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XXII ExpoPPGIm
Reunião Anual do Programa de Pós-graduação em Imunologia UFBA
10 a 12 de agosto de 2022

Instituto de Ciências da Saúde
Universidade Federal da Bahia – Campus Vale do Canela

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RESUMOS

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XXII EXPOPPGIM

Reunião Anual do Programa de Pós-graduação em Imunologia UFBA 10 a 12 de agosto de 2022

Instituto de Ciências da Saúde Universidade Federal da Bahia – Campus Vale do Canela

PROGRAMAÇÃO

10 de agosto, quarta-feira 09:00 h - Abertura. Silvia Lima Costa e Vitor Antônio Fortuna

09:00 h - Abertura. Silvia Lima Costa e Vitor Antônio Fortuna

09:00 às 10 :00- Conferência Plenária. Moderador Alex Torres

***Mycobacterium tuberculosis* explora a via endógena do receptor de ácido retinóico para modular as respostas mielóides.** André Luiz Barbosa Báfica (UFSC)

10:00 às 12:00 h – Mesa redonda: Avanços no Entendimento da Relação entre Patógeno/ Hospedeiro. Moderador Maria de Fatima Dias Costa

Biologia molecular e imunidade contra microrganismos patogênicos e doenças crônicas e em condições de disbiose. Leonardo Augusto de Almeida (UNIFAL-MG)

Disbiose oral: da sinergia polimicrobiana à subversão do sistema imunitário. Soraya Castro Trindade (UEFS-BA)

Infecção neurológica por *Neospora caninum*: relação entre e via das quinureninas e imunomodulação. Maria de Fatima Dias Costa (UFBA)

14:00 às 15:00 h – Conferência Plenária. Moderador Songeli Menezes Freire

Genômica como ferramenta de One Health. Vasco Ariston Azevedo (UFMG)

15:00-17:00 h – Sessão de Poster Discentes PPGIm I.

Moderadores Soraya Castro Trindade e Victor Diogenes Amaral da Silva

17-18:00 h - Conferência Plenária. Moderador Luciana Santos Cardoso

Inflamação na Patogênese da Leishmaniose Cutânea Disseminada. Edgar Marcelino de Carvalho Filho (IGM/Fiocruz-BA, HUPES/UFBA)

11 de agosto, quinta-feira

09:00- às 10 :00 – Conferência Plenária. Moderador Simone Gracia Macambira

O Lado Obscuro do Laboratório: o que está acontecendo no Laboratório Seco. Artur Trancoso Lopo de Queiroz (IGM/Fiocruz-BA)

10:00 às 12:00 h – Mesa Redonda: Imunopatologia e terapia I. Moderador Silvia Lima Costa

Mecanismos e possíveis tratamentos para Mucosite. Tatiani Uceli Maioli (UFMG)

Propriedades neuroimunomoduladoras de flavonoides: uma ação potencial como adjuvantes para o tratamento do glioblastoma. Silvia Lima Costa (UFBA

Efeitos neuroprotetores e antineuiflamatórios de compostos naturais em modelos de estudo da Doença de Parkinson. Victor Diogenes Amaral da Silva (UFBA)

14:00-15:00 h - Conferência Plenária. Moderador Roberto José Meyer Nascimento

BCG recombinante expressando genes do SARS-CoV-2 protege parcialmente contra à COVID-19. Sergio Costa Oliveira (UFMG)

15:00 às 17:00 h – Sessão de Poster Discentes PPGIm II.

Moderadores Deise Vilas Boas e Victor Diogenes Amaral da Silva

17:00-18:00 h - Conferência Plenária. Moderador Luis Pacheco

Genome-phenome and host-pathogen interactions – based development of candidate drugs and vaccines against pathogenic microorganisms. Sandeep Tiwari (UFMG)

12 de agosto, , sexta-feira

09:00- às 10:00 – Conferência Plenária. Moderador Victor Diogenes Amaral da Silva

Os efeitos da privação de sono na dor e resposta imune pós-operatória: o que os modelos animais nos ensinam? Maira Assunção Bicca (John Hopkins School of Medicie, USA)

10:00 às 12:00 h – Mesa Redonda: Imunopatologia e terapia II. Moderador Vitor Antônio Fortuna

Corpúsculos e mediadores lipídicos na resposta inflamatória em modelo murino de anemia falciforme Jaime Ribeiro (IGM/Fiocruz-BA)

Terapia microbiana no controle do tumor de mama murino. Patricia Paiva Corsetti (UNIFAL-MG)

Terapia Celular Aplicada à Imunologia. Vitor Antônio Fortuma (UFBA)

14:00- 15:00 h – Conferência Plenária V. Moderador Soraya Castro Trindade

Aplicações e desafios da Probiogenômica. Rodrigo Dias Carvalho (UFBA-PV)

15:00 às 16:00h – Apresentação do Programa de Pós-graduação em Imunologia

Premiações de Posteres. Moderadores Silvia Lima Costa e Vitor Antônio Fortuna

16: 00-17:00 h – Celebração 40 Anos do LabImuno. Laboratório de Imunologia e Biologia Molecular do Instituto de Ciências da Saúde da UFBA: 40 anos de Contribuição no Diagnostico e na Pesquisa em Imunologia. Roberto Meyer Nascimento (UFBA).

17:00h Encerramento

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APRESENTAÇÃO

O Programa de Pós-graduação em Imunologia (PPGIm) há mais de 30 anos, vem formando recursos humanos de excelência, capacitados para as atividades de ensino e pesquisa em Imunologia e áreas correlatas, muitos já absorvidos por instituições da Bahia e de outros estados. O PPGIm tem realizado reuniões científicas visando difusão do conhecimento científico e integração acadêmica com a graduação e a pós-graduação da própria UFBA e outras IES. A ExpoPPGIm, Reunião Anual do Programa, já se tornou um evento tradicional, que acontece a cada ano, com a primeira edição no ano 2000, constituindo um fórum de integração de profissionais, pesquisadores e jovens cientistas, alunos de graduação e pós-graduação da UFBA e outras IES do Estado da Bahia, do Brasil e de outros Países com interesse no amplo domínio da Imunologia. O objetivo da ExpoPPGIm é divulgar conhecimento científico em Imunologia e áreas correlatas, gerado localmente, na Bahia, no Brasil, e outros países, tendo como público-alvo estudantes de graduação e pós-graduação, pesquisadores da UFBA e outras IES e profissionais da área. Esta XXII Edição da ExpoPPGIm que aconteceu entre os dias 10 e 12 de agosto de 2022 foi realizada nas instalações do Instituto de Ciências da Saúde e contou com a participação como palestrantes além de pesquisadores da própria UFBA, pesquisadores vinculados a outras instituições de ensino e pesquisa da Bahia e do Brasil, que apresentaram palestras em 4 sessões temáticas, relacionadas às linhas de pesquisa do Programa. Ainda, durante o evento, discentes do Programa apresentaram e discutiram sobre seus projetos de pesquisa em desenvolvimento distribuídos em e sessões pôster, e assim também contribuindo para a integração acadêmica e a difusão do conhecimento científico em Imunologia e seus correlatos.

RESUMOS SESSÕES DE POSTER

EVALUATION OF IGF-1 OVEREXPRESSION AS A STRATEGY TO POTENTIALIZE THE NEUROREGENERATIVE EFFECT OF HUMAN MESENCHYMAL CELLS

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Introduction: Mesenchymal stromal cells (MSCs) are a heterogeneous population of cells with broad potential for clinical applications due to the anti- inflammatory, anti-apoptotic, antimicrobial, immunomodulatory and anti-fibrotic properties already described. However,

they are expanded in fetal bovine serum (FBS), containing media more broadly as less proliferative, and expression more generic in scope. The modification of MSCs for the expression of factors shows promising results in cell therapy. IGF-1 acts in the regulation of neurogenesis, cognition and recovery during the damage process in ischemic stroke. **Objectives:** Define a protocol for the generation of genetically modified mesenchymal stem cells with high potency for use in cell therapy. **Material and Methods:** Synthesized IGF-1 plasmids were coupled to an ampicillin-resistant vector (AmpR) for selection of transformed bacteria. MSC- IGF-1 were generated by nucleofection and characterized by cytometry expressing 98% CD90, 96% CD73, 91% CD105 and 0.3% negative markers. Tests were performed to ensure cell viability, cell morphology, cell cycle and growth curve, as well as a test to evaluate the immunomodulatory potential of the generated MSCs, such as mixed leukocyte reaction and lymphoproliferation assay. **Results and discuss:** When comparing the culture in SBF and the lysate, we observed that there is no difference in morphology, but the expression of beta-galactosidase was increased in the culture with lysate. The experiments to evaluate cell proliferation and immunosuppression, as well as analyzes of cytokine production still need to be performed.

Conclusions: The results suggest further investigation into the behavior of cell modification, as well as the immunomodulatory and neuroregenerative potential of IGF-1 overexpression.

Key Word: Mesenchymal cells, Immunoregulation, Cell therapy

Support: FAPESB

IL5RA GENE VARIANTS ARE ASSOCIATED WITH ASTHMA AND ATOPY PHENOTYPES IN A BRAZILIAN POPULATION

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Introduction: Asthma affects approximately 339 million people worldwide. It is a heterogeneous disease determined by interactions between genetic and environmental factors. Symptoms such as wheezing, dyspnea, and cough result from variable airway obstruction caused by inflammation. The IL-5 receptor, expressed mainly on eosinophils, plays a crucial role in the pathogenesis of the eosinophilic phenotypes of asthma and respiratory allergies. Many genetic studies have identified variants in this gene associated with asthma susceptibility in other populations. **Objective:** Investigate genetic variants in the interleukin-5 receptor alpha subunit gene (*IL5RA*), associated with asthma phenotypes and atopy markers in the mixed population of Salvador-BA. **Material and Methods:** Genomic DNA from 1094 patients from the Bahia Asthma Control Program (ProAR) was genotyped using the Illumina Multi Ethnic Global Array chip. All patients underwent skin tests for the most common inhaled allergens in the region. Total immunoglobulin E concentration was determined by nephelometry. Dominant and additive logistic regression models were used for association analysis using PLINK 1.9. Comparisons between genetic groups were analyzed using the GraphPad Prism 8, and *in silico* functional analyzes were performed using Genotype-Tissue Expression (GTEx Portal) version 8. **Results and Discussion:** The G allele of rs163551 is negatively associated with asthma in the ProAR population (OR = 0.76). On the other hand, it seems to increase the chances of asthmatic individuals having severe asthma (OR = 1.51), as does the G allele of rs340831 (OR = 1.55). Both appear to contribute to increased *IL5RA* gene expression in whole blood, according to GTEx expression quantitative trait (eQTL) loci data. The presence of the A allele (rs17885926) seems to contribute to patients with severe asthma having an adequate response to the bronchodilator (OR = 0.08). However, this allele is associated with an increased chance of ProAR individuals being allergic to mites and cockroaches (OR = 3.81). **Conclusions:** Variants in the *IL5RA* are associated with asthma and atopy in the ProAR population. Investigating them may provide answers about the different pathophysiological mechanisms of the disease and assist in the stratification of patients towards personalized treatments in the Brazilian population.

Keywords: Asthma, variants, phenotypes, eosinophilia.

Support: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

EFEITO IN VITRO DO EXTRATO DAS FOLHAS DE LIPPIA ORIGANOIDES KUNTH NA PRODUÇÃO DE IL-10 POR CÉLULAS DE INDIVÍDUOS COM PERIODONTITE.

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Abstract

Introduction: Periodontitis is an inflammatory disease characterized by the progressive destruction of periodontal tissues, caused mainly by microorganisms such as Porphyromonas gingivalis. This microorganism causes an inflammatory reaction resulting in the production of Interleukin-10 (Il-10). Conventional treatment is scaling and subgingival root planing, however, in some cases, the sites continue to show disease progression. In this perspective, the search for natural products with antibacterial activity in the fight against diseases that affect the oral cavity has been considered, especially with the emergence of multiresistant strains to antibiotics.The use of Lippia origanoides Kunth in its treatment is promising, as it has anti-inflammatory activity.andantimicrobial. However, the knowledge of its immunomodulatory capacity is not well elucidated. **Objectives:** The present study evaluated the in vitro effect of the leaves extract of Lippia origanoides Kunth on the production of Il-10 by peripheral blood cells of individuals with periodontitis. **Methods:** Research participants were recruited from the UEFS dental clinic.The extract of the leaves of L. origanoides Kunth was obtained by maceration with methanol and concentrated by rotary evaporation, provided by the Laboratory of Chemistry of Natural and Bioactive Products.After periodontal examination, blood from volunteers was collected and cells were cultured with Porphyromonas gingivalis antigens, with and without the presence of Lippia origanoides Kunth leaf extract. The dosage of IL-10 in the culture supernatant was performed by enzyme immunoassay. The data obtained were evaluated with ANOVA and Games-Howell post-hoc tests. **Results:** Nine individuals diagnosed with periodontitis participated in the study. The presence of P. gingivalis and L. origanoides extracts, used in cultures separately or simultaneously, determined a higher concentration of IL-10 in the supernatant, when compared to the concentration of cells without stimulation. However, a statistically significant difference was only observed in the concentration of IL-10 stimulated by the P. gingivalis extract ($p=0.004$). **Conclusions:** Porphyromonas gingivalis extract induced an increase in IL-10 production by human peripheral blood cells. The extract of the leaves of L. origanoides does not seem to interfere in this production.

Keywords: periodontitis; immunomodulation; cytokines.

Support: Fundação de Amparo à Pesquisa do Estado da Bahia.

FLAVONOID AGATHISFLAVONE MODULATES MICROGLIA FOR AN ANTI INFLAMMATORY AND NEUROPROTECTIVE PROFILE.

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Introduction: Neuroinflammation is one of the mechanisms responsible for the emergence of neurodegenerative diseases (NDD), inducing activation of glial cells, such as microglia. In the central nervous system, microglia orchestrate the inflammatory response to various insults, acquiring a pro-inflammatory cytotoxic profile that can exacerbate brain damage. However, considering the modulation of microglia plasticity of their inflammatory response to injury may also promote stages of inflammation resolution and tissue regeneration. Agathisflavone, a biflavonoid purified from *Poincianella pyramidalis* (Tul.) has demonstrated anti inflammatory and neuroprotective properties in in vitro models of NDD.

Objectives: Here, we investigated the effects of agathisflavona directly in microglial cells submitted to inflammatory damage in view to elucidate mechanisms of neuroprotection associated to modulation of inflammatory response. **Material and Methods:** Microglia were isolated from cortical primary cultures of newborn Wistar rats and were exposed to *Escherichia choli* lipopolysaccharide (LPS,10 ng/mL) and treated or not with agathisflavone (1- 10µM), for 24h. To investigate possible neuroprotective effects of agathisflavona treatment, differentiated PC12 neuronal cells were exposed to the microglia secretoma (MS) derived from cultures in each experimental condition. **Results and Discussion:** We observed that the inflammatory stimulus with LPS induced the microglia to assume an activated cellular state with pro-inflammatory profile characteristic (increased CD68), confirmed by phenotypic changes with more rounded or amoeboid cells. However, when treated with agathisflavone, microglia up-regulated expression of CD206 (anti- inflammatory) and down-regulated CD68 expression, as well presented mainly more branched-like phenotype, in addition to a reduction in the expression of inflammatory mediators IL-6, IL1-b, TNF, NRLP3 and chemokines CCL5 and CCL2, characterizing change to an anti inflammatory state. Moreover, we observe the preservation of neurites and regulation in the expression of β-tubulin III and Caspase-3 in PC12 cells exposed to MS derived from agathisflavona and agathisflavona plus LPS treated cultures.

Conclusions: Together, these data reinforce the capacity of the flavonoid in reprograming microglia

to a neuroprotective anti-inflammatory profile standing out as a promising molecule for the treatment or prevention of neurodegenerative diseases.

Keywords: Neuroprotection, Anti-inflammatory, Flavonoids.

Funding: CAPES, FAPESB and CNPq

GUT MICROBIOME DIVERSITY AND GENETIC VARIANTS OF GPR41 AND GPR43 IN A POPULATION OF BRAZILIAN ASTHMATICS

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Introduction: The gut microbiota can influence immune responses at distant sites, such as the lung, via multiple mechanisms and plays several important roles in the development, regulation, and maintenance of healthy immune response. Several studies have linked unbalanced of the gut microbiota with an altered risk of asthma later in life. The development of asthma and allergy is also related to the western lifestyle, underlying the important role of the environment in the pathogenesis of these diseases. Studies have identified that different diets produce an infinity of specific metabolites that can influence the immune response. Several dietary metabolites, particularly fatty acids, influence inflammation through a diverse family of G protein-coupled receptors (GPCRs). GPCRs for short-chain fatty acids such as GPR43 and GPR41 play key roles in promoting intestinal homeostasis and regulating inflammatory responses. **Objectives:** To assess microbial diversity from the microbiota in stool samples and to associate genetic polymorphisms of GPR41 and GPR43 in asthmatic individuals. **Material and methods**: This project is part of a multicenter study conducted in five countries. A total of 57 stool samples were collected from each subject (29 samples from asthmatics and 28 samples from non-asthmatics individuals) the bacterial 16S rDNA targeting the V4 region was amplified using PCR and sequenced by Illumina MiSeq high-throughput sequencing. The bioinformatics analysis was conducted using QIIME2 (version 2021.4) and data visualization and analysis using R (version 4.1.0). The analysis of genetic variants was performed with DNA extracted from peripheral blood of individual's and genotyping was executed using the TaqMan technique in the QuantStudio 12k Flex equipment. **Results and conclusions:** The richness and diversity of the microbial community, i.e. alpha diversity, in asthmatics was lower than that in non-asthmatics, although no significant difference in Observed ASVs and Shannon index was observed. Beta diversity analysis was performed by Bray– Curtis dissimilarity analysis, indicated a significant difference in beta diversity between the two groups. Although without statistical significance, it was possible to observe in the analyzed polymorphisms that the polymorphic allele is associated with the risk of developing T2 asthma. This study supports information of the microbial diversity and richness of species among asthmatics and non- asthmatics individuals.

Keywords: asthma, microbiome, sequencing, gut microbiota

Support: FAPESB, ERC: European Research Council

EVALUATION OF IMMUNOMODULARORY EFFECTS OF PHYSALIS ANGULATA IN TUMORAL CELLS C6 OF GLIOBLASTOMA

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Introduction: Glioblastomas are high grade glial cell brain tumors that have a poor prognosis. They have a great capacity for migration, proliferation and invasion into brain tissue, which reduces the chances of treatment success. New therapeutic targets are studied in order to increase the efficacy of treatments and decrease side effects. *Physalis angulata* is a plant species rich in chemical components and promising for the pharmaceutical industry. It has among many proven benefits, the antitumor action promoted by physalins. **Objectives:** Study the immunomodulatory action of the ethanolic extract of *Physalis angulata* on murine glioblastoma C6 tumor cell line. **Material and Methods:** Cytotoxicity was evaluated by the MTT method. Nitric oxide was dosed by Griess method. Cell migration was analyzed by migration assay. Cell morphology was evaluated by immunocytochemistry with EGFR immunolabeling and Rosenfeld staining method. Protein expression was evaluated by Western blotting method. **Results and Discussion:** Through the MTT assay, the EEPA was cytotoxic above the concentration 5 µg/mL, so the concentrations 0.5, 1 and 2.5µg/mL were chosen for modulation of the following experiments. In the morphological analysis by immunocytochemistry, a decrease in EGFR expression was found in concentrations 1 and 2.5µg/mL. As for Rosenfeld, in concentrations 1 and 2.5µg/mL we have a smaller amount of cells and presence of smaller and thinner prolongations, and smaller cell body when compared to controls. Western blotting showed a lower expression of EGFR in the tested concentrations when compared to the control. **Conclusions:** The results obtained in this study may indicate a reduction in tumor expression when modulated with EEPA.

Keywords: glioma; antitumoral activity; Physalis angulata. physalins.

Support: Capes

INVOLVEMENT OF THE *MTOR* GENE AND ITS VARIANTS IN THE SEVERITY OF COVID-19

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Abstract

Introduction: COVID-19 disease severity is associated with an exacerbated and uncontrolled systemic inflammatory response resulting from cytokine storm. The mTOR pathway has been shown to be affected by SARS-CoV-2 and hyperactivated in severe patients which suggest that dysregulation of this pathway might play an important role in poor prognosis of disease. In addition, the genetic background of patients could possibly contribute to this outcome. **Objectives:** To investigate the involvement of MTOR gene on COVID-19's severity in the Brazilian population. **Methods:** Severe and mild COVID-19 individuals were recruited. Blood samples and sociodemographic data were collected. DNA was extracted and MTOR SNP rs2295079 was genotyped. **Results and Conclusions:** In our population, we found that older and male individuals were prevalent in the severe group, within this group 35.9% were admitted to ICU and 19.7% have died of COVID-19. Majority of patients with ongoing comorbidities such as hypertension, diabetes and cardiopathy were present in the severe group and these analyses were statistically significant. The rs2295079 was not associated with COVID-19 severe outcome in this population. It is expected that this study will help to understand more the influence of genetic variants of the MTOR gene on the severity of COVID-19.

Keywords: mTOR; COVID-19; severe; polymorphisms.

Support: PPSUS/FAPESB 02/2020 and CAPES 2021.

MOLECULAR MEDIATORS SECRETED BY MESENCHYMAL STEM CELLS ACCELERATED SKIN REPAIR IN EXPERIMENTAL SICKLE CELL WOUND MODEL

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Introduction: Sickle cell anemia is a hemoglobinopathy characterized by a mutation in the beta-globin chain of the hemoglobin, generating hemoglobin S. Erythrocytes with a sickle cell phenotype have difficulty moving through the capillaries, causing secondary complications such as chronic leg ulcers (UCL). Clinical cases of UCL constitute an important public health problem, presenting higher costs of health services as a result of the treatment and management of complications resulting from non-healing. Due to their ability to secrete bioactive molecules involved in angiogenesis and tissue repair, Adipose tissue mesenchymal stem cells (ASC) are important for the treatment of non-healing wounds. **Objectives:** The aim of this study was to evaluate the effects of ASC secretome on wound healing in mice with sickle cell anemia. **Methods:** Secretome collected from adipose tissue-derived mesenchymal stromal culture was administered to dorsal full-thickness wounds on sickle cell anemia mice (Townes model, HbSS) (CEUA ICS 131/2018 e CEUA FIOCRUZ 021/2019). The secretome's therapeutic effect was analyzed in wound healing model through wound reduction rate, gene expression analysis by RT-PCR, histological and immunofluorescence assay. **Results:** Wounds treated with ASC secretome showed improved healing over 7 days (n=08). The proteomic profile demonstrated pro-angiogenic growth factor and tissue remodeling mediators were detected in ASC secretome. Histological assay showed a reduction in the inflammatory infiltrate, an increase in the number of fibroblasts ($P<0.0001$) and in the epidermis thickness ($P=0.0091$) at the wound's lesions treated with the ASC secretome. Immunofluorescence analysis and RT-PCR are still under investigation. **Conclusion:** These preliminary data suggest that ASC secretome has important properties for the treatment of skin ulcers and can be a promising alternative for the regenerative medicine.

Support: FAPESB, CNPq and PIBIC-UFBA.

Keywords: ASC, chronic wounds, cell therapy, sickle cell anemia.

DRIED WHOLE BLOOD SPOTS VIABILITY FOR ANTI-HEV IGM AND IGG HUMAN COMMERCIAL ELISA KIT - PRELIMINARY RESULTS

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Introduction: Hepatitis E virus (HEV) develops an infectious disease that affects the liver, which can lead to mild or moderate acute conditions. As the main transmission route is fecal-oral, through contaminated water or food, endemic control relies on hygiene and basic sanitation. Pigs are cited as the main natural reservoir. Human diagnosis is performed by means of serological identification of anti-HEV IgM and IgG. Because it is a disease with a low incidence and its main natural reservoir is related to swine farming, the diagnostic test entails the need to transport the samples to a central laboratory or transfer the patient. The use of filter paper for storing and transporting dried blood samples is an established routine in the SUS for prenatal screening of similar infections. **Objectives:** To evaluate the feasibility of using dried blood samples on filter paper for HEV seroreactivity test using ELISA commercial kit. **Materials and Methods:** The project was approved by CEP-HUPES (CAAE: 13814419.6.1001.0049). Whole blood samples were collected with EDTA and then spots of 60uL were applied on filter paper (S&S 903). Reactivity tests were realized with a conventional HEV IgG ELISA kit (Mikrogen). Plasm samples were diluted according to the manufacturer's recommendation and one 3mm diameter filter paper picot was eluted in 150uL with respective kit diluent. Six positive samples and six negative samples were used for each ELISA test, comparing picots and plasm results. **Results and Discussion:** Among positive samples, O.D. values were evidenced for the picot about half than presented in plasm. However, considering the cutoff for each test, there was no change between positive and negative results. HEV tests are not part of common surveillance by the Brazilian Health System. Besides other tests such as HVB being standardized with one picot, preliminary results indicate that for HEV tests will be necessary a higher concentration of picots for conventional diagnostic kits. Standardizing this method will allow easier sample collection in isolated areas, contributing for SUS covering. Conclusion: Filter paper as a screening diagnosis for transport, storage and serological testing of HEV has real feasibility. More tests are needed to standardize and validate the methodology.

Keywords: HEV; ELISA; Dried Whole Blood; Filter Paper.

Support: LabImuno; CAPES; PIBIC-UFBA; CNPq; FAPESB; PPGIm;
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HETEROLOGOUS EXPRESSION OF *DERMATOPHAGOIDES PTERONYSSINUS* ALLERGEN DER P 5

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Abstract ExpoPPGIm UFBA 2022 Introduction: Allergic diseases are mostly triggered by allergens. One of the main sources of IgE-reactive proteins are the house dust mites (HDM), mainly those belonging to the genus *Dermatophagoides sp*., which are known for its global incidence. However, the group 5 allergen from *Dermatophagoides pteronyssinus* (Der p 5) lacks studies on its clinical importance in tropical and subtropical regions of the globe. **Objectives:** To induce the heterologous expression of the allergen Der p 5 **Materials and methods:** The shortened Der p 5 sequence was sent for synthesis and cloning into the expression vector pET3a. Transformation was performed using the chemocompetent *E. coli* BL 21 (DE3) *star* strain*,* through heat shock transformation. Induction of expression was performed with 0.5 mM IPTG on a small scale (10 mL LB media) to standardize the best expression conditions. Scale-up (1L) of the induction was performed for 4 h at 37 ºC, at 220 rpm. The solubility of the recombinant Der p 5 (rDer p 5), was evaluated using a lysis buffer (50 mM Sodium Phosphate, pH 8). Cell lysis was performed by sonication, using a frequency of 40Hz in an ice bath. Following centrifugation, the supernatant was collected. The sediment was resuspended in a 6M urea solution and centrifuged again. Transformation, expression, and protein solubility were confirmed by SDS-PAGE and Western blot. In the case of the latter, a pool of sera from mice allergic to *D. pteronyssinus* was used to verify the recombinant's ability to bind IgG antibodies. **Results and Discussion:** rDer p 5 expression was confirmed by the presence of an overexpressed band with a molecular weight (MW) around 12 kDa, which was similar to the theoretical one of 11.95 kDa. The extracted rDer p 5 was completely soluble, highlighting the absence of the protein in the sediment solubilized with urea. These findings were confirmed by Western blot analysis. . **Conclusion:** rDer p 5 was satisfactorily expressed in *E. coli* in a soluble form, which bond to antibodies in sera from *D. pteronyssinus* allergic mice. Future studies using human sera to detect IgE reaction will settle the protein as a recombinant allergen.

Keywords: house dust mite, recombinant protein, allergy

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FUNCTIONAL CHARACTERIZATION OF THE ELASTASE ENZYME FROM SCHISTOSOMA MANSONI AND EVALUATION OF ITS ROLE IN THE DEVELOPMENT OF THE IMMUNE RESPONSE TO THE PARASITE

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Abstract

Introduction: In Brazil, over seven million people are infected by *Schistosoma mansoni*. *S. mansoni* parasite has a complex life cycle and the host infection occurs by the active penetration of cercariae through the skin. This penetration process starts a several immune mechanisms which are different between individual who has been infected for the first time and individual who had previous contact with the parasite antigens. Among the *S. mansoni* antigens, the protein involved in the penetration process: serine protease elastase (SmCE) has been identified as the most abundant and most important protease in the process. Despite that, the trigger to the initial response against infection remains unknown. **Objectives:** Characterize the *Schistosoma mansoni* elastase enzyme and evaluate its importance in the development of the immune response to the parasite in healthy individuals and previously infected ones**. Methods:** Once the recombinant protein was expressed, we performed an enzymatic assay with the chromatogenic substrate for 24h in some different pHs and protein concentrations. With these results we did another incubation, change the substrate concentration to determinate the Vmax and Km of the enzyme. Human peripheral blood mononuclear cells were incubated for 48 hours with the SmCE and a viability test was made, the supernatant was used to determinate the optimal and sub-optimal concentration of the protein for cytokines assays as well. **Results and Conclusions**: The best protease activity was found in the concentration of 650µg/mL at pH 9, and its Vmax and Km was 0.02568mM/min and 0.04089mM respectively. Viability test show about 52% of viable cells in the presence of 100 µg/mL of SmCE and the optimal concentration was 6.2µg/mL. This experiment concluded so far that in higher concentration the SmCE protein is cytotoxic to cells, thus the optimal concentration will be used for this project.

Keywords: *Schistosoma mansoni,* elastase, enzyme, cercaria, infection

Support: CNPq, FAPESB (APP0099/2016)

INVESTIGATION OF THE NEUROPROTECTIVE AND ANTI-NEUROINFLAMMATORY POTENTIAL OF MARINE SPONGES

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INTRODUCTION: Neurodegenerative diseases are characterized by the progressive loss of neurons, resulting in disability and death. They have different etiologies, but some show similar components, such as oxidative stress and exacerbated inflammation. Oxidative stress leads to cell death through mitochondrial dysfunction, causing bioenergetic imbalance with subsequent neuronal damage and brain injury, associated with neuroinflammation, orchestrated mainly by glial cells, that contributes to the progression of neurodegeneration. Hence, the search for new therapies from natural compounds aims to discover new neuroprotective substances with neuroprotective and anti-neuroinflammatory effects. **OBJECTIVES:** To analyze cytotoxicity of extracts from marine sponges to neuronal cells, and to determine the best candidates, considering the viability parameters. **METHODOLOGY:** Cultures of neuronal PC12 cells were treated with a total of 23 different extracts (0.1 to 200 µg/mL) obtained with different solvents (methanol, ethyl acetate and chloroform) from 9 species of sponges from the coast of Salvador, Bahia in Brazil, and cell viability was determined after 24 h treatment by MTT test. **RESULTS AND CONCLUSIONS:** Most extracts showed toxicity only at the highest concentrations of 100 and 200 µg/mL adopted, but chloroform and methanolic extracts did not show cytotoxicity at concentrations of 0.1, 1 and 10 µg/mL. Moreover, cultures treated with the C1, F1, I1 and J1 chloroform extracts and with the F3 and H3 methanolic extracts, presented the greater amounts of cells that metabolized MTT. Ethyl acetate extracts did not show significant results in the evaluated parameters. These results encourage continuity of studies in neuroinflammation models to determine extracts and its components best candidates and potential application for neurodegenerative diseases.

KEYWORDS: Neuroinflammation, marine sponges, neuroprotection, anti- inflammatory

SUPPORT: CNPq

PROSPECTING FOR PROTEINS AND EPITOPES OF *CORYNEBACTERIUM PSEUDOTUBERCULOSIS* FOR THE DEVELOPMENT OF A MULTI-EPITOPE IMMUNOGEN

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Introduction: *Corynebacterium pseudotuberculosis* is a Gram-positive, facultative intracellular pathogen known to cause diseases of veterinary importance. Among these diseases is Caseous Lymphadenitis (CLA), a disease that affects goats and sheep, causing abscess formation in lymph nodes and internal organs and, consequently, economic losses for breeders. Prophylaxis is the most cost-effective alternative for the control of infectious diseases; however, there is no effective vaccine yet against CLA. Several *in silico* methodologies are contributing to the selection of molecular targets aiming the development of therapeutic strategies, diagnostic methods and recombinant immunogens. **Objectives:** The present work aimed to use immunoinformatics tools to develop and characterize potentially immunogenic chimeric proteins that combine epitopes of antigenic proteins secreted by *C. pseudotuberculosis*. **Methods:** The antigenic proteins RpfB, SlpA, Nlpc/P60 and CP40 were selected from literature search and evaluated for their intraspecific conservation and homology with proteins from the goat and sheep hosts. Subsequently, epitopes of MHC-I, MHC- II and B cells present in these proteins were predicted and evaluated, and those that were shown to be overlapping with each other were selected for the construction of chimeric proteins. Five chimeric proteins were proposed with different combinations of these epitopes and fused to the adjuvant lipopeptide LprA. Physicochemical, allergenicity and antigenicity parameters were predicted and evaluated for these proteins and their variations without the adjuvant LprA. The chimeric protein with the highest immunogenic potential was submitted to the modeling and refinement of its three-dimensional structure, for which the binding affinity to immune mediators such as the TLR2 receptor will be predicted. **Results and Conclusions:** Five chimeric protein variations were designed combining T and B cell epitopes predicted for antigens secreted by *C. pseudotuberculosis*. One variation stood out for its stability and antigenic potential, and its tertiary structure was predicted and refined *in silico*. It was predicted that this multi- epitope protein is soluble and non-allergenic, thus suitable for heterologous expression in *Escherichia coli* and vaccine formulation. Future steps of this work include the prediction of the affinity of this protein to the TLR2 receptor and heterologous expression for further characterization.

Keywords: corynebacteria, immunoinformatics, sheep and goat farming, vaccination.

Support: CAPES

EFFECT OF *LIPPIA INSIGNIS* LEAF EXTRACT ON IFN-G PRODUCTION BY PERIPHERAL BLOOD MONONUCLEAR CELLS OF INDIVIDUALS WITH PERIODONTITIS.

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Abstract

Introduction: Periodontitis is a destructive inflammatory reaction characterized by inflammation and subsequent loss of tissue from dental support and may result in loss of dental unit. It is triggered by key pathogens, such as *Porphyromonas gingivalis*, which initiate the host's inflammatory and immune response, increasing the concentration of innate and adaptive immunity cytokines. The treatment for periodontitis aims to reduce the accumulation of biofilm and eliminate infections, and can thus be associated with the administration of antibiotics and antiseptics. However, the use of these chemical agents may have adverse effects, such as microbial resistance. This is one of the reasons why the use of natural products as an alternative for the treatment of diseases has been highlighted. **Objectives:** To evaluate whether the extract of the leaves of the plant species *Lippia insignis* has an immunomodulatory effect on the production of interferon-g cytokines (IFN-g) by peripheral blood cells of patients with and without periodontitis. **Methods:** Peripheral blood cells were obtained from individuals with and without periodontal disease that met the eligibility criteria of this study and these were grown in wells with the following stimuli: mitogen (PWM); extract from the leaves of *L. insignis*; sonicated extract of *P. gingivalis*; extracts of *L. insiginis* and *P. gingivalis* simultaneously, besides the well without stimuli. The dosage of the cytokine IFN-g was measured by the Immunoenzymatic Assay ELISA. **Results:** There was a statistically significant difference in IFN-g production between the groups only when the cells were cultured with PWM. No difference was observed in the production of this cytokine when cells were stimulated with the extract of the leaves of *L. insignis* (p=0.93) or with the extract of *P. gingivalis* (p=0.89), when compared to its basal production, without stimulus. **Conclusions**: *The extract from the leaves of L. insignis does not interfere with the production of IFN-g by peripheral blood cells.*

Keywords: Periodontal disease, *Lippia insignis*, IFN-g

Support: CNPq

INVOLVEMENT OF COMPONENTS OF THE TRYPTOPHAN PATHWAY IN THE ANTI-NEUROINFLAMMATORY EFFECTS OF FLAVONOID AGATHISFLAVONA

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Introduction: Tryptophan (Trp/W) is an essential amino acid important for the synthesis of proteins and neurotransmitters such as serotonin and melatonin. Trp is bound to serum albumin and the remainder is freely available in the blood and is able to cross the blood-brain barrier and can be transformed into bioactive molecules by CNS cells. In inflammatory processes, cells such as macrophages, astrocytes and microglia produce indoleamine 2, 3-dioxygenase (IDO), enzyme responsible for the transformation of Trp into kynurenines (KYN). KYN can undergo the action of kynuriniases, and the enzyme kynurenine 3-monoxygenase (KMO) produces quinolinic acid (QUIN), important in the formation of nicotinamide, a component of the NAD+ hydrogen transport. Metabolites of this pathway, such as QUIN and kynurenic acid (KINA), can modulate the expression of several cytokines, chemokines and their receptors in astrocytes, with an important role in neuroinflammation. The flavonoid agathisflavone (bis-apigenin), has demonstrated neurogenic, neuroprotective and anti-neuroinflammatory properties, however mechanism of action are still few elucidated **Objectives:** This work investigated the possible role of Trp pathway in the agathisflavona effects in an in vitro model of neuroinflammation. **Methods:** : Isolated microglia and mixed glial (astrocytes and microglia) primary cultures obtained from newborn rats (P2) were modulated with agathisflavone (1 µM) in the presence or not of LPS (1 µg/mL), QUIN (500 nM), or with the IDO inhibitor, 1-methyl tryptophan. It was observed that LPS and QUIN induced toxicity, evidenced by the MTT test, and morphological changes in glial cells, evidenced by immunocytochemistry, characterizing gliosis, effects also observed in cultures modulated with IDO inhibitor, and reversed in cultures also treated with agathisflavone. **Results and Conclusions** Components of the tryptophan pathway may be associated with anti-neuroinflammatory effects of the flavonoid agathisflavona.

Keywords: Tryptophan; kynurenines; agathisflavone (bis-apigenin)

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IGE REACTIVITY OF *BLOMIA TROPICALIS* MAJOR ALLERGENS AND HYBRID PROTEINS THEREOF IN A TRIAD OF COUNTRIES

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Abstract

Introduction: Chronic respiratory diseases display worldwide distribution and they are considered social and economic burdens. Allergens from dust mite, such as *Blomia tropicalis,* are important triggers and their binding to IgE lead to allergic symptoms. A treatment approach in healthcare includes allergen specific- immunotherapy and our research group has developed hypoallergenic hybrid candidates, termed BTH1 and BTH2. Both are based in the two major allergens Blo t 5 and Blo t 21. **Objective:** To measure the IgE reactivity of the recombinant proteins rBlo t 5, rBlo t 21, BTH1 and BTH2, in sera of subjects from Brazil, Colombia and Ecuador. **Material and Methods:** IgE binding capacity was tested by indirect ELISA. One hundred and ninety-six subjects were included: 90 (including 26 non-atopics) from Brazilian adults, 46 (10 non-atopics) from Colombian children, and 60 (13 non-atopics) from Ecuadorian children. Atopy was defined as follows: 1) Brazil and Colombia - clinical history of allergic disease with both positive skin prick test and presence of specific IgE (sIgE) to *B. tropicalis* extract (BtE); 2) Ecuador - clinical history of allergic disease and presence of specific sIgE to *B. tropicalis* (by in-house ELISA). Allergic disorders were classified by severity using Global Initiative against Asthma criteria. **Results and Discussion:** ELISA measurements confirmed the IgE reaction against BtE in sera from atopic donors of the three countries. Out of this positive reactive sera, 81.25%, 88.89% and 81.82% of the sera from Brazilian, Colombian and Ecuadorian donors, respectively, reacted to rBlo t 5. Sixty-three percent, 75.00% and 72.73% of sera with anti-BtE antibodies from Brazilian, Colombian and Ecuadorian patients, respectively, reacted to rBlo t 21. We observed a significant decrease in IgE binding to BTH2 compared to both parental allergens and BTH1. Although the absorbance values of parental allergens and BTH1 in severe asthma phenotype were statistically higher than the other phenotypes, no significant findings were observed for sIgE against BTH2. These findings highlight BTH2 as the best vaccine candidate, even for asthmatic patients. **Conclusions:** Blo t 5 and Blo t 21 were identified as major allergens in sera from Latin America and BTH2 is a hypoallergenic protein.

Keywords: Allergy, Blo t 5, Blo t 21, hypoallergen, Latin America.**Support:** Fapesb (APP0099/2016), CNPq (164990/2020-8 e 403336/2021-0);

EFFECT OF NICOTINE ON THE ACTIVATION OF AUTOPHAGY AND PROTECTION AGAINST AMINOCHROME IN ASTROCYTES

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Introduction: Parkinson's Disease (PD) is the second most common neurodegenerative disease in the world. However, there is still no effective therapy for curing or prevention of progressive degeneration in the nigrostriatal system. Conventional treatments are based on promoting physiological levels of dopamine and control ofsymptoms. Some therapies based on neuroprotective action- such as coenzyme Q10 administration have been successful in preclinical studies, but not in clinical trials. This may be related to the mistaken use of preclinical study models, which are not related to the cause of PD. Among the hypotheses that lead to the discovery of the cause of neuronal loss in PD, the neurotoxic effect generated by a molecule derived from dopamine oxidation, aminochrome, has been considered, and it has been used as a model-inducing neurotoxin. On the other hand, nicotine is a compound derived from Nicotiana tabacum, which has been attributed a neuroprotective action and association with a lower risk of developing PD. **Objectives:** In this study, we evaluated the effect of nicotine on the activation of autophagy in astrocytes and its involvement with neuroprotection.**Methodology:** We used Wild type and transfected astrocytes from U251 human lineage of submitted to treatment with nicotine, for further investigation of the protective effect against treatment with aminochrome. The mtt test was performed to assessed a viability curve in cells treated with nicotine for 24. In addition, LC3 and P62 protein expression analyzes were performed by Western blot in cells treated with nicotine at a concentration of 0.1 µM for 24 h, and at concentrations of 0.1 and 10 uM for a period of 2 h, 4 h and 6 h.A viability test was also performed in U251 cells with suppression of α- synuclein treated with aminochrome, for 48h, at concentrations ranging from 0.01 to 100 µM. **Results:** in this study we observed that in U251 Wild Type, only the concentration of nicotine 500µM presented a toxic effect, however, no static differences were observed in the expression of LC3 and P62 proteins. On the other hand, in U251 with α-synuclein suppression, it was observed that the highest concentrations of the aminochrome are toxic to the cells. **Conclusion:** In this sense, further studies will be needed to clarify the effect on the expression of autophagy markers in cells subjected to stress condition by treatment with aminochrome. This study is in progress to assess whether autophagy participates in the mechanisms of the neuroprotective action of nicotine in this experimental model of Parkinson's disease.

Keywords: Parkinson's disease; astrocytes; nicotine; neuroprotection.

Support: CNPQ; Fapesb

EVALUATION OF GENES: PSGL-1/SELPLG, ITGA-4, ARG-1, NOS-2 IN TOTAL LEUKOCYTES AND THEIR CORRELATION WITH SEVERITY IN PATIENTS WITH COVID-19

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INTRODUCTION: COVID-19, a disease caused by the SARS-COV-2 virus, has its pathophysiology related to hyperinflammation and immunothrombosis. Recent research correlates the enzymes arginase-1 (ARG-1), nitric oxide synthase (NOS2), α4β1 integrin (ITGA4) and P-selectin-1 (SELPLG) as possible molecules involved in dysregulated immune responses. The immunopathological mechanisms involving these genes in the severity of COVID-19 are still under investigation. **OBJECTIVE:** To evaluate the expression of ARG-1, NOS2, ITGA4 and SELPLG genes in total leukocytes from patients with COVID-19. **MATERIAL AND METHODS:** In the present case-control study submitted and approved by CONEP (Opinion No: 4,014,165) patients with positive PCR for SARS-CoV-2 were included, grouped into mild and severe disease. Whole blood was collected and mRNA was isolated from total leukocytes. The RT-qPCR assay was performed to analyze relative gene expression (2-ΔCT). **RESULTS AND DISCUSSION:** Males (n=38; OR=2.77) and elderly (n=32; OR=7.04), both with p<0.0001, were more likely to have a serious outcome. Comorbidities associated with the severe outcome were: hypertension (n=23; OR= 2.57) p<0.026, diabetes mellitus (n=27; OR=16.26), cardiovascular diseases (n=27; OR= 24.39), both with p<0.0001. The counting of the RBC indices between the mild vs. severe groups: red blood cells; hemoglobin and hematocrit (%), showed anemia in patients with a severe outcome, p<0.0001. Platelet count was significantly higher in critically ill patients, p< 0.001. Results showed leukocytosis for the severe outcome p<0.0001, and a positive correlation between neutrophilia and lymphopenia (r=0.78), p<0.0001. Analysis of gene expression indicated that the relative expression of the SELPLG gene was higher in the mild and severe groups (p<0.005 - p<0.01, respectively), compared to the endogenous gene HPRT-1. Comparison of medians indicated a trend towards greater expression in the severe group. The ARG-1 genes; NOS2 and ITGA-4 are under-expressed (p>0.05). ROC curve analysis for SELPLG at two 1:150 dilutions with AUC=0.79; p>0.006 (58.82% – 83.33%), and 1:300 dilution AUC=0.76; p>0.01(80%–78.57%), showed significant diagnostic value. **FINAL CONSIDERATIONS:** The results evidence the age group, comorbidities and dysregulated hematological parameters and the overexpression of SELPLG associated with thrombocytosis and immunothrombosis, highlighting that SELPLG may be useful as a biomarker for severity in COVID-19.

KEYWORDS: COVID-19, Leukocytes, SELPLG

NEGATIVE CORRELATION OF IL-12P70 WITH AGING IN COPD

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Introduction: The immune response in COPD and aging share similar mechanisms, with changes that lead to a decline in the adaptive response and stimulation of the innate immune system, resulting in a pro-inflammatory state. **Objectives:** The aim of study was to evaluate the impact of aging on immunological and clinical markers in COPD patients. **Methods:** Individuals diagnosed with COPD through spirometry were recruited at the Pneumology Service of the Edgard Santos University Hospital–Federal University of Bahia (HUPES- UFBA), located in the city of Salvador (Bahia, Brazil). Clinical and functional parameters were determined during medical care. Cytokine levels were determined in serum. Cytokines IL-6, IL-8, IL-12p70 and IL-1□ were quantified by flow cytometry using a commercial kit (BD Biosciences- CBA KIT- HU INFLAMMATION). This study was reviewed and approved by the Research Committee ethics (Protocol 4.113.435). **Results and Conclusions**: Forty-one subjects were included in this study The participants mean age was 62 (□5) years. Twenty-nine (71%) subjects were hospitalized due acute exacerbation of COPD. According to GOLD criteria, there were 20% of COPD patients in stage A, 34% in stage C, and 46% in stage D. Serum levels of cytokines IL-12p70, IL-1□,IL-6 and IL-8 showed mean 10.2 (□2.7), 3.6 (□1.7), 3.8 (□2.4) and 2.4 (□11.3) pg/mL, respectively. Age was negatively correlated with IL-12p70 levels (p=0.005; r=-0.4) and positively correlated with IL-1□ levels (p= 0.04; r=0.3). Moreover, age was associated positively with COPD severity (p=0.01; r=0.38). These findings could have important implication in COPD since a positive association of IL-1□ levels with age may represent the persistence of neutrophilic inflammation in this disease, and a negative association of IL-12p70 may imply a decreased ability to produce cytokines in the face of infection by pathogens. More studies are needed to clarify the risk of exacerbation by infection at different concentrations of IL-12p70 at different ages.

Keywords: COPD, Aging and cytokines.

Support: No support.

INFORMATIONAL MARKERS OF ANCESTRY ASSOCIATED WITH THE IMMUNE RESPONSE IN INDIVIDUALS INFECTED WITH SARS-COV-2

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Abstract

Introduction: COVID-19 disease is caused by SARS-COV-2 which can have severe and mild clinical manifestations. Ancestry Information Markers (AIM) are genetic indicators that have a >30% differential frequency between different geographically distinct populations and can be used to infer ancestry in mixed populations. The Brazilian population is tri-hybrid, as it is the product of the miscegenation of Europeans, Africans and Amerindians. Assessing ancestral contribution may provide a better understanding of SARS-COV-2 infection in these distinct ethnic groups. **Objective**: To describe the cellular profile and genotypic profile of AIM in individuals infected with SARS-CoV-2 with severe and mild clinical presentations. **Methods**: Cross-sectional, case-control study. Fifty- six subjects with severe and mild symptoms were included, and the samples underwent separation of PBMCs. Part of the cells was destined for cytometry and another part was submitted to the extraction of genomic DNA. Genotyping was performed by PCR for markers (AT3I\D, Sb19.3, APO and PV92). Statistical analyzes were performed using the SPSS program, using the ANOVA test, comparing the lymphocyte medians with the clinical presentation. **Results and Conclusion**: There was homogeneity between the ancestral profile (presence of the marker) and the severe and mild groups, which was expected, given that Brazil is a mixed-race country. There was statistical significance between the lymphocyte profile in comparison with the severe and mild groups, with $p < 0.05$. The increase in the lymphocyte profile of individuals in the severe group may be related to the increase in the exacerbation of the immune response, which is already well described as a predictor of clinical worsening.

Keywords: Ancestry Informational Markers; SARS-CoV-2;

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IDENTIFICATION OF ENVIRONMENTAL AND IMMUNOLOGICAL FACTORS RELATED TO CHILDHOOD BEHAVIOR DISORDERS

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Abstract

Introduction: Behavior disorders are characterized by changes in cognition, emotional or behavioral regulation. Childhood represents a key period for the establishment of brain regulatory patterns and it is possible to observe the development of internalizing and externalizing behaviors. At this stage, socio- environmental and immunological factors were shown to be related to behavioral changes. **Objectives:** The present study pretends to identify children with signs of internalizing and externalizing behavior disorders in a population sample and to test their associations with sociodemographic, environmental factors and cytokine levels in the peripheral blood of individuals. **Material and Methods:** A total of 1,364 children in this case-control, recruited by the SCAALA project (Social Changes, Asthma and Allergy in Latin America) were included in the present study. Questionnaires on socio-environmental and economic data created by the SCAALA project were applied, in addition to the CBCL questionnaires (internalizing and externalizing symptoms), SRQ-20 (Common Mental Disorders in mothers/caregivers) and community violence questionnaire. Cytokines (IL-10, IL-5, IL-13 and IFN-γ) from peripheral blood were measured by ELISA. **Results and Discussion:** Normality was tested on internalization, N=450/31.1%, and externalization score data, N=425/ 29.4% (normal distribution, cut off=64) and cytokine data (non-normal distribution). The χ2 test revealed an association between internalization and externalization and socio-environmental factors, such as: monthly family income ($P_{internalization}$= $2x10^{-2}$; $P_{externalization}$=10^{-3}), violent abuse (Pinternalization=$8x10^{-7}$; Pexternalization=$2x10^{-7}$), non-violent abuse ($P_{internalization}$=10^{-13}; $P_{externalization}$=10^{-23}), SRQ-20 ($P_{internalization}$=$4x10^{-15}$; $P_{externalization}$=$4x10^{-9}$) and nonviolent discipline ($P\ internalization$=10^{-3}; $P_{externalization}$ = $8x10^{-4}$), in addition to the association between

externalization and maternal schooling ($P_{externalization}$= $2x10^{-2}$). These results suggest that social factors are important for characterizing behavioral outcomes. Cytokine data was categorized into immunophenotypes (groups of individuals that expressed high, intermediate, or low concentrations of the evaluated cytokines). An association was observed between externalizing symptoms and immunophenotypes (Pexternalization = $2x10^{-2}$), showing that immunological factors may be involved in the development of externalizing symptoms in children. **Conclusions:** Socioenvironmental and immunological factors are associated with childhood behavior outcomes in our population, which corroborates other findings in the literature. Less subjective markers such as these maybe, in the future, considered auxiliary for the diagnosis of behavioral disorders in childhood.

Keywords: childhood, behavior disorders, immunophenotypes, socio- environmental components, intra-family violence.

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DETERMINING IMMUNOLOGICAL REFERENCE RANGES VALUES TO HEALTHY INDIGENOUS BRAZILIANS AT DOURADOS, MATO GROSSO DO SUL

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ABSTRACT

Introduction: The establishment of reference values for a subset of leukocytes is commonly used in clinical practice and ethnic variations are strongly associated with the development of diseases. In Brazil, indigenous people are vulnerable to infections and few studies describe the health and disease conditions of this population. **Objectives:** The aim of this study was to provide reference values for leukocyte subsets of healthy indigenous people living in Mato Grosso do Sul. **Methods:** A total of 115 indigenous Brazilian adults were included in the study, the majority being female (72%). Anti-CD14 and anti-CD16 monoclonal antibodies were used to identify monocyte subpopulations, anti-CD3+, anti-CD4+, anti-CD8+ and anti-CD45+ for T lymphocyte subpopulations, anti-CD5, anti-CD19 and anti-CD20 for B lymphocytes and anti-CD16+ and anti-CD56+ for Natural Killers cells and anti-CD45RO, anti-CD45RA and anti-HLA-DR to differentiate memory cells, naive cells and cell activation. **Results and Conclusions:** The results presented the reference values of total T and B lymphocytes, T CD4+, T CD8+, natural killer cells, monocytes and dendritic cells, providing an immunological profile for the population in question. In the present study, the ratio of CD4+ / CD8+ cells was higher in females than in males, and the relative values of natural killer cells were lower in females. When comparing different groups according to age, there was a slight increase in the values of T CD3+, T CD4+ and T CD8+, in the older groups. To date, cell reference values for indigenous people are non-existent in Brazil and the reference range for immune cells presented in this pioneering study will bring relevant contributions to the clinical and laboratory evaluation of the Brazilian indigenous population.

Keywords: Reference range, Indigenous Brazilians, Lymphocytes, Monocytes Support: CNPq, CAPES

EFFECT OF *LIPPIA ORIGANOIDES* KUNTH EXTRACT ON IL-6 PRODUCTION BY INDIVIDUALS WITH PERIODONTITIS: IN VITRO STUDY

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Introduction: Periodontitis is a chronic, inflammatory and infectious disease that affects periodontal tissues. The inflammatory process is triggered and perpetuated by Gram-negative bacteria, such as *Porphyromonas gingivalis*, that elicit an exacerbated host response, with the production of the pro-inflammatory cytokine IL-6. Currently, the treatment of periodontitis consists of the mechanical elimination of the infectious foci, however, chemical methods are sought. Antibiotics lead to the resistance of microorganisms, so the replacement by phytotherapics, such as *Lippia origanoides* Kunth, may be promising, as it has biotechnological potential and antimicrobial activity. However, the mechanisms of action of this plant have not yet been fully elucidated. **Objective:** To evaluate, in vitro, the effect of the extract of the leaves of *L. origanoides* Kunth on the production of Il-6 by cells of individuals with periodontitis. **Methodos:** A bank of volunteers assisted at the dental clinic of the Universidade Estadual de Feira de Santana in 2018 was used. Patients received the periodontal diagnosis and the whole blood cell were cultured during 48h with the methanolic extract from the leaves of the plant and with *P. gingivalis* antigens. The IL-6 cytokine was quantified in the culture supernatants using the ELISA. **Results:** The group with periodontitis had a higher concentration of IL-6 in the supernatant of cells cultured only with the culture medium ($p=0.04$) or with the extract of the leaves of *L. origanoides* ($p=0.03$), when compared to the group without periodontitis. There was an increase in the production of IL-6 in cells stimulated with *P. gingivalis* in relation to the production of cells without stimulation ($p<0.01$) or stimulated with

L. origanoides ($p<0.01$). **Conclusion:** people with periodontitis have a greater susceptibility to IL-6 production. However, the presence of the extract from the leaves of *L. origanoides* does not seem to alter the production of this cytokine.

Keywords: cytokines; immunomodulation; periodontal disease

Support: FAPESB

THE INFLUENCE OF TEMPERATURE ON ASTROCYTE VIABILITY IN PRIMARY CULTURES OF NEWBORN RATS

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Introduction: Astrocytes are macroglia cells, despite having functions and shared morphologies, they present heterogeneity resulted from the microenvironments in which it is established. Astrocytes are essential in providing nutrients, supporting neuronal cells and synapses, reuptake excess neurotransmitters, neuronal plasticity, removing reactive oxygen species, and contributing to the integrity and permeability of the BBB, neurogenic control functions, synapses, neuronal growth, and survival. These astrocytes respond to injury through reactive astrogliosis. This process occurs in the presence of neuropathology or tissue damage to the CNS (Central Nervous System). In this response, the main morphological changes that occur are hypertrophy, exacerbated proliferation, changes in prolongations, the release of pro- inflammatory cytokines, and increased expression of the GFAP marker. Given the diversity of astrocytes, it is not surprising that the context in which their dysfunction occurs is also an important issue for various pathological scenarios. Therefore, we asked if high temperatures, a very common feature in many infections, could induce astrogliosis. **Objectives**:To evaluate the influence of temperature on astroglial reactivity. To do this, we analyzed the effects of heat stress on the expression of astrocyte markers, viability, and effects upon this heat insult on modulation of the astrocyte response. **Material and Methods:** To investigate a possible effect of temperature, primary cultures of astrocytes were prepared from two-day postnatal rats and subjected to a temperature of 42 degrees Celsius for 30 minutes. After this period, the cultures were replaced at 37°C in C02 for another 24 hours. The experiment was ended by fixing the cells in ice-cold methanol for 10 minutes to perform immunocytochemistry for GFAP and DAPI markers. **Results and Discussion**: The data obtained indicate that high temperature, at 42 degrees Celsius, for 30 minutes, induces astrogliosis, increasing the expression of GFAP in purified cultures of astrocytes by approximately 40% as we can verify by immunostaining experiments. **Conclusions**: Complementary assays are being carried out to verify the levels of cell proliferation and toxicity induced by different temperatures and incubation times in order to understand the effects of high temperatures and fever on the astrocytic and inflammatory response.

Keywords: astrocytes.response inflammatory.high temperatures.reactive astrogliosis.

Support: CNPq.

EVALUATION OF ANTIOXIDANT AND ANTI-NEUROINFLAMMATORY ACTIVITY OF FLAVONOIDS AND SYNTHETIC DERIVATIVES AGAINST INFLAMMATORY DAMAGE IN GLIAL CELLS

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Introduction: Neuronal degeneration can be contained by glial cells through the homeostatic control of toxic and inflammatory mechanisms that occur in the central nervous system. Loss of homeostasis leads to increased oxidative stress and inflammation, associated with neurodegenerative diseases (NDD). In this context, polyphenolic compounds with antioxidant and anti-inflammatory properties, such as flavonoids, are promising candidates for complementary therapies for NDD; **Objectives:** This work evaluated, in vitro, the cytotoxicity and antioxidant mechanisms of flavonoids and synthetic derivatives, associated with the control of the glial inflammatory response. **Methods:** The cellular antioxidant activity of the flavonoids chrysin, apigenin, roifolin, hesperidin naringin, naringenin and prenylated synthetic derivatives was determined by free radical scavenging reactions (DPPH). The cytotoxic effects of the compounds (1-100 µM) were determined in human GL-15 and mouse C6 glioma cell cultures by MTT assay and differential interference contrast (DIC) microscopy. Primary astrocyte cultures, obtained from Wistar rats (P0-2), were subjected or not to inflammatory damage with LPS (1 µg/mL), and after 24 h, treated or not with flavonoids and derivatives (10 µM) for aditional 24 h; phenotype and cell viability were determined by DIC and MTT, and levels of the inflammatory mediator nitric oxide (NO) were determined in the culture medium by the Griess reaction. **Results and Conclusions:** The flavonoids hesperidin, apigenin and the diprenylated synthetic derivative of naringenin, at a concentration of 1 µM, showed higher scavenging of the DPPH radical than the Trolox standard, in addition to maintaining the viability of the cells of the primary astrocyte cultures. These flavonoids reduced LPS-induced NO levels, an effect also observed after treatment with the synthetic monoprenylated derivative of naringenin. The determination of the antioxidant mechanisms of flavonoids and synthetic derivatives involved in neuroinflammation will contribute to the development of new complementary therapies for NDD.

Keywords: flavonoids; glial cells; antioxidant, neuroinflammation

Support: CAPES, CNPq and FAPESB.

IMMUNOREGULATORY EFFECT OF RECOMBINANT PROTEINS ON PERIPHERAL BLOOD MONONUCLEAR CELLS FROM INDIVIDUALS ALLERGIC TO *BLOMIA TROPICALIS*

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Abstract

Introduction: Allergic diseases remain a worldwide healthcare problem. The immune response against allergens is mainly based on the production of Th2 cytokines. For treatment, allergen immunotherapy is an option and our research group has developed a hypoallergen, termed BTH2. The hybrid protein achieved essential efficacy parameters, but the need for adjuvants was observed. In previous studies, *T. Trichiura* helminth proteins (rTtMIF and rTtFBPA) immunoregulated Th response by decreasing the production of IL-5 and IL-13, and increasing IL-10. **Objective:** To investigate the immunoregulatory potential of recombinant proteins BTH2, rTtMIF and rTtFBPA in co-cultures of human peripheral blood mononuclear cells (PBMC). **Material and Methods:** Heterologous expression of BTH2, rTtMIF and rTtFBPA was performed using different strains of *E. coli*. Proteins were purified by different chromatographic methods. A primary PBMC culture was performed to determine the optimal and suboptimal concentration of recombinant proteins and positive controls. The MTT method was used to assess cell viability. PBMC cultures were performed with 6 allergic volunteers, in which the recombinant proteins were co-cultured with *B. tropicalis* extract (BtE) or LPS to evaluate the production of cytokines IL-10, IL- 5, IL-13, IL-1β, IFN-γ and TNF. **Results and Discussion:** All proteins significantly inhibited the production of IL-1β in the co-culture with LPS, while in the co-culture with BtE, there was significant inhibition of IL-13 and IL-5. IL-10 and IFN-γ were not significantly inhibited in both co-cultures. TNF, in contrast, was significantly increased in the presence of recombinant proteins. The association of the three proteins led to a higher inhibitory effect with rTtMIF and rTtFBPA appearing to be the main cause. Considering all cytokines analysed, it was observed a Th1-biased and/or a regulatory immune response, as described in other studies. The non-inhibition of IL-10 was an interesting outcome due to its anti-inflammatory nature. Moreover, the inhibition of Th2 cytokines is another compelling finding given the role of IL-5 and IL-13 during allergic inflammation. **Conclusions:** The recombinant proteins BTH2, rTtMIF and rTtFBPA showed promise as immunoregulators *in vitro*. Therefore, the hypoallergen was confirmed as an immunoregulatory molecule and rTtMIF and rTtFBPA as important immunoregulatory adjuvants for future immunotherapy applications.

Keywords: Allergy, MIF, FBPA, PBMC, Cytokines.

Support: Fundação de Apoio à Pesquisa do Estado da Bahia (APP0099/2016)

EVALUATION OF IMMUNE-RELATED GENES LINKED TO THE SUSCEPTIBILITY AND SEVERITY OF COVID-19 IN BRAZILIANS

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Introduction: The COVID-19 pandemic has had a significant impact on society, and despite the efforts implemented to contain the disease, it still has a wide distribution, with different clinical manifestations. This clinical variability may be associated with the genetic patterns of the host, since polymorphisms in specific genes can influence the responses triggered. Thus, it is important to understand the genetic profile presented by different populations in order to clarify the factors associated with the severity and susceptibility of the disease. **Objectives:** This study aims to investigate the genotypic profiles of individuals with COVID-19 in different Brazilian populations. **Methods:** The methodological design comprises two large groups: group 1, composed of 290 individuals, from laboratory and hospital collaborations from different locations in the state of Bahia. Group 2 includes 1590 individuals from the Edgar Santos University Hospital (HUPES) survey. The genes were selected based on previous studies linked to COVID-19 susceptibility, such as *ABO*, *ACE*, *ACE2*, *TMPRSS2*, *LZTFL1* and *TNFA* and used as targets for a candidate gene approach proposed in this study. Markers on such genes are being typed using a RT-PCR QuantStudio 12K platform. **Results and Conclusions:** As partial results, we have concluded the standardization and just completed the genotyping process in Group 1. The next steps will be run logistic regression analysis in order to verify the association of each studied SNP with COVID-19 using PLINK. Perspectives include replicating the most significant associations in Group 2 and performing in silico analysis in order to better elucidate the main findings of our study.

Keywords: COVID-19, SARS-COV-2, polymorphisms, SNPs, genotyping.

Support: CAPES.

VARIANTS OF THE *RORA* GENE ARE ASSOCIATED WITH ATOPIC AND EOSINOPHILIC ASTHMA IN A SALVADOR POPULATION.

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Introduction: Asthma is a chronic inflammatory disease and is a heterogeneous condition determined by interactions between genetic and environmental factors. The type 2 immune response in asthma triggered by ILC2 can lead to increased IgE and eosinophilia due to the production of IL-4, IL-5, and IL-13. ILC2s require the ROR-alpha, a transcription factor specific to these cells. In this context, this work aimed to investigate genetic variants in the RORA gene associated with asthma phenotypes in the population of Salvador - BA. **Methods**: Was collected the whole blood from 1,094 patients from the Asthma Control Program in Bahia (ProAR), DNA was extracted using the FlexiGene Kit (Qiagen), and mRNA was extracted using the PureLink Kit (Thermo Fisher) and converted to cDNA using the SuperScript IV Kit (Thermo Fisher). Genotyping was performed using the MEGA chip (Illumina), and RT-PCR was performed using the pre-synthesized Taqman® gene expression assay. Total IgE concentration was determined by nephelometry, and cytokine dosage was performed using Luminex®. Dominant and additive logistic regression models were used for association using PLINK 1.9. Comparisons between genotypes were analyzed using GraphPad Prism 8, and functional data in silico were performed using GEO – NCBI. **Results and Conclusions**: The G allele of rs56397838 was associated with protection (OR = 0.50) for atopic asthma and related to increased RORA expression. The C allele of rs2289163 was associated with protection (OR = 0.53) for atopic asthma and is related to a decrease in plasma IL-13. In contrast, the G allele of rs809736 is associated with risk (OR = 1.42) for eosinophilic asthma and contributes to the increase in plasma eosinophils and total serum IgE. Further investigations into the RORA gene may provide answers about its participation in the different pathophysiological mechanisms of asthma and help discover new personalized treatments in the Brazilian people.

Keywords: Asthma, atopy, SNVs.

Funding: CAPES, CNPq.

EFFECT OF *LIPPIA ORIGANOIDES KUNTH* LEAF EXTRACT ON IL1B PRODUCTION BY CELLS OF INDIVIDUALS WITH PERIODONTITIS

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Abstract Introduction: Periodontitis is a chronic multifactorial inflammatory disease associated with a dysbiotic interaction between the biofilm present on the dental surface and periodontal tissues. *Porphyromonas gingivalis* is considered a key pathogen in the disease, being associated with periodontal destruction. This dysbiotic biofilm can stimulate the production of proinflammatory cytokines, such as IL-1b, whose presence has been correlated with the

pathogenesis and severity of periodontal disease. Historically, medicinal plants are used in phytotherapy and in the discovery of new drugs, an example is the genus *Lippia L.*, with bioactive properties that promote the decrease of bacterial load and contribute significantly to the improvement of oral health. **Objectives**: To identify the immunomodulatory potential of the extract of the leaves of *Lippia origanoides Kunth*. **Methods:** Volunteers recruited at the dental clinic of the State University of Feira de Santana (UEFS) were classified according to periodontal parameters in two groups : with periodontitis and without periodontitis. Whole blood cells were cultured with the extract of *P. gingivalis* and the extract of the leaves of *Lippia origanoides Kunth*. IL-1b was quantified in the supernatants using immunoenzymatic assay method (ELISA). Descriptive analysis of the clinical characteristics of individuals through the chi-square test (categorical variables) and Student's t-test (continuous variables). **Results:** Statistically significant difference was observed between the groups with and without periodontitis in the production of IL-1b by peripheral blood cells cultivated with the crude sonicated extract of *P. gingivalis*. Cells cultured with *P. gingivalis* presented higher IL-1b concentration in their supernatant than those cultured without stimulation ($p<0.01$) or under stimulation of *L. origanoides* extract ($p<0.01$). There was no statistically significant difference between the production of IL-1b induced by *Porphyromonas* and that induced by the combination of the two extracts. **Conclusions:** The presence of the extract of *L. origanoides* in the culture didn´t decrease the production of IL-1b induced by *P. gingivalis*.

Keywords: Lippia, IL-1b, Periodontite

Support: CNPq/PIBITI

ORAL INFECTION BY *T. GONDII* PROMOTES CHANGES IN THE INTESTINAL WALL OF RATS THROUGH THE IMMUNE AND INFLAMMATORY RESPONSE IN THE CHRONIC PHASE.

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Introduction and Objectives: Currently, toxoplasmosis is treated with the chemotherapeutic agents pyrimethamine and sulfadiazine, which inhibit essential enzymes for the synthesis of *Toxoplasma gondii* DNA. However, overuse has resulted in the selection of resistant strains of the parasite. Therefore, the aim of this study is to investigate the immunomodulatory effect of the herbal drug *Echinacea purpurea* on the colon mucosa of rats infected with *T. gondii*. **Methods**: The experimental protocol was approved by CEUA-UEM (7633021018). Twenty-four *Rattus norvegicus* were randomly divided into four experimental groups (n=6): one uninfected and untreated control group (GC); one infected and untreated (GC-INT); one uninfected and treated with *E. purpurea* (GC-EP100); one infected and treated with *E. purpurea* (GI-EP100). The infected groups were orally inoculated with 500 sporulated oocysts of *T. gondii* (RH strain, genotype I). Rats in the GC- EP100 and GI-EP100 groups were treated orally with 100 mg/kg *E. purpurea* daily for 30 days before and after inoculation. Thirty days after infection, the rats were sacrificed and colon segments were collected for standard histological, histochemical, and immunohistochemical procedures. The segments were then dehydrated, diaphanized, and embedded in paraffin to obtain 4 µm semiserial cross sections that were stained with toluidine blue to count the mast cells, and immunohistochemistry was used to evaluate enterochromaffin cells and mast cells expressing serotonin (5-HT). Quantification of enterochromaffin cells and serotonergic mast cells was performed in 50 microscopic fields using a 40× objective. **Results and Conclusions**: Chronic infection induced changes in the distribution of total mast cells and serotonin- expressing mast cells and enterochromaffin cells in the colon mucosa of rats (5- HT +). Compared with the control group, the number of total mast cells and 5-HT + mast cells increased in rats GC-INT, GC-EP100 and GI -EP100 ($p < 0.01$). The number of 5-HT + enterochromaffin cells in the colonic epithelium of GC- INT, GC-EP100 and GI -EP100 mice ($p < 0.05$) was also higher than in the control group.

Keywords: Toxoplasmosis, RH strain, herbal drug.

Support: Fundação de Amparo à Pesquisa do Estado da Bahia-FAPESB

EFFECT OF *LIPPIA INSIGNIS* MOLDENKE EXTRACT ON IL-10 PRODUCTION OF INDIVIDUALS WITH PERIODONTITIS.

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Introduction: Periodontitis is a multifactorial disease that affects the protective and supporting tissues of the teeth through the inflammatory response of the host to the presence of dysbiotic subgingival biofilm. The response is triggered through a cascade, characterized by the influx of neutrophils and the production of inflammatory interleukins, such as IL-1β and IL-8, and anti-inflammatory ones, such as IL-10. The treatment of periodontitis is performed mainly through scaling and root planing, brushing and flossing associated or not with chemical agents, such as antibiotics. However, that's drug class can generate deleterious effects to the individual's body and therefore new alternatives are being investigated for the treatment of periodontitis. In this context, medicinal plants, such as those of the Lippia genus, especially *Lippia insignis* Moldenke, have promising biotechnological potential for drug formulation. **Objective:** This work aimed to investigate whether the extract of leaves of *L. insignis* Moldenke can modulate the production of IL-10 in cells of individuals with and without periodontitis. **Methods:** A database with information from clinical evaluations, including periodontal examination, of volunteers assisted at the dental clinic of the State University of Feira de Santana in 2018 was used. Extracts from the leaves of the plant were obtained in their raw form and transformed into methanolics so that they could be used. The IL-10 cytokine was quantified in the whole blood culture supernatants of the research participants, using the ELISA. For the characterization of the groups, a descriptive analysis referring to the clinical characteristics of the individuals was carried out. **Results**: Ten individuals diagnosed with periodontitis were included in the study. An increase in the concentration of IL-10 in the supernatant of the cultures of the cells cultivated in all stimulus conditions was observed, when compared to the basal concentration (without stimulus, however there was only a statistically significant difference in the supernatant of cells cultivated with the *P. gingivalis* extract and *L. insignis* extract simultaneously (p=0.016). **Conclusion:** *L. insignis* leaf extract and *P. gingivalis* extract potentiate IL-10 production by human peripheral blood cells.

Keywords: Cytokines; *Lippia insignis*; Periodontitis.

Support: CNPq.

A PREDICTIVE GENETIC PANEL IN ASTHMA USING MACHINE LEARNING

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Introduction: Asthma is a chronic inflammatory condition that results in hyperreactivity and in episodes of wheezing, shortness of breath, coughing, and/or chest tightness. This disease is heterogeneous and defined by the history of symptoms such airway inflammation, smooth-muscle contraction, epithelial sloughing, mucous hypersecretion, bronchial hyperresponsiveness, and mucosal edema. Identifying the genetic variations associated with asthma and discovering the molecular interactions between the omics that confer the risk of developing this disease will help us to unravel and better understand the biological pathways involved in the pathogenesis of asthma. **Objective**: In this work, we established a predictive genetic panel for asthma using machine learning methods. **Material and Methods**: It was selected three feature selection methods: the Boruta algorithm (feature selection wrapper algorithm, whose kernel is Random Forest); the 200 best markers from GWAS according to their respective p-values; and, the Elastic Net regression. It was choose ten different algorithms for classification: K- Nearest Neighbor (KNN), Naive Bayes (NB), Artificial Neural Networks (ANN), Support Vector Machine (SVM), Classification and Regression Trees (CART), C5.0, Bagging, AdaBoost, Random Forest (RF), and XGBoost. The predictive panel was built based on the sum of the scores of each algorithm, with a cut-off point at the first median that gave at least 80% accuracy. **Results and Discussion**: We observed that the two methods of selection of Boruta and GWAS variables were statistically similar when comparing the averages of the generated test accuracies exposed in table 2 (81.03% and 79.85%), while the Elastic Net method obtained the worst overall performance (52.87%). The predictive genetic panel was closed with 62 SNVs, with 80.2% accuracy, 78.3% sensitivity and 82.1% specificity through the Support Vector Machine algorithm. The selected markers transit between known SNVs and not yet described in the literature. Now, it is possible to focus on SNVs not yet described and to try to understand how they may be involved in the pathophysiology of asthma. **Conclusion**: The method is able to classify asthma and non-asthma effectively and can be a tool to assist in the prediction and/or diagnosis of asthma, contributing to the personalization of clinical management.

Keyword: asthma, machine learning, SNV, prediction, panel.

Support: CNPq.PRONEM/FAPESB.

EFFECT OF *LIPPIA INSIGNIS* LEAVES EXTRACT ON IL-13 PRODUCTION BY PERIPHERAL BLOOD MONONUCLEAR CELLS OF INDIVIDUALS WITH PERIODONTITIS.

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Abstract Introduction: Periodontitis has multifactorial etiology and is characterized by immunoinflammatory events in response to the presence of a dysbiotic biofilm and, if left untreated, can lead to damage tissues of the tooth, possibly culminating in tooth loss. The increase in some molecules and cytokines, such as IL-13, can assist in the destruction of these supporting tissues. The most used treatment in the most severe cases of the disease are the surgical approach and pharmacotherapy, however the overuse of this can lead to

drug resistance, so it is important the search for alternatives, such as the use of medicinal plants, among species of the genus Lippia, abundant in the Northeast region of Brazil. Given the antimicrobial and anti-inflammatory properties of these plants, their use has been investigated for the treatment of the disease as adjuvant to mechanical control, already widely recommended. **Objectives**: Evaluate the modulator effect of *Lippia insignis* leaf extract on IL-13 production by peripheral blood mononuclear cells (PBMC) of individuals with periodontitis. **Material and Methods:** Participants were volunteers over 18 years old with at least four teeth in the mouth and patients with systemic disorders, current pregnancy, treatment periodontal current or previous periodontal, current or previous smoking, use of antibiotics and anti-inflammatories in the last six months prior to collection were not included. Peripheral blood mononuclear cells from a pre-existing sample bank, cultured with the extract of the leaves of *L. insignis,* were tested by immunoassay to compare the IL-13 concentrations in PBMC supernatants cultured with the plant extract and with the extract of a periodontopathogenic bacterium (*Porphyromonas gingivalis*). **Results:** There was no statistically significant difference in the production of IL-13 by the cells of individuals with and without the diagnosis of periodontitis. There was no change in the production of this cytokine in cells cultivated with the extract of the leaves of *L. insignis*. **Conclusion:** *Lippia insignis* leaf extract does not appear to affect IL-13 production beyond its basal levels.

Keywords: Periodontitis; IL-13; *Lippia insignis*.

Support: PIBIC/FAPESB.

SEP7 GENE VARIANTS ARE ASSOCIATED WITH PERIODONTITIS

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Introduction: Periodontal diseases result from significant interactions between the inflammatory immune response and the dental biofilm causing an exacerbated inflammation of the adjacent tissues responsible for supporting the teeth. Environmental and genetic aspects are related to the individual's degree of susceptibility to develop periodontitis, since some genetic variations are associated with the host's response to dysbiotic dental biofilm. In this way, genetics, lifestyle and associated environmental factors, directly interfere in the composition of the biofilm, as well as in the individual's inflammatory immune response, forming a diverse biological phenotype. The *SEPT7* gene was associated with periodontitis in a Genomic Wide Association Study (GWAS) for Periodontal Disease in individuals from Salvador-BA. **Objectives:** Investigate the association of genetic variants of the *SEPT7* gene with the presence of periodontal disease. **Material and Methods:** 506 individuals of both sexes, aged

≥ 18 years, participating in the *Programa para o Controle da Asma na Bahia (ProAR)* had their periodontal parameters evaluated according to the criteria of Gomes Filho et al. (2007) and were classified by the presence (117 individuals, 26.9%) or absence (389 individuals, 73.9%) of periodontitis. Genotyping was accomplished using the Illumina Multi-Ethinic AMR / AFR-8 chip, this one with approximately 2.5 million genetic variants. Logistic regression in three models – dominant(dom), additive(add), and recessive(rec) used PLINK 1.9 software (adjustments for age, obesity, asthma, mouth breathing, flossing and principal component of ancestry). The stipulated quality control was MAF>0.01 and HWE>0.05. **Results and Discussion:** Two variants were associated in the 3 models as a risk factor for the presence of PD (rs10232178 Additive OR:1.79; 95%CI:1.28–2.52; p-value:7.66x10-4; Dominant OR:2.00; 95%CI:1.26–3.17; p-

value:0.0033; Recessive OR:2.31; 95%CI:1.17-4.53; p-value:0.0154) and (rs2893514 Additive OR:1.71; 95%CI:1.23-2.39; p-value:0.0015; Dominant OR:1.98; 95%CI:1.25-3.13; p-value:0.0037; Recessive OR:2.02; 95%CI:1.06-

3.88; p-value:0.0338) according to the adopted criterion. SEPT7 protein is essential for cytokine in fibroblasts, the main cells of the periodontal ligament. The presence of polymorphisms in the gene of this protein may affect its function. **Conclusions:** In the population studied, the genetic polymorphisms rs10232178 and rs2893514 of *SEPT7* are associated as a risk factor to the presence of periodontal disease in additive, dominant and recessive models.

Keywords: Polymorphism, gene, SEPT7, periodontal disease.

Support: CAPES, UFBA, FADBA

GENETIC PANEL GENERATED BY MACHINE LEARNING PREDICTS RISK OF SEVERE EXACERBATION IN BRAZILIAN ASTHMA PATIENTS

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Introduction: Severe exacerbations of asthma are the main contributors to the increase in health costs related to asthma, morbidity and mortality. However, there is a need for additional predictors for this outcome. **Objectives:** The aim was to evaluate the performances of ten machine learning algorithms in the prediction of severe asthma frequent exacerbations using top SNVs from a previous Genome Wide Association Study (GWAS) with severe asthma exacerbations in individuals with moderate to severe asthma. **Material and methods:** This study was carried out with 364 Brazilians with moderate to severe asthma of the ProAR cohort. Genotyping was performed using the Illumina Multi-Ethnic Global Array (MEGA, Illumina) in 399 exacerbators cases and 328 non-exacerbators controls. After performing a GWAS for severe asthma exacerbators, the variants with p value < 0.05 were filtered and the prediction models were built using the following algorithms: K-nearest neighbors (KNN), Naive Bayes, Artificial neural networks, Support Vector Machine, Bagging, AdaBoost, Classification and Regression Trees (CART), C5.0, Random Forest and XGBoost. **Results and Discussion:** After the integration of all algorithms, the best predictive algorithm was the XGBoost. The final panel had 89 variants, that were considered the most important markers for the XGBoost algorithm to effectively predict the chances of being an exacerbator among individuals with asthma, with an overall accuracy of 80%, an Area Under the Curve (AUC) of 91%, a specificity of 72% and a sensibility of 86%. **Conclusion:** Our results suggest a genetic panel with 89 variants for identification of the exacerbators, among patients with moderate to severe asthma. More studies are needed to assess the functional effect of these variants in the risk of exacerbation of asthma.

Key words: asthma, severe exacerbations, GWAS, Machine Learning

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CIRCUNVENTING THE THERAPEUTIC FAILURE OF PENTAVALENT ANTIMONY IN LEISHMANIA BRAZILIENSIS INFECTIONS IN MURINE MACROPHAGES BY INHIBITING ABC TRANSPORTERS

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ABSTRACT

Introduction: A cutaneous leishmaniasis (LC), caused by *Leishmania braziliensis*, is a a wide spectrum disease with clinical presentations, characterized by the presence of one or more skin ulcers with high edges. The most important limitation of leishmanicidal drugs is a high rate of treatment failure, the emergence of drug- resistant parasites and patients abandoning treatment. The host genes associated with multidrug resistance (MDR), ABCB1 and ABCC1 are more expressed in lesions of patients with LC when compared to healthy skin. The increased activity of these proteins may be associated with therapeutic failure and the use of inhibitors in conjunction with the pentavalent antimony Glucantime (SbV), may prevent the efflux of drugs in the host's macrophages. **Objectives:** The objective was to evaluate the activity of ABC transporters in primary murine macrophages infected with *L. brasiliensis* strains in collaboration with Dr. Fasel, at the University of Lausanne, Switzerland. **Material and Methods:** We verified the activity of ABC transporters in the macrophages after infection with *L. braziliensis* strains by flow cytometry technique. We utilized the MDR Gold flow cytometry kit, that provides a rapid, sensitive and quantitative method to monitor the activity of the three most clinically important MDR proteins: MDR 1, MRP1/2 and BCRP. **Results and Discussion:** The macrophages infected with *L. braziliensis* showed less fluorescense compared to non infected cells, possibly by increasing activity of ABCB1 (MDR1) and ABCC1 (MRP) causing the efflux of the probe. **Conclusion:** The infection of *L. braziliensis* in primary murine macrophages seems to activate the ABC transporters, causing the MDR profile and the failure of treatment with SbV. The development of protocols with the association of SbV and the inhibitors of MDR1 and MRP could reduce the costs of new courses of therapy.

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INFLUENCE OF T. CRUZI COINFECTION ON THE IMMUNE RESPONSE AND CLINICAL OUTCOME OF PATIENTS WITH CUTANEOUS LEISHMANIASIS

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Introduction. In several areas of Latin America, the geographic distribution of cutaneous leishmaniasis (CL) overlaps with areas of Chagas disease transmission ranging from 12 to 70% of patients with clinical symptoms of leishmaniasis. Studies show a difference in the expression of T cells in LC and ML coinfected with Trypanosoma cruzi in relation to patients with isolated leishmania. **Objective**. To assess whether the immune response of patients with CL caused by L. braziliensis and co-infected with T. cruzi is associated with clinical evolution. **Materials and methods**. The case-control was performed with one hundred and eighty sera from patients with CL caused by L. braziliensis enrolled for this study. Trypanosoma cruzi-specific chimeric proteins were determined to detect co-infection with Chagas disease by the ELISA technique. **Results and Discussion**: Twenty patients with CL coinfected with T.cruzi were identified, all with higher anti-leishmania antibody titers compared to patients infected with leishmania alone. IL-6 production was also higher in the group of coinfected patients. There was no statistical difference in the production of IFN- γ, TNF, IL-1β and granzyme B between coinfected CL and T.cruzi patients. Regarding the clinical outcome, fourteen (70%) of the coinfected individuals failed antimony therapy, while six patients (30%) cured the treatment. **Conclusions**. These results indicate that co-infection may interfere with the individual's immune response and clinical evolution to Leishmania infection.

Keywords: Leishmaniasis; Chagas disease; coinfection; Immune response **Support**: National Institute of Science and Technology - Tropical Diseases (INCT-DT).

STUDY OF THE ANTIGLIOMA AND IMMUNOMODULATORY EFFECTS OF FLAVONOIDS RELATED TO AHR INTERACTION

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INTRODUCTION: Glioblastoma (GBM) is the most common and aggressive neoplasm in the primary brain tumor. The transcription factor AhR (aryl hydrocarbon receptor) constitutively activation promotes the differentiation of cells and increase expression of resistance genes, putting AhR antagonism as a target in cancer chemotherapy. Naturally occurring compounds such as flavonoids can act as AhR ligands. Studies show that these natural ligands modulate AhR activity by altering metabolic pathways involved in tumor growth. The anti-tumor potential of flavonoids and their immunomodulatory activity in glioma cells has been investigated and the pharmacological potential of these drugs have encouraged studies in alternative therapy for GBM. **OBJECTIVES:** This study aimed to better define the antitumor mechanisms of flavonoids and possible association of its antiglioma activity with the capacity to act as AhR antagonists. **MATERIAL AND METHODS:** Natural flavonoids, whose anti glioma effects have already been demonstrated, such as naringenin (NAR), agathisflavone (FAB) and chrysin (CHR) were tested as AhR antagonists at increasing non-cytotoxic concentrations of 10, 20 and 30 µM, using the induction of CYP1A1 mediated EROD activity assay in MCF7 cells, as a marker of Ah- responsiveness. Cultures were also treated with the flavonoid dilution vehicle DMSO (0.01%) and TCDD (2nM), a known strong AhR agonist. Cell viability was determined by methylene blue assay. U87 glioma cells were treated with CHR (30µM) and NAR (30µM) to quantify gene expression levels related to canonical AhR activity. **RESULTS AND DISCUSSION:** CYP1A1- mediated EROD activity assay showed, pretreatment with CHR, NAR and FAB at 30µM concentration, for 2h, to be powerful antagonists in the presence of a strong agonist of the receptor (TCDD), for 6h. Also, U87 treated with CHR (30µM) and NAR (30µM) showed reduction of expression levels of AHR, TIPARP and CYP1B1 genes compared to positive (TCDD) and negative (DMSO) controls. **CONCLUSIONS:** Such regulations showed to be dose dependent. The characterization of the molecular mechanisms of flavonoids related to antagonistic effect on AhR and its role in chemosensitivity, will contribute to sustain their application as adjuvant for GBM treatments.

Keywords: glioma; glial cells; flavonoids; aryl hydrocarbon receptor; immunomodulation **Support:** CAPES, CNPq and FAPESB

EVALUATION OF TYPE 1 INTERFERON RECEPTOR AND INTERLEUKIN 17-A EXPRESSION IN PATIENTS WITH COVID-19

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Introduction: COVID-19, caused by the SARS-CoV-2 virus, is a severe acute respiratory disease which emerged in Wuhan (China) in late 2019 and quickly becoming a global pandemic. Recent studies have shown that impaired response of type-1 IFNs (IFN-α and its receptors) in COVID-19 infection, as well as deregulated expression of the cytokine IL-17A are important for the development of cytokine storm. Moreover, the activation of human endogenous retroviruses (HERVs) may be related to severity of COVID- 19, but their contribution to COVID-19 severity is still under investigation. **Objective:** To analyze the expression of IFN-α genes and their receptors (INFAR1/INFAR2), IL-17A and HERVs (HERV-K /HERV-W) in the peripheral blood of patients with mild and severe forms of COVID-19. **Methods**: A case-control study, with 117 patients with a diagnosis confirmed by qRT-PCR, of which 59 participants in the case group and 58 in the control group. We collected whole blood and performed the isolation of mRNA from total leukocytes. The RT-qPCR assay was performe to analyze the relative expression of genes ($2^{-\Delta CT}$). **Preliminary Results:** Among the sample studied, 65.5% of the patients were male and 30% of elderly patients were in the severe group (**** p<0.0001). Considering comorbidities, the patients showed the presence of at least one pre-existing chronic disease, with hypertension being the most common comorbidity present in 23 (39,7%) patients. Compared with mild patients, patients with severe COVID-19 had significantly decreased levels of red blood cells, hemoglobin and percentage of hematocrit (*** p< 0,001). Correlation analysis showed that lymphopenia with a negative association with neutrophilia (r=0.78; p<0.0001). Comparison of the medians of the INFAR1 and IL-17A genes indicated a trend towards greater expression in the severe group (both with * p<0.05). ROC analysis for INFAR1 and IL-17A demonstrated AUC, sensitivity and p-value (0.81;0.77,95%CI; *p<0.05, respectively) resulting in positive diagnostic value. **Final Considerations:** Overall, our results demonstrate that the segment most affected by COVID-19 comprises the male, elderly, with hypertension and high expression of INFAR1 and IL-17A in critically ill patients, which may be a reflection of the exacerbated immune response. The findings suggest the potential use of the INFAR1 and IL- 17A genes as biomarkers for severity in COVID-19.

Keywords: COVID-19. INFAR1. IL-17A.

Support: FAPESB, CNPq and PIBIC-UFBA.

HUMAN SERORREACTIVITY TO DIFFERENT ANTIGENS OF *CORYNEBACTERIUM PSEUDOTUBERCULOSIS* – PRELIMINARY RESULTS

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Introduction: caseous lymphadenitis is a disease caused by *Corynebacterium pseudotuberculosis* (*C. pseudotuberculosis)* well described in small ruminants. Some *C. pseudotuberculosis* antigens (VD57, PknG and SodC) have been used in the Immunology Laboratory (Labimuno group) of the Federal University of Bahia (UFBA) to evaluate goat or sheep infection using *in house* methods. Human infection with *C. pseudotuberculosis*, although with low frequency, has been described in several countries. Lymphadenitis and pneumonia were observed in individuals who have contact with these infected animals and/or their derivate products or with the laboratory personal working with bacteria, however, there is no serological diagnostic kit available to detect the infection. Our group showed some antigen of Three-Phase Partitioning (TPP) PAT10 to be reactive in human infection. **Objective:** identify the reactivity of different antigenic preparations of *C. pseudotuberculosis* in human infection. **Material and Method:**

C. pseudotuberculosis PAT10 and VD57 strains were grown in Brain Heart Infusion (BHI) broth and culture supernatants were treated by TPP method. Recombinant protein rPknG *C. pseudotuberculosis* expressed in BL21 StarTM (DE3) strain of Escherichia coli (Invitrogen) and purified by affinity chromatography, according to the protocols established by the our group. Reactivity test were realized by Western blotting (WB) in NC membrane after 12% SDS-PAGE. Standard molecular weight (Thermo Scientific 26616). The samples used were from individuals who reported work/ management of small ruminants on farms. Human sera were diluted 1:10 and conjugate 1:250. **Results and Discussion:** In preliminary analysis by WB with TPP VD57 antigen, different from the peril of fewer bands or non-reactivity in samples from the non-contact group, samples from the contact group showed band reactivity between 25 and 130kDa as observed in the TPP PAT10 preparation. From the analysis of WB with rPknG from C. pseudotuberculosis, recognition was observed in a test sample from the contact group. **Conclusions:** Among the antigenic preparations, different antigenicity could be observed between the control and contact groups in the preliminary tests. An increase in the number of samples from the control and contact groups and the inclusion of rSodC preparation in future analyses is foreseen.

Keywords: *Corynebacterium pseudotuberculosis, rPknG, PAT10, VD57, Western blotting, antigenicity***Support:** LabImuno; CAPES; PIBIC-UFBA; CNPq; FAPESB; PPGIm; Fundação Maria Emília; NECBA-HUPES-UFBA; UFBA.

ANALYSIS OF RISK FACTORS ASSOCIATED TO TOXOCARA SPP., INFECTION IN A PROSPECTIVE STUDY (2005 – 2013)

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Abstract

Introduction: *Toxocara spp.,* are helminths responsible to development of human toxocariasis. The accidental egg ingestion of these helminths leads to development of third larval stage, hence in gut wall entrance and then migration through the organs. In this migration process, the larvae can reach many organs causing the production of Th2 and Th1 cytokines, eosinophilia, raised IgE which culminating in deleterious effects to organisms. Many risk factors are associated with this infection, for instance, age, gender, salary incoming, and habitation. **Objectives:** This study aimed to identify the risk factors associated with *Toxocara* spp., infection through the years (2005 – 2013) in the SCAALA population. **Material and Methods:** Were used 926 sera to identify IgG anti-*Toxocara* positivity by indirect ELISA, using sensitized plates with excreted-secreted of *Toxocara* spp., antigen. The sera were absorbed with *Ascaris lumbricoides* antigen to avoid cross-reactivity, after that the diluted sera were added in the plates and incubated for 1h, anti-IgG was added and incubated for 1h, followed by the streptavidin addition and incubation for 30 min. The OPD chromogen was used to reveal the reaction and the plates were read at 450nm in spectrophotometer. **Results:** The infection prevalence at 2005 was 48% while in 2013 was 53%, the new cases in 2013 was 25 % and the remission case from 2005 to 2013 was 21%. In 2005 we found risk factor association to *T. canis* infection and age and presence of cat/dog at home. We found association to *T. canis* infection with increasing of mother scholarity, salary incoming and street pavement as a protective factor. In comparation, at 2013 we did not find any risk factors to *T. canis* infection, but we found association with increasing to mother scholarity and street pavement as a protective factor. **Conclusions:** In this study, we could identify that the increasing of incoming, scholarity and living conditions are important features to raise the protective factor against *Toxocara spp.,* infection.

Keywords: Toxocara, Risk Factors, Eosinophilia.

Support: CAPES; FAPESB (APP0099/2016)

INTERSECTION OF GENETIC MECHANISMS UNDERLYING PRIMARY AUTOINFLAMMATORY DISORDERS AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C)

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Introduction: Multisystem Inflammatory Syndrome in Children (MIS-C) occurs 2- 5 weeks after SARS-CoV-2 infection and manifests as a severe and uncontrolled inflammatory response that affects multiple organs. The genetic and immunological mechanisms associated with this syndrome have not yet been fully clarified, but several pathways have been suggested**. Objective:** To identify rare genetic variants involved in MIS-C, consolidating the view on the influence of genetic factors on the development of this condition. **Material and methods:** We performed Whole Exome Sequencing (WES) on 21 previously healthy children with MIS-C to identify genetic mechanisms underlying this condition. Single Nucleotide Variants (SNVs) underwent a multi-level prioritization framework, focusing on genes related to primary autoinflammatory disorders. **Results and Discussion:** This analysis revealed 11 missense or splicing heterozygous variants in 8 different genes. Among them, rare and highly pathogenic mutations at *ADAM17* (Patient 8: rs61754178; Patient 14: rs1200631089; Patient 19: rs144458353) and *TRIM22* (Patient 10: rs114191522) were highlighted as strong candidate MIS-C-causing variants. *ADAM17* encodes a member of the ADAM (a disintegrin and metalloprotease domain) family, which is implicated in processing the tumor necrosis factor alpha (TNF-α). Furthermore, this protease may play a role in SARS-CoV-2 infection, since it cleaves the Angiotensin Converting Enzyme 2 (ACE2), the main cellular receptor for SARS- CoV-2. On the other hand, the expression of *TRIM22* is controlled by interferons, restricting viral infection (such as HIV, HBV, HCV and Influenza A) via either regulating innate signaling pathways or serving as an antiviral factor. **Conclusions:** Rare and potentially pathogenic variants in coding regions of the *ADAM17* and *TRIM22* genes may contribute to the occurrence of the multisysteminflammatory syndrome associated with COVID-19. More studies are needed to establish the functional effect of these genetic variants on MIS-C development.

Keywords: MIS-C; Hyperinflammation; SARS-CoV-2; Genetics.

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VARIANT IN THE *ADCY9* IS NEGATIVELY ASSOCIATED WITH SEVERE ASTHMA EXACERBATIONS AND NEUTROPHILIA.

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Introduction: Asthma is a chronic inflammatory disease of the lower airways determined by environmental and genetic factors. Severe asthma exacerbations are a worsening of asthma symptoms that require an urgent action by the patient and physician to prevent hospitalization or death from asthma. One of the possible causes of recurrence of asthma attacks may be interindividual genetic variations. Immunogenetic is the study of the genetic basis of the immune response. It is important to study genes involved in the immunopharmacological pathway of the disease, such as *ADCY9*. **Objective:** To evaluate genetic variants in the *ADCY9* gene with phenotypes of asthma exacerbations in a population of Salvador. **Material and Methods:** Patients with severe asthma attacks were recruited from emergency care units in Salvador/Ba. DNA was extracted from whole blood. Genotyping of rs2601814, rs2601796 in *ADCY9* were performed in

172 individuals using Taqman assay. Logistic regression was performed for asthma outcomes (exacerbations, asthma control and immunological markers in the blood). Analyzes were performed using Plink 1.9, SPSS 20, and RStudio software. **Results and Discussion:** The G allele of rs2601814 was negatively associated with oral corticosteroid use (OR 0.62 CI 0.40-0.97 and negatively with lack of asthma control according to the ACQ-6 questionnaire (OR 0.56 CI 0.35- 0.92). Individuals with this variant also had lower levels of neutrophils in their blood. It has already been described in the literature that the level of neutrophils is directly related to the number of asthma exacerbations. **Conclusion:** The rs2601814 is associated with severe asthma exacerbations and may be associated with a differentiated response to treatment. Functional impact studies should be carried out to better understand the mechanism by which this variant act.

Key words: Asthma, Attack, Variant.

Support CNPq, CAPES, PROAR, UFBA.

EVALUATION OF THE THERAPEUTIC POTENTIAL OF MESENCHYMAL STEM CELLS OVEREXPRESSING G-CSF FOR CLINICAL USE

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Abstract

Introduction: The stem cell therapy has been considered a promising regenerative medical treatment for spinal cord injury. The proliferative and functional activity of mesenchymal stem cells (MSC) is destined to decrease during the senescence process. Recently, several strategies have been explored to rejuvenate senescent MSCs and improve their functions. We evaluate the genetic modification to overexpress G-CSF and replacement of fetal bovine serum (FBS) with platelet lysate. **Objectives:** To evaluate a protocol for the generation of genetically modified mesenchymal stem cells with high potency to use in cell therapy. **Methods:** The MSC were isolated from human umbilical cord (UC) and characterized in P4 by surface markers and genetic monitoring by karyotyping. MSC culture were suplemented with 10% SBF or platelet lysate. Senescence markers were evaluated by fluorescence and cell proliferation evaluated by luminescence according to the Cell Titer Glow kit. The immunoregulatory potential was evaluated through the cultivation of PBMC with MSC-G-CSF culture supernatant. **Results and Conclusions:** MSC-UC derived express 100% CD90, 100% CD73, 95,8% CD105 and 0,6% of negative markers and normal karyotyping. The replacement of FBS by platelet lysate didn't affect cell morphology, however, we observe an increase in the proliferative capacity and expression of Beta-galactosidase. Regarding the immunoregulatory potential, we observe stimulation of lymphocytes by MSC-G-CSF when compared to controls. Confirmatory experiments need to be performed, as well as cytokine and factor analyses.

Keywords: Mesenchymal stem cells; Genetic modification; G-CSF

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VARIANTS AT *NLRP12*, *IL17RC*, *IFNA10* AS GENETIC FACTORS FOR MULTISSYSTEMIC INFLAMMATORY SYNDROME IN PREVIOUSLY HEALTHY INDIVIDUALS

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Introduction: Multisystem inflammatory syndrome in children (MIS-C) is a severe complication of SARS-CoV-2 infection. Studies have been developed to identify the genetics determinants of MIS-C. **Objectives:** To identify genetic variants that are determinant for MIS-C. **Material and Methods:** This is descriptive study of patients without previous comorbidities, diagnosed with MIS- C in Salvador (BA, Brazil) and Recife (PE, Brazil), based on the Centers for Disease Control and Prevention (CDC, USA) diagnostic criteria. Clinical and laboratory data were collected from medical records, as well as DNA samples were collected to perform whole exome sequencing. Variants prioritization was carried out focusing on 126 human genes that encode proteins involved in the mechanisms by which SARS-CoV-2 modulates immune responses, from a list available in the Reactome database (DOI:10.3180/R-HSA-9694516.1). **Results and Discussion:** 21 patients with MIS-C participated of this study; of these, 62% (n=13) were male and 67% (n=14) were declared as brown. The median age was 8 years (IQR, 5-12). In addition to fever > 38º C, observed in 100% of patients, the most prevalent symptoms were abdominal pain (74%), followed by skin rash (57%) and dyspnea (57%). The main outcome was shock, observed in 48% of patients. When prioritizing coding variants in genes that participate of the SARS- CoV-2 infection process, we identified rare, deleterious variants potentially involved in the development of MIS-C in 38% (n=8) of the individuals studied. Remarkably, 5 of 21 (24%) patients had functional mutations in the *NLRP12* gene, located at 19q13.42, which encodes a cytoplasmic protein involved in suppression of inflammatory responses in activated monocytes. We also identified three mutations in the *IL17RC* gene, located at 3p25.3, which encodes one of the IL-17 receptor chains. Furthermore, we also identified a nonsense variant in the *IFNA10* gene, located in at 9p21.3, which encodes the IFN-α10 factor. **Conclusion:** Rare and deleterious mutations in coding regions of the *NLRP12*, *IL17RC* and *IFNA10* genes may contribute to the occurrence of MIS-C

Keywords: MIS-C, SARS-CoV-2; Genetics.

Support: FIOCRUZ Support Foundation (FIOTEC). INOVA/FIOCRUZ Program (2020). Process number: 48402174317383.

THE IMMUNE HUMORAL RESPONSE IN SARS-COV-2 INFECTION AND ITS POTENTIAL CLINICAL APPLICATION

Abstract

Introduction: In 2019, the first records of the SARS-CoV-2 disease (COVID-19) occurred, which spread rapidly around the world, forcing the World Health Organization (WHO) to declare a pandemic state. As the pandemic progressed, several variants of concern have been identified, causing several epidemic waves. Along with the emergence of these new variants, new questions have also arisen about the effectiveness of the humoral immune response of individuals who were previously infected, especially about the ability of neutralizing antibodies to prevent. **Objective:** To elucidate the kinetics of the humoral immune response in COVID-19, exploring the cytokine profile involved in the switch of different antibody subclasses, as well as their recognition of SARS CoV-2 proteins. **Material and Methods:** We collected serum samples from 300 patients positive for SARS-CoV-2 (RT-PCR), admitted to the emergency center of Hospital Aeroporto. Patients were followed up after hospital discharge and new serum collections were performed 1, 3, 6 and 12 months after admission. Anti- S1 IgG antibodies were measured by ELISA. Patients were classified into two groups (acute and chronic), with the following classifications: mild, moderate and severe. **Results and Discussion:** We identified that patients who had moderate or severe disease in the chronic phase had increased production of IgG anti-S1 from SARS-CoV-2, compared to patients who had mild, moderate or severe disease in acute phase or patients with mild symptoms in the chronic phase. These results suggest a dysregulation of the immune system in patients with more serious complications. **Conclusions:** Patients who express higher amounts of IgG in response to viral S1 may be producing immunoglobulin subclasses that are less efficient in fighting the infection.

Keywords : COVID-19, Antibodies, IgG, Spike.

Support: Fiocruz Support Foundation (FIOTEC). INOVA/FIOCRUZ Program (2020). Process Number: 48401626961258.

CYTOTOXICITY OF DIFFERENT CONCENTRATIONS OF THE ETHANOLIC EXTRACT OF PHYSALIS ANGULATA IN PC12 CELL CULTURES

Washington Santos Antunes[1,2], Brenda Valério Souza[1,2], Silvia Lima Costa[2], Alexandre Moraes Pinheiro[1]

Veterinary Biochemistry and Immunology Laboratory, Federal University of Recôncavo da Bahia, Bahia, Brazil.
Neurochemistry Laboratory, Neurochemistry Laboratory, Federal University of Bahia, Salvador, Bahia, Brazil.

Introduction: Physalis angulata is a plant that can be found in tropical and subtropical regions, where it is used in folk medicine for the treatment of numerous diseases. Several studies using different components of P. angulata proved anti-inflammatory, antiparasitic, antioxidant and protective action.

Objectives: Therefore, the present work sought to evaluate the effects of the crude ethanolic extract of P. angulata (EEPA) in cell cultures of the PC12 lineage. **Methods**: EEPA was produced from the stems of P. angulata. The cytotoxicity of different concentrations of EEPA was determined using the MTT assay. To evaluate cell morphology and cell proliferation, Rosenfeld dye was used. ImageJ v.1.53e software was used to count the cells. To verify the immune response, nitric oxide levels were analyzed, determined by measuring nitrite using the Griess method. The results were analyzed by the statistical program GraphPadPrism 7.0 and the data were expressed as mean ± standard deviation of the mean of the evaluated parameters. **Results and Conclusions**: Treatment with EEPA at concentrations 0.5; 1; 5 µg/mL suggest that there was no cytotoxicity or reduction in the number of PC12 cells. The extract caused morphological changes in cells at all concentrations, the most noticeable being the contraction of the cell body. NO production was reduced at all concentrations, mainly at 0.5µg/mL. The data obtained in our work suggest that EEPA can negatively modulate NO production and change the morphology of PC12 cells.

Keywords: Central Nervous System. Herbal medicine. PC12.

Support: CAPES, UFS, PPGIm, LabNq.

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VII INTERNATIONAL SYMPOSIUM OF NEUROCHEMISTRY AND PATHOPHYSIOLOGY OF THE GLIAL CELL
XI SYMPOSIUM OF UPDATES ON PHARMACOLOGY AT UFBA

OUTUBRO 11 – 14, 2022
Institute of Health Sciences – Salvador
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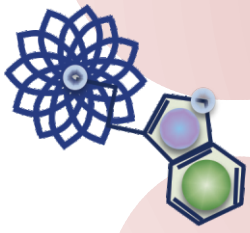

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PROGRAM

October 11th

09:00 a.m. – 7:00 p.m. (on line)

Mini-course *(online)* – Knowledge Bases of Research in Neurochemistry.

Laboratory of Neurochemistry and Cell Biology (LabNq- ICS/UFBA), School of Advanced Studies in Neurochemistry (EAEN)

Morphofunctional aspects of Central Nervous System (CNS) Cells. Balbino Lino dos Santos e Suzana Braga

In vitro Study Models of CNS cells under physiological and pathological conditions. Silvia Lima Costa e Ravena Nascimento.

In vivo Study Models of CNS Pathologies. Victor Diogenes Amaral da Silva and Juciele Valeria Oliveira

October 12th

09:30 – 12:00 a.m.

Presentation of undergraduate students and young doctors. Moderators: Maria de Fatima Costa and Clarissa Schitine.

Role of glucocorticoid receptors in agathisflavone signaling in an in vitro model of neuroinflammation in glial cells. Áurea Maria Alves Nunes Almeida, MPhil in Immunology, Federal University of Bahia.

Amyloid fibers and inflammation: induction of extracellular neutrophil networks in a murine model. Thyago Rubens Cardim Pires, PhD in Biochemistry, Federal University of Rio de Janeiro.

Effects of flavonoid rutin in Parkinson's disease animal model induced by aminochrome. Fillipe Mendes de Araújo, PhD in Immunology, Federal University of Bahia.

Opening *(online)*. Silvia Lima Costa

Lecture *(online)* - The plasticity of myelination glia in the white matter. Prof. Dr. Arthur Morgan Butt (University of Portsmouth, King's College London, UK)

Thematic Session *(online)* - Pathophysiology of Brain Diseases and Therapy I

The translocator protein TSPO is prodromal to mitophagy loss in neurotoxicity. Michelangelo Campanella (University of London, UK).

Fractalkine enhances oligodendrocyte regeneration and remyelination in a cuprizone demyelination mouse model. Anastasia Voronova (University of Alberta, CN)

Deciphering reactive astrogliosis in Alzheimer's disease brains. Igor Fontana (Karolinska Institute, SE

October 13th

Lecture *(online)* - Cell plasticity governs by AhR. David Gilot (University of Rennes I, FR).

09:00-10:00- Poster Session II *(online)* - Presentation of works by undergraduate and graduate students

Thematic Session *(presential)* - Pathophysiology of Brain Diseases and Therapy II

Modulation of Autophagy in Neurodegenerative Diseases Associated with Aging. Rodrigo Ureshino (University of São Paulo).

Imaging Brain Glucose Metab olism. Eduardo Zimmer (Federal University of Rio Grande do Sul)

If you don't know, now you know; astrocytes participate in the remyelination process. Markley Silva (Heinrich Heine University, GR).

Lecture *(presential)* – Glia: cell-cell interactions in health and disease. Vivaldo Moura Neto (State Institute of the Brain Paulo Niemeyer). **15:30 h Closure**

Lecture *(presential)* - Purinergic signalling in neurodegeneration and brain diseases. Alexander Henning Ulrich (University of São Paulo).

October 14th

Lecture *(online)* - Targeting myelin and oligodendrocyte dysfunction: new hopes and challenges for treating neurodegenerative diseases. Maria Pia Abbracchio (University of Milan, IT)

Poster Session III *(presential)*. Presentation of works by undergraduate and graduate students

Thematic Session *(presential)* - Chemistry and Neuropharmacology of Natural Products

Lectins: biological applications and structural correlations. Claudener Souza Teixeira (University of Cariri).

Synthesis of natural and non-natural flavonoids for biological evaluation. Mauricio Morares Victor (Federal University of Bahia).

Aminochrome and molecular mechanisms in Parkinson's disease and utility to study neuroprotective compounds. Victor Diogenes Amaral da Silva (Federal University of Bahia)

Award for Best Posters and Closing

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Yohana de Barros Fernandes; Gabriele Domingos Jardim; Juliana da Silva Carvalho; Vivaldo Moura Neto; Juliana de Mattos Coelho Aguiar.

PRESENTATION

The 7th International Symposium on Neurochemistry and Pathophysiology of the Glial Cell took place in part virtually, through the Zoom Platform, in part at the Institute of Health Sciences, Federal University of Bahia in Salvado-Bahia, Brazil, from the 11th to the 14th October 2022. The event feature besides local researchers the participation of renowned speakers from Brazil, from the Americas and Europe, which presented the various topics of research in Neurochemistry, Pathophysiology, Neuro and Immunopharmacology and all its related. During the meeting it was presented and discussed advances in the understanding of aspects of neurochemistry, immunology, physiology, and pathophysiology of diseases that affect the nervous system and about the understanding of molecular targets for drug discovery, organized in conferences, scientific session also composed by young researchers, as well as virtual and presential poster sessions. Around 200 participants attended the meeting, between undergraduate students and graduate students, as well as researchers and professionals, which will bring the possibility of interaction of the local academic and scientific community with renowned researchers, encouraging scientific and technological exchanges.

ABSTRACTS POSTER SECTIONS

BBB PERMEABILITY AND INCREASED LEVELS OF AMINO ACIDS IN CSF ARE ASSOCIATED WITH BRAIN ALTERATIONS IN RATS WITH ACUTE LIVER FAILURE

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Introduction: Acute liver failure (ALF) is a life-threatening medical condition that often leads to hepatic encephalopathy (HE). The pathogenesis of HE implicates hyperammonemia, astrocyte dysfunction and glutamatergic system imbalance. Animals and humans with HE have shown elevated cerebrospinal fluid (CSF) levels of glutamine and glutamate, which may be associated with brain impairment. **Objective:** In this study, we aim to evaluate the relationship between blood-brain barrier (BBB) integrity and CSF amino acid levels with the neurological status of rats after subtotal hepatectomy. **Methods:** Adult male Wistar rats underwent a subtotal hepatectomy (removing 92% of hepatic mass or SHAM group) and were divided into 4 (four) cohorts. They were assessed according to: i) ALF following surgery (24h) by measuring plasma levels in liver function tests; ii) HE development by monitoring the rats through a neurological scale following surgery (up to 72h); iii) BBB impairment following surgery (24h) by measuring CSF albumin and amino acid levels and in vivo Evans Blue penetration into the brain; iv) Mortality rate by measuring amino acid levels following surgery (12h) and monitoring the rats following surgery (up to 72h after). **Results:** Animals with ALF presented severe neurological impairment and high mortality rates when compared to the SHAM group. We performed a hepatic function test 24 hours after subtotal hepatectomy, which demonstrated a significant increase of AST, ALT, Total Bilirubin, Direct Bilirubin, Prothrombin time and Ammonia levels in blood. Additionally, the increase of amino acids, glutamine, and albumin levels in CSF as well as of Evans Blue penetration into the brain tissue was correlated with the neurological grades of HE, indicating signs of impaired BBB permeability induced by ALF. Furthermore, the animals' mortality rate showed a positive correlation with the increase of amino acid levels in CSF following subtotal hepatectomy (12h). **Conclusion**: We present new evidence correlating increased levels of amino acids in CSF with impaired BBB permeability in an experimental model of ALF. Our data highlight the potential role of amino acid levels in CSF, especially glutamine, for detection purposes even in the early stages of HE and suggest that these molecules offer prognostic value for patients progressing to coma and death.

Keywords: Acute liver failure, Hepatic encephalopathy, Cerebrospinal Fluid, Amino Acids, Albumin, Blood-brain barrier, Glutamine.

Support: This work was supported by Brazilian agencies and grants: CNPq, CAPES, FAPERGS, Brazilian Institute of Neuroscience/FINEP, INCT/Excitotoxicity and Neuroprotection (465671/2014-4). The authors declare no competing financial interests.

ROLE OF KYNURENINE PATHWAY IN THE NEUROPROTECTIVE EFFECT OF RUTIN AGAINST AMINOCHROME CYTOTOXICITY

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Introduction: Neuroinflammation, aminochrome (AM) cytotoxicity, and changes in kynurenine pathway (KP) have been described as pathological alterations associated with dopaminergic degeneration in Parkinson's Disease (PD). On the other hand, rutin is a flavonoid with anti-inflammatory, antioxidant and neurogenic action. However, the role of Kynurenine pathway in the neuroprotective effect of rutin against aminochrome cytotoxicity has never been investigated. **Objective:** To analyze morphological aspects and the kynurenine pathway in glial cells treated with rutin and/ or AM. **Method:** Rat brain glial cells were treated with AM (25 µM) for 24 hours and then treated with rutin (1 µM) for an additional 24 h. Morphological Analysis were performed by microscopy using Rosenfeld's staining with immersion in the dye for 20 min, while the evaluation of glial acid fibrillary protein (GFAP) expression was performed by immunostaining for GFAP antibody and visualization with fluorescence microscopy, and the analysis of KP was performed in secretomes by high performance liquid chromatography (HPLC) (UltiMate™ 3000, Thermo Scientific) in a reversed phase column (C18) at 22°C with the solvents: (A) Methanol, (B) Acetonitrile (C) Water, with detection of eluates between 280-360 nm and 320 nm, comparing them with the standards quinolinic acid, kynurenic acid, 3-hydroxykynurene and tryptophan (SIGMA). **Results and Conclusions:** The results show that AM promoted significant damage in cell culture, predominance of fusiform and amoeboid morphologies, the latter typical of reactive microglia phenotypes; all these morphological changes were reversed with rutin treatment. Furthermore, it was observed that AM modulation also caused a reduction in GFAP expression, and release of quinolinic acid (QUIN) and 3-hydroxykynurenine acid (3HK) metabolites of the kynurenine pathway associated with cell damage, different from what was presented by the rutin-treated (R) and AM + R-treated groups that showed increased GFAP expression and peaks compatible with kynurenic acid (KYNA), a protection-related metabolite. The results showed that rutin is able to attenuate the changes induced by AM in astrocytes, suggesting its potential for treatment of neuroinflammation.

Keywords: Rutin, Aminochrome, neuroinflammation and the kynurenine pathway.

Support: CAPES, CNPQ, and Fapesb.

MOLECULAR INTERACTIONS BETWEEN APIGENIN AND THE NRLP-3 INFLAMMASOME COMPLEX: USING BIOINFORMATICS IN THE ANALYSIS OF ANTI-INFLAMMATORY POTENTIAL

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Introducion: NLRP3 integrates the inflammasome and together with ASC and Caspase-1, form a multiprotein structure that initiates inflammation, and its configuration remains essential for immune defenses. However, inflammation itself in various tissues is the factor that produces the pathophysiology of NLRP3-associated diseases. Apigenin is a flavonoid, which may have a therapeutic effect against inflammatory diseases. **Objectives:** This study aims to evaluate in silico if proteins associated with the pathway of activation and execution of the NLRP3-inflammassome complex are targets of apigenin. **Methods:** The AutoDockTools, AutoDockVina and Discovery Studio programs were used. The MCC950 and ML132 were used as comparison for positive control for inhibition of the NLRP3 and Caspase, respectively. **Results and Conclusions:** It was observed that apigenin interacted with 15 aminoacids of the NACHT domain of the NLRP3 very close to the binding site of the pharmacological inhibitor of the ATPase activity of the NLRP3 inflammasome, MCC950. This proximity indicates a likely inhibitory activity of the flavonoid. Regarding the tests of apigenin with BRCC3, it was found that 12 aminoacids participated in this interaction, which did not occur in the JAMM binding domain of BRCC3 with NLRP3. This result does not rule out further possible indirect inhibition pathways, since the interaction found was favorable. Tests of apigenin with the adaptor protein ASC showed interaction of 7 aminoacids of the PYD domain. This may indicate ability of apigenin to interfere with ASC-NLRP3 binding which would possibly inhibit the NLRP3 inflammasome. In tests with Caspase-1, its inhibitor ML132 was used as a parameter. Apigenin did not interacted with aminoacids in common with its inhibitor, nor with any aminoacid of the active site of Caspase-1, and cannot be classified, through these results, as capable of causing its inhibition. Nonetheless, its binding with Caspase-1 happened in the CARD domain, which is where the protein binds to ASC in a CARD-CARD interaction, thus, there is a possibility of apigenin interfering in this interaction, given its affinity with this domain, by intercepting the activation of the NLRP3 inflammasome. Further in vitro and in vivo studies are needed to confirm other mechanisms and pathways of action of the flavonoid in inhibiting the inflammasome.

Kaywords: Inflammation; Apigenin; Molecular Docking; NLRP3.

Support: CNPq.

INVESTIGATION OF THE NEUROPROTECTIVE POTENTIAL OF APLYSINA FULVA AND AF-H1

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Introduction: Neurodegenerative diseases are characterized by the progressive and irreversible loss of neuronal function, resulting from the exacerbated activation of glial cells, with the secretion of cytokines, chemokines and neurotoxic factors causing exacerbated inflammation and oxidative stress to contain the damage. Upon subsequent contact with the damage, these cells assume an inflammatory profile, where there is production of high levels of inflammatory mediators, such as TFN-α and IL-1β, in addition to the production of reactive oxygen and nitric oxide species, resulting in neuronal death. Thus, the search for new therapies aims to discover natural compounds with anti-inflammatory and neuroprotective effects, such as marine sponges, products rich in anticancer and/or anti-inflammatory agents. **Objectives:** To evaluate the neuroprotective profile of the extract of the species Aplysina Fulva and pure substance isolated from it in neuronal cells. **Methodology:** PC12 cell cultures were induced to damage with LPS at 1 and 5 µg/mL for 2 hours and then treated with methanolic extract of the sponge Aplysina Fulva at concentrations of 0.1.1 and 10 µg/mL, as well as the substance isolates of the same species, AF-H1 at concentrations of 1 and 10 µM for 24 h. Viability was determined by MTT assay and morphological analysis by phase contrast and Rosenfeld staining. **Results and Conclusions:** The cultures induced to the damage and later treated with the extract of Aplysin Fulva and isolated substance, presented greater cellular viability in relation to the control and appear to protect the neuronal cells.

Keywords: Neuroinflammation. marine sponges, anti-inflammatory, neuroprotection

Support: The support of this work is due to the National Council for Scientific and Technological Development (CNPq), the Fundação de Amparo a Pesquisa do Estado da Bahia (FAPESB), the Coordination for the Improvement of Higher Education Personnel (CAPES) and the Federal University of Bahia (UFBA)

INVESTIGATION OF THE NEUROPROTECTIVE POTENTIAL OF FLAVONOID APIGENIN CONJUGATED WITH B-CYCLODEXTRINS IN SPINAL CORD INJURY MODELS

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Introduction: Spinal cord injury is defined as a temporary or permanent interruption of spinal cord function, and it is associated with significant morbidity and mortality. Inflammation is one of the factors that increases the lesion area, aggravating the neurological deficits. Treatment strategies vary according to the stage of spinal cord injury, however current therapies are limited. The literature presents different models of studies in the central nervous system in which apigenin has shown beneficial effects. Despite this, there is little research on the neuroprotective role of apigenin in spinal cord injury. **Objectives:** To evaluate the neuroprotective effects of the flavonoid apigenin and conjugates of apigenin with β-cyclodextrins in spinal cord injury models. The specific objectives are to evaluate the cytotoxicity of apigenin and its conjugates to determine the best candidates considering viability parameters; to evaluate the effect of apigenin and the best conjugates on the neuroprotective response of spinal cord cells in the ex vivo model of spinal cord trauma; and to characterize the morphological response of cells treated with the different conjugates in the in vitro and ex vivo model of spinal cord injury. **Materials and methods:** The cytotoxicity of the apigenin and conjugates of apigenin with β-cyclodextrins was evaluated through MTT assay to identify the best compounds. The i*n vitro* spinal cord model was subjected to injury by chemical and physical methods and, later, was treated with the best apigenin conjugates. The analysis of cell morphology and phenotypes was performed by phase contrast microscopy and Rosenfeld staining. **Results:** Three conjugates look promising when compared to apigenin. Apigenin conjugates increased cell viability and reversed LPS-induced chemical damage. **Conclusions:** Apigenin conjugates appear to protect neural cells from damage caused by inflammation from spinal cord injury.

Keywords: apigenin; neuroprotection; spinal cord injury Support This work was supported by the Research Support Foundation of the State of Bahia (Fundação de Amparo à Pesquisa do Estado da Bahia – FAPESB), the National Council for Scientific and Technological Development (Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPq) and the Higher Education Personnel Improvement Coordination (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – CAPES).

INFLUENCE OF CANNABIS SATIVA CONSUMPTION ON GLIAL CELLS: IMPLICATIONS FOR EPIGENETICS AND NEURODEVELOPMENT

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Introduction: Cannabis sativa is mainly used recreationally and therapeutically. There are several phytocannabinoids present in it, but the most investigated are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), recognized for their psychotropic and therapeutic effects, respectively. The action of these phytocompounds at the cellular level raises questions about their function linked to receptors present in glial cells. **Objective:** The objective of this review is to understand the mechanisms of these receptors present in glial cells that result in phenotypic alterations, mainly associated with neurodevelopment and epigenetic alterations. **Methodology:** Some descriptors such as "cannabinoids and neurodevelopment", "THC effects", among others, were used in databases such as Scopus, Science Direct and Pubmed. Inclusion criteria defined articles related to the use of THC in glial cells. **Discussion:** CB1 and CB2 receptors are highly expressed in glial cells. Astrocytes and neurons express more CB1 receptors, while microglia express more CB2 receptors. THC is specific for CB1 and CB2, unlike cannabidiol which can bind to other receptors such as 5HT1A. Studies show that exposure to THC caused morphological changes in astrocytes, in addition to increasing inflammatory markers and microglial activation. Cannabidiol had the ability to reduce astrocytic activity in insults. Epigenetically, behavioral and molecular problems have been found in the offspring of rats where the parents had exposure to cannabinoids before and during mating, as in the disruption of the offspring's dopamine circuits. THC can cross the placental barrier and this influences the abnormal development of the fetal endocannabinoid system, decreasing the amount of receptors. Its use in adolescence may reduce astroglial markers, synaptic markers and neurotransmitters such as glutamate in some areas of the brain. **Conclusion:** CBD and THC have actions related to receptors that are bound, whether endocannabinoids or not, and this may justify their effects. These receptors will initiate activation processes according to the stimulus and will present a phenotype according to the glial cell affected. Evidence demonstrates direct influences of prenatal and postnatal cannabis use (during the cortical development phase) on offspring or on the individual itself, particularly glial cells, but research on epigenetics and neurodevelopment needs to be clarified.

Keywords: "endocannabinoids"; "glial cells"; "cannabinoids"; "neurodevelopment"; "epigenetics".

Suport: CNPq.

EFFECT OF NICOTINE IN ASTROCYTES AND ITS INVOLVEMENT ON NEUROPROTECTION IN PARKINSON'S DISEASE

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Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disease in the world. However, there is still no effective therapy for cure or prevention of the progressive neuronal loss in the nigrostriatal system. Conventional treatments are based on promotion of physiological levels of dopamine and control of symptoms. Some therapies based on neuroprotective action – such as coenzyme Q10 administration have been successful in preclinical studies, but not in clinical trials. This may be due to the lack of pre-clinical translational study models. Studies have been suggested aminochrome, a molecule derived from dopamine oxidation, has been considered a neurotoxin able to induce all of molecular alterations associated with PD pathogenesis. On the other hand, there is epidemiological evidence of potential protective effect of nicotine for PD, and studies showed protective effect of nicotine against aminochrome cytotoxicity in neuronal cells. However, the effect of nicotine in astrocytes in PD study model induced by aminochrome is not clear. **Objectives:** In this study, we evaluated the effect of nicotine on the activation of autophagy in astrocytes and its involvement with neuroprotection. **Methodology:** We used astrocytes from U251 human cell lineage, Wild type or transfected (pBABE alpha-syn – nYFP), submitted to treatment with nicotine and/ or aminochrome. The MTT test was performed to assess the cell viability. In addition, analyze of LC3 and P62 protein expression was performed by Western blot. **Results:** In the present study, we observed that most of conditions of nicotine treatment (0.0001 – 750 µM, for 24 h) did not induced cytotoxicity in Wild Type U251 cells. Meanwhile, 20 µM nicotine for 24 h was cytotoxicity for transfected U251 cells. The treatment with 0.1 µM nicotine for 48h U251 cells did not induced changes in the expression of LC3 and P62. On the other hand, it was observed that treatment with 25 – 75 µM aminochrome for 48h and 72h is toxic to transfected U251 cells . Moreover, we observed that nicotine in concomitant treatment with aminochrome was protective for transfected U251 cells. **Conclusion:** In this sense, we conclude that nicotine is protective for astrocytes with alpha-synuclein dysfunction against cell damage induced by aminochrome. Further studies will be needed to clarify the effect of nicotine on the expression of autophagy markers in cells subjected to treatment with aminochrome.

Keywords: Parkinson's disease; astrocytes; nicotine; neuroprotection.

Support: CNPQ; Fapes, CAPES

IN SILICO ANALYSIS OF MOLECULAR INTERACTIONS BETWEEN CANNABIDIOL AND THE NLRP3 INFLAMMASOME

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Introduction: NLRP3 is an intracellular protein belonging to the NLR family, composed of three domains, which are: the pyrin domain, also called PYD, the leucine-rich repeat domain, LRR and the central nucleotide binding domain, NATCH. Its role in the body's defense can trigger an inflammatory response, forming a multiprotein complex called inflammasome. This complex is directly linked to the innate immune system, playing several roles related to the protection of the human body. However, the exacerbation of this inflammasome can cause a homeostatic imbalance, activating and aggravating various inflammatory diseases. Thus, some substances have been tested in order to clarify their inhibition potential against this exacerbated reaction, for example, cannabidiol, which is one of the most commonly studied cannabinoids, derived from the cannabis sativa plant, used for the treatment of various pathologies, especially those of a neurological and carcinogenic nature. **Objectives:** This study aims to demonstrate the inhibitory potential of cannabidiol against the NLRP3 inflammasome complex and the desubiquitinase proteins BRCC3, ASC and Caspase-1. **Material and methods:** AutodockTools and AutodockVina were used for molecular docking. For visualization and analysis of the results, the Discovery Studio Visualizer software was used. **Results and discussion:** A binding energy of – 7.4 kcal/mol was obtained through the interaction between NLRP3-Cannabidiol, establishing interactions with the Walker A motif, demonstrating bonds with 15 amino acids, indicating that it has inhibitory potential against to the inflammasome, as it was compared with the control inhibitor MCC950. The docking of the BRCC3 protein with the ligand Cannabidiol obtained binding energy of – 7.0 kcal/mol, however, there was no interaction with the active site of the protein. In the interaction between Caspase protein and Cannabidiol, a binding energy of – 6.8 kcal/mol and interactions with 12 amino acids were obtained, forming conventional bonds of Hydrogen, Pi-sigma, Pi-Alkyl and Van der Waals. Faced with the interaction between ASC protein and Cannabidiol, a low interaction of – 5.3 kcal/mol was demonstrated, despite the amino acids that established interactions being within the active domain of the protein. **Conclusions:** Cannabidiol has the potential to inhibit the inflammasome, similarly to the control inhibitor MCC950, however, this same potential cannot be observed with the other proteins, requiring further studies to better demonstrate these interactions.

Keywords: NLRP3, Inflamassoma, Cannabidiol, Molecular Docking, Caspase-1.

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ANTIGLIOMA ACTIVIY OF FRACTIONS FROM LEPIDIUM MEYENII (PERUVIAN MACA)

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Introduction: Lepidium meyenii is a plant that has several medicinal properties as antioxidant, anti-inflammatory and antitumor activity, however, it is the first study that evaluates antiglioma effect from this plant. Also, many chemical compounds from L. meyenii extracts have already been identified as macamides, alkaloids and glucosinolates. Still, few studies show the correlation between the chemical compound and biological activities from this plant **Objective:** To do a bioguided fractionation of L. meyenii extract by evaluation of antiglioma activity. **Methods:** The extract was obtained from the root of the plant by maceration in ethyl acetate. A bioguided fractionation of the extract was performed by evaluating the antiglioma activity against C6 cell line and cell viability was evaluated by MTT assay. The crude extract was subject a liquid chromatography using silica gel. Then, the most active fractions were subjected to a liquid chromatography using sephadex. **Results and discussion:** From the crude extract it was obtained thirteen fractions. The antiglioma activity from all thirteen fractions was tested and the percentual of viable cells varied from 130 to 83% after 24 hours of treatment and after 48 hours of treatment the percentual varied from 113 to 65%. The fraction number six was the most active and it was chosen to be fractionated by a liquid chromatography using sephadex and eleven fractions were obtained. The antiglioma activity from these fractions was evaluated and the percentual of viable cells varied from 95 to 0.12% after 48h of treatment. **Conclusion:** Our data show that L. meyenii has a high antiglioma potential against C6 cells and it suggest that this plant may have potential clinic applications in glioma therapy.

Keywords: Peruvian Maca, Metabolomics, Natural Products.

Support: UFBA, FAPESB, CNPq and CAPES

SYNTHESIS OF NATURAL AND NON-NATURAL BIFLAVONOIDS FROM CITRUS SINENSIS BIOMASS WASTE

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Introduction: Biflavonoids are natural polyphenols. Amentoflavone 7 is a natural biflavonoid isolated from plants such as Taxus baccata, Torreya nucifera, and Garcinia xanthochymus. It has exhibited many bioactivities, including leishmanicidal, neuroprotective, antioxidant, and antimicrobial. Due to its limited natural abundance, it has been synthesized to solve the low availability. The syntheses of 7 found in the literature are biomimetic, reported to initiate from hydroxylated acetophenone and a substituted benzaldehyde in a long and expensive route. Changing to a sustainable strategy, using non-glycosylated flavonoids from biomass as starting material allows syntheses of natural and non-natural biflavonoids from an advanced and bioavailable intermediate. **Objectives:** Here, we described synthetic studies on the total synthesis of amentoflavone 7 and other non-natural biflavonoids from biomass. **Methods:** Hesperidin 1 was obtained from the extraction of albedo from Citrus sinensis using refluxing EtOH. The glycosylated flavone was oxidized to diosmin 2, which suffered the following transformations: ii) alkylation and sugar hydrolysis, iii) methylation, and iv) dealkylation reactions furnishing 3. **Results and Conclusions:** Using our synthetic route was possible to obtain 3 in 5 steps with a 14% overall yield. Then is aimed to synthesize the amentoflavone 4 and the non-natural biflavonoids 5 employing C-C cross-coupling reactions. After obtaining the substances will be studied the yields to optimize them.

Keywords: Total synthesis, Amentoflavone, Waste biomass, Flavonoid

Support: CAPES, CNPq, INCT, CIEnAm, UFBA, GPSQ

THE ROLE OF RUTIN AS A POSSIBLE INHIBIDOR IN SILICO OF NRLP3'S INFLAMATORY PATHWAY.

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Introduction: Inflammation is one of the most important processes to support life but is also the key to the pathogenesis of multiple degenerative diseases, like Parkinson's disease and Alzheimer's disease. One of the main regulation pathways of inflammation is through the NRLP3 complex, an inflammasome, that along with other proteins, acts generating pro-inflammatory cytokines and can be a good pharmacologic target to regulate inflammation. Flavonoids, innate anti-inflammatory polyphenols derived from vegetables and plants, are being researched as a possible inhibitor of this pathway. **Objectives:** This paper aims to analyze the interactions between Rutin and the NRLP3 complex, and if this flavonoid has any inhibition capabilities. **Methods:** Using docking softwares as AutoDockTools, AutoDockVina, Discovery Studio and the tridimensional models collected in the PubChem and AlphaFold websites, we made in silico simulations of interactions between rutin and the NRLP3 inflammasome, specifically in the NACHT domain, which has a proven in vivo inhibitor named MCC950, that was used as a positive control experiment. **Results and Conclusions:** this experiment revealed that the interaction between the Rutin and the NRLP3 complex amounts to – 10,6 kcal/mol of Gibbs free energy. It showed that 21 amino-acids participated in this interaction and that 24 bonds were made, namely 8 Van der Waals bonds, 13 Hydrogen bonds and 3 Pi-Alky bonds. The control experiment had – 9,7 kcal/mol of Gibbs free energy. There were 16 amino acids, 23 bonds made, namely 7 Hydrogen bonds, 3 Carbon-hydrogen bonds, 2 Pi-cation bonds, 6 Van der Waals bonds, 4 Pi-alquil bonds and 1 Alquil bond. Also, of the 16 amino acids participating in the control experiment, 15 of the same amino acids were participating in the interaction of rutin and the inflammasome. Analyzing the data and comparing with the control results, we can stipulate that the rutin interaction had more relevant bonding energy, that it bonds with the same amino acids but one, that it docks in the same or near site of the control and that the quantity and quality of the bonds were superior. In conclusion, this work suggests Rutin as a potential inhibitor of NRLP3 inflammatory pathway.

Keywords: Neurodegenerative; Molecular docking; Rutin; NRLP3; Inflammation.

Support: Brazilian's National Council for Scientific and Technological Development (CNPQ).

THE ROLE OF ACTIVE AND REACTIVE ENTERIC GLIAL CELLS TO COLORECTAL TUMOR CELLS

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Introduction: In normal physiological conditions, the enteric glial cell (EGC) is essential to numerous functions, such as the regulation of the intestinal epithelial barrier (IEB). However, in a pathological condition, enteric glia become reactive and assume a pro-inflammatory role, expressing markers such as NFKB and overexpressing S100b. It has already been described that, in the colorectal cancer context, the glial cells act promoting the proliferation of tumor stem cells, stimulating the tumorigenesis and expressing factors such as PGE2 and IL-1. **Objectives:** Our project aims to comprehend how EGC becomes reactive when facing inflammatory and tumoral insults, and the implication of this reactive state to the IEB and colorectal cancer. **Methods:** We made culturing experiments of the colorectal tumor lineage HCT116 with or without conditioned medium of cells of the EGC lineage challenged with LPS or with the conditioned medium of HCT116 itself. We also performed a cell viability assay by MTT, subjecting HCT116 under different conditions involving treatment with conditioned medium of EGC, conditioned medium of LPS-treated EGC and the HCT116-treated EGC. **Results and discussion:** Our preliminary results indicate that, under conditions where the factors secreted by EGC were present, there was less cell proliferation, indicating a protective role for enteric glia. This work will allow us to understand the role of EGC in its normal or reactive state in the maintenance of IEB and against colorectal tumors.

Keywords: Enteric glia, colorectal tumor, cancer, intestinal epithelial barrier

Support: CNPq, FAPERJ

IN SILICO ANALYSIS OF MOLECULAR INTERACTIONS BETWEEN FLAVONOID AGATHISFLAVONE WITH INFLAMMATION-NLRP3

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Introduction: Inflammation is one of the most important processes for the development and progression of diseases. Many studies consider the participation of NLRP3 in the pathogenesis of metabolic, autoimmune and neurodegenerative diseases. Due to the ability of the NLRP3 inflamasum to release pro-inflammatory cytokines it has become a potential inhibitory target for the treatment of inflammatory disorders. Identifying ways to prevent the progression of inflammation can be beneficial to minimize data from these diseases. Flavonoids are a class of polyphenol compounds present in plant species that have great pharmacological potential. **Objective:** To evaluate in syl the interaction of agathisflavone with the proteins of the nlrp3 inflamasome in order to verify whether these proteins are molecular targets of flavonoid agathisflavone promoting its inhibition. **Methodology:** AutoDockTools, AutoDockVina. and Discovery Studio software were used. In the sense of comparison, the MCC950 was used as a positive inhibitor control for NLRP3 and the ML132 inhibitor for caspase-1, since they have already been shown in vivo and in vitro. **Result and Conclusion:** The NLRP3-agathisflavone interaction showed binding energy of – 10.6 kcal/mol with 17 interacting amino acids and showed great similarity with the positive control MCC950, demonstrating great pharmacological potential of flavonoid nlrp3 protein. In the BRCC3-agathisflavone interaction the energy was – 8.6 kcal/mol with 10 interacting amino acids, but the linker did not connect to the ACTIVE JAMM site of BRCC3. In the ASC protein, agathisflavone obtained energy of – 7.6 kcal/mol with 9 amino acids binding to the PYD domain, which may be indicative that the linker infers in the PYD-PYD interaction of the ASC with the NLRP3. In caspase-1, agathiflavone interacted with 14 amino acids between the CARD and p10 protein domain with energy of – 8.5 kcal/moln, entertaining flavonoid, with no resemblance to positive CONTROL ML132, but with the possibility of interfering in the CARD-CARD interaction of caspase-1 and NLRP3. Further in vitro and in vivo studies are necessary to actually elucidate the flavonoid's action in inhibiting the components that make up the NLRP3 inflamasome.

Keywords: Agathisflavone; Inflammation; Molecular Docking; NLRP3 Financial

Support: PIBIC-CNPq

INFLUENCE OF LPS AND TLR4 IN L-DOPA-INDUCED DYSKINESIA

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Introduction: The gold pharmacological treatment for Parkinson's disease is L-DOPA, which improves the motor impairment typical of this disease. However, a massive problem of L-DOPA chronic treatment is L-DOPA-induced dyskinesia (LID), which is a group of abnormal movements that, once appeared, presents every time L-DOPA is in its plasma's peak dose. Our group observed that LID has a neuroinflammatory compound, shown by higher expression of the inflammatory markers inducible nitric oxide synthase, cyclooxygenase-2, gliosis, and cytokines. Inflammogens such as lipopolysaccharide (LPS) can exacerbate LID, while anti-inflammatory drugs can reduce it. **Objectives:** Our goal was to link neuroinflammatory aspects of LID to the well-known inflammatory pathway of toll-like receptor 4 (TLR4), by activating it with LPS. **Material and methods:** We used adult male C57/BL mice with 6-OHDA striatal lesion (15µg) or sham. Experimental groups were divided with similar lesion intensities (with exception of low-lesion animals, used as an independent group) by the apomorphine rotational test (0,5 mg/kg s.c.). Then, they received a unique injection of LPS (0,1mg/kg i.p.) and the day after, L-DOPA (25mg/kg + benserazide 10 mg/kg i.p) was given for 15 days and abnormal voluntary movements were scored. This project was approved by animal experimentation ethics committee (2020.1.561.58.6). **Results:** the lps/l-dopa group presented increased lid levels in all analyzed days compared to veh/l-dopa (with similar lesion intensities). The group with lower striatal lesion received LPS and had an increase in LID from day 5, presenting similar LID manifestation to treated with Veh/L-DOPA (with higher lesion intensity). No difference was found for TLR4 and MyD88 protein expression at dorsal striatum, analyzed by western blot. **Conclusion:** LPS exacerbates LID in both high and low-lesioned mice. It is necessary to analyze other intermediates of the TLR4 pathway to confirm the participation of this receptor in this disorder.

Keywords: Neuroinflammation, dyskinesia, L-DOPA, Parkinson's Disease, TLR4.

Support: CNPq, CAPES, Fapesp.

THE ROLE OF THE NLRP3 INFLAMMASOME IN THE DEVELOPMENT OF DEPRESSIVE DISORDERS

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Departamento e Laboratório: Faculdade de Ensino Superior da Amazônia Reunida, Redenção – Pará, Brasil.

Introduction: Depression is a serious global health problem, being the fourth non-fatal disease in the world, so it is important to understand the pathophysiological mechanisms of this pathology. Evidence suggests that the central nervous system (CNS) resident immune cells, microglia, are involved in the pathogenesis of depression. Furthermore, receptors such as the NLRP3 inflammasome are being postulated as pathways related to the pathophysiology of depression. However, the activation of this receptor in hippocampal microglia remains unclear. **Objectives:** to understand the role of the NLRP3 inflammasome expressed in microglia in the development of depression. **Methods:** This is a systematic literature review, using the electronic databases of indexed journals: MEDLINE, ScienceDirect and LILACS. Inclusion criteria were: systematic review articles published in the last 5 years. The descriptors considered were: NLRP3 inflammasome, microglia, depressive disorder. Articles that did not systematically address the topic were excluded. **Results and Conclusions:** Depression is considered a microglial disease, since the contributions made by microglia to regulate inflammation, synaptic plasticity and the formation of neural networks are affected in depression. Evidence indicates that microglial cells are distributed in the hippocampus and prefrontal cortex, which are brain regions that play a critical role in regulating mood and behavior. Microglial activation is a mediator in neuroinflammatory processes for the elimination of pathogens and damaged cells that activate immune-inflammatory pathways by increasing the production of cytokines such as interleukin (IL)-1β. The NLRP3 receptor is an intracellular multiprotein complex responsible for a series of innate immune processes associated with infection, inflammation and autoimmunity. Analyzes suggest that depression and chronic stress activate the GR-NF-κB-NLRP3 signal pathway in hippocampal microglia and eventually mediate the cascade reaction of inflammatory factors, mainly IL-1β. The activated NLRP3 inflammasome exacerbates the pathology and accelerates the progression of neurodegenerative diseases, which needs to be tightly controlled. Therefore, it is still unclear whether the NLRP3 inflammasome is activated in the hippocampal microglia during chronic stress and depression, and this is just a new perspective for the development of new antidepressants.

Keywords: depressive disorder, microglial activation, NLRP3 inflammasome, neuroinflammation and pathophysiology.

TRANSLOCATOR PROTEIN (TSPO) AS POTENTIAL BIOMARKER OF PARKINSON'S DISEASE: A SYSTEMATIC REVIEW OF THE LITERATURE

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Introduction: the 18 kda translocator protein (tspo), located in the outer mitochondrial membrane, is present in most peripheral tissues and minimally expressed in surveilling microglia in a healthy brain. Its expression is strongly positively regulated in microglia activated in neuroinflammation. TSPO has been studied for over three decades using cutting edge techniques, such as positron emission tomography (PET) and autoradiography, leading to great advances in the understanding of pathological role of microglial activation and neuroinflammation in neurodegenerative diseases. The use of radioligands to study TSPO promote investigation of its expression in both in vivo and in vitro, and recent evidence demonstrates the increased expression of TSPO in patients with Parkinson's Disease (PD). In this systematic review, an overview of the studies on the identification of neuroinflammation through the expression of TSPO is presented, as well as the annual growth of applications of measurement techniques, focusing on its potential as a biomarker of neuroinflammation in PD. **Objectives:** to present an overview of studies on identification of neuroinflammation in pd through the expression of tspo. **Material and methods:** exploratory scientific prospecting was carried out considering publications in the pubmed database, using the **Keywords:** "(tspo or pbr or pk11195 or pbr28) and (parkinson's disease)". **Results and discussion:** it was identified 100 articles using tspo as a biomarker in neuroinflammation. Among them, 45 articles were studies with radioligand with affinity for TSPO for detection of neuroinflammation in patients or in study models of PD. These articles were published between the years 1991 to 2021. **Conclusions:** in this study we observed an annual growth of applications of measurement techniques. In addition, through the collected data, it was possible to identify PK11195, PBR28 and FEPPA as the main radioligands and PET as the main techniques used to identify this protein. It is possible to conclude that TSPO has emerged as an important biomarker of neuroinflammation in PD , and support the understand on different stages of PD progression.

Keywords: translocator protein (tspo); peripheral benzodiazepine receptor (pbr); neuroinflammation; parkinson's disease.

THE INFLUENCE OF TEMPERATURE ON ASTROCYTE VIABILITY IN PRIMARY CULTURES OF NEONATE RATS

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INTRODUCTION It is known that astrocytes present extensive heterogeneity of their functions, but we can identify them by the presence of the marker GFAP, which expands in cases of injury or nerve damage. This is because astrocytes respond to injury through reactive astrogliosis, an attempt to maintain neural activities and minimize damage, being the main regulator of the inflammatory immune response. In this process several events occur, such as fever, which is the elevation of body temperature, but continuous fever or failure in thermoregulation may result in hyperthermia, generating deleterious damage that can lead to death. By inducing an imbalance in the environment, high temperature may be a triggering factor for reactive astrogliosis, and the use of containment measures, such as antipyretics, may mitigate this response. We analyzed the effect of heat stress on astrocyte marker expression, viability and the effect of antipyretic on modulating the astrocyte response. METHODS The cell model started from primary cultures of neonate rats. The heat shock protocol was used to induce stress to this culture and the proposed treatment was the addition of an antipyretic/antipyretic. From the execution of this protocol, tests were performed to evaluate astroglial reactivity under the exposed conditions. RESULTS Through immunocytochemistry we verified that the control cultures showed reactivity, considered as basal reactivity. The heat shock cultures showed increased reactivity, demonstrating that the damage potentiated the astrocyte response. The heat shock and treatment cultures showed a reduction in the level of astroglial response. Western blot assays resulted in a characteristic protein expression profile. Among the conditions, the groups that were exposed to heat stress showed higher concentration of expressed proteins after labeling with anti GFAP. This may represent astrocyte response upon such injury. CONCLUSION The present results indicate that high temperatures stimulate astroglial reactivity. Further assays are needed to characterize the astrocyte response.

ANTIOXIDANT AND ANTINEUROINFLAMMATORY ACTIVITY OF FLAVONOIDS AND SYNTHESIS DERIVATIVES IN GLIAL CELLS

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Introduction: Astrocytes participate in multiple aspects of brain function, including redox regulation. However, the overproduction of reactive species or defects in detoxification, results in reactive astrogliosis promoting changes in cellular homeostasis, generating an inflammatory loop. In this context, flavonoids, with antioxidant and anti-inflammatory properties, are promising candidates for complementary therapies for Neurodegenerative Diseases (NDD). **Objective:** To evaluate, in vitro, the cytotoxicity and antioxidant mechanisms of flavonoids and prenylated synthesis derivatives, associated with the control of the glial inflammatory response. **Methodology:** Flavonoids and prenylated synthetic derivatives were evaluated for antioxidant activity through DPPH (cell-free) radical scavenging, glutathione (GSH) depletion assay and superoxide dismutase (SOD). Cytotoxicity (1-100 µM) determined in cultures of astrocytic cells GL-15, C6 and primary culture, obtained from Wistar rats (P0-2) (Protocol nº 6731220818/ID 000058), evaluated by the MTT assay and microscopy (DIC). Primary astrocyte cultures were exposed or not to inflammatory damage with LPS (1µg/mL) for 24h and then treated or not with flavonoids and prenylated derivatives (10µM). Measured in the culture supernatant (Griess), the inflammatory mediator nitric oxide (NO) and the cellular phenotype analyzed by Rosenfeld. **Results:** Hesperidin (1µM) showed potent antioxidant action in scavenging the DPPH radical compared to standard trolox. There was an increase in the levels of GSH promoted by naringenin and its derivatives, when compared to DMSO 0.05%. In the evaluation of SOD, LPS promoted a greater increase in enzymatic activity. Naringenin, its derivatives and hesperidin also induced an increase in SOD, however, in a discrete way. In MTT, apigenin (GL-15), chrysin (C6) and hesperidin (astrocytes) promoted a reduction in cellularity and cell viability (100 µM). LPS promoted a reduction in prolongations, cell body retraction (Rosenfeld) and an increase in NO. The co-treated molecules significantly reduced NO levels. Chrysin, hesperidin and the monoprenylated derivative preserved the extensions, cell body and density of astrocytes, attenuating the progression of damage caused by LPS. **Conclusion**: Thus, flavonoids and synthetic derivatives have antioxidant and anti-neuroinflammatory capacity in glial cells and further studies are needed to elucidate other mechanisms to contribute to the development of complementary therapies for DND.

Key-words: flavonoids; glial cells; antioxidant, neuroinflammation.

Support: FAPESB, CAPES, CNPq, LabNq

NEUROPROTECTIVE AND BEHAVIORAL EFFECT OF RUTIN AFTER AMINOCROME-INDUCED STRIATAL INJURY IN A RAT MODEL WITH PARKINSON'S DISEASE

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Introduction: Aminochrome is a compound produced in Substance Nigra pars compacta (SNpc) dopaminergic neurons during the neuromelanin formation. Studies sugests its role in the progression of Parkinson's disease (PD) due to its ability to induce oxidative stress, alpha-synuclein accumulation, and neuroinflammation. On the other hand, rutin is a flavonoid with anti-inflammatory, antioxidant and neuroprotective properties recognized in the literature. **Objectives:** The present study investigated the behavioral and neuroprotective effect of rutin in an *in vivo* model of PD induced by aminochrome. **Methods**: For this, Male Wistar rats (280g–330g) were divided into four groups: control (CTR), 10 mg/kg rutin (RUT), 6 nmol aminochrome (AMI), and aminochrome+rutin (AMI + RUT) to perform stereotaxis and injection of aminochrome or saline solution into the striatum (ICS – CEUA 114/2016). Animals were treated with daily oral dosis of rutin for 14 days and behavioral tests were performed on the 14th day after single aminochrome injection. Samples of SNpc were colected and fixed with 4% paraformaldehyde for immunohistochemistry for microglia (IBA1+) and dopaminergic neurons (TH+). **Results**: The open field test showed animals from AMI group presented a reduction in the total frequency of rearing when compared with CTR group ; The plus maze test showed animals from AMI + RUT group presented increased frequency of open arm entries, when compared with animals from AMI group ; and animals from RUT group presented higher time spent in the closed arm when compared with CTR group . The immunohistochemical analyzes showed that aminochrome reduced the viability of TH+ cells in AMI group, when compared with CTR group, and AMI + RUT group. The number of IBA1+ cells did not change significantly between the groups. On the other hand, there was a considerable increase in microglia-neuron interactions in the aminochrome group compared with CTR and AMI + RUT group . **Conclusions:** The behavioral consequences of a unilateral lesion in SNpc induced by aminochrome injection in the striatum have not yet been well described, therefore, this study contributes to the characterization of a new study model of PD and to clarify the therapeutic potential of rutin in the disease.

Keywords: Bahavioral changes, aminochrome, neuroprotection, rutin.

Funding: CNPQ, FAPESB.

SESAMOL IMPROVES SURVIVAL IN MURINE MODEL OF CEREBRAL MALARIA

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Introduction: Cerebral malaria is the most severe infectious manifestation caused by Plasmodium falciparum, presenting complex neuropathological mechanisms such as cerebral ischemia, neuroinflammation, oxidative stress, blood-brain barrier impairments and the development of neurocognitive sequelae. Sesamol is a natural phenolic compound extracted from sesame seeds (Sesamum indicum). Studies prove its antioxidant, anti-inflammatory and neuroprotective properties, proving to be a possible ally in the treatment of damages caused by cerebral malaria. **Objectives:** Evaluate the performance of Sesamol as a Neuroprotective agent in cases of experimental cerebral malaria induced by Plasmodium Bergei ANKA (PbA) in mice. **Methods:** The effect of Sesamol (20mg/kg) against murine cerebral malaria pathology was evaluated using Swiss mice, aged between 6-8 weeks and weighing 25-30g. Cerebral malaria was induced by the ANKA strain of Plasmodium Berghei and the animals were divided into the following experimental groups: Control, Sesamol, PbA and PbA+Sesamol. The PbA+Sesamol group was treated with intraperitoneal injection of Sesamol for 7 consecutive days. The body weight of the mice was checked daily throughout the course of the disease. Parasitemia levels started to be verified from the 3rd day after infection, with one day intervals, by counting infected cells in blood smears obtained from blood samples. Behavioral and motor changes were evaluated using the SHIRPA protocol, which evaluate neuropsychic aspects; reflexes and sensory functions; tone and strength and motor activity. **Results and Conclusions:** The animals treated with Sesamol obtained a significant increase in the survival curve and showed fewer cognitive deficits compared to the untreated animals, even both groups showing similar parasitemia levels. On the 7th post-infection day, 60% of the individuals in the PbA group died, with no deaths in the PbA+Sesamol group. From the 8th to the 9th post-infection day, 100% of the untreated group died. Treated animals group showed lower cognitive deficits and survived until the 21th post-infection day. Such results demonstrate the protective effect of Sesamol against the damages caused by cerebral malaria in murines.

Keywords: Sesamol, neuroprotective, cerebral malaria, antioxidant, infection, survival.

Support: Laboratory of Experimental Neuropharmacology (LNE); Federal University of Pará (UFPA); Amazonian foundation for study and research (FAPESPA).

IMMEDIATE EFFECT OF OBESOGENIC DIET ON PREFRONTAL CORTEX

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Introduction: Pregnancy, lactation and early childhood are understood as the critical period of development. Studies show that consumption of a high-fat diet during these periods can lead to neurodegenerative diseases, although until now the effect of obesogenic diet on oxidative balance in prefrontal cortex is not totally undersdood in juvenile male rats.**Objectives:** Evaluate the effects of an obesogenic maternal diet on the oxidative balance of the prefrontal cortex of the offspring at 30 days of age. **Material and methods:** Approved by the ethics committee (protocol n° 0090/2021). The pregnant rats received, during pregnancy and lactation, a commercial diet or an obesogenic diet, rich in fat and carbohydrates, with free access to condensed milk. After lactation (21 days), male rats were used in the experiments, divided into two experimental groups: Control (C) and Obesogenic (O). Analyzes in the prefrontal cortex were performed on the 30th day of life. Data were expressed as Mean ± SEM and compared using the t-test with GraphPad Prism 6.0 software; significance was set at 5% ($p<0.05$) for all analyses. **Results and discussion:** Our data showed an increase in lipid peroxidation in obesogenic group (C:0.295 ± 0.03; O:0.632 ± 0.06; N=6; p=0.0002) and protein oxidation (C:7.57 ± 0.78; O:28.63 ± 5.99; N=6; p=0.0024). In addition we observed a decrease in SOD activity (C:2.51 ± 0.21; O:1.58 ± 0.11; N=6; p=0.0075), CAT (C:0.130 ± 0.03; O:0.052 ± 0.01; N=6; p= 0.0430) and GST (C:0.157 ± 0.004; O:0.130 ± 0.009; N=6; p=0.0432). The non-enzymatic antioxidant defense evaluated by the sulfhydryls showed no significant difference. **Conclusions:**Our data indicate that an obesogenic maternal diet induces negative effect in the oxidative balance in the prefrontal cortex of juvenile rats, increasing the risk of neurodegenerative diseases in adulthood.

Keywords: Obesogenic Diet, Oxidative Stress, Prefrontal Cortex.

Support: FACEPE, CNPq, CAPES.

EFFECTS OF A MATERNAL OBESOGENIC DIET ON OXIDATIVE BALANCE IN THE HIPPOCAMPUS OF MALE RATS

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Introduction: The consumption of foods rich in fats has been increasingly, in addition to highly processed food. Studies already show that nutritional insults during development can cause metabolic disturbances in offspring which may be linked to a higher incidence of neurodegenerative disease in adulthood. **Objectives:** Evaluate the effects of a maternal obesogenic diet on the oxidative balance in the hippocampus of the offspring at 60 days of age. **Material and methods:** Wistar rats, age 90-120 days, weight 220-250g, divided after pregnancy into a control group (n=8) that received commercial diet and an obesogenic group (n=8) that received a high-fat (31.5%) diet and high carbohydrate (49.4%) content. The diet was offered during pregnancy and lactation, at 21 days males rats were weaned into a control group (CT) and an obesogenic group (OB) and at 60 days the animals were sacrificed and the hippocampus collected. The study was approved by the Ethics Committee on the Use of Animals (CEUA) of the UFPE (nº 0061/2019). Lipid peroxidation, protein oxidation, superoxide dismutase-SOD, catalase-CAT, glutathione-S-transferase-GST and REDOX status (GSH/GSSG) were evaluated. Results were presented using Student's t-test and shown as mean ± SEM considering $p < 0.05$. Statistical analyzes were performed using the Graphpad prism program, version 6.0 for windows. **Results and discussion:** The OB group had a higher lipid peroxidation in relation to the CT (CT: 17.63 ± 3.756; OB: 30.58 ± 1.758; N=4; p= 0.0354). In antioxidant defense SOD activity (CT: 147.8 ± 6.620; OB: 58.28 ± 18.20; N=4; p=0.0099) and CAT (CT: 0.2380 ± 0.0190; OB: 0.0099) 0840 ± 0.01 N=4 p= 0.0149) were decreased in the OB group. GST and sulfhydryls showed no significant differences between groups. **Conclusions:** Our data showed that an obesogenic maternal diet induce imbalance in oxidative status in the hippocampus at 60 days of age, which may be associated with a higher risk of neurodegenerative diseases in adulthood.

Keywords: Obesogenic Diet, Oxidative Stress, hippocampus.

Support: FACEPE, CNPq, CAPES

THE ROLE OF LAMININ AND PTEN IN THE NEUROGENIC POTENTIAL OF ENTERIC GLIA

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Introduction: The enteric nervous system (ENS) constitutes the intrinsic innervation of the digestive system. Enteric neurons and glial cells (EGCs) that compose the ENS form the myenteric and submucosal plexus. EGCs have important functions. The EGC differentiation into neurons is well known in vitro and some situations of injury in vivo. However, signaling pathways involved in this process are still not known. Laminin is an extracellular matrix protein present in the muscular layers of the intestinal wall, and the EGCs are found in the midst of this laminin network. PTEN is a phosphatase that inhibits PI3K/AKT signaling. In ex vivo myenteric plexus culture, PTEN inhibition increases EGC proliferation and differentiation into neurons. In our previous work, Veríssimo et al (2019), we showed that, when culturing EGCs, most of the cells after 3 days consisted of GFAP-positive EGCs and only a minority were double positive for GFAP and βIIItubulin. After seven days, most had dual expression of GFAP and βIIItubulin, which indicates that the EGCs were under transdifferentiation into neurons, a process that has its rate reduced when cells are cultured on polylaminin, suggesting that this can inhibit the neuronal differentiation of CGEs from adult mice. **Objective:** To investigate the differentiation potential of EGC in vitro, the role of laminin in this process, and the relationship with PTEN activity. **Material and methods:** EGCS cultures from Swiss or C57BL/6 mouse on fibronectin or poly-laminin substrate. The cells will be evaluated by immunofluorescence and western-blotting, for the expression of glial (GFAP and S100β) and neuronal (βIIItubulin and HUC/D) markers, as well as the presence of PTEN, active or inactive form, and also AKT (pathway effector). **Results and Conclusions:** Our initial data indicate an increase in proliferation in the presence of fetal bovine serum, which also interferes with cell morphology. The percentage of cells doubly labeled for GFAP and βIIItubulin is being evaluated. In a next step we will have the analysis for PTEN, phospho-PTEN. We believe that the PI3k/AKT pathway may be involved through PTEN in activating the neurogenic potential of enteric glia.

Keywords: Enteric glia, neurogenesis, laminin.

Support: CNPq, FAPERJ

HIGH-VOLUME EXERCISE ASSOCIATED WITH ULTRA-ENDURANCE RUNNING MODIFIED THE ASTROCYTIC GFAP ISOFORM PROFILE

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Introduction: evidence shows how harmful ultra-endurance exercise (TE) can be for some organs, including the brain. Recent research has focused on trying to understand the molecular mechanisms associated with this damage. **Objective:** the aim of this study was to investigate whether high-volume exercise under moderate intensity can induce systemic metabolic changes and cerebellar astroglial reactivity, and if these effects can be intensified by TE. **Methods:** forty-five adult male rats were divided into 6 groups: control (C), control + TE (C-TE), moderate training volume (MV), MV+TE, high volume (HV) and HV+TE. A treadmill run was performed 5x a week at moderate intensity. This training period was kept on 30 min/day (MV) or gradually increased to 90 min/day (HV) for 3 months, followed or not by UE. Twenty-four hours after the training or UE the rats were sacrificed and serum and cerebellar tissue were obtained. Corticosterone and creatine kinase (CK) levels were quantified in the serum. Lipid peroxidation (LP) and GFAP isoform profile were analyzed in the cerebellum. Experimental protocol was approved by Ethics Committee on the Use of Animals of UFPE (0035/2017). **Results:** high-volume training increased corticosterone and CK levels compared to control (p=0.05), but this effect was not modified by TE. However, UE increased CK levels in the MV-TE vs. CT-TE groups (p=0.03). UE also modified GFAP isoform expression profile in the cerebellum: Increased levels of the 50 kDa isoform were observed in the C-TE and MV-TE groups compared to C and MV, which was accompanied by a reduction in the 42 kDa (~40%) and 39 kDa isoform (~26%). In the HV-ET group, the 50 KDa isoform amount was reduced 40–60% compared to the other groups and the 39 KDa isoform, increased sevenfold. Increased LP levels were detected in the cerebellum of the HV group but this effect was intensified by UE only in the MV-TE group. **Conclusion:** high volume per se was able to induce cerebellar LP and inflammation. However, when UE was associated with this training, changes were seen in the reactive profile of astrocytes, increasing the levels of non-phosphorylated GFAP isoforms, suggesting astrocytic functional impairment.

Keywords: cerebellum; high volume exercise; lipoperoxidation, glial reactivity.

Support: CAPES e CNPq.

EXPRESSION AND ACTIVITY OF GLUTAMATE TRANSPORTER XCG IN PRIMARY CULTURE OS COCHLEAR GLIAL CELLS

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Introduction: In the peripheral nervous system, glial cells are majorly recognized for their role in myelination and trophic support, however, recent evidence has shown that glial cells contributes to the neurotransmission through the regulation of extracelular glutamate. One of the main transport systems in the nervous system is glutamate, divided into sodium-dependent (xAG) and independent (xCG) transporters. In the peripheral auditory pathway, glutamate is the main neurotransmitter that mediates excitatory synapses, and disturbances in its release or uptake leads to excitotoxicity and cell death. However, despite glutamatergic excitotoxicity is closely related to hearing losses, little is known about the role of Cochlear Glial Cells (CGCs) in the glutamate transport. **Objective:** Demonstrate the presence of glutamate transport systems in Cochlear Glial Cells. **Material and methods:** Primary CGC cultures from Balb/c mice cochleae (P1-P2) were performed, according to the local ethics committee (Nº 6211241117). Cells were maintained in DMEM+10% FBS for 7 days in a CO2 stove (37ºC, 5% CO2) and then submitted to glutamate release and uptake assays. Extracellular glutamate was measured by High Performance Liquid Chromatography. Protein levels were measured through the Bradford method. Immunostaining was performed using an anti-xCT primary antibody and nuclei marker DAPI. Statistical analysis was performed using Student's T Test and One Way ANOVA, considering $p<0.05$ and images were processed with ImageJ. **Results and discussion:** CGCs showed a glutamate uptake of ≋30% in the NaCl group and ≋70% in the LiCl group, demonstrating the contribution of both glutamate transporter systems. Also, CGCs exposed to the xCG transporter substrate (cysteine 500µM), generated a ≋65% reduction in glutamate uptake and a ≋250% increase in glutamate release when compared to the control group, suggesting a possible xCG activity in CGCs. Inhibition of the xCG transporter with α-aminoadipic (αAA), a competitive inhibitor of the transporter, reduced glutamate uptake by ≋75% compared to the control group. Furthermore, cell exposure to αAA and cysteine was similar (≋85%) to our previous results. In addition, our immunostaining results demonstrated that CGCs expresses the xCG transporter. **Conclusions:** Collectively, our work demonstrated the contribution of the xCG system in the cochlea, supporting the hypothesis that CGCs may play a prominent role in the auditory system.

Keywords: Glial Cells, Cochlea, Glutamate transporters.

Support: CNPq and CAPES.

INVESTIGANTING THE MOLECULAR MECHANISMS RELATED TO ANTIGLIOMA EFFECTS OF FLAVONOIDS IN INTERACTION WITH AHR

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Introduction: The anti-tumor potential of flavonoids and their immunomodulatory activity in glioma cells has been investigated and the pharmacological potential of these drugs have encouraged studies in alternative therapy for glioblastoma (GBM). The conventional treatment for GBM includes tumor removal surgery, radiotherapy and chemotherapy. However, tumor characteristics, such as the fast growth, rapid proliferation and the induction of immunosuppression, contributes to a great recurrence after treatment. Studies demonstrated that, in adition to a poor prognosis, the transcription factor, aryl hydrocarbon receptor (AhR), constitutively activated in tumor cells is related to chemo and immunoresistance. AhR activation promotes the differentiation of cells and increase expression of resistance genes, putting AhR antagonism as a target in cancer chemotherapy. AhR antagonists, as the naturally occurring compounds, reduce tumor cell viability. **Objectives:** This study aimed to better define the antitumor mechanisms of flavonoids by selection of the best candidate to act as AhR antagonists. **Material and methods:** Flavonoids, whose anti-glioma effects have already been demonstrated, such as naringenin (NAR), agathisflavone (FAB) were tested as AhR antagonists at increasing non-cytotoxic concentrations of 10, 20 and 30 µM by induction of CYP1A1 mediated EROD activity assay in pretreated MCF7 cells, as a marker of Ah – responsiveness. Cultures were also treated with DMSO (0.01%) and TCDD (2nM), a known strong AhR agonist. Cell viability was determined by methylene blue assay. To investigate the potential antagonism of the candidates in glioma cells, U87 were treated with CHR (30µM) and NAR (30µM) to quantify gene expression levels related to canonical AhR transcriptional activity. **Results and discussion:** Results from CYP1A1 – mediated EROD activity assay demonstrated a dose dependent regulation. NAR and FAB at 30µM concentration, showed to be powerful antagonists in the presence of a strong agonist of the receptor (TCDD), for 6h. Also, U87 treated with CHR (30µM) and NAR (30µM) showed reduction of expression levels of AHR, TIPARP and CYP1B1 genes compared to positive (TCDD) and negative (DMSO) controls. **Conclusions:** In view of the therapeutic potential of flavonoids, this study will contribute to knowledge about the mechanism of action in terms of molecular signaling via AhR and sustain their application as adjuvant for GBM treatments.

Keywords: glioma; glial cells; flavonoids; aryl hydrocarbon receptor; immunomodulation.

Support; CAPES, CNPq and FAPESB.

PHYTOCHEMICAL AND ANTIOXIDANT ACTIVITY OF BEE POLLEN PRODUCED BY *TETRAGONISCA ANGUSTULA* A DURING DRY SEASON IN THE CAATING OF BAHIA STATES, BRAZIL

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Introduction: Oxidative stress and neuroinflammation are contributing factors in the pathogenesis of various diseases that compromise quality of life, such as neurodegenerative diseases. Phytoactive antioxidant defense modulators have been promising, *in vitro* studies of neurodegenerative diseases. The bioproducts of this bee, such as honey, propolis, geopropolis and bee pollen are used for medicinal, cosmetic and nutraceutical purposes. Bee bioproducts (honey, propolis and geopropolis) have shown antioxidant potential. However, little is known about the antioxidant activity of compounds present in bee pollen. **Objectives:** To investigate the antioxidant activity and phytochemical profile of pollen produced by *Tetragonisca angustula* (Jataí). **Methods:** This is a qualitative/quantitative *in vitro* experimental study, in which the ethanolic extract (EEP) of bee pollen produced by *Tetragonisca angustula*, collected at the end of the dry period of the caating of Bahia states, Brazil. The evaluation of antioxidant activity was performed using the DPPH radical capture method. For phytochemical investigation, polyphenols were determined using the Folin-Ciocalteu reagent, in addition, saponins were determined and the presence of flavonoids was also investigated by means of the Shinoda Reaction or Cyanidin. **Results and Conclusions:** A yield content of pollen extract of 70.95% was observed. Qualitative phytochemical tests performed with EEP showed the presence of saponins and flavonoids (specifically flavones). The percentage of scavenging of DPPH• Radicals for the 3 mg/mL dose was 12.52% (SD 3.9); at 6 mg/ml it was 25.42% (SD 0.7); 12 mg/mL was 35% (SD 6.4) and 18 mg/mL was 65% (SD 1.8). The Jataí bee pollen contains compounds with antioxidant potential, which opens therapeutic and prophylactic possibilities in the prevention of oxidative damage.

Keywords: Stingless bee. Antioxidant. Neurodegeneration. Stress oxidative. Phytotherapy.

Support: Foundation for Research Support of the State of Bahia (FAPESB).

EVALUATION OF ESTROGEN-MEDIATED NEUROPROTECTION IN A CELLULAR MODEL OF TAUOPATHY

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Introduction: The abnormal presence of hyperphosphorylated tau protein and the consequent formation of neurofibrillary tangles is the main characteristic of a group of neurodegenerative diseases, known as tauopathies, with Alzheimer's disease being the most prevalent, so therapeutic interventions are desirable to remove the pathological tau protein. **Objectives:** To characterize a neuronal lineage (SH-SY5Y) that overexpresses the human tau protein isoform 0N4R and the mutated tau P301L, searching for estrogen receptor agonists/antagonists that lead to a decrease in the overexpressed tau protein. **Methods:** To induce tau protein overexpression in SH-SY5Y cells, an advanced inducible expression system produced with Lenti-X TM Tet-On® (Clontech) was used. Cell viability was evaluated in the SH-SY5Y strain with overexpression of tau protein (WT-tau-0N4R) by flow cytometry, at 24, 48 and 72 hours. The morphological aspect of organelles (lysosomes and mitochondria) was observed by Confocal Microscopy. A screening of a library with 42 compounds (Tocris Bioscience ®) was performed. Protein expression was analyzed by Western blot. **Results and Conclusions:** The Tet On inducible expression system was effective in overexpressing tau protein, observed at 24, 48 and 72 hours, with a significant difference in protein expression compared to controls without system activation. Analysis of lysosomes and mitochondria revealed that overexpression of tau protein affected the morphology of such organelles, compared to negative controls. Activation of the tau protein overexpression system at 24, 48 and 72 hours did not affect cell viability. Screening of a library of compounds that act on nuclear and membrane estrogen receptors (Tocris Bioscience ®) revealed 10 compounds that reduced the overexpressed tau protein by more than 50%. The best compounds in the library approved by the FDA (*Food Drug Administration*) belong to the following classes: selective estrogen receptor modulators, aromatase inhibitors and estrogen receptor agonists. The results demonstrate that the evaluation of estrogen receptor regulation in cytoprotection is relevant to design new pharmacological therapies for dementia, such as that occurs in Alzheimer's Disease.

Keywords: Alzheimer's Disease; tau protein; Tauopathies; estrogens; SH-SY5Y**.**

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EARLY NEUROCHEMICAL ALTERATIONS IN THE BRAIN OF MICE INFECTED WITH PLASMODIUM BERGHEI (ANKA)

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Introduction: Neurobehavioral deficits are symptoms associated with cerebral malaria (CM), the main complication of Plasmodium falciparum infection. However, there are few datas that describe the neurochemical alterations in the central nervous system (CNS) related to this condition. Glutamate and gamma amino-butyric acid (GABA) represent the main excitatory and inhibitory neurotransmitters in the CNS, respectively, and the imbalance in glutamatergic and GABAergic synapses are closely linked to different cognitive and motor disorders observed during the developmental of CM. **Objectives:** The objective of the work was to evaluate changes in the levels of GABA and glutamate in cerebrum and cerebellum of animals infected with Plasmodium berghei ANKA strain (PbA) **Methods:** Swiss mice were intraperitoneally infected with 106 PbA-pRBCs. Mice were observed for parameters as blood parasitemia and survival curve. Clinical sings were assessed using Rapid Murine Coma and Behavior scale (RMCBS) protocol. Quantification of GABA e Glutamate extracellular levels in cerebrum and cerebellum was performed with High-Performance Liquid Chromatography on days 3, 5 and 7 post infection (d.p.i). Data was analyzed using one way ANOVA followed by Tukey-Kramer post hoc. **Results and Conclusion:** Our data showed motor and behavioral impairment assessed by RMCBS protocol in infected animals with PbA on day 3, 5 e 7 d.p.i. Disorders in gait, balance, motor performance, aggression, touch escape and hygiene-related behavior parameters was observed since early stages of infection. On 7th d.p.i, PbA-infected mice started to succumb to CM. Survival curve and clinical signs was followed by low percentage of parasitemia (<20%). Significant increase in glutamate levels was observed on day 3 (>100%), day 5 and day 7 d.p.i (>300%) in cerebrum of infected animals. Same was observed in cerebellum on day 3 and 5 d.p.i. GABA extracellular increased on day 3 and 5 d.p.i, returning to control levels on day 7. In cerebellum, it was detected no changes in GABA extracellular levels. This data showed for the first time neurological impairments associated with neurochemical alterations in GABAergic and glutamatergic neurotransmission since early stages of infection. The results suggest a role of both neurotransmitters in the development of neurological signs in CM.

Key words: Cerebral Malaria, Neurological impairment, neurochemistry, GABA, glutamate.

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CAN DVL ACT AGAINST GLUTAMATERGIC EXCITOTOXICITY?

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Introduction: DVL is a mannose/glucose binding lectin extracted from the seeds of *Dioclea violacea*, popularly known as mucunã or bull's eye. This lectin is known to have biological activities such as antitumor, antinociceptive and anti-inflammatory through its carbohydrate recognition domain, which provides the interaction of DVL with target cells and molecules. In addition to the carbohydrate recognition domain, DVL has a hydrophobic domain capable of modulating biological activities, this domain has already been described in other similar lectins interacting with non-protein amino acids, such as α-aminobutyric acid (ABU) and γ-aminobutyric acid (GABA). Considering the molecular similarity between these non-protein amino acids and glutamate, we hypothesized that DVL possibly interacts with glutamate, which is the main excitatory neurotransmitter of the central nervous system and is related to several diseases and neural disorders. **Objective:** to evaluate the interaction of DVL with glutamate via the amino acid binding domain and to evaluate its effect against glutamatergic excitotoxicity. **Material and methods:** *Dioclea violacea* seeds were collected in the city of Vargem Grande – MA. The lectin was purified on a sephadex g-50 column and subsequently fluorescence spectroscopy, hemagglutinating activity and inhibition of hemagglutinating activity in the presence of glutamate were performed. **Results and discussion:** DVL at concentrations of 2.3 uM interacts with glutamate (0.17mM – 1.45 mM) and its hemagglutinating activity and inhibition by carbohydrates is not affected by the presence of glutamate at a concentration of 100 uM. Evidencing that the activity of the amino acid binding domain of DVL does not interfere with the activity of the carbohydrate recognition domain. Thus, enabling the use of the amino acid binding domain of DVL as a promising biological tool in the fight against glutamatergic toxicity. **Conclusion**: Therefore, these findings conclude that biological assays with astrocytes and neurons are crucial for the validation of this new natural product for the treatment of diseases related to glutamate excitotoxicity.

Keywords: Natural compound, neural cells, lectin, glutamate, toxicity.

Support: National Council for Scientific and Technological Development – CNPQ

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PROTECTIVE EFFECTS OF LUTEIN IN DROSOPHILA EXPERIMENTAL MODEL OF PARKINSON´S DISEASE

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Introduction: Lutein is a xanthophyll carotenoid obtained from various foods and it is a versatile phyto-nutraceutical compound. Recent basic and clinical studies have investigated its antioxidant and anti-inflammatory effects for prevention of chronic diseases but only few studies analyzed its effects on experimental models of Parkinson´s disease. **Objective:** In the present study, using a Drosophila melanogaster experimental model of Parkinson´s disease we tested the hypothesis that lutein could be protective reducing iron and nitric oxide levels involved in rotenone-induced neurodegeneration and locomotor impairment. **Methods:** Drosophila melanogaster from both sexes 3-4 days old were exposed to a diet with rotenone (500 µg/ml) in the absence and presence of lutein (0.25, 0.5, 1.0 and 2.0 mg/ml) for seven days. The mortality index was analyzed every 12 h, and negative geotaxis motor test and biochemical assays were carried out to assess lipid peroxidation, iron and nitric oxide levels. Results: Rotenone reduced the survival percentage (40% compared to control $p< 0.05$), the climbing time in the negative geotaxis test (75%) and increased iron (35%), nitric oxide (25%) and lipid peroxidation (40%) levels in the tissues. Lutein reverted the toxic effects of rotenone, improving locomotor parameters, lowering malonaldehyde, iron and nitric oxide production. **Discussion and conclusion:** The findings reinforce that lutein can be considered a promising caratenoid for treatment of rotenone-induced neural damage, indicating a potential beneficial effect on ferroptosis and inflammatory cell damage. Further study on this role is in progress to address this issue.

Keywords: antioxidant, lutein, rotenone, Drosophila melanogaster

Suport: CNPQ e CAPES

EFFECT OF NON-PERIODIC ACOUSTIC STIMULUS ON REFRACTORY EPILEPSY NETWORKS

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Introduction: Epilepsy is a public health problem that affects about 50 million people worldwide. Although several efforts have been employed for the development of new drugs for the disease, approximately one third of patients present pharmacoresistance, which refers to the need to develop adjuvant therapies. Recently, a non-periodic electrical stimulus (NPS) has been developed, focusing on the hypersynchronous characteristic of the illness. Such stimulation has been shown to be effective for several animal models of focal and generalized epilepsy, supporting future studies in humans. From the NPS, the non-periodic acoustic stimulus (NPAS) was developed and demonstrated clinical effects in patients with refractory epilepsy. **Objectives:** to evaluate whether there is an end result of NPAS on synchrony, connectivity and topology of dynamic functional networks in persons with refractory epilepsy. **Methodology:** construction of functional brain networks through dynamic graphs and the aggregated static network; acquisition of electroencephalographic (EEG) data of individuals with refractory epilepsy (n = 8) and using motif synchronization as a method of association. Treatment outcomes were evaluated in the acute phase and after five days after the NPAS. **Results:** There was a significant reduction in functional connectivity during the acute phase of treatment, followed by an elevation of measurements on the fifth day of treatment, before re-stimulation, which was accompanied by a trend towards an increase in the variability of path length and betweenness centrality; maintenance of nodes relevant to the network was noted for all states; in addition, there was a significant cognitive improvement after treatment. **Conclusions:** Taken together, these findings support an effect of the intervention on functional connectivity and synchrony of dynamic networks in subjects with refractory epilepsy, in addition to evidencing a probable reorganization of their brain networks. A greater variability of measures related to the architecture of brain networks, concomitantly with the maintenance of node hubs, may justify these findings. Future investigations may shed light on the topological variability of this stimulation modality.

Keywords: Epilepsy. Functional brain networks. Non-periodic acoustic stimulation. Functional connectivity. Topology.

Support: Coordination for the Improvement of Higher Education Personnel (CAPES).

USE OF CANNABIS SATIVA EXTRACTS IN MULTIPLE SCLEROSIS: A SYSTEMATIC REVIEW OF CLINICAL STUDIES

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Introduction: Multiple sclerosis (MS) is characterized as an autoimmune neurological disease that affects the central nervous system (CNS), leading to destruction of the myelin sheath, compromising nerve signal transmission. Common to MS and other neurodegenerative diseases, neuroinflammation is a phenomenon that has been explored. Studies show that patients with exacerbated neuroinflammation have a worse prognosis. On the other hand, findings have shed light on the role of the endocannabinoid system (SEC) in modulating neuroinflammation. Added to this, the development of medicinal products from Cannabis sativa has made possible the pharmacological management of this neuromodulatory system. **Objective:**Therefore, the present study aimed to evaluate the effectiveness and safety of using whole extracts obtained from C. sativa flowers for the treatment of MS symptoms. **Methodology:** Therefore, a systematic analysis of clinical studies published in the last five years was carried out that evaluated the treatment of MS from the modulation of the SEC with the medicinal use of C. sativa extracts. **Results and Conclusions:** Based on the analysis of evaluation instruments, the studies demonstrated the pharmacotherapeutic potential of C. sativa, decreasing the spasticity numerical rating scale in all evaluated studies. Furthermore, the treatments were well tolerated, with few adverse effects and provided clinical improvement in most of the patients evaluated. In view of the large number of patients unresponsive to other treatments, the modulation of ECS by C. sativa extracts may offer a therapeutic alternative in the treatment of chronic CNS diseases such as MS.

Keywords: Cannabis sativa. Multiple sclerosis. Neuroinflammation.

ANTIVIRAL EFFECTS OF CURCUMIN IN 2D AND 3D CULTURE OF SH-SY5Y INFECTED WITH SARS-COV-2

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Abstract: COVID-19, caused by SARS-CoV-2, uses ACE2 (Angiotensin-Converting Enzyme 2) receptor to invade host cells. SARS-CoV-2 can infect neuronal cells, causing several symptoms such as memory loss, anosmia and brain inflammation. Curcuminoids (Me08 e Me23), derived from Curcuma Longa (CL), have anti-inflammatory and antioxidant properties. Among the three curcuminoids, curcumin (CUR), CL's active principle, has antiviral capacity. **Objective:** investigate the therapeutic and antiviral effects of cur and curcuminoids in sars-cov-2 replication in sh-sy5y 2d and 3d overexpressing ace2. **Methods:** sh-sy5y were transduced with lentivirus to overexpress ace2 (sh-ace2). Cell viability, after treatment with Me08-Me23 and CUR, was assessed by flow cytometry for 28 days and by MTT assay in 3D and 2D cultures, respectively. Gene expression of ACE2 and TMPRSS2 and viral replication was assessed by qPCR. **Results and Conclusions:** the viability of sh-sy5y and sh-ace2 spheroids increased 76% and 67% ($p<0.05$), respectively, after 21 days of cultivation. SH-ACE2 spheroids presented 21% less viable cells, compared to SH-SY5Y, after 7 days. In order to evaluate the effects of Me08, Me23 and CUR on cell viability in 2D and 3D cell cultures, a dose-response curve was developed. 2D and 3D cell cultures treated with Me08 did not exhibit significant difference in viability. Conversely, Me23 treatment(90 µM) in 2D cell reduced the viability($p<0.001$). In 3D cultures, a reduction in the viability was also observed in all concentrations (60-180 µM, $p<0.00001$), after Me23 treatment. 2D cell cultures showed lower viability after treatment with CUR (2.8x10^-2 and 1.4x10^-2 mg/mL). We also observed a reduction in the spheroid's viability after treatment with CUR (9x10^-2 mg/mL, $p<0.00001$). No significant differences in the ACE2 and TMPRSS2 expression was observed in 2D cultures of sh-sy5y after treatment. However, Me23 reduced the SARS-CoV-2 replication in SH-ACE2 cells. The present study investigated the effect of curcuminoids me08 e me23 and cur in 2d and 3d cultures of sh-ace2 and control sh-sy5y. It was not observed differences in ACE2 and TMPRSS2 expression after treatment with curcuminoids and CUR. Me23 reduced the SARS-CoV-2 replication in SH-ACE cells, which broadens the potential study perspectives on curcuminoids and COVID-19.

Keywords: Curcumin, curcuminoids, spheroids, SARS-CoV-2, SH-SY5Y

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EVALUATION OF THE EFFECT OF BLOCKING AMPA/KAINATE-TYPE GLUTAMATERGIC RECEPTORS IN A MURINE MODEL OF CEREBRAL MALARIA

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Introduction: Cerebral Malaria (CM), one of the most severe complications of the infection caused by *Plasmodium Falciparum*, is characterized by hemorrhagic events due to obstruction of the cerebral microvasculature and breakdown of the blood-brain barrier (BBB) causing metabolic changes that results in severe neurological damage. Among the metabolic changes involved is the increase in glutamate levels, which results in tissue damage by excitotoxicity. Studies show that AMPA/Cainate glutamatergic receptors have a strict relationship with the functionality of the blood-brain barrier. Based on this, the objective of this work was to evaluate the effect of AMPA/Cainate blockade in a murine model of CM, using the antagonist a DNQX (6,7-dinitroquinoxaline-2-3dione). **Material and methods:** C57BL/6 mice were infected intraperitoneally with 10^6 of erythrocytes parasitized with the ANKA strain of Plasmodium berghei (PbA) (CEUA nº 62112417). The animals were treated with DNQX blocker 2mg/kg (1h after infection from the 1st to the 4th day). We evaluated survival, parasitemia and performed the brain vascular permeability assay. **Results and discussion:** Our results showed that the treatment with DNQX increased the survival of the animals. Analysis of parasitemia showed that there was no significant difference between the groups. In the vascular permeability test, it was found that the treatment of DNQX significantly enriched the vascular extravasation in the animals. **Conclusion:** Blockade of AMPA/Cainate receptors in murine attenuated the damage to the BBB, increasing the survival of the animals.

Keywords: cerebral malaria; blood brain barrier; DNQX; *Plasmodium.* **Support:** CAPES.

BIFLAVONOID AGATHISFLAVONE CONTROL REACTIVE ASTROGLIOIS AND INDUCES REGENERATION OF NEURONS ASSOCIETED WITH INCREASED EXPRESSION OF GLT-1 GLATAME TRANSPORTER IN A MODEL OF TRAUMATIC BRAIN INJURY

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Introduction: Traumatic Brain Injury (TBI) is a complex and multifactorial pathology, being a major cause of death and disability for humans. Immediately after TBI, astrocytes and microglia react with complex morphological and functional changes known as reactive gliosis and forms, in the area immediately adjacent to the lesion, the glial scar, the major barrier to neuronal regeneration in the central nervous system. The flavonoid agathisflavone (bis-apigenin) has been shown to have neurogenic, neuroprotective and anti-inflammatory effects, demonstrated in *in vitro* models of glutamate-induced toxicity, neuroinflammation, demyelination and trauma. However, the mechanisms mediating agathisflavone action in TBI models are still poorly understood. **Objective:**The present study investigated the effect of agathisflavone in neuronal integrity and in the modulation of astrocytes response in an ex vivo model. **Methodology:** Microdissections from the encephalon of Wistar rats (P6-8), were prepared and subjected to mechanical injury prior to treatment with agathisflavone (5µM), and in the daily changes of the culture medium by 3 days or maintained in control conditions (DMSO0.005%). For cell phenotype and morphology analyses, the cells were immunolabeled for β-III-tubulin (neurons), GFAP (astrocytes). **Results:** In the lesion area of the untreated groups, decreased immunostaining of β-III tubulin was observed, as well as gliosis in the extension of the edge of the lesion, increase of GFAP expression, and formation of the typical TBI glial scar. On the other hand, in the injured tissue treated with agathisflavone the expression of GFAP and the extension of the glial scar were reduced and with the increase of neurons in the area and edge of the lesion. **Conclusion**:These results indicate that the flavonoid was able to modulate gliosis and increase the population of neuronal cells and the migration of neurons to the region of brain injury putting in perspective its use in complementary therapies for TBI.

Keywords: Traumatic brain injury, Agathisflavone, Astrogliosis, Microglia

Support:: CAPES, FAPESB and CNPq.

DEVELOPMENT AND CHARACTERIZATION OF POLYMERIC NANOPARTICLES OF POLY-L-LACTIC ACID (PLA) LOADED WITH VITAMIN D WITH THERAPEUTIC POTENTIAL FOR NEURODEGENERATIVE DISEASES

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Introduction: Vitamin D (VD) deficiency is increasingly associated with the worsening progression of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's, and multiple sclerosis, for example. Beyond its roles in calcium homeostasis and bone health, VD plays important features in the central nervous system, as in enhancing the neural microenvironment, promoting anti-inflammatory effects, and impacting on proliferation and differentiation of glial cells. Hence, considering the influence of VD on different physiological mechanisms, our study intends to use a nanotechnological approach to improve VD's efficiency and therapeutic potential in the context of neurodegenerative disorders. **Objectives:** The present study focuses on the development and characterization of a polymeric nanoparticle system incorporated with VD as a novel approach to neurodegenerative disease treatments and/or supplementation. **Methods:** To obtain the nanocarriers we used a standardized adapted method of emulsification-solvent evaporation. Nanoparticles were tested related to their diameter sizes, polydispersity index (PdI), zeta potential (ZP), and stability over seven successive weeks. We also evaluated encapsulation efficiency (EE) in the first trials together with the other parameters. **Results and Conclusions:** The results achieved so far demonstrate good stability for seven consecutive weeks, diameter sizes ranging from 256 to 266 nm, PdIs all below 0.3, ZP mean of 4.97 mV (± 0.68), and EE higher than 97%. From the foregoing, the data collected is satisfactory and presents good properties according to literature, besides that, the project needs to follow up on other experiments needed for a better understanding of the drug-loaded nanoparticle's interactions in a living system (i.e. cell culture and animal models).

Keywords: Neurodegenerative Diseases; Vitamin D; Nanotechnology.

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EFFECT OF METABOTROPIC GLUTAMATE RECEPTOR 5 (MGLUR5) BLOCK ON THE EXPERIMENTAL CEREBRAL MALARIA INDUCED BY PLASMODIUM BERGHEI (ANKA)

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Introduction: Cerebral malaria (CM) is a complication resulting from Plasmodium falciparum infection, which can be lethal if not treated. One of the characteristics present in individuals who survive CM is long-term neurocognitive and motor sequelae, however the mechanisms that lead to these impairments are still poorly understood. Within this perspective, we will seek to evaluate the glutamatergic system, as it is altered in several neurological disorders that are also observed in cerebral malaria. Since the activation of the metabotropic glutamate receptor 5 (mGluR5) is widely associated with damaging events to the parenchyma and brain vasculature, and is expressed both in neurons and glial cells, we aim to evaluate the implications of mGluR5 modulation in the pathogenesis of CM. **Objective:** Therefore, the objective will be to evaluate the effect of blocking mGluR5 in experimental cerebral malaria. **Material and methods:** Primary, Swiss mice will be infected intraperitoneally with 106 PbA-pRBCs. Parameters as survival curve, parasitemia, body weight and clinical signs will be monitored. Animals will be treated with the selective mGluR5 MPEP antagonist (1h before infection and 1st – 3th day post). For the behavioral assessment, Rapid Murine Coma and Behavior Scale (RMCBS) protocol will be used, associating the clinical signs of the disease with those presented in the experimental model, as well as Open Field test. Tests will be performed on days 3, 5 and 7 after infection (d.p.i). **Results and discussion:** Regarding previous work, in our results we expect to observe an attenuation of the clinical halllmarks of the disease in the animals treated with the mGluR5 inhibitor leading to increased survival rate. Accordingly, we intend to assess the contribution of this receptor at the cellular level, evaluating the role of neuronal and glial cells in the development of cerebral malaria. **Conclusions:** In conclusion, we expect that the modulation of glutamatergic activity through its metabotropic receptor 5 may elucidate the participation of this system in the pathophysiology of the disease.

Keywords: Glial Cells, Cerebral Malaria, Glutamate System, Metabotropic Glutamate Receptor 5.

Support: CNPq and CAPES.

STUDY OF THE ROLE OF CX43 ON ENTERIC GLIAL CELLS IN INFLAMMATION OF INTESTINAL EPITHELIAL CELLS

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Introduction: Enteric Glial Cells (EGC) and enteric neurons compose the Enteric Nervous System. Mucosal EGCs play an important role in controlling the integrity of the Intestinal Epithelial Barrier (IEB) by reducing the permeability and as a defense in inflammation. However, in some cases EGC becomes reactive, releasing pro-inflammatory cytokines and S100B protein, that in high concentrations contributes to the fragility of the IEB and intestinal inflammation. Communication between EGCs occurs through connexin43 (cx43) channels. In addition, some factors may be released by these Cx43 hemichannels. Ablation of Cx43 in EGC results in increased fluid in feces, which indicates a role of these hemichannels in IEB regulation. **Objectives:** To investigate in vitro the role of cx43 in the EGCs response and its consequences for colon epithelial cells, against inflammation promoted by lipopolysaccharide (LPS). **Material and methods:** Interaction of the EGC lineage – CRL2690, with intestinal epithelial cells of the Caco-2 lineage, through co-culture experiments and culture of one cell type with the conditioned medium of the other cell type, with or without treatment with LPS, and cx43 inhibitor (43gap26). Immunofluorescence and western blotting for detection of Caco-2 and EGC proteins. ELISA for S100B. Cell viability (MTT) and proliferation will be evaluated in both cell types. **Results and discussion:** Caco-2 showed no significant difference in cell viability when exposed for 24h to LPS, or to the conditioned media of EGC, LPS-treated EGC, or HCT116 conditioned media-treated EGC; EGC showed decreased cell viability about 10% when exposed to LPS and 43gap26 and expressed twice as much S100b in the presence of LPS. Treatment with LPS plus cx43 inhibitor in EGC seems not to change cx43 expression. Caco-2 treated with LPS shows discontinuity sites in ZO-1 expression zones. However, in co-culture with EGC, LPS does not cause these failures in the occlusion zones between Caco-2 cells, but failures regions are there if co-culture is treated with LPS and 43gap26. **Conclusions:** EGCs seems to protect IEB from inflammatory insults, which is mitigated when cx43 pathways are inhibited. These data suggest that factors secreted by cx43 hemichannels of EGC play an important role in this protection.

Keywords: Enteric Glial Cells, Inflammation, Reactivity, Connexin43, Enteric Nervous System

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