Building a better antipsychotic drug by treating schizophrenia's cause

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The classic symptoms of schizophrenia – paranoia, hallucinations, the inability to function socially—can be managed with antipsychotic drugs. But exactly how these drugs work has long been a mystery.

Now, researchers at Pitt have discovered that antipsychotic drugs work akin to a Rube Goldberg machine— that is, they suppress something that in turn suppresses the bad effects of schizophrenia, but not the exact cause itself. In a paper published in this week's *Journal of Neuroscience,* they say that pinpointing what's actually causing the problem could lead to better avenues of schizophrenia treatment that more directly and efficiently target the disease.

"In the past five years or so, we've really started to understand what may be going wrong with the schizophrenic brain," says Anthony Grace, Distinguished Professor of Neuroscience and professor of psychology in Pitt's School of Arts and Sciences and professor of psychiatry in the Pitt School of Medicine, who is senior author of the paper.

Schizophrenia is made up of three different types of symptoms. Positive symptoms, which are added onto a "normal" personality, include hallucinations and delusions, such as hearing voices, thinking people are after you, or thinking you're being targeted by aliens. Those are the classic symptoms of schizophrenia and the ones antipsychotic medications work on best. Grace says these are the symptoms most likely related to a neurotransmitter called dopamine.

The other two categories of symptoms are negative (what's missing from the normal personality—the ability to interact socially or hold down a job; some emotional flattening) and cognitive (the ability to think linearly or concentrate on one thing at a time). These two really aren't addressed well by antipsychotic drugs. "Blocking the dopamine system seems to fix classic hallucinations and delusions a whole lot better than it fixes the other problems," says Grace.

Grace has been studying the role dopamine plays in the schizophrenic brain since 1978. It's long been known that after several weeks of treatment with antipsychotic drugs, dopamine-producing neurons are inactivated. "It would suggest to us that in schizophrenia there is not too much dopamine, but rather the dopamine system is too responsive," says Grace.

Therefore, by inactivating the neurons, this overresponsivity should be able to be treated. "If there were just too much dopamine in the brain, one would expect the biggest treatment effect would be at the beginning and then it would diminish," Grace says.

But the actual effect is different—it builds over a couple days and then is constant; you don't get the tolerance you'd get with other drug treatments. This didn't fit with clinical observation. "Patients respond in the first few days, but we took weeks to see results in our normal animals," Grace says.

Grace's team developed a rat model that approximates some of the key features of schizophrenia. Rats exhibit the same symptoms one would expect from schizophrenia: sensory processing, cognition, and hyperresponsivity to amphetamines. When team members looked at this animal model and used these antipsychotic drugs, they found that what takes weeks to occur in a normal rat happens in a couple days in these schizophrenia-model rats. "It fits very well with the time course we see

in human patients," says Grace.

What causes this to be the case? Grace hypothesizes that it's the schizophrenic brain's dopamine system working overtime. "Our recordings of dopamine neurons suggest that the dopamine system is turned up too high," says Grace. "That fits with human imaging studies in schizophrenics showing the dopamine system is overreacting."

Currently available antipsychotic drugs work by blocking dopamine receptors and stopping dopamine neurons from firing. "Using these drugs, we're fixing the overreactivity by causing the neurons to be inactive," says Grace. "It would be better to fix overreactivity by correcting what causes it.

"It's like fixing a car that's going too fast by taking out the engine instead of lifting your foot off the gas."

Getting Closer to the Source: The Hippocampus?

"What we're doing today, using antipsychotic drugs currently available, is putting a sort of patch several steps downstream from where we think the problem is," says Grace. "By using these animal models, we can start to work backwards to figure out why the drugs are having the effects they do. The next step to look further back and try to fix the problem at its source"

In the schizophrenic brain, it's not just the dopamine system that's hyperresponsive. The hippocampus is also hyperactive. Grace's research shows that this hippocampal hyperactivity probably causes the dopamine system to go into overdrive.

Grace recently published a paper in the journal Neuropsychopharmacology in which he looked at a novel compound that

works on another neurotransmitter, called GABA.

"What we found in animal models and others have found postmortem in schizophrenic patients is that the hippocampus is lacking a certain type of GABA-ergic [GABA-producing] neuron that puts the brakes on the system," says Grace. "What we're trying to do is fix the GABA system that's broken and, by doing that, stabilize the system so the dopamine system responses are back to normal, so that we can actually fix what's wrong rather than trying to patch it several steps downstream.

"The dopaminergic system is easier because we have a good handle on what's going on," he adds. "Cognitive symptoms are more complex. We're trying to get a handle on how to approach those. Hopefully we can use some of this novel compound that we think is going to fix more of the symptoms and test in these domains."

After 30 years of studying dopamine and the schizophrenic brain, Grace is gratified to be getting an idea of just how antipsychotic drugs are addressing what we think is wrong with the dopamine system. It's not just simply blocking receptors, it's more complex and inactivates neurons that are hyprerresponsive.

"This is consistent with the hypothesis that the hippocampus is overdriving the system, and antipsychotics are just pushing it over the edge to shut it down," he says. "This gives us an idea of where to go to make a better antipsychotic drug."

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