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REVIEW ARTICLE

Relevance of 5-HT_{2A} Receptor Modulation of Pyramidal Cell Excitability for Dementia-Related Psychosis: Implications for Pharmacotherapy

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Abstract

Psychosis occurs across a wide variety of dementias with differing etiologies, including Alzheimer's dementia, Parkinson's dementia, Lewy body dementia, frontotemporal dementia, and vascular dementia. Pimavanserin, a selective serotonin 5-HT_{2A} receptor (5-HT_{2A}R) inverse agonist, has shown promising results in clinical trials by reducing the frequency and/or severity of hallucinations and delusions and the risk of relapse of these symptoms in patients with dementia-related psychosis. A literature review was conducted to identify mechanisms that explain the role of 5-HT_{2A}Rs in both the etiology and treatment of dementia-related psychosis. This review revealed that most pathological changes commonly associated with neurodegenerative diseases cause one or more of the following events to occur: reduced synaptic contact of gamma aminobutyric acid (GABA)-ergic interneurons with glutamatergic pyramidal cells, reduced cortical innervation from subcortical structures, and altered 5-HT_{2A}R expression levels. Each of these events promotes increased pyramidal cell hyperexcitability and disruption of excitatory/inhibitory balance, facilitating emergence of psychotic behaviors. The brain regions affected by these pathological changes largely coincide with areas expressing high levels of 5-HT_{2A}Rs. At the cellular level, 5-HT_{2A}Rs are most highly expressed on cortical glutamatergic pyramidal cells, where they regulate pyramidal cell excitability. The common effects of different neurodegenerative diseases on pyramidal cell excitability together with the close anatomical and functional connection of 5-HT_{2A}Rs to pyramidal cell excitability may explain why suppressing 5-HT_{2A}R activity could be an effective strategy to treat dementia-related psychosis.

Key Points

Most pathological changes in neurodegenerative diseases cause degradation of inhibitory controls, resulting in neuronal cell hyperexcitability and leading to psychotic behaviors.

5-HT_{2A}Rs are highly expressed in these same neuronal cells and play a crucial role in regulating their excitability in both normal and diseased states.

Suppressing 5-HT_{2A}R activity could therefore help control the neuronal hyperexcitability and accompanying psychotic behaviors found in many neurodegenerative diseases.

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1 Introduction

Dementia afflicts nearly 50 million people worldwide [1], with dementia-related psychosis (DRP) affecting ~25% of those who have dementia. DRP is typified by hallucinations and delusions, causes substantial distress to both patients and caregivers, increases healthcare costs, and contributes to higher mortality rates. The most common neurodegenerative dementing illnesses are Alzheimer's disease (AD), dementia with Lewy bodies (DLB), Parkinson's disease (PD) dementia (PDD), vascular dementia (VaD), and frontotemporal dementia (FTD), which account for ~65–70% (AD), 14% (DLB), 10% (VaD), 7% (PDD), and < 1% (FTD) of the ~2.3 million DRP cases in the United States [2–8].

Genetic evidence implicates serotonin (5-HT)$_{2A}$ receptors (5-HT_{2A}Rs) as having a role in both the emergence and treatment of DRP. A variety of studies have linked genetic polymorphisms in the 5-HT_{2A}R genetic locus to psychotic symptoms and behavioral disturbances in dementia [9], but this correlation is not universally accepted and may be influenced by other factors [10]. Nevertheless, at least with respect to schizophrenia, twin studies show that

schizophrenia is highly heritable, while a number of studies have shown associations between polymorphisms in the 5-HT_{2A}R gene and overall risk of developing schizophrenia, deficits in sensorimotor gating, and response to antipsychotic treatments (reviewed in [11]).

Studies with agents that activate 5-HT_{2A}Rs, as well as selective 5-HT_{2A} inverse agonists, provide further evidence that this receptor is important for both the emergence and treatment of psychotic symptoms, and by inference, dementia-related psychosis. Visual hallucinations (VHs) are a common symptom in subjects with neurodegenerative disease, particularly PD and DLB, but also AD [12]. Qualitatively, these symptoms are similar to the effects of hallucinogenic drugs like lysergic acid diethylamide (LSD) which are known to activate 5-HT_{2A} receptors. Several studies have demonstrated that co-administration of ketanserin, a selective 5-HT_{2A} antagonist, can block the psychotropic effects of LSD and psilocybin [13, 14].

The realization that the highly effective antipsychotic drug clozapine had considerably higher affinity for 5-HT_{2A}Rs over D_2 dopamine receptors [15] was one of first events demonstrating the importance of 5-HT_{2A}Rs as therapeutic targets for psychosis in a field dominated by the dopamine hypothesis of schizophrenia. This discovery spurred the development of a large number of new antipsychotics, termed second generation or atypical antipsychotics, whose most common shared property is high affinity for 5-HT_{2A}Rs [16].

Because of their utility for treating schizophrenia, atypical antipsychotics, and certain atypical antidepressants like trazodone that also inhibit 5-HT_{2A}Rs [17], have been used off label to treat psychosis associated with neurodegenerative disease, but with mixed success, especially when the detrimental effects of these drugs on subjects with dementia are considered [18–21]. For example, of the atypical antipsychotics aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone that have been examined in controlled studies for the treatment of PD psychosis, only clozapine has consistently shown antipsychotic efficacy, an effect Meltzer et al. attributed to 5-HT_{2A}R antagonism, stating, "5-HT_{2A} receptor blockade is the most likely basis for the effectiveness of clozapine" [22]. Interestingly, of the atypical antipsychotics, clozapine has amongst the highest selectivity for 5-HT_{2A}Rs over D_2 receptors [16], and therefore the low doses typically used to treat PD psychosis may achieve relatively selective targeting of 5-HT_{2A}Rs.

Several randomized, well-controlled clinical trials have also been conducted to evaluate the efficacy of atypical antipsychotics (e.g., risperidone, olanzapine, quetiapine, and aripiprazole) in the treatment of the behavioral and psychological symptoms of AD (reviewed in [21]). Systematic reviews of these studies have been mixed regarding the overall benefit versus the relative risks of these medications [19, 23]. A meta-analysis of atypical antipsychotics in the treatment of AD psychosis found that these drugs were associated with increased rates of parkinsonism, sedation, edema, chest infections, stroke (with odds ratios of 2.5–3.0), and mortality (with odds ratios of 1.5–1.7) [24]. A separate meta-analysis among patients treated with atypical antipsychotics for 6–12 weeks reported a doubling of the expected rate of cognitive deterioration [19]. Therefore, in exchange for treating the psychosis, use of these agents in DRP may exacerbate key symptoms of the underlying primary disease. The aforementioned side effects may stem from the fact that these drugs target many other receptors besides 5-HT_{2A} such as dopaminergic, histaminergic, adrenergic, and muscarinic receptors.

Clinical investigations of the selective 5-HT_{2A}R antagonists/inverse agonists M100907 (volinanserin) [25, 26] and SR46349B (eplivanserin) [27] showed statistically significant reductions in total positive and negative syndrome scores in subjects with schizophrenia [11], although both drugs had numerically inferior efficacy compared with haloperidol in these studies. Additionally, ritanserin, a selective 5-$HT_{2A/2C}$ inverse agonist/antagonist, had statistically significant effects compared with placebo on the Scale for the Assessment of Negative Symptoms in subjects with predominantly negative symptoms, although this was a small trial (34 subjects), which limits the conclusions that can be drawn [28]. In addition to demonstrating potential therapeutic benefits, no worsening of extrapyramidal symptoms was observed in these studies. Each of these drugs primarily act through 5-HT_{2A}Rs, and in the case of ritanserin, secondarily through 5-HT_{2C}Rs, and unlike marketed antipsychotics, lack affinity for other receptors including D_2 dopamine receptors. Although none of these drugs are approved for use, these data helped establish the importance of 5-HT_{2A}Rs in psychosis, and selective 5-HT_{2A}R inverse agonists as a treatment for schizophrenia that does not cause motoric side effects. More recently, roluperidone has shown promising efficacy for treating negative symptoms of schizophrenia [29], while lumateperone is approved for schizophrenia [30]. While both of these drugs primarily block 5-HT_{2A}Rs, roluperidone also targets sigma-2 receptors, while lumateperone partially blocks D2 dopamine receptors at therapeutic doses [29, 30].

Pimavanserin is a selective 5-HT_{2A}R inverse agonist/antagonist with lesser activity at 5-HT_{2C}Rs, and no appreciable activity at over 70 other targets tested. Pimavanserin has demonstrated antipsychotic properties in preclinical models, and was recently the first drug approved for treating hallucinations and delusions associated with PD [31]. In a phase II clinical study in schizophrenia, pimavanserin augmented the antipsychotic efficacy of low-dose risperidone but not haloperidol [32]. A subsequent phase III

clinical trial examining pimavanserin as adjunctive treatment to atypical antipsychotic drug therapy failed to meet the primary endpoint, although significant benefits were noted against negative symptoms, a potential indication still being pursued. Pimavanserin was effective at reducing the frequency and/or severity of hallucinations and delusions associated with PD [33] and AD [34]. Although the prespecified primary endpoint of efficacy at 6 weeks was met, the separation between placebo and pimavanserin groups was no longer statistically significant at 12 weeks in the AD trial, due primarily to an increased placebo response at that time point. In both PD and AD trials, further analysis of subgroups revealed that efficacy was greater in PD patients who were cognitively impaired as indicated by lower Mini-Mental State Examination scores [35] and in AD patients with more severe psychiatric symptoms [36]. Significantly, pimavanserin was well tolerated in PD and AD patients, did not cause motoric side effects, and did not worsen cognition in AD subjects over 12 weeks of drug administration [34, 36], a timeframe in which atypical antipsychotic drugs do worsen cognition [19]. Recently, it was announced that pimavanserin significantly reduced the risk of psychotic relapses in a trial enrolling subjects diagnosed with a variety of dementias including AD, PD, DLB, FTD, and VaD [37–39]. These data suggest that selectively targeting 5-HT$_{2A}$Rs has the potential to treat hallucinations and delusions across multiple forms of DRP.

The data described above implicating 5-HT$_{2A}$Rs in DRP generally, and the recent positive clinical trial results with pimavanserin prompted a literature review to identify mechanisms that explain the role of 5-HT$_{2A}$Rs in both the etiology and treatment of DRP. The fact that about half of all people with dementia have mixed pathology, with frequent co-occurrence of neuropathological changes usually associated with AD, DLB, and vascular brain injury [40], together with the fact that many of the psychotic symptoms commonly experienced by dementia patients are qualitatively similar across different dementias [41, 42], were additional motivating factors to attempt to elucidate common mechanisms linking 5-HT$_{2A}$Rs to DRP. For this narrative review, searches were conducted in PubMed for papers written in English, with no date limits, to identify relevant papers that focused on the expression, localization, and normal function of 5-HT$_{2A}$Rs, and the impacts of common neurodegenerative processes on 5-HT$_{2A}$R–expressing cells, particularly cortical glutamatergic pyramidal cells where the densest concentrations of 5-HT$_{2A}$Rs are found. Common themes emerged showing an anatomical and functional connection of 5-HT$_{2A}$Rs to pyramidal excitability and that various types of protein aggregation and cortical denervation that occur in neurodegenerative disease promote pyramidal cell hyperexcitability.

2 Brain Regions Implicated in DRP Coincide with Areas of High 5-HT$_{2A}$R Expression

The 5-HT$_{2A}$R subtype is highly expressed across all the major lobes of the cortex, including frontal, parietal, temporal, occipital (visual), and entorhinal cortices (Fig. 1), typically at levels 50–200% higher than the next most abundant serotonergic receptor subtype, the 5-HT$_{1A}$ receptor [43].

The frontal, temporal, and parietal lobes of the cortex are also among the brain regions affected in DRP. For example, several studies in AD subjects, including both postmortem analysis and functional imaging, have helped to define the areas of the brain where the effects of neurodegeneration lead to the emergence of hallucinations and delusions. These regions include the frontal lobes, where white matter lesions were associated with active delusions [44]; the dorsolateral frontal cortex, anterior cingulate cortex, parietal cortex, and ventral striatum, where hypoperfusion was implicated in hallucinations and delusions [45]; and the frontal, temporal, and parietal lobes, where AD patients with VHs also showed hypoperfusion [46].

A postmortem evaluation of the neuropathology in patients diagnosed with DLB, PDD, and PD found that the occurrence of VHs in these patients was correlated with high densities of Lewy bodies in the temporal lobe and amygdala [47]. α-Synuclein aggregates in the cortical lobes were found to strongly correlated with VHs in PD and DLB patients [48]. Lewy body load was significantly higher across frontal, temporal, and parietal cortical areas in PD patients with VHs than in those without VHs [49]. Other studies confirmed Lewy body load was significantly higher in the frontal and temporal cortices of patients who had had VHs, and showed increased atrophy within frontal lobes of DLB patients with hallucinations compared to those without [48, 50, 51].

A magnetic resonance imaging (MRI) study comparing PD patients with VHs to PD patients without VHs and to a control group showed the greatest grey matter reductions in the PD patients with VHs, specifically in the parietal lobe [52]. Grey matter includes interneurons that provide inhibitory control; thus, losing grey matter may promote pyramidal cell hyperexcitability. Other studies have shown that disinhibition in discrete areas of the visual cortex produces distinct types of VHs [53, 54]. The frontal lobe plays a key role in the control of focalized attention; impairment of this region leading to poor perception and attention has been invoked to explain VHs in PD and DLB [55]. In sum, these studies suggest that pathological changes in brain regions with high levels of 5-HT$_{2A}$Rs may underlie many hallucinations and delusions associated with neurodegenerative dementing illnesses in the elderly.

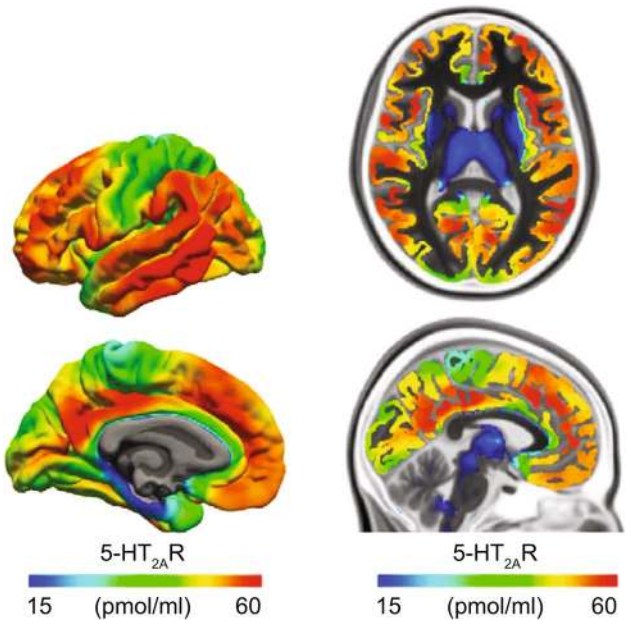

Fig. 1 Density maps for 5-HT_{2A} receptors. From Beliveau V, Ganz M, Feng L, Ozenne B, Højgaard L, Fisher PM, et al. A high-resolution in vivo atlas of the human brain's serotonin system. J Neurosci. 2017;37(1):120–8. Used with permission of *J Neurosci*. Permission conveyed through Copyright Clearance Center, Inc

3 5-HT_{2A}Rs Regulate Glutamatergic Pyramidal Cell Excitability

At the cellular level, the highest expression of 5-HT_{2A}Rs is found on the apical dendrites of glutamatergic pyramidal cells in both cortical [56] and subcortical [57] structures important for cognition, mood, and memory. Jakab and Goldman-Rakic also proposed that "probably all glutamatergic pyramidal cells express 5-HT_{2A} receptors" [56]. Stahl proposed that excessive glutamatergic pyramidal cell output may drive psychotic symptoms [58].

5-HT_{2A}R activation excites glutamatergic pyramidal cells by depolarizing them, leading to spontaneous excitatory postsynaptic potentials, and by inhibiting after-hyperpolarizing currents, which also contributes to increasing pyramidal cell excitability [59]. Jakab and Goldman-Rakic proposed a 'gating function' for 5-HT_{2A}Rs to regulate information flow through glutamatergic pyramidal cell apical dendrites, facilitating excitatory neurotransmission in glutamatergic pyramidal neurons engaged in information processing [56]. They speculated that excessive 5-HT_{2A}R activation may be disruptive, causing dysfunctional gating of apical dendritic ion channels and resulting in psychotic behavioral states. According to their model, in a psychotic state, the glutamatergic pyramidal cells are unable to return to a resting firing mode but remain hyperactive.

Subsequently, Jakab and Goldman-Rakic experimentally determined that 5-HT_{2A}Rs are also expressed in large and medium-size parvalbumin-positive (also calbindin-positive) gamma aminobutyric acid (GABA)-ergic interneurons known to specialize in the perisomatic inhibition of glutamatergic pyramidal cells [60]. These interneurons have long axons that innervate the soma of glutamatergic pyramidal cells in different cortical columns and which are crucial for regulating cortical excitatory/inhibitory (E/I) balance [61]. There are two subclasses of parvalbumin-positive interneurons, chandelier cells and basket cells. Chandelier cells innervate the axon initial segment of glutamatergic pyramidal cells, and basket cells synapse onto the soma and proximal dendrites of glutamatergic pyramidal cells; both express 5-HT_{2A}Rs [57]. Significantly, the axon initial segment links the glutamatergic pyramidal cell body to the axon where action potentials are initiated.

5-HT primarily increases the excitability of the 5-HT_{2A}R–containing glutamatergic pyramidal cells at the apical dendritic field [62], where the concentrations of 5-HT_{2A}Rs are high [56], but it can also suppress glutamatergic pyramidal cell firing by activating the 5-HT_{2A}R–containing perisomatic inhibitory neurons. Net E/I balance on synaptic transmission may be influenced by the magnitude and duration of 5-HT_{2A}R activation [63]. Thus, losing GABA-ergic interneuron function in neurodegenerative diseases can shift the influence of 5-HT_{2A}Rs to excessive excitation even when some 5-HT_{2A}Rs are lost (discussed in the following section).

4 Neurodegenerative Processes Promote Glutamatergic Pyramidal Cell Hyperexcitability

Disinhibition of neural structures leading to loss of E/I balance is a hypothesis explaining the causes and origins of hallucinations [48]. When neurodegeneration occurs, E/I balance can be destroyed through loss of GABAergic interneurons, disruption of synaptic contacts between GABAergic interneurons and glutamatergic pyramidal cells, and changes in expression levels of 5-HT_{2A}Rs. Importantly, the structures affected by neurodegeneration largely overlap with the structures described above that express 5-HT_{2A}Rs.

Accumulated β-amyloid (Aβ) disrupts synaptic transmission, perturbs E/I balance, and contributes to cognitive decline in AD [64–66]. Busche and coworkers showed that neuronal E/I balance is disrupted by Aβ plaques and that the proportion of hyperexcitable neurons is very well correlated with both the development of amyloid plaques and the proximity to those plaques [67, 68]. Preclinically, transgenic mice that overexpress Aβ also show hyperexcitation

in individual neurons in cortical and hippocampal networks [67, 69]. At pathologically relevant concentrations (based on levels found in patients and animal models of AD) [70], soluble Aβ peptides cause neuronal hyperexcitation in cultured neurons [69, 71, 72].

Mechanistically, Ren and coworkers showed that one of the targets of Aβ leading to neuronal hyperexcitability is parvalbumin-positive interneurons [66], which express 5-HT$_{2A}$Rs (discussed in Sect. 3; see Jakab and Goldman-Rakic [60]). Using whole cell recordings, Ren et al. found that addition of soluble Aβ causes hyperexcitability of glutamatergic pyramidal cells in mouse brain slices derived from the anterior cingulate cortex. By recording both interneurons and glutamatergic pyramidal cells, it was shown that disruption of the inhibitory input from the parvalbumin-positive interneurons by Aβ was responsible for the E/I imbalance and hyperexcitability of glutamatergic pyramidal cells [66].

Additional detailed examples of the dysregulation of glutamatergic pyramidal cell excitability by Aβ have been described. Using amyloid precursor protein/presenilin 1 transgenic mice, immunofluorescent staining and confocal microscopy revealed losses in GABAergic innervation of glutamatergic pyramidal cells contacted with or enveloped by Aβ plaques, particularly at the axon initial segment [73]. Similarly, postmortem analysis of cortical brain tissue from AD patients showed that Aβ plaques disrupt perisomatic contact of 5-HT$_{2A}$R–expressing parvalbumin-positive interneurons with glutamatergic pyramidal cells [74]. Since these perisomatic synapses exert a strong inhibitory influence on glutamatergic pyramidal cell output, losing them may promote hyperactivity of the neurons in contact with plaques.

Aβ can also increase neuronal excitability indirectly through its effects on other receptors and neurotransmitters. For example, Chen et al. found that Aβ impairs nicotinic activation of GABAergic inhibitory inputs to cortical glutamatergic pyramidal neurons, leading to E/I imbalance and disruption of working memory [75]. This demonstrates another way Aβ disrupts E/I balance and also reinforces the idea that loss of cholinergic input (specifically, loss of acetylcholine [ACh]), as often occurs in AD and PD, would also disrupt E/I balance in the cortex (Disscussed in Sect. 6).

Hyperphosphorylated tau (P-tau) protein aggregates are also a key feature of AD. Like Aβ, it may be soluble forms of P-tau rather than aggregation of P-tau into neurofibrillary tangles that drive pathogenesis (see [76]). Crimins et al. used a transgenic mouse model of tauopathy (rTg4510 mice carrying the tau P301L mutation) and performed electrophysiological measurements complemented with confocal microscopy to examine the effects of P-tau on neuronal excitability [77]. They compared neurons derived from young (1–3 months) mice with very early tauopathy to old (9–13 months) mice with advanced tauopathy. Increases in neuronal excitability were seen in neurons from both young and aged transgenic mice compared with wild-type mice. Given its role as a microtubule-associated protein, the authors speculated that P-tau–induced trafficking abnormalities along microtubule and actin networks impair dendritic delivery of hyperpolarization cyclic nucleotide–gated channels, altering the electrophysiological properties of the neuron, even at early stages of the disease.

With disease progression, P-tau also causes losses of GABAergic interneurons to further disrupt E/I balance. For example, in apolipoprotein E transgenic mice, loss of GABAergic interneurons occurs in a tau-dependent manner, and, with that, a concomitant reduction of miniature inhibitory postsynaptic currents and impairment of learning and memory [78]. Likewise, Levenga et al. showed that GABAergic function in the hippocampus is impaired by tau [79]. Using transgenic mice expressing human tau P301L, tau expression was correlated with increased excitatory postsynaptic potentials in the hippocampus, indicating an E/I imbalance. Levenga et al. showed that the E/I imbalance could be normalized with zolpidem, a GABAa agonist, implicating reduced GABAergic interneuron function as the cause [79]. Tau-induced increases in neuronal excitability are compounded when there is also accumulation of Aβ [80].

P-tau is also associated with other forms of dementia, such as some forms of frontotemporal lobar dementia (FTLD) (see Noble et al. [81]), as well as dementias derived from repetitive mild traumatic brain injury and chronic traumatic encephalopathy (see Takahata et al. [82]). Therefore, the mechanisms described above may also be relevant for explaining the same behavioral disturbances that occur in these other disorders. A study employing transgenic mice expressing human tau with an FTD-associated mutation (V337M) found that the mice had impaired expression and synaptic localization of *N*-methyl-D-aspartate receptors (NMDARs) [83]. The authors hypothesized that NMDAR hypofunction contributed to the behavioral disturbances they observed. As evidence, they demonstrated that D-cycloserine, an NMDAR modulator that enhances NMDAR function, normalized behavior in these mice. It is known that the highly selective 5-HT$_{2A}$R inverse agonist M100907 potentiates NMDAR-mediated neurotransmission through cortical and hippocampal glutamatergic pyramidal cells [84, 85].

Similarly, in DLB, where VHs are quite common, significant losses of parvalbumin-positive interneurons occur throughout the hippocampus, which is speculated to be a result of α-synuclein accumulation or a consequence of calcium toxicity and/or impaired mitochondrial function [86]. A recent review of VHs in synucleinopathies indicates how α-synuclein may disrupt E/I balance through effects on glutamate and GABA signaling by enhancing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor function and suppressing NMDA receptor function, as

well as through degeneration of cholinergic, dopaminergic, and serotonergic signaling [87].

Cerebrovascular disease, vascular lesions, and various vascular risk factors, including hypertension and hypercholesterolemia, have been shown to be associated with greater incidence of psychotic symptoms, even in pathologically defined AD subjects [88, 89]. As discussed in Sect. 1, the underlying pathology causing DRP is often mixed, and this is particularly true of VaD, which is very frequently associated with AD. Although a mechanistic link between vascular risk factors and vascular lesions in causing psychosis has not been established [90], vascular deposition of Aβ may promote blood vessel occlusion in the brain, a process called cerebral amyloid angiopathy. Conversely, cerebral hypoperfusion created by carotid artery occlusion increases the rate of formation of Aβ fibrils and Aβ plaques in transgenic mice expressing human amyloid precursor protein [91]. These findings suggest that events occurring in AD and VaD may promote each other.

Preclinical models of cerebrovascular disease recapitulate some of the pathophysiological changes seen in humans, but mechanistic studies specifically linking cerebrovascular disease to the emergence of psychotic symptoms are lacking. Shibata and coworkers showed occluding the carotid artery to have a fairly specific effect on working memory but no significant effects on a variety of other behavioral endpoints, including prepulse inhibition, which is considered to be an index of psychosis [92]. Cerebral amyloid angiopathy has been modeled in animals [93], but effects of cerebral amyloid angiopathy on preclinical indices of psychosis have not been reported.

Despite the lack of a clear mechanism explaining how VaD causes hallucinations and delusions, empirically, risperidone, which has potent 5-HT_{2A}R inverse agonist activity [16], is effective in controlling psychosis in many forms of dementia, including VaD [94]. A case report showed clozapine to be effective against psychotic delusions in a patient with VaD in whom haloperidol and quetiapine were not [95]. Clozapine has one of the highest ratios of 5-HT_{2A}R to dopamine D_2 receptor activity of the atypical antipsychotic drugs [16]. A limitation of these studies is that both risperidone and clozapine are active at many other receptor targets, so one cannot be certain that their effects are mediated solely through 5-HT_{2A}Rs. A preclinical study showed that administration of the 5-HT_2 receptor antagonists pirenperone, cinanserin, and ritanserin to rats significantly reduced the cognitive impairment in a working memory task caused by transient forebrain ischemia, although one cannot conclude how they might address psychotic symptoms from this study [96]. Postmortem binding studies showed increased expression of 5-HT_{2A}Rs in VaD [97], which is also frequently the case in PD psychosis.

5 Chronic Inflammation Reduces Parvalbumin-Positive Interneurons and Glutamatergic Pyramidal Cell Hyperexcitability

Chronic inflammation and oxidative stress contribute to disrupting E/I balance between glutamatergic pyramidal cells and GABAergic interneurons in the prefrontal cortex (PFC) [98]. It has been proposed that neuroinflammation, oxidative stress, and NMDA receptor hypofunction impair the normal development of parvalbumin GABAergic interneurons (which express 5-HT_{2A}Rs, discussed in Sect. 3), leading to the behavioral disturbances and cognitive impairment associated with schizophrenia [99]. Chronic inflammation, oxidative stress and exposure to pro-inflammatory cytokines in early life may contribute to faulty neurodevelopment, particularly reduced development of inhibitory interneurons, leading to altered E/I balance characteristic of schizophrenia [100, 101].

The mechanistic links of chronic inflammation and oxidative stress to psychosis are analogous to the other mechanisms described above. Parvalbumin-positive GABAergic interneurons are particularly vulnerable to chronic inflammation and oxidative stress due to their high rates of metabolism [102, 103]. These neurons, also termed 'fast-spiking interneurons', require high metabolic activity and hence contain many mitochondria to sustain such fast firing. Damage to or loss of these neurons (decreased interneuron population) will result in disinhibition of glutamatergic pyramidal cells, loss of neural synchronization, and psychosis phenotypes, much in the same way the protein aggregates common to neurodegenerative diseases lead to the same outcome (described above).

Experimentally, the harmful effects of inflammation and oxidative stress on GABAergic interneurons have been shown in a number of different models, including genetic, environmental, and pharmacological models [104]. Although many of these studies did not specifically model psychosis, they illustrate how chronic inflammation affects neuronal populations, neuropsychiatric behaviors, and cognition.

For example, acute intracerebroventricular administration of soluble Aβ oligomers to rats caused sustained increases in inflammatory markers (tumor necrosis factor [TNF]-α, interleukin [IL]-1β), decreases in synaptic markers (PSD-95, SNAP-25) and loss of parvalbumin-positive interneurons in the frontal cortex [105]. Functionally, models of schizophrenia were not investigated, but Aβ treatment caused memory impairment in the rats. Interestingly, the loss of neurons caused by Aβ infusion was fairly specific to parvalbumin interneurons, as the overall number of neurons was not significantly affected. This is consistent with the notion that

parvalbumin interneurons are particularly vulnerable to the effects of chronic inflammation.

Direct, continuous intracerebroventricular infusion of TNF-α over a 7-day period to mice, coupled with noise exposure, caused significant loss of cortical parvalbumin-positive interneurons and impaired pre-pulse inhibition [106]. The combination of TNF-α infusion and noise exposure, but neither alone, was correlated with microglial activation as evidenced by morphological deramification. Impaired pre-pulse inhibition is a common feature in subjects with schizophrenia.

Traumatic brain injury in mice caused by blast exposure led to increased expression of TNF-α, microglial activation, and loss of parvalbumin-positive inhibitory interneurons [107]. These pathologic changes resulted in increased excitatory and reduced inhibitory synaptic transmission as measured primarily by the frequencies of miniature excitatory postsynaptic currents and miniature inhibitory postsynaptic currents in CA1 pyramidal cells, respectively. Administration of the TNF-α inhibitor 3,6′-dithiothalidomide reduced levels of TNF-α close to the levels seen in sham control mice, prevented parvalbumin-positive interneuron loss, and restored E/I balance.

Chronic treatment of rodents with NMDA receptor antagonists like phencyclidine are commonly used models of schizophrenia because they cause cognitive deficits and deficits in social interactions. The pathological basis for these behavioral changes may stem from reductions in parvalbumin-positive GABAergic interneuron expression caused by phencyclidine [108]. Interestingly, in another study examining the effects of chronic exposure to phencyclidine, cortical parvalbumin-positive interneuron loss in rats was reversed by clozapine but not haloperidol [109]. Chronic phencyclidine administration to mice causes an inflammatory response characterized by astrocyte and microglial activation and upregulation of the proinflammatory cytokine IL-1β [110], a possible mechanistic link between phencyclidine treatment and parvalbumin-positive interneuron loss.

6 Cortical Denervation Promotes Glutamatergic Pyramidal Cell Hyperexcitability and Changes in 5-HT$_{2A}$R Expression

Aβ, tau, and α-synuclein reduce monoaminergic signaling in the cortex by damaging the cell bodies originating from the basal forebrain and brain stem that produce these neurotransmitters, a process called cortical denervation. Cortical denervation is a prominent feature of AD [111] but is also important in PD [112, 113], DLB [114], and FTD [115]. Frequently, multiple transmitter systems are affected, with alterations of absolute levels and relative ratios between neurotransmitters. Cortical denervation disrupts glutamatergic pyramidal cell E/I balance and contributes to cognitive impairment and other comorbid symptoms like depression.

ACh is highly relevant for dementia. Loss of cholinergic signaling is a hallmark of AD and also a prominent feature of PD and DLB [116]. Anticholinergic (antimuscarinic) drugs are well known to cause hallucinations, especially VHs, whereas acetylcholinesterase inhibitors reduce psychotic symptoms in some demented patients, including those with PD [117] and DLB [118].

ACh maintains E/I balance in part through α_7-nicotinic receptors expressed on GABAergic interneurons. Loss of cholinergic innervation may therefore result in decreased output of these interneurons, causing disinhibition of glutamatergic pyramidal cells [119]. The propensity of schizophrenic patients to smoke cigarettes may represent attempts to self-medicate with nicotine, which would activate α_7-nicotinic receptors. ACh activation of M_1 muscarinic ACh receptors potentiates NMDA receptor function, and therefore a loss of ACh may contribute to the NMDA receptor hypofunction believed to underlie some of the symptoms of psychosis [120]. Tissue-specific knockout of M_1 muscarinic receptors eliminates ACh activation of parvalbumin-positive interneurons, disrupting the synchrony of gamma oscillations representing coordinated activation of glutamatergic pyramidal cells important for learning, memory, and attention [121].

A large study conducted by the Alzheimer's Disease Neuroimaging Initiative showed that neurodegeneration in the basal forebrain preceded and was correlated with subsequent progression to cortical neurodegeneration [111]. Disease progression was followed for 2 years in patients with mild cognitive impairment, patients with mild cognitive impairment who progressed to AD at the end of 2 years, patients with AD, and age-matched healthy controls using MRI and measurements of cerebrospinal fluid levels of $A\beta_{1-42}$. The results showed the emergence of volumetric changes in the basal forebrain that followed closely or were coincident with changes in cerebrospinal fluid $A\beta_{1-42}$ but which clearly preceded changes in entorhinal cortex volume. This implies that increases in $A\beta_{1-42}$ damage the basal forebrain early in disease progression. It contains structures crucial for the production of ACh, and thus damage to the basal forebrain could cause a loss of ACh. Loss of cholinergic signaling in the visual cortex is correlated with VHs in AD [122]. Loss of cholinergic innervation of the visual cortex also occurs in DLB and may even exceed losses seen in AD [123].

Dopamine is also an important neurotransmitter in dementia, with loss of dopamine featured in FTD and DLB as well as PD [112, 115]. There is clinical and experimental evidence of a nigrostriatal deficit in many cases of FTD, with loss of presynaptic dopaminergic neurons, reduced dopamine levels, reduced dopamine active transporter

binding, and abnormal dopamine receptor binding. In addition to extrapyramidal motor features, degeneration of dopaminergic tracts, especially the mesocortical pathway, could contribute to behavioral symptoms of FTD [115].

The neurotoxin 6-hydroxy dopamine (6-OHDA) is used to model PD because in the presence of norepinephrine reuptake inhibitors, this compound is selectively transported into dopamine neurons, where it destroys them. Using this model, Wang and coworkers found that complete unilateral 6-OHDA lesioning of the substantia nigra and partial lesioning of the ventral tegmental area (VTA) in rats increases the mean firing rate and number of bursts per spike of glutamatergic pyramidal neurons in the medial PFC [124], subsequently demonstrating that the increased glutamatergic pyramidal cell firing was caused by reduced firing of inhibitory GABAergic interneurons [125]. Since dopamine neurons projecting from the VTA contact GABAergic interneurons in the medial PFC [126, 127], and these interneurons express dopamine receptors [128, 129], losing dopamine innervation from the VTA would reduce interneuron activity, effectively disinhibiting glutamatergic pyramidal cells in the PFC.

Many of the behavioral effects of 6-OHDA lesioning of the substantia nigra resemble the rodent surrogates of psychosis. Lesioned rats displayed augmented spontaneous head-twitch response, a behavior highly correlated with 5-HT_{2A}R activation by hallucinogenic drugs, sensorimotor gating deficits (loss of prepulse inhibition, a feature seen in schizophrenic subjects), and augmented hyperactivity responses to amphetamine [130]. In all cases, these behaviors were normalized by pimavanserin and M100907 but not by the selective 5-HT_{2C}R antagonist SB242084. This study was consistent with previous studies showing upregulation of 5-HT_{2A}R signaling in animal models of PD employing dopamine neuron lesioning [131, 132] and in human patients with PD [133, 134]. Interestingly, intracerebroventricular infusion of Aβ peptide fragments produced virtually the same behavioral phenotypes as the 6-OHDA lesioning study, behaviors that were also normalized by pimavanserin and M100907, demonstrating how diverse pathological changes can produce similar neuropsychiatric symptoms [135].

Postmortem analysis of PD patients with dementia revealed marked reductions in noradrenergic innervation and reduced norepinephrine levels compared with age-matched neurologically normal controls [112]. These losses were observed throughout the brain, including in the visual-associated cortex. Similarly, loss of norepinephrine is a feature of FTD [115]. Release of norepinephrine into the medial PFC, either through stimulation of the locus coeruleus or by direct application of norepinephrine, has inhibitory effects on neuronal activity [136, 137]. These results suggest depletion of norepinephrine would contribute to increased neuronal excitability.

5-HT dysfunction occurs in disorders involving FTLD [115]. Interestingly, differences are seen in the effects on 5-HT_{2A}R expression depending on which clinical disorder one looks at, with decreases seen in FTD but increases seen in the related syndrome progressive supranuclear palsy. Subjects with PD also have reduced serotonergic innervation in certain brain regions [112]. The degeneration of serotonergic neurons from the Raphe nuclei as well as loss of some 5-HT receptor–containing glutamatergic pyramidal cells that occurs in PD can result in upregulation of 5-HT_{2A}Rs on the remaining glutamatergic pyramidal cells [58].

Compensatory upregulation of both D_1- and D_2-type dopamine receptors results from dopamine denervation that occurs in PD [138]. Upregulation of striatal dopamine receptors (denervation supersensitivity) occurs whether nigrostriatal dopamine denervation is caused by the neurodegenerative process of PD or by selective dopamine neuron lesioning in animal models of PD [139]. In addition, as described above, loss of dopamine also leads to upregulation of serotonergic signaling and 5-HT_{2A}Rs. These changes result in intrinsic increases in patient susceptibility to behavioral disturbances as well as increased sensitivity to dopamine replacement therapies.

Altered ratios of different monoamines may also predispose to VHs. In a postmortem analysis, DLB patients who had VHs could be distinguished from those who did not by a higher ratio of dopamine and 5-HT metabolites to choline acetyl transferase (ChAT) levels [140]. All of these parameters were lower than normal controls, but the ratios differed greatly. For example, the 5-hydroxyindoleacetic acid/ChAT ratios were 9.3, 3.1, and 4.6 for DLB with VHs, DLB without VHs, and normal controls, respectively. Perry and colleagues speculated that "effective treatment of hallucinations with serotonin receptor blockers would lend credence to the hypothesis that monoaminergic-cholinergic imbalance is responsible for the emergence of hallucinations," though they further speculated that such patients "might be more responsive to cholinergic replacement therapy" [140].

Figure 2 depicts the effects of neurodegeneration and denervation on glutamatergic pyramidal cell excitability.

7 5-HT_{2A}R Expression and Its Relevance for DRP

In PD, increased expression of 5-HT_{2A}Rs (or 5-HT_{2A}R binding potential) has been associated with the prevalence of hallucinations and delusions [133]. Using positron emission tomography, Ballanger and coworkers found that the 5-HT_{2A}R binding potential was nearly twice as high in brain structures associated with visual stimulus and cognitive

processing in patients with PD and VHs as in patients with PD but without VHs.

Other publications support the Ballanger study. In postmortem binding studies, Chen and coworkers reported increased 5-HT$_{2A}$R binding in the orbitofrontal and temporal cortex of PD patients compared with age-matched controls [141], and Huot et al. observed significant increases in 5-HT$_{2A}$R binding in the inferotemporal cortex of PD patients with VHs compared with PD patients without VHs [134]. Finally, Rasmussen and coworkers used radioligand binding with [^{3}H]MDL 100.907 together with western blotting for α-synuclein in postmortem studies to show that increased 5-HT$_{2A}$R expression in the frontal cortex was accompanied by increased α-synuclein in subjects who had PD [142]. A possible explanation for increased 5-HT$_{2A}$R expression is that it is a compensatory increase in response to lower 5-HT levels seen in PD [112].

Binding studies on postmortem tissue from frontal and temporal cortices obtained from patients with various forms of VaD or mixed AD/VaD showed that, in certain VaD cases, the expression levels of 5-HT$_{2A}$Rs (and 5-HT$_{1A}$Rs) in the temporal cortex were significantly increased relative to control subjects, whereas there were no significant changes in the frontal cortex [97]. Given the role of 5-HT$_{2A}$Rs in the perception and processing of visual information, excessive activation of 5-HT$_{2A}$Rs in the temporal cortex and/or an imbalance of 5-HT$_{2A}$R signaling in this region relative to other regions may promote formation of VHs. The authors speculated that it would be important to determine whether upregulation of 5-HT$_{2A}$Rs (and 5-HT$_{1A}$Rs) is associated with noncognitive symptoms like psychosis [112].

The situation is different in other forms of dementia, for which studies have typically found reduced expression of 5-HT$_{2A}$Rs, particularly in AD [143–145] and animal models of AD [146]. However, although overall 5-HT$_{2A}$R expression levels are lowered, the balance of 5-HT$_{2A}$R expression levels may be altered between different cell types that modulate excitability (e.g., glutamatergic pyramidal cells vs GABAergic interneurons) or compared with other receptors that influence excitability (e.g., 5-HT$_{1A}$ or 5-HT$_3$). As described above, 5-HT$_{2A}$Rs are expressed on both GABAergic interneurons and glutamatergic pyramidal cells, and frequently there is disproportionate loss of GABAergic interneurons relative to glutamatergic pyramidal cells in neurodegenerative diseases. In such situations, one could have an overall loss of 5-HT$_{2A}$Rs but the ratio of 5-HT$_{2A}$R expression would be shifted away from inhibitory cells, more toward excitatory cells, theoretically promoting E/I imbalance.

Examples of regionally specific changes in 5-HT$_{2A}$R expression have been described [97, 147]. Cheng and coworkers compared cortical expression levels of 5-HT$_{2A}$Rs in postmortem brain tissue derived from patients with AD, PD, PDD, DLB, and DLB plus VHs versus a control group of patients with no history of neurological or psychiatric disease [147]. Six different layers of the temporal cortex were examined. 5-HT$_{2A}$R expression was reduced in all groups and across all layers examined compared with the control

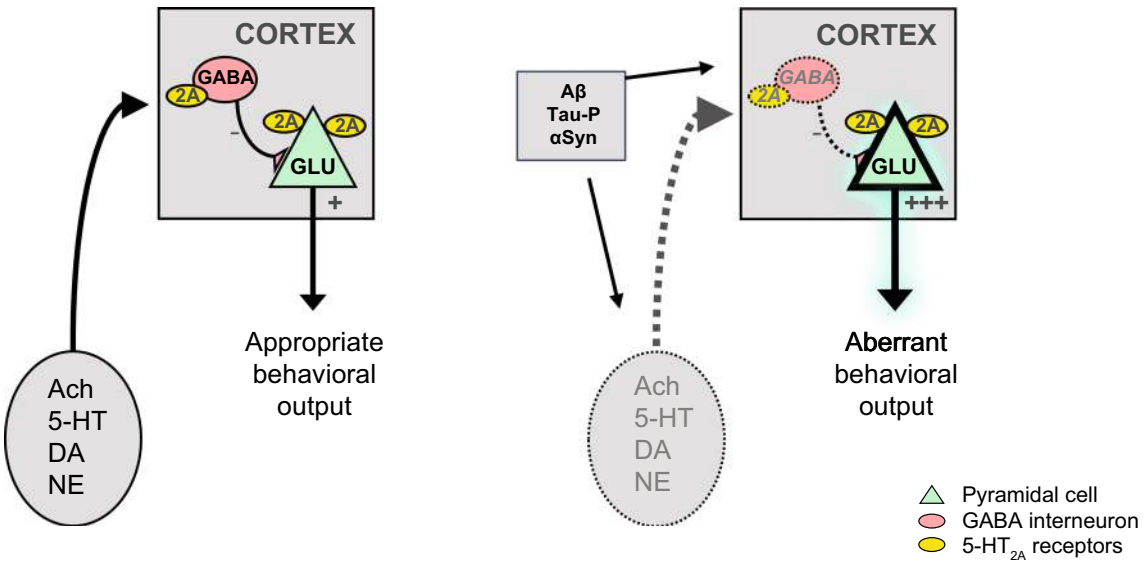

Fig. 2 Innervation of the cortex by neurons containing acetylcholine (*ACh*), serotonin (*5-HT*), dopamine (*DA*), and norepinephrine (*NE*) that originate from subcortical cell bodies. Accumulation of β-amyloid (*Aβ*), P-tau, and α-synuclein (*αSyn*) leads to reduced monoaminergic cortical input and loss of GABAergic interneurons or GABAergic interneuron synaptic contact with glutamatergic pyramidal cells, as depicted by dashed lines and grey font. Together, these changes disrupt excitatory/inhibitory balance, promoting aberrant behavior. *5-HT* serotonin, *GABA* gamma aminobutyric acid, *GLU* glutamate

group. However, there were marked differences in the 5-HT_{2A}R levels between layers, as well as highly significant differences in 5-HT_{2A}R expression in certain cortical layers across patients with different disease histories. Layers C and E, which correspond to cortical layers III and V, each contain many glutamatergic pyramidal cells and were the layers with the highest expression, consistent with other reports [43, 56]. In the DLB plus VHs group, 5-HT_{2A}R expression in layers C and E was much better preserved than in both the other layers and in the DLB patients without VHs. Thus, although the overall expression of 5-HT_{2A}Rs was reduced in every case, in DLB patients who had VHs, the ratio of 5-HT_{2A}Rs expressed in cortical layers containing a high concentration of excitatory cells was increased relative to the other cortical layers.

Changes in the ratio of 5-HT_{2A}Rs to other neurotransmitter systems have been described. The absolute levels of 5-HT_{2A}Rs were lower in DLB patients who had VHs than in normal subjects (33 vs 42 fmol/mg); however, the ratio of 5-HT_{2A}Rs to ChAT was ~20 in DLB patients with VHs compared with 5 in normal controls, and 4 in DLB without VHs [140]. These results indicate an increased ratio of serotonergic to cholinergic signaling in DLB patients with VHs despite the fact that overall expression of 5-HT_{2A}Rs is lower.

5-HT_{2A}R expression increases substantially in activated astrocytes in people with AD, FTD, Huntington's disease, and other pathological states [148]. Whether astrocyte upregulation of 5-HT_{2A}Rs represents a physiological response to or a consequence of these diseases and whether or not increased 5-HT_{2A}R expression in astrocytes exacerbates disease pathology is unknown. As described above, there is a clear link between chronic inflammation, loss of parvalbumin-positive interneurons, and deregulated E/I balance, and thus it is interesting to speculate whether suppressing 5-HT_{2A}R activity would restore E/I balance by impacting neuroinflammation. Regardless, this example again shows how neurodegenerative disease may have unequal effects on 5-HT_{2A}R expression in different cell types.

Finally, Beliveau et al. observed that in cortical regions, mRNA levels of 5-HT_{2A}Rs were almost twice as high as other investigated targets and linearly correlated with 5-HT_{2A}R protein levels [43]. The authors speculated that high mRNA levels enable rapid regulation of synaptic 5-HT_{2A}R levels, consistent with a dynamic role for 5-HT_{2A}Rs in controlling synaptic activity. The very linear and shallow correlation curve of protein expression (abscissa) with mRNA (ordinate) in cortical regions suggests small changes in transcription could cause large changes in protein expression of 5-HT_{2A}Rs in the cortex (see Fig. 5D in Beliveau et al. [43]). This is relevant for DRP, in which expression levels of 5-HT_{2A}Rs are frequently altered.

8 Conclusion

Pimavanserin effectively reduced hallucinations and delusions associated with DRP in multiple clinical studies, which included patients with the major forms of dementia, and was well tolerated by elderly fragile patients in the studies [33–37, 149]. The purpose of this review was to identify mechanisms that explain the role of 5-HT_{2A}Rs in both the etiology and treatment of DRP. The main finding is that despite the diverse pathological changes associated with different types of neurodegenerative disease and dementia, many of these pathological changes promote glutamatergic pyramidal cell hyperexcitability and loss of E/I balance, effects that predispose to psychosis. The close anatomical and functional connection of 5-HT_{2A}Rs with glutamatergic pyramidal cell excitability are reasons why suppressing 5-HT_{2A}R activity may be an effective strategy to reduce psychosis across different dementia subtypes.

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Declarations

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