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Extending the family: Roles for uptake₂ 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 distribution](#) and 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, "Uptake₁" process (since attributed to the [norepinephrine transporter](#) (NET)), a lower-affinity, cocaine-insensitive, corticosterone-sensitive clearance mechanism, termed "Uptake₂". Since those days, a large body of research has examined the role of the Uptake₁ family of transporters (also including [serotonin](#) and [dopamine transporters](#), SERT

and DAT, respectively) in brain, but relatively little is known about the roles of the Uptake₂ transporters in brain. Key findings, however, indicate that the view of monoamine clearance in the brain, mediated exclusively by the high-affinity Uptake₁ transporters, is incomplete, and that a better understanding of Uptake₂ 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 Uptake₂ mechanisms;
- b) Demonstration of Uptake₂-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 Uptake₂ transporters, to a greater extent than their Uptake₁ 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 Uptake₂. For example:

- 1. What is the specific role of each Uptake₂ 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 Uptake₁ and Uptake₂ transporters to [monoamine release](#) and clearance are in their infancy. Substrate specificity and transport efficiency varies among the Uptake₂ 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 Uptake₂ 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 Uptake₂ 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 immunoelectron 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 β 1-adrenergic receptors, and subsequent activation of G_s-cAMP signaling from the Golgi apparatus ([Irannejad et al., 2017](#)).

4. How do the Uptake₂ 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 Uptake₂ 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.

References

[Baganz et al., 2008](#)

N.L. Baganz, R.E. Horton, A.S. Calderon, W.A. Owens, J.L. Munn, L.T. Watts, N. Koldzic-Zivanovic, N.A. Jeske, W. Koek, G.M. Toney, L.C. Daws **Organic cation transporter 3: keeping the brake on extracellular serotonin in serotonin-transporter-deficient mice** Proc. Natl. Acad. Sci. U. S. A., 105 (2008), pp. 18976-18981

[Cui et al., 2009](#) M. Cui, R. Aras, W.V. Christian, P.M. Rappold, M. Hatwar, J. Panza, V. Jackson-Lewis, J.A. Javitch, N. Ballatori, S. Przedborski, K. Tieu **The organic cation transporter-3 is a pivotal modulator of neurodegeneration in the nigrostriatal dopaminergic pathway** Proc. Natl. Acad. Sci. U. S. A., 106 (2009), pp. 8043-8048

[Duan and Wang, 2010](#) H. Duan, J. Wang **Selective transport of monoamine neurotransmitters by human plasma membrane monoamine transporter and organic cation transporter 3** J. Pharmacol. Exp. Ther., 335 (2010), pp. 743-754

[Engel et al., 2004](#) K. Engel, M. Zhou, J. Wang **Identification and characterization of a novel monoamine transporter in the human brain** J. Biol. Chem., 279 (2004), pp. 50042-50049

[Gasser et al., 2006](#) P.J. Gasser, C.A. Lowry, M. Orchinik **Corticosterone-sensitive monoamine transport in the rat dorsomedial hypothalamus: potential role for organic cation transporter 3 in stress-induced modulation of monoaminergic neurotransmission** J. Neurosci., 26 (2006), pp. 8758-8766

[Gasser et al., 2017](#) P.J. Gasser, M.M. Hurley, J. Chan, V.M. Pickel **Organic cation transporter 3 (OCT3) is localized to intracellular and surface membranes in select glial and neuronal cells within the basolateral amygdaloid complex of both rats and mice** Brain Struct. Funct., 222 (2017), pp. 1913-1928

[Graf et al., 2013](#)

E.N. Graf, R.A. Wheeler, D.A. Baker, A.L. Ebben, J.E. Hill, J.R. McReynolds, M.A. Robble, O. Vranjkovic, D.S. Wheeler, J.R. Mantsch, P.J. Gasser **Corticosterone acts in the nucleus accumbens to enhance dopamine signaling and potentiate reinstatement of cocaine seeking** J. Neurosci., 33 (2013), pp. 11800-11810

[Grundemann et al., 1998](#) D. Grundemann, B. Schechinger, G.A. Rappold, E. Schomig **Molecular identification of the corticosterone-sensitive extraneuronal catecholamine transporter** Nat. Neurosci., 1 (1998), pp. 349-351

[Grundemann et al., 2003](#) D. Grundemann, C. Hahne, R. Berkels, E. Schomig **Agmatine is efficiently transported by non-neuronal monoamine transporters extraneuronal monoamine**

transporter (EMT) and organic cation transporter 2 (OCT2) J. Pharmacol. Exp. Ther., 304 (2003), pp. 810-817

[Horton et al., 2013](#)

R.E. Horton, D.M. Apple, W.A. Owens, N.L. Baganz, S. Cano, N.C. Mitchell, M. Vitela, G.G. Gould, W. Koek, L.C. Daws **Decynium-22 enhances SSRI-induced antidepressant-like effects in mice: uncovering novel targets to treat depression** J. Neurosci., 33 (2013), pp. 10534-10543

[Irannejad et al., 2017](#) R. Irannejad, V. Pessino, D. Mika, B. Huang, P.B. Wedegaertner, M. Conti, Z.M. von

Functional selectivity of GPCR-directed drug action through location bias Nat. Chem. Biol., 13 (2017), pp. 799-806

[Koepsell et al., 2007](#)

H. Koepsell, K. Lips, C. Volk **Polyspecific organic cation transporters: structure, function, physiological roles, and biopharmaceutical implications** Pharm. Res., 24 (7) (2007), pp. 1227-1251

[McReynolds et al., 2017](#)

J.R. McReynolds, A. Taylor, O. Vranjkovic, T. Ambrosius, O. Derricks, B. Nino, B. Kurtoglu, R.A. Wheeler, D.A. Baker, P.J. Gasser, J.R. Mantsch **Corticosterone potentiation of cocaine-induced reinstatement of conditioned place preference in mice is mediated by blockade of the organic cation transporter 3** Neuropsychopharmacology, 42 (2017), pp. 757-765