The Vesicular Monoamine Transporter

April 15, 2008 | Bipolar Disorder [1], Schizophrenia [2], Geriatric Psychiatry [3], Alcohol Abuse [4]

The vesicular monoamine transporter (VMAT) is a membrane-embedded protein that transports monoamine neurotransmitter molecules into intraneuronal storage vesicles to allow subsequent release into the synapse. By accumulating both newly synthesized neurotransmitter molecules and freshly returned neurotransmitter molecules from the synapse, VMAT function plays a critical role in the signaling process between monoamine neurons. The VMAT exists in 2 distinct forms: VMAT1 and VMAT2.

VMAT1, previously known as the chromaffin granule amine transporter, is found in extraneural tissues including the chromaffin cells of the adrenal medulla and endocrine and paracrine cells of the GI tract. VMAT2, previously known as the synaptic vesicular monoamine transporter, is primarily located in neuronal cells of the central, peripheral, and enteric nervous system. Although VMAT2 is also present in the chromaffin cells of the adrenal medulla, it is the VMAT form of primary psychiatric interest. However, interesting recent evidence suggests that VMAT1 may also be present in the human brain, perhaps concentrated in the substantia nigra.

Mechanisms of VMAT2
VMAT2 is the only molecule able to selectively recognize and transport all of the biogenic amine neurotransmitters across biomembranes. In this way, the VMAT2 is distinct from the plasma membrane neurotransmitter transporters (dopamine [DAT], serotonin [SERT], and norepinephrine [NET]), which selectively move only 1 of the neurotransmitters from the synapse into the cell. It is also distinct from the many monoamine receptors that respond selectively to individual neurotransmitters based on the receptor type's cellular location and the signaling proteins with which it couples. Thus, VMAT2 is not selective; the DAT, SERT, and NET are selective for each neurotransmitter, while numerous receptor subtypes respond to the individual monoamines in highly individualized ways. One would predict the most narrow and specialized effects to occur through receptor activation, and the most widespread effects through VMAT2 function.

Even though monoamine neurons represent a relatively small proportion of neurons in the brain, they are of great psychiatric and neurological significance. Unfortunately, at this time, the interpretation of VMAT2 function remains complex, and a considerable amount of the available experimental data predate VMAT2 cloning and are based on whole brain experiments rather than simpler systems using complementary DNA expressed in nonneuronal cells or dissected neurons. Thus, many aspects of the VMAT2 function and pharmacology have not been fully determined.

VMAT physiology
Like plasma membrane transporters, such as DAT, SERT, and NET, VMAT2 displays a similar size and molecular topography with 12 transmembrane domains and both tails located in the interior. Surprisingly, however, there is limited amino acid homology and the VMAT is more closely related to other transporter families, such as the multi-drugresistant transporter family. VMAT physiology is distinct from plasma membrane transporters in several important ways:

- It uses an $\text{H}^+$ ion (proton) gradient energetically to transport substrates rather than the $\text{Na}^{++}\text{K}^+$ gradient used by DAT, SERT, and NET.
- The extracellular environment for VMAT is actually cytoplasmic, and the cytoplasmic face is
The Vesicular Monoamine Transporter
Published on Psychiatric Times
(http://www.psychiatrictimes.com)

The Vesicular Monoamine Transporter
Published on Psychiatric Times
(http://www.psychiatrictimes.com)

actually intravesicular.13

• The access of substrates and drugs to the VMAT is more complicated, because it requires transport of the substrate or drug molecule across the plasma membrane into the cell as a first step, either via diffusion or coupled to a plasma membrane transporter.

Thus, access of VMAT drugs or substrate sequestration into the intracellular vesicle involves a kinetic interaction between the plasma membrane transporter and VMAT, with complex ramifications that remain to be delineated.

Currently all drugs known to bind to the VMAT inhibit its function, similar to the manner in which antidepressants and stimulants affect SERT, NET, or DAT. Thus, VMAT ligands are best referred to as inhibitors, rather than antagonists, since the existence of direct agonist drugs, which bind to and increase VMAT activity, is not proved. However, indirect agonists, which affect the trafficking of the VMAT into and out of functional position, are likely to be discovered, as has been the case with plasma membrane transporters.14-18 Although VMAT agonists, direct or indirect, have not been identified, theoretically, this class of drugs has applications as neuroprotective agents, particularly in a dopaminergic condition such as Parkinson disease in which loose dopamine may be neurotoxic, and for substance abuse treatment by modulating dopamine-related reward.19,20 A recent preliminary experiment has claimed that bupropion may have a VMAT2 stimulatory effect, but confirmation that the apparent effect is mediated solely through a VMAT2 interaction that could be accomplished in intact human participants remains a considerable project.21

Recent genetic studies suggest that some regions of the VMAT2 gene might vary in a way that could serve as a genetic substrate for susceptibility to schizophrenia, bipolar disorder, or alcoholism.6,22-26 Such observations could become of great significance, but remain inconclusive until larger population-based studies support and further illuminate the results.

Therapeutics
Currently, 2 VMAT inhibitors are available in the United States for clinical use: reserpine (Figure), available since 1957, and tetrabenazine, available as an orphan drug and recently recommended for approval by the FDA. Reserpine, the best-known VMAT ligand, has been used in traditional medicine in India for centuries. Reserpine is derived from the Rauwolfia plant species and has one of the most complex structures of all known natural alkaloids.27 It binds to the amine substrate site of the VMAT with high affinity and irreversibly blocks the uptake of monoamines into secretory vesicles.28 Its use in modern Western medicine began in the 1950s as an antihypertensive and an antipsychotic agent. Subsequently, a syndrome of depression and lethargy induced by reserpine, and the nearly simultaneous discovery of the therapeutic efficacy of tricyclic antidepressants, led to the formulation of the biogenic amine hypothesis of depression.8

Reserpine is currently used as a second-line antihypertensive agent and is also approved for use in psychotic disorders. Reserpine is rarely used in the United States for hypertension because of its adverse effects and the many alternative therapies. However, it remains common abroad because it is economical. At present, the most likely clinical scenario to be encountered by the North American psychiatrist involving VMAT is an international visitor taking reserpine for hypertension.

Reserpine is still used for the treatment of psychosis in patients with troublesome extrapyramidal effects from dopamine receptor antagonists. In rare instances, a trial of reserpine might be warranted in a younger patient who has psychotic episodes and has serious choreiform or athetotic movements associated with profound tardive dyskinesia. It is more usual to treat elderly patients who have advanced tardive dyskinesia with large doses of antipsychotics, which suppress the abnormal movements, although worsening the underlying pathophysiology (Table 1).

Tetrabenazine has recently been approved in the United States for the treatment of choreiform movements in Huntington disease. Tetrabenazine is also available internationally for the management of other hyperkinetic disorders. It is not clear why tetrabenazine is more effective than reserpine in chorea, but the effect may be related to its greater activity in dopaminergic neurons, which might involve antagonistic activity on dopamine receptors beyond VMAT2 effects (Table 2).29

Cautions
The therapeutic use of these drugs in hypertension, psychosis, and chorea needs to be very carefully monitored for psychiatric complications. Although occasionally useful for these indications, VMAT2 inhibitors are accompanied by adverse effects that might precipitate psychiatric evaluations, particularly depressed mood, suicidal thoughts, and suicidal behaviors. In one case series, 18% of the patients treated with reserpine for hypertension were found to have depressive symptoms after an average exposure of 4.5 months. Unfortunately, in the largest clinical trial of tetrabenazine in patients with Huntington disease, 1 of the 22 study participants committed suicide. An interesting and unanswered question is how so many participants actually avoid depressive symptoms.

VMAT2 inhibitors have been used clinically as diagnostic tools. Several ligands appear useful as positron emission tomography agents in clinical medicine. Neuronal loss has been documented in Parkinson disease and after methamphetamine abuse, and increased monoaminergic innervation has been detected in Tourette syndrome using the radioligand dihydrotetrabenazine (DTBZ), a related metabolite of tetrabenazine. Bohnen and colleagues found a 0.5% age-related decline in striatal DTBZ binding in normal participants and significant correlation between DTBZ-binding asymmetry and clinical asymmetry in patients in the early stages of Parkinson disease. Caution is necessary, however, because interpretation of alterations in VMAT2 binding can be problematic, since total VMAT2 binding could reflect either the total number of neurons or the number of VMAT molecules per neuron. The regulation of total vesicle number and VMAT2 expression per vesicle remain unresolved and controversial topics.

DTBZ binding and VMAT2 immunoreactivity were found to be decreased in postmortem brain tissue from a large series of cocaine users compared with matched nonusers. Follow-up studies based on dopaminergic cell counting indicate that the decrease was caused by neuronal loss rather than a decrease in the VMAT content of individual neurons, which was not altered in in situ hybridization experiments. VMAT2 diminution was related to increased signs of depressive disorders, a complication of long-term cocaine use. In addition to decreased VMAT2 measures and cell loss, the same cocaine users displayed increased binding to the DAT, most likely related to an increase of DAT on the neuronal surface. Such a simultaneous up-regulation is postulated to decrease transsynaptic signaling and mitigate the effects of excessive synaptic dopamine (Table 3).

These dopaminergic adaptations may contribute to depression and withdrawal symptoms after cessation of cocaine use, perhaps more than to long-term craving. Withdrawal and sustained depression versus long-term craving, although related, may best be thought of as distinct aspects of cocaine dependence that may require unique therapies.

**Experimental therapies**

Both reserpine and tetrabenazine have been researched as treatments for cocaine and methamphetamine dependence, because each drug should theoretically diminish dopamine-based signaling and its role in eventual reward. Such an effect appears to parallel recent findings that disulfiram, a dopamine synthesis inhibitor, is helpful for cocaine dependence. Thus, antidopaminergic approaches might be tailored for those patients who are particularly troubled by the intensity of an acute cocaine "rush." Unfortunately, these treatments might also increase the risk of withdrawal symptoms and depression. Interestingly, alterations in VMAT2 function have been found to affect ethanol intake in animals.

Recently, Riddle and colleagues have demonstrated that methamphetamine and cocaine can alter VMAT2 trafficking and function through mechanisms that might contribute to symptoms and potentially could be reversed for therapeutic effect. In addition, animal studies with a newly designed VMAT2 inhibitor, lobeline and related analogs, which may have additional effects other than VMAT2 inhibition, suggest that this group of drugs decreases behavioral response to methamphetamine, while also decreasing self-administration. Furthermore, a new class of ligands for the VMAT2, structurally unique 3-amino-2-phenylpropene derivatives, is being developed with potential effects that have yet to be explored.

Drugs that could enhance VMAT2 function might be neuroprotective. Heterozygous knockout mice show hypersensitivity to the neurotoxic effects of VMAT2 substrates, such as MPP⁺, and they display more than double the dopamine cell loss compared with their wild-type littermates. Other studies indicate that blockage or loss of VMAT2 function may contribute to accelerated neuronal loss.
However, drug therapies that target VMAT2 function must alter the function of an intracellular target, which is perhaps more elusive and difficult to uniquely manipulate than a target molecule that protrudes through the cell wall. Although complex, the therapeutic possibilities are exciting.

Biographical vignette

The Nobel laureate Ernest Hemingway, whose writings widely influenced 20th century ideas about adventure and heroism, received reserpine treatment for several years in the late 1950s. During this time, he was frequently discouraged and slowly lost weight and physical strength. He found it difficult to concentrate on his writing or achieve an acceptable artistry.

Hemingway was often irritable and bickered frequently with his wife. He was disheartened by his inability to resolve pressing financial obligations and a legal dispute with the IRS.

Hemingway was obsessed with suicide, and clearly envisioned it as the ultimate act of self-control. When Ernest was 29, his father Clarence--a physician--committed suicide using his own Civil War revolver.

On November 30, 1959, Hemingway was admitted for psychiatric care. By this time, the deleterious effects of reserpine had been recognized, and the drug was discontinued. A course of electroconvulsive therapy (ECT) was begun that lasted through January 1960. Hemingway improved and returned home to Ketchum, Idaho. He immediately immersed himself in several difficult writing projects, including finishing the novel, The Garden of Eden, for which he had amassed over 2000 manuscript pages. This novel was a project the 61-year-old Hemingway, recovering from ECT and years of heavy drinking and severe depression, was unable to adequately complete.

During this period, he provided advice to Fidel Castro about managing the US media, but Hemingway was discouraged when Castro evoked Hemingway's name as supporting executions he ordered. In addition, it became clear that Hemingway would not be able to return to his beloved home in Cuba nor was he able to make progress with his financial problems or IRS dispute. He was rehospitalized in April and received further ECT sessions. He appeared suddenly brighter in June and was discharged home. After an apparently happy homecoming, he shot himself the next morning.52

Clearly, a number of biological, psychological, and situational factors contributed to Hemingway's depression and suicide. His relapse and ultimate suicide occurred many months after the physiological effects of reserpine had abated. However, the protracted course of his depression and its damaging effects on his marriage, financial situation, and confidence in his ability to work might have been repairable at an earlier stage if reserpine had been discontinued sooner.

References: References

40. Little KY, Sharda AV, Stowers PN, Cassin BJ. VMAT2 mRNA levels in human cocaine users. In press.

Source URL: [http://www.psychiatrictimes.com/articles/vesicular-monoamine-transporter](http://www.psychiatrictimes.com/articles/vesicular-monoamine-transporter)

Links:
[2] [http://www.psychiatrictimes.com/schizophrenia](http://www.psychiatrictimes.com/schizophrenia)
[5] [http://www.psychiatrictimes.com/authors/karley-y-little-md](http://www.psychiatrictimes.com/authors/karley-y-little-md)
[6] [http://www.psychiatrictimes.com/authors/anish-v-sharda-md-mph](http://www.psychiatrictimes.com/authors/anish-v-sharda-md-mph)