

# GABA Transporters

## Key References

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## Overview

Fast synaptic transmission requires a mechanism for rapid removal of transmitter molecules from the synaptic cleft, a task most often accomplished by transmitter clearance or degradation. High affinity transport proteins fulfill this role for a variety of neurotransmitters including GABA, the major inhibitory neurotransmitter in the CNS. GABA transporters utilize sodium and chloride electrochemical gradients to enable GABA sequestration in presynaptic nerve terminals and surrounding glia. Reversal of GABA transport, caused by high cytosolic sodium, may be physiologically relevant in retinal cells, cerebral neurons and Bergman glia where calcium-independent GABA release has been observed. Functional, structural and sequence conservation place these transporters within the larger family of sodium- and chloride-dependent transport proteins.

As GABA transporter activities were initially discovered, categorization was accomplished according to sensitivities to pharmacological agents and apparent localization to specific cell types. This vital work led to the broad classifications of 'neuronal' and 'glial' GABA transporters as a useful first approximation. Subsequent cloning of a number of transporter cDNAs, and delineation of the pharmacological sensitivities and regional distributions of each, resolved a number of discrepancies arising from strict adherence to the previous nomenclature. Four transporters have been identified that transport GABA with varying affinities and are referred to as GAT-1, GAT-2, GAT-3 (or GAT-B) and BGT-1. Nipecotic acid serves as a universal inhibitor of and substrate for the GABA transporters with the exception of BGT-1. The most abundant, GAT-1, found principally in neurons, but also in specialized glia, transports GABA with high

affinity and is inhibited by cis-1,3-amino-cyclohexane carboxylic acid (ACHC) and L-diaminobutyric acid (L-DABA). Predominantly localized to pia mater and arachnoid complex, GAT-2 transports GABA with relatively high affinity and is inhibited by  $\beta$ -alanine. GAT-3, identified in both neuronal and glial cells, transports both GABA and  $\beta$ -alanine with relatively high affinity. Expressed in neurons throughout the brain, BGT-1 transports GABA at moderate affinity and the osmolyte betaine at low affinity. Additional pharmacological studies in heterologous high-level expression systems are now providing a new framework from which to probe the physiological roles of the individual GABA transport proteins.

Structural motifs common to these four GABA transporters include 12 transmembrane-spanning domains (TM), intracellular N- and C-termini, a large extracellular loop between TMs 3 and TM 4 having multiple potential glycosylation sites, and potential regulation on intracellular consensus phosphorylation sites. Pore-loop structures may also arise between TM 3 and TM 4 and also between TM 7 and TM 8.

A synaptic vesicle GABA transporter having ten TM domains and expressed in both GABAergic and glycinergic neurons has also been cloned. This transporter is inhibited most potently by vigabatrin ( $\gamma$ -vinyl-GABA), weakly by nipecotic acid and glycine, and utilizes both the Dy and DpH components of the proton electrochemical gradient ( $\Delta\mu_{H^+}$ ) to accomplish vesicular GABA uptake. In addition, glycine may be a potential substrate for this carrier.

The clinical relevance of GABA transporter modulation has arisen from extensive data suggesting that select anticonvulsants

exert a majority of their effects at these transport sites. The number of transporters expressed in certain temporal lobe regions and the resulting potential for depolarization-induced transport reversal may also be of particular relevance in the clinical sphere of epilepsy. Because disruptions in GABAergic transmission have been implicated not only in epilepsy, but also in affective disorders and schizophrenia, each member of this family has become a potential target for pharmacological intervention. In addition, tiagabine has pronounced effects on promoting slow-wave sleep making the GABA transporters potential targets for the treatment of sleep disruptions. With the exception of GAT-1, highly selective and potent inhibitors of each subtype have not been identified, although the potential for therapeutic benefit appears promising. Recent work with EF1502, an analog of exo-THPO with affinity for both mGAT-1 and mGAT-2, suggests that mGAT-2-selective inhibitors may have utility in treating epilepsy. Selective inhibitors or potentiators of individual GABA transporter subtypes may provide avenues for the fine tuning of GABA tonus in select CNS locales.

# GABA Transporters

<b>CURRENTLY ACCEPTED NAME</b>	GAT-1 (GABA transporter type 1)	GAT-2 (GABA transporter type 2)	GAT-3 (GABA transporter type 3)	BGT-1 (Betaine transporter)	VGAT (Vesicular GABA transporter)
<b>ALTERNATE MURINE NAME</b>	mGAT-1	mGAT-3	mGAT-4	mGAT-2	VIAAT
<b>STRUCTURAL INFORMATION</b>	599 aa (human)	602 aa (rat)	632 aa (human)	614 aa (human)	525 aa (rat)
<b>UPTAKE SUBSTRATES</b>	GABA ( <b>A2129</b> )	GABA ( <b>A2129</b> ), β-Alanine ( <b>A7752</b> )	GABA ( <b>A2129</b> ), β-Alanine ( <b>A7752</b> )	GABA ( <b>A2129</b> ), <sup>a</sup> Betaine ( <b>B3501</b> )	GABA ( <b>A2129</b> )
<b>UPTAKE INHIBITORS</b>	Nipecotic acid ( <b>211672</b> ) <sup>b</sup> L-DABA ( <b>D8376</b> ), Guvacine ( <b>G007</b> ) <sup>b</sup> EGYT-3886, ACHC <sup>b</sup> NNC 05-2045 <sup>e</sup> THPO, CI-966, SKF 89976A, NO-711 ( <b>N142</b> ), <sup>c</sup> Tiagabine, <sup>c</sup> LU-32-176B <sup>h</sup> EF1502 <sup>i</sup>	Nipecotic acid ( <b>211672</b> ), <sup>b</sup> L-DABA ( <b>D8376</b> ), Guvacine ( <b>G007</b> ), <sup>b</sup> EGYT-3886	Nipecotic acid ( <b>211672</b> ), <sup>b</sup> L-DABA ( <b>D8376</b> ), EGYT-3886, SNAP-5114 <sup>d</sup>	EGYT-3886, NNC 05-2045, <sup>e</sup> NNC 05-2090, <sup>f</sup> EF1502 <sup>i</sup>	Nipecotic acid ( <b>211672</b> ), <sup>b</sup> Vigabatrin ( <b>V8261</b> ) <sup>g</sup>
<b>TISSUE EXPRESSION</b>	Retina, limbic system, basal forebrain, cortex layers IV – V, cerebellar cortex, thalamus, hypothalamus, interpeduncular nucleus, inferior colliculus, substantia nigra, striatum, pons, medulla (neurons and specialized glia)	Liver, kidney arachnoid complex, pia mater	Thalamus, hypothalamus, amygdala region of pyriform cortex, inferior colliculus, pons, brainstem, deep cerebellar nuclei, cerebral cortex, basal forebrain, striatum, hippocampus, cerebellar cortex (neurons and glia)	Liver, kidney, cerebellum, cerebral cortex, amygdala, caudate nucleus, corpus callosum, hippocampus, hypothalamus, substantia nigra, subthalamic nucleus, thalamus	GABA and glycine containing presynaptic boutons in brain
<b>PHYSIOLOGICAL FUNCTION</b>	Transport of GABA	Transport of GABA	Transport of GABA and β-alanine	Transport of GABA and betaine	Transport of GABA
<b>DISEASE RELEVANCE</b>	Epilepsy, sleep disorders	Not known	Epilepsy	Epilepsy	Not known

## Abbreviations

**ACHC:** *cis*-1,3-Aminocyclohexane carboxylic acid

**CI-966:** [1-[2-bis[4-(Trifluoromethyl)phenyl]-methoxy]ethyl]-1,2,5,6-tetrahydro-3-pyridine carboxylic acid

**L-DABA:** L-Diaminobutyric acid

**EF1502:** [N-[4,4-bis(3-Methyl-2-thienyl)-3-butenyl]-3-hydroxy-4-(methylamino)-4,5,6,7-tetrahydrobenzo[d]isoxazol-3-ol]

**EGYT-3886:** [(+)-2-Phenyl-2-[(dimethylamino)ethoxy]-(1R)-1,7,7-trimethylbi-cyclo[2.2.1]heptan]

**LU-32-176B:** [N-[4,4-bis(4-Fluorophenyl)-butyl]-3-hydroxy-4-amino-4,5,6,7-tetrahydrobenzo[d]isoxazol-3-ol]

**NNC 05-2045:** 1-(3-(9H-Carbazol-9-yl)-1-propyl)-4-(4-methoxyphenyl)-4-piperidinol

**NNC 05-2090:** 1-(3-(9H-Carbazol-9-yl)-1-propyl)-4-(2-methoxyphenyl)-4-piperidinol

**NO-711:** 1-(2-(((Diphenylmethylene)amino)oxyethyl))-1,2,4,6-tetrahydro-3-pyridine-carboxylic acid

**SKF 89976A:** N-(4,4-Diphenyl-3-butenyl)-3-piperidinecarboxylic acid

**SNAP-5114:** (S)-1-[2-[tris(4-Methoxyphenyl)methoxy]ethyl]-3-piperidinecarboxylic acid

**THPO:** 4,5,6,7-Tetrahydro-isoxazolo[4,5-c]-pyridin-3-ol

## FOOTNOTES

**a** Relative affinity of BGT-1 for GABA is several fold higher than for betaine (93 μM and 398 μM, respectively).

**b** These compounds are also substrates.

**c** Potent and selective inhibitors of GAT-1 with IC<sub>50</sub> values of 40-70 nM.

**d** Selective inhibitor of GAT-3 with an IC<sub>50</sub> value of 5 μM.

**e** Selective inhibitor of GAT-3 and BGT-1 with K<sub>i</sub> values of 1.6-6.1 μM.

**f** Selective inhibitor of BGT-1 with a K<sub>i</sub> value of 1.4 μM.

**g** Vesicular GABA transporter is inhibited by vigabatrin with an IC<sub>50</sub> similar to that for GABA (7.5 μM and 4.75 μM, respectively)

**h** Selective inhibitor of mGAT-1 with an IC<sub>50</sub> value of 4 μM.

**i** Selective inhibitor of mGAT-1 with an IC<sub>50</sub> value of 4 and 22 μM, respectively.

For complete information, please visit the [Sigsal Handbook of GATs and mGATs](https://www.sigsal.com/) (<https://www.sigsal.com/>)