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Antidepressant Role in Modulating Neurotransmitter Imbalance to Improve Cognitive Impairment in Patient with Alzheimer's Disease

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ABSTRACT

The present article delves into the complex correlation among neurotransmitter dysregulation, antidepressant therapy, and Alzheimer's disease (AD). Progressive cognitive decline and neuropsychiatric symptoms are the outcome of AD, the predominant type of dementia, which is characterized by pathological manifestations of β-amyloid plaques and hyperphosphorylated tau tangles. Amyloid plaque formation, tau protein phosphorylation, oxidative stress, and other pathophysiological processes are all aided by dysfunctional neurotransmitters such as acetylcholine, histamine, gamma-aminobutyric acid, and serotonin. On the other hand, medications that treat depression and AD patients turn out to be very important. These include selective noradrenaline reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs) and atypical antidepressants. Depression and neurologic disorders are correlated in both directions, supporting this treatment approach. The effects of antidepressants include reducing the production of amyloid plaque, improving cognitive function, stimulating neurogenesis, and increasing the levels of monoamine and brain-derived neurotrophic factor (BDNF) in synapses.

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Introduction

The main type of dementia, Alzheimer's disease, is thought to start developing years before symptoms appear [1]. β-amyloid senile plaques and neurofibrillary tangles containing hyperphosphorylated tau protein are its pathological hallmarks [2]. The neuropsychiatric hallmarks of Alzheimer's disease include progressive memory loss, cognitive impairment, language problems, and visuospatial problems [3]. The pathogenesis of Alzheimer's disease is influenced by abnormal neurotransmitter function, which includes acetylcholine, histamine, gamma-aminobutyric acid, and serotonin. These abnormalities result in tau protein phosphorylations, oxidative stress, and the formation of amyloid plaques [4-5]. On the other hand, antidepressants—such as atypical antidepressants, selective noradrenaline reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs)—are essential for treating Alzheimer's patients who also have depression [6]. The two-way relationship between neurologic disorders and depression supports this strategy [7]. Antidepressants reduce the production of amyloid plaque, improve memory and learning, boost neurogenesis, and raise the levels of monoamine and brain-derived neurotrophic factor (BDNF) in synapses [6].

Discussion

The neurotransmitter imbalances linked to Alzheimer's disease (AD) include disturbances in the cholinergic, serotonergic, noradrenergic, and dopaminergic systems [8]. In patients with AD, these imbalances play a role in neuropsychiatric symptoms and cognitive impairment. Antidepressants may be able to help with this neurotransmitter dysregulation, according to recent research. Neurotransmitter activity in the brain is modulated by antidepressants, including cholinesterase inhibitors, mirtazapine, and selective serotonin reuptake inhibitors (SSRIs) [8,9,10]. For example, serotonin levels are raised by SSRIs, which affects mood and cognitive function [9]. The cholinergic neurotransmission that is essential for cognitive function is enhanced by cholinesterase inhibitors [8]. Through its action on serotonergic and adrenergic receptors, mirtazapine exhibits neuromodulatory properties [10].

Interconnection Between Depression and Cognitive Decline

Strong data suggests that depression is probably a dementia risk factor, early symptom, and complication. Depression might be a prodromal symptom of dementia, according to a different systematic review and meta-analysis [11]. Additionally, depression and anxiety may result from the neurodegeneration of brain areas and neural circuits responsible for emotion regulation in AD patients [12]. Many biological mechanisms are shared by depression and dementia, which could explain their complex interplay [13]. First, pro-inflammatory cytokines, acute phase reactants (APRs) such as CRP, and microglial activation, which indicates chronic neuroinflammation, are elevated in depressed patients [14]. The advancement of AD may be fueled by inflammation [15]. In

addition, depression raises adrenal glucocorticoids which have negative effects on the nervous system [16]. In animal models, they increase tau accumulation and amyloid precursor protein which are characteristics of AD [17]. They also cause hippocampal atrophy which is a crucial alteration in AD [18,19]. Additionally, as previously mentioned, growth factors like BDNF, which promote neurogenesis and plasticity, are decreased in AD and depression [20].

Mechanisms of Action of Antidepressants

The goal of all antidepressant families is to raise the concentrations of specific neurotransmitters, primarily dopamine, norepinephrine, and serotonin [21]. However, the methods by which this effect is achieved differ. The class of antidepressants known as monoamine oxidase inhibitors (MAOIs) was the first to be identified [22]. They work by preventing monoamine oxidases from acting. Serotonin, norepinephrine, and dopamine are broken down by these enzymes and are released into the synaptic cleft, where they are then reabsorbed [23]. However, by preventing their reuptake back into the pre-synaptic neuron, tricyclic antidepressants (TCAs) raise the amounts of these neurotransmitters in the brain [24]. Similarly, the transporters that allow certain classes of drugs to reuptake their corresponding neurotransmitters are also blocked by these drugs, such as SSRIs, SNRIs, and NDRIs. Some families (atypical antidepressants, for example) use different mechanisms, such as blocking the reuptake of neurotransmitters, agonizing or opposing certain receptors, and changing the neurotransmission of glutamate and GABA [25].

Serotonin Modulation and Cognitive Enhancement

Serotonergic systems are important for memory and cognition, and Alzheimer's disease (AD) is associated with memory decline due to dysregulation of these systems [26]. By stimulating important brain regions, particularly the prefrontal cortex and the hippocampus, these systems have a profound effect on cognition [27]. Serotonin (5-HT) is essential for social connections, working memory, attention, and reversal learning in humans, and it plays a critical role in the hippocampus in these areas [26,28]. In the prefrontal cortex, 5-HT is necessary for critical functions like working memory and attention. Serotonin's interaction with particular receptors, such as 5-HT1A and 5-HT2A, is crucial for promoting cognitive function in the hippocampus and prefrontal cortex [26]. By precisely controlling the release of neurotransmitters like glutamate and dopamine in the prefrontal cortex, serotonin enhances neural network performance [28]. Working memory, attention, and executive functioning are all markedly improved by this subtle modulation [27]. Concurrently, serotonin stimulates long-term potentiation in the hippocampus by altering synaptic plasticity, especially in the CA1 area [29]. This process is essential for information encoding and retrieval. The well-coordinated receptor-mediated processes as a whole are responsible for the proven cognitive benefits in both brain areas [26, 29]. When it comes to treating cognitive deficits linked to Alzheimer's disease (AD), selective serotonin reuptake inhibitors (SSRIs) have shown great promise [30]. Chronic SSRI use, such as that of fluoxetine and sertraline, has been shown to have significant positive effects on people with AD. These effects include improved memory and cognitive function, a decrease in depressive symptoms, and an overall improvement in quality of life [31]. Remarkably, this long-term use corresponds with a noticeable decrease in amyloid-beta (Aβ) plaques, a characteristic feature of AD pathology, indicating a possible function in preventing cognitive decline [26]. Certain SSRIs display unique neuroprotective properties. citalopram, for instance, has exhibited efficacy in reducing Aβ peptide levels and inhibiting the growth of existing plaques [32]. A well-known SSRI called fluoxetine has been linked to larger hippocampus size as well as increased expression of proteins involved in the CREB/BDNF signalling pathways [33,34]. Furthermore, fluoxetine has been shown to be effective in lowering levels of soluble Aβ peptide in a variety of biological compartments [31,33, 34]. It has also been shown to have memory-enhancing properties, particularly in spatial memory, at the behavioural and cognitive levels [33,34]. The medication also stops synaptic protein loss and stops amyloid precursor protein (APP) from getting phosphorylated, which lowers the amount of Aβ peptide that is produced [31,34]. By decreasing tau hyperphosphorylation, a characteristic of AD pathology, escitalopram, another particular SSRI, has demonstrated its neuroprotective potential via the Akt/GSK-3β and 5-HT1A serotonergic receptor pathways [32,34]. Within the SSRI class, paroxetine improves behaviorally, lowers Aβ peptide levels, and treats tau protein problems in AD patients [35]. As an additional SSRI, fluvoxamine significantly improves memory in AD by blocking γ-secretase activity and thereby lowering the production of Aβ peptide [34,36].

Combined, these diverse neuroprotective effects of SSRIs—which include decreased Aβ plaques, altered tau phosphorylation, and preserved synaptic proteins—highlight the drugs' potential as a viable and adaptable therapeutic option for reversing cognitive decline associated with Alzheimer's disease [27].

Acetylcholine Modulation and Cognitive Enhancement

Acetylcholine appears to be a critical component in the regulation of cognitive processes, apart from serotonin. Acetylcholine (ACh) is a neurotransmitter in the central cholinergic system that binds to muscarinic and nicotinic receptors selectively. Acetylcholinesterase (AChE) can degrade ACh [37]. Acetylcholine is primarily involved in memory, attention, and learning, in contrast to serotonin's function in mood regulation [38]. Many parts of the central nervous system (CNS) work together to form memories, and the hippocampus is one of the key players. The hippocampus is actively regulated by cholinergic neurons that originate from a variety of brain areas, including the medial septum, intervals, basal forebrain, and prefrontal cortex [37,39,40]. Acetylcholine (ACh) is the primary mediator in the cholinergic nervous system and the first neurotransmitter discovered. It is essential to the processes involved in memory and learning [37,38]. Studies have demonstrated that mAChR, which are located in the dorsal hippocampus (DH) and retrosplenial cortex (RSC), are essential for the encoding and retrieval of contextual memory [41-43]. Memory formation in particular depends on hippocampal M3 receptors as well as the cooperative activity of RSC M1 and M3 receptors. Furthermore, it was found that, in terms of memory retrieval, the inactivation of multiple M1–M4 mAChR in DH or RSC causes a more marked impairment than the inactivation of a single receptor subtype [43]. These findings, in particular, highlight how important it is to coactivate multiple mAChR in order to successfully retrieve contextual memories that were acquired remotely as well as those that were acquired recently. Studies aiming for greater receptor specificity were typically found to be less successful than those focusing on multiple receptor subtypes, suggesting that mAChR functions in concert with other receptors to regulate different aspects of memory processes [41,44,45]. Numerous studies have consistently demonstrated that people with AD and age-related memory decline typically exhibit a characteristic loss of cholinergic neurons in the hippocampus, which is often accompanied by a notable reduction in acetylcholine (ACh) levels [37,46]. Research on both humans and animals indicates a strong correlation between the build-up of amyloid β peptide (Aβ) in extracellular spaces and intracellular neurofibrillary tangles, even though the exact pathophysiology of

AD is still unknown. By lowering choline acetyltransferase levels, Aβ negatively impacts ACh synthesis and release. It also disrupts cholinergic receptor signalling by binding with high affinity to α7 nicotinic acetylcholine receptors (nAChRs) and promoting the abnormal activation of mGluR5, which contributes to the pathological dysfunction of muscarinic acetylcholine receptors (mAChR) in the perirhinal cortex. Lastly, Aβ reduces the amount of cholinergic neurons. Furthermore, Aβ functions as an allosteric modulator, augmenting the enzyme butylcholinesterase, which hydrolyzes acetylcholine [46-50]. As a reversible and selective inhibitor of acetylcholinesterase (AChE), donepezil is presently licensed for the treatment of Alzheimer's disease (AD) symptoms [51-54]. The catalytic active site (CAS) and the peripheral anionic site (PAS), which are linked by a hydrophobic gorge, are the two main binding sites of acetylcholinesterase (AChE) as revealed by its X-ray crystallographic structure. Through its exclusive orientation from the CAS to the PAS, donepezil bridges this chasm [54]. This process consists of reducing the amount of β-amyloid plaque and blocking the breakdown of the neurotransmitter acetylcholine (ACh), which attempts to make up for the brain's lack of ACh. According to clinical trials, donepezil has been shown to improve cognitive function in people with mild to moderately severe AD and to be very well tolerated without having any negative effects on the liver [55,56].

BDNF and Antidepressant-Mediated Cognitive Benefits

The potential role of antidepressants in mitigating cognitive impairment in Alzheimer's disease has been studied, and it appears that their mode of action involves modulating Brain-Derived-Neutrophic Factor (BDNF) [57]. BDNF has been found to be a critical component that protects against neurodegeneration, especially when Alzheimer's disease is present [58]. Moreover, Alzheimer's disease, dementia, and cognitive impairment have all been connected to abnormalities in BDNF signalling [59]. The etiology of amnestic mild cognitive impairment and its progression to Alzheimer's disease has been linked to the interaction between single nucleotide polymorphisms (SNPs) and BDNF gene promoter methylation [60]. Furthermore, in the central nervous system (CNS), BDNF plays a crucial role in a number of processes, including neurogenesis, neuronal differentiation, neuroprotection, neuro-regeneration, and synaptic plasticity. Decreased levels of BDNF have been linked to a number of CNS disorders, including Alzheimer's disease [57,59,61].

Moreover, antidepressant therapies have been demonstrated to increase brain-derived neurotrophic factor (BDNF) levels and promote neurogenesis in the hippocampal regions of patients suffering from depressive disorders (Figure 1) [62,63]. Ketamine's antidepressant effects may be due to glutamate modulation through NMDA and AMPA receptors, which increases synaptic plasticity and produces BDNF [64]. Furthermore, acute cortisol alterations that influence the BDNF response have been connected to the antidepressant effect of ayahuasca [65]. Moreover, the Val66Met polymorphism in BDNF has been linked to Alzheimer's disease [66], indicating a possible hereditary impact on BDNF function in the development of cognitive impairment into Alzheimer's disease. Nonetheless, a study that focused on the BDNF Val66Met polymorphism's sex-dependent effects revealed that the gender differences in its effects on cognitive decline may exist [67].

BDNF has demonstrated that through activating the TrKB receptor, it influences the growth and flexibility of glutamatergic and GABAergic synapses [68]. Also, antidepressant-induced elevations in BDNF levels in the hippocampal regions affect both pre- and post-synaptic elements, changing the efficiency of synapses by modifying pre-synaptic neurotransmitter release and raising post-synaptic neurotransmitter sensitivity [64,69]. Furthermore, it has been demonstrated that antidepressants raise BDNF mRNA and protein levels in the hippocampal and cerebral cortex [70]. The decrease in histone acetylation in the BDNF promoter regions is the cause of this increase [71]. As a result, BDNF has a complex role in controlling the release and activity of various neurotransmitters, including glutamate, gamma-amino butyric acid (GABA), and dopamine [64,68,71,72]. Studies have emphasized how important BDNF is for regulating neurotransmitter dynamics [72]. As a result, BDNF has a complex role in controlling the release and activity of various neurotransmitters, including glutamate, gamma-amino butyric acid (GABA), and dopamine [71,72]. Antidepressants work by enhancing the cerebral cortex's TrKB receptor signalling, a process that is BDNF-dependent and essential for the modulation of neurotransmitters [73]. Numerous research studies have demonstrated that antidepressants, including ketamine and selective serotonin reuptake inhibitors (SSRIs), directly interact with the TrKB receptor, thereby influencing levels of BDNF [73,74]. Both the production and the release of BDNF are influenced by serotonin, and serotonin activation has the ability to promote BDNF synthesis and release [75]. Because SSRIs prevent serotonin from being reabsorbed, they maintain the activation of the serotonin pathways, which increases BDNF synthesis and causes its release [75,76].

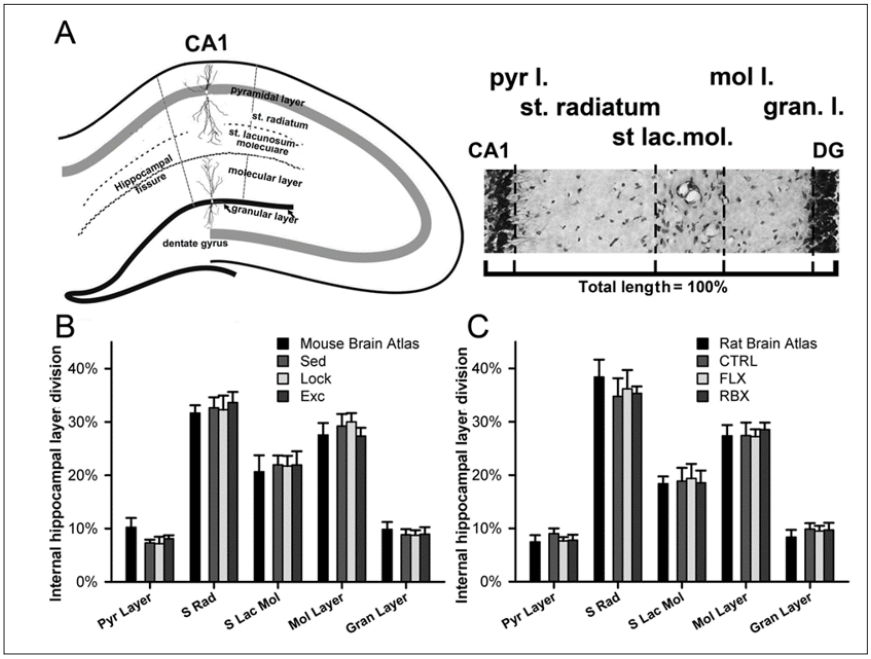

Figure: The authors obtained permission to use the figure from the publication: Physical Exercise and Antidepressants Enhance BDNF targeting in Hippocampal Ca3 Dendrites: Further Evidence of a Spatial Code for BDNF Splice Variants

A graphic depiction of the approach used to measure the thickness of hippocampus layers is shown in Figure 1. Specifically, Panel A provides a schematic diagram that delineates the area that was used for the thickness assessment. Continuing, the measurement reference for Panels B and C was determined by setting the distance as 100% between the bases of the DG Granular layer and the CA1 Pyramidal cell layer. The relative thickness of a number of dendritic and somatic strata, including Stratum Radiatum (S Rad), Stratum Lacunoso Molecularis (S Lac Mol), and Molecular Layer (Mol Layer), was then computed. Examples of these strata include the Pyramidal cell layer (Pyr Layer) and Granular layer (Gran Layer). Regarding the impact of antidepressants on these findings, it's important to note that this research has shown a possible relationship between antidepressant use and alterations in hippocampal structure. This suggests that antidepressant administration may promote neurogenesis and dendritic branching in the hippocampus, which may improve cognition in patients with Alzheimer's disease [77].

Glutamate Pathways: Antidepressant Interventions

Synaptic strength and shape are significantly influenced by the glutamatergic pathway, specifically N-methyl-D-aspartate receptor (NMDAR) activation, which modifies long-term synaptic plasticity associated with cognitive processes [78]. Pyramidal neurons in the hippocampal region receive CREB signals upon calcium (Ca2+) entry through NMDARs and L-type Ca2+ channels, which supports cognitive functions [79]. Glutamate packing into synaptic vesicles is facilitated by vesicular glutamate transporters (VGLUT1-3), and variations in their expression are a sign of glutamatergic neuron activity [80].

Reduced levels of VGLUT1 and VGLUT2 are seen in specific brain regions when AD is present, indicating abnormalities in glutamatergic transmission [78]. Reduced glutamic acid content, receptor binding, and glutamatergic synapse loss are all associated with the etiology of Alzheimer's disease, which is linked to glutamatergic network disruption [81]. Soluble Aβ oligomers in Alzheimer's disease phosphorylate tau and interfere with glutamatergic networks, leading to synaptic dysfunction [82]. Aβ42, a subtype of Aβ, binds to synaptosomes in the forebrain and modifies the NMDA subunits NR1 and NR2B within postsynaptic density complexes [83]. Aβ oligomers that are soluble cause mitochondrial dysfunction by inducing NMDA-dependent Ca2+ currents and cell death [84]. Aβ oligomers appear to have a detrimental effect on synaptic plasticity by suppressing LTP in hippocampus brain slices [85]. Neurodegeneration and extrasynaptic NMDAR overactivation are related [78]. While using direct receptor blockers like ketamine and MK-801 may result in enhanced dopamine release, excess glutamate activity, particularly through NMDA receptors, is a major cause of rapid nerve injury [78]. Moreover, glycine and d-serine function on NMDA receptors as co-agonists [86]. By modifying NMDA neurotransmission and focusing on these co-agonist sites, researchers hope to enhance cognitive functioning [87]. For instance, supplementing with d-serine has shown promise in improving learning capacity in older adults and mitigating cognitive losses linked to immunological challenges [86].

Conclusion

Antidepressants may play a therapeutic role in Alzheimer's disease (AD) due to the complex relationship between neurotransmitter imbalances and cognitive decline. Antidepressants have neuroprotective effects by targeting important neurotransmitter systems like acetylcholine and serotonin. This helps to mitigate pathological features of AD such as tau hyperphosphorylation and amyloid-beta plaques. Moreover, their influence on levels of Brain-Derived Neurotrophic Factor (BDNF) stimulates neurogenesis and synaptic plasticity, providing a holistic strategy to alleviate cognitive impairments in AD. The fact that antidepressants can affect a wide range of neurotransmitters, including glutamate, acetylcholine, and serotonin, demonstrates their extensive impact on the complex neurobiology of Alzheimer's disease. Even though it is still difficult to fully comprehend the complexities of neurotransmitter modulation and how they specifically affect AD pathology, current research shows promise for creating focused interventions that will lessen cognitive impairment in those suffering from this crippling neurodegenerative disease.

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