REVIEW —Current Perspective—

Strategy for Modulation of Central Dopamine Transmission Based on the Partial Agonist Concept in Schizophrenia Therapy

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ABSTRACT—The dopamine system is known to be closely involved in brain neuronal dysfunction and in diseases such as Parkinson's disease, Tourette's syndrome, attention deficit hyperactive disorder, generation of pituitary tumors and schizophrenia. According to the classical dopamine hypothesis on the pathology of schizophrenia, conventional antipsychotics has D₂ dopamine receptor antagonistic profiles. However, the use of typical antipsychotics has several limitations; that is, some patients do not respond to them, they can even worsen negative symptoms, and they can provoke unacceptable extrapyramidal and endocrine side effects. To produce effective antipsychotics with reduced side effects, partial agonists to D₂ dopamine receptors (D₂ receptors) have been developed. Despite the effectiveness of partial agonists for pre- and post-synaptic D₂ receptors, administration of such drugs results in inconsistent clinical effects to ameliorate the symptoms of schizophrenia. Thus, strategies for obtaining ideal effective antipsychotics with reduced side effects are considered in this short review with respect to the intrinsic efficacies and affinities of the partial agonists, based on the partial agonist concept.

Keywords: Dopamine receptor, Antipsychotic, Partial agonist, Intrinsic efficacy, Affinity, Schizophrenia

1. Introduction

Schizophrenia is a chronic psychiatric illness with two major types of symptoms, positive symptoms such as hallucinations and delusions and negative symptoms such as amotivation, apathy and asociality. The different types and courses of schizophrenic symptoms indicate a disease caused by multiple neurochemical abnormalities. Although the ultimate causes of schizophrenia remains unknown, since the clinically effective antipsychotics commonly block dopamine receptors (1), it has been thought that schizophrenia is caused by the up-regulated condition of dopamine neuronal activity. Thus, the main property of typical antipsychotics has been the pharmacological antagonism of D₂-like dopamine receptors (D₂-like receptors) (1). However, some patients are considered unresponsive to these typical antipsychotics (2). Especially, in schizophrenia predominantly expressing negative symptoms, a dopamine deficit rather than an excess has been hypothesized. Accordingly, a typical antipsychotic, haloperidol, cannot

ameliorate and can even worsen some symptoms (3) and a nonselective dopamine agonist could be effective. Indirect dopamine agonists like L-dopa or D-amphetamine generally increase the central dopaminergic function, which was reported to have beneficial effects on some negative symptoms in several cases (4, 5). Furthermore, typical antipsychotics have serious side effects. For example, they cause extrapyramidal dysfunction inducing Parkinsonian symptoms that would be due to the blockade of D₂ dopamine receptors (D₂ receptors) in the striatum. They also induce hyperprolactinemia through the blockade of D₂ receptors in the pituitary. In the search for antipsychotics that are effective against both positive and negative symptoms and have reduced side effects, the following three approaches have been undertaken. Firstly, at least 5 distinct dopamine receptor subtypes (D₁ – D₅) have been found by molecular biological techniques. Not only the D₂ receptors but also some other subtypes are preferentially distributed in the limbic area or frontal cortex of the brain where they might be involved in mental illness either by themselves or by interaction with one another. Some antipsychotics developed recently might possess significant affinities to dopa-

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mine receptor subtypes rather than the D₂ receptors. Indeed clozapine, a potentially effective antipsychotic with reduced side effects, shows an approximately tenfold higher affinity to the D₄ receptors than the D₂ receptors (6). In addition, Lidow et al. speculated that balancing opposing actions through D₁ and D₂ receptors is the key to optimal drug therapy (7). Secondly, systems other than the dopaminergic system (e.g., glutamatergic, cholinergic, serotonergic, peptidergic and GABAergic systems) could be involved in the pathogenesis of schizophrenia. Clozapine has potent affinity to the 5-HT_{2A} receptors as well as D₄ receptors (8), and levels of glutamate receptor subunits are reported to be changed by chronic treatment with antipsychotics (9). Thirdly, this short review describes partial agonists that target the D₂ receptors in discrete regions of the CNS with intermediate to high affinities and negligible intrinsic efficacies.

2. Dopaminergic system in the CNS

The dopaminergic system in the brain is well known to be associated with cognitive, motive, motor and endocrine functions. There are three major pathways in the brain. One is the nigrostriatal pathway which arises in dopamine-synthesizing neurons of the substantia nigra compacta and projects to the dorsal striatum. This pathway contains as much as 80% of all the dopamine in the brain with the highest level in the striatum, the area most enriched in nerve terminals. This pathway is involved in the control of movement, and its degeneration causes Parkinsons disease, characterized by tremors, rigidity and akinesia. The other major pathways in the brain are the mesocortical and mesolimbic pathways that arise in the ventral tegmental area and project to the frontal cortex and the limbic areas such as the nucleus accumbens and the olfactory tubercle, which are involved in motivated behavior, and these systems may be the targets of antipsychotics. The tuberoinfundibular pathway arises in cells of the periventricular and arcuate nuclei of the hypothalamus and projects to the intermediate lobe of the pituitary to control the secretion of α -melanocyte-stimulating hormone from melanotroph cells and to the median eminence of the hypothalamus where dopamine is released and reaches the anterior pituitary via the portal system to control the secretion of prolactin from lactotroph cells.

Dopamine exerts its multiple actions via specific receptors. To date, at least five dopamine receptor subtypes have been distinguished by molecular cloning techniques, all of which belong to a family of seven transmembrane domain G-protein coupled receptors (10, 11). They are grouped as two major subfamilies, D₁- and D₂-like receptors, according to structure as assessed from deduced amino acid sequences and their pharmacological profiles such as the similarities of the binding affinities of the ligands. The

D₁-like receptor subfamily consists of D₁ and D₅ receptors and the D₂-like receptor subfamily, D₂, D₃ and D₄ receptors. D₁-like receptors are positively linked to adenylyl cyclase, while D₂-like receptors are generally negatively linked to this enzyme. In contrast to D₁-like receptors, the D₂-like receptors have several introns in the coding region of their genes and mRNA isoforms generated by alternative splicings. Two functional isoforms of D₂ receptor mRNA, called D_{2L} and D_{2S} receptor mRNAs, have been found, the former of which is identified by the existence of 29 amino acids in the putative third intracellular domain compared to the latter isoform (12, 13). Although these two isoforms are distributed unevenly through the brain, they have similar pharmacological profiles that are not distinguished by the dopaminergic ligands, and the events that regulate the splicing of the D₂ receptor gene are not yet understood.

3. Autoreceptors as targets of antipsychotics

The D₂ receptors are expressed predominantly in the caudate putamen, nucleus accumbens and olfactory tubercle, and the D₃ receptors are expressed in more restricted regions of the brain such as the islands of Calleja, a few septal nuclei, the hypothalamus and a few regions of the thalamus and cerebellum. The mRNAs of both receptors are also expressed in the substantia nigra pars compacta and in the ventral tegmental area, where dopamine neuronal somas project to discrete regions of the brain. These mRNAs disappear on treatment with dopamine neuronal toxin 6-hydroxy-dopamine, indicating that the D₂ and D₃ receptors are located in the dopamine neurons as autoreceptors (14).

Generally, autoreceptors regulate their own neuronal activities by a negative feedback mechanism. Two types of autoreceptors are located in the neuronal cell soma (somatodendritic autoreceptors) and neuronal terminus (pre-synaptic receptors). The former exists in the substantia nigra and the ventral tegmental area and the latter in the striatum, limbic area and cortex in the case of the dopaminergic system. The stimulation of pre-synaptic receptors inhibits the synthesis and release of neurotransmitters, while the stimulation of somatodendritic autoreceptors leads to an inhibition of the neuronal firing rate, which is the case also in the dopaminergic system. Indeed, studies have found that agonists for the D₂ or D₃ receptors inhibit dopamine release from the nerve terminals (15). The contribution of the D₃ receptors to dopamine autoreceptor function, however, might be small because it was reported that D₂ receptors-but not D₃ receptors-deficient mice show dopamine autoreceptor dysfunction (16, 17).

Consequently, it has been hypothesized that a selective stimulation of the dopamine autoreceptors by autoreceptor-selective agonists can decrease the synthesis and release of dopamine and neuronal activity and thus ameliorate the positive symptoms of schizophrenia. While a typical anti-

psychotic such as haloperidol blocks dopaminergic transmission completely to induce extrapyramidal side effects, an autoreceptor agonist, which merely diminishes the tone of the dopaminergic system is thought to be free from such side effects. Therefore, autoreceptor-selective agonists (pramipexole, roxindole, etc.) that do not interfere with post-synaptic receptors have been developed in the past years. However, administration of autoreceptor-selective agonists such as talipexole, roxindole and pramipexole have yielded clinically inconsistent results and did not result in a significant improvement of positive symptoms (18). Rather, schizophrenic symptoms could be worsened by an autoreceptor agonist because it might also stimulate post-synaptic receptors if it is not completely selective to pre-synaptic autoreceptors alone or if it is used at higher doses. The dopaminergic autoreceptors are the D₂ receptors, which are identical to the post-synaptic D₂ receptors despite the possibility of a different interaction with the different second messenger systems. As a matter of course, it is thought to be difficult for ligands to distinguish between the autoreceptors and the post-synaptic receptors. The autoreceptor-selective agonist even showed considerable intrinsic activity at denervated and thus supersensitized post-synaptic receptors (19). Furthermore, autoreceptors could be easily down regulated. As reported previously, an autoreceptor non-selective agonist, *n*-propyl-norapomorphine, produced antipsychotic effects after acute but not chronic administrations (20). This appears to be a very rapid tolerance to the antipsychotic effects probably due to the down regulation of the dopamine autoreceptors. Since the therapeutic action of antipsychotics takes a longer time to develop, with such a long administration schedule, the predominant antipsychotic effects of the drugs will be post-synaptically rather than pre-synaptically mediated.

4. Partial agonists as ideal antipsychotics

A number of dopamine receptor partial agonists have been developed for use as antipsychotics. A partial agonist is a compound that displays a large range of intrinsic activities at the same receptors depending on the conditions and model used during the development of the compound (21). Such a drug displays potent agonistic effects at the pre-synaptic D₂ receptors, which have a high receptor reserve (22), whereas at a similar concentration, it fails to display agonism at the post-synaptic D₂ receptors, which have virtually no receptor reserve. The intrinsic efficacy of a dopamine-receptor partial agonist depends on the sensitivity and responsiveness of the dopamine receptors influenced by its occupancy. That is to say, a partial agonist may act as a dopamine receptor agonist in the substantia nigra and the ventral tegmental area, where the D₂ receptors exist as somatodendritic autoreceptors and the amount of endogenous dopamine is relatively low, and as an antagonist at

the post-synaptic D₂ receptors in the striatum, the limbic areas and pituitary, where the amount of endogenous dopamine is high. The pre-synaptic dopamine D₂ receptors in the latter brain area may have a high receptor reserve for such a drug to act as an agonist. The prototypical drug of this group is preclamol, (-)-3-(3-hydroxyphenyl)-*N*-*n*-propyl-piperidine (3-PPP). The rational principle of this approach has been an apparent agonistic effect on the autoreceptors to inhibit dopamine synthesis and release and reduced endocrinal and extrapyramidal side effects because of inactivity for post-synaptic receptors. However, as mentioned above, autoreceptor-selective agonists have inconsistent antipsychotic effects and can even provoke positive symptoms. This is thought to be due to the down regulation of the autoreceptors and the substantial agonistic effects on the post-synaptic receptors. Thus, on repeated administration of antipsychotics, the contribution of post-synaptic receptors rather than autoreceptors should be considerable. It is likely that the intrinsic efficacies of most partial agonists have been too high, and that an ideal antipsychotic should have been weaker or even have negligible intrinsic efficacy at the D₂ dopamine receptors.

In this respect, OPC-14597 (aripiprazole), a quinolinone derivative which has been demonstrated to be clinically useful as an antipsychotic drug with reduced extrapyramidal motor and endocrinal side effects, is an interesting recent development. This compound is a congener of OPC-4392 but has much less intrinsic efficacy (23).

We found that aripiprazole competed against [³H]spiperone binding with 100-fold more affinity than [³H]SCH23390 binding and inhibited GTPase activities induced by the D₂ agonist quinpirole in rat striatum membranes, indicating that this compound exerted high affinity for the post-synaptic D₂ receptor antagonist, similar to the conventional antipsychotic haloperidol. Nevertheless, in contrast to haloperidol, the chronic administration of aripiprazole did not increase [³H]spiperone binding or the D₂ receptor mRNA in rat brain striatum (24). We also investigated the D₂ receptors in the rat pituitary. The chronic administration of haloperidol greatly increased [³H]spiperone binding and the amount of D₂ receptor mRNA, which indicates that the receptors were up-regulated following repeated administration of the antagonist. Aripiprazole, conversely, decreased [³H]spiperone binding and D₂ receptor mRNA levels in the rat pituitary (25). These results might be reflected in the clinical properties of aripiprazole's effect on schizophrenic symptoms with reduced extrapyramidal and endocrinal side effects.

In spite of the common pharmacological properties of haloperidol and aripiprazole, namely, high affinity post-synaptic antagonism, there are differences in their effects on the D₂ receptors in the striatum on chronic treatment. Two distinctive factors are involved. Firstly, haloperidol

has no intrinsic activity in the D_2 receptors in the striatum, while aripiprazole has some intrinsic efficacy. This means that aripiprazole is a partial agonist for the D_2 receptors and thus acts as an agonist on autoreceptors and as an antagonist on post-synaptic D_2 receptors. Another group has demonstrated that aripiprazole works as a partial agonist in the rat pituitary (26). Secondly, aripiprazole has adequate affinity for D_2 receptors. The K_i value of aripiprazole was 38 nM for [3H]spiperone binding in our assay, which shows a high affinity to the D_2 receptors, but somewhat lower than that of haloperidol. Haloperidol has been reported to show K_i values of 0.6 – 1.2 nM for D_2 receptors. In another study, aripiprazole had a K_i value of 4.7 nM, which is rather mild compared to haloperidol, with a K_i of 0.41 nM in rat striatal membranes (23).

Figure 1 shows a scheme describing the mode of action of an ideal antipsychotic in the dopaminergic system in the brain. Dopaminergic neuronal systems in the brain have D_2 autoreceptors, which are the somatodendritic autoreceptors and the pre-synaptic autoreceptors, and the post-synaptic D_2 receptors. The somatodendritic autoreceptors are located in the substantia nigra and ventral tegmental area. The post-synaptic D_2 receptors and the pre-synaptic autoreceptors are located in the striatum and the limbic area where dopamine neurons innervate and dopaminergic neuronal terminals exist. The pre-synaptic autoreceptors have a high receptor reserve, in contrast to the post-synaptic receptors. The partial agonist could bind the pre-synaptic autoreceptors to act as a potent agonist. At the somatodendritic autoreceptors, the amount of endogenous dopamine is so

low that the partial agonist could bind to act as an agonist. These effects depress the dopaminergic neuronal activity, which may effectively ameliorate the positive symptoms of schizophrenia. However, these autoreceptors are easily down-regulated by repeatedly administering agonists. At the post-synaptic receptors, since significant amounts of endogenous dopamine exist and there is no receptor reserve, partial agonists with low intrinsic efficacy act as an antagonist to provoke the antipsychotic effects. The potency of the intrinsic efficacy of the partial agonist is important because if it is high, it will exacerbate the positive symptoms. Furthermore, the occupancy of the post-synaptic D_2 receptors by the partial agonist in the striatum or the limbic area depends on the affinity of the partial agonist. In the striatum, a high level of endogenous dopamine exists. Conventional antipsychotics such as haloperidol with super high affinity to the D_2 receptors could block the post-synaptic D_2 receptors completely despite the existence of much endogenous dopamine, to induce the extrapyramidal side effects. Partial agonists with a relatively low affinity to the D_2 receptors fail to compete for the endogenous dopamine and could not bind the post-synaptic D_2 receptors in the striatum. In the limbic area, a low level of endogenous dopamine could allow drugs with a range of affinities to occupy the post-synaptic D_2 receptors and exert antipsychotic effects as D_2 receptor antagonists because of their low intrinsic activities. Thus, partial agonists with little intrinsic activity and adequate affinity could make for an ideal antipsychotic drug with reduced side effects.

Fig. 1. A scheme describing the mode of action of the partial agonist as an ideal antipsychotic in the dopaminergic system in the brain.

5. Conclusion

Partial agonists with adequate intrinsic efficacies and affinities for D₂ receptors may be ideal antipsychotic drugs with potency to ameliorate schizophrenic symptoms and with reduced extrapyramidal and endocrinal side effects. It is suggested that the fine-tuning of the intrinsic efficacy and the affinity is an important strategy for defining an optimal antipsychotic based on the dopamine D₂-receptor partial agonist concept. Such receptor partial agonists could offer a novel tool for modulation of dopaminergic transmitter systems in the CNS, the systems that are implicated most frequently in the pathogenesis of schizophrenia. Furthermore, the regulation of dopaminergic receptor subtypes other than D₂ and the involvement of neuronal systems other than the dopaminergic system should be considered in therapy for schizophrenia, especially for the negative symptoms.

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