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Mini Review

An Overview of the Links between Behavioral Disorders and Alzheimer's Disease

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Abstract

Cumulative evidence shows that innate immunity participates in the pathogenesis of Alzheimer´s disease. This implies that activation of microglia by the so called "damaged signals" triggers a cascade of pathological molecular events thus leading to hyperphosphorylation and oligomerization of the tau protein in the brain, which is associated with cognitive impairment and loss of memory. However, from the pathophysiological point of view, Alzheimer´s disease is significantly more complex in inducing the loss of memory. As initial events in the pathogenesis of this neurodegenerative disease, alterations in the dopaminergic pathway together with serotonin depletion in the elderly lead to late onset depressive phenomena according with recent evidences. These events seem to occur prior to neuroimmunomodulatory alterations that lead to a final oligomerization of tau protein in the course of neurofibrillary tangles formation. It is critical to analyze both affective disorders and mood changes with the cognitive impairment in the context of Alzheimer´s disease.

INTRODUCTION

Neurodegenerative disorders including Alzheimer´s disease (AD), constitute a major puzzle to medicine and society when considering their progressive incidence and impact in public health, and the slow progress in searching for diagnosis and therapeutic approaches [1]. Fortunately, significant advances have been achieved about their pathogenesis and the alterations in the signaling pathways involved in communication between glial and neuronal cells in the brain [2,3]. Important information exists on the storage of cognitive information, processes underlying human cognition and acquisition of memory. In AD, for example, the neuroimmunomodulation theory largely explain the sequence of events derived from innate immunities that lead to tau oligomerization and formation of paired helical filaments and tangles [2].

However, Alzheimer's pathology involves changes not only in memory but also emotional events such as empathy, mood, humor, which appear to integrate well with cognitive processes [4]. In this context, experimental evidence supports the existence of molecular/cellular alterations in sophisticated pathways of molecular connectivity between the dopaminergic cortex and dopamine release with the functional organization of the hippocampus [5]. On the basis of these reports and the multifactorial origin of AD, we hypothesize that behavioral disorders is an important step of the early pathological alterations associated with the symptoms of AD. Here, we briefly reviewed the structural and cellular basis for the functional connections between emotional and cognitive phenomena and their pathological alterations in AD.

ALZHEIMER´S DISEASE AND MOOD DISORDERS

AD has been associated with loss of memory, which is regarded as a main feature and trait of the disorder. However, such non-cognitive symptoms as anxiety, apathy, psychosis, depression appear to be involved in the AD. These disorders negatively affect the life quality of patients and caregivers [4-6]. Moreover, neuropsychiatric symptoms can be present in 80% of AD patients, and the depression is the most frequent alteration among them, with a prevalence of 50% of cases [7]. Controversial evidence, due to the diversity of the design of the studies and the difficulty for distinguish between AD and depression, does not allow a consensus to ascertain if the depression is just a risk factor, and an early event in AD progression [8,9]. In fact, studies show a higher presence of neurofibrillary tangles (NFTs) and senile plaques (SP) in the hippocampus of AD patients with a

history of major depression, compared with AD patients without a depressive background. Besides, there is an increase in NFTs and SP of *post mortem* AD brains that present comorbidity with depression, as compared with those without the neuropsychiatric component [10,11].

On the other hand, patients suffering from depression have showed hippocampal atrophy [12]. In this context, late stage of depression and AD share mutual genetic factors, including the involvement of BDNF, ApoE, IL-1, and methylenetetrahydrofolate reductase (MTHFR), while inflammatory pathways are activated in both disorders [13,14]. Depressive episodes are influenced by dopamine and reduction of serotonin in brain, while AD has been associated with loss of serotonergic neurons and a reduction in the levels of 5-hydrotryptamine (5-HT) of post mortem brains with this disease [15,16]. As it was suggested by Butzlaff and Ponimaskin [17], serotonin receptors 5-HT4R, 5-HT6R and 5-HT7R, could modulate the activity of two essential proteins in tau phosphorylation: GSK-3β and CDK5 respectively, which could lead to NFT formation, triggering microgial activation according with the neuroimmunomodulation theory [2,18,19]. Furthermore, Yun et al. [20], showed that an antagonist of 5-HT6R is capable of rescue memory deficit and attenuate the expression levels of astrocytes and microglia in an AD mouse model, sustaining the role of serotonin in degeneration and microglial activation. Concomitantly, dopamine production is deeply reduced in brains of AD, as well as the levels of its receptors [21]. In addition, it has been recently determined that the loss of dopamine affects memory dysfunction in a transgenic mouse of AD [22]. Because AD has a multifactorial pathogenesis, we hypothesize that depression is an important step of the early pathological alterations which are associated with the symptoms in AD. In a healthy brain, dopamine is continuously released to the hippocampus, which connects mood feelings with cognitive processes [23,24]. In AD, a decrease in the dopaminergic levels plus a serotonin diminution would trigger depression which is regarded as a prodromal symptom of AD. In this context, the alterations generated by late onset of depression appears to have an impact on the hippocampus, thus inducing the inflammatory events, activating microglial cells that trigger overproduction of pro-inflammatory factors, as described in earlier time about the conceptual scheme of our neuroimmunomodulation theory [2,3,18].

CROSS-TALKS BETWEEN THE DOPAMINERGIC CORTEX AND THE HIPPOCAMPAL NEURONS

As mentioned about the links between the release of dopamine in the dopamine areas and the neurons from the hippocampus, both brain areas appear to be functionally interconnected. Within a mind-brain perspective, this means a bridge between the brain substrate for emotions and the substrate for rational processes. Recent studies pointed toward deep brain stimulation (DBS) in the medial forebrain bundle, which is associated with the reward system, in order to promote an improvement in a depressive-like rat model. They were capable to obtain not only an anti-depression response but also an increase of dopamine D2 receptors and dopamine transporters, in the areas of the hippocampus and the pre-frontal cortex [25]. These findings suggest a functional mechanism of the dopaminergic system in behavioral disorders of the hippocampal area, which is the primary structure affected by the neuroinflammatory mechanisms triggered by "damage signals" in AD, in agreement with the neuroimmune modulation theory [2,3]. The frontal cortex is also reported as a zone affected in cognition disorders. In this region, the blockade of D3 dopamine receptors has been associated with pro-cognitive activity in rodents and primate models and proposed as a possible therapy for AD [5,26,27]. In the meantime, it seems that improvement in cognition processes is related to cAMP/PKA/CREB signaling in the hippocampus, which also presents D3 receptors [28-32]. In fact, knockout mice for D3 receptor present an improved spatial memory and an increased CREB phosphorylation in the hippocampus, suggesting an enhancement in memory consolidation [33]. Other brain regions which constitutively express D3 receptors, seem to regulate memory processes, attention, emotions, motivation and reward. Neurons projecting their neurites from the nucleus accumbens (NAc) are enriched in D3 receptors and are innervated by dopaminergic neurons from the ventral tegmental area (VTA), which in turn, also receive NAc projections. Moreover, NAc processes reach the entorhinal and PFC and, receive projections from the cortex, hippocampus and the amygdala [34]. In other AD models, dopamine has been a target for the enhancement of memory tasks and the control of the associated cognitive impairment. In 2012, Guzman-Ramos and their collaborators [35] performed the microdialysis of dopamine reuptake blocker in cortical and hippocampal regions of a triple transgenic mouse model of AD (3xTg-AD). Moreover, cortical release of this neurotransmitter specifically in the insular cortex was able to attenuate the memory and cognitive impairment [35]. Furthermore, a recent study indicated that the gradual loss of dopaminergic neurons in an AD mouse model (Tg2576) characterized by memory and reward dysfunction [26]. It is known that dopamine D1 and D2 receptors are expressed in specific hippocampal areas, suggesting their role together with acetylcholine in memory processes [36,37]. More interesting D2 receptor antagonists have been proved as neuroprotective agents against tau toxicity and its aggregation [38] (Figure 1).

These observations seem to be connected with a series of evidence linking electric and magnetic induction in some regions of the brain, not only with the emergence of a minimal stages of consciousness or vegetative state but also with differential levels of serotonin and dopamine agents [39-42]. Previous reports have linked the dopaminergic system with brain damage and cognitive disorders [43-45].

DOPAMINERGIC SYSTEM IN BEHAVIORAL DISORDERS AND AD

According with the ideas outlined in the precedent paragraphs, an important cross- talk exists between the dopaminergic pathway involved in mood activities and neurons from the hippocampal domain and entorhinal cortex. Research shows that behavioral and mood disorders have been associated with AD phenotypes. In 1993, Rohling and Scogin [46] reported the correlative effect between depression and memory deficiencies. Today, we know that there are many reports with data related to the same phenotypes, giving us insights on the possible effects of the early AD event in behavioral or mood disorder conditions

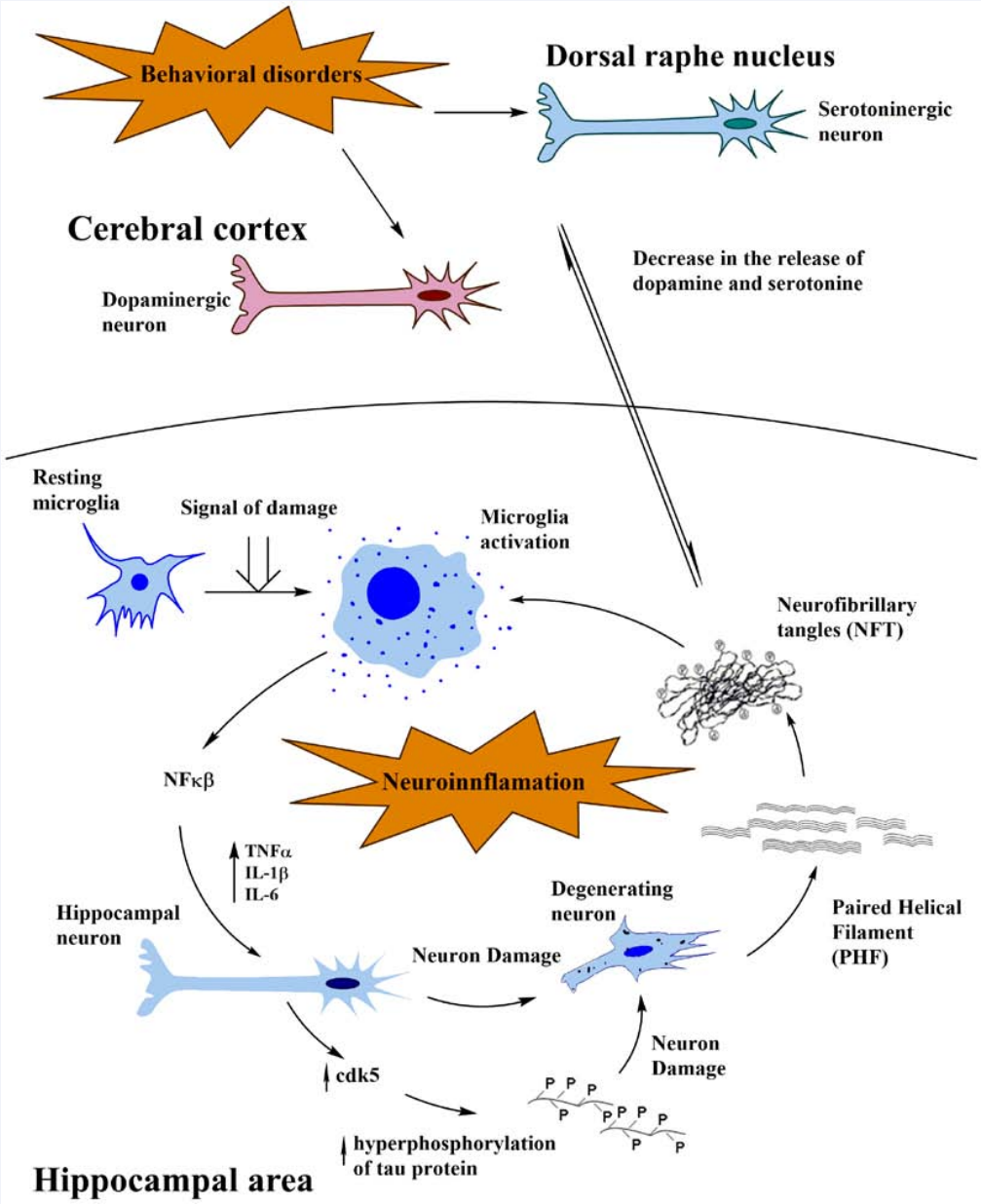

Figure 1 Schematic representation of concerted action of dopaminergic/serotonergic decrease-neuroinflammation hypothesis on Alzheimer´s pathogenesis. Molecular and cellular events occurring at the dopaminergic area and dorsal raphe nucleus, linked with behavioral and mood alterations results in dopamine/serotonergic reduction. This event appears to activate the neuroinflammatory cascade at the hippocampal level, by stimulating microglial cells and as a consequence, promoting the release of pro-inflammatory factors that in turn activate protein kinases such as CDK5, tau phosphorylation, oligomerization into paired helical filaments and neuronal death. This may explain that late depression involving decrease in dopamine and serotonin decrease occur as early events, prior to deregulation of microglia-neuronal cells cross talks and activation of the neuroinflammatory cascade.

[47]. Since we have linked the hippocampal deterioration with a compromised behavioral state and mood disorders, it is interesting to pay attention to the evidence of the involvement of the glutamate system. Recent research has suggested ketamine, as a glutamatergic promoter, aimed to improve depressive or bipolar conditions [48].

Altogether, these reports suggest the importance of several neurotransmitters related to the interest regions in AD, indicating a paramount cross-talking between these neurotransmitters and functions such as memory, behavioral and cognition affections. It has already been shown that the progress of AD associated with neuronal death processes are preceded by pathological tau aggregation [2]. Therefore, the greatest interest from the therapeutic point of view is to search for compounds being capable of interfering with abnormal tau aggregation, as well as compounds that have a neuroprotective capacity, in order to ameliorate the degree of injury and prevent continuous cell damage. These studies on the connectivity between the

dopaminergic pathway and the hippocampal area will be critical in the search for therapeutic solutions for AD.

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