MINI REVIEW

GABA_A receptors as targets for anaesthetics and analgesics and promising candidates to help treat coronavirus infections: A mini-review

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Funding information
Australian Research Council,
Grant/Award Number: LP160100560

Abstract
GABA is a major inhibitory neurotransmitter that regulates the balance between excitatory and inhibitory circuits in the human nervous system. The GABA receptors are divided into three main subtypes, GABA_A, GABA_B, and GABA_C (also termed GABA rho) receptors. GABA_A receptors are pentameric ligand-gated ion channels widely expressed throughout the central and peripheral nervous system. The activation of GABA_A receptors results in opening of an anion-selective channel that mainly gates chloride ions and allows them to flow into the neuron, causing hyperpolarization of the cell membrane that dampens neural excitability. This makes GABA_A receptors critical anaesthetic and analgesic targets for existing as well as for the development of novel drugs. In this review, we first summarize the biochemical properties of GABA_A receptors and the clinical anaesthetics and analgesics targeting the receptors. In a forward-looking section, we summarize the emerging role of GABAergic signalling in treatment of COVID-19 related infections. Finally, we discuss the opportunities arising from targeting specific and unique subunit interfaces for the development of novel anaesthetics and analgesics leading to more efficient therapies.

KEYWORDS
anaesthetic, analgesic, COVID-19, GABA receptor, ion channel

1 | INTRODUCTION

γ-Aminobutyric acid (GABA) is an important inhibitory neurotransmitter in the human body and was first discovered in the 1950s.1 The neurotransmitter GABA is formed from glutamate which again is biosynthesised glutamine (Figure 1). GABA is widely distributed in the mammalian central nervous system (CNS) and in plant tissue. Neurons containing GABA in the brain (GABAergic neurons) account for about 20–30% of the total number of neurons, and most of them are interneurons, which makes GABA one of the most crucial inhibitory neurotransmitters.1 Insufficient GABAergic activity can cause numerous neuropathological disorders including pain.1 The GABA receptors discovered so far are divided into three major groups, GABA_A, GABA_B, and GABA_C (also
termed GABA\(_\rho\) receptors.\(^2\) GABA\(_\rho\) receptors are pentameric ligand-gated ion channels (pLGICs) that mainly mediate rapid synaptic activity.\(^2\) The activation of the receptors can result in opening of an anion-selective channel that mainly gates chloride ions and allows them to flow into the neuron, causing hyperpolarization of the cell membrane that dampens excitability of GABAergic neurons (Figure 1). GABA\(_B\) receptors belong to the family C of G-protein-coupled receptors, which operate as dimers composed of GABA\(_\beta1\) and GABA\(_\beta2\) subunits to transform synaptic neurotransmitter signals into a cellular response through the binding and activation of heterotrimeric G proteins.\(^3\) GABA\(_B\) receptors signal through three different pathways, voltage-gated Ca\(^{2+}\) channels, G protein-activated inwardly-rectifying K\(^+\) channels (GIRK), and adenylyl cyclase, and the effect of this signalling is blockage of neurotransmitter release and hyperpolarization of neurons.\(^4\) GABA\(_C\) receptors are considered a subclass of GABA\(_\rho\)Rs and are therefore also often referred to as GABA\(_\rho\) receptors and exist in three different subtypes, \(\varphi 1\)–\(3\). In addition, the GABA transporter (GAT) plays a vital role in GABAergic signalling. It transports GABA against a concentration gradient through the cell membrane and thereby reduces the GABA concentration in the synaptic cleft.\(^5\)

In this review, we describe the biochemical properties of GABA\(_\rho\) receptors and the clinical anaesthetics and analgesics targeting the receptors, and we discuss the potential additive/synergistic effects of these drugs from a view of their different binding sites. In a forward-looking section, we summarize the emerging role of GABAergic signalling in relation to COVID-19 infections. Finally, we discuss the opportunities arising from targeting specific and unique subunit interfaces for the development of novel anaesthetics and analgesics leading to more efficient therapies with fewer adverse effects.

### 2 | BIOCHEMICAL PROPERTIES OF GABA\(_\rho\) RECEPTORS

A possible impediment to drug design is a lack of structural information for most GABA\(_\rho\) receptors. The discovery of the 3D structure of GABA\(_\rho\) receptors marks the beginning of a revolution in developing new drugs.\(^6\) Functional GABA\(_\rho\) receptors are assembled of five homologous subunits from a pool of 19 subunits (\(\alpha 1\)–\(6, \beta 1\)–\(3, \gamma 1\)–\(3, \delta, \varepsilon, \pi, \rho 1\)–\(3\) and \(\theta\)) encoded by corresponding genes.\(^7\) The assembled subunits form different types of GABA\(_\rho\) receptors, among which the most common receptor subtype is composed of 2\(\alpha\), 2\(\beta\), and 1\(\gamma\) subunit, in brief \(\alpha 2\beta2\gamma\).\(^7\) Recent cryogenic electron microscopy structures have confirmed the assembled receptor stoichiometry to be organized as “\(\beta-\alpha-\beta-\gamma\)” in a counterclockwise orientation when viewed from the extracellular side (Figure 2A). When viewed perpendicular to the channel direction, each subunit has an extracellular domain (ECD), a transmembrane domain (TMD) and an intracellular domain (ICD, not shown) (Figure 2B). The drugs discussed below bind to the ECD and TMD of the receptor to exert their anaesthetic and analgesic effects.

The physiological significance of GABA\(_\rho\) receptors is reflected in their ability to modulate many different signalling pathways by controlling membrane potentials.
They are widely expressed in the central and peripheral nervous system to regulate the afferent excitability and nociception. When GABA binds to GABAA receptors, it results in opening of an anion selective channel that mainly gates chloride ions and allows them to flow into the neuron, causing hyperpolarization of the cell membrane that dampens excitability of GABAergic neurons. Oppositely, antagonizing GABAergic signalling prevents membrane hyperpolarization and causes hyper-nociceptive effects. For instance, animal tests have shown that treatment with the GABAA antagonist bicuculline enhances nociceptive signalling and behavioural reactivity.

3 | MERITS AND DEMERITS FOR ANALGESICS AND ANAESTHETICS TARGETING GABAA RECEPTORS

At present, most of the sedative and analgesic drugs that act on GABA receptors can be roughly divided into two major types, agonists and positive allosteric modulators (PAMs). Agonists activate the receptor fully or partially by binding to the GABA binding site while PAMs produce anaesthetic and analgesic effects by enhancing the effects produced by endogenous GABA. These are drugs such as benzodiazepines, barbiturates, volatile anaesthetics, and neurosteroids.

3.1 | Benzodiazepines

One of the major drug classes targeting GABA receptors with analgesic effect commonly used clinically is benzodiazepines (BDZs), a class of psychotropic drugs with a core chemical structure consisting of a phenyl group fused to a diaza heterocyclic ring. The classical high affinity BDZ binding site is situated in the receptors ECD in the interface between an α and a γ subunit in a position equivalent to the β-α interfaces where GABA is binding. The α1, α2, α3, and α5 subunits have a high affinity for BDZs, while α4 and α6 subunits have no affinity for BDZs and are often referred to as being BDZ-insensitive. Low affinity BDZ binding sites have also been reported in the β-α interfaces and in the γ-β interface in the TMD. However, much less is known about the influence of these binding sites on the pharmacological profile of BDZs compared to the classical BDZ site. It has been shown that α1β2γ2 receptors mediate the sedative, anticonvulsant, and anterograde amnestic actions of BDZs. BDZs have various pain indications (e.g., muscle spasms pain caused by CNS diseases) and can be used for surgical anaesthesia. The neurological effects of BDZs are dose-dependent. At low doses, they have anxiolytic effects, and as the dose increases, sedation and forgetfulness appear, and finally, anaesthesia is induced. Chloridiazepoxide was the first BDZ drug to be introduced in 1960. It has a sedative, antianxiety, and weak analgesic
actions. Since then, extensive research on chlordiazepoxide has led to the introduction of diazepam, midazolam, and remimazolam.

Diazepam is among the most successful BDZ drugs, which is efficacious in treating a wide spectrum of central nervous system disorders, including anxiety and epilepsy. It sets the standard for pharmacotherapy of BDZs in potency, the onset of action, and safety. Nordiazepam, temazepam, and oxazepam are active metabolites of diazepam, which may accumulate after repeated administration, leading to prolonged sedation and posing a significant risk to patients with impaired renal function. Therefore, continuous intravenous diazepam is rarely used to sedate patients in the ICU. Midazolam is a short-acting BDZ-derivative with anxiolytic, amnestic, anticonvulsant, hypnotic, and sedative properties. The onset duration of midazolam is short, and it has no continuous analgesic effect on its own, however, continuous application can cause the accumulation of active metabolites (α-hydroxymidazolam), leading to prolonged sedation. Remimazolam is an ester-based BDZ derivative with the characteristics of the parent compounds midazolam and remifentanil. The presence of an ester functionality in remimazolam makes it prone to hydrolysis by esterases and produces an inactive metabolite containing a carboxylic acid moiety that is hydrophilic and easily excreted which means less residual drug after end of infusion and this makes remimazolam particularly suitable for surgical sedation. A multicentre, randomized, non-inferiority, phase III trial established a non-inferior sedation success rate of remimazolam compared with propofol in patients undergoing upper gastrointestinal endoscopy. The result showed that remimazolam allows faster recovery from sedation compared to propofol.

BDZs bind to the interface between α and γ subunits on GABA_A receptors and generally do not discriminate significantly between different receptor subtypes. The side effects, such as drowsiness, tolerance, dependence, the risk of withdrawal, and adverse effects on cognition, are inevitable, limiting the potential broader clinical application of BDZs. To reduce the side effects of BDZs, researchers put effort into developing novel drugs that target specific subtypes of GABA_A receptors. A class of non-benzodiazepine hypnotic fast-acting medicines that act on GABA_A receptors has been developed, known as “Z drugs,” including zolpidem, zaleplon, and eszopiclone. It is worth noting that zolpidem, zaleplon, and some other sedative and hypnotic compounds, such as indoplon and abecanide, show preferential selectivity for α1β2 receptors, which significantly reduce the side effects. Moreover, several preclinical drugs targeting GABA_A receptor α2/3 subunits, such as Saniona’s NS11394 and MSD’s L838417, have shown sound analgesic effects in animal experiments.

3.2 Barbiturates

Barbiturates exhibit a spectrum of GABA_A receptor-mediated activities, including sedative, anxiolytic, hypnotic, and anti-convulsant effects. The discovery of barbiturates and research into their derivatives have been important for the development of modern anaesthesia. Two important binding sites for barbiturates in the GABA_A receptor’s TMD have been identified at the α-β and γ-β interfaces. Pentothal was a commonly used barbiturate, but it is rarely used today due to its many disadvantages, such as changes of the metabolism of other drugs metabolized in the liver, accumulation of active metabolites in kidneys and associated renal failure, and pain, secondary endothelial damage and inflammation from intravenous injection. Thiopental and methohexitol are ultra-short acting derivatives of barbiturates. They are mainly used in obstetrics for induction of caesarean sections under general anaesthesia. Besides, other barbiturates with longer-acting effects are available for specialist use, including amobarbital, phenobarbital, and butobarbital. Phenobarbital remains explicitly popular as an anti-epileptic drug. At low concentrations it potentiates the receptor’s response to GABA, while at high concentrations, it evokes direct allosteric activation through binding sites in the TMD. This property makes barbiturates dangerous and potentially lethal as they can cause severe cardiovascular and respiratory depression in overdose. Therefore, barbiturates are only used in patients who cannot tolerate or do not respond to other drugs.

3.3 Anaesthetics

Propofol is the most widely used intravenous general anaesthetic and can directly activate GABA_A receptors at high concentrations. It binds to the domain defined by the β(M286) residue at the β(+)/α(−) interface in the TMD and the β(Y143) residue near the β(−) surface in the junction between the extracellular and transmembrane domains. Affinity labelling and mutagenesis results for propofol suggest that in addition to the β-α sites, there may be additional sites at other subunit interfaces, and/or at the TMD-ECD junction. Propofol has some characteristics of an ideal sedative, including the advantages of rapid onset and short duration of action, which is especially suitable for patients who need frequent neurological examinations. An open-label randomized controlled trial revealed that sedation with propofol results in significantly fewer ventilator days compared to lorazepam. However, propofol infusion syndrome from cumulative doses of propofol is a risk factor that should be considered by clinicians. It can often lead to cardiac failure, rhabdomyolysis, metabolic acidosis, and kidney
failure and may potentially be fatal. A multicentre ICU database analysis further supports these data: Out of more than 3000 patients, those receiving propofol infusion had lower mortality and shorter ICU stays than those receiving midazolam or lorazepam.26 Besides, the antioxidant properties of propofol may provide cardioprotection as suggested based on rat studies.27 However, propofol also has some disadvantages. Up to 30% of patients experience propofol-related injection pain during intravenous injection of propofol. As a sedative, propofol has a "narrow therapeutic window," which may cause a sudden transition from sedation to general anaesthesia. Also, propofol reduces the sensitivity of central chemoreceptors to hypercapnia so that dose-dependent respiratory depression may occur after administration. Also, propofol can cause dose-related cardiovascular depression, decreased sympathetic tone, decreased vascular resistance, and subsequent hypotension, making propofol unfavourable for non-specialist applications. In recent years, several water-soluble analogues of propofol have been developed to avoid the shortcomings of propofol. Fospropofol is a water-soluble prodrug of propofol, which is activated by endotheial alkaline phosphatase. Fospropofol is suitable for monitored anaesthesia care for adult patients undergoing diagnostic or therapeutic procedures, and for outpatients and day surgery. A single loading dose can endure the entire surgical process. Furthermore, since fospropofol is a water-soluble preparation, the incidence and severity of injection pain is less, and it is less prone to bacterial growth and contamination than propofol. In an open-label multicenter trial, 60 patients receiving mechanical ventilation were randomly divided into three groups: fospropofol intravenous injection and infusion for 12 h; fospropofol infusion only for 12 h; and propofol infusion only for 12 h. The results show that fospropofol is effective and well-tolerated when used for short-term sedation.28 Notably, the delay of clinical effects must be considered when using fospropofol (metabolic activation of the prodrug in vivo takes time) to avoid excessive injection leading to more profound sedation than desired. Given propofols binding to a site in the receptor's transmembrane region and distinct from that of benzodiazepines, synergistic/additive effects of propofol and benzodiazepines have been reported and are potentially dangerous and highly dependent on GABA concentrations.19

Etomidate is another commonly used intravenous general anaesthetic that can rapidly induce general anaesthesia by positively modulating GABA_A receptors.29 It binds to the same site as propofol on GABA_A receptors. Etomidate can maintain haemodynamic stability in patients with cardiovascular diseases, and therefore, is commonly substituted for propofol in cases where cardiovascular or respiratory depression is a concern.30 Recently, a double-blind, randomized clinical trial showed that in patients undergoing coronary artery bypass graft surgery with low ejection fraction, diazepam is more favourable in terms of haemodynamic stability compared to propofol, and etomidate can be used safely for induction of anaesthesia in patients with impaired ventricular function.31 The primary defect of etomidate is that administration for rapid sequence intubation is associated with higher rates of adrenal insufficiency and mortality in patients with sepsis.32 Recently, studies have found that an etomidate analogue methoxy carbonyl etomidate (MOC-etomidate) does not inhibit the function of the adrenal cortex. It enhances GABA_A receptor signaling in rats and constitutes a fast-metabolism hypnotic with similar haemodynamic stability as etomidate.33 However, the fly in the ointment is that MOC-etomidate can be rapidly hydrolyzed by esterases to form carboxylic acid metabolites, which easily accumulate in patients with renal failure. Cyclopropyl methoxy carbonyl etomidate (CPMM or ABP-700) is a second-generation etomidate analogue developed after MOC-etomidate was studied in animals. ABP-700 aims to solve the problem of accumulation of carboxylic acid metabolites of MOC-etomidate in the kidneys of patients with renal failure. Animal experiments conducted in tadpoles revealed that ABP-700 has better potency and a longer half-life than MOC-etomidate in rats, long-term infusion does not cause changes in half-life, and the carboxylic acid changes metabolites of ABP-700 are not accumulated in the CNS.34 Besides, the recovery of sedation after using ABP-700 is faster than propofol and easier to control. A preliminary phase I study of ABP-700 showed that a single bolus injection of 0.25 and 0.35 mg/kg of ABP-700 could provide satisfactory clinical effects, and it is still safe at doses as high as 1 mg/kg.35

### 3.4 Neurosteroids

The δ-containing GABA_A receptors are capable of sensing low concentrations of GABA in the intercellular fluid and producing tonic inhibition. The importance of tonic inhibition in regulating states of consciousness and pain transduction is supported by the fact that δ-containing GABA_A receptors are promising targets for anaesthetics and analgesics, for example, propofol is a positive allosteric modulator of α5- and δ-containing GABA_A receptors leading to enhanced tonic conductance, which is widely used for anaesthesia and analgesia in bronchoscopy.36 Neurosteroids are potent positive allosteric modulators of the δ-containing GABA_A receptors to exert their biological effects on the regulation of neuronal
Evidence revealed that the tonic inhibitory neurotransmission mediated by α4βδ GABA_A receptors could be modulated by neurosteroids. Some binding sites of neurosteroids on GABA_A receptors have been identified by using site-directed mutagenesis and electrophysiology, including α1V227, T236, Q241, N407, and β3Y284, and it remains to be seen if neurosteroids bind to sites that directly involve γ or δ subunits. Neurosteroids have been found to have a wide range of clinical effects, including sedation, analgesia, anticonvulsant effects, pressure and stress relief, and cognitive improvement, which have prompted the development of synthetic neurosteroids. For instance, alfaxalone (alfaxan) is a progesterone-derived neuroactive steroid and a non-competitive GABA_A receptor agonist used for general anaesthesia. Its metabolite allopregnanolone has the characteristics of fast onset, fast metabolism, and is relatively safe but may cause mild cardiovascular and respiratory depression. Alfaxalone is used currently in veterinary practice as an induction agent for anaesthesia and as an injectable anaesthetic. A phase I trial compared the efficacy and safety of alfaxalone and propofol and concluded that the new aqueous alfaxalone formulation has similar pharmacodynamic properties to its analogue progesterone, and it has a similar sedative effect compared to propofol. However, a faster cognitive functional recovery is observed. Furthermore, the new aqueous alfaxalone formulation does not cause injection pain and cardiopulmonary inhibition.

4 | GABA_A RECEPTORS STIMULATION PREVENT DISEASE PROGRESSION IN COVID-19

The role of GABAergic signalling in relation to immune response has regained interest during the COVID-19 pandemic. GABA_A receptors are expressed in antigen-presenting cells (APCs) and activation of these receptors can hyperpolarize APCs, thereby reducing their activity. This may lead to a reduction in the body’s inflammatory response. Further, GABA_A receptors have been found in alveolar macrophages, and the application of GABA_A receptor agonists and PAMs (i.e., GABA and diazepam) reduce the production of pro-inflammatory molecules after lipopolysaccharide (LPS) stimulation. The specific type of GABA_A receptors expressed on APCs and alveolar macrophages is not determined yet. However, polymerase chain reaction (PMR) was used to screen human peripheral blood mononuclear cells (PBMC) and Jurkat cells for the presence of GABA_A receptor subunit mRNAs. Positive signals were detected for the α1, α3, β2, β3, δ and ε subunit mRNAs in both cell populations. In addition, a study of the bronchial asthma mouse model showed that the inhibition of GABA_A receptor subunit π (GABRP) could reduce the differentiation of airway epithelial progenitor cells into goblet cells, leading to reduced inflammation.

Coronavirus mouse hepatitis virus-1 (MHV-1) causes pneumonia in mice and shares pathological characteristics with human COVID-19 infection. A recent study administered GABA to MHV-1-infected mice and found that mice that received GABA immediately after inoculation with MHV-1 had mild pneumonia symptoms and eventually all recovered. When GABA treatment was started 3 days after MHV-1 infection, the severity of the disease was also significantly reduced. The study revealed that the activation of GABA receptors prevents the development of severe pneumonia and death in mice caused by MHV-1 infection and suggests that GABA_A receptors stimulation potentially could help prevent disease progression in COVID-19 and other coronavirus strains infections in humans. Another study performed animal experiments in susceptible inbred A/J mice to test whether oral treatment with GABA could modulate the MHV-1-induced pneumonitis. The research revealed that MHV-1-inoculated control mice became severely ill (over 60% succumbed to the infection), whereas mice that received GABA immediately after MHV-1 inoculation became only mildly ill and all of them recovered. In addition to GABA, similar experiments were conducted using the GABA_A agonist homotaurine, and led to similar results. Treatment with the GABA_A R-specific agonist homotaurine significantly reduced the severity of pneumonitis and death rates in MHV-1-infected mice. However, the similar effect was not observed in the mice treated with GABA_A R-specific agonist baclofen, indicating that the therapeutic effects were mediated primarily through GABA_A receptors.

In addition to animal tests, a recent clinical study revealed that GABA levels were significantly reduced in COVID-19 patients and GABA plasma levels allowed for stratification of COVID-19 patients with high sensitivity and specificity. These results strongly suggest a correlation between GABA and COVID-19. However, the anti-inflammatory mechanism by which GABA_A receptor stimulation prevents disease progression in COVID-19 should be further explored.

5 | CONCLUSIONS AND PERSPECTIVES

The GABAergic system is a critical target for anaesthetics and analgesics. Since GABA_A receptors are widely distributed in the central and peripheral nervous system,
many drugs targeting GABA<sub>A</sub> receptors are currently used in clinical practice. However, their side effects (i.e., addictive effect and drug dependence) due to lack of true subtype selectivity limit their potential broader clinical application. Therefore, the development of more selective drugs is imminent. Although this is promising in theory, the complexity and a plethora of subtypes have hampered significant progress so despite knowing about the roles of different subtypes for many years, the successful development of receptor truly selective drugs that can exert the desired efficacy without causing side effects has not yet to be realized. There is currently a structural revolution happening 3D structures of GABA<sub>A</sub> receptors are becoming available. This may guide development of novel analgesics and anaesthetics that target specific and selective drugs is imminent. Although this is promising in theory, the complexity and a plethora of subtypes have hampered significant progress so despite knowing about the roles of different subtypes for many years, the successful development of receptor truly selective drugs that can exert the desired efficacy without causing side effects has not yet to be realized. There is currently a structural revolution happening 3D structures of GABA<sub>A</sub> receptors are becoming available. This may guide development of novel analgesics and anaesthetics that target specific and unique subunits or subunit interfaces for the development of novel anaesthetics and analgesics. In addition, more and more studies have proven the relationship between the GABAergic system and the prognosis of COVID-19. Considering that drugs targeting GABA<sub>A</sub> receptors are proven to be safe from many years of clinical applications, we should further explore their mechanism of action in relation to immune response.

**ACKNOWLEDGEMENTS**

This work was supported by funding from the Australian Research Council (LP160100560). Open access publishing facilitated by The University of Sydney, as part of the Wiley - The University of Sydney agreement via the Council of Australian University Librarians.

**CONFLICTS OF INTEREST**

The authors declare no competing interests.

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How to cite this article: Luo Y, Balle T. GABA\(_A\) receptors as targets for anaesthetics and analgesics and promising candidates to help treat coronavirus infections: A mini-review. Basic Clin Pharmacol Toxicol. 2022;131(6):443-451. doi:10.1111/bcpt.13798