

REVIEW

THE ROLE OF γ -HYDROXYBUTYRIC ACID IN THE TREATMENT OF ALCOHOLISM: FROM ANIMAL TO CLINICAL STUDIES

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Abstract — Since its discovery nearly 40 years ago, γ -hydroxybutyric acid (GHB) has attracted several waves of scientific interest due to new developments in the knowledge of its mechanisms of action and ideas for its potential use in clinical practice. Its effects have been claimed to treat different psychiatric conditions, but over time its use has become limited to a few specific situations (e.g. sedating patients in non-painful surgical procedures and narcolepsy). New interest in the drug derives from its potential use in the treatment of alcoholism. Recent studies demonstrated a marked effect of the substance in suppressing ethanol (ETOH) withdrawal symptoms and in reducing craving for alcohol, compared to other available drugs. However, GHB has to be given under very careful supervision because of its side-effects, including the risk of abuse and dependence and possible interference with the metabolic pathways of endogenous GHB and ETOH. This short review discusses these and related issues and we hope that it will stimulate further interest in GHB.

INTRODUCTION

γ -Hydroxybutyric acid (GHB), a short-chain fatty acid which closely resembles the inhibitory neurotransmitter γ -aminobutyric acid (GABA), has a number of diverse neuropharmacological and neurophysiological effects (Snead, 1977; Vayer *et al.*, 1987). Interest in this compound has arisen because it is found naturally in animal brain (Giarman and Roth, 1964), specifically in the hypothalamus and basal ganglia (Snead and Morley, 1981), in human brain (Doherty *et al.*, 1978), as well as in extraneuronal rat tissue (Nelson *et al.*, 1981). The concentrations naturally present in brain suggest a physiological role for the compound (Walters and Roth, 1977; Roth *et al.*, 1980).

Although GHB has been termed a 'GABA agonist' (Meldrum, 1981), evidence is accumulating that GHB might function as a neurotransmitter

or a neuromodulator in the mammalian central nervous system (CNS) in its own right (Benavides *et al.*, 1982; Vayer *et al.*, 1987). Moreover, GHB has been shown also to interfere with the activity of the dopamine, serotonin, acetylcholine, and opioid systems (Gessa *et al.*, 1968; Spano and Przegalinsky, 1973; Snead and Bearden, 1980).

Evidence of a relationship between the actions of ethanol (ETOH) and GHB has appeared since the late 1960s. ETOH potentiates the 'sleeping time' induced by GHB administration in mice and rats (Ban *et al.*, 1967; McCabe *et al.*, 1970). An *in vivo* action of ETOH on endogenous GHB concentration has been reported (Roth, 1970). Subsequently, acute ETOH administration in pharmacologically relevant concentrations has been shown in rats to decrease GHB in some brain areas (Poldrugo, 1987). In the past decade, the mechanism of the interaction between GHB and ETOH has become clearer and, recently, GHB has been introduced in clinical practice for alcoholism management. The present report will update the relationship between these two sub-

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stances with the aim of clarifying the potential use of GHB in the treatment of alcoholism.

GENETIC AND BIOLOGICAL INTERACTIONS

γ -Butyrolactone (GBL), a precursor of GHB (Lettieri and Fung, 1978), induced a longer loss of righting reflex (LRR) in long-sleep mice (LS-line) selectively bred for greater sensitivity to ETOH than in the less sensitive short-sleep mice (SS-line). A low dose of GBL produced biphasic effects on locomotor activity. Both the initial depressant action and the later increase in activity were greater in LS, than SS, mice (Dudek and Fanelli, 1980). These results were more recently replicated in Sardinian alcohol-preferring rats (sP), a rat line selectively bred for high preference for ETOH (Colombo *et al.*, 1998). The same line of rats showed an increased activity in GHB on the binding sites present in cortical membranes (Frau *et al.*, 1995) and a decrease in voluntary ETOH intake after ingestion of GHB in its lactone form (Fadda *et al.*, 1983). This effect was assumed to be mediated by dopamine, since GHB and its analogues, when administered to animals in doses that produce behavioural depression, cause a significant increase in brain dopamine (Gessa *et al.*, 1966). Animals addicted to ETOH for prolonged periods indeed show a tolerance to the dopaminergic effect of GBL administration (Liljequist and Engel, 1979; Nowycky and Roth, 1979).

METABOLIC INTERACTIONS

(a) Biochemical background

Formation and metabolism of GHB. The metabolic pathways of synthesis and degradation of GHB have been extensively studied in rat brain more than in the liver. The metabolic steps likely to occur are depicted in Fig. 1. In rat brain, it has been clearly demonstrated that GHB is formed from GABA *in vivo* (Gold and Roth, 1977). GABA is transaminated to succinic semialdehyde (SSA) and the latter is reduced to GHB. Different NADPH- and NADH-dependent SSA reductases responsible for GHB formation have been described (Anderson *et al.*, 1977). This is a minor metabolic route for GABA; SSA, instead,

is mainly oxidized to succinic acid (SA), which then enters the Krebs cycle.

Glutamic acid, which is transformed to GABA by L-glutamic acid decarboxylase, has been related to GHB formation in animal brain (Santaniello *et al.*, 1978). 1,4-Butanediol (1,4-BD) is also a precursor of GHB (Sprince, 1969; Snead *et al.*, 1982). Alcohol dehydrogenase (ADH) (EC 1.1.1.1.) present in liver of animals and humans has been claimed to be responsible for the conversion of 1,4-BD to GHB (Bessman and McCabe, 1972; Taberner *et al.*, 1972; Pietruszko *et al.*, 1978). However, this reaction probably involves two enzymatic steps. The first step, which is regulated by ADH, is responsible for the formation of γ -hydroxybutyraldehyde, which is then converted to GHB (Poldrugo and Snead, 1986).

GHB, once formed, disappears from brain with a half-life of 5 min. GHB (Doherty *et al.*, 1975) and 1,4-BD (Gessner *et al.*, 1960) are converted to SSA and SA. The reaction converting GHB to SSA is regulated by an NADP⁺- and NAD⁺-dependent GHB dehydrogenase of cytosolic location in brain and liver (Kaufman and Nelson, 1981). In animal and human liver, an action of ADH in the conversion of GHB to SSA has been postulated (Vree *et al.*, 1975, 1978; Poldrugo *et al.*, 1989). Finally, an SSA dehydrogenase (succinate-semialdehyde: NAD⁺ oxidoreductase; EC 1.2.1.16.) (SSADH), a highly purified enzyme responsible for the conversion of SSA to SA, has been isolated in brain (Cash *et al.*, 1977).

It is also possible that a minor GHB portion is degraded through a β -oxidative pathway to 3,4-dihydroxybutyrate (DHB) (Walkenstein *et al.*, 1964; Jakobs *et al.*, 1981).

(b) Experimental data

Studies *in vitro* of the interaction between GHB and ETOH are conflicting. ETOH and the alcohol dehydrogenase inhibitor pyrazole (PY), (Theorell *et al.*, 1969) were found to have no effect on the brain reductase responsible for the conversion of succinic semialdehyde (SSA) to GHB (Anderson *et al.*, 1977). Alcohol dehydrogenase (ADH) has been proposed to have a minimal (Tabakoff and von Wartburg, 1975) or a prominent (Taberner, 1974) action on the reduction of SSA to GHB in brain; the same enzyme does not affect the conversion of the GHB to SSA (Kerkut and

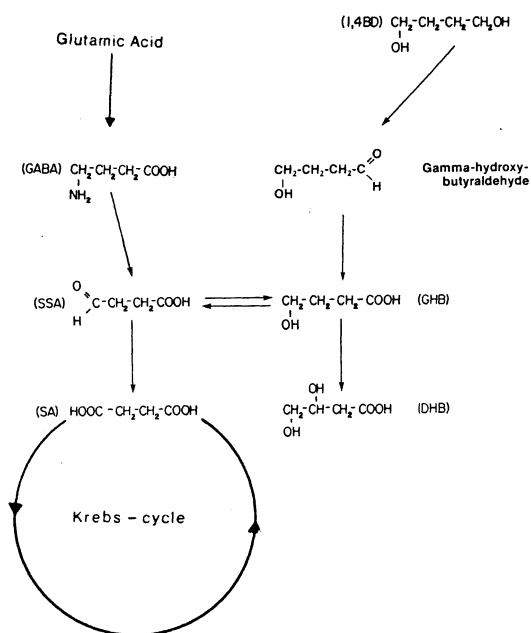


Fig. 1. Metabolic pathways of γ -hydroxybutyric acid.

Taberner, 1971). Subsequent studies have demonstrated that ETOH and PY do not interfere with the enzymes responsible for GHB formation and degradation in animal brain (Doherty *et al.*, 1975; Gold and Roth, 1977; Poldrugo and Snead, 1985). ETOH, instead, inhibits the NADH-dependent formation of GHB from SSA competitively as well as the NAD^+ -dependent degradation of GHB in the liver (and both reactions are blocked by PY), suggesting involvement of ADH (Poldrugo *et al.*, 1989). Indeed, horse liver ADH is also able to degrade GHB *in vitro* (Poldrugo *et al.*, 1989).

Another precursor of GHB is 1,4-butanediol (1,4-BD) (Sprince, 1969; Snead *et al.*, 1982). This substance is present in animal neural and extraneural tissues (Bergelson *et al.*, 1966; Snead *et al.*, 1986) and in humans (Barker *et al.*, 1985). The metabolic source of 1,4-BD is unknown. Exogenously administered 1,4-BD is quickly converted to GHB (Poldrugo and Snead, 1984a). ETOH was found to inhibit GHB formation from 1,4-BD in rat brain and liver homogenates (Poldrugo and Snead, 1986). Although ADH is responsible for this reaction in animal and human liver (Bessman and McCabe, 1972; Taberner *et al.*, 1972;

Pietruszko *et al.*, 1978), in rat brain an enzyme other than ADH is involved, since the reaction is competitively inhibited by ETOH and not by PY (Poldrugo and Snead, 1986).

In vivo, GHB and ETOH interact both in animals and humans. Chronic ETOH ingestion in rats increases the endogenous GHB content in the liver, but not in the brain (Poldrugo and Snead, 1984b). Contrary to what has been reported previously (Roth, 1970), there is no effect in the brain, except in the striatum, where its content is decreased after acute ETOH administration (Poldrugo, 1987). ETOH also exerts an action on 1,4-BD concentrations. Continuous ETOH administration increases endogenous 1,4-BD liver content in rats (Poldrugo *et al.*, 1985a); acute ETOH administration, instead, decreases GHB concentration following 1,4-BD administration in rats (Poldrugo and Snead, 1984a) and Rhesus monkeys (Vree *et al.*, 1975).

In humans, GHB administration *per os* has been reported to increase the concentration of endogenous ETOH present in the blood of detoxified male chronic alcoholics (Burov *et al.*, 1983). This is a natural compound, which has been implicated in the mechanism of action of ETOH in animals (Liopo *et al.*, 1991; Poldrugo *et al.*, 1991) and humans (Ostrovsky, 1986; Ostrovsky *et al.*, 1989). The degradation time of either GHB or ETOH when administered simultaneously is also prolonged in alcoholics (Vree *et al.*, 1976; Hoes *et al.*, 1978), an action attributed to competition for liver ADH (Vree *et al.*, 1975, 1978) in which the circadian rhythm is still preserved (Hoes *et al.*, 1981).

PHARMACOLOGICAL INTERACTION

The pharmacological profiles of GHB and ETOH show a close similarity. Both drugs exert dose-dependent biphasic effects, ranging from locomotor stimulation to sedation (Maitre, 1997) and possess anxiolytic (Krsiak *et al.*, 1974) and reinforcing (Koob *et al.*, 1994) properties. Furthermore, GHB and ETOH have similar discriminative stimulus effects, as demonstrated by symmetrical generalization in a recent drug discrimination study (Colombo *et al.*, 1995).

In animals, some authors have shown that the administration of GHB inhibits the behavioural

effects produced by low doses of ETOH (Cott *et al.*, 1976; Liljequist *et al.*, 1980). Higher doses of ETOH potentiate the behavioural effects of GHB and GBL, as measured by the duration of 'sleeping time' (Ban *et al.*, 1967; McCabe *et al.*, 1970). Pre-treatment of mice with GHB has been shown to decrease the dose of ETOH required for anaesthesia without increasing toxicity (Serebryakov, 1965).

In humans, low doses of GHB and ETOH have been reported to have more of an additive than a synergistic effect (Mattila *et al.*, 1978). In pharmacokinetic studies, higher doses of GHB were able to inhibit the elimination rate of ETOH (Vree *et al.*, 1978). This could explain the respiratory arrest which has been more recently reported after the ingestion of GHB and heavy ETOH intake (Einspruch and Clark, 1992).

PY increases the behavioural effects of GHB (Benton *et al.*, 1974), but decreases the behavioural effects of 1,4-BD (Bessman and McCabe, 1972; Taberner *et al.*, 1972). Prior administration of ETOH is able to suppress 1,4-BD conversion to GHB as assessed through behavioural, electrical, biochemical, and toxicological investigations (Poldrugo and Snead, 1984a).

TOXICOLOGICAL EFFECTS

The most relevant effects of GHB are the marked electroencephalographic (EEG) and behavioural changes produced in animals. These changes consist of a 'trance-like' state associated with paroxysmal electrical activity. This was initially thought to represent a 'sleep' state (Helrich *et al.*, 1964), but evidence has accumulated indicating that the EEG and behavioural changes induced by GHB represent a form of seizure, rather than sleep which Winters and Spooner (1965) subsequently called 'non-convulsive seizure'. Since then, studies have demonstrated that GHB-induced stupor and LRR were associated with spiking on the EEG and 'petit mal' epilepsy (Snead *et al.*, 1976). A role for GHB, as for other short-chain fatty acids, in the pathogenesis of coma accompanying hepatic encephalopathy (where stupor is seen with striking EEG changes), and also in pathologic sleep (e.g. Kline-Levin syndrome) and neurological diseases (e.g. Huntington's chorea) has also been suggested (Snead, 1977; Roth *et al.*, 1979). More strikingly,

GHB has been implicated in an inborn error of metabolism with marked mental retardation and abnormal urinary GHB output (Jakobs *et al.*, 1981; Divry *et al.*, 1983).

The LD₅₀ of GHB (and 1,4-BD) varies from 1 to 2 g/kg body wt (Laborit, 1964; Sprince, 1969; Vickers, 1969). There are no data regarding histological damage after acute (Marcus *et al.*, 1967) or chronic (Nowycky and Roth, 1979) GHB administration. However, the use of the substance as a health food to promote body building led to several cases of poisoning in humans (Food and Drug Administration Agency, 1991a,b; Thomas *et al.*, 1997). Side-effects depended on dosage and included drowsiness, hypnagogic state, amnesia, involuntary movements, 'seizure-like' activities, and a comatose state. The severity of symptoms was potentiated by the presence of ETOH.

The acute (Hinrichs *et al.*, 1948) and chronic (Knyshova, 1968) administration of 1,4-BD, the precursor most suitable for GHB experiments, instead, results in histological damage to brain, liver, and kidney. Simultaneous administration of ETOH potentiates this toxic effect and a role for endogenous 1,4-BD in contributing to the toxic effects of ETOH has been postulated (Poldrugo *et al.*, 1985a,b).

CLINICAL STUDIES

(a) GHB use in conditions other than alcoholism

Great clinical interest arose in the 1960s when the GHB molecule was introduced as a novel anxiolytic drug. Its use was proposed, through uncontrolled clinical studies, in anxiety and depressive disorders (Danon-Boileau *et al.*, 1962; du Couedic *et al.*, 1964; Rinaldi *et al.*, 1967) and in psychotic patients (Tanaka *et al.*, 1966). Since then, its use has been restricted to sedating patients in non-painful surgical procedures (Vickers, 1969; McLennan and Parry, 1983) and in the treatment of narcolepsy (Mamelak *et al.*, 1986).

(b) GHB use in alcoholism

Several preclinical studies stimulated researchers to investigate the possible use of GHB in the clinical treatment of ETOH addiction. GHB has been shown to inhibit voluntary ETOH consumption in sP rats (Fadda *et al.*, 1983), and suppress tremors and convulsions following acetaldehyde administration in mice (Andronova and Barkov,

1981) and ETOH withdrawal in physically alcohol-dependent rats (Poldrugo and Snead, 1984a; Fadda *et al.*, 1989).

In humans, a double-blind study demonstrated that oral administration of a low dose (50 mg/kg body wt) was very effective in suppressing the ETOH withdrawal syndrome (Gallimberti *et al.*, 1989). The same research group, later, showed that short-term treatment with GHB *per os* (50 mg/kg divided into 3 daily doses for 3 months) was more effective than placebo in increasing the number of abstinent days and in reducing the number of daily drinks and signs of ETOH craving in alcoholic patients (Gallimberti *et al.*, 1992).

A neurotransmitter/neuromodulator function of GHB, mimicking the central effects of ETOH, was proposed indicating the same rationale for using GHB in the treatment of alcoholism as in the use of methadone for heroin addiction. GHB has also been tested in a very preliminary study conducted in ETOH and heroin addicts (Zolesi *et al.*, 1994).

More recently, the same dosage of GHB has been given to alcoholics for 6 months (Addolorato *et al.*, 1995) followed by a 1-year drug-free period (Addolorato *et al.*, 1996). Abstinence from ETOH and craving were considered as outcome measures. At the same time, tolerability and safety of the drug were tested. The presence of the drug improved the abstinence rate during the 6-month treatment period and this effect continued during the drug-free period. The drug was safe in general and this was confirmed by the improvement in values of laboratory markers of alcoholism (Addolorato *et al.*, 1997a). Side-effects of vertigo, increased sleepiness, and fatigue were reported in 30% of patients, but these resolved after 2–3 weeks of GHB use and did not recur thereafter.

The optimal dosage of the drug is not yet defined since GHB absorption and elimination are capacity-limited both in experimental animals and alcoholic patients (Vree *et al.*, 1978; Arena and Fung, 1980; Ferrara *et al.*, 1992). The first-pass metabolism is also strongly implicated in the apparently poor oral bioavailability of GHB (Lettieri and Fung, 1976). Very recent studies have demonstrated the advantage of the further partition of the total dose of GHB into six instead of three daily doses in non-respondent alcoholics (Addolorato *et al.*, 1998a,b). A more rational way to overcome this limitation would be to adjust the drug regime to the individual GHB degradation

curve (or to find other ways of predicting GHB metabolism); or by producing a sustained-release form of GHB.

(c) Potential of abuse

In animals, both GHB and ETOH exert dose-dependent biphasic effects. Low doses of GHB produce euphoria in humans, but higher doses produce sedation. Although the drug, at the doses used for the treatment of alcoholism, is well tolerated, its euphoric effects make it attractive as a drug of abuse.

In fact, a craving for GHB in weaning alcoholics using low doses and resulting in 10% of subjects abusing the drug, with a voluntary increase of dosage six to seven times the recommended levels, has been reported in controlled studies (Addolorato *et al.*, 1996; 1997b). In these cases, if the abuse of GHB was reported immediately by the family members and the drug withdrawn or reinstated at the dosage previously planned, patients reported signs of mild anxiety and insomnia disappearing in about 1 week. Thus, these observations support the potential efficacy of GHB in alcoholism management, but suggest its use under strict clinical surveillance and supervision by members of the family and of alcohol rehabilitation programmes. Because of the risk of abuse, the dosage of the drug should not be increased (e.g. in non-responders).

Recently, others have published a number of case reports on GHB abuse and physical dependence after the drug was wrongly assumed to induce euphoric, sedative, and anabolic effects (Galloway *et al.*, 1997).

GENERAL CONCLUSIONS AND COMMENTS

Evidence has accumulated on the very close similarities of actions exerted by ETOH and GHB on the CNS. Although the precise scientific basis of these similarities has yet to be defined, they have been corroborated by biochemical, genetic, physiological, and pharmacological studies.

Endogenous alcohols are a natural target of ADH in animals and humans. One of these is 1,4-BD which is also a minor source of GHB. Both substances are normally present in humans and both are substrates for ADH in the liver. Results derived from research (Poldrugo *et al.*, 1985b) and reconsideration of previous lethal

experiences using 1,4-BD (Hinrich *et al.*, 1948) have definitely discouraged the use of this diol as a prodrug for the treatment of alcoholics. The last experimental use of the substance was 20 years ago (van Dalen *et al.*, 1978).

Among available drugs, GHB has remarkable effects in suppressing the ETOH withdrawal syndrome (Poldrugo, 1997) and in reducing craving for alcohol in humans (Gallimberti *et al.*, 1992; Addolorato *et al.*, 1996). The clinical studies available at present indicate that GHB could have an important role in the treatment of alcoholism. However, the use of GHB beyond the detoxification period must be approached with caution and under clinical monitoring.

The simple structure of GHB (and its limited patentability) have until recently discouraged drug companies from conducting appropriate clinical trials. Interestingly, the same reasons (being a natural and inexpensive compound), prompted its use in alcoholics in the former Soviet Union. However, the intake of GHB (*per os* in a syrup formulation) has been limited by the observation that it quickly led to dependence (Y. N. Burov, personal communication). These addictive properties have recently been confirmed in the United States. In addition, the presence of epilepsy and/or the concomitant use of anti-epileptic drugs should be ascertained carefully (as contraindications) before using GHB.

Another aspect to take into consideration is that of genetics. The data accumulated in animals on the genetic background of the relationship between ETOH and GHB actions could have implications for humans. Some subjects may have differences in binding sites for GHB which are regulated genetically. Others may differ in GHB metabolism, e.g. because of differences in liver and gastric ADH; in the latter case with evident gender implications. Future research should better define if alcoholics differ in responses to GHB (e.g. looking at individual EEG responses to GHB or GHB metabolism) with the aim of characterizing the subgroups of alcoholics who would benefit more from the drug.

Another reason for concern is the difficulty in defining the optimal GHB regime because of its short-lived effects and due to the fact that ADH and other liver enzymatic activities are altered in alcoholics. The long-term use of GHB in alcoholics could interfere with endogenous 1,4-BD

metabolism leading to possible effects which have not yet been tested experimentally. Also, there is the assumption that concomitant intake of ETOH and GHB could increase the concentration of both compounds in the body with consequent potentiation of effects. Taking into account the metabolism of the drug, a slow release form of GHB with a prolonged action could increase the rate of positive outcome in alcoholism treatment.

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