10-1-2017

Extending the Family: Roles for Uptake$_2$ Transporters in Regulation of Monoaminergic Signaling

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Accepted version. *Journal of Chemical Neuroanatomy*, Vol. 83-84 (October 2017): 107-108. DOI.

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Extending the family: Roles for uptake$_2$ transporters in regulation of monoaminergic signaling

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Monoamine transporters determine not only the amplitude, duration, and physical spread of released monoamines, but also the intracellular distributionand metabolic fates of their substrates. While most studies of monoamine transport have focused on the high-affinity, sodium-dependent transporters and, to a lesser degree, on the vesicular monoamine transporters, it has long been recognized that another, kinetically and pharmacologically distinct, group of transporters plays a role in monoamine clearance. Early studies of catecholamine uptake in cardiovascular tissue described, in addition to the high-affinity, cocaine-sensitive, "Uptake$_1$" process (since attributed to the norepinephrine transporter(NET)), a lower-affinity, cocaine-insensitive, corticosterone-sensitive clearance mechanism, termed "Uptake$_2$". Since those days, a large body of research has examined the role of the Uptake$_1$ family of transporters (also including serotoninand dopamine transporters, SERT

and DAT, respectively) in brain, but relatively little is known about the roles of the Uptake$_2$ transporters in brain. Key findings, however, indicate that the view of monoamine clearance in the brain, mediated exclusively by the high-affinity Uptake$_1$ transporters, is incomplete, and that a better understanding of Uptake$_2$ transporters and their contributions to the disposition of monoamines is necessary. These findings included:

a)Identification of a group of transporters, the organic cation transporters (OCT1-3) (Koepsell et al., 2007, Grundemann et al., 1998) and the plasma membrane monoamine transporter (PMAT) (Engel et al., 2004) as Uptake$_2$ mechanisms;

b)Demonstration of Uptake$_2$-like, corticosterone-sensitive, transport of serotonin (Baganz et al., 2008), histamine (Gasser et al., 2006) and dopamine (Graf et al., 2013) in brain;

c)Brain expression of OCTs and PMAT. This is particularly interesting given that Uptake$_2$ transporters, to a greater extent than their Uptake$_1$ counterparts, are multi-specific – capable of transporting serotonin, norepinephrine, epinephrine, dopamine, and, unlike any other monoamine transporter, histamine and the trace amines (Duan and Wang, 2010, Grundemann et al., 2003).

Despite these advances, fundamental questions remain, questions which are still being answered for the uptake1 transporters, and are only beginning to be addressed for Uptake$_2$. For example:

•1. What is the specific role of each Uptake$_2$ transporter in regulating both the extracellular concentrations and the intracellular disposition of monoamines? *Ex vivo* studies have demonstrated the substrate specificity of these transporters, but *in vivo* experiments examining the relative contributions of Uptake$_1$ and Uptake$_2$ transporters to monoamine releaseand clearance are in their infancy. Substrate specificity and transport efficiency varies among the Uptake$_2$ transporters, indicating that each of these transporters may play distinct roles in regulating signaling by any particular monoamine.

2. How are the expression, subcellular localization, and activity of the Uptake$_2$transporters regulated? This includes examination of potential effects of development, life experience, disease processes, and drug exposure on transporter expression and distribution.

3. What are the cellular (cell type) and subcellular distributions of each Uptake$_2$ transporter, including their spatial relationships to monoamine receptors and the enzymes of monoamine metabolism. This information is critical for the development of models describing the contribution of these transporters to monoamine signaling. A recent study using immuno-electron microscopy to examine the subcellular distribution of OCT3 revealed, in addition to the expected plasma membrane localization in astrocytes, neurons and endothelial cells, unexpected localization of the transporter to mitochondrial and nuclear membranes, suggesting novel signaling mechanisms or roles in regulation of metabolism (Gasser et al., 2017). Along these lines, very recently a role for OCT3 in the transport of epinephrine into the Golgi apparatus was shown to be important for activation of Golgi pools of β1-adrenergic receptors, and subsequent activation of G_s-cAMP signaling from the Golgi apparatus (Irannejad et al., 2017).

4. How do the Uptake$_2$ transporters contribute to disease processes, and how might they be targeted for therapeutic strategies? A small number of studies have indicated roles for OCT3 in treatment-resistant depression (Horton et al., 2013), neurodegenerative disease (Cui et al., 2009), and in the ability of stress and corticosterone to increase relapse vulnerability in cocaine addicts (Graf et al., 2013, McReynolds et al., 2017).

The answers to these and other questions will allow the integration of Uptake$_2$transporters into current models of monoamine clearance, resulting in a more complete understanding of monoamine signaling, and may lead to the development of novel therapeutic strategies.

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