Chapter 7
Organic Cation Transporters (OCTs) as Modulators of Behavior and Mood

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Abstract The organic cation transporters (OCTs) fulfill important functions in the absorption and excretion of endogenous compounds and xenobiotics in peripheral organs, which have been well documented. Two OCT subtypes, OCT2 and OCT3, are also expressed in the brain and predominant in aminergic projection regions. The last decade has seen substantial advances in our understanding of the implication of these transporters in a range of integrated functions of the central nervous system. Various approaches exploiting pharmacological inhibitors and mutant mice models for OCTs have disclosed that they are involved in particular in behaviors related to osmoregulation, anxiety, stress, antidepressant action and addiction. We summarize in this chapter recent developments on the roles of OCTs in central nervous system, focusing on mood-related behaviors.

Keywords Organic cation transporter • Brain • Osmoregulation • Anxiety • Stress • Antidepressants • Addiction

Abbreviations

5-HT	Serotonin
D22	Decynium 22
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

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Introduction

Organic cation transporters (OCTs) belonging to the SLC22 family fulfill important roles in the absorption and excretion of endogenous compounds and xenobiotics in peripheral organs, which have been well documented. Three main OCT subtypes (OCT1, OCT2 and OCT3) were identified by molecular cloning, followed by their pharmacological characterization in heterologous expression systems. Studies over time showed that a large number of endogenous and exogenous substances can interact with these transporters as substrates or inhibitors. OCT ligands include various therapeutic drugs such as antivirals, cytostatics, antidiabetics and antihistaminergic agents, as well as hormones and neurotoxins [1, 2]. Interestingly, certain metabolites and neurotransmitters were also shown to be transported by OCTs, in particular the biogenic monoamines dopamine (DA), serotonin (5-hydroxytryptamine, 5-HT), norepinephrine (NE), epinephrine and histamine [3–8].

Aminergic neurotransmitters modulate fundamental integrated behaviors related to mood, aggression, attention, motor function, motivation and reward. An important step in the control of the action of monoamines at the synapse is their rapid reinternalization into the presynaptic terminals by high-affinity reuptake transporters, DAT, NET and SERT, for DA, NE and 5-HT, respectively [9]. In agreement with this fundamental role in amine clearance, the high-affinity transporters are the principal targets of potent psychoactive drugs including psychostimulants and several commonly used antidepressants. The finding that OCTs can transport monoamines, albeit with lower affinity than the classical reuptake transporters, opened stimulating perspectives for the identification of novel mechanisms modulating central behaviors and therapeutic innovation.

Convincing data concerning the role of OCTs in the central nervous system was obtained only in the last decade. The study of the contribution of these transporters to monoamine clearance in vivo in the brain was complicated by their wide substrate specificity and their low-affinity, making difficult to distinguish their activity from that of the high-affinity transporters, much more easily detected. The creation of mouse mutants deficient for these transporters [10–12] was an essential step in the understanding of their role in neurotransmitter clearance in the brain of live animals. Since then, the number of specialized central functions implicating OCTs has been steadily expanding and will probably continue to expand in the coming years. This chapter provides an overview of the general knowledge on the role of OCTs in various behaviors and integrated functions, ranging from salt-intake regulation to mood-related behaviors and addiction.

OCTs Modulate Aminergic Neurotransmission

The OCTs display the low-affinity kinetics and overall characteristics of uptake$_2$, a catecholamine uptake system detected earlier in peripheral tissues with sympathetic innervation [13, 14]. In contrast with the high-affinity transporters [15], transport by

OCTs is independent of Na^+ and Cl^- ions and highly sensitive to the cyanine dye derivatives disprocynium 24 (D24) and decynium 22 (D22) [16, 17]. The properties of OCT3 were found to resemble most accurately those of uptake$_2$, in particular regarding sensitivity to corticosteroids and 0-methylated catecholamines [5, 6, 8, 18, 19].

Although predominantly expressed in peripheral tissues, two subtypes, OCT2 and OCT3, are expressed in the central nervous system [4, 6, 8, 18, 20–26]. The first hints that these OCTs could be implicated in monoamine transport in the brain originated from studies using selective inhibitors as discriminatory pharmacological tools. By high-speed chronoamperometry, L. Daws and colleagues demonstrated the existence in rat hippocampus of a 5-HT clearance component sensitive to the local application of D22 and corticosterone [27, 28], both previously described to interact with OCTs. Remarkably, this component could be only detected in conditions of pharmacological blockade [27] or genetic [28] invalidation of SERT. In another study, P. Gasser and collaborators showed that the OCT substrate histamine, for which no high-affinity transporter has been identified, could accumulate in rat dorsomedial hypothalamus minces, and that this accumulation was sensitive to corticosterone, 5-HT, estradiol and D22 [29]. By the use of microdialysis, it was also shown that extracellular 5-HT levels in rat medial hypothalamus were notably increased by D22 perfusion [30].

Subsequently, the use of mouse mutants harboring an invalidated OCT2 or OCT3 gene allowed to tease apart the contribution of these transporters in monoamine transport in the brain and in central functions. A number of neurochemical studies confirmed the importance of both these transporters in the modulation of monoamine neurotransmission in the brain with, however, some differences in the nature of the neurotransmitters implicated. The analysis of tissue content of monoamines by high-performance liquid chromatography showed that OCT3 deletion leads to decreased intracellular levels and increased turnover of these neurotransmitters, with a preferential impact on DA content and metabolism compared to the other monoamines [24]. In rats, in agreement with a role of OCT3 in DA clearance, inhibition of OCT3 through infusion of antisense oligonucleotides into the third ventricle was shown to increase extracellular DA levels in nucleus accumbens and prefrontal cortex [31] as well as methamphetamine-induced hyperactivity, a behavioral response relying on the activation of dopaminergic pathways [32]. In contrast, OCT2 was found to be more selective of 5-HT and NE, as supported by a set of neurochemical and electrophysiological evidence. OCT2 deletion was associated with significant reductions in the content in brain tissue concentrations of 5-HT and NE [25], suggesting a role for this transporter in the preferential uptake of these two amines in vivo. This hypothesis was further supported by functional studies evaluating monoamine transport activity ex vivo, in cell suspensions from highly-expressing brain regions, in conditions where the high-affinity transporters are inhibited. These experiments showed a significant decrease in D22-sensitive 5-HT and NE uptake in OCT2 mutant mice, whereas DA uptake appeared less affected [25]. This decrease in ex vivo uptake could not be explained by modifications in the expression of other high or low-affinity transporters, as shown by quantification by ligand binding and immunoautoradiography. Consolidating these findings, combined

microiontophoresis and electrophysiology studies revealed dramatic consequences of OCT2 deletion on monoamine clearance in vivo in dorsal hippocampus [25]. These studies showed that the recovery of the firing activity of CA3 pyramidal neurons after 5-HT and NE application was significantly decreased in OCT2-deleted mice treated with the dual 5-HT/NE antidepressant venlafaxine. Besides revealing a key role of OCT2 in monoamine clearance, these findings indicate that this transporter modulates postsynaptic neuron activity in vivo when the SERT and NET are pharmacologically inactivated. Taken together, the above studies suggest that OCTs function as an alternate monoamine clearance mechanism in brain areas lacking the high-affinity transporters, at distance from the aminergic nerve endings, or when these high-affinity transporters are saturated or inhibited, as may be the case after antidepressants or psychostimulants administration (Fig. 7.1).

Distribution and Functional Specialization of Brain OCTs

OCT2 and OCT3 show a similar expression pattern in the brain. As expected for monoamine transporters, both are expressed in aminergic nuclei such as raphe, locus coeruleus and tuberomammillary nucleus. However, a distinguishing feature of these low-affinity transporters is their predominant expression in the major brain areas receiving aminergic innervation, like the cortex, hippocampus, thalamus, hypothalamus, amygdala and hindbrain [4, 23–26]. Contrarily to the classical reuptake transporters enriched in nerve terminals, OCT2 and OCT3 are expressed in the cells bodies and processes (of neurons and occasionally astrocytes) in these projection regions [24, 33], thus strategically positioned to internalize monoamines postsynaptically. This potential role in postsynaptic uptake is compatible with the known mode of transmission of monoamines, which may diffuse away from the site of liberation to reach remote targets [34–36] and with the high capacity of OCTs, which may compensates for low-affinity. In agreement with the participation of OCTs in aminergic clearance in physiological conditions, OCT2 and OCT3 knockout mice show diminished monoamine contents in several brain regions compared to wild-type mice, in absence of any pharmacological treatment [24, 25]. Interestingly, a similar decrease in monoamine levels was previously found in DAT, SERT and NET knockout mice brain [37–39].

In spite of their comparable general distribution, OCT2 and OCT3 also show varying expression levels and selective expression within restricted brain areas. Contrarily to OCT2, OCT3 is highly expressed in circumventricular organs (CVO) [22, 23] and in the dopaminergic nuclei substantia nigra [40]. At the cellular level, while both transporters are principally located in neurons, OCT3 was also detected in astrocytes in certain areas such as dorsomedial hypothalamus nucleus and substantia nigra. These subtle differences in expression could reflect the need for selective clearance within an area. As summarized above, OCT2 seems to prefer 5-HT and NE in vivo [25], while OCT3 appears more specialized for DA in several brain areas [24] except in dorsomedial hypothalamus nucleus [29]. Differential OCT expression could thus allow a precise tuning of clearance according to the

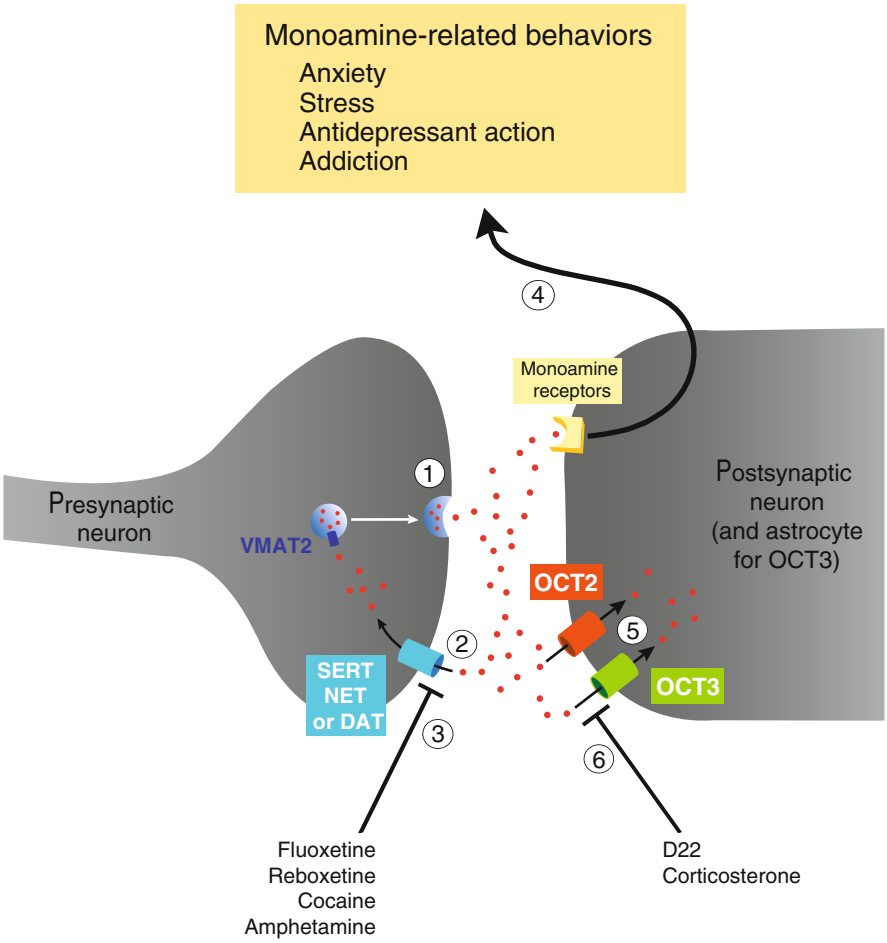

Fig. 7.1 Schematic representation of the role of OCTs in monoamine clearance in the brain. Monoamines (5-HT, NE or DA) are transported into the synaptic vesicles by the vesicular transporter 2 (VMAT2) and released in the synaptic cleft by exocytosis (*1*). High-affinity uptake transporters (SERT, NET and DAT) control the clearance of extracellular monoamines by ensuring their reinternalization into the pre-synaptic terminals (*2*). Pharmacological inhibition of these high-affinity uptake transporters by antidepressants and psychostimulants (*3*) increases the extracellular concentration of monoamines, modulating central behaviors (*4*). OCT2 and OCT3 (*5*) located on proximal or distal post-synaptic sites contribute to clearance when the high-affinity transporters are saturated, inhibited or absent. OCT blockers such as decynium 22 (D22) and corticosterone (*6*) potentiate the neurochemical and behavioral effects (*4*) of high-affinity transporter inhibitors (*3*)

nature of the aminergic afferent fibers received by the brain regions. A body of work over the last years has revealed the role of the brain OCTs in a number of integrated functions (Fig. 7.2). Although the roles of OCT2 and OCT3 are far from being fully understood, these studies implicate these two subtypes in somewhat different behaviors, which may be determined by their anatomical and functional specialization.

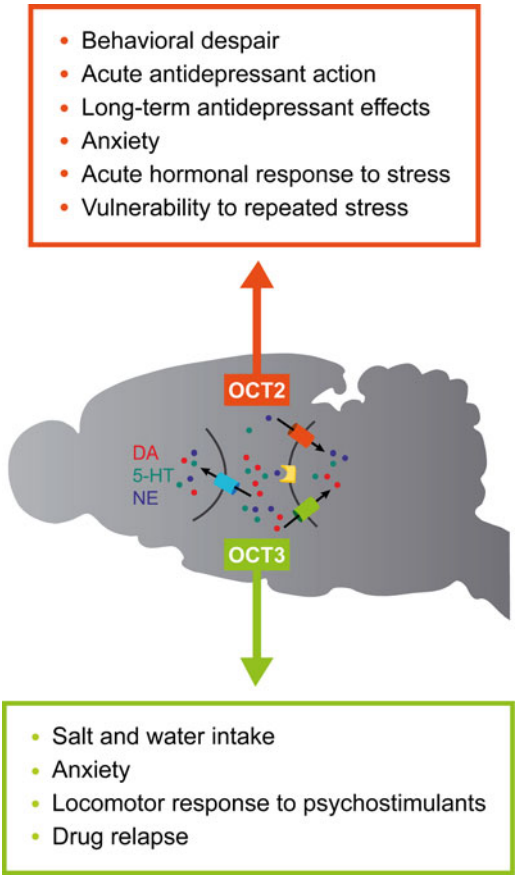

Fig. 7.2 Schematic summary of the roles of OCTs in central behaviors in rodents. OCT2 (in *red*) and OCT3 (in *green*) participate in monoamine (DA, 5-HT and NE) clearance in the brain in addition to the high-affinity transporters, thereby modulating their extracellular levels. OCT2 was shown to be implicated in behavioral despair, acute and long-term antidepressant effects, anxiety, and stress response and vulnerability. OCT3 was shown to be implicated in salt and water intake, anxiety, locomotor response to psychostimulants and drug abuse relapse

Role in Integrated Behaviors

Salt and Water Intake

One of the earliest demonstrations of the role of OCT3 in central functions directly proceeds from its peculiar distribution. This transporter is highly expressed in CVOs such as area postrema and subfornical organ (SFO), structures located at the blood–brain interface and controlling fluid exchange and osmotic homeostasis [23]. This initial observation led to challenge the role of OCT3 in the processing of osmotic information in the brain. Concerted sodium and water balance regulation is a complex function implicating osmoreceptors for blood-borne information located in the sensory CVOs and secondary neural circuits in forebrain and hindbrain, all interconnected. In agreement with the expression profile of this transporter, mice lacking OCT3 show an abnormal salt ingestion behavior, in particular increased preference for hypertonic saline under sodium depletion and water deprivation conditions.

Furthermore, induction of the c-Fos protein was established as a reliable indicator of neural activation in osmosensitive and relay regions. Specifically, modifications of this functional response in mice exposed to salt deprivation can be detected by quantitating the number of c-Fos expressing cells in these structures. Under conditions of salt deprivation, c-Fos induction in the SFO, where OCT3 is highly expressed, was found significantly decreased in OCT3-deficient mice in comparison with wild-type animals, reflecting a blunted neural response in this structure [23]. This study demonstrates that OCT3 modulates the neural and behavioral responses to variations in osmolarity in the environment. However, how OCT3 achieves this modulation remains to be determined. The SFO neurons themselves are sensitive to variations in extracellular osmotic pressure, presumably through the activation of ionic channels, but salt-intake is also subject to extensive control by secondary neural circuits and neuroendocrine signaling. Based on its fundamental properties, it seems unlikely that OCT3 could be implicated in osmolarity sensing per se, but rather that it could play a role in modulation of the primary neural response, either within the SFO or by afferent connections [23]. Several forebrain regions implicated in relaying osmoregulatory responses express OCT3 at a low level. Thus, OCT3 could also be required for activation of secondary neural circuits participating in the response, or for correct neurotransmission between osmosensitive structures and these relay regions [23]. The CVOs and in particular the SFO have been proposed to participate in sympathetic-mediated hypertension [41]. It will interesting to determine in the coming years whether OCT3 function may influence blood pressure in various conditions and possibly predisposition to hypertension, as suggested for other components controlling both osmolarity sensing within CVOs and salt-intake behavior [42].

Mood-Related Behaviors

Anxiety

The role of the OCTs in mood was intensively studied, instigated by the fact that these transporters could transport biogenic amines. Alterations in anxiety-related behaviors were found in mice mutants for OCT2 [25] or OCT3 [24, 43], as expected from the involvement of aminergic neurotransmission pathways systems in these behaviors [44]. OCT2 knockout mice showed decreased anxiety-related behavior in two distinct paradigms, the elevated O-maze and the novelty-suppressed feeding test [25]. This anxiolytic phenotype was confirmed in the open-field, with the mutants showing significant increases in the time and spontaneous locomotor activity in the center of the field, and no change in activity at the periphery [25]. Contrasting with this clear phenotype, inconsistent observations were found after OCT3 genetic deletion, with decreased anxiety levels found in one mice line [43] and increased anxiety levels found in another [24]. The causes for this discrepancy are unclear but might be linked to the genetic background of the mice lines, a

parameter that may influence the expression of diverse molecules participating in aminergic signaling. In particular, the existence of eventual variations in the expression of monoamine uptake transporters was not explored in the two mice lines. The activity of the high-affinity 5-HT reuptake transporter, SERT, may for instance modulate anxiety-related behaviors [45]. In spite of these contradictions, these results point to a role of OCT3 activity in anxiety-related behavior in mice. Reinforcing this possibility, an OCT3 variant with decreased NE transport capacity was identified in patients with the anxiety-related obsessive-compulsive disorder [46, 47].

Stress Response and Vulnerability

Several studies demonstrate that the brain OCTs modulate the physiological response to stress in mammals, although the exact mechanisms of this action remain unclear. As mentioned earlier, OCTs expressed in heterologous systems can be inhibited by the stress hormone corticosterone, contrarily to the high-affinity monoamine transporters [5, 6, 19, 48, 49]. These observations laid the basis for the idea that interactions between OCTs and corticosterone could somehow play a part in the biological processes occurring during stress. One of the brain OCTs, OCT2, was detected in brain regions implicated in the response to stress, like the prelimbic and infralimbic cortices, hippocampus, amygdala, dorsomedial and arcuate nuclei of hypothalamus, paraventricular nucleus of the thalamus and pituitary, as well as in the adrenals [25, 26]. The above-mentioned circuits have been shown to modulate, through direct and indirect connections with the paraventricular nucleus (PVN) and periPVN regions, the activation of the hypothalamic-pituitary-adrenocortical (HPA) axis, which culminates in corticosteroid secretion [50, 51]. In agreement with this localization, OCT2 was found to profoundly modulate the hormonal response to acute stress. In particular, OCT2 knockout mice showed important increases in circulating corticosterone concentrations following acute stress, as well as modifications of HPA axis function at basal state [26].

Interactions between genetic and environmental factors like exposure to stress play an important role in the pathogenesis of mood-related psychiatric disorders, including major depressive disorder and post-traumatic stress disorder [52, 53]. In rodents, chronic stress paradigms such as unpredictable chronic mild stress (UCMS) can mimic these noxious effects, inducing progressive neurobiological and behavioral anomalies resembling symptoms of human depression [54, 55]. It was thus hypothesized that their increased hormonal response to acute stress could confer to OCT2 knockout mice vulnerability to repeated stressful conditions. Indeed, during UCMS, the OCT2 mutants developed more intensely than wild-type mice several depression-related phenotypes involving self-care, social interaction, spatial memory and stress-sensitive spontaneous behavior [26]. Along with these behavioral anomalies, the mutants also showed significant variations of brain glycogen synthase kinase-3β (GSK3β) signaling, an intracellular pathway highly sensitive to stress [26, 55]. Interestingly, GSK3β signaling anomalies have also been associated

with major depression [56] and depressive-like behavior in rodents [57]. Taken together these data indicate that in rodents OCT2 can directly modulate the molecular and hormonal events occurring during acute stress and attenuate the harmful consequences of chronic stress. These biological processes may not be without consequences for human disorders. A prediction, which remains to be tested, is that pharmacological or genetic inhibition of OCT2 could enhance vulnerability to repeated adverse events, leading to stress-related disorders. This could occur for instance during prolonged treatment with antivirals, cytostatics and antidiabetics inhibiting OCTs [58, 59], or in individuals with genetic polymorphisms in the OCT2 gene affecting transport activity.

While the above-mentioned experiments illustrate that the OCTs exert a control over corticosterone release in the blood stream, other studies also suggest that the reverse may also hold true and that this hormone could reciprocally impair OCT-mediated clearance in vivo. In support of this possibility, the influx of histamine in dorsomedial hypothalamus nucleus minces was shown to be inhibited by corticosterone [29]. Since to date no high-affinity transporter for histamine has been identified and this amine is selectively transported by OCT2 and OCT3, the authors of the study suggested that during acute stress direct inhibition of OCTs by corticosterone could increase extracellular monoamine levels in this brain area [29]. A similar mechanism was proposed by Baganz and collaborators, who demonstrated by cyclic voltametry the existence of a corticosterone-sensitive 5-HT clearance component in hippocampus of SERT knockout mice [28]. Repeated swim stress was also found to attenuate 5-HT clearance in the same brain region in normal but not adrenalectomized mice, demonstrating that endogenous corticosterone release was implicated [60]. Moreover, supporting the implication of OCTs, repeated swim stress was found to decrease histamine clearance in hippocampus [60]. Blockade of the OCTs, rather than regulation of expression of this specific transporter, was proposed to be the underlying cause of this decrease in histamine transport, since it was associated with only a slight decrease in protein OCT3.

The involvement of OCT2 was not investigated in the latter study, yet recent observations suggest that monoamine uptake mediated by this transporter as well could be affected by corticosterone in physiological conditions [26]. In vivo microiontophoretic electrophysiology was used to assess the consequences on hippocampal monoamine clearance of the systemic administration of corticosterone. In this experimental set-up, subchronic corticosterone administration had an inhibitory effect on 5-HT and NE clearance in presence of venlafaxine, a dual SERT and NET inhibitor, in the hippocampus of wild-type mice but not OCT2 knockout mice. Altogether, these studies suggest that endogenous corticosterone in physiological conditions may modulate the activity of OCT2, OCT3 or both in certain brain areas. Such a mechanism could contribute to the biological processes underlying the response to stress, by directly impacting on aminergic signaling. In the case of OCT2, modulation of its activity by corticosterone would also provide a novel feed-forward mechanism by which this hormone could enhance its own release in the blood stream. However, direct interaction between OCT and corticosteroids in vivo still remains to be demonstrated. Indeed, corticosterone induces a number

of alterations in the brain [61] which could influence by diverse other mechanisms the expression or the activity of low or high-affinity transporters at the plasma membrane and account for the observations reported above.

Antidepressant Response and Efficacy

A number of antidepressants traditionally used to treat depression modulate 5-HT and NE neurotransmission, especially the activity of the high-affinity reuptake transporters. This has provided the underlying rationale for the long-lived "monoamine" hypothesis, which stipulates that toning-down of 5-HT and NE signaling occurs during depression, which may be restored by long-term antidepressant treatment [62]. Mainstream antidepressants do not however provide positive treatment outcomes for all patients. In this context, low-affinity monoamine transporters of the brain such as the OCTs represent promising novel pathways to develop alternate therapeutic approaches.

Some of the biological processes that underlie the effects of antidepressants can be investigated in detail using animal models. Behavioral despair paradigms like the tail suspension (TST) and the forced-swim (FST) tests have been used during decades to measure what is commonly called "depressive-like" behavior. These tests evaluating immobility during exposure to inescapable stress show high predictive value for evaluating antidepressants efficacy. However, they do not reflect symptoms of depression per se but the state of resignation of the animals [63]. The OCT inhibitor D22 was shown to decrease immobility in the TST when applied in the hippocampus of SERT-deficient mice [28], suggesting that brain OCTs could control this behavior. Likewise, intracerebral infusion of an OCT3 antisense RNA to reduce OCT3 function was shown to decrease immobility in the same paradigm [32]. OCT2 knockout mice, on the other hand, showed a marked increase in immobility in the TST and the FST [25], suggesting an opposite role to OCT3 for this transporter. Unraveling the neurochemical mechanisms underlying these contrasting roles may however prove to be difficult, since multiple neurotransmission pathways and components in the brain can influence performance in these rudimentary paradigms [64].

Both OCT2 and OCT3 appear to modulate the acute action of 5-HT/NE reuptake antidepressants on behavioral despair. Infusion of antisense OCT3 RNA in mice brain was found to increase the anti-immobility action of imipramine in the FST [32]. This observation implicating OCT3 in acute antidepressant action contrasts with another study, which proposed this transporter was not implicated in the effects of three antidepressants, fluvoxamine, fluoxetine and desipramine in the TST [60]. In the latter study, however, OCT3 blockade was tentatively achieved by repeated swim-stress and not monitored, and only one dose of antidepressant was tested, which may explain this discrepancy. Supporting a role of OCTs in constraining the short-term antidepressant action, normetanephrine, a NE metabolite and potent inhibitor of uptake$_2$, was shown to accentuate the releasing effects of venlafaxine on extracellular NE in rat cortex, as well as on immobility in the FST [65]. A similar effect was found in mice with D22, which was shown to increase the anti-immobility action of a subactive dose of fluvoxamine in the TST [66].

OCT2 as well seems to be involved in the short-term effects of 5-HT/NE antidepressants [25]. OCT2 knockout mice showed compared to wild-type mice striking modifications in the effects in the FST of the dual 5-HT/NE reuptake inhibitor venlafaxine and of the SERT- and NET-selective reuptake inhibitors, citalopram and reboxetine. In particular, genetic deletion of OCT2 increased sensitivity to the anti-immobility action of low doses of each of these antidepressants. This genetic deletion also had complex consequences on the action of higher doses of the same antidepressants, such as increasing the anti-immobility action of reboxetine and decreasing that of citalopram [25]. These observations could be related to the way each antidepressant modulates given aminergic neurotransmission pathways and how OCT2 disruption interferes with these pathways in different brain regions. Additional investigations will be needed to clarify these fine mechanisms.

As mentioned earlier, the tests evaluating resignation used in the above-mentioned studies fall far from reproducing the symptoms of depressive disorders. Furthermore, immobility in the FST or TST in rodents is influenced by the pharmacological blockade or genetic invalidation of numerous components controlling central neurotransmission [64]. Therefore, despite their complexity, well-validated long-term models of depression such as UCMS represent invaluable tools to investigate the complex neurobiological anomalies underlying this disorder. Another relevant paradigm, chronic corticosterone exposure, was used to gain insight into the role of OCT2 in antidepressant response. As for UCMS, rodents exposed to chronic corticosterone develop anhedonia, increased anxiety and social aversion [25, 67]. As human depression, these stable alterations induced by corticosterone may be reversed by long-term but not acute antidepressant treatment. In these experiments, chronic corticosterone administration induced depression-like anomalies in both wild-type and OCT2 knockout mice [25]. As expected, the administration of the dual antidepressant venlafaxine in a second phase reversed the anomalies induced by chronic corticosterone in wild-type mice. In contrast, the anomalies developed in OCT2 knockout mice remained insensitive to venlafaxine treatment, demonstrating that this transporter was essential for long-term antidepressant efficacy [25].

This long-term effect contrasts strikingly with the role of OCT2 in the FST. The explanation for this apparent contradiction may reside in the fact that the beneficial effects of antidepressants, which appear only after several weeks of treatment, involve different mechanisms than their short-term action. Specific neurotrophic and neurochemical processes occur during long-term treatments with NE and 5-HT/NE antidepressant [67, 68], for instance the desensitization of 5-HT1A autoreceptors [69] and the decrease in the firing of NE neurons in the locus coeruleus [70, 71]. In addition, OCT2 knockout mice show constitutive alterations in the expression of 5-HT1A receptors and of the SERT, which may also participate in long-term resistance to venlafaxine [25]. In the future, a better understanding of the neurochemical mechanisms underlying the role of OCT2 in antidepressant action may be gained by the investigation of the firing properties of raphe (5-HT) and locus coeruleus (NE) neurons and the activation state of monoamine receptors in these pathways. In any event, these findings emphasize the importance of OCT2 in the long-term antidepressant action. Since OCT2 appears to have a similar distribution in human and in rodent brain [4], it may be speculated that variations in the activity

of this transporter in humans might contribute to antidepressant resistance and, importantly, that antidepressant efficacy should be amenable to modulation by manipulation of this activity.

Addiction

DA is one of the central players in the effects of drugs of abuse. All psychoactive drugs increase DA release in the striatum and nucleus accumbens, an action mediating in part their locomotor and addictive properties [72]. In agreement with its involvement in DA signaling in the nigrostriatal and mesolimbic pathways, OCT3 has been implicated in the locomotor response to psychostimulants and in addictive behavior. In a study by Kitaichi and co-workers, intracerebral infusion of OCT3 antisense RNA in mice was found to increase the locomotor response to methamphetamine [32]. This attenuating action of OCT3 on drug-induced locomotion was confirmed in another study using OCT3-deficient mice, which showed enhanced response of the psychostimulants amphetamine and cocaine at high doses, supporting a role for this transporter when the high-affinity transporters are inhibited [24].

OCTs were also recently shown to be involved in the effects of stress on addictive behaviors. Chronic stress is a well-known risk factor for the development of addiction. In particular, craving in presence of drug-associated stimuli is perceived as increased by drug addicts during periods of stress [73], an effect that can be reproduced in rodents. In an exciting study, Graf and colleagues demonstrated that footshock stress could enhance cocaine-induced reinstatement of drug seeking behavior in rats [74]. This enhancing action of stress on reinstatement of drug seeking, found with a subthreshold dose of cocaine, was dependent upon corticosterone secretion, as shown by adrenalectomy, and mimicked by intra-accumbens infusion of either corticosterone or the uptake$_2$ blocker normetanephrine. A set of complementary experiments indicates that these effects of stress involve blockade of DA clearance in the nucleus accumbens. These findings identify a novel mechanism by which corticosterone enhances the effects of cocaine on DA transmission by decreasing OCT-mediated clearance in the nucleus accumbens. Consistent with the implication of this mechanism in drug relapse in humans, a previous study reported a correlation between single nucleotide polymorphisms in the OCT3 gene and the development of polysubstance use in patients with methamphetamine dependence [75].

Drug Action at Brain OCTs

A large proportion of therapeutic drugs is composed of organic cations, a number of which can interact with OCTs, at least in heterologous expression systems [2]. Molecules acting on central nervous system with the potential to inhibit OCTs include antidepressants [8, 21, 76–79], psychostimulants like cocaine, amphetamine

and 3,4-methylenedioxy-methamphetamine (MDMA) [8, 80] and NMDA receptor antagonists, like phencyclidine, MK-801, ketamine, memantine and amantadine [4, 80, 81]. Several classes of adrenergic ligands also functionally interact with both OCTs and α-adrenoceptors, two families that share close anatomical and functional relationships. The potent cyanine-related OCT inhibitors behave as α-adrenoceptor antagonists and, reciprocally, a number of other α- and β-adrenoceptor agonists and antagonists inhibit diverse OCT subtypes [2, 19, 82]. This promiscuity between pharmacophores recognizing α-adrenoceptors and OCTs raises the possibility that some adrenergic ligands could act concomitantly on OCT-mediated monoamine uptake and at α-adrenoceptors in sympathetically-innervated tissues or the CNS, either in a cooperative or opposite manner. Finally, various neurotoxins such as *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine (DSP-4) [82], 1-methyl-4-phenylpyridinium (MPP^+) [33, 83] and paraquat [84] have also been shown to interact with the OCTs. For the two latter, it was shown that these interactions underlie in part their neurotoxic effects in the brain [33, 84].

Besides compounds intended to act on CNS, various drugs aimed at peripheral targets could also influence central OCT activity. In this line we can mention the antiacid cimetidine [85], the antimalarial drug quinine [86], the antiviral drugs acyclovir, lamivudine, abacavir and azidothymidine (AZT) [58, 87], antidiabetics like metformin [59], cytostatics like cisplatin [88] and the antispasmodic trospium [89]. Whether these different categories of therapeutic drugs inhibit OCTs in the brain remains uncertain, considering their low affinity and the high first-pass effect of organic cations [90]. Several lines of data support however this possibility. First, higher concentrations of some of these drugs in the brain compared to circulation could allow local interaction with the brain OCTs [77]. Second, high-affinity binding sites for some of these compounds may have gone undetected in OCTs, as documented for abacavir and AZT [87]. Third, most inhibition constants at OCTs were defined previously using artificial and not endogenous substrates, but these constants seem to vary depending on the substrate tested [91]. Finally, the affinity of these ligands for OCTs could be influenced differentially by the environment in vivo than in vitro and thus differ in vivo from those established in heterologous expression systems. The identification of interactions between the above-mentioned drugs and OCTs in vivo is an arduous task, complicated by the multiplicity of their targets and actions. If these interactions do occur in the brain, the administration of these molecules could on the long-term affect central neurotransmission, leading to unexpected and potentially undesirable secondary effects.

Conclusion and Perspectives

In recent years, a substantial body of evidence has accumulated suggesting that OCTs function as an alternate monoamine clearance system in the brain, in addition to the high-affinity monoamine transporters. These studies have disclosed that this transporter family participates in a variety of integrated central functions in rodents,

ranging from salt-intake regulatory behavior to stress response and antidepressant efficacy. It can be hypothesized that genetic and epigenetic-based variations in the activity of the brain OCTs in humans could influence individual predisposition to various disorders such as hypertension, anxiety and depression as well as the response to antidepressant therapies. Another indirect consequence of these findings might be that prolonged treatments with routinely used therapeutics could increase vulnerability to the above-mentioned disorders, through interaction with these low-affinity transporters. In the future, the design of molecules capable of modulating selectively the activity of OCTs may lead to the development of novel therapeutic strategies in several clinical fields, in particular for the treatment of mood disorders.

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References

1. Koepsell H, Schmitt BM, Gorboulev V. Organic cation transporters. Rev Physiol Biochem Pharmacol. 2003;150:36–90.
2. Koepsell H, Lips K, Volk C. Polyspecific organic cation transporters: structure, function, physiological roles, and biopharmaceutical implications. Pharm Res. 2007;24(7):1227–51.
3. Breidert T, Spitzenberger F, Grundemann D, Schomig E. Catecholamine transport by the organic cation transporter type 1 (OCT1). Br J Pharmacol. 1998;125(1):218–24.
4. Busch AE, Karbach U, Miska D, Gorboulev V, Akhoundova A, Volk C, et al. Human neurons express the polyspecific cation transporter hOCT2, which translocates monoamine neurotransmitters, amantadine, and memantine. Mol Pharmacol. 1998;54(2):342–52.
5. Grundemann D, Koster S, Kiefer N, Breidert T, Engelhardt M, Spitzenberger F, et al. Transport of monoamine transmitters by the organic cation transporter type 2, OCT2. J Biol Chem. 1998;273(47):30915–20.
6. Grundemann D, Schechinger B, Rappold GA, Schomig E. Molecular identification of the corticosterone-sensitive extraneuronal catecholamine transporter. Nat Neurosci. 1998;1(5):349–51.
7. Grundemann D, Liebich G, Kiefer N, Koster S, Schomig E. Selective substrates for non-neuronal monoamine transporters. Mol Pharmacol. 1999;56(1):1–10.
8. Wu X, Kekuda R, Huang W, Fei YJ, Leibach FH, Chen J, et al. Identity of the organic cation transporter OCT3 as the extraneuronal monoamine transporter (uptake2) and evidence for the expression of the transporter in the brain. J Biol Chem. 1998;273(49):32776–86.
9. Torres GE, Gainetdinov RR, Caron MG. Plasma membrane monoamine transporters: structure, regulation and function. Nat Rev Neurosci. 2003;4(1):13–25.
10. Zwart R, Verhaagh S, Buitelaar M, Popp-Snijders C, Barlow DP. Impaired activity of the extraneuronal monoamine transporter system known as uptake-2 in Orct3/Slc22a3-deficient mice. Mol Cell Biol. 2001;21(13):4188–96.
11. Jonker JW, Wagenaar E, Mol CA, Buitelaar M, Koepsell H, Smit JW, et al. Reduced hepatic uptake and intestinal excretion of organic cations in mice with a targeted disruption of the organic cation transporter 1 (Oct1 [Slc22a1]) gene. Mol Cell Biol. 2001;21(16):5471–7.
12. Jonker JW, Wagenaar E, Van Eijl S, Schinkel AH. Deficiency in the organic cation transporters 1 and 2 (Oct1/Oct2 [Slc22a1/Slc22a2]) in mice abolishes renal secretion of organic cations. Mol Cell Biol. 2003;23(21):7902–8.

13. Iversen LL. The uptake of catecholamines at high perfusion concentrations in the rat isolated heart: a novel catechol amine uptake process. Br J Pharmacol. 1965;25:18–33.
14. Bonisch H. Extraneuronal transport of catecholamines. Pharmacology. 1980;21(2):93–108.
15. Graefe K-H, Bonisch H. The transport of amines across the axonal membranes of noradrenergic and dopaminergic neurons. In: Trendelenburg U, Weiner N, editors. Handbook of experimental pharmacology. Berlin: Springer-Verlag; 1988.
16. Russ H, Sonna J, Keppler K, Baunach S, Schomig E. Cyanine-related compounds: a novel class of potent inhibitors of extraneuronal noradrenaline transport. Naunyn Schmiedebergs Arch Pharmacol. 1993;348(5):458–65.
17. Russ H, Staust K, Martel F, Gliese M, Schomig E. The extraneuronal transporter for monoamine transmitters exists in cells derived from human central nervous system glia. Eur J Neurosci. 1996;8(6):1256–64.
18. Grundemann D, Babin-Ebell J, Martel F, Ording N, Schmidt A, Schomig E. Primary structure and functional expression of the apical organic cation transporter from kidney epithelial LLC-PK1 cells. J Biol Chem. 1997;272(16):10408–13.
19. Hayer-Zillgen M, Bruss M, Bonisch H. Expression and pharmacological profile of the human organic cation transporters hOCT1, hOCT2 and hOCT3. Br J Pharmacol. 2002;136(6):829–36.
20. Gorboulev V, Ulzheimer JC, Akhoundova A, Ulzheimer-Teuber I, Karbach U, Quester S, et al. Cloning and characterization of two human polyspecific organic cation transporters. DNA Cell Biol. 1997;16(7):871–81.
21. Kekuda R, Prasad PD, Wu X, Wang H, Fei YJ, Leibach FH, et al. Cloning and functional characterization of a potential-sensitive, polyspecific organic cation transporter (OCT3) most abundantly expressed in placenta. J Biol Chem. 1998;273(26):15971–9.
22. Haag C, Berkels R, Grundemann D, Lazar A, Taubert D, Schomig E. The localisation of the extraneuronal monoamine transporter (EMT) in rat brain. J Neurochem. 2004;88(2):291–7.
23. Vialou V, Amphoux A, Zwart R, Giros B, Gautron S. Organic cation transporter 3 (Slc22a3) is implicated in salt-intake regulation. J Neurosci. 2004;24(11):2846–51.
24. Vialou V, Balasse L, Callebert J, Launay JM, Giros B, Gautron S. Altered aminergic neurotransmission in the brain of organic cation transporter 3-deficient mice. J Neurochem. 2008;106(3):1471–82.
25. Bacq A, Balasse L, Biala G, Guiard B, Gardier AM, Schinkel A, et al. Organic cation transporter 2 controls brain norepinephrine and serotonin clearance and antidepressant response. Mol Psychiatry. 2012;17(9):926–39.
26. Couroussé T, Bacq A, Belzung C, Guiard B, Balasse L, Louis F, et al. Brain organic cation transporter 2 controls response and vulnerability to stress and GSK3β signaling. Mol Psychiatry. 2015;20(7):889–900.
27. Daws LC, Montanez S, Owens WA, Gould GG, Frazer A, Toney GM, et al. Transport mechanisms governing serotonin clearance in vivo revealed by high-speed chronoamperometry. J Neurosci Methods. 2005;143(1):49–62.
28. Baganz NL, Horton RE, Calderon AS, Owens WA, Munn JL, Watts LT, et al. Organic cation transporter 3: keeping the brake on extracellular serotonin in serotonin-transporter-deficient mice. Proc Natl Acad Sci U S A. 2008;105(48):18976–81.
29. Gasser PJ, Lowry CA, Orchinik M. 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. 2006;26(34):8758–66.
30. Feng N, Lowry CA, Lukkes JL, Orchinik M, Forster GL, Renner KJ. Organic cation transporter inhibition increases medial hypothalamic serotonin under basal conditions and during mild restraint. Brain Res. 2010;1326:105–13.
31. Nakayama H, Kitaichi K, Ito Y, Hashimoto K, Takagi K, Yokoi T, et al. The role of organic cation transporter-3 in methamphetamine disposition and its behavioral response in rats. Brain Res. 2007;1184:260–9.
32. Kitaichi K, Fukuda M, Nakayama H, Aoyama N, Ito Y, Fujimoto Y, et al. Behavioral changes following antisense oligonucleotide-induced reduction of organic cation transporter-3 in mice. Neurosci Lett. 2005;382(1–2):195–200.

33. Cui M, Aras R, Christian WV, Rappold PM, Hatwar M, Panza J, et al. The organic cation transporter-3 is a pivotal modulator of neurodegeneration in the nigrostriatal dopaminergic pathway. Proc Natl Acad Sci U S A. 2009;106(19):8043–8.
34. Bunin MA, Wightman RM. Quantitative evaluation of 5-hydroxytryptamine (serotonin) neuronal release and uptake: an investigation of extrasynaptic transmission. J Neurosci. 1998;18(13):4854–60.
35. Mundorf ML, Joseph JD, Austin CM, Caron MG, Wightman RM. Catecholamine release and uptake in the mouse prefrontal cortex. J Neurochem. 2001;79(1):130–42.
36. Mitchell K, Oke AF, Adams RN. In vivo dynamics of norepinephrine release-reuptake in multiple terminal field regions of rat brain. J Neurochem. 1994;63(3):917–26.
37. Jones SR, Gainetdinov RR, Jaber M, Giros B, Wightman RM, Caron MG. Profound neuronal plasticity in response to inactivation of the dopamine transporter. Proc Natl Acad Sci U S A. 1998;95(7):4029–34.
38. Bengel D, Murphy DL, Andrews AM, Wichems CH, Feltner D, Heils A, et al. Altered brain serotonin homeostasis and locomotor insensitivity to 3, 4-methylenedioxymethamphetamine ("Ecstasy") in serotonin transporter-deficient mice. Mol Pharmacol. 1998;53(4):649–55.
39. Xu F, Gainetdinov RR, Wetsel WC, Jones SR, Bohn LM, Miller GW, et al. Mice lacking the norepinephrine transporter are supersensitive to psychostimulants. Nat Neurosci. 2000;3(5):465–71.
40. Gasser PJ, Orchinik M, Raju I, Lowry CA. Distribution of organic cation transporter 3, a corticosterone-sensitive monoamine transporter, in the rat brain. J Comp Neurol. 2009;512(4):529–55.
41. Osborn JW, Hendel MD, Collister JP, Ariza-Guzman PA, Fink GD. The role of the subfornical organ in angiotensin II-salt hypertension in the rat. Exp Physiol. 2012;97(1):80–8.
42. Zhang B, Li M, Wang L, Li C, Lou Y, Liu J, et al. The association between the polymorphisms in a sodium channel gene SCN7A and essential hypertension: a case-control study in the northern Han Chinese. Ann Hum Genet. 2015;79(1):28–36.
43. Wultsch T, Grimberg G, Schmitt A, Painsipp E, Wetzstein H, Breitenkamp AF, et al. Decreased anxiety in mice lacking the organic cation transporter 3. J Neural Transm. 2009;116(6):689–97.
44. Millan MJ. The neurobiology and control of anxious states. Prog Neurobiol. 2003;70(2):83–244.
45. Murphy DL, Moya PR, Fox MA, Rubenstein LM, Wendland JR, Timpano KR. Anxiety and affective disorder comorbidity related to serotonin and other neurotransmitter systems: obsessive-compulsive disorder as an example of overlapping clinical and genetic heterogeneity. Philos Trans R Soc Lond B Biol Sci. 2013;368(1615):20120435.
46. Lazar A, Walitza S, Jetter A, Gerlach M, Warnke A, Herpertz-Dahlmann B, et al. Novel mutations of the extraneuronal monoamine transporter gene in children and adolescents with obsessive-compulsive disorder. Int J Neuropsychopharmacol. 2008;11(1):35–48.
47. Fontenelle LF, Mendlowicz MV, Versiani M. The descriptive epidemiology of obsessive-compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30(3):327–37.
48. Zhang L, Schaner ME, Giacomini KM. Functional characterization of an organic cation transporter (hOCT1) in a transiently transfected human cell line (HeLa). J Pharmacol Exp Ther. 1998;286(1):354–61.
49. Gorboulev V, Shatskaya N, Volk C, Koepsell H. Subtype-specific affinity for corticosterone of rat organic cation transporters rOCT1 and rOCT2 depends on three amino acids within the substrate binding region. Mol Pharmacol. 2005;67(5):1612–9.
50. Herman JP, Figueiredo H, Mueller NK, Ulrich-Lai Y, Ostrander MM, Choi DC, et al. Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. Front Neuroendocrinol. 2003;24(3):151–80.
51. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci. 2009;10(6):397–409.
52. Mazure CM, Bruce ML, Maciejewski PK, Jacobs SC. Adverse life events and cognitive-personality characteristics in the prediction of major depression and antidepressant response. Am J Psychiatry. 2000;157(6):896–903.

53. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci. 2009;10(6):434–45.
54. Surget A, Saxe M, Leman S, Ibarguen-Vargas Y, Chalon S, Griebel G, et al. Drug-dependent requirement of hippocampal neurogenesis in a model of depression and of antidepressant reversal. Biol Psychiatry. 2008;64(4):293–301.
55. Gourley SL, Wu FJ, Kiraly DD, Ploski JE, Kedves AT, Duman RS, et al. Regionally specific regulation of ERK MAP kinase in a model of antidepressant-sensitive chronic depression. Biol Psychiatry. 2008;63(4):353–9.
56. Karege F, Perroud N, Burkhardt S, Schwald M, Ballmann E, La Harpe R, et al. Alteration in kinase activity but not in protein levels of protein kinase B and glycogen synthase kinase-3beta in ventral prefrontal cortex of depressed suicide victims. Biol Psychiatry. 2007;61(2):240–5.
57. Polter A, Beurel E, Yang S, Garner R, Song L, Miller CA, et al. Deficiency in the inhibitory serine-phosphorylation of glycogen synthase kinase-3 increases sensitivity to mood disturbances. Neuropsychopharmacology. 2010;35(8):1761–74.
58. Takeda M, Khamdang S, Narikawa S, Kimura H, Kobayashi Y, Yamamoto T, et al. Human organic anion transporters and human organic cation transporters mediate renal antiviral transport. J Pharmacol Exp Ther. 2002;300(3):918–24.
59. Kimura N, Masuda S, Tanihara Y, Ueo H, Okuda M, Katsura T, et al. Metformin is a superior substrate for renal organic cation transporter OCT2 rather than hepatic OCT1. Drug Metab Pharmacokinet. 2005;20(5):379–86.
60. Baganz N, Horton R, Martin K, Holmes A, Daws LC. Repeated swim impairs serotonin clearance via a corticosterone-sensitive mechanism: organic cation transporter 3, the smoking gun. J Neurosci. 2010;30(45):15185–95.
61. de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci. 2005;6(6):463–75.
62. Charney DS. Monoamine dysfunction and the pathophysiology and treatment of depression. J Clin Psychiatry. 1998;59 Suppl 14:11–4.
63. Porsolt RD, Brossard G, Hautbois C, Roux S. Rodent models of depression: forced swimming and tail suspension behavioral despair tests in rats and mice. Curr Protoc Neurosci. 2001;Chapter 8:Unit 8.10A.
64. Cryan JF, Mombereau C, Vassout A. The tail suspension test as a model for assessing antidepressant activity: review of pharmacological and genetic studies in mice. Neurosci Biobehav Rev. 2005;29(4–5):571–625.
65. Rahman Z, Ring RH, Young K, Platt B, Lin Q, Schechter LE, et al. Inhibition of uptake 2 (or extraneuronal monoamine transporter) by normetanephrine potentiates the neurochemical effects of venlafaxine. Brain Res. 2008;1203:68–78.
66. Horton RE, Apple DM, Owens WA, Baganz NL, Cano S, Mitchell NC, et al. Decynium-22 enhances SSRI-induced antidepressant-like effects in mice: uncovering novel targets to treat depression. J Neurosci. 2013;33(25):10534–43.
67. David DJ, Samuels BA, Rainer Q, Wang JW, Marsteller D, Mendez I, et al. Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression. Neuron. 2009;62(4):479–93.
68. Surget A, Tanti A, Leonardo ED, Laugeray A, Rainer Q, Touma C, et al. Antidepressants recruit new neurons to improve stress response regulation. Mol Psychiatry. 2011;16(12):1177–88.
69. Beique J, de Montigny C, Blier P, Debonnel G. Effects of sustained administration of the serotonin and norepinephrine reuptake inhibitor venlafaxine: I. in vivo electrophysiological studies in the rat. Neuropharmacology. 2000;39(10):1800–12.
70. Yanpallewar SU, Fernandes K, Marathe SV, Vadodaria KC, Jhaveri D, Rommelfanger K, et al. Alpha2-adrenoceptor blockade accelerates the neurogenic, neurotrophic, and behavioral effects of chronic antidepressant treatment. J Neurosci. 2010;30(3):1096–109.
71. Szabo ST, Blier P. Effects of the selective norepinephrine reuptake inhibitor reboxetine on norepinephrine and serotonin transmission in the rat hippocampus. Neuropsychopharmacology. 2001;25(6):845–57.
72. Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. Annu Rev Neurosci. 2006;29:565–98.

73. Preston KL, Epstein DH. Stress in the daily lives of cocaine and heroin users: relationship to mood, craving, relapse triggers, and cocaine use. Psychopharmacology (Berl). 2011;218(1): 29–37.
74. Graf EN, Wheeler RA, Baker DA, Ebben AL, Hill JE, McReynolds JR, et al. Corticosterone acts in the nucleus accumbens to enhance dopamine signaling and potentiate reinstatement of cocaine seeking. J Neurosci. 2013;33(29):11800–10.
75. Aoyama N, Takahashi N, Kitaichi K, Ishihara R, Saito S, Maeno N, et al. Association between gene polymorphisms of SLC22A3 and methamphetamine use disorder. Alcohol Clin Exp Res. 2006;30(10):1644–9.
76. Grundemann D, Gorboulev V, Gambaryan S, Veyhl M, Koepsell H. Drug excretion mediated by a new prototype of polyspecific transporter. Nature. 1994;372(6506):549–52.
77. Haenisch B, Drescher E, Thiemer L, Xin H, Giros B, Gautron S, et al. Interaction of antidepressant and antipsychotic drugs with the human organic cation transporters hOCT1, hOCT2 and hOCT3. Naunyn Schmiedebergs Arch Pharmacol. 2012;385(10):1017–23.
78. Wu X, Huang W, Ganapathy ME, Wang H, Kekuda R, Conway SJ, et al. Structure, function, and regional distribution of the organic cation transporter OCT3 in the kidney. Am J Physiol Renal Physiol. 2000;279(3):F449–58.
79. Urakami Y, Akazawa M, Saito H, Okuda M, Inui K. cDNA cloning, functional characterization, and tissue distribution of an alternatively spliced variant of organic cation transporter hOCT2 predominantly expressed in the human kidney. J Am Soc Nephrol. 2002;13(7):1703–10.
80. Amphoux A, Vialou V, Drescher E, Bruss M, La Cour CM, Rochat C, et al. Differential pharmacological in vitro properties of organic cation transporters and regional distribution in rat brain. Neuropharmacology. 2006;50(8):941–52.
81. Goralski KB, Lou G, Prowse MT, Gorboulev V, Volk C, Koepsell H, et al. The cation transporters rOCT1 and rOCT2 interact with bicarbonate but play only a minor role for amantadine uptake into rat renal proximal tubules. J Pharmacol Exp Ther. 2002;303(3):959–68.
82. Amphoux A, Millan MJ, Cordi A, Bonisch H, Vialou V, Mannoury la Cour C, et al. Inhibitory and facilitory actions of isocyanine derivatives at human and rat organic cation transporters 1, 2 and 3: a comparison to human alpha 1- and alpha 2-adrenoceptor subtypes. Eur J Pharmacol. 2010;634(1–3):1–9.
83. Shang T, Uihlein AV, Van Asten J, Kalyanaraman B, Hillard CJ. 1-Methyl-4-phenylpyridinium accumulates in cerebellar granule neurons via organic cation transporter 3. J Neurochem. 2003;85(2):358–67.
84. Rappold PM, Cui M, Chesser AS, Tibbett J, Grima JC, Duan L, et al. Paraquat neurotoxicity is mediated by the dopamine transporter and organic cation transporter-3. Proc Natl Acad Sci U S A. 2011;108(51):20766–71.
85. Okuda M, Saito H, Urakami Y, Takano M, Inui K. cDNA cloning and functional expression of a novel rat kidney organic cation transporter, OCT2. Biochem Biophys Res Commun. 1996;224(2):500–7.
86. Budiman T, Bamberg E, Koepsell H, Nagel G. Mechanism of electrogenic cation transport by the cloned organic cation transporter 2 from rat. J Biol Chem. 2000;275(38):29413–20.
87. Minuesa G, Volk C, Molina-Arcas M, Gorboulev V, Erkizia I, Arndt P, et al. Transport of lamivudine [(-)-beta-L-2′,3′-dideoxy-3′-thiacytidine] and high-affinity interaction of nucleoside reverse transcriptase inhibitors with human organic cation transporters 1, 2, and 3. J Pharmacol Exp Ther. 2009;329(1):252–61.
88. Ciarimboli G, Ludwig T, Lang D, Pavenstadt H, Koepsell H, Piechota HJ, et al. Cisplatin nephrotoxicity is critically mediated via the human organic cation transporter 2. Am J Pathol. 2005;167(6):1477–84.
89. Wenge B, Geyer J, Bonisch H. Oxybutynin and trospium are substrates of the human organic cation transporters. Naunyn Schmiedebergs Arch Pharmacol. 2011;383(2):203–8.
90. Shugarts S, Benet LZ. The role of transporters in the pharmacokinetics of orally administered drugs. Pharm Res. 2009;26(9):2039–54.
91. Thevenod F, Ciarimboli G, Leistner M, Wolff NA, Lee WK, Schatz I, et al. Substrate- and cell contact-dependent inhibitor affinity of human organic cation transporter 2: studies with two classical organic cation substrates and the novel substrate cd2+. Mol Pharm. 2013;10(8):3045–56.