Valbenazine MOA and TD MOD Video

FEMALE SPEAKER: Monoamines such as dopamine are essential for many brain functions, including mood, cognition, and motor control. Healthy dopaminergic neurotransmission involves a careful balance between adequate neurotransmitter release into the synaptic cleft and removal of neurotransmitters from the synapse. Several proteins, including vesicular monoamine transporters, or VMAT, reuptake transporters, and presynaptic autoreceptors are critical to this balance.

Dopamine is released from the presynaptic neuron and then binds to receptors located on the presynaptic and/or postsynaptic cell membrane. Dopamine may also be recycled, and along with newly synthesized dopamine, be packaged into synaptic vesicles by vesicular monoamine transporters. Packaged dopamine is then ready for subsequent release, thereby promoting synaptic neurotransmission.

There are two types of vesicular monoamine transporters. Only VMAT2 is found in the central nervous system. Throughout the following animation, we will focus specifically on VMAT2 and its relationship to the movement disorder tardive dyskinesia.

Within the nigrostriatal pathway, synaptic neurotransmission involving the monoamine dopamine is critical for sustaining normal motor control. When dopamine release, reuptake, metabolism, and vesicular packaging are balanced, movement is smooth and controlled. However, if the delicate balance of dopaminergic neurotransmission in nigrostriatal areas is disrupted, movement disorders such as tardive dyskinesia may result.

Symptoms of tardive dyskinesia include involuntary movements of the face, trunk, and extremities. One way in which dopaminergic neurotransmission may become aberrant in the nigrostriatal region is through prolonged exposure to antipsychotics and other antidopaminergic treatments such as metoclopramide. Antipsychotics aimed to reestablish a balance in dopaminergic neurotransmission via antagonism of postsynaptic dopamine D2 receptors in mesolimbic areas.

By blocking these mesolimbic dopamine D2 receptors, antipsychotics are often quite effective for ameliorating symptoms of psychosis. However, antipsychotic actions are not confined solely to the mesolimbic area. Chronic antipsychotic-induced lowering of dopaminergic neurotransmission outside of the mesolimbic pathway, and particularly in the nigrostriatal area, may cause an upregulation or a hypersensitivity of dopamine D2 receptors.

This dopamine D2 receptor hypersensitivity is hypothesized to underlie the pathophysiology of tardive dyskinesia. One possible approach to addressing dopamine hypersensitivity is the inhibition of VMAT2. Blocking VMAT2 transporters decreases the packaging of dopamine into synaptic vesicles, leading to less dopamine being released from the presynaptic neuron into the synaptic cleft.

With less dopamine release from the presynaptic cell, there is less dopamine available in the nigrostriatal area to interact with hypersensitive dopamine D2 receptors. In this way, dopaminergic neurotransmission is normalized, despite the antipsychotic-induced hypersensitization of dopamine D2 receptors. This mechanism of VMAT2 inhibition is hypothesized to reduce tardive dyskinesia.

Valbenazine capsules is a unique vesicular monoamine transporter 2 or VMAT2 specific inhibitor indicated for the treatment of adults with tardive dyskinesia. Valbenazine is metabolized into two major metabolites, including (+) alpha-dihydortetrabenazine. In vitro data indicate that valbenazine and its metabolite (+) alpha-dihydortetrabenazine inhibit VMAT2 selectively and specifically without affecting

other components of monoaminergic neurotransmission such as postsynaptic dopamine or serotonin receptors.

Although the mechanism of action of valbenazine in the treatment of TD is unknown, by inhibiting the VMAT2, valbenazine is thought to decrease dopamine release into the synapse. Decreased stimulation of hypersensitive D2 receptors in the motor striatum may reduce tardive dyskinesia.