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Review

Behavioral and Neuropsychiatric Disorders in Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is the most frequent type of dementia in the elderly, severely affecting functional and executive skills of subjects suffering from this disease. Moreover, the distress of caregivers as well as the social implications constitute a critical issue for families. Furthermore, cognitive impairment, along with behavioral disorders and neuropsychiatric symptoms are characteristics of AD. Although these are present with variations in prevalence, intensity, and progression, an important core of them is visible before cognitive impairment, especially depression and apathy, which affect at least 50% of patients. The most updated literature shows that depression and/or behavioral and neuropsychiatric symptoms (BNS) are part of the initial phase of the disease rather than just a risk factor. Thus, mood disorders are associated with anomalies in specific brain regions that disturb the normal balance of neurotransmission. This in turn is linked with an inflammatory pathway that leads to microglial activation and aggregated neurofibrillary tangle formation, finally triggering neuronal loss, according to our neuroimmunomodulation theory. Altogether, inflammation and tau aggregation are observed in preclinical stages, preceding the BNS of patients, which in turn are exhibited earlier than cognitive and functional impairment detected in AD. This review is focused on the latest insights of cellular and molecular processes associated with BNS in asymptomatic early-onset stages of AD. An important medical research focus is to improve quality of life of patients, through prevention and treatments of AD, and the study of behavioral disorders and early event in AD pathogenesis has a major impact.

Keywords: Alzheimer's disease, apathy, asymptomatic stages, behavioral disorders, neuroimmunomodulation, neuroinflammation, neuropsychiatric symptoms

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder, characterized by progressive neuronal loss and cognitive impairment [1–4], is the most frequent type of dementia worldwide, affecting the life quality of patients and their families [5, 6]. For this reason, AD is nowadays a relevant issue in global health policies with a profound economic impact in society [7]. AD is considered as a late onset disease, being identified around 65 years old and, existing very few cases associated to hereditable mutations (2–10%), hence being mostly sporadic [6]. The mechanisms that trigger AD are not fully elucidated, however there are two pathologic hallmarks of AD; the presence of extracellular plaques of amyloid-β (Aβ) peptide of 39 to 42 amino acid residues, and the formation of intracellular paired helical filaments (PHF) and neurofibrillary tangles (NFT), composed of hyperphosphorylated tau protein [8–10]. By means of

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imaging and cerebrospinal fluid (CSF) technology, these marks have been observed even 15–20 years before clinical or symptomatic phases [11, 12]. One of the most compelling theories in AD is the unifying theory of neuroimmunomodulation, which point to persistent microglial activation that lead to microtubule destabilization, damage in axonal transport, synaptic alterations and finally neuronal death. In turn, this causes the accumulation of pathological tau on the extracellular space after its liberation, which would cause the reactivation of microglia, exacerbating the cellular damage [13–16]. Recently, it has been determined that a necroptosis pathway lead to neuronal loss in a mice model of AD, as evidenced by using biomarkers observed in postmortem brains of AD patients, process that has been attributed as a result of inflammation, although it has not been fully elucidated [17]. Besides, necroptosis has a relation with phosphorylated tau, but not with Aβ markers, supporting the importance of altered tau protein as trademark of the disease [17, 18]. The progression of symptoms of AD is not completely characterized, mainly because the use of different scales, the subjectivity of caregiver's inquiries and other tools, added to the diverse nomenclature used in literature, becoming difficult to find a "standardized" description of general symptomatology. For research purposes, the National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines, suggest the classification of AD on three recognizable stages: preclinical, mild cognitive impairment due to AD, and dementia due to AD [1, 19, 20]. On the other hand, through diverse scales as Mini-Mental State Examination (MMSE), Clinical Dementia Rating Scale (CDR), Global Deterioration Scale (GDS) and others, the symptomatic stages of AD have been clinically classified in general terms as middle, moderate and advanced dementia, according to severity of symptoms. Similarly in AD has been recognized a preclinical stage without identification of cognitive or executive damage in subjects with a high probability of developing dementia of AD type [21–23]. Thus, the evidence shows that at least, it is possible to differentiate between a preclinical or asymptomatic stage in AD, and a clinical or symptomatic phase [21, 24], which can vary according to every AD subject, due to his own medical history, comorbidity, and demographic origin [25]. In this context, this review will explore mainly the preclinical or asymptomatic stages and the onset or early phases of AD.

Although, there are variations depending of patients, cognitive and functional damage is clearly described in the development of AD, as a gradual and progressive deterioration in at least two cognitive or functional aspects, such as agnosia, aphasia and apraxia, and the capacity to elaborate a plan, including the evident impairment in working or episodic memory [26]. Otherwise, BNS are variable and sporadic throughout the disease [26, 27], but an important group of them are present at early stages, before the clinical diagnosis of cognitive impairment, as will be described below [28–30]. Then, we can turn to the current knowledge of cellular and molecular insights on preclinical and onset stages of AD, mainly associated to the BNS, as a useful and necessary target. This approach may help to find mechanisms to improve quality of life of AD patients and their caregivers, and as a key point of research to prevent or treat effectively the disease.

BEHAVIORAL DISORDERS IN ALZHEIMER'S DISEASE

Behavioral alterations are common at different stages of AD and other neurodegenerative diseases, reaching 80–90% of prevalence [31, 32]. Reports have catalogued the disruption in conduct and mood with different terminologies, but according to the most integrative nomenclature, we will refer to behavioral and neuropsychiatric symptoms to mention the heterogeneous group of cognitive disturbances exhibited in AD patients and other dementias. AD encompass a broad spectrum of BNS, that are often present with more than one symptom together, observing in 50% of patients at least four of them at the same time [33–35]. Considering the difficulties to differentiate between them, non-standardized scales, and the subjectivity of assays, authors has tried to unify and compile the prevalence of the most observed BNS in AD, establishing that the most frequent BNS are apathy and depression [22, 36–40]. AD subjects also show agitation and aggressiveness, anxiety, sleep disturbances, delusion, and in a minor rate, hallucinations, appetite changes and euphoria (see Fig. 1) [22, 36, 37, 39, 40]. Apathy, the loss of interest or motivation, is the most common BNS documented in AD, increasing it frequency through the progress of disease, from 42% in early stages to 90% in severe AD [41]. Apathy has been associated with high levels of tau and phosphorylated tau in CSF of AD patients, and correlated with NFT burden in the anterior cingulated cortex of postmortem AD brains, but not whit senile plaques (SP) [42, 43].

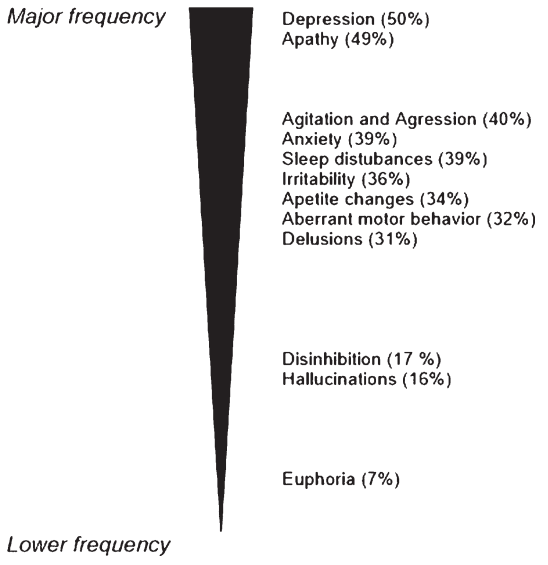


Fig. 1. Behavioral and neuropsychiatric symptoms in AD.

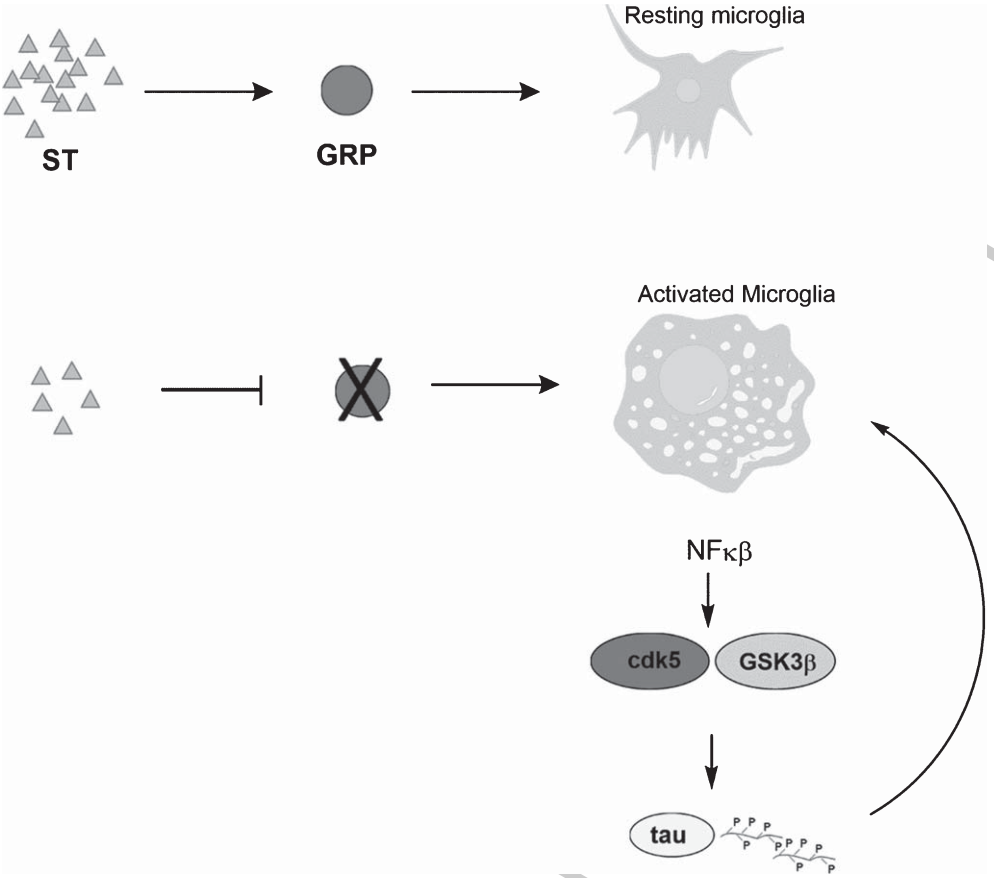
Previous background has been related to atrophy of temporal cortex, besides of dopaminergic disturbances in preclinical prodromal AD [44, 45]. Apathy can also be experienced together with depression [46]. Depression is vastly documented in AD, and its prevalence is variable, but reach 50% of prevalence in AD subjects [47], being one of its prodromal symptoms [29]. Patients with AD and depression, shows stronger presence of NFT and SP in postmortem brains, atrophy in hippocampus and alterations of serotonergic pathways, as will be discussed below [40, 48–50]. Besides, a correlation between alterations in executive functions and the severity of depression and anxiety has been observed in patients with mild cognitive impairment (MCI), who can turn into an AD. In the meantime, subjects that present MCI together with anxiety, defined as the excessive apprehension and feeling of foreboding [51], show a correlation between this symptom and the concentrations of $A\beta_{42}$ peptide and total tau protein in CSF [52]. Meanwhile, agitation and aggression, noticed as an excessive motor activity associated with feeling of inner tension and physical and verbal insults, by screeches, strikes and nibbles, respectively [30, 51], has also been associated with higher levels of phosphorylated tau in postmortem AD brains and CSF [53, 54]. Besides, a correlation exists between $A\beta_{39\text{-}42}$ marker in CSF and the level of aggressiveness in AD patients [55]. Sleep disturbances, are noticed in 25% to 50% of AD population, often before of cognitive impairment [56], and are considered together with appetite changes one the most influential causes of institutionalization [57]. Similarly, delusions and hallucinations, classified as psychotic symptoms, are frequently related with the caregiver distress [51, 58], even, correlating with a faster cognitive deterioration and an increment in mortality [59, 60]. In addition, there is an increase in SP, NFT, and higher levels of phosphorylated tau, also being associated with diminution in serotonergic system [61, 62]. A longitudinal study with cognitively normal subjects who later develop diverse grades of dementia with AD, showed that BNS appear in three differentiable periods, starting with irritability, depression and sleep disturbances, followed by apathy, anxiety, agitation, appetite changes and other phases, including delusions, hallucinations, and aberrant motor behavior [29]. Coincidently, depression and apathy have been usually documented in early stage of AD, while delusions and hallucinations, are present preferably in moderate and advanced stages of the disease [30, 38]. The intensity of BNS increased over the time, however these are variable and episodic [22], and BNS have been directly associated with a diminishing in survival rates [63]. Severity of BNS has a correlation with cognitive and functional impairment in patients with AD [22, 37, 40, 64], even though this is controversial. A non-linear relationship between the BNS and cognitive decline has been found [65]. Nonetheless, AD subjects show a faster deterioration of BNS when the CSF markers has been detected in preclinical stages of disease [29, 66]. Thus, updated and considerable evidence shows that BNS are part of early stages of AD, correlating with pathological marks, and preceding the cognitive impairments [28, 29, 36, 67].

NEUROINFLAMMATION AND BEHAVIORAL DISORDERS IN ALZHEIMER'S DISEASE

The innate immune cells, microglia and astrocytes, are the mediators of inflammatory pathways on central nervous system (CNS) [68–70]. Particularly, participation of microglia and inflammation in the pathogenesis of AD has been well established [13, 70–75]. Neuroimmunomodulation theory proposed that a persistent activation of microglia lead to neuronal damage and death, producing the release of pathological tau toward the extracellular environment, which trigger in turn the microglial activation, promoting thus a feedback mechanism that generate

a continuous cellular damage. Microglial activation causes the generation of nuclear factor-κβ (NF-kB), sparking the expression and release of proinflammatory cytokines, leading to an increase of activity and expression of serine-threonine kinase glycogen synthase kinase 3beta (GSK-3β), and cyclin-dependent kinase 5 (CDK5) proteins, which phosphorylate the microtubule-associated protein tau. This affects tau normal function, and leads to NFT formation in AD [13–15, 71, 74]. Two morphologic and functional aspects of microglia have been shown in neurodegenerative diseases, starting with an adaptive reaction aiming at restoring brain integrity and becoming in injurious process through chronic inflammation [72, 76–78]. The neuroimmune role and neuronal link is supported by genetic changes and epigenetic signals conserved in mouse and human, and corroborated by recent genome-wide analysis (GWAS) and other "omics" findings [79, 80]. In AD mice, microglia and complement mediate the synaptic loss in early stages of the disease, prior to Aβ deposition [81]. It has been previously established that inflammation, has a correlation with cognitive decline in patients with AD [75].

Regarding BNS and microglia, activation of the later has been related to a deficit in social interactions [82]. Meanwhile, inflammation markers have been correlated with depression, neurological symptoms and chronic behavior, in patients with traumatic brain injuries as compared to control groups [82, 83]. Last year, a novel GSK-3β inhibitor, was able of reduce inflammation and improve the cognitive and social alterations in a 5XFAD AD mouse model [84]. Alike, apathy, anxiety, depression and agitation in AD were associated with an increase of systemic tumor necrosis factor α (TNF-α), detected in serum of mild to severe AD patients [85, 86]. The group of Holmgren et al. [87], found an association between the levels of diverse cytokines present in CSF of patients with dementia, discovering that anti-inflammatory interleukin-10 (IL-10) cytokine levels were inversely proportional to neuropsychiatric inventory (NPI) scores of agitation, depression and sleep disturbances. Thus, prompting a protective role of it, while the soluble IL-1 receptor type II (sIL-1RII) levels show correlation with apathy symptoms. In the specific group of AD patients, IL-6 levels presented an inverse correlation with anxiety [87]. The delivery of agents that promote the activation of microglia in humans, like lipopolysaccharide (LPS) or endotoxins, trigger behavioral and mood changes, specially depression, which correlates with high levels of proinflammatory cytokines in blood [88, 89]. In a similar way, overexpression of interleukin 1beta (IL-1β), deletion of microglia-specific fractalkine receptor (CX3CR1), and LPS administration, have shown to exacerbate the tau accumulation in AD mice [90–92]. While LPS administration in rats, induce microglial activation and depressive behavior, the effect can be prevented by selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) [93–95]. As will be described in the next paragraphs, the serotonergic signaling has been previously documented to be involved in depression and mood disorders associated to AD [67, 96, 97]. Importantly, a recent research found that depressive behavior triggered by intracerebroventricular injections of Aβ oligomers in mice, is mediated by inflammation through microglial cells activation in hippocampus, decreasing 5-HT levels in hippocampus and prefrontal cortex [98]. Thus, a link between serotonin decrease and inflammatory factors released by microglia, has been clearly established in AD [98]. We propose a possible mechanism (please refer to Fig. 2) that would explain the indubitable but still enigmatic relationship between serotonergic neurotransmission, inflammation and BNS in AD, supporting even more that depression and BNS are part of the disease [28, 29, 36, 67]. Besides, the microglial activation in early stages of AD has been described. Recently, a new trial of AD patients, using the microglial activated marker 18F-DPA-714 together with amyloid imaging positron emission tomography (PiB-PET), demonstrated that microglia is active in prodromal and early stages of the pathology in the temporal-lateral cortex, suggesting a protective role [99]. Moreover, a microglial marker, which triggers the receptor expressed on myeloid cells 2, sTREM2, was found highly expressed in CSF of early symptomatic stages AD patients, also correlated with an increment of CSF total tau and phosphorylated tau. These findings were previously demonstrated in a cross-sectional multicenter study [100]. Altogether, Aβ deposition, tau hyperphosphorylation, microglial activation and inflammatory signals are observed in AD patients before "clinical diagnosis", and could explain the development of BNS on early stages of disease. Markers that documented the disturbances of serotonin *in vivo* in preclinical or early stages of disease, are suggested to corroborated this possible mechanism, but recent evidence show that serotonin transporters are effectively decreased in cortex and limb in patients that suffer MCI in comparison to healthy subjects [101].



Considering this context, experimental evidence supports the existence of molecular/cellular alterations in sophisticated pathways of molecular connectivity, mainly between the cortex/thalamus and dopamine/serotonin release with the functional organization of the hippocampus in AD [102]. On the basis of these reports and the multifactorial origin of AD, there has been already published that behavioral disorders are an important step on the early pathological alterations which are associated with AD symptoms. This review the structural and cellular basis for the functional connections between emotional and cognitive phenomena and their pathological alterations in AD [67].

MOLECULAR AND FUNCTIONAL LINKS BETWEEN BEHAVIORAL DISORDERS AND ALZHEIMER'S DISEASE

Patients suffering from depression have showed hippocampal atrophy [103]. In the same way, late stage of depression and AD share mutual genetic factors, including the involvement of brain-derived neurotrophic factor (BDNF), Apolipoprotein E (ApoE), interleukin-1 (IL-1), and methylenetetrahydrofolate reductase (MTHFR), while inflammatory pathways are activated in both disorders [104, 105]. 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 postmortem brains with this disease [106, 107]. As it was suggested by Butzlaff and Ponimaskin [108], 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 microglial activation accordingly with the neuroimmunomodulation theory [13, 14, 74]. Furthermore, Yun and collaborators [109], showed that an antagonist of 5-HT6R is capable of rescuing memory deficit and attenuate the expression levels of astrocytes and microglia in an AD mouse model, sustaining the role of serotonin in activating the neuroinflammatory pathway (Fig. 2) with the subsequent neuronal degeneration. Concomitantly, dopamine production is deeply reduced in brains of

AD, as well as the levels of its receptors [110]. In addition, it has been recently determined that the loss of dopamine affects memory dysfunction in a transgenic mouse of AD [111]. 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 [112, 113]. 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 microglia cells that trigger overproduction of pro-inflammatory factors, as described in earlier time about the conceptual scheme of the neuroimmunomodulation theory [14, 74, 114].

As mentioned, the links between the release of dopamine in the dopamine areas and the neurons from the hippocampus, seems 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 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 [115]. 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 neuroinflammation mechanisms triggered by "damage signals" in AD, in agreement with the neuroimmunemodulation theory [14, 114]. 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 [102, 116, 117]. 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 [118–122]. 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 [123]. Other brain regions which constitutively express D3 receptors, seems 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, 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 [124]. 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 [125] 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 [125]. Furthermore, a recent study indicated that the gradual loss of dopaminergic neurons in an AD mouse model (Tg2576) characterized by memory and reward dysfunction [116]. It is known that dopamine D1 and D2 receptors are expressed in specific hippocampal areas, suggesting their role together with acetylcholine in memory processes [126, 127]. More interesting, D2 receptor antagonists have been proven as neuroprotective agents against tau toxicity and its aggregation [128].

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 [129–132]. Previous reports have linked the dopaminergic system with brain damage and cognitive disorders [133–135].

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 the entorhinal cortex. Research shows that behavioral and mood disorders have been associated with AD phenotypes. In 1993, Rohling and Scogin [136] 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 [29]. 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 [137]. The effect of ketamine, an anesthetic which induce an unconsciousness state response represented by gamma oscillations in the thalamocortical area [138], is observed in the cat hippocampus evoking an altered EEG profile also in this area [139]. Similar effects are observed by the use of NMDA receptors antagonists in the thalamus, presenting more activity in CA1 and delta oscillations [140], which mimics the same characteristics observed in schizophrenic patients [141], another prevalent neurological disorder.

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, and 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 [14]. 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 neurotransmitters pathways and the hippocampal area will be critical in the search for therapeutic solutions for AD.

CONCLUSION

The cause of AD remains unclear; however, recent investigations supports that neuroimmunomodulation pathway provide a great contribution to clear up the onset and progression of the disease, triggering behavioral, neuropsychiatric symptoms and posterior cognitive impairment. Experimental approaches are necessary to contribute to the characterization and understanding of BNS, mainly at early stages, taking advantage of the incipient development of biomarkers to identify this prodromal phase, useful tools to prevent or treat effectively AD in the near future.

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