CHAPTER I

INTRODUCTION

Gamma-hydroxybutyric acid (GHB, 4-hydroxybutanoate, 4-hydroxybutyric acid) is a naturally occurring substance in the brain where it is synthesized locally from gamma-aminobutyric acid (GABA) by the action of GABA aminotransferase and succinic semialdehyde reductase (Maitre, 1997). Exogenous GHB was initially developed as an intravenous anesthetic agent and was sold in the U.S. in health food stores as a performance enhancing additive in bodybuilding formulas. Later on, as GHB's euphoric and hallucinogenic properties were known, it became a fashionable club drug. In 1990, following widespread reports of GHB-related coma and seizures, the U.S. Food and Drug Administration (FDA) banned its distribution. In 2000, GHB was added to the list of Schedule I controlled substance in the U.S. (Walters, 2002). Despite being banned by the FDA, GHB is still widely available in the underground drug market. In addition, gamma-butyrolactone (GBL) and 1,4-butanediol, analogs of GHB, are substituted for it and are marketed as dietary supplement in health food stores, sport nutrition stores and on the Internet (Walters, 2002).

GBL is converted into GHB in the presence of sodium or potassium hydroxide, and the reaction is complete in under an hour. Furthermore, once ingested, these analogs of GHB are rapidly metabolized to GHB. GBL is converted to GHB *in vivo* by a rapidly acting lactonase found in blood and liver with a half-time of less than 1 minute. 1,4-butanediol is converted to GHB by alcohol dehydrogenase and aldehyde dehydrogenase. Because of the efficient conversion of both GBL and 1,4-butanediol, their toxicological profiles are analogous to that of GHB (Kerrigan, 2001a). The primary pathway for GHB elimination involves conversion to succinic semialdehyde that is subsequently converted to succinate. Succinate then enters the Krebs cycle and is ultimately expired as carbon dioxide. A small fraction of GHB is metabolized to succinate via a beta oxidation pathway in the liver before entering the Krebs cycle. A negligible amount of GHB is eliminated in urine (Mason and Kerns, 2002).

Factors that seem to contribute to the abuse potential of GHB and its metabolic precursors include its purported anabolic effects, its hypnotic effects, and its ability to incapacitate women for purposes of sexual assault. GHB produces a state of relaxation and tranquility accompanied by feelings of calmness, mild euphoria. Despite these positive feelings attributed to the use of the drugs. As the dose of the drugs is increased, a steep increase in adverse effects may occur. Overdoses with these drugs can result in life-threatening symptoms of CNS depression, coma, respiratory depression, apnea, bradycardia, hypotension, and seizures (Li, Stokes, and Woeckener, 1998). According to the Drug Abuse Warning Network (DAWN), GHB emergency department mentions have increased from 56 in 1994 to 3,340 in 2001. Since 1990, the U.S. Drug Enforcement Administration (DEA) has documented more than 15,600 overdoses and law enforcement encounters and 72 deaths relating to GHB. The FDA has released reports and warning conveying the adverse health consequences of GHB, GBL, and 1,4-butanediol. Ingestion of products containing these substances has been linked to at least 122 serious illnesses and 3 deaths (Kerrigan, 2001a). The FDA has issued warnings for both GBL and 1,4-butanediol, stating that the drugs have a potential for abuse and are a public health danger (Walters, 2002).

Wisotsky (1999) has reported that tetrahydrofuran (THF) is also one of GHB-related chemicals. THF is an organic solvent used in the synthesis of GBL and 1,4-butanediol (National Toxicology Program, 1998; Rhodium, 2003; The Good Reverend Drone, 2003). Recently, increasing inquiries regarding these syntheses have appeared (Morris, 2000; Nicholson and Balster, 2001). Anonymous (2000) has explained the structural comparison of GBL, 1,4-butanediol and THF. Each of these compounds shares the same 4-carbon backbone and differences between them are due to different functional groups at the C-1 and C-4. Hydrolysis of GBL opens the 5-membered ring of the 4-carbon backbone, forming GHB. Conversions of these structures are as follows: the conversion of 1,4-butanediol to THF can be accomplished by dehydrolysis. THF can be converted to GBL via oxidation. Alternatively, oxidation and dehydrolysis can convert 1,4-butanediol directly to GBL. Finally, GBL can be converted into GHB by hydrolysis with sodium hydroxide (Figure 1-1).

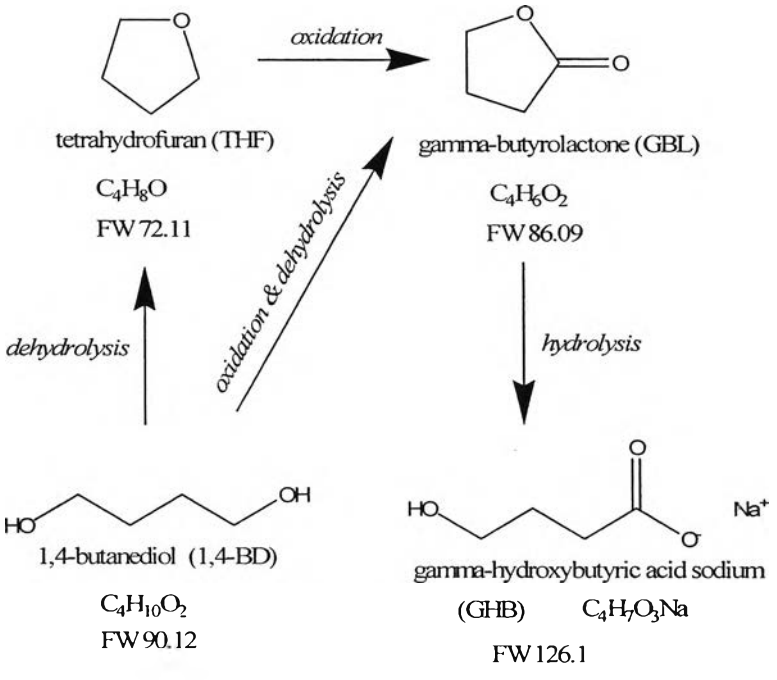

FIGURE 1-1 The Conversion of GHB-Related Chemicals.

Tetrahydrofuran pathway map was proposed by Bjerke (2002). THF is converted to GHB through enzymatic oxidizing activity of tetrahydrofuran hydroxylase, 2-hydroxy-tetrahydrofuran isomerase, 2-hydroxytetrahydrofuran dehydrogenase, butyrolactone hydrolase, and 4-hydroxybuteraldehyde dehydrogenase or auto-oxidation (Figure 1-2)

The literature contains little information on the pharmacology and toxicology of THF. Bamford et al. (1970) demonstrated the intravenous anesthetic activity of THF in mice. Marcus et al. (1976) reported THF (21 mmol/kg, i.p.) induced rat EEG high amplitude, slow wave activity, loss of righting reflex, manifested myoclonic jerks and vibrissae movements to tactile stimulation. THF induced progression of EEG and behavioral changes with characteristic of generalized non-convulsive epilepsy similar to that produced by 4-hydroxybutyric acid and butyrolactone.

Acute exposure to high concentration of THF may cause nausea, dizziness, headache, central nervous system depression and may cause hypotension, coma, and death (Thomson Micromedex, 2004a). Overdose of GHB can cause life-threatening effects similar to acute THF toxicity, such as the central nervous system depression, respiratory depression, apnea, hypotension, coma and death (Teter and Guthrie, 2001; Thomson Micromedex, 2004b). In Thailand, the Thai Food and Drug

Administration reported one-woman death and seven seriously ill victims from drinking wine which contains GBL, tetrahydrofuran (THF), and acetonitrile or methyl cyanide (Kaopatumtip, 2003; Nation multimedia group, 2003). Cartigny et al. (2001) have reported the investigation by ^{1}H nuclear magnetic resonance (^{1}H NMR) spectroscopy of biological fluids in a case of intentional poisoning with THF. The presence of GHB was detected in serum and urine. This could indicate that GHB could have been produced from THF and a metabolic link between the two compounds may exist.

Since no published experiments concerning the neuropharmacological properties of THF exist (Hazardous Substances Databank, 2002; Moody, 1991), the investigation of the central nervous system effects of THF in comparison to GBL will provide more information of THF neuropharmacology, and awareness to the abuse of THF.

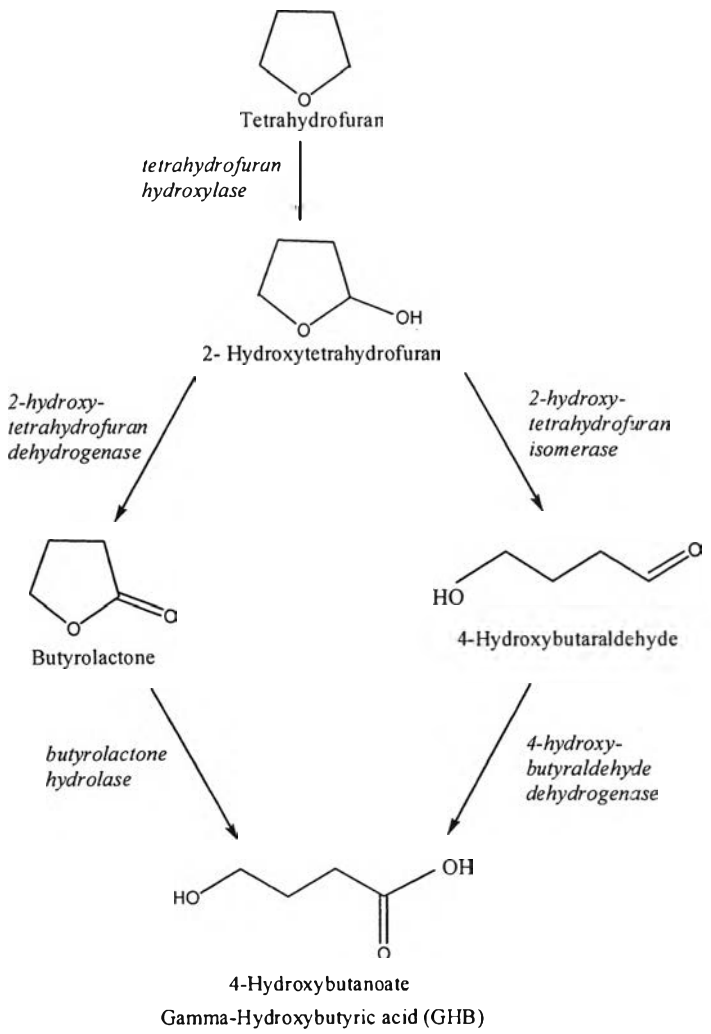

FIGURE 1-2 Tetrahydrofuran Pathway Map (Bjerk, 2002).

Research Hypothesis

The neuropharmacological effects of tetrahydrofuran (THF) display a similar profile to those of gamma-butyrolactone (GBL) and may be possibly related to the mechanism involving $GABA_B$ or GHB specific receptor.

Conceptual Framework

To study behavioral effects of tetrahydrofuran (THF) in comparison to those of GBL. It is possible that THF can exert its central nervous system actions in similar fashion to gamma-butyrolactone (GBL) and/or gamma-hydroxybutyric acid (GHB) and mediate these actions through $GABA_B$ or GHB specific receptor (Figure 1-3).

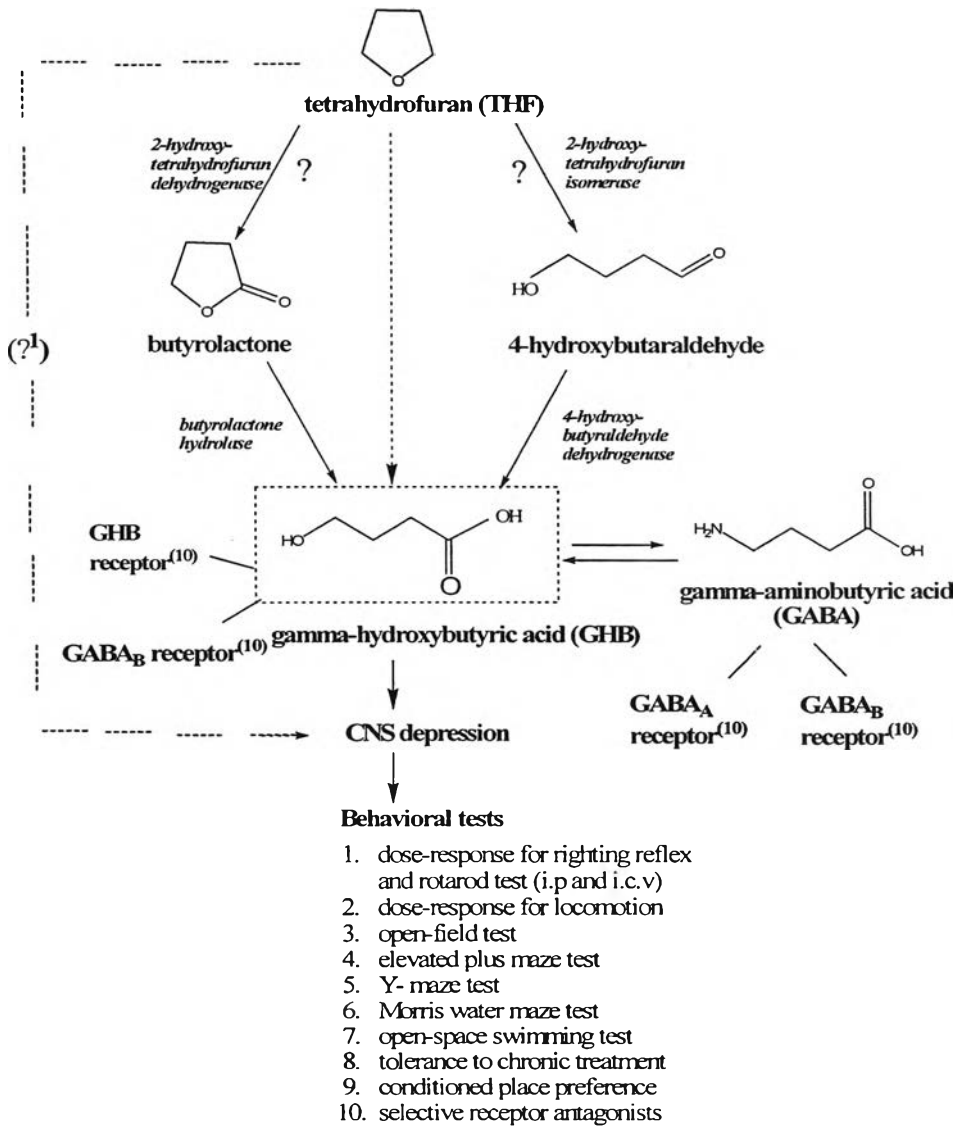

FIGURE 1-3 The Conceptual Framework of Neuropharmacological Profiles of Tetrahydrofuran Research.