GABA transporters

Overview: Plasma membrane-located GABA transporters (provisional nomenclature as adopted for human GABA transporters) are members of the solute carrier family 6 (SLC6) of sodium- and chloride-dependent neurotransmitter receptor transporters that includes the monoamine and glycine transporters (Chen *et al*., 2004). The members of this superfamily share a structural motif of 12 TM segments (Palacín *et al*., 1998) that has been confirmed by the crystal structure of a bacterial homolog ($LeuT_{Aa}$) of the Na^+/Cl^--dependent neurotransmitter transporters from *Aquiflex aeolicus* (Yamashita *et al*., 2005). The activity of GABA-transporters located upon both neurones and glia serves to terminate phasic GABA-ergic transmission, maintain low ambient extracellular concentrations of GABA and recycle GABA for reuse by neurones. Nonetheless, ambient concentrations of GABA are sufficient to sustain tonic inhibition mediated by high-affinity $GABA_A$ receptors in certain neuronal populations (Semyanov *et al*., 2004). A structurally and functionally distinct vesicular transporter representing the SCL32 family [VGAT/VIAAT (ENSG00000101438); McIntire *et al*., 1997; Sagne *et al*., 1997; Gasnier, 2004], subject to inhibition by vigabatrin, is responsible for concentrating GABA (and glycine) within synaptic vesicles.

Nomenclature	GAT-1	GAT-2	GAT-3	BGT-1
Other names	mGAT-1, SLC6A1	mGAT3, SLC6A16	mGAT4, GAT-B, SLC6A11	mGAT2, SLC6A12
Ensembl ID	ENSG00000157103	ENSG00000010379	ENSG00000132164	ENSG00000111181
Endogenous substrates	GABA	GABA, β-alanine	GABA, β-alanine	GABA, betaine
Selective inhibitors (IC_{50})	NNC-711 (0.04 μM), SKF89976A (0.13 μM), CI-966 (0.26 μM), tiagabine (0.8 μM), EF1500 (2 μM) (*R*)-EF1502 (4 μM), LU32176B (4 μM), (*S*)-EF1502 (120 μM)	–	SNAP-5114 (6.6 μM)	NNC052090 (1.4 μM), (*R*)-EF1502 (22 μM), (*S*)-EF1502 (34 μM), LU 32176B (>100 μM)
Probes	[^{3}H]Tiagabine	–	–	–
Stoichiometry	2 Na^+: 1 Cl^-: 1 GABA	–	≥2 Na^+: 2 Cl^-: 1 GABA	3 Na^+: 1 (or 2) Cl^-: 1 GABA

SNAP-5114 is only weakly selective for GAT-3, with IC_{50} values in the range 20 to >30 μM at GAT-1, GAT-2 and BGT-1, whereas NNC052090 has at least an order of magnitude selectivity for BGT-1 [see Schousboe *et al*. (2004a) and Clausen *et al*. (2006) for reviews]. (*R*)-(1-{2-[tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl)acetic acid is a recently described compound that displays 20-fold selectivity for GAT-3 over GAT-1 (Fülep *et al*., 2006). In addition to the inhibitors listed, EGYT3886 is a moderately potent, although non-selective, inhibitor of all cloned GABA transporters (IC_{50} = 26–46 μM; Dhar *et al*., 1994). Diaryloxime and diarylvinyl ether derivatives of nipecotic acid and guvacine that potently inhibit the uptake of [^{3}H]GABA into rat synaptosomes have been described (Knutsen *et al*., 1999). Several derivatives of *exo*-THPO (e.g. *N*-methyl-*exo*-THPO and *N*-acetyloxyethyl-*exo*-THPO) demonstrate selectivity as blockers of astroglial, versus neuronal, uptake of GABA [see Schousboe *et al*. (2004b) and Clausen *et al*. (2006) for reviews]. GAT-3 is inhibited by physiologically relevant concentrations of Zn^{2+} (Cohen-Kfir *et al*., 2005).

Abbreviations: CI966, [1-[2-[bis-4(trifluromethyl)phenyl]methoxy]ethyl]-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid; **EF1500**, *N*-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-hydroxy-4-amino-4,5,6,7-tetrahydrobenzo[*d*]isoxazol-3-ol; **EF1502**, *N*-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-hydroxy-4-(methylamino)4,5,6,7,tetrabenzo[*d*]isoxazol-3-ol; **EGYT3886**, (-)-2-phenyl-2-[(dimethylamino)ethoxy]-(1*R*)-1,7,7-trimethylbicyclo [2.2.1]heptane; *exo*-THPO, 3-hydroxy-4-amino-4,5,6,7-tetrahydro-1,2-benzisoxazol; **LU32-176B**, *N*-[4,4-bis(4-fluorophenyl)-butyl]-3-hydroxy-4-amino-4,5,6,7-tetrahydrobenzo[d]isoxazol-3-ol; **NNC711**, 1-2-(((diphenylmethylene)amino)oxy)ethyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid hydrochloride; **NNC052090**, 1-(3-(9*H*-carbazol-9-yl)-1-propyl)-4-(2-methoxyphenyl)-4-piperidinol; **SKF89976A**, 1-(4,4-diphenyl-3-butenyl)-3-piperidinecarboxylic acid

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