Monoamines, Nigrostriatal Pathway, and Antipsychotics

FEMALE SPEAKER: The monoamines, including dopamine, serotonin, and norepinephrine, are essential for many brain functions, including, mood, cognition, and motor control. Healthy monoaminergic 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, reuptake transporters, and presynaptic autoreceptors-- are critical to this balance.

A monoamine is released from the presynaptic neuron and then binds to receptors located on the presynaptic and/or postsynaptic cell membrane. Using a negative feedback mechanism, binding of monoamine to presynaptic auto receptors slows down further release of monoamines from the presynaptic neuron.

Additionally, reuptake transporters regulate monoaminergic neurotransmission by removing excess monoamines from the synaptic cleft and back into the presynaptic cell. Once inside the presynaptic neuron, monoamines may be broken down by the enzyme monoamine oxidase. The synthesis of monoamines is mediated, in part, by various hydroxylase enzymes.

Monoamines may also be recycled, and along with newly synthesized monoamines, be packaged into synaptic vesicles by vesicular monoamine transporters. Packaged monoamines are then ready for subsequent release, thereby promoting synaptic neurotransmission.

There are two types of vesicular monoamine transporters. Both VMAT1 and VMAT2 are located in the periphery. Whereas, VMAT2 is the only VMAT 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.

One way in which dopaminergic neurotransmission may become apparent in the nigrostriatal region is through prolonged exposure to antipsychotics. Antipsychotics aim 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 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 some, but not all 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 hyper sensitization of dopamine D2 receptors. This mechanism of VMAT2 inhibition is hypothesized to reduce tardive dyskinesia.