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An overview of the pathophysiology of agitation in Alzheimer's dementia with a focus on neurotransmitters and circuits

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Abstract

Alzheimer's dementia (AD) is a progressive, neurodegenerative disease often accompanied by neuropsychiatric symptoms that profoundly impact both patients and caregivers. Agitation is among the most prevalent and distressing of these symptoms and often requires treatment. Appropriate therapeutic interventions depend on understanding the biological basis of agitation and how it may be affected by treatment. This narrative review discusses a proposed pathophysiology of agitation in Alzheimer's dementia based on convergent evidence across research approaches. Available data indicate that agitation in Alzheimer's dementia is associated with an imbalance of activity between key prefrontal and subcortical brain regions. The monoamine neurotransmitter systems serve as key modulators of activity within these brain regions and circuits and are rendered abnormal in AD. Patients with AD who exhibited agitation symptoms during life have alterations in neurotransmitter nuclei and related systems when the brain is examined at autopsy. The authors present a model of agitation in Alzheimer's dementia in which noradrenergic hyperactivity along with serotonergic deficits and dysregulated striatal dopamine release contribute to agitated and aggressive behaviors.

Introduction

There are an estimated 6.5 million adults aged 65 years and older living with Alzheimer's dementia (AD) in the United States, and this population is expected to double by 2050.[1] Neuropsychiatric symptoms (NPS) commonly occur over the course of AD and are among the most disabling aspects of the disease. Among NPS, agitation is one of the most prevalent and distressing. Approximately 45% of community-dwelling patients and 53% of nursing home residents exhibit agitated behaviors during the course of AD, and agitation has been observed across mild to severe stages of the disease.[2,3]

Agitation is defined by the International Psychogeriatric Association as a syndrome occurring in patients with a cognitive impairment or dementia syndrome; manifesting as excessive motor activity, verbal aggression, or physical aggression associated with emotional distress that is persistent or recurrent for at least 2 weeks; producing behaviors severe enough to produce excess disability; and not being attributable to another disorder.[4] Agitation is characterized by disruptive or aggressive behaviors such as shouting, cursing loudly, kicking, shoving, and hitting. Agitation may place the patient and the caregiver in danger of harm. Agitation in Alzheimer's dementia is associated with significant negative patient outcomes, including accelerated disease progression, functional decline, increased institutionalization, and increased mortality.[5–7] Additionally, agitation in Alzheimer's dementia is linked to high caregiver burden and increased health care resource utilization and costs.[6–8]

Characterizing the pathophysiology of agitation contributes to understanding the biology of the clinical manifestation of AD and is important for developing potential treatments for agitation in Alzheimer's dementia. AD is a progressive, neurodegenerative disease characterized by β-amyloid protein (Aβ) plaques, tau protein pathology, and neurodegeneration.[9] Accumulating evidence indicates that NPS may be caused by dysfunction within specific neural circuits affected by these pathologies; both structural and functional changes have been identified within key prefrontal and subcortical regions in patients with agitation in Alzheimer's dementia.[10,11] The norepinephrine (NE), serotonin (5-HT), and dopamine (DA) monoamine neurotransmitter systems are important modulators of activity within these brain regions and circuits and are markedly impacted by AD pathological changes.[12–16] Dysfunction of the monoamine neurotransmitter systems may contribute to agitation symptoms by disrupting the balance of prefrontal and subcortical activity in circuits required for normal behavioral function. Monoamine neurotransmitter systems may represent key targets for the potential improvement of agitation symptoms in AD.

This review synthesizes research observations into a proposed pathophysiology of agitation in Alzheimer's dementia, focusing on the potential role of monoamine neurotransmitter systems and related circuits. We first examine how an imbalance between prefrontal and subcortical activity may underlie agitation symptoms in patients with AD. We then explore how monoamine neurotransmitter systems may contribute to dysfunction in these brain regions, examining noradrenergic, serotonergic, and dopaminergic system function in patients with AD and the evidence linking these systems with agitation symptoms. For each system, we synthesize the available evidence to provide a hypothetical model of the neurobiological basis of agitation symptoms. We discuss the potential role of other neurotransmitter systems, including glutamate and γ-aminobutyric acid (GABA), and comment on emerging treatments for agitation in Alzheimer's dementia and their therapeutic targets.

Prefrontal and Subcortical Dysfunction in Agitation in Alzheimer's Dementia

Behavior involves a balance between bottom-up reactive responses to stimuli, referred to as emotional drive, and top-down control mechanisms that allow for the regulation of these responses, referred to as executive control.[17,18] This balance arises from activity within a complex circuitry involving cortical and subcortical brain regions, with the prefrontal cortex (PFC) and amygdala emerging as key nodes of these circuits. The PFC guides many aspects of executive control, including attention and working memory, emotional regulation, and response inhibition, while the amygdala—a key node within the limbic system—plays a central role in the orchestration of emotional responses to sensory input.[17–19] These regions share dense reciprocal connections, with the PFC downregulating reactive processes driven by the amygdala.[17,18]

Disruption of the balance between the PFC and subcortical regions is believed to contribute to NPS, including agitation in Alzheimer's dementia.[10,11,17] Evidence from structural and functional imaging studies as well as postmortem analyses indicates that pathology within specific brain regions, including the PFC and amygdala, may increase the risk of agitation. One study of postmortem brain tissue found that neurofibrillary tangle (NFT) burden in the left orbitofrontal cortex was associated with both agitation and chronic aberrant motor behavior; no relationship with amyloid pathology was observed.[20] A second study found that the ratio of phosphorylated to total tau within the PFC positively correlated with aggression.[21] Similarly, structural magnetic resonance imaging (MRI) studies of patients with AD have found that agitation, aggression, and aberrant motor behavior were associated with greater gray matter atrophy in the PFC and amygdala.[22–24] Agitation has been linked to pathology in other brain regions involved in emotional processing, including the anterior cingulate cortex and insula.[20,22,25] In a study of patients with AD, cerebrospinal fluid (CSF) levels of both total and phosphorylated tau were associated with greater agitation, while there was no relationship between levels of the 42-amino acid isoform of Aβ protein ($A\beta_{1-42}$), a biomarker of amyloid pathology, and agitation.[26] Although AD is characterized by both tau and amyloid pathology, these data suggest that tau-mediated pathology may be more influential in the biology of agitation in Alzheimer's dementia.

Functional magnetic resonance imaging (fMRI) studies have provided further evidence of an imbalance of activity between the PFC and subcortical brain regions in patients with agitation. Fluorodeoxyglucose (FDG) positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies of patients with AD have demonstrated that agitation, aggression, and aberrant motor behavior are associated with hypoperfusion and decreased glucose metabolism within the PFC, as well as within other regions, including the parietal, temporal, and cingulate cortices and insula.[27–30] Conversely, agitation is associated with elevated amygdala reactivity to emotional stimuli. An fMRI study showed that patients with AD had a significantly greater amygdala response to both neutral and fearful faces compared to elderly controls and that amygdala responses to familiar neutral faces were positively correlated with severity of agitation and irritability symptoms.[31]

Collectively, these findings indicate that agitation in Alzheimer's dementia may arise from an imbalance between executive control, mediated by the PFC, and emotional drive, mediated by subcortical regions, including the amygdala (Figure 1). This imbalance may arise in part from the accumulation of tau pathology and neurodegeneration within key brain regions. A consequence of this pathology is the dysfunction of the monoamine neurotransmitter systems, which modulate the activity of neural circuits throughout the brain and show substantial alterations over the course of AD. The following sections review evidence suggesting that monoamine neurotransmitter system dysfunction may contribute to agitation symptoms.

Monoamine System Dysfunction in Agitation in Alzheimer's Dementia

The noradrenergic, serotonergic, and dopaminergic systems originate primarily in brainstem nuclei and project throughout the brain to modulate the activity of numerous brain regions, including prefrontal and subcortical regions.[12–14] The balance of these systems is dynamic, with reciprocal connections existing among

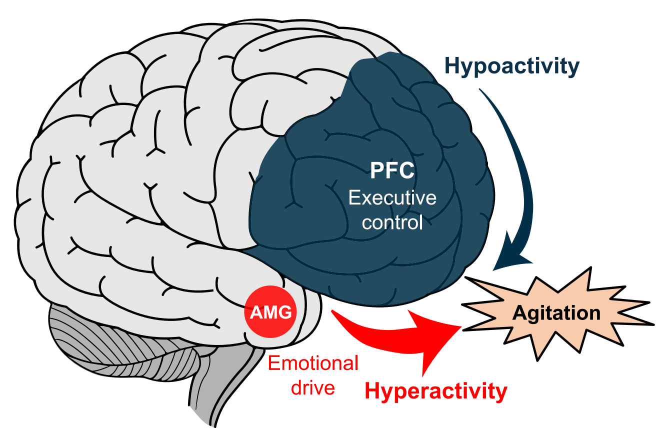

Figure 1. Hypothesized imbalance between executive control (mediated by prefrontal regions) and emotional drive (provided by subcortical regions, including the amygdala) underlying agitation symptoms in patients with Alzheimer's dementia. Abbreviations: AMG, amygdala; PFC, prefrontal cortex.

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monoaminergic nuclei and their target regions as well as among different monoamine systems.[12,16,18]

Norepinephrine

The noradrenergic system plays a key role in facilitating emotional responses, including arousal and responses to salient stimuli, the stress response, and fear and anxiety behaviors.[12,32] The locus coeruleus (LC) is the primary source of NE in the brain, with LC neurons projecting to key regions, including the PFC and amygdala.[12,32] The activity of LC neurons is in turn modulated by reciprocal projections from these target regions, with NE release being driven by the amygdala and regulated by the PFC.[12,18,32] Among the neurotransmitter systems examined in this review, a particularly robust body of evidence implicates noradrenergic hyperactivity in the pathophysiology of agitation in Alzheimer's dementia.

The noradrenergic system is severely impacted over the course of AD. The LC is among the first brain regions impacted in AD, with tau pathology and NFTs observed during the earliest stages of the disease and neuron loss occurring as the disease progresses.[9,33] Following the loss of LC neurons, the noradrenergic system undergoes changes that may compensate for neuronal loss and preserve NE signaling based on the following observations.[15] First, despite the loss of LC neurons in AD, CSF levels of NE and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) have generally been reported to be unchanged or elevated relative to healthy controls.[34–37] This may be due to increased NE synthesis by the remaining LC neurons, as supported by the finding of increased expression of tyrosine hydroxylase, the rate-limiting step in NE synthesis, in the LC neurons of patients with AD.[38] Second, increased α_1-adrenoceptor expression—considered to be a response to decreased NE levels—has been observed in the hippocampus and PFC in patients with AD.[38,39] Third, AD is associated with increased sprouting of dendrites and axonal projections to the hippocampus and PFC by the remaining LC neurons.[38–40]

Several lines of evidence from patients with AD indicate that compensatory changes in NE signaling following LC neurodegeneration are associated with agitation symptoms. First, agitation has been associated with greater severity of LC neuron loss. One study reported a negative correlation between number of LC neurons and aggression,[41] while a more recent study found an increased risk of agitation to be associated with greater NFT burden during early stages of the disease when NFTs are largely confined to the transentorhinal cortex and brainstem regions, including the LC.[42] Second, despite the loss of LC neurons, positive correlations have been reported between NE levels within the PFC and aggression and between CSF levels of MHPG and behavioral symptom severity.[43,44] Studies of these relationships are inconsistent, and several failed to find significant associations between NE or MHPG levels and aggression.[45–48] Third, agitation is associated with changes in NE receptor expression and function that may occur in response to the loss of LC neurons.[49] Finally, studies using yohimbine or clonidine to challenge the noradrenergic system in patients with AD indicate that agitation and aggression may be associated with greater responsiveness of the noradrenergic system. In one study, patients with AD showed greater increases in agitation compared to controls following yohimbine administration that correlated with CSF epinephrine levels.[50] In a second study, aggression was elevated in patients with a blunted growth hormone (GH) response to clonidine, which is thought to reflect noradrenergic system overactivity, compared to patients with a preserved GH response.[51]

Noradrenergic system hyperactivity may impair prefrontal function and drive amygdala activity in part through the activation of α_1-adrenoceptors. One study examining α_1-adrenoceptor binding in the PFC found that both receptor density and receptor affinity were positively associated with aggression in patients with AD.[49] Evidence suggests that PFC neurons are highly sensitive to changing NE levels, which are mediated in part by the activation of different classes of adrenoceptors as the disease progresses. Low to moderate levels of NE engage high-affinity α_2-adrenoceptors.[18] However, increasing NE levels lead to the desensitization of α_2-adrenoceptors, particularly α_{2C}-adrenoceptors, and engage lower-affinity α_1-adrenoceptors.[18,52] Within the PFC, activation of α_1-adrenoceptors is associated with impaired functioning.[18] In contrast, amygdala function is enhanced by activation of α_1-adrenoceptors and stimulation of LC terminals, as demonstrated by increased fear- and anxiety-related behaviors in rodent studies, while antagonism of these receptors produces the opposite effect.[53–55] Consistent with these findings, agents that act as α_1-adrenoceptor antagonists have been reported to improve agitation and aggression in patients with AD compared to placebo.[56–58]

The hypothesized role of noradrenergic system dysfunction in agitation in Alzheimer's dementia is summarized in Figure 2. Following the loss of neurons in the LC, the noradrenergic system undergoes compensatory changes, including increased NE synthesis and sprouting of axonal projections by LC neurons with elevated expression of α_1-adrenoceptors in the PFC.[38,39] Given the opposing effects of elevated NE levels on PFC versus amygdala function and the evidence linking elevated noradrenergic system activity to agitation behaviors, increased NE signaling may contribute to agitation in patients with AD by impairing the executive and supervisory function of the PFC and increasing amygdala activity.

Serotonin

AD is associated with marked serotonergic system deficits. The raphe nuclei of the brainstem, which are the major sources of 5-HT in the brain, show tau pathology during early stages of the disease

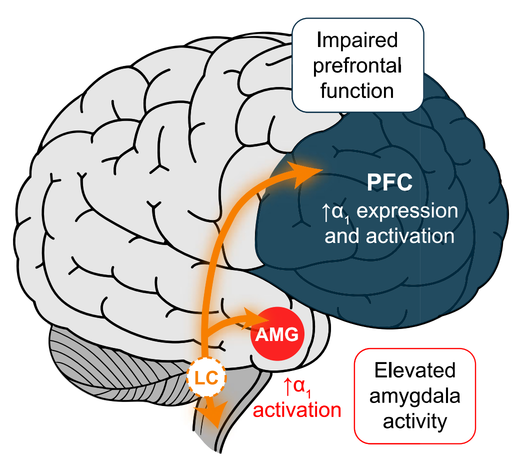

Figure 2. Hypothetical model of noradrenergic system dysfunction underlying agitation in Alzheimer's dementia. Neurodegeneration of LC neurons is accompanied by compensatory increases in noradrenergic system activity, including increased NE synthesis and sprouting of axonal projections by LC neurons and increased α_1-adrenoceptor expression in the PFC. This increase in NE signaling could impair PFC function and increase amygdala activity through the activation of α_1-adrenoceptors. Dashed orange circle indicates NE neuron loss. Bolded orange arrows indicate increased NE release. Abbreviations: AMG, amygdala; LC, locus coeruleus; NE, norepinephrine; PFC, prefrontal cortex.

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and eventual loss of 5-HT neurons and their projections.[9,16] Corresponding to this loss of 5-HT neurons, decreased levels of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) have been reported in CSF and in multiple brain regions, including the PFC, amygdala, hippocampus, and temporal cortex.[16,43,59] Decreased levels of 5-HT receptors have been reported in multiple brain regions, including decreased levels of 5-HT_{1A} receptors in the frontal cortex and hippocampus.[16,60]

The serotonergic system plays a key role in regulating aggression and impulsivity, with decreased central 5-HT signaling being associated with increased aggression.[13,61] This may occur in part through the modulation of PFC and amygdala activity, as functional imaging studies of healthy adults show that lowered central 5-HT levels via acute tryptophan depletion can alter PFC activity, increase amygdala reactivity to emotional stimuli, and impact prefrontal-amygdala connectivity.[62,63] Dysfunction of the serotonergic system is poised to contribute to agitation behaviors by further disrupting PFC and amygdala function.

Several studies have reported relationships between decreased 5-HT or 5-HIAA levels and agitation. One postmortem study associated overactivity in life, consisting of high ratings for walking more, walking aimlessly, and trailing or checking on carers, with decreased prefrontal 5-HT levels.[59,64] Additional studies have reported negative correlations between agitation and 5-HIAA levels, particularly in the hippocampus but also in the PFC.[43,46,48] Treatment with a selective serotonin reuptake inhibitor (SSRI) has been reported to reduce agitation in patients with AD.[65] Decreased expression of 5-HT receptors, particularly in the temporal cortex, has been linked to agitation in patients with AD. One study reported a negative correlation between aggression and 5-HT_{1A} receptor density in the temporal cortex,[66] with the same research group reporting a similar trend in the hippocampus, although this result did not reach statistical significance.[60] Another study reported that overactivity, as defined above, was predictive of reduced 5-HT_6 receptor levels in the temporal cortex.[67] Agitation and aggression are associated with abnormal responses to serotonergic system challenge as indicated by greater increases in prolactin concentrations following fenfluramine—a serotonin-releasing agent, agonist of the serotonin 5-HT_2 receptors, and σ_1 receptor positive modulator—administration.[68,69]

The effects of 5-HT are mediated by 7 families of 5-HT receptors (5-HT_1 to 5-HT_7) expressed on both excitatory glutamatergic neurons and inhibitory interneurons.[13] 5-HT_{1A} receptors within the PFC and amygdala appear to be particularly important for modulating behaviors relevant to agitation, including aggression and impulsivity. In rodents, stimulation of 5-HT_{1A} receptors in the PFC reduced aggression and impulsivity,[13,70] while stimulation of 5-HT_{1A} receptors in the amygdala decreased amygdala activity as well as fear- and anxiety-related behaviors.[71,72] In healthy adults, PET imaging studies using a radioligand selective for the 5-HT_{1A} receptor have shown correlations between aggressive or impulsive traits and 5-HT_{1A} binding in the PFC and amygdala.[73,74] Finally, treatment with an agent acting as a 5-HT_{1A} partial agonist has been reported to improve agitation symptoms in patients with AD.[57,58]

The hypothesized role of serotonergic system dysfunction in agitation in Alzheimer's dementia is summarized in Figure 3. The role of 5-HT signaling in regulating activity of key neural circuits combined with evidence of serotonergic system deficits in both agitation-related behaviors and AD suggests that 5-HT signaling deficits may contribute to agitation in patients with AD by contributing to the disruption of PFC and amygdala function. The key role of the 5-HT_{1A} receptor in regulating aggression and impulsivity suggests that these behaviors and agitation in Alzheimer's dementia may be mediated in part by altered activation of these receptors.

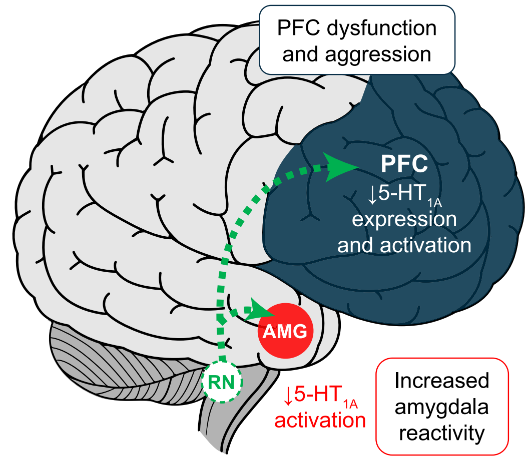

Figure 3. Hypothetical model of serotonergic system dysfunction underlying agitation in Alzheimer's dementia. Loss of 5-HT inputs to the PFC combined with decreased 5-HT_{1A} receptor expression and activation may contribute to PFC dysfunction and aggression, while loss of 5-HT inputs to the amygdala could result in increased amygdala reactivity via decreased 5-HT_{1A} activation. Dashed green circle indicates 5-HT neuron loss. Dashed green arrows indicate decreased 5-HT release. Abbreviations: 5-HT, serotonin; AMG, amygdala; PFC, prefrontal cortex; RN, raphe nuclei.

Dopamine

Historically, the dopaminergic system has been viewed as being relatively spared in AD compared to the other monoamine neurotransmitter systems.[16] More recent studies suggest that, while AD is associated with relatively little loss of DA neurons, dopaminergic system dysfunction may contribute to cognitive deficits and NPS associated with AD. Recent imaging studies have reported that patients with AD exhibit disrupted connectivity of the mesocorticolimbic DA system, consisting of dopaminergic projections from the ventral tegmental area (VTA) to cortical and limbic areas.[14,75]

Relative sparing of dopaminergic projections in the context of serotonergic system disruption provides a foundation for the dysregulation of DA release, contributing to agitation and aggression.[16] Specifically, serotonergic projections to the substantia nigra (SN) and VTA regulate DA release from DA neurons.[76,77] Given the evidence linking agitation in Alzheimer's dementia to serotonergic system deficits, a decrease in 5-HT levels predicts an altered striatal DA release in response to specific stimuli.

The dopaminergic system is involved in a number of processes, including the regulation of voluntary movement and reward processing.[78,79] Increased activation of the dopaminergic system has been linked to agitation and aggression, with rodent studies showing that aggression was associated with striatal DA release and activation of D_2 receptors, while antagonism of striatal D_2 receptors decreased aggression.[80–82] Similarly, treatment with agents acting as D_2 receptor partial agonists or antagonists has been reported to improve agitation and aggression in patients with dementia.[57,58,83]

The potential role of dysregulated DA release in agitation is supported by studies in patients with AD. Several studies reported that aggression was associated with relative preservation of the dopaminergic system as indicated by higher CSF and plasma concentrations of the DA metabolite homovanillic acid and greater cell count in the SN.[84–86] Recently, agitation was linked with

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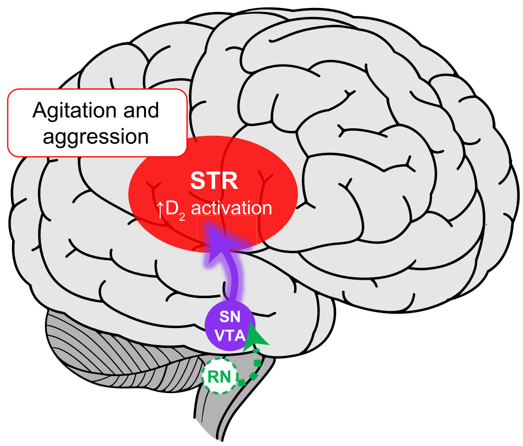

Figure 4. Hypothetical model of dopaminergic system dysfunction underlying agitation in Alzheimer's dementia. Preserved dopaminergic projections combined with a loss of regulation of DA release by serotonergic neurons could result in activation of striatal D_2 receptors, which are implicated in agitated and aggressive behaviors. Dashed green and solid purple circles indicate 5-HT neuron loss and DA neuron preservation, respectively. Dashed green and bolded purple arrows indicate decreased 5-HT release and increased DA release, respectively. Abbreviations: 5-HT, serotonin; DA, dopamine; RN, raphe nuclei; SN, substantia nigra; STR, striatum; VTA, ventral tegmental area.

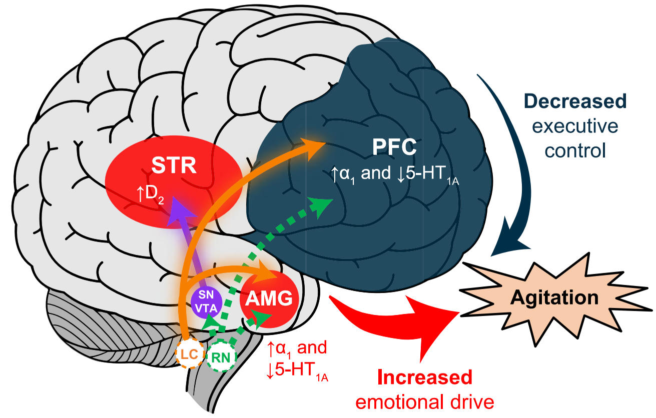

Figure 5. Hypothetical model of monoamine neurotransmitter system dysfunction underlying agitation in Alzheimer's dementia. Increased NE signaling combined with 5-HT signaling deficits may contribute to PFC dysfunction and increased amygdala reactivity through the increased activity of α_1-adrenoceptors and decreased activity of 5-HT_{1A} receptors. Dysregulated DA signaling may contribute to agitation and aggression via activation of striatal D_2 receptors. Collectively, these effects contribute to an imbalance between executive control and emotional drive. Dashed orange and green circles indicate NE and 5-HT neuron loss, respectively. Solid purple circle indicates DA neuron preservation. Bolded orange and purple arrows indicate increased NE and DA release, respectively. Dashed green arrows indicate decreased 5-HT release. Abbreviations: 5-HT, serotonin; AMG, amygdala; DA, dopamine; LC, locus coeruleus; NE, norepinephrine; PFC, prefrontal cortex; RN, raphe nuclei; SN, substantia nigra; STR, striatum; VTA, ventral tegmental area.

increased functional connectivity between the VTA and the hippocampus and cerebellum, supporting a potential role of altered DA release in agitation in Alzheimer's dementia.[14]

The hypothesized role of dopaminergic system dysfunction in agitation in Alzheimer's dementia is summarized in Figure 4. The dopaminergic system is less severely impacted by AD pathology compared to the other monoamine neurotransmitter systems, and there is some evidence that agitation may be associated with relative preservation of DA signaling. Preservation of DA signaling combined with serotonergic system deficits could give rise to dysregulation of DA release in the striatum, contributing to increased agitation and aggression.

Summary of monoamine neurotransmitter system dysfunction in agitation in Alzheimer's dementia

The potential roles of the monoamine neurotransmitter systems in agitation in Alzheimer's dementia are summarized in Figure 5. This evidence-based model suggests that agitation arises from an imbalance between executive control mediated by prefrontal brain regions and emotional drive provided by subcortical brain regions, including the amygdala.[10,11] AD is associated with marked alterations in the monoamine neurotransmitter systems, providing the basis for this imbalance.[14–16] Noradrenergic system hyperactivity combined with serotonergic system deficits may result in PFC dysfunction and elevated amygdala reactivity, while dysregulated DA release in the striatum may contribute to agitated and aggressive behaviors.

Other Neurotransmitter Systems

While evidence suggests that disruption of the monoamine neurotransmitter systems may be a key aspect of agitation in Alzheimer's dementia pathophysiology, disruption of other neurotransmitter systems, such as glutamate and γ-aminobutyric acid (GABA), may also contribute to agitation symptoms.

Glutamate is the primary excitatory neurotransmitter in the brain, with glutamatergic projections from the PFC providing top-down control over subcortical regions, including the amygdala.[17] AD is associated with dysfunctional glutamate transmission, which may contribute to agitation and aggression by disrupting frontal cortex function (Figure 6).[87] Patients with AD show reduced glutamate reuptake in multiple brain regions, including the frontal cortex, possibly reflecting interference by Aβ plaques with the function of glutamate transporters.[87,88] Decreased reuptake could result in elevated glutamate levels as indicated by studies reporting elevated CSF levels of glutamate and its precursor

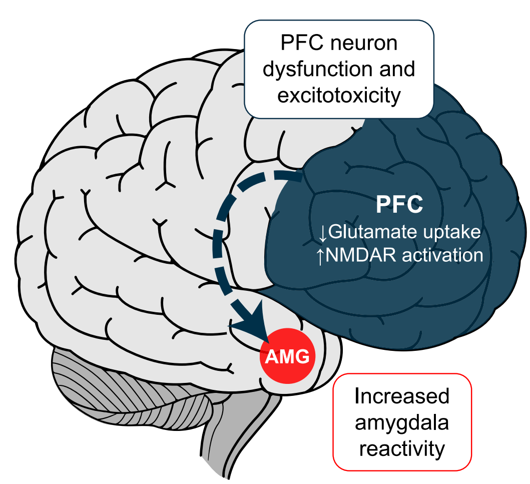

Figure 6. Hypothetical model of glutamatergic system dysfunction underlying agitation in Alzheimer's dementia. Decreased glutamate reuptake may contribute to increased NMDAR activation, resulting in PFC neuron dysfunction and excitotoxicity. Decreased top-down regulation from the PFC may result in increased amygdala reactivity. Dashed blue arrow indicates decreased PFC regulation of the amygdala. Abbreviations: AMG, amygdala; NMDAR, *N*-methyl-D-aspartate receptor; PFC, prefrontal cortex.

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glutamine in patients with AD.[89] Elevated glutamate levels may disrupt frontal cortex function, with elevated levels impairing normal cognitive processes and extreme elevations driving excitotoxicity through extrasynaptic glutamate *N*-methyl-D-aspartate (NMDA) receptors.[87,88] Agents acting as NMDA receptor antagonists improve agitation in patients with AD.[90]

GABA is the primary inhibitory neurotransmitter in the brain.[91] During normal brain activity, activation of excitatory glutamatergic neurons and inhibitory GABAergic interneurons maintains a balance of activity within neural circuits.[91,92] While GABAergic neurons and receptors have been viewed as being more resistant to AD pathology than other systems, recent research indicates that the GABAergic system undergoes substantial changes in AD.[92] Tau pathology and neurodegeneration of GABAergic interneurons have been observed in multiple brain regions, including the hippocampus and cortex, along with decreases in brain and CSF levels of GABA.[91,92] Disruption of GABAergic neuron function may lead to an imbalance between excitation and inhibition within neural circuits, potentially contributing to cognitive impairments and behavioral disturbances in AD.[91,92]

Insights From Emerging Pharmacological Treatments

The increasing prevalence of AD and the burden of agitation in Alzheimer's dementia for patients and caregivers alike underscore the need for new therapies that can address NPS, including agitation in patients with AD. One agent, brexpiprazole, has been approved by the US Food and Drug Administration (May 2023) for the treatment of agitation associated with dementia due to Alzheimer's disease, and 6 agents being developed for treatment of agitation symptoms in patients with AD are in phase 3 clinical trials (as per the federal database ClinicalTrials.gov on September 25, 2023): dexmedetomidine (α_2-adrenoceptor agonist), citalopram (SSRI), masupirdine (5-HT_6 antagonist), AVP-786 (dextromethorphan plus quinidine), AXS-05 (dextromethorphan plus bupropion), and nabilone (cannabinoid partial agonist). Consistent with the proposed role of monoamine neurotransmitter system dysfunction in agitation in Alzheimer's dementia, 2 of the 6 agents currently in phase 3 clinical trials, along with brexpiprazole, act on the noradrenergic, serotonergic, or dopaminergic systems.

Brexpiprazole has a high affinity for noradrenergic α-adrenoceptors, in addition to its high affinity for serotonergic and dopaminergic receptors. Brexpiprazole acts as an antagonist at α_{1B}-adrenoceptors while also serving as a partial agonist at 5-HT_{1A} serotonergic and D_2 dopaminergic receptors.[57,93] Additionally, brexpiprazole acts as an antagonist at α_{2C}-adrenoceptors and 5-HT_{2A} serotonergic receptors.[93] Hypothetically, α_{1B}-adrenoceptor antagonism and 5-HT_{1A} partial agonism may support PFC function and reduce amygdala function by blocking the deleterious effects of elevated NE and restoring 5-HT signaling, while D_2 receptor partial agonism may regulate striatal DA activity.

Dexmedetomidine is an α_2-adrenoceptor agonist currently used in intensive care units for its sedative properties and has been proposed as an acute treatment for agitation.[94] Consistent with the hypothesized role of noradrenergic hyperactivity in agitation in Alzheimer's dementia, the effects of dexmedetomidine are thought to be mediated by the activation of presynaptic α_2-autoreceptors, which inhibit NE release.[95]

Citalopram is an SSRI whose clinical benefits are primarily associated with its S-enantiomer (escitalopram).[65,96] The efficacy of SSRIs is believed to be driven in part by the desensitization of somatodendritic 5-HT_{1A} autoreceptors ultimately resulting in increased 5-HT release in target regions, which is consistent with the hypothesized role of serotonergic system deficits in agitation in Alzheimer's dementia.[97]

Although not currently in phase 3 clinical trials as per ClinicalTrials.gov, prazosin is a centrally acting α_1-adrenoceptor antagonist previously shown to improve behavioral symptoms in AD patients with agitation and aggression.[56] Hypothetically, antagonism of postsynaptic α_1-adrenoceptors may address agitation symptoms by preventing the effects of noradrenergic hyperactivity.

Four of the 6 agents in phase 3 clinical trials act on targets beyond the monoamine neurotransmitter systems. Masupirdine is a serotonin 5-HT_6 receptor antagonist whose efficacy may arise from modulation of neurotransmitters implicated in agitation, including glutamate, GABA, and NE, as well as acetylcholine.[98,99]

AVP-786 is the deuterated form of AVP-923, a combination of the NMDA receptor antagonist and σ_1 receptor agonist dextromethorphan and the cytochrome P450 2D6 (CYP2D6) inhibitor quinidine.[100] AXS-05 is a combination of dextromethorphan and the NE and DA reuptake inhibitor and CYP2D6 inhibitor bupropion.[90] NMDA receptor antagonism may reduce agitation by protecting against the effects of elevated glutamate transmission, such as disrupted frontal cortex function.

Nabilone is a synthetic cannabinoid that acts as a partial agonist at cannabinoid CB_1 and CB_2 receptors.[101] Nabilone may indirectly influence the neurotransmitter systems implicated in agitation, as the endocannabinoid system modulates the activity of other neurotransmitter systems, including the monoamine, glutamatergic, and GABAergic systems.[102] Cannabinoid receptors are expressed in brain regions associated with monoaminergic signaling, including the amygdala, cerebral cortex, basal ganglia, and striatum, and evidence suggests that cannabinoid receptor expression is correlated with tauopathy and subsequent neurodegeneration.[102,103]

Limitations

One limitation of this review is the potential impact of other NPS, as patients with dementia frequently experience multiple NPS.[104] While this review focused on studies of patients with agitation in Alzheimer's dementia, it is possible that the study results were influenced by the presence of additional NPS.

A second limitation is that the proposed pathophysiology of agitation in Alzheimer's dementia discussed in this review does not distinguish between domains of agitation, which include excessive motor activity, verbal aggression, and physical aggression, as it has been suggested that different aspects of agitation may arise from different structural and functional deficits.[4,10,78] While there has been relatively little study of the pathophysiology associated with different domains of agitation, several studies discussed in this review provide potential insights. PFC dysfunction was associated with multiple forms of agitation, including aggression and aberrant motor behavior, as well as physical and verbal agitation, suggesting that loss of executive control may contribute to multiple agitation domains.[20,23,27,28,30] Additionally, several studies reported that alterations in the noradrenergic system were associated with aggressive behavior but not overactivity or physically nonaggressive behavior, suggesting that noradrenergic system dysfunction may be particularly important in the development of verbal or physical aggression.[41–43,49] Further study of the pathophysiology underlying different agitation domains would improve understanding of the neurobiological basis of NPS in AD.

Conclusion

This review synthesized research observations to provide a hypothetical model for the pathophysiology of agitation in Alzheimer's dementia with a focus on the monoamine neurotransmitter systems. Agitation may arise from disrupted top-down executive control and elevated bottom-up emotional drive mediated by prefrontal and subcortical brain regions, respectively. The monoamine neurotransmitter systems are key modulators of these brain regions and show marked alterations in AD. Noradrenergic hyperactivity along with serotonergic deficits and dysregulated dopamine release may contribute to agitation symptoms by disrupting the balance between executive control and emotional drive. These neurotransmitter abnormalities may point to development of specific types of agents useful in the control of agitation.

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