Role of $\alpha_1$ adrenergic antagonism in the mechanism of action of iloperidone: reducing extrapyramidal symptoms

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ISSUE:
The low incidence of extrapyramidal side effects associated with the atypical antipsychotic iloperidone may be linked to its unique binding profile of high affinity antagonism of both $\alpha_1$ adrenergic receptors and serotonin 2A receptors.

Take-Home Points

1. Extrapyramidal symptoms (EPS) such as Parkinsonism, dystonia, and akathisia are frequent side effects of antipsychotic drugs, and are thought to be due to blockade of D$_2$ dopamine receptors in the nigrostriatal dopamine pathway.

2. Second-generation antipsychotics are "atypical" because they do not cause EPS to the same extent as conventional antipsychotics—an action that has been attributed to potent serotonin 5HT$_{2A}$ antagonism. Because 5HT$_{2A}$ antagonism prevents 5HT-induced excitation of pyramidal neurons in the prefrontal cortex, this hypothetically results in downstream release of dopamine in the striatum that partially reverses the D$_2$ dopamine receptor blockade there, thus reducing EPS.

3. These same pyramidal neurons are also regulated by $\alpha_1$ adrenergic receptors, and when blocked, $\alpha_1$ adrenergic antagonism also hypothetically causes additional downstream release of striatal dopamine.

4. Iloperidone has a unique combination of potent $\alpha_1$ adrenergic antagonism plus 5HT$_{2A}$ antagonism, which may explain its very low association with EPS.

All antipsychotics block D$_2$ dopamine receptors and 5HT$_{2A}$ serotonin receptors.$^1$ Actions at other receptors differentiate the pharmacology of one atypical antipsychotic from another.$^1$ In the case of iloperidone, the pharmacologic action that distinguishes it most from other atypical antipsychotics is its potent antagonism of $\alpha_1$ adrenergic receptors; in fact, this property is the most potent of all the pharmacologic actions of iloperidone.$^1$–$^3$ Perhaps the most distinguishing clinical property of iloperidone is its low placebo level of inducing extrapyramidal side effects (EPS).$^4$–$^5$ Examining the regulation of dopamine release by pyramidal neurons can provide a hypothetical link between potent $\alpha_1$ adrenergic antagonism, 5HT$_{2A}$ antagonism, and low EPS.

5HT$_{2A}$ Receptor Antagonism

The key to understanding why antipsychotics are atypical is to understand the pharmacology of 5HT$_{2A}$ receptors, and the significance of what happens when they are blocked by atypical antipsychotics.$^1$ 5HT$_{2A}$ receptors located on cortical pyramidal neurons are excitatory and can thus enhance downstream glutamate release (Figure 1). Glutamate in turn regulates downstream dopamine release, so stimulating (Figure 1) or blocking (Figure 2) 5HT$_{2A}$ receptors can therefore also regulate downstream dopamine release.$^1$

5HT$_{2A}$ receptors are brakes on dopamine release in the striatum

5HT$_{2A}$ stimulation of cortical pyramidal neurons by serotonin (Figure 1, box 1) hypothetically blocks...
**Figure 1.** Stimulatory actions of serotonin at 5HT2A receptors

Cortical 5HT2A Receptors Decrease Dopamine Release

- Decreased DA release
  - Nucleus accumbens

- Brainstem neurotransmitter centers

**Figure 2.** Antagonist actions at 5HT2A receptors disinhibit downstream dopamine release to reduce extrapyramidal side effects

Blocking Cortical 5HT2A Receptors Increases Dopamine Release

- Increased DA release
  - Nucleus accumbens

- Brainstem neurotransmitter centers

**Figure 3.** Stimulatory actions of norepinephrine at α1 adrenergic receptors

Stimulatory actions of norepinephrine at α1 adrenergic receptors

- Increased DA release
  - Nucleus accumbens

- Brainstem neurotransmitter centers

**Figure 4.** Antagonist actions at α1 adrenergic receptors disinhibit downstream dopamine release to reduce extrapyramidal side effects

Antagonist actions at α1 adrenergic receptors disinhibit downstream dopamine release to reduce extrapyramidal side effects

- Decreased DA release
  - Nucleus accumbens

- Brainstem neurotransmitter centers

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downstream dopamine release in the striatum. It does this via stimulation of glutamate release in the brainstem that triggers release of inhibitory GABA there (Figure 1, box 2). Release of dopamine from neurons in the striatum is thus inhibited.

5HT2A antagonism cuts the brake cable

5HT2A antagonism of cortical pyramidal neurons by an atypical antipsychotic interferes with serotonin by applying its braking action to dopamine release via 5HT2A receptors (Figure 2, box 1). Thus, 5HT2A antagonism in the cortex hypothetically stimulates downstream dopamine release in the striatum. It does this by reducing glutamate release in the brainstem, which in turn fails to trigger the release of inhibitory GABA at dopamine neurons there (Figure 2, box 2). Release of dopamine from neurons downstream in the striatum is thus disinhibited, which should theoretically mitigate EPS.

5HT2A receptor antagonism theoretically makes an antipsychotic atypical: low EPS

Normally, serotonin reduces dopamine release from the striatum by actions of serotonin at the various 5HT2A receptors discussed above (Figure 1). Atypical antipsychotics have 2 principle actions: blockade of both D2 receptors and 5HT2A receptors.1,6 When D2 receptors are blocked by the D2 antagonist actions of the atypical antipsychotic, there are EPS if occupancy of D2 receptors reaches 80% or more.1 This is exactly what happens with a conventional antipsychotic. However, atypical antipsychotics have a second property, namely to block 5HT2A receptors, which, as discussed above, increases dopamine release in the striatum (Figure 2). The result of this increased dopamine release is that dopamine competes with drug at D2 receptors in the striatum, and reduces the D2 receptor binding there below 80% to more like 60%, which is enough to reduce extrapyramidal symptoms.7 This is the hypothesis that is most frequently linked to the explanation for the mechanism of the most important distinguishing clinical properties of atypical antipsychotics, namely low EPS with comparable antipsychotic actions.

α1 Adrenergic Antagonism

Due to the presence of stimulatory α1 adrenergic receptors on the same glutamate neurons that contain stimulatory 5HT2A receptors,7 it is possible that blockade of α1 adrenergic receptors may have the same downstream effects as blockade of 5HT2A receptors, and that this could hypothetically contribute to the reduction of EPS seen with agents having potent α1 adrenergic antagonist actions. This is suggested by the fact that preclinical studies show that norepinephrine acting at postsynaptic α1 receptors (Figure 3) can stimulate the same pyramidal neurons in the prefrontal cortex that serotonin acting at postsynaptic 5HT2A receptors stimulate (see Figure 1).7 By analogy, therefore, if blocking 5HT2A receptors reduces EPS by the downstream actions of such neurons (Figure 2), it may be possible that blocking α1 receptors on these same neurons would also reduce EPS (Figure 4). α1 adrenergic receptors are co-localized with 5HT2A receptors on pyramidal neurons in the prefrontal cortex8 and regulate several downstream neurotransmitters including dopamine.9–14

α1 adrenergic receptors are brakes on dopamine release in the striatum

α1 adrenergic receptor–mediated stimulation of cortical pyramidal neurons by norepinephrine (Figure 3) hypothetically blocks downstream dopamine release in the striatum.7–15 It does this hypothetically via stimulation of glutamate release in the brainstem that triggers release of inhibitory GABA there (Figure 3) analogous to how 5HT does this same action (Figure 1). Release of dopamine from neurons in the striatum is thus inhibited.

α1 adrenergic antagonism cuts the brake cable

α1 adrenergic antagonism of cortical pyramidal neurons by an atypical antipsychotic interferes with norepinephrine by applying its braking action to dopamine release via α1 adrenergic receptors (Figure 4, box 1). Thus, α1 adrenergic antagonism in the cortex hypothetically would stimulate downstream dopamine release in the striatum. It would do this by reducing glutamate release in the brainstem, which in turn fails to trigger the release of inhibitory GABA at dopamine neurons there (Figure 4, box 2). Release of dopamine from neurons downstream in the striatum is thus disinhibited, which should theoretically mitigate EPS, analogous to how 5HT is thought to have this same action (Figure 2, box 2).

Iloperidone

Iloperidone is one of the newer atypical antipsychotics with 5HT2A/D2 antagonist properties.1–6 One of its most distinguishing clinical properties is a very low
level of EPS associated with its use. Its most distinguishing pharmacological property is its potent \( \alpha_1 \) antagonism. Although it is unknown why iloperidone, like quetiapine and clozapine, has a low incidence of EPS, it may be in part due to the fact that all 3 of these agents have high affinity for \( \alpha_1 \) receptors as well as for 5HT\(_2A\) receptors. Theoretically, low EPS has been linked both to high affinity for 5HT\(_2A\) receptors (Figures 1–3) and to high affinity for \( \alpha_1 \) adrenergic receptors. One outlier to this theory is risperidone, which has relatively high \( \alpha_1 \) receptor binding, but nevertheless has higher rates of EPS.

**Summary**

In summary, the combination of a potent blockade of both 5HT\(_2A\) and \( \alpha_1 \) receptors is a novel hypothesis for the low EPS of iloperidone, clozapine, and quetiapine. The very low, placebo-level incidence of EPS associated with iloperidone may thus be explained not only by its 5HT\(_2A\) antagonist properties, which are shared with every other member of the atypical antipsychotic class, but also by combining this action with the most potent \( \alpha_1 \) antagonist action of any atypical antipsychotic.

**References**