Gamma-Hydroxybutyrate (GHB) and its derivatives: A new and novel neuroactive drug of abuse

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There has been increasing attention in the abuse of gamma-hydroxybutyrate (GHB), with some evidence in other parts of the world especially the United States. In vitro and animal research models show that, while GHB shares certain properties with some depressant drugs abusive to central nervous system, it also has unique aspects of its pharmacology including actions at a specific neural receptor which probably mediates many of its effects. So far, the assessment of the abusive potential of GHB with standard animal models has not yielded a picture of a highly abusive substance, and little testing of the drug in human has been done. Very little systematic data exist on the tolerance and dependence of GHB, but both have been seen in human users. Quantitative data on the prevalence of GHB abuse is incomplete, but various qualitative measures indicate that a mini-epidemic of GHB abuse began in the late 1980s and continues to the present. GHB is often included with the group of the so-called 'club drugs', which can be used as an intoxicant. It also has been used as a growth promoter and sleep-aid agent, also implicated in cases of 'date rape', usually in combination with alcohol. Undoubtedly the easy availability of GHB and some of its precursors has contributed to its popularity. With as yet unknown consequences for the scope of the public health problem, recent changes in the control status of GHB in the US may reduce its availability. Experts on drug abuse need to familiarize themselves with GHB since it has a potentiality to be a new type of problem of drug abuse with some unique properties.

Keywords: Gamma-hydroxybutyrate, GHB, Gamma-butyrolactone, GBL, Novel neuroactive drug, New type of drug abuse.

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Objective:

This review highlights the biochemistry, neuropharmacology, and toxicology of the naturally-occurring fatty acid derivative, gamma-hydroxybutyrate (GHB). GHB is derived from gamma-aminobutyric acid (GABA) and is proposed to function as an inhibitory chemical transmitter in the central nervous system. The purposes of this review also focus on the social effect of this substance and urge the public to aware of its increasing abuse potential.

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ภัยคุกคามที่มีจุดประสงค์เพื่อให้บุคคลทางสาธารณสุข ผู้มีอำนาจที่เกี่ยวข้องในการควบคุมการใช้ยาในทางที่ถูกต้อง และประชาชนได้ทราบและทราบข้อมูลของการ GHB และบุคคลที่มีผู้สนใจ แนวทางที่จะมีการใช้ยาในทางที่เหมาะสมและอาจเป็นการเสพติดขั้นสูงที่นำไปสู่ปัญหาทางสังคม และสาธารณสุข

คำสำคัญ: แอมโมเนียมของไบไนโตริทเรท แอมโมเนียมไบไนโตริทเรท ยาออกฤทธิ์ต่อจิตประสาทต่างๆ ยาที่ใช้ในการปล่อยทางเพศ
Gamma-Hydroxybutyrate (GHB; 4-hydroxybutyrate, 4-hydroxybutyric acid) is a central neuromodulator synthesized locally from Gamma-aminobutyric acid (GABA) which is an endogenous constituent of mammalian brains. Synthetic GHB was initially developed as anesthetic agents and was sold in the US in health food store as a performance enhancing additive in bodybuilding formulas. However in 1990, the US Food and Drug administration (FDA) banned its distribution due to its widespread reports of poisoning and adverse reactions. In 2000, GHB was placed into schedule I of the Federal Controlled Substance Act.\(^1\)

**Abusive use of GHB**

Despite being banned by the FDA, GHB is still widely available in the underground drug market. There are analogs of GHB: Gammabutyrolactone (GBL) and 1,4-butanediol which are marketed as dietary supplements in health food stores, sport nutrition stores and on the internet. GBL is converted into GHB in an alkaline environment such as in the presence of sodium or potassium hydroxide and the reaction is complete in under an hour. Additionally, once digested these analogs of GHB are rapidly metabolized to GHB \textit{in vivo} by a rapidly acting lactonase found in the blood and liver. 1,4-butanediol is converted to GHB by alcohol dehydrogenase and aldehyde dehydrogenase. Due to the efficient conversion of both GBL and 1,4-butanediol, their toxicological profiles are essentially analogous to that of GHB.\(^2\)

Factors that seem to contribute to the addictive potential of GHB and its metabolic precursors include its purported anabolic effects, its hypnotic effects and its ability to incapacitate victims (mostly women) for purposes of sexual assault. GHB produces a state of relaxation and tranquility accompanied by feelings of calmness, mild euphoria. As the dose of these drugs is increased, a sharp 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.\(^3\) 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 US Drug Enforcement Administration (DEA) has documented more than 15,600 overdoses and law enforcement encounters and 72 deaths related to GHB. The FDA has released reports and warning conveying the adverse health consequences of GHB, GBL, and 1,4-butanediol. Ingestion of the products containing these substances have been linked to at least 122 serious illnesses and three deaths.\(^2\) 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.\(^1\)

**Situation in Thailand**

In 2003, the Food and Drug Administration of Thailand reported death of a woman and seven cases of serious illness resulted from drinking wine that contains GBL, tetrahydrofuran (THF), and acetonitrile or methyl cyanide.\(^4\)\(^5\) The wine was in a lot of 144 bottles which two foreigners had been hired to mail the bottles to the US but the company was unable to send it.\(^4\)
Biotransformation of GHB and THF

Comparing the structures of GBL with 1, 4-butanediol and THF, it was found that each of these compounds share the same 4-carbon backbone and the differences between them are due to the 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 structure 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.

The literature contains little information on the pharmacology and toxicology of THF. Bamford, et al. demonstrated the intravenous anesthetic activity of THF in mice. Marcus, et al. reported THF (21 mmol/kg i.p.) induced EEG high amplitude in rats, slow wave activity with a latency of 2 min, loss of right reflex, manifested myoclonic jerks and vibrissae movements to tactile stimulation. THF-induced progression of EEG and behavioral changes the characteristic of generalized non-convulsive epilepsy similar to that produced by 4-hydroxybutyric acid and butyrolactone.

Cartigny, et al. reported an investigation by 1H nuclear magnetic resonance (1H NMR) spectroscopy of biological fluids in a case of intentional poisoning THF. The presence of GHB was detected in serum and urine. This could indicate that GHB could be produced from THF and a metabolic link between the two compounds may exist.

Acute exposure to high concentrations of THF may affect the central nervous system to produce effects such as behavioral sedation and narcosis in mammals, gastrointestinal tract like nausea, vomiting and diarrhea and may cause respiratory depression, coma, and death. Overdose of GHB can cause life-threatening effects similar to acute THF toxicity, such as respiratory depression, apnea, hypotension, coma and death. Currently there are no antidotes to treat GHB overdose or THF toxicity. Knowledge about the biotransformation of THF to GHB could be useful in designing pharmacological interventions.

Gamma-hydroxybutyric acid and its precursor

The sodium salt of GHB has a molecular formula of C4H7NaO3 and a molecular weight of 126.09. It is a naturally occurring derivative of the major CNS inhibitory neurotransmitter, Gamma aminobutyric acid (GABA). GHB appears to have no legitimate use as an industrial chemical. Importantly, gamma-butyrolactone (GBL) and 1,4-butanediol, two GHB precursor molecules, one used extensively in chemical manufacturing. GBL is known by the chemical names 2(3H)-furanone and 1,4-butanediol has a synonym of 1,4-tetramethylene glycol. GBL and 1,4-butanediol are both chemical precursor and metabolic precursor of GHB. They have been marketed as 'legal' alternatives to the FDA-banned GHB, GHB has been studied outside the United States as a potential treatment for narcolepsy, sleep apnea, opiate withdrawal and alcohol withdrawal and dependence.

Additionally, apart from GBL and 1, 4-butanediol the most recent precursor to have appeared is tetrahydrofuran (THF). A recent survey of Internet sites related to GHB indicates a potential in the clandestive manufacture of GHB. Currently, there
is increasing inquiries regarding the synthesis of 1, 4-butanediol, and THF is also mentioned.\(^{(12)}\)

THF is one of the GHB-related chemicals.\(^{(13)}\) There are many references for the synthesis of GBL from THF by chemical experiments.

**Endogenous GHB in the brain**

GHB is a short-chain fatty acid that occurs naturally in the mammalian brain at a concentration of 1-4 microns.\(^{(14)}\) Gamma-aminobutyric acid (GABA) is believed to be the primary precursor of GHB in the brain. It is synthesized by a specific pathway that transforms GABA into succinic semialdehyde via GABA-transaminase activity, then succinic semialdehyde is converted into GHB by a NADPH-dependent enzyme succinic semialdehyde reductase (SSR). However, GHB can be reconverted back to SSA via GHB dehydrogenase and the GHB derived SSA can be converted back to GABA. SSA can also be metabolized by succinic semialdehyde dehydrogenase (SSADH) to succinic acid which then enters the Krebs cycle (Figure 1).\(^{(2)}\)

GHB has many properties that suggest this compound might play a role in the brain as a neurotransmitter or neuromodulator. The presence of GHB receptor is suggested by specific high-affinity \(^{(3)}\)GHB binding sites that occur in the brain with the highest density found in the hippocampus allowed by the cortex and then the thalamus.

![Figure 1. The biotransformations of GHB and its precursors\(^{(2)}\)](image-url)
GHB also binds to the GABA<sub>B</sub> receptor. The relevance of this remains unknown but it suggests that some of the pharmacological actions of GHB are weak but selective agonist of GABA<sub>B</sub> receptor.

GHB can be metabolized in vivo to GABA and trans-4-hydroxycrotonic acid, which are pharmacologically active at GABA<sub>B</sub> and GHB receptor, respectively. Many of the pharmacological and clinical effects of exogenously administered GHB are mediated via the GABA<sub>B</sub> receptor, where GHB might act both directly as a partial agonist and indirectly through GHB-derived GABA. GHB appears to be a weak GABA<sub>B</sub> receptor agonist, with an affinity for the GABA receptor in the millimolar range. Therefore the high concentration of GHB in the brain that would increase following exogenous administration could activate GABA<sub>B</sub> receptor.

Alternatively, GHB could activate the GABA<sub>B</sub> receptor indirectly via its conversion to GABA. This hypothesis could explain that the high concentration of GHB is required to produce GABA<sub>B</sub> receptor-mediated effects because of high micromolar to low millimolar concentration of GABA receptors. The possibility of GHB-derived GABA playing a role when the concentration of GHB is high as would be the case in GHB abuse and toxicity.

Pharmacokinetics of GHB

GHB is rapidly absorbed, freely crosses the blood-brain-barrier with an onset of action within 15 minutes according to the laboratory testing in animals and humans. The half-life of GHB is 22-28 minutes after an oral dose of GHB 25 mg/kg and the free fraction of GHB in plasma indicating a lack of significant plasma protein binding. Owing to the short half-life, there is no accumulation of GHB with repeated dosing and GHB doses up to 100 mg/kg are no longer detectable in the blood from 2-8 hours or in the urine after 8-12 hours. In summary, it has been suggested that regardless of the dose given, the elimination of GHB is rapid, even in those with compromised liver function; GHB is completely eliminated within 4-6 hours after ingestion.

For GBL and 1,4-butanol, they were metabolized to GHB (Figure 1), and thus have similar pharmacologic and toxic effects as GHB. GBL is converted to GHB in vivo by a rapidly acting lactonase found in blood and liver which the half-life take approximately 1 minute in animal GBL given per orally, intraperitoneally or intravenously is capable of producing higher concentration of GHB in rat brain and blood than an equimolar amount of GHB administered by the same route. It was noted that GHB blood concentration fell more rapidly after GHB than GBL administration. Roth and Giarnam suggested that GBL was found to concentrate more in the lean muscle than did GHB. This depot pool of the drug appears to be metabolized more slowly because it is not readily accessible to enzyme involving in its biotransformation and slowly release back into the blood stream. This tissue, in turn, may act as a reservoir for GBL and extend its duration of action.

1, 4-Butanol is converted to GHB by alcohol dehydrogenase, and aldehyde dehydrogenase via an intermediate, 4-hydroxybutanal. Pyrazole, an inhibitor of alcohol dehydrogenase competitively blocks the oxidation of 1,4-butanol by the rat liver supernatant. Administration in vivo of
pyrazole to the rat prevents the appearance of GHB, a 1,4-butanediol metabolite, in the blood.

**Dose related effects**

The primary dose-related effects of GHB are related to CNS depression, with GHB, very small dosage differences can cause greatly different effects. The difference between the dose required to produce sleep and the dose required to produce coma or death is usually less than 1 gram.

For a person weighing 140 lbs: 2 gm usually results in relaxation, decreased heart rate and respiration and motor impairment, 2 - 4 gm will usually bring about severe intoxication, 5 - 6 gm usually leads to coma, 6 gm will normally result in respiratory arrest.

In terms of mg/kg dose, 10 mg/kg GHB is capable of producing amnesia and hypotonia of the skeletal muscles resulting from the depression of neurons in the spinal cord. At 20-30 mg/kg, GHB promotes a normal sequence of rapid eye movement (REM) and non-REM (slow-wave) sleep, which lasts from 2-3 hours. At 40-50 mg/kg intravenously or orally, GHB produces a state of somnolence, which appears within 5-15 minutes. Anesthesia is associated with the doses of 50 mg/kg, and doses that are higher than 50 mg/kg are associated with coma, as well as decreased cardiac output, respiratory depression, and seizures. These effects are more pronounced with the co-ingestion of CNS depressants, particularly ethanol. The pharmacological and clinical actions of GHB are summarized in Table 1.

### Table 1. Pharmacological and clinical actions of GHB.

<table>
<thead>
<tr>
<th>GHB Doses</th>
<th>Physiological responses</th>
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</thead>
<tbody>
<tr>
<td><strong>Physiological and toxicological effects of single doses in rats.</strong></td>
<td></td>
</tr>
<tr>
<td>5 - 30 mg/kg i.p.</td>
<td>Hyperthermia</td>
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<tr>
<td>150 mg/kg i.p.</td>
<td>Anxiolytic activity</td>
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<tr>
<td>200 - 400 mg/kg i.p.</td>
<td>Sedation, absence-like seizures</td>
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<tr>
<td>400 - 750 mg/kg i.p.</td>
<td>Hypothermia, loss of righting reflex, apnea</td>
</tr>
<tr>
<td>500 - 1600 mg/kg i.p.</td>
<td>Coma</td>
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<tr>
<td>1700 mg/kg i.p.</td>
<td>Respiratory depression, LD₅₀</td>
</tr>
<tr>
<td><strong>Clinical and Toxicological effects of single doses in humans</strong></td>
<td></td>
</tr>
<tr>
<td>10 mg/kg p.o.</td>
<td>Anxiolysis, amnesia, hypotonia</td>
</tr>
<tr>
<td>20 - 30 mg/kg i.v. (50-60) mg/kg p.o.)</td>
<td>Unconsciousness, anesthetic adjuvant</td>
</tr>
<tr>
<td>60 - 100 mg/kg p.o.</td>
<td>Coma, epileptic seizures, respiratory depression</td>
</tr>
</tbody>
</table>
Toxicological analysis

Routine toxicological screening tests do not detect GHB-related compounds because of efficient transformation of GHB’s precursors. Toxicological analysis of GBL and 1, 4-butanediol in vivo, is commonly targeted towards GHB. In vitro the process of conversion of GHB to GBL has been readily used for toxicological analyses. GBL is more amenable to conventional methods of extraction and gas chromatography compared with GHB, which is considerably more polar and less volatile. GHB can be analyzed directly using either liquid-liquid or solid-phase extraction techniques. Due to its small size and polar moieties, the extracts tend to be non-specific, and therefore derivatization prior to chromatographic analysis is necessary.

Early gas chromatographic analyses were developed for the measurement of endogenous GHB in tissue. Samples were heated in the presence of acids, converting GHB to GBL, and the process was capable of measuring GHB concentration as low as 1.45±0.22 nmol/g (0.183 ± 0.028 mg/L) (N = 4) of brain tissue in the rat. Subsequent gas chromatography – mass spectrometry (GC-MS) assays were developed specifically for measuring GHB in human plasma and urine concentration as low as 0.2 and 0.1 mg/L, respectively. However, the technique also required conversion of GHB to GBL. GC-MS assays allowing direct measurement of GHB in urine and blood with detection limits of 0.5-2 mg/L without GBL conversion have been developed.

A high-performance liquid chromatography assay also has the advantage of being able to measure both GHB and GBL. This may be useful for measuring drugs in the overdose setting when GBL has been ingested and partially metabolized to GHB, resulting in both drugs being present. Cartigny, et al. and Imbenotte, et al. have applied nuclear magnetic resonance (NMR) spectroscopy to identify and quantify GHB in serum and urine directly.

GHB and dopamine

Many experiments have firmly established that GHB perturbs the followings: the firing rates of dopaminergic neurons, dopamine release, dopamine synthesis, levels of dopamine and its major metabolites. However, GHB appears either to inhibit or to stimulate dopamine functions, depending on the following factors, i.e. GHB doses, routes of administration, animal species, brain latencies, technique of measure and type of anesthesia.

GHB and GABA neurotransmission

Systematically administered GHB at low doses produces pharmacological responses specifically mediated by GHB receptors and blocked by GHB receptor antagonist. However, most of the behavioral and biochemical responses induced by GHB occur only when its brain level increase more than 50–200 fold their endogenous values.

At these high dose GHB specific binding sites are probably saturated, and it is likely to interacts with other systems. At about 5–10 mg/Kg i.p., GHB increased the spontaneous firing rate of prefrontal cortex neurons recorded in urethane-anesthetized rats; on the contrary at higher doses (160 – 320) mg/kg i.p., it decreased the activities. The selective GHB receptor antagonist NCS–382 blocked the effects of the low doses, but left those of high doses unchanged.
In vivo reports suggest that GHB can also modulate GABAA response: the GABAA receptor agonists musimol exacerbated GHB – it induced absence seizures whereas the antagonist flumazenil, attenuated the anxiolytic effect of GHB.\(^{(38)}\) The fact that high doses of GHB mimic GABA-mediated responses could be explained by a GHB mediated control of GABA release, the re-transformation of GHB in a GABA or GHB is a structural analogue of GABA that could bind to GABA receptors.\(^{(16)}\)

**Biotransformation**

**GHB addiction and withdrawal**

The clinical presentation of GHB withdrawal ranges from mild clinical anxiety, agitation, tremors, and insomnia to profound disorientation, increasing paranoia with auditory and visual hallucination, tachycardia, elevated blood pressure, and extraocular motor impairment.\(^{(32)}\) Studies in rodents are in concordance with the clinical data. After repeated treatment with GHB for 14 days, mice developed tolerance to the hypolocomotion effects of the drug. Martellotta, et al.\(^{(33)}\) and Fattore, et al.\(^{(34)}\) have evaluated that GHB possesses rewarding properties are achieved through conditioned place of preference and intravenous self-administration.

**Clinical management of GHB intoxication**

Management of acute GHB intoxication focuses on alleviating symptoms and providing support for airway management, i.e. mechanical ventilation, prevention of aspiration and measures to counter bradycardia are also commonly required. Due to the rapid absorption of GHB, gastric lavage, gastric lavage or activated charcoal may be ineffective. There are no widely accepted antidotes to GHB, although physostigmine, a choline esterase inhibitor, has shown some promise as a reversal agent. The opiate and GABA antagonists, naloxone and flumazenil, are ineffective. Spontaneous recovery from GHB overdose is common, usually within a few hours.\(^{(30)}\) Therapeutic intervention with the GABAb receptor antagonist CGP-35348 increased survival to 36.4 % in animals. However, treatment with the GHB receptor antagonist NCS-382 was much more effective, resulting in a survival rate of 61.5 %.\(^{(31)}\) These data suggest that both the GABA receptor and GHB receptor are involved in the pathogenesis of CNS manifestation of GHB ingestion.

**Conclusion**

Gamma-hydroxybutylate and its derivatives are new neuroactive drugs that have been used as anesthetic agents and anabolic drugs for many years. However, nowadays, there have been many reports about their morbidity, mortality due to misuse of the substances for certain purposes such as sexual seduction or ‘date rape’, or in the night club where they are so-called ‘club drugs’ to enhance the mood. Gamma-hydroxybutyrate and its derivatives are usually consumed with alcohol which can lead to slight sedation, coma and fatal respiratory depression according to the dosage of intake. These substances are unable to be detected by routine toxicological screening due to the efficient biotransformation of their precursors. Nevertheless, there are specific investigation techniques that can be used to detect the substances directly: derivatization, silylation and then using either liquid-liquid or solid-phase extraction techniques. Additionally, in vitro conversion of GHB
to GBL has been used for toxicological analysis as well because GBL is more amenable to conventional methods of extraction and gas chromatography than GHB.

In the treatment of GHB intoxication, the clinical management focuses on symptomatic and supportive basis because there is no specific antidote for GHB intoxication. Decontamination technique such as gastric lavage or activated charcoal may not be able to help much because of its rapid absorption property. However, spontaneous recovery from GHB overdose is usually common within a few hours.

Lastly, there is increasing misuse of these substances due to insufficient control of distribution and availability of neuroactive drugs. These new neuroactive drugs are highly potential to be one of the major public health and social problems unless there is enough awareness and proper control of them.

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กิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์

ท่านสามารถได้รับการรับรองอย่างเป็นทางการสำหรับกิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์ กลุ่มที่ 3 ประเภทที่ 23 (ศึกษาด้วยตนเอง) โดยศูนย์การศึกษาต่อเนื่องของแพทย์ จุฬาลงกรณ์มหาวิทยาลัย ตามเกณฑ์ของศูนย์การศึกษาต่อเนื่องของแพทย์แห่งประเทศไทย (ชมพ.) จากการรายงานความเรื่อง “แก๊มมาไฮโดรอกซีบิวтрат (GHB) สารออกฤทธิ์ต่อประสาทด้วยเนื้อที่กับน้ำมันไว้ในทางที่มีผล” โดยตอบคำถามข้างล่างนี้ ท่านมีคุณสมบัติของด้วยแบบฟอร์มคำตอบท้ายคำถาม โดยสามารถตรวจสอบจำนวนเครดิตได้จาก http://www.ccme.or.th

คำถาม - คำตอบ
1. What is the sign and symptom of Gamma-hydroxybutyrate (GHB) intoxication?
   a. CNS depression
   b. Bradycardia
   c. Seizure
   d. Respiratory depression
   e. All of above are the clinical symptoms of GHB intoxication

2. What substance can be detected in the serum and urine of the Tetrahydrofuran (THF) poisoning patient?
   a. Gamma-hydroxybutyrate (GHB)
   b. Gamma-butyrolactone (GBL)
   c. 1,4-butanediol
   d. Tetrahydrofuran (THF)
   e. All of above can be found in the serum and urine

3. What is the direct chemical and metabolic precursor of GHB?
   a. 1,4-butanediol
   b. Gamma-butyrolactone (GBL)
   c. 1,4-tetramethylene glycol
   d. All of above
   e. None of above

คำตอบ ส่งรับแบบมือเรื่อง "แก๊มมาไฮโดรอกซีบิวтрат (GHB) สารออกฤทธิ์ต่อประสาทด้วยเนื้อที่กับน้ำมันไว้ในทางที่มีผล"
จุฬาลงกรณ์มหาวิทยาลัย ปีที่ 48 ฉบับที่ 7 เดือนกรกฎาคม พ.ศ. 2547
รหัสการศึกษาต่อเนื่อง 3-23-201-9010/0407-(1012)
ชื่อ - นามสกุลผู้ขอ CME credit..........................................................เลขที่ใบประกอบวิชาชีพเวชกรรม...........................................
ที่อยู่..........................................................
4. What is the primary precursor of GHB in the brain?
   a. Gamma-aminobutyric acid (GABA)
   b. Succinic semialdehyde
   c. Trans-4-hydroxycrotonic acid
   d. 1,4-butanediol
   e. Tetrahydrofuran (THF)

5. How to detect the GHB-related compound from biological specimen properly?
   a. Routine toxicological screening test
   b. Extraction and gas chromatography
   c. Liquid-liquid phase extraction technique
   d. Solid-phase extraction technique
   e. All b, c and d techniques are the proper technique