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Electrical activity of sensory pathways in female and male geriatric Rhesus monkeys (*Macaca mulatta*), and its relation to oxidative stress

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ABSTRACT

Synapses loss during aging has been related to decreased neuronal excitability and reduced electrophysiological activity in the nervous system, as well as to increased brain damage. Those physiological and biochemical alterations have been related to the oxidative stress increase associated with old age. The main substrate of lipid peroxidation (LPX) in the central and peripheral nervous systems are the myelin sheaths, and their damage generates a delayed nerve conduction velocity. However, studies in which the neural conduction velocity is related to changes in the redox state are still lacking. Therefore, our aim was to correlate the sensory neural pathways delay in healthy geriatric Rhesus monkeys (*Macaca mulatta*) with the oxidative stress associated with physiological aging. Twenty-four monkeys were divided into four groups according to age and gender. Auditory, visual, and somatosensory evoked potentials were obtained. Superoxide dismutase, catalase, and glutathione peroxidase enzymatic activity, as well as LPX, were determined from blood samples. Our results showed significant differences between the older and younger age groups in all neural generators of the different sensory pathways evaluated, along with an increase in LPX and the antioxidant enzymatic activities. It suggests that, even though the enzymatic activity was found to be higher in older monkeys, probably as a compensatory effect, it was not enough to avoid LPX damage and the declined electric activity associated with age.

1. Introduction

Brain aging is a complex process that is characterized by morphological and neurochemical alterations. Currently, one of the most important challenges in aging biology is to understand the mechanisms involved in this progression, in order to relate the biochemical alterations to the functional decline during old age (Sims-Robinson et al., 2013; Di Penta et al., 2013). It is known that, during the normal aging process, there is a continuous synapses loss, which leads to significant neurophysiologic alterations that modify several electrophysiological parameters (Dickstein et al., 2007; Watson et al., 2012; Ibáñez-Contreras et al., 2011b, 2014b). In order to conduct the information among cells and tissues, the systems that are in charge of information registration and analysis must be in optimal conditions to allow the interaction of the organisms with their habitat, and are, therefore, essential for the adaptation to their environment (Hof et al., 2002; Watson et al., 2012; Ibáñez-Contreras et al., 2016).

Oligodendrocytes (OLG) interaction with neurons, due to myelin production, favors the action potential saltatory propagation, a phenomenon that greatly increases the axonal conduction velocity. Myelin loss or degeneration produces neuronal axons demyelination, thus delaying the nerve conduction rate at a central level (Dickstein et al.,

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2007; Watson et al., 2012; Ibáñez-Contreras et al., 2011a, 2016).

In the last decades, it has been discovered that, during aging, different mechanisms induce OLG damage and death. Among them are mitochondrial dysfunction, axonal transport deterioration, trophic support reduction, high iron levels and readily oxidable substrates, antioxidant enzymes low production, Ca^{2+} homeostasis alteration, increased microglial activation, etc. (Bongarzone et al., 1995; Smith et al., 1999; Dewar et al., 2003; Haynes et al., 2006; Sims-Robinson et al., 2013). All these features together might deteriorate the information and communication systems in detriment of the organism. For that reason, studying and preventing sensory decline during aging is relevant, not only due to its high incidence, but also because of its detrimental effects on the organisms' health span (Sala-Llonch et al., 2014; Ibáñez-Contreras et al., 2016). The evoked potentials (EP), which denote the cortical responses to sensory peripheral stimulus, have been proved to be a powerful tool to analyze the auditory, visual, and somatosensory pathways in Non-human primates (NHP). The main importance of this method is the opportunity to continuously survey the performance of the nerve elements that might be damaged or altered with age (Ibáñez-Contreras et al., 2016).

A common factor that has been related to decreased neuronal excitability, and reduced electrophysiological activity in the nervous system (NS), along with increased brain damage, is oxidative stress (Yan, 2014; Csiszar et al., 2012; Harman, 1956). Lipid peroxidation (LPX) modifies membrane enzymes, receptors, and proteins within channels, causing alterations in the transport systems, which result in increased ion permeability, thus accelerating neuronal damage (Gonzalez-Fraguela et al., 2000), membrane degradation, and cell death (Bongarzone et al., 1995; Smith et al., 1999; Haynes et al., 2006; Marotti et al., 2010).

It has been assumed that the neurophysiological alterations described above are related to oxidative stress and to the damage to biomolecules during aging. However, there are still very few studies that relate the changes in the sensory pathways neural conduction velocity to the modification of the redox state.

NHP have been used as one of the main animal models to study normal brain aging, as well as neurodegenerative diseases, due to their phylogenetic closeness to humans (Nagahara et al., 2010; Kemnitz, 2011; Toledano et al., 2012; Ibáñez-Contreras et al., 2011a, 2011b). Our group has been working with a NHP healthy geriatric cohort for several years (Solís-Chávez et al., 2014; Hernández-Godínez et al., 2011, 2012, 2014; Ibáñez-Contreras et al., 2011a, 2014a, 2014b, 2016). Therefore, this model offers an extraordinary opportunity to study the normal physiology of brain aging (Hof et al., 2002; Qin et al., 2006; Willette et al., 2010; Kemnitz, 2011; Collier et al., 2011; Castro et al., 2012; Didier et al., 2016).

The aim of this work was to determine the sensory pathways and the brain electric activity, using EP, in a captive population of healthy geriatric Rhesus monkeys (*Macaca mulatta*), and to relate them to the systemic antioxidant enzymatic activity, and LPX during physiological aging. Auditory, visual, and somatosensory EP were measured in male and female Rhesus monkeys from different age groups. Our results showed a delayed electrical activity associated to age; no significant differences were found between genders. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), as well as LPX, were determined from blood samples. Although the enzymatic activity was found to be higher in older monkeys, probably as a compensatory effect, it was not enough to avoid the LPX damage and the delayed electrical activity associated with age.

2. Material and methods

2.1. Animals

Twenty-four Rhesus monkeys (*Macaca mulatta*) were used. The monkeys were housed in captivity in PIMVS facilities (Proyecto CAMINA A.C.), registration number DGVS-PIMVS-CR-IN-1014-D.F./08 at SEMARNAT (Environmental and Natural Resources Secretary). All animals' procedures were strictly carried out according to Mexican Official Ethics Standard NOM-062-ZOO-1999, and were also approved by the Internal Committee of Laboratory Animals Care and Use, as well as the Ethics and Research Commissions of CAMINA A.C. Research Center and APREXBIO S.A.S. de C.V.

The animals were divided into four areas, each area conformed an independent social group to promote animal welfare. The rooms' building materials consisted of concrete floors. All surfaces were covered with ceramic tiles, and the outer walls were a wire mesh, firmly anchored to the walls and floors, in order to provide the animals with a natural photoperiod. The ceilings offered a secure waterproof covering, and the doors were locked to ensure the safety of both the animals and their handlers. Automatic water dispensers and feed tanks were placed outside the walls of each area to avoid food contact with feces and urine.

The NHP were divided into four age groups consisting of 6 animals, each with 3 males and 3 females. Group 1: geriatric monkeys, over 25 years of age; group 2: average age, 20 years; group 3: average age, 15 years; group 4: young monkeys, 7 years old, on average (Table 1). Monkeys were fed according to their corporal weight with Monkey chow Purina 5045® (Monkey Diet 5038, PMI Nutrition International, St Louis, MO) five times a day, and water was available ad libitum.

For individual handling, chemical contention was necessary, so Tiletamine-Zolazepam (Zoletil® Laboratory Virbac Carros, France) 4 $mg \cdot kg^{-1}$ i.m. was used, as reported previously (Ibáñez-Contreras et al., 2011a, 2016). Tiletamine-Zolazepam was used because it offers a higher clinical safety margin for the animals, mainly those in the older groups. Since it is known that dissociative agents and tranquilizers, like the benzodiazepines, generate electrophysiological changes, only a single anesthetic dose was administered intramuscularly for the recording of each sensory pathway. This was done in all cases, and the animals presented palpebral, corneal, pupillary, and swallowing reflexes, as well as segmental reflexes. All animals were sedated using the same anesthetic mixture for their electrophysiological recording, as well as for their blood sampling. The body temperature was kept at 38 ± 1 °C during the whole procedure using a thermostatic mattress.

2.2. Neurophysiological assays

All monkeys included in this study were healthy, without any acute disease noted, as determined by the diagnostic set Pocket Plus LED the Welch Allyn (Welch Allyn Latin America 2500 NW 107th Ave #300, Doral, FL 33172). All animals evaluated had clear optics and a healthy-appearing fundus. Animals showing significant visual problems, or any experimental record that might have altered the results, were not included in the current study. None of the animals used in this study exhibited signs of glaucoma or had any retina pathologies like hemorrhage, macular degeneration or cicatrization. Otoscopic examinations were used in the animals' inclusion criteria. The monkeys' ear channels were not occluded, and none of them had an ototoxic drug treatment history. The animals' ear canals were cleaned of debris when necessary,

Table 1
Population information of the 24 Rhesus monkeys used in this study.

SEX	Group	N	Age range (yr)	Mean	Median
Females	1	3	23.6–27.0	25.4 ± 1.70	25.6
	2	3	18.9–21.4	20.3 ± 1.28	20.7
	3	3	14.5–15.8	15.1 ± 0.65	15
	4	3	6.8–7.9	7.3 ± 0.55	7.2
Males	1	3	24.4–27.8	25.7 ± 1.83	24.9
	2	3	20.4–21.0	20.66 ± 0.30	20.6
	3	3	14.8–16.6	15.46 ± 0.98	15
	4	3	7.3–7.9	7.66 ± 0.32	7.8