Introduction

Astrocytes, which are known to be the most abundant cell type in the human brain, work as key players in various central nervous system (CNS) activities. Details of astrocyte CNS activity have been described in several excellent reviews.\(^1\)\(^\text{-}\)\(^9\) For example, astrocytes produce lactate from glucose to feed to neurons as their energy source utilizing astrocytic monocarboxylate transporter 1 (MCT1) and MCT4 (export), and neuronal MCT2 (uptake), respectively. This is the so-called lactate shuttle. Another example is the formation of the tripartite synapse.\(^5\)\(^\text{-}\)\(^7\) It has been observed that numerous, but not all, numbers of synapses are surrounded by astrocytes in the hippocampus,\(^6\) whereby astrocytes are considered to play essential roles in neurotransmitter clearance in the synaptic cleft. In the tripartite synapse, two astrocyte-specific transporters, namely, excitatory amino acid transporter 1 (EAAT1) and EAAT2 (glutamate transporters (GLAST and GLT-1) in rodents, respectively) significantly contribute to the uptake of the released glutamate into astrocytes, leading to the termination of excitation signals. Similarly, another astrocyte-enriched transporter glycine transporter-1 (GlyT-1) is reported to be primarily involved in glycine clearance at the synapse. Since glycine is a known co-agonist of N-methyl-D-aspartate (NMDA) receptor, GlyT-1 function is indispensable for fine-tuning NMDA activities.

Consistent with their physiological importance in maintaining CNS homeostasis, functional impairments of astrocyte transporters are often associated with various CNS diseases.\(^5\)\(^\text{-}\)\(^7\) For example, the functional insufficiency of EAAT2 results in an elevation of glutamate concentration at the synapse, eventually inducing excitotoxicity. Therefore, EAAT2 functional enhancers, such as ceftriaxone and LDN/OSU-0212320, are expected to facilitate glutamate clearance to reduce such toxicity. In this way, EAAT2 has drawn significant attention in CNS drug development for the treatment of such diseases as amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease.\(^8\) Furthermore, because astrocytes utilize various types of plasma membrane transporters in order to fulfill their pleiotropic roles, it can be expected that drug-targetable astrocyte transporters are not limited to EAAT2. Obviously, GlyT-1 has been regarded as another drug target transporter,\(^9\)\(^\text{-}\)\(^10\)

Key words astrocyte; transporter; drug development; central nervous system

Received January 23, 2017

It has become widely acknowledged that astrocytes play essential roles in maintaining physiological central nervous system (CNS) activities. Astrocytes fulfill their roles partly through the manipulation of their plasma membrane transporter functions, and therefore these transporters have been regarded as promising drug targets for various CNS diseases. A representative example is excitatory amino acid transporter 2 (EAAT2), which works as a critical regulator of excitatory signal transduction through its glutamate uptake activity at the tripartite synapse. Thus, enhancement of EAAT2 functionality is expected to accelerate glutamate clearance at synapses, which is a promising approach for the prevention of over-excitation of glutamate receptors. In addition to such well-known astrocyte-specific transporters, cumulative evidence suggests that multi-specific organic ion transporters (i.e., organic cation/anion transporters [OCTs/OATs], carnitine/organic cation transporters [OCTNs], and organic anion transporting polypeptides [OATPs]) are also functionally expressed in astrocytes. Even though identification and characterization of their physiological/pathophysiological roles in astrocytes are in the initial stage, the findings obtained so far indicate that OCT3 and plasma membrane monoamine transporter are significantly involved in the clearance of biogenic amine neurotransmitters in the synaptic cleft, and that OCTN2 and OATP1C1 provide a cellular entry gate for carnitine/acetyl-l-carnitine and thyroxine, respectively. Therefore, organic ion transporters, including those mentioned above, are expected to become emerging pharmacological targets for various CNS diseases. With such expectations in mind, this review will briefly summarize the functional expression of organic ion transporters in astrocytes.

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Fig. 1. A Summary Illustration of Functional Expression of Organic Ion Transporters in Astrocytes

Representative astrocytic organic anion transporters described in this review (OATP1C1, OCT3, OCTN2, and PMAT), and their functions, are summarized. Well-established astrocyte transporters (MCT1, MCT4, EAAT1, EAAT2, and GlyT1) and their functions are also shown. MCT2 is known to be a neuronal lactate uptake transporter, and glucose transporter 1 (GLUT1) is regarded as a primary glucose uptake transporter expressed in astrocytes. The question mark (?) indicates that while several transporters, including MCT8, are thought to be involved in thyroid hormone efflux, their details remain undetermined. Synapse is depicted on the right side. Thick arrows show preferential transport processes. Ac-Car, acetyl-L-carnitine; Car, carnitine; DA, dopamine; DIO2, Type II iodothyronine deiodinase; E, epinephrine; Glc, glucose; Glu, glutamate; Gly, glycine; H, histamine; 5-HT, 5-hydroxytryptamine (serotonin); Lac, lactate; NE, norepinephrine; T3, triiodothyronine; T4, thyroxine (or tetraiodothyronine); Pyr, pyruvate.

Table 1. $K_m$ Values of OCT3, PMAT, OCTN2, and OATP1C1 for Their Typical Substrates

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Substrate</th>
<th>$K_m$ (µM)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT3</td>
<td>MPP$^+$</td>
<td>166 (human)</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Dopamine</td>
<td>1033 (human)</td>
<td>16, 24</td>
</tr>
<tr>
<td></td>
<td>Serotonin</td>
<td>988, 510 (human)</td>
<td>16, 24, 26</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine</td>
<td>510, 629, 923, 2630 (human)</td>
<td>15, 16, 24, 26</td>
</tr>
<tr>
<td></td>
<td>Epinephrine</td>
<td>240, 458 (human)</td>
<td>16, 24</td>
</tr>
<tr>
<td></td>
<td>Histamine</td>
<td>220, 641 (human)</td>
<td>16, 24</td>
</tr>
<tr>
<td>PMAT</td>
<td>MPP$^+$</td>
<td>33, 111 (human)</td>
<td>24, 73, 77</td>
</tr>
<tr>
<td></td>
<td>Dopamine</td>
<td>201, 329, 406 (human)</td>
<td>24, 73, 77</td>
</tr>
<tr>
<td></td>
<td>Serotonin</td>
<td>114, 116, 283 (human)</td>
<td>24, 73, 77</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine</td>
<td>1078, 2606 (human)</td>
<td>24, 77</td>
</tr>
<tr>
<td></td>
<td>Epinephrine</td>
<td>951, 15323 (human)</td>
<td>24, 77</td>
</tr>
<tr>
<td></td>
<td>Histamine</td>
<td>4379, 10471 (human)</td>
<td>24, 77</td>
</tr>
<tr>
<td>OCTN2</td>
<td>L-Carnitine</td>
<td>4.3 (human)</td>
<td>38, 79</td>
</tr>
<tr>
<td></td>
<td>D-Carnitine</td>
<td>10.9 (human)</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Acetyl-L-carnitine</td>
<td>8.5 (human)</td>
<td>78</td>
</tr>
<tr>
<td>OATP1C1</td>
<td>Thyroxin</td>
<td>0.09 (human)</td>
<td>59, 60, 80</td>
</tr>
<tr>
<td></td>
<td>Reverse triiodothyronine</td>
<td>0.13 (human)</td>
<td>59, 80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.18, 0.34 (mouse)</td>
<td>59, 80</td>
</tr>
</tbody>
</table>
xCT (the cysteine/glutamate exchanger) seems to be another.\textsuperscript{13}

Besides these amino acid transporters, organic ion transporters are also promising candidates as drug-targetable astrocyte transporters. Unlike the above-mentioned astroglia-specific transporters, the expression of organic ion transporters is not always limited to astrocytes (as described later); therefore, their potential as a pharmacological target in astrocytes has yet to be established. However, their functions in astrocytes have been demonstrated, and recent advances have pointed to the importance of taking into consideration astrocytic organic ion transporter functions in future CNS drug development.

Thus, with the expectation that astrocytic organic ion transporters will establish their presence in CNS drug development, this review will briefly summarize their expression profiles and functions in astrocytes. Additionally, we discuss their potential to become a therapeutic target, while cautionary notes in astrocytic organic ion transporter studies are summarized, as well as their functions.

2. ORGANIC CATION TRANSPORTERS

2.1. Organic Cation Transporter 3 (OCT3) Two extracellular monoamine clearance systems in monoaminergic neurons have been observed. One is the uptake\textsubscript{1} system, which consists of high-affinity, low-capacity Na\textsuperscript{+}- and Cl\textsuperscript{−}-dependent norepinephrine, dopamine, and serotonin transporters (NET, DAT, SERT, respectively). The other is the uptake\textsubscript{2} system, which is a low-affinity, high-capacity Na\textsuperscript{+}- and Cl\textsuperscript{−}-independent monoamine transport process. The uptake\textsubscript{2} system has been thought to be mediated by the molecularly-unidentified extraneuronal monoamine transporter (EMT) predominantly expressed in glia.\textsuperscript{12} However, in the late 1990s, a series of molecular cloning and functional expression analysis of transporters strongly suggested that organic cation transporter 3 (OCT3, SLC29A3) is likely to be a molecular entity of the EMT.\textsuperscript{13–15}

\textit{In situ} hybridization and immunohistochemical analyses using rat or mouse brain have demonstrated that, in addition to its neuronal expression in the cerebellum, subfornical organ, dorsal raphe, hippocampus, and other brain regions,\textsuperscript{13,16–19} OCT3 is also expressed in astrocytes in several brain regions, such as the substantia nigra, striatum, hippocampus, and hypothalamic nuclei.\textsuperscript{17,19} Astrocytic OCT3 expression has also been reported in human brain sections\textsuperscript{18,20} and in primary human astrocytes.\textsuperscript{20–22} However, the absence of OCT3 expression in astrocytes has also been observed in some brain areas (such as the cerebellum), and primary human astrocytes are not always positive for OCT3 expression.\textsuperscript{19,23} Therefore, OCT3 appears to be expressed in astrocytes heterogeneously.

OCT3 is a Na\textsuperscript{+}- and Cl\textsuperscript{−}-independent transporter, and has shown to be capable of transporting 1-methyl-4-phenylpyridinium ion (MPP\textsuperscript{+}), dopamine, norepinephrine, epinephrine, 5-hydroxytryptamine (5-HT), and histamine.\textsuperscript{16,24} Given these functions, it is considered likely that, by working together with high-affinity type transporters, astrocytic OCT3 actively participates in the synaptic clearance of these transmitters. This notion may be related to the findings that OCT3 knock-out mouse, at least slightly, show increased anxiety and sensitivity to psychostimulants.\textsuperscript{17} Therefore, as Schildkraut and Mooney have proposed,\textsuperscript{25} it can be postulated that the inhibition of OCT3 is expected to enhance the efficacy of anti-depressant or anti-psychotic drugs.

Details of previous research efforts regarding the above-mentioned proposal has been summarized in the review article.\textsuperscript{22} Additionally, a recent study has shown that several anti-depressant drugs, such as desipramine and sertraline, can inhibit OCT3-mediated norepinephrine or 5-HT uptake.\textsuperscript{26} Furthermore, Horton et al.\textsuperscript{27} have reported that, while decynium-22 (D22, a potent inhibitor of “uptake\textsubscript{2}“) alone does not effectively work as an anti-depressant, the compound significantly enhances the anti-depressant effects of fluvoxamine (a selective serotonin reuptake inhibitor, SSR1). Furthermore, this incremental effect was significantly attenuated in OCT3 knock-out mouse, indicating that OCT3 participates in D22’s pharmacological action.

Collectively, the findings obtained so far strongly support the idea that the inhibition of OCT3 activity is a promising approach for improving the therapeutic efficacy of current anti-depressant drugs. However, specification of the roles played by astrocytic OCT3 is confounded by its region-restricted expression profile, and by the presence of neuronal OCT3. Therefore, characterization of how astrocyte OCT3 contributes to the D22’s effects is a challenge for future research.

On the other hand, the importance of astrocytic OCT3 function has been highlighted in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-mediated dopaminergic neurotoxicity in mice. Cui et al.\textsuperscript{19} have proposed the following model: MPTP is metabolized to MPP\textsuperscript{+} in astrocytes, which is in turn released from the cells via OCT3, and then taken up by dopaminergic neurons via DAT. Therefore, understanding the roles of OCT3 in astrocytes is important not only for CNS pharmacology, but also for CNS toxicology.

2.2. Plasma Membrane Monoamine Transporter (PMAT) While OCT3 is a transporter responsible for the uptake\textsubscript{3} system (practically synonymous with EMT), the current understanding of the uptake\textsubscript{3} system is that it encompasses a series of low-affinity, high-capacity Na\textsuperscript{+} and Cl\textsuperscript{−}-independent transporters for the biogenic amines.\textsuperscript{13} Accordingly, another transporter carrying uptake\textsubscript{3} system characteristics has been cloned: the plasma membrane monoamine transporter (PMAT, also known as equilibrative nucleoside transporter 4, SLC29A4).\textsuperscript{20}

PMAT is a relatively new organic cation transporter, originally cloned from the human brain.\textsuperscript{29} PMAT has been shown to exhibit similar transporter characteristics to those of OCT3 (for more details, please see the review article\textsuperscript{30}). Like OCT3, PMAT can transport MPP\textsuperscript{+}, dopamine, norepinephrine, epinephrine, 5-HT, and histamine, and is strongly inhibited by D22.\textsuperscript{29,30} However, it should be noted that the substrate preference of PMAT is different from that of OCT3: OCT3 exhibits higher transport activity levels towards norepinephrine, epinephrine, and histamine, whereas PMAT prefers to transport dopamine and 5-HT.\textsuperscript{24} This difference suggests that the role of PMAT in the clearance of biogenic amines at synapses is different from that of OCT3.

As with OCT3, it has been reported that PMAT is expressed in various brain regions in the mouse,\textsuperscript{29} where its predominant localization can be found in neurons.\textsuperscript{24,31} Recently, however, evidence for PMAT’s expression and functions (histamine and MPP\textsuperscript{+} uptake) has been provided in primary
and immortalized human astrocytes.\textsuperscript{20,22,23} Therefore, it is probable that PMAT also serves as an astrocyte organic cation transporter.

Considering the neurotransmitter uptake activity of PMAT, it is not surprising to assume PMAT may be a target of certain CNS drugs, in a similar manner to that of OCT3. For example, in addition to OCT3, the functional inhibition of PMAT by D22 may also be involved in its anti-depressant augmenting effects.\textsuperscript{27} However, currently it is difficult to separately evaluate the contribution of each transporter to the action of D22.

To summarize, it is considered likely that astrocytic PMAT plays a crucial role in biogenic amine clearance in both the normal and pathological brain, thus suggesting that PMAT has significant potential to become a pharmacological target in several brain diseases. In order to further enhance the feasibility of uptake\textsubscript{c} system-targeted drugs (e.g., anti-depressant drugs), it is important to develop ways whereby astrocytic OCT3 and PMAT functions are independently evaluated. In this view, the identification of selective inhibitors (like lopinavir, a recently identified PMAT-specific inhibitor\textsuperscript{27}), are expected to contribute to the clarification of transporter-specific function in astrocytes.

2.3. Other Organic Cation Transporters Regarding other members of the OCT family, results obtained so far suggest that OCT1 (SLC22A1) is not significantly expressed in the brain, if at all, but OCT2 (SLC22A2) appears to be expressed. Although OCT2 mRNA expression in rat cultured astrocytes has been reported,\textsuperscript{33} several studies have identified that OCT2 is primarily expressed in neurons.\textsuperscript{34–36} Therefore, it is possible that significance of OCT2 function in astrocytes might be only marginal. Nevertheless, its neuronal expression and functional redundancy with OCT3 and PMAT should be noted in relevant studies.

OCT asides, carnitine/organic cation transporters (OCTN1 and OCTN2, SLC22A4 and SLC22A5, respectively) are the different family of organic cation transporters. With different substrate selectivity from those of OCTs and PMAT, OCTN1 and OCTN2 can transport various cationic/amphipathic compounds, such as d-carnitine, L-carnitine (carnitine), acetyl-L-carnitine, ergothioneine, and drugs like verapamil and oxaliplatin.\textsuperscript{27}

OCTN2 is a Na\textsuperscript{+}-dependent high-affinity carnitine transporter.\textsuperscript{38} Carnitine is an essential molecule for the transport of fatty acid into mitochondria, where fatty acids are oxidized to produce acetyl-CoA as an energy source. Therefore, it is considered likely that OCTN2 activity is closely linked with tissue energy homeostasis.

Brain distribution of OCTN2 is not clearly known at present, but Inazu \textit{et al.}\textsuperscript{39} first showed functional OCTN2 expression in rat astrocytes. This has been further supported by subsequent reports of OCTN2 in rats\textsuperscript{40,41} and humans.\textsuperscript{23} The presence of OCTN2 in astrocytes seems reasonable, since astrocytes require substantial amounts of energy to fulfill their roles. Panov \textit{et al.}\textsuperscript{22} have hypothesized that, in line with the fact that perisynaptic processes of astrocytes hold large numbers of mitochondria,\textsuperscript{43} fatty acid β-oxidation is the preferable process for acetyl-CoA production, by which astrocytes accomplish large-scale production of lactate and ATP at the same time. And in fact, fatty acid oxidation in astrocytes has been proven to date.\textsuperscript{44,45} Therefore, OCTN2 may play the determinant role of carnitine availability for the fatty acid β-oxidation process.

In addition to carnitine, acetyl-L-carnitine, which is another endogenous OCTN2 substrate, is also known to be a physiologically multi-talented molecule, not simply an energy source. It can be used for amino acid synthesis,\textsuperscript{46} and acts as a nutraceutical with anti-oxidative effects.\textsuperscript{47,48} Consistently, acetyl-L-carnitine is expected to ameliorate several brain disease conditions, such as depression\textsuperscript{49} and ischemia.\textsuperscript{50} Considering that the important target site of these acetyl-L-carnitine actions is astrocytes, the functional activation of astrocytic OCTN2 should be a beneficial approach for the treatment of several brain diseases.

Meanwhile, OCTN1 exhibits differential substrate specificity (e.g., significant transport ability toward ergothioneine, but not to carnitine\textsuperscript{51}). Thus, physiological roles of OCTN1 are assumed to be clearly different from those of OCTN2. It has been shown that OCTN1 is expressed in neurons,\textsuperscript{52,53} but there is no report describing its function in astrocytes to date. However, in our unpublished observation, OCTN1 mRNA expression has been found in human primary astrocytes. It is worth further examining OCTN1 existence in human astrocytes.

3. ORGANIC ANION TRANSPORTERS

Representative multi-specific organic anion transporter families include organic anion transporters (OATs), organic anion transporting polypeptides (OATPs), and MCTs. It has been well described that several MCT members are functionally expressed in the brain; see also other excellent reviews for details.\textsuperscript{54,55} By contrast, to date there is no clear evidence for the functional expression of well-characterized OAT members (namely, OAT1–3) in astrocytes. Thus, this section focuses solely on OATPs expressed in astrocytes.

OATP1C1 (also known as OATP14 or OATP-F, SLC01C1) has exhibited a functional expression in astrocytes, as evidenced during efforts to explore the identification of a sulfonfrodamine 101 (SR101, an anionic fluorescence compound) uptake transporter in hippocampus astrocytes. It has been shown that hippocampal astrocytes can be efficiently labeled with SR101, but the uptake system involved had been unknown.\textsuperscript{56} However, Hülsmann’s group has recently clarified that SR101-labelling intensity is severely reduced in the presence of rifampicin and dehydroepiandrosterone sulfate, which are OATP substrates/inhibitors,\textsuperscript{57} and SR101-labelled astrocytes mostly disappeared in Oatp1c1-knockout mice.\textsuperscript{58}

OATP1C1 is a multi-specific organic anion transporter, but its primary substrates are thyroid hormones, with the highest activity towards 3,5,3',5'-tetraiodothyronine (thyroxine, T\textsubscript{4}),\textsuperscript{59,60} The thyroid hormone transporting ability of OATP1C1 is in good agreement with the critical roles of astrocytes in CNS thyroid hormone homeostasis. Brain cells utilize thyroid hormones of both peripheral and CNS origin. Because brain type 2 deiodinase expression is restricted in astrocytes,\textsuperscript{61} T\textsubscript{4} is converted to the active form 3,5,3'-triiodothyronine (T3), primarily in astrocytes in the brain. Then, T3 either binds to thyroid hormone receptors (TR\textsubscript{α} and TR\textsubscript{β}) in astrocytes or is released into extracellular fluids, whereby other brain cells can take up the hormone.

It has been known that thyroid hormones regulate a variety
of physiological functions of astrocytes.\textsuperscript{62,63} Briefly, thyroid hormones promote astrocyte maturation and regulate extracellular matrix synthesis and growth factor secretions.\textsuperscript{64,65} T3 enhances the expression levels of astrocytic glutamate transporters (GLAST and GLT-1).\textsuperscript{66} Furthermore, thyroid hormones indirectly affect neuronal differentiation and function through their action in astrocytes. For example, it has been observed that T3-primed astrocytes express higher levels of heparan sulfate proteoglycans, which provide neurite outgrowth effects.\textsuperscript{67}

Therefore, OATP1C1 expressed in astrocytes is likely to be a molecule actively taking part in brain thyroid hormone action, and its functional modification may have therapeutic potential in some brain diseases. However, it is also true that other thyroid hormone transporters have been identified, such as MCT8, MCT10 and L-type amino acid transporters (LATs),\textsuperscript{68} in all of these, mRNAs are expressed in astrocytes (unpublished observation). Thus, the clarification of OATP1C1-specific roles in CNS thyroid hormone homeostasis will be an important challenge in future studies.

In addition to OATP1C1, other OATP members may work as astrocyte organic anion transporters. While there is no report showing the expression of OATP1B1/Oatp1b members in astrocytes, recently Oatpl\textsubscript{a4} and Oatpl\textsubscript{a5} mRNA, and OATP2B1 mRNA expression has been reported in cultured rat and human astrocytes, respectively.\textsuperscript{23,69} Moreover, OATP3A1 and 4A1 mRNA can also be detected in primary human astrocytes (unpublished observation). While characterization of their function in astrocytes awaits further studies, it is possible that the functions of such OATP members may contribute to the pharmacological action of both current and future CNS drugs.

4. CAUTIONARY NOTES ON ASTROCYTE ORGANIC ION TRANSPORTER STUDIES

For future astrocytic organic ion transporter studies aimed at drug discovery, it is important to provide two important cautionary notes: one is astrocyte heterogeneity, and the other inter-species differences of the transporters. As for astrocyte heterogeneity, several lines of evidence have shown that morphologically different subsets of astroglial populations exist within the brain (such as protoplasmic and fibrous astrocytes), and their functions are also assumed to be different.\textsuperscript{70–72} Even in a morphologically-similar astrocyte subset, roles may differ in a region-dependent or developmental stage-dependent manner. Given these points, it is not surprising to see that the astrocytic expression of organic ion transporters is region- or stage-specific. However, to date, only limited information regarding brain distribution profiles of astrocytic organic ion transporters is available, even in rodents. Therefore, further detailed investigation regarding the matter is strongly encouraged, the results of which will be fundamental information for the precise characterization of the physiological/pathophysiological roles of organic ion transporters.

Roughly speaking, there are three types of species differences. The first is a functional (qualitative) difference. It has been shown that rat OCT3 is much more sensitive to inhibition by \textit{d}-amphetamine and ketamine (>100-fold), but less sensitive to MK-801, compared with human OCT3.\textsuperscript{66} Similarly, although to a lesser extent, differences in the inhibition properties of D22 have been observed between human and mouse PMATs.\textsuperscript{73} As suggested by these reports, even though the physiological roles of OCT3 and PMAT appear to be mostly conserved among species, their inhibitor (and substrate) recognition preference must be, at least slightly, different, depending on their intrinsic amino acid sequences.

The second difference is in expression profiles. This issue has not been clearly appreciated in the study of astrocytic transporters, and therefore, currently, no appropriate example can be provided. However, it has been shown that OATP1C1 is abundantly expressed in rodent, but not in human, blood–brain barrier.\textsuperscript{74,75} This fact invites attention to quantitative species differences in other organic ion transporters in astrocytes.

Finally, the existence of species-specific family members should be noted. A clear example is that while OCTN3 is a rodent member of the OCTN family, and expressed in rat astrocytes,\textsuperscript{76} humans do not appear to have this member.\textsuperscript{37}

Currently, the understanding of species differences of astrocytic organic ion transporters is premature. However, since this is critically important in the appropriate translation of pre-clinical results into clinical trials in drug development, extensive research efforts should be made to fully clarify these inter-species distinctions.

5. CONCLUSION

Accumulating evidence of the functional expression of organic ion transporters in astrocytes makes it likely that these transporters have significant potential to become pharmacological targets for various CNS diseases. The multi-substrate nature of organic ion transporters, along with non-fatal phenotypes identified by knockout mouse, imply that these transporters would not play a fatal, but rather a fine-tuning role in various CNS activities. Furthermore, it is expected that not only functional boosting, but also the inhibition of the transporter functions are feasible approaches in the development of new CNS drugs.

However, the identification and characterization of astrocytic organic ion transporters is still in the initial stage. Even for EMT transporters (OCT3 and PMAT), their physiological and pathophysiological roles remain to be fully established. It is true that broad substrate specificity of transporters, as well as their yet unestablished intra-brain expression characteristics, have made it difficult to precisely understand how they work in astrocytes and which diseases they are involved in. Therefore, in order to further specify their roles, elaborative research efforts, with the above-described cautionary notes in mind, are unequivocally necessary. These include the development of astrocyte-specific transporter(s) knockout mouse and transporter-specific inhibitors, scrutiny of their region- and cell type-specific expression profiles, and human-oriented examination. In these efforts, extra-astrocytic expression of the transporters should be taken into consideration.

Despite the various challenges that lie in ahead, we hope this review will stimulate additional astrocytic organic ion transporter studies that will contribute to further understanding of their physiological/pathophysiological roles, as well as to the development of manipulation strategies to modify their functions. We believe that such research advances will in turn lead to the discovery of new CNS drugs targeted to astrocytic
organic ion transporters.

Conflict of Interest The authors declare no conflict of interest.

REFERENCES


