The Potential Role of Dopamine D3 Receptors in Major Depressive Disorder

The Burden of Major Depressive Disorder

Major depressive disorder (MDD) is a complex mental disorder characterized by core symptoms of persistent low mood and a loss of interest or pleasure in activities previously enjoyed.[1] MDD can significantly diminish an individual's quality of life, often impacting various aspects of daily living, including social interactions and occupational activities. According to the World Health Organization, depression is projected to be the largest contributor to the global disease burden by 2030, affecting approximately 300 million people worldwide.[2]

While the recommended first-line treatment for patients with MDD is antidepressant therapy, some patients may not achieve remission with their initial treatment.[3] In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which examined the effectiveness of some switch or augmentation strategies used for patients with MDD whose symptoms were not sufficiently addressed with their initial antidepressant treatment, only about 50% achieved initial response, while only about 33% achieved remission.[4] Often, patients may experience residual symptoms, including anhedonia. In a separate analysis of the STAR*D data, over 90% of patients who had achieved remission reported still experiencing at least one residual symptom, including anhedonia.[5] The presence of residual symptoms has been shown to be associated with negative patient outcomes, including higher levels of disability, increased risk of relapse, and shorter time to relapse.[6-8]

Anhedonia: A Persistent and Disabling Symptom of Depression

Anhedonia, defined as a loss of interest in and/or the capacity to experience pleasure in previously enjoyed activities, is a core diagnostic criterion of MDD. It affects an estimated 70% of patients with MDD and may persist even after initial treatment with traditional antidepressants.[9]

Anhedonia can lead to greater levels of disability in patients with MDD and is often associated with greater impairment in executive functioning and increased risk for suicidal ideation.[9] Functional neuroimaging and pathophysiological studies have implicated dysfunction of the mesolimbic dopaminergic pathway **(Figure 1)**, particularly in regions associated with reward and motivation, with symptoms of anhedonia.[10,11]

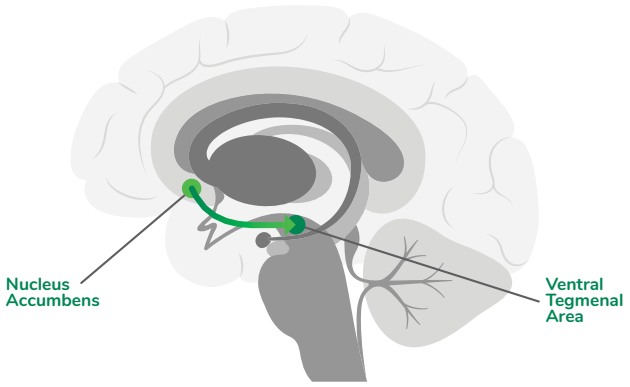

Figure 1. Mesolimbic dopamine pathway.

Role of Dopamine Signaling in MDD

Research on the pathophysiology of MDD has centered on the monoamine (MAO) hypothesis. The MAO hypothesis suggests that a dysregulation of key neurotransmitters, including serotonin, dopamine, and norepinephrine, within the synapse of neuronal cells may affect or underlie mood alterations observed in patients with MDD.[12] In fact, the hypothesis that dysregulation of serotonin plays a role in the etiology of depressive symptoms has helped inform the development of antidepressants that target the serotonergic pathways to help address symptoms of depression.[13] Dopamine, specifically, has been hypothesized to be dysregulated in the mesolimbic dopaminergic pathway, which is involved in reward processing among other functions. This dysregulation of the dopamine reward system may underlie the motivational deficits and anhedonia observed in depression.[11,14] Decreased extracellular dopamine has been proposed as a driver of depressive symptoms.[11]

The Dopamine D3 Receptor

Dopamine signaling in the brain is mediated by five dopamine receptors, grouped into the D1-like (D1, D5) and D2-like (D2, D3, D4) families **(Figure 2)**.[11,15] D3 receptors, a member of the D2-like dopamine receptor family, may play a key role in the regulation and manifestation of depressive symptoms in MDD.[11,16]

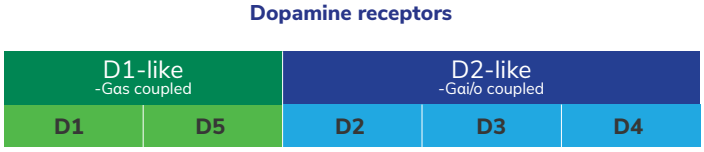

Figure 2. Dopamine receptor families.

D3 receptors are primarily located in limbic regions, including the nucleus accumbens and other components of the mesolimbic pathway, where they are thought to regulate motivation, reward processing, and cognitive functions **(Figure 3)**.[16] As described above, dysfunction of dopaminergic neurotransmission within the limbic system may contribute to anhedonia, loss of motivation, and psychomotor retardation, common key symptoms of MDD.[17] Additionally, D3 receptor modulation has been shown to hypothetically contribute to cognitive improvements, including attention, working memory, and executive function.[18]

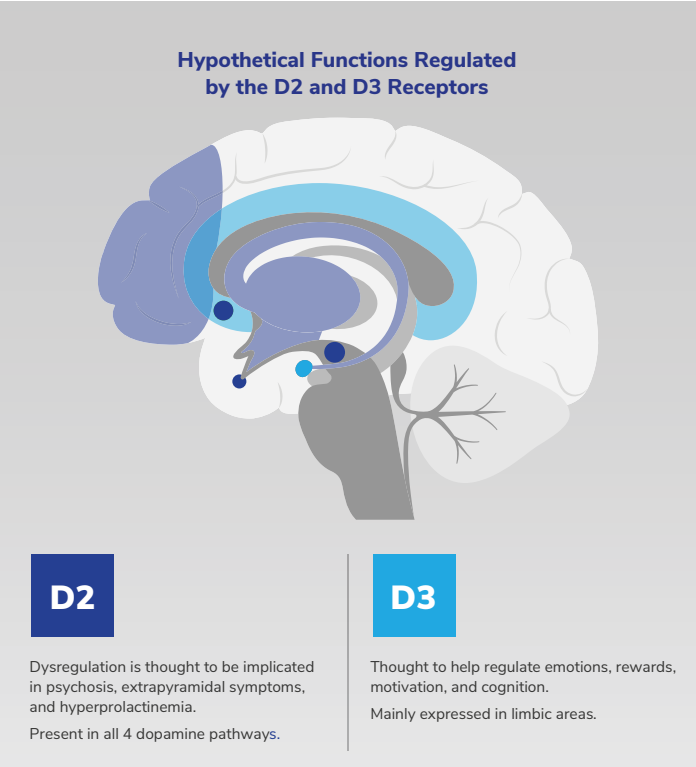

Figure 3. Location and hypothetical functions regulated by the D2 and D3 receptors.[16]

Even small alterations in D3 receptor function can potentially lead to physiological changes, highlighting their sensitivity and importance in neural regulation.[15] D3 receptors can be found in both the presynaptic and postsynaptic regions, modulating both dopamine synthesis and release.[11] Due to its high affinity for dopamine, D3 autoreceptors in the presynaptic neuron can be activated by low tonic dopamine levels. This is thought to create a negative feedback loop to inhibit further dopamine release, which may contribute to dopaminergic underactivity theoretically associated with MDD **(Figure 4A)**.[16]

Blocking D3 receptors through D3 receptor antagonism, particularly presynaptically, may lead to disinhibition of dopamine release in the limbic system **(Figure 4B)**, thus enhancing dopaminergic tone in reward-related brain regions. This may theoretically help reduce symptoms of anhedonia observed and help improve motivation and pleasure.[1]

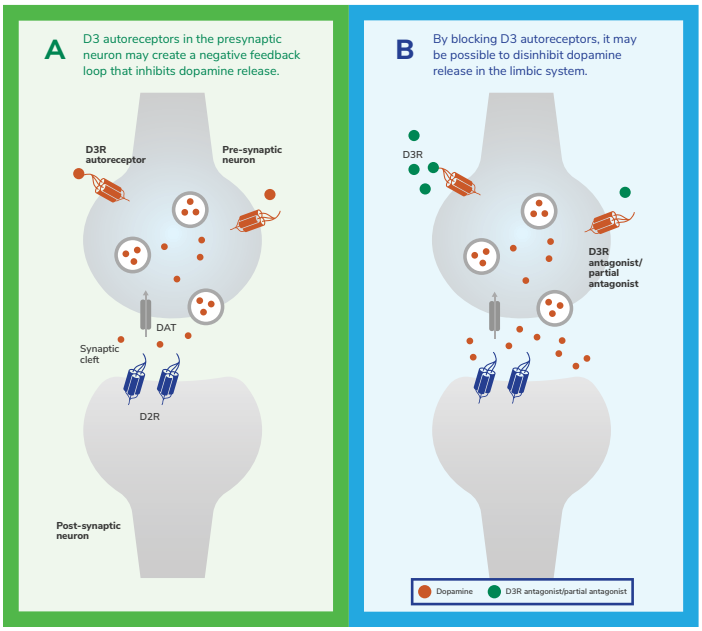

Figure 4. Proposed regulation of D3 receptors at synapses.[19] Adapted from Banks ML, et al. *Addict Biol.* 2024;29(2):e13369. D2R = dopamine 2 receptor, D3R = dopamine 3 receptor, DAT = dopamine transporter.

A better understanding of how dopamine receptors function and are regulated within the dopamine pathways thought to be involved in MDD can be beneficial in helping healthcare providers appropriately manage MDD.

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