VESICULAR MONOAMINE TRANSPORTERS

Most of us learn that monoamines are packaged in the axonal terminal/ending in storage vesicles. Depending upon the neuron, when an action potential causes the influx calcium at that ending, one or another monoamine is released into the synaptic cleft. In dopamine producing cells storage vesicles of dopamine fuse with the cell membrane and release dopamine. The same is true of the other monoamines, i.e. serotonin, norepinephrine, epinephrine, and histamine.

The question many of us failed to ask is, 'Well, how does the dopamine, etc, get into these storage vesicles?" The answer is interesting. For some time, if I thought about it at all, I assumed that the monoamines were synthesized right there in the axonal terminal, but that was both wrong and lazy. Monoamines are synthesized in the cytoplasm in the cell body as are other neurotransmitters of psychiatric interest such as acetylcholine, GABA, glycine, and glutamate.

The monoamine neurotransmitters are dependent on a transporter-track to transport them through to the axon ending/terminal. These mechanisms are referred to as vesicular monoamine transporters. As noted, some non-monoamines require transport from the cytoplasm before their eventual exocytosis, however, focusing on the monoamines, we find that a specific single protein, identified as vesicular monoamine transporter 2 (VMAT2), mediates their transport. *[VMAT1 works primarily in the periphery].* So a molecule, like serotonin, is synthesized in the cytoplasm of the cell body, but must be moved by this transport system in order to be funneled to the vesicle.

Knowledge of this has sparked interest in studying these vesicular transporters and by extension, has led to speculations about how the manipulation of these systems might be found clinically useful. Clinicians and researchers from specialties such as drug addiction, neurology, cardiology, and psychiatry, have pondered how this transport-system knowledge might yield clinical benefits for patients. For at least 30 years, pharmacologic researchers have known that reserpine inhibits this system thus accounting for the drop in blood pressure it was known to cause. This VMAT2 inhibition also accounts for depression as a side effect. Amphetamine, on the other hand, acts on this system to release more monoamines leading to

stimulation. A relatively new drug (available May of 2017) that has caught my attention is valbenazine (Ingressa) which is the latest pharmacologic effort to treat, modify, ameliorate iatrogenic tardive dyskinesia (TD). Valbenazine is a drug that is synthesized from tetrabenazine, the first drug to effectively treat TD (Meyer, 2017). Valbenazine and its metabolites only have affinity for VMAT2 thus do not have the tolerability issues of tetrabenazine nor the more complicated dosing schedule. By inhibiting VMAT2, valbenazine reduces the 'flow' of dopamine to storage vesicles, which reduces exocytotic release of dopamine, which reduces the symptoms of TD.

So, one more thing to contemplate when administering or prescribing certain psychotropic drugs. As I note once before in this column, my pharmacologic education has been two steps forward and one step backwards as I am constantly reminded of how much I do not know. But if you are reading this, you are probably a bit younger than I am, and can look forward to many "aha" moments ahead. It will be interesting where the understanding of VMAT2 inhibition will take us.

Meyer, J. M. (2017) Valbenazine for tardive dyskinesia. Current Psychiatry, 16(5): 40-45.