Review
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The Role of the SLC Transporters Protein in the Neurodegenerative Disorders

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The solute carrier (SLC) superfamily is one of the major sub-groups of membrane proteins in mammalian cells. The solute carrier proteins include more than 400 different membrane-spanning solute carriers organized with 65 families in the human. In solute carrier family neurons, neurotransmitter is considered to be a pharmacological target of neuropsychiatric drugs because of their important role in the recovery of neurotransmitters such as GABA, glutamate, serotonin, dopamine and noradrenaline and regulation of their concentration in synaptic regions. Therefore, solute carrier transporters play vital and different roles in neurodegenerative disorders. In this article, the role of solute carrier transporters in neurodegenerative disorders such as Alzheimer disease, amyotrophic lateral sclerosis, Huntington disease, Parkinson's diseases, depression, post-traumatic stress disorder, dementia, schizophrenia, and Epilepsy reviewed and discussed to see how defects or absences in SLC transporter cause neurodegenerative disorders. In this review, we try to summarize what is known about solute carriers with respect to brain distribution and expression. The review summarizes current knowledge on the roles of solute carrier transporters in neurodegenerative disorders.

KEY WORDS: Solute carrier; Amyotrophic lateral sclerosis; Alzheimer disease; Post-traumatic stress disorder; Depression.

INTRODUCTION

Genes encoding the membrane protein, one of the largest gene groups in human and mouse genome, are claimed to be more than 10% of genes encoding all genes [1]. Solute carriers (SLCs) proteins, one of the major subgroups of membrane proteins that control the transport of exceptional substances such as sugar, amino acids, nucleotides, inorganic ions, lipids, and drugs on the cell membrane, include more than 400 different membrane-spanning SLCs organized with 65 families in the human [2]. Many of these membrane proteins act as coupled symporters (co-transporters) using downhill ion (H^+ or Na^+) gradients as a pushing force to transport the substrate to cells against the concentration gradient [3].

The transported molecule moves towards the low concentration region through the membrane and reaches equilibrium. Other members of the SLC family function as antiporters with substrate-binding sites, while the remaining members show channel-like properties. It is known that ion exchangers cause pH alterations around the cell surface. Therefore, when combined with Na^+/K^+ ATPase, they negate the load balance by making the intracellular membrane potentially negative. The transition of the molecule through membranes is facilitated either by changing load balance or pH [4]. In SLC family neurons, the neurotransmitter is considered to be neurodegenerative disorders such as schizophrenia (GABA, GLYT, and SERT), epilepsy (GABA and BGT), anxiety (GABA and SERT), depression (SERT and NAT), and Parkinson disease (DAT), amyotrophic lateral sclerosis (GLT) [5]. In particular, irregularities in SLC polymorphism play role in the mechanism of neurological and neuropsychiatric disorders by altering transport expression, malfunction, and regulation in the neurotransmitter system (Fig. 1).

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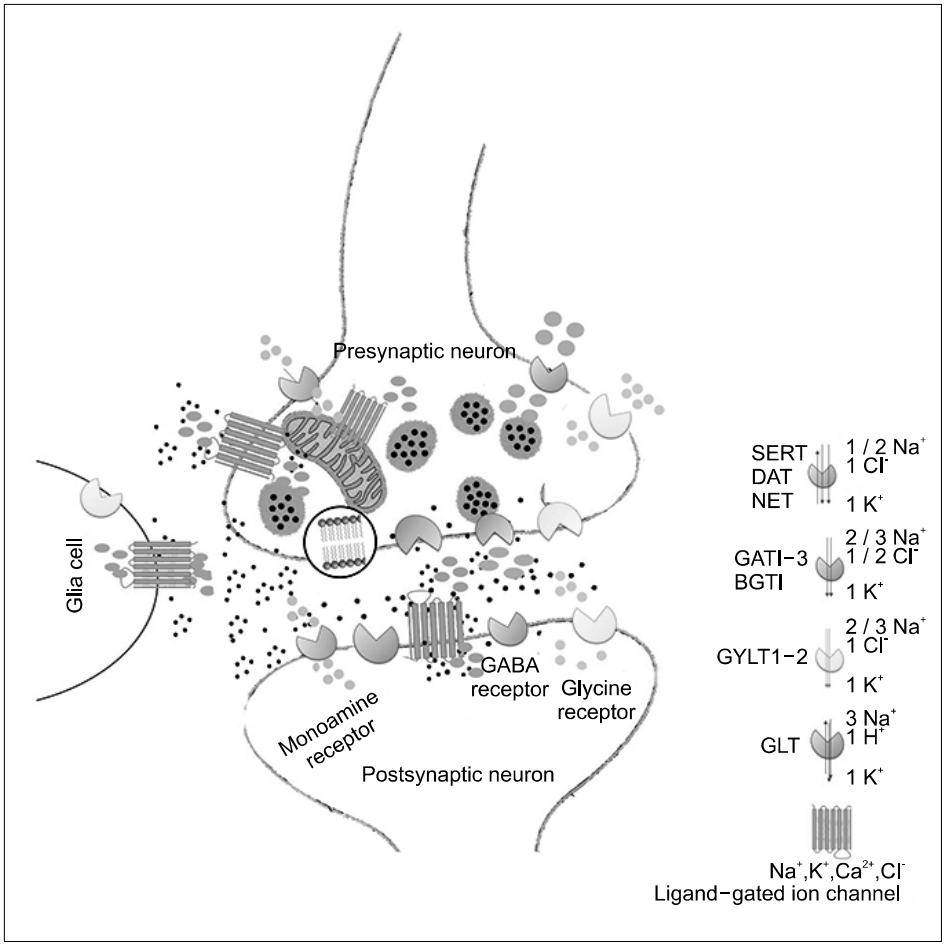

Fig. 1. A schematic representation of the physiologic function of solute carriers (SLCs) and their role in synaptic transmission in the central nervous system. SLC transporters are critical in the termination of synaptic transmission for amino acid neurotransmitters in addition to their role in providing essential nutrients and osmolytes to neurons and glial cells. Dopamine, serotonin, noradrenaline, glycine, and GABA are removed by neurotransmitter sodium symporters. The monoamine transporters (NET, SERT, and DAT) are localized to extra-synaptic sites, whereas GATs, GLYTs, and osmolyte transporter (BGTs), are localized to synaptic and extra-synaptic sites in addition to glial cells. Inhibition of NET, SERT, and DAT transporters by drugs reduces the clearance of neurotransmitters from the synapse, thus increasing their stay time in the synaptic cleft. The resulting increased concentrations of monoamines in the synaptic cleft improve receptor occupancy, leading to increased activation of ligand-gated ion channels. GLTs play a major role in maintaining the extracellular glutamate concentration at low levels and to protect neurons from the excitotoxic action of glutamate. Due to their crucial role in keeping basal concentrations of neurotransmitters low, malfunction, improper, or dysfunction of these transporters may lead to developing neurodegenerative disorders.
Neurotransmitter transporters (GAT [γ-aminobutyric acid], GYLT [glycine], and monoamine trasporter DAT [dopamine], NET [noradrenaline], SERT [serotonin]). Osmolyte transporter, BGT (betaine). Neutral amino acid transporter, GLT (glutamate).

SOLUTE CARIERS' TRANSPORTER FAMILY

The localization of SLC proteins in the brain is shown in Table 1. neurotransmitters in the brain that are released into the synapse are taken back to presynaptic neurons via SLC1 and 6 carriers [2]. SLC1 family has two subfamilies that encode glutamate transporters (SLC1A1, 2, 3, 6, and k) and neutral aminoacid transporters (SLC1A4 and 5). SLC2 members like 1, 2, 3, 6, 8, 10, and 13 are expressed in the brain. SLC5 human genes encoding SGLT proteins with the exception of SLC5A4, 5, and 7 are all expressed in the brain [6,7]. SLCA1-7 human genes are members of the high-affinity glutamate and neutral amino acid transporter family. SLC1A5 and 7 are known not to show any expression in the human brain. SLC1A1 encodes glutamate carrier called EAAC1 (also known as EAAT3). EAAC1 is a neuronal type-high affinity glutamate carrier. They are predominantly expressed in neurons in various brain regions, particularly in the hippocampus, cerebral cortex, striatum, superior colliculus, and thalamus [8].

Table 1. The distribution of solute carrier (SLC) proteins in the brain and the disorders in which play a role

Gene name	Protein name	Brain tissue expression	Disorders
SLC1			HD, epilepsy, AD, ALS, schizophrenia [3], dementia
SLC1A1	EAAC1 EAAT3	Neurons [9]	HD, epilepsy, AD [9]
SLC1A2	GLT1 EAAT2	Astrocytes [9]	AD, PD, ALS [9], dementia
SLC1A3	GLAST EAAT1	Astrocytes, cerebellar Bergmann glia [9]	AD, HD, ALS, epilepsy [9]
SLC1A4	ASCT1 SATT	Neurons	
SLC1A5	ASCT2 AAAT	Neurons	
SLC1A6	EAAT4	Cerebellum (pukinje cells) on postsynaptic dendritis spines [9]	
SLC1A7	EAAT5	Retinal neurons	
SLC2A4	GLUT4	Hippocampus, neurons	Stress [7]
SLC5A1	SGLT1	Hypothalamic neurons in rat brain [82]	
SLC5A2	SGLT2	Hypothalamic neurons in rat brain [82]	
SLC5A3	SMIT1	Hypothalamic neurons in rat brain [82]	
SLC5A6	SMVT	Hypothalamic neurons in rat brain [82]	
SLC5A8	SMCT	Hypothalamic neurons in rat brain [82]	
SLC5A9	SGLT4	Hypothalamic neurons in rat brain [82]	
SLC5A10	SGLT5	Hypothalamic neurons in rat brain [82]	
SLC5A11	SMIT2	Hypothalamic neurons in rat brain [82]	
SLC5A12	SMCT2	Hypothalamic neurons in rat brain [82]	
SLC5A4	SGLT3	Cholinergic neurons in human brain and hypothalamic neurons in rat brain [82]	
SLC6			Epilepsy [21], schizophrenia, depression [3]
SLC6A1	GAT1	Brain	Epilepsy [21], schizophrenia [21], anxiety [82]
SLC6A2	NET	Non adrenergic neuronal somata, axons, dendrites	Depression [3,82]
SLC6A3	DAT	Dopaminergic neurons,	PD [21,82], PTSD [79], depression [3]
SLC6A4	SERT	Brain	Anxiety [82], depression [3]
SLC6A5	GLYT2	Glycinergic neurons, Golgi cells, brainstem, cerebellum	Depression [3], schizophrenia [21]
SLC6A6	TAUT	Brain	
SLC6A7	PROT	Glutamatergic neurons, hippocampus	
SLC6A8	CT1	Ubiquitous all tissues	
SLC6A9	GLYT1	Brain	Schizophrenia [21,82], depression [3]
SLC6A11	GAT3	Gabaergic neurons, glia	Epilepsy [21]
SLC6A12	BGT1	Brain	Epilepsy [21]
SLC6A13	GAT2	Meninges, ependyma, choroid plexus	Epilepsy [21]
SLC6A15		Amygdala, putamen, corpus callosum in human brain and hippocampus in rat brain	Stress [78], depression
SLC6A17		Brain	
SLC6A20		Brain	
SLC7A3	CAT3	Neurons [22]	
SLC7A4	CAT4	Brain [22]	
SLC7A5	LAT2	Brain [22]	
SLC7A6	yLAT	Brain [22]	
SLC7A8	LAT2	Brain [22]	
SLC7A10	ASC1	Brain [22]	
SLC7A11	xCT	Brain [22]	
SLC8A1	NCX1	Specific splice variants found in brain	
SLC8A2	NCX2	Abundant in neurons in all parts of the brain	
SLC8A3	NCX3	At lower levels in some brain regions	

Table 1. Continued 1

Gene name	Protein name	Brain tissue expression	Disorders
SLC10A4	P4	Cholinergic neurons	AD, epilepsy [3]
SLC11A1	NRAMP1		AD, PD [3]
SLC11A2	DMT1		PD [3]
SLC12A2	NKCC1	Ubiquitous in all tissues [28]	Epilepsy [3], HD
SLC12A4	KCC1	Ubiquitous in all tissues [28]	
SLC12A5	KCC2	Neurons [28]	Epilepsy [3], HD
SLC12A7	KCC4	Extensive limited in brain [28]	Epilepsy [3]
SLC13A3	NaC3	Brain	
SLC13A5	NaC2	Brain	
SLC15A3	PHT2	Brain	
SLC15A4	PHT1	Brain	
SLC16A2	MCT8	Brain	
SLC16A5	MCT6	Brain	
SLC16A7	MCT2	Brain	
SLC16A9	MCT9	Brain	
SLC16A14	MCT14	Brain	
SLC17A2	NPT3	Brain	
SLC17A6	VGLUT2	Neurons	
SLC17A7	VGLUT1	Neurons	
SLC17A8	VGLUT3	Neurons, glia	
SLC17A9	VNUT	Neurons	
SLC18A2	VMAT2	All CNS aminergic neurons	
SLC18A3	VAChT	Cholinergic neurons	
SLC18B1	C6orf192	Brain	
SLCO1A2	OATP1A2	Brain	
SLCO1C1	OATP1C1	Blood-brain barrier	
SLC22A1	OCT1	Blood-brain barrier	
SLC22A2	OCT2	Blood-brain barrier, neurons	
SLC22A3	OCT3	Neurons, glial cells, plexus choroideus	
SLC22A15	FLIPT1	Brain	
SLC22A17	BOIT	Brain	
SLC22B1	SV2A	Subcortex (basal ganglia, thalamus)	
SLC22B2	SV2B	Hippocampus, cortex	
SLC22B3	SV2C	Striatum, substantia nigra, pons/medulla oblongata, olfactory bulb	
SLC22B4	SVOP	Brain	
SLC22B 5	SVOPL	Brain	
SLC23A2	SVCT2	Neurons	
SLC24A2	NCKX2	Brain	
SLC24A3	NCKX3	Brain	
SLC24A4	NCKX4	Brain	
SLC25			Epileptic encephalopathy [3]
SLC25A2	ORC2[a]	Brain	
SLC25A3	PHC	Brain	
SLC25A4	ANT1	Brain	
SLC25A5	ANT2	Brain	
SLC25A6	ANT3	Brain	
SLC25A8	UCP2	Hypothalamus, pituitary, brainstem [33]	
SLC25A10	DIC		
SLC25A12	AGC1		
SLC25A14	UCP5 BMCP1	Hypothalamus, hippocampus, thalamus, amygdale in the mice brain [33]	
SLC25A15	ORC1	Brain	

Table 1. Continued 2

Gene name	Protein name	Brain tissue expression	Disorders
		Brain	
SLC25A18	GC2	Brain	
SLC25A19	DNC	Brain	
SLC25A20	CAC	Brain	ALS
SLC25A22	GC1	Brain	
SLC25A23	APC2	Brain	
SLC25A25	APC3	Brain	
SLC25A27	UCP4	Brain	
SLC25A33		Brainstem, thalamus, corpus callosum, hippocampus brainstem, thalamus in the rat brain [33]	
SLC25A40		Cerebellum, olfactory bulb, cerebral cortex, midbrain, pons [33]	
SLC25A41	APC4	Olfactory bulb, pons, midbrain, cerebellum [33]	
SLC25A42		Pons, midbrain, thalamus [33]	
SLC25A44		Hindbrain, cerebellum, pons, midbrain, hypothalamus, corpus callosum [33]	
SLC25A46		Hindbrain, cerebellum, pons, midbrain, hypothalamus, corpus callosum [33]	
SLC26A9	SLC26A9	Brain	
SLC26A11	SUT1	Brain	
SLC27A1	FATP1	Brain	
SLC27A4	FATP4	Brain	
SLC28A2	CNT2	Brain	
SLC29A4	ENT4	Brain	
SLC30A3		Brain	
SLC30A4		Brain	
SLC30A10		Brain	Dementia [5,48], PD, AD [16]
SLC31		Brain	Degenerative neuronal disease [3]
SLC33A1	CTR1	Brain	
SLC35F3		Cerebellum	
SLC35F4		Cerebellum	
SLC36A1	PAT1	Brain	
SLC37A3	SPX3	Brain	
SLC38A1	SNAT1	Brain	
SLC38A4	SNAT4	Brain	
SLC38A5	SNAT5	Brain	
SLC38A6	SNAT6	Brain	
SLC38A7	SNAT7	Brain	
SLC38A8	SNAT8	Brain	
SLC38A10	N/A	Brain	
SLC39			Neurodegeneration [3], PD, AD
SLC39A4	ZIP4	Hippocampus, neurons	
SLC39A10	ZIP10	Brain	
SLC39A12	ZIP1	Brain	
SLC40A1	FPN1		PD
SCL41A2	RhBG	Cerebellum	PD
SLC44A1	CTL1	Brain	
SLC44A5	CTL5	Brain	
SLC45A1	SLC45A1	Brain	
SLC45A4	SLC45A4	Brain	
SLC49A1	FLVCR1	Brain	
SLC49A2	FLVCR2	Brain	
SLC49A3	MFSD7	Brain	
SLC52A2		Brain	

Table 1. Continued 3

Gene name	Protein name	Brain tissue expression	Disorders
SLC56A4	SFXN4	Brain	
SLC56A5	SFXN5	Brain	
SLC57		Brain	ALS [3]
SLC57A1	NIPA1	Brain	
SLC59A1	MFSD2A	Brain	
SLC60A2	MFSD4B	Brain	
SLC61A1	NPC1	Cortex, hypothalamus, cerebellum	

EAAC, excitatory amino acid carrier; EAAT, excitatory amino acid transporter; ASCT, amino acid transporter; DAT, dopamine transporter; PHT, phosphate transporter; GAT, GABA transporter; GLT, glutamate transporter; GLYT, glycine transporters; MCT, monocarboxylate transporter; NCX, Na^+/Ca^{2+}; NET, noradrenaline transporter; NRAMP, natural resistance-associated macrophage protein; OATP, organic anion transporter; SERT, serotonin transporter; SGLT, sodium glucose cotransporter 2 (SGLT-2); Zip, zinc transporter; ALS, amyotrophic lateral sclerosis; PD, Parkinson's disease; HD, Huntington disease; AD, Alzheimer disease.
Empty areas show that there is no study about the SCL protein.
[a]Ornithine carrier.

Studies on EAAC1 knock-out mice showed no improvement in neurological symptoms and neurodegeneration [9]. Besides, significant low spontaneous locomotor activity was found in homozygous mutants of knock-out mice [9]. SLC1A2 encodes glial type-high affinity glutamate transporter which is called glial glutamate transporter and glutamate synthase (GLT1) (also known as an excitatory amino acid carrier, EAAT2). This multi-pass membrane protein is required to terminate the postsynaptic effect of glutamate by rapidly removing glutamate release from the synaptic cleft, as well as preserves glutamate concentrations below toxic concentrations to prevent neuronal damage [10]. EAAT2 is particularly expressed in the cortex, hippocampus, and astrocytes of various brain regions. In the histological analysis, GLT1 knock-out mice showed neuronal degeneration in the hippocampal CA1 region, indicating the neuroprotective role of GLT1 [9]. It has also been reported that GLT1 knock-out mice have similar behavioral patterns and dramatic fatal spontaneous epileptic seizures as N-methyl-D-aspartate (NMDA)-induced seizures [11]. SLC1A3, also known as EAAT1, encodes glutamate GLAST. is a glial type-high affinity glutamate carrier which is especially seen in cerebellum [9]. While GLAST knock-out mice can coordinate simple movements, it is reported that in more difficult movement dysfunction occurs in parallel with the abnormality in cerebellum [9]. SLC1A4 encodes the Na^+ dependent neutral amino acid carrier ASCT1 (also known as SATT) [12,13]. In the brain, ASCT1 is preferably expressed in glial cells with L-serine biosynthetic enzyme 3-phosphoglycerate dehydrogenase. Therefore, large amounts of L-serine are synthesized and stored in glial cells. The L-serine release is achieved by changing the structure of the extracellular substrate due to alterations in ASCT1. This change assumes that neurons will meet their metabolic needs through the transport of small glial born neutral amino acids [14]. This change assumes that neurons will meet their metabolic needs through the transport of small glial born neutral amino acids. ASCT1 shows a broad expression in the brain. SLC1A5 encodes a second isoform of the ASC transport system called ASCT2 (also known as AAAT). ASCT2 carries glutamate with low affinity and ASCT2 mediated glutamate transport increases at low pH [15]. Similar to ASCT1, ASCT2 mediates Na^+ dependent mandatory substrate amino acid change [16]. SLC1A6 encodes the neuronal high-affinity glutamate transporter EAAT4, which is expressed in purkinje cells in the cerebellum, mainly on postsynaptic dendritic spines [17,18]. The SLC1A7 gene encodes the EAAT5 protein and the members of the SLC4 family such as 3, 4, 7, 8, and 10 are distributed in the brain. They have a role in bipolar disorder through Li^+ channels in epilepsy by affecting GABA and chloride channels [19,20].

All SLC6 are also referred to as neurotransmitter transporters. These transporters provide regulation of neurotransmitter homeostasis in the central nervous system (CNS) [21]. SLC6 family transporters are known to make a balance between inhibitory neurotransmitters, GABA and glycine, and excitatory neurotransmitter glutamate.

Many subtypes of the SLC7 gene family are expressed in the brain. Particularly, they play an important role in diseases like schizophrenia and Parkinson's disease (PD)

by influencing the distribution of the amine or amino acid structured neurotransmitter precursor known as L-DOPA [22,23].

The SLC11 (NRAMP) family members catalyze the passage of metal ions like Fe^{2+} through the cell membrane. Fe^{2+} is really important for the development of the brain and takes place in many important functions such as neurotransmission and myelination. Fe^{2+} deficiency during development may have a significant negative impact on brain development and cognition that may lead to a chronic neurological disorder. On the other hand, abnormal levels of Fe^{2+} have been reported in brain regions in neurodegenerative diseases like PD, Hallervorden-Spatz syndrome, Huntington disease (HD) and Alzheimer disease (AD) [24,25]. SLC11A2 mediated Fe^{2+} transport has been suggested to be involved in neuronal degeneration in PD and AD [26,27].

The family of SLC12 chloride carriers contributes to ion currents in various tissues, especially in the brain, kidney and choroid plexus. Seven of the 9 members of this family are well known. Na^+: K^+: $2Cl^-$ cotransporter 1 (NKCC1) is really important for the function of both central and peripheral nervous systems. The activity of NKCC1 helps to protect the extracellular areas of the brain and the environment of cerebrospinal fluid. NKCC1 expression in neurons is regulated by low expression in mature neurons and high in immature neurons. In the adult peripheral nervous system, NKCC1 is intensely expressed in primary sensory neurons and root ganglia. Although K^+: Cl^- cotransporter (KCC) 1, KCC3 and low levels of KCC4 is expressed in the brain, their expression is not limited to the nervous system, as opposed to the neuronal-specific KCC2. KCCs have been associated with sickle cell anemia, cancer growth and as well as neurological diseases. KCC2 expression is high in the hippocampus, cerebellum, and brain stem neurons [28]. Among the members of the SLC superfamily, organic anion transporting polypeptide plays an important role in the transport of both endo-xenobiotics, including numerous drugs throughout the superfamily (OATPs) plasma membranes [29]. It is known that there are eleven OATPs in humans. On this basis, human and rodent OATPs are composed of 6 families (OATP1-6) and each family may have sub-families such as OATP1A, OATP1B, OATP1C. Expressions of OATPs have generally been identified in epithelial or endothelial cells of each organ and some OATPs such as OATP1C1 specific to the rat brain have limited expression in other specific organs. Commonly expressed OATP2A1, OATP3A1 and OATP4A1 were determined by mRNA in all tissues in human [29,30]. OATP1C1, a member of the OATP1 family, is expressed in glial cells throughout the hypothalamus. Moreover, prostaglandin transporter OATP2A1 is one of the ubiquitous OATP which is known to be expressed in neurons, astrocytes, epithelial and endothelial cell layers [30]. OATP3A1, which is localized in neuron and frontal cortex, has the highest expression level in the brain and also found in many tissues. Expression of OATP5A1 and OATP6A1 in the brain were determined with mRNA analysis [29].

Organic cation transporter 3 (OCT3) encoded by SLC22A3 and SCL6A4 encoded serotonin transporter (SERT) has a high and low affinity, respectively during serotonin transport [31]. In SERT knock-out mice, the transcription level of SLC22A3 increased in the hippocampus and no such change was determined in other brain regions [32]. This regulation of SLC22A3 plays an important role in the recruitment of serotonin in the absence of SLC6A4 and may fully obscure the in vivo effect of SERT.

SLC25 proteins that act as carriers of a wide variety of molecules, are the largest SLC family with 46 members (SLC25A1-46) known as mitochondrial carriers [33]. The most of the SLCs are highly expressed in brain regions such as hypothalamus, pituitary, hippocampus, thalamus, amygdala, and brainstem, but are also present intensely in the periphery [34-38]. These proteins have been reported to play a vital role in neuronal signaling for energy production in healthy neurons [39].

In humans, there are two important Zn^{2+} carrier family known as SLC30 (ZnT) and SLC39 (ZIP) family which provide cellular Zn^{2+} homeostasis. The SLC39 contains 14 members and they are the transmembrane carriers which pump the extracellular Zn^{2+} and Cu^{2+} into the cell. Additionally, recent studies have showed that ZIP family proteins have important role in Fe^{2+} transport [40]. Zn^{2+} and Cu^{2+} play an important role in vital biological processes like growth, development and neuron functions. SLC30A3 transfers Zn^{2+} to synaptic vesicles in the brain. Interestingly, SLC30A3 expression in the brain is independent of the availability of dietary Zn^{2+} and may be important in conservation of brain Zn^{2+} during Zn^{2+} deficiency. However, the expression of SLC30A3 decreases with aging, and this process progresses faster in

patients suffering from neurodegenerative AD [41,42]. Thus, it seems likely that a loss of synaptic accumulation and subsequent release of Zn^{2+} play a role in AD pathogenesis [41]. Increased expression of SLC30A1, SLC30A4, and SLC30A6 was observed in AD patients. Chronic perturbation of Cu^{2+} homeostasis causes neuronal degeneration [43]. Microglia has been shown to upregulate SLC31A1 in response to interferon-γ activation. Increased Cu^{2+} uptake and trafficking by microglia may have a neuroprotective role in AD [27].

Among the Mg^{2+} carriers, SLC family 41 (SLC 41) has three members known as A1, A2 and A3. Although SLC41 is distributed in various tissues and organs, it is expressed in brain and provides Na^{+}/Mg^{2+} activity. Na^{+}/Mg^{2+} activity is obvious in various avian and mammalian cell types like hepatocytes, neurons and glial cells. Degradation or irregularity of Na^{+}/Mg^{2+} exchanger may alter the systemic and intracellular Mg^{2+} homeostasis and participate in the pathogenesis of various diseases related to hypertension, ischemic heart disease, neurodegeneration, inflammation and preeclampsia/eclampsia [27].

DISORDERS

Given the basic physiological roles of the SLC carriers, it is not surprising that defects in a single carrier lead to a serious disease. The dysfunction of SLCs is associated with countless neurodegenerative disorders (see Table 1).

Alzheimer Disease

Amyloid-β (Aβ) peptide aggregation or oligomerization, known to be supported in the presence of Zn^{2+} is one of the reasons affecting the pathogenesis of AD. Zn^{2+} is transmitted to the brain via SLC39 family carriers. Studies revealed that, the time course expression change of dZip1, an orthologue of human SLC39 family transporter hZIP1 in Drosophila, was recovered in brains of Aβ42 flies when compared with normal control flies. Researchers assume that modulating the expression level of dZip1 may affect the accumulation of Zn^{2+} in the brain and, accordingly, alter the pathological process of AD [44]. Recently, it has been determined that hippocampus-dependent learning and memory functions are not only based on synaptic plasticity of glutamatergic synapses, but also inhibitory GABA-secreting interneurons are required [45]. The closed link between inhibition of learning and memory is also obvious in neurodegenerative disease like Alzheimer's disease mouse model restoring inhibition rescues the associated memory deficits [45]. Divalent cations play a strong role in the pathogenesis of AD and can also regulate the Aβ peptide cluster formation. Proton-divalent cation carriers encoded by SLC11A1 and SLC11A2 are expressed in the brain as well as regulate ion homeostasis from endosomal compartments. SLC11A1 also has pleiotropic effects on pro-inflammatory responses that may be important in AD [46].

Dementia

Lewy body dementia, the second most common neurodegenerative dementia in the elderly, is characterized by Lewy neurites and Lewy bodies which formed by abnormal a-synuclein accumulation in the brainstem, limbic system, and cortical regions [47]. Glutamate transporter SLC family 1, member 2 (GLT1/EAAT2) that is expressed in astrocytes, regulates glutamate levels in synapse and plays an important role in the prevention of excitotoxic neuronal damage in certain neurodegenerative diseases. Modified mRNA and/or protein expression in glutamate transporters have been reported in transgenic models of AD [47]. Neurodegenerative diseases have been suggested to be associated with cellular stress like oxidative stress and endoplasmic reticulum (ER) stress. For instance, the positive immunoreactivity of phosphorylated PERK and eIF2a, modulators of the ER stress response pathway, was observed in the substantia nigra of PD patients [7]. Accumulation of ER stress or reactive oxygen species causes cell death of dopaminergic neurons. Although SLC30A10 has been shown to play a protective role against oxidative stress, SLC30A10 and cellular stress are thought to be related to neurodegenerative diseases. The mechanism for the cause of neurodegenerative diseases associated with cellular stress and SLC30A10 has not yet been fully elucidated; besides decreased SLC30A10 levels were determined in the brains of AD patients. Although the loss of function of SLC30A10 causes Parkinsonism, the role of SLC30A10 in the cellular cause of ER stress that may be associated with PD is unknown. In a study, the SLC30A10 mutation has been shown to cause Parkinsonism, and an autopsy of the AD patient's brain showed a decrease in SLC30A10 [5,16]. On the other hand, oxidative stress or ER stress has been reported to be related to the cause of neurodegenerative disease. In an-

other study, slc30a10 expression was observed in the cerebral cortex, hippocampus, midbrain, cerebellum and spinal cord of the rat brain. Slc30a10 has also been localized to the dopaminergic neurons of the substantia nigra, glutamatergic neurons of the striatum, and cerebral cortex neurons. Previous studies have demonstrated that the protective role of SLC30A10 against oxidative stress and the relationship between cellular stress and SLC30A10 has not yet been fully elucidated [48].

Amyotrophic Lateral Sclerosis (ALS)

ALS is the most common adult motor neuron disease leading to muscle paralysis and death within 3–5 years of onset. ALS is a progressive neurodegenerative disease characterized by degeneration of motor neurons in the primary motor cortex, brain stem, and spinal cord [49]. To date, many mechanisms have been described in motor neuron degeneration in ALS. Molecular indicators of glutathione excitotoxicity, impaired axonal transport, oxidative stress, mitochondrial dysfunction, growth factor deficiency, protein aggregation, abnormal RNA metabolism, and apoptosis were observed in the human brain, spinal cord, and transgenic disease models long before the onset of symptoms. Excessive glutamate leading to neuronal degeneration is thought to be one of the pathogenesis of ALS, a fatal neurodegenerative disorder caused by selective death of motor neurons in the brain and spinal cord [50,51]. Riluzol, a drug that is used to treat ALS, inhibits the activation of postsynaptic neurons that prevent glutamate release and reduce glutamate-induced sodium ecototoxicity [50]. Loss of EAAT1 was observed in patients with ALS. Riluzole was found to increase the transport activity of SLC1A3, which takes extracellular glutamate from the synapses and thus reduces glutamate levels in the synaptic cleft [52,53]. In another study, riluzole has been shown to stimulate glutamate uptake by increasing the level of SLC1A1 excitatory amino acid carrier in astroglial cells. Similar to EAAT1, EAAT2, the major glutamate carrier in astrocytes, has been reported to reduce the level of glutamate in the synaptic cleft, thereby alleviating excitotoxicity. The neurodegenerative diseases that may benefit from the upregulated EAAT2 function include epilepsy, stroke, and neurotrauma, as well as AD, ALS and PD. All of these diseases have been associated with a decrease in EAAT2 protein expression levels [52-55]. A decrease in glutamate transporter activity has been reported due to decreased GLT1 (EAAT2) isoform in motor and sensory cortex in patients with sporadic ALS [9]. A decrease in glutamate transporter activity has been reported due to decreased GLT1 (EAAT2) isoform in motor and sensory cortex in patients with sporadic ALS [9]. For these reasons, the development of a drug that enhances the activity of EAAT2 represents a promising approach to the development of a CNS. According to the mRNA analysis, the previous studies show that the expression of EAAT2 decreased in the spinal cord, motor cortex in ALS's patients [56,57]. The SLC25A20, a member of the large mitochondrial carrier family, catalyzes transport through the inner mitochondrial membrane. The production of ATP, calcium homeostasis and the regulation of mitochondria-associated apoptosis are reported in ALS. Abnormalities in the morphology and biochemistry of the cortex, spinal cord and muscles were observed in patients with ALS [58-60].

Huntington Disease

HD is a deadly neurodegenerative disease that cannot be treated today. Although HD is classically regarded as a motor disorder, it is also characterized by progressive motor coordination disorder and involuntary movements resulting from neurodegeneration of the striatum. HD patients experience cognitive and behavioral disorders such as learning and memory, due to impairment of cortex and hippocampus many years before the onset of motor symptoms. Additionally, similar symptoms are observed in HD mouse models [61]. While HD patients show hippocampal memory and learning deficits, changes in excitatory synaptic plasticity and spatial cognition in the hippocampus have been reported in HD mouse models [62-64].

Hippocampus excitatory synaptic plasticity changes and degeneration in spatial cognition are reported to occur in HD mouse models [65-69]. Proteomic studies have shown that the gene encoding the KCC2, slc12A5, is highly rich in the Huntington protein (Htt) proteome [25,26]. In the mouse study, by using isoform-specific amplification of slc12a5 (KCC2) and slc12a2 (NKCC1), it has been found out that KCC2 protein expression decreased in the hippocampus as it was affected by Htt [61].

Parkinson's Disease

SLC41A1, which has recently been identified as a part of a new PD susceptibility locus named PARK16, has

been reported in the pathophysiology of PD, preeclampsia, and nephronophthisis-associated ciliopathies. After that, rare PD-associated coding variants of SLC41A1, ie p.A350V, p.L146G, p.P480P and c.552 + 50G> A, were identified [44]. Studies have shown that nigrostriatal dopamine loss is important in the distinctive features of PD. SLC6A3 is known to play an important role in dopamine reuptake in striatal [70]. Allelic variants in SLC6A3 are located in PD by modulating gene expression and may increase the risk of PD by interacting with the occupational pesticide. SLC6A3/DAT1 genotype has also been found to have a significant effect on fronto-striatal activation and performance in PD. Therefore, SLC6A3 is thought to be associated with PD development by modulating the metabolism of dopamine [71]. A number of different evidences suggest that the overlapping clinical, genetic, and pathological features of PD, MSA and ALS may be caused by a common potential pathogenic pathway. Firstly, epidemiological studies have indicated that some patients with ALS have parkinsonian symptoms and also the increase in the number of PD patients thought to enhance the risk of developing ALS. Moreover, as ALS and MSA show clinical overlaps, all other evidence suggests that all these diseases occur with the combination of abnormal and improperly folded proteins. Disruption of SLC40A1 mediated Fe^{2+} flow from neurons is thought to be one of the pathogenesis of PD [72-74]. Disruption of SLC40A1-mediated Fe^{2+} flow from neurons may also contribute to the pathogenesis of PD [75].

Depression

Drugs used to treat depression can be classified according to their possible targets. For example, monoamine reuptake inhibitors containing serotonin-selective reuptake inhibitors and noradrenaline reuptake inhibitors inhibit neurotransmitter carriers. Over the past few decades, the development of new antidepressants has been moved from "chance of discovery" to single-targeted strategies and then to multiple target strategies. Several carriers in the SLC6 family have important roles in taking monoamines into the synapses of the CNS. Although they all show overlapping substrate specificity, these include NET (SLC6A2), DAT (SLC6A3), and SERT (SLC6A4), all of which are carriers of noradrenaline, dopamine, and serotonin (also known as 5-hydroxytryptamine). Drug-mediated inhibition of these carriers reduces the clearance of monoamine neurotransmitters from the synapse and thus increases the residence time in the synaptic cleft. As a result, increased concentrations of monoamines in the synaptic cleft increase receptor invasion, leading to increased activation of ligand-gated ion channels and modulation of G-protein-bound receptor signaling. However, the mechanisms by which such drugs ultimately exert antidepressant effects are not yet completely clear [21,76]. Glycine has important roles in neuronal inhibition and stimulation in the CNS. It acts as an inhibitor neurotransmitter by activating ionotropic glycine receptors, providing chloride ions to hyperpolarize the postsynaptic membrane. Glycine also binds to excitatory NMDA receptors to provide receptor activation with glutamate. Glycine carriers such as GLYT1 (also known as SLC6A9) and GLYT2 (also known as SLC6A5) on neurons, astrocytes, and glial cells regulate extracellular glycine levels in the brain and thereby regulate NMDA receptor activity [77].

SLC6A15, a neutral amino acid transporter expressed in neurons, is recommended as a candidate gene for major depression and stress vulnerability with glutamate content, a key neurotransmitter regulating stress response in the hippocampus [78]. A single nucleotide polymorphism in this gene shows all the markers of altered volume, glutamate levels, and hypothalamus-pituitary-adrenal axis activity and major depression [78].

In a study of chronic social stress where a conventional slc6a15 knock-out mouse line and a virus-mediated hippocampal slc6a15 overexpression mice were used, both slc-knock-out mice and a virus-mediated hippocampal slc6a15 overexpression mice were reported to have lower anxiety and depressive behaviors compared to stressed wild-type offspring, after chronic social stress. These findings suggest that the deletion of slc6a15 changes the HPA axis activation following chronic social stress and reduces the negative behavioral consequences of chronic social stress. In addition, the expression levels of GluR1 in hippocampus, particularly in dentate gyrus, were reported to be significantly affected by levels of slc6a15. The results of the study showed that slc6a15 levels affect HPA axis activation under chronic stress conditions, regulating anxiety and depressive behaviors and affecting GluR1 expression in hippocampus [78].

Post-Traumatic Stress Disorder (PTSD)

PTSD is a complex disorder characterized by three symptom clusters including re-experiencing, avoidance, and hyperarousal. SLC6A3 (also known as DAT1 or DAT) and it is a biologically relevant candidate gene for PTSD. SLC6A3 encodes a dopamine transporter, a member of the sodium- and chloride-dependent neurotransmitter transporter family, which plays a key role in the regulation of dopaminergic neurotransmission by removing dopamine from the synaptic cleft [79]. The role of dopamine in the etiology of PTSD is supported by increased urine and plasma dopamine levels. This shows a significant correlation between dopamine concentration and severity of PTSD symptoms. The complexity of the relationship between SLC6A3 and PTSD may be related, not only to genetic but also to the evidence that epigenetic factors constitute the risk of mental illness. Epigenetic disorder plays a role in the pathogenesis of various psychiatric disorders such as depression, schizophrenia, and PTSD. The study investigating how genetic and epigenetic, molecular variation in the SLC6A3 locus affect the risk of PTSD, it has been reported that SLC6A3 39UTR VNTR polymorphism significantly increased the lifetime risk of PTSD. It has also been shown that participants with high DNA methylation provide preventive new evidence for interaction with genetic and epigenetic variation affecting PTSD risk, which significantly increases the risk of the disease. The results of the study support the 9R allele of SLC6A3 39UTR VNTR polymorphism as a risk allele for PTSD compared to homozygous 10R genotype in PTSD [80].

Schizophrenia

Glycine has an important role in neuronal inhibition and stimulation in CNS. Glycine binds to excitatory NMDA receptors to provide receptor activation with glutamate. Glycine carriers such as GLYT1 (also known as SLC6A9) and GLYT2 (also known as SLC6A5) on neurons, astrocytes, and glial cells regulate levels of extracellular glycine in the brain and thereby regulate NMDA receptor activity. According to the glutamate hypothesis of schizophrenia, the symptoms of the disease are caused by insufficient glutamatergic (NMDA) signaling and therefore GLYT1 inhibitors have been developed to increase the NMDA signal in this disorder to inhibit glycine reuptake in NMDA receptors and to increase glycine levels [2].

Epilepsy

Epilepsy is one of the most common neurological disorders in the population up to 1%. It is a complex genetic disease, and many different gene families are actively being investigated as a potential response to antiepileptic drugs. Decreased KCC2 expression in mouse models of intractable epilepsy and in human patients with temporal lobe epilepsy is additional evidence for its role in the regulation of neuronal excitability [28]. In a study, it has been shown that the synaptic protein SLC10A4 affects the sensitivity to cholinergic chemo-convulsant and the absence of SLC10A4 induces the altered function of neural networks and possibly epileptic vulnerability [81,82].

CONCLUSION

In this review, it has been emphasized that SLC proteins are of great importance in the elucidation of neurodegenerative disorder mechanism due to their important role in the synaptic regulation of the neurotransmitters. Therefore, this review will also contribute to the regulation of existing treatments and the creation of new treatment options, with the non-radical treatment of SLC proteins.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Asli Aykaç, Ahmet Özer Şehirli. Data acquisition: Asli Aykaç, Ahmet Özer Şehirli. Formal analysis: Asli Aykaç, Ahmet Özer Şehirli. Supervision: Asli Aykaç, Ahmet Özer Şehirli. Writing—original draft: Asli Aykaç, Ahmet Özer Şehirli. Writing—review & editing: Asli Aykaç, Ahmet Özer Şehirli.

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