

# GABA, Gamma-aminobutyric acid

## Table of Contents

summary

Chemical Structure

Function in the Brain

Physiological Effects

- Role in Stress and Anxiety

- Sleep Regulation

- Impact on Neurological and Psychiatric Disorders

- Side Effects and Considerations

GABA Receptors

- GABAA Receptor

- GABAB Receptor

- Ligands and Modulation

- Role in Neurophysiology

Clinical Relevance

- Schizophrenia

- Epilepsy

- Other Mental Health Disorders

Research and Future Directions

History

Dietary Sources of GABA

- Major Food Sources

- Fermented Foods

- GABA in Beverages

- Bioavailability and Research Considerations

Dysregulation and Disorders

- Common Disorders Associated with GABA Dysregulation

  - Anxiety Disorders

  - Autism Spectrum Disorders

  - Alzheimer's Disease

  - Epilepsy

# Neurodegenerative Disorders

## Rett Syndrome

Check <https://storm.genie.stanford.edu/article/1155997> for more details

Stanford University Open Virtual Assistant Lab

The generated report can make mistakes.

Please consider checking important information.

The generated content does not represent the developer's viewpoint.

## summary

Gamma-aminobutyric acid (GABA) is a crucial neurotransmitter in the central nervous system, primarily recognized for its role as the chief inhibitory neurotransmitter in mammals. GABA is synthesized from glutamate through the enzyme glutamate decarboxylase and is essential for maintaining the balance between excitation and inhibition within neuronal circuits. This neurotransmitter operates predominantly through two receptor types: the ionotropic GABAA receptors, which facilitate rapid inhibition, and the metabotropic GABAB receptors, which mediate slower, sustained inhibitory effects.[\[1\]\[2\]\[3\]](#).

GABA's significance extends to various physiological processes, including the regulation of mood, anxiety, stress responses, and sleep patterns. Dysregulation of GABAergic signaling is implicated in a multitude of neuropsychiatric disorders such as schizophrenia, anxiety disorders, epilepsy, and mood disorders, highlighting its critical role in maintaining mental health and cognitive function.[\[2\]\[4\]\[3\]\[5\]](#). Notably, GABA's inhibitory actions are vital for controlling neuronal excitability, and alterations in its transmission can lead to various clinical manifestations, underscoring the importance of GABA in neurophysiology.

Controversies surrounding GABA include the debate over the efficacy of exogenous GABA supplementation and its ability to cross the blood-brain barrier, with emerging research suggesting a more complex relationship between dietary GABA and its neurological effects than previously understood.[\[1\]\[6\]](#). Additionally, ongoing studies are investigating the potential connections between gut microbiota and GABA synthesis, further complicating the narrative surrounding this important neurotransmitter.[\[7\]\[8\]](#). As research continues to unfold, GABA remains a focal point in understanding both the biological underpinnings of neurological health and the development of novel therapeutic strategies for various disorders.

## Chemical Structure

GABA (gamma-aminobutyric acid) is primarily found as a zwitterion, which means that it carries both a positive and a negative charge due to its amino and carboxyl functional groups, respectively[\[1\]](#). The conformation of GABA is influenced by its environment; in the gas phase, a highly folded conformation is energetically favored due to electrostatic attractions between the charged groups, with stabilization estimated

at about 50 kcal/mol based on quantum chemistry calculations[1]. In the solid state, GABA adopts an extended conformation, characterized by a trans configuration at the amino end and a gauche configuration at the carboxyl end, arising from packing interactions with neighboring molecules[1].

In solution, GABA exhibits conformational flexibility, existing in five different forms—some folded and some extended—due to solvation effects[6]. This flexibility is crucial for its biological function, as it allows GABA to bind to various receptors in different conformations[6]. The primary synthesis pathway of GABA involves its conversion from glutamate through the enzyme glutamate decarboxylase (GAD), which utilizes pyridoxal phosphate (the active form of vitamin B6) as a cofactor[1][6].

Moreover, GABA can also be synthesized through a secondary pathway from putrescine via diamine oxidase and aldehyde dehydrogenase[1]. Historically, it was believed that exogenous GABA could not cross the blood-brain barrier; however, recent research suggests that this notion requires further investigation to clarify[1][6].

## Function in the Brain

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system (CNS) and plays a crucial role in maintaining the inhibitory-excitatory balance necessary for proper brain function. GABA modulates neuronal activity predominantly through two receptor subtypes: ionotropic GABAA receptors and metabotropic GABAB receptors[2]. GABAA receptors, which are pentameric ligand-gated chloride channels, rapidly hyperpolarize neurons, thus inhibiting excitatory signals[9][2]. Conversely, GABAB receptors, which are G-protein-coupled receptors located extrasynaptically, provide prolonged inhibition by activating potassium channels and inhibiting calcium channels[2].

GABA's primary function in the brain encompasses regulating behaviors related to cognition, emotion, and motivation[2][4]. Approximately 30% to 40% of neurons in the brain are GABAergic, meaning they release GABA to communicate between neurons[4]. GABA's activity is critical for controlling movement, speech, and overall behavioral responses, including reflexes[10]. It helps to alleviate painful sensations and is involved in mood regulation, sleep induction, and relaxation[10][11].

The dynamic nature of GABAergic signaling is influenced by the developmental expression of the KCC2 transporter, which regulates intracellular chloride levels. Initially, high intracellular chloride concentrations make GABAergic signaling excitatory, but as KCC2 expression increases during development, GABA shifts to its inhibitory role[2][7]. This switch is significant for synaptic plasticity and neuronal circuit formation, as GABAergic interneurons play a pivotal role in shaping the network dynamics of excitatory and inhibitory interactions in the brain[12][7].

Moreover, abnormalities in GABA signaling have been implicated in various neuropsychiatric disorders, including schizophrenia, anxiety, and mood disorders[3][4][5]. Dysfunction in GABAergic transmission can lead to imbalances that affect cognitive functions and emotional regulation, highlighting the importance of GABA in maintaining mental health[3][4].

# Physiological Effects

## Role in Stress and Anxiety

Gamma-aminobutyric acid (GABA) is a crucial neurotransmitter in the central nervous system, primarily known for its inhibitory effects. Its role in regulating the physiological response to stress is significant, as GABAergic neurons project to the paraventricular nucleus (PVN) of the hypothalamus, which is essential in controlling the hypothalamus-pituitary-adrenal (HPA) axis and the associated release of stress hormones such as cortisol.[\[2\]](#) Dysregulation of GABAergic processes has been linked to various stress-related disorders, including anxiety and depression, which stem from a malfunction in brain circuits that regulate emotional responses to perceived threats.[\[13\]\[14\]](#).

## Sleep Regulation

Research indicates that GABA plays an important role in promoting sleep, with GABA activity being closely tied to sleep onset and maintenance.[\[4\]](#) Studies have demonstrated that GABA supplements may help improve sleep quality, reducing sleep onset latency and enhancing overall sleep satisfaction.[\[15\]\[4\]](#) However, results are mixed, and while some interventions show promising outcomes, others fail to establish statistically significant differences when compared to control groups.[\[15\]](#).

## Impact on Neurological and Psychiatric Disorders

GABA's effects extend to various neurological and psychiatric conditions. Reduced levels of GABA are associated with disorders such as Huntington's disease and epilepsy, where insufficient GABA activity can lead to excessive neural excitation and subsequent seizures.[\[16\]\[17\]](#) Moreover, abnormalities in GABAergic neurotransmission have been implicated in cognitive deficits observed in neurodevelopmental disorders and schizophrenia, where the modulation of GABA signaling may provide therapeutic avenues for managing symptoms.[\[18\]\[3\]](#).

## Side Effects and Considerations

While GABA supplements and analogs can provide benefits, they are not without side effects. Common adverse effects include sedation, dizziness, gastrointestinal upset, and muscle weakness.[\[19\]\[20\]](#) Notably, some individuals may experience neuropsychiatric reactions such as anxiety, agitation, and cognitive impairment, particularly when using benzodiazepines that enhance GABA activity.[\[21\]\[14\]\[17\]](#) As such, it is crucial to consult healthcare providers before using GABA-related products to ensure their appropriateness for individual health circumstances.[\[20\]](#).

## GABA Receptors

GABA receptors are a class of receptors that respond to the neurotransmitter gamma-aminobutyric acid (GABA), which serves as the principal inhibitory neurotransmitter in the mature vertebrate central nervous system. There are two primary classes of GABA receptors: GABAA and GABAB. The GABAA receptors are ligand-gated ion channels, while GABAB receptors are G protein-coupled receptors, also referred to as metabotropic receptors[\[22\]\[23\]](#).

## GABAA Receptor

The GABAA receptor (GABAAR) is an ionotropic receptor that mediates rapid inhibitory neurotransmission. When GABA binds to the GABAA receptor, the receptor channel opens, allowing chloride ions (Cl<sup>-</sup>) to flow into the neuron, leading to hyperpolarization and neuronal inhibition. This quick action is crucial for regulating neuronal activity and maintaining nervous system stability. For instance, during an epileptic seizure, the activation of GABAA receptors can help counteract excessive neuronal excitation, alleviating seizure symptoms[\[24\]\[23\]](#).

The GABAA receptor is composed of a pentameric arrangement of different subunits, with 19 identified subunit genes in humans, including six alpha ( $\alpha 1-6$ ), three beta ( $\beta 1-3$ ), three gamma ( $\gamma 1-3$ ), and others[\[25\]](#). This structural diversity allows for a range of functional and pharmacological properties. The receptor operates by being selectively permeable to chloride ions and, to a lesser extent, bicarbonate ions upon activation[\[23\]](#).

## GABAB Receptor

The GABAB receptor, unlike GABAA, functions as a metabotropic receptor and is involved in slower inhibitory processes through G-protein signaling pathways. GABAB receptors play a significant role in modulating neurotransmitter release and regulating excitability in neuronal circuits[\[22\]\[26\]](#).

## Ligands and Modulation

Various ligands can bind to GABA receptors, modulating their activity. These ligands can be classified as orthosteric agonists and antagonists, which interact with the primary binding site where GABA binds, or as allosteric modulators, which bind to different sites on the receptor, influencing its activity indirectly[\[27\]\[25\]](#). Orthosteric agonists, such as gaboxadol and muscimol, activate the receptor and increase Cl<sup>-</sup> conductance, while antagonists like bicuculline inhibit GABA's effects, reducing Cl<sup>-</sup> conductance[\[26\]](#).

Allosteric modulators can either enhance (positive allosteric modulators, PAM) or inhibit (negative allosteric modulators, NAM) the receptor's response to GABA. Substances such as benzodiazepines and barbiturates are examples of PAMs that increase the efficacy of GABA transmission, thereby serving as anxiolytics and sedatives[\[25\]\[3\]](#).

## Role in Neurophysiology



GABA receptors, particularly the GABAA subtype, are vital for maintaining the excitatory/inhibitory balance in the brain. Disruptions in this balance are associated with various neurological disorders, including epilepsy and anxiety disorders. The developmental changes in GABA's function from excitatory in neonates to inhibitory in adults highlight the dynamic role of GABAergic signaling in brain maturation and function[28][6].

## Clinical Relevance

GABA, or gamma-aminobutyric acid, plays a crucial role in several psychiatric and neurological disorders, underscoring its clinical relevance. It functions primarily as an inhibitory neurotransmitter in the central nervous system, and its dysregulation has been linked to various conditions, including schizophrenia and epilepsy.

### Schizophrenia

Schizophrenia is a multifactorial psychiatric disorder that affects approximately 0.5–1% of the global population, characterized by positive symptoms (hallucinations and delusions), negative symptoms (lack of communication and social interaction), and cognitive disturbances (Lewis and Lieberman, 2000)[3]. Impairments in GABAergic signaling have been implicated in the pathophysiology of schizophrenia. Studies have shown alterations in GABA receptor subunit glycosylation in the brains of individuals with schizophrenia, which may contribute to dysfunctional neurotransmission (Mueller et al., 2015)[25]. Specifically, a reduction in the expression levels of GABA transporter genes, such as NKCC1 and KCC2, has been observed in schizophrenia-like animal models, suggesting a potential link between GABA dysregulation and the disorder (Larimore et al., 2017)[3].

### Epilepsy

Epilepsy is another significant clinical condition where GABA's role is critical. Characterized by recurrent seizures due to abnormal brain electrical activity, epilepsy affects around 65 million people worldwide (Schwartzkroin and Prince, 1980)[3]. An imbalance between excitatory and inhibitory signals, often attributed to impaired GABAergic signaling, is a hallmark of epilepsy (Ben-Ari et al., 1979)[3]. Clinical evidence supports that many antiepileptic drugs target GABA receptors, highlighting the importance of GABA modulation in managing seizure disorders. Mutations in GABA receptor subunit genes have been linked to various idiopathic forms of epilepsy, indicating that GABA dysfunction can result in impaired neuronal communication and increased seizure susceptibility (Kostopoulos et al., 1983)[3].

### Other Mental Health Disorders

GABA's role extends beyond schizophrenia and epilepsy; it has also been implicated in major depressive disorder (MDD) and anxiety disorders. Dysregulation of GABAergic signaling is thought to contribute to the pathophysiology of MDD,

with chronic stress leading to alterations in GABA transmission in the prefrontal cortex (Williams et al., 2020)[25]. In anxiety disorders, GABA receptor modulators, such as benzodiazepines, are commonly used as anxiolytics, demonstrating the neurotransmitter's importance in treating anxiety-related symptoms (Parviz et al., 2014)[6].

## Research and Future Directions

Recent research has significantly expanded our understanding of gamma-aminobutyric acid (GABA) and its potential therapeutic applications. Some new antidepressants have been found to act through the GABAergic system, highlighting GABA's role in mood regulation and mental health management[29]. This research suggests that GABA modulation could provide new avenues for treating conditions like major depressive disorder, particularly in light of findings that demonstrate the effectiveness of alternative interventions such as yoga and coherent breathing on thalamic GABA levels[30].

Moreover, studies have begun to explore the implications of gut microbiota in the production of GABA. Emerging evidence indicates that human gut microbiota can synthesize GABA, potentially influencing the gut-brain axis and offering insights into the connection between gut health and neurological function[7][8]. This suggests that GABA could serve as a functional link between the microbiome and brain activity, which could have far-reaching implications for both mental and physical health[31].

In addition, the development of combinational therapies targeting both N-methyl-D-aspartate receptors (NMDARs) and GABAB receptors (GABABRs) has shown promise in alleviating various pathologies across multiple diseases, potentially paving the way for more comprehensive treatment strategies[2].

Furthermore, the role of dietary components, such as glutamic acid, in modulating GABA levels and its subsequent effects on conditions like obesity and depressive symptoms is being actively investigated. This research could lead to novel dietary interventions for enhancing GABA production[32][33].

As research progresses, it will be essential to address the efficacy and safety of GABA supplementation, given that some individuals are already exploring these options for anxiety and other health conditions[34]. Before considering GABA supplements, medical professionals generally recommend trying established treatments, which underscores the importance of further investigation into the role of GABA in therapeutic contexts. The future directions in GABA research may thus hold significant promise for advancing our understanding of its multifaceted role in health and disease.

## History

Gamma-aminobutyric acid (GABA) was first synthesized in 1883, initially recognized as a metabolic product in plants and microorganisms[24]. It was not until 1950 that significant advances were made in understanding its role within mammalian biology. Researchers at Washington University School of Medicine, Eugene Roberts and

Sam Frankel, employed newly-developed chromatography techniques to analyze protein-free extracts from mammalian brains, leading to the discovery that GABA is metabolized from glutamic acid and accumulates within the central nervous system of mammals[24][6].

Following this breakthrough, GABA remained relatively under-studied until 1957 when Canadian researchers identified it as a key inhibitory component in extracts from the brain and spinal cord, referring to it as Factor I[6]. The functionality of GABA was further elucidated in 1959 when studies demonstrated its action at inhibitory synapses on crayfish muscle fibers, revealing that GABA acts by stimulating inhibitory nerve pathways. Notably, this inhibitory action could be blocked by picrotoxin, indicating a specific mechanism of action[6].

The foundational research conducted during this period laid the groundwork for the recognition of GABA as a crucial inhibitory neurotransmitter in the mammalian nervous system, with further studies confirming its presence and roles in various biological systems.

## Dietary Sources of GABA

Gamma-aminobutyric acid (GABA) is an important neurotransmitter found in various foods that can potentially influence its levels in the body. Dietary sources of GABA are diverse, encompassing a range of vegetables, legumes, grains, and fermented products.

### Major Food Sources

Several food categories are recognized for their GABA content. Cruciferous vegetables such as broccoli, cabbage, cauliflower, and Brussels sprouts are notable sources[10][34]. Legumes, particularly soybeans and adzuki beans, also contribute significantly to GABA intake[35]. Additionally, mushrooms and leafy greens, including spinach, tomatoes, and sweet potatoes, have been identified as good sources of GABA[10][35][36].

### Fermented Foods

Fermented foods play a crucial role in GABA availability. Products like yogurt, kefir, kimchi, miso, and tempeh contain naturally occurring GABA, as the fermentation process can enhance its levels[10][35]. Fermented cereals, sourdough breads, and certain cheeses are also recognized for being enriched with GABA, further diversifying dietary options[15].

### GABA in Beverages

Certain beverages are also sources of GABA. For instance, green, black, and oolong teas have been noted for their GABA content, offering a flavorful way to potentially increase GABA levels through diet[35].



## Bioavailability and Research Considerations

Despite the presence of GABA in these foods, research regarding the effectiveness of dietary GABA in significantly influencing brain levels remains inconclusive[35]. Ongoing studies are needed to better understand how GABA from food sources interacts with the human body, particularly regarding its transport to the brain and overall efficacy in enhancing cognitive functions or alleviating stress[15]. Nonetheless, including GABA-rich foods in a balanced diet may support overall health and wellness.

## Dysregulation and Disorders

Dysregulation of the GABAergic system is implicated in a variety of neurological and psychiatric disorders, highlighting the critical role of gamma-aminobutyric acid (GABA) in maintaining excitatory/inhibitory balance in the brain[15]. This imbalance is associated with numerous conditions, including anxiety, depression, autism spectrum disorders (ASD), Alzheimer's disease, and epilepsy[2][26].

## Common Disorders Associated with GABA Dysregulation

### Anxiety Disorders

GABA dysfunction is notably present in anxiety disorders, where decreased GABAergic activity may contribute to heightened neuronal excitability and anxiety symptoms. Benzodiazepines, which enhance GABA receptor activity, are commonly used in treating these disorders, providing rapid relief of anxiety symptoms[37]. However, long-term use must be carefully monitored due to potential dependency and withdrawal issues[20].

### Autism Spectrum Disorders

Research has demonstrated a reduced expression of KCC2 and NKCC1, two crucial chloride transporters involved in GABAergic signaling, in both ASD patients and preclinical models[2]. Inhibiting NKCC1 has shown promise as a therapeutic strategy, alleviating symptoms associated with ASD, Alzheimer's disease, and stress-related disorders[2][25]. This suggests a potential common molecular mechanism underlying these conditions related to GABA signaling.

### Alzheimer's Disease

Alzheimer's disease is characterized by cognitive decline and is also associated with GABA dysregulation. Alterations in GABAergic transmission may exacerbate cognitive dysfunction in individuals with stress-related disorders, indicating that GABAergic pathways could be targeted for therapeutic interventions in Alzheimer's disease[2][26].

# Epilepsy

GABA receptor mutations have been implicated in various forms of epilepsy, including Dravet syndrome. These mutations can lead to abnormal receptor trafficking and reduced inhibitory signaling, resulting in increased seizure susceptibility[25]. Furthermore, the relationship between GABA deficiency and epileptogenesis emphasizes the importance of maintaining balanced GABAergic activity for seizure management[26].

## Neurodegenerative Disorders

The GABAergic system also plays a critical role in neurodegenerative diseases such as Huntington's chorea and amyotrophic lateral sclerosis (ALS). GABA deficiency in these conditions is linked to increased neuronal excitability and cognitive decline[26][38]. In ALS, a significant reduction in GABAergic neurons has been associated with more severe motor impairments, highlighting the necessity of GABA for motor control[26].

## Rett Syndrome

Rett syndrome, a developmental disorder primarily affecting females, shows an imbalance between excitatory and inhibitory neurotransmission due to mutations in the MeCP2 gene. Studies indicate that reduced KCC2 expression in Rett patients parallels findings in other ASD-related conditions, further implicating GABAergic dysregulation in the disorder's symptomatology[2][3].

## References

- [1]: [a review Production of gaba \(<sup>3</sup>-aminobutyric acid\) by microorganisms](#)
- [2]: [GABA - Wikipedia](#)
- [3]: [A paradoxical switch: the implications of excitatory GABAergic ...](#)
- [4]: [The GABAB Receptor—Structure, Ligand Binding and Drug ... - MDPI](#)
- [5]: [GABA Benefits and How to Boost It - Verywell Health](#)
- [6]: [A List of Foods with the Highest GABA - Livestrong.com](#)
- [7]: [The role of GABA neurotransmitter in the human central nervous ...](#)
- [8]: [Gamma-aminobutyric acid as a potential postbiotic mediator in the ...](#)
- [9]: [GABA Signaling: Therapeutic Targets for Neurodegenerative ... - MDPI](#)
- [10]: [Dysregulation of GABAergic Signaling in Neurodevelopmental ...](#)
- [11]: [Molecular mechanisms of metabotropic GABA B receptor function](#)
- [12]: [Anxiety disorders and GABA neurotransmission: a disturbance of ...](#)
- [13]: [Review Altered Connectivity in Depression: GABA and Glutamate ...](#)
- [14]: [The Effect of Oral GABA on the Nervous System: Potential for ... - MDPI](#)
- [15]: [GABA - Physiopedia](#)

- [16]: [What are GABA receptor agonists and how do they work?](#)
- [17]: [GABA Receptor Positive Allosteric Modulators - StatPearls - NCBI](#)
- [18]: [Gamma Aminobutyric Acid: Uses and Effects of GABA Supplement](#)
- [19]: [Gamma-aminobutyric acid analogs - Drugs.com](#)
- [20]: [BENZODIAZEPINES: THE GOOD, THE BAD, AND THE UGLY](#)
- [21]: [GABA receptor - Wikipedia](#)
- [22]: [Structure and function of cerebral GABAA and GABAB receptors](#)
- [23]: [Overview of GABA Metabolism - Creative Proteomics](#)
- [24]: [GABAA receptors: structure, function, pharmacology, and related ...](#)
- [25]: [Role of GABA pathway in motor and non-motor symptoms in ...](#)
- [26]: [GABAA receptor - Wikipedia](#)
- [27]: [Distinct Roles of GABAA and GABAB Receptors in Balancing and ...](#)
- [28]: [The emergence of antidepressant drugs targeting GABAA receptors](#)
- [29]: [Do GABA Supplements Actually Reduce Anxiety? - Verywell Health](#)
- [30]: [Bifidobacterium adolescentis as a key member of the human gut ...](#)
- [31]: [Gut microbial GABA imbalance emerges as a metabolic signature in ...](#)
- [32]: [Gut microbiota-derived gamma-aminobutyric acid improves host ...](#)
- [33]: [Supplementation with high-GABA-producing Lactobacillus ...](#)
- [34]: [GABA: Benefits, side effects, and more - Medical News Today](#)
- [35]: [Gamma-Aminobutyric Acid \(GABA\): What It Is, Function & Benefits](#)
- [36]: [GABA foods and natural sources - Methyl-Life](#)
- [37]: [Resolving the Paradox of Long-Term Benzodiazepine Treatment](#)
- [38]: [What is GABA? | Mental Health America](#)