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Role of organic cation transporters (OCTs) in the brain

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ABSTRACT

Organic cation transporters (OCTs) are polyspecific facilitated diffusion transporters that contribute to the absorption and clearance of various physiological compounds and xenobiotics in mammals, by mediating their vectorial transport in kidney, liver or placenta cells. Unexpectedly, a corpus of studies within the last decade has revealed that these transporters also fulfill important functions within the brain. The high-affinity monoamine reuptake transporters (SERT, NET and DAT) exert a crucial role in the control of aminergic transmission by ensuring the rapid clearance of the released transmitters from the synaptic cleft and their recycling into the nerve endings. Substantiated evidence indicate that OCTs may serve in the brain as a compensatory clearance system in case of monoamine spillover after high-affinity transporter blockade by antidepressants or psychostimulants, and in areas of lower high-affinity transporter density at distance from the aminergic varicosities. In spite of similar anatomical profiles, the two brain OCTs, OCT2 and OCT3, show subtle differences in their distribution in the brain and their functional properties. These transporters contribute to shape a variety of central functions related to mood such as anxiety, response to stress and antidepressant efficacy, but are also implicated in other processes like osmoregulation and neurotoxicity. In this review, we discuss the recent knowledge and emerging concepts on the role of OCTs in the uptake of aminergic neurotransmitters in the brain and in these various physiological functions, focusing on the implications for mental health.

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1. Introduction

Organic cation transporters (OCTs) are polyspecific facilitated diffusion transporters that contribute to the absorption and clearance of various physiological compounds and xenobiotics in mammals, by mediating their vectorial transport in kidney, liver or placenta cells (Koepsell, Gorboulev, Karbach, & Arndt, 2000). Unexpectedly, a corpus of studies within the last decade has revealed that these transporters also serve important functions within the brain. Since 1994, three OCT subtypes (OCT1, OCT2 and OCT3) have been isolated by cloning from

Abbreviations: 5-HT, serotonin; D22, decynium22; DA, dopamine; DAT, dopamine transporter; FST, forced-swim test; NE, norepinephrine; NET, norepinephrine transporter; OCT, organic cation transporter; SERT, serotonin transporter; SFO, subfornical organ; TST, tail suspension test; —/—, null.

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diverse organs and included in the SLC22 transporter family, within the large Major Facilitator Superfamily. The study of their basic pharmacological properties in cultured cells and *Xenopus* oocytes provided evidence that these transporters accept as substrates a variety of positively charged endogenous substances and drugs, ranging from hormone-like compounds to antiviral and antihistaminergic agents (Koepsell, Schmitt, & Gorboulev, 2003). These substrates can be translocated across the cell membrane bidirectionally, driven by their concentration gradient and by the membrane potential, independently of the H^+ and Na^+ gradients (Koepsell et al., 2003). Early studies showed that OCTs also transport the biogenic monoamines serotonin (5-hydroxytryptamine, 5-HT), norepinephrine (NE), dopamine (DA) and histamine (Breidert, Spitzenberger, Grundemann, & Schomig, 1998; Busch et al., 1998; Grundemann, Koster, et al., 1998; Grundemann, Schechinger, Rappold, & Schomig, 1998; Wu et al., 1998; Grundemann, Liebich, Kiefer, Koster, & Schomig, 1999). Contrary to OCT1 (Amphoux et al., 2006), the two subtypes OCT2 and OCT3 are expressed in the brain (Gorboulev et al., 1997; Grundemann et al., 1997; Busch et al., 1998; Grundemann, Koster, et al., 1998; Grundemann, Schechinger, et al., 1998; Wu et al., 1998), leading to intense speculation concerning their potential role in the nervous system.

The monoaminergic pathways control fundamental physiological functions within both central and peripheral nervous systems. Although fine interactions between these distinct neuroanatomical systems are required for the adequate tuning of most functions, 5-HT tonus has been preferentially associated with modulation of mood, aggression, appetite, sleep, sexual activity, pain and thermoregulation, NE with arousal, attention, mood and stress and DA with control of motor function, motivation and reward, mood and cognition. As a consequence, transporters modulating the general homeostasis of these pathways are bound to affect heavily these fundamental behaviors. In line with this concept, a number of psychoactive drugs, including several antidepressants and psychostimulants, target the high-affinity 5-HT, NE and DA transporters. These high-affinity reuptake transporters exert a crucial role in the control of aminergic transmission by ensuring the rapid clearance of the released transmitters from the synaptic cleft and their recycling into the nerve endings. The seminal discoveries that OCTs transported monoamines, albeit with much lower affinity than the classical reuptake monoamine transporters, opened mesmerizing perspectives for the identification of novel mechanisms controlling neurotransmission and for therapeutic innovation. However, the shift from this hypothetical vision to substantiated convictions on the roles of OCTs in the central nervous system took place only progressively in the last decade. For this delay we can incriminate the intrinsic pharmacological properties of OCTs (low-affinity, polyspecificity) and the lack of pharmacological tools allowing the differentiation between subtypes. Adding to these difficulties, the determination of specific functions for OCTs in the brain was hampered by the masking effect of the high-affinity transporters, much more readily detected in the brain, and themselves carrying out heterologous uptake (i.e. uptake of non-cognate neurotransmitter). We had to wait for functional studies and mouse mutants deficient for one or several of these transporters (Jonker et al., 2001; Zwart, Verhaagh, Buitelaar, Popp-Snijders, & Barlow, 2001; Jonker, Wagenaar, Van Eijl, & Schinkel, 2003) to see evidence that OCT activity in live animals may influence not only drug absorption at the periphery but also neurotransmitter clearance in the brain. Since then, our knowledge concerning specialized functions that these transporters play in the central nervous system has increased over the years, bringing to light similarities as well as complementarities with the classical reuptake transporters.

This review highlights the major milestones that led to the understanding of the role of OCTs in the clearance of aminergic neurotransmitters in the brain, mood-related and addictive behaviors and disposal of neurotoxins in the brain, focusing on the implications for mental health.

2. Organic cation transporters as an alternate monoamine clearance system in the brain

2.1. Neurochemical and functional evidence

On the basis of their general properties, OCTs were assimilated since their cloning with uptake$_2$, a peripheral catecholamine removal system. Contrasting with the high-affinity Uptake$_1$ system of nerve terminals (Graefe & Bonisch, 1988), Uptake$_2$ is a sodium and chloride-independent, low-affinity, high-capacity system found in sympathetically innervated tissues such as the heart, smooth muscle and glandular cells (Iversen, 1965; Bonisch, 1980). OCT3 in particular was found to reflect most accurately the properties of uptake$_2$, including selective inhibition by corticosteroids and O-methylated catecholamines and sensitivity to nanomolar concentrations of the cyanine dye derivatives disprocynium24 and decynium22 (D22) (Grundemann et al., 1997; Grundemann, Koster, et al., 1998; Grundemann, Schechinger, et al., 1998; Wu et al., 1998; Hayer-Zillgen, Bruss, & Bonisch, 2002). Similar low-affinity monoamine transport systems were detected in the brain well before the identification of OCTs by molecular cloning. NE and the model substrate isoprenaline were shown to accumulate in rat cerebral cortex slices (Hendley, Taylor, & Snyder, 1970; Wilson, Grohmann, & Trendelenburg, 1988), displaying overall features of peripheral Uptake$_2$. Consistent with the existence of a central Uptake$_2$ system, the residual MPP^+ uptake observed after suppression of Uptake$_1$ by cocaine was shown to be sensitive to the selective Uptake$_2$ inhibitor disprocynium24 (Russ, Sonna, Keppler, Baunach, & Schomig, 1993; Russ, Staust, Martel, Gliese, & Schomig, 1996). Other studies also revealed distinct components for DA uptake in rat striatal preparations (Mireylees, Brammer, & Buckley, 1986) and prefrontal cortex (Wayment, Schenk, & Sorg, 2001). While some of these early observations may be explained by the strong promiscuity for substrate selectivity between the high-affinity transporters – DA can be transported by the NET and SERT (Larsen et al., 2011) and NE by the DAT and SERT (Vizi, Zsilla, Caron, & Kiss, 2004) – a role for OCT devoted solely to peripheral transport had to be reconsidered. Since, it has become increasingly clear that OCTs are major actors of monoamine transport *in vivo* in the brain.

Much of the evidence for the implication of OCTs in central monoamine clearance initially came from studies exploiting selective inhibitors. P. Gasser and collaborators found that *ex vivo* accumulation in rat dorsomedial hypothalamus minces of the OCT substrate histamine could be inhibited by corticosterone, 5-HT, estradiol and the cyanine inhibitor D22 (Gasser, Lowry, & Orchinik, 2006), a profile evoking OCT3 pharmacological properties. In a microdialysis study, the NE metabolite and potent OCT inhibitor normetanephrine was found to potentiate the venlafaxine-mediated increase in extracellular NE levels in rat frontal cortex (Rahman et al., 2008). More recently, perfusion of D22 in rat medial hypothalamus by microdialysis was shown to increase strongly local extracellular 5-HT levels, an effect accentuated by acute stress (Feng et al., 2010). A fundamental contribution to the study of monamine clearance *in vivo* was made by Daws et al. (2005), who developed an elegant method based on high-speed chronoamperometry allowing the detection of a 5-HT clearance component in rat hippocampus after SERT pharmacological blockade. Subsequently, these authors demonstrated that this 5-HT clearance component persisted in mutant mice lacking the SERT and was impaired by local application of D22 or corticosterone (Baganz et al., 2008). In a more recent study also using voltammetry, acute administration of corticosterone was found to diminish DA clearance in the nucleus accumbens of rats treated beforehand with a DAT inhibitor (Graf et al., 2013). Such findings point toward the existence of undefined transporters that could in some circumstances control 5-HT and DA clearance, yet did not allow teasing apart the precise nature of the transporters implicated. Both OCT2 and OCT3 are potentially blocked by D22 (Hayer-Zillgen et al., 2002). Yet another organic cation transporter expressed in the brain, plasma