ROLE OF 5-HT2C RECEPTORS IN DYSKINESIA

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ABSTRACT

By integrating knowledge gained by pharmacogenetic, neuroanatomical and pharmacological studies, a model can be constructed how serotonin (5-HT) affects the vulnerability to induce tardive dyskinesia. From neuroanatomical studies, it can be concluded that 5-HT inhibits the release of dopamine (DA) within the dorsal striatum by affecting 5-HT2C receptors and also within the ventral striatum and prefrontal cortex by affecting 5-HT2A receptors. However, considering the low affinity of DA for its receptors, it is unlikely that the so released DA is able to displace atypical antipsychotics from DA D2 and D3 receptors. 5-HT2C receptors and, to a lesser extent, 5-HT2A receptors, have constitutive activity and therefore, atypical antipsychotics can have inverse agonistic effects. It is hypothesized that decreasing the activity of 5-HT2 receptor carrying medium spiny neurons (MSNs) within the dorsal striatum represents the mechanism showing how atypical antipsychotics have limited ability to cause tardive dyskinesia.

Keywords: Tardive dyskinesia, Extrapyramidal system, Medium spiny neurons, 5-HT2C receptors, Inverse agonism.

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INTRODUCTION

Dyskinesia is a movement disorder characterized by involuntary, repetitive and irregular motions that affect the mouth and face and/or the limbs and trunk [1, 2]. Dyskinesia can occur spontaneously, particularly in elderly patients [3, 4], and in persons with schizophrenia [5-7], in Huntington's disease and in a variety of other neurological disorders [8], and can be drug-induced [9]. The usage of antipsychotic drugs and levodopa, in particular has been associated with dyskinesia. Tardive dyskinesia (TD) is a well-known complication of long-term treatment with dopamine (DA) blocking agents, predominantly antipsychotic drugs [10]. Levodopa-induced dyskinesia (LID) is a common consequence of the long-term treatment of Parkinson's disease with levodopa [11-14].

Both LID and TD are believed to be caused by a dysregulation of the DAergic neurotransmitter system. A well-accepted model of LID states that the mechanism underlying these movements is related to pulsatile stimulation of postsynaptic DA receptors [14]. A classical model of the pathogenesis of TD explains this movement disorder to be a super sensitivity response to chronic DA blockade [15]. However, the 5-HTergic system is also believed to be involved [15-18].

Seven types of serotonin (5-hydroxytryptamine; 5-HT) receptors have been found, all but one (5-HT3) being g-protein coupled [19-21]. Most of these are divided into several subtypes. For their role in dyskinesia, 5-HT1A, 5-HT2A and 5-HT2C receptors have been most extensively studied. Stimulation of 5-HT1A receptors result in increased influx of K+ ions and hyperpolarization of the membrane, and so to the inhibition of neurotransmission while 5-HT2A and 5-HT2C receptors have opposite activity [19-24].

Pharmacogenetic studies describe an association between polymorphisms of the genes coding for the 5-HT2A (HTR2A) and 5-HT2C (HTR2C) receptor protein and the prevalence of tardive dyskinesia. The results appear to be conflicting [25], however. The 23Ser allele of the Cytochrome P450 variants of HTR2C (rs6318) was associated with an increased risk of TD and Parkinsonism [26-30]. The HTR2C is found on the long arm of the X-chromosome, Xq24 [31]. Males, therefore, are hemizygous, so always homzygous. Al Hadithy et al. demonstrated there was a significant association between carriers of the 23Ser allele of HTR2C and Parkinsonian bradykinesia in males, but not in females [26]. Wilfert et al. did not find a correlation between TD and 23Ser male carriers when they were analyzed separately [30]. Orofical and limb-truncal TD scores, however, were statistically significantly higher in male patients carrying combinations of the 9Ser variant of the DA D3 (DRD3) gene and 23Ser allele of HTR2C [30]. This may correspond to the findings of Segman et al. who found no association with 23Ser male carriers, but the highest oro-facial dyskinesia scores were found in combined carriers of 9Gly DRD3 and 23Ser HTR2C (not specified for males and females) [29]. Gunes et al. who studied only male subjects with several types of EPS (Parkinsonism, dystonia, and/or dyskinesia), observed a strong association with 23Ser HTR2C carriers [28]. It should be emphasized that the drug treatments probably differed between studies. Gunes et al. excluded all patients who were using atypical drugs, while the other authors included patients who were on atypical antipsychotics [26,27,30]. Unfortunately, Segman et al. did not specify the antipsychotics used by their patient population, but they studied Jewish patients recruited from several centers in Israel [29, 32].

Atypical antipsychotics are assumed to cause less Parkinsonism and TD by blocking 5-HT2A and/or 5-HT2C (5-HT2A/2C) receptors [33-36]. Therefore, the differences between the results of these studies may at least be partly explained by the concurrent use of 5-HT2A/2C blocking agents by at least some of the patients, which apparently decrease the differences between carriers and non-carriers. In future studies, users of 5-HT2A/2C blocking agents should be excluded from analysis.

In this article, we will try to explain the association between being a carrier of this 23Ser HTR2C, and the likelihood of developing TD by describing the distribution and physiological role of this receptor.

Anatomical considerations

5-HT is, together with DA, norepinephrine (NE) and histamine (H), one of the lesser abundant neurotransmitters of the central nervous system (CNS), which are used by about 2% of the CNS nerve cells [19]. Cell bodies of 5-HTergic neurons are primarily localized in the brainstem (fig. 1). Apart from these proper raphe nuclei, three other nuclei have been described [37]. These nuclei are usually located in the midline (raphe” from Greek ῥαψις) of the brainstem (fig. 1). Apart from these proper raphe nuclei, three other nuclei have been described [37]. These nuclei are usually located in the midline (raphe” from Greek ῥαψις) of the brainstem (fig. 1). There is, however, evidence that the raphe nuclei may be found at different levels of the brainstem, and may be involved in different functions [38]. One of the raphe nuclei is the dorsal raphe nucleus, located in the dorsal medulla oblongata, and is involved in the regulation of autonomic functions, such as blood pressure and heart rate [39]. Another is the median raphe nucleus, located in the midline of the brainstem, and is involved in the regulation of sleep and wakefulness [40]. The third is the lateral raphe nucleus, located in the lateral medulla oblongata, and is involved in the regulation of somatic functions, such as temperature regulation and movement [41].

In the brainstem, 5-HTergic neurons project to various brain regions, including the hypothalamus, amygdala, hippocampus, and prefrontal cortex [42]. These neurons have been implicated in a variety of functions, such as mood regulation, learning and memory, and stress response [43]. The exact role of 5-HTergic neurons in the brainstem is not yet fully understood, but it is clear that they play an important role in the regulation of autonomic functions [44].

5-HTergic neurons in the brainstem also project to the striatum, the basal ganglia, and the thalamus [45]. These projections are involved in the regulation of motor function, and have been implicated in the pathogenesis of Parkinson's disease and TD [46]. The exact role of 5-HTergic neurons in the striatum is not yet fully understood, but it is clear that they play an important role in the regulation of motor function [47].

In summary, the 5-HTergic system plays a crucial role in the regulation of autonomic functions, mood, learning and memory, stress response, and motor function. The exact role of 5-HTergic neurons in the brainstem is not yet fully understood, but it is clear that they play an important role in the regulation of autonomic functions. The exact role of 5-HTergic neurons in the striatum is not yet fully understood, but it is clear that they play an important role in the regulation of motor function.
within the spinal cord and one up through the medial forebrain bundle to the striatum and cerebral cortex [19, 37]. Within the brainstem, 5-HTergic nuclei are connected to the DAergic substantia nigra, pars compacta (SNc) and ventral tegmental nucleus (VTA), to adrenergic (NE using) locus coeruleus and nucleus tractus solitarius and to other 5-HTergic raphe nuclei [19, 37].

In order to understand how 5-HT2 receptors modify Parkinsonism and TD, the exact localization of 5-HT2A and 5-HT2C receptors within several areas of the brain should be considered. This localization is not entirely clear within the cerebral cortex [36, 38]. 5-HT2A receptors are abundantly present in the telencephalon (olfactory system, cerebral cortex, basal forebrain, neostriatum, and hippocampus), and occur in the diencephalon and brainstem [36]. 5-HT2C receptors are more abundant and more widely expressed than 5-HT2A receptors, but the two types of receptors often co-exist [36].

Within the cerebral cortex, 5-HT2A receptors are localized on pyramidal cells, on Gamma Amino Butyric Acid (GABA)ergic interneurons, and pre-synaptically on axons of (probably) monoaminergic cells (fig. 3). However, although results are conflicting, 5-HT2C receptors are probably not present on fast-spiking (i.e. GABAergic) interneurons of the cerebral cortex [36, 38, 39]. Within the basal ganglia, 5-HT2A and 5-HT2C receptors are co-localized within medium-sized spiny projection neurons (MSNs) of both direct and indirect pathways of the extrapyramidal circuit (fig. 2 and 4) [36]. Moreover, both 5-HT2A and 5-HT2C receptors are present on cholinergic, glutamatergic, and DAergic axon terminals [38]. The simultaneous role in GABAergic interneurons is less clear. 5-HT acts on 5-HT2C receptors when stimulating striatal fast-spiking interneurons, which are the most numerous class of GABAergic interneurons there [40]. To the best of our knowledge, a physiological role has never been established for 5-HT2A receptors. Within the upper brainstem, 5-HT2C receptors are restricted to GABAergic neurons, at least within pars reticulata and pars compacta (SNc) of the substantia nigra (fig. 5). Only few 5-HT2C receptor positive cells were observed within the VTA [41]. However, 5-HT2A receptors were more often present within neurons in the VTA than those in the SNc [42]. Within the VTA, 5-HT2A receptors are unevenly distributed and more prevalent in rostral and mid parts [43]. They are co-localized with DAergic neurons throughout the VTA, but they also co-localized with non-DAergic cells [43]. These differences in the distributions of 5-HT2A and 5-HT2C receptors may explain the various effects of 5-HT agonists and antagonists in different parts of the midbrain. Within the VTA, they predominantly act on 5-HT2A receptors with a direct effect on DAergic neurons, while within the SNc, they predominantly act on 5-HT2C receptors of GABAergic interneurons.

It can be concluded that 5-HT inhibits the activity of DA terminals within the dorsal striatum, mainly by affecting 5-HT2C receptors. It inhibits DA activity within the ventral striatum and frontal cortex mainly by affecting 5-HT2A receptors.
Table 1: Receptor-binding affinities (expressed as Ki values) of several atypical antipsychotic agents in comparison to haloperidol

<table>
<thead>
<tr>
<th></th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Ziprasidone</th>
<th>Sertindole</th>
<th>Aripiprazol</th>
<th>Asenapine</th>
<th>Risperidon</th>
<th>Paliperidon</th>
<th>Pipamperon</th>
<th>Ritanserin</th>
<th>Haloperidol</th>
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<tr>
<td>D1</td>
<td>85</td>
<td>31</td>
<td>455</td>
<td>9.5</td>
<td>12</td>
<td>265</td>
<td>1.4</td>
<td>75</td>
<td>670</td>
<td>-</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>D2</td>
<td>125</td>
<td>11</td>
<td>160</td>
<td>4.8</td>
<td>0.45</td>
<td>0.34</td>
<td>1.4</td>
<td>3</td>
<td>4.0</td>
<td>124</td>
<td>70</td>
<td>1</td>
</tr>
<tr>
<td>D3</td>
<td>473</td>
<td>49</td>
<td>340</td>
<td>7.2</td>
<td>12</td>
<td>0.8</td>
<td>0.42</td>
<td>10</td>
<td>7.5</td>
<td>-</td>
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<td>2</td>
</tr>
<tr>
<td>D4</td>
<td>9</td>
<td>27</td>
<td>1600</td>
<td>32</td>
<td>11</td>
<td>44</td>
<td>1.1</td>
<td>7</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>D5</td>
<td>235</td>
<td>90</td>
<td>1738</td>
<td>152</td>
<td>-</td>
<td>1675</td>
<td>-</td>
<td>16</td>
<td>29</td>
<td>-</td>
<td>-</td>
<td>147</td>
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<tr>
<td>5-HT1A</td>
<td>12</td>
<td>4</td>
<td>220</td>
<td>0.4</td>
<td>0.2</td>
<td>3.4</td>
<td>0.07</td>
<td>0.6</td>
<td>0.25</td>
<td>7</td>
<td>1.0</td>
<td>78</td>
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<tr>
<td>5-HT1C</td>
<td>8</td>
<td>11</td>
<td>615</td>
<td>1.3</td>
<td>0.51</td>
<td>15</td>
<td>0.034</td>
<td>26</td>
<td>71</td>
<td>54</td>
<td>9.3</td>
<td>3085</td>
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<tr>
<td>α1</td>
<td>7</td>
<td>19</td>
<td>7</td>
<td>10</td>
<td>1.4</td>
<td>57</td>
<td>1.2</td>
<td>2</td>
<td>4.0</td>
<td>62</td>
<td>97</td>
<td>46</td>
</tr>
<tr>
<td>H1</td>
<td>6</td>
<td>7</td>
<td>11</td>
<td>47</td>
<td>440</td>
<td>61</td>
<td>1.0</td>
<td>155</td>
<td>10</td>
<td>&gt;&gt;</td>
<td>35</td>
<td>3630</td>
</tr>
<tr>
<td>M₁</td>
<td>1.9</td>
<td>1.9</td>
<td>120</td>
<td>&gt;&gt;</td>
<td>260</td>
<td>&gt;&gt;</td>
<td>&gt;&gt;</td>
<td>&gt;&gt;</td>
<td>3570</td>
<td>2.500</td>
<td>-</td>
<td>1475</td>
</tr>
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</table>

Aripiprazole [Abilify package insert]; asenapine [50]; olanzapine [Zyprexa package insert]; paliperidone [51]; pipamperone [52, 53]; ritanserin [54]; sertindole [55]; ziprasidone [Gideon package insert]; DS: [22, 56, 57].
How antagonizing 5-HT2 receptor does limits Parkinsonism and dyskinesia

An initial model to explain how atypical antipsychotics cause less extrapyramidal side effects than classical drugs was related to the observation that antagonists of 5-HT2 receptors block the inhibition of release of DA by 5-HT from striatal slices in vitro [44]. It was suggested that 5-HT had this effect by stimulating 5-HT2 receptors on DAergic terminals. Later, it was shown that numerous atypical antipsychotics stimulate the release of DA more potently in the mediofrontal cortex and mesocorticolimbic innervated areas than in the striatum [45]. This is not only attributed to direct effects on DAergic terminals, but also influencing their origins within the midbrain. However, 5-HT2 receptors mediate an inhibitory effect on the release of DA within the dorsal and ventral striatum [45, 46]. As has been stated above, both 5-HT2A and 5-HT2C receptors have an excitatory effect [19-21], so blocking these receptors with atypical antipsychotics would result in inhibition of the DAergic cell bodies/terminals and therefore, result in inhibition of DA release. This apparent contradiction can be explained by their localization on GABAergic inhibitory interneurons [47].

Stimulation of these interneurons results in inhibition of the activity of DAergic cells and nerve terminals; blocking these 5-HT2 receptors would result in increased release of DA [49]. Based on this study, it was believed that atypical antipsychotics induce the release of DA to such an extent that some of the DA D2 receptor blockades by the antipsychotic drug was reversed [48]. However, an important pharmacological reason causes doubt concerning this mechanism. As can be seen in table 1, apart from clozapine, quetiapine, and pipamperone, most atypical antipsychotics are potent DA D2 receptor antagonists. DA itself has an affinity in the micromolar range [49]. It is difficult to understand how the even massive release of DA would be able to displace most atypical antipsychotics to a sufficient degree from their DA D2 receptor. In fact, this mechanism would overload the putamen with DA leading to an increase in oxidative stress. This may result in an increase of TD by causing damage to mid-sized GABAergic projection neurons (MSNs) [10].

Apart from promoting DA release from striatal DAergic fibers, 5-HT2 receptors may modulate the activity of striatal GABAergic projection neurons (MSNs) directly (fig. 4). These receptors are present on MSNs of both direct and indirect pathways. A special characteristic of these receptors can explain why 5-HT2 antagonists diminish Parkinsonism and decrease the likelihood of developing dyskinesia: these receptors prominently signal for cellular effector mechanisms in the absence of ligands [38, 58], and 5-HT2C receptors may have higher constitutive activity than 5-HT2A. In this situation, a ligand binding to the receptor may also act as an inverse agonist; i.e., changing the activity of the receptor in the opposite direction instead of increasing or blocking it. This occurred when this receptor was bound by atypical antipsychotics [22, 30]. This may also explain the findings from genetic studies. In these cases, the genetic variant (of 5-HT2A or 5-HT2C receptors) with increased constitutive activity would have greater benefit and the variant with decreased or absent constitutive activity would have less benefit due to the complete blockade of these receptors by atypical antipsychotic drugs. In the absence of receptor blockers (usage of classical antipsychotics), carriers of a variant with no constitutive activity would have a significant advantage. As is shown in table 1, most atypical antipsychotics are both 5-HT2A and 5-HT2C antagonists. Inverse agonism is somewhat more likely with 5-HT2C than 5-HT2A receptors [19, 39]. Moreover, these receptors may also explain the prevention of TD by having a direct influence on MSNs and/or an indirect effect on corticostriatal projections. Inverse agonistic effects (less activation) on MSNs of the indirect pathway could explain the occurrence of less Parkinsonism as well as protection against excitotoxic toxicity [10].

CONCLUSION

Considering the distribution of these receptors and the low affinity of DA to receptors of the DA D2 receptor family, it seems unlikely that atypical antipsychotics have a low potential to cause Parkinsonism by increasing DA release within the striatum. Only clozapine, quetiapine and pipamperone have such low affinity to the D2 receptors that DA could successfully compete with them for binding to this receptor.

An exception may be binding to the Ser9Gly DRD3 variant (rs6280) of the DA D3 receptor [59]. The homogenous Gly variant has been associated with four-fold greater DA binding affinity in vitro [60] and the DA D3 receptor is characterized by an extraordinarily large binding affinity for DA [61]. It should be emphasized, however, that DA D3 receptors are largely confined to the ventral striatum [61], while the site of action of TD inducing mechanisms should be the putamen [10]. So, even in this case, promoting DA release is an unlikely mechanism to overcome antipsychotic drug-induced Parkinsonism. Furthermore, even when DA would have sufficient affinity to compete with antipsychotics for binding to the homogenous Ser9Gly variant of the DA D3 receptor, it is difficult to understand how this activation could overcome the remaining blockade of DA D2 and D4 receptors within the dorsal striatum.

Whether the affinity of atypical antipsychotics to DA D1 and D5 receptors is sufficiently low to have these drugs displaced by extra released DA (table 1), is not certain, but definitely more likely: this could be related to the cognitive effects of atypical antipsychotics [22]. Moreover, the release of DA within the prefrontal cortex has a higher magnitude than that within the dorsal striatum possibly by the involvement of 5-HT2A receptors [45]. The release of DA within the prefrontal cortex and striatum may be relevant in case of antidepressant drugs because these agents have a very low affinity to DA receptors [62].

So, when the promoting of DA release is not the best explanation for the reduced capability of 5-HT2 receptor antagonists to induce Parkinsonism and TD in comparison to classical antipsychotics, an alternative explanation comes into view. We want to hypothesize that this is caused by blocking the constitutive excitatory activity of 5-HT2 receptors on striatal MSNs (fig. 4). This would decrease the activation of both direct and indirect extrapyramidal pathways, thereby reducing the risk of Parkinsonism, especially when the direct pathway is still activated by stimulation of DA D1 carrying MSNs. At the same time it would lower the vulnerability of these medium spiny neurons (MSNs) to neurotoxicity resulting from oxidative stress, therewith preventing TD [10].

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

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