

# Mechanisms for Enhancing GABAergic Activity

$\gamma$ -aminobutyric acid (GABA) is the most important inhibitory neurotransmitter in the central nervous system and is widely distributed throughout the brain. GABA binds to three principal receptors, each of which is involved in different physiologic functions:

● GABA-A receptors mediate fast inhibitory synaptic transmissions; they regulate neuronal excitability (e.g., seizure threshold) and rapid mood changes (e.g., anxiety, panic, and response to stress). GABA-A receptors are targets of benzodiazepines, barbiturates, and ethanol, all of which have sedative effects.<sup>1,2</sup>

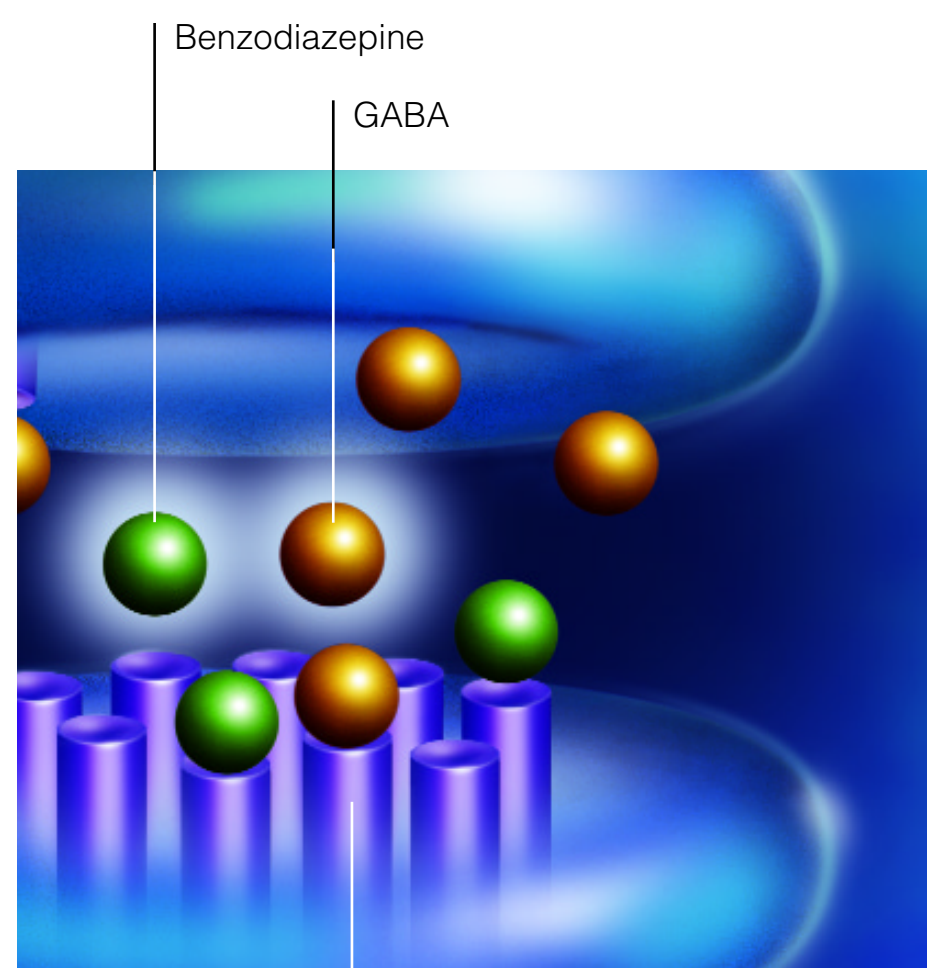
● GABA-B receptors mediate slow inhibitory potentials; they appear to be important in memory, mood (depression), and pain.<sup>3</sup>

● GABA-C receptors — their physiologic role has not been described.

## MECHANISM 1

### Agonism of GABA-A receptors

The effects of benzodiazepines are due primarily to allosteric agonism at the GABA-A receptor.<sup>1,2</sup>

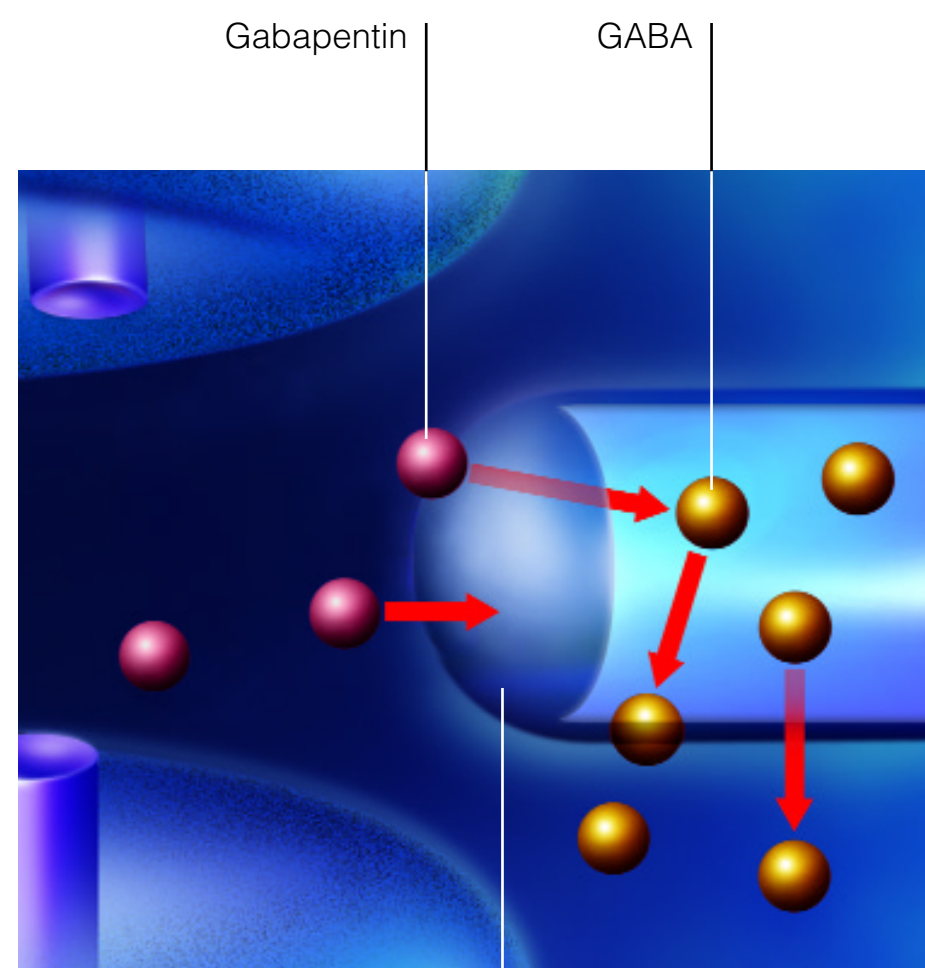


GABA-A receptor

## MECHANISM 2

### Increased release of GABA from glial cells

Gabapentin appears to have multiple modes of action, including increasing GABA release from glial cells, increasing GABA synthesis by enhancing the activity of glutamic acid decarboxylase (GAD), weakly binding to calcium channels and, at high concentrations, inhibiting the action of GABA transaminase.<sup>4,5</sup>

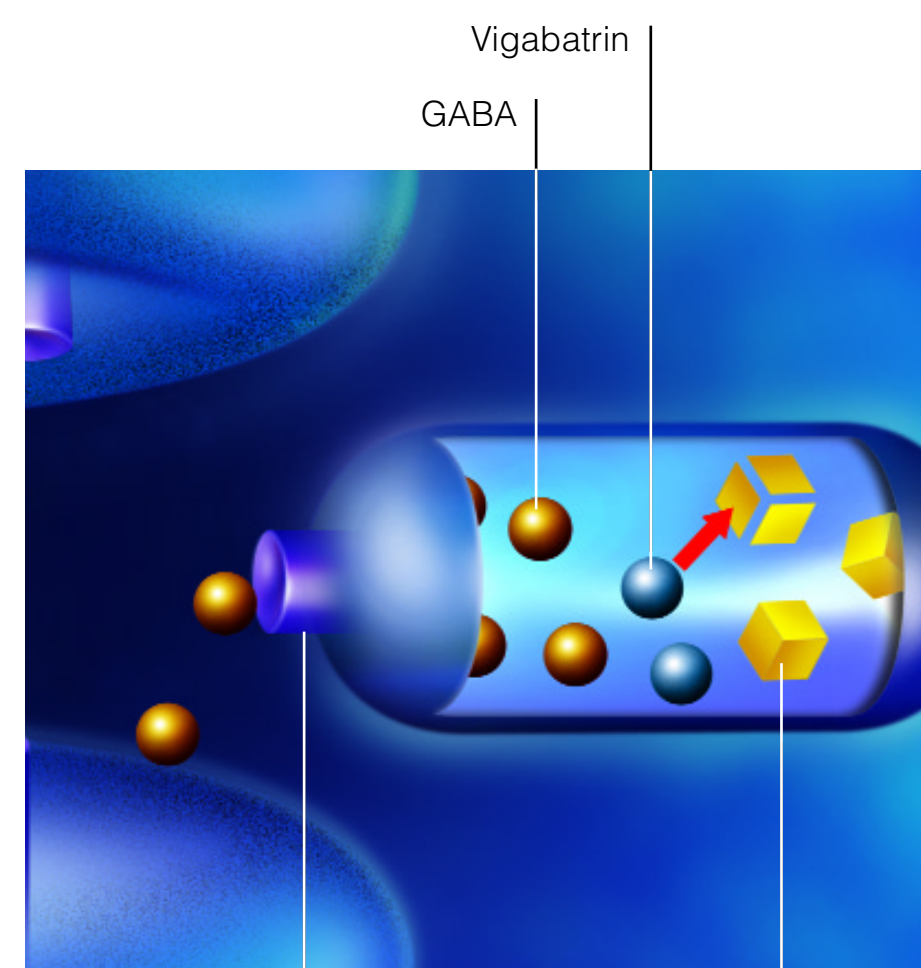


Glial cell

## MECHANISM 3

### Inhibition of the enzymatic breakdown of GABA

Vigabatrin (not approved for U.S. use) works primarily and valproate works in part by inhibiting GABA transaminase, the enzyme that metabolizes GABA after its reuptake by the GAT-1 transporter.<sup>4</sup>



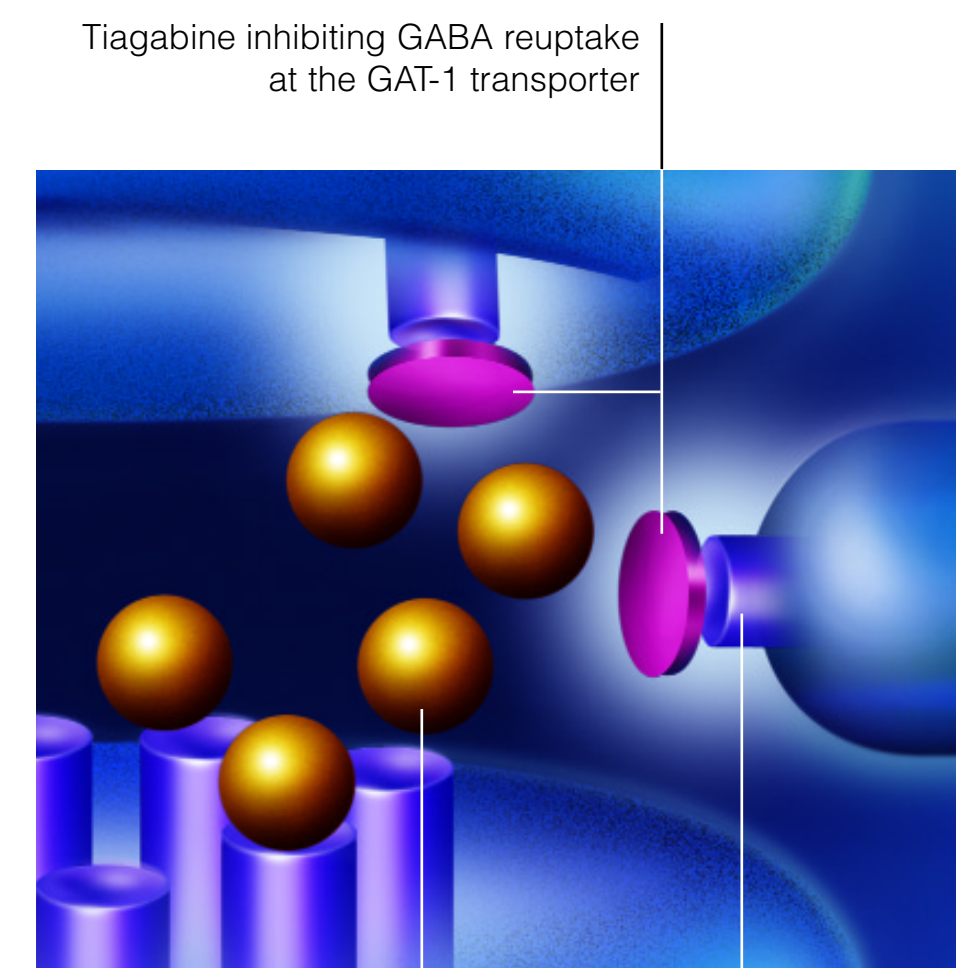
GAT-1 GABA transporter

GABA transaminase

## MECHANISM 4

### Selective inhibition of GABA reuptake

SGRIs inhibit the action of GAT-1 transporters, increasing the amount of available GABA without increasing the total amount of GABA in the CNS and without affecting physiologic control of GABA release.<sup>6</sup> The only SGRI currently available is tiagabine.



GABA

GAT-1 GABA transporter

**References** 1. Neilson EB, Suzdak PD, Andersen KE, et al. Characterization of tiagabine (NO-328), a new potent and selective GABA uptake inhibitor. *Eur J Pharmacol.* 1991;257-266. 2. Borden LA, Murali Dhar TG, Smith KE, et al. Tiagabine, SK&F 89976-A, CI-996, and NNC-711 are selective for the cloned GABA transporter GAT-1. *Eur J Pharmacol.* 1994;219-224. 3. Meldrum BS, Chapman AG. Basic mechanisms of Gabitril (tiagabine) and future potential developments. *Epilepsia.* 1999;40(Suppl 9):S2-S6. 4. Ketter TA, Post RM, Theodore WH. Positive and negative psychiatric effects of antiepileptic drugs in patients with seizure disorders. *Neurology.* 1999;53(Suppl 2):S53-S67. 5. Taylor CP. Mechanisms of action of gabapentin. *Rev Neurol (Paris).* 1997;153(Suppl 1):S39-S45. 6. Schmidt D, Gram L, Brodie M, et al. Tiagabine in the treatment of epilepsy — a clinical review with a guide for the prescribing physician. *Epilepsy Res.* 2000;41:245-251.

