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REVIEW

γ-HYDROXYBUTYRIC ACID (GHB) AND ITS CHEMICAL MODIFICATIONS: A REVIEW OF THE GHBergic SYSTEM

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γ-Hydroxybutyric acid (GHB) and its chemical modifications: a review of the GHBergic system. A. WASZKIELEWICZ, J. BOJARSKI. Pol. J. Pharmacol., 2004, 56, 43–49

γ-Hydroxybutyric acid (GHB) is a naturally occurring substance with function of an inhibitory neurotransmitter in the central nervous system in mammals. GHB can be used as a medicine in narcolepsy (Xyrem) and for general anesthesia (sodium oxybate). It is also a popular drug of abuse, causing coma, addiction and severe withdrawal syndrome, and, therefore, demanding thorough studies on the GHBergic system and expanded research on toxicology of this compound. The aim of this review is to present the proved and some suggested mechanisms of its action from pharmacological point of view, which may help to properly treat intoxication or other pathological states caused by GHB ingestion. Some new GHB derivatives studied for analogous action and their present use are also described.

Key words: *γ-hydroxybutyric acid, 1,4-butanediol, γ-butyrolactone, NCS-382*

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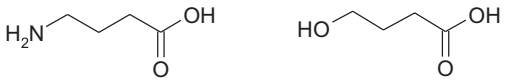
Introduction

The γ-hydroxybutyric acid (GHB) is a structural analog of the γ-aminobutyric acid (GABA).



GABA GHB

It is an endogenous substance with function of an inhibitory neurotransmitter in the central nervous system in mammals. Its natural concentration in the human brain is 0.3 mmol/g. However, the compound is able to pass the blood-brain barrier, which is unique for a neurotransmitter, and, thus, its concentration in cerebrospinal fluid (CSF) can be enlarged. The main mechanism of its action consists in binding to a specific presynaptic GHB receptor which is coupled to a G protein [34]. Its further effect relies upon a decrease in adenyl cyclase activity.

A receptor complex of GHB-$GABA_B$ has also been reported and GHB was proved to be an agonist of most $GABA_B$ receptors [5]. The third observed mechanism involves an allosteric action on the calcium channels [19].

Under physiological conditions, GHB originates from GABA which is metabolized by a transaminase to succinic semialdehyde and then by a dehydrogenase to GHB. Nevertheless, most of GABA is transformed to succinic acid which enters the Krebs cycle (Fig. 1).

Neuropharmacological action

GHB can be found in both nerve and somatic cells and in body fluids such as blood and CSF. However, its function in the body outside the nervous system remains unknown.

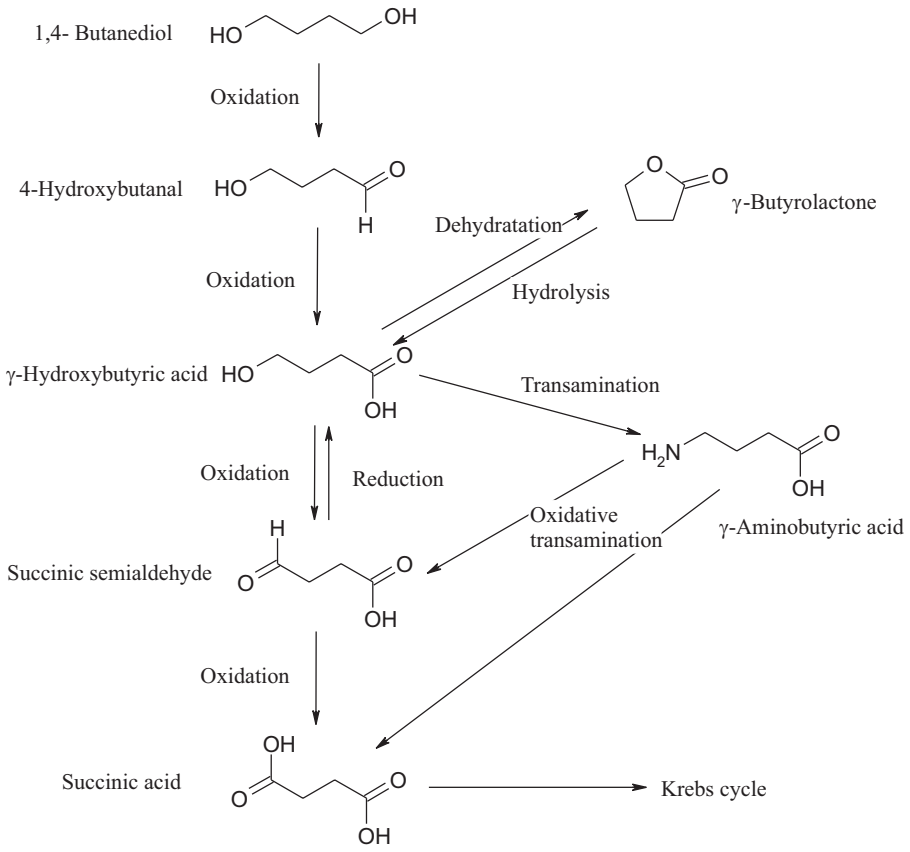


Fig. 1. Metabolism of γ-hydroxybutyric acid, γ-aminobutyric acid, 1,4-butanediol and γ-butyrolactone

The cerebral cortex

Stimulation of the GHB-$GABA_B$ receptor complex in the frontal lobe of the cerebral cortex probably leads to absence seizures [2] due to inhibition of Ca^{2+} uptake (stimulated by K^+ ions). Moreover, agonism at presynaptic $GABA_B$ receptor results in lowered GABA release leading to the absence seizures mentioned above [14, 33]. Another result of the $GABA_B$ agonism is the hypnotic effect [37].

An increase in endogenous acetylcholine level has been reported after GHB administration as well as an increase in serotonin synthesis and metabolism [31].

In the 1970s it was observed that morphine elevated the GHB level and that GHB and morphine had synergic effect in producing euphoria [30]. Later, it was demonstrated that GHB increased synthesis of enkephalins, and that GHB-induced EEG change was reversed by naloxone [29]. Moreover, GHB was proved not to stimulate the μ, δ and κ opioid receptors [25].

In the temporal lobe, in the hippocampus, which is responsible for memory and learning, agonistic action at the $GABA_B$ receptors leads to guanyl cyclase activation, increase in cGMP level, and consequently to hyperpolarization of hippocampal neurons. Such action is responsible for amnesia due to GHB ingestion.

The thalamus

A decrease in the excitatory postsynaptic potentials in the thalamus has been reported. Such action is responsible for the anesthetic effect of GHBNa used as sodium oxybate (Somsanit) [9]. It is suspected that the GHB-$GABA_B$ receptor complex also can be formed in the ventrobasal nucleus in the thalamus and is responsible for absence seizures [1].

The hypothalamus

Administration of GHB results in activation of tyrosine hydroxylase and, as a result, the larger amount of dopamine is synthesized. Nevertheless, small doses of the drug decrease and its large doses increase secretion of dopamine [5].

Secretion of dopamine in the striatum is decreased independently of the GHB dose.

The limbic system

The limbic system is responsible for the mood. Frequent stimulation of the reward system, especially the extended amygdala, which includes the shell and the nucleus accumbens, with the same substance leads to addiction [27]. Such mechanism also concerns GHB ingestion [16].

The cerebellum

There are so few GHB receptors in the cerebellum that the effect of their stimulation is merely noticeable. What is observed in this structure is that GHB decreases the synthesis of nitric oxide, resulting in sudden reversible increase in blood pressure in the brain.

The spinal cord

Intraspinal GHB administration leads to hyperpolarization of neurons in the spinal cord [26].

The metabolic and endocrinologic effects

Inhibitory effect of GHB on the GABA-ketoglutaric acid transaminase leads to a decrease in glucose catabolism and greater tolerance of hypoxia [35]. Such an action can be considered as an advantage of GHB use in resuscitation [17].

Another effect of the drug consists in increasing the growth hormone level, which was the reason why GHB became popular among body-builders [31].

Toxicology

Only 1% of GHB is excreted with urine in the unchanged form [13]. Therefore, in order to measure its concentration in blood or urine, it is essential to use advanced chromatographic methods. One of them, using gas chromatography/mass spectrometry (GC/MS), allows to measure as small drug concentrations as 0.1 mg/l in plasma and 0.2 mg/l in urine, however, it requires conversion of GHB to γ-butyrolactone (GBL) (acidification of samples) [10]. Another GC/MS analysis, which does not require the mentioned conversion, can be used for samples within the concentration range between 0.5–2.0 mg/l [8, 18]. If a patient has ingested GBL which was partially converted to GHB in blood, it may be the easiest to use high performance liquid chromatography (HPLC) [13]. Another analytical procedure has recently been developed by Kimura et al. [15] due to the need for higher sensitivity of tests. In addition, a new ultra-rapid procedure seems promising, because a valid result of the test is accessible within 1 h [36].

GHB is rapidly metabolized to succinic semialdehyde and then to succinic acid which enters the Krebs cycle (Fig. 1) and the final metabolic products are CO_2 and H_2O. Therefore, 4–6 h after the GHB ingestion it may be impossible to measure its concentration in urine [20, 28].

Acute intoxication can be entirely cured within 6 h in cases when it does not impair respiratory activity [22].

Some dose- and blood concentration-effect relationships are summarized in Tables 1 and 2.

Chemical modifications of GHB

Trans-4-hydroxycrotonic acid (T-HCA) (I)

T-HCA was proved to be an endogenous substance in the CNS [3]. It is able to bind to the GHB receptor and it was the first compound that showed properties required for a substance to be capable of reacting with the GHB receptor. Firstly, the active form of the compound must be non-lactonic. Secondly, there is small tolerance of the distance between the carboxyl and the hydroxyl groups.

1,4-Butanediol (II)

1,4-Butanediol is much more lipophilic than GHB. Therefore, it passes through the blood-brain barrier much faster and clinical effects are observed sooner than after GHB ingestion. However, in the CNS it is transformed to GHB as it is shown in Figure 2. It should be noticed that administration of any alcohol dehydrogenase inhibitor, such as ethanol or 4-methylpyrazole, prevents the sedative effect from development after GHB ingestion. Disulfiram, which is an inhibitor of aldehyde dehydrogenase, partially abolishes the sedative effect. Therefore, it seems that 1,4-butanediol (1,4-BD) acts after being metabolized to GHB and/or to GABA [4, 38].

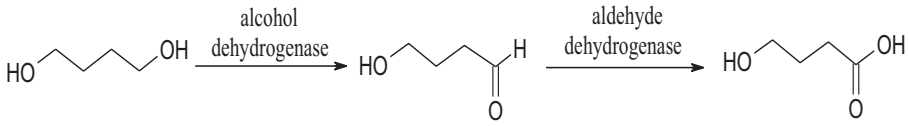
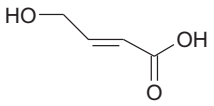
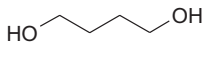


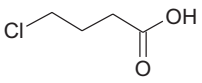
Fig. 2. 1,4-Butanediol metabolism to γ-hydroxybutyric acid



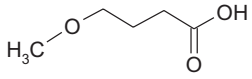
trans-4-hydroxycrotonic acid (**I**)



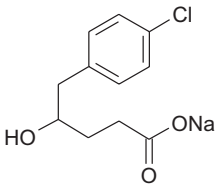
1,4-butanediol (**II**)



4-chlorobutyric acid (**III**)

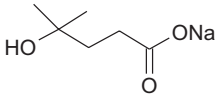


4-metoxybutyric acid (**IV**)



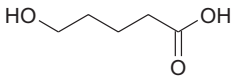
NCS-356

sodium 4-hydroxy-5-*p*-chlorophenylpentanoate (**V**)



UMB68

sodium 4-hydroxy-4-methylpentanoate (**VI**)



UMB58

5- hydroxypentanoic acid (**VII**)

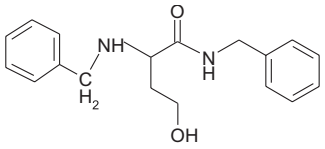
Fig. 3. GHB-related compounds

Table 1. The relationship between the dose and the effect of GHB in patients [6]

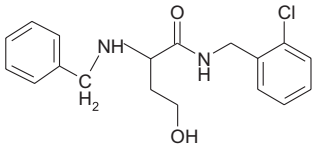
Dose (g)	Effect
below 0.7	euphoria, sociability
0.7–1.4	short amnesia
1.5–2.1	weariness and sleep
2.1–3.5	intensification of the above effects
3.5–4.9	hypnosis, hypotonia, weak analgesia

Table 2. The relationship between the GHB concentration in blood and the state of consciousness in patients [12]

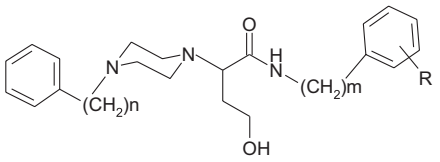
GHB concentration in blood (mg/l)	State of consciousness
over 260	patients in coma and did not react to pain stimuli
156-260	patients asleep and did react to pain stimuli
52-156	patients showed spontaneous movements and occasionally opened their eyes
below 52	patients woke up



N-benzylamide of α-(benzylamine)-γ-hydroxybutyric acid (**VIII**)



N-(*o*-chlorobenzyl)-amide of α-(benzylamine)-γ-hydroxybutyric acid (**IX**)



α-(4-Phenylpiperazine)-γ-hydroxybutyric acid and
α-(4-benzylpiperazine)-γ-hydroxybutyric acid derivatives (**X**)

n = 0 or 1
m = 1 or 2 (for m = 2 R = H)
R = H, 2-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3,4-$(OCH_3)_2$

Fig. 4. Antiepileptic derivatives of γ-hydroxybutyric acid

C_4-substituted derivatives

Both 4-chlorobutyric acid (**III**) and 4-methoxybutyric acid (**IV**) have stronger ability to cause absence seizures [21] (Fig. 3).

NCS-356, sodium 4-hydroxy-5-*p*-chlorophenylpentanoate (**V**), is a specific GHB receptor agonist used for receptor studies. However, it is rapidly metabolized in the organism [37].

The following compounds have been studied for both GHB receptor agonism and their potential metabolism [37]. Both UMB68 (**VI**) and UMB58 (**VII**) are specific GHB receptor agonists. UMB68, sodium 4-hydroxy-4-methylpentanoate, is not metabolized by oxidases due to a change in the primary alcohol group (GHB) into the tertiary one (UMB68). Therefore, it is used for GHB receptor studies. UMB58, 5-hydroxypentanoic acid, can be another compound proving the tolerance of the distance between the carboxyl and the hydroxyl group in the acid for the GHB receptor agonism.

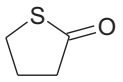
Both compounds: N-benzyl-α-(benzylamine) -γ-hydroxybutanamide (**VIII**) and N-(*o*-chlorobenzyl)-α-(benzylamine)-γ-hydroxybutanamide (**IX**) (Fig. 4) have been synthesized within the American Antiepileptic Drug Development (ADD) program and chosen as effective and the least toxic among this group of substances. Within the range of promising compounds, there are also α-(4-phenylpiperazine)-γ-hydroxybutyric acid and α-(4-benzylpiperazine)-γ-hydroxybutyric acid derivatives (**X**) [19].

Cyclic compounds

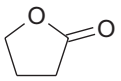
Among cyclic compounds tested for their influence on different seizures, there are γ-thiobutyrolactone (**XI**) and GBL (**XII**) (Fig. 5). The former has the potential of causing *grand mal* seizures [21] and the latter, as GHB precursor, causes *petit mal* seizures. It is suspected that GBL is first hydrolyzed to GHB in blood by the serum esterases, then the GHB passes through the blood-brain barrier and in the CNS it reacts with the GHB receptor.

NCS-382

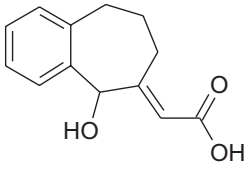
The pharmacological GHB receptor antagonist, NCS-382 (6,7,8,9-tetrahydro-5-[H]benzocyclo-hepten-5-ol-4-ylideneacetic acid) (**XIII**) (Fig. 5), and especially its (R)-isomer [7], is accessible in NIDA



γ-Thiobutyrolactone (**XI**)



γ-Butyrolactone (GBL) (**XII**)



NCS-382 (6,7,8,9 tetrahydro-5-[H]benzocyclohepten-5-ol-4-ylideneacetic acid) (**XIII**)

Fig. 5. Cyclic derivatives of GHB

(National Institute on Drug Abuse) for studies on the GHBergic system. It is able to antagonize GHB action, up to a certain GHB dose, due to the other mechanisms of action reported for GHB [24]. NCS-382 is also able to antagonize seizures of different sources other than those caused by GHB, although clinical data do not suggest that the effectiveness is always satisfactory [32].

Valproic acid and ethosuximide

The GHB dehydrogenase inhibitors, valproic acid (Depakene, Valproate, Valrelease) and ethosuximide (Zarontin), which are common antiepileptic medicines, intensify all the effects observed after administration of GHB [11, 23]. The effect is observed due to inhibited GHB metabolism.

Conclusions

The recent 40 years of studies on pharmacological aspects of GHB action in mammalian brain have brought a large amount of information concerning the GHB synaptic system and the role of its agonists in the brain. However, certain problems, such as the distribution of the GHB-$GABA_B$ complex or different sensitivity of $GABA_B$ receptors, still remain unsolved. Certain substances with proved action on the GHBergic system require further studies and much more specific data are expected. Nevertheless, the development of analytical procedures to test GHB, 1,4-BD and/or GBL is impressive as it seems to meet requirements of emergency toxicology departments.

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