



Organic Cation Transporters in Brain Catecholamine Homeostasis

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Abstract

Catecholamines, including dopamine, norepinephrine, and epinephrine, are modulatory transmitters released from specialized neurons throughout the brain. Collectively, catecholamines exert powerful regulation of mood, motivation, arousal, and plasticity. Transporter-mediated uptake determines the peak concentration, duration, and physical spread of released catecholamines, thus playing key roles in determining the magnitude and duration of their modulatory effects. Most studies of catecholamine clearance have focused on the presynaptic high-affinity, low-capacity dopamine (DAT), and norepinephrine (NET) transporters, which are members of the uptake₁ family of monoamine transporters. However, recent studies have demonstrated that members of the uptake₂ family of monoamine transporters, including organic cation transporter 2 (OCT2), OCT3, and the

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plasma membrane monoamine transporter (PMAT) are expressed widely throughout the brain. In contrast to DAT and NET, these transporters have higher capacity and lower affinity for catecholamines and are multi-specific, each with the capacity to transport all catecholamines. The expression of these transporters in the brain suggests that they play significant roles in regulating catecholamine homeostasis. This review summarizes studies describing the anatomical distribution of OCT2, OCT3, and PMAT, their cellular and subcellular localization, and their contribution to the regulation of the clearance of catecholamines in the brain.

Keywords

Catecholamine · Clearance · Dopamine · Epinephrine · Norepinephrine · OCT1 · OCT2 · OCT3 · Organic cation transporter · PMAT · Uptake

1 Introduction

Early studies of catecholamine clearance mechanisms revealed the presence of two kinetically and pharmacologically distinct uptake processes in cardiovascular tissue: Uptake₁, a low capacity ($V_{\max} = 1.22$ nmol/min/mg tissue), high-affinity ($K_d = 0.27$ μ M) transport process inhibited by cocaine and desipramine; and Uptake₂, a high capacity ($V_{\max} = 100$ nmol/min/mg tissue), low-affinity ($K_d = 252$ μ M) process insensitive to cocaine and desipramine, but inhibited by corticosterone and normetanephrine (Iversen 1965; Iversen and Salt 1970). Subsequent studies identified the proteins responsible for these two processes in cardiac tissue as the norepinephrine transporter (NET) for uptake₁ (Pacholczyk et al. 1991) and, for uptake₂, a protein initially named the extraneuronal monoamine transporter (EMT) (Gründemann et al. 1998b), and subsequently identified as the third member of the organic cation transporter (OCT) family, OCT3 (Wu et al. 1998). It is now understood that uptake₁ and uptake₂ are two families of monoamine transporters: the uptake₁ family containing the sodium-dependent norepinephrine (NET), dopamine (DAT), and serotonin (SERT) transporters; and the uptake₂ family containing three organic cation transporters (OCT1, 2, and 3) and the plasma membrane monoamine transporter (PMAT). Each of the uptake₂ transporters has been identified in brain tissue (Amphoux et al. 2006; Gasser et al. 2006, 2009; Vialou et al. 2007), suggesting that, in areas where they are expressed, these transporters may play important roles in the disposition of monoamines in the brain, and thus may contribute to the regulation of monoaminergic neurotransmission. This review describes studies examining the roles of uptake₂ transporters in the regulation of catecholamine homeostasis and signaling in the brain.

2 Transport of Catecholamines by Uptake₂ Transporters: Cell Culture Studies

Studies of monoamine transport by uptake₂ transporters exogenously expressed in cultured cells have demonstrated that all of the uptake₂ transporters can transport catecholamines and that each transporter displays a distinct substrate specificity profile (Amphoux et al. 2006; Schömig et al. 2006; Duan and Wang 2010). OCT3 preferentially transports norepinephrine, epinephrine, and dopamine, all with similar efficiencies (V_{\max}/K_m) (Duan and Wang 2010). OCT2 preferentially transports epinephrine, with much lower transport of dopamine and norepinephrine (Gründemann et al. 1998a; Amphoux et al. 2006). PMAT strongly prefers dopamine and serotonin, which it transported with five- to sevenfold greater efficiency than any other monoamine (Duan and Wang 2010). Of the catecholamines, OCT1 preferentially transports epinephrine, with lower transport of dopamine and only weak transport of norepinephrine (Braidert et al. 1998). It is important to note that there is considerable variation in reported transport efficiencies between studies and that direct comparisons of transport efficiencies in cell culture studies are difficult due to variation in transporter expression, etc. Nonetheless, these studies indicate that OCT2, OCT3, and PMAT have the potential to contribute to the regulation of catecholamine homeostasis in the brain.

Studies of catecholamine transport by neuronal and glial cells in primary culture confirm roles for uptake₂ transporters while at the same time revealing the complexity of catecholamine uptake in more naturalistic systems. Uptake of the neurotoxin 1-methyl-4-phenylpyridinium (MPP⁺) by cultured cerebellar granule neurons (CGNs) is inhibited by decynium-22 (D-22) as well as by corticosterone, aldosterone, estradiol, and other steroids, but not by DAT inhibitors (Shang et al. 2003; Hill et al. 2011). The expression of mRNA for OCT1, OCT3, and PMAT, but not for NET or DAT, in CGNs confirms that catecholamine clearance in these cells is the function of multiple transport processes. Similarly, cultured astrocytes express mRNA for both OCT3 and NET (Inazu et al. 2002, 2003; Takeda et al. 2002), indicating that both uptake₁ and uptake₂ can contribute to catecholamine clearance in a single cell type. Understanding the specific roles of a given transporter in regulating catecholamine signaling will require information about its subcellular localization, including its spatial relationship to catecholamine receptors.

3 Expression and Localization of Uptake₂ Transporters in Brain

With the exception of OCT1, all of the uptake₂ transporters are widely expressed in the brain. OCT1 mRNA is barely detectable in most brain regions except for cerebellum and some white matter tracts (Amphoux et al. 2006; Hill et al. 2011). Here, we review the literature describing OCT3, OCT2, and PMAT localization in the central nervous system.

3.1 OCT3

In situ hybridization and immunohistochemical studies have shown that OCT3 is expressed widely throughout the rat brain. Particularly high levels of mRNA and protein expression have been observed in layer II of all cortical areas, especially retrosplenial, insular, and piriform cortex; in striatum, hippocampus, and cerebellum; and in periventricular organs including the subfornical organ, choroid plexus, fornix, and OVLT (Vialou et al. 2004; Amphoux et al. 2006; Gasser et al. 2009). OCT3 expression has been observed in neurons (Hill and Gasser 2013; Vialou et al. 2004), including cerebellar, hippocampal, and olfactory granule neurons (Cui et al. 2009; Gasser et al. 2009; Hill et al. 2011), striatal medium spiny neurons (Graf et al. 2013), and VTA dopaminergic neurons (Mayer et al. 2018). The transporter is also expressed in non-neuronal cells, including ependymal cells (Gasser et al. 2006, 2009); vascular endothelial cells in the brain (Li et al. 2015); and glial cells, including microglia (Gasser et al. 2016; He et al. 2017), oligodendrocytes (Gasser et al. 2009); and astrocytes (Cui et al. 2009; Gasser et al. 2016). The detection of OCT3 in brain astrocytes in situ is consistent with studies demonstrating OCT3 expression and function in human (Inazu et al. 2002) and rat (Perdan-Pirkmajer et al. 2012) astrocytes in primary culture.

3.2 OCT2

Immunohistochemical studies have demonstrated that OCT2 is widely distributed throughout the mouse brain, but is particularly enriched in prelimbic, infralimbic, cingulate and motor cortices, as well as in amygdala, periventricular thalamus (PVT), and hippocampus, including CA1, CA2, and CA3 regions (Bacq et al. 2012; Couroussé et al. 2015). OCT2 was expressed in most noradrenergic neurons in the locus coeruleus but was not detected in the dopaminergic VTA or substantia nigra (Bacq et al. 2012). In these studies, OCT2 expression was exclusively neuronal, with no evidence for astrocytic expression. This is in contrast with cell culture studies, which identified strong OCT2 mRNA expression in cultured rat astrocytes (Perdan-Pirkmajer et al. 2012).

3.3 PMAT

Immunohistochemical and in situ hybridization studies have identified PMAT mRNA and protein expression distributed throughout the brain, with particularly high expression in cerebellum, olfactory bulb, and medial septum. Interestingly, PMAT was expressed only in some, but not all, catecholamine cell groups. Most locus coeruleus noradrenergic neurons expressed PMAT, but the transporter was poorly expressed in dopaminergic cell groups. These studies also examined the expression of PMAT in specific neuronal subtypes. They identified high levels of PMAT expression in glutamatergic neurons including mitral cells in the olfactory

bulb, cholinergic neurons in striatum, hindbrain, and medial septum; and hippocampal and cerebellar granule cells (Dahlin et al. 2007; Vialou et al. 2007; Hill et al. 2011; Wang 2016).

4 Roles for Uptake₂-Mediated Transport in Brain Catecholamine Homeostasis: In Vivo and Ex Vivo Studies

Evidence that uptake₂ transporters play significant roles in shaping catecholamine homeostasis in the brain comes from studies using *ex vivo* uptake assays, microdialysis, voltammetry, or chronoamperometry to measure the effects of pharmacological or genetic manipulations on extracellular dopamine or norepinephrine dynamics. The most common compounds used to inhibit uptake₂ transporters and thereby test their involvement in monoamine clearance are the adrenal steroid hormone corticosterone and the quinoline derivative 1, 1'-diethyl-2,2'-cyanine iodide (decynium-22; D-22). All uptake₂ transporters are acutely inhibited by corticosterone and other steroids, though they differ in their sensitivities (for review, see Gasser and Lowry 2018; Benton et al. (this volume)). OCT3 and OCT2 are much more sensitive to corticosterone ($IC_{50} = 0.1 \mu\text{M}$ (OCT3), $1 \mu\text{M}$ (OCT2)) than is PMAT ($IC_{50} = 500 \mu\text{M}$). D-22 inhibits OCTs and PMAT with IC_{50} of approximately $0.1 \mu\text{M}$ (Engel and Wang 2005). However, studies have demonstrated that D-22 has significant actions at other targets. These effects include antagonism at $\alpha 1$ adrenoceptors (Russ et al. 1996) and more recently, D2 dopamine receptors (Lloyd et al. 2019). It is important to note that D-22 has been shown in chronoamperometry studies to inhibit monoamine (serotonin) clearance at very low concentrations of D-22 ($\sim 0.05 \mu\text{M}$) (Baganz et al. 2008; Horton et al. 2013), while the D-22-induced antagonism of dopamine D2 receptors was observed at very high concentrations ($25 \mu\text{M}$) (Lloyd et al. 2019). Thus, D-22 is an effective inhibitor of monoamine uptake, but off target actions of D-22 should be considered in studies of extracellular catecholamine concentrations. Experiments using these compounds must be carefully designed and must consider dose/concentration, as well as information about the expression of uptake₁ and uptake₂ transporters in the brain region where measurements are being taken.

Strong evidence that uptake₂ transporters contribute to catecholamine homeostasis comes from studies of mice genetically engineered to lack individual transporters. OCT2-deficient mice display decreased tissular norepinephrine levels in hippocampus, cortex, striatum, and brainstem and, in *ex vivo* uptake assays, hippocampal and cortical tissue from these mice display decreased D-22-sensitive norepinephrine uptake (Bacq et al. 2012). OCT3-deficient mice exhibit significantly lower tissular concentrations of dopamine in olfactory bulb, cortex, striatum, ventral tegmental area (VTA)/substantia nigra (SN), thalamus/hypothalamus and brainstem; and of norepinephrine in VTA/SN (Vialou et al. 2008). Methamphetamine and the neurotoxin 1-methyl-4-phenylpyridinium (MPP⁺), two dopamine-releasing agents, induce larger, longer lasting increases in striatal dopamine concentrations in OCT3-deficient mice than in wild-type mice (Cui et al. 2009), suggesting a role for

OCT3 in dopamine clearance in this area. In the only study to examine monoamine transport in PMAT-deficient mice, choroid plexus tissue from PMAT-deficient mice accumulated significantly less dopamine than tissue isolated from wild-type mice (Duan and Wang 2013). Together, these studies indicate that the clearance of extracellular catecholamines in the central nervous system is mediated by both uptake₁ and uptake₂ transporters.

A large number of studies have examined the effects of uptake₁ and uptake₂ inhibitors, alone and in combination, on extracellular catecholamine concentrations using microdialysis or electrochemical techniques. Several of these studies have examined potential joint contributions of OCT3 and DAT to dopamine clearance in the striatum. Graf and colleagues showed that systemic injection of a low dose of cocaine (2.5 mg/kg), administered alone, had no effect on extracellular dopamine concentrations. However, when preceded by an injection of corticosterone, this same dose of cocaine caused significant increases in extracellular dopamine (Graf et al. 2013). The dose of corticosterone administered in these studies (2.5 mg/kg) results in plasma corticosterone concentrations that mimic those induced by exposure to stress (Graf et al. 2013). Microdialysis studies have reported that the concentration of corticosterone in brain tissue during stress reaches approximately 100 nM (Droste et al. 2008, 2009; Qian et al. 2012), a concentration previously shown to inhibit OCT3-mediated transport (Gasser et al. 2006). Thus, the studies of Graf and colleagues implicate OCT3 in the regulation of dopaminergic transmission in this region. However, it is likely that OCT2 and PMAT, both of which are expressed in the striatum, also contribute to dopamine clearance in this area. In other microdialysis studies, direct administration of D-22 into the striatum of nigrostriatal lesioned rats markedly enhanced L-DOPA-induced increases in extracellular dopamine concentrations (Sader-Mazbar et al. 2013). Although the results of this study are consistent with a role for uptake₂ in striatal dopamine clearance, the high concentration of D-22 administered (50 μM) means that other, non-transport mechanisms, including DA D2 receptor antagonism (Lloyd et al. 2019), may contribute to the observed increases in dopamine.

Fast-scan cyclic voltammetry (FSCV) and high-speed chronoamperometry are electrochemical techniques that can monitor catecholamine concentrations on a sub-second timescale, thus allowing quantification of clearance rates. Studies using FSCV in the rat striatum have provided strong evidence that OCT3, as well as DAT, mediates dopamine clearance in this region. These studies examined the effects of the DAT inhibitor GBR12909, in the presence or absence of corticosterone, on the clearance of electrically induced increases in dopamine in the nucleus accumbens of anesthetized rats (Graf et al. 2013). Systemic injection of GBR12909 alone significantly decreased NAc dopamine clearance (increases in full width at half height (FWHH), apparent K_m , and tau, all indicating decrease clearance). Once the effects of DAT blockade had stabilized, injection of corticosterone, but not vehicle, further decreased dopamine clearance (further increases in FWHH, apparent K_m , and tau) (Graf et al. 2013). These studies revealed for the first time in an in vivo setting, the presence of corticosterone-sensitive, DAT-independent clearance of dopamine. Subsequent studies used FSCV to examine the effects of corticosterone and cocaine

on NAc dopamine clearance in awake and behaving animals. In these studies, injection of corticosterone alone significantly increased the duration and magnitude of spontaneous dopamine transients, indicating that, even in the NAc, where DAT is very densely expressed, corticosterone-induced inhibition of DA clearance can be observed in the absence of DAT blockade. Further, in these studies, administration of low-dose cocaine alone had no effect on the amplitude, and only slightly increased the duration, of dopamine transients. However, when administered after corticosterone, this dose of cocaine robustly increased both amplitude and duration of dopamine transients (Wheeler et al. 2017). These studies clearly demonstrate that both uptake₁ (DAT-mediated) and uptake₂ (likely OCT3-mediated) processes work to shape catecholamine signals *in vivo*.

The relative contributions of uptake₁ and uptake₂ to catecholamine clearance likely vary regionally, resulting from region-specific patterns of transporter expression and catecholamine release. Holleran et al. (2020) used FSCV in slices of basolateral amygdala and nucleus accumbens to describe region-specific expression of DAT and OCT3, and regional differences in the contributions of uptake₁ and uptake₂ transporters to catecholamine clearance, in the nucleus accumbens (NAc) and basolateral amygdala (BLA) (Holleran et al. 2020). While OCT3 was expressed at similar levels in both regions, DAT expression was much greater in the NAc than in the BLA. Consistent with this expression pattern, the uptake₂ inhibitor corticosterone inhibited a greater proportion of catecholamine clearance in the BLA, while the DAT/uptake₁ inhibitor cocaine inhibited clearance in the NAc. In the hippocampus, where both uptake₁ and uptake₂ transporters are expressed, locally administered D-22 (at very low doses) enhanced desipramine-induced increases in norepinephrine concentrations measured by high-speed chronoamperometry, suggesting that regulation of catecholamine homeostasis in this region is also mediated by both classes of transporter (Bowman et al. 2020).

5 Subcellular Localization of Uptake₂ Transporters

The subcellular localization of a transporter, particularly its spatial relationship to receptors and transmitter release sites, is a critical determinant of the degree to which it regulates neurotransmission. While no studies have directly examined the co-localization of any uptake₂ transporter with catecholamine receptors or its proximity to catecholamine release sites, immuno-electron microscopy studies have demonstrated that OCT3 is positioned to exert significant influence over the temporal and physical spread of released monoamines (Gasser et al. 2016). In these studies, OCT3 was localized to plasma membranes of dendritic spines in amygdala, in some cases adjacent to axonal processes consistent with the morphology of catecholamine release sites. OCT3 was also observed in plasma membranes of neuronal somata, axonal profiles, and astrocyte processes surrounding axodendritic and axospinous profiles. Positioned at these sites, OCT3-mediated transport may be an important determinant of the degree to which released catecholamines activate receptors on pre- and post-synaptic cells.

Interestingly, OCT3 was also observed in a variety of endomembranes in both neurons and glia, including outer nuclear membranes, Golgi, mitochondrial, and vesicular membranes (Gasser et al. 2016). The localization of OCT3 to outer nuclear membranes is consistent with studies demonstrating nuclear localization of adrenergic receptors in cardiac myocytes (Boivin et al. 2006; Wu et al. 2014). Vesicular and Golgi localization are consistent with recent studies in non-neuronal cells demonstrating OCT3-mediated transport is required for activation of adrenergic receptors localized to these endomembranes (Irannejad et al. 2017). In the only other electron microscopic study of an uptake2 transporter, OCT2 was also observed densely localized to synaptic vesicles in spinal cord cholinergic neurons (Nakata et al. 2013). Mitochondrial localization raises the possibility that OCT3 may mediate access of catecholamines to mitochondrial monoamine oxidase for metabolism, though this hypothesis has not been tested.

6 Summary

By regulating the duration, physical spread, peak concentrations, and intracellular disposition of released catecholamines, transport processes determine the extent to which catecholamine receptors are activated and, thus, the extent to which catecholamines exert neuromodulatory influences over surrounding synapses. While clearance of released catecholamines was once believed to be solely mediated by the high-affinity, low-capacity dopamine and norepinephrine transporters (DAT and NET), the studies reviewed here have demonstrated that OCT2, OCT3, and PMAT are expressed throughout the brain in a variety of cell types and have begun to reveal how these transporters act, alone and in concert with NET and DAT, to influence catecholaminergic neurotransmission.

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