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PHYSIOLOGICAL AGING OF THE CENTRAL NERVOUS SYSTEM: LITERATURE REVIEW.

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ABSTRACT

The accelerated process of population aging raises the interest of science for a better understanding of the physiological changes that occur in the human body over time. The central nervous system (CNS) is the biological system most affected by this process, since it is responsible for the command of virtually all functions. The main objective of this article is to develop the scientific content of the Central Nervous System and the degenerative process of neurons, and general structures, occurring during the aging process. This research is justified by observations made in the course of expertise in neuroscience, where I presented a constant interest on the physiological aging process of the human body. The research was conducted in the period from July 2012 to January 2013, where data were collected to describe the aging process, specifically the central nervous system. Preferably, the texts were analyzed from 2000, with some references of the 90s. Despite the small found in the literature regarding the physiological aging central nervous system are clear to biotransformations, resulting from the aging process, resulting in frames cognitive impairment, functional motor.

KEYWORDS: Central nervous system, aging, degeneration.

1. INTRODUCTION

Aging is characterized by a decline in organic functions that causes various modifications throughout the organism, leading to a reduction in the functional capacity of the elderly (MORELLI; REBELATTO, 2004).

According to the National Center for Health Statistics (2008), life expectancy has risen sharply over the last century. There is a projection that around 2030, there will be more people over 60 years of age (22%) than people under 18 years of age (21%). Biological aging is defined as a set of alterations occurring in the human body, in which there is the involvement of all systems: musculoskeletal, cardiorespiratory, neurological and digestive (MENDONÇA, 2006).

These variations are dependent on several factors such as lifestyle, socioeconomic conditions and chronic diseases. On the other hand, the concept "biological" relates to aspects in the molecular, cellular, tissue and organic planes of the individual, whereas the psychic concept is the relation of the cognitive and psychoactive dimensions, interfering in the personality and affection (FECHINE & TROMPIERI, 2012; 2006).

According to the World Health Organization (2015), the average life expectancy1 in the world has increased by 5 years between 2000 and 2015, the highest growth since the 1960s, and now the global average life expectancy is 71.4 years. The increase in life expectancy has revealed the appearance of degenerative deficits and neurological changes that evolve with advancing age (BERNHARDI, 2005).

In Brazil, statistics show that by 2020, the country will have 32 million people over 60 years old (IBGE, 2010). This is a worrying fact, since Brazil will be the sixth country with the largest population of older people in the world until the year 2025 (BRAZIL, 2014).

The accelerated process of population aging raises the interest of science for a better understanding of the physiological changes that occur in the human body over time. The central nervous system (CNS) is the biological system most affected by this process, as it is responsible for the control of virtually all the internal and external functions of the body (CANSADO, 2002). Aging compromises the ability of the central nervous system (CNS) to perform signal processing of sensory systems, which are responsible for maintaining body balance, decreasing adaptive reflex modifications (DORNELES & SILVA & MOTA, 2015).

Due to the importance of the CNS in the human organism (mentioned in the previous paragraph), the main objective of this article is to increase the scientific collection on the CNS and the degenerative process of neurons and general structures during the aging process. And as a specific objective, to describe the main functional and physiological changes occurring during the physiological aging of the central nervous system.

This research is justified, through observations made during the course of neuroscience specialization, where I "presented" a constant interest in the physiological process of aging of the human body; there is a range of scientific research on aging, but few reports and research have the Physiological Aging of the CNS in detail. Based on the problematic raised, this research will give more details, on the subject mentioned above.

The research was developed, from July 2012 to January 2016, where data were collected that describe the aging process, specifically the central nervous system. Texts from the 90s onwards were analyzed, with some older references, from 1987 and 1988, since many articles analyzed emphasized only the most advanced view of the authors cited, neglecting the state of the art history of the subject matter.

The collection took place in a virtual environment, at the bases of Scielo, Lilac and at the collection of the Central Library of the University of Amazonia.

2 FUNCTIONAL AND PHYSIOLOGICAL ALTERATIONS OF THE CENTRAL NERVOUS SYSTEM DURING AGING

In the past, it was rare for people to live longer than 50 years. Thus, we have not developed the use of the brain in old age. Cerebral aging, therefore, is a relatively new phenomenon in human history and evolution (SOUZA, 2002). The natural degeneration of the nervous system should not be confused with dementias or cognitive diseases. For most neurons remain healthy until the individual's death, plus the volume, size, and amount of neurons decrease. This process can lead to a lower speed of impulses, impairing memory and reflexes related to movements (CARTER, 2009).

The physiological changes intrinsic to aging are subtle, incapable of generating any incapacity in the initial phase, although, over the years, they will cause increasing levels of limitations to the performance of basic activities of daily living (ESQUENAZI; SILVA & GUIMARÃES, 2014).

All physiological changes related to the aging process are consequences of changes in the biochemical processes associated with these systems. Biochemical CNS changes lead to physiological changes, both macroscopically and microscopically.

In biological terms, aging is considered a progressive and irreversible manifestation, which structurally and functionally affects the individual. It does not necessarily determine the presence of diseases, but it compromises the body's responses to a homeostatic imbalance, which predisposes to the development of pathologies (MORAES, MORAES & LIMA, 2010).

Several physiological and structural modifications occur in the brain throughout life, they are multifactorial changes, many of which contribute to the loss of strength and imbalance in elderly people and are potentiated when associated with pathological processes (ESQUILINE, SILVA & GUIMARÃES, 2014).

The functional and physiological alterations of aging accompany the morphological changes. Functional decline may be evidenced by the decrease in the rate of work of the individual with advancing age (HOFFMANN, 2002).

In this case, within macroscopic changes of the CNS, we have the macrostructures and their biotransformations.

The Central Nervous System (CNS) is the stimulus, command and response-triggering portion formed by the brain and spinal cord, protected by the skull and spine (STILES, 2000). The brain is composed of three parts (brain, cerebellum and brainstem). The brainstem also has three divisions: mesencephalon, bridge and bulb (GUYTON & HALL, 2017).

In the brain (brain, cerebellum and trunk) are the centers that control from our emotions, our understanding and our language, to those that control our simpler movements. It contains the organs responsible for our sense of smell, taste, sight and hearing (HYFLICK, 1997).

More than any organ the brain has great sensitivity to the oxygen that it receives through the arterial blood, being that its lack produces in very short time serious lesions. Hence the reason cerebrovascular diseases are so important (STILES, 2000).

The spinal cord is a continuation of the final portion of the brain or brainstem and lies within the spinal column and ends at the level of the lumbar region. It contains the nerve fibers that are born in the periphery (skin, muscles and joints, for example) and that carry information to the brain and also the fibers that come from the brain and carry information to the organs, muscles, joints (SCHNEIDER, 1998).

The aging of brain nerve cells (neurons) starts around the age of 30 years. This process leads to a loss of cells with consequent decrease in brain weight (SCHNEIDER, 1998).

The most important changes in aging occur in the brain. The brain decreases in volume and weight. There is a reduction of 5% at 70 years and about 20% at 90 years of age. A certain degree of cortical atrophy occurs, with a consequent volumetric increase of the ventricular system, which is well evidenced by a tomographic study (CANÇADO; HORTA, 2006).

In the macroscopic scope, it is also possible to notice a weight reduction of the encephalon around 1.4 to 1.7% per decade, from approximately 25 years. It is important to emphasize that this weight loss occurs earlier in women compared to men (GARBELLINI, 2007).

An explanation for this event may be related to the decline of estrogen in women from menopause. In rats, estrogen levels are related to dendritic spine density, number of spines and synapses (BERNHARDI., 2005). Erickson et al. (2006) indicate that estrogen levels are associated with neuroprotection, growth and neural function.

In general, the brain volume reduces by up to 200cm³. At 90 years of age, the encephalon is approximately 10% smaller than the age of 30 years. The para-hippocampal cortex suffers volume reduction in about 10% between 40 and 86 years; the lentiform nucleus reduces from 21.4 to 36.8% between 35 and 60 years, and the nucleus caudate 24.6% (STOKES, 2000). In this case, the reduction of the para-hippocampal cortex has resulted in complications such as difficulty in storing new memories.

According to Stiles (2000), there is a decrease in blood irrigation due mainly to the narrowing of the arteries and consequently there is a decrease in cellular function, which leads to a decrease in brain activity leading, for example, the death of several neurons with different functions.

Areas such as the caudate and lentiform nuclei - mentioned above - form the striatum of the nuclei of the base, being responsible for the control of voluntary movement and motor planning, the reduction of these areas may be related to the reduced speed with which the elderly can carry out the movements (NETO et al., 2001).

Reduction of brain mass is associated with neuronal loss, which is not uniform in all brain areas (STOKES, 2000). This loss occurs especially in the cortex of the pre-central rotations, which is the voluntary motor area, and temporal spins also in the cerebellum cortex (RIBEIRO, 1994).

The cerebral white matter is reduced in the anterior parts of the corpus callosum (frontal and temporal interhemispheric fibers), from the age of 65 years. CT scan shows areas of decreased white matter density after 70 years, which may be related to hypoperfusion (GARBELLINI, 2007).

There is also enlargement and increase of the mean volume of the ventricles in 16ml between 18 and 40 years, and 56ml over 61 years (NETTO, BRITO, 2001).

There is also an increase in cerebrospinal fluid volume and changes in the meninges, especially in the arachnoid, where there is fibrosis thickening in the paraassagital area after 60 years. The cerebellum also undergoes weight loss and hypotrophy of the three cortical layers. Finally, there is hypotrophy of the brainstem (PITTELA, 1994). These characteristics are possible evidences of the alterations related to the general functioning, that occur in the organism in the process of aging, disadjusting its homeostasis (STOKES, 2000).

Accompanying this reduction of weight and volume, we observe anatomical changes in various structures of the nervous system. Table 1 presents some of these changes, derived from the advancement of age, relating them to the authors who cited them.

Table 1. Central Nervous System Changes.

AUTHOR/ STRUCTURE	BORGE, HERNÁNDEZ, EGEA (1999)	HAYFLICK (1997)	MORA, PORRAS (1998)	LENT, (2001)	OLIVEIRA (2001)	CANÇADO, HORTA, (2002)
Cortical grooves	Increase	Enlargement	Increase in size	More open and deep	Dilated	Extension and deepening
Convolutions	Decrease	Reduction	Decrease	Thinner	_	Width Reduction
Brain Ventricles	Dilation	_	Increase in Volume	_	Dilated	Extends and increases volume
Brain clefts	_	_	_	_	Wide	Length
Basal Tanks	_	_	_	_	Dilated	Length
White Substance	_	_	Decreases Volume	_	Reduction Generating Leucariose	Reduction Generating Leucariose
Meninges	_	_	_	_	_	Thickening
Perivascular Spaces		–	–	–	Increase in size and quality	–

Sources: Borge, Hernádez & Egea, 1999; Hayflick, 1997; Mora & Porras, 1998; Lent, 2001; Oliveira, 2001; Cançado & Horta, 2002.

The increase or decrease of the brain regions, causes important homeostatic disorders in the aging process. Since each region of the CNS is responsible for the command of a region of the body or a cognitive function. In this case the understanding of the functions of the microscopic regions of the CNS is also necessary because the specific physiological knowledge of the aging process in these areas may be the key to delay some of the discomforts that occur with advancing age.

Lino et al. (2015) points out that among the physiological changes, there is a decrease in brain activity that causes a decrease in reflexes and sensitivity, with a direct influence on the reduction of the intellectual capacity of the elderly, causing changes in attention.

The physiological aging of the CNS, microscopically, results from the normal and gradual loss of nerve cells and / or the gradual accumulation of chemical changes, which results in disturbances of the function of the specific chemical systems (CARVALHO; FILHO; NETTO, 1994).

A normal brain is made up of billions of nerve cells that communicate through neuronal circuits, which generate electrical and chemical signals that are transmitted from neuron to neuron to realize thought, memory and feeling. Among the neurons there are substances called neurotransmitters that help the passage of electrical flow between them (ANDRADE, 1987).

Cell death, neuronal hypotrophy or loss of white matter can be considered as the main causes of the nervous system changes associated with aging. Until the 1950s and 1960s, studies overestimated neuronal loss, but it is now known that this loss is not massive, with many neurons decreasing in size in relation to the reduction of their numbers, and the increase of the population of small neurons (MENDONÇA, 2006).

The loss of neuronal is more evident in the prefrontal cortex, responsible for decision making. There is also a reduction in the number of neurons of 5.4% per decade, from the age of 30, which shows a possible decrease in the capacity to store new information in memory (CARVALHO; NETTO, 1994).

The reduction is also evidenced in the number of synapses, which declines by about 50% in the eighth decade of life compared to the fifth and sixth decades. This synaptic loss is observed in the pre-motor cortex, not occurring in the post-central motor cortex. A compensation mechanism, however, leads to an increase in the extent of the remaining synapses (BRITO, 2013).

Thus, as a result of these alterations, the nerve conduction velocity is reduced, having a decrease of 15% between the fifty and eighty years (HERNÁDEZ & EGEA, 1999).

Among the morphological changes caused by the aging process in the nervous system, changes in dendrites and synapses become relevant due to their importance in the process of formation and maintenance of memory and the arrival of information to neurons (BORGE, HERNÁDEZ & EGEA, 1999). The progressive decrease of the dendritic tree and, consequently, of the synapses, is one of the causes of cerebral atrophy.

This decrease seems to occur in a heterogeneous way (MORA & PORRAS, 1998). However, parallel to neuronal death, a dendritic tree grows. This dendritic increase is a compensatory mechanism known as neural plasticity and it acts more effectively until the seventh decade of life decreasing in the following decades (MORA & PORRAS, 1998; CANÇADO & HORTA, 2002).

Neural hypotrophy is marked by the retraction of the cellular body with reduction of its functional capacity, probably due to modifications in its cytoarchitecture as well as in the transmission capacity (CARTER, 2009).

Cerebral myelin content begins to decline after the age of 20 and, together with the above-mentioned changes and changes in the neurotransmitters, myelin degeneration may lead to a decrease in the rate of neural conduction in the afferent and efferent pathways and difficulty processing in regions of the cerebral cortex where speed is very important. Nerve conduction velocity is 10 to 15% slower in the elderly (MENDONÇA, 2006).

Although this loss seems to explain the propensity for falls as a result of slower input of sensory information into the system, or a delayed motor response time, a connection between deficiency in a part of the system and the total function of the individual has not been proven (BRITO, 2013).

2.1 LIPOFUSCINS

One of the "marks" of aging in the nerve cell is the presence of the lipofucsin pigment, this pigment is also observed in cardiac, liver and striatal muscle cells in paralyzed or immobilized extremities. It results from the perioxidation of the polyunsaturated lipids of the biological membranes (MORA & PORRAS, 1998).

Lipofuscins are residual pigmentary bodies, which accumulate in neurons, glial cells and capillary endothelium, being found in the inferior olivary nucleus, cerebellar nucleus, thalamus nuclei, pale globe, red nucleus, cranial nerve motor nuclei and large neurons of the pre-central gyro (CANÇADO & HORTA, 2002).

These pigments are formed through phagocytosis of cellular constituents (autophagocytosis) that will be polymerized and peroxidized in secondary lysosomes (ANDRADE, 1987). Some of these lysosomes will give rise to such lipofuscin pigments, and the accumulation will occur differently according to the brain region and age. These substances generally begin to form around middle age, in regions such as the motor nuclei of the cranial pairs and in large regions of the precentral gyrus (SILVERTHORN, 2010). The effect of this accumulation is not yet known, and is not necessarily associated with cell death, but could contribute to the cellular degeneration that occurs in the physiological aging process (PITTELA, 1994).

2.2 NEUROTRANSMISSORS SYSTEM

During aging there is a decrease in production, release and metabolism of neurotransmitters, as well as reductions in concentrations of secondary messengers and enzymes involved in cascades of signal transduction (PITTELA, 1994). One of the major causes of cognitive decline over time is this decline. As protein synthesis is affected over time, and the action of neurotransmitters occurs through enzymes and membrane receptors (proteins), changes in neurotransmitters may follow - functional changes (BERNHARDI M., 2005), or results of atrophy and neuronal death (MORA & PORRAS, 1998). Among the enzymes affected are those responsible for sequestering free radicals and regulating calcium homeostasis. Calcium regulates functions such as the synthesis and release of neurotransmitters, neuronal excitability and protein phosphorylation. In the aged brain there is a significant increase of intracellular calcium, ultimately causing cell death (HOFFMANN, 2002). There is also a decrease in the levels of acetylcholine, dopamine and serotonin, gamma-aminobutyric acid (GABA) (Table 2) and endorphins (KHALSA, 1997) on cholinergic receptors (CANADO & HORTA, 2002). Canada and Horta (2002) report that there is a change, but it does not refer either to the decrease or to the increase, which is mentioned by Cançado & Horta (2002). This variation can be explained by the different years of the research and thus, consequent advances in the techniques of evaluation.

Table 2. Transformations in Neurotransmitters.

NEUROTRANSMITTER	AUTHORS	AMENDMENTS INDICATED	REGION
Acetylcholine	KHALSA, 1997. MORA & PORRAS, 1998. CANÇADO & HORTA , 2002	Decreases	Basal Nucleus of Meyert and cortex.
Dopamine	MORIGUCHI, & MORIGUCHI, 1998. KHALSA, 1997. MORA & PORRAS, 1998. CANÇADO & HORTA , 2002	Decreases	Black substance and caudate nucleus
Noradrenaline	KHALSA, 1997. CANÇADO & HORTA , 2002	Decreases Increase	Cortex and locule ceruleus
Serotonin	OLIVEIRA & FURTADO,1999. KHALSA, 1997. CANÇADO& HORTA, 2002	Decreases	Cortex and raphe nuclei
GABA	MORIGUCHI, & MORIGUCHI, 1998. MORA & PORRAS, 1998. CANÇADO & HORTA, 2002. OLIVEIRA & FURTADO,1999.	Decreases	Lower olivine nucleus and caudate nucleus

Sources: **Moriguchi & Moriguchi, 1988; Khalsa, 1997; Mora & Porras, 1998; Cançado & Horta, 2002.**

This reduction of neurotransmitters affects several regions of the brain, especially in the brainstem and in regions where dopaminergic and noradrenergic axons terminate (nuclei of the base, hypothalamus and cerebral cortex) (OLIVEIRA & FURTADO, 1999) and acetylcholinergics (MORA & PORRAS, 1998).

In dopaminergic pathways there is a decrease in dopaminergic receptor density and a significant change in dopamine levels, from the age of seventy-five in the striatum. The pathways present a decrease in acetylcholinergic receptors in the striatum and also the enzyme acetylcholine transferase, responsible for the synthesis of acetylcholine in the cerebral cortex, striatum and hippocampus (MORA & PORRAS, 1998).

Many of these changes are observed both in individuals affected by pathologies and in those where the aging process occurs in a normal way (HORAFLICK, 1997; MORA & PORRAS, 1998; LENT, 2001; CANÇADO & HORTA, 2002).

This point, according to Mora and Porras (1998), is a factor that hinders scientific investigation about the aging process of the nervous system, since it is often not possible to differentiate whether a change is due to aging itself, or to the some concomitant pathology.

2.3 NEURAL AND NARROW FIBER PLATES

The senile plaques, identified just over 100 years ago, are also called neuritic plaques, dendritic plaques and amyloid plaques. They are presented as spherical structures with a central beta-amyloid protein nucleus, located in the external part of the neuron (CANSADO, 2002).

Plates are heterogeneous in shape and composition. Diffuse plaques predominate in the normal elderly and appear to produce no tissue damage (SOUZA, 2002). In contrast, neuritic plaques incorporate neuritic material (axons, dendrites and degenerate synapses), often present positive immunoreactivity for Tau protein, appear to have a neurotoxic effect and predominate in cases of dementia. They are found in large amounts in Alzheimer's disease (GARBELLINI, 2007).

Neurofibrillary tangles, also known as neurofibrillary tangles, correspond to the loss of the normal cytoskeleton of the microtubules and neurofilaments, due to the hyperphosphorylation of the Tau protein (microtubule stabilizer). Consequent changes occur in the cellular functions dependent on these structures (retrograde and anterograde intracellular transport). They have as main component the Tau protein and other proteins associated with microtubules, ubiquitin and beta-amyloid. This is absent in the elderly who do not have dementia (STEVES; DOWD, 1997).

The description of the microscopic changes of the CNS demonstrates the complexity of this human structure, bringing information about biotransformation related to age, of neural components responsible for functions such as emotion, reasoning, memory, among others, related to the behavior of the individual.

In this study we have observed controversies of authors, who report in different years, results of researches without specific definitions. Difficult reliable connections between: structural deficit and function. Therefore, there should be more studies that clearly address how the CNS has aged so that coherent alternatives can be sought to avoid or reduce disorders that affect the independence and quality of life of the elderly.

3. FINAL CONSIDERATIONS

The physiological changes related to the aging process occurring in the central nervous system are part of the process of normal aging senescence due to the passage of time - and do not always mean important physical and social imbalances in the daily life of the elderly individual.

However, it is a fact that 40% of the functional problems affecting aging people are related to the changes and biotransformations occurring in the central nervous system, causing signs such as: difficulty in storing new information and difficulty in performing certain functional movements.

Despite the small literature on the physiological aging of the central nervous system, the approach and the description of the changes resulting from this process are clear, considered as senescence, provoking pictures of decreased motor cognitive and functional capacity and as a general consequence the decrease of the quality of life of individuals in this age group.

It is also concluded from the literature described in authors such as: Hoffmann, Carter, Brito and others, that all complications from aging that affect and cause disorders in the elderly are derived from the dimimution of stimuli and commands from the nervous system central. In this case, methods that could stimulate, neuronal growth, decreased degeneration and increased brain plasticity, could minimize such changes.

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