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Glycine's Role in Driving the Cognitive Symptoms of CIAS

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Dr. Harvey:
Hi, this is CMD on ReachMD and I'm Dr. Philip Harvey. Here with me today is Dr. Martin Strassnig.

We're going to talk about the glutamatergic NMDA receptor, and we also need to talk about what is the role of glycine in NMDA receptor activity and its consequences, including cognitive impairment in schizophrenia.

Dr. Strassnig:
Thanks, Phil. Glycine really supports excitatory neuronal signaling through glutamate in the cortex of the CNS [central nervous system]. Right? What it really does, it acts as an inhibitor in neurotransmitter and glycinergic neurons, mainly in the hindbrain, which is the lower parts of the brain. But more importantly here, it acts as a co-agonist for NMDA receptors in excitatory glutamatergic neurotransmission, primarily in the forebrain, that is the higher brain centers, including the frontal lobe. Now, the crucial molecule here is the glycine transporter 1, GlyT-1,which controls the release and reuptake of glycine which is expressed in both glia and presynaptic neurons. Now, what happens is that glutamate is released during an action potential and binds to AMPA receptors, causing certain conformational changes, and this triggers an action potential that excites other neurons. Now, magnesium, for example, dissociates from NMDA receptors at this point, allowing glutamate and glycine here to bind and open the NMDA receptor channel, leading to influx of calcium and sodium, which increases the likelihood of a response to future signaling. I think this signaling, I think it is crucial because this process is known as synaptic plasticity and is crucial for learning and memory.

Now, in addition to that, NMDA receptors, and by proxy glycine, provide excitatory input to inhibitory GABAergic interneurons, which is a separate concept, but it is crucial for cortical network function and excitement/inhibition balance. It creates neural oscillations and synchronizes the brain for cognitive function and sensory processing. Right? All of which, by the way, is impaired in schizophrenia.

Dr. Harvey:
Well, Martin, that was a very interesting and comprehensive description of NMDA receptor activity, and it highlights the tremendous complexity of the NMDA receptor system. We have landed on the idea of glycine and glycine transport as ways to manipulate the NMDA receptor, because a lot of previous efforts in increasing activity in NMDA have not worked. People have tried agonists, they have tried allosteric modulation, they have tried using direct glycine agonism, as well, as a strategy to increase the obligatory activity and the co-transmission, and none of those things succeeded. It's probably the case that by inhibiting transport with the GlyT1 inhibitor, you get a more naturalistic manipulation of the receptor system wherein you actually, just like a serotonin receptor transport antagonist and SSRI [selective serotonin reuptake inhibitor] has a better antidepressant effect than a serotonin agonist does, this sort of regulates the regulation of the receptor system and allows it to function more normally. I think one of the things that gives you good potential with that is by inhibiting transport, you're still not intrinsically affecting the rest of the system; you're just pushing a little bit more glycine into the

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system, allowing the neuron to take advantage of that, and then to continue to signal onto the GABAergic interneurons. So I think this is a strategy that's very compelling, especially given the history of lack of success at other attempts to manipulate the very important NMDA glutamate receptor of hypoactivity, of which causes all kinds of downstream problems as we've heard of in other podcasts.

So thanks very much. This has been a great bite-sized discussion. And thanks for listening.

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