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Review

Healthy brain aging: Interplay between reactive species, inflammation and energy supply

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ABSTRACT

Brains' high energy expenditure with preferable utilization of glucose and ketone bodies, defines the specific features of its energy homeostasis. The extensive oxidative metabolism is accompanied by a concomitant generation of high amounts of reactive oxygen, nitrogen, and carbonyl species, which will be here collectively referred to as RONCS. Such metabolism in combination with high content of polyunsaturated fatty acids creates specific problems in maintaining brains' redox homeostasis. While the levels of products of interaction between RONCS and cellular components increase slowly during the first two trimesters of individuals' life, their increase is substantially accelerated towards the end of life. Here we review the main mechanisms controlling the redox homeostasis of the mammalian brain, their age-dependencies as well as their adaptive potential, which might turn out to be much higher than initially assumed. According to recent data, the organism seems to respond to the enhancement of aging-related toxicity by forming a new homeostatic set point. Therefore, further research will focus on understanding the properties of the new set point(s), the general nature of this phenomenon and will explore the limits of brains' adaptivity.

1. Introduction

Since living organisms are open thermodynamic systems, they need energy to maintain their organization and functioning. This is very true for the brain, the most complicated animals' organ. High energy expenditure of the brain (in mammals, the brain amounts to about 2% of body weight but consumes about 25% of glucose and 20% of oxygen absorbed by the organism) and utilization of the specific energy sources (mainly glucose and to a lesser extent ketone bodies (KB)) defines specific features of the brain metabolism. The situation is further complicated by high amounts of polyunsaturated fatty acid residues in brain lipids. The extensive oxidative metabolism is accompanied by production of high amounts of reactive oxygen (ROS), nitrogen (RNS), and carbonyl (RCS) species (collectively called RONCS), which the brain has to cope with during the entire life of an individual. The levels of products of interaction between RONCS and diverse cellular components increase during the life span and this increase is recognized as a critical signature of aging. An association between the levels of free radicals and aging laid the basis of free radical theory of aging proposed by Harman (1956). Decades of studies of aging and processes involving reactive species of oxygen and other elements led to recently proposed classifications of oxidative stresses (Lushchak, 2014) which in this paper we will try to adapt to description of aging process.

In many cases, aging-related increase of RONCS levels stimulates proinflammatory processes. Over recent years, the inflammatory processes occurring in the aging brain have attracted a lot of attention mostly because of their association with several age-related diseases such as stroke, vascular dementia, epilepsy, schizophrenia, Alzheimer's and Parkinson's diseases. This led to an assumption about the detrimental role of aging-related inflammation, causing an impairment of memory and cognition or even neurodegeneration. However, the recent studies in centenarians have shown that individuals, who have largely avoided chronic pathologies, had strongly increased plasma levels of pro-inflammatory cytokines IL-6, IL-18, paralleled by higher blood

Abbreviations: AD, Alzheimer's disease; AGEs, advanced glycation end products; BBB, blood-brain barrier; BDNF, brain-derived nerve growth factor; CML, carboxymethyllysine; CMRg, cerebral metabolic rate of glucose; DAMPs, damage-associated molecular patterns; GLUT, glucose transporter; GPx, glutathione-dependent peroxidase; IL, interleukin; KB, ketone bodies; LGs, lipofuscin granules; MCT, monocarboxylic acid transporter; NF-κB, nuclear factor kappa-B; Nrf2, NF-E2-related factor 2; PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors; RAGE, receptor for AGEs; SOD, superoxide dismutase; RCS, reactive carbonyl species; RNS, reactive nitrogen species; ROMS, ROS-modified substances; RONCS, reactive oxygen/nitrogen/carbonyl species; RONS, reactive oxygen/nitrogen species; ROS, reactive oxygen species; ROSISP, ROS-induced ROS-sensitive parameter; TBARS, thiobarbituric acid-reactive substances; TNF-α, tumor necrosis factor α

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levels of potent anti-inflammatory molecules, such as transforming growth factor β (TGF-β) or cortisol (Franceschi and Campisi, 2014). Therefore, healthy aging seems to require a proper balance between pro- and anti-inflammatory factors rather than stand-alone reduction in the level of proinflammatory cytokines (Franceschi et al., 2017).

The age-associated increase of RONCS levels and products of their interaction with organisms' components in concert with other processes accompanying brain aging may potentially lead to a shortage in glucose and oxygen consumption. Mosconi (2013) hypothesized that "a deficit in the utilization of glucose, rather than reduced glucose availability, is involved in some late onset AD (Alzheimer's disease) cases". Similar processes may characterize normal brain aging. This deficit may be associated with reduced brain capability to convert external energy to substrates required for ATP biosynthesis, mainly due to dysfunction of mitochondria (Cunnane et al., 2011) and, to a lesser extent, an impairment of transport systems for carbohydrates and carbonic acids. Such perturbations of energy homeostasis along with increased inflammation and endoplasmic reticulum stress cause so-called metabolic stress (Uranga et al., 2010). Age-promoted metabolic stress along with enhanced steady-state level of RONCS may cause multiple pathological changes in the aging brain. Some products of nonenzymatic interaction of RONCS with cellular components, such as, for example, advanced glycation end products (AGEs) and advanced lipooxidation end products are pro-inflammatory, closely interacting with the immune system via so-called pattern recognition receptors (PRRs).

In this article, we describe biochemical and immune system-related changes accompanying healthy brain aging and discuss the mechanisms by which the aging brain is adapting to new circumstances.

2. Classifications of stresses induced by reactive species

Under normal conditions, organisms maintain a delicate balance between generation and elimination of reactive species as well as prevention of their formation (Lushchak, 2014; Sies, 2014, 2015, 2017). However, being generally well counterbalanced by defense systems at the global level, locally RONCS attack nearby located cellular components causing the formation of RONCS-modified molecules. The latter can be eliminated in two ways: either by degradation, or by cellular repair systems. However, a certain portion of RONCS-modified molecules can avoid elimination and form bigger aggregates, which may enter autoxidation, thus becoming ROS generators themselves (Grimm et al., 2011; Lushchak, 2014; Sies, 2017; Sies et al., 2017). Such aggregates may include modified proteins, lipids, carbohydrates, and possibly nucleic acids, forming so-called aging pigment lipofuscin (Grimm et al., 2011).

Recently we proposed two systems for classification of oxidative stresses: the time course-based and the intensity-based ones (Lushchak, 2014). Within the time course-based classification the term "acute oxidative stress" denotes an increase in the steady-state ROS level lasting from minutes to hours, whereas if it lasts longer, "chronic oxidative stress" takes place (Fig. 1A). During chronic oxidative stress, the steady-state ROS level might be either slightly higher, or even very similar to that encountered before the stress induction. Furthermore, after the end of the stress-inducing event the steady-state ROS level may not return into the initial corridor and stabilize at higher so-called quasi-stationary level. Strictly speaking, chronic oxidative stress may not be a stress at all, because classically stress is defined as a relatively fast response of the organism to a stressor, but rather to reflect a change of the "set point" of the organism adapting to a new steady-state ROS level. Moreover, under some circumstances the ROS level may decrease, resulting in acute and chronic reductive stress (Fig. 1A; Lushchak, 2011). However, to date the information on reductive stress is scarce and therefore it will not be discussed here in detail.

The second proposed classification of oxidative stresses it based on their intensity (Fig. 1B; Lushchak, 2014). At very low concentration/intensity of the inducer, it is impossible to register the development of oxidative stress by conventional methods. There is no obvious increase in the level of ROS or ROS-modified substances (ROMS) as well as so-called ROS-induced ROS-sensitive parameters (ROSISP). Such stress is called basal oxidative stress (Zone I, Fig. 1B). A further increase in the level of oxidative stress inducers causes so-called low intensity oxidative stress (Zone II, Fig. 1B). During this phase, one can measure a reliable increase in the level of ROS-modified cellular components. At initial phase of low intensity oxidative stress, ROSISP level increases due to ROS-induced upregulation, whereas later it decreases due to predominance of damaging ROS effects. At some point ROSISP level reaches so-called "no observed effect point" or "zero equivalent point" where inducer effects on ROSISP are not visible. Further increase in the level of oxidative stress inducers enhances the level of ROS-modified substances accompanied by a decrease of ROSISP below the initial or basal level. This is called strong/severe oxidative stress (Zone III, Fig. 1B). Finally, at the highest level of inducers, ROSISP level reaches a minimum, whereas ROMS level reaches a maximum and the very high intensity oxidative stress takes place (Zone IV, Fig. 1B). In the latter case, ROMS reach a maximum probably due to exhaustion of substances, which can be attacked by ROS. Because it seems that the proposed full classification system is too complicated for regular application, it can be more practical to use a simplified one. According to this classification, mild oxidative stress takes place when ROSISP and ROMS increase compared to control levels, whereas strong oxidative stress takes place when levels of ROSISP are lower and that of ROMS are higher than during mild oxidative stress. A similar scheme was used by Uranga et al. (2010), who described normal aging as a process, mainly preserving existing structures, accompanied by a low speed decline of metabolic functions, low intensity oxidative stress, and low level inflammation, whereas at diverse pathologies, such as cognitive decline, these processes are of higher intensity. Recently, Sies (2017) proposed to apply general Selye's theory of stress to oxidative stresses and coined terms "oxidative eustress" and "oxidative distress". This generally well corresponds to our simplified classification of oxidative stresses (see above; Lushchak, 2014).

The above classifications of oxidative stress may help to describe the processes happening during brain aging. Moreover, similar logics can be used to describe so-called nitrosative stress caused by RNS, like nitric oxide (·NO), nitrous oxide (N_2O), peroxynitrite ($ONOO^-$), and their derivatives as well as carbonyl stress caused by RCS like methylglyoxal or glyoxal. If the concept of nitrosative stress, particularly in the brain, was developed virtually in parallel with the one of oxidative stress (Bolaños et al., 2004; Nakamura et al., 2007), carbonyl stress concept was developed later. In the initial work, T. Miyata and colleagues defined it as a situation "resulting from either increased oxidation of carbohydrates and lipids (oxidative stress) or inadequate detoxification or inactivation of reactive carbonyl compounds derived from both carbohydrates and lipids by oxidative and nonoxidative chemistry" (Miyata et al., 1999). The authors associated RCS, AGEs and carbonyl stress mainly with chronic failure of kidney and urinic toxicity. Nowadays, however, there is a lot of evidence about considerable overlap between carbonyl and oxidative stresses (for review see Semchyshyn and Lushchak, 2012). Growing body of recent evidences also suggests that carbonyl stress, like oxidative one, may accelerate the rate of aging, development of age-related disturbances and cognitive decline (Dmitriev and Titov, 2010; Li et al., 2013).

Next, let us discuss nonenzymatic interactions of ROS-modified substances (RONCS) with each other and with other components of living organisms. For brevity, here and below reactive oxygen/nitrogen species will be collectively called RONS. Like RONS-promoted modifications, glycation is a nonenzymatic process, which accompanies many enzymatic processes and cannot be avoided or tightly controlled by the organism. Because of its significant impact on homeostasis, glycation is likely involved in normal aging, age-related diseases, and their complications. Monnier and Cerami (1981) postulated a causative role of glycation in aging and put forward the "glycation hypothesis of