Brain aging: insights into neuron-glia interactions

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Abstract
Aging begins at maturity and is characterized by increasing deviations from an ideal functional state. One major reason for this is thought to be oxydatif stress. The brain is particularly susceptible to oxidative damage. Besides neurons, glial cells, a major family of neural cells, are directly involved in vital brain functions and particularly in the brain antioxidant defence. This review brings insights into the potentialities of these glial cells to protect neurons and into their contribution to the brain aging process.

Keywords: Glial function. Oxidative stress. Neuroprotection. Aging.

INTRODUCTION

Aging is an irreversible process that begins at maturity and is characterized by increasing deviations from an ideal functional state. Many changes occur as an animal ages. To name a few, proteins become modified and cross-linked, somatic mutations accumulate, stress resistance decreases, and the probability of death increases. Among the prime candidates responsible for this is thought to be oxidative stress, that means, oxidative damage to macromolecules and lipid membranes, caused by superoxydes and other free radicals resulting from aerobic metabolism (SOHAL; WEINDRUCH, l996). It has been hypothesized that brain aging results from a progressive inability to cope with such insults as oxidative stress and inflammation. This damage can be partially but never completely counteracted by mechanisms for elimination of free radicals as well as turnover of macromolecules. Besides oxidative damage, extrachromosomal circular DNAs and nucleolar fragmentation, could also be a general cause of cellular aging (WOOD, 1998).

Does aging depends only on the rates of cell-autonomous processes, or is there a systematic clock that regulates aging of the organism as a whole, or is it both: systemic controls which affect life span by regulating rates of cellular aging remains an opened question.

Although deleterious changes inevitably accumulate, their rate of accumulation and the resulting life spans are genetically controlled. Two kinds of genes could affect aging rates: those genes that directly affect intracellular mechanisms for protection, turnover and repair of macromolecules and cell membranes; a second class would include genes that systemically control metabolic rates or response to environmental stress.

What begins to emerge from recent studies is that an increase in longevity accompanies increases in stress resistance, consequent to cell-autonomous processes of free-radical elimination and repair (ARKING et al., 1996; SHOOK;

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BROOKS; JOHNSON, 1996). Non-genetic evidence, for a relationship between aging and metabolism, comes from observations that dietary restriction (DR) can substantially increase the life spans of numerous tested animals (CASADESUS; SHUKITT-HALE; JOSEPH, 2002; LANE, et al., 2002; MATTISON et al., 2003). Systemic controls may therefore regulate rates of the intracellular enzymatic processes to protect against, for example, oxidative damage and its effects, the efficiency of these cellular mechanisms, in turn, dictates the aging rate.

BRAIN AGING

The brain is particularly susceptible to oxidative damage. Neural cells use multiple mechanisms to maintain the integrity of nerve cell circuits and facilitate responses to environmental demands, promoting the recovery of function after injury. The mechanisms include production of cytokines, expression of various cell-survival promoting proteins, protection of the genome by telomerases and DNA repair proteins and also potential mobilization of precursor cells to replace damaged neurons and glia.

The aging process challenges such protective and restorative mechanisms, often with devasting consequences as Alzheimer's and Parkinson's diseases or stroke. Genetic and environmental factors superimposed upon the aging process, can determine whether brain aging is successful or unsuccessful. Mutations in genes overwhelm endogenous neuroprotective mechanism. On the other hand, neuroprotective mechanisms can be bolstered by dietary and behavioural modifications (MATTSON et al., 2002). At the cellular and molecular levels, successful brain aging can be facilitated by activating signals to which neurons respond by upregulating the expression of neurotrophic factors. Neural stem cells reside in the adult brain; they may respond to environmental demands, and be capable of replacing lost or dysfunctional neurons and glial cells in the aging brain. In fact, molecular and cellular biology of brain aging is revealing a remarquable capacity within brain cells for adaptation to aging and resistance to disease. In aged rodents, surprisingly little evidence is found for major cell loss in life. Additionally, it has been suggested that even some loss of neurons, observed in specific brain areas, triggered compensatory mechanisms of growth and remodelling, and the surviving cells sprout and replace lost connections.

However, human and non-human primate brains show undeniable cognitive declines during normal aging. Here again, there is no significant cortical neuronal loss with age and no correlation between the frequency of senile plaques and cognitive status (PETERS, 2002). Neurons of the neocortex show few signs of aging; nevertheless, some pyramidal cells lose branches and synapses and this underlines a certain regional heterogeneity in the aging process. At the same time, the glial limiting membrane thickens. There are decreases in the level of some neurotransmitters and receptors. The brain myelin sheaths are thinning and show signs of breakdown, causing a slowing of conduction along nerve fibers, disrupting the timing in neuronal circuits. Myelin-forming oligodendrocytes develop swelling along their processes and gane dense inclusions. Microglial cells and astrocytes increase in number (MOUTON et al., 2002), and become phagocytic.

ASTROCYTES AND AGING

Astrocytes are directly involved in the brain defence. They represent a major cell population in the brain and are involved in many functions vital for brain. They are present at strategic positions in the brain: near blood vessels, along meninges, around synapses and constitute their own networks projecting at long distances. They regulate glucose entry into the brain and have the capacity either to stock it as glycogen, or to furnish energetic metabolites to neurons in response to specific signals. They control ion

and amino acid neurotransmitter homeostasis at the synaptic level. They protect neurons against Glu excitotoxicity, reactive oxygen and nitrogen species, toxins of endo- and exogenous origin.

Although many of the voltage-sensitive ion channels and neurotransmitter receptors of neurons are found in glia, these cells lack the membrane properties required to fire action potentials. Nevertheless, channels and transporters allow glia to sense indirectly the level of neuronal activity by monitoring activity-dependent changes in the chemical environment shared by the two cell types.

A new physiological concept for transmission of information in the brain has been proposed, involving the astroglial network and Gap junctions (NEWMANN; ZAHNS, 1997; SMITH, 1994; VERKHRATSKY; ORKLAND; KETTENMANN, 1998). There may exist preferred astroglial circuits in the brain. Astroglial cells communicate through a widely extended network via intracellular waves of Ca++, but also via intercellular diffusion of chemical messengers like inositol phosphate (IP3) and ATP. In addition, by releasing neurotransmitters and other extra cellular signalling molecules, astrocytes can at distance affect neuronal excitability and synaptic transmission and perhaps coordinate activity across networks of neurons. Reversely, neuronal stimuli regulate a wide range of glial activities including their proliferation and differentiation.

What might be the role of these glial cells in neuronal aging? There is an increase in glial cell proliferation in some areas of the aging brain; the significance of this phenomenon is not yet well understood. The classical notion that astroglial cell proliferation with aging, characterized as astrogliosis, implicating a response to neuronal death, does not take into consideration glial cell modifications which may contribute to neuronal cell disfunctions in certain brain areas. The possibility that glial cells do not provide the required signals for neuronal homeostasis, and do not assume neuronal protection warrants further attention. Astrocytes from aging brain continue to function normally with respect to several parameters. They continue to express some degree of plasticity but with time, this plasticity declines and cell homeostasis appeared impaired (GROVE et al., 1996). These cells may undergo several critical periods in their regulatory functions during a life span.

Astrocytes protect neurons against Glutamate-induced excitotoxicity through exchanges of Glutamine for Glutamate (FIGURE 1); basal Glutamate (Glu) uptake by astrocytes increase with age (GOTTFRIED et al., 2002), but exposure to hydrogen peroxide, an oxidative metabolite, highly decreases its uptake. Such alterations in Glu homeostasis can contribute to the understanding of some consequences of excitotoxicity and of oxidative stress during brain aging.

Oxydative damage, and initial oxidative modifications by glycation or another cause, in astrocytes, can lead to a neurodegenerative cascade. As an exemple, a loss of activity of glutamine synthetase (GS), an astroglial specific enzyme, which neutralizes actively Glutamate and ammonium ions (FIGURE 1), and consumes 98% of the ammonia entering the brain, was paralleled by increases in brain carbonyl content in proteins. A working hypothesis is that reduced GS activity results from oxidative damage (OLIVER et al., 1990). Deficits of this key enzyme, could lead to excess ammonia levels and a consequent astroglial hypertrophy, to a glutamine deficit with further metabolic consequences or even to direct neurotoxicity due to an excess of excitatory amino acids. Inhibition of GS also diverts glutamate taken up from the synaptic cleft by astrocytes, to aketoglutarate through glutamate dehydrogenase which further produces ammonia, inhibiting enzymes of the citric acid cycle.

Astrocytes protect neurons against reactive oxygen deleterious effects by a high modulable expression of catalase associated with GSH peroxydase, two enzymes directly involved in free oxygen radicals neutralization; this astroglial metabolism declines with aging (FIGURE 2).

Astrocytes also protect neurons by storing excess iron and by brushing away from the brain tissue damaged cell constituents such as aged mitochondria, peroxidized membranes and nitrated proteins (SREBRO; DZIOBEK, 2001) and such capacity still lowered.

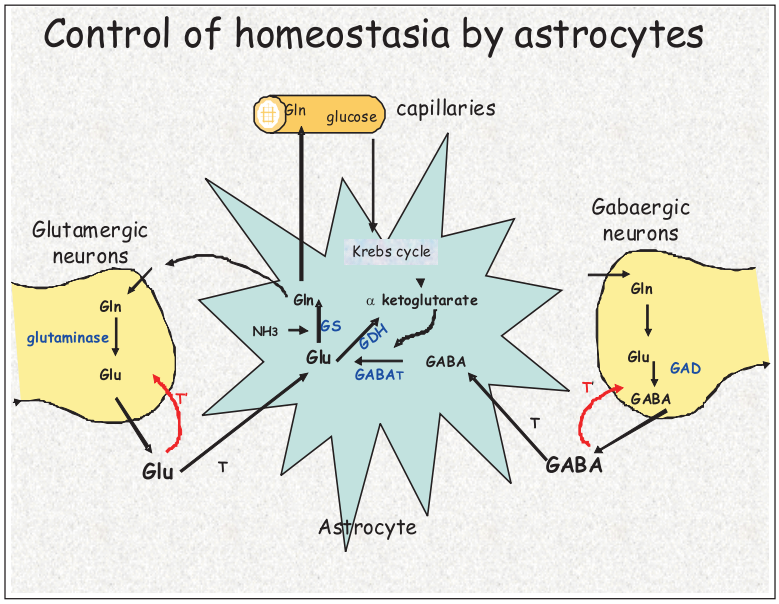

FIGURE 1 – Control of Homeostasia by Astrocytes.
Astrocytes can take up (T) actively Glutamate (Glu) and GABA released by Glutamergic or Gabaercic nerve endings. They can metabolize both of them. GABA is transformed by transamination (GABA-T) to Glu and neutralized into Glutamine (Gln) by Glutamine synthetase (GS) which by the way, neutralizes ammonium ions. Gln is released into the extracellular space and can be taken up by nerve endings, where it serves as precursor for Glu through glutaminase, or for GABA when Glutamate decarboxylase (GAD) is present in the pre-synaptic compartment.
Glu can also serve as substrate for Glutamate Dehydrogenase (GDH) and join the Krebs cycle.

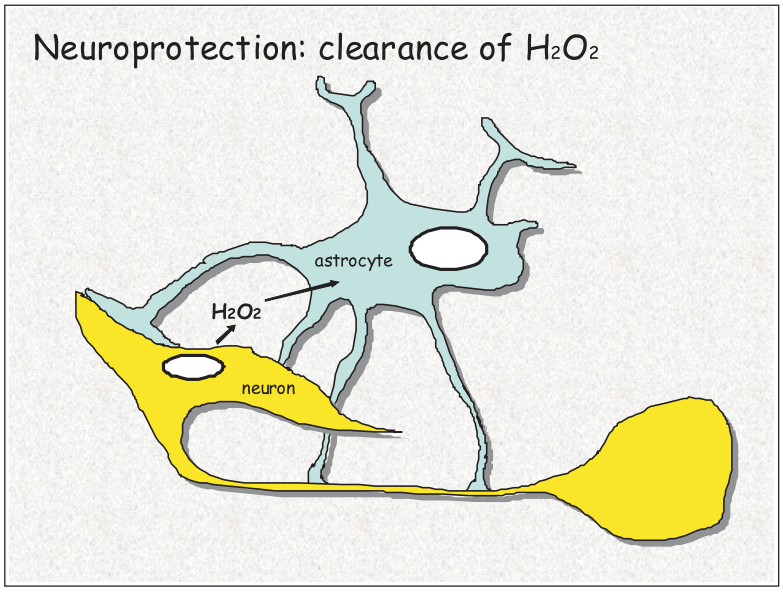

FIGURE 2 – Neuroprotection: Clearance of H_2O_2
Astrocytes can tak2e up an excess of hydrogen peroxyde (H_2O_2) released by neurons. H_2O_2 released is in excess and consequent to an associated effect of neuronal Superoxyde dismutase (SOD) and of Glutathion (GSH) Peroxydase. Astrocytes can take up this excess of H_2O_2 and neutralize it to water, via the cooperation of a highly modulated Catalase and of an astroglial GSH Peroxydase.

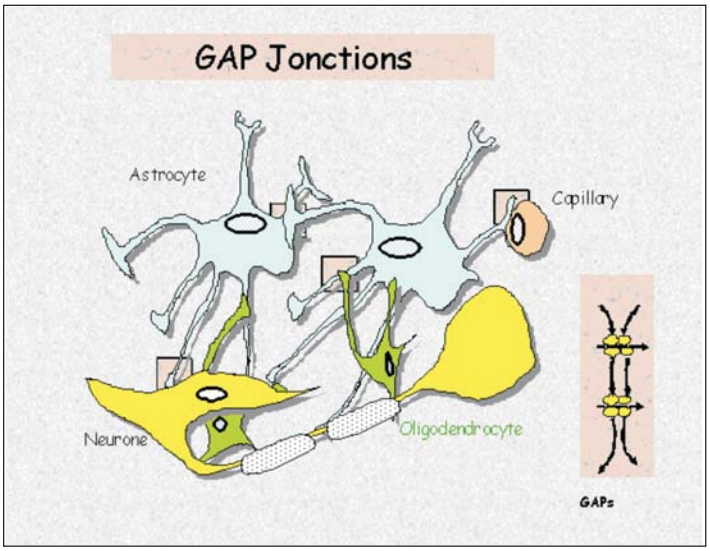

FIGURE 3 – GAP Jonctions
Astrocytes can communicate through homotypic GAP junctions (pink squares), along an astroglial network and can transfert informations at large distances. They can also communicate with oligodendrocytes and neurons through heterotypic GAP junctions and transfert signals to these cells.

Aging in the brain is also associated with the species, with specific phenotypic changes in the astroglial population, which include increased expression of a major component of its gliofilaments, the Glial Fibrillary Acidic Protein (GFAP) (RIOL; FAGES; TARDY, 1992; NICHOLS et al., 1993; TARDY et al., 1993; LAPING et al., 1994; KOHAMA et al., 1995). Upregulation of GFAP expression is one of the main characteristics of the astrocytic reaction commonly observed after CNS lesion (LE PRINCE et al., 1993) in specific brain regions (NICHOLS, 1993) and an increased GFAP-mRNA is associated with increased mRNAs per astrocyte in the outer molecular layer of the aging dentate gyrus. (YOSHIDA et al., 1996; MORGAN et al., 1999). The astrocyte response is of central importance following CNS injury and can either promote or deter recovery of neural function (MATHEWSON; BERRY, 1985; ORDY et al., 1993; GARCIA-ESTRADA et al., 1995; LEFRANÇOIS et al., 1997; COSTA et al., 2002). Vascular damage and reactive gliosis were found colocalized with amyloid deposits in Alzheimer disease (AD) brains. Localisation of the C-terminal of amyloid precursor protein (APP) and of amyloid peptide within ischemic astroglial cells underlines the involvement of APP and of astrocytes in the pathogenesis of ischemia (PLUTA, 2003).

The signals which regulate astroglial reactivity begin to be known, but the exact role of the reactive astrocytic hypertrophy is still a matter of speculation (TARDY, 2002).

Reducing astrocyte reactivity during both, post-trauma regeneration, as well as during aging, has been proposed to indirectly represent an increase in neuronal well being.

This has been obtained with diet restriction (DR) in rats, where GFAP expression was lowered in the hippocampus and hypothalamus of diet-restricted rats compared to ad libidum fed controls (NICHOLS; FINCH; NELSON, 1995; MAJOR et al., 1997), but also with corticoids (O'CALLAGAN; BRINTON; MCEWEN, 1991), testosterone (DAY et al., 1998) and estradiol (STONE et al., 1998).

OLIGODENDROCYTES AND AGING

Another component of macroglia is oligodendrocyte. The main function of oligo-

dendrocytes, is the formation of a myelin sheath around most of axons in the CNS. Oligodendrocytes appeared also involved in clustering of sodium channels at the node of Ranvier, during axogenesis (KAPLAN et al., 1997). They also participate to development and regulation of axonal calibre and maintenance of axons.

Myelin allowed the propagation of action potentials in neurons over large distances at high velocity. Disruption of myelin sheaths could contribute to cognitive impairment such as that observed during the normal aging process. The content of intact myelin fraction decreased in aging consequent to an increased breakdown of intact myelin. However, increased cyclic nucleotide-3'-phosphodiesterase (CNPase) and myelin proteins, in response to myelin degradation, suggest remyelinisation (SLOANE et al., 2003) and may be related to the presence of oligo. progenitors in adult mammalian CNS which may differentiate into oligodendrocytes (BLIGHT, 1998). This potentiality appears particularly important for remyelination during the aging process, but requires further investigations.

MICROGLIA ACTIVATION IN AGING

In contrast to macroglia, which derived embryologically from ectodermal precursors, within the central nervous system, microglia derived from bone marrow monocyte precursors. Microglia constitute a widely distributed network of immunoprotective cells. They respond to neuronal impulse activity and mediate neuro-immune interactions. During the last decade, it has become clear that the functions traditionally ascribed to microglia,(to dispose of dead cells and debris and to mediate inflammatory states), are only a fraction of a much wider repertoire of functions spanning from brain development to aging and neuropathology (POLAZZI; CONTESTABILE, 2002). In the healthy brain, neurons release signals related to the suppression of immunological properties of microglia , and the derangement from this physiological equilibrium in aging and disease, may be deleterious.

The loss of specific communications between damaged neurons and microglia allowed the activated microglia to escape neuronal control and give rise to persistant inflammation and to release of free radicals and inflammatory cytokines. During normal aging, brains show general feature of chronic inflammation. The neuro-inflammatory process observed in aging, can be considered in the context of the similar and more intense changes in Alzheimer disease (AKIYAMA et al., 2000; FINCH; LONGO, 2000). Activated microglial cells are present in brains of Parkinsonian patients and may be involved in the pathology (KOUTSILIERI et al., 2002).

Concerning physiological aging, astroglial activation appears to begin at middle age, that means several months before any neuronal loss was detected, astroglial activation may therefore not be really considered as secondary to neuronal death but also not sufficient for microglial activation. In aging, microglial activation could be related to changes in electrical activities, including ion channels sensitivity to extracellular potassium, to increased cytokines like TNF (GEHRMANN et al., 1993), or to epileptiform seizures (SHAW; PERRY; MELLANBY, 1994), blocking conduction and inducing GFAP (CANADY; HYSON; RUBEL et al., 1994). In white matter, microglial activation during aging might be rather a cause or consequent of alterations in oligodendroglia associated with chronic progressive demyelination . Oxidized lipids in myelin sheaths could be one of the various factors inducing microglial activation (BRUCE-KELLER et al., 1999) and inflammatory processes observed in brain aging.

CONCLUSION

With the increasing demands placed in our society to perform better, for longer, efforts are going on to limit or even reverse the declines that emerge from growing old. Currently, knowledge about neuronal disfunction, during both normal aging and neurodegenerative

diseases progresses. Among the candidates responsible for producing a great part of these deleterious effects, are free radicals. The vital implication of glial cells in the suppression of oxidative stress (OS) and its correlated preservation of neuronal function and associated cognitive and motor performance during aging is of crucial importance. Involved in physiological aging, OS is also significantly enhanced in Parkinson Disease (PD). OS-dependent aggregation of proteins in the form of advanced glycation end products can be imaged in Lewy bodies at a time when no phenotype of a neurodegenerative disorder is evident. Toxin-induced neurodegeneration in PD animal models can be blocked by antioxidants. Finch et al. (2002), recently proposed a convergence of the inflammatory and oxidative damage as a hypothesis of aging with the idea that early outcome of aging may depend on how early stage "smouldering gero-inflammatory process" are kindled by the external environment, as well as by physiological influences such as diet and hormones.

Experiments with caloric restriction (CR), in aging rats showed normalisation in the astroglial and the microglial activation (MORGAN et al., 1999). Food restriction reduces oxygen consumption, lowers thyroid hormone levels, blood glucose levels and as a consequence, decreases the accumulation of oxidized products (SELL; KLEINMAN; MONNIER, 2000). Thus, elucidation of the biological mechanisms of CR in brain, and particularly on neuron-glial interactions during the adult life span as well as development of alternative strategies to yield similar benefits appeared of primary importance.

Envelhecimento do cérebro: reflexões sobre interações neuro-gliais

Resumo

O envelhecimento começa na maturidade e se caracteriza pelos crescentes desvios do estado funcional ideal. Supõe-se que o principal motivo dessas mudanças seja o estresse oxidativo. O cérebro é extremamente susceptível a danos oxidativos. Além dos neurônios, as células gliais, a principal família das células neurais, estão diretamente envolvidas com as funções vitais do cérebro, especialmente na defesa antioxidante do cérebro. Este trabalho aborda aspectos relativos ao potencial que as células gliais têm para proteger os neurônios e sua contribuição para o processo de envelhecimento do cérebro.

Palavras-chave: *Função glial. Estresse oxidativo. Neuroproteção. Envelhecimento.*

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