Current Topics

Recent Advances in 5-Hydroxytryptamine (5-HT) Receptor Research: How Many Pathophysiological Roles Does 5-HT Play via Its Multiple Receptor Subtypes?

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The serotonergic nervous system plays crucial roles in regulating psycho-emotional, cognitive, sensorimotor and autonomic functions. It is now known that multiple serotonin (5-hydroxytryptamine; 5-HT) receptors regulate extrapyramidal motor functions, which are implicated in pathogenesis and/or treatment of various neurological disorders (e.g., Parkinson’s disease and drug-induced extrapyramidal motor deficits). Specifically, antagonism of 5-HT1A/1B receptors alleviates antipsychotic-induced extrapyramidal side effects (EPS) by relieving the 5-HT2A/2C receptor-mediated inhibition of nigral dopaminergic neuron activity and striatal dopamine release. Indeed, many of the second generation antipsychotics (e.g., risperidone, perospirone and olanzapine) commonly possess potent 5-HT1A/1B blocking actions which contribute to their atypical antipsychotic property. In addition, activation of 5-HT1A receptors also improves antipsychotic-induced EPS and motor disabilities in animal models of Parkinson’s disease. Microinjection studies revealed that stimulation of postsynaptic 5-HT1A receptors in the striatum or motor cortex plays an important role in the antiparkinsonian actions. Furthermore, recent studies demonstrated that antagonism of 5-HT1A and 5-HT3 receptors alleviates extrapyramidal motor disorders while 5-HT3, 5-HT4, and 5-HT7 receptors are mostly inactive. These results encourage drug discovery research into new 5-HT receptor ligands that could improve current therapies for extrapyramidal motor disorders.

Key words extrapyramidal disorder; serotonergic system; serotonin receptor; striatum; dopaminergic system

1. INTRODUCTION

The serotonergic nervous system plays crucial roles in regulating diverse physiological activities including psycho-emotional, cognitive, sensorimotor and autonomic functions.1–3) Serotonin (5-hydroxytryptamine; 5-HT) neurons are mainly located in the raphe nuclei and send axons to various regions of the brain including the cerebral cortex, limbic region, basal ganglia, diencephalon and the spinal cord. The serotonergic neurotransmission is mediated by multiple 5-HT receptors, which are classified into 7 families (5-HT1 to 5-HT7) consisting of at least 14 subtypes (5-HT1A,1B,1D,1E,1F, 5-HT2A,2B,2C , 5-HT3, 5-HT4, 5-HT5A,5B, 5-HT6, and 5-HT7).4,5)

Among 5-HT receptor subtypes, 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT1F, 5-HT5A,5B, and 5-HT7 receptors are coupled to Gq/o protein and inhibit adenylate cyclase activity, cAMP formation and protein kinase A (PKA) activity. 5-HT2A, 5-HT2B, and 5-HT2C receptors are Gi coupled and enhance phosphatidylinositol (PI) turnover by activating phospholipase C, which consequently stimulates protein kinase C- and Ca2+/calmodulin-cascades. 5-HT3, 5-HT4, and 5-HT7 receptors are Gq-coupled receptors and activate adenylate cyclase and PKA cascades. Furthermore, 5-HT1 receptors function as channel-type receptors which elicit cation influx (e.g., Na+, K+, and Ca2+) upon stimulation. All 5-HT receptors act as postsynaptic receptors, in addition, 5-HT1A, 5-HT1B, and 5-HT1D receptors also act as presynaptic 5-HT autoreceptors which negatively regulate 5-HT neuronal activity.3–5) Specifically, 5-HT1A autoreceptors are located on the cell bodies and dendrites of 5-HT neurons in the raphe nuclei and inhibit the firing of 5-HT neurons. 5-HT1B or 5-HT1D receptors are located on the nerve terminals of 5-HT neurons, where they inhibit release and synthesis of 5-HT.

It is now known that the serotonergic system plays an important role in regulating extrapyramidal motor functions that are implicated in the pathogenesis of various neurological disorders including Parkinson’s disease and drug-induced extrapyramidal motor disorders.5–8) Extrapyramidal motor functions are primarily regulated by the basal ganglia (e.g., striatum and globus pallidus), which forms the basal ganglia-thalamus-cerebral cortex neural network.5,8) In the striatum, medial spiny neurons (γ-aminobutyric acid (GABA)ergic output neurons) receive excitatory glutamatergic input from the motor cortex as well as excitatory innervation of acetylcholine-ergic interneurons within the striatum (Fig. 1). In addition, these neurons receive inhibitory dopaminergic input from the substantia nigra. When the synaptic transmission of nigrostriatal dopaminergic neurons is impaired by neurodegeneration (e.g., Parkinson’s disease) or D2 receptor antagonists (e.g., antipsychotic-induced extrapyramidal side effects, EPS), it causes diverse motor deficits such as akinesia, bradykinesia, rest tremor, muscle rigidity, and dystonia.5,8) Serotonergic

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neurons derived from the dorsal and median raphe nuclei innervate to the basal ganglia as well as the motor cortex and modulate the incidence and magnitude of extrapyramidal motor disorders. Specifically, 5-HT\textsubscript{1A}, 5-HT\textsubscript{2A/2C}, 5-HT\textsubscript{3}, and 5-HT\textsubscript{6} receptors reportedly play crucial roles in modulating antipsychotic-induced EPS and/or motor disabilities in animal models of Parkinson's disease.\textsuperscript{3,6–8} In this article, we review the functional roles and mechanisms of 5-HT receptors in modulating extrapyramidal motor disorders and discuss their therapeutic potential against CNS disorders.

2. ROLES OF 5-HT RECEPTORS IN MODULATING EXTRAPYRAMIDAL MOTOR DISORDERS

2.1. 5-HT\textsubscript{1A} Receptors

Brain regions that contain high densities of 5-HT\textsubscript{1A} receptors include the raphe nuclei and limbic regions such as the hippocampus, amygdala, and lateral septum. 5-HT\textsubscript{1A} receptors are also expressed in the cerebral cortex, basal ganglia (e.g., striatum) and diencephalon (e.g., thalamus and hypothalamus) at low to moderate densities.\textsuperscript{1,4,8,9} As described above, 5-HT\textsubscript{1A} receptors inhibit adenylate cyclase activity, which leads to inhibition of the cAMP-PKA cascade. In addition, 5-HT\textsubscript{1A} receptors activate G protein-gated inwardly rectifying K\textsuperscript{+} (GIRK) channels, which consequently hyperpolarize the target neurons and inhibit the neuronal activity.\textsuperscript{1,3–5}

Several studies demonstrated that activation of 5-HT\textsubscript{1A} receptors improves antipsychotic-induced EPS and motor disabilities in animal models of Parkinson's disease.\textsuperscript{10–16} In our studies, 5-HT\textsubscript{1A} agonists (e.g., 8-hydroxy-2-(di-n-propylamino)-tetralin and tandospirone) ameliorated haloperidol-induced bradykinesia and catalepsy with potencies similar to those of antiparkinsonian agents (e.g., trihexyphenidyl and L-3,4-dihydroxyphenylalanine (L-DOPA)).\textsuperscript{13,14} Consistently with these anti-EPS actions, 5-HT\textsubscript{1A} agonists reversed striatal Fos protein expression induced by haloperidol, indicating that 5-HT\textsubscript{1A} receptors counteract D\textsubscript{2} receptor blockade by antipsychotics in the striatum.\textsuperscript{14,15}

Earlier studies showed that microinjection of 5-HT\textsubscript{1A} agonists into the raphe nuclei attenuated antipsychotic-induced catalepsy, suggesting that activation of presynaptic 5-HT\textsubscript{1A} autoreceptors can reduce EPS.\textsuperscript{11} (Fig. 1 and Table 1). On the

![Fig. 1. Action Mechanisms of 5-HT\textsubscript{1A} Agonist in Modulating Extrapyramidal Motor Disorders](image)

5-HT\textsubscript{1A} agonist can improve extrapyramidal motor disorders by stimulating both post-synaptic and pre-synaptic 5-HT\textsubscript{1A} receptors. Stimulation of post-synaptic 5-HT\textsubscript{1A} receptors reduces the activity of striatal neurons directly by hyperpolarizing the GABAergic medial spiny neurons or indirectly by inhibiting the acetylcholinergic interneurons in the striatum, which leads to improvement of extrapyramidal motor disorders. Microinjection of 5-HT\textsubscript{1A} agonist into the cerebral cortex also reduces the activity of striatal neurons by inhibiting glutamatergic cortico-striatal neurons. In addition, stimulation of pre-synaptic 5-HT\textsubscript{1A} autoreceptors inhibits serotonergic neuron activities in the raphe nuclei and thereby attenuates the functions of 5-HT\textsubscript{2A/2C}, 5-HT\textsubscript{3}, and 5-HT\textsubscript{6} receptors, which leads to improvement of extrapyramidal motor disorders. DA: dopamine, Glu: glutamate, ACh: acetylcholine, mACh: muscarinic acetylcholine.

<table>
<thead>
<tr>
<th>5-HT receptor</th>
<th>Mechanisms in modifying extrapyramidal disorder</th>
<th>Therapeutic strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT\textsubscript{1A} receptor</td>
<td>Inhibition of cortico-striatal glutamatergic neurons&lt;br&gt;Reduced glutamine release in the striatum&lt;br&gt;Inhibition of striatal (medium spiny) neurons and/or cholinergic interneurons&lt;br&gt;Inhibition of raphe serotoninergic neurons by stimulating 5-HT\textsubscript{1A} autoreceptors</td>
<td>Agonism (Partial agonism)</td>
</tr>
<tr>
<td>5-HT\textsubscript{2A/2C} receptor</td>
<td>Inhibition of dopaminergic neurons in the substantia nigra&lt;br&gt;Inhibition of dopamine release in the striatum&lt;br&gt;Activation of cholinergic interneurons in the striatum</td>
<td>Antagonism</td>
</tr>
<tr>
<td>5-HT\textsubscript{3} receptor</td>
<td>Activation of striatal neurons ?</td>
<td>Antagonism</td>
</tr>
<tr>
<td>5-HT\textsubscript{6} receptor</td>
<td>Activation of cholinergic interneurons in the striatum</td>
<td>Antagonism</td>
</tr>
</tbody>
</table>
other hand, several studies demonstrated that the anti-EPS actions of 5-HT$_{1A}$ agonists were resistant against denervation of 5-HT neurons by 5-HT neurotoxins (e.g., p-chlorophenylalanine), indicating that activation of postsynaptic 5-HT$_{1A}$ receptors also ameliorates EPS.$^{10,12,13}$ In addition, it is known that local microinjection of 5-HT$_{1A}$ agonists into the striatum or cerebral cortex (i.e., motor cortex) attenuates extrapyramidal disorders.$^{10}$ (Fig. 1 and Table 1). Therefore, it is postulated that activation of 5-HT$_{1A}$ receptors ameliorates antipsychotic-induced EPS by inhibiting neural activity in the striatum, motor cortex and raphe nuclei (Fig. 1). Since inhibition of corticostriatal glutamatergic transmission by N-methyl-D-aspartate (NMDA) antagonists reportedly counteracted the striatal D$_2$ blocking action (i.e., Fos expression) of antipsychotics and reduced their EPS,$^{17,18}$ it is possible that activation of cortical 5-HT$_{1A}$ receptors alleviates EPS by inhibiting cortico-striatal glutamatergic neurons. In addition, activation of 5-HT$_{1A}$ autoreceptors can reduce EPS by reducing serotonergic activity, which facilitates EPS symptoms via 5-HT$_{2A/C}$, 5-HT$_3$, and 5-HT$_{6}$ receptors (Fig. 1). Furthermore, 5-HT$_{1A}$ agonists are known to improve extrapyramidal disorders elicited by dopaminergic neurotoxins (e.g., 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)), indicating that 5-HT$_{1A}$ receptors alleviate EPS via non-dopaminergic mechanisms.$^{5-8,16}$

### 2.2. 5-HT$_{2A/C}$ Receptors

5-HT$_{2A}$ and 5-HT$_{2C}$ receptors are highly expressed in the brain.$^{59}$ Specifically, 5-HT$_{2A}$ receptors are expressed at a high density in the forebrain regions such as the cerebral cortex, olfactory tubercle and limbic regions (e.g., nucleus accumbens, hippocampus). 5-HT$_{2C}$ receptors are distributed in various brain regions including the cortex, limbic regions, and basal ganglia (e.g., striatum and substantia nigra).

It is well documented that 5-HT$_{2A/C}$ antagonists attenuate antipsychotic-induced extrapyramidal disorders and motor deficits in Parkinson’s disease patients.$^{19-21}$ 5-HT$_{2A/C}$ antagonists reverse various responses of striatal neurons to antipsychotics (D$_2$ antagonists) such as increases in acetylcholine release, metabolic turnover of dopamine and Fos expression in the striatum, supporting the EPS-ameliorating actions of 5-HT$_{2A/C}$ antagonists.$^{70}$ It is postulated that blockade of 5-HT$_{2A/C}$ receptors alleviates EPS by relieving 5-HT$_{2A/C}$ receptor-mediated inhibition of dopamine release in the striatum, and of neural firing of nigral dopamine neurons.$^{20-23}$ (Fig. 2 and Table 1). Although the precise subtype(s) of 5-HT$_3$ receptors play at least in part a crucial role in modulating extrapyramidal motor functions are still uncertain, several studies suggest that 5-HT$_{2C}$ receptors play at least in part a crucial role in modulating extrapyramidal motor functions.

### 2.3. 5-HT$_3$ Receptors

5-HT$_3$ receptors compose a hetero-pentamer consisting of 5-HT$_{3A}$ to 5-HT$_{3E}$ subunits and function as cation (Na$^+$, K$^+$, and Ca$^{2+}$)-permeable channels.$^{4,27}$ Therefore, activation of 5-HT$_3$ receptors depolarizes postsynaptic membranes and excites the target neurons. 5-HT$_3$ receptors are also located on the nerve terminals of various neurons and modulate neurotransmitter release (e.g., acetylcholine, glutamate, GABA, and dopamine).

Previous studies showed that 5-HT$_3$ receptor antagonists (e.g., ondansetron and granisetron) reduced haloperidol-induced EPS (e.g., catalepsy and bradykinesia)$^{28-30}$ Recent clinical studies also showed that ondansetron significantly reduced the incidence and severity of antipsychotic-induced EPS (e.g., akathisia and parkinsonism) in patients with chronic schizophrenia.$^{31,32}$ In our studies, activation of the serotonergic system by 5-hydroxytryptophan (5-HTP) significantly potentiated haloperidol-induced catalepsy and this 5-HTP-potentiated EPS was also suppressed by systemic treatments or intrastriatal microinjections of ondansetron.$^{29}$ These findings indicate that postsynaptic 5-HT$_3$ receptors in the striatum are involved in the induction or potentiation of extrapyramidal disorders and blockade of the striatal 5-HT$_3$ receptors can alleviate antipsychotic-induced EPS (Fig. 2 and Table 1). How-

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**Fig. 2. Action Mechanisms of 5-HT$_{2A/C}$, 5-HT$_3$, and 5-HT$_6$ Antagonists in Modulating Extrapyramidal Motor Disorders**

Blockade of 5-HT$_{2A/C}$ receptors alleviates extrapyramidal disorders by increasing dopamine release in the striatum and by activating dopamine neurons in the substantia nigra. 5-HT$_3$ receptors are expressed in the striatal acetylcholinergic interneurons and their blockade inhibits acetylcholinergic interneurons and thereby GABAergic medial spiny neurons in the striatum, which leads to the improvement of extrapyramidal disorders. Although the information is still limited, 5-HT$_3$ antagonist seems to improve extrapyramidal disorders by inhibiting striatal neurons. DA: dopamine, Glu: glutamate, ACh: acetylcholine, mACh: muscarinic acetylcholine.
ever, a recent study has shown that 5-HT₃ receptors did not alter the activity of cholinergic interneurons in the striatum.²⁶ Thus the functional mechanisms of 5-HT₃ receptors in modulating extrapyramidal motor disorders are still uncertain and remain to be clarified.

2.4. 5-HT₆ Receptors 5-HT₆ receptors are predominantly expressed in the brain, specifically in the basal ganglia (e.g., striatum and nucleus accumbens), limbic regions (e.g., olfactory tubercles and hippocampus), and cerebral cortex.⁴ Although an early study reported that the 5-HT₆ antagonist Ro 04-6790 failed to affect haloperidol-induced catalepsy,³³ we recently demonstrated that the 5-HT₆ antagonist SB-258585 alleviated haloperidol-induced bradykinesia and catalepsy.²⁹,³⁰ In addition, the EPS-potentiating action of 5-HTP was also blocked by systemic injection of SB-258585 or its microinjection into the striatum, implying that blockade of the striatal 5-HT₆ receptors is at least in part involved in alleviating antipsychotic-induced EPS (Fig. 2 and Table 1). The anti-EPS actions of 5-HT₆ antagonists were further supported by electrophysiological studies showing that 5-HT₆ receptors are expressed in the striatal acetylcholine interneurons, where 5-HT₆ receptors excite acetylcholine neurons. Since activation of striatal acetylcholine neurons evokes extrapyramidal disorders, it is conceivable that 5-HT₆ antagonists alleviate antipsychotic-induced EPS by inhibiting acetylcholinergic activity in the striatum (Fig. 2 and Table 1).

2.5. Other 5-HT Receptors Although information is limited, other 5-HT receptor subtypes (e.g., 5-HT₄, 5-HT₅, and 5-HT₆ receptors) seem to have no significant roles in modulating extrapyramidal motor disorders.²⁹ In our studies, neither antagonist for 5-HT₄ (GR-125487), 5-HT₆ (SB-69951), nor 5-HT₇ (SB-269970) receptors affected against induction of antipsychotic-induced EPS.²⁹

3. CONCLUSION AND PERSPECTIVE

Extrapyramidal motor disorders are the core symptom of Parkinson’s disease and the most frequently observed side effects of antipsychotics in the treatment of schizophrenia and related psychotic diseases. In this article, we reviewed the functional roles and mechanisms of the serotonergic system in modulating extrapyramidal motor disorders. Among 5-HT receptor subtypes, 5-HT₁A, 5-HT₂A/2C, 5-HT₃, and 5-HT₆ receptors play crucial roles in regulating extrapyramidal motor functions. Specifically, stimulation of 5-HT₁A receptors and blockade of 5-HT₂A/2C, 5-HT₃, or 5-HT₆ receptors improve abnormalities of extrapyramidal motor functions. It is therefore conceivable that 5-HT₁A agonists or antagonists for 5-HT₂A/2C, 5-HT₃, or 5-HT₆ receptors may become novel antiparkinsonian agents in the treatment of Parkinson’s disease or schizophrenia. These agents may be especially useful as adjunctive therapy with current medications. In addition, multimodal agents with actions for current therapeutic targets (e.g., dopamine D₂ receptors) and those for 5-HT₁A, 5-HT₂A/2C, 5-HT₃, and 5-HT₆ receptors may be useful in these disease settings. Such new agents or therapeutic strategies may overcome limitations of clinical efficacy and/or improve adverse reactions in the current treatment of extrapyramidal motor disorders.

REFERENCES


