Targeting dopamine in depression

By Tim Fulmer, Senior Writer

Canadian researchers have designed a peptide that blocks interactions between dopamine receptors and shows antidepressant effects in rodent models of depression.¹ The team is optimizing the peptide to increase its bioavailability and get it across the blood brain barrier.

The neurotransmitter most commonly associated with depression is serotonin, with at least one major class of marketed antidepressants—the selective serotonin reuptake inhibitors (SSRIs)—targeting levels of the neurotransmitter in the synapse. However, a large proportion of patients fail to respond or show only partial responses to such drugs, which has prompted a search for other causes of depression.

One candidate is dopamine, a neurotransmitter that plays key roles in brain regions associated with reward, motivation, pleasure and drive.

Because many depression symptoms involve loss of motivation and drive, a number of researchers have speculated that disruptions in dopamine pathways may play at least as large a role in the disorder as impaired serotonin signaling.²

To better understand dopamine's role, a team of Toronto researchers led by Fang Liu focused on dopamine receptors in the brain. Previous work by his lab and others had shown that the dopamine D1 receptor and dopamine D2 receptor can form dimeric complexes on the surface of neurons.^{3,4} It was unclear, however, whether those complexes played a role in depression.

Liu is senior scientist at the **Centre for Addiction and Mental Health** and associate professor of psychiatry at the **University of Toronto**.

To find a potential link between the dopamine D1 and D2 receptors and depression, Liu and colleagues studied postmortem brain tissue from depressed patients and nondepressed controls.

They found that the ratio of D1-D2 receptor dimers to D1 receptor monomers was significantly greater in depressed patients than in controls ($p < 0.05$). The researchers reasoned that aberrant upregulation of D1-D2 dimer formation could play a role in the disease and that blocking this process could have an antidepressant effect.

To test that hypothesis, the researchers designed a peptide that targeted the protein-protein interaction region of the D1 and D2 receptors. The peptide was also fused to the cell membrane transduction domain of the HIV tat protein to increase its cell permeability.

Next, the peptide was infused into the prefrontal cortex of rats undergoing the forced swim test, a standard rodent model of acute depression. The peptide significantly decreased anxiety-associated immobility compared with saline ($p < 0.05$).

In a rat model of chronic depression, animals had more D1-D2 dimers in the prefrontal cortex and striatum than nondepressed control rats ($p < 0.01$). Intracerebroventricular injection of the peptide into the prefrontal cortex of the rats significantly lowered depressive behavior compared with that in controls ($p < 0.01$).

The authors wrote that their study provides "...the first direct evidence implicating the D1R-D2R complex in the pathology of depression and also identifies an interfering peptide with antidepressant-like effects."

The findings were published in *Nature Medicine*.

Moving forward, the Toronto researchers will look at two potential ways of disrupting the D1-D2 receptor complex. One approach involves modifying and optimizing the peptide described in the paper. This includes improving its bioavailability and delivery into the brain, corresponding author Liu told SciBX.

"The second option we plan to explore should avoid the potential problems associated with delivering a peptide to the brain. We hope to

develop a small molecule that mimics the effects of the peptide by using the D1-D2 interaction site as the drug target," said Liu.

Liu declined to disclose details.

The paper's findings are covered by patent applications, and the IP is available for licensing through Toronto's **MaRS Innovation Centre**, according to Liu.

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COMPANIES AND INSTITUTIONS MENTIONED

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