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# Not Just Dopamine: An Overview of Neurotransmitters and Circuits Implicated in Schizophrenia

**Announcer:**
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**Dr. Citrome:**
Hello, I'm Dr. Leslie Citrome, Clinical Professor of Psychiatry and Behavioral Sciences at New York Medical College in Valhalla, New York. Let's talk about the Neurotransmitters and Circuits Implicated in Schizophrenia. It's not just a dopamine story, although dopamine is central. It's not the only way of addressing the symptoms of schizophrenia. So let's review.

For over the past half century, we have believed that psychosis, particularly auditory hallucinations and delusions, are the result of hyperactivation of something called the mesolimbic pathway. This is the pathway in our brains from the ventral tegmental area to the ventral striatum. And that has been our working hypothesis as to why dopamine receptor antagonists work in reducing hallucinations and delusions. Block those receptors, you block those symptoms.

However, the story is a bit more complicated. Modern imaging techniques have implicated another pathway. This is from the substantia nigra to something we call the associative striatum. And this has changed the world a little bit in terms of how we conceptualize dopaminergic circuitry in human brains. So we have a total of five different circuits that we're now familiar with, with dopamine. We have the mesocortical pathway, that explains negative symptoms and cognitive impairment as well as depression. We have the mesolimbic pathway, which has undergone some modification, which is explanatory for some negative symptoms. We have our new nigrostriatal pathway 1 that goes from part of the substantia nigra to the associative striatum, which explains psychosis. We have our traditional nigrostriatal pathway which explains movement disorders when we see them in people receiving antipsychotics, and we have the tuberoinfundibular pathway that explains prolactin elevation with some of our antipsychotics.

So let's acknowledge this new nigrostriatal pathway to the associative striatum as a new advance in the science of understanding dopamine. When we block dopamine receptors in parts of the striatum that may help with hallucinations and delusions, we also block dopamine D2 receptors elsewhere that can cause problems. So if we block dopamine D2 receptors in the dorsal striatum, we have collateral damage. That is, the induction of movement problems such as drug-induced Parkinsonism, or eventually the production of tardive dyskinesia. If we block postsynaptic dopamine D2 receptors in the hypothalamic pituitary pathway, we can cause hyperprolactinemia. So perhaps there are other ways of addressing psychotic symptoms that don't involve dopamine receptor blockade.

Let's take a look elsewhere. What about glutamate receptors? Now glutamate pathways are actually a way of addressing psychosis. How do we manage to explain that? Well, it turns out that psychosis in schizophrenia may be the result of hypofunctional glutamate receptors, NMDA receptors, specifically on GABA interneurons in the cortex. Now GABA is an inhibitory neurotransmitter. So if you have a hypofunctional NMDA receptor on an inhibitory neurotransmitter where we actually lose the brakes, so to speak, and we have overactivation of downstream glutamate, which can result in increases in dopamine going to the pathways where we don't want it to,

leading to psychosis.

Clozapine actually has an interesting potential mechanism of action of addressing hypofunctional NMDA receptors by making glycine more available at the NMDA receptor. Glycine is necessary for that NMDA receptor to operate. So clozapine may work in part through that. So glutamate is certainly an approach that we can actually think about in terms of drug development that does not involve postsynaptic dopamine D2 blockade. Up to now, that's all we've been able to do.

With the glutamatergic pathway, well, we have an opening here of addressing hypofunctional NMDA receptors. And currently, there are phase 3 studies in place of iclepertin, a glycine transporter type 1 inhibitor, that is specifically being looked at for cognition.

We can further antagonize serotonin 5HT2A receptors, that may actually address dopamine downstream, and with the avoidance of direct dopamine D2 blockade. Now, we have some second-generation antipsychotics that already do that pretty well. Lumateperone, in particular, has actually higher affinity to 5HT2A than to D2. But we have this other antipsychotic, so to speak, pimavanserin, which actually has no dopamine D2 receptor antagonism. It's almost exclusively a 5HT2A receptor antagonist, and it's used to treat Parkinson's disease psychosis, and in development to be used adjunctively to antipsychotics in schizophrenia.

But there are other novel ways of addressing psychosis that we haven't talked about yet. There's the muscarinic cholinergic hypothesis of schizophrenia that's been around since the 1950s. And we know that cholinergic systems directly modulate dopaminergic and glutamatergic pathways. If we can modulate this, we can perhaps control psychotic symptoms without directly blocking postsynaptic dopamine D2 receptors. There is a medication in development in phase 3, that is a combination of xanomeline, a M1/M4 receptor agonist and trospium, a muscarinic antagonist. And together, they can be used to decrease psychotic symptoms, and relatively tolerable in that way, because the trospium added to the xanomeline helps mitigate against some of the GI side effects that we would otherwise expect with cholinergic agonism. So this combination actually seems to work. And clinical trials have resulted in positive effects in terms of psychotic symptom reduction, so stay tuned for that one.

Another novel approach is trace amines and their receptors. So trace amines are endogenous chemical messengers. They're referred to as false neurotransmitters as they're not released from the neuron when the neuron fires. They're structurally similar to mono amine neurotransmitters such as dopamine and norepinephrine and serotonin. They're expressed at very low levels. But the trace amine-associated receptors are very interesting. They were discovered not that long ago. And they help modulate these mono amines that are implicated in schizophrenia. TAAR1 is the most studied trace amine-associated receptor, and it can dimerize with dopamine receptors, and lead to alterations in dopaminergic signaling, ultimately resulting perhaps in the reduction of psychotic symptoms as evidence in a phase 2 trial of medicine called ulotaront. So stay tuned for that one.

So both approaches I just mentioned, the muscarinic approach and the TAAR1 approach, can reduce symptoms of schizophrenia without direct dopamine D2 receptor blockade.

Thank you for your attention.

**Announcer:**
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