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Review article

GABA and its receptors' mechanisms in the treatment of insomnia

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ABSTRACT

Insomnia has now become a major health problem of global concern, with about 1/3 of the population suffering from sleep problems, a proportion that is still rising year by year. Most of the therapeutic drugs for insomnia currently used in clinical practice are not developed in a targeted manner, but are discovered by chance, and have unavoidable side effects such as addiction. Finding a safer and more effective therapeutic drug has become an urgent need for current research.

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. It can ameliorate Insomnia, Alzheimer's disease, Parkinson's disease, Epilepsy, and other neurological disorders. Various mechanisms have been reported for GABA to ameliorate insomnia, such as GABAA receptor modulation, GABAB receptor modulation, inhibition of neuroinflammatory responses, repair of oxidative damage, and inter-regulation of the circadian rhythm hormone melatonin. GABA is a potential therapeutic target in the prevention and treatment of insomnia.

This paper reviews mechanisms of GABA and its receptors in insomnia diseases and the potential of GABA analogs application and discusses the research progress of GABA as a promising therapeutic drug for insomnia diseases. This will help the development of novel targeted GABA-like drugs and provide new ideas and methods for the clinical treatment of insomnia.

1. Introduction

Insomnia is a common condition characterized by difficulty falling asleep, excessive dreaming, early waking, and daytime fatigue. Studies show that 29.8 % of people in the United States had trouble sleeping between 2017 and 2022, and about 27 % of the global population suffered from sleep problems in 2021 [1]. Insomnia has become a major public health problem of global concern. Chronic insomnia can seriously damage health, destroying immune function, reducing cognitive function, and greatly increasing the risk of other diseases, such as anxiety, depression, cardiovascular disease, dementia, etc. [2,3], which puts a huge mental stress and economic

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burden on the family and society. Current treatments for insomnia can be divided into pharmacological and non-pharmacological treatments. Non-pharmacological treatments, i.e. Cognitive Behavioral Therapy (CBT-I), are recommended first-line treatments, but are difficult to be promoted and applied in the clinic due to the shortage of specialized doctors, high time cost and economic cost.

Most patients with insomnia use drug therapy, with benzodiazepines being the most commonly used medications, such as diazepam, eszopiclone, and alprazolam. However, the unclear pathogenesis of insomnia complicates the development of hypnotic drugs that effectively target its underlying mechanisms. Consequently, these medications often lead to various side effects, such as addiction, withdrawal symptoms, and daytime fatigue, which can significantly harm both physical and mental health [4]. Therefore, finding a safer and more effective treatment has become an urgent need for research.

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system. It has sedative-hypnotic, memory-enhancing, anxiolytic, antidepressant, antiepileptic and analgesic effects. Studies have shown its ability to improve Insomnia, Alzheimer's disease, Parkinson's disease, Epilepsy and other neurological disorders [5–9]. Due to the diversity of subunit combinations, GABA receptors have very rich subtypes, particularly GABAA receptors, which include α1-6, β1-3, γ1-3, δ, π, ε, θ, ρ, and σ subunits. These subunits assemble into a limited number of pentameric receptors, typically with a stoichiometry of two α subunits, two β subunits, and one γ subunit. Among these, δ and ε subunits can replace the γ subunit, and the σ subunit can replace the β subunit [10]. Additionally, there is a unique type of GABAA receptor, known as the GABAC receptor, composed of five ρ subunits. In contrast, GABAB receptors are composed of two subunits, b1 and b2 [11]. GABA acts on these different receptor subtypes with different focuses. In addition, GABA can regulate macrophages and microglia, inhibit the activation of related inflammatory pathways such as the NF-κB signaling pathway and reduce the release of inflammatory factors, thus inhibiting neuroinflammation and playing a neuroprotective role [12,13]. It has also been shown that GABA inhibits reactive oxygen species, scavenges free radicals, reduces malondialdehyde concentration to resist oxidative damage, and inter-regulates with melatonin, which has a circadian rhythm, to improve insomnia [14–16]. Previously, benzodiazepines were widely used in the treatment of insomnia. In recent years, certain new GABA receptor agonists have been identified that play a role primarily in sedative anesthesia, such as nitrous oxide, isoflurane, sevoflurane, desflurane, isoproterenol, etomidate, methohexital, and sodium thiopental (Fig. 1).

This paper reviews mechanisms of GABA for insomnia and the potential of GABA analogs application, which can help the development of novel targeted GABA analogs and provide new ideas and methods for the clinical treatment of insomnia.

2. The link between the physiological role of GABA and insomnia

2.1. Physiological functions of GABA

GABA is one of the major inhibitory neurotransmitters regulating sleep in the mammalian central nervous system, with hypnotic, sedative and anxiolytic functions. Glutamate (Glu), on the other hand, is the main excitatory neurotransmitter in the central nervous system, which mainly acts in the cerebral cortex, hippocampus, cerebellum and thalamus, and is involved in the initiation and maintenance of sleep and wakefulness. Transmission of GLU and GABA in the CNS controls the neural excitatory/inhibitory balance to keep the brain in an optimal state for optimal function.

Previous studies have shown that humans have two types of GABA receptors: fast-acting ionotropic GABAA receptors (GABAARs) and slow-acting metabotropic GABAB receptors (GABABRs). Of these, activation of GABAARs has sedative-hypnotic, anxiolytic, antidepressant, antiepileptic, and analgesic effects [17], whereas GABABRs have been associated with several behavioral and central nervous system disorders, including epilepsy, depression, anxiety, panic, and sleep disorders [18].

2.2. Relationship between GABA and insomnia

Under physiological, conditions, GABA functions in a dynamic equilibrium with GLU, which has an excitatory effect on neurons,

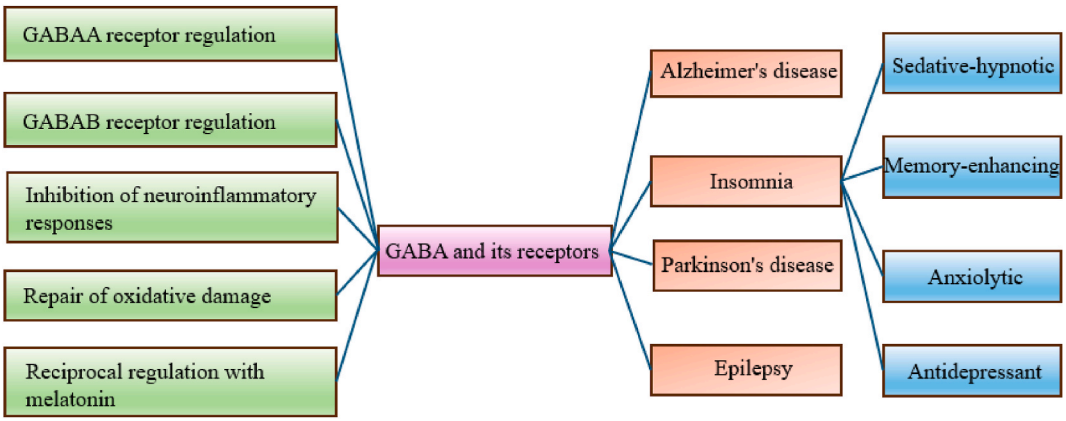

Fig. 1. GABA and its receptors in insomnia.

but in excess produces neurotoxicity, leading to neuronal death and neurological disorders [19]. GABA is produced by the enzyme glutamic acid decarboxylase (GAD) that catalyzes the decarboxylation of Glu, and the production of GABA produces an inhibitory effect on the excitatory properties of GLU in order to maintain the neural excitability/inhibition balance [20]. Studies have shown that insomniac mice have up-regulated GABA expression in vivo through treatment, with a decrease in GLU content and an increase in the GABA/Glu ratio, resulting in sedative and hypnotic functions and improved insomnia [21].

GABA has ameliorative effects on different types of insomnia. Studies have shown that the excitation of GABAergic neurons induces NREM sleep and inhibits REM sleep, while its inhibition produces sustained wakefulness [22]. Several studies of oral natural or biosynthetic GABA administration to insomniacs have found that, for the dose needed to improve insomnia, biosynthetic GABA ranges from 100 to 300 mg; oral GABA has shown improvements in sleep onset and maintenance, morning drowsiness, and recovery of fatigue scores in insomniacs and facilitates the natural induction of sleep, but it requires a minimum of 1 week of GABA use to achieve the effect [23–25]. This suggests that GABA may need to be used over a long period of time to have an effect on improving insomnia. Additional studies have shown that herbal extracts can enhance the sedative and anxiolytic effects of GABA by increasing GABA concentrations, activating GABA receptors, and promoting GABAergic signaling in the brain [26]. For example, Zizyphus jujuba Mill var. spinosa can increase GABA synthesis, and its extract sanjoinine A can activate GABAA receptors and enhance chloride influx in cerebellar granule cells [27]. Similarly, other herbs such as valerian [28] and Ipomoea orizabensis [29] also exhibit comparable GABA-modulating properties. Being from natural plant sources, they are safer for long-term use.

3. Therapeutic mechanisms of GABA and its receptors in insomnia

In addition to the fast-acting ionotropic GABAA receptors (GABAARs) and the slow-acting metabotropic GABAB receptors (GABABRs), there is a recently discovered class of GABAC receptors (GABACRs) that share the same structure as GABAARs, and thus are also categorized as GABAARs. GABAAR regulation is one of the four key mechanisms of approved insomnia treatments and is currently the most extensively studied class of GABA receptors. (the other three mechanisms are melatonin receptor agonism, histamine 1 receptor antagonism, and hypothalamic secretin/eosin antagonism) [30]. In addition to this, many studies have found that GABA amelioration of insomnia may be associated with biological processes such as inhibition of nervous system inflammation, repair of oxidative damage, neuroprotection and melatonin regulation [16,31].

3.1. GABAA receptor regulation

Studies have shown that activation of GABAARs has sedative-hypnotic, anxiolytic, antidepressant, antiepileptic, and analgesic effects [17]. GABAARs are the main type of GABA receptors in the brain, and they are ligand-gated pentameric chloride ion channels composed of five subunits. The typical composition is two α, two β, and one γ subunits, with the δ and ε subunits taking the place of the γ subunit, and the σ subunit taking the place of the β subunit. Activation of GABAARs allows chloride ions to enter the cell, leading to

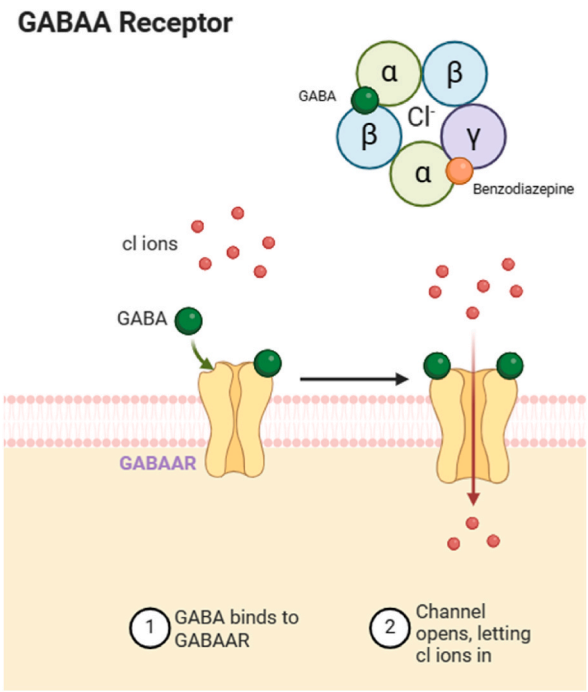

Fig. 2. Structure, binding site and mechanism of action of GABAA receptors.

hyperpolarization of the neuron, which exerts an inhibitory effect on neurotransmission and relieves hyperexcitability [18,32,33]. Previous studies have focused on synaptic GABAARs, which mediate rapid inhibition. In contrast, recent studies have found the presence of extrasynaptic GABAARs, which have a high affinity for GABA, can acutely sense changes in peripheral GABA levels, and mediate slower tone overall inhibitory effects [34]. This suggests that, in addition to exerting a rapid inhibitory effect, activation of GABAARs may also provide a sustained inhibitory effect to prevent excitatory neural overactivation. Several studies have shown that the majority of GABAARs subtypes α1β2γ2, α3β3γ2, and α2β3γ2 receptors are expressed in the CNS to a lesser extent [35].

There are multiple binding sites on GABAARs, including GABA-binding sites, benzodiazepine-binding sites, non-benzodiazepine drug-binding sites, and alcohol-binding sites [36–38]. These binding sites play a role in regulating the activity of GABAARs. For example, benzodiazepine binding sites located in the α and γ subunit binding sites can enhance GABA inhibition by decreasing the concentration of GABA required to open chloride channels [39]. Notably, certain drugs, such as barbiturates and ethanol, can potentiate inhibition by increasing chloride inward flow or directly opening chloride channels, which can lead to fatal drug overdose [39] (Fig. 2).

Several recent studies have reported GABAC Receptors (GABACRs), which are often considered as an isoform of GABAARs due to the similar compositional structure. Unlike the GABACRs, GABACRs are ligand-gated pentameric chloride channels composed of five p-subunits. When activated, GABACRs produce rapid synaptic inhibition [39–41]. The GABAC-ρ1 receptor was found to play an important role in sleep-wake behavior in rats [42].

3.2. GABAB receptor regulation

Studies have shown that GABABRs are associated with a number of behavioral and central nervous system disorders, including depression, anxiety, epilepsy, panic, and sleep disorders [43]. GABABRs consist of two subunits, GABAB1 and GABAB2.Both subunits are composed of three structural domains: the flytrap structural domain (VFT) in the extracellular N-terminal region, the seven-helix transmembrane structural domain (7TM), and the C-terminal intracellular tail [44]. The GABAB1 subunit has multiple isoforms, of which GABAB1a and GABAB1b are the most abundant isoforms encoded by the same gene, respectively [45]. The interaction between GABAB1 and GABAB2 subunits occurs through noncovalent interactions between N-terminal leaflet structures within the VFT. The GABAB1a subunit differs from the other subunits by the presence of two Sushi structural domain repeats (Sushi 1 and Sushi 2) in its N-terminal region, which play a role in intracellular sorting and transport to the axon [46].

The orthostatic binding site for ligand binding is in the VFT of the GABAB1 subunit. The 7TM structural domain of the GABAB2

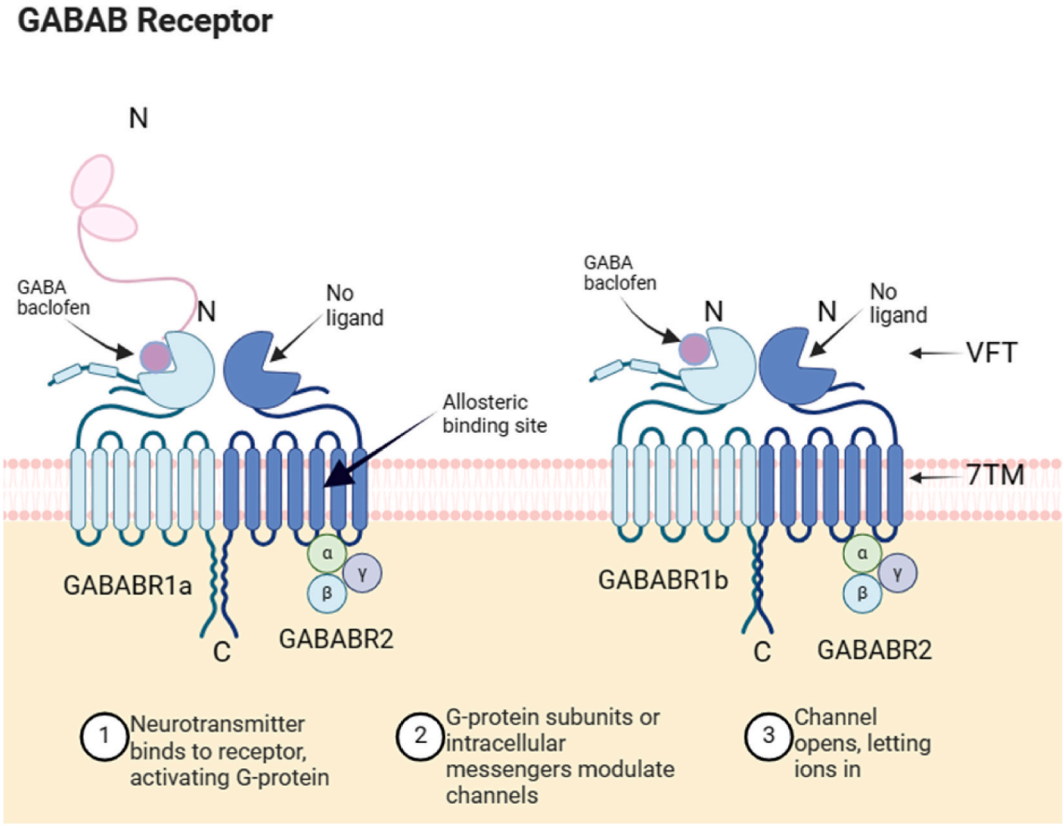

Fig. 3. Structure, binding site and mechanism of action of GABAB receptors.

subunit is responsible for recruiting G proteins and hosting the sub stable binding site, which influences the affinity of ligand binding to the R1 subunit [47]. To function properly, GABABR requires the formation of R1/R2 heterodimers [48]. These receptors are anchored to the plasma membrane at the presynaptic and postsynaptic terminals and regulate calcium and potassium channel activity through interactions with G proteins and adenylate cyclase [49]. When agonists bind to postsynaptic GABABRs, potassium efflux increases, producing a slow inhibitory potential that hyperpolarizes the membrane and generates an inhibitory postsynaptic potential that provides sustained inhibition (Fig. 3).

Although there has been some research on GABABRs, there are currently few drugs targeting this receptor. Baclofen is the only GABAB receptor agonist currently approved for clinical use. It is used as a muscle relaxant and antitussive. However, it has been shown that baclofen and its modifier PAMs show anxiolytic effects in animal cognitive models and are thought to reverse the anxiety response induced by addiction-related withdrawal, whereas GABABRs antagonists show antidepressant effects in a variety of animal models [11]. Although the allosteric modulator PAMs enhanced the sedative effects of baclofen, the binding mode and molecular mechanisms of the alter modulators remain rather uncertain, and multiple alter modulator binding sites may exist. More and more in-depth studies are needed in the future.

4. GABA protects nerves in insomnia disorders by inhibiting neuroinflammation-apoptosis

4.1. Insomnia and neuroinflammation-apoptosis

Both autonomic dysfunction and an imbalance in sleep homeostasis contribute to insomnia. When pathological changes of inflammation and apoptosis occur in nerve cells, they cause autonomic dysregulation, disturbing sleep homeostasis and leading to insomnia. Conversely insomnia leads to activation of the immune system which causes pathological changes in nerve cells such as inflammation and apoptosis, in which the production of inflammatory mediators disrupts the delicate balance required for neurophysiological action and adversely affects memory, neuroplasticity and neurogenesis [50], which interact with each other.

It has been reported that patients with insomnia have higher levels of inflammatory factors in their bodies compared to those with regular sleep schedules [51]. Additionally, short sleep duration in patients with chronic insomnia is associated with peripheral inflammasome disorders [52]. Studies have shown that IL-1β and TNF-α expression is significantly enhanced and brain-derived neurotrophic factor (BDNF) expression is attenuated in the brain tissue of chronic sleep-restricted rats [53], whereas in humans, acute sleep deprivation also enhances the levels of pro-inflammatory cytokines such as IL-6 and TNF-α [54]. In addition, many symptoms caused by sleep deprivation, such as lethargy, fatigue, poor cognitive performance, and increased sensitivity to pain, can be induced by injections of exogenous IL-1 or TNF [55,56]. The correlation between inflammation and insomnia is evident. Several classical sleep regulatory substances can directly or indirectly modulate inflammation [57], such as IL-1β, TNF-α, and growth hormone-releasing hormone (GHRH) for non-rapid eye movement (NREM) sleep, and prolactin and nitric oxide (NO) for rapid eye movement (REM) sleep. Neuroinflammation is a major pathological feature of insomnia [58]. Furthermore, in bacterial models, GABA deficiency loses its ability to block neurodegeneration, whereas in situ supplementation confers neuroprotective activity, suggesting that GABA plays a neuroprotective role in the host [59]. GABA-rich chickpea milk protects neuroendocrine PC-12 cells from manganese chloride-induced injury, improves cell viability, and reduces lactate dehydrogenase release [60]. On the other hand, GABA receptor agonists are also neuroprotective against cerebral ischemic injury. Administration of the GABAB receptor agonist baclofen significantly attenuated neuronal damage and inhibited cell-damaging autophagy by up-regulating the Bcl-2/Bax ratio and increasing the activation of Akt, GSK-3β, and ERK, which inhibit cell-damaging autophagy [61]. In a kainic acid (KA)-induced seizure model in rats, co-activation of GABA receptor agonists (felicitin and baclofen) achieves neuroprotection by attenuating the Fas/FasL apoptotic signaling pathway, inhibiting erythrocyanine-induced increase in thioredoxin reductase activity, inhibiting procaspase-3 activation,

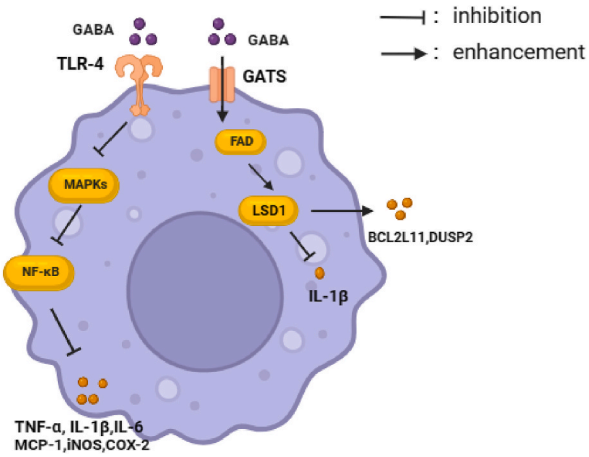

Fig. 4. Mechanisms of GABA inhibition of inflammation in macrophages.

and decreasing caspase-3 cleavage [62].

4.2. Mechanism of action of GABA in regulating brain immune cells

Inhibition of neuroinflammation, apoptosis, and injurious autophagy and thus neuroprotection is an important idea in the treatment of insomnia. Among them, the process of inhibiting neuroinflammation is the most critical. Numerous studies have shown that GABA is involved in inhibiting the process of neuroinflammatory response [63,64], and in macrophages, microglia and astrocytes, GABA has been found to inhibit the release of inflammatory factors by affecting NF-κB signaling and thus exerting an inhibitory effect on neuroinflammation [13].

GABA has the power to lessen the generation of pro-inflammatory mediators, control the release of inflammatory substances from immune cells, and alleviate the symptoms of inflammation. Research has demonstrated that GABA attaches competitively to the TLR4 receptor in macrophages, where it blocks the activation of MAPKs and NF-κB signaling pathways [65], This, in turn, prevents the release of inflammatory factors that suppress inflammation, including IL-1β, IL-6, tumor necrosis factor α (TNF-α), and monocyte chemotactic protein-1 (MCP-1). Furthermore, it has been noted that the FAD-LSD1 signaling pathway is augmented, Bcl2l11 and Dusp2 expression is elevated, IL-1β production is decreased, and the GAT transporter carries GABA into macrophages [66] (Fig. 4).

Microglia are innate immune cells of the central nervous system, and in the healthy brain they play an important role in development, plasticity, cognition, and homeostasis in vivo, and their dysfunction or malactivation affects a variety of signaling pathways thereby impairing learning, memory, and other basic cognitive functions [67]. The most important of these is the pro- and anti-inflammatory potential of microglia. Their M1 functional state is associated with pro-inflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α), whereas their M2 functional state is associated with anti-inflammatory cytokines (e.g., IL-4 and IL-10) [68]. It has been shown that both pro-inflammatory and anti-inflammatory genes are up regulated upon microglia activation [69]. GABA acts on GABAB receptors to inhibit microglia reactive responses to pro-inflammatory stimuli, such as lipopolysaccharide (LPS), which leads to inhibition of the relevant inflammatory pathways mediated by NF-κB and p38MAP kinase, and reduces the release of IL-6, TNFα [70]. Excess GABA has been found to mediate hippocampal microglia activation through NLRP3 inflammasome and NF-κB signaling pathways. This process releases the inflammatory factor IL-1β, leading to neuroinflammation, which can be reversed by inhibitors related to inflammatory signaling pathways [71]. Further studies are needed to find out how to make GABA-activated microglia play more roles in anti-inflammation (Fig. 5).

In addition, GABA activates the γ-aminobutyric acid B (GABAB) receptor. This activation inhibits the nuclear factor-kappa B (NF-κB) and p38 mitogen-activated protein kinase (p38MAPK) signaling pathways [72], reducing IL-1βproduction in astrocytes and attenuating neuroinflammation [73].

In summary, the NF-κB signaling pathway is critical in the process of GABA exerting its role in regulating neuroinflammation on macrophages, astrocytes and microglia, and may be a key therapeutic target for inhibiting neuroinflammation and improving insomnia diseases. More studies on GABA-mediated anti-inflammatory mechanisms should be carried out in the future to provide a basis for the development of targeted therapeutic drugs to inhibit neuroinflammation and improve insomnia diseases.

4.3. GABA repairs oxidative damage in insomnia disorders

Decrease in GABA neurons leads to redox dysregulation. Changes in cellular redox status affect the activity of transcription factors,

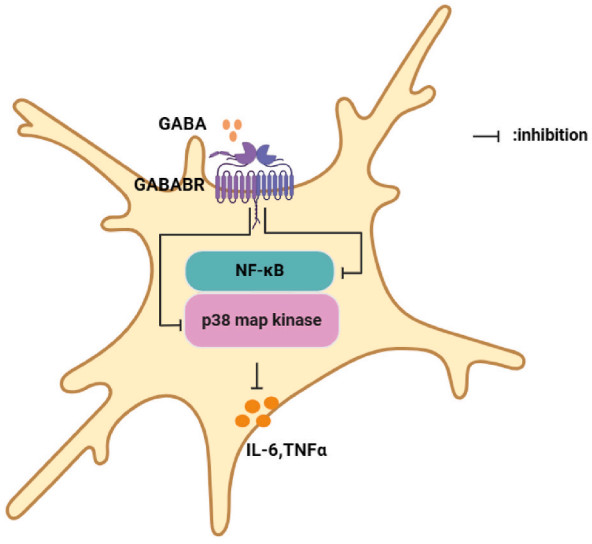

Fig. 5. Mechanisms of GABA inhibition of inflammation in microglia.

kinases, and phosphatases, which regulate various aspects of neurodevelopment and synaptic plasticity, leading to disorders such as Alzheimer's disease, Depression, and Cognitive impairment [15,74,75].

It has been shown that GABA can repair this damage. The mechanism may involve GABA's regulation of glycogen synthase kinase (GSK)-3β and the antioxidant nuclear factor nuclear factor erythroid 2-related factor 2 (NRF2) [76], which helps maintain the cell's redox state(Table 1). The tonic GABA response recorded from hippocampal CA1 pyramidal cells was significantly and reversibly augmented in both the high endogenous H2O2 and high exogenous H2O2 models, and this augmentation was abrogated by extracellular antioxidants [77]. In contrast, other studies have observed a protective effect of GABA against H2O2-induced oxidative stress in pancreatic cells [76] and human umbilical vein endothelial cells [14], which enhances antioxidant defenses by reducing cell death and inhibiting ROS production. It has been shown that glutathione has significant antidepressant effects, and the possible mechanism is through enhanced activation of GABAA receptors and inhibition of GABAB receptors [78]. Under physiological conditions, GABA has been reported to capture reactive intermediates during lipid peroxidation and react with malondialdehyde, thereby inhibiting the formation of advanced lipid oxidation end products and exerting antioxidant effects [79]. In the rat acute status epilepticus model, GABA administration significantly reduced malondialdehyde levels. It also increased superoxide dismutase and glutathione peroxidase activities in the cerebral cortex and hippocampus, scavenging free radicals and protecting tissues from oxidative damage [15]. In addition, GABA was found to attenuate oxidative stress-mediated cellular damage and restore the antioxidant function of the thyroid gland in fluoride-exposed mice [80].

GABA-rich germinated brown rice extract was found to significantly scavenge hydroxyl radicals and thiobarbituric acid actives in cell-free and treated media, indicating its ability to scavenge free radicals both directly and indirectly [81]. Both GABA-enriched cheese and GABA-enriched fermented soy protein bio composite edible film had strong antioxidant properties [82].

In conclusion, GABA is an important antioxidant that may exert antioxidant effects in neurological disorders by scavenging free radicals, decreasing malondialdehyde concentration, increasing glutathione peroxidase and catalase activities, increasing GSK-3β levels, repairing oxidative stress damage, and increasing the nuclear mass ratio of the transcription factor NRF2 (Fig. 4). Therefore, GABA may be a promising agent for the prevention or treatment of neurological diseases associated with oxidative damage.

4.4. GABA affects melatonin secretion in insomnia disorders

Melatonin is a circadian hormone synthesized and secreted by the pineal gland, which is involved in the regulation of autonomic function and circadian rhythms. GABA supplementation has been reported to promote sleep by increasing serotonin/melatonin levels in the blood of rats through the serotonergic system [83]. A Kalsbeek et al. found that retina-mediated photoactivation of supraoptic nucleus neurons induced the release of GABA from supraoptic nucleus efferent nerve endings, which led to pineal gland inhibition of melatonin release [84]. In turn, melatonin increases GAD67 protein levels and promotes GABA synthesis in accelerated aging OXYS rats [85]. The two interact to produce therapeutic effects on insomnia and other neurological disorders. Melatonin attenuates PTSD-like behaviors such as anxiety and depression and restores serum GABA levels in mice, and melatonin receptor 1 mediates this therapeutic effect [16]. Melatonin inhibits sympathetic vasodilatory tone by potentiating GABAA receptor activity and inhibiting the activity of presympathetic neurons in the hypothalamic paraventricular nucleus (PVN), an inhibitory effect mediated by GABAA receptors [86]. Melatonin inhibits sympathetic vasodilatory tone by potentiating GABAA receptor activity and inhibiting the activity of hypothalamic paraventricular nucleus (PVN) pre-sympathetic neurons, and this inhibition is mediated by GABAA receptors. In Alzheimer's disease (AD), melatonin allows AD patients to enter REM sleep more quickly by modulating GABA receptors [87]. Melatonin also regulates GABA in PMS, effectively alleviating PMS symptoms such as sleep disturbances, depression, and cognitive impairment [88,89] (Fig. 6).

5. Relationship between GABA and other medications for insomnia

Although Cognitive Behavioral Therapy (CBT) is the recommended first-line treatment for insomnia, it has always been difficult to carry out in clinical practice due to high time costs, consultation fees, lack of specialized doctors, and poor patient compliance. Except for some people in developed countries or regions, most people around the world prefer to accept medication to treat their insomnia. The medications that are currently effective in the treatment of insomnia include serotonin, norepinephrine, dopamine, orexin, melatonin, histamine, and adenosine, in addition to the GABA class of drugs. Although some studies claim that benzodiazepines increase health risks, benzodiazepines - the GABA class of drugs - as the only FDA-approved medications for clinical use in the treatment of insomnia, have advantages that cannot be replaced or surpassed by any other medication.

Table 1
Pathways of GABA antioxidant.

Pathways	Effect	References
GSK-3β levels	promotion	[76]
Nuclear mass ratio of the transcription factor NRF2	promotion	[76]
Free radicals ROS	inhibition	[14,76]
Malondialdehyde concentration	inhibition	[15,79]
Glutathione peroxidase	promotion	[15]
Catalase activities	promotion	[15]
Oxidative stress damage	inhibition	[15]

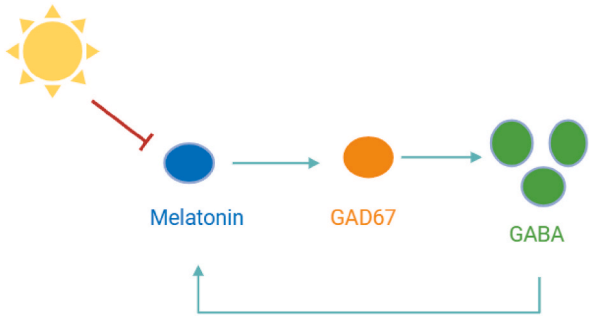

Fig. 6. Mechanism of mutual regulation of GABA and melatonin.

First, other new insomnia treatment drugs have been found to be superior in only one specific aspect during research, and not superior to the GABA class of drugs in key areas of efficacy, safety, and so on. A Lancet study comparing insomnia medications noted that in acute insomnia, dexzopiclone, an anti-insomnia medication that targets GABA receptors, performed best in terms of improving sleep quality, tolerability (discontinuation due to any adverse event), and acceptability (discontinuation for any reason); in long-term insomnia, safety is a concern. The histamines Doxepin and seltorexant, although tolerated to some extent, have yet to excel in terms of efficacy, safety, and acceptability. Melatonin and the melatonin-like hypnotic ramelteon, on the other hand, have not been seen to be of overall benefit [90].

Second, GABA analogs have been shown to be highly effective in improving insomnia with a wide range of actions, and the functions of many subunits have been reported (Table 2). The GABA class of drugs includes benzodiazepines and Z-drugs. Benzodiazepines are often used not only for the treatment of insomnia, but also for a variety of indications, including generalized anxiety disorder, panic disorder, social phobia, and seizures. For the short-term treatment of insomnia, benzodiazepines with moderate half-lives, such as temazepam and chlordiazepoxide, have better acceptability than short- or long-acting compounds [91]. Z-drugs (e.g., zolpidem, zaleplon, eszopiclone) are commonly used for the short-term treatment of insomnia. These medications can significantly improve symptoms of difficulty falling asleep and are associated with a lower risk of drug dependence and reduced daytime drowsiness compared to traditional benzodiazepines. However, long-term use may lead to side effects and dependence. Z-drugs work through a similar mechanism to benzodiazepines, primarily by enhancing the activity of the neurotransmitter γ-aminobutyric acid (GABA) to produce sedative and hypnotic effects [92,93].

Finally, most of the GABA-based drugs currently commonly used in the clinic were not developed by targeting but discovered by chance, and we should study the anti-insomnia mechanism of GABA more deeply and develop more GABA-targeted drugs in order to circumvent the existing known side effects as much as possible and to improve the safety of the clinical use of GABA-based anti-insomnia drugs.

Table 2
The roles of select GABA receptor subunits.

Receptor subunit	Post-activation effects	References
gabaaα 1	Sedation, Amnesia	[94]
gabaaα 2	Anxiolysis	[95]
gabaaα 3	Anxiolysis	[95]
gabaaα 5	Amnesia, Learning/memory	[96]
gabaaα 6	Trigeminal-related Pain, Migraine,Essential tremor, schizophrenia,stress-associated disorders, depression, Anxiety disorders, Alcohol use disorder	[97–99]
gabaaβ1	schizophrenia, bipolar disorder, Major depression	[100]
gabaaβ2	Sedation, Effects of anesthetic, epilepsy	[101]
gabaaβ3	Effects of anesthetics, epilepsy	[35,97]
gabaaγ2	Anxiety, epilepsy	[102]
gabaaγ3	alcohol dependence	[103]
gabaaδ	Effects of anesthetics, Learning/memory	
gabaaε	Epilepsy	[104]
gabaaπ	the female reproductive system, Ovarian, breast, gastric, cervical, and pancreatic cancers	[105,106]
gabaaθ	Bipolar disorder, Migraine,essential tremor	[107–109]
gabab1	Depression,anti-obesity,anticonvulsant effects(epilepsy), drug addiction,	[110–113]
gabab 2	alleviate the anxiety,	[114]
gabaaρ1/ gabacρ1	alcohol dependence, sleep disorders, memory and learning facilitation, anxietyrelated disorders,	[115]
gabaaρ2/ gabacρ2	analgesia	[116]

6. Research perspectives on GABA in insomnia

GABA is an important inhibitory neurotransmitter that balances neural hyperexcitability during insomnia. There is evidence that the use of GABA-rich functional foods can improve symptoms of depression, insomnia, cognitive impairment, and memory loss (Table 3). GABA preparations have great research value and broad application prospects as biomarkers or drugs for the treatment of insomnia. But how to translate the theoretical strategy into practical treatment? Based on animal models it is not difficult to find that it is feasible to improve or reverse the onset of insomnia by enhancing the expression of GABA-mediated corollary signaling pathways such as drugs developed by targeting some GABA receptor subunits. However, there is a lack of evidence-based support for the safety of GABA drugs, leading to skepticism and limited clinical use. Even though these drugs are FDA-approved, doctors are hesitant to prescribe them, resulting in an increase in the avoidance of these medications.On the other hand, GABA drugs (benzodiazepines such as diazepam, eszopiclone, and alprazolam, etc.) do have some adverse effects such as withdrawal, fatigue, etc., which are not suitable for long-term use; however, the research and development of targeted GABA drugs (non-benzodiazepines such as dexrazopipilone tablets) has greatly reduced such adverse effects, which shows us the direction of improvement and hope. Therefore, in the future, we should not only enhance the clinical safety testing of existing GABA analogs, but also focus on the research and development of targeted drugs. To this end, we must continue to dig deeper into the mechanism of GABA in the treatment of insomnia.

It is now known that GABA regulates macrophages, astrocytes and microglia to inhibit the release of inflammatory factors. Mechanistic studies have identified a common key signal in this process of inhibiting inflammation in all three: NF-κB signaling. So what exactly is the role of NF-κB signaling and how does it play its role? In addition, microglia are the immune cells of the brain, and when activated, both pro- and anti-inflammatory genes are upregulated, both inhibiting and promoting inflammation, so how does GABA fit into this to achieve inhibition of inflammatory factor release? Although some studies have suggested that it may be related to NF-κB signaling [70,72], the exact mechanism is unclear.

In addition, GABA has been found to inhibit neuronal damage by increasing the activation of Akt, GSK-3β and ERK, significantly reducing neuronal damage; maintain the redox state of neuronal cells through the regulation of glycogen synthase kinase (GSK)-3β and the antioxidant-related nuclear factor redox-related factor 2 (NRF2), which play a neuroprotective role. The neuroprotective effects of GABA are closely related to the regulation of inflammation, autophagy, and redox reactions, but how do these three interconnections affect each other, and how does GABA link the three? There are no relevant reports yet.

In conclusion, there is a lack of clinical drug safety studies in insomnia patients, especially in the application of GABA formulations. Therefore, we urgently need more translational work to maximize the clinical potential of GABA analogs in insomnia disorders. In addition, we also hope to make more efforts in the study of mechanisms related to insomnia diseases, so as to expand the understanding of the molecular pathogenesis of insomnia diseases, and to provide new ideas for the future development of safer GABA-targeted drugs for the treatment of insomnia diseases.

7. Conclusion

GABA is the major inhibitory neurotransmitter in the brain and has an important balancing effect on neural hyperexcitability and neurological damage in insomnia. This paper reviews the chemical structure, each binding site, and the roles of different receptor subunits of the GABAA receptor, a pentameric chloride ion-gated channel, and the G protein-coupled GABAB receptor. The mechanisms of neuroprotective effects exerted by GABA in inhibiting neuroinflammation and repairing oxidative damage, as well as the association with melatonin, were elucidated. However, there is still a lack of clinical trials on existing GABA drugs and further molecular mechanism studies on GABA, a lack of studies on NF-κB signaling, a key molecule in GABA inhibition of inflammation, a lack of exploration of the relationship between GABA and melatonin circadian rhythms, a lack of studies on the mechanism of action of the newly discovered GABAB receptor and a more limited study on the mechanism of action of the GABAB receptor. The research on the mechanism of action of GABAB receptor is also limited.

In the future, more clinical trials should be conducted to evaluate the safety of GABA analogs in current use, and more epidemiologic investigations should be conducted to follow up and validate the relevance of GABA analogs to insomnia treatment. In addition, more attention should be paid to the molecular mechanism of action of GABA in the future, such as to the key inhibitory inflammatory molecule NF-κB signaling, the corresponding mechanism of GABA and melatonin circadian rhythm, and the mechanism of action of GABAC receptor and GABAB receptor.

Just like the success of the GABA-targeted drug dexzopiclone tablets, we believe that exploratory research on the mechanism of GABA treatment for insomnia will aid in the development of more targeted drugs, which will be of great significance to the insomnia population.

Table 3
Effects of GABA in different products on the nervous system.

Source	Effect	References
Gaba-rich Monascus-fermented product	Preventing depression	[117]
Gaba powder from natural fermentation using lactic acid bacteria	Prevention of sleep disorder	[24]
Gaba-enriched fermented Laminaria japonica product	Preventing cognitive impairment in the elderly	[118]
GABA-rich fermented milk	Relieves anxiety and improves sleep	[119]

CRediT authorship contribution statement

Wenwen Zhu: Writing – original draft. **Lishan Huang:** Data curation. **Hanxing Cheng:** Software. **Nanxi Li:** Formal analysis. **Bin Zhang:** Data curation. **Wenbin Dai:** Software. **Xiao Wu:** Visualization. **Dechou Zhang:** Visualization. **Wenzhan Feng:** Software. **Sen Li:** Writing – review & editing. **Houping Xu:** Writing – review & editing, Conceptualization.

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Not applicable. No data was used for the research described in the article.

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Not applicable. Because this is a review based on published literature.

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References

[1] H. Di, Y. Guo, I. Daghlas, L. Wang, G. Liu, A. Pan, et al., Evaluation of sleep habits and disturbances among US adults, 2017-2020, JAMA Netw. Open 5 (11) (2022) e2240788.
[2] Y.E. Dean, M.A. Shebl, S.S. Rouzan, B.A.A. Bamousa, N.E. Talat, S.A. Ansari, et al., Association between insomnia and the incidence of myocardial infarction: a systematic review and meta-analysis, Clin. Cardiol. 46 (4) (2023) 376–385.
[3] N. Mookerjee, N. Schmalbach, G. Antinori, S. Thampi, D. Windle-Puente, A. Gilligan, et al., Comorbidities and risk factors associated with insomnia in the elderly population, J Prim Care Community Health 14 (2023) 21501319231168721.
[4] S. Uzun, O. Kozumplik, M. Jakovljević, B. Sedić, Side effects of treatment with benzodiazepines, Psychiatr. Danub. 22 (1) (2010) 90–93.
[5] J.V. Andersen, A. Schousboe, A. Verkhratsky, Astrocyte energy and neurotransmitter metabolism in Alzheimer's disease: integration of the glutamate/GABA-glutamine cycle, Prog Neurobiol 217 (2022) 102331.
[6] S. Kim, K. Jo, K.B. Hong, S.H. Han, H.J. Suh, GABA and l-theanine mixture decreases sleep latency and improves NREM sleep, Pharm. Biol. 57 (1) (2019) 65–73.
[7] N.I. Bohnen, J. Barr, R. Vangel, S. Roytman, R. Paalanen, K.A. Frey, et al., GABA(A) receptor benzodiazepine binding sites and motor impairments in Parkinson's disease, Brain Sci. 13 (12) (2023).
[8] Y. Feng, Z.H. Wei, C. Liu, G.Y. Li, X.Z. Qiao, Y.J. Gan, et al., Genetic variations in GABA metabolism and epilepsy, Seizure 101 (2022) 22–29.
[9] M.A.P. Fontes, G.C. Vaz, T.Z.D. Cardoso, M.F. de Oliveira, M.J. Campagnole-Santos, R.A.S. Dos Santos, et al., GABA-containing liposomes: neuroscience applications and translational perspectives for targeting neurological diseases, Nanomedicine 14 (3) (2018) 781–788.
[10] A. Ghit, D. Assal, A.S. Al-Shami, D.E.E. Hussein, GABA(A) receptors: structure, function, pharmacology, and related disorders, J. Genet. Eng. Biotechnol. 19 (1) (2021) 123.
[11] L.S.M. Evenseth, M. Gabrielsen, I. Sylte, The GABA(B) receptor-structure, ligand binding and drug development, Molecules 25 (13) (2020).
[12] M. Llansola, Y.M. Arenas, M. Sancho-Alonso, G. Mincheva, A. Palomares-Rodriguez, M. Doverskog, et al., Neuroinflammation alters GABAergic neurotransmission in hyperammonemia and hepatic encephalopathy, leading to motor incoordination. Mechanisms and therapeutic implications, Front. Pharmacol. 15 (2024) 1358323.
[13] D.Y. Abg Abd Wahab, C.H. Gau, R. Zakaria, M.K. Muthu Karuppan, A.R. Bs, Z. Abdullah, et al., Review on cross talk between neurotransmitters and neuroinflammation in striatum and cerebellum in the mediation of motor behaviour, BioMed Res. Int. 2019 (2019) 1767203.
[14] Z. Zhu, Z. Shi, C. Xie, W. Gong, Z. Hu, Y. Peng, A novel mechanism of Gamma-aminobutyric acid (GABA) protecting human umbilical vein endothelial cells (HUVECs) against H(2)O(2)-induced oxidative injury, Comp. Biochem. Physiol. C Toxicol. Pharmacol. 217 (2019) 68–75.

[15] Y. Deng, W. Wang, P. Yu, Z. Xi, L. Xu, X. Li, et al., Comparison of taurine, GABA, Glu, and Asp as scavengers of malondialdehyde in vitro and in vivo, Nanoscale Res. Lett. 8 (1) (2013) 190.
[16] Z. Xu, W. Li, Y. Sun, W. Jin, L. Yu, J. Yang, et al., Melatonin alleviates PTSD-like behaviors and restores serum GABA and cortisol levels in mice, Psychopharmacology (Berl). 240 (2) (2023) 259–269.
[17] G.R. Dawson, N. Collinson, J.R. Atack, Development of subtype selective GABAA modulators, CNS Spectr. 10 (1) (2005) 21–27.
[18] N.G. Bowery, A.L. Hudson, G.W. Price, GABAA and GABAB receptor site distribution in the rat central nervous system, Neuroscience 20 (2) (1987) 365–383.
[19] R. Machado-Vieira, L. Ibrahim, I.D. Henter, C.A. Zarate Jr., Novel glutamatergic agents for major depressive disorder and bipolar disorder, Pharmacol. Biochem. Behav. 100 (4) (2012) 678–687.
[20] S.M. Sears, S.J. Hewett, Influence of glutamate and GABA transport on brain excitatory/inhibitory balance, Exp. Biol. Med. 246 (9) (2021) 1069–1083.
[21] N. Li, J. Liu, M. Wang, Z. Yu, K. Zhu, J. Gao, et al., Sedative and hypnotic effects of Schisandrin B through increasing GABA/Glu ratio and upregulating the expression of GABA(A) in mice and rats, Biomed. Pharmacother. 103 (2018) 509–516.
[22] X. Yu, W. Li, Y. Ma, K. Tossell, J.J. Harris, E.C. Harding, et al., GABA and glutamate neurons in the VTA regulate sleep and wakefulness, Nat. Neurosci. 22 (1) (2019) 106–119.
[23] P. Hepsomali, J.A. Groeger, J. Nishihira, A. Scholey, Effects of oral gamma-aminobutyric acid (GABA) administration on stress and sleep in humans: a systematic review, Front. Neurosci. 14 (2020) 923.
[24] A. Yamatsu, Y. Yamashita, T. Pandharipande, I. Maru, M. Kim, Effect of oral γ-aminobutyric acid (GABA) administration on sleep and its absorption in humans, Food Sci. Biotechnol. 25 (2) (2016) 547–551.
[25] J.I. Byun, Y.Y. Shin, S.E. Chung, W.C. Shin, Safety and efficacy of gamma-aminobutyric acid from fermented rice germ in patients with insomnia symptoms: a randomized, double-blind trial, J. Clin. Neurol. 14 (3) (2018) 291–295.
[26] Y. Shi, J.W. Dong, J.H. Zhao, L.N. Tang, J.J. Zhang, Herbal insomnia medications that target GABAergic systems: a review of the psychopharmacological evidence, Curr. Neuropharmacol. 12 (3) (2014) 289–302.
[27] Y. Ma, H. Han, J.S. Eun, H.C. Kim, J.T. Hong, K.W. Oh, Sanjoinine A isolated from Zizyphi Spinosi Semen augments pentobarbital-induced sleeping behaviors through the modification of GABA-ergic systems, Biol. Pharm. Bull. 30 (9) (2007) 1748–1753.
[28] G. Trauner, S. Khom, I. Baburin, B. Benedek, S. Hering, B. Kopp, Modulation of GABAA receptors by valerian extracts is related to the content of valerenic acid, Planta Med. 74 (1) (2008) 19–24.
[29] I. León-Rivera, M. Herrera-Ruiz, S. Estrada-Soto, C. Gutiérrez Mdel, I. Martínez-Duncker, G. Navarrete-Vázquez, et al., Sedative, vasorelaxant, and cytotoxic effects of convolvulin from Ipomoea tyrianthina, J. Ethnopharmacol. 135 (2) (2011) 434–439.
[30] O. Bruni, L. Ferini-Strambi, E. Giacomoni, P. Pellegrino, Herbal remedies and their possible effect on the GABAergic system and sleep, Nutrients 13 (2) (2021).
[31] A. Ahnaou, W. Drinkenburg, Sleep, neuronal hyperexcitability, inflammation and neurodegeneration: does early chronic short sleep trigger and is it the key to overcoming Alzheimer's disease? Neurosci. Biobehav. Rev. 129 (2021) 157–179.
[32] J.M. Cénat, C. Blais-Rochette, C.K. Kokou-Kpolou, P.G. Noorishad, J.N. Mukunzi, S.E. McIntee, et al., Prevalence of symptoms of depression, anxiety, insomnia, posttraumatic stress disorder, and psychological distress among populations affected by the COVID-19 pandemic: a systematic review and meta-analysis, Psychiatr. Res. 295 (2021) 113599.
[33] D.J. Nutt, A.L. Malizia, New insights into the role of the GABA(A)-benzodiazepine receptor in psychiatric disorder, Br. J. Psychiatry 179 (2001) 390–396.
[34] M. Farrant, Z. Nusser, Variations on an inhibitory theme: phasic and tonic activation of GABA(A) receptors, Nat. Rev. Neurosci. 6 (3) (2005) 215–229.
[35] P.J. Whiting, GABA-A receptor subtypes in the brain: a paradigm for CNS drug discovery? Drug Discov. Today 8 (10) (2003) 445–450.
[36] R.W. Olsen, GABA(A) receptor: positive and negative allosteric modulators, Neuropharmacology 136 (Pt A) (2018) 10–22.
[37] M.D. Wang, M. Rahman, D. Zhu, T. Bäckström, Pregnenolone sulphate and Zn2+ inhibit recombinant rat GABA(A) receptor through different channel property, Acta Physiol. 188 (3–4) (2006) 153–162.
[38] B.A. Vega Alanis, M.T. Iorio, L.L. Silva, K. Bampali, M. Ernst, M. Schnürch, et al., Allosteric GABA(A) receptor modulators-A review on the most recent heterocyclic chemotypes and their synthetic accessibility, Molecules 25 (4) (2020).
[39] U. Rudolph, H. Möhler, Analysis of GABAA receptor function and dissection of the pharmacology of benzodiazepines and general anesthetics through mouse genetics, Annu. Rev. Pharmacol. Toxicol. 44 (2004) 475–498.
[40] W. Sieghart, G. Sperk, Subunit composition, distribution and function of GABA(A) receptor subtypes, Curr. Top. Med. Chem. 2 (8) (2002) 795–816.
[41] J. Bormann, A. Feigenspan, GABAC receptors, Trends Neurosci. 18 (12) (1995) 515–519.
[42] M.M. Naffaa, S. Hung, M. Chebib, G.A.R. Johnston, J.R. Hanrahan, GABA-ρ receptors: distinctive functions and molecular pharmacology, Br. J. Pharmacol. 174 (13) (2017) 1881–1894.
[43] D.P. Li, H.L. Pan, Role of GABAB receptors in autonomic control of systemic blood pressure, Adv. Pharmacol. 58 (2010) 257–286.
[44] L. Chun, W.H. Zhang, J.F. Liu, Structure and ligand recognition of class C GPCRs, Acta Pharmacol. Sin. 33 (3) (2012) 312–323.
[45] K. Kaupmann, K. Huggel, J. Heid, P.J. Flor, S. Bischoff, S.J. Mickel, et al., Expression cloning of GABA(B) receptors uncovers similarity to metabotropic glutamate receptors, Nature 386 (6622) (1997) 239–246.
[46] B. Biermann, K. Ivankova-Susankova, A. Bradaia, S. Abdel Aziz, V. Besseyrias, J.P. Kapfhammer, et al., The Sushi domains of GABAB receptors function as axonal targeting signals, J. Neurosci. 30 (4) (2010) 1385–1394.
[47] J. Kniazeff, T. Galvez, G. Labesse, J.P. Pin, No ligand binding in the GB2 subunit of the GABA(B) receptor is required for activation and allosteric interaction between the subunits, J. Neurosci. 22 (17) (2002) 7352–7361.
[48] M. Margeta-Mitrovic, Y.N. Jan, L.Y. Jan, Function of GB1 and GB2 subunits in G protein coupling of GABA(B) receptors, Proc. Natl. Acad. Sci. U.S.A. 98 (25) (2001) 14649–14654.
[49] M. Gassmann, B. Bettler, Regulation of neuronal GABA(B) receptor functions by subunit composition, Nat. Rev. Neurosci. 13 (6) (2012) 380–394.
[50] R. Yirmiya, I. Goshen, Immune modulation of learning, memory, neural plasticity and neurogenesis, Brain Behav. Immun. 25 (2) (2011) 181–213.
[51] A. Syauqy, C.Y. Hsu, H.H. Rau, A.L. Kurniawan, J.C. Chao, Association of sleep duration and insomnia symptoms with components of metabolic syndrome and inflammation in middle-aged and older adults with metabolic syndrome in Taiwan, Nutrients 11 (8) (2019).
[52] J. Wang, X. Wu, W. Liang, M. Chen, C. Zhao, X. Wang, Objective short sleep duration is related to the peripheral inflammasome dysregulation in patients with chronic insomnia, Nat. Sci. Sleep 12 (2020) 759–766.
[53] M.R. Zielinski, J.M. Krueger, Sleep and innate immunity, Front Biosci (Schol Ed) 3 (2) (2011) 632–642.
[54] M. Lekander, A.N. Andreasson, G. Kecklund, R. Ekman, M. Ingre, T. Akerstedt, et al., Subjective health perception in healthy young men changes in response to experimentally restricted sleep and subsequent recovery sleep, Brain Behav. Immun. 34 (2013) 43–46.
[55] F. Kapsimalis, G. Richardson, M.R. Opp, M. Kryger, Cytokines and normal sleep, Curr. Opin. Pulm. Med. 11 (6) (2005) 481–484.
[56] F. Obal Jr., J.M. Krueger, Biochemical regulation of non-rapid-eye-movement sleep, Front. Biosci. 8 (2003) d520–d550.
[57] J.M. Krueger, The role of cytokines in sleep regulation, Curr. Pharmaceut. Des. 14 (32) (2008) 3408–3416.
[58] M.R. Zielinski, A.J. Gibbons, Neuroinflammation, sleep, and circadian rhythms, Front. Cell. Infect. Microbiol. 12 (2022) 853096.
[59] A. Urrutia, V.A. García-Angulo, A. Fuentes, M. Caneo, M. Legüe, S. Urquiza, et al., Bacterially produced metabolites protect C. elegans neurons from degeneration, PLoS Biol. 18 (3) (2020) e3000638.
[60] W. Li, M. Wei, J. Wu, X. Rui, M. Dong, Novel fermented chickpea milk with enhanced level of γ-aminobutyric acid and neuroprotective effect on PC12 cells, PeerJ 4 (2016) e2292.
[61] L. Liu, C.J. Li, Y. Lu, X.G. Zong, C. Luo, J. Sun, et al., Baclofen mediates neuroprotection on hippocampal CA1 pyramidal cells through the regulation of autophagy under chronic cerebral hypoperfusion, Sci. Rep. 5 (2015) 14474.
[62] X.W. Wei, H. Yan, B. Xu, Y.P. Wu, C. Li, G.Y. Zhang, Neuroprotection of co-activation of GABA receptors by preventing caspase-3 denitrosylation in KA-induced seizures, Brain Res. Bull. 88 (6) (2012) 617–623.

[63] A. Cabrera-Pastor, M. Llansola, C. Montoliu, M. Malaguarnera, T. Balzano, L. Taoro-Gonzalez, et al., Peripheral inflammation induces neuroinflammation that alters neurotransmission and cognitive and motor function in hepatic encephalopathy: underlying mechanisms and therapeutic implications, Acta Physiol. 226 (2) (2019) e13270.
[64] K. Chen, T. Palagashvili, W. Hsu, Y. Chen, B. Tabakoff, F. Hong, et al., Brain injury and inflammation genes common to a number of neurological diseases and the genes involved in the genesis of GABAnergic neurons are altered in monoamine oxidase B knockout mice, Brain Res. 1774 (2022) 147724.
[65] D.H. Ngo, Q.T. Tran, Y.S. Kim, N.T.N. Hang, D.N. Ngo, T.S. Vo, GABA-enriched rice bran inhibits inflammation in LPS-stimulated macrophages via suppression of TLR4-MAPK/NF-κB signaling cascades, J. Food Biochem. 46 (12) (2022) e14421.
[66] J. Fu, Z. Han, Z. Wu, Y. Xia, G. Yang, Y. Yin, et al., GABA regulates IL-1β production in macrophages, Cell Rep. 41 (10) (2022) 111770.
[67] T.L. Tay, J.C. Savage, C.W. Hui, K. Bisht, M. Tremblay, Microglia across the lifespan: from origin to function in brain development, plasticity and cognition, J Physiol. 595 (6) (2017) 1929–1945.
[68] F.O. Martinez, S. Gordon, The M1 and M2 paradigm of macrophage activation: time for reassessment, F1000Prime Rep 6 (2014) 13.
[69] A.M. Osman, Y. Sun, T.C. Burns, L. He, N. Kee, N. Oliva-Vilarnau, et al., Radiation triggers a dynamic sequence of transient microglial alterations in juvenile brain, Cell Rep. 31 (9) (2020) 107699.
[70] M. Lee, C. Schwab, P.L. McGeer, Astrocytes are GABAergic cells that modulate microglial activity, Glia 59 (1) (2011) 152–165.
[71] L. Lang, B. Xu, J. Yuan, S. Li, S. Lian, Y. Chen, et al., GABA-mediated activated microglia induce neuroinflammation in the hippocampus of mice following cold exposure through the NLRP3 inflammasome and NF-κB signaling pathways, Int. Immunopharm. 89 (Pt B) (2020) 106908.
[72] F. Liu, Y.Y. Zhang, N. Song, J. Lin, M.K. Liu, C.L. Huang, et al., GABA(B) receptor activation attenuates inflammatory orofacial pain by modulating interleukin-1β in satellite glial cells: role of NF-κB and MAPK signaling pathways, Brain Res. Bull. 149 (2019) 240–250.
[73] Y. Xia, F. He, X. Wu, B. Tan, S. Chen, Y. Liao, et al., GABA transporter sustains IL-1β production in macrophages, Sci. Adv. 7 (15) (2021).
[74] A. Wilkaniec, J.B. Strosznajder, A. Adamczyk, Toxicity of extracellular secreted alpha-synuclein: its role in nitrosative stress and neurodegeneration, Neurochem. Int. 62 (5) (2013) 776–783.
[75] P. MacMullin, N. Hodgson, U. Damar, H.H.C. Lee, M.Q. Hameed, S.C. Dhamne, et al., Increase in seizure susceptibility after repetitive concussion results from oxidative stress, parvalbumin-positive interneuron dysfunction and biphasic increases in glutamate/GABA ratio, Cerebr. Cortex 30 (12) (2020) 6108–6120.
[76] X. Tang, R. Yu, Q. Zhou, S. Jiang, G. Le, Protective effects of γ-aminobutyric acid against H(2)O(2)-induced oxidative stress in RIN-m5F pancreatic cells, Nutr. Metab. 15 (2018) 60.
[77] A. Penna, D.S. Wang, J. Yu, I. Lecker, P.M. Brown, D. Bowie, et al., Hydrogen peroxide increases GABAA receptor-mediated tonic current in hippocampal neurons, J. Neurosci. 34 (32) (2014) 10624–10634.
[78] A.L. Dafre, J.M. Rosa, A.L.S. Rodrigues, M.P. Cunha, Multiple cellular targets involved in the antidepressant-like effect of glutathione, Chem. Biol. Interact. 328 (2020) 109195.
[79] Y. Deng, L. Xu, X. Zeng, Z. Li, B. Qin, N. He, New perspective of GABA as an inhibitor of formation of advanced lipoxidation end-products: it's interaction with malondiadehyde, J. Biomed. Nanotechnol. 6 (4) (2010) 318–324.
[80] H. Yang, R. Xing, S. Liu, H. Yu, P. Li, Analysis of the protective effects of γ-aminobutyric acid during fluoride-induced hypothyroidism in male Kunming mice, Pharm. Biol. 57 (1) (2019) 29–37.
[81] N.D. Md Zamri, M.U. Imam, S.A. Abd Ghafar, M. Ismail, Antioxidative effects of germinated Brown rice-derived extracts on H2O2-induced oxidative stress in HepG2 cells, Evid Based Complement Alternat Med 2014 (2014) 371907.
[82] T. Hagi, H. Nakagawa, H. Ohmori, K. Sasaki, M. Kobayashi, T. Narita, et al., Characterization of unique metabolites in γ-aminobutyric acid-rich cheese by metabolome analysis using liquid chromatography-mass spectrometry, J. Food Biochem. 43 (11) (2019) e13039.
[83] S.D. Dutta, D.K. Patel, K. Ganguly, K.T. Lim, Effects of GABA/β-glucan supplements on melatonin and serotonin content extracted from natural resources, PLoS One 16 (3) (2021) e0247890.
[84] A. Kalsbeek, R.A. Cutrera, J.J. Van Heerikhuize, J. Van Der Vliet, R.M. Buijs, GABA release from suprachiasmatic nucleus terminals is necessary for the light-induced inhibition of nocturnal melatonin release in the rat, Neuroscience 91 (2) (1999) 453–461.
[85] D.V. Telegina, A.K. Antonenko, A.Z. Fursova, N.G. Kolosova, The glutamate/GABA system in the retina of male rats: effects of aging, neurodegeneration, and supplementation with melatonin and antioxidant SkQ1, Biogerontology 23 (5) (2022) 571–585.
[86] Q. Yu, Q. Guo, S. Jin, C. Gao, P. Zheng, D.P. Li, et al., Melatonin suppresses sympathetic vasomotor tone through enhancing GABA(A) receptor activity in the hypothalamus, Front. Physiol. 14 (2023) 1166246.
[87] M.A. Cruz-Aguilar, I. Ramírez-Salado, M. Hernández-González, M.A. Guevara, A.P. Rivera-García, EEG coherence and power spectra during REM sleep related to melatonin intake in mild-to-moderate Alzheimer's disease: a pilot study, Int. J. Neurosci. 133 (4) (2023) 441–449.
[88] W. Yin, J. Zhang, Y. Guo, Z. Wu, C. Diao, J. Sun, Melatonin for premenstrual syndrome: a potential remedy but not ready, Front. Endocrinol. 13 (2022) 1084249.
[89] Z. Zareie, F. Tabatabaei Yazdi, S.A. Mortazavi, Development and characterization of antioxidant and antimicrobial edible films based on chitosan and gamma-aminobutyric acid-rich fermented soy protein, Carbohydr. Polym. 244 (2020) 116491.
[90] F. De Crescenzo, G.L. D'Alò, E.G. Ostinelli, M. Ciabattini, V. Di Franco, N. Watanabe, et al., Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis, Lancet 400 (10347) (2022) 170–184.
[91] M.E. Hirschtritt, M. Olfson, K. Kroenke, Balancing the risks and benefits of benzodiazepines, JAMA 325 (4) (2021) 347–348.
[92] V.C. Abad, C. Guilleminault, Insomnia in elderly patients: recommendations for pharmacological management, Drugs Aging 35 (9) (2018) 791–817.
[93] N. Gunja, The clinical and forensic toxicology of Z-drugs, J. Med. Toxicol. 9 (2) (2013) 155–162.
[94] R.M. McKernan, T.W. Rosahl, D.S. Reynolds, C. Sur, K.A. Wafford, J.R. Atack, et al., Sedative but not anxiolytic properties of benzodiazepines are mediated by the GABA(A) receptor alpha1 subtype, Nat. Neurosci. 3 (6) (2000) 587–592.
[95] K.S. Smith, E. Engin, E.G. Meloni, U. Rudolph, Benzodiazepine-induced anxiolysis and reduction of conditioned fear are mediated by distinct GABAA receptor subtypes in mice, Neuropharmacology 63 (2) (2012) 250–258.
[96] L.J. Martin, A.A. Zurek, J.F. MacDonald, J.C. Roder, M.F. Jackson, B.A. Orser, Alpha5GABAA receptor activity sets the threshold for long-term potentiation and constrains hippocampus-dependent memory, J. Neurosci. 30 (15) (2010) 5269–5282.
[97] P.R. Kramer, L.L. Bellinger, Reduced GABAA receptor α6 expression in the trigeminal ganglion enhanced myofascial nociceptive response, Neuroscience 245 (2013) 1–11.
[98] E.J. Rodríguez-Palma, Y.E. De la Luz-Cuellar, A.M. Islas-Espinoza, A.E. Félix-Leyva, S.I. Shiers, G. García, et al., Activation of α6-containing GABAA receptors induces antinociception under physiological and pathological conditions, Pain 164 (5) (2023) 948–966.
[99] W. Sieghart, L.C. Chiou, M. Ernst, J. Fabjan, M.S. M, M.T. Lee, α6-Containing GABA(A) receptors: functional roles and therapeutic potentials, Pharmacol. Rev. 74 (1) (2022) 238–270.
[100] S.H. Fatemi, T.D. Folsom, R.J. Rooney, P.D. Thuras, Expression of GABAA α2-, β1- and ε-receptors are altered significantly in the lateral cerebellum of subjects with schizophrenia, major depression and bipolar disorder, Transl. Psychiatry 3 (9) (2013) e303.
[101] C.C. Hernandez, X. Tian, N. Hu, W. Shen, M.A. Catron, Y. Yang, et al., Dravet syndrome-associated mutations in GABRA1, GABRB2 and GABRG2 define the genetic landscape of defects of GABA(A) receptors, Brain Commun 3 (2) (2021) fcab033.
[102] E. Todd, K.N. Gurba, E.J. Botzolakis, A.K. Stanic, R.L. Macdonald, GABAA receptor biogenesis is impaired by the γ2 subunit febrile seizure-associated mutation, GABRG2(R177G), Neurobiol. Dis. 69 (2014) 215–224.
[103] D.M. Dick, H.J. Edenberg, X. Xuei, A. Goate, S. Kuperman, M. Schuckit, et al., Association of GABRG3 with alcohol dependence, Alcohol Clin. Exp. Res. 28 (1) (2004) 4–9.
[104] F. Markus, C. Angelini, A. Trimouille, G. Rudolf, G. Lesca, C. Goizet, et al., Rare variants in the GABA(A) receptor subunit ε identified in patients with a wide spectrum of epileptic phenotypes, Mol Genet Genomic Med 8 (9) (2020) e1388.

[105] R.M. Karvas, S. McInturf, J. Zhou, T. Ezashi, D.J. Schust, R.M. Roberts, et al., Use of a human embryonic stem cell model to discover GABRP, WFDC2, VTCN1 and ACTC1 as markers of early first trimester human trophoblast, Mol. Hum. Reprod. 26 (6) (2020) 425–440.
[106] I.I.A. Juvale, Z. Hassan, A.T.C. Has, The emerging roles of π subunit-containing GABA(A) receptors in different cancers, Int. J. Med. Sci. 18 (16) (2021) 3851–3860.
[107] R. Breuer, M.L. Hamshere, J. Strohmaier, M. Mattheisen, F. Degenhardt, S. Meier, et al., Independent evidence for the selective influence of GABA(A) receptors on one component of the bipolar disorder phenotype, Mol. Psychiatr. 16 (6) (2011) 587–589.
[108] F. Fernandez, T. Esposito, R.A. Lea, N.J. Colson, A. Ciccodicola, F. Gianfrancesco, et al., Investigation of gamma-aminobutyric acid (GABA) A receptors genes and migraine susceptibility, BMC Med. Genet. 9 (2008) 109.
[109] E. García-Martín, C. Martínez, H. Alonso-Navarro, J. Benito-León, O. Lorenzo-Betancor, P. Pastor, et al., Gamma-aminobutyric acid GABRA4, GABRE, and GABRQ receptor polymorphisms and risk for essential tremor, Pharmacogenetics Genom. 21 (7) (2011) 436–439.
[110] O.F. O'Leary, D. Felice, S. Galimberti, H.M. Savignac, J.A. Bravo, T. Crowley, et al., GABAB(1) receptor subunit isoforms differentially regulate stress resilience, Proc. Natl. Acad. Sci. U.S.A. 111 (42) (2014) 15232–15237.
[111] H. Badshah, I. Ullah, S.E. Kim, T.H. Kim, H.Y. Lee, M.O. Kim, Anthocyanins attenuate body weight gain via modulating neuropeptide Y and GABAB1 receptor in rats hypothalamus, Neuropeptides 47 (5) (2013) 347–353.
[112] I. Ullah, H. Badshah, M.I. Naseer, H.Y. Lee, M.O. Kim, Thymoquinone and vitamin C attenuates pentylenetetrazole-induced seizures via activation of GABAB1 receptor in adult rats cortex and hippocampus, NeuroMolecular Med. 17 (1) (2015) 35–46.
[113] L.H. Jacobson, F.F. Sweeney, K. Kaupmann, O.F. O'Leary, M. Gassmann, B. Bettler, et al., Differential roles of GABAB1 subunit isoforms on locomotor responses to acute and repeated administration of cocaine, Behav. Brain Res. 298 (Pt B) (2016) 12–16.
[114] Y. Lu, C.J. Li, C. Chen, P. Luo, M. Zhou, C. Li, et al., Activation of GABAB2 subunits alleviates chronic cerebral hypoperfusion-induced anxiety-like behaviours: a role for BDNF signalling and Kir3 channels, Neuropharmacology 110 (Pt A) (2016) 308–321.
[115] Y.A. Blednov, J.M. Benavidez, M. Black, C.R. Leiter, E. Osterndorff-Kahanek, D. Johnson, et al., GABAA receptors containing ρ1 subunits contribute to in vivo effects of ethanol in mice, PLoS One 9 (1) (2014) e85525.
[116] R. Tadavarty, J. Hwang, P.S. Rajput, P.J. Soja, U. Kumar, B.R. Sastry, Are presynaptic GABA-Cρ2 receptors involved in anti-nociception? Neurosci. Lett. 606 (2015) 145–150.
[117] C.Y. Chuang, Y.C. Shi, H.P. You, Y.H. Lo, T.M. Pan, Antidepressant effect of GABA-rich monascus-fermented product on forced swimming rat model, J. Agric. Food Chem. 59 (7) (2011) 3027–3034.
[118] S.N.S. Reid, J.K. Ryu, Y. Kim, B.H. Jeon, Corrigendum to "the effects of fermented laminaria japonica on short-term working memory and physical fitness in the elderly", Evid Based Complement Alternat Med 2018 (2018) 1764038.
[119] L. Yu, X. Han, S. Cen, H. Duan, S. Feng, Y. Xue, et al., Beneficial effect of GABA-rich fermented milk on insomnia involving regulation of gut microbiota, Microbiol. Res. 233 (2020) 126409.