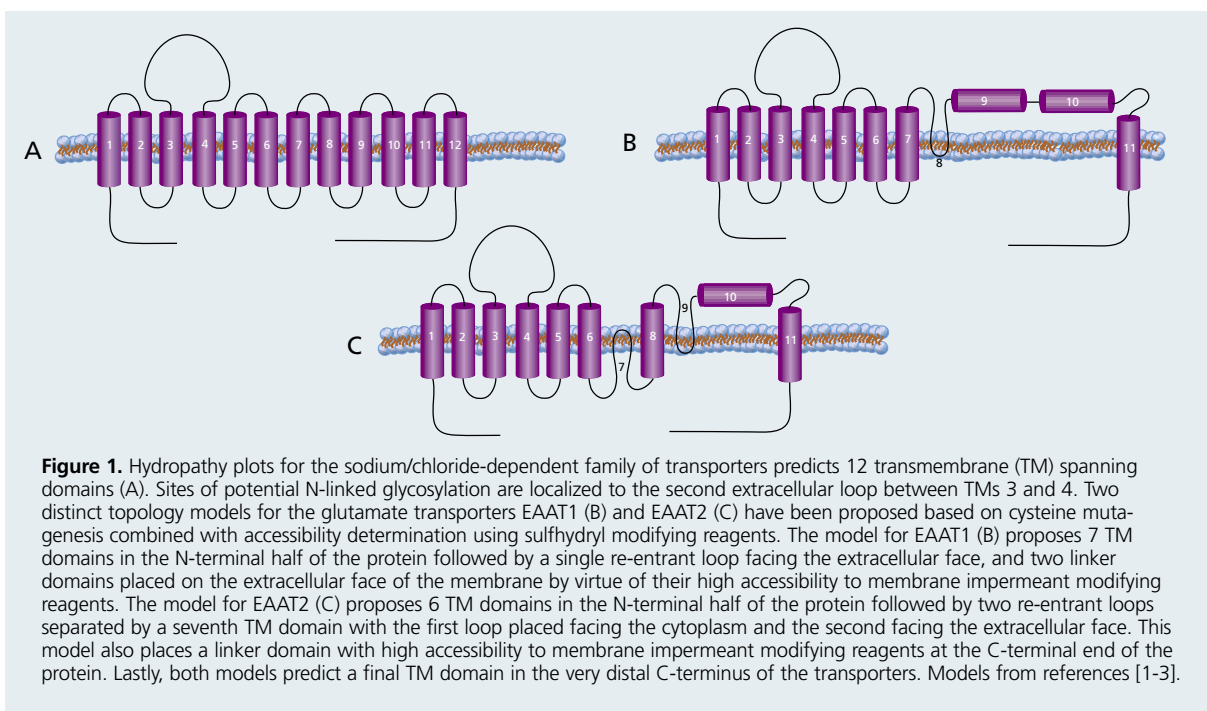


# Neurotransmitter Transporters: Two Busy Families

John Dunlop

Inactivation of the amino acid and biogenic amine neurotransmitters is achieved by their active removal from synapses by plasma membrane neurotransmitter transporters. Two distinct transporter gene families have been identified; the sodium-dependent glutamate transporter family and the sodium/chloride-dependent family encompassing the transporters for GABA (Prod. No. [A 2129](#)), glycine (Prod. No. [G 7403](#)), serotonin (Prod. No. [H 9523](#)), norepinephrine (Prod. No. [A 9512](#)) and dopamine (Prod. No. [H 8502](#)). Common to both families, substrate transport is driven largely by the energy of the sodium-electrochemical gradient and there is co-transport of sodium with substrate translocation. An important mechanistic difference between the two families is the counter-transport of potassium,

with respect to the functional properties of neurotransmitter transporters which go beyond the primary function of substrate binding and translocation. These include the dynamic regulation of the transporters by substrates (and other transporter ligands), phosphorylation and accessory proteins. This review will focus on the basic pharmacology, acute regulation, and identified protein:protein interactions of the neurotransmitter transporter family members. Finally, it should be noted that a number of transporters exhibit channel-like activity, distinct and uncoupled from the ionic requirements for substrate translocation, and potentially exist in monomeric and oligomeric forms. The functional significance of these two properties is not yet well understood.



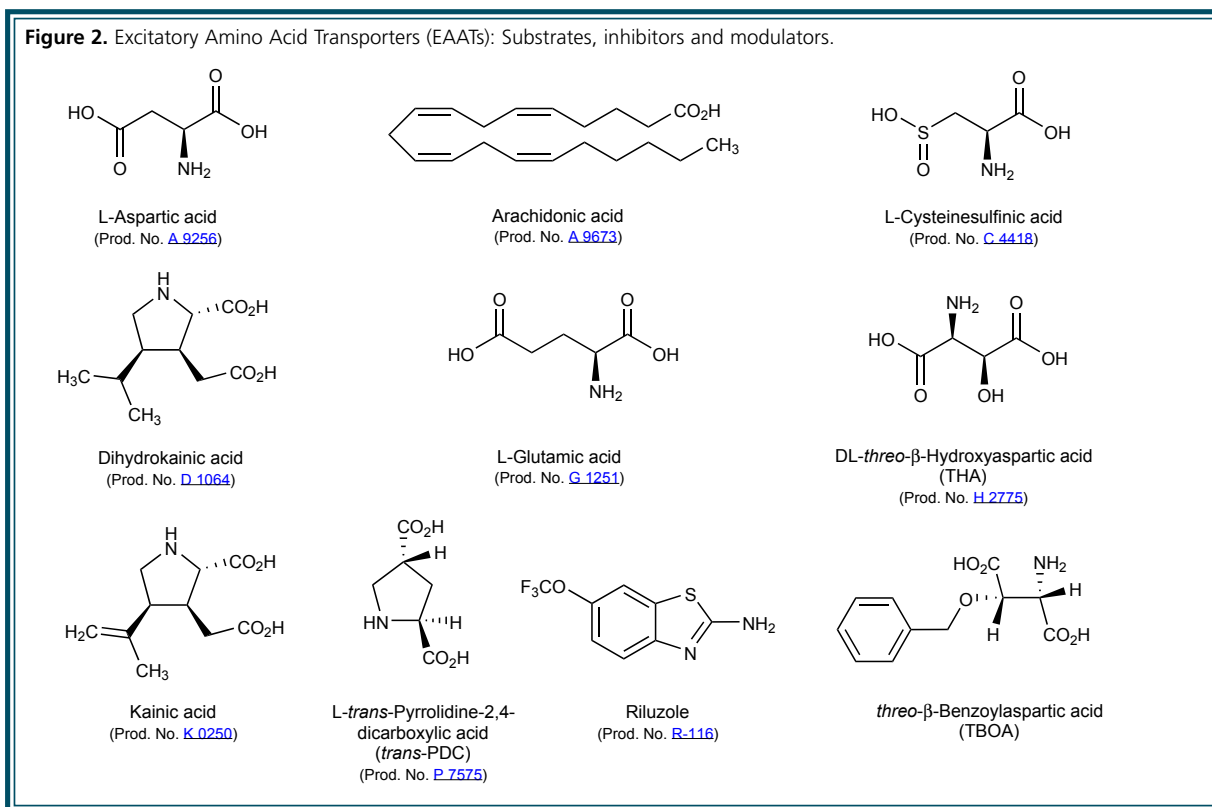
restricted to the glutamate transporters, and the co-transport of chloride, restricted to the sodium/chloride-dependent family. In addition, sequence homologies are high within each family, but are divergent between families. Moreover, the predicted membrane topology of the sodium/chloride-dependent family of transporters is consistent with 12 transmembrane-spanning domains (Figure 1A) [1]. However, there is controversy concerning the topology of the glutamate transporters; in particular, the C-terminal half of the protein (Figures 1B, 1C) [2,3]. Despite the diversity of substrates and the structural and mechanistic distinctions between families, several common family traits have emerged

## About the Author

**John Dunlop** received his Ph.D. from the University of St. Andrews where he studied in the laboratory of Dr. Roger Griffiths and characterized the neurochemical properties of a number of sulfur-containing glutamic acid analogs. In 1992, he joined the Biochemical Pharmacology group at Wyeth Research in Taplow, UK where he established a number of *in vitro* neurotransmitter release and G protein-coupled receptor (GPCR) signaling assays. In 1995, he relocated to Wyeth-Ayerst (presently Wyeth Research) in Princeton, USA where he is currently a Principal Scientist in the Neuroscience division. He is currently responsible for a research group that focuses on drug discovery targets including GPCRs and glutamate transporters.

## Neurotransmitter Transporters...(continued)

**Figure 2.** Excitatory Amino Acid Transporters (EAATs): Substrates, inhibitors and modulators.



### Sodium-Dependent Glutamate Transporter Family: Excitatory Amino Acid Transporters (EAATs)

L-Glutamic acid (Prod. No. [G 1251](#)) is the predominant excitatory neurotransmitter in the mammalian central nervous system (CNS). Reuptake of glutamic acid is important not only for the termination of glutamatergic neurotransmission, but also for the maintenance of low extracellular glutamic acid levels below a threshold required to elicit excitotoxicity. The existence of multiple glutamate transporter subtypes was originally inferred by the heterogeneity of radio-labeled glutamate transport in synaptosomal preparations derived from various brain regions [4,5]. Almost simultaneously, three distinct glutamate transporters, referred to as GLAST (GLutamate/ASpartate Transporter), GLT-1 (GLutamate Transporter) and EAAC1 (Excitatory Amino Acid Carrier), were cloned [6-8], confirming the presence of multiple subtypes. Subsequently, human homologs for each of these subtypes were isolated and the designation excitatory amino acid transporter (EAAT) was adopted for the human clones EAATs 1-3, respectively [9]. Identification of two additional subtypes, EAATs 4 and 5 [10,11], completes the currently known siblings. The EAAT designation recognizes the multiple excitatory amino acid substrates including L-glutamic acid, L-aspartic acid (Prod. No. [A 9256](#)) and L-cysteine sulfinate (Prod. No. [C 4418](#)).

Pharmacological tools to discriminate between the EAATs are somewhat limited with only kainic acid (Prod. No. [K 0250](#)) and dihydrokainic acid (Prod. No. [D 1064](#)) available as selective inhibitors of the EAAT2 subtype [9]. Unfortunately, the use of the former compound as a selective EAAT2 blocker is limited by its ionotropic glutamate receptor activity. Of the five glutamate transporter subtypes, EAAT2, predominantly localized to astroglial cells, is the subtype commonly considered to represent the family quantitatively, both in terms of expression level and contribution to total uptake capacity. Generally speaking, the most frequently used uptake inhibitors, including L-trans-pyrrolidine-2,4-dicarboxylic acid (Prod. No. [P 7575](#)) [12], threo-hydroxyaspartic acid (Prod. No. [H 2775](#)) [13] and threo-β-benzoylaspartic acid (TBOA) [14], are essentially non-selective across the subtypes and therefore provide tools for the inhibition of total net uptake rather than the discrimination of individual transporter subtypes. One hallmark of EAAT2 is the enhancement of transport activity observed in the presence of arachidonic acid (Prod. No. [A 9673](#)) in both *Xenopus* oocytes and recombinant expression systems [15,16], although paradoxically, arachidonic acid decreases the transport activity of the purified transporter reconstituted in liposomes [17]. Recent data suggest that the glutamate transporter may be a target for the neuroprotective and anti-convulsant compound riluzole

## Neurotransmitter Transporters...(continued)

(Prod. No. [R-116](#)). This agent, which possesses many potential modes of action including modulation of glutamate receptors and ion channel activity, has recently been shown to stimulate glutamate uptake in synaptosomes isolated from spinal cord [18].

Beyond the primary function of binding and translocation of substrate, glutamate transporters and their cousins in the sodium/chloride-dependent family are regulated at multiple levels, including by the substrate itself (and other transporter ligands), by phosphorylation via protein kinases and by their interaction with accessory proteins. These multiple levels of regulation may control the availability of functional transporters at the cell surface by both acutely affecting the transport activity and controlling their trafficking to and from the plasma membrane. The participation of the substrate L-glutamic acid in the regulation of glutamate transporters was first demonstrated for the GLAST (EAAT1) subtype where incubation of glial cultures in the presence of glutamic acid led to an increase in its cell surface expression and corresponding transport activity [19]. Similar regulation of EAATs 1-4 by glutamic acid has been observed, although increases in transporter activity following glutamic acid treatment are not always associated with increased cell surface expression of transporter protein [20].

Many studies have evaluated the effect of phosphorylation on the activity and cell surface expression of glutamate transporters, although conflicting results have arisen from many different laboratories. Generally, phorbol ester activation of protein kinase C (PKC) results in either an increase or decrease in transport activity which is sometimes associated with up-regulation or internalization of the transporter(s). GLAST is reported to be down-regulated following direct phosphorylation of the transporter protein after PKC activation with phorbol ester [21]. In the case of EAAT2, the data is most conflicting with reports of both PKC-mediated up- and down-regulation or even a lack of effect on both activity and cell surface expression [22-24]. Similarly, EAAC1 is rapidly up-regulated in C6 glioma cells following activation of PKC [25,26], yet it is down-regulated in *Xenopus* oocytes [27]. Up-regulation of EAAC1 in C6 glioma cells has also been reported in response to treatment with platelet-derived growth factor (PDGF, Prod. No. [P 8147](#)), suggesting that activation of tyrosine kinase and phosphatidylinositol 3-kinase (PI3K, Prod. No. [P 8615](#)) signaling cascades contribute to its regulation [28]. It seems clear that phosphorylation does play an important role in the regulation of glutamate transporters, although the use of different model systems has produced conflicting results, indicating that cellular context

has an impact on the outcome of such studies. With this in mind, it will be important to assess these aspects of regulation with transporters that have been expressed in a more native environment.

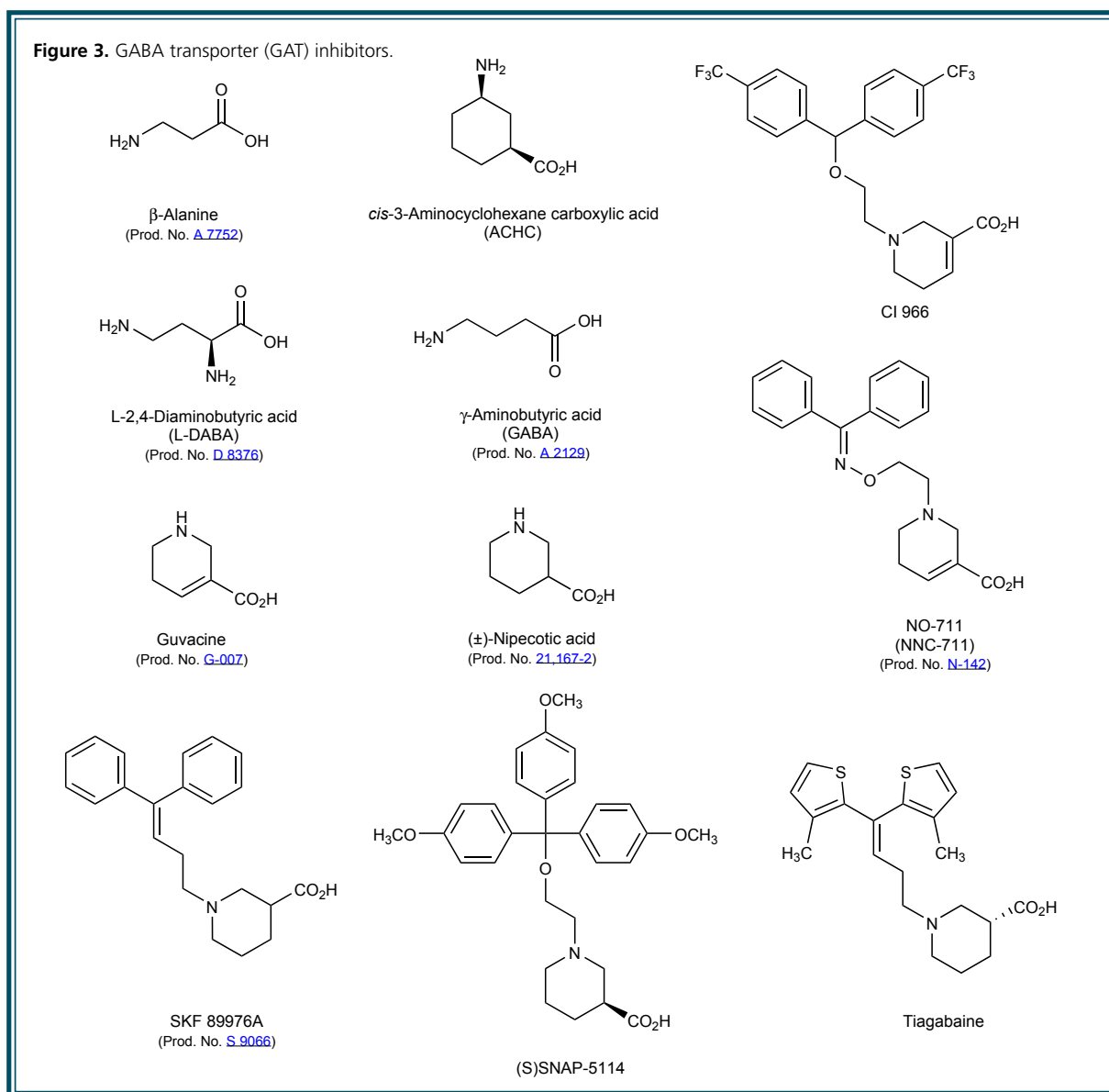
Recently, a number of glutamate transporter accessory proteins have been identified, adding further to the complexity of transporter regulation. Glutamate transport associated protein 3-18 (GTRAP 3-18) negatively regulates the functional activity of EAAT3 [29], while GTRAP41 and GTRAP48 are positive regulators of EAAT4, producing an increase in total EAAT4 transport capacity when co-expressed by a mechanism attributed to increased cell surface expression of the transporter protein [30]. The LIM protein Ajuba interacts with EAAT2 without influencing the functional transport activity and is proposed to act as a scaffolding or trafficking partner [31].

### Sodium/Chloride-Dependent Family: GABA ( $\gamma$ -Aminobutyric Acid) Transporters (GATs)

GABA is the predominant inhibitory neurotransmitter in the mammalian CNS. Similar to the glutamate transporter family history, multiple GABA transporters were originally proposed based on the pharmacology and kinetics of GABA transport in a number of CNS derived preparations, particularly the differences between neuronal and astrocytic uptake [32]. Molecular cloning techniques have subsequently confirmed the existence of multiple GABA transporter subtypes. The GABA transporter, GAT-1, was the first neurotransmitter transporter to be cloned. The cDNA for GAT-1 was identified after purification of GABA transporter protein, partial amino acid sequencing and design of oligonucleotide probes to screen a rat brain cDNA library [33]. Subsequent, sequence homology screening has produced additional GABA transporter subtypes (in addition to those for glycine and biogenic amines as discussed below) including GAT-2 and GAT-3 [34], BGT-1, a betaine/GABA transporter [35] and TAUT, a taurine/GABA transporter [36]. The betaine and taurine transporters display high- and low-affinity for GABA, respectively.

GABA uptake into primary cultures of neurons and astrocytes has been shown to exhibit different pharmacological profiles based on the inhibitory potencies measured for a number of uptake blockers including nipecotic acid (Prod. No. [21.167-2](#)), guvacine (Prod. No. [G-007](#)),  $\beta$ -alanine (Prod. No. [A 7752](#)), 2,4-diaminobutyric acid (Prod. No. [D 8376](#)) and *cis*-3-aminocyclohexane carboxylic acid [32].

## Neurotransmitter Transporters...(continued)



These agents and other more recently developed lipophilic derivatives with anti-convulsant properties, including tiagabine (NO-328), NNC-711 (NO-711, Prod. No. [N-142](#)), SKF-89976A (Prod. No. [S 9066](#)) and CI-966, have later been shown to exhibit selectivity for the GAT-1 subtype when studied in heterologous expression systems [37]. Agents selective for the other subtypes are limited, with the two nipecotic acid derivatives, NNC 05-2045 and NNC 05-2090, described as non-GAT-1 preferring based on synaptosomal uptake studies [38], and (S)-SNAP-5114 reported to display 4-fold selectivity for GAT-3 over GAT-2 [39].

Similar to EAAT2 in the glutamate transporter family, GAT-1 is the subtype commonly considered to represent the family quantitatively. Its regulation has been

studied in some detail revealing an important interaction between the neurotransmitter release and reuptake machinery. Phorbol ester treatment of *Xenopus* oocytes expressing GAT-1 induces an increase in the  $V_{max}$  for GABA transport, an effect attributed to the trafficking of intracellular transporters to the cell surface [40]. Syntaxin 1A, a protein present in the neuronal plasma membrane and involved in the docking and fusion of synaptic vesicles during the release process, interacts with GAT-1 as a positive regulator of its surface expression [41]. Paradoxically, syntaxin 1A negatively regulates GAT-1 functional transport activity, indicating that GAT-1 regulation by interaction with syntaxin 1A is complex. GABA appears to be involved in regulating this complex process since GABA transporter substrates up-regulate transporter

## Neurotransmitter Transporters...(continued)

activity by a mechanism postulated to involve relieving the negative influence of syntaxin 1A on functional activity [42-45]. It is clearly a very exciting development to establish a partnership between a protein known to regulate release of the neurotransmitter and one responsible for its retrieval. GAT-2 and GAT-3 regulation has been documented in the context of targeted sorting in MDCK cells, with localization to the basolateral and apical surfaces, respectively [46]. Importantly, a C-terminal motif has been identified as a sorting determinant for GAT-2 and GAT-3, and in the case of GAT-3, a PDZ-like interaction domain has been noted, suggesting that protein:protein interactions might be important in the regulated expression of this subtype.

### Glycine Transporters (GLYTs)

Glycine is a major inhibitory neurotransmitter in the spinal cord and brain stem, and a co-agonist of the NMDA subtype of excitatory glutamate receptor that is widely distributed throughout the CNS. Two glycine transporter subtypes have been cloned and designated GLYT1 and GLYT2 [47-50]. Tissue distribution studies support a correlation between GLYT1 expression with NMDA glutamate receptors and GLYT2 with the strychnine-sensitive inhibitory glycine receptor, suggesting the two distinct subtypes control the availability of glycine at its two principle sites of action. Pharmacological discrimination of GLYT1 and GLYT2 is achieved using sarcosine (N-methylglycine; Prod. No. [S 7672](#)) and the derivative ALX 5407 ((R)-(N-[3-(4'-fluorophenyl)-3-(4'-phenylphenoxy)propyl]sarcosine), both of which are selective for the GLYT1 subtype [51]. In addition, high concentrations of the tricyclic antidepressant amoxapine (Prod. No. [A-129](#)) inhibit GLYT2 to a greater extent than GLYT1, while doxepin (Prod. No. [D 4526](#)), amitriptyline (Prod. No. [A 8404](#)) and nortriptyline (Prod. No. [N 7261](#)) are equipotent at both subtypes [52].

Regulation of GLYTs has been less extensively characterized than for the EAATs or the GATs. The cloned GLYT1 transporter expressed in HEK cells is down-regulated following treatment with phorbol esters, indicating modulation by PKC [53]. In C6 glioma cells, the endogenous glycine uptake system is inhibited by treatment with arachidonic acid, although no similar reports have appeared with the cloned subtypes [54]. In common with the GAT-1 subtype, syntaxin 1A is an important binding partner for the glycine transporters [55]. Transient co-expression of either transporter with syntaxin 1A in COS cells resulted in a decreased capacity for glycine uptake. In synaptosomal preparations, depolarizing

conditions initiated cell surface trafficking followed by retrieval of GLYT2. Furthermore, the membrane insertion step was prevented when syntaxin 1A was inactivated by treatment with botulinum neurotoxin C (Prod. No. [B 1036](#)) [56]. These results suggest an important role once again for syntaxin 1A in the regulation of the neurotransmitter transporter life cycle.

### Norepinephrine, Dopamine and Serotonin Transporters (NETs, DATs and SERTs)

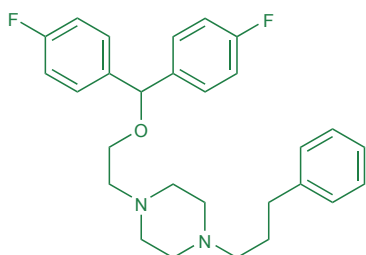
Unlike their amino acid relatives, a single transporter protein accounts for the reuptake of each of the biogenic amines norepinephrine, dopamine and serotonin. First to be isolated by expression cloning was the norepinephrine transporter (NET) [1], followed by the dopamine (DAT; Prod. No. [D-209](#)) [57,58] and the serotonin (SERT) [59] transporters using approaches combining both expression and homology cloning. Some degree of substrate promiscuity exists between these transporters, e.g., dopamine is also a substrate for NET while serotonin is also a substrate for DAT. A rich pharmacology exists for the biogenic amine transporters by virtue of their interaction with many drugs that are used in the treatment of psychiatric diseases and drugs of abuse such as cocaine (Prod. No. [C 5776](#)) and amphetamines (Prod. Nos. [A 5880](#), [A 1263](#)).

Pharmacologically, NET is characterized by its sensitivity to the tricyclic antidepressants desipramine (Prod. No. [D 3900](#)), nortriptyline (Prod. No. [N 7261](#)) and imipramine (Prod. No. [I 7379](#)), and its insensitivity to the serotonin reuptake inhibitor citalopram (Prod. No. [C 7861](#)) [1]. In comparison, potent inhibition by GBR 12909 (Prod. No. [D-052](#)) and mazindol (Prod. No. [M 2017](#); also a potent blocker of NET) are distinguishing pharmacological characteristics of DAT [57], while the selective serotonin reuptake inhibitors (SSRIs) fluoxetine (Prod. No. [F-132](#)), paroxetine, fluvoxamine (Prod. No. [F 2802](#)) and citalopram are potent blockers of SERT [59] and exert much weaker (or no) inhibitory activity on either NET or DAT. Compounds with mixed pharmacologies also exist, for example, venlafaxine, which blocks both NET and SERT and is used clinically to treat depression and generalized anxiety disorder. Cocaine and amphetamine interact with all three transporters with varying potencies exhibiting a preference, based on IC<sub>50</sub> values for inhibition of substrate transport, for NET followed by DAT and then SERT.

## Neurotransmitter Transporters...(continued)

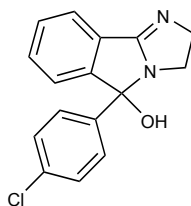
Figure 4. Biogenic amine transporter inhibitors.

DAT Preferring



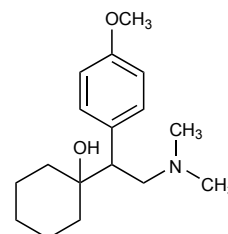
GBR 12909  
(Prod. No. [D-052](#))

DAT/NET Preferring



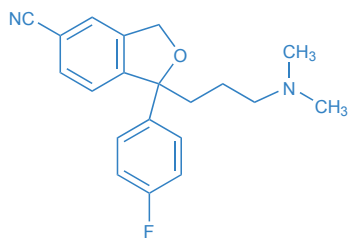
Mazindol  
(Prod. No. [M-2017](#))

NET/SERT Preferring



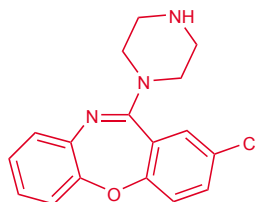
Venlafaxine

SERT Preferring

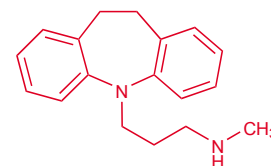


Citalopram  
(Prod. No. [C-7861](#))

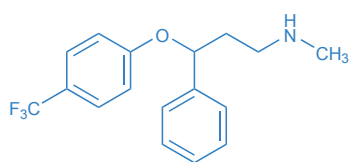
NET Preferring



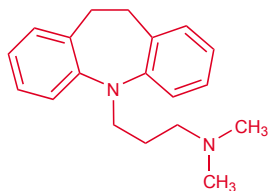
Amoxapine  
(Prod. No. [A-129](#))



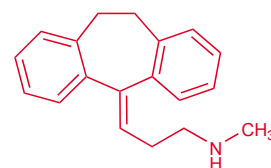
Desipramine  
(Prod. No. [D-3900](#))



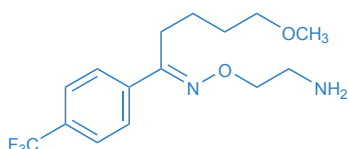
Fluoxetine  
(Prod. No. [E-132](#))



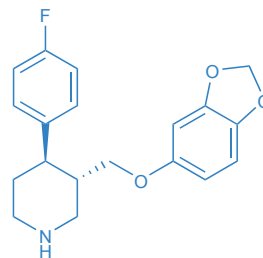
Imipramine  
(Prod. No. [L-7379](#))



Nortriptyline  
(Prod. No. [N-7261](#))



Fluvoxamine  
(Prod. No. [F-2802](#))



Paroxetine

## Neurotransmitter Transporters...(continued)

NET, DAT and SERT have similar regulatory mechanisms controlling both functional transport activity and cell surface expression to those described above for the amino acid neurotransmitter transporters. Using heterologous expression systems, it has been demonstrated that activation of PKC leads to a decrease in the transport activity of NET, DAT and SERT attributed to an internalization of the transporter protein(s) [60-62]. In the case of SERT, there is evidence for direct phosphorylation of the transporter protein [63]. In contrast, PKC-dependent internalization of DAT can occur in the absence of direct phosphorylation [64], implicating accessory phosphoproteins in this component of its regulation. Additional regulatory mechanisms for DAT have been revealed using inhibitors of tyrosine kinase [65] and PI3K [66], that both produce decreases in net transport activity associated with transporter removal from the cell surface. Conversely, activation of the PI3K signaling pathway following insulin treatment resulted in an increase in DAT activity and cell surface expression [66].

As described for the amino acid transporters, regulation of the biogenic amine transporters by their endogenous substrates is emerging as an important mechanism for controlling both their functional activity and cellular trafficking. Substrates for SERT, including serotonin, amphetamine and fenfluramine (Prod. Nos. [F 8507](#), [F-112](#), [F-113](#)), reduce the phosphorylation of transporter protein and internalization following activation of PKC by phorbol ester [67]. This provides for a use-dependent regulation of SERT expression (and function) by maintaining the transporter on the cell surface when extracellular clearance of available serotonin is required. Conversely, in the case of DAT, substrates such as dopamine and amphetamine reduce transporter activity by promoting internalization. In contrast, the inhibitor cocaine blocks this effect [68] and itself produces an increase in net uptake capacity by promoting cell surface expression [69]. Consistent with the negative regulation of DAT by substrates observed in the recombinant studies, both methamphetamine (Prod. No. [M 8750](#)) and methylenedioxymethamphetamine (MDMA, 'Ecstasy'; Prod. Nos. [M 6403](#), [M-139](#))

### Neurotransmitter Transporter Research Tools Available from Sigma-RBI

#### Dopamine Transport (DAT) Inhibitors

<a href="#">D-044</a>	Amfolenic acid
<a href="#">B-138</a>	BTCP HCl
<a href="#">B-102</a>	Bupropion HCl
<a href="#">C-124</a>	$\beta$ -CFT naphthalenesulfonate (WIN 35,428)
<a href="#">C-156</a>	D-CPT tartrate (WIN 35,065-2)
<a href="#">C-207</a>	4'-Chloro-3 $\alpha$ -(diphenylmethoxy)tropane HCl
<a href="#">D-205</a>	4',4'-Difluoro-3 $\alpha$ -(diphenylmethoxy)tropane HCl
<a href="#">D-209</a>	Dopamine transporter, human
<a href="#">D-052</a>	GBR 12909 diHCl
<a href="#">G 9659</a>	GBR 12935 diHCl
<a href="#">G-120</a>	GYKI 52895
<a href="#">T 3146</a>	Trimipramine maleate

#### Norepinephrine Transport (NET) Inhibitors

<a href="#">A-129</a>	Amoxapine
<a href="#">D 3900</a>	Desipramine HCl
<a href="#">M 9651</a>	Maprotiline HCl
<a href="#">N-151</a>	Nisoxetine HCl
<a href="#">N 7261</a>	Nortriptyline HCl
<a href="#">P 8813</a>	Protriptyline HCl
<a href="#">T 7947</a>	Tomoxetine HCl

#### Serotonin Transport (SERT) Inhibitors

<a href="#">A-164</a>	Alaproclate HCl
<a href="#">C-155</a>	nor- $\beta$ -CIT
<a href="#">C 7861</a>	Citalopram HBr
<a href="#">C 7291</a>	Clomipramine HCl
<a href="#">F-132</a>	Fluoxetine HCl
<a href="#">F 1553</a>	S(+)-Fluoxetine HCl
<a href="#">F 1678</a>	R(-)-Fluoxetine HCl
<a href="#">F 2802</a>	Fluvoxamine maleate

<a href="#">F-133</a>	Norfluoxetine HCl
<a href="#">Q-109</a>	6-Nitroquipazine maleate
<a href="#">T 6154</a>	Trazodone HCl
<a href="#">Z-101</a>	Zimelidine diHCl

#### Mixed DAT/NET/SERT Inhibitors

<a href="#">A 8404</a>	Amitriptyline HCl
<a href="#">D 4526</a>	Doxepin HCl
<a href="#">M 2017</a>	Mazindol
<a href="#">I-119</a>	Indatraline HCl (Lu 19-005)
<a href="#">I 7379</a>	Imipramine HCl
<a href="#">N 1530</a>	Nomifensine maleate

#### GABA Transport Substrates

<a href="#">A 7752</a>	$\beta$ -Alanine
<a href="#">B 3501</a>	Betaine HCl

#### GABA Transport Inhibitors

<a href="#">D 8376</a>	L-DABA diHCl
<a href="#">G-007</a>	Guavacine HCl
<a href="#">N-142</a>	NO-711 HCl
<a href="#">211672</a>	Nipecotinic acid
<a href="#">V 8261</a>	Vigabatrin

#### Excitatory Amino Acid Transport Inhibitors

<a href="#">D 1064</a>	Dihydrokainic acid
<a href="#">H 2775</a>	threo-Hydroxyaspartic acid
<a href="#">K 0250</a>	Kainic acid
<a href="#">P 7575</a>	trans-2,4-Pyrrolidine-2,4-dicarboxylic acid

#### Glycine Transport Inhibitors

<a href="#">S 7672</a>	Sarcosine
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## Neurotransmitter Transporters...(continued)

decrease DAT function *in vivo* [70,71]. Taken together, these observations have important implications for the interpretation of drug action, since these agents can no longer simply be viewed as inhibitors of the transport process.

Dynamic regulation of the biogenic amine transporters likely involves many accessory proteins that regulate both their activity and their trafficking. A number of binding partners have been identified. Of particular significance with respect to an involvement in the targeting of transporter proteins is the demonstration that the PDZ domain containing protein PICK1 strongly interacts with both DAT and NET (weaker with SERT) in both recombinant expression systems and cultured neurons [72]. Whether PICK1 acts simply as a general targeting and anchoring partner, or also participates in the dynamic regulation of transporter function and expression, remains to be determined. Another identified partnership is between SERT and protein phosphatase 2A (Prod. No. [P 9989](#)). In this case, an interaction is believed to be involved in the regulation of transporter activity and surface expression which is influenced by the substrate serotonin [73]. Clearly, the identification of additional binding partners for SERT and other members of the neurotransmitter transporter families is an area of current focus and will undoubtedly lead to a greater understanding of the biology of these transporters.

### Other Family Activities

Like most modern day families, both the sodium-dependent and sodium/chloride-dependent neurotransmitter families maintain hectic lifestyles. Add to this busy schedule the capacity for certain transporter subtypes to exhibit channel-like properties [74], distinct from their substrate binding and translocation function, and matters become even more complicated. Whether these various activities are achieved by each transporter protein working alone (monomeric), or in close collaboration with their counterparts (oligomeric forms), is an area likely to receive increased attention in the future. Recent observations that support the oligomeric assembly of SERT [75] and EAAT3 [76] offer the new challenge of ascribing the various functional activities of these transporters to these different structures. More family secrets undoubtedly await future discovery.

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