VMAT2 and Parkinson’s disease: harnessing the dopamine vesicle

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Abstract

Despite a movement away from dopamine-focused Parkinson’s disease (PD) research, a recent surge of evidence now suggests that altered vesicular storage of dopamine may contribute to the demise of the nigral neurons in this disease. Human studies demonstrate that the vesicular monoamine transporter 2 (VMAT2; SLC18A2) is dysfunctional in PD brain. Moreover, studies with transgenic mice suggest that there is an untapped reserve capacity of the dopamine vesicle that could be unbridled by increasing VMAT2 function. Therapeutic manipulation of VMAT2 level or function has the potential to improve efficacy of dopamine derived from administered levodopa, increase dopamine neurotransmission from remaining midbrain dopamine neurons and protect against neurotoxic insults. Thus, the development of drugs to enhance the storage of release of dopamine may be a fruitful avenue of research for PD.

Keywords
dopamine; L-DOPA; Parkinson’s disease; vesicle; VMAT2

Parkinson’s disease (PD) is a dramatic and progressive movement disorder where quick fluid motions are replaced by slowness and leaden rigidity. Nearly 60 years ago, Ehringer and Hornykievicz identified the depletion of dopamine as a central hallmark to the disease [1]. In the following decades, a great deal of effort has been exerted to restore dopamine function in PD. More recently, some have suggested that the study of dopamine-mediated

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Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.
No writing assistance was utilized in the production of this manuscript.
dysfunction in PD is an elusive and unrewarding pursuit, likening these dopamine-centric research strategies to beating a dead horse [2]. We agree that PD is much more than just a dopaminergic disorder; however, it is impossible to dismiss the selective degeneration of nigral dopamine neurons and the efficacy of levodopa (L-DOPA) therapies in PD. After all, L-DOPA remains the primary treatment for millions of PD patients and continues to provide awakenings in disease sufferers. In light of recent evidence from both animal and clinical studies, we argue that this proverbial horse that is synaptic dopamine handling in the pathogenesis of PD is not dead, nor is it ready to be put out to pasture.

Dopamine handling & PD

L-DOPA restores the underlying dopamine deficit in the PD brain, addressing the primary motor symptoms of the disease with striking effectiveness in most patients. L-DOPA is converted to dopamine by dopa decarboxylase in the neuronal cytosol; this new dopamine is then packaged into synaptic vesicles, tiny storage compartments for neurotransmitter, so that the dopamine can be released into the synapse for neurotransmission. However, the treatment window of L-DOPA is often limited due to the eventual onset of side effects, such as dyskinesias. As it stands today, the research community is at a loss as to why L-DOPA-induced dyskinesias appear throughout the course of treatment, and clinicians often delay escalation of L-DOPA doses to widen this treatment window. We pose the question now: what if dopamine neurons could more efficiently package, store and release this newly made dopamine? Since most of the brain’s dopamine is stored in synaptic vesicles, improvements to dopamine packaging into the vesicle could more efficiently use L-DOPA and extend the treatment window. A few key players in the neuron terminal mediate these dopamine dynamics, perhaps the most important of which is the focus of this piece: the vesicular monoamine transporter 2 (VMAT2; SLC18A2).

VMAT2 as a wrangler of synaptic dopamine

VMAT2 is an H\(^+\)-ATPase antiporter that packages monoamines (dopamine, norepinephrine, serotonin, epinephrine and histamine) into small synaptic and dense core vesicles for their subsequent release from the neuron [3]. Through this transmitter storage, VMAT2 also acts to sequester potentially harmful cytosolic dopamine. Dopamine molecules left unpackaged are vulnerable to the creation of reactive oxygen species including hydroxyl radicals, superoxide, hydrogen peroxide and also dopamine-quinones that can result in function-altering cysteiny1 adducts on cellular proteins [4]. Interestingly, VMAT2 is evolutionarily related to a family of toxin-extruding antiporters found in bacteria [5], so it is no surprise that VMAT2 levels have been shown to modify dopamine neuron vulnerability to additional toxic insults, including those by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin (MPTP) and methamphetamine [6]. Indeed, VMAT was originally identified by its ability to protect cells from the toxicity of MPP\(_+\), the metabolite of the dopaminergic toxicant and PD model, MPTP [7].

Mouse models of altered VMAT2 function

The modulation of synaptic vesicle filling and function is perhaps best represented in mouse models of varying VMAT2 levels. Although a complete loss of VMAT2 is lethal [8–10],

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*Expert Rev Neurother.* Author manuscript; available in PMC 2015 June 24.
mice with a 95% reduction in VMAT2 (VMAT2-deficient mice) survive into adulthood. However, these VMAT2-deficient animals experience dramatic dopamine depletion, progressive loss of dopamine neurons and α-synuclein accumulation [11]. Thus, reductions in vesicular storage are detrimental to the dopamine system. Luckily, the converse is also true: increased vesicular function is beneficial to the dopamine system. Mice with elevated VMAT2 levels (VMAT2-HI) have an increased capacity for the storage of dopamine in their neurons, which results in increased total dopamine levels, increased dopamine release and protection from neurotoxic insult by MPTP [12]. This means that a small molecule capable of enhancing VMAT2 function may increase neuronal dopamine output, while also protecting those cells from intracellular stressors. These findings from the VMAT2-HI mice provide a crucial stepping stone to understanding the uppermost limits of the dopamine vesicle, suggesting that VMAT2 modulation may be a viable therapeutic approach to address deficits in neurotransmitters like dopamine.

**VMAT2 function in human disease**

Multiple groups have reported the importance of vesicular function in human parkinsonism. Over 50 years after the key finding from the Ehringer and Hornykievicz [1], Piffl *et al.* reported that post-mortem PD brains show dramatically reduced VMAT2-mediated vesicular filling, greater than what could be explained by terminal loss alone [13]. This demonstrates that impaired packaging of dopamine into vesicles may be a key player in the disease process. These results also complement recent findings, including higher cytosolic dopamine turnover in PD patients [14] and a familial VMAT2 mutation that dramatically reduces vesicular filling and causes an infantile parkinsonian condition with profound motor and cognitive impairments [15]. Additionally, there is mounting evidence that increased VMAT2 level or function protects against PD. Glatt *et al.* demonstrated that a gain in VMAT2 function protects against the development of PD [16]. Brighina *et al.* associated two SNPs in the promoter region of the VMAT2 gene with a reduced PD risk, suggesting that increases to VMAT2 level confer protection to the disease [17]. Thus, vesicular function may oppose the vulnerability of midbrain dopamine neurons to other factors that influence PD outcome, whether genetic (PD-associated mutations) or environmental (toxic insult).

**Therapeutic potential of vesicular modulation**

It is time to revisit the idea of optimizing the function of existing dopamine neurons in the PD brain [18]. By manipulating vesicular filling through increased VMAT2 level or function, the benefits in a PD patient would be threefold: improved efficacy of newly synthesized dopamine via L-DOPA treatment, increased dopamine neurotransmission from remaining dopamine neurons and protection from either exogenous or endogenous neurotoxic insults. With the latest work from our lab and others, it appears to be more plausible than ever before to take advantage of the malleable nature of the synaptic dopamine vesicle.

Interestingly, the VMAT2-HI mice mentioned above also show improved outcomes on measures of depressive and anxiety-like behaviors, both of which are likely mediated by monoamines beyond just dopamine [12]. Thus, it is possible that a VMAT2-targeted
therapeutic strategy may have beneficial effects in other monoamine-deficient diseases like depression, for example. Alternatively, ligands that are also selective for plasma membrane transporters (DAT on dopamine neurons, SERT on serotonin neurons or NET on norepinephrine neurons) would allow for more transmitter system-specific VMAT2 modulation. Finally, one must not forget that other mediators of vesicular dopamine storage may provide alternate targets for the development of therapeutics. In this way, our understanding of the benefits of increased VMAT2 function could serve as a proxy for another vesicular protein target.

**VMAT2 in the winner’s circle**

In conclusion, the delicate balance of dopamine in the neuronal terminal is a complicated game of keeping the neurotransmitter in the right place at the right time. Too much dopamine left unpackaged, and the cytosolic environment becomes precarious. With too little dopamine in the system, the neurons lose signaling efficacy, which manifests itself as a parkinsonism-like behavior. Luckily, there appears to be a ‘dopamine sweet spot’ where one can take advantage of an additional vesicular capacity, thereby improving L-DOPA efficacy, increasing transmitter output and protecting cells from toxic insult. Based on the latest clinical findings on vesicular storage and PD risk, mouse models of varying VMAT2 levels may better reflect the human spectrum of vesicular filling and dopamine homeostasis than we previously realized. With the recent focus on newly uncovered genetic associations with PD, there has been movement away from dopamine, a.k.a., the dead horse. However, the recent findings discussed here would suggest that the horse isn’t anywhere near being dead. In fact, it is moving into the gates, ready for the next race.

**Biographies**

Kelly M Lohr

![Kelly M Lohr](image)

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References


