Review

Does stimulation of 5-HT_{1A} receptors improve cognition in schizophrenia?

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Abstract

Cognitive impairment is a key feature of schizophrenia and may be the most important determinant of outcome in schizophrenia. This impairment is diffuse and may reflect abnormalities in frontal cortex, hippocampus and other brain regions. While deficits in glutamatergic, GABAergic, dopaminergic and cholinergic impairment have received the most attention as the basis of this impairment, there are many reasons for considering the role of serotonin (5-HT) in contributing to these deficits. This may be via its influence on dopaminergic, cholinergic, glutamatergic and GABAergic function, as well as various growth factors that have been implicated in schizophrenia. Of the 14 known serotonin receptors, the 5-HT_{1A} receptor is a key candidate for mediating at least some of the influence 5-HT has on cognition. 5-HT_{1A} receptors are upregulated in postmortem specimens from patients with schizophrenia, suggesting a deficit in 5-HT_{1A} function in this disorder. Atypical but not typical antipsychotic drugs stimulate the efflux of dopamine from cortex by a 5-HT_{1A}-dependent mechanism. A series of studies from this laboratory involving the 5-HT_{1A} partial agonists tandospirone and buspirone have reported a modest ability of these agents to improve some domains of cognition in patients receiving typical or atypical antipsychotic drugs. Preclinical studies have been mixed in regard to the ability of 5-HT_{1A} partial agonists to improve cognition in various paradigms; some studies report that 5-HT_{1A} antagonists are effective to improve cognition. Aripiprazole, clozapine, olanzapine, perospirone, quetiapine risperidone, and ziprasidone are examples of atypical antipsychotic drugs which are either direct or indirect 5-HT_{1A} agonists which have been shown to improve cognitive function in patients with schizophrenia. Further study is needed to determine the role of the 5-HT_{1A} receptor to improve cognitive function in schizophrenia.

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1. Introduction

Cognitive impairment is almost universal in patients with schizophrenia, with over 85% of patients with this disorder showing clinically significant impairment in some but not all domains of cognition, including attention, working memory, declarative memory, speeded motor performance, and executive function [1]. It is well established that this impairment is the strongest determinant of functional outcome in schizophrenia [2]. Typical antipsychotic drugs have minimal benefit on cognition in schizophrenia in most studies (see Ref. [3] for review). Conversely, most, but not all studies have found that atypical antipsychotic drugs, e.g. aripiprazole, clozapine, quetiapine, olanzapine, risperidone, and ziprasidone have greater efficacy to improve cognition than the typical antipsychotic drugs, e.g. haloperidol [4–6]. These drugs share in common the ability to block serotonin (5-HT)_{2A} receptors and to block dopamine (DA) receptor transmission. With
the exception of aripiprazole and the main metabolite of clozapine, N-desmethylclozapine, which are partial DA agonists, they are D2 receptor antagonists, with affinities for the D2 receptor which are weaker than their affinities for the 5-HT2A receptors. We have summarized the evidence concerning differences among the atypical antipsychotic drugs with regard to their ability to improve cognition [4]. Head-to-head comparisons such as a recent study comparing clozapine and ziprasidone [7] sometimes show advantages for one atypical over another but there have been too few such studies to have confidence as to the findings.

There is considerable animal evidence in a variety of paradigms that atypical antipsychotic drugs are more effective than typical antipsychotic drugs in reversing deficits in tasks that involve working memory or long-term memory [8,9]. In addition to being inverse agonists (antagonists) at 5-HT2A receptors, some atypical antipsychotic drugs, including aripiprazole, bifeprunox, clozapine, perospirone, quetiapine and ziprasidone are serotonin (5-HT)1A partial agonists, while others are inferred to be indirect 5-HT1A agonists in that some of the key actions, including the ability to enhance DA and acetylcholine (ACh) efflux in the medial prefrontal cortex, a region known to be important for cognition, are blocked by the 5-HT1A antagonist (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl] -N-(2-pyridyl)cyclohexanecarboxamide (WAY100635) [10–12]). However, these results have not been consistently replicated [13]. It has been suggested the 5-HT1A receptor stimulation can improve memory deficits in depression [14]. Some but not all of the atypical antipsychotic drugs are also 5-HT2C, 5-HT6, and 5-HT7 receptor antagonists. These 5-HT receptors, particularly the 5-HT2C and 5-HT6 receptors, may have an important role in cognition, through their ability to modulate the release of cortical and hippocampal DA and acetylcholine [15]. It is beyond the scope of this article to consider the roles of these other types of 5-HT receptors in mediating the action of atypical antipsychotic drugs to improve cognition. As will be discussed below, there is considerable evidence that 5-HT1A, and 5-HT2A receptors have a reciprocal relationship on many neurobiological processes, including the activity of pyramidal neurons in cortex and hippocampus. It seems likely that for schizophrenia, the 5-HT2A receptor is more important than the 5-HT1A receptor in terms of both pathophysiology and mechanism of action of antipsychotic drugs, as there is more and more evidence accumulating for an intimate relationship between 5-HT2A receptor function and glutamatergic activity [116]. Nevertheless, the role of 5-HT1A receptors remains of keen interest. Based upon these and other data to be considered below, there have now been several reviews of the role of 5-HT1A receptors in schizophrenia, including consideration of their importance for cognitive impairment [17,18].

2. 5-HT1A Receptors and 5-HT1A agonist administration in schizophrenia

This background is relevant to understanding studies which have utilized buspirone, a 5-HT1A partial agonist introduced as an anxiolytic, in patients with schizophrenia receiving typical antipsychotic drugs, such as haloperidol [19–22]. Most studies involving buspirone in doses of 10–100 mg/day, report a beneficial effect on psychotic symptoms or parkinsonism, or both [20–22]. These findings are supported by a small, randomized, placebo-controlled, double-blind study of buspirone, conducted by the authors’ group [23], which found a trend level improvement in positive symptoms, as measured by the Brief Psychiatric Rating Scale Positive symptom scale, in subjects given buspirone 30 mg/day for 6 months.

A key issue in interpreting the results of 5-HT1A Partial agonist administration in preclinical or clinical studies is whether they act on presynaptic or postsynaptic 5-HT1A Receptors, both, or possibly, neither, as none of the available agents are entirely specific for 5-HT1A receptors. The presynaptic 5-HT1A receptor is an autoreceptor located on cell bodies of raphe neurons; stimulation leads to inhibition of firing of 5-HT neurons and a decrease in the release of 5-HT from nerve terminals in terminal regions such as the hippocampus [24]. Stimulation of postsynaptic 5-HT1A receptors, located on cortical pyramidal neurons as well as GABAergic interneurons, generally leads to hyperpolarization of neurons, and diminished release of glutamate or GABA. This effect of 5-HT1A receptor stimulation is opposite to the depolarizing effect of stimulation of 5-HT2A receptors. Postsynaptic 5-HT1A receptors are abundant in the hippocampus, frontal cortex, entorhinal cortex and the amygdala, all of which have been implicated in various aspects of schizophrenia. Postsynaptic 5-HT1A receptors have been shown to inhibit the entry of Ca2+ into nerve terminals, which should serve to reduce/inhibit the release of neurotransmitters such as GABA, ACh and glutamate [25]. The reciprocal effects of 5-HT1A and 5-HT2A receptors on cortical neurons are the most likely basis for the similarity in clinical and preclinical studies of the effects of 5-HT1A agonists and 5-HT2A antagonists. There is extensive evidence indicating that 5-HT1A receptor agonists and 5-HT2A receptor antagonists produce similar neurochemical and behavioral effects on a variety of measures [26]. Chronic buspirone treatment to rodents has been found to differentially and reciprocally regulate 5-HT1A and 5-HT2A receptor mRNA and binding sites in the CA1 and CA2 regions of the rat hippocampus, whereas both upregulated 5-HT1A and 5-HT2A receptors in the dentate gyrus and CA3 and CA4 regions of the hippocampus [27]. Meneses and Hong [28] have suggested that stimulation of presynaptic 5-HT1A receptors is the likely basis for improvement in cognition from 5-HT1A agonists. This work is discussed elsewhere in this volume.

2.1. Postmortem studies

Postmortem studies have reported 5-HT1A receptor density is increased in frontal and temporal cortices in schizophrenia [29–34]. Subsequent PET studies [35,36] confirmed an increase in cortical 5-HT1A receptor binding in schizophrenia. We identified the high-affinity [3H]8-OH-DPAT binding sites which correspond to the 5-HT1A receptor component coupled to G-proteins in human postmortem prefrontal cortex, and found an 80% elevation of the high-affinity sites in subjects with schizophrenia [34]. These studies could find no evidence that this was due to antipsychotic drug treatment. The increased density of 5-HT1A receptors may represent upregulation secondary to diminished 5-HT1A receptor stimulation [32,34]. Whether this presumptive decrease in stimulation of 5-HT1A receptors and subsequent increase in 5-HT1A receptor density is related to the cognitive impairment in patients with schizophrenia remains to be determined.

2.2. Effect of augmentation with 5-HT1A agonists on cognition in schizophrenia

Sumiyoshi and colleagues conducted a series of pilot studies of the effects of the addition of tandospirone, a 5-HT1A partial agonist and azapirone derivative [37,38], to ongoing treatment with small to moderate doses of typical antipsychotic drugs (mainly haloperidol), on cognitive function in patients with schizophrenia [39–41]. The addition of tandospirone (30 mg/day), but not placebo, to typical antipsychotic drugs for 4–6 weeks, was found to improve executive function in one study [39,40] and verbal learning and memory in another [39–41].

Buspirone, 30 mg, neither improved or impaired cognition in healthy human subjects [42]. On the other hand, Yasuno et al.
[43], reported that acute (60 min) administration of a relatively high dose of tandospirone (60 mg/day), impaired verbal memory in healthy volunteers. They also found a lower dose (30 mg/day) of tandospirone slightly impaired memory performance in normals [43]. This discrepancy between the findings of Yasuno et al. [43] and ours may be due to differences in the treatment regimen (acute vs. chronic), subjects studied (normal controls vs. patients with schizophrenia), or a combination of the above [44].

Switching patients with schizophrenia to ziprasidone [45] or perospirone [46], two atypical antipsychotic drugs which are 5-HT1A partial agonists, from typical antipsychotics, improved some aspects of verbal memory in subjects with schizophrenia. Adjunctive use of tandospirone with perospirone produced additional enhancement of verbal learning and memory in a single subject [47].

We have recently reported additional evidence for the beneficial effect of augmentation therapy with 5-HT1A agonists in schizophrenia by conducting a randomly assigned placebo-controlled double-blind study to determine if the addition of buspirone would enhance cognitive function in subjects with schizophrenia treated with atypical antipsychotic drugs [48]. Patients with schizophrenia, who had been treated with an atypical antipsychotic drug for at least 3 months, were randomly assigned to receive either buspirone, 30 mg/day (a small to moderate dose), or matching placebo for 6 months. Several cognitive domains, including attention, verbal learning and memory, and executive function, as well as psychopathology, were assessed. Buspirone outperformed placebo in improving the performance on the Digit Symbol Substitution Test, a measure of attention/speeded motor performance as well as an index of general cognitive function [49]. It is noteworthy that none of the cognitive domains assessed showed deterioration after augmentation with buspirone. Scores on the Brief Psychiatric Rating Scale (total, positive subscale) were improved during treatment with buspirone but not placebo, but the effects did not reach statistical significance.

2.3. Further consideration of mechanism of action of 5-HT1A agonists to improve cognition in schizophrenia

The possible mechanisms underlying the cognitive benefits of 5-HT1A agonists, besides the ability of these agents to enhance the release of DA and acetylcholine in the prefrontal cortex and hippocampus, can be mentioned here. First, the ability of 5-HT1A receptors to alter the release of glutamate and GABA provides a basis for the role of 5-HT in controlling cognitive process suberved by the prefrontal cortex [50]. Diminished GABA release in response to activation of inhibitory 5-HT1A (or 5-HT1B) heteroreceptors on GABAergic interneurons may facilitate hippocampal ACh and striatal DA release, respectively, which could compensate for possible deficiencies of these neurotransmitters in these brain areas [62]. Second, the 5-HT1A agonist F13714, or the antipsychotics, clozapine, ziprasidone and aripiprazole, that are partial agonists at 5-HT1A receptors, has been shown to protect against excitotoxin-induced striatal lesions in the rat [51]. This finding suggests that 5-HT1A agonism may have a neuroprotective effects against pathological processes which may contribute to some of the cognitive impairment in schizophrenia. Third, a recent study [52] suggests the facilitating influence of the 5-HT1A agonist tandospirone on anaerobic metabolism in the prefrontal cortex, suggesting a novel mechanism by which 5-HT1A receptor agonism ameliorates deficits in some key domains of cognition in subjects with schizophrenia. The ability of systemic administration of risperidone at doses of 1 and 2 mg/kg to increased ACh release in the prefrontal cortex is antagonized by systemic administration of high doses (WAY100635) but not by a low dose (0.1 mg/kg) of the antagonist which antagonizes preferentially presynaptic 5-HT1A autoreceptors. Furthermore, local application of WAY100635 into the prefrontal cortex also attenuated risperidone-induced increases in ACh efflux. WAY100635 alone did not affect acetylcholine release in the prefrontal cortex. These results suggest that risperidone increases ACh release in the prefrontal cortex by stimulation of postsynaptic 5-HT1A receptors. We also demonstrated an important influence of 5-HT1A receptors on muscarinic mechanisms that may be of importance to cognitive impairment in schizophrenia [53]. The ability of the M1 receptor agonist, 4-[3-(4-butylpiperidin-1-yl)-propyl]-7-fluoro-4H-benzo[1,4]oxazin-3-one (AC260584), to increase the release of acetylcholine and dopamine in the rat medial prefrontal cortex and hippocampus was attenuated by the muscarinic M1 receptor antagonist telenzepine (3 mg/kg, s.c.) but not by the 5-HT1A receptor antagonist N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]-N-(2-pyridyl) cyclohexanecarboxamide (WAY100635, 0.2 mg/kg, s.c.). However, the increase in dopamine release produced by 10 mg/kg AC260584 was blocked by both telenzepine and WAY100635.

The evidence from both preclinical and clinical studies, reviewed above, indicates 5-HT1A receptors are an interesting, if not entirely convincing, target for the management of cognitive disturbances of schizophrenia. It must be noted that there is some evidence that 5-HT1A receptor blockade is more likely to be of benefit in alleviating cognitive impairment than 5-HT1A receptor stimulation [54,55,56]. WAY-101405 is a silent 5-HT1A antagonist which was recently reported to be effective in multiple rodent models of learning and memory, including novel object recognition and reversing the memory deficits induced by scopolamine [57]. In vivo microdialysis studies in the dorsal hippocampus of freely moving adult rats demonstrated that acute administration of WAY-101405 increased extracellular ACh levels [57]. Novel antipsychotic compounds with efficacy at 5-HT1A receptors, e.g. F156063, SLV313, SSR181507, and bifeprunox [58–61] which are in development as treatments for schizophrenia, will provide further tests of whether 5-HT1A agonism is useful or possibly harmful for cognitive function. The ability of these newer agents to enhance cognitive function appears to be promising but further study is needed [62,63]. While there are other 5-HT receptors, e.g. 5-HT2C, 5-HT5 which hold promise for improving cognition in patients with schizophrenia and perhaps other disorders with cognitive impairment as well, [64,65,66] the 5-HT1A receptor is clearly one that has the most evidence to support its potential as a target for schizophrenia at the current time.

In conclusion, there are several clinical studies which indicate that 5-HT1A agonism may be beneficial to improve cognition in some patients with schizophrenia. There is, in fact, no evidence that the authors are aware of that 5-HT1A agonism can impair cognition in schizophrenia. This is consistent with some but not all preclinical studies of the ability of 5-HT1A agonists and antagonists to modulate memory and learning in various animal paradigms.

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