Dopamine System Stabilizers, Aripiprazole, and the Next Generation of Antipsychotics, Part 1

"Goldilocks" Actions at Dopamine Receptors

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Issue: *A new class of antipsychotics, called dopamine system stabilizers (DSSs), is emerging that stabilizes dopamine neurotransmission by binding to dopamine-2 receptors in a way that is not too stimulating, not too antagonizing, but just right.*

In Pursuit of the Ideal Antipsychotic: "Goldilocks" Actions

Psychosis occurs when too much dopamine exists in the synapses, and the action, akin to Goldilocks's first bowl of soup, is "too hot." Every antipsychotic that reduces the positive symptoms of psychosis such as delusions and hallucinations does so by blocking dopamine D_2 receptors, most likely those of the mesolimbic dopamine pathway.[1] Unfortunately, the blocking is often nonspecific, which is typical of conventional antipsychotic actions. Thus, when D_2 receptors in the nigrostriatal dopamine pathway are also blocked, a penalty is paid in motor side effects, namely extrapyramidal reactions, pseudoparkinsonism, and ultimately, tardive dyskinesia. The blocking causes levels that are too low or "too cold" (like Goldilocks's second bowl of soup).

Ever since the motor complications of conventional antipsychotics were recognized, attempts have been made to preserve their therapeutic effects but reduce their motor side effects—aiming for a synaptic soup that is "just right." One approach has been to reduce psychotic symptoms with a mechanism other than blocking D_2 receptors, but these attempts have been unsuccessful to date. The successful approach has been the one that changes the way a drug binds to D_2 receptors, creating that "just right" combination of antipsychotic effects without motor side effects. Not only do the atypical antipsychotics achieve this goal, but so may a new generation of agents, and by a novel mechanism called dopamine system stabilization.

What is dopamine system stabilization?

A new concept for the action of antipsychotic drugs that do not induce motor side effects is dopamine system stabilization.[2–9] The brain normally stabilizes dopamine neurotransmission by attaining a balance between presynaptic and postsynaptic D_2 receptor stimulation. These 2 mechanisms act together: presynaptic dopamine receptors are stimulated, and dopamine release at specific postsynaptic sites is turned off, thus reducing excessive dopamine activation in parts of the brain where the concentration is too high yet permitting normal dopamine activity in other parts of the brain. The presynaptic D_2 receptors responsible for regulating dopamine release are less sensitive in detecting dopamine than are postsynaptic D_2 receptors, so physiologic neurotransmission continues until dopamine levels build up sufficiently to stimulate the presynaptic D_2 receptors, thereby turning off further dopamine release.

In the brain, regional differences may occur in the activity of dopamine neurons and the sensitivity of various presynaptic and postsynaptic D_2 receptors to dopamine, especially during disease states and as a consequence of various drug treatments. The concept of dopamine system stabilization is based on preserving or enhancing dopaminergic neurotransmission where it is low ("too cold") and reducing dopaminergic neurotransmission where it is too high ("too hot"). In terms of treating psychosis, the goal is to reduce hyperactive dopamine neurons that mediate psychosis and at the same time enhance underactive dopamine neurons that mediate negative and cognitive symptoms (mesocortical pathway) while preserving physiologic function in dopamine neurons that regulate motor movement and prolactin—all in the same brain at the same time.

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How does a drug stabilize dopamine?

When dopamine is dysregulated in psychoses (e.g., schizophrenia), dopamine system stabilizers (DSSs), which bind to D_2 receptors in a manner that can be either stimulating or antagonizing, are helpful.[3] These stabilizers are far different from receptor antagonists, which always block the action of dopamine completely and reduce output from D_2 receptors ("too cold"), and very different from dopamine itself, which is a full agonist at D_2 receptors that creates maximum action (if the amount is high enough), making the receptors "too hot." DSSs, on the other hand, theoretically create the desired dopamine balance. Thus, when dopamine activity is too cold, a DSS increases dopamine output, but to a level not as hot as real dopamine. In the presence of maximum dopamine, DSSs reduce the amount until it is "just right."

Pharmacologically, this mechanism is known as partial agonist action, which means activation at low dopaminergic tone and inhibition at high dopaminergic tone, thus stabilizing dopamine output from either direction.[10,11] Molecularly, the exact mechanism of partial agonist binding to D_2 receptors remains somewhat obscure but is hypothesized to exploit differences in D_2 receptors presynaptically vs. postsynaptically, in various brain regions, or in their affinities, distribution, density, and tightness of coupling to a physiologic output.

Clinically, the term *partial agonist* may be misinterpreted because "partial" can imply weak or incomplete. DSSs, however, are not less effective than other types of antipsychotics. The prototypical member of this class, aripiprazole (also known as OPC-14597 or Abilitat), has been found to reduce psychosis as effectively as other antipsychotics without causing motor side effects in schizophrenia.[3]

Other agents in this class include (–)-3-PPP [(–)-3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine] (i.e., preclamol), (–)-OSU6162, DU-127090, and WAY-135452 (or DAB-452).[6–9] These agents all have preclinical profiles as DSSs, with partial D_2 agonist effects pharmacologically that predict antipsychotic actions without motor side effects. The trick is to find an agent that allows sufficient dopamine action in nigrostriatal pathways to prevent motor side effects from developing while reducing dopamine sufficiently in mesolimbic pathways to produce antipsychotic actions. With the right amount of dopamine system stabilization, one can achieve an antipsychotic action without motor side effects. Early clinical development of several DSSs is ongoing or imminent, and testing of aripiprazole is in late stages.

Take-Home Points

- Classical neuroleptics, known as conventional antipsychotics, bind to D_2 receptors throughout the brain as powerful, long-acting antagonists.
- Second-generation antipsychotics, known as atypical antipsychotics, bind better to D_2 receptors in parts of the brain that control psychosis than in parts of the brain that cause motor side effects. Such differential binding is a consequence of reduction of D_2 receptor antagonism where it is not desired, either by simultaneous blockade of $5\text{-}HT_{2A}$ receptors, or by short-acting blockade at D_2 receptors, called "hit-and-run" antagonism.
- Third-generation antipsychotics are dopamine system stabilizers (DSSs). They block D_2 receptors sufficiently where dopamine activity needs to be reduced (mesolimbic pathway), and thereby produce an antipsychotic action. However, DSSs do not simultaneously reduce dopamine activity in those brain regions where normal dopamine levels are needed (nigrostriatal pathway) and thus do not cause motor side effects. DSSs may even provide a modest boost in dopamine activity in areas of the brain where it needs to be increased (mesocortical pathway), and thus improve the negative and cognitive symptoms of schizophrenia.

Summary

Dopamine system stabilizers are a potential new class of antipsychotic agents without motor side effects. All known effective antipsychotics act at D_2 receptors. A novel concept for an antipsychotic without motor side effects is to stabilize these receptors rather than block them harshly.

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