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Review Article

HISTORY OF SODIUM OXYBATE – A REVIEW

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ABSTRACT

Gamma Hydroxybutyric acid (GHB), also known as 4-hydroxybutanoic acid and sodium oxybate is a naturally occurring substance found in the human central nervous system as well as in wine, beef, small citrus fruits, and almost all animals in small amounts. It is also categorized as an illegal drug in many countries. It is currently regulated in Australia and New Zealand, Canada, most of Europe and in the US.

Key Words: Gamma Hydroxybutyric acid (GHB), 4-hydroxybutanoic acid, Sodium oxybate, History.

INTRODUCTION

GHB as the sodium salt, known as sodium oxybate, is sold by Jazz Pharmaceuticals under the name Xyrem to treat cataplexy and excessive daytime sleepiness in patients with narcolepsy. GHB has been used in a medical setting as a general anesthetic, to treat conditions such as insomnia, clinical depression, narcolepsy, and alcoholism, and to improve athletic performance. It is also used as an intoxicant (illegally in many jurisdictions) or as a date rape drug.GHB is naturally produced in the human body's cells and is structurally related to the ketone body beta-hydroxybutyrate. As a supplement/drug, it is used most commonly in the form of a salt, for example sodium gamma-hydroxybutyrate (Na.GHB, sodium oxybate, or under the brand name Xyrem.) or potassium gamma-hydroxybutyrate (K.GHB, potassium oxybate). GHB is also produced as a result of fermentation, and so is found in small quantities in some beers and wines.

Succinic semialdehyde dehydrogenase deficiency is a disease that causes GHB to accumulate in the blood. Sodium oxybate (Xyrem) is the sodium salt of gamma hydroxybutyrate (GHB). Xyrem 500mg/ml solutions licensed for the treatment of cataplexy in adult patients with narcolepsy. Cataplexy is an abrupt, reversible decrease in muscle tone caused by emotion, reported by approximately 75%of patients with narcolepsy. The term narcolepsy is used to describe a syndrome comprising of symptoms: cataplexy, hypnologic hallucinations and sleep paralysis Sodium oxybate is indicated for the treatment of cataplexy in adult patients with narcolepsy. It is considered to act in a different way to the only other the licensed medication, clomipramine, for this indication. Cataplexy is an abrupt, reversible decrease in muscle tone caused by emotion and is reported in approximately 75% of patients with narcolepsy.

Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB) and is a schedule 4 (part 1 CD Benz) controlled drug in the UK. Sodium oxybate is associated with dose-related improvements in the symptoms of narcolepsy and reductions in the number of attacks of cataplexy. The most significant improvements/reductions were seen in patients taking 9g/day. These effects have been demonstrated for treatment periods of 12 months or longer. The most commonly reported adverse effects of sodium oxybate included headache, nausea and dizziness. No withdrawal effects were seen in trials. Abrupt withdrawal leads to a gradual increase in the number of cataplexy attack.

Oxybate (GHB) is a metabolite of γ-aminobutyric acid (GABA) which is synthesised and accumulated by neurons in the brain. It is present at μM concentrations in all brain regions investigated as well as in several peripheral organs, particularly in the gastro-intestinal system. Neuronal depolarization releases GHB into the extracellular space in a Ca2+-dependent manner. A family of GHB receptors in rat brain have been identified and cloned and most probably belong to the G-protein-coupled receptors. High-affinity receptors for GHB are present only in neurones, with a restricted specific distribution in the

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hippocampus, cortex and dopaminergic structure so frat brain.

In general, stimulation of these receptors with low (physiological) amounts of GHB induce hyperpolarisation in dopaminergic structures with a reduction of dopamine release. However, in the hippocampus and frontal cortex, GHB seems to induced polarization with an accumulation of Cgmp and an increase in inositol phosphate turnover. However, at higher (therapeutic) exposures, GHB receptors are saturated and probably desensitized and down regulated. Such GHB dopaminergic hyperactivity, strong sedation with anaesthesia and EEG changes those are consistent with normal sleep. The pathogenesis of narcolepsy is still unknown, but an imbalance between monoamines and acetylcholine is generally accepted.

Recent research has found a marked reduction of the neuropeptide hypocretin type 1 in the cerebrospinal fluid of a majority of patients and a global loss of hypocretins in postmortem brain tissue of narcoleptic subjects. The hypocretins are synthesized by a small group of neurons predominantly located in the lateral hypothalamic and perifornical regions of the hypothalamus. The hypothalamic system directly and strongly innervates and potently excites noradrenergic, dopaminergic, serotoninergic, histaminergic and cholinergic neurones.

The effect of GHB on this system has not been investigated. However, the available data indicate that its mode of action is likely to relate to non-specific dopaminergic stimulation rather than the hypocretin system. Formal nonclinical pharmacology studies to investigate the primary pharmacodynamics have not been conducted by the applicant, rather a comprehensive review of the scientific literature has been conducted. The publications included have been selected based on their relevance to the proposed indications, based on evidence of efficacy from early clinical studies.

In addition, animal models of cataplexy and narcolepsy are continuing to be developed, but have not yet been fully validated. Little nonclinical information is available on its effects on narcolepsy in general, and cataplexy in particular. Available, directly relevant data, from the published literature, has been reviewed but the current understanding of the role of GHB in the CNS does not provide a mechanistic explanation of the positive clinical effects reported in the dossier.

GHB had no effect on cataplexy in dogs with hereditary narcolepsy when administered as a single dose of 500mg/kg i.v. or 50mg/kg/day p.o. for 3 consecutive days. However, although such dogs have amutation of the type 2 hypocretin receptor, the clinical relevance of this model remains to be established. Moreover, a dose of 75mg/kg/day for atleast 14 days is required for efficacy in humans. Though the precise mode of action is unknown, these sedative properties of GHB and its effects on sleep may play a role in the efficacy observed in humans. Evidence from a human clinical study (Study OMC-SXB-20) where GHB was administered to narcoleptic patients and overnight poly somno grams(PSG) were recorded, suggests that GHB modifies sleep architecture, specifically a dose-related increase in Stage 3 & 4 slow wave sleep (SWS, deltasleep). The cause of human narcolepsy and cataplexy is, as yet, unknown. Recent evidence points to the loss of hypocretin-containing neurones, possibly due to autoimmune attack, as a likely cause (Scammell 2003). Hypocretin is a neuro transmitter that has roles amongst others, in sleep-wake regulation. Alterations in hypocretin neurotransmission have also been observed in mouse and models of narcolepsy, although no studies have been undertaken with GHB in these models.

GHB reaches much higher concentrations in the brain and activates GABAB receptors, which are primarily responsible for its sedative effects. GHB receptors are densely expressed in many areas of the brain, including the cortex and hippocampus, and these are the receptors that GHB displays the highest affinity for. There has been somewhat limited research into the GHB receptor; however, there is evidence that activation of the GHB receptor in some brain areas results in the release of glutamate, the principal excitatory neurotransmitter. Activation of both the GHB receptor and GABA (B) is responsible for the addictive profile of GHB. GHB's effect on dopamine release is biphasic, low concentrations stimulate dopamine release via the GHB receptor Higher concentrations inhibit dopamine release via GABA(B) receptors as do other GABA(B) agonists such as baclofen. After an initial phase of inhibition, dopamine release is then increased via the GHB receptor. This explains the paradoxical mix of sedative and stimulatory properties of GHB, as well as the so-called "rebound" effect, experienced by individuals using GHB as a sleeping agent, where in they awake suddenly after several hours of GHB-induced deep sleep. That is to say that, overtime, the concentration of GHB in the system decreases below the threshold for significant GABAB receptor activation and activates predominantly the GHB receptor, leading to wakefulness [1-5].

Medical use

The only common medical applications for GHB today are in the treatment of narcolepsy and more rarely alcoholism [6,7]. GHB is the active ingredient in a prescription medication called Xyrem (sodium oxybate). Xyrem is approved by the U.S. Food and Drug Administration (FDA) for the treatment of cataplexy associated with narcolepsy [8] and Excessive Daytime Sleepiness (EDS) associated with narcolepsy.

Recreational use

GHB is a CNS depressant used as an intoxicant.[9,10] It has many street names, including "Georgia Home Boy", "Juice", "Liquid Ecstasy", "Mils", "G", "Liquid X", and "Liquid G", as well as "Fantasy" and the reordered initialism GBH. Its effects have been described anecdotally as comparable with alcohol and

ecstasy use, such as euphoria, disinhibition, enhanced sensuality and empathogenesis. At higher doses, GHB may induce nausea, dizziness, drowsiness, agitation, visual disturbances, depressed breathing, amnesia, unconsciousness, and death. The effects of GHB can last from 1.5 to 3 hours, or even longer if large doses have been consumed [11]. Consuming GHB with alcohol is dangerous as it can lead to vomiting in combination with unrouseable sleep, a potentially lethal combination [12].

In general, the doses used recreationally are between 500 mg and 3,000 mg. When used as a recreational drug, GHB may be found as the sodium or potassium salt, which is a white crystalline powder, or as GHB salt dissolved in water to form a clear solution. The sodium salt of GHB has a salty taste [11]. Other salt forms such as calcium GHB and magnesium GHB have also been reported, but the sodium salt is by far the most common.

Some chemicals convert to GHB in the stomach and blood stream. GBL, or gamma-butyrolactone, is one such prodrug. Other prodrugs include 1,4-butanediol. There may be additional toxicity concerns with these precursors. 1,4-B and GBL are normally found as pure liquids, although they may be mixed with other more harmful solvents when intended for industrial use, e.g., as paint stripper or varnish thinner.

GHB can be easily manufactured at home with very little knowledge of chemistry, as it only involves the mixing of its two precursors, GBL and an alkali hydroxide (such as sodium hydroxide) to form the resulting GHB salt. Due to the ease of manufacture and the availability of its precursors, its production is not done in relatively few illicit laboratories like most other synthetic drugs, but in private homes by low level producers instead. While available as a prescription for rare and severe forms of sleep disorders such as narcolepsy in some other countries, notably most of Europe, GHB was banned (in the U.S.) by the FDA in 1990. However, on 17 July 2002, GHB was approved for treatment of cataplexy, often associated with narcolepsy. GHB is "colourless and odorless" [13].

Club and rave scene use

GHB is often taken because users find that it enhances their experiences of being in a club, party, or rave; small doses of GHB can act as a stimulant and aphrodisiac. GHB is sometimes referred to as G, liquid ecstasy, liquid X, or liquid E due to its tendency to produce euphoria and sociability and its use in the dance party scene [14]. Despite this nickname, GHB has entirely separate chemical and pharmacological modes of action compared to ecstasy.

Sports and athletics

FDA warning against products containing GHB and its prodrugs.

Some athletes also use GHB, as GHB has been shown to elevate human growth hormone in vivo.[15] The growth hormone elevating effects of GHB are mediated through muscarinic acetylcholine receptors and can be prevented by prior administration of pirenzepine, a muscarinic acetylcholine receptor blocking agent [16].

As certain succinate salts have been shown to elevate growth hormone in vitro [17] and because GHB is metabolized into succinate some people have suggested this may play a role in the growth hormone elevations from GHB. There is however currently no evidence to show that succinate plays any role in the growth hormone elevations from GHB.

As a date rape drug

Like alcohol and potent benzodiazepines such as Rohypnol (the trade name of a potent hypnotic benzodiazepine, flunitrazepam), GHB has been labeled as a date rape drug [6]. The sodium form of GHB has an extremely salty taste but, as it is colourless and odorless [13], it has been described as "very easy to add to drinks"[13] that mask the flavor. GHB has been used in cases of drug-related sexual assault, usually when the victim is vulnerable due to intoxication with a sedative, generally alcohol [18]. It is difficult to establish how often GHB is used to facilitate rape as it is difficult to detect in a urine sample after a day, and many victims may not recall the rape until sometime after this [19][20], although GHB can be detected in hair [21]. Hair testing can be a useful tool in court cases and/or for the victim's own information. Over-the-counter urine test kits only test for date rape drugs that are benzodiazepines, which GHB is not. To detect GHB in urine, the sample must be taken within 8–12 hours of GHB ingestion, and cannot be tested at home. GHB can be detected in hair for months after GHB ingestion. Other drugs, such as muscle relaxers (Carisoprodol for example) are sometimes mixed with GHB. Therefore, it can be beneficial to request that the hair sample is tested for multiple drugs.

There have been several high profile cases of GHB as a date rape drug that receive national attention. In early 1999 a 15 year old girl, Samantha Reid of Rockwood, MI, died from GHB poisoning. Reid's death inspired the legislation titled the "Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000." This is the law that made GHB a schedule 1 controlled substance [22].

GHB, produced as a sodium salt (sodium oxybate), may provide a noticeable salty character to the drink, although individual sensitivity to the taste of salt varies.[23] GHB can also be produced as different salts, some of which may not have a taste as distinctive as the sodium salt (e.g., magnesium oxybate), or much less commonly in the unstable free-acid form [24].

Adverse effects

Combination with alcohol

In humans, GHB has been shown to inhibit the elimination rate of alcohol. This may explain the respiratory arrest that has been reported after ingestion of both drugs [25]. A review of the details of 194 deaths

attributed to or related to GHB over a ten-year period found that most were from respiratory depression caused by interaction with alcohol or other drugs [26].

Reported deaths

One report has suggested that Xyrem (pharmaceutical GHB, or "Sodium Oxybate") overdose may be fatal, based on deaths of three patients who had been prescribed the drug [27]. However, for two of the three cases, post-mortem GHB concentrations were 141 and 110 mg/L, which is within the expected range of concentrations for GHB after death, and the third case was a patient with a history of intentional drug overdose [28].

One publication has investigated 226 deaths attributed to GHB [29]. Of 226 deaths included, 213 suffered cardiorespiratory arrest and 13 suffered fatal accidents. Seventy-one deaths (34%) had no co-intoxicants. Postmortem blood GHB was 18–4400 mg/L (median=347) in deaths negative for co-intoxicants.

GHB is produced in the body in very small amounts, and blood levels may climb after death to levels in the range of 30–50 mg/L.[30] Levels higher than this are found in GHB deaths. Levels lower than this may be due to GHB or to postmortem endogenous elevations.

A UK parliamentary committee commissioned report found the use of GHB to be less dangerous than tobacco and alcohol in social harms, physical harm and addiction [31].

Treatment of overdose

Overdose of GHB can be difficult to treat because of its multiple effects on the body [5,32,33]. GHB tends to cause rapid unconsciousness at doses above 3500 mg, with single doses over 7000 mg often causing life-threatening respiratory depression, and higher doses still inducing bradycardia and cardiac arrest. Other side-effects include convulsions (especially when combined with stimulants), and nausea/vomiting (especially when combined with alcohol) [10].

The greatest life threat due to GHB overdose (with or without other substances) is respiratory arrest [2,10]. Other relatively common causes of death due to GHB ingestion include aspiration of vomitus, positional asphyxia, and trauma sustained while intoxicated (e.g., motor vehicle accidents while driving under the influence of GHB).[citation needed] The risk of aspiration pneumonia and positional asphyxia risk can be reduced by laying the patient down in the recovery position. People are most likely to vomit as they become unconscious, and as they wake up. It is important to keep the patient/friend awake and moving, plus do not allow them to be alone as death through vomiting can easily happen. Frequently they will be in a good mood but this does not mean they are not in danger. GHB overdose is a medical emergency and immediate assessment in an emergency department is needed.

Convulsions from GHB can be treated with diazepam or lorazepam,[10] even though these are also CNS depressants they are GABAA agonists, whereas GHB is primarily a GABAB agonist, so the benzodiazepines do not worsen CNS depression as much as might be expected [citation needed].

Because of the faster and more complete absorption of GBL relative to GHB, its dose-response curve is steeper, and overdoses of GBL tend to be more dangerous and problematic than overdoses involving only GHB or 1,4-B. Any GHB/GBL overdose is a medical emergency and should be cared for by appropriately trained personnel.

A newer synthetic drug SCH-50911, which acts as a selective GABAB antagonist, quickly reverses GHB overdose in mice [34]. However, this treatment has yet to be tried in humans, and it is unlikely that it will be researched for this purpose in humans due to the illegal nature of clinical trials of GHB, and the lack of medical indemnity coverage inherent in using an untested treatment for a life-threatening overdose [original research?].

Detection of use

GHB may be quantitated in blood or plasma to confirm a diagnosis of poisoning in hospitalized patients,[10] provide evidence in an impaired driving arrest or to assist in a medicolegal death investigation. Blood or plasma GHB concentrations are usually in a range of 50–250 mg/L in persons receiving the drug therapeutically (during general anesthesia), 30–100 mg/L in those arrested for impaired driving, 50–500 mg/L in acutely intoxicated patients and 100–1000 mg/L in victims of fatal overdosage. Urine is often the preferred specimen for routine drug abuse monitoring purposes. Both gamma-butyrolactone (GBL) and 1,4-butanediol are converted to GHB in the body [35-37].

Neurotoxicity

In multiple studies, GHB has been found to impair spatial and working learning and memory in rats with chronic administration [38-41]. These effects are associated with decreased NMDA receptor expression in the cerebral cortex and possibly other areas as well [38].

Pedraza et al. (2009) found that repeated administration of GHB to rats for 15 days drastically reduced the number of neurons and non-neuronal cells in the CA1 region of the hippocampus and in the prefrontal cortex. With doses of 10 mg/kg of GHB, they were decreased by 61% in the CA1 region and 32% in the prefrontal cortex, and with 100 mg/kg, they were decreased by 38% and 9%, respectively. It is interesting to note that GHB has biphasic effects on neuronal loss, with lower doses (10 mg/kg) producing the most neurotoxicity, and higher doses (100 mg/kg) producing less.

Pretreatment with NCS-382, a GHB receptor antagonist, prevents both learning/memory deficits and neuronal loss in GHB-treated animals, suggesting that

GHB's neurotoxic actions are mediated via activation of the GHB receptor [41]. In addition, the neurotoxicity appears to be caused by oxidative stress [41-43].

Addiction

Although there have been reported fatalities due to GHB withdrawal, reports are inconclusive and further research is needed [44]. Addiction occurs when repeated drug use disrupts the normal balance of brain circuits that control rewards, memory and cognition, ultimately leading to compulsive drug taking [45,46].

Colombo reports that rats forced to consume massive doses of GHB will intermittently prefer GHB solution to water, but notes that "no rat showed any sign of withdrawal when GHB was finally removed at the end of the 20-week period" or during periods of voluntary abstinence [47,48].

Withdrawal

GHB has also been associated with a withdrawal syndrome of insomnia, anxiety, and tremor that usually resolves within three to twenty-one days [44,49,10]. The withdrawal syndrome can be severe producing acute delirium and may require hospitalization in an intensive care unit for management [10]. The mainstay of treatment for severe withdrawal is supportive care and benzodiazepines for control of acute delirium, but larger doses are often required compared to acute delirium of other causes (e.g. > 100 mg/d of diazepam). Baclofen has been suggested as an alternative or adjunct to benzodiazepines based on anecdotal evidence and some animal data [50]. However, there is less experience with the use of baclofen for GHB withdrawal, and additional research in humans is needed. Baclofen was first suggested as an adjunct because benzodiazepines do not affect GABAB receptors and thus have no cross-tolerance with GHB while baclofen, which works via GABAB receptors, is cross-tolerant with GHB and may be more effective in alleviating withdrawal effects of GHB [51].

GHB withdrawal is not widely discussed in text books and some psychiatrists, general practitioners, and even hospital emergency physicians may not be familiar with this withdrawal syndrome [52].

Endogenous production

Cells produce GHB by reduction of succinic semialdehyde via the enzyme succinic semialdehyde dehydrogenase. This enzyme appears to be induced by cAMP levels [53], meaning substances that elevate cAMP, such as forskolin and vinpocetine, may increase GHB synthesis and release. People with the disorder known as succinic semialdehyde dehydrogenase deficiency, also known as gamma-hydroxybutyric aciduria, have elevated levels of GHB in their urine, blood plasma and cerebrospinal fluid [54].

The precise function of GHB in the body is not clear. It is known, however, that the brain expresses a large amount of receptors that are activated by GHB [55]. These receptors are excitatory and not responsible for the sedative effects of GHB – they have been shown to elevate the principle excitatory neurotransmitter—glutamate [56]. The benzamide antipsychotics—amisulpride, sulpiride—have been shown to bind to this receptor in vivo [57]. Other antipsychotics were tested and were not found to have an affinity for this receptor. It is a precursor to GABA, glutamate, and glycine in certain brain areas [58]. GHB has neuroprotective properties and has been found to protect cells from hypoxia [59].

Natural fermentation by-product

GHB is also produced as a result of fermentation and so is found in small quantities in some beers and wines, in particular fruit wines. However, the amount of GHB found in wine is insignificant and not sufficient to produce any effects [60].

Pharmacology

GHB has at least two distinct binding sites [61] in the central nervous system. GHB is an agonist at the newly characterized GHB receptor, which is excitatory [62,63] and it is a weak agonist at the GABAB receptor, which is inhibitory [63]. GHB is a naturally occurring substance that acts in a similar fashion to some neurotransmitters in the mammalian brain [64]. GHB is probably synthesized from GABA in GABAergic neurons, and released when the neurons fire.[63] If taken orally, GABA itself does not effectively cross the blood-brain-barrier [65].

GHB induces the accumulation of either a derivative of tryptophan or tryptophan itself in the extracellular space, possibly by increasing tryptophan transport across the blood–brain barrier. The blood content of certain neutral amino-acids, including tryptophan, is also increased by peripheral GHB administration. GHB-induced stimulation of tissue serotonin turnover may be due to an increase in tryptophan transport to the brain and in its uptake by serotonergic cells. As the serotonergic system may be involved in the regulation of sleep, mood, and anxiety, the stimulation of this system by high doses of GHB may be involved in certain neuropharmacological events induced by GHB administration.

However, at therapeutic doses, GHB reaches much higher concentrations in the brain and activates GABAB receptors, which are primarily responsible for its sedative effects [66]. GHB's sedative effects are blocked by GABAB antagonists.

The role of the GHB receptor in the behavioural effects induced by GHB is more complex. GHB receptors are densely expressed in many areas of the brain, including the cortex and hippocampus, and these are the receptors that GHB displays the highest affinity for. There has been somewhat limited research into the GHB receptor; however, there is evidence that activation of the GHB receptor in some brain areas results in the release of glutamate, the principal excitatory neurotransmitter [56].

Drugs that selectively activate the GHB receptor cause absence seizures in high doses, as do GHB and GABA (B) agonists [67].

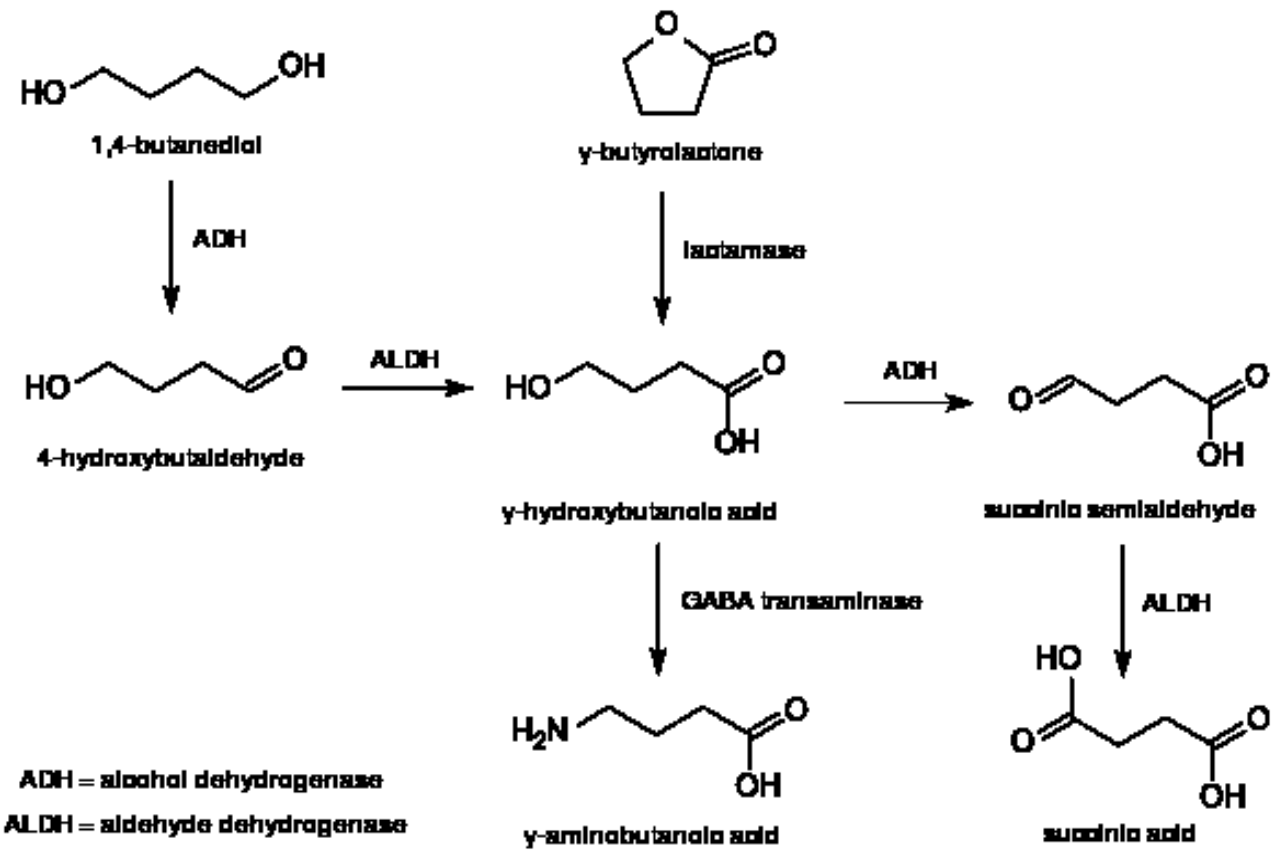
Activation of both the GHB receptor and GABA (B) is responsible for the addictive profile of GHB. GHB's effect on dopamine release is biphasic [68]. Low concentrations stimulate dopamine release via the GHB receptor [69]. Higher concentrations inhibit dopamine release via GABA (B) receptors as do other GABA (B) agonists such as baclofen and phenibut [70]. After an initial phase of inhibition, dopamine release is then increased via the GHB receptor. Both the inhibition and increase of dopamine release by GHB are inhibited by opioid antagonists such as naloxone and naltrexone. Dynorphin may play a role in the inhibition of dopamine release via kappa opioid receptors [71].

This explains the paradoxical mix of sedative and stimulatory properties of GHB, as well as the so-called "rebound" effect, experienced by individuals using GHB as a sleeping agent, wherein they awake suddenly after several hours of GHB-induced deep sleep. That is to say that, over time, the concentration of GHB in the system decreases below the threshold for significant GABAB receptor activation and activates predominantly the GHB receptor, leading to wakefulness.

Recently, analogs of GHB, such as 4-hydroxy-4-methylpentanoic acid have been synthesised and tested on animals, in order to gain a better understanding of GHB's mode of action [72]. Analogues of GHB such as 3-methyl-GHB, 4-methyl-GHB and 4-phenyl-GHB have been shown to produce similar effects to GHB in some animal studies, but these compounds are even less well researched than GHB itself. Of these analogues, only 4-methyl-GHB (γ-hydroxyvaleric acid, GHV) and its prodrug form gamma-valerolactone (GVL) have been reported as drugs of abuse in humans, and on the available evidence seem to be less potent but more toxic than GHB, with a particular tendency to cause nausea and vomiting.

Other prodrug ester forms of GHB have also rarely been encountered by law enforcement, including 1,4-diacetoxybutane, methyl-4-acetoxybutanoate, and ethyl-4-acetoxybutanoate, but these are, in general, covered by analogue laws in jurisdictions where GHB is illegal, and little is known about them beyond their delayed onset and longer duration of action. The intermediate compound 4-hydroxybutaldehyde is also a prodrug for GHB; however, as with all aldehydes this compound is caustic and is strong-smelling and foul-tasting; actual use of this compound as an intoxicant is likely to be unpleasant and result in severe nausea and vomiting.

Fig 1. Metabolic breakdown pathways shown for GHB can run in either direction, depending on the concentrations of the substances involved, so the body can make its own GHB either from GABA or from succinic semialdehyde



Under normal physiological conditions, the concentration of GHB in the body is rather low, and the pathways would run in the reverse direction to what is shown here to produce endogenous GHB. However, when GHB is consumed for recreational or health promotion purposes, its concentration in the body are much higher than normal, which changes the enzyme kinetics so that these pathways operate to metabolise GHB rather than producing it.

History

Synthesis of the chemical GHB was first reported in 1874 by Alexander Zaytsev [73], but the first major research into its use in humans was conducted in the early 1960s by Dr. Henri Laborit to use in studying the neurotransmitter GABA [74]. It quickly found a wide range of uses due to its minimal side-effects and short duration of action, the only difficulties being the narrow therapeutic dosage range and the dangers presented by its combination with alcohol and other nervous system depressants.

GHB was widely used in France, Italy, and other European countries for several decades as a sleeping agent and an anesthetic in childbirth but problems with its abuse potential and development of newer drugs have led to a decrease in legitimate medical use of GHB in recent times. In the Netherlands, GHB could be bought as aphrodisiac and euphoriant in a smartshop for several years, until several incidents caused it to become regulated. The only common medical applications for GHB today are in the treatment of narcolepsy and more rarely alcoholism. In the typical scenario, GHB has been synthesized from γ-butyrolactone (GBL) by adding sodium hydroxide (lye) in ethanol or water.

A popular children's toy, Bindeez (also known as Aqua Dots, in the United States), produced by Melbourne company Moose, was banned in Australia in early November 2007 when it was discovered that 1,4-butanediol (1,4-B), which is metabolized into GHB, had been substituted for the non-toxic plasticiser 1,5-pentanediol in the bead manufacturing process. Three young children were hospitalized as a result of ingesting a large number of the beads, and the toy was recalled [75].

Legal status

In the United States, it was placed on Schedule I of the Controlled Substances Act in March 2000. However, when sold as Xyrem, it is considered a Schedule III substance but with Schedule I trafficking penalties, one of several drugs that are listed in multiple schedules [2,76]. On 20 March 2001, the Commission on Narcotic Drugs placed GHB in Schedule IV of the 1971 Convention on Psychotropic Substances [77]. In the UK it was made a class C drug in June 2003.

In Hong Kong, GHB is regulated under Schedule 1 of Hong Kong's Chapter 134 Dangerous Drugs Ordinance. It can only be used legally by health professionals and for university research purposes. The substance can be given by pharmacists under a prescription. Anyone who supplies the substance without prescription can be fined HK$10000. The penalty for trafficking or manufacturing the substance is a HK$150,000 fine and life imprisonment. Possession of the substance for consumption without license from the Department of Health is illegal with a HK$100,000 fine and/or 5 years of jail time.

In New Zealand and Australia, GHB, 1,4-B and GBL are all Class B illegal drugs, along with any possible esters, ethers and aldehydes. GABA itself is also listed as an illegal drug in these jurisdictions, which seems unusual given its failure to cross the blood–brain barrier, but there was a perception among legislators that all known analogues should be covered as far as this was possible. Attempts to circumvent the illegal status of GHB have led to the sale of derivatives such as 4-methyl-GHB (gamma-hydroxyvaleric acid, GHV) and its prodrug form gamma-valerolactone (GVL), but these are also covered under the law by virtue of their being "substantially similar" to GHB or GBL and; so importation, sale, possession and use of these compounds is also considered to be illegal.

In Chile, GHB is a controlled drug under the law "Ley de substancias psicotropicas y estupefacientes" (psychotropic substances and narcotics). In Norway [78] and in Switzerland [79], GHB is considered a narcotic and is only available by prescription under the trade name Xyrem (Union Chimique Belge S.A.). Xyrem (Alcover) is also used therapeutically in Italy for treatment of alcohol withdrawal and dependence [80].

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