General Overview of Organic Cation Transporters in Brain

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Abstract

Inhibitors of Na^+/Cl^- dependent high affinity transporters for norepinephrine (NE), serotonin (5-HT), and/or dopamine (DA) represent frequently used drugs for treatment of psychological disorders such as depression, anxiety, obsessive-compulsive disorder, attention deficit hyperactivity disorder, and addiction. These transporters remove NE, 5-HT, and/or DA after neuronal excitation from the interstitial space close to the synapses. Thereby they terminate transmission and modulate neuronal behavioral circuits. Therapeutic failure and undesired central nervous system side effects of these drugs have been partially assigned to neurotransmitter removal by low affinity transport. Cloning and functional characterization of the polyspecific organic cation transporters OCT1 (*SLC22A1*), OCT2 (*SLC22A2*), OCT3 (*SLC22A3*) and the plasma membrane monoamine transporter PMAT (*SLC29A4*) revealed that every single transporter mediates low affinity uptake of NE, 5-HT, and DA. Whereas the organic transporters are all located in the blood brain barrier, OCT2, OCT3, and PMAT are expressed in neurons or in neurons and astrocytes within brain areas that are involved in behavioral regulation. Areas of expression include the dorsal raphe, medullary motoric nuclei, hypothalamic nuclei, and/or the nucleus accumbens. Current knowledge of the transport of monoamine neurotransmitters by the organic cation transporters, their interactions with psychotropic drugs, and their locations in the brain is reported in detail. In addition, animal experiments including behavior tests in wildtype and knockout animals are reported in which the impact of OCT2, OCT3, and/or PMAT on regulation of salt intake, depression, mood control, locomotion, and/or stress effect on addiction is suggested.

Keywords

Antidepressants · Monoamine neurotransmitters · Neurotransmitter reuptake inhibitors · OCT1 · OCT2 · OCT3 · Organic cation transporters · PMAT · Psychotropic drugs

Abbreviations

5-HT	5-Hydroxytryptamine (serotonin)
ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorders
BBB	Blood–brain barrier
BLA	Basolateral amygdala complex

CP	Choroid plexus
CSF	Cerebrospinal fluid
CSFBB	CSF–blood barrier
DA	Dopamine
DAT	Dopamine transporter
DMH	Dorsomedial hypothalamus
FST	Forced swim test
GABA	γ-Aminobutyric acid
HPA	Hypothalamic-pituitary-adrenal
KO	Knockout
METH	Methamphetamine
MPP	1-Methyl-4-phenylpyridinium
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NAC	Nucleus accumbens
NE	Norepinephrine
NET	Norepinephrine transporter
NTS	Nucleus tractus solitarii
OCD	Obsessive-compulsive disorder
OCT	Organic cation transporter
PD	Parkinson's disease
PMAT	Plasma membrane monoamine transporter
RTI-55	3β-(4-iodophenyl)-tropane-2-carboxylic acid
SERT	Serotonin transporter
SN	Substantia nigra
SSRI	Selective serotonin reuptake inhibitor
TEA	Tetraethylammonium
UCMS	Unpredictable chronic mild stress
VMH	Ventromedial hypothalamic nucleus
WT	Wildtype

1 Introduction

Neuronal networks in the brain control complex cerebral functions such as learning, reasoning, mood control, motivation, and motoric coordination. These networks consist of neurons that release specific neurotransmitters upon activation at their synapses that are detected by receptors in postsynaptic membranes. The secreted neurotransmitters are taken up by cognate transporters located extrasynaptically in neuronal terminals where they are packed into intracellular vesicles for future neuronal release. This synaptic, "wiring-type" activation is accompanied by activation of receptors on more distant neurons occurring via neurotransmitters that diffuse out of the synaptic cleft. This activation of remote receptors by "volume transmission" imposes a much higher degree of complexity and regulatory options. In addition to other mechanisms including cerebral effects of hormones, volume transmission activation of neighboring neurons contributes to overarching psycho-

emotional or psycho-behavioral effects, such as increased severity of depression or increased remission in addicts during prolonged stress. Volume transmission mediated activation is shaped by neurotransmitter uptake via local specific and nonspecific neurotransmitter uptake systems.

This present article is an introductory overview of biomedical functions of polyspecific low affinity uptake systems supplementing neurotransmitter reuptake by specific monoamine neurotransmitter transporters. The properties and biomedical impact of high affinity Na^+/Cl^- dependent transporters for noradrenaline/norepinephrine (NE), dopamine (DA), and serotonin (5-HT) are shortly recalled. Thereafter, functional properties, sites of expression, and selectivity of neurotransmitters and psychotropic drugs of the low affinity organic cation transporters OCT1-3 and PMAT that are expressed in brain are compiled. *In vivo* experiments in rodents are listed that shed light on the impact of these transporters during psychiatric disorders. Discussing these data, the limitations of the employed methodological tools are outlined. This overview intends to serve as an introductory guide for the more specialized presentations in this volume. In this overview, detailed data concerning sites of cerebral expression, neurotransmitter substrates, interacting psychotropic drugs, and partially selective inhibitors of organic cation transporters are compiled. It is apparent that the current data are rather fragmentary and that more investigations are warranted to obtain a better understanding of the roles of organic cation transporters in the brain during health and psychiatric disorders.

2 High Affinity Na^+/Cl^- Dependent Monoamine Neurotransmitter Transporters

2.1 Locations in the Brain and Transport Properties

The high affinity monoamine neurotransmitter transporters NET (*SLC6A2*), DAT (*SLC6A3*), and SERT (*SLC6A4*) are expressed in noradrenergic, dopaminergic, and serotoninergic neurons, respectively (Kristensen et al. 2011; Torres et al. 2003). They are essential for synaptic neurotransmission and influence neuronal crosstalk. NET, DAT, and SERT are localized to cell bodies, dendrites, and neurites of their cognate neurons in many brain areas (Table 1). Noradrenergic, dopaminergic, and serotoninergic neurons may lie close together and may be functionally connected (Hoffman et al. 1998; Liprando et al. 2004). In the neurites, the monoamine neurotransmitter transporters are mainly localized in presynaptic plasma membranes close to synapses (Hoffman et al. 1998; Nirenberg et al. 1997a; Pickel and Chan 1999; Tao-Cheng and Zhou 1999; Zhou et al. 1998) (Fig. 1). NET, DAT, and SERT are Na^+/Cl^- cotransporters of NE, DA, and 5-HT that show some overlapping neurotransmitter selectivity (Table 2). For example, NE and DA are transported by human NET (hNET) and human DAT (hDAT) (Carboni et al. 1990; Giros et al. 1994; Moron et al. 2002). The monoamine neurotransmitter transporters exhibit transmitter/Na^+/Cl^- stoichiometries of 1:1:1 (NET), 1:2:1 (DAT), and 1:1:1 (SERT) (Kristensen et al. 2011; Torres et al. 2003). In SERT cotransport of 5-HT with Na^+

Table 1 Brain areas where monoamine neurotransmitter transporters and organic cation transporters have been detected in rats and/or mice

Transporter	Cellular location	Location in the brain
Net (*Slc6a2*)	Noradrenergic neurons	Nuclei of medulla oblongata, raphe nuclei, striatum, locus coeruleus, thalamus, hypothalamus, hippocampus, amygdala, cerebral cortex
Dat (*Slc6a3*)	Dopaminergic neurons	Ventral tegmental area, basal midbrain ganglia, striatum, SN, pallidum, claustrum, medial forebrain bundle, nigrostriatal bundle, lateral habenula, zona incerta, hypothalamic dorsomedial arcuate nucleus, median eminence, amygdala, NAC, olfactory bulb, olfactory tubercle, cingulate cortex, prefrontal cortex
Sert (*Slc6a4*)	Endothelial cells of BBB, serotonergic neurons	BBB, nuclei of medulla oblongata, raphe nuclei, locus coeruleus, tegmental nuclei, cochlear and olivary nuclei, cerebellum, SN, nucleus ruber, pallidum, caudate nucleus, putamen, hypothalamus (dorsomedial nucleus, septal nuclei), olfactory bulb, olfactory nuclei, forebrain cortex, hippocampus, NAC, amygdala
Oct1 (*Slc22a1*)	Endothelial cells of BBB	BBB, CP, hippocampus
Oct2 (*Slc22a2*)	Endothelial cells of BBB, neurons, epithelial cells of CP, ependymal cells	BBB, CP, raphe nuclei, locus coeruleus, cerebellum, thalamus, hypothalamus, median eminence, cerebral cortex, hippocampus, amygdala
Oct3 (*Slc22a3*)	Endothelial cells of BBB, neurons, astrocytes, non-astrocyte glial cells, ependymal cells	BBB, CP, nuclei of medulla oblongata, pontine nuclei, NTS, raphe nuclei, locus coeruleus, tegmentum, cerebellum, striatum, SN, circumventricular organs including the area postrema, subfornical organ, subcommissural organ, pineal gland, thalamus, hypothalamus, lateral septum, olfactory bulb, cerebral cortex, hippocampus, subiculum, NAC, amygdala
Pmat (Slc29a4)	Endothelial cells of BBB, pericytes, astrocytes, neurons	BBB, nuclei of medulla oblongata and mesencephalon, nuclei of rhombencephalon, inferior olivary complex, raphe nuclei, pontine nuclei, cerebellum, striatum, pallidum, SN, nucleus ruber, putamen, septum, thalamus, hypothalamus, olfactory bulb,

(continued)

Table 1 (continued)

Transporter	Cellular location	Location in the brain
		olfactory tubercle, cerebral cortex, hippocampus, amygdala

Net: (Lorang et al. 1994; Pacholczyk et al. 1991; Schroeter et al. 2000; Torres et al. 2003), **Dat**: (Cerruti et al. 1993; Ciliax et al. 1995; Freed et al. 1995; Hersch et al. 1997; Hoffman et al. 1998; Holleran et al. 2020; Lorang et al. 1994; Nirenberg et al. 1996, 1997a, b; Revay et al. 1996; Torres et al. 2003), **Sert**: (Bengel et al. 1998; Brust et al. 2000; Hoffman et al. 1998; Pickel and Chan 1999; Qian et al. 1995; Sur et al. 1996; Tao-Cheng and Zhou 1999; Zhou et al. 1998) (Bengel et al. 1998; Brust et al. 2000; Cerruti et al. 1993; Chang et al. 1996; Hoffman et al. 1998; Pickel and Chan 1999; Qian et al. 1995; Sur et al. 1996; Tao-Cheng and Zhou 1999; Torres et al. 2003; Zhou et al. 1998), **Oct1**: (Baganz et al. 2008; Choudhuri et al. 2003; Duan and Wang 2013; Lin et al. 2010; Sekhar et al. 2019; Wu et al. 2015b),**Oct2**: (Amphoux et al. 2006; Bacq et al. 2012; Choudhuri et al. 2003; Courousse et al. 2014; Lin et al. 2010; Sweet et al. 2001; Wu et al. 2015b)**, Oct3**: (Amphoux et al. 2006; Baganz et al. 2008; Chaves et al. 2020; Cui et al. 2009; Gasser et al. 2006, 2009, 2017; Graf et al. 2013; Haag et al. 2004; Hill and Gasser 2013; Holleran et al. 2020; Mayer et al. 2018; Miura et al. 2017; Nakayama et al. 2007; Schmitt et al. 2003; Sweet et al. 2001; Vialou et al. 2004, 2008; Wu et al. 1998a; Wyler et al. 2015) **Pmat**: (Dahlin et al. 2007, 2009; Sekhar et al. 2019; Vialou et al. 2007; Wu et al. 2015a)

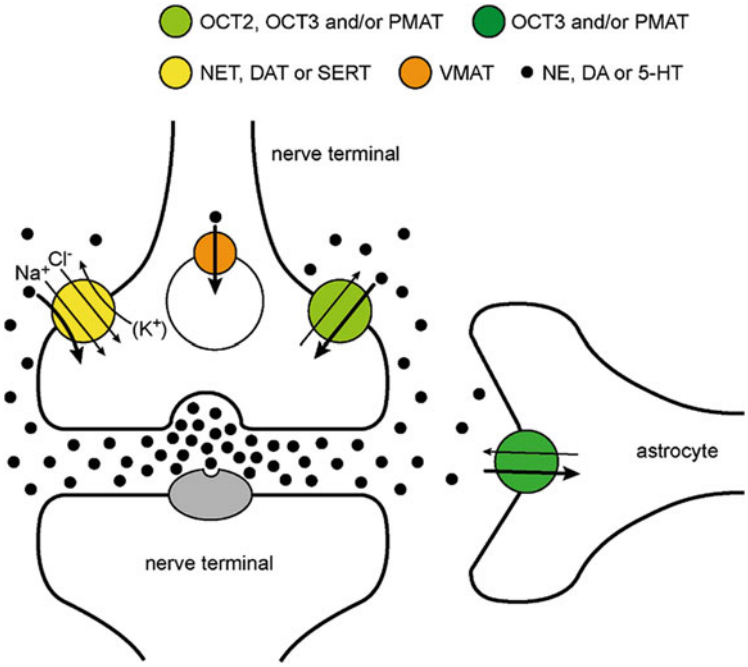

Fig. 1 Schematic depiction of locations of monoamine neurotransmitter transporters in cerebral neurons and glial cells. The indicated high affinity transporters NET, DAT, and SERT are expressed in their different cognate neurons. OCT2, OCT3, and PMAT or OCT3 and PMAT may be expressed in identical or different neurons and astrocytes. The indicated neurotransmitter concentrations simulate a post-excitatory situation

Table 2 K_m values of cationic neurotransmitters transported by high affinity neurotransmitter transporters and organic cation transporters from humans and rodents

Compound		K_m [μM] NET/Net	DAT/Dat	SERT/Sert	OCT1/Oct1	OCT2/Oct2	OCT3/Oct3	PMAT/Pmat
Norepinephrine	Human Rat (Mouse)	0.46–2.6 1.4 (4)	20		t 800	1,500–5,450 2,100, 4,400 (t)	182–2,630 1,900 (336, 566)	1,078, 2,606 (515)
Epinephrine	Human Rat (Mouse)				t 1,100	420 1,370, 1,900	240, 458 1,500	951
Dopamine	Human Rat (Mouse)	0.67	1.2–2.5 0.3–1.2 (2.0)		t 19–600	390–1,400 2,100 (n.t.d.)	800, 1,033 1,500 (785)	201–406 271 (160, 466)
Serotonin	Human Rat (Mouse)		t	0.2–1 0.32 (0.40)	197 38, 900	80, 290 760, 3,600 (313)	900, 988 500 (430)	114–283 93, 231 (120)
Histamine	Human Rat (Mouse)				t 99	520–1,300 278, 890 (111)	180–641 540 (1,670)	4,379 3,620 (1,520)

t transported, *n.t.d.* no transport detected

Norepinephrine: (Amphoux et al. 2006; Bacq et al. 2012, Busch et al. 1998; Chen et al. 2014; Daws 2009; Duan and Wang 2010; Engel et al. 2004; Giros et al. 1994; Gründemann et al. 1998a, b; Miura et al. 2017; Muck et al. 2007; Pacholczyk et al. 1991; Paczkowski et al. 1999; Song et al. 2019), **epinephrine**: (Amphoux et al. 2006; Duan and Wang 2010; Gründemann et al. 1998a, b), **dopamine**: (Amphoux et al. 2006; Daws 2009; Bednarczyk et al. 2003; Busch et al. 1996, 1998; Campbell et al. 2019; Duan and Wang 2010; Engel et al. 2004; Giros et al. 1991, 1992, 1994; Gründemann et al. 1998a; Kilty et al. 1991; Miura et al. 2017; Shimada et al. 1991; Shirasaka et al. 2017; Sitte et al. 1998; Wu and Gu 1999; Zolk et al. 2009a), **serotonin**: (Amphoux et al. 2006; Daws 2009; Blakely et al. 1991; Boxberger et al. 2014; Busch et al. 1996, 1998; Chang et al. 1996; Chen et al. 2014; Duan and Wang 2010; Engel et al. 2004; Gründemann et al. 1998a; Kristensen et al. 2011; Miura et al. 2017; Shirasaka et al. 2017; Zhou et al. 2002), **histamine**: (Amphoux et al. 2006; Arndt et al. 2001; Bednarczyk et al. 2003; Busch et al. 1996, 1998; Duan and Wang 2010; Miura et al. 2017; Usui et al. 2016; Yoshikawa and Yanai 2017)

and Cl^- is additionally coupled with antiport of K^+. The inwardly directed concentration gradients of Na^+ and Cl^- and the outwardly directed K^+ gradient provide large driving forces for transmitter uptake allowing a dramatic intracellular accumulation of NE, DA, and 5-HT at low extracellular concentrations of neurotransmitters.

2.2 Physiological Roles

The central role of the Na^+/Cl^- dependent monoamine neurotransmitter transporters is the rapid removal of neurotransmitters that are released during neurotransmission (Kristensen et al. 2011; Torres et al. 2003). Thereby, neurotransmission is terminated, and presynaptic nerve terminals are supplied with neurotransmitters for replenishment of presynaptic vesicles via vesicular neurotransmitter transporters. This is essential for maintenance and fine-tuning of neurotransmission. In addition, the monoamine neurotransmitter transporters participate in the control of ambient concentrations of NE, DA, and 5-HT which modulate ontogeny of neurons in the embryo, regulation of neuronal properties in adults, and crosstalk between neurons (Daws and Gould 2011). Based on these features, it is not surprising that monoamine neurotransmitter transporters are involved in diverse central nervous system functions. For example, NET regulates learning, memory, attention, mood control, motoric functions, and responses to stress. Mice in which NET was removed showed decreased NE tissue concentrations in various brain areas, decelerated NE clearance after activation of noradrenergic neurons, and an increased response to behavioral despair (Xu et al. 2000). DAT participates in the regulation of DA neurotransmission that is involved in motor activity, cognition, emotion, motivation, and reward behavior. Functional failure and dysregulation of DAT have been associated with neurological and psychiatric disorders including schizophrenia, depression, Parkinson´s disease (PD), attention deficit hyperactivity disorder (ADHD), bipolar disease, autism spectrum disorders (ASD), and drug addiction (Bowton et al. 2014; Dreher et al. 2009; Hamilton et al. 2013; Mazei-Robinson and Blakely 2006; Mazei-Robison et al. 2005). DAT knockout (KO) mice exhibited slowed removal of DA from the extracellular space surrounding dopaminergic neurons and increased hyperlocomotion (Giros et al. 1996). Also, the 5-HT releasing serotonergic system that is modulated by SERT is involved in various brain functions (Deneris and Wyler 2012; Lesch et al. 2012; Lesch and Waider 2012), including cognition, motor activity, mood control, aggression, appetite, and sleep. Mice in which SERT was removed showed decreased 5-HT concentrations in several brain areas and exhibited improved learning during a reversal task (Bengel et al. 1998; Brigman et al. 2010). Noteworthy, NET, DAT, and SERT collaborate to regulate central nervous system circuits controlling mood, attention, psychological drive, and reward behavior. This is, between others, due to overlapping neurotransmitter selectivity of the monoamine neurotransmitter transporters, closely associated noradrenergic, dopaminergic, and serotonergic neurons, and neuronal volume transmission (Sulzer and Edwards 2005; Torres et al. 2003; Zhou et al. 2002, 2005; Zoli et al. 1998).

2.3 Psychoactive Drugs That Interact with Na^+/Cl^- Dependent Monoamine Neurotransmitter Transporters

Compounds interacting with NET, DAT, and/or SERT have psychoactive effects (Mika et al. 2013; Torres et al. 2003). They are employed for treatment of ADHD, depression, addiction, pain, and obsessive-compulsive disorder (OCD). Many of these compounds are also substrates and/or inhibitors of organic cation transporters. These drugs are depicted in Table 3. Amphetamine is a stimulant that induces excitement, euphoria, and the feeling of wakefulness but may create dependence. It increases the synaptic concentrations of DA, NE, and 5-HT at cognate synapses by different mechanisms including stimulation of monoamine transporter mediated neurotransmitter release and inhibition of neurotransmitter reuptake (Jones et al. 1998; Mazei-Robison et al. 2008; Sitte and Freissmuth 2015; Sulzer et al. 1995; Torres et al. 2003). The selective NE reuptake inhibitor, atomoxetine, exhibits psychomotor effects and is approved for treatment of ADHD. Selective SERT inhibitors (SSRIs) like citalopram and fluoxetine and compounds that inhibit SERT and NET (amitriptyline, clomipramine, doxepin, imipramine, and desipramine) have complex psychotropic effects such as mood enhancement, sedation, and anxiolysis. They are used in the treatment of depression, anxiety, and related disorders. SSRIs and clomipramine are recommended for treatment of OCDs (Pittenger and Bloch 2014). Fluoxetine, amitriptyline, doxepin, imipramine, and desipramine are also used for treatment of chronic pain (Mika et al. 2013).

3 Emergence of the Concept That Low Affinity Monoamine Neurotransmitter Transporters Operate in Brain

3.1 Pioneering Demonstration of Low Affinity Noradrenaline Transport in the Heart

In 1965 Iversen described transporter mediated low affinity uptake of epinephrine and NE in addition to high affinity uptake in rat hearts (Iversen 1965). He named the low affinity uptake "uptake 2" in contrast to high affinity "uptake 1". In addition to much higher K_m values determined for uptake 2, differences in inhibitor selectivity were observed. For example, in contrast to uptake 1, uptake 2 did not discriminate between stereoisomers of epinephrine and NE. Moreover, evidence was provided for different transport properties of both systems. Whereas uptake but no efflux of epinephrine and NE was observed for uptake system 1, bidirectional transport was demonstrated for uptake system 2. Employing fluorescence microscopy, uptake 2 mediated transport was localized to heart muscle cells (Clarke et al. 1969; Iversen 1971).

Table 3 Apparent K_m values for drug uptake, IC_{50} or K_i values for drug inhibition of monoamine neurotransmitter uptake by human sodium-dependent monoamine neurotransmitter and/or organic cation transporters or K_D values for binding

	***K*m** (*IC*50 /*K*i) $\underline{K_D}$ [μM]						
Drug, therapeutic effect, *mechanism*	NET	DAT	SERT	OCT1	OCT2	OCT3	PMAT
Amphetamine, stimulant, *stimulation of DA release and inhibition of DA uptake via DAT, inhibition of NET*	**t** (0.06–0.20)	**0.7, 0.8** (0.39–2.3)	(38)	(97,202)	**0.8, 534** (0.7–145)	(24–460)	
Metamphetamine, stimulant, *stimulation of NE and DA release*		(0.2)		(0.3, 400)	**2.1** (1.2, 58)	(247, 300)	
Atomoxetine, treatment of ADHD, *inhibition of NET, NMDA receptor antagonist*	(0.005)	(0.69)	(0.15)		(3.5-20)		
Citalopram, antidepressant, analgetic, *inhibition of SERT*	(30) $\underline{4.1}$	(10) $\underline{28}$	**0.009** (0.001, 0.005) $\underline{0.001}$	(3, 19)	(12)	(145)	(117)
Fluoxetine, antidepressant, analgetic, *inhibition of SERT*	(1, 2) $\underline{0.24}$	(19.5) $\underline{3.6}$	(0.007, 0.020) $\underline{0.0008}$	**t** (3–6)	(17–57)		(11-28)
Sertraline, antidepressant, *inhibition of SERT*	$\underline{0.42}$	$\underline{0.025}$	$\underline{0.0003}$			(7.4)	(5.1, 14)
Amitriptyline, antidepressant, analgetic, *inhibition of SERT and NET*	(0.1) $\underline{0.035}$	(3.0) $\underline{3.3}$	(0.015, 0.036) $\underline{0.004}$	(3.5–17)	(0.5–14)	(>100)	(23)
Clomipramine, antidepressant, treatment of obsessive, compulsive disorders, *inhibition of SERT and NET*	(0.054) $\underline{0.038}$	(3.0) $\underline{2.2}$	(0.00004 0.00014) $\underline{0.0003}$	(5, 19)			
Doxepin, antidepressant, analgetic, *inhibition of SERT and NET*	$\underline{0.030}$	$\underline{12}$	$\underline{0.068}$	(1.5, 12)	(0.25–13)		
Imipramine, antidepressant, analgetic, *inhibition of SERT and NET*	(0.07–0.14) $\underline{0.037}$	(25) $\underline{8.5}$	(0.005-0.020) $\underline{0.001}$	(6–37)	(0.4–6)	(11, 42)	(21)

Desipramine, active metabolite of imipramine, antidepressant, analgetic, *inhibition of NET and SERT*	(0.004–0.01) 0.0008	(13–79) 3.2	(0.04–0.16) 0.018	(5–57)	(16)	(0.7–68)	(15, 33)
Sulpiride, antidepressant, antipsychotic, *dopamine receptor antagonist*				**260**	**26, 187**	**160**	
Berberine, antidepressant, *inhibitor of monoamine oxidase*				**15**	**1.0, 4.4** (0.4–0.9)	**2.2** (0.4–10)	
Trimipramine, anxiolytic, sedative, *antagonist of neurotransmitter receptors*				(28)	(0.44)		(12)
Buspirone, anxiolytic, *serotonin receptor agonist and dopamine receptor antagonist*					(8.6-69)		
Apomorphine, anti-Parkinson, *DA receptor agonist*				(21)	**t**		
Benztropine, anti-Parkinson, a*cetylcholine receptor antagonist, inhibition of uptake by NET and DAT*	(0.3, 0.8)	(0.04, 0.06)	(47)		(0.3–13)		
Memantine, anti-Parkinson, treatment of AD, *NMDA receptor antagonist*				(4, 27)	**34** (7.3)	(236)	
Procyclidine, anti-Parkinson, *acetylcholine receptor antagonist*					(<0.1)		
Selegiline, anti-Parkinson, *inhibition of monoamine oxidase*					**t**		
Amisulpride, antipsychotic, *dopamine receptor antagonist*				**31**	**168**	**192**	
Chlorpromazine, antipsychotic, *antagonist of various neurotransmitter receptors*				(2.6–52)	(2.6, 14)		
Chlorprothixene, antipsychotic, *antagonist of various neurotransmitter receptors*					**t**		
Clozapine, antipsychotic, *antagonist of various neurotransmitter receptors*							(13)
Haloperidol, antipyschotic, *antagonist of various neurotransmitter receptors*				(142)			(11)
Olanzapine, antipsychotic, *antagonist of various neurotransmitter receptors*					(<1)		(149)
Perphenazine, antipsychotic, *dopamine receptor antagonist*				**t**			

(continued)

Table 3 (continued)

Drug, therapeutic effect, *mechanism*	K_m (IC_{50} /K_i) K_D [μM]						
	NET	DAT	SERT	OCT1	OCT2	OCT3	PMAT
Promazine, antipsychotic, *antagonist of various neurotransmitter receptors*				(17)			
Risperidone, antipsychotic, *antagonist of various neurotransmitter receptors*							(7.0)
Phenytoin, anticonvulsant, *sodium channel blocker*						(0.75)	
Clomacran, hypnotic, *GABA receptor antagonist*					(<1)		
Zolpidem, hypnotic, *allosteric activator of GABA receptor*					(0.15)		
Ketamine, anesthetic, hypnotic, *NMDA receptor blocker*				**74**[a]	**34**[a]	**53**[a], **365**	
Morphine, analgetic, *opioid receptor agonist*				**3.4** (4.2, 28)		(538)	
Diphenhydramine, antiemetic, sedative, *histamine receptor antagonist, inhibitor of SERT*				**t** (3.4, 4.1)	(5.8–21)		
Domperidone, antiemetic, *dopamine receptor antagonist*				(33)	(7.9)		
Granisetron, antiemetic, *serotonin receptor antagonist*					(4.3)		
Metoclopramide, antiemetic, *dopamine receptor antagonist*				**t** (16, 95)	**t**		
Ondansetron, antiemetic, *serotonin receptor antagonist*				(1.2–64)	(0.9–16)	(1.7, 17)	
Scopolamine, antiemetic, *acetylcholine receptor antagonist*				(6.7)	(541)	(218)	

[a]Measured in presence of an inwardly directed proton gradient

Drugs which have not been tested for transport or could not be identified as substrates are only indicated if an IC_{50} or K_i value <20 μM was determined for at least one organic cation transporter. For determination of IC_{50} values substrate concentrations far below their K_m values were employed

t transported, K_D values for replacement of binding of [^{3}H]imipramine to SERT, [^{3}H]nisoxetine to NET, and [^{3}H]WIN3428 to DAT were measured (Tatsumi et al. 1997)

Amphetamine: (Amphoux et al. 2006; Eshleman et al. 1994; Giros et al. 1992, 1994; Kristensen et al. 2011; Pacholczyk et al. 1991; Sitte et al. 1998; Wagner et al. 2017; Wu and Gu 1999; Wu et al. 1998a; Zhu et al. 2010), **Metamphetamine:** (Eshleman et al. 1994; Wagner et al. 2017; Wu et al. 1998a)**, Atomoxetine:** (Kristensen et al. 2011; Sandoval et al. 2018), **Citalopram**: (Ahlin et al. 2008; Apparsundaram et al. 2008; Nies et al. 2011; Owens et al. 1997; Pacholczyk et al. 1991; Tatsumi et al. 1997; Torres et al. 2003; Zhou et al. 2007), **Fluoxetine**: (Boxberger et al. 2014, 2018; Engel et al. 2004; Haenisch and Bönisch 2010;

Kristensen et al. 2011; Owens et al. 1997; Sandoval et al. 2018; Tatsumi et al. 1997; Tzvetkov et al. 2018; Zhou et al. 2007; Zhu et al. 2012, 2018), **Sertraline**: (Haenisch and Bönisch 2010; Tatsumi et al. 1997; Zhou et al. 2007; Zhu et al. 2012), **Amitriptyline**: (Ahlin et al. 2008; Belzer et al. 2013; Giros et al. 1992; Hacker et al. 2015; Haenisch and Bönisch 2010; Matthaei et al. 2016; Owens et al. 1997; Pacholczyk et al. 1991; Sandoval et al. 2018; Sata et al. 2005; Tatsumi et al. 1997; Torres et al. 2003; Tzvetkov et al. 2013; Zolk et al. 2009a), **Clomipramine**: (Ahlin et al. 2008; Apparsundaram et al. 2008; Hendrickx et al. 2013; Millan et al. 2001; Tatsumi et al. 1997), **Doxepin**: (Belzer et al. 2013; Chen et al. 2017a; Hacker et al. 2015; Mika et al. 2013; Tatsumi et al. 1997; Zolk et al. 2009a), **Imipramine**: (Ahlin et al. 2008; Belzer et al. 2013; Haenisch and Bönisch 2010; Hendrickx et al. 2013; Kido et al. 2011; Owens et al. 1997; Pacholczyk et al. 1991; Paczkowski et al. 1999; Sandoval et al. 2018; Tatsumi et al. 1997; Torres et al. 2003; Tzvetkov et al. 2013; Wu et al. 2000; Zhu et al. 2012, 2018; Zolk et al. 2009a), **Desipramine**: (Ahlin et al. 2011; Ahlin et al. 2008; Chen et al. 2017a; Engel et al. 2004; Giros et al. 1992, 1994; Gorboulev et al. 1997; Haenisch and Bönisch 2010; Owens et al. 1997; Pacholczyk et al. 1991; Paczkowski et al. 1999; Tatsumi et al. 1997; Torres et al. 2003; Wu et al. 1998a, 2000; Zhang et al. 1998; Zhu et al. 2012; Zolk et al. 2009a), **Sulpiride**: (Bai et al. 2017; dos Santos Pereira et al. 2014; Li et al. 2017; Takano et al. 2017), **Berberin**: (Nies et al. 2008; Sun et al. 2014), **Trimipramine**: (Ahlin et al. 2008; Hacker et al. 2015; Haenisch and Bönisch 2010), **Buspirone**: (Sandoval et al. 2018), **Apomorphine**: (Ahlin et al. 2008; Hendrickx et al. 2013), **Benztropine**: (Giros et al. 1992; Kristensen et al. 2011; Pacholczyk et al. 1991; Sandoval et al. 2018), **Memantine**: (Ahlin et al. 2008; Amphoux et al. 2006; Busch et al. 1998; Hendrickx et al. 2013), **Procyclidine**: (Kido et al. 2011), **Selegiline**: (Hendrickx et al. 2013), **Amisulpride**: (dos Santos Pereira et al. 2014), **Chlorpromazine**: (Ahlin et al. 2011; Ahlin et al. 2008; Bednarczyk et al. 2003; Belzer et al. 2013; Zolk et al. 2009b)**, Chlorprothixene**: (Hendrickx et al. 2013), **Clozapine**: (Haenisch and Bönisch 2010), **Haloperidol**: (Ahlin et al. 2008; Haenisch and Bönisch 2010) **Olanzapine**: (Haenisch and Bönisch 2010; Kido et al. 2011), **Perphenazine**: (Hendrickx et al. 2013), **Promazine**: (Ahlin et al. 2008), **Risperidone**: (Haenisch and Bönisch 2010), **Phenytoin**: (Hasannejad et al. 2004), **Clomacran**: (Kido et al. 2011), **Zolpidem**: (Hacker et al. 2015), **Ketamine**: (Hendrickx et al. 2013; Keiser et al. 2018), **Morphine**: (Ahlin et al. 2008; Tzvetkov et al. 2013; Zhu et al. 2018), **Diphenylhydramine**: (Belzer et al. 2013; Boxberger et al. 2014, 2018; Müller et al. 2005; Zolk et al. 2009b), **Domperidone**: (Wittwer et al. 2013), **Granisetron**: (Wittwer et al. 2013), **Metoclopramide**: (Ahlin et al. 2008; Hendrickx et al. 2013; Matthaei et al. 2016), **Ondansetron**: (Ahlin et al. 2008; Kido et al. 2011; Tzvetkov et al. 2013; Tzvetkov et al. 2012; Wittwer et al. 2013; Zhu et al. 2018), **Scopolamine**: (Chen et al. 2017b; Hendrickx et al. 2013)

3.2 Reasons for the Need of Low Affinity Monoamine Neurotransmitter Transporters in Brain

Monoamine neurotransmitters released at synapses do activate not only postsynaptic receptors but also neuronal auto-receptors and receptors on nearby neurons. The synaptic "wiring transmission" allows rapid activation of neuronal circuits whereas the activation of remote neurons promoted by the so-called volume transmission occurs much more slowly and serves complex integrative and regulatory functions (Bunin and Wightman 1999; Smiley et al. 1994; Zoli et al. 1998). The concentration of monoamine neurotransmitters within and around synaptic clefts varies considerably (Bunin and Wightman 1998; Clements 1996). In the resting state, concentrations are in the low nanomolar range and are similar within and around synaptic clefts (Mathews et al. 2004). After neuronal activation, neurotransmitter concentrations within synaptic clefts and in remote tissue regions may be largely different. They depend on various factors that include firing rate, time after firing, anatomy of the synaptic cleft, density of cognate neurons as well as densities, properties, and locations of related neurotransmitter transporters (Bunin and Wightman 1998; Clements 1996; Garris and Wightman 1994). The concentration of DA and NE in synaptic clefts of cognate neurons after neuronal activation has been estimated to be in the millimolar range (Bunin and Wightman 1998; Garris et al. 1994). Outside synaptic clefts, the monoamine neurotransmitter concentration ranges from nanomolar to the low millimolar range (Williams and Millar 1990; Zoli et al. 1998). Because monoamine neurotransmitter concentrations close to the synapses are frequently orders of magnitude higher compared to the K_m values of the ambient high affinity neurotransmitter transporters (see Table 2), low affinity monoamine neurotransmitter transporters are required to enable an effective removal of neurotransmitters after nerve excitation. The coexistence of the low and high affinity neurotransmitter transporters enables a rapid location- and function-dependent adjustment of monoamine neurotransmitter concentrations. In the presence of drugs that inhibit high affinity monoamine neurotransmitter transporters, the neurotransmitter concentrations are increased, and their reuptake by low affinity transporters gains special importance (Daws 2009).

3.3 First Data Indicating That OCTs Translocate Monoamine Neurotransmitters and Are Expressed in Brain

Two years after the first cloning of the polyspecific organic cation transporter OCT1 from the rat (rOCT1) (Gründemann et al. 1994), it was observed that rOCT1 also mediates low affinity transport of monoamine neurotransmitters (Busch et al. 1996). Whereas early publications reported no expression of rOCT1 in the brain, cerebral expression of OCT2 in rats (rOCT2) was demonstrated by RT-PCR (Gründemann et al. 1997). In 1998, it was reported that human organic cation transporter 2 (hOCT2) is expressed in neurons of several brain areas and mediates low affinity transport of NE, 5-HT, DA, and histamine (Busch et al. 1998). In the same year,

cloning and broad expression of OCT3 from rats (rOCT3) and humans (hOCT3), including expression in brains and hearts, was reported (Gründemann et al. 1998b; Kekuda et al. 1998; Wu et al. 1998b). It was observed that hOCT3 transported epinephrine and NE in addition to other organic cations and that tetraethylammonium (TEA) transport by rOCT3 was inhibited by DA and 5-HT (Gründemann et al. 1998b; Wu et al. 1998a). Since rOCT3 and hOCT3 are also expressed in the heart, it was concluded that OCT3 is responsible for "uptake 2" as described by Iversen (1965). Because plasma membrane monoamine transporter PMAT that transports epinephrine and NE is also expressed in the heart (Engel et al. 2004), PMAT may also contribute to "uptake 2" in the heart.

4 Organic Cation Transporters Expressed in Brain

4.1 Basic Functional Properties of OCT1–3 (*SLC22A1–3*) and PMAT (*SLC29A4*)

The organic cation transporters OCT1, OCT2, OCT3, and PMAT are facilitated diffusion systems that translocate structurally different organic cations in both directions across the plasma membrane (Koepsell 2020; Wang 2016). The driving forces for cellular uptake by these transporters are the transmembrane concentration gradient of transported cation and the inside negative membrane potential. Extracellular protons also stimulate transport of organic cations by PMAT. OCT1, OCT2, OCT3, and PMAT accept a variety of structurally different organic cations as substrates, including monoamine neurotransmitters. In addition, they are inhibited by various organic cations and neutral compounds that are not transported. The substrate and inhibitor specificities of the four organic cation transporters overlap. Mutagenesis experiments and tertiary structure homology modeling of OCT1 and OCT2 indicate that these transporters, and probably also the highly homologous OCT3, contain substrate binding regions with partially overlapping cation binding sites within a large binding cleft (Koepsell 2019, 2020). After binding of one or two cationic substrates to one or two transport relevant binding sites within the inner part of the outward-open cleft, the transporter undergoes conformational changes including a state in which the substrates are occluded, triggering an inward-open state that allows the intracellular release of the substrates. The OCTs also contain high affinity cation binding sites that are accessible extracellularly and may modulate organic cation transport and sensitivity of inhibitors. The complex tertiary structure of the cation binding region containing interacting binding sites for structurally different cations and the existence of high affinity cation binding sites promoting structural changes within the substrate binding region provide a rationale why the sensitivity of inhibitors is often influenced drastically by the molecular structure and the concentration of transported cations (Koepsell 2019, 2020; Nies et al. 2011).

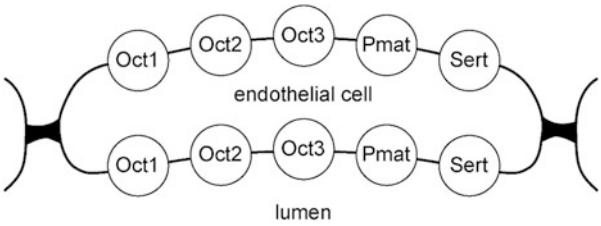

Fig. 2 Expression of Oct1, Oct2, Oct3, and Pmat in endothelial cells of the BBB identified in rodents. The indicated membrane locations of Oct1-3 and Pmat are suggested by immunohistochemical data (Oct1, Oct2, Oct3, Pmat) or presumed (Sert)

4.2 OCT1 (*SLC22A1*) in Brain

In the human brain, mRNA of OCT1 was detected by RT-PCR (Duan and Wang 2013; Gorboulev et al. 1997). OCT1 mRNA was also detected in the hippocampus of mice and in the choroid plexus (CP) of mice and rats (Baganz et al. 2008; Choudhuri et al. 2003; Duan and Wang 2013). A relatively low expression of OCT1 was observed in small blood vessels isolated from brains of humans, rats, and mice (Chaves et al. 2020; Geier et al. 2013; Lin et al. 2010; Sekhar et al. 2019; Wu et al. 2015b). In cultured rat brain endothelial cells, rOct1 was located to the luminal and abluminal membranes with higher luminal expression (Lin et al. 2010). The monoamine neurotransmitter transporters expressed in endothelial cells of rodents including their presumed plasma membrane location are depicted in Fig. 2.

Like the other organic cation transporters that are also expressed in the blood–brain barrier (BBB) (Table 1) including the novel organic cation transporter OCTN2 (*SLC22A5*), multidrug and toxin exclusion proteins MATE1 (*SLC47A1*) and MATE2-K (*SLC47A2*), which transport 5-HT and/or sulpiride (Koepsell 2020), OCT1 may be involved in translocation of organic cations across the BBB in both directions. It has been demonstrated that OCT1/Oct1 transports NE, 5-HT, DA, acetylcholine, and histamine like OCT2, OCT3, and PMAT (Breidert et al. 1998; Busch et al. 1996) (Table 2). The biomedical relevance of OCT1 and the other organic cation transporters in the BBB has not been resolved. Considering the overlapping specificity of the transporters, the biomedical relevance may be limited to individual drugs preferred by OCT1 and specific therapeutic situations, meaning situations in which other transporters are inhibited by drugs. Because blood concentrations of monoamine neurotransmitters and histamine are generally lower compared to their respective concentrations in the brain, their uptake into the brain has probably no biomedical relevance. In contrast, efflux of 5-HT across the BBB by the organic cation transporters may play a role in neuronal serotonergic regulation of microvascular blood flow and BBB permeability (Cohen et al. 1996; Leybaert 2005). Brain capillaries are associated with serotonergic nerve terminals that often originate from neurons in raphe nuclei and form tripartite neurovascular units together with astrocytes (Cohen et al. 1996; Reinhard et al. 1979). During serotonergic regulation of blood flow, 5-HT is released at the capillaries and activates 5-HT receptors at the endothelial cells (Parsons 1991). The activation is terminated by 5-HT uptake into

the endothelial cells where it may be degraded by monoamine oxidase (Kalaria and Harik 1987; Maruki et al. 1984). 5-HT uptake into the endothelial cells is mediated by SERT (Brust et al. 2000) and probably also by the low affinity organic transporters enabling efficient 5-HT uptake within a large concentration range.

Psychoactive, antiemetic, and analgetic drugs have been identified as substrates and/or inhibitors of human OCT1 and the other organic cation transporters (Table 3). Human OCT1 may be involved in cerebral uptake of fluoxetine, amisulpride, perphenazine, and morphine but probably not in uptake of amisulpride since the plasma concentrations of amisulpride in patients are much lower compared to the K_m value for uptake by hOCT1 (Table 3). Drug–drug interactions at the levels of OCT1 and/or the other organic cation transporters in the BBB may decrease transporter mediated drug uptake into the brain. Of note, the IC_{50} values presented in Table 3 have been determined with relatively high concentrations of model substrates such as tetraethylammonium (TEA) or 1-methyl-4-phenylpyridinium (MPP). Hence, these IC_{50} values may be orders of magnitude higher than the IC_{50} values for inhibition of transported drugs. As outlined above, the affinity for inhibition of OCTs is highly dependent on the molecular structure and concentration of the transported drug, and high affinity inhibition may occur when the concentration of the transported drug is far below its respective K_m (Koepsell 2019, 2020).

4.3 OCT2 (*SLC22A2*) in Brain

4.3.1 Locations in Brain

In the human brain hOCT2 was detected in pyramidal cells of hippocampus and occipital cortex and in the caudate nucleus (Busch et al. 1998). In microvessels isolated from human, rat, and mouse brain OCT2 was identified and located to luminal and abluminal membranes of the endothelial cells (Geier et al. 2013; Lin et al. 2010; Wu et al. 2015b). In rats and mice, expression of OCT2 was also observed in choroidal epithelial cells and localized to their apical membrane (Amphoux et al. 2006; Choudhuri et al. 2003; Duan and Wang 2013; Sweet et al. 2001). *In situ* hybridization in rats revealed rOct2 related staining at the borders between brain ventricles and parenchyma suggesting expression in ependymal cells (Amphoux et al. 2006). In the rat, rOct2 mRNA was also observed in granular cells of cerebellum and in granular and pyramidal cells of the hippocampal CA1, CA2, and CA3 regions (Amphoux et al. 2006). In mice, cerebral location of Oct2 protein was investigated in detail by immunohistochemistry employing Oct2-KO mice as negative controls (Bacq et al. 2012; Courousse et al. 2014). Expression of mouse Oct2 (mOct2) was observed in raphe nuclei, locus coeruleus, thalamic paraventricular nucleus, and hypothalamic dorsomedial, ventromedial, and arcuate nuclei. As in rats, mOct2 protein was also detected in the median eminence, in CA1, CA2, and CA3 regions of hippocampus, as well as in amygdala, and in various cortical regions such as precentral and cingulate gyri, prelimbic cortex, and infralimbic regions of prefrontal cortex. Co-labeling revealed that mOct2 was expressed in most noradrenergic neurons of the locus coeruleus and in a fraction of the serotonergic neurons of the dorsal raphe nucleus (Bacq et al. 2012).

4.3.2 Specificity for Transport of Monoamine Neurotransmitters and Interaction with Psychiatric Drugs

Like OCT1, OCT3, and PMAT, OCT2 accepts NA, epinephrine, DA, 5-HT, and histamine as substrates (Table 2). For uptake of NE by both hOCT2 and rOct2, diverging K_m values were reported. They range between 1.5 and 5.5 mM offering no indication of species related differences. These K_m values are at least 500 times higher than the K_m values reported for NE uptake by hNET. For DA uptake by hOCT2 or rOct2 diverging and overlapping K_m values between 0.39 and 2.1 mM were reported. These values are at least 150 times higher than the K_m values measured for hDAT and at least 1,000 times higher compared to the K_m values reported for rat Dat (rDat). K_m values of 0.08 and 0.29 mM were reported for uptake of 5-HT by hOCT2 while K_m values of 0.76 and 3.6 mM were reported for uptake of 5-HT by rOct2, suggesting a lower affinity of the rat transporter. The low K_m value of 0.08 mM reported for hOCT2 is 80 times higher than the K_m value reported for 5-HT uptake by human SERT (hSERT). For uptake of epinephrine by hOCT2, a K_m value of 0.4 mM has been reported that is about three times lower than the lower value reported for rOct2. Similar K_m values ranging between 0.28 and 1.3 mM were determined for histamine uptake by hOCT2 and rOct2. The data suggest complementary functions of OCT2 and coexpressed high affinity monoamine neurotransmitter transporters.

Transport by hOCT2 has been demonstrated for various psychotropic drugs including the stimulants amphetamine and metamphetamine, the antidepressant sulpiride, the antipsychotic amisulpride, and the anesthetic ketamine (Table 3). Considering the low plasma concentrations of psychotropic drugs in patients in relation to the determined K_m values for OCT2 (Table 3), OCT2 probably only participates significantly in translocation of amphetamine, metamphetamine, and ketamine across the BBB. Psychoactive drugs that have been shown to inhibit OCT2 (Table 3) may be also transported and OCT2 could be relevant for their uptake into brain. If OCT2 mediated drug uptake across the BBB turns out to be significant, the possibility of drug–drug interactions at OCT2 should be considered. As discussed for OCT1, OCT2 mediated drug uptake across the BBB may be inhibited by very low concentrations of coadministered drugs that also interact with OCT2. Psychoactive drugs in the brain interstitium may also inhibit OCT2 mediated uptake of monoamine neurotransmitters into neurons, because the relatively high IC_{50} values for hOCT2 shown in Table 3 do not exclude high affinity inhibition of neurotransmitter *in vivo* (Koepsell 2019, 2020).

4.3.3 Presumed Biomedical Functions

Employing Oct2 knockout (KO) mice, cerebral functions of mOct2 were investigated (Bacq et al. 2012; Courousse and Gautron 2015). In the hippocampus of Oct2-KO mice the *in vivo* clearance of iontophoretically applied NE and 5-HT was observed to be reduced compared to wildtype (WT) mice if uptake by NET and SERT was blocked (Bacq et al. 2012; David et al. 2003). This indicates the capability of mOct2 to participate in the adjustment of interstitial concentrations of 5-HT and NE. Using animal models for psychiatric disorders, data were obtained

suggesting that OCT2 is relevant for the performance of serotonergic circuits that are related to anxiety and depression.

After removal of Oct2, mice showed signs for decreased anxiety and increased depression-related behaviors. Decreased anxiety was suggested using the open field test, the O-maze test, and a test on feeding behavior after food application in a novel adverse environment. Compared to WT, Oct2-KO mice stayed in an open field longer, spent more time in the elevated open arms area in the O-maze test, and showed a reduced latency to feed in a novel environment. As paradigms for depression, the time periods of immobility after exposure to unescapable stress were tested in forced swim test (FST) and tail suspension tests. Whereas inhibitors of SERT and NET had no effects in Oct2-KO mice compared to WT mice, the time periods of immobility, indicating despair, were increased. These data indicate a complex, not yet understood impact of OCT2 mediated modulation of neurotransmitter homoeostasis on depression.

Chronic stress leading to increased levels of corticosterone is considered a risk factor for the onset of depression. Since OCT2 is expressed in neuronal circuits that trigger corticosterone secretion via activation of the hypothalamic-pituitary-adrenocortical axis, the effect of mOct2 removal on corticosterone secretion in response to acute stress was tested (Courousse and Gautron 2015; Krishnan and Nestler 2008). After acute stress, the brain induced increase of corticosterone secretion observed in Oct2-KO mice was higher compared to WT. This indicates an attenuating effect of Oct2 mediated neurotransmitter transport on stress induced corticosterone secretion. The effect of mOct2 removal on the vulnerability of mice for depression in response to unpredictable chronic mild stress (UCMS) was studied by analyzing the deterioration of coat state, emergence of spatial memory deficits, and decline of social behavior (Courousse and Gautron 2015). After UMCS conditions, an accelerated deterioration of the coat state, a higher deficit in spatial memory, and enhanced social deficits were observed in Oct2-KO mice compared to WT mice. These data suggest that depression-like behavior induced by chronic stress is blunted by OCT2 mediated neurotransmitter transport via decrease of corticosterone secretion.

4.4 OCT3 (*SLC22A3*) in Brain

4.4.1 Locations in Brain

When successful cloning of OCT3 from humans (hOCT3) and rats (rOct3) was reported, expression of OCT3 in brain and placenta was emphasized (Gründemann et al. 1998b; Kekuda et al. 1998). In the human brain, expression of OCT3 was detected in microvessels, CP, neurons of the substantia nigra (SN) and cerebellum, and in astrocytes (Cui et al. 2009; Duan and Wang 2013; Geier et al. 2013; Yoshikawa et al. 2013). In rodents, Oct3 expression was observed in many brain areas (Table 1) (Amphoux et al. 2006; Cui et al. 2009; Gasser et al. 2006, 2009, 2017; Graf et al. 2013; Haag et al. 2004; Hill and Gasser 2013; Nakayama et al. 2007; Sweet et al. 2001; Vialou et al. 2004; Wu et al. 1998a). Rat Oct3 was identified in pontine nuclei, nucleus tractus solitarii (NTS), raphe nuclei, locus coeruleus, colliculi of tectum, SN, circumventricular organs, and pineal gland. In rats, Oct3

was also detected in cerebellum, striatum, thalamus (anterodorsal, posterior paraventricular, lateral geniculate, arcuate nuclei), hypothalamus (dorsomedial and ventromedial nuclei), lateral septum, various regions of cerebral cortex, olfactory bulb, hippocampus, subiculum, nucleus accumbens (NAC), amygdala including the basolateral amygdala complex (BLA), and CP. ROct3 was observed in granular and Purkinje cells in the cerebellum, and in granular and pyramidal cells in the hippocampus. Employing immunohistochemical double labeling in area postrema and subfornical organ, expression of rOct3 was observed in neurons but not in astrocytes (Vialou et al. 2004). In contrast, in the dorsomedial hypothalamus (DMH) expression of rOct3 was detected in glial-like cells (Gasser et al. 2006). In the pineal gland, expression of rOct3 was observed in pinealocytes (Vialou et al. 2004). Moreover, rOct3 was located in ependymal cells (Gasser et al. 2006, 2009; Nakayama et al. 2007; Vialou et al. 2004) and in brain microvessels (Chaves et al. 2020). In mice, Oct3 (mOct3) was demonstrated in the BBB, in ependymal cells, and in many of the brain areas where expression of rOct3 was also observed in rats (Cui et al. 2009; Gasser et al. 2017; Vialou et al. 2008). Like rOct3, mOct3 was mainly located in neurons. In pars compacta of SN, expression of mOct3 was demonstrated in dopaminergic neurons (Vialou et al. 2008) whereas in the dorsal raphe, mOct3 was expressed in serotonergic neurons (Wyler et al. 2015). In various brain areas such as neostriatum, SN, and hypothalamus, expression of mOct3 was detected in astrocytes (Cui et al. 2009; Vialou et al. 2008). The expression of rOct3 and mOct3 in neurons, astrocytes, non-astrocyte glial cells, and capillary endothelial cells was confirmed with electron microscopic immunostaining in BLA of rat and mice (Gasser et al. 2017). In the endothelial cells, rOct3 and mOct3 were located to the luminal and abluminal plasma membrane (Fig. 2). In neurons, rOct3/mOct3 related immunoreactivity was observed at somatic plasma membranes, intracellular membranes, neurites and dendrites whereas the staining in glial cells was associated with somatic plasma membranes and cell processes (Gasser et al. 2017).

4.4.2 Specificity for Transport of Monoamine Neurotransmitters and Interaction with Psychiatric Drugs

Like the other organic cation transporters, OCT3 of humans and rodents transports NE, epinephrine, DA, 5-HT, and histamine (Table 2). For uptake of NE, epinephrine, DA, and histamine by hOCT3 similar K_m values were reported as for hOCT2. Similar K_m values were determined for uptake of NE by hOCT3 compared to human PMAT (hPMAT), higher K_m values for uptake of DA and 5-HT by hOCT3 versus hPMAT, and lower K_m values for uptake of histamine by hOCT3 versus hPMAT. Comparing OCT3 from humans and rats, the K_m values for NE, 5-HT, and DA were similar whereas an approximately threefold higher K_m value for epinephrine uptake by rOct3 compared to hOCT3 was determined. Like hOCT2, the K_m values for uptake of monoamine neurotransmitters by hOCT3 are orders of magnitude higher compared to hNET, hDAT, and hSERT. OCT3 extends the capacity for neurotransmitter reuptake in brain. Regional differences in expression compared to OCT1, OCT2, and PMAT and differences in regulation including the high sensitivity of OCT3 to corticosterone (Table 4) effectuate the diversification of neurotransmitter reuptake in brain.

Table 4 IC_{50} values for inhibition of cation uptake by organic cation transporters of humans and rodents by partial selective inhibitors

Compound		IC_{50} [μM]						
		NET/Net	DAT/Dat	SERT/Sert	OCT1/Oct1	OCT2/Oct2	OCT3/Oct3	PMAT/Pmat
Decynium 22	Human				0.98–12	0.1–10	0.09, 0.2	0.1–1.1
	Rat				0.36, 11			0.31
	(Mouse)	(35)	(13)	(7.9)	(5.3)	(0.43)		(0.48, 0.59)
Corticosterone	Human				7.0–22	5.4–80	0.12–0.62	430–1,059
	Rat				72, 151	4, 4.2	4.9, >10	
	(Mouse)	(840)	(364)	(445)		(8.7)	(11)	(n.i.d.)
β-Estradiol	Rat				>100	85	1.1	
Lopinavir	Human	n.i.d.	n.i.d.	36	174	n.i.d.	n.i.d.	1.4
	Rat							1.0
Mepiperhenidol	Rat				7.1	474		
Methylisoprenaline	Human							26
	Rat				37	2,600		
	(Mouse)			(8.4)	(8.4)	(>100)		
Amantadine	Human				10, 236	27, 28	>1,000	
	Rat				12	82	>1,000	
Phencyclidine	Human				4.4	25	333	
	Rat				0.16	16	3	
Memantine	Human				3.7, 27	7.3, 34	236	
	Rat				1.7	73	295	
RTI-55	Human	0.003, 0.023	0.003, 0.030	0.019, 0.0005				>100

n.i.d. no inhibition detected

Decynium 22: (Engel and Wang 2005; Engel et al. 2004; Floerl et al. 2020; Fraser-Spears et al. 2019; Gorboulev et al. 1997; Gründemann et al. 1994; Haenisch and Bönisch 2010; Hayer-Zillgen et al. 2002; Miura et al. 2017; Shirasaka et al. 2017; Zhang et al. 1998), **corticosterone**: (Arndt et al. 2001; Engel and Wang 2005; Engel et al. 2004; Fraser-Spears et al. 2019; Gründemann et al. 1998b, 2002; Hayer-Zillgen et al. 2002; Minematsu et al. 2010; Miura et al. 2017; Wu et al. 1998a; Zhang et al. 1998), **β-estradiol**: (Wu et al. 1998a), **lopinavir**: (Duan et al. 2015; Usui et al. 2016), **mepiperhenidol**: (Arndt et al. 2001), **O-methylisoprenaline**: (Arndt et al. 2001; Koepsell et al. 2007), **amantadine**: (Amphoux et al. 2006; Bednarczyk et al. 2003; Busch et al. 1998), **phencyclidine**: (Amphoux et al. 2006), **memantine**: (Ahlin et al. 2008; Amphoux et al. 2006; Busch et al. 1998), **RTI-55 (3β-(4-iodophenyl)-tropane-2-carboxylic acid)**: (Duan and Wang 2013; Torres et al. 2003)

Concerning OCT3 mediated transport of psychoactive drugs, transport has only been reported for sulpiride, berberine, amisulpride, and ketamine. The K_m values for transport of these drugs by hOCT3 are similar to those for transport by hOCT2 (Table 3). Twelve additional psychoactive drugs (amphetamine, metamphetamine, citalopram, sertraline, amitriptyline, imipramine, desipramine, memantine, phenytoin, morphine, ondansetron, and scopolamine) have been identified as inhibitors of hOCT3 but have not been tested for transport.

4.4.3 Presumed Biomedical Functions

Physiological and biomedical functions of OCT3 in brain were investigated employing rodents in which Oct3 was removed by genetic knockout or downregulated by antisense RNA technology. Some experiments were performed in combinations with inhibitors. Effects on physiological and psychological behaviors were measured using behavioral tests. In addition, effects of stress and treatment with stimulants were investigated. Moreover, the role of Oct3 in toxic degeneration of dopaminergic neurons was explored.

After Oct3 removal in mice, the concentrations of DA and NE in the SN and the ventral tegmental area and the concentration of histamine in thalamus and hypothalamus were decreased (Vialou et al. 2008). Employing cocaine and corticosterone as inhibitors the involvement of Oct3 in the clearance of catecholamines (DA and NE) after neuronal activation was investigated in rats (Holleran et al. 2020). Cocaine is a high affinity inhibitor of DAT whereas corticosterone inhibits rOct3 and rOct2 with higher affinity compared to rPmat (Table 4). After electric stimulation, the clearance rate of catecholamines in NAC and BLA was decreased by both cocaine and corticosterone. Since Oct3 but not Oct2 was detected in NAC (Table 1) these data suggest that Oct3 is critically involved in clearance of catecholamines.

In Oct3-KO mice the spontaneous ingestion of hypertonic saline in response to withdrawal of water and application of the sodium-wasting diuretic furosemide was 40% higher compared to WT mice (Vialou et al. 2004). These data suggest an impact of Oct3 on the regulation of osmolarity in neuronal circuits that involve neurons that are located in the subfornical organ, area postrema, hypothalamic paraventricular nuclei, and the NTS where rOct3 is expressed (Table 1).

The forced swim test (FST) was used on mice to elucidate whether Oct3 has an impact on depression. In the FST the time of immobility indicating behavioral despair was decreased when cerebral expression of mOct3 was decreased by injection of mOct3 antisense RNA into the third ventricle (Kitaichi et al. 2005). This suggests an anti-depressive effect due to impaired mOct3 mediated neurotransmitter removal from interstitial space.

Moreover, complementary functions of OCT3 and SERT were investigated. In Sert-KO mice, the expression of mOct3 was increased in hippocampus but not altered in cerebral cortex, striatum, brainstem, and cerebellum (Baganz et al. 2008; Schmitt et al. 2003). In contrast to WT, decynium 22 decreased the clearance rate of 5-HT injected into the CA3 region of the hippocampus in Sert-KO mice (Baganz et al. 2008). This is consistent with an inhibition of Oct3 mediated 5-HT uptake after elimination of Sert but could also be due to inhibition of 5-HT uptake by Oct2

(Table 4). The clinical impact of 5-HT transport by OCT3 and/or OCT2 during compromised function of SERT was suggested by the observation that decynium 22 decreased depressive-like behavior in Sert-KO mice measured in the tail suspension test (Baganz et al. 2008).

The impact of OCT3 on effects of the stimulants metamphetamine (METH) and amphetamine was explored. In mice and rats, the stimulative effect of METH on locomotion with and without downregulation of Oct3 was investigated (Kitaichi et al. 2005; Nakayama et al. 2007). It was observed that the METH induced stimulation of locomotion was amplified when the expression of mOct3/rOct3 was reduced by injection of Oct3 antisense RNA into the third ventricle. The application of METH to rats caused an increase of the interstitial DA concentration in prefrontal cortex and NAC, and this DA increase was reinforced when the expression of rOct3 was downregulated suggesting reuptake of DA by rOCT3 (Nakayama et al. 2007). After treating mice with amphetamine, an increase of neuronal activity of dopaminergic neurons was observed that was associated with an increase of DA in the vicinity of the dopaminergic neurons (Mayer et al. 2018). This increase of DA was blunted by decynium 22. The effect of decynium 22 was apparently due to inhibition of Oct3 because it was not observed in mOct3-KO mice. Supported by the observation that amphetamine stimulated cyanine 22-inhibitable MPP^+ efflux from MPP^+-preloaded neurons of the superior ganglion, the hypothesis was raised that amphetamine stimulates OCT3-mediated efflux of DA from dopaminergic neurons (Mayer et al. 2018).

Furthermore, the impact of OCT3 on cocaine addiction was investigated in rats in which expression of rOct3 was demonstrated in neurons of the NAC (Gasser et al. 2009). Glutaminergic and dopaminergic neuronal circuits in NAC have been shown to be involved in relapse of recovering cocaine addicts (Bachtell et al. 2005; Madayag et al. 2010). In addicts, the probability of relapse is increased by environmental factors associated with stress that activates the hypothalamic-pituitary-adrenal (HPA) axis and leads to an increase of plasma cortisol in humans and plasma corticosterone in rodents (Sinha et al. 2003). In rats, the impact of corticosterone sensitive Oct3 in NAC on stress related cocaine reward was investigated by measuring drug-seeking behavior after a period of cocaine self-administration that was followed by extinction and reinstatement (Graf et al. 2013). The reinstatement was primed with one administration of cocaine with and without preceding stress that had been induced by electrical foot-shock treatment. It turned out that dopamine receptor blockers blunted stress-increased reinstatement behavior. A stress-like effect was observed when corticosterone was applied systemically or injected into the NAC. In addition, it was observed that corticosterone decreased the dopamine clearance in the NAC. Evidence for the involvement of mOct3 was provided by the demonstration that cocaine-primed corticosterone-induced reinstatement of reward-like behavior observed in WT mice could not be detected in Oct3-KO mice.

Finally it was investigated in mice whether Oct3 in SN and striatum contributes to death of dopaminergic neurons after ingestion of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Cui et al. 2009). MPTP is a protoxin that is metabolized to toxic MPP^+ (Javitch et al. 1985). In nigrostriatum MPP^+ is taken up by

dopaminergic neurons via Dat where it induces neuronal death causing Parkinson's disease (Dauer and Przedborski 2003; Javitch et al. 1985). Cui and coworkers observed that mOct3 is expressed in astrocytes in the vicinity of dopaminergic neurons (Cui et al. 2009). MPTP is transported into astrocytes and metabolized to MPP^+, and MPP^+ is released into the interstitial space via mOct3. The astrocytes tolerate the emerging intracellular MPP^+ concentrations. After removal of mOct3, the decay of dopaminergic neurons in nigrostriatum after application of MPTP was reduced indicating a critical involvement of mOct3 in neuronal poisoning (Cui et al. 2009).

4.5 PMAT (*SLC29A4*) in Brain

4.5.1 Locations in Brain

PMAT is broadly expressed in brain. In humans, PMAT was detected in the BBB, CP, medulla oblongata, pons, cerebellum, SN, putamen, caudate nucleus, cerebral cortex, hippocampus, and NAC (Dahlin et al. 2009; Duan and Wang 2010, 2013; Engel et al. 2004; Geier et al. 2013; Sekhar et al. 2019). In all regions except the caudate nucleus, the mRNA abundance of human PMAT (hPMAT) was higher compared to hOCT3 (Duan and Wang 2010). Human PMAT was located to the endothelial cells in the BBB (Sekhar et al. 2019), to the luminal membrane of choroid epithelial cells (Duan and Wang 2013), and to neurons (Dahlin et al. 2007; Engel et al. 2004). Expression of hPMAT was also observed in primary cultured human astrocytes (Yoshikawa et al. 2013). Also in rodents, Pmat was detected in the BBB, the CP, and various brain regions (Dahlin et al. 2007; Sekhar et al. 2019; Vialou et al. 2007; Wu et al. 2015a). In rodents, Pmat was observed in brain areas that contain diverse neuron populations, particularly cholinergic, glutamatergic, GABAergic, and noradrenergic neurons. In rodents, expression of Pmat was assigned to many specific locations (Dahlin et al. 2007; Vialou et al. 2007). Between others, Pmat was detected in several motor nuclei of medulla oblongata and mesencephalon including NTS, in specific areas of rhombencephalon (dorsal raphe, motor nuclei, medial vestibular nuclei), in the inferior olivary complex, in pontine nuclei, in cerebellar cortex, in ventral striatum, in lateral and ventral pallidum, in pars compacta of SN, in nucleus ruber, in ventral tegmental area, caudate putamen, septum (indusium griseum, diagonal band of Broca, and triangular nucleus), in thalamic nuclei (anteromedial, anterodorsal, and reticular nuclei), in hypothalamic nuclei (dorsomedial, lateral mammillary, tuberomammillary, arcuate, circular, and supraoptic nuclei), in the olfactory system (bulbus and olfactory tubercle), in various areas of cerebral cortex (amongst others telencephalon, piriform, lateral entorhinal, ectorhinal, insular, and temporal cortex), in hippocampus (regions CA1–CA3, dentate gyrus), and in amygdala (for example, in lateral amygdaloid nucleus). The immunostaining of Pmat was observed in neurons and astrocytes (Wu et al. 2015a). Immunohistochemical colocalization of mouse Pmat (mPmat) in striatum indicated mPmat in somata and fibers of most neurons (Dahlin et al. 2007). Co-labeling of rat brain using immunohistochemistry and *in situ*

hybridization revealed that rat Pmat (rPmat) was observed in many cholinergic but only few dopaminergic neurons (Vialou et al. 2007). In microvessels isolated from the brains of rats and mice Pmat was located to the luminal and abluminal membrane of endothelial cells (Wu et al. 2015a).

4.5.2 Specificity for Transport of Monoamine Neurotransmitters and Interaction with Psychiatric Drugs

Like OCT1-3, PMAT transports NE, DA, 5-HT, epinephrine, and histamine (Table 2). The K_m values are similar for NE uptake by hPMAT, hOCT2, and hOCT3. They are higher for histamine uptake by hPMAT compared to hOCT2 and hOCT3 but lower for uptake of DA and 5-HT by hPMAT compared to hOCT3. Psychotropic drugs have not been tested for transport by PMAT, however, citalopram, fluoxetine, sertraline, amitriptyline, imipramine, desipramine, trimipramine, clozapine, haloperidol, olanzapine, and risperidone were identified as inhibitors (Table 3). Additional experiments are required to elucidate whether PMAT is involved in drug uptake across the BBB, across the CSF–blood barrier (CSFBB) and/or into neurons, and whether clinically relevant drug–drug interactions exist in the brain.

4.5.3 Presumed Biomedical Functions

The strong expression of PMAT in various brain areas, the BBB, and the CSFBB implicates relevant biomedical functions. In the BBB, PMAT may be critically involved in removal of toxic compounds such as MPP^+ and MTPT from the brain (Fig. 2). PMAT may mediate uptake into the endothelial cells across the abluminal membrane and – at low intracellular pH – also efflux across the luminal membrane into the blood (Itagaki et al. 2012; Okura et al. 2011). In the luminal membrane of choroid epithelial cells PMAT is supposed to play a dominant role for cerebral clearance of toxic compounds and of histamine across the CSFBB (Duan and Wang 2013; Usui et al. 2016). Being expressed in astrocytes, PMAT may be also engaged in the clearance of histamine from the extracellular space close to histaminergic neurons (Yoshikawa et al. 2013).

Hosford and coworkers provided data from rats suggesting that 5-HT uptake by rPmat in the NTS is critically involved in cardiovascular regulation (Hosford et al. 2015). A stimulation of vagal afferents that slowed heartbeat and decreased blood pressure promoted release of 5-HT from serotonergic neurons in the NTS leading to a transient increase of 5-HT in the interstitial space. The 5-HT increase was unaffected by the SSRI citalopram but was reinforced by decynium 22. The slowdown of heartbeat after vagal stimulation was not influenced by citalopram but amplified by decynium 22. Since the clearance of locally applied 5-HT in NTS was slowed down by decynium 22 but not altered by corticosterone that inhibits rOct3 but probably not rPmat (Table 4), the effects of decynium 22 after vagal stimulation were assigned to Pmat.

Gilman and coworkers compared locomotor activity, anxiety-like behavior, and stress coping behaviors between Pmat-KO mice and WT mice using various behavioral tests (Gilman et al. 2018). With exception of a small gender independent

increase of anxiety-related behavior in heterozygous Pmat-KO mice and a mild increase in active coping behavior in female homozygous KO mice, no significant effects of Pmat removal were observed. Additional studies are required to elucidate whether the observed effects are due to compensatory upregulations in the KO mice or indicate a minor impact of Pmat on these behavior disorders when the other monoamine transporters are functional.

Changed functions of PMAT in the brain may also contribute to the emergence of ASD (Garbarino et al. 2019). ASD is a complex disorder comprising social behavior deficits and restrictive repetitive behavior that may be associated with anxiety, mood disorders, attention deficit, and hyperactivity. ASD is thought to be caused by changed 5-HT signaling in the brain during embryonic development that affects the maturation of serotonergic circuits. Amongst others, disturbed 5-HT signaling may be a consequence of dysregulation of cerebral 5-HT concentrations that may be caused by changed 5-HT reuptake. In eight of 284 patients with ASD three inherited non-synonymous mutations were identified in hPMAT that are extremely rare in non-diseased control individuals (Adamsen et al. 2014). Two mutations induced an impairment of hPMAT mediated 5-HT transport. The data suggest that changed function and expression of hPMAT may contribute to the emergence of ASD.

4.6 Potential of Inhibitors to Distinguish Between Transport by Different Organic Cation Transporters

The overlapping expression and selectivity of monoamine neurotransmitter transporters represent serious obstacles in determining the contributions of individual transporters to cerebral functions. This can be achieved by *in vivo* experiments in combination with genetic transporter knockout, decrease of transporter expression by antisense technology, and/or inhibition of transporters with selective inhibitors. Each of these methods has limitations. Specifically, these limitations are compensatory expression of transporters with overlapping selectivity in knockout animals, incomplete decrease of transporter expression by antisense technology, and usage of inhibitors with inadequate selectivity. In Table 4, IC_{50} values are compiled that have been reported to inhibit cation uptake by human and rodent monoamine neurotransmitter transporters. Conspicuously, none of the inhibitors have been tested for all relevant transporters in humans, rats, and mice. Comparing human transporters, it is noteworthy that the reported IC_{50} values vary considerably. The differences are thought to be due to usage of different substrates and substrate concentrations for inhibition experiments as discussed earlier (Koepsell 2019, 2020). Species differences between humans and rodents also exist. For example, whereas corticosterone has an at least 8.7-fold lower IC_{50} value for hOCT3 compared to hOCT2, the IC_{50} values for rOct3 and rOct2 are not different. Unfortunately, for mouse transporters, only few IC_{50} values have been reported. In summary, for a valid distinction between individual monoamine transporters with inhibitors, the functionally relevant IC_{50} values should be known. Strictly spoken, these should be the IC_{50} values for inhibition of transport by the transporter of the investigated species using

the substrate of interest at its biomedically relevant concentration. On the basis of existing data, it may be argued that it is possible to distinguish between transport by PMAT/Pmat and OCT3/Oct3 in humans and rodents using corticosterone, between hPMAT and the other transporters in humans using lopinavir, between Oct1 and Oct2 in rodents using methylisoprenaline, between OCT3/Oct3 and OCT2/Oct2 in humans and rats using amantadine, and between hPMAT and the high affinity Na^+/Cl^- dependent monoamine neurotransmitter transporters in human using RTI-55.

5 Conclusions

Sophisticated experiments in rodents have indicated the impact of organic cation transporters on complex cerebral functions like anxiety, mood control, and motor activity and on their modulatory functions during medical treatment of psychiatric disorders. These data implicate the possibility of developing a new generation of more effective psychoactive drugs that inhibit monoamine neurotransmitter reuptake by high and low affinity neurotransmitter transporters (Orrico-Sanchez et al. 2020). By critically appraising previous achievements and calling attention to the incompleteness of the current data basis, we hope to stimulate future investigations in this research area. The validation of current knowledge that is nearly exclusively based on experiments with rodents, for humans is a great challenge for the future. This can be achieved by employing defect mutations in human transporters and/or drugs with molecular characterized targets.

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