gamma-Aminobutyric acid

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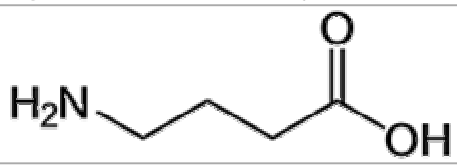
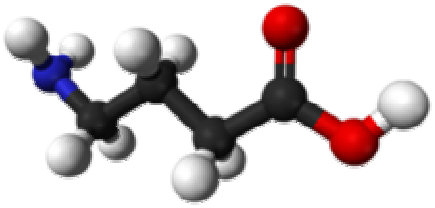
(Redirected from Gamma-aminobutyric acid)

γ-Aminobutyric acid (
/ˈgæmə əˈmiːnoʊbjuːˈtɪrɨk ˈæsɨd/ *GAM-ə ə-MEE-noh-bew-TIRR-ik*; or **GABA** /ˈgæbə/)
is the chief inhibitory neurotransmitter in the mammalian central nervous system. It plays a role in regulating neuronal excitability throughout the nervous system. In humans, GABA is also directly responsible for the regulation of muscle tone.[2]

Although chemically it is an amino acid, GABA is rarely referred to as such in the scientific or medical communities, because the term "amino acid," used without a qualifier, conventionally refers to the alpha amino acids, which GABA is not, nor is it ever incorporated into a protein.

In spastic diplegia in humans, GABA absorption becomes impaired by nerves damaged from the condition's upper motor neuron lesion, which leads to hypertonia of the muscles signaled by those nerves that can no longer absorb GABA.

Contents

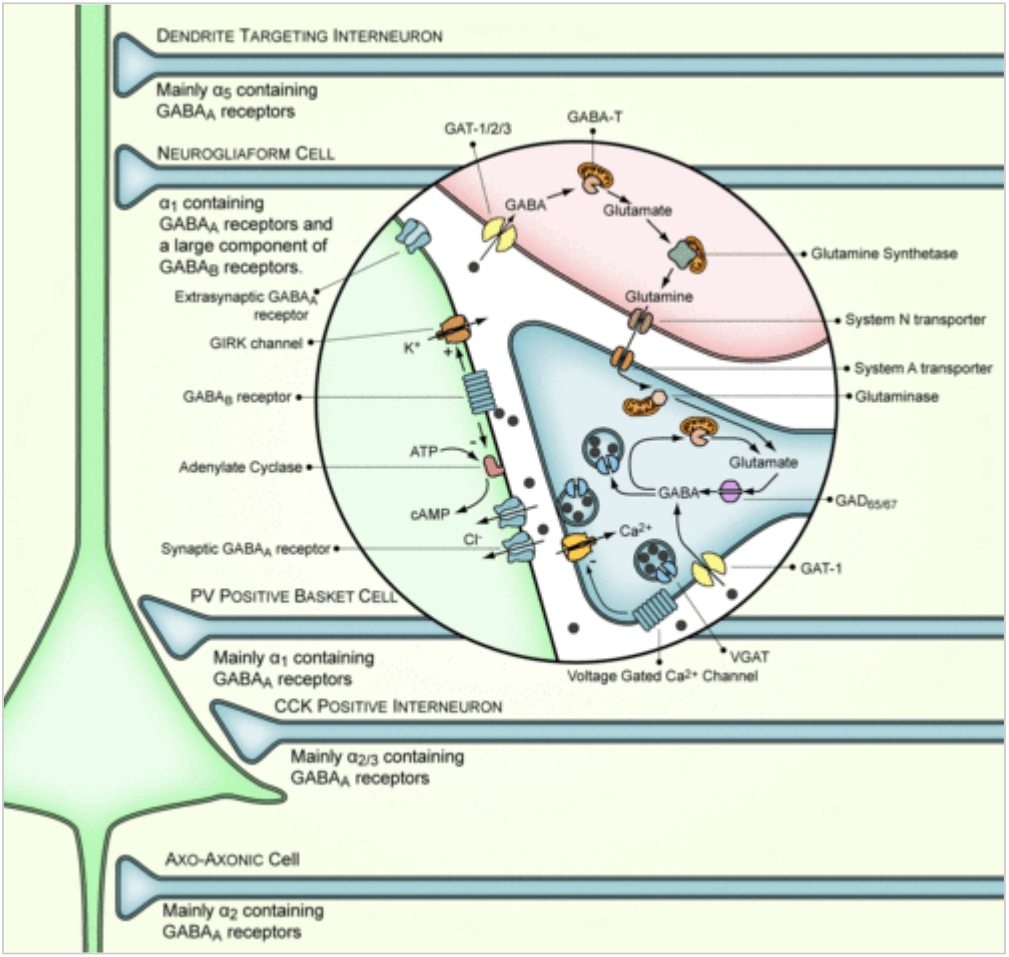
***gamma*-Aminobutyric acid**	
	
	
IUPAC name	
4-aminobutanoic acid	
Identifiers	
CAS number	56-12-2 ✓
PubChem	119
ChemSpider	116 ✓
UNII	2ACZ6IPC6I ✓
DrugBank	DB02530
KEGG	D00058 ✓
MeSH	gamma-Aminobutyric+Acid
ChEBI	CHEBI:59888 ✓
ChEMBL	CHEMBL96 ✓
IUPHAR ligand	1067
Jmol-3D images	Image 1 (http://chemapps.stolaf.edu/jmol/jmol.php?model=C%28CC%28%3DO%29O%29CN)
SMILES	
InChI	
Properties	
Molecular formula	$C_4H_9NO_2$
Molar mass	103.12 g/mol

Function

Neurotransmitter

Melting point	203.7 °C, 477 K, 399 °F
Acidity (pK_a)	4.23 (carboxyl), 10.43 (amino)[1]
✓(what is this?) (verify) Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)	
Infobox references	

In vertebrates, GABA acts at inhibitory synapses in the brain by binding to specific transmembrane receptors in the plasma membrane of both pre- and postsynaptic neuronal processes. This binding causes the opening of ion channels to allow the flow of either negatively charged chloride ions into the cell or positively charged potassium ions out of the cell. Depending on which ion channels open, the membrane potential is either hyperpolarized or repolarized. This action results in a negative change in the transmembrane potential, usually causing hyperpolarization. Two general classes of GABA receptor are known: $GABA_A$ in which the receptor is part of a ligand-gated ion channel complex, and $GABA_B$ metabotropic receptors, which are G protein-coupled receptors that open or close ion channels via intermediaries (G proteins).



The production, release, action, and degradation of GABA at a stereotyped GABAergic synapse

Neurons that produce GABA as their output are called GABAergic neurons, and have chiefly inhibitory action at receptors in the adult vertebrate. Medium Spiny Cells are a typical example of inhibitory CNS GABAergic cells. In contrast, GABA exhibits both excitatory and inhibitory actions in insects, mediating muscle activation at synapses between nerves and muscle cells, and also the stimulation of certain glands.[3] In mammals, some GABAergic neurons, such as chandelier cells, are also able to excite their glutamatergic counterparts.[4]

$GABA_A$ receptors are ligand-activated chloride channels; that is, when activated by GABA, they allow the flow of chloride ions across the membrane of the cell. Whether this chloride flow is excitatory/depolarizing (makes the voltage across the cell's membrane less negative), shunting (has no effect on the cell's membrane) or inhibitory/hyperpolarizing (makes the cell's membrane more negative) depends on the direction of the flow of chloride. When net chloride flows out of the cell, GABA is excitatory or depolarizing; when the net chloride flows into the cell, GABA is inhibitory or hyperpolarizing. When the net flow of chloride is close to zero, the action of GABA is shunting. Shunting inhibition has no direct effect on the membrane potential of the cell; however, it minimises the effect of any coincident synaptic input essentially by reducing the electrical resistance of the cell's membrane (in essence, equivalent to Ohm's law). A developmental switch in the molecular machinery controlling concentration of chloride inside the cell – and, hence, the direction of this ion flow – is responsible for the changes in the functional role of GABA between the neonatal and adult stages. That is to say, GABA's role changes from excitatory to inhibitory as the brain develops into adulthood.[5]

Brain development

For the past two decades, the theory of excitatory action of GABA early in development was unquestioned based on experiments in vitro, on brain slices. The main observation was that in the hippocampus and neocortex of the mammalian brain, GABA has primarily excitatory effects, and is in fact the major excitatory neurotransmitter in many regions of the brain before the maturation of glutamateergic synapses.[5][6]

However, this theory has been questioned based on results showing that in brain slices of immature mice incubated in artificial cerebrospinal fluid (ACSF) (modified in a way that takes into account the normal composition of the neuronal milieu in sucklings by adding an energy substrate alternative to glucose, beta-hydroxybutyrate) GABA action shifts from excitatory to inhibitory mode.[7] This effect has been later repeated when other energy substrates, pyruvate and lactate, supplemented glucose in the slices' media.[8] The effects of beta-hydroxybutyrate were later confirmed for pyruvate[9] and for lactate.[10] However it was argued that the concentrations of the alternative energy substrates used in these experiments were non-physiological and the GABA-shift was instead caused by changes in pH resulting from the substrates acting as "weak acids". These arguments were later rebutted by further findings[11][12] showing that changes in pH even greater than that caused by energy substrates do not affect the GABA-shift described in the presence of energy substrate-fortified ACSF and that the mode of action of beta-hydroxybutyrate, pyruvate and lactate (assessed by measurement NAD(P)H and oxygen utilization) was energy metabolism-related.[13]

In the developmental stages preceding the formation of synaptic contacts, GABA is synthesized by neurons and acts both as an autocrine (acting on the same cell) and paracrine (acting on nearby cells) signalling mediator.[14][15]

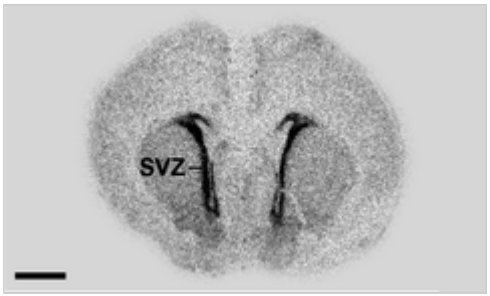
GABA regulates the proliferation of neural progenitor cells[16][17] the migration[18] and differentiation [19][20] the elongation of neurites[21] and the formation of synapses.[22]

GABA also regulates the growth of embryonic and neural stem cells. GABA can influence the development of neural progenitor cells via brain-derived neurotrophic factor (BDNF) expression.[23] GABA activates the $GABA_A$ receptor, causing cell cycle arrest in the S-phase, limiting growth.[24]

Beyond the nervous system

GABAergic mechanisms have been demonstrated in various peripheral tissues and organs including, but not restricted to the intestine, stomach, pancreas, Fallopian tube, uterus, ovary, testis, kidney, urinary bladder, lung, and liver.[26]

In 2007, an excitatory GABAergic system was described in the airway epithelium. The system activates following exposure to allergens and may participate in the mechanisms of asthma.[27] GABAergic systems have also been found in the testis[28] and in the eye lens.[29]



GABA-producing GAD67 enzyme in the brain slice at 1st postnatal day, with the highest expression in subventricular zone (svz). From Popp et al., 2009.[25]

Structure and conformation

GABA is found mostly as a zwitterion, that is, with the carboxy group deprotonated and the amino group protonated. Its conformation depends on its environment. In the gas phase, a highly folded conformation is strongly favored because of the electrostatic attraction between the two functional groups. The stabilization is about 50 kcal/mol, according to quantum chemistry calculations. In the solid state, a more extended conformation is found, with a trans conformation at the amino end and a gauche conformation at the carboxyl end. This is due to the packing interactions with the neighboring molecules. In solution, five different conformations, some folded and some extended, are found as a result of solvation effects. The conformational flexibility of GABA is important for its biological function, as it has been found to bind to different receptors with different conformations. Many GABA analogues with pharmaceutical applications have more rigid structures in order to control the binding better.[30][31]

History

Gamma-aminobutyric acid was first synthesized in 1883,[*citation needed*] and was first known only as a plant and microbe metabolic product. In 1950, however, GABA was discovered to be an integral part of the mammalian central nervous system.[32]

Synthesis

GABA does not penetrate the blood-brain barrier; it is synthesized in the brain. It is synthesized from glutamate using the enzyme L-glutamic acid decarboxylase and pyridoxal phosphate (which is the active form of vitamin B6) as a cofactor via a metabolic pathway called the GABA shunt. This process converts glutamate, the principal excitatory neurotransmitter, into the principal inhibitory neurotransmitter (GABA).[33][34]

Pharmacology

Drugs that act as allosteric modulators of GABA receptors (known as GABA analogues or *GABAergic* drugs) or increase the available amount of GABA typically have relaxing, anti-anxiety, and anti-convulsive effects.[35][36] Many of the substances below are known to cause anterograde amnesia and retrograde amnesia.[*citation needed*]

In general, GABA does not cross the blood-brain barrier,[37] although certain areas of the brain that have no effective blood-brain barrier, such as the periventricular nucleus, can be reached by drugs such as systematically injected GABA.[38] At least one study suggests that orally administered GABA increases the amount of Human Growth Hormone.[39] GABA directly injected to the brain has been reported to have both stimulatory and inhibitory effects on the production of growth hormone, depending on the physiology of the individual.[38]

GABAergic Drugs

- $GABA_A$ receptor ligands
  - Agonists/Positive allosteric modulators: alcohol,[40][41][42] barbiturates, benzodiazepines, carisoprodol, chloral hydrate, etomidate, glutethimide, L-theanine, kava, methaqualone, muscimol, neuroactive steroids, z-drugs, propofol, scullcap, valerian, volatile/inhaled anaesthetics.
  - Antagonists/Negative allosteric modulators: bicuculline, cicutoxin, flumazenil, furosemide, gabazine, oenanthotoxin, picrotoxin, Ro15-4513, thujone.
- $GABA_B$ Receptor Ligands
  - Agonists: baclofen, GBL, GHB,[43] phenibut.
  - Antagonists: phaclofen, saclofen.
- GABA reuptake inhibitors: deramciclane, hyperforin, tiagabine.
- GABA-transaminase inhibitors: gabaculine, phenelzine, valproate, vigabatrin, Lemon balm (Melissa officinalis).[44]
- GABA analogues: pregabalin, gabapentin.
- Others: GABA (itself), L-glutamine, picamilon, progabide, tetanospasmin.

GABA as a supplement

A number of commercial sources sell formulations of GABA for use as a dietary supplement, sometimes for sublingual administration. These sources typically make claims that the supplement has a calming effect. No scientific assessment of such claims exists, but because of the extensive evidence that GABA does not cross the blood-brain barrier at significant levels[37], their validity is doubtful.

See also

- Germinated brown rice
- Spasticity
- Spastic diplegia, a GABA deficiency neuromuscular neuropathology

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