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Review Article

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The Pathogenesis of Memory and Its Causes

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Abstract

Objective: *to evaluate the memory phenomenon when synchronizing an area of the brain interacting with the external environment.*

Introduction: *Dr. Dale Bredesen estimates that there will be more than 160 million individuals with Alzheimer's dementia in the world by 2050. Amnesia in temporal lobe epilepsy indicates that the hyperactive excitability generated in this temporal lobe impairs the ability to memorize, destabilizing the rhythm in relative to the other brain lobes.*

Methodology*: through literature review it is assessed that there is a working relationship between the region on the cortical side of the brain and the contralateral homotopic cortex.*

Results and discussion: *the types of amnesia are classified in a first group whose organic causes predominate. We must not forget the danger of the accumulation of non-functional proteins that can precede the formation of beta-amyloid aggregates. They replicate more intensely than an infectious agent does, because they do not need genetic material for their multiplication.*

Conclusion: *the first group may also be due to the lack of memory consolidation (sleep disorders, lack of mnemic exercise, malnutrition, infection or other conditions). There is a second group whose psychological causes predominate. Studies on the hormone DHEA (dehydroepiandrosterone) can help improve these neurodegenerative processes.*

Keywords: Alzheimer's Dementia; Amnesia; Dehydroepiandrosterone

Introduction

The neuroendocrine system is related to the environment through categories of synchronization. The preservation of memory is also related to a whole biochemical process proportional to the anti-aging effect. Arnaldo Paiva Neto calls the term "revolutionary pathways" to designate "neuroactive steroids" [1]. Dr. Jay Glaser conducted studies on the hormone DHEA (dehydroepiandrosterone) whose level declines in direct proportion to increasing age [2]. This substance peaks around the age of 25 and falls at an increasing rate to 5% of its maximum around the last year of life. We have a reservoir of DHEA that we are provided at birth, every time we produce adrenaline and cortisol we use a little of that reservoir. DHEA administration is related to the reversal of aging in mice, with anticancer and glycemic control effects in patients with diabetes mellitus. We compare this mechanism to people who look in the mirror and find themselves "older" at times and "younger" at other times. When we talk about vascular dementia, we have to consider the atherosclerotic effects and the degradation of collagen of the layer of the arteries.

We can cite dementia due to vitamin B12 deficiency. Vitamin B12 and folic acid allow the demethylation of methionine, while Tran sulfurization depends on vitamin B6. The oxidative action of aging on DNA is cumulative; however, the rates of antioxidation are changeable according to our lifestyle [3]. The genes that were active during wakefulness resume their activities in REM sleep and there is a process that converts short-term memories into long-term memories: called "memory consolidation" [4]. Many people find it difficult to reconcile the phases from sleep rest to daily activities with the geological and social cycle. Variations in ambient light are passed on to hypothalamic nuclei (brain structures related to so-called "biological clocks") and synchronize changes from day to night with body temperature, food or liquid intake, sexual activity and behaviors that become cyclical in 24 hours. Synchronization occurs between an area or lobe of the brain interacting with the external environment and, for research purposes, we classify this mechanism of synchrony between the nervous system and the external environment as "category 1".

In medical practice, disorders that affect category 1 are exemplified in patients who report irregular "sleep", since they are unable to sleep at the same time because they perceive longer cycles than

24 hours or even because of what we call "poor preparation" to sleep (which requires a dark environment, without noise, comfort and other conditions). Marquioli studies the emotional repercussion that modulates mnemic processes and that occurs in the face of this poor hygiene [5]. During REM sleep, theta rhythm brainwaves between 4 and 7 Hz (related to states of disappointment, frustration or degenerative diseases) are particularly evident in the results of the electroencephalogram. By inhibiting selected pathways during sleep, contextual memory is impaired (such as, for example, remembering where an object was the day before). The genes that were active during wakefulness resume their activities in REM sleep and there is a process that converts short-term memories into long-term memories.

Methodology

We conducted a literature review with the objective to evaluate the phenomenon of memory in the face of synchronization between an area of the brain interacting with the external environment. We must not forget the danger of the accumulation of non-functional proteins that can precede the formation of beta-amyloid aggregates. We based our studies on Dr. Dale E. Bredesen [6]. The hospital experience allowed us to group patients theoretically, between the periods from 2015 to 2019. We know that practice and theory should complement each other, but it is not a simple task to reconcile real issues with the most subjective model of disease. We declare no conflicts of interest; we operate in the Public Health System (SUS) without external financial involvement.

Results and Discussion

Extracellular concentrations of adenosine in the cholinergic region of the basal forebrain increased during spontaneous wakefulness. These concentrations decrease during slow-wave sleep. Progressive peaks occur with prolonged awakening. The basal forebrain (or BF) poses a presence of cholinergic, GABAergic and glutamatergic neurons. All three BF neuronal subtypes project to the cortex and are implicated in cortical arousal and sleep-wake control. The optical stimulation of basal forebrain (BF) cholinergic neurons in mice increases local acetylcholine levels and wakefulness. One of the effects of oxidative stress by adenosine dates back to one of the causes of Alzheimer's disease that relates to low levels of acetylcholine in the brain. Cellular multiplication occurs due to greater replication capacity and lower action of apoptotic mechanisms. Studies have shown that "selective" stimulation of these cholinergic neurons favor the transition between NREM sleep and wakefulness, implicating cholinergic projections to cortex in wake promotion.

Studies by Arnaldo Paiva Neto classify the memorization process as "category 1 of synchronization mechanisms" that is established between occurrences in the external environment and in the organism itself that generates nervous stimuli from them (through the biochemical energy of the impulses nervous) [7]. These stimuli are taken to the central nervous system to be later converted into stored memories. These impulses travel in the fraction of a second, the individual resynchronizes with the new stimuli from the external environment and the delayed remains of the previous stimulus make up the memory. In Alzheimer's disease, the toxic effects of the beta-amyloid peptide may be mediated by A2 adenosine receptors [8]. The deposition of this peptide proliferates more intensely than an infectious mechanism confronting the category 1 synchronization mechanism. It has been found that this substance can produce more of itself without the need for genetic material (a substance known as prions).

Severino (2009) points out another favorable aspect to adenosine, which is the mechanism of activation of A2 receptors contrary to atherosclerosis. In addition, researchers argue that the substance is important immunomodulatory agent. Vitamin "Q10" also known as "ubiquinone oxidoreductase" has been used to reduce the α-tocopheroxy radical to α-tocopherol. In this logic, coenzyme Q10 inhibits the incorporation of the free radical into the fatty acids of the cell membrane: a phenomenon known as "lipid peroxidation" or "lipoperoxidation". In this way, it avoids the destruction of its structure that would culminate in apoptosis. Examples of free radicals include superoxide radicals and hydroxyl groups, which are highly reactive and unstable. In nanoseconds, they trigger reactions that damage biological components [9]. Loscalzo adds that reactive oxygen species can initiate the lipoperoxidation process on the surface of endothelial cells and that they are related to a variety of diseases that involve oxidative stress (such as Alzheimer's disease).

There is a synchronized activation of different brain regions that interact, acting together in the face of certain physiological functions. By convention, we can call this operation together as "category 2 in the classification of synchronization mechanisms". In focal epilepsy in which a location in the brain has an electrical discharge more intense than normal and which makes its activity much more differentiated than in other areas, the pathological mechanism refers to "marked loss of synchrony of brain areas with each other". In medical practice, it is common for pathophysiology to compromise both categories of synchronization to varying degrees and mixed patterns. For theoretical purposes, we systematize the Chrono biological hypotheses according to the predominance of the main pathways that generate the considered phenomena.

Depression points to hypoactive or less stimulated areas compared to hyper synchronized discharges observed in juvenile myoclonic epilepsy, in which Rayleigh's analysis showed a difference in activity and temperature acrophases [10]. Category 2 of synchronization can suffer impairment in depressive disorders in which there is a reduction in REM sleep latency and cholinergic hyperactivity, according to Nofzinger [11]. In contrast, in Alzheimer's dementia there is a reduction in the period of REM sleep and cholinergic hypo activity, according to Cook [12]. Both diseases reflect in desynchronized patterns of activities in brain areas that require more harmony in the sequential process of proper functioning and sufficiently optimized to promote better integration of the nervous system with the other systems of the human organism. Precisely this debate is opened by Silveira, when the existence of the timer system that integrates the central nervous system [10].

We grouped the patients into two groups: 1. Patients with dementia by secondary causes and; 2. Patients with dementia by primary causes. Among the reversible dementias (secondary or pseudo-dementia), we consider vascular causes (post-stroke or ischemic microangiopathies), depression, hypothyroidism, vitamin B12 deficiency (after bariatric surgery, atrophic gastritis or intestinal inflammation), infections (neurosyphilis or HIV), illicit or even licit drugs (such as benzodiazepines, clonazepam), trauma with complications, and normal pressure hydrocephalus (dementia, apraxia and urinary incontinence). Irreversible dementias derive from origins such as Alzheimer's disease, Lewy body disease, parkinsonism, frontotemporal disease (early atrophy and neuronal loss). Dr. Dale E. Bredesen compared the 36 different factors that cause Alzheimer's disease with 36 holes in a roof of a building. In

the brain structure, there are multiple damaged areas diffusely like the roof of the damaged building (since we are not considering a focal pattern of disease).

Arnaldo Paiva Neto affirmed that we could classify the types of amnesia into two large groups: in the first group, organic causes predominate, and in the second, psychological causes prevail [13]. Forgetfulness by organic causes (in turn) can be divided into two distinct subtypes: "subtype A" which refers to structural (vascular, trauma, ischemic, neoplastic, chronic infectious, severe TBI and other sources that damage the marks of the memories formed in a certain location in the Central Nervous System or CNS). Such a marker consists of the formation of protein complexes by biophysical and biochemical changes imprinted on the nervous tissue (called "engrams"). Still for organic causes, there is the "subtype B" of amnesia that refers to the lack of memory consolidation (due to sleep disturbances, lack of mnemonic exercises or malnutrition or deficiency states, depression, state of acute confusion or delirium, convulsions, acute infections, mild TBI and other pictures with insufficient stimuli for memory consolidation, with a greater chance of being reversible, even before the respective engrams were formed). The aging process (by itself) already leads to decreased vision and space skills, decreased numbers of neurons, synapses, receptors, cortical volume, metabolic rate, and blood flow.

Arnaldo Paiva Neto calls the term "category 3" referring to the hormonal variations by function of the glands that interact with the nervous system [14]. The daily stress represented by cortisol peaks sabotages our ideal functioning. Faced with constant changes in cortisol levels, we consider adaptogenic medications that revert the aging process and apoptosis. From the vascular point of view, the use of acetylsalicylic acid, beta-blockers and calcium channel antagonists stands out. Some scientists have studied revolutionary pathways of pharmacological action. We call these pathways a "21st-century tripod": based on "neuroactive esteroids", "neurogenesis" and "anti-tumor", as example ixolaris that blocks primary tumor growth and glioblastoma angiogenesis (still in the studies). Arnaldo considers the conclusions: there is an inhibitory influence of corticosterone on the expression of PSA-NCAM; PregS enhances neurogenesis through the expression of PSA-NCAM (in the hippocampal region); AlloP produces an effect opposite the mechanism of action of PregS, reducing hippocampal neurogenesis. However, AlloP favors the effects of decreased neuronal death after traumatic brain injury [13].

Conclusion

Based on Holecek, our medical practice made it possible to reaffirm that supplementation with nutrients for a period of 35 days can reverse the oxidative stress [15]. Glycosylated hemoglobin values decrease in diabetics supplemented with antioxidants. In clinical practice, we gain improved metabolic control. We corroborate the "trophic signals" needed to delay the symptoms of amnesia. Protein molecules produced within neuronal cells are transported to their surface (on the plasma membrane). Receivers are formed. These bind to molecules of substances called "neurotrophins", especially in the area of the basal forebrain. Synaptic strengthening compounds include "brain derived neurotrophic factor" (BDNF), which is a neurotrophin that promotes neuronal survival. This action may be increased by regular exercise, vitamin D, folic acid, "neuroactive" steroids (e.g. dehydroepiandrosterone or DHEA) and docosahexaenoic acid or DHA.

There is an evidence that bone marrow cells migrate to white matter, hippocampal neurons and cerebral cortex participating in tissue regeneration, primarily linked to memory formation [16, 6]. Dr. Dale E. Bredesen realized that the receptor without the trophic linker induces cells to die. While the presence of a ligand bound to P75NTR completely disables the suicidal cell mechanism. In such a way, the complex "key and lock" occurs [17, 18]. That is, "addiction receptors" culminate in neuronal death (when beta-amyloid meets exactly the "antitrophin" criteria). The structures of the Lewy bodies may also exert the "antitrophin" function. There are hyaline centers surrounded by light halos, normally observed in black matter neurons (which explains parkinsonism) and in neurons of the locus coeruleus (which is related to negative emotions and is influenced by noradrenaline). Presynaptic alphasinuclein is suspected to be the major involved in the formation of these corpuscles, which also exert neurotoxic effects and undergo strong genetic influence [19-23]. There is greater benefit for individuals with Lewy body associated disease with the use of acetylcholinesterase inhibitor medications.

There is a complexity related to the accumulation of substances like adenosine that act indirectly in mechanisms of gene activation or gene repression. In mammals, there is also the mechanism called "dose compensation", in which one of the X chromosomes is inactivated in the cells of female mammals. Therefore, oxidative and antioxidative reactions present cumulative product dynamics that allow advances and regressions in the gene manifestations. The aging process itself is not constant but varies according to biochemical and hormonal conditions. We suggest that there is a relationship between "serum DHEA levels / serum cortisol levels" that can be used to correlate with quality of aging, as well as in neurodegenerative diseases.

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