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γ-Hydroxybutyric Acid: Pharmacokinetics, Pharmacodynamics, and Toxicology

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Abstract

Gamma-hydroxybutyrate (GHB) is a short-chain fatty acid present endogenously in the brain and used therapeutically for the treatment of narcolepsy, as sodium oxybate, and for alcohol abuse/withdrawal. GHB is better known however as a drug of abuse and is commonly referred to as the "date-rape drug"; current use in popular culture includes recreational "chemsex," due to its properties of euphoria, loss of inhibition, amnesia, and drowsiness. Due to the steep concentration-effect curve for GHB, overdoses occur commonly and symptoms include sedation, respiratory depression, coma, and death. GHB binds to both GHB and $GABA_B$ receptors in the brain, with

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Her current position is SUNY Distinguished Professor and Chair of the Department of Pharmaceutical Sciences at the University at Buffalo. She had the privilege of being a graduate student with Dr. Gerhard Levy and a postdoctoral fellow with Dr. K. Sandy Pang, joining the Department of Pharmaceutical Sciences at the University at Buffalo in 1985 as their first woman faculty member. It has been her privilege to have very talented graduate students and postdoctoral fellows in her laboratory over the years, including the two coauthors of this review. Both have continued to contribute significantly in the drug transporter field with research, publications, presentations, and contributions to national/international scientific societies.

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Melanie was a graduate student and postdoctoral fellow in the Morris laboratory graduating with her PhD in 2010 and having an appointment as Research Assistant Professor in the Department of Pharmaceutical sciences from 2013 to 2015. She is currently an Assistant Professor in the Thomas J. Long School of Pharmacy, University of the Pacific. During her time in the Morris laboratory, as well as after leaving, we published 11 manuscripts, most recently a review on monocarboxylate transporters published in 2020. While a graduate student in the Department of Pharmaceutical Science, she was recognized with a Graduate Student Teaching award (2007) and the UB Pharmaceutics Graduate Scholar Award (2010). She received conference travel awards for AAPS and ASPET and was a 2010 recipient of the AAPS Graduate Symposium in Pharmacokinetics, Pharmacodynamics, and Drug Metabolism. In 2017, she was recognized with an AACP New Investigator Award. She is currently the chair of the AAPS Drug Transporter Community.

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Bridget was a graduate student in the Morris laboratory, graduating in 2013. Her current position is Principal Research Scientist, Eli Lilly and Company. During her time in Morris laboratory, she published 11 manuscripts; additionally, we published a chapter on Membrane Drug Transporters in both the 7th and 8th editions of the textbook Foye's Principles of Medicinal Chemistry. Bridget's research accomplishments during her graduate program were recognized by an AAPS Graduate Student Research Symposium Award (2012) in Pharmacokinetics, Pharmacodynamics, and Drug Metabolism (PPDM) and Clinical Pharmacology and Translational Research (CPTR), Presidential Symposium Speaker for the ASPET-Upstate New York Pharmacology Association meeting in May 2012 and UB Department of Pharmaceutical Sciences Graduate Student Award in 2012. She is currently Chair Elect of the AAPS Drug Transporter Community.

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pharmacological/toxicological effects mainly due to $GABA_B$ agonist effects. The pharmacokinetics of GHB are complex and include nonlinear absorption, metabolism, tissue uptake, and renal elimination processes. GHB is a substrate for monocarboxylate transporters, including both sodium-dependent transporters (SMCT1, 2; SLC5A8; SLC5A12) and proton-dependent transporters (MCT1–4; SLC16A1, 7, 8, and 3), which represent significant determinants of absorption, renal reabsorption, and brain and tissue uptake. This review will provide current information of the pharmacology, therapeutic effects, and pharmacokinetics/pharmacodynamics of GHB, as well as therapeutic strategies for the treatment of overdoses.

Keywords

$GABA_B$ receptors addiction; monocarboxylate transporters; narcolepsy; overdose treatment strategies; pharmacology; toxicity

INTRODUCTION

γ-Hydroxybutyric acid (GHB) is an endogenous short-chain fatty acid ($C_4H_8O_3$) present in the central nervous system (CNS) (Fig. 1) (1) and an analog of y-aminobutyric acid (GABA), a major inhibitory neurotransmitter in the CNS. GHB was first synthesized in 1874 but was not investigated for a potential clinical use until the 1960s when the French biochemist Henri Laborit tested GHB as an analog for the inhibitory CNS neurotransmitter GABA that was capable of crossing the blood-brain barrier (2). The US Food and Drug Administration (FDA) in 2002 approved GHB in its salt form as sodium oxybate ($C_4H_7NaO_3$), for the treatment of narcolepsy associated with cataplexy in adults (1,3); in 2019, it was approved for use in children over 7 years of age. GHB has been approved in other countries for other therapeutic purposes. Currently, GHB is marketed in Austria and Italy for the treatment of alcohol withdrawal as Alcover® (4). A recent review indicates that sodium oxybate is an effective, well-tolerated, and safe treatment for withdrawal and relapse prevention treatment in alcohol-dependent patients (5). GHB is also approved for use as an anesthetic in Germany where it is marketed as Somsanit® (4). Additionally, GHB was marketed as a dietary supplement and used as a sleep aid and growth hormone enhancer. Despite these numerous clinical applications, the therapeutic utility of GHB has been overshadowed by its high prevalence of abuse. Over-the-counter sales of GHB were banned in 2000 due to reports of respiratory depression and deaths following its abuse, and it was classified through the US Controlled Substances Act as a Schedule I drug. GHB was also classified as a Schedule III controlled substance in the USA for its therapeutic use in narcolepsy in 2002.

GHB is exploited illicitly for many desirable effects including euphoria, decreased inhibition, and growth hormone release (1). The abuse of GHB (known as Fantasy, Liquid Ecstasy, G) carries the risk of several severe adverse effects such as sedation, respiratory depression, hypothermia, coma, and even death (1). Ingestion of GHB dietary supplements starting in the 1980s, by body builders and athletes as a steroid alternative, due to its growth hormone–stimulating effects, led to abuse and addiction. GHB became a popular rave drug often abused at clubs and dance parties, where it was frequently co-ingested with alcohol

and other drugs of abuse. A survey of 131 GHB users reported that alcohol was co-ingested by 58% of individuals, and the risk of hospital treatment increased among GHB users following alcohol co-ingestion (6). Co-ingestion of ketamine and opiates has also been documented with GHB abuse (1,7). Ketamine (street names of Special K, Kit Kat) is a dissociative anesthetic that can have respiratory depressant effects similar to GHB and has been reported to be co-ingested with GHB by 30% of users (6). MDMA (3,4-methylenedioxymethamphetamine) is a member of the class of amphetamines and is a widely abused psychostimulant drug, very often co-abused with GHB (8). GHB is most commonly referred to as a "date-rape drug," since it can be added to alcoholic drinks as it is colorless and nearly without taste, and ingestion results in sedation, euphoria, decreased inhibitions, enhanced sex drive, and anterograde amnesia.

GHB continues to be listed on NIDA's "Commonly Abused Drugs," and DAWN reports over the past decade indicate consistent abuse of GHB. However, it is also well known that problems exist with the documentation of GHB abuse, which is underreported. In view of concerns about the ongoing diversion of therapeutic GHB for illicit purposes and illicit trade of the GHB precursors γ-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) (Fig. 1), the World Health Organization (WHO) Expert Committee on Drug Dependence critically reviewed GHB at its 35th meeting in June 2012 (9), and a 2018 theme issue in Current Drug Metabolism focused on GHB/GBL abuse (10). The reports highlight the use of "GHB kits" and recipes for synthesis available on the internet and in books. In the WHO report, a publication by Griffiths and Johnson (11) was cited, indicating that GHB was ranked second only to pentobarbital with respect to toxicity, when taking into account withdrawal severity, cognitive impairment, and, in particular, lethality after overdose. The WHO report states "The steep dose-response curve of GHB could also cause problems in terms of the user selecting the required dosage or taking subsequent doses in quick succession." The report concluded that the overall data indicate that "the abuse of and dependence on GHB continues to be a public health problem." As well, the European Drug Emergencies Network reported GHB as the fourth most commonly abused drug after heroin, cocaine, and cannabis (2013–2014). Consistent with these findings, recent publications that have surveyed the use of drugs of abuse have indicated continuous use of GHB, and deaths due to its overdose, and recent reports of overdoses from the UK in 2018 (12). A recent report investigated GHB-associated deaths in London over a 4-year period from January 2011 to December 2015 (13). There was a 119% increase in GHB-associated deaths in 2015 compared with those in 2014, which can be contrasted to only a 25% increase in cocaine-associated and 10% increase in MDMA-associated deaths in the same time (13). GHB was found to be in the top five drugs involved with emergency department visits by the European Drug Emergencies Network; GHB was associated with 711 visits, more than amphetamines (593 visits), over a 1 year period (2013–2014) (1). Accidental overdose of GHB also presents a real threat as the compound is used to facilitate sexual assault and due to its expanded clinical uses including as treatment of pediatric narcolepsy type 1 (1,14).

A 2019 report from the UK indicates that misuse of GHB or its prodrugs GBL and 1,4-BD has increased greatly since the early 1990s, particularly among lesbian, gay, bisexual, and transgender individuals in recreational and sexual settings for what is commonly referred to as chemsex or "party and play" (10). GHB use among gay and bisexual men has increased in

recent years, as GHB is commonly cited as a sexual-enhancement drug. A prospective observational study of Australian gay and bisexual men found that 19.5% had a history of GHB use; overdose was reported by 14.7% of users and was more common among men who used GHB at least monthly (15). Recreational drugs commonly associated with chemsex along with GHB/GBL include crystal methamphetamine, mephedrone, and ketamine (16). Abuse of GHB and its resulting toxicity due to the steep concentration–effect relationship of GHB and its co-ingestion with alcohol and other drugs of abuse remain a societal problem.

GHB Pharmacology

GHB is both a precursor and metabolite of the neurotransmitter GABA and is present in the brain in μM concentrations. GHB binds to at least two distinct populations of low- and high-affinity binding sites in the brain. The physiological effects of GHB are mediated through binding to its own GHB receptor, identified as a subset of $GABA_A$ receptors characterized by the α4, δ, and β1 subunits (17–19); [^{3}H]GHB binding to the GHB receptor is specific, saturable, and pH-dependent with optimum binding at pH 5.5. GHB is thought to act as a neuromodulator in the brain at endogenous concentrations (20). Kinetic and pharmacological studies have focused on binding in the brain using [^{3}H]-GHB as a ligand, identifying binding with K_d values for GHB in the nM and μM ranges, for both rats and humans (21), similar to endogenous GHB concentrations in brain tissue. GHB-induced epileptic generalized absence seizures were absent in mice and rats after knock-down of δ subunit of $GABA_A$. The small-molecule ligand NCS-382 ((E)-2-(5-hydroxy-5,7,8,9-tetrahydro-6H-benzo[7]annulen-6-ylidene)acetic acid), an analog of γ-hydroxybutyric acid, can bind to the GHB receptor with higher affinity than GHB and can inhibit the uptake of GHB by GHB receptors. Other inhibitors are described by Bay *et al.* (17). GHB binding sites have also been reported in other tissues, including heart, pancreas, liver, and kidneys of rats, although the physiological functions of these peripheral GHB sites are unknown (21). Additionally, studies have demonstrated the ability of GHB to affect the release of neurotransmitters in the brain, including GABA, glutamate, and dopamine, which may contribute to its effect (22–24). While some studies indicate the involvement of the GHB receptor in the pharmacological effects of GHB, many studies have demonstrated that the behavioral/pharmacological/toxicological effects of GHB are attributed to action at $GABA_B$ receptors.

Toxicological effects of GHB, and its prodrugs GBL and 1,4-BD, include sedation, hypothermia, respiratory depression, and fatality, and can be attributed to agonism at $GABA_B$ receptors (19,25–27). The therapeutic use of GHB in reducing the symptoms of narcolepsy is due to the GHB-mediated stimulation of slow-wave “deep sleep” with no effect on REM sleep (28). The typical dose for this clinical indication is 4.5 g daily at bedtime in two divided doses 4 h apart. GHB is a partial weak agonist of the $GABA_B$ receptor, although with much lower affinity than for its own receptor, with K_d values estimated to be in the range of μM to mM (29–32). The $GABA_B$ receptor is an obligate heterodimer, which functions as a G protein–coupled receptor (33). When activated, this receptor produces inhibitory responses at both presynaptic and postsynaptic sites. Presynaptically, $GABA_B$ activation inhibits calcium influx, thereby preventing the release of neurotransmitters (33). Postsynaptically, the activation of $GABA_B$ results in the activation of

G protein–activated potassium (GIRK or Kir3) channels, which allow the efflux of potassium producing slow inhibitory postsynaptic currents (33). GHB binding to $GABA_B$ receptors increases brain concentrations of the endogenous neurosteroids 3a,5a-tetrahydroprogesterone (3a,5a-THP) and 3a,5a-tetrahydrodeoxycorticosterone (3a,5a-THDOC) in rats (17), which may play a role in its pharmacological effects. The administration of $GABA_B$ receptor antagonists, 2S)(+)-5,5-dimethyl-2-morpholineacetic acid (SCH50911) and (3-aminopropyl)(cyclohexylmethyl)phosphinic acid (SGS742, CGP46381), completely prevents the sedative/hypnotic and respiratory depressive effects and lethality of GHB in mice (19,25–27). SCH50911 was also capable of completely abolishing the sedative/hypnotic effect of the $GABA_B$ receptor agonist, baclofen (19). Additional studies have demonstrated a lack of sedative/hypnotic and hypothermic effects following the administration of 1000-mg/kg GHB intraperitoneally to $GABA_B$ receptor-deficient mice (18,25). Studies from our laboratory have further shown that GHB produces a dose-dependent decline in breathing frequency and lethality in rats, which can be completely abolished by pretreatment with the $GABA_B$ receptor antagonists, SCH50911 and SGS742 (Fig. 2) (26). SCH50911 is a potent $GABA_B$ receptor antagonist that has an IC_{50} in rat brain of 1.1 μM (34,35). SCH50911 displays selectivity for the $GABA_B$ receptor and is able to penetrate the CNS, which makes it a useful compound for use as a $GABA_B$ receptor antagonist *in vivo* (34). SGS742 is another potent $GABA_B$ antagonist with an IC_{50} of 38 μM, and although it is less potent than SCH50911, it still has a higher affinity for $GABA_B$ receptors than GHB (36). SGS742 is currently in a phase II trial for the treatment of succinic semialdehyde dehydrogenase deficiency (SSADH), a rare neurological disorder characterized by lack of one of two enzymes involved in the breakdown of GABA in the brain, resulting in increased concentrations of both GABA and GHB. SGS742 has been shown to be effective in altering sedation and respiratory depression produced by both intravenously and orally administered GHB *in vivo* in rats. The compound reduces sleep time in rats, and ataxia and muscle relaxation in baboons, and precipitates withdrawal symptoms in chronic administration of the GBL (37–39). These reports confirm the involvement of the $GABA_B$ receptors in the pharmacological and toxicological effects of GHB. However, it is of note that the effects of GHB differ from those of the $GABA_B$ agonist baclofen, indicating the presence of subsets of $GABA_B$ receptors or the influence of other neurotransmitter receptors including GHB receptors (40,41). Rats are able to distinguish between GHB and baclofen in drug discrimination studies, providing support for differing mechanisms (42). Additionally, chronic baclofen use is not associated with addiction, and it is not as effective as GHB in treating narcolepsy symptoms (41).

GHB Metabolism

GHB metabolism is complex and involves multiple reversible pathways. Endogenous GHB is formed as part of the GABA shunt pathway within the brain with approximately 1–2% of the pathways' flux resulting in GHB production (43). Endogenous GHB concentrations range from 2 to 5 μM in all brain regions (22), but significantly higher concentrations are achieved following exogenous GHB consumption. Less than 2% of a therapeutic dose of GHB is excreted in the urine indicating that metabolism represents the major clearance pathway (44). Multiple pathways for GHB metabolism have been identified within the brain;

however, there is little or no information on the contribution of additional tissues to GHB metabolism.

Figure 3 illustrates the known metabolic routes for GHB. GHB is rapidly formed following consumption of the GHB prodrugs 1,4-butanediol and GBL, which are also considered drugs of abuse (45–47). GBL can be converted to GHB prior to ingestion with a strong base, or after ingestion via blood lactonases. 1,4-butanediol is converted to 4-hydroxybutyraldehyde via alcohol dehydrogenase (ADH), which is subsequently converted to GHB via aldehyde dehydrogenase (48). Metabolism of 1,4-butanediol is inhibited by fomepizole, a known ADH inhibitor leading to reduced systemic concentrations of GHB following pretreatment with fomepizole (48). GABA is metabolized to succinic semialdehyde (SSA) via GABA transaminase, which is then further reduced by SSA reductase to form endogenous GHB (49,50). GHB is metabolized within the body by distinct enzymes located in the cytosol and the mitochondria. Within the cytosol, GHB dehydrogenase converts GHB to SSA (51), which can either be taken up into the mitochondria or be converted within the cytosol to GABA (as part of the GABA shunt pathway) (49,50). GHB dehydrogenase has been identified as aldo-ketoreductase 1A1 (AKR1A1) in HepG2 cells; when AKR1A1 expression was knocked down with siRNA, GHB dehydrogenase activity was reduced by 82% (52). GHB is converted to SSA within the mitochondria via GHB transhydrogenase (also known as D-2-hydroxyglutarate transhydrogenase), which is coupled to the conversion of α-ketoglutarate to D-2-hydroxyglutaric acid (47,51). α-Ketoglutarate can be converted to glutamate, which can subsequently be converted to GABA, thereby completing the GABA shunt pathway (53). Within the mitochondria, SSA is metabolized to succinic acid by SSA dehydrogenase (ALDH5A1) (54); succinic acid subsequently enters the Kreb's cycle and is excreted as carbon dioxide and water (55). GHB accumulation occurs in SSA dehydrogenase deficiency, suggesting that the conversion of GHB to SSA and entry into the Kreb's cycle are the primary metabolic pathway for GHB (45,50,56). Cytosolic GHB dehydrogenase likely represents the main pathway for the conversion of GHB to SSA, as its inhibition by valproate and ethosuximide causes accumulation of GHB within the brain (57,58). GHB transhydrogenase, which converts GHB to SSA within the mitochondria, is not sensitive to inhibition by valproate and therefore is a minor pathway for GHB metabolism (57). SSA may be converted to 4,5-dihydroxyhexanoate within the mitochondria (59); however, the enzyme responsible for this reaction has not been determined. In addition, the β-oxidation spiral has been proposed as an excretion pathway for GHB resulting in the formation of dicarboxylic acids such as 3.4-dihydroxybutyric acid and glycolic acid (60,61).

Metabolism of GHB has primarily been evaluated in brain homogenates and crude synaptosomal membranes. AKR1A1 (GHB dehydrogenase) is ubiquitously expressed with high expression in the liver, suggesting that hepatic metabolism is likely the primary route of metabolism for exogenous GHB (62); however, quantitative analysis of the contribution of the liver to GHB metabolic clearance has not been conducted. Endogenous GHB concentrations are measurable in numerous peripheral tissues suggesting that GHB metabolism may not be restricted to the liver and brain. Mechanistic studies to elucidate GHB metabolism and metabolite kinetics in additional tissues including the liver, kidney, and intestine are necessary.

Monocarboxylate Transporters

Monocarboxylate transporters facilitate the transport of lactate and other monocarboxylates, and therefore play an important role in cellular metabolism and homeostasis.

Proton- and sodium-dependent monocarboxylate transporters (MCTs/SMCTs) are involved in the uptake and efflux of GHB in biologically important tissues and barriers, including the kidney, intestine, and blood-brain barrier (BBB) (63). Transporters are critically important for GHB pharmacokinetics due to the pKa of GHB (pKa = 4.7), which results in almost complete ionization of GHB at physiologic pH. MCT/SMCT expression governs the extent of GHB renal excretion, absorption, and brain and tissue distribution (64–67).

Proton-dependent monocarboxylate transporters belong to the SLC16A family, with 14 members identified based on sequence homology (68). Only four members of this transporter family (MCT1–4) demonstrate proton-dependent transport and facilitate the transport of important endogenous monocarboxylates, including lactate, pyruvate, and ketone bodies (69,70). MCTs have a ubiquitous distribution in the body with variable expression depending on the specific isoform (70). Figure 4 is based on a recent review on MCTs by Felmlee *et al.* (70) that provides a detailed discussion of MCT tissue distribution. MCT1, the predominant isoform, is ubiquitous in its distribution in the body. Of importance in the distribution of GHB, MCT1 is expressed on the apical membrane of the liver and the basolateral membrane of the kidney and intestine (63,70,71). MCT2 demonstrates a more restricted tissue distribution but is present in the kidney, intestine, and other tissues including heart and skeletal muscle (70,72). MCT3 also exhibits a restricted tissue distribution, being present at the basolateral membrane of the retinal pigment epithelium and choroid plexus cells (70,71). MCT4 is present on the basolateral membrane of kidney and intestine, as well as in other tissues including skeletal muscle, heart, and lungs. MCT1 is the only isoform expressed at the BBB, with expression demonstrated at the apical and basolateral membranes in rats (73). MCT1 is also present on choroidal epithelial cells in humans and rats, present at both the apical and basolateral membranes in rats (71). Within the brain, MCT2 expression has been detected on neurons and astrocytes, although there are species differences, and MCT4 is mainly localized on astrocytes (74). Therefore, the proton-dependent MCTs 1–4 are responsible for the transport of GHB, as well as endogenous monocarboxylates such as L-lactate and other exogenous drugs including salicylate, valproic acid, and atorvastatin (8) in most tissues, including across the BBB and blood-CSF barrier, and in neurons and astrocytes within the brain.

SMCTs belong to the SLC5A family, with two members, SMCT1 (SLC5A8) and SMCT2 (SLC5A12), with neither having sequence homology with SLC16A members. SMCT1's molecular structure differs from MCTs in that it has 7 transmembrane spanning domains with an extracellular amino terminus and an intracellular carboxyl terminus (75). SMCT1 protein expression has been identified in the kidney, intestine, brain, retina, and thyroid gland (76–80). SMCT1 is expressed in the kidney cortex and outer medulla, with expression localized to the apical membrane of the S2 and S3 segments of the proximal tubules, while SMCT2 is localized to the apical membrane of the S1 segment (81). In the intestine, SMCT1 and SMCT2 are expressed on the brush border membrane. SMCTs are expressed in the brain in neurons (SMCT1) and astrocytes and glia (SMCT2) (82). Although there is no structural

similarity between SMCTs and MCTs and the transport mechanisms differ, SMCTs share many substrates with proton-coupled MCTs, including D- and L-lactate, pyruvate, butyrate, and ketone bodies. A number of exogenous drugs are substrates for SMCT1, including GHB, benzoate, and salicylates; however, the pharmacological significance of SMCT2 is unknown (83). GHB has a higher affinity for SMCT1 than for MCT1, with a reported K_m value of 0.68 mM (84).

Transport of GHB via Monocarboxylate Transporters—Transport of GHB is pH- and concentration-dependent in rat kidney membrane vesicles, human kidney HK-2 cells, Caco-2 cells, FRTL-5, and rat MCT1-transfected MDA-MB231 cells, and is inhibited by known MCT substrates/inhibitors such as lactate, pyruvate, and α-cyano-4-hydroxycinnamate (CHC) (72,84–86). In rat kidney membrane vesicles, saturable uptake of GHB was demonstrated across the basolateral and brush border membranes and was inhibited by MCT/SMCT inhibitors (72). GHB transport was pH- and sodium-dependent, suggesting that MCTs and SMCTs are involved in active renal reabsorption of GHB (72); however, only MCT1 and MCT2 protein expressions were confirmed in the vesicles. Consistent with rat kidney membrane vesicles, transport of GHB in HK-2 cells was saturable and inhibited by MCT inhibitors (85), suggesting the role of MCT inhibitors in the renal reabsorption of GHB in both humans and rats. Following knock-down of MCT1 protein expression via siRNA in HK-2 cells, the uptake of L-lactate and GHB was significantly decreased (85), suggesting that MCT1 is the predominant transporter for GHB uptake in the kidney. GHB is a substrate for MCT2 and MCT4; however, the reductions in transport following knock-down were minimal compared to the reduction in transport following MCT1 knock-down (85). The presence of MCT1–4 protein expression was confirmed in Caco-2 cells, and GHB transport characteristics in these cells are consistent with proton-dependent MCT-mediated transport (86). In rat thyroid follicular (FRTL-5) cells, GHB transport was pH- and sodium-dependent with a K_m for sodium-dependent transport of 0.68 mM, which is consistent with SMCT1-mediated transport (84). In rat MCT1-transfected MDA-MB231 cells, the K_m for MCT1-mediated transport of GHB was found to be 4.6 mM (72). GHB affinity for MCT1 demonstrates pH dependence (87). In red blood cells, the K_m for GHB transport shifted from 2.2 to 17.0 mM, when the extracellular pH was raised from pH 6.5 to 7.4 (87). This suggests that the K_m for GHB transport will vary dependent on the tissue microenvironment.

GHB Transport at the BBB—Of the MCT/SMCT isoforms known to transport GHB, only MCT1 is expressed at the BBB in mice, rats, monkeys, and humans (71). GHB transport at the BBB was demonstrated to be saturable and carrier-mediated using *in situ* brain perfusion with a K_m value of 11 mM (65). This is consistent with MCT1 transporter kinetics in RBCs in the absence of a pH gradient (87). Furthermore, GHB transport was inhibited by known MCT1 substrates and inhibitors, including lactate, pyruvate, and CHC (65). GHB transport kinetics were investigated in *in vitro* models of the rat and human BBB, RBE4, and hCMEC/D3 cells. These cell lines have been demonstrated to express MCT1 (88,89). GHB transport was concentration- and pH-dependent in RBE4 and hCMEC/D3 cells with K_m values of 23.3 mM and 18.1 mM at pH 7.4 (90). MCT1-mediated uptake of

GHB was inhibited in RBE4 cells by CHC and L-lactate (64,90) and in hCMEC/D3 cells by L-lactate (90) at concentrations obtained with *in vivo* GHB doses in rats.

GHB Pharmacokinetics

As a therapeutic agent, the pharmacokinetics of GHB have been well described in humans. GHB is marketed in the USA in the form of sodium oxybate under the brand name Xyrem®. In humans, GHB exhibits dose-dependent pharmacokinetics, even at therapeutic concentrations (91–93). The nonlinear kinetics of GHB are due to saturable oral absorption, saturable metabolism, and saturable renal reabsorption (94,95). Dose-dependent pharmacokinetics have also been reported in rats and baboons (92,96). Compared to that in humans, pharmacokinetics in rats demonstrate similar nonlinearity attributed to saturable oral absorption, saturable metabolism, and saturable renal reabsorption as described below (94,96,97).

Absorption—MCTs/SMCTs are expressed in the intestine in multiple species, including rats, non-human primates, and humans, and are likely responsible for the observed saturable oral absorption of GHB (86). One clinical study reported dose-dependent oral absorption of GHB, with Tmax values increasing with increasing dose, suggesting saturable GHB absorption (92). In an evaluation of administration of GHB in doses of 200–1600 mg/kg orally in rats, the GHB Cmax increased less than proportionally with dose, and Tmax increased with dose, also suggesting saturable absorption of GHB in rats (96). This can be observed from similar subsequent experiments in rats shown in Fig. 5. *In situ* experiments using everted rat gut confirmed saturable intestinal transport of GHB at high mM concentrations (97). The oral administration of L-lactate with oral GHB in rats interestingly delayed the absorption of GHB, with no significant change in overall exposure, suggestive of the role of MCTs in GHB absorption and their high capacity in the intestine (98). The prolonged absorption of GHB after intragastric administration has also been observed in baboons, similar to rats, consistent with MCT-mediated absorption of GHB (97,100). Estimation of GHB bioavailability is confounded by its nonlinear pharmacokinetics. However, in rats, negligible GHB was detected in feces following oral administration, suggesting a high fraction absorbed and consistent with the high capacity of MCTs in the intestine (98).

Distribution—Due to the ubiquitous expression of MCTs, it is likely that MCTs are involved in the distribution of GHB into tissues. The tissue distribution of GHB was assessed in rats (66), showing highest partitioning in kidney, with partition coefficients of < 1 in all other tissues. Tissue- and dose-dependent partitioning was observed, and L-lactate administration had tissue-specific effects on partitioning, consistent with the involvement of various MCT isoforms in different tissues and the bidirectional nature of MCTs. As MCT1 is highly expressed in RBCs, the dose-dependent partitioning of GHB into RBCs was separately assessed and was unexpectedly linear in rats across dose ranges that demonstrate nonlinear renal clearance (87). This is in part attributed to the higher K_m value for MCT1 determined at blood pH (7.4), compared to other physiological sites, including the lumen of the proximal tubule (i.e., ~ 6.5).

As the site of GHB action and a known tissue with MCT expression, GHB partitioning into brain has been assessed in rats in various studies. Total partition coefficients in brain are < 1 and dependent on the brain region, being somewhat higher in hippocampus and frontal cortex compared to whole brain (66,101). Unbound partitioning in extracellular fluid (ECF) of the frontal cortex was also assessed in rats using microdialysis, similarly reporting low partitioning coefficients in ECF of < 0.1 across intravenous doses of 400–800 mg/kg (64,90). Intravenous administration of MCT inhibitors to rats has demonstrated a decrease in GHB brain partitioning, consistent with the role of MCTs at this barrier and may be due to either direct inhibition or potential trans-stimulation of MCT-mediated transport (64,74).

While such assessments on tissue distribution are not possible in humans, MCT expression is widespread in both humans and rats. Plasma protein binding has also been demonstrated to be similar between species (fraction unbound of ~ 1) (94,102).

Clearance

Metabolic Clearance.: Numerous reports indicate that the oral clearance of GHB decreases with increasing dose in humans, indicating saturable metabolism of GHB, even at therapeutic plasma concentrations (91–93). Metabolism is the primary route of GHB elimination in humans, as very little is excreted unchanged in the urine (102). The proposed metabolic pathways for GHB are shown in Fig. 3 and described above. In rats, similarly to humans, the total and metabolic (non-renal) clearance decrease with increasing dose following IV and oral administration, as shown in Tables I and II, and the pharmacokinetics demonstrate Michaelis-Menten kinetics following IV administration (Fig. 6) (94). Through the use of pharmacokinetic modeling, the *in vivo* metabolic K_m value for GHB in rats has been estimated to be in the range of 54–579 μg/ml or approximately 0.5–5 mM (96,103–105).

Renal Clearance.: In humans, only 2–6% of GHB is excreted unchanged following an oral therapeutic dose (92). Since the fraction unbound in human plasma of GHB is ~ 1, it is assumed that GHB undergoes glomerular filtration, and the lack of elimination of GHB into urine can be attributed to almost complete renal reabsorption. In rats, renal clearance is similarly negligible at low doses and at plasma concentrations similar to those used therapeutically in humans (Table I); however as shown after both IV and oral administration in rats, it becomes the predominant route for its elimination at higher doses (Tables I and II) (94,106). In rats, the increased GHB renal clearance with increases in dose suggests that GHB undergoes saturable, carrier-mediated renal reabsorption (94). Administration of MCT inhibitors, including L-lactate, pyruvate, and dietary flavonoids, results in increased renal clearance of GHB in rats, further indicating saturable active renal reabsorption of GHB and that this process involves transport by MCTs (Tables I and II) (94,104,107). In humans, while renal clearance is nearly negligible at therapeutic oral doses, administration of L-lactate to humans significantly increased the renal clearance of GHB, consistent with a similar role of MCTs in the active renal reabsorption of GHB in humans, as in rats, shown in Table I (94).

Pharmacokinetics of GHB Precursors.: As a lactone, the GHB precursor GBL is rapidly converted to GHB via lactonases in the blood, and following GBL administration to rats and baboons, only GHB is detectable in plasma (108). As such, the disposition of GBL *in vivo* is likely irrelevant; however, the properties of GBL in the intestine, prior to systemic exposure, represent important differences with this agent compared to GHB itself. The everted rat gut studies mentioned above also evaluated the intestinal transport of GBL and interestingly demonstrated transport of GBL in these gut preparations to be much higher than GHB, lacking evident saturation of transport (97). Rat studies evaluating oral administration of equimolar doses of GHB and GBL demonstrate superior absorption of GBL compared to GHB with higher GHB C_{max} values following GBL administration compared to GHB itself (Fig. 5) (109). Similar behavior of GHB following GBL absorption has been demonstrated in baboons (109). As GBL is undetectable in plasma following administration, it is unlikely that toxicodynamic effects of GBL are relevant *in vivo*. Additionally, intracerebroventricular administration of GBL in rats demonstrated no pharmacological effects of this agent, when avoiding systemic conversion to GHB (110). Therefore, toxicodynamic effects of concern following overdose of GBL are those of formed GHB.

Conversely, plasma concentrations of 1,4-butanediol (BD) are measurable following oral administration to rats, baboons, and humans along with those of GHB (111,112). Following an oral dose of 25 mg/kg BD to healthy volunteers, the oral clearance of BD showed high interindividual variability, as did the ratio of GHB:BD (113). A correlation was found in that subjects with lower clearance and lower GHB:BD carried variant alleles for the ALD gene. The mean GHB:BD plasma AUC ratio was 49 in this study, and mean plasma Cmax of GHB was greater than that of BD by over 10-fold, suggesting that the toxicological effects can likely be attributed to those of GHB. Additionally, in the same study with GBL, BD demonstrated no effect following intracerebroventricular administration in rats (110). The dose-dependent pharmacokinetics of BD were assessed in rats and were nonlinear, and pharmacokinetic modeling indicated that the bioconversion of BD to GHB was complete, via the two-step conversion through alcohol dehydrogenase, followed by aldehyde dehydrogenase. Similarly, the pharmacokinetics of BD were nonlinear following oral administration to baboons. However, unlike GHB, in both rats and baboons, the Tmax of BD occurred rapidly, at all doses (111,112).

GHB Overdose

Overdose of GHB can lead to serious adverse effects such as nausea, sedation, dizziness, seizure, respiratory depression, hypothermia, coma, and death (114). There are numerous reports in the clinic of GHB-related fatality among drug abusers. Currently, there is no antidote for the treatment of GHB overdose and treatment is limited to supportive care including mechanical ventilation to overcome respiratory depression observed in cases of overdose. Physostigmine, naloxone, and activated charcoal have been tried as antidotes but demonstrated little to no effect (98,115,116). Therefore, there is an urgent need to develop potential treatment strategies for the treatment of GHB overdose, alone and when it is co-ingested with other common club drugs.

Additionally, there is the potential for enhanced toxicity when GHB is administered with other drugs of abuse. In a recreational setting, GHB and GBL are typically not ingested alone and alcohol co-ingestion occurs in the majority of cases (115,117). In rats, GHB induced a decrease in respiratory frequency with a compensatory increase in tidal volume; co-administration of ethanol partially prevented the compensatory tidal volume increase and resulted in increased rate of fatality (39). Co-ingestion of ketamine and opiates has also been documented with GHB abuse (1,7). Ketamine can have respiratory depressant effects similar to GHB and has been reported to be co-ingested with GHB by 30% of users (6). Availability of ketamine may increase, since the therapeutic use of ketamine is increasing with its recent approval as an anti-depressant. Opioids including oxycodone and fentanyl are μ-opioid receptor agonists that can cause similar toxicities as GHB including respiratory depression, coma, and death (118–120).

Although the relative contribution of MCT1 and SMCT1 to the renal reabsorption of GHB has not been determined *in vivo*, it has been demonstrated that inhibition of MCTs can increase GHB CL_R, alter brain penetration, and reverse the effects of GHB on sleep time (measured by return of righting reflex), respiratory depression, and lethality (26,64,66,94,98). Animal studies with MCT inhibitors L-lactate and the flavonoid luteolin demonstrated significant increases in the renal and total clearances of GHB following its administration at high doses (104,107). Treatment with L-lactate also resulted in a significant decrease in the sedative/hypnotic effects of GHB and an improvement in GHB-induced respiratory depression in rats (26). A proof of concept study in humans utilized an infusion of the MCT1 inhibitor, L-lactate, and demonstrated a significant increase in GHB renal excretion (Table I) (99). Due to the minimal contribution of renal clearance at therapeutic doses assessed, the increase in renal clearance did not result in increased total clearance. This effect was similar to that observed at low oral doses in rats; however, the data in rats suggest that at higher doses, more relevant to overdose, the increase in renal clearance does translate into increased total clearance of GHB. The similarities between human and rat pharmacokinetics suggest that at high doses in humans, increased renal clearance with MCT inhibition should result in increased total clearance of GHB from the body. Specifically for L-lactate, the increase in renal clearance in humans and rats required a very high dose, which may limit the use of this MCT inhibitor for overdose treatment; however, the data support MCT inhibition as an overdose strategy in humans.

In addition to the inhibition of active renal reabsorption of GHB in the kidney, MCT inhibition may play an important role in blocking the entry of GHB into the brain, which is its site of action (64,65,74). Recent studies using *in vivo* microdialysis have demonstrated that L-lactate administration as a bolus followed by a continuous intravenous infusion to rats treated with GHB resulted in a decrease in plasma as well as frontal cortex ECF concentrations when compared to GHB alone (64). The reduction in plasma and frontal cortex ECF GHB concentrations was greater with a higher dose of lactate (64). This higher lactate dose also significantly reduced the unbound GHB brain ECF to plasma partition coefficient, whereas no such change was observed with lower lactate doses. These data suggest that L-lactate at higher doses can alter the BBB transport of GHB and represents a potential treatment strategy for GHB overdose (64). The K_m value for GHB uptake has been shown to be higher at pH 7.4 when compared to pH 6.5 in red blood cells (87).

As the physiologically relevant pH at the BBB is 7.4, higher concentrations of L-lactate may be required to inhibit MCT-mediated transport of GHB across the BBB, compared with the intestine or kidneys where a lower physiological pH represents a driving force for absorption or reabsorption, respectively. Consistent with the reduction in plasma and brain ECF concentrations of GHB, L-lactate also significantly reduced GHB-induced sleep time measured as difference between return and loss of righting reflex (64). L-lactate was also able to inhibit GHB uptake into RBE4 cells in *vitro* at pH 7.4 at concentrations of 5 and 10 mM (64). The renal clearance of GHB was also increased by L-lactate administration due to inhibition of MCT-mediated active reabsorption in the proximal tubule of kidney, as demonstrated previously. These results together suggest that the transport of GHB across the BBB is mediated by MCTs. Since MCT1 is the predominant transporter expressed in the BBB, it is most likely responsible for the observed effects.

Subsequent pre-clinical work investigated more potent MCT1 inhibitors, AR-C15585 and AZD3965. Both compounds were identified by AstraZeneca, in an effort to synthesize potent and selective MCT1 inhibitors as immunosuppressants and as anti-cancer agents (121,122). AR-C155858 and AZD3965 are both highly potent MCT1 inhibitors with K_i values of 2.3 and 1.6 nM, respectively (123,124). AZD3965 exhibits 6-fold selectivity for MCT1 over MCT2 and does not have activity against MCT3 or MCT4 (122). Similarly, AR-C155858 is 4-fold more selective for MCT1 than MCT2 and does not inhibit MCT4 (123). In rats, treatment with AR-C155858 5 min after GHB administration prevented the respiratory depressant effects, reduced plasma exposure, and increased CL_R of an intravenous dose of GHB (Table I and Fig. 7) (95). A similar effect was observed with AR-C155858 treatment following an oral dose of GHB. When AR-C155858 was administered 5 or 60 min after GHB, there was a decrease in exposure mediated by an increase in CL_R (95). AZD3965 administration 60 min after IV or oral GHB administration results in decreased respiratory depression (125). Additionally, brain concentrations of GHB after AZD3965 administration were significantly decreased in rats, suggesting that a major effect of MCT1 inhibition is due to decreased uptake of GHB into the brain (125). The ability of AZD3965 to impact GHB TK even when the administration was delayed indicated that MCT1 inhibition with a potent inhibitor was a promising strategy for GHB overdose treatment.

Addiction to GHB

Chronic treatment of drugs associated with addiction causes an increase in the neuronal activity of the mesocorticolimbic dopamine system. The actions of GHB on dopamine (DA) are mediated predominantly via the low-affinity binding of GHB to the $GABA_B$ receptors in the mesocorticolimbic DA system, and the addictive properties of GHB may represent the result of differential actions of GHB on DA and $GABA_B$ neurons. GHB is readily self-administered by rats and mice, and early drug discrimination studies conducted in rats indicated that GHB and its prodrugs GBL and BD are addictive $GABA_B$ agonists (126,127). Animals were clearly able to distinguish ethanol, baclofen, or diazepam from GHB and did not substitute them for GHB, suggesting differences in receptors involved in the reinforcing/addictive properties of these drugs (128,129). Rats that were chronically administered GHB showed tolerance after 3–6 days of daily administration and withdrawal symptoms (130,131). GHB and its prodrugs GBL and BD can also maintain self-administration in

baboons, indicating the potential for physical dependence (37,132–134). Administration of a $GABA_B$ antagonist results in withdrawal symptoms including tremors, vomiting, jerks, increased aggression, and increased duration to complete fine-motor tasks. Peak spontaneous withdrawal symptoms occur within 6–72 h following chronic administration of GHB or GBL. This is similar to that reported in humans following chronic GHB or GBL use (135).

Dependence liability of GHB was initially considered to be low for sodium oxybate (< 1%), and initial studies after clinical administration of GHB in patients with narcolepsy have not shown any cases of misuse or tolerance. However, further studies have indicated the potential for the drug to be mentally and physically addictive. Regular GHB use may result in dependence in weeks, and GHB withdrawal is known to cause autonomic dysfunction with severe CNS symptoms. Abrupt withdrawal can produce a range of neurological symptoms including tremor, anxiety attacks, confusion, seizures, and memory loss. These initial symptoms may progress to severe delirium with auditory and visual hallucinations and cardiovascular effects including tachycardia and hypertension (136). The withdrawal syndrome of GHB, GBL, or BD closely resembles that of other sedative-hypnotic agents (136). Brunt *et al.* (2014) (135) summarized the withdrawal symptoms from published studies; these consisted of tremor (67%), hallucinations (63%), tachycardia (63%), insomnia (58%), anxiety (46%), hypertension (44%), seizures (7%), and rhabdomyolysis (7%), plus one death. Additionally, little is known about treatment effectiveness for GHB-addicted subjects. Benzodiazepines, barbiturates, and antipsychotic medication have been used for treatment of withdrawal symptoms, and in such severe cases of GHB withdrawal, treatment with high doses of predominantly benzodiazepines is generally used. However, in many cases, these treatment regimens have proven ineffective. In the “Dutch GHB Monitor” study, 274 patients with GHB dependence were followed during treatment for GHB detoxification over the period of 2010 to 2012. After 3 months of follow-up, 65% of the patients in this study reported a relapse in GHB abuse (137). A newer treatment regimen in the Netherlands follows the recommended medication-assisted treatment for opioid addiction and treats GHB withdrawal with pharmaceutical GHB (Xyrem) with tapering of doses over time.

CONCLUSIONS

GHB is used therapeutically for the treatment of narcolepsy and for withdrawal symptoms in alcoholics. However, since the 1990s, there have been reports of GHB abuse in recreational settings and GHB has been referred to as a “date-rape drug.” One of the probable reasons for the abuse of GHB and, therefore, associated problems with toxicity and addiction is the relative ease to manufacture GHB and easy accessibility of its precursors. While physiological effects of GHB are due to binding to GHB receptors in the brain, pharmacological and toxicological effects of GHB are predominantly due to binding to $GABA_B$ receptors, effects that can be reversed by $GABA_B$ receptor antagonists. The pharmacokinetics of GHB are complex and involve capacity-limited absorption, metabolism, tissue distribution, and renal elimination. Monocarboxylate transporters represent major determinants of absorption, renal clearance, and tissue uptake, including uptake into the brain, its site of action. Toxicity and death after GHB overdoses in pre-clinical studies can be reversed by MCT1 inhibitors, indicating their potential use for the treatment of clinical GHB overdoses. Clinical studies, based on scale-up from physiologically based pharmacokinetics

and pharmacodynamics models, are needed to implement MCT1 inhibition for the treatment of overdoses.

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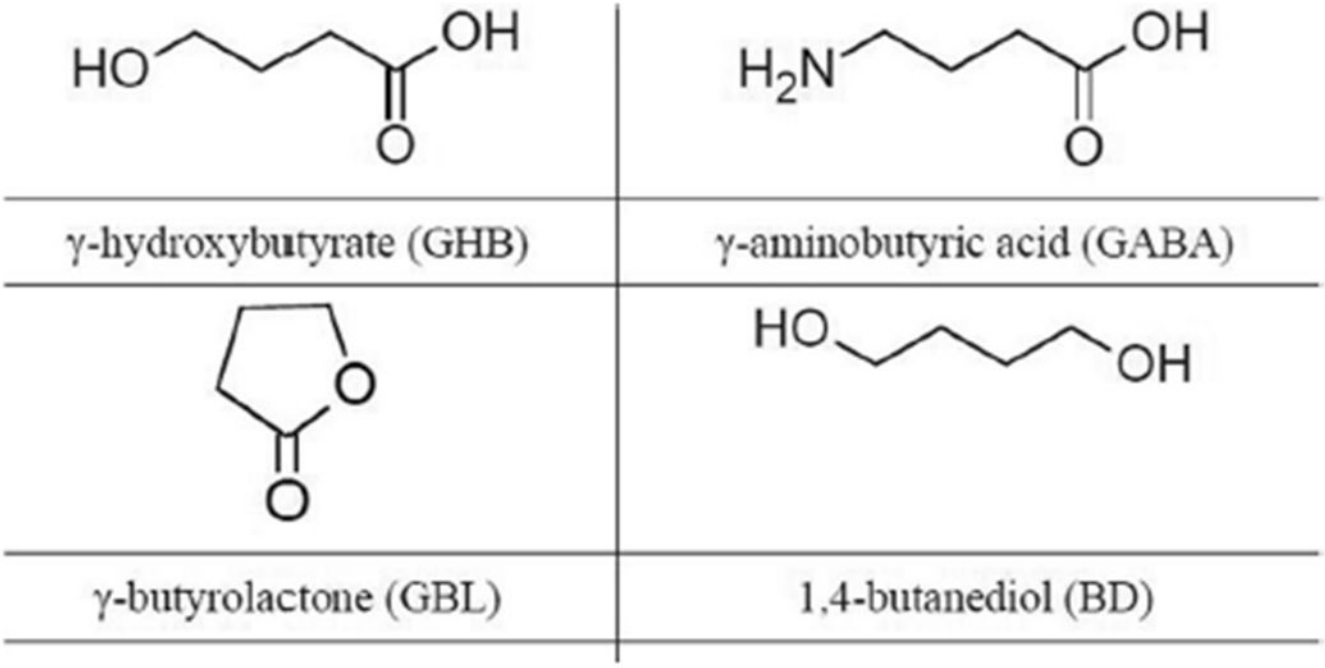

Fig. 1.
Chemical structures of GHB, and its precursors GABA, GBL and 1,4-BD

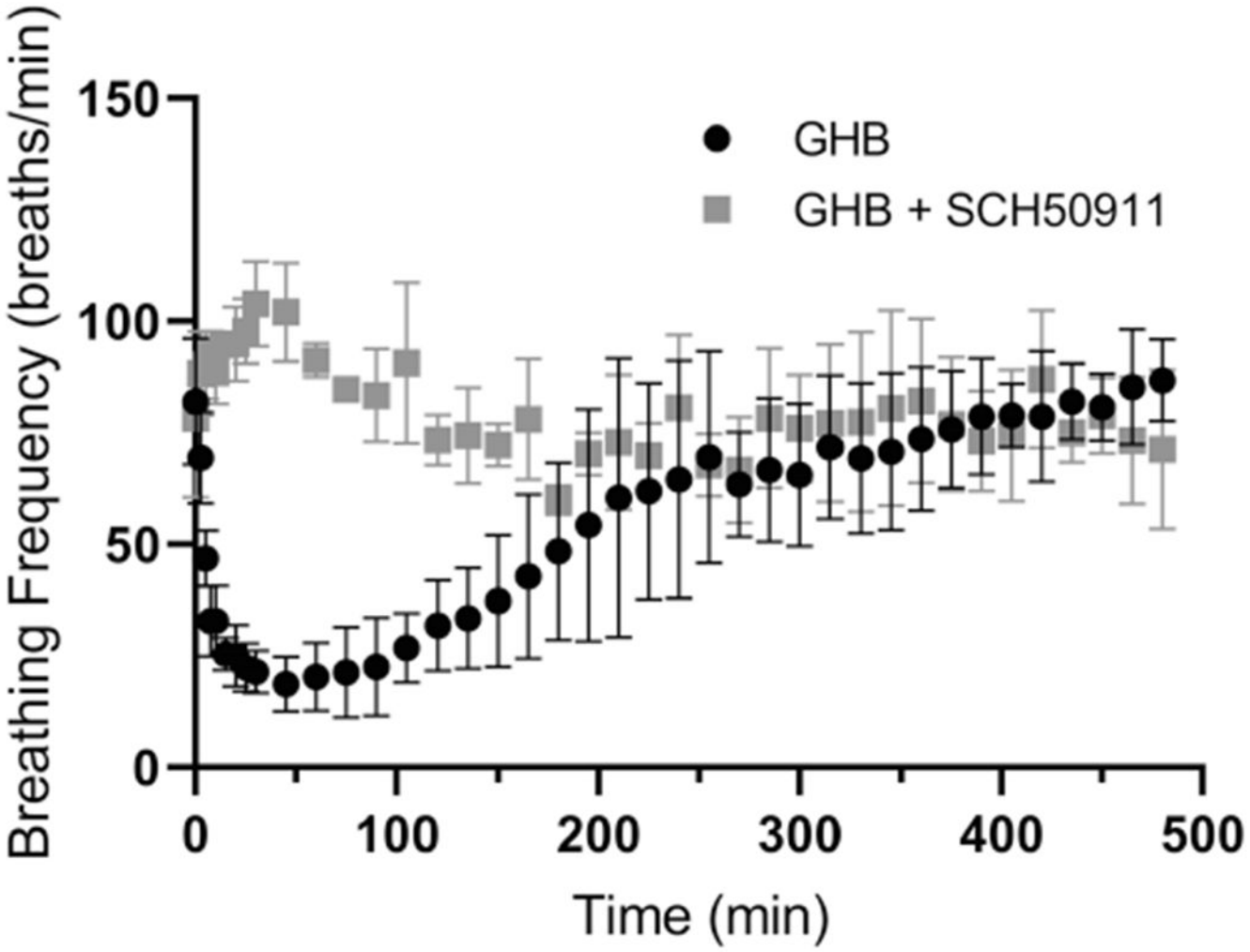

Fig. 2.

Impact of $GABA_B$ receptor inhibition on GHB inducedrespiratory depression. GHB (1500mg/kg) was administered intravenously,alone and after pretreatment with the $GABA_B$ receptor antagonist SCH50911(150mg/kg). Inhibitor was administered intravenously 5min beforeGHB. Data are presented as mean±S.D.; *n*=to 5.Figure and caption adapted from (26)

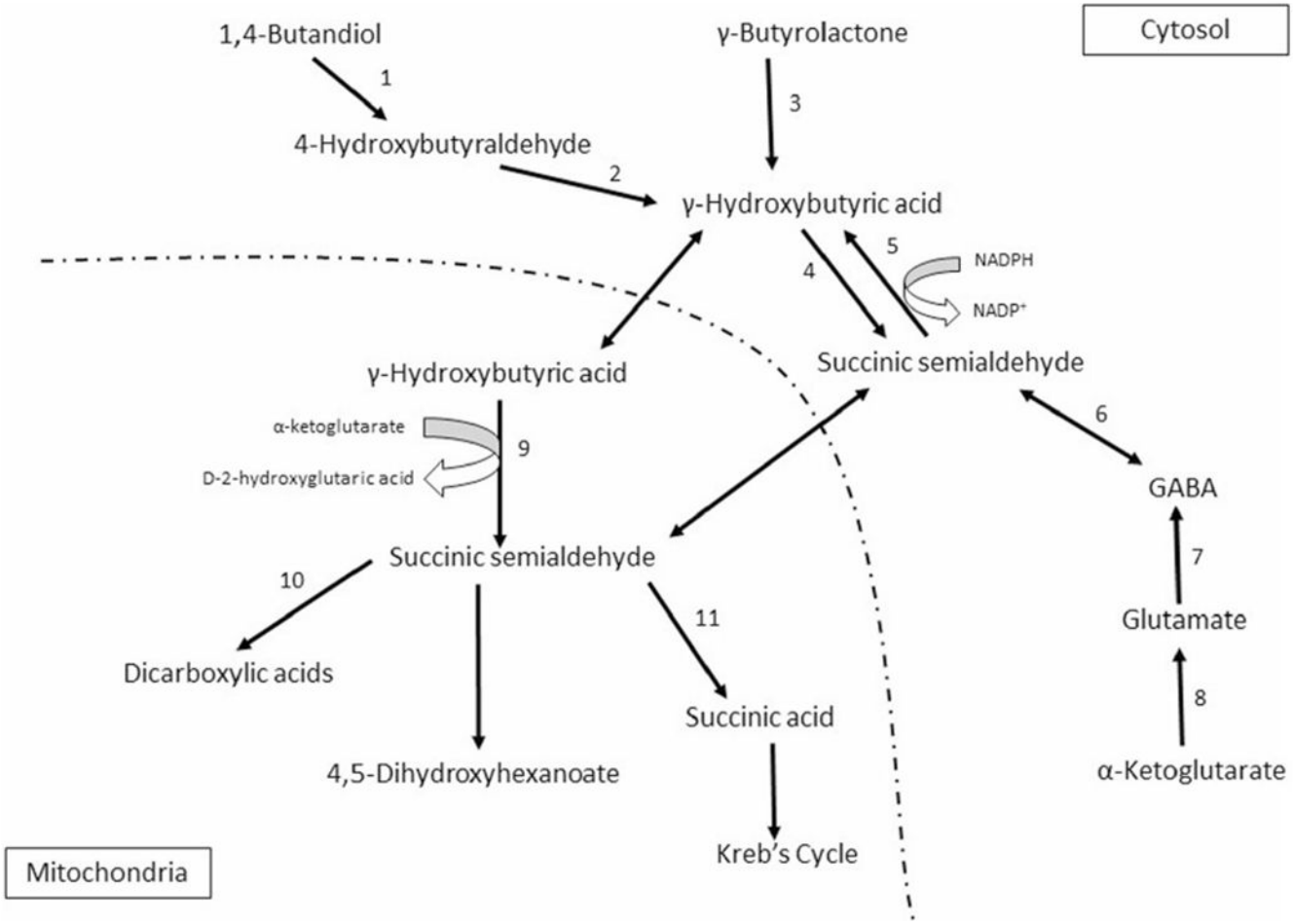

Fig. 3.

Metabolism of GHB. Enzymes: 1, Alcohol dehydrogenase; 2, Aldehydedehydrogenase; 3, Blood lactonases; 4, GHB dehydrogenase (AKR1A1); 5, Succinicsemialdehyde reducatase; 6, GABA transaminase; 7, Glutamate decarboxylase; 8,Glutamate dehydrogenase; 9, GHB transhydrogenase; 10, β-oxidation spiral; 11,Succinic semialdehyde dehydrogenase (ALDH5A1)

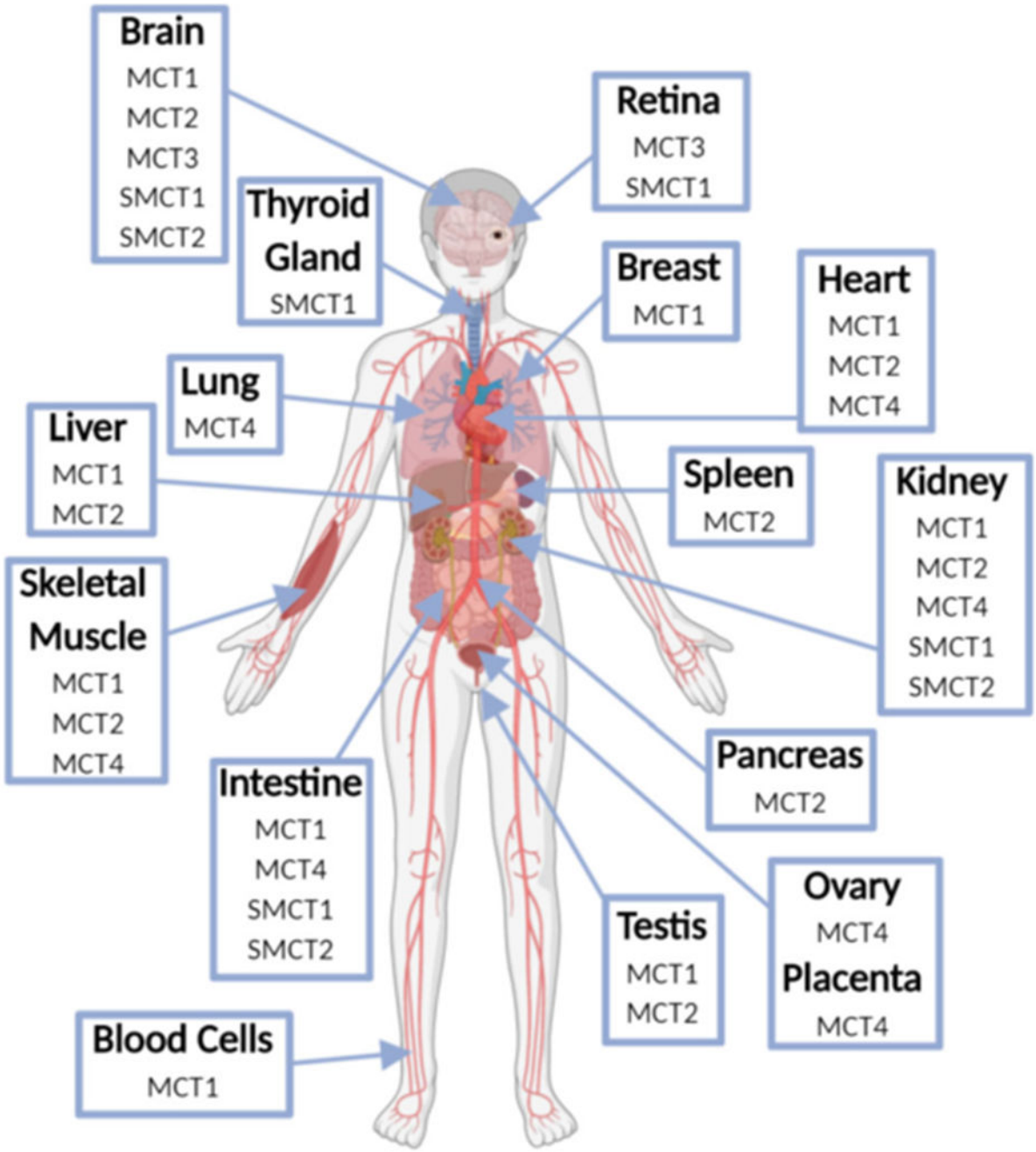

Fig. 4.
Tissue distribution of MCTs and SMCTs in humans. (Data from references 70–80)

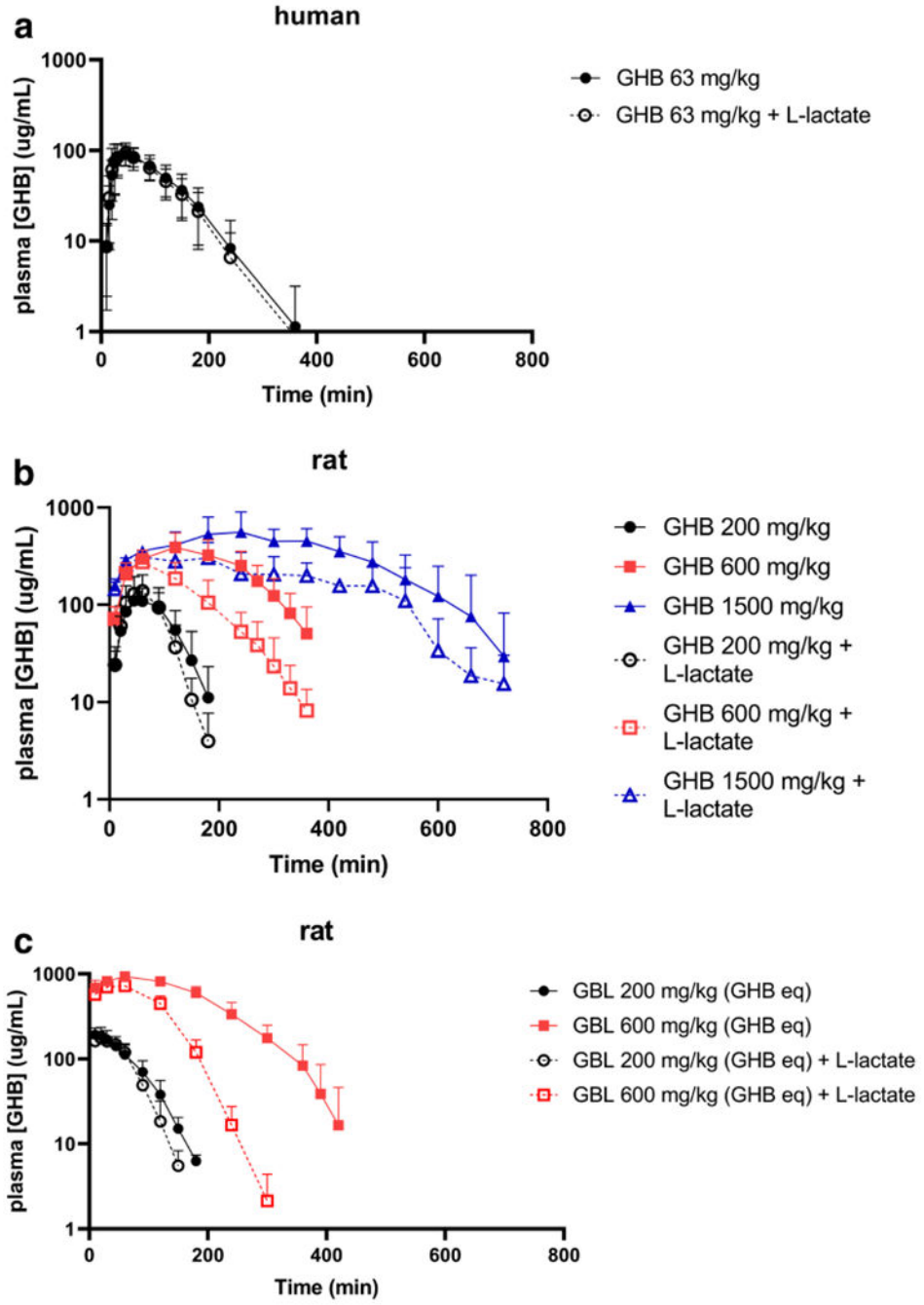

Fig. 5.

Oral pharmacokinetics of GHB in rats and humans, with and withoutadministration of MCT inhibitor L-lactate (**a**and **b**) and of GHB following GBLadministration in rats, with and without administration of MCT inhibitorL-lactate (**c**). Rat figures adaptedfrom (98). Data in humans arefrom the study described in (99). Data are presentedas mean ± S.D.;n=7 to 10 in rat studies. Humanpharmacokinetic data are from 10 healthy volunteers

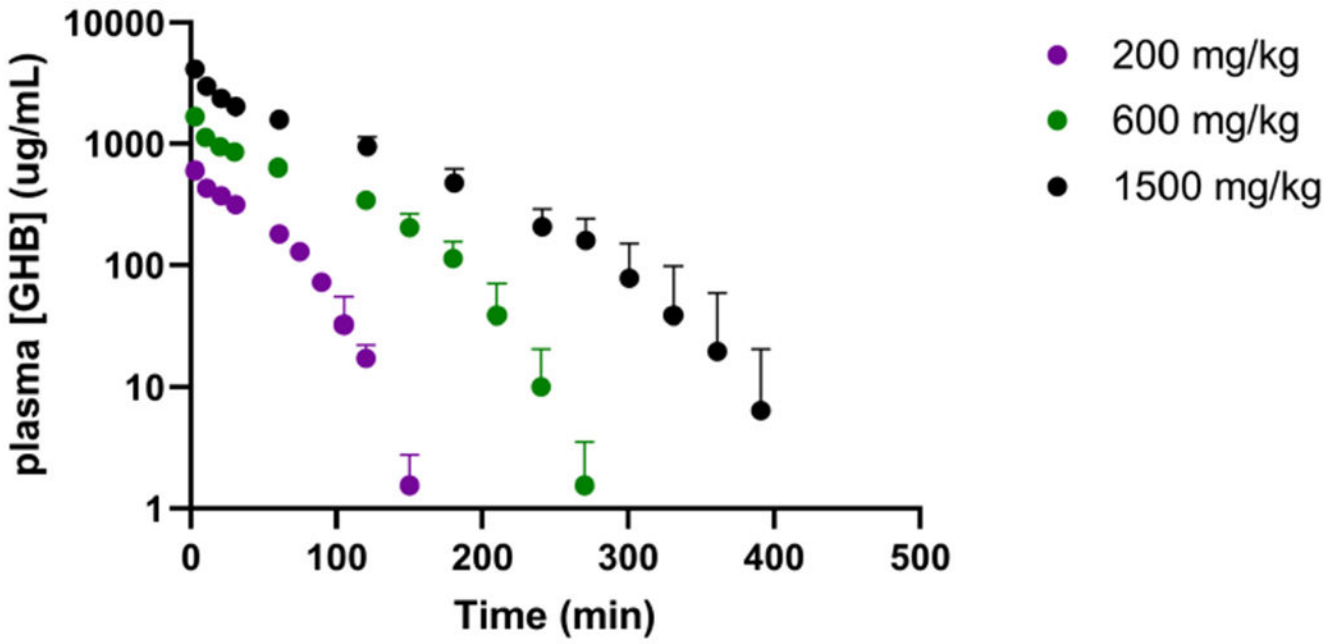

Fig. 6.

Plasma concentrations of GHB after intravenous administration of GHB in rats. Datapresented as mean ± S.D., *n*=4–9.Figure and caption adapted from (26). Data are presentedas mean ± S.D.;*n*=4 to 6

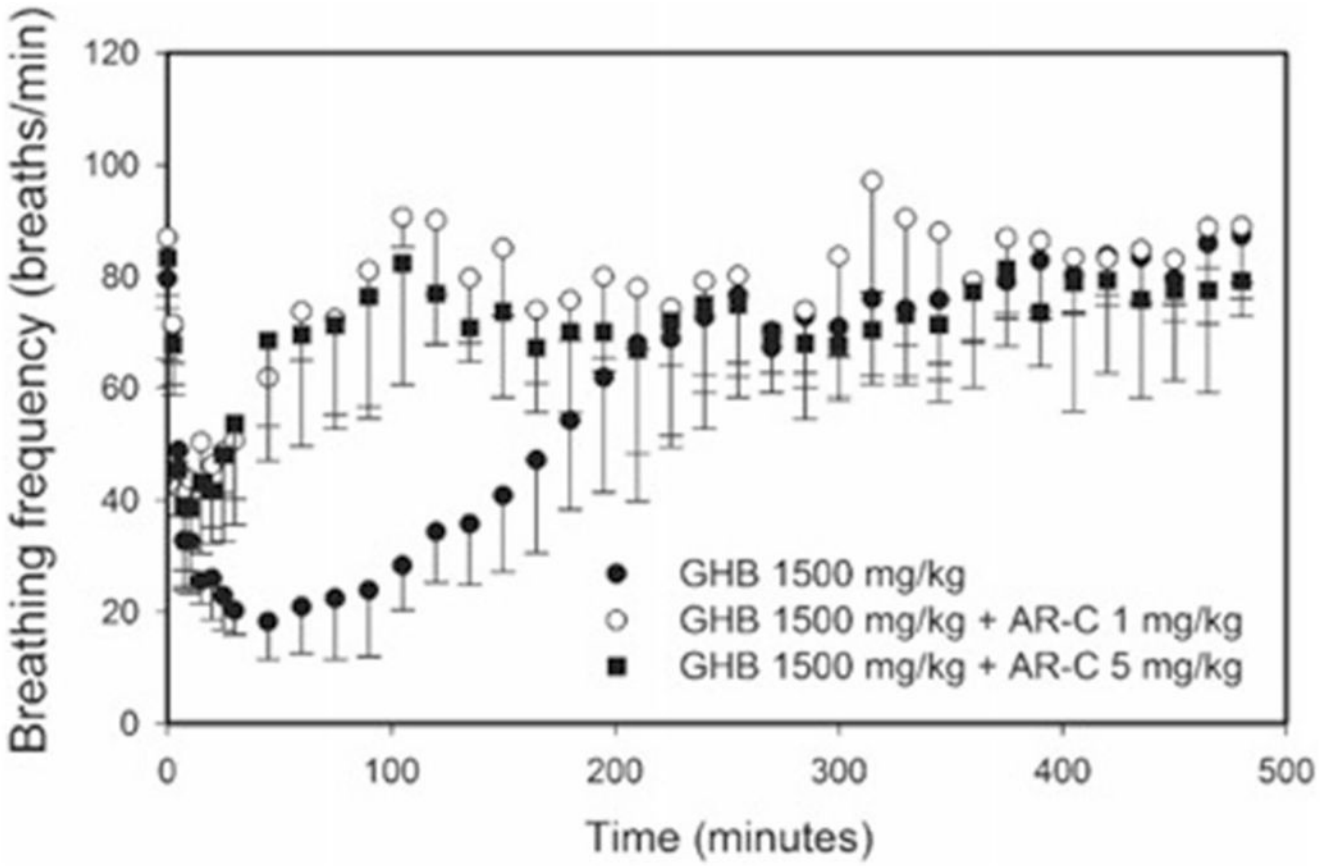

Fig. 7.

Effect of increased clearance due to MCT inhibition by AR-C155858 onGHB-induced respiratory depression. Dose of GHB is 1500mg/kg IV AR-C155858was administered 5min after GHB. Figure adapted from (95). Extent of increaserenal and total clearance by AR-C155858 shown in Table I. Data arepresented as mean±S.D.; n=4 to 6

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Table I.

Dose-Dependent Oral Pharmacokinetics of GHB in Rats and Comparison of L-Lactate Effect on the Oral Pharmacokinetics of GHB in Rats and Humans. Adapted from (98) and (). Plasma GHB concentration profiles from these studies are shown in Fig. 5. Data are presented as mean (S.D.); $n = 7$ to 10 in rat studies. Human pharmacokinetic data are from 10 healthy volunteers

	Rat			Human
GHB alone				
Dose (mg/kg)	200	600	1500	63 mg/kg
CL/F (ml/kg/min)	18.5 (6.3)	7.64 (2.8)	6.36 (1.1)	4.86 (1.8)
CL_R (ml/kg/min)	0.194 (0.098)	0.867 (0.51)	1.62 (0.63)	0.105 (0.053)
% excreted	1.0	11.3	25.5	2.2
GHB with L-lactate				
CL/F (ml/kg/min)	20.9 (9.0)	15.7 (4.9)*	12.2 (1.4)*	4.86 (1.6)
CL_R (ml/kg/min)	0.48 (0.40)*	1.73 (0.92)*	2.48 (0.84)	0.146 (0.063)*
% excreted	2.3	11.0	20.3	3.2*

CL/F total oral clearance, CL_R renal clearance, *CLNR* non-renal (metabolic) clearance, *% excreted*, percent of dose excreted unchanged in urine

*Significantly different from GHB alone ($P < 0.05$)

Table II.

Dose-Dependent Pharmacokinetics of GHB Following IV Administration and Effects of MCT Inhibitors (adapted from (26) and (95)). Data are presented as mean (S.D.); $n = 7–10$

GHB dose	200 mg/kg	600 mg/kg	1500 mg/kg	1500 mg/kg + L-lactate	1500 mg/kg + AR-C155858 1 mg/kg	1500 mg/kg + AR-C155858 5 mg/kg
Cl (ml/kg/min)	7.60 (0.29)	6.00 (0.74)	5.16 (0.70)	6.40 * (0.62)	9.25 * (0.75)	9.42 * (0.98)
Cl_R (ml/kg/min)	0.444 (0.20)	1.68 (0.75)	3.18 (0.66)	4.22 * (0.63)	7.09 * (0.94)	7.44 * (1.07)
% excreted	6%	27%	61%	66%	77% *	79% *

Cl total clearance, CL_R renal clearance, % *excreted,* percent of dose excreted unchanged in urine

* Significantly different from GHB 1500 mg/kg

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