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Modulating the Bipolar Circuit: Striatal Dopamine and the Muscarinic Opportunity

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Dr. Rubio:
This is CE on GLC Education. Hello, I am Jose Rubio, and here with me today is Dr. Tang.

Dr. Tang, what do we know about the neurocircuitry of bipolar disorder?

Dr. Tang:
Well, bipolar disorder involves dysregulation across multiple neurotransmitter systems and neurocircuits. So it's actually decades ago that a cholinergic-adrenergic balance hypothesis was proposed by Janowsky et al that suggests that cholinergic dominance was related to depressive states, whereas adrenergic dominance, so that's an increase in norepinephrine and dopamine, was related to manic states. And we've seen since then that this cholinergic-adrenergic balance hypothesis has actually been borne out by a lot of the pharmacologic studies recently. So, for example, studies that show scopolamine, which is an anticholinergic, has some antidepressant properties in bipolar disorder, and also on the other side, we've seen that dopamine agonists like amphetamines, for example, can actually precipitate manic episodes.

Dr. Rubio:
So how does our understanding of mania's neurobiology, specifically dopamine, point us towards muscarinic receptors as a new therapeutic target?

Dr. Tang:
Well, so we've seen that dopamine overactivity has been found on a lot of those studies. So, in particular, manic and mixed states have been characterized by higher striatal dopamine synthesis capacity, as shown on some of those PET studies. And particularly, we see this in the striatum.

In addition, we also know that muscarinic circuits, so cholinergic muscarinic circuits, are a part of the modulation of some of those dopaminergic circuits in the striatum. So muscarinic receptors, particularly M1 and M4, are actually located in these same striatal circuits and can decrease dopaminergic transmission by decreasing both presynaptic dopamine release as well as by opposing dopamine signaling in the postsynaptic neurons.

Xanomeline-trospium has been recently introduced as a first-in-class novel antipsychotic agent, and it is a selective agent that acts as

an M1/M4 agonist. So there's been two recent phase 3 trials, BALSAM-1 and BALSAM-2, that are currently under way, actually evaluating xanomeline-trospium for the treatment of acute mania or mania with mixed features in bipolar disorder.

Dr. Rubio:
So it'll be interesting to see what comes up in those studies, but certainly from the perspective of mechanisms, based on what we know about traditional antipsychotics, it seems that the M1/M4 agonism is a viable avenue to address manic symptoms, right? In the way that they share some commonalities with psychosis and their involvement of dopamine. So I think that that's very interesting.

Dr. Tang:
Yeah, that's right.

Well, actually, what we know about the currently available treatments for bipolar disorder, both with the antipsychotic treatments as well as the mood stabilizers, is that all of them actually target the dopaminergic system, either directly or indirectly, so it does make sense as a pharmacologic approach that if we're able to modulate those striatal dopaminergic circuits and signals with upstream M1/M4 agonism, that this would make sense as a pharmacologic approach to targeting bipolar disorder, and particularly manic episodes in bipolar disorder.

So this is exactly the kind of approach that's being tested in the BALSAM-1 and the BALSAM-2 studies right now, looking at bipolar disorder. So we'll see if this novel class of antipsychotics might be effective in bipolar disorder as well.

Dr. Rubio:
Very interesting scientific premise, and yeah, looking forward to learning about those results. Well, this has been a great micro discussion. Our time is up. Thanks a lot for listening.

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