

From the street to the brain: neurobiology of the recreational drug γ -hydroxybutyric acid

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γ -Hydroxybutyric acid (GHB) is a short-chain fatty acid that occurs naturally in the mammalian brain and is formed primarily from the precursor γ -aminobutyric acid (GABA). The properties of GHB suggest that it has a neuromodulatory role in the brain and has the ability to induce several pharmacological and behavioral effects. GHB has been used clinically as an anesthetic and to treat alcoholism and narcolepsy. Furthermore, GHB has emerged recently as a major recreational drug of abuse. GHB appears to have dual mechanisms of action in the brain. Biochemical data suggest that the intrinsic neurobiological activity of GHB might be mediated through the GHB receptor, which is separate and distinct from the GABA_B receptor. However, many of the pharmacological and clinical effects of exogenously administered GHB, including the properties of addiction, tolerance, withdrawal and intoxication, are probably mediated via the GABA_B receptor, where GHB might act both directly as a partial agonist and indirectly through GHB-derived GABA.

γ -Hydroxybutyric acid (GHB) was synthesized in 1960 and was used initially as an anesthetic drug [1]. In the 1970s, GHB was found to be beneficial in the treatment of the sleep disorder narcolepsy [2]. GHB was manufactured in the USA during the late 1980s and was marketed as a dietary supplement in the 1990s. At that time, body builders started to use GHB and its prodrug γ -butyrolactone (GBL) because of the growth hormone-releasing effect of GHB. Subsequently, the addictive properties of both GHB and GBL became apparent [3]. By the late 1990s GHB had become a popular drug used in clubs and gained significant notoriety as a major drug of abuse and as a date rape drug [4]. The Food and Drug Administration banned the sale of non-prescription GHB in 1990 and on 13 March 2000 GHB was classified as a schedule I drug [5]. However, GBL is still available in health food stores and can be converted easily to GHB.

Current 'street' names for GHB include G, liquid ecstasy, grievous bodily harm, Georgia home boy, gib, liquid X, soap, easy lay, salty water, scoop and nitro [5]. GHB abuse has arisen because of the euphoria, disinhibition and heightened sexual awareness that are claimed to be associated with its use [4]. GHB overdose has been reported to result in coma, cardiorespiratory depression, seizures and death [4]. Currently, no specific antidote for GHB intoxication exists and the exact mechanism(s) of action of GHB is not clear [6]. In this article, we will review the neurobiology of endogenous GHB, the effect of exogenous administration of GHB and the evidence that GHB has multiple mechanisms of action in the brain, including activation of both the γ -aminobutyric acid type B (GABA_B) receptor and a separate GHB-specific receptor.

Endogenous GHB in the brain

GHB is a short-chain fatty acid that occurs naturally in the mammalian brain at a concentration of 1–4 μ M [7]. The primary precursor of GHB in the brain is γ -aminobutyric acid (GABA). GHB is formed in the brain from GABA-derived succinic semialdehyde (SSA) via a specific succinic semialdehyde reductase (SSR). GHB can be reconverted back to SSA via GHB dehydrogenase, and the GHB-derived SSA can be converted back to GABA [7]. SSA can also be metabolized by succinic semialdehyde dehydrogenase (SSADH) to succinic acid. Mutant mice in which the SSADH enzyme is deleted display high levels of GHB and GABA [8]. GHB has many properties that suggest that this compound might play a role in the brain as a neurotransmitter or neuromodulator. These characteristics include a discrete, subcellular anatomical distribution for GHB and its synthesizing enzyme in neuronal presynaptic terminals. SSR is present in GABA-containing neurons, which suggests that GHB and GABA might colocalize in certain inhibitory nerve terminals [9] and raises the possibility of a GHB-derived pool of GABA.

The presence of a GHB receptor is suggested by specific, high-affinity [³H]GHB binding sites that occur in the brain, with the highest density found in the hippocampus, followed by the cortex and then the thalamus. The binding

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kinetics of this site correlate with the physiological concentrations of GHB in brain because there is a high-affinity GHB binding site with a dissociation constant (K_D) of 30–580 nM and a low-affinity site with a K_D of ~ 1.5 – 16.0 μ M. The anatomical distribution of [3 H]GHB binding correlates with GHB turnover and displays a distinct ontogeny. GHB binding is a postnatal event, appearing in the third postnatal week of life [7]. GHB is released by neuronal depolarization in a Ca^{2+} -dependent fashion and a Na^+ -dependent GHB uptake system has been demonstrated in brain. Furthermore, an active vesicular uptake system has been reported that is most probably driven by the vesicular inhibitory amino acid transporter – the same transporter that mediates the uptake of GABA and glycine [10]. Although GHB has been proposed as a biologically active neuromodulator [7], the precise function of endogenous GHB in the brain is unknown.

Recently, Andriamampandry and colleagues cloned a putative GHB receptor that is activated by GHB and is coupled to G proteins [11]. However, this newly cloned receptor displays no affinity for the specific GHB receptor antagonist NCS382 (see Chemical names), which suggests the presence of an NCS382-insensitive subtype of the GHB receptor.

GHB addiction and withdrawal

The recent surge in the use of GHB as a major recreational drug has led to reports of addictive properties of this compound in humans [4,12]. In addition, GHB withdrawal symptoms similar to those observed in ethanol withdrawal have been reported in humans [13,14]. In the majority of these cases, tolerance to GHB occurred. Studies in rodents are in concordance with the clinical data. Thus, rats treated chronically with GHB exhibit tolerance and withdrawal [15,16], and develop conditioned place preference, which suggests a rewarding effect of GHB [17,18]. There is some evidence that the addictive properties of GHB might be mediated through the $GABA_B$ receptor. For example, GHB self-administration has been shown to be blocked by administration of the $GABA_B$ receptor agonist baclofen [19].

Although there is some disagreement about the quality of the evidence [20], GHB appears to be effective in the treatment of alcohol withdrawal [21,22]. However, relapse rates are high and there are reports that administration of GHB in the treatment of alcohol withdrawal can subsequently lead to GHB addiction or withdrawal [23–25].

Distinct GHB and $GABA_B$ receptors

The $GABA_B$ receptor is a heterodimer in which the $GABA_{B(1)}$ receptor dimerizes with the $GABA_{B(2)}$ receptor to form a functional $GABA_B$ receptor [26]. The $GABA_B$

receptor couples to various effector systems through a signal-transducing G protein. Presynaptically, activation of $GABA_B$ receptor autoreceptors (located on GABA-containing neurons) and heteroreceptors (located on other neurotransmitter-releasing neurons) has been reported to inhibit neurotransmitter release through inhibition of Ca^{2+} channels. Postsynaptically, $GABA_B$ receptor activation produces slow inhibitory postsynaptic potentials via G-protein-coupled inward rectifying K^+ channels (GIRK) [26].

Many of the pharmacological and clinical effects of exogenously administered GHB, including the properties of addiction and tolerance, are probably mediated via the $GABA_B$ receptor, where GHB might act both directly as a partial agonist and indirectly through GHB-derived GABA. GHB appears to be a weak $GABA_B$ receptor agonist [12,27], with an affinity for the $GABA_B$ receptor in the millimolar range [28], which is well above the 1–4 μ M physiological concentrations of GHB in the brain [7]. Therefore, the high concentrations of GHB in the brain that would accrue following exogenous administration could activate $GABA_B$ receptors.

Alternatively, GHB could activate the $GABA_B$ receptor indirectly via its conversion to GABA [7] (Figure 1). This hypothesis could explain the inordinately high concentration of GHB required to produce $GABA_B$ receptor-mediated effects because high micromolar to low millimolar concentrations of GHB are required to produce enough GHB-derived GABA to activate $GABA_B$ receptors [29]. The conversion of GHB to GABA can be inhibited by ethosuximide and valproate. When these two drugs are included in binding assays, GHB no longer competes with [3 H]GABA for binding at the $GABA_B$ receptor [29]. Although some studies using concentrations of GHB below 100 μ M have failed to provide support for the GHB-derived GABA hypothesis [30], the possibility of GHB-derived GABA playing a role when the concentration of GHB is inordinately high (Figure 1), as would be the case in GHB abuse and toxicity, has not been fully addressed experimentally.

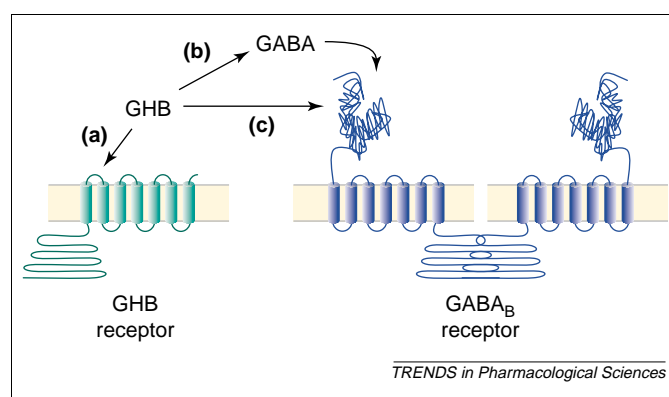


Figure 1. γ -Hydroxybutyric acid (GHB) has multiple mechanisms of action in the brain. (a) Physiologically relevant concentrations (1–4 μ M) of GHB activate at least two subtypes of the GHB receptor: NCS382-sensitive and -insensitive subtypes [11]. (b) In addition to binding to the GHB receptor, at supra-physiological concentrations (high micromolar to low millimolar) a sufficient quantity of GHB might be metabolized to GABA, which then activates the $GABA_B$ receptor [7]. (c) At supra-physiological levels, GHB itself might bind to the $GABA_B$ receptor [12].

Chemical names

CGP35348: (3-aminopropyl)(diethoxymethyl)phosphinic acid

CGP36742: (3-aminopropyl)butylphosphonic acid

NCS382: (2E)-(5-hydroxy-5,7,8,9-tetrahydro-6H-benzo[α] [7]annulen-6-ylidene)ethanoic acid

There are several lines of evidence to support the hypothesis that the GHB receptor is not the same as the GABA_B receptor (Table 1). GABA_B receptor agonists do not displace [³H]GHB binding [31,32] and the ability of GHB to displace [³H]baclofen binding is weak [12,27]. GHB and its antagonist NCS382 [7] do not compete for [³H]GABA binding in autoradiographic binding assays on rat brain sections [31]. Furthermore, the ontogeny [33,34] and regional distribution [7,33,35] of the GHB receptor and the GABA_B receptor are different. In addition, neither [³H]GHB nor the GHB receptor antagonist [³H]NCS382 have affinity for the GABA_{B(1)} receptor, the GABA_{B(2)} receptor or the GABA_{B(1)} receptor–GABA_{B(2)} receptor heterodimer in recombinant HEK cells [36].

From a physiological perspective, GHB can activate GABA_B receptor heterodimers coexpressed with Kir3 channels in *Xenopus* oocytes, but only with an EC₅₀ of ~5 mM [28], which is one thousand times more than the physiological concentration of GHB in brain. Similarly, millimolar concentrations of GHB are required to mimic the postsynaptic effects of baclofen on the GABA_B receptor, and this electrophysiological effect of GHB is blocked by a specific GABA_B receptor antagonist but not by the GHB receptor antagonist NCS382 [37,38]. Indeed, it has been proposed that there is no electrophysiological evidence from *in vitro* investigations to support the idea that there is a neuronal GHB receptor-mediated electrophysiological response [39].

Dose response of GHB

Given the low *K_D* of GHB for the GHB receptor and the high median inhibitory concentration (IC₅₀) of GHB for the GABA_B receptor relative to the physiological concentration of GHB in brain, the determination of the relationship between dose and response is crucial to understanding the mechanism of action of endogenous versus exogenously administered GHB. The clinical and experimental effects of GHB are dose dependent (Table 2). In humans, low doses (10 mg kg⁻¹) induce short-term anterograde amnesia, and drug abuse is possible. Doses of 20–30 mg kg⁻¹ result in drowsiness and sleep, whereas doses of 50 mg kg⁻¹ lead to general anesthesia, with no analgesia. Dosages higher than 50 mg kg⁻¹ can result in coma, cardiorespiratory depression, seizures and death [40,41].

In rat or other rodent experimental models, dose-dependent effects are also observed for GHB. Doses of

10–50 mg kg⁻¹ cause memory deficits and anxiolytic effects, whereas doses ranging from 75 to 200 mg kg⁻¹ induce absence seizures that can be blocked by both GABA_B receptor antagonists and GHB receptor antagonists [42,43]. The threshold level of GHB in the brain that is associated with GHB-induced absence seizures is 240 μM. These effects can be blocked by both GABA_B receptor antagonists and GHB receptor antagonists. A GHB dose of 200–300 mg kg⁻¹ induces stupor and high voltage slowing on an electroencephalogram (EEG). As the GHB dose increases above 300 mg kg⁻¹ and brain levels of GHB exceed 500 μM, coma and EEG burst-suppression occur, which can be blocked by GABA_B receptor antagonists, but not by the GHB receptor antagonist NCS382. The median lethal dose (LD₅₀) of GHB in rat is 1.7 G kg⁻¹ [43,44].

Neuromodulatory effects of GHB

GHB concentrations in the brain that exceed the physiological levels of GHB by 2–3 orders of magnitude both saturate GHB receptors and produce GABA_B receptor-mediated functional perturbations in the brain. Hence, the GHB–GABA_B receptor interaction has potential relevance for mechanisms of GHB addiction, tolerance, abuse, toxicity and other effects of exogenously administered high doses of GHB. However, GABA_B receptor-mediated mechanisms cannot explain the specific properties of endogenous GHB in the brain [7], and can only partially explain the effects of lower doses of GHB (e.g. experimental absence seizures) [44,45]. Similarly, electrophysiological studies in rodent brain slices have demonstrated dual effects of GHB depending on whether the concentration of GHB was at physiological or supra-physiological levels. The effects of physiological concentrations of GHB are blocked by the GHB receptor antagonist NCS382 [7,45,46], whereas the electrophysiological effects of millimolar concentrations of GHB are blocked by GABA_B receptor antagonists, but not by the GHB receptor antagonist [47,48].

Physiologically relevant concentrations of GHB have been shown to inhibit forskolin-stimulated increases in cAMP levels in the cortex and hippocampus [34]. This effect of GHB might be due to activation of a G-protein-coupled receptor because GHB stimulated [³⁵S]GTPγS binding and low-*K_m* GTPase activity. The effect of GHB on cAMP levels was detected in presynaptic synaptosomal fractions but not in synaptoneurosomal fractions, which contain primarily postsynaptic proteins. Furthermore,

Table 1. Differences between the GHB receptor and the GABA_B receptor^{a,b}

Parameter	GHB receptor	GABA _B receptor
GHB antagonist	High affinity	No affinity
GHB	High affinity	Low affinity
Baclofen (GABA _B receptor agonist)	No affinity	High affinity
G-protein coupled	Yes	Yes
Cerebellum	No binding	High density
Hippocampus	High density	Moderate density
Cortex	Layer I–III	Layer IV–VI
Thalamus	Moderate density	High density
Ontogeny	Appears postnatal week 3	Present at birth
Effects on forskolin-stimulated cAMP	Inhibits	Inhibits

^aAbbreviation: GHB, γ-hydroxybutyric acid.

^bData are from studies in rodents described in [31,33,34].

Table 2. Dose response of GHB^a

Dose or concentration of GHB	Physiological effect [44]
Oral dose (humans) [3–6]	
10 mg kg ⁻¹	Short-term amnesia
20–30 mg kg ⁻¹	Sleep and drowsiness
50–60 mg kg ⁻¹	Coma, cardiorespiratory depression, seizures
Systemic dose (rodents)	
10–50 mg kg ⁻¹	Memory impairment
75–200 mg kg ⁻¹	Absence seizures, spike-and-wave discharges on EEG (threshold brain concentration for this effect is 240 µM)
200–300 mg kg ⁻¹	Stupor, EEG slowing
> 300 mg kg ⁻¹	Coma, EEG burst suppression; isoelectric period increases with dose
1.7 g kg ⁻¹	LD ₅₀
In vitro changes [7,12,27,44]	
Nanomolar to low micromolar	Activate the GHB receptor
Low micromolar	Alter GABA and glutamate release
Millimolar	Activate the GABA _B receptor; might be converted to physiologically active concentrations of GABA

^aAbbreviations: EEG, electroencephalogram; GHB, γ-hydroxybutyric acid.

these effects occurred after postnatal day 21, when specific [³H]GHB binding is detected. Because presynaptic cAMP is known to be functionally coupled to neurotransmitter release, endogenous GHB might modulate neurotransmitter release. Indeed, *in vivo* microdialysis studies indicate that GHB induces a robust decrease in the basal and K⁺-evoked release of GABA [49–51] and glutamate [52].

Although the biochemical and microdialysis data suggest that endogenous GHB activates a presynaptic GHB receptor to modulate GABA and glutamate release, the electrophysiological data fail to support such a hypothesis [39]. However, there are two broad problems with the literature on the electrophysiological effects of GHB. First, the threshold concentration of GHB for GABA_B receptor-mediated effects in *in vitro* electrophysiological experiments appears to be ~1 mM [47]. Second, most slice recordings are performed in brains taken from rats [39] that are 12–22 days old. Although the GABA_B receptor is present in the brains of animals of this age, the GHB receptor does not appear until 15–18 days of age in rats and does not reach adult levels until the 4th and 5th weeks of postnatal age in this species [33]. Hence, the absence of a GHB receptor-specific electrophysiological response in a brain slice from a rat younger than 15–18 days is to be expected and does not exclude the presence of a functional GHB receptor in older animals.

GHB and dopamine

GHB has long been known to have an effect on dopamine systems in the brain. Chronic treatment with GHB results in upregulation of dopamine D1 and D2 receptor mRNA expression in brain regions rich in GHB receptors [53]. Acute treatment with GHB inhibits dopamine release [54]. The attenuation of dopamine neurotransmission that follows GHB administration might underlie the loss of locomotor activity that can occur in humans and experimental animals. Rodent studies have shown that GHB given in various supra-physiological doses, ranging from 200 to 800 mg kg⁻¹, can lead to sedation and a dose-dependent decrease in motor activity [53,55,56]. These effects were shown to be antagonized effectively by pretreatment with GABA_B receptor antagonists [55]. Carai

et al. [57] have reported similar findings and demonstrated that the GHB-induced loss of motor activity was associated with a highly significant decrease in striatal 3-methoxytyramine (3-MT) concentrations. Because dopamine is inactivated in the synaptic cleft by the action of catechol-O-methyltransferase resulting in 3-MT formation, these observations provide further evidence that GHB might act to inhibit dopamine release. Pretreatment with the GABA_B receptor antagonists CGP35348 and CGP36742 not only antagonized the GHB-induced motor effects but also antagonized the loss of striatal 3-MT [58]. Collectively, the above data strongly suggest that GHB-induced inhibition of dopamine release is mediated by the GABA_B receptor.

GHB and reward

The mechanism of the addictive properties of GHB is not clear. At a molecular level, chronic GHB exposure would probably desensitize GHB and GABA_B receptors, as has been demonstrated *in vitro* [59,60], thus reducing their ability to inhibit neurotransmitter release. Hence, under conditions of chronic GHB intake, it is possible that compensatory mechanisms could occur that offset the inhibition of dopamine release and could in fact result in an increase in dopamine, GABA and/or glutamate release. This scenario could contribute to the addictive properties of GHB.

GHB and progesterone

Evidence from microdialysis studies in rats suggests that exogenous administration of GHB elevates brain concentrations of the hormone progesterone in a dose-dependant fashion [61]. However, again, large doses of GHB were required for this effect, which was blocked by a GABA_B receptor antagonist but not by a GHB receptor antagonist. Furthermore, the GHB-induced increase in progesterone levels was mimicked by baclofen. The ability of GHB to elevate levels of progesterone has relevance to GABA-mediated transmission because the progesterone metabolite allopregnanolone is a positive allosteric modulator of the GABA_A receptor [62]. Conceivably, GHB modulation

of progesterone levels could contribute to changes in cognition and mood across the menstrual cycle [63].

Therapeutic intervention for GHB intoxication

The data reviewed above suggest that high concentrations of GHB can result in activation of the GABA_B receptor and that the resultant effect can be blocked by GABA_B receptor antagonists, but not by GHB receptor antagonists. Because levels of GHB are inordinately high during GHB intoxication, it would seem logical that blockade of the GABA_B receptor might be an effective acute treatment for GHB overdose. However, studies of mice that lack the gene encoding SSADH (SSADH^{-/-}) suggest that GHB intoxication might involve GHB receptors in addition to GABA_B receptors [8]. This mutant animal is characterized by inordinately elevated concentrations of brain GHB and GABA, which makes it a potential model of chronic GHB abuse. During a critical period from postnatal days 16 to 22 SSADH^{-/-} mice exhibit ataxia and develop generalized tonic-clonic seizures that lead to rapid death. Therapeutic intervention with the GABA_B receptor antagonist CGP35348 increased survival to 36.4% of animals. However, treatment with the GHB receptor antagonist NCS382 was much more effective, resulting in a survival rate of 61.5% [64]. These data suggest that both the GABA_B receptor and GHB receptor are involved in the pathogenesis of CNS manifestations of GHB ingestion. Elevation of GHB in brain would saturate the GHB receptor. In addition, the GABA_B receptor would be maximally stimulated by a combination of GHB, a weak GABA_B receptor agonist, and the GHB-derived GABA (Figure 1). Hence, an effective treatment strategy for GHB intoxication and abuse might well involve blockade of both receptors.

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