PROCEEDING

Aripiprazole, a novel antipsychotic agent : Dopamine D_2 receptor partial agonist

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Abstract : It is obvious that DA is an important neurotransmitter *in vivo*. It is involved in a variety of physiological processes such as mental processes, motor function and hormone regulation. In this context, it is quite understandable that a DA D_2 receptor antagonist that inhibits the DA D_2 receptor regardless of the state of activity of dopaminergic neurotransmission and inhibit the physiological function of DA can have a variety of adverse effects. In contrast to DA D_2 antagonists, aripiprazole acts as an antagonist at the DA D_2 receptor in the state of excessive dopaminergic neurotransmission, while it acts as an agonist at the DA D_2 receptor in the state of low dopaminergic neurotransmission, and thus attempts to bring the state of dopaminergic neurotransmission to normal. This activity of aripiprazole to regulate dopaminergic neurotransmission is physiologically reasonable, and can be regarded as a stabilizing effect, for which aripiprazole is called a dopamine system stabilizer J. Med. Invest. 52 Suppl. : 284-290, November, 2005

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INTRODUCTION

Schizophrenia is a mental illness that appears from the adolescent period. Its morbidity rate is estimated at about 1% of the population with no interracial differences. It is now characterized as a illness that progresses repeating the relapse-remission cycle, and a collapse of personality occurs in severe cases. It consists of two major symptoms. One is the "positive symptoms" that express such abnormal behavior as defined in the following diagnostic terms: "hallucination," "delusion," and "agitation." The other is the "negative symptoms" that are classified using the following diagnostic terms: "blunted affect," "emotional withdrawal," and "apathy." In addition, the "positive symptoms" mostly emerge at an acute phase of the illness, and the "negative symptoms" generally emerge at its chronic phase (1) . The cause and pathophysiological basis of schizophrenia are currently unclear, and various hypotheses about the cause have been proposed, for example, genetic disorder, neuro-developmental disorder from infancy, disorder of glutamatergic neurotransmission, and dopaminergic neuronal disorder, and so on. However, there is no hypothesis at present that sufficiently explains the pathphysiological and neurobiological basis (2) . Schizophrenic patients are now treated with typical and atypical antipsychotic agents in clinics, which have an antagonistic effect at dopamine (DA) D_2 receptors.

Fifty years has passed since the initial report of the antipsychotic activity of chlorpromazine in 1952. The cause of schizophrenia still remains unknown but has been hypothesized to be excessive activity of dopaminergic neurotransmission, and in the mid 1970s, the "DA hypothesis of schizophrenia" was proposed (3). Based on this hypothesis, many DA receptor antagonists were developed. It is generally known that these so-called typical antipsychotics are effective against the positive symptoms, but have weak activity against the negative symptoms.

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In terms of safety, this class of drugs is associated with extrapyramidal side effects such as akathisia, dystonia and parkinsonian movement disorders, as well hyperprolactinemia (4, 5). In the late 1980's, while the DA hypothesis itself was being modified (6, 7), there were additional proposals that other neural systems such as the serotonergic system and glutamatergic system may also be involved in the pathogenesis of schizophrenia, thus complicating the hypothesis that schizophrenia is due to abnormalities in DA neurotransmission (8) . New drugs developed in the 1990s were clozapine, which established the concept of atypical antipsychotics, risperidone, which is a serotonin-dopamine antagonist (SDA) , olanzapine and quetiapine, and in 2000, ziprasidone was introduced. Among the shortcomings of the typical antipsychotics, these antipsychotics largely solved the problem of extrapyramidal side effects (8, 9) . However, on the other hand, the atypical antipsychotics are associated with problems of weight gain, lipid metabolism abnormalities, excessive sedation, and cardiac QT prolongation, so that there has existed a need for antipsychotics with better safety and tolerability.

At Otsuka Pharmaceuticals, based on the DA hypothesis, we have focused on drug discovery for compounds with inhibitory activity on the dopaminergic neurotransmission, which are different from the traditional agents, and have studied DA autoreceptor agonists since the 1970s. We have focused on agents to regulate neurotransmission, which act as agonists at the presynaptic DA autoreceptor and as antagonists at the postsynaptic DA D_2 receptor, and as a result developed aripiprazole, which is a DA D_2 receptor partial agonist (10-12). Aripiprazole was approved by the US FDA in November 2002 for schizophrenia and in the expanded 25 countries in the Europe by the European Commission (EC) in June 2004. Additionally in September 2004, it received a supplemental approval for the indication of acute manic episode of bipolar disorder by FDA. An application for approval is currently pending in Japan for schizophrenia as an indication. Aripiprazole is a small molecule with 3, 4-dihydro-2-(1H)-quinolinone as the backbone (Figure 1) and has attracted attention as the world's first novel antipsychotic that is a DA D_2 receptor partial agonist (13-15). In this review, we discuss the activity of aripiprazole as a DA D_2 receptor partial agonist and discuss the utility of DA D_2 receptor partial agonists in schizo-phrenia.

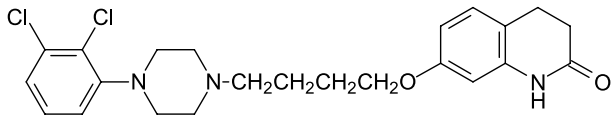

Figure 1 Structural formula of aripiprazole

DA D_2 RECEPTOR PARTIAL AGONIST ACTIVITY

Substances that bind specifically to the receptor, such as neurotransmitter, hormones or centrally acting drugs are called ligands. The concept of a partial agonist is not a new concept but has been in existence for a long time as a concept that explains the reactions mediated by ligands bound to the receptor and the receptor. Simply, a DA D_2 receptor partial agonist has affinity toward the DA D_2 receptor and an intrinsic activity that is less than the activity of the endogenous full agonist DA (that is, it can bind to the DA D_2 receptor and cause a similar set of reaction but the magnitude of the reaction is smaller than DA). These effects differ from the traditional typical and atypical DA D_2 receptor antagonists. The partial agonist activity of aripiprazole at the DA D_2 receptor has been demonstrated in the 4 *in vitro* and *ex vivo* studies described below.

1) An *in vitro* receptor binding study was conducted using a Chinese hamster ovary (CHO) cell membrane expressing the recombinant human DA D_2 receptor. The DA D_2 receptor agonist had higher affinity to the DA D_2 receptor in the G-protein-coupled state when compared to the DA D_2 receptor in the G-protein-uncoupled states (16) . Aripiprazole differs from the DA D_2 receptor antagonist haloperidol and as with the DA D_2 receptor partial agonist terguride, has about a 2-fold higher affinity to the DA D_2 receptor in the G-protein-coupled state than that in the G-protein-uncoupled state. In addition, aripiprazole had far higher affinity to the DA D_2 receptor compared to the endogenous neuro-transmitter DA (Table 1) (10) . These data suggest that aripiprazole is a DA D_2 receptor partial agonist.

2) Studies were conducted *in vitro* with CHO cell line expressing the recombinant human DA D_2 receptor (10) and rat primary cultures of anterior pituitary cells (unpublished). In both studies, the aripiprazole stimulated the DA D_2 receptor and the maximum stimulatory effect was smaller than the full agonist DA. In the studies conducted with the CHO cells expressing the recombinant human DA D_2 receptor, aripiprazole antagonized the stimulatory effect of DA to the level of aripiprazole (10) (Figure 2). These data indicate that the aripiprazole is a partial agonist with intrinsic activity that is less than the full agonist.

Table 1 Affinity of antipsychotics to dopamine D_{2L} receptor in the G-protein-coupled or uncoupled state

Drug		Ki value (nM)		
		[^{125}I]-7-OH-PIPAT (A)	[^{3}H]-Spiperone (B)	Ki (B) / Ki (A)
Agonist	Quinpirole	9.5 ± 1.5	634 ± 151	67
	Dopamine	17 ± 1.0	576 ± 192	34
Partial agonist	S-(-)-3-PPP	56 ± 4.5	1034 ± 231	18
	Terguride	0.16 ± 0.01	0.36 ± 0.04	2
	Aripiprazole	0.34 ± 0.02	0.70 ± 0.22	2
Antagonist	Butaclamol	0.43 ± 0.09	0.16 ± 0.01	0.4
	Haloperidol	0.30 ± 0.06	0.16 ± 0.02	0.5

n=2 to 4. The data shown is a mean ± SE of n=3 or 4, or in the case of n=2, then the mean of ± 1/2 range. [^{125}I]-7-OH-PIPAT binding was measured for dopamine D_{2L} receptor in the G-protein-coupled state, while [^{3}H]-spiperone binding was measured for dopamine D_{2L} receptor in the G-protein-uncoupled state. (Reference 2)

3) Using the CHO cells expressing the recombinant human DA D_2 receptor, we conducted *in vitro* studies on spare receptors. Using the alkylating agent EEDQ to partially inactivate the DA D_2 receptor, at the concentration of EEDQ that has no effect on the maximum inhibitory effect on cAMP accumulation by DA, the maximum inhibitory effect of aripiprazole on cAMP accumulation decreased dramatically (10) . These data indicate that spare DA receptors exist, while such receptors do not exist for aripiprazole. Thus, aripiprazole can be considered to be DA D_2 receptor partial agonist.

4) We studied the effect of aripiprazole *ex vivo* on the presynaptic DA D_2 autoreceptor, which regulates the activity of tyrosine hydroxylase, a rate-determining step in DA biosynthesis. Because the presynaptic DA D_2 autoreceptor has many spare receptors while the postsynaptic DA D_2 receptor has essentially no spare receptors, a DA D_2 receptor partial agonist acts as an agonist at the presynaptic site but as an antagonist and not as an agonist at the postsynaptic site (17,18). In animals treated with reserpine or γ-butylolactone, aripiprazole, like the DA D_2 receptor partial agonist S-(-)-3-PPP (19) , inhibited the increase in DA biosynthesis and showed DA D_2 autoreceptor agonist activity (11). These results indicate that aripiprazole is a DA D_2 receptor partial agonist.

REGULATION OF DOPAMINERGIC NEUROTRANSMISSION BY DA D_2 RECEPTOR PARTIAL AGONIST ACTIVITY

The DA D_2 receptor partial agonist activity is a characteristic that is not seen with the existing typical or atypical antipsychotics, DA D_2 receptor antagonists. In contrast to the DA D_2 receptor antagonists that act generally at the DA D_2 receptor regardless of the activity of the *in vivo* dopaminergic neurotransmission and inhibit the action of DA at the D_2 receptor completely at a high dose, the DA D_2 receptor partial agonist acts as an antagonist at the DA D_2 receptor in the state of excessive dopaminergic neurotransmission, while it acts as an agonist at the DA D_2 receptor in the state of low dopaminergic neurotransmission (20) . The *in vitro* and *in vivo* studies indicated that the DA D_2 receptor partial agonist aripiprazole acts as a DA D_2 receptor antagonist in the states of the excessive dopaminergic neurotransmission and as a DA D_2 receptor agonist in the state of the low dopaminergic neurotransmission (Figure 2) (10, 11, 21).

AFFINITY AND EFFECTS AT OTHER RECEPTORS

Table 2 shows the affinity of aripiprazole at various receptors. Aripiprazole has the highest affinity to the DA D_2 receptor, and also has high affinity to the DA D_3 receptor, and the serotonin 5-HT_{1A} and 5-HT_{2A} receptors. Aripiprazole also acts as a partial agonist at the D_3 receptor(12) and the 5-HT_{1A} receptor(22) and as an antagonist at the 5-HT_{2A} receptor(23). Aripiprazole at the serotonin 5-HT_{2A} receptor acts as a partial agonist with low intrinsic activity (12.7% of 5-HT), and at the serotonin 5-HT_{2B} receptor acts as an inverse agonist (12).

Aripiprazole has relatively high affinity to the serotonin 5-HT_{2A} receptor (Ki value : 3.4 nM), but

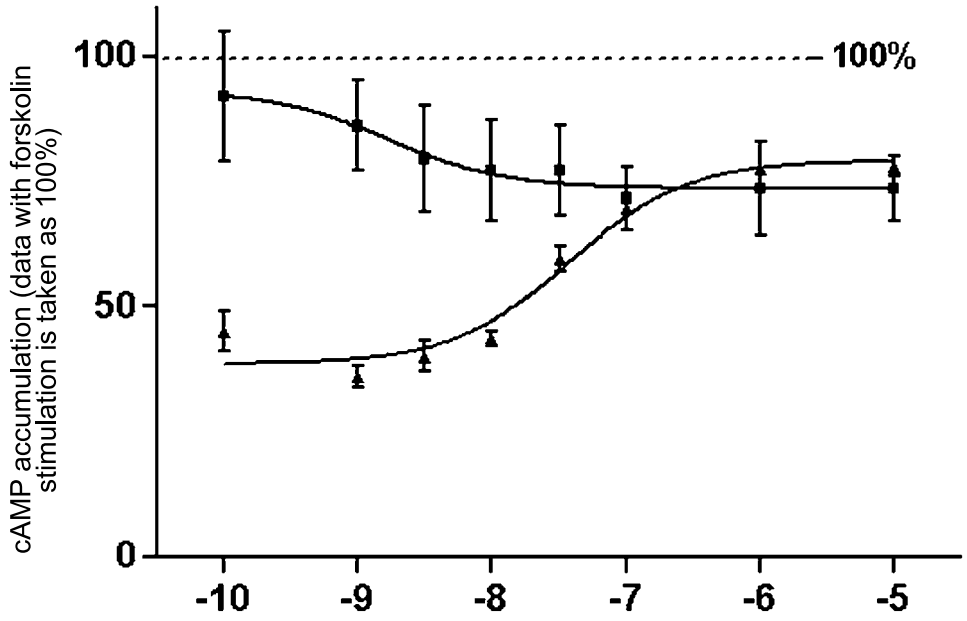

Figure 2 Agonist and antagonist activities of aripiprazole at the dopamine D_2 receptor using cAMP accumulation after forskolin stimulation as an index
In the presence of 10 μM EEDQ, Chinese hamster ovary cells expressing the human dopamine D_{2L} receptor were incubated to partially inactivate the dopamine D_2 receptor. After removing the EEDQ by washing, the effect of aripiprazole on forskolin-induced cAMP accumulation was measured in the absence (■) and presence (▲) of dopamine at 100 nM. The data shown is the mean ± 1/2 range of 2 experiments. (Reference 2)

its affinity to the DA D_2 receptor is 10-fold higher (Ki value : 0.34 nM). The SDA-type antipsychotics have a relatively higher affinity to the 5-HT_{2A} receptor than to the D_2 receptor, and it has been hypothesized that this is a requirement for clinical utility as an atypical agent (8) . According to this hypothesis, aripiprazole would not be an SDA-type agent. As far as we are aware, there have been 3 reports from different research institutions on the effect of aripiprazole on intracerebral DA release in the rat brain using the intracerebral microdialysis method. There are 2 reports involving the medial prefrontal cortex. One study reported that aripiprazole had no effect on DA release (24) . In the other study, aripiprazole promoted DA release in the medial prefrontal cortex, but the DA release promoting effect was seen only at the intermediate dose among the 4 doses selected. The effect was mild and without dose-dependence (25) . There is also 1 report on the frontal cortex ; aripiprazole had a mild but dose-dependent effect of decreasing the DA release (26). There are 2 reports on the striatal system ; in one report aripiprazole had no effect on DA release (24), while in the other there was a slight dose-dependent inhibition of the DA release (26) . These data indicate that aripiprazole differs not only from the SDA-type antipsychotics but also the conventional antipsychotics in that it has essentially no effect of promoting DA release from presynaptic sites. The lack of promotion of DA release by aripiprazole is postulated to be due to the presynaptic DA D_2 receptor autoreceptor agonist activity based on the DA D_2 receptor partial agonist activity.

Aripiprazole has low affinity to the adrenergic α_1 receptor involved in sedation and orthostatic hypotension and histamine H_1 receptor involved in sedation and weight gain, and extremely low affinity to the muscarinic receptor involved in anti-cholinergic side effects (visual disturbance, thirst, constipation, urination disorder, and cognitive disorder) (Table 2).

5 UTILITY OF ARIPIPRAZOLE IN THE TREATMENT OF SCHIZOPHRENIA

In short-term placebo-controlled studies conducted overseas (27-29), aripiprazole improved positive and negative symptoms in patients with acute exacerbation, and prevented relapse in a 26-week long-term placebo-controlled study (30). In a 52-week long-term study (31) , its improvement in positive symptoms was equivalent to haloperidol and was better against negative symptoms and depressive symptoms. It had a low incidence of extrapyramidal effects and was shown to have little effects on the blood prolactin level and weight gain, which have been seen with other agents (13, 14,

Table 2 Binding characteristics of antipsychotics

Receptor	Aripiprazole	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Haloperidol
D_1	265	290	580	52	1,300	130	120
D_2	0.34	130	2.2	20	180	3.1	1.4
D_3	0.8	240	9.6	50	940	7.2	2.5
D_4	44	47	8.5	50	2,200	32	3.3
5-HT_{1A}	1.7	140	210	2,100	230	2.5	3,600
5-HT_{2A}	3.4	8.9	0.29	3.3	220	0.39	120
5-HT_{2C}	15	17	10	10	1,400	0.72	4,700
5-HT_6	214	11	2,000	10	4,100	76	6,000
5-HT_7	39	66	3.0	250	1,800	9.3	1,100
Alpha 1	57(rat)	4.0	1.4	54	15	13	4.7
Alpha 2	791(rat)	33	5.1	170	1,000	310	1,200
H_1	61	1.8	19	2.8	8.7	47	440
M_1	>10 μM (IC_{50},bovine)	1.8	2,800	4.7	100	5,100	1,600

Unless specifically noted, the values indicate the Ki value (nM) at the expressed human receptor. The Ki values (nM) for antipsychotics other than aripiprazole are taken from Reference 26.

32-35).

A hypothesis based on the pathophysiological research has suggested that the mesolimbic dopaminergic neurotransmission is in a hyperactivated state in schizophrenic patients (4-6) . Antipsychotics have the DA D_2 receptor antagonist effect and improve positive symptoms by inhibiting the postsynaptic DA D_2 receptor in the mesolimbic dopaminergic neurons and at the same time have extrapyramidal side effects and hyperprolactinemia by inhibiting the postsynaptic DA D_2 receptor in the substantia nigra and tuberoinfundibular dopaminergic neurons respectively (4, 5) . In schizophrenia, the mesolimbic dopaminergic neurotransmission is in a hyperactive state, while the tuberoinfundibular dopaminergic neurotransmission is in normal state and substantia nigra dopaminergic neurotransmission is actually in a suppressed state (6) . In addition, it has been reported that postsynaptic DA D_2 receptors (D_2 receptor on the prolactin-secreting cells in the anterior pituitary) on the tuberoinfundibular dopaminergic neurons have spare receptors (36) . Aripiprazole acts as an antagonist on the mesolimbic postsynaptic DA D_2 receptor and thus improves the positive symptoms by inhibiting the excessive dopaminergic neurotransmission. At the same time, it does not completely inhibit the neurotransmission at the postsynaptic DA D_2 receptor in the substantia nigra and also has no inhibitory effect at the postsynaptic DA D_2 receptor in the tuberoinfundibular system, so that there are less extrapyramidal side effects and no hyperproalctinemia. In schizophrenia, it is thought that the decreased dopaminergic neurotransmission in the prefrontal cortex leads to the expression of negative symptoms (6,7) , and aripiprazole has agonist activity at the postsynaptic DA D_2 receptor in the prefrontal cortex in the state of low dopaminergic neurotransmission and improve the negative symptoms by improving the low neurotransmission.

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