Aripiprazole: What Is the Role of Dopamine D_2 Receptor Partial Agonism?

Aripiprazole is the first clinically available atypical antipsychotic drug that utilizes partial agonism at the dopamine D_2 receptor to achieve an atypical antipsychotic profile. The extent to which the atypical profile of aripiprazole is mediated solely by its partial agonism at the dopamine D_2 receptor versus its actions at many other G-protein-coupled receptors has been a subject of some discussion (1). Clinically, aripiprazole has been shown to have similar efficacy to haloperidol, risperidone, and olanzapine in treating positive and negative symptoms (1, 2). Its effects on cognition have been reported to be similar to those of olanzapine except for producing greater improvement in verbal learning (3). It is the very low incidence of extrapyramidal symptoms and the absence of elevated prolactin levels that clinically distinguish aripiprazole from most other antipsychotic drugs.

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Pharmacological studies demonstrate that, depending on the assay, aripiprazole can be a high-affinity partial agonist, a full agonist, or an antagonist at the dopamine D_2 receptor; the consensus of binding studies suggests that it is a high-affinity partial agonist at the dopamine D_{2S} and D_{2L} receptors. It is also a high-affinity partial agonist at the dopamine D_3 and serotonin 5-HT_{1A} receptors, a high-affinity antagonist at the serotonin 5-HT_{2A} and 5-HT_{2B} receptors, a moderate-affinity weak partial agonist at the 5-HT_{2C} receptor, and a high-affinity weak partial agonist at the 5-HT_7 receptor. In addition, aripiprazole has moderate affinity at the α_{1A}, α_{1B}, and α_{2C} adrenoreceptors and histamine H_1 receptors (1, 4). The pharmacological profile of aripiprazole differs from both typical and second-generation atypical antipsychotic drugs in being a partial agonist as opposed to an antagonist or inverse agonist at the dopamine D_2 receptor. Second-generation atypical antipsychotic drugs have been distinguished from typical antipsychotic drugs by a high 5-HT_2:D_2 affinity ratio (usually 10 nM or higher) and a low affinity for the dopamine D_2 receptor (5). In contrast, aripiprazole has a low 5-HT_2:D_2 affinity ratio (less than 1.0) and a high affinity for the dopamine D_2 receptor (1.0 nM or less). Studies in animals suggest that aripiprazole's partial agonism stabilizes dopamine D_2 receptor-mediated neurotransmission; in hyperdopaminergic states, aripiprazole behaves more like an antagonist blocking the effects of increased dopamine levels, while in a hypodopaminergic state it produces agonist effects (1, 6). Aripiprazole's low level of catalepsy is partially reversed by 5-HT_{1A} antagonists, suggesting that its partial agonism at the 5-HT_{1A} receptor plays a significant role in the low incidence of extrapyramidal symptoms observed clinically (1, 2, 5, 7). These studies suggest that aripiprazole's atypical profile is mediated in large part by its partial agonism at the dopamine D_2 and 5-HT_{1A} receptors; 5-HT_{2A} receptor antagonism may play a role as well (1, 5).

In the current issue of the *Journal,* Mamo et al. use positron emission tomography (PET) imaging studies of dopamine D_2, 5-HT_2 and 5-HT_{1A} receptors in subjects with schizophrenia to examine the pharmacological basis for the low incidence of extrapyramidal symptoms observed with aripiprazole. Their results show that unlike typical antipsychotic drugs, which produce therapeutic effects at >65% D_2 occupancy and extrapyramidal symptoms at occupancies >80%, therapeutic doses of aripiprazole produce more than 80% to more than 90% occupancy without inducing extrapyramidal

symptoms in most subjects, consistent with Yokoi et al.'s study in healthy subjects (8). [^{11}C]Raclopride was used to estimate dopamine D_2 receptor occupancy; it is an antagonist that binds with equal affinity at high- and low- agonist affinity states of the dopamine D_2 receptor and does not distinguish between agonist and antagonist actions of aripiprazole. Although aripiprazole has high D_2 receptor occupancy at clinically utilized doses, its partial agonism likely produces a much lower level of functional antagonism of D_2 receptor-mediated neurotransmission than seen with full antagonists (6). Unlike second-generation atypical antipsychotic drugs, aripiprazole occupied considerably lower levels of 5-HT_2 receptors than D_2 receptors, which is consistent with its lower in vitro affinity for the 5-HT_2 receptor. Low occupancy of 5-HT_{1A} receptors, 16% on average, was seen. The authors suggest that dopamine D_2 receptor partial agonism is likely the pharmacological basis for aripiprazole's atypical antipsychotic profile. However, the measurement of 5-HT_{1A} receptor occupancy by aripiprazole using [^{11}C]WAY100635, a 5-HT_{1A} antagonist, probably does not give an accurate estimate of the functional role of aripiprazole's partial agonism at the 5-HT_{1A} receptor in mediating its atypical profile. Previous studies in humans that utilized [^{11}C]WAY100635 to measure occupancy of 5-HT_{1A} receptors by agonists or partial agonists have found either low or no significant apparent occupancy despite the presence of side effects related to 5-HT_{1A} agonism (9, 10). There may be several reasons for these observations, including a large number of spare receptors, a small fraction of 5-HT_{1A} receptors being in the high-affinity agonist configuration, and the possibility that [^{11}C]WAY100635 and agonists bind to different sites on the 5-HT_{1A} receptor causing [^{11}C]WAY100635 to be insensitive to agonist binding. Given aripiprazole's high affinity and partial agonism for the 5-HT_{1A} receptor (1, 4), the increased cataleptogenic potency of aripiprazole following 5-HT_{1A} receptor blockade (7), and the insensitivity of [^{11}C]WAY100635 PET studies to 5-HT_{1A} agonists (9, 10), the available evidence suggests that both dopamine D_2 and 5-HT_{1A} partial agonism are important factors in aripiprazole's freedom from extrapyramidal symptoms. The moderate level of 5-HT_2 blockade seen may provide additional benefit, but this is unclear. Aripiprazole appears to follow in the functional footsteps of second-generation atypical antipsychotic drugs in targeting dopamine D_2-mediated and serotonergic neurotransmission, but adds partial agonism at the dopamine D_2 receptor as an additional mechanism of action.

The article by Shim et al. in the current issue of the *Journal* reports that adjunctive aripiprazole administration to subjects with schizophrenia receiving haloperidol therapy reverses both the haloperidol-induced hyperprolactinemia and the sexual dysfunction associated with increased prolactin secretion in a large fraction of subjects. The results of this article demonstrate that aripiprazole functions as a partial dopamine D_2 receptor agonist in humans. Its high affinity for the dopamine D_2 receptor allows it to successfully compete with haloperidol while providing sufficient agonism to reverse the haloperidol-induced hyperprolactinemia.

In conclusion, the articles by Mamo et al. and Shim et al. in this issue of the *Journal* highlight the role of dopamine D_2 receptor partial agonism in the atypical profile of aripiprazole. While aripiprazole appears to modulate dopaminergic and serotonergic neurotransmission in a manner similar to that of second-generation atypical antipsychotic drugs, its partial D_2 receptor agonism provides decreased liability for extrapyramidal symptoms and hyperprolactinemia. Development of future atypical antipsychotic drugs will hopefully provide drugs that act at additional therapeutically efficacious sites, thereby reducing the number of therapeutic nonresponders and produce additional decrements in negative symptoms and improvement in cognitive deficits.

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