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BRAINSTORMS—Clinical Neuroscience Update

Role of α1 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 α1 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 α1 adrenergic receptors, and when blocked, α1 adrenergic antagonism also hypothetically causes additional downstream release of striatal dopamine.
4. Iloperidone has a unique combination of potent α1 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 α1 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 α1 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 $5HT_{2A}$ receptors

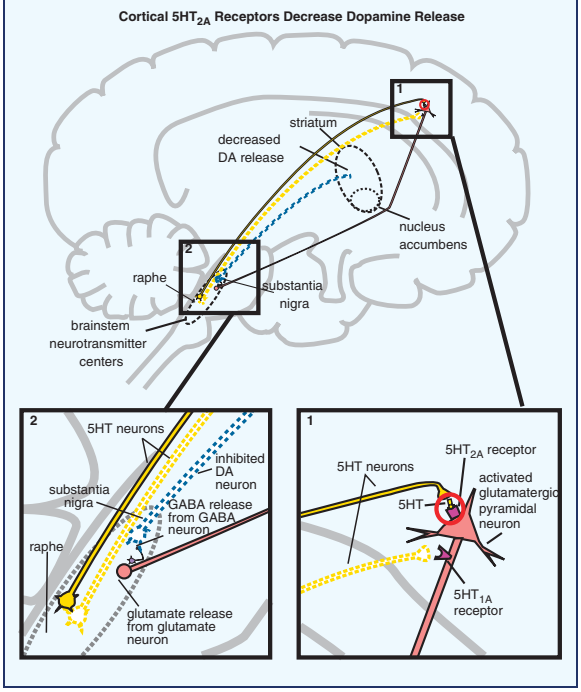


Figure 2. Antagonist actions at $5HT_{2A}$ receptors disinhibit downstream dopamine release to reduce extrapyramidal side effects

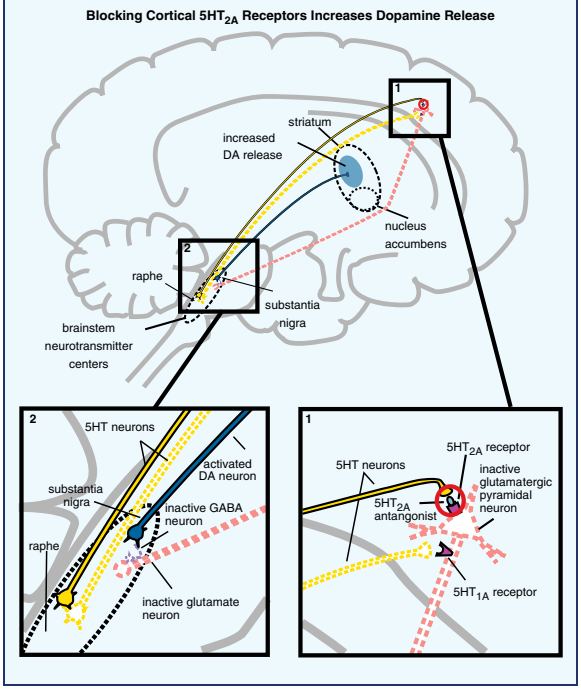


Figure 3. Stimulatory actions of norepinephrine at α1 adrenergic receptors

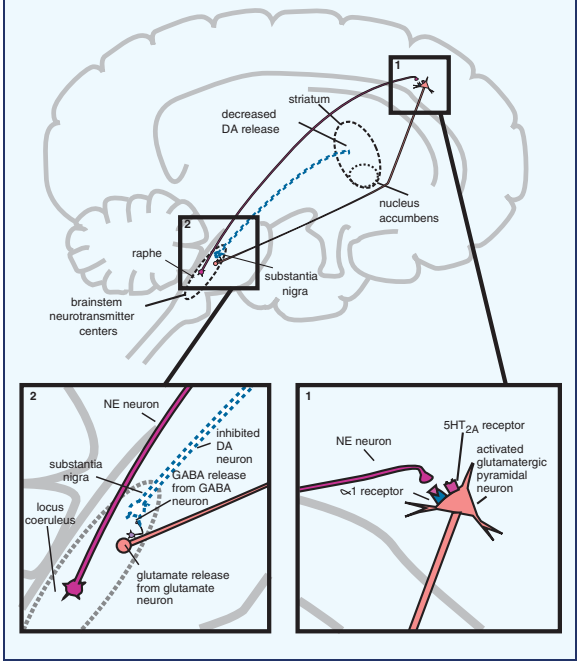
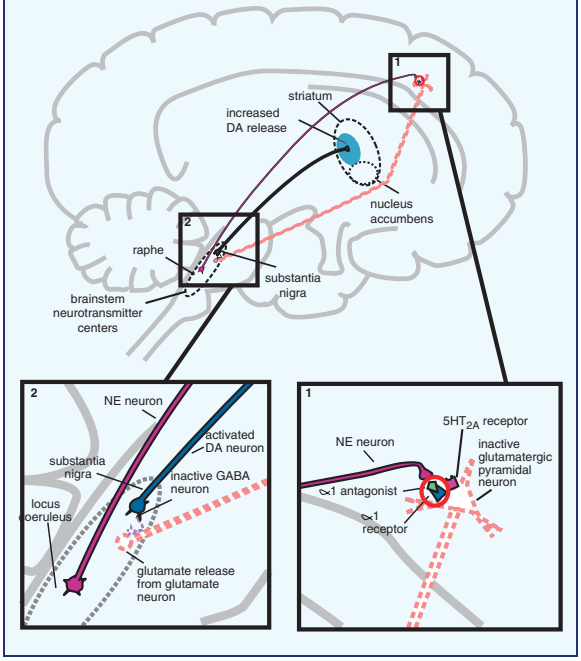


Figure 4. Antagonist actions at α1 adrenergic receptors disinhibit downstream dopamine release to reduce extrapyramidal side effects



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.

5HT$_{2A}$ antagonism cuts the brake cable

5HT$_{2A}$ antagonism of cortical pyramidal neurons by an atypical antipsychotic interferes with serotonin by applying its braking action to dopamine release via 5HT$_{2A}$ receptors (Figure 2, box 1). Thus, 5HT$_{2A}$ 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.

5HT$_{2A}$ receptor antagonism theoretically makes an antipsychotic atypical: low EPS

Normally, serotonin reduces dopamine release from the striatum by actions of serotonin at the various 5HT$_{2A}$ receptors discussed above (Figure 1). Atypical antipsychotics have 2 principle actions: blockade of both D_2 receptors and 5HT$_{2A}$ receptors.[1,6] When D_2 receptors are blocked by the D_2 antagonist actions of the atypical antipsychotic, there are EPS if occupancy of D_2 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 5HT$_{2A}$ 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 D_2 receptors in the striatum, and reduces the D_2 receptor binding there below 80% to more like 60%, which is enough to reduce extrapyramidal symptoms.[1] 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 5HT$_{2A}$ receptors,[7] it is possible that blockade of α1 adrenergic receptors may have the same downstream effects as blockade of 5HT$_{2A}$ 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 5HT$_{2A}$ receptors stimulate (see Figure 1).[7] By analogy, therefore, if blocking 5HT$_{2A}$ 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 5HT$_{2A}$ receptors on pyramidal neurons in the prefrontal cortex[8] 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 5HT$_{2A}$/D_2 antagonist properties.[1–6] One of its most distinguishing clinical properties is a very low

level of EPS associated with its use.[1–5] Its most distinguishing pharmacological property is its potent α1 antagonism.[1–3,6] 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 α1 receptors as well as for $5HT_{2A}$ receptors.[1,2,15] Theoretically, low EPS has been linked both to high affinity for $5HT_{2A}$ receptors (Figures 1–3) and to high affinity for α1 adrenergic receptors.[1,2,15] One outlier to this theory is risperidone, which has relatively high α1 receptor binding, but nevertheless has higher rates of EPS.

Summary

In summary, the combination of a potent blockade of both $5HT_{2A}$ and α1 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 α1 antagonist action of any atypical antipsychotic.

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