International Journal of
Clinical Pharmacology & Pharmacotherapy
Review Article Open Access

The GABAergic System: An Overview of Physiology, Physiopathology and Therapeutics

Rafael Antonio Vargas
School of Medicine, Universidad Antonio Nariño, Bogotá, Colombia

Abstract

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system, where it is widely distributed. GABA has an important role in neurodevelopment, and depending on the period of development, its action can be excitatory or inhibitory. In prenatal stages, GABA is excitatory, and in the adult stage, GABA acquires an inhibitory function in the nervous system and modulates the function of other organs and systems including the endocrine system and the immune system. Disorders in the function of GABA are responsible for various pathologies, both neurological and non-neurological, and include epilepsy, anxiety, depression, schizophrenia, endocrine disorders and immunological disorders. In the present narrative review, we show that the activity of GABA depends on the synthesis, degradation, membrane transport and the presence of specific GABA receptors, present in both nervous tissue and non-neural tissue. We describe general aspects of the physiology, physiopathology, and pharmacotherapeutics of the GABA system, and finally, we emphasize that although there are multiple GABAergic therapeutic options, more research is required into the GABA system since future applications may be broad.

Publication History:

Received: November 01, 2018
Accepted: December 27, 2018
Published: December 29, 2018

Keywords:

GABA, GABA agonists, GABA antagonists, GABA pathophysiology, GAD 65/67, GABA-T

Introduction

Gamma-aminobutyric acid (GABA) is the most important brain inhibitory neurotransmitter with key roles in the regulation and function of many cortical and subcortical circuits. These aspects mean that alterations in the GABAergic function can be determinative in the development of multiple pathologies, and the GABAergic function is a key target in therapeutic strategies. The present work is a narrative review of the existing literature. We performed a search in databases such as PubMed, Scopus and Google Scholar using the key terms GABA, GABA agonists, GABA antagonists, and GABA pathophysiology. Based on the results obtained, the information was analyzed, organized and presented, focusing on three issues: general aspects of GABA, the pathophysiology of GABA, and GABAergic pharmacology and therapeutics.

General Aspects of GABA Neurotransmission

The synthesis of GABA is carried out through a three-stage process involving three enzymes: glutamate decarboxylase (GAD), GABA transaminase (GABA-T) and succinate semialdehyde dehydrogenase (SSADH). This cycle is called the GABAergic shunt: glutamine glutamate GABA, and glucose is the source of the carbons (Figure 1). From glucose, glutamate is synthesized, which is derived from the Krebs cycle and this in turn will give rise to GABA. The enzyme glutamate decarboxylase (GAD), which requires pyridoxal phosphate as a cofactor, produces GABA by catalyzing the decarboxylation of glutamate. This cytoplasmic enzyme has two subtypes, GAD 65 and GAD 67; it is found in a large proportion of the interneurons and in non-neural tissue such as liver, pancreas and kidney. GADs are used as markers to identify GABAergic circuits. After its synthesis, the GABA is stored in vesicles that go to the presynaptic terminals where it is released in a calcium-dependent mechanism after a nervous stimulus depolarizes the synaptic terminal. The released GABA reaches the postsynaptic neuron where it binds to specific receptors. GABA that does not interact with the receptors is taken up to be metabolized, either by the presynaptic neuron or by the glial cells. Reuptake is performed by a GABA cytoplasmic membrane transporter (GAT) of which four subtypes have been identified (GAT 1-4). Inside the cell, GABA is degraded to succinic semialdehyde through the action of enzymes GABA-T and SSADH, and then to succinate (Figure 1). The GABA-T enzyme is present throughout the nervous system in neurons, glial cells and ependymal cells [Bak, Goto, 1-3].

GABAergic circuits

GABA is the main inhibitory neurotransmitter in postnatal life and is found throughout the central nervous system, mainly in interneurons. GABAergic neurons are part of extensive neural circuits that connect structures such as the cerebral cortex, the hippocampus, the limbic system, the olfactory bulb, the basal ganglia, thalamus, hypothalamus, brain stem nuclei, and pituitary gland. In the cerebellum, GABA is also present in important structures, especially in Purkinje neurons, which are GABAergic neurons. The most studied GABAergic connections are those that connect the striatum with the brain stem and cerebellar cortex. The connections between the hypothalamus and adenohypophysis have also been extensively studied. In recent years, it has been shown that GABA can also be synthesized in non-neural tissue such as pancreatic islets, adrenal glands, testes, ovaries, placenta, uterus and cells of the immune system such as macrophages, monocytes and T cells [4-7].

GABAergic receptors

There are three types of GABA receptors that have been identified by analogous substances that partially or totally reproduce the GABAergic response. Initially, two types of receptors were identified, which were called GABA-A and GABA-B (Figure 1). GABA-B was identified by

***Corresponding Author:** Dr. Rafael Antonio Vargas, School of Medicine, Universidad Antonio Nariño, Bogotá, Colombia; E-mail: antonio.vargas@uan.edu.co

Citation: Vargas RA (2018) The GABAergic System: An Overview of Physiology, Physiopathology and Therapeutics. Int J Clin Pharmacol Pharmacother 4: 143. doi: https://doi.org/10.15344/2456-3501/2018/142

using baclofen (beta-p-chlorine phenyl GABA), an analogue of GABA that activates the GABA-B and GABA-A receptors that were identified by using bicuculline. Subsequently, a third receptor was identified that was not sensitive to classical substances and was named GABA-C. It is currently accepted that there are three receptors for GABA: two fast-acting receptors, GABA-A and GABA-C, and one with slow action, GABA-B [8-11]. The GABA-A receptor is a pentameric chloride-type ionotropic channel receptor that has five different subunits, each one with isoforms, which generate 19 subunits: alpha subunit (α1-6 isoforms), beta subunit (β1-3 isoforms), gamma subunit (γ1-3 isoforms), and subunits delta (δ), epsilon (ε), theta (θ), pi (π) and rho (isoforms ρ1-3). A GABA-A receptor is composed of the combination of five subunits to form a chloride-permeable channel. Most receptors contain two alpha subunits, two beta subunits and one gamma subunit. The receptor has specific binding sites for GABA and for analogous substances. Depending on the combination of subunits, the efficacy of the GABA agonist site and the affinity for the additional allosteric sites changes. Each subunit has four transmembrane hydrophobic domains embedded in the cell membrane, designated M1, M2, M3 and M4. Each oligomeric complex has a site corresponding to the ion channel, which is a channel of chlorine and additional allosteric binding sites for other substances that modulate the action of GABA: benzodiazepines, barbiturates, steroids, zinc and ethanol [11,12]. High and low affinity sites for GABA have been identified in the structure of the channel. The high affinity site is modulated by drugs that bind to additional allosteric sites. The low affinity site is antagonized by the benzodiazepines. Researchers have also identified a site for exogenous agonists such as benzodiazepines and a site for inverse agonists that reduces the flow of chlorine induced by GABA (beta carbolines). There are also binding sites to partial agonists (cyclopyrrolones), binding sites for selective antagonists (bicuculline), and sites of nonselective antagonists (flumazenil). The activation of GABA-A receptors generates a chlorine inlet current, which induces a hyperpolarization of the cell membrane and therefore inhibits nerve impulse conduction. This is reflected in the presence of postsynaptic inhibitory potentials (IPSPs).The GABA B receptor is a heterodimer coupled to a G protein, meaning that it belongs to the family of metabotropic receptors. This receptor is a membrane protein that consists of 7 transmembrane hydrophobic domains; several isoforms of this receptor have been described, designated GABA B1a, GABA B1b and GABA B2. At the brain level, there is a difference in the expression of these receptor subtypes [13,14]. In general, the GABA-B receptor is anchored in the plasma membrane of both the presynaptic terminal and postsynaptic terminal and modulates the activity of calcium channels and potassium channels by an interaction with protein G and adenylyl cyclase. The binding of an agonist to the presynaptic GABA-B receptor decreases the calcium intake, which induces a lower concentration of calcium and therefore a lower release of excitatory neurotransmitters such as glutamate, thereby reducing glutamatergic excitatory activity. On the other hand, the activation of the postsynaptic GABA-B receptor by a GABAergic agonist increases the potassium efflux to the extracellular medium, producing a slow inhibitory potential, which hyperpolarizes the membrane and generates IPSPs [15-17]. The GABA-C receptor is an ionotropic receptor that was isolated in the vertebrate retina. GABA-C receptors were characterized as GABA receptors that do not respond to the GABA analogs bicuculline or baclofen. They are receptors that regulate chlorine channels generating IPSPs [18].

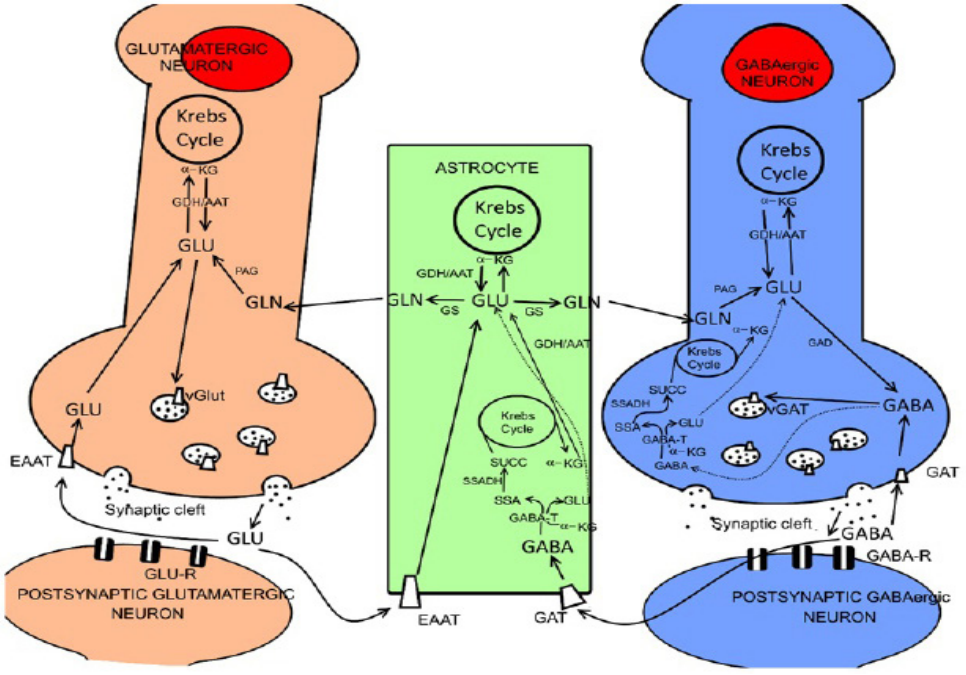

Figure 1: GABA synthesis. The synthesis of GABA is part of glutamate/GABA-glutamine cycle an intracellular process in which GABA or glutamate from neurons are uptake by astrocytes. Subsequently, astrocytes synthesize and release glutamine a precursor of GABA and glutamate synthesis. GABAergic neurons synthesize GABA from glucose and others precursors, including pyruvate and others amino acids. α-KG: α-keto-glutarate; EAAT: excitatory amino acid transporter; GABA-T: GABA transaminase; GABA-R: GABA receptor; GAD: glutamate decarboxylase; GAT: GABA Transporter; GDH/AAT: glutamate dehidrogenase/aspartate aminotransferase; GLN: glutamine; GLU: glutamate; GLU-R: glutamate receptor; GS: glutamine synthetase; PAG: glutaminase; Succ: succinate; SSA: succinic semialdehyde; SSADH: succinate semialdehyde dehydrogenase; vGAT: vesicular GABA transporter; vGlut: vesicular glutamate transporter

Functional aspects of GABA

The neurotransmitter GABA is considered to be an inhibitory neurotransmitter since activating its receptors reduces nerve transmission. In the case of the ionotropic GABA-A and C receptors, the influx of chlorine into the cell, due to the chemical gradient and the Nerst potential for chlorine (20 mM vs 110 mM; ECl = −70 mV), causes a hyperpolarization of the cell membrane, which generates IPSPs. However, this is not true in embryonic cells because in this circumstance, intracellular chlorine is elevated with respect to extracellular chlorine (80–120 vs 110 mM). This is due to the early expression of the cotransporter for sodium, potassium and chlorine called NKCC1, which favors the accumulation of intracellular chlorine. Therefore, in embryonic neurons, GABA causes a strong depolarization, because when activating the GABA-A receptor, a chlorine efflux current is produced, which generates a depolarization that has been called giant potentials. For this reason, at this stage, the GABA neurotransmitter is excitatory and apparently is key in the formation and development of brain circuits [19,20]. The factor that changes the embryonic (excitatory) to mature (inhibitory) phenotype in the neuron is the expression of a chlorine and potassium cotransporter called KCC2, which decreases the intracellular chlorine, which allows the current GABA-A to activate the current. Chlorine entry hyperpolarizes the membrane. In the case of postsynaptic GABA-B receptors, hyperpolarization is due to the indirect activation of potassium channels, which generates a potassium outflow and thus hyperpolarization. In the presynaptic terminal, the GABA-B receptor modulates calcium channels and decreases calcium entry, thus causing less release of excitatory neurotransmitters such as glutamate. The final result is that GABA inhibits nerve transmission mediated by glutamate and other excitatory neurotransmitters in the different neuronal circuits of the cerebral cortex, either by hyperpolarizing the postsynaptic cell membrane or by reducing the release of excitatory neurotransmitters from the presynaptic terminal. The GABA receptors have different locations; they can be located in the synapse or positioned in extrasynaptic territories, which allows for the generation of two types of responses: a fast postsynaptic potential (fast IPSP), characteristic of the action of GABA on synaptic ionotropic receptors and a slow (slow IPSP) that is dependent on the action of GABA that diffuses and acts on extrasynaptic receptors [21]. However, there are also numerous subtypes of GABAergic interneurons in circuits of the cerebellum, the basal ganglia and many areas of the cerebral cortex that have specific biophysical properties and contribute to the diversity of responses related to GABAergic tone. However, GABA does not only act as a neurotransmitter; its roles as a neurohormone, trophic factor and immunomodulator have also been described, and these roles make GABA a multifunctional molecule [11].

GABA and balance inhibition-excitation

The general function of GABA in the different circuits is to generate a balance between the excitatory impulses in the different circuits, through a presynaptic or postsynaptic inhibitory effect, which, when reducing neuronal excitability, is considered to act as an inhibitory tone. It is suggested that this modulating activity is reflected in the synchronized oscillatory activity of neuronal circuits, which can be the basis of multiple cognitive functions that include perception, attention, memory and learning. Macroscopically, these oscillatory patterns of cortical circuits are reflected in the electroencephalogram in high-frequency oscillatory activity such as gamma rhythms with frequencies of 30-100 Hz and beta frequencies of 13-30 Hz [22]. These rhythms fluctuate normally in physiological conditions and are altered in pathological situations. Some depressant chemicals of the central nervous system increase this inhibitory tone through modulation of the GABA receptors in the presynaptic or postsynaptic neurons. An example are some nervous system depressants such as benzodiazepines or alcohol. Other drugs reduce the flow of calcium in the neurons by reducing the release of various neurotransmitters such as noradrenaline, glutamate and substance P, which causes various responses including pain inhibition. Drugs such as pregabalin and gabapentin have been used in the treatment of pain, but they are also used in the treatment of pathologies as diverse as anxiety, epilepsy and other neuropathies [23,24].

GABA and sleep

There are many neurotransmitters that participate in the phenomenon of sleep and the sleep-wake cycle: neurotransmitters such as glutamate, noradrenaline, serotonin and histamine can be part of excitatory circuits of alertness and wakefulness; endorphins, acetylcholine and of course GABA participate actively in the inhibitory circuits to trigger sleep. GABA apparently participates in both REM and non-REM sleep [25-27]. Sleep is a complex phenomenon that, by generating a restriction of neuronal activity, apparently favors detoxification and functional recovery at the cellular level. Sleep is part of a fundamental biological cycle common to many species: the sleep-wake cycle. This cycle includes three phases: wakefulness, sleep with rapid eye movements (REM sleep) and sleep without rapid eye movements (non-REM sleep) and is the result of the participation of various neural circuits in the reticular formation of the brain stem to the cortex that have both excitatory and inhibitory characteristics [26,27].

GABA and neurodevelopment

The role of GABA in postnatal brain development processes has been studied in animal models where the development of the somatosensory and visual cortex has been explored [18,19]. Cortical activity and its postnatal development depends on a balance between excitatory circuits and inhibitory circuits. It has been observed that the administration of agonist substances or GABA antagonists modifies the structure of cerebral cortical units, namely, the cortical columns. This has been studied in rodents, where it was observed that the infusion of benzodiazepines expands the distance between the cortical columns of the visual cortex, while the antagonists reduce the distance between the columns [28,29]. These structural and cortical modifications can be key in processes such as learning, memory and processing of sensory and motor information [22,25,30].

GABA in the neuroendocrine system

One of the additional functions of GABA is as a neurohormone. It has been reported that GABA inhibits the release of gonadotropin releasing hormone (GnRH), and it inhibits the release of prolactin, although its inhibitory effect is less potent than that of dopamine. It has been shown that a decrease in GABA together with an increase in glutamate coincides with the high release of GnRH during puberty. At a peripheral level, GABA participates in the activity of ovaries and testes by regulating the release of estrogen, progesterone and the process of spermatogenesis [7]. However, in fish it has been observed that an injection of GABA causes an increase in the release of GnRH and LH and inhibits the activity of dopaminergic cells. It has also been observed that by inhibiting GABA transaminase there is an increase of GABA in the pituitary gland and elevation of gonadotropin levels in

plasma. Apparently the changes in GABA are cyclic and are regulated by estrogen levels, since estradiol produces a decrease in GABA levels [31,32]. GABA and synthetic enzymes such as GAD are also present in other endocrine tissues. In the islets of Langerhans in the pancreas, the beta cells produce this neurotransmitter. Here, GABA seems to have a cytoprotective effect, since it has been observed that it reduces the apoptosis of beta cells and favors their proliferation [33]. At the level of the digestive tract, the presence of cells reactive to GABA, especially at the level of the pyloric sphincter and small intestine, has also been described, which could mean that GABA can act as a neurotransmitter and intestinal hormone [34]. Some studies have shown that GABA can stimulate gastric secretion in rodent models [35]. More recently, the existence of a brain-gut axis has been proposed in which microbiota in the digestive tract can modify levels of neurotransmitters such as dopamine, norepinephrine, serotonin and GABA [36].

GABA as an immunomodulator

In recent years, multiple studies have shown that GABA can be synthesized, stored and released by the immune system. Cells of the immune system such as macrophages, monocytes and T lymphocytes express GABA-A and B receptors, GAD and transporters for GABA. The activation of GABA receptors, at a non-neural level, requires much lower concentrations than those present in the nervous system. At the peripheral level, GABA can modulate the activity of the immune system by activating or inhibiting cytokine secretion, decreasing the proliferation of T cells and modifying the migration of defense cells. In animal models it has been observed that a decrease in the expression of GAT increases the proliferation of T cells and the production of cytokines [4-6,37].

GABA and cardiovascular regulation

The modulating effect of GABA in cardiovascular regulation circuits located in the central nervous system at the brain stem level has been widely studied in multiple models. The administration of GABAergic agents in the nervous system produces a decrease in heart rate and blood pressure by reducing the sympathetic tone. This response can be reversed by GABA antagonists such as bicuculline [26,38-40]. In a recent work, by using a zebrafish model, we found that GABA modifies the variability of heart rate (HRV) in larvae, probably by central action [41]. GABA has also been identified at the level of structures of the peripheral nervous system such as the sympathetic ganglia, but its role in cardiovascular regulation at this level is not clear and research is needed to establish the regulatory mechanisms. This information proposes a possible therapeutic approach to cardiovascular pathologies with substances that act peripherally and selectively [1,38,42,43].

Pathophysiology of Gaba, Neurological and Non-Neurological Diseases

GABA is implicated in a large number of diseases including anxiety and stress disorders [44], pain [24], musculoskeletal disorders [1], sleep disorders, depression, addiction and withdrawal syndromes, seizure syndrome, encephalopathies, hepatic disorders, memory and learning disorders, hormonal disorders such as premenstrual syndrome and more recently a role of GABA in schizophrenia, depression and Alzheimer's disease has been revealed [25,45].

GABA and neurological disorders, Convulsive syndrome

A convulsive syndrome is a multi-causal phenomenon in which a relatively common phenomenon is the decrease or absence of neuronal inhibition mediated by GABA. The decrease of inhibitory GABAergic tone is associated with an increase in neuronal excitability that favors the hyper synchronization of neuronal electrical activity and the appearance of convulsive episodes. This can trigger numerous pathological processes such as epileptic states. Studies in humans have shown that the expression of the transporter for GABA is diminished in the hippocampus of epileptic patients, which probably leads to the increase of GABA in the synaptic cleft; as a response, the internationalization of GABA receptors into the cytoplasm (down regulation) and their reduction in number in the cell membrane occurs and this decreases the response to GABA and increases the action of excitatory neurotransmitters [Goto, 46-48].

GABA and affective disorders

Experimental evidence shows a relationship between impaired GABAergic function and affective disorders such as stress, anxiety, depression and addictive behaviors, especially related to alcoholism.

Anxiety, depression and GABA

Anxiety and depression are disorders of affect that often occur simultaneously in the same patient and some researchers have suggested that both pathologies may have a similar pathophysiological mechanism. It has been proposed that a reduction of GABAergic tone may be present in both anxiety disorders and more complex pathologies such as major depression [Pehrson, 45]. Studies of cerebral functional images in patients with depression have shown lower levels of GABA at the cortical level and in experimental models in rats it has been observed that a decrease in the expression of GABA-A receptors generates a pattern of behavior similar to anxiety. GABA has also been implicated in the pathophysiology of panic disorder along with serotonin and dopamine [45].

Alcoholism and GABA

The neurobiological effects of alcoholism, such as acute and chronic intoxication, convulsive episodes, psychotic states, Wernicke-Korsakoff syndrome and alcohol-fetal syndrome, are the expression of the effects and consequences of ethanol, a GABAergic agonist, on the glutamatergic system. Acute consumption of ethanol facilitates GABAergic transmission (by increasing the conductance of chlorine through the GABA receptor) and inhibits glutamatergic function (by decreasing cathonic conductance through the NMDA receptor). Paradoxically, the development of tolerance associated with the chronic consumption of ethanol leads to a reduction in GABAergic function and an increase in glutamatergic activity. The prolonged inhibition of the NMDA receptor by ethanol results in the development of super sensitivity, and acute withdrawal of ethanol causes a marked increase in the activity of postsynaptic neurons that include various circuits such as the dopaminergic, noradrenergic and glutamatergic system that can lead to neurotoxicity by glutamate [49,50].

GABA and cognitive disorders. Schizophrenia

GABA has also been implicated in the pathophysiology of schizophrenia [51, Schmidt]. Recent studies carried out in autopsies of patients with schizophrenia indicate that the GABA function is

diminished in brain areas that present structural changes observed in computerized axial tomography and magnetic resonance studies. These reported structural changes are associated with the patient's negative symptoms, poor premorbid functioning and decreased turnover of dopamine and serotonin. There are other findings, both in schizophrenic patients and in animal models, related to GABA: reduction in the density of GABAergic neurons, structural alterations of the receptors and disorders in the reuptake of this neurotransmitter. This accumulated evidence suggests the participation of GABA in the genesis of this disease and we have proposed models that propose an interaction of the GABAergic and dopaminergic system in the pathophysiology of schizophrenia [52,53, Benes].

Immune system and GABA. Autoimmune pathologies

The neurotransmitter GABA has also been implicated in disorders related to autoimmunity that include multiple sclerosis, diabetes mellitus type 1, rheumatoid arthritis, asthma, and sepsis. In patients with multiple sclerosis it has been found that serum levels of GABA are decreased. In animal models of rheumatoid arthritis and obesity, the administration of GABAergic agents decreases the inflammatory response [4-6]. In diabetes mellitus type 1, it has been suggested that the destruction of beta cells may be mediated by proinflammatory and cytotoxic activity of T cells, which would coincide with a reduction in GABAergic function; it has been suggested that GAD can act as an autoantigen [7,54,55]. GABA could also play an important role in conditions such as sepsis, where a massive release of cytokines can cause a patient's condition to rapidly deteriorate [56,57]. Similarly, in other pathologies with an immunological component such as in asthma, it has been suggested that the production of GABA in the respiratory epithelium may be aprotective factor since it apparently induces bronchial smooth muscle relaxation, but the underlying mechanisms are still unclear [58].

Pharmacology and Therapeutics of Gaba

The use of chemical substances that act on the GABA system is not new; in fact, the first sedative-acting agents developed more than 100 years ago act on the GABAergic system, namely barbiturate substances derived from barbituric acid [59]. Based on the knowledge of the structure, function and participation of GABA and its recipients in various pathologies, mechanisms of action of conventional multiple drugs traditionally used in clinical practice have been clarified, for which mechanisms of action were not previously known, but they have also been used to develop new therapeutic alternatives that target GABA and its actions (Table 1).

GABA-A agonists include barbiturates (pentobarbital, secobarbital, phenobarbital), classical and new benzodiazepines (diazepam, alprazolam, flurazepam, imidazenil, triazolam), ethanol, neurosteroids, muscimol and topiramate. Neurosteroids are a group of interesting substances because they are metabolites derived from steroid hormones that can apparently be synthesized in the nervous system. Derivatives of progesterone and corticosterone produce hypnotic, sedative and anxiolytic effects [60,61]. One of these steroids is the anesthetic alfaxalone that acts as a potent modulator of GABA. Other steroidal derivatives are: allopregnanolone, alo tetra hydroxycorticosterone, androstanediol, ethiocolanone, pregnenolone and dehydroepiandrosterone [23]. The ability of neurosteroids to modulate the function of GABA could explain the different responses to the administration of GABAergic agents when administered to men or women and the symptoms of anxiety that occur with the abrupt suspension of corticosteroids administered chronically. GABA A antagonists are experimental agents such as beta carbolines, picrotoxin, bicuculline, and pentylenetetrazole; these agents are characterized by blocking GABA effects and producing anxiety states to convulsions. Also in this group should be considered flumazenil, a drug used as an antidote in poisonings by benzodiazepines (Table 1).

TARGET	TYPE	MECHANISM	EFFECT	DRUGS	REFERENCES
GABA SYNTESIS (GAD)	Blocker	Reduces GABA synthesis	Reduces inhibitory tone	Hidracines, valproic acid.	[32, 69]
	Activator	Reactive synthesis of GABA	Reduces excitatory tone	Piridoxine.	[32, 69]
TRANSPORT (GAT)	Blocker	Prevents GABA reuptake	Increase inhibitory tone	Vigabatrin, valproate, tiagabine, diaminobutyric acid, nipocotic acid and guvacine	[32, 51, 52, 53, 69]
DEGRADATION (GABA-T)	Inhibitor	Blocks GABA degradation	Increase inhibitory tone	Vigabatrine, valproic acid.	[70]
GABA-A RECEPTOR	Agonist	Increases chlorine entry by GABA-A receptor	Inhibition (rapid IPSP). Increase inhibitory tone.	BZD, barbiturates alcohol, neurosteroids, muscimol, abecarnil, topiramate.	[17, 23, 25, 27, 28, 29, 32, 48, 49, 61,64, 65, 66, 69, 71, 72, 77, 82, 89]
	Antagonist	Decreases chlorine permeability. Reduces inhibitory tone	Excitatory tone predominates	Picrotoxin, bicuculline, pentylenetetrazole, flumazenil.	[23, 27, 29, 65, 66, 69, 71, 72]
GABA B RECEPTOR	Agonist	Increases potassium output postsinapsis Reduces calcium entry presynapsis	Inhibition (slow IPSP) Reduces neurotransmitter release	Baclofen, 3-APPA, 3-APMA.	[10, 15, 16, 17, 18, 32, 37, 54, 65, 66, 69, 73, 74, 86, 90]
	Antagonist	Reduces inhibitory tone	Excitatory tone predominates	Saclofen, ácido amino-valérico.	[15, 16, 17, 18, 19, 65, 66, 69, 86]

Table 1: Pharmacology of GABA. The therapeutic targets, mechanisms of action, final effects on GABAergic transmission and pharmacological agents can be observed.

3-APMP: 3-aminopropyl(methyl)phosphonic acid; 3-APPA: 3-aminopropylphosphonic acid; BZD: benzodiazepines; GABA-T: GABA transaminase; GAD: glutamate decarboxylase enzyme; GAT: GABA transporter; IPSP: inhibitory postsynaptic potential.

For GABA-B receptors, the number of available drugs is lower. Baclofen is the agonist par excellence, while antagonists are saclofen and valeric amino acid. With the direct action of these agents on GABAergic receptors, phasic GABAergic inhibition is modulated, which depends on the release of GABA and its action on synaptic receptors [60].

GABAergic action can also be modulated by acting on the synthesis, degradation and / or transport systems (Table 1). With these agents the inhibitory tone is modulated without directly acting on GABAergic receptors, causing a fleeting or prolonged effect of GABA on their areas of influence. This can positively or negatively modulate the GABAergic tonic inhibition. Some drugs can increase the inhibitory tone by activating synthetic enzymes (GAD), as happens with pyridoxine, a cofactor of GAD, and whose deficiency can generate seizures. GABAergic tone is also increased by inhibiting degradation enzymes such as GABA-T (valproate, vigabatrin, gabaculin, phenelzine) or by inhibiting the GAT membrane transporter (tiagabine, deramciclane, adhyperforin, hyperforin). The inhibitory tone can be reduced by inhibiting the GABA synthesis enzyme, GAD 65/67, with hydrazines.

From the clinical point of view, understanding the function of GABAergic neurons and their participation in pathological disorders is key in clinical areas such as neurology, psychiatry and rehabilitation because a large number of anxiolytics, muscle relaxants, sedatives and anticonvulsants exert their pharmacological action by acting on receptors or enzymatic systems; however, new clinical areas and therapeutic proposals based on the findings of recent years have emerged.

Clinical Applications

Anticonvulsants: GABAergic agents are an option in the treatment of epilepsy in order to increase the inhibitory tone to reduce neuronal cortical hyperexcitability [55]. The mechanism of these agents varies and includes GABA agonist drugs such as benzodiazepines or barbiturates. Agents that modify transport and metabolism that include inhibitors of the GABA transporter or pyridoxine as a cofactor of GAD can be considered to act as an anticonvulsant in cases of seizures due to pyridoxine deficiencies (see Table 1). Sodium valproate is an inhibitor of semialdehyde succinic dehydrogenase and GABA transaminase; its mechanism of action is to inhibit enzymes that are related to the degradation of GABA and therefore it maintains the necessary levels of GABA. Another strategy is to block the reuptake of GABA by presynaptic neurons, which is achieved with substances such as diaminobutyric acid, nipecotic acid and guvacine [46,47,62].

Sleep disorders: Many GABAergic agents have sedative and hypnotic actions and many of them have been used with that intention, such as barbiturates, benzodiazepines to anesthetic agents and alcohol. With the contribution of molecular biology to identify subtypes of subunitsit has been possible to establish that the expression pattern of subunits determines the predominance of a particular effect. Apparently, the presence of alpha 1 subunits results in a greater sedative effect and the presence of alpha2 / alpha3 subunits produces a greater anxiolytic effect [25,63].

Anxiety and depression: Given that it is postulated that anxiety and depression are clinical situations that may be present in the same patient and that GABA may be participating in its genesis, many GABAergic agents have been used for the treatment of anxiety and as coadjutants in the treatment of depression [43,64-66].

Schizophrenia: In patients diagnosed with schizophrenia, a reduction in the number of GABAergic type of interneurons has been found in post mortem studies. More recently, it has been suggested that deficiencies in the expression of the α2 subunit of the GABA-A receptor could be involved in the genesis of schizophrenia, learning disorders, chronic pain and drug dependence [60]. Early intervention with GABAergic agents at this level, much less aggressive than traditional neuroleptics, could delay the onset of symptoms and the progression of schizophrenia [52,53,65-67].

Abnormal movements, spasticity and analgesia: For the management of spasticity[68],a GABA B agonist has traditionally been used to modulate muscle tone in situations in which it presents, such as in upper motor neuron and / or basal ganglia lesions [9,69]. GABA and its receptors are present in circuits responsible for coordinating the perception and response to painful stimuli. The antinociceptive effect of GABA agonists has been demonstrated in various animal models. It has also been shown that in some types of chronic pain there is a decrease in the GABAergic inhibitory tone in the circuits responsible for the processing of sensory information related to pain [24]. However, the use of GABAergic agents as analgesics is limited because the response varies depending on the type of pain and its time of evolution. Additionally, side effects occur such as sedation, which in turn is directly related to the analgesic effect [70-71]. Some medications that have been used for pain control include baclofen, diazepam, pentobarbital, progesterone-derived neurosteroids, and ethanol [72-74].

Immunomodulator: As previously mentioned, GABA has been implicated in some autoimmune pathologies, which implies that parallel to its inhibitory function in the nervous system, it has a modulating function on the immune system [75]. In patients with Stiffman syndrome (rigid person syndrome) which is associated with autoimmune diabetes mellitus and seizures, anti-GAD antibodies have been found and therefore reduced levels of GABA [76]. In some experimental models of autoimmune encephalitis, the stimulation of GABAergic tone reduces the progressive paralysis that occurs due to the inflammatory process [5,36]. Some studies with benzodiazepines have shown that this GABA agonist agent plays a role in the regulation of the production of corticosteroids by the adrenal cortex and central nervous system in stress situations; however, extensive studies are required to establish the therapeutic potential of GABAergic agents [77,78].

Asthma: In some experimental models in which hyperresponsiveness of the airway is induced by some type of allergen (ovalbumin, for example), in which there is overproduction of mucus, an increase in the synthesis of GABA and an increase in the expression of GABA-A receptors is observed. This suggests an excitatory role for GABA at this level. Also in humans, there is an increase in the expression of GAD and GABA-A receptors after exposure to allergens. The intranasal application of GABA antagonists reduces the overproduction of nasal mucus induced by allergens [Forkuo, 79]. However, GABA-B receptors also have an important role in inhibiting bronchoconstriction stimulated by acetylcholine or cytokines; it has been shown that the use of GABA-B receptor agonists could have a protective effect in asthma [80,81]. However, additional studies on these responses are required as well as studying if there is any connection between asthma and emotional states such as stress and anxiety typical of many asthmatic patients.

Digestive disorders: Although less studied, the presence of GABA in the digestive tract can be evidenced when using GABA agents in the treatment of diseases characterized by disorders of gastric secretion or intestinal motility. The secretory function of the gastrointestinal tract seems to be modulated by GABA, since there are studies in animal models that show that the application of GABA in the central nervous system decreases the vagal tone and thereby reduces gastric acid secretion mediated by acetylcholine, which reduces significant and dose-dependent ulcers caused by stress [82]. The use of GABA agonists, such as pentobarbital, in the treatment of irritable bowel syndrome reduces pain and improves digestive symptoms [83]. Similarly, baclofen, a GABA-B agonist, has been used to increase gastric emptying in animal models of delayed gastric emptying induced by dipyrone [84]. Similarly, the theory of the bowel brain axis raises the possibility of acting on the microbiota to modify affective and / or cognitive disorders [85,86, Kelly]. However, more studies are required to confirm or reject these hypotheses.

Conclusions

Research and current knowledge show that GABA is a versatile molecule, which, besides being a key inhibitory neurotransmitter in the development and function of the nervous system, can perform other tasks in nonneural tissue, either as a neurohormone or as a neuroimmunomodulator. This makes GABA one of the fundamental molecules of the neuroimmunoendocrine system, which can become a potential therapeutic target for the treatment of a large number of pathologies related to this system. However, it is necessary to carry out more research, both basic research and clinical research, to confirm or rule out its therapeutic usefulness.

Competing Interests

The author declare that there is no competing interests regarding the publication of this article.

References

1. Bak LK, Schousboe A, Waagepetersen HS (2006) The glutamate/GABA-glutamine cycle: aspects of transport, neurotransmitter homeostasis and ammonia transfer. J Neurochem 98: 641-653.
2. Goto T, Matsuo N, Takahashi T (2001) CSF glutamate/GABA concentrations in pyridoxine-dependent seizures: etiology of pyridoxine-dependent seizures and the mechanisms of pyridoxine action in seizure control. Brain Dev 23: 24-29.
3. Bowery NG, Brown DA, White RD, Yamini G (1979) [3H] gamma-Aminobutyric acid uptake into neuroglial cells of rat superior cervical sympathetic ganglia. J Physiol 293: 51-74.
4. Bowery NG, Brown DA (1974) Depolarizing actions of gamma-aminobutyric acid and related compounds on rat superior cervical ganglia in vitro. Br J Pharmacol 50: 205-218.
5. Walsh JM, Bowery NG, Brown DA, Clark JB (1974) Metabolism of gamma-aminobutyric acid (GABA) by peripheral nervous tissue. J Neurochem 22: 1145-1147.
6. Alam S, Laughton DL, Walding A, Wolstenholme AJ (2006) Human peripheral blood mononuclear cells express GABAA receptor subunits. Mol Immunol 43: 1432-1442.
7. Bhat R, Axtell R, Mitra A, Miranda M, Lock C, et al. (2010) Inhibitory role for GABA in autoimmune inflammation. Proc Natl Acad Sci USA 107: 2580-2585.
8. Dionisio L, José De Rosa M, Bouzat C, Esandi MDC (2011) An intrinsic GABAergic system in human lymphocytes. Neuropharmacology 60: 513-519.
9. Gladkevich A, Korf J, Hakobyan VP, Melkonyan KV (2006) The peripheral GABAergic system as a target in endocrine disorders. Auton Neurosci Basic Clin 124: 1-8.
10. Bowery NG, Hill DR, Hudson AL (1983) Characteristics of GABAB receptor binding sites on rat whole brain synaptic membranes. Br J Pharmacol 78: 191-206.
11. Bowery NG, Hill DR, Hudson AL (1985) [3H](-)Baclofen: an improved ligand for GABAB sites. Neuropharmacology 24: 207-210.
12. Bowery NG, Hudson AL, Price GW (1987) GABAA and GABAB receptor site distribution in the rat central nervous system. Neuroscience 20: 365-383.
13. Carter CRJ, Kozuska JL, Dunn SMJ (2010) Insights into the structure and pharmacology of GABAA receptors. Future medicinal chemistry 2: 859-875.
14. D'Hulst C, Atack JR, Kooy RF (2009) The complexity of the GABAA receptor shapes unique pharmacological profiles. Drug Discov Today 14: 866-875.
15. Chronwall BM, Davis TD, Severidt MW, Wolfe SE, McCarson KE, et al. (2001) Constitutive expression of functional GABA(B) receptors in mIL-tsA58 cells requires both GABA(B(1)) and GABA(B(2)) genes. J Neurochem 77: 1237-1247.
16. Kaupmann K, Malitschek B, Schuler V, et al. (1998) GABA(B)-receptor subtypes assemble into functional heteromeric complexes. Nature 396: 683-687.
17. Bormann J (2000) The "ABC" of GABA receptors. Trends Pharmacol Sci 21: 16-19.
18. Bowery NG, Brown DA (1997) The cloning of GABA(B) receptors. Nature 386: 223-224.
19. Hill DR, Bowery NG, Hudson AL (1984) Inhibition of GABAB receptor binding by guanyl nucleotides. J Neurochem 42: 652-657.
20. Qian H, Dowling JE (1993) Novel GABA responses from rod- driven retinal horizontal cells. Nature 361: 162-164.
21. Cherubini E, Ben-Ari Y (2011) The immature brain needs GABA to be excited and hyper-excited. J Physiol 589: 2655-2656.
22. Wang DD, Kriegstein AR, Ben-Ari Y (2008) GABA regulates stem cell proliferation before nervous system formation. Epilepsy Curr Am Epilepsy Soc 8: 137-139.
23. Sigel E, Steinmann ME (2012) Structure, function, and modulation of GABA(A) receptors. J Biol Chem 287: 40224-40231.
24. Möhler H (2007) Molecular regulation of cognitive functions and developmental plasticity: impact of GABAA receptors. J Neurochem 102: 1-12.
25. Carta MG, Bhat KM, Preti A (2012) GABAergic neuroactive steroids: a new frontier in bipolar disorders? Behav Brain Funct BBF 8: 61.
26. Neto FL, Ferreira-Gomes J, Castro-Lopes JM (2006) Distribution of GABA receptors in the thalamus and their involvement in nociception. Adv Pharmacol 54: 29-51.
27. Chebib M, Hanrahan JR, Mewett KN, Duke RK, Johnston GAR, et al. (2004) Ionotropic GABA receptors as therapeutic targets for memory and sleep disorders. Annu Rep Med Chem 39: 13-23.
28. Pal D, Mallick BN (2010) GABA-ergic Modulation of Pontine Cholinergic and Noradrenergic Neurons for REM Sleep Generation. GABA and Sleep Springer Basel.
29. Reite M (2011) GABA and Sleep: Molecular, Functional and Clinical Aspects. Am J Psychiatry 168: 755.
30. Hensch TK, Fagiolini M, Mataga N, Stryker MP, Baekkeskov S, et al. (1998) Local GABA circuit control of experience-dependent plasticity in developing visual cortex. Science 282: 1504-1508.
31. Hensch TK, Stryker MP (2004) Columnar architecture sculpted by GABA circuits in developing cat visual cortex. Science 303: 1678-1681.
32. Möhler H (2011) The rise of a new GABA pharmacology. Neuropharmacology 60: 1042-1049.
33. Kah O, Trudeau VL, Sloley BD, Chang JP, Dubourg P, et al. (1992) Influence of GABA on Gonadotrophin Release in the Goldfish. Neuroendocrinology 55: 396-404.

34. Trudeau VL, Kah O, Chang JP, Sloley BD, Dubourg P, et al. (2000) The inhibitory effects of (gamma)-aminobutyric acid (GABA) on growth hormone secretion in the goldfish are modulated by sex steroids. J Exp Biol 203: 1477-1485.

35. Tian J, Dang H, Chen Z, Guan A, Jin Y, et al. (2013) γ-Aminobutyric acid regulates both the survival and replication of human β-cells. Diabetes 62: 3760-3765.

36. Jessen KR, Hills JM, Limbrick AR (1988) GABA immunoreactivity and 3H-GABA uptake in mucosal epithelial cells of the rat stomach. Gut 29: 1549-1556.

37. Piqueras L, Martinez V (2004) Peripheral GABAB agonists stimulate gastric acid secretion in mice. Br J Pharmacol 142: 1038-1048.

38. Strandwitz P (2018) Neurotransmitter modulation by the gut microbiota. Brain Res 1693: 128-133.

39. Jin Z, Mendu SK, Birnir B (2013) GABA is an effective immunomodulatory molecule. Amino Acids 45: 87-94.

40. Bowery NG, Hudson AL (1979) Gamma-Aminobutyric acid reduces the evoked release of [3H]-noradrenaline from sympathetic nerve terminals [proceedings]. Br J Pharmacol 66: 108P.

41. DeFeudis FV (1982) The link between analgesia and cardiovascular function: roles for GABA and endogenous opioids. Prog Neurobiol 19: 1-17.

42. Szczepanska-Sadowska E, Cudnoch-Jedrzejewska A, Ufnal M, Zera T (2010) Brain and cardiovascular diseases: common neurogenic background of cardiovascular, metabolic and inflammatory diseases. J Physiol Pharmacol Off J Pol Physiol Soc 61: 509-521.

43. Vargas RA (2017) Effects of GABA, Neural Regulation, and Intrinsic Cardiac Factors on Heart Rate Variability in Zebrafish Larvae. Zebrafish 14: 106-117.

44. Ito T, Hioki H, Nakamura K, Tanaka Y, Nakade H, et al. (2007) Gamma-aminobutyric acid-containing sympathetic preganglionic neurons in rat thoracic spinal cord send their axons to the superior cervical ganglion. J Comp Neurol 502: 113-125.

45. Llewellyn-Smith IJ (2002) GABA in the control of sympathetic preganglionic neurons. Clin Exp Pharmacol Physiol 29: 507-513.

46. Stachowicz K, Brański P, Kłak K, van der Putten H, Cryan JF, et al. (2008) Selective activation of metabotropic G-protein-coupled glutamate 7 receptor elicits anxiolytic-like effects in mice by modulating GABAergic neurotransmission. Behav Pharmacol 19: 597.

47. Pehrson AL, Sanchez C (2015) Altered γ-aminobutyric acid neurotransmission in major depressive disorder: a critical review of the supporting evidence and the influence of serotonergic antidepressants. Drug Des Devel Ther 9: 603-624.

48. Smith KS, Rudolph U (2012) Anxiety and depression: mouse genetics and pharmacological approaches to the role of GABA(A) receptor subtypes. Neuropharmacology 62: 54-62.

49. Chen JWY, Naylor DE, Wasterlain CG (2007) Advances in the pathophysiology of status epilepticus. Acta Neurol Scand 115: 7-15.

50. Errington AC, Gibson KM, Crunelli V, Cope DW (2011) Aberrant GABA(A) receptor-mediated inhibition in cortico-thalamic networks of succinic semialdehyde dehydrogenase deficient mice. PloS One 6: e19021.

51. Pearl PL, Gibson KM, Cortez MA, Wu Y, Carter Snead O 3rd, et al. (2009) Succinic semialdehyde dehydrogenase deficiency: lessons from mice and men. J Inherit Metab Dis 32: 343-352.

52. Cheong JH (2017) Neurobiological Factors Involved in the Formation of Alcoholism. Yakhak Hoeji 6: 326-334.

53. Zhu EC, Hu Y, Soundy TJ (2017) Genetics of Alcoholism. South Dakota Medicine 70: 225-227.

54. Paz HR (2005) Modelos fisiopatológicos de la esquizofrenia; de dopamina a glutamato, de glutamato a GABA. Rev Chil Neuro-Psiquiatr 43: 314-328.

55. Schmidt MJ, Mirnics K (2015) Neurodevelopment, GABA system dysfunction, and schizophrenia. Neuropsychopharmacology 40: 190-206.

56. Wassef AA, Dott SG, Harris A, Brown A, O'Boyle M, et al. Critical review of GABA-ergic drugs in the treatment of schizophrenia. J Clin Psychopharmacol 19: 222-232.

57. Wassef A, Baker J, Kochan LD (2003) GABA and schizophrenia: a review of basic science and clinical studies. J Clin Psychopharmacol 23: 601-640.

58. Benes FM (2015) The GABA system in schizophrenia: cells, molecules and microcircuitry. Schizophr Res 167: 1-3.

59. Michelsen BK, Petersen JS, Boel E, Møldrup A, Dyrberg T, et al. (1991) Cloning, characterization, and autoimmune recognition of rat islet glutamic acid decarboxylase in insulin-dependent diabetes mellitus. Proc Natl Acad Sci USA 88: 8754-8758.

60. Tian J, Yong J, Dang H, Kaufman DL (2011) Oral GABA treatment downregulates inflammatory responses in a mouse model of rheumatoid arthritis. Autoimmunity 44: 465-470.

61. Neethling WML, Hodge AJ (2010) The effect of diazepam on myocardial function and coronary vascular tone after endotoxemia in the isolated rat heart model. Inflamm Res 59: 907-913.

62. Wheeler DW, Thompson AJ, Corletto F, Reckless J, Loke JC, et al. (2011) Anaesthetic impairment of immune function is mediated via GABA(A) receptors. PloS One 6: e17152.

63. Gallos G, Townsend E, Yim P, Virag L, Zhang Y, et al. (2013) Airway epithelium is a predominant source of endogenous airway GABA and contributes to relaxation of airway smooth muscle tone. Am J Physiol Lung Cell Mol Physiol 304: 191-197.

64. Ticku MK, Olsen RW (1978) Interaction of barbiturates with dihydropicrotoxinin binding sites related to the GABA receptor-ionophore system. Life Sciences 22: 1643-1651.

65. Kerr DI, Ong J (1992) GABA agonists and antagonists. Med Res Rev 6: 593-636.

66. Krogsgaard-Larsen P, Christensen AV (1980) GABA Agonists and Antagonists. In Annual Reports in Medicinal Chemistry. Academic Press 15: 41-50.

67. Valdivia Álvarez I, Abadal Borges G (2005) Epilepsia de difícil control en Pediatría: Nuevas drogas antiepilépticas. Rev Cuba Pediatría.

68. Lancel M, Steiger A (1999) Sleep and Its Modulation by Drugs That Affect GABA(A) Receptor Function. Angew Chem Int Ed Engl 38: 2852-2864.

69. Möhler H (2006) GABA(A) receptor diversity and pharmacology. Cell Tissue Res 326: 505-516.

70. Möhler H (2012) The GABA system in anxiety and depression and its therapeutic potential. Neuropharmacology 62: 42-53.

71. Rudolph U, Möhler H (2014) GABAA Receptor Subtypes: Therapeutic Potential in Down Syndrome, Affective Disorders, Schizophrenia, and Autism. Annu Rev Pharmacol Toxicol 54: 483-507.

72. Engin E, Liu J, Rudolph U (2012) □2-containing GABA(A) receptors: a target for the development of novel treatment strategies for CNS disorders. Pharmacol Ther 136: 142-152.

73. Rivera Díaz RC, Arcila Lotero MA, Campuzano Escobar D. Baclofeno intratecal para el tratamiento de la espasticidad. Reporte de caso con revisión temática. Rev Colomb Anestesiol 41: 229-235.

74. Dario A, Tomei G (2004) A benefit-risk assessment of baclofen in severe spinal spasticity. Drug Saf Int J Med Toxicol Drug Exp 27: 799-818.

75. Enna SJ, McCarson KE (2006) The role of GABA in the mediation and perception of pain. Adv Pharmacol 54: 1-27.

76. McCarson KE, Enna SJ (2014) GABA Pharmacology: The Search for Analgesics. Neurochem Res 39: 1948-1963.

77. Franklin KBJ, Abbott FV (1993) Pentobarbital, diazepam, and ethanol abolish the interphase diminution of pain in the formalin test: Evidence for pain modulation by GABAA receptors. Pharmacol Biochem Behav 46: 661-666.

78. Frye CA, Duncan JE (1994) Progesterone metabolites, effective at the GABAA receptor complex, attenuate pain sensitivity in rats. Brain Res 643: 194-203.

79. Taira T, Kawamura H, Tanikawa T, Iseki H, Kawabatake H, et al. (1995) A New Approach to Control Central Deafferentation Pain: Spinal Intrathecal Baclofen. Stereotact Funct Neurosurg 65: 101-105.

80. Bhat R, Axtell R, Mitra A, Miranda M, Lock C, et al. (2010) Inhibitory role for GABA in autoimmune inflammation. Proc Natl Acad Sci 107: 2580-2585.

81. Solimena M, Folli F, Aparisi R, Pozza G, De Camilli P, et al. (1990) Autoantibodies to GABA-ergic Neurons and Pancreatic Beta Cells in Stiff-Man Syndrome. N Engl J Med 322: 1555-1560.

82. Peričić D, Manev H, Boranić M, Poljak-Blaži M, Lakić N, et al. (1987) Effect of Diazepam on Brain Neurotransmitters, Plasma Corticosterone, and the Immune System of Stressed Rats. Ann N Y Acad Sci 496: 450-458.

83. Ferrarese C, Appollonio I, Bianchi G, Frigo M, Marzorati C, et al. (1993) Benzodiazepine receptors and diazepam binding inhibitor: A possible link between stress, anxiety and the immune system. Psychoneuroendocrinology 18: 3-22.

84. Forkuo GS, Nieman AN, Yuan NY, Kodali R, Yu OB, et al. (2017) Alleviation of multiple asthmatic pathologic features with orally available and subtype selective GABAA receptor modulators. Molecular pharmaceutics 14: 2088-2098.

85. Xiang YY, Wang S, Liu M, Hirota JA, Li J, et al. A GABAergic system in airway epithelium is essential for mucus overproduction in asthma. Nat Med 13: 862-867.

86. Chapman RW, Hey JA, Rizzo CA, Bolser DC (1993) GABAB receptors in the lung. Trends Pharmacol Sci 14: 26-29.

87. Tohda Y, Ohkawa K, Kubo H, Muraki M, Fukuoka M, et al. (1998) Role of GABA receptors in the bronchial response: studies in sensitized guinea-pigs. Clin Exp Allergy 28: 772-777.

88. Bhargava KP, Gupta GP, Gupta MB (1985) Central GABA-ergic mechanism in stress-induced gastric ulceration. Br J Pharmacol 84: 619-623.

89. Clotet J, Piñero E, Hatem L, Esaa M, Gutierrez J, et al. (2007) Efectividad del tratamiento con agonistas gaba a (Pentobarbital) en el síndrome de intestino irritable con dolor: Año 2005. GEN 61: 277-280.

90. Collares EF, Vinagre AM (2005) Effect of the GABA B agonist baclofen on dipyrone-induced delayed gastric emptying in rats. Braz J Med Biol Res 38: 99-104.

91. Burokas A, Arboleya S, Moloney RD, Peterson VL, Murphy K, et al. (2017) Targeting the microbiota-gut-brain axis: prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice. Biol Psychiatry 82: 472-487.

92. Dinan TG, Cryan JF (2017) The microbiome-gut-brain axis in health and disease. Gastroenterol Clin North Am 46: 77-89.

93. Kelly JR, Clarke G, Cryan JF, Dinan TG (2016) Brain-gut-microbiota axis: challenges for translation in psychiatry. Annals of Epidemiology 26: 366-372.