CNS: Inhibitory Neurotransmitters: GABA and GLYCINE

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GABA or Gamma Amino Butyric Acid

GABA or Gamma amino butyric acid is the main inhibitory neurotransmitter in the central nervous system (CNS) mainly in the brain. 30 – 40% of CNS neurons are GABAergic neurons. GABA concentration is more in the nigrostriatal system, hypothalamus and hippocampus. Other GABAergic neurons are short interconnecting neurons. GABA concentration is higher in CNS than any other neurotransmitter. It is very less in peripheral tissues.

The overall excitability of CNS depends up on the sum total discharge from main excitatory Glutaminergic neurons and primary inhibitory GABAergic neurons. Ongoing level of neuronal activity is regulated by the balance between excitatory Glutaminergic inputs and inhibitory GABAergic activity. If the balance swings in favour of GABA, then sedation, amnesia and ataxia appear. On the other hand, the mildest attenuation of the GABAergic system results in arousal, anxiety, restlessness, insomnia and exaggerated reactivity. The main functions of GABA areregulation of muscle tone, anxiety, cognition and pain.
In the developing brain GABA can function as excitatory neurotransmitter. *Van den Pol An et al* found that in developing hypothalamic neurons, glutamate can inhibit the excitatory actions of GABA.

Most of the CNS depressant drugs namely Anxiolytics, Sedatives, Hypnotics, General anaesthetics and Anti epileptics exert their actions by facilitating or enhancing GABAergic inhibitory transmission.

Anxiety disorders such as panic attacks, seizure disorders, and numerous other conditions including addiction, headaches, Parkinson's syndrome and cognitive impairment are all related to low GABA activity.

**GABA Biosynthesis, Storage, Release, Removal and Degradation**

- GABA is directly biosynthesized from L-glutamate by the action of glutamic acid decarboxylase (GAD). This GABA-synthesizing enzyme is found only in the GABAergic neurons. Vitamin B6 derivative, pyridoxal phosphate is required as a co factor in GABA synthesis. Severe Vitamin B6 deficiency leads to convulsions. GABA synthesis is increased when energy production through citric acid cycle is low. This is a protective feedback inhibition.
- GABA is stored in synaptic vesicles by vesicular GABA transporter (VGAT) and is released through exocytosis when the presynaptic membrane is depolarized.
- GABA reuptake into presynaptic terminals and/or into surrounding astrocytes by GABA transporters (GATs) is the primary mechanism of removal and this reuptake is inhibited by guvacine and nipecotic acid.
- GABA is catalysed by GABA-transaminase (GABA-T) to yield glutamate with the production of succinic semi aldehyde, converted into succinic acid. Vigabatrine can inhibit GABA-T and increases GABA levels at the synapse.

**Functional role of GABA**

**Pain:** GABAergic neurons are also found in the spinal cord dorsal horn regions and in supraspinal areas which are involved in the perception of pain. GABA receptor agonists exhibit antinociceptive properties in a variety of animal models of pain. GABA receptor agonists, as
well as inhibitors of GABA uptake or metabolism, are clinically effective in treating pain. GABA\textsubscript{A} agonist, CGP 35024, induces antinociception at doses well below those that cause sedation. Activation of GABA receptors decrease the response to painful stimuli. Analgesia produced by GABA\textsubscript{A} agonists may be supraspinal mediated. The GABA\textsubscript{B} agonist baclofen produces analgesia through both spinal and supraspinal actions.

**Anxiety:** Low GABA levels are associated with several psychiatric and neurological disorders, including anxiety. Benzodiazepines, Barbiturates and Alcohol all bind to GABA receptors to increase its’ post-synaptic inhibitory effect and reduce anxiety. Benzodiazepines bind allosterically to the GABA receptor and have their own binding site. Additionally, Benzodiazepine inverse agonists such as Flumazenil decrease effects of GABA and cause anxiety. Mutation and down-regulation of GABA receptors in Alcoholics and Alcohol withdrawals was shown to cause marked anxiety and this further confirm the role of the GABAergic system in anxiety.

**Depression:** Low GABA levels have been found in patients suffering from various forms of depression and GABAergic drugs offer an effective treatment for depression, various antidepressant drugs have been shown to be effective for depression by affecting not only monoamine and serotonin activity, but also by increasing brain GABA levels.

**Memory:** Central GABAergic system is also critically involved in cognitive processes, especially memory. Many human and animal studies showed that benzodiazepine receptor agonists impair memory formation. Conversely drugs that decrease GABA function can have memory-enhancing properties.

**Epilepsy:** The mechanisms of most anti-epileptic drugs involve direct or indirect GABA enhancement. The drugs act in a variety of ways by increasing GABAergic inhibition (benzodiazepines, phenobarbital, valproate), inhibiting GABA reuptake (tiagabine), increasing synaptic GABA concentration through inhibition of GABA-T (vigabatrine).

**Sleep:** GABA\textsubscript{A} receptors are highly expressed in the thalamus, a region of the brain involved with sleep processes. GABA-agonist drugs, such as zolpidem and temazepam are sedatives used in the treatment of insomnia.
**Movement Disorders:** Tourette Syndrome, Parkinson’s Disease, Tardive Dyskinesia. GABAergic pathways are involved in the pathophysiology of various movement disorders. Baclofen, a synthetic GABA analogue, exerts antispasmodic effects and useful in Tourette syndrome. The GABA-agonists zolpidem and gabapentin are found to be beneficial in Parkinson’s disease, while the GABA-agonist vigabatrine provides benefit for tardive dyskinesia and other movement disorders.

**GABA Receptors**

There are two types of GABA receptors. Ionotropic GABA receptors (GABA$_A$ and GABA$_C$) and Metabotropic GABA receptors (GABA$_B$). Most abundant GABA receptors in the CNS are ionotropic GABA$_A$ receptors.

Ionotropic GABA receptors (GABA$_A$ and GABA$_C$) are present post-synaptically, coupled to chloride ion channel. Activation of these receptors leads to Fast inhibitory postsynaptic potential (IPSPs) which causes hyperpolarisation of post synaptic membrane by opening chloride channels and allowing chloride influx. Peri synaptic slow inhibitory effects are produced by activation of extrasynaptic GABA$_A$ receptors, which are activated by low levels of GABA that diffuse into cerebrospinal fluid and interstitial spaces.

GABA$_A$ receptors are pentameric transmembrane proteins to form a central ion pore surrounded by five subunits. GABA$_A$ receptor-channel activation occurs when two molecules of GABA binds to two receptor’s agonist sites. GABA$_C$ receptors are formed by three subunits and present in the retina. No drugs currently in use target GABA$_C$ receptors. Prolonged occupation of the agonist sites by GABA leads to receptor desensitization.

Certain endogenous steroids, known as neurosteroids rather than acting through nuclear receptors, alter GABA$_A$ receptor function by binding to allosteric sites on the receptor protein, causing increased GABA$_A$ receptor activation. Another endogenous substance that enhances GABA$_A$ receptor activity is oleamide, induces sleep, in part through potentiation of GABA$_A$ receptors.

**Metabotropic GABA receptors** (GABA$_B$) are G protein-coupled receptors and are found mainly in the spinal cord both presynaptically and postsynaptically. The GABA$_B$ receptors interact with G proteins, leading to directly activation of $K^+$ channels and inhibition of voltage-
gated Ca\(^{2+}\) channels. Presynaptic “autoreceptors” modulate neurotransmitter release by reducing Ca\(^{2+}\) influx, while postsynaptic GABA\(_B\) receptors produce slow IPSPs through activation of G protein-activated “inward rectifier” K\(^{+}\) channels. These inhibitory actions are mediated through inhibition of adenylate cyclase. Baclofen is a GABA\(_B\) receptor agonist, used to treat spasticity.

**Drugs acting on GABA receptors**

**Anxiolytics and Hypnotics:** Benzodiazepines, Barbiturates

**General anaesthetics:** Intravenous and volatile anesthetics

**Antiepileptics:**

GABA agonists: Benzodiazepines, Barbiturates, Valproate, Gabapentin

Tiagabine, blocking the reuptake of GABA via transporter inhibition.

Vigabatrine can inhibit GABA-T

**Centrally acting muscle relaxants:** Benzodiazepines, Baclofen

**Agonists and antagonists of GABA receptors**

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Glycine

Glycine is the main inhibitory neurotransmitter in the brainstem and spinal cord and regulates motor and sensory functions. Glycine is also present in the forebrain and promotes the actions of glutamate, thus serves both inhibitory and excitatory functions in the CNS.

Glycine is formed from serine by the enzyme serine hydroxymethyltransferase (SHMT) and released from nerve endings through exocytosis and reuptake via Na+/Cl−-dependent, high-affinity glycine transporters.

Glycine receptor resembles GABA<sub>A</sub> receptor, it is a ligand gated chloride channel. Activation of the receptor leads to fast post synaptic hyperpolarisation, causes fast IPSP there by inhibition. Beta alanine and taurine are less potent agonists at glycine receptors. Strychnine acts as an antagonist. Tetanus toxin inhibits the releases of glycine from neurons.

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