

γ -Hydroxybutyrate Conversion into GABA Induces Displacement of GABA_B Binding that is Blocked by Valproate and Ethosuximide¹

VIVIANE HECHLER, CHARLINE RATOMPONIRINA and MICHEL MAITRE

L.N.M.I.C., UPR 416 CNRS, Centre de Neurochimie, Strasbourg Cedex, France

Accepted for publication January 30, 1997

ABSTRACT

γ -Hydroxybutyrate (GHB) has been reported to be a ligand for GABA_B receptor(s), although with low or very low affinity (IC₅₀ = 150–796 μ M). In addition, several reports argue for a role of GHB via GABA_B receptors in both *in vivo* and *in vitro* electrophysiological experiments. In the present study, we demonstrate that the inhibition of GHB's conversion into GABA by rat brain membranes blocks the ability of GHB to interfere with GABA_B binding. In particular, the inhibition of GHB dehydroge-

nase by valproate or ethosuximide and the blockade of GABA-T by aminooxyacetic acid induce the disappearance of the GABA-like effect of GHB at GABA_B, but also at GABA_A, receptors. This finding could explain the misinterpretation of *in vitro* or *in vivo* experiments where GHB possesses a GABA-like effect. But in addition, it is postulated that the normal metabolism of GHB in brain induces GABA_B mechanisms that could be blocked by the administration of valproate or ethosuximide.

GHB is a naturally occurring substance that is located in almost all brain regions (Vayer *et al.*, 1988), together with succinic semialdehyde reductase, the enzyme responsible for its synthesis. However, it is thought to play a direct functional role only in some restricted brain areas, a view supported by the heterogeneous distribution of its receptor sites. These are located largely in the cortex, hippocampus and thalamus, together with dopaminergic brain structures including the dorsal and ventral striatum, olfactory tracts, A₉, A₁₀ and A₁₂ (Hechler *et al.*, 1992). The major part of the hypothalamus, pons-medulla and cerebellum are totally devoid of high-affinity binding sites for GHB, as are peripheral tissues such as liver, muscles and kidneys. Specific high-affinity GHB binding sites have also been found in cell membranes prepared from human brain (Snead and Liu, 1984). This binding does not require Na⁺ and is not displaceable by GABA, muscimol, baclofen, isoguvacine, dopamine or picrotoxin, but only by GHB and structurally related analogs (Benavides *et al.*, 1982).

Electrophysiological studies have shown an effect of GHB on about 50% of the cells examined in the nigro-striatal pathway (Harris *et al.*, 1989), in the neocortical region (Olpe and Koella, 1979) and in the parietal cortex (Kozhechkin, 1980). When used at low doses *in vivo* (5–10 mg/kg), GHB induces a depolarizing effect that is blocked by the GHB receptor antagonist NCS-382 (Godbout *et al.*, 1995). How-

ever, when used at higher doses both *in vivo* and *in vitro* (in general ≥ 100 μ M *in vitro* and ≥ 300 mg/kg *in vivo*), GHB induces a membrane hyperpolarization that is bicuculline-resistant (Olpe and Koella, 1979) but that has been reported to be sometimes inhibited by GABA_B antagonists (CGP 35 348 or CGP 55 845) (Xie and Smart, 1992; Williams *et al.*, 1995; Ito *et al.*, 1995). The number of GHB-responsive neurons appears to be much lower than the number of GABA-responsive neurons in the brain regions investigated. The neuronal hyperpolarization induced by GHB *in vivo* or after incubation of brain tissue slices with GHB probably explains the decrease in dopaminergic neuronal activity resulting in a decreased dopamine release in the nigro-striatal pathway after administration of GHB (Walters *et al.*, 1973). Baclofen has similar effects on dopaminergic neurons (Da Prada and Keller, 1976).

Thus GHB induces specific physiological responses that are dependent on its interaction with GHB receptors that are distinct from GABA_B receptors in kinetics, pharmacology, distribution and ontogeny (Benavides *et al.*, 1982; Hechler *et al.*, 1992; Snead, 1994). However, a possible GABAergic contribution to the pharmacological effects of GHB must be considered. This contribution can be explained by a direct interaction of GHB with GABA_B sites, because GHB displaced GABA_B binding with an IC₅₀ value of 100–200 μ M (Bernasconi *et al.*, 1992), 500 μ M (Ito *et al.*, 1995) or 796 μ M (Ishige *et al.*, 1996). These values largely exceed endogenous GHB levels in brain, which peaked at maxima of 5 to 6 μ M (Vayer *et al.*, 1988).

Received for publication September 3, 1996.

¹ This work was supported by a grant from DRET 93-172.

ABBREVIATIONS: GHB, γ -hydroxybutyrate; SSA, succinic semialdehyde; GABA-T, γ -aminobutyrate transaminase

Several authors have suggested that labeled GABA is formed *in vivo* after the administration of labeled GHB with no increase in GABA concentration (see, for example, DeFeudis and Collier, 1970), although one group has suggested that brain GABA levels are increased (Della Pietra *et al.*, 1966). In our hands, [³H]-GHB is consistently transformed into [³H]-GABA by brain extract (Vayer *et al.*, 1985). This conversion is due to the coupled effect of GHB dehydrogenase and NADP to yield succinic semialdehyde (SSA); then GABA-T activity transaminates SSA into GABA. GHB dehydrogenase is a cytosolic enzyme that is inhibited by a wide range of antiepileptic compounds, including barbiturates, valproate, ethosuximide and trimethadione (Kaufman and Nelson, 1991). Most of these compounds, when administered to rats, induce an accumulation of GHB in the brain (Snead *et al.*, 1980).

The purpose of this study was to demonstrate that, under the conditions used for *in vitro* GABA_B binding experiments, under *in vivo* conditions and in experiments carried out with brain slices or cell cultures, GHB is partially degraded by brain extract into GABA, which then displaces GABA_B binding. In our experiments, GHB degradation into GABA was prevented by GHB dehydrogenase inhibition with either valproate or ethosuximide or by GABA-T inhibition with aminooxyacetic acid.

Materials and Methods

Animals. Male Wistar rats weighing 250 to 300 g were killed by a blow on the head; their brains were rapidly extracted and used as starting material. Procedures involving animals and their care were conducted in conformity with national and international regulations (decree n° 87848, October 19, 1987, and EEC council directive 86/609, QJ L 358, December 12, 1987).

GABA_B binding to rat brain membranes. The methods of Hill and Bowery (1981, method 1) and of Bernasconi *et al.* (1992, method 2) were used to assess the ability of GHB to displace GABA_B binding. Method 1 was used in general, but method 2 was adopted in some experiments because an IC₅₀ value of 150 μM was measured for GHB under these conditions. Crude synaptic membranes (P₂ fraction) were prepared from total brain or from cerebrum or cerebellum. In method 2, the vesicular preparation was further purified by centrifugation on 0.8 M buffered sucrose. After hypoosmotic shock, the membranes were centrifuged and frozen at -20°C overnight (method 1) or for 2 days (method 2). After several incubations and washings at ambient temperature, the pellets were used for GABA_B binding determinations. Incubations were carried out in 600 μl of buffer (50 mM Tris-HCl, 2.5 mM CaCl₂, pH 7.4) at ambient temperature with 25 nM [³H]-GABA (Dupont-NEN, France, 7.4 Ci/mmol), Isoguvacine (100 μM, final concentration) and GHB (concentrations from 10 μM to 5 mM) were added. In some experiments, media were supplemented with valproate or ethosuximide at a final concentration of 1.5 mM. Nonspecific binding was determined in the presence of 100 μM baclofen.

GABA_A binding in the presence of GHB. The effect of GHB on GABA_A binding was tested using [³H]-muscimol (19 Ci/mmol, Dupont-NEN). Membranes were prepared from a crude synaptosomal/mitochondrial fraction of rat brain according to the method of Olsen *et al.* (1981). GABA_A receptor binding was measured by a rapid filtration assay at 0-4°C in Na⁺-free buffer. [³H]-muscimol was included at 25 nM (final concentration) with or without 0.1 mM nonradioactive GABA. Samples containing 1 mg of protein in an assay volume of 600 μl were incubated 15 min at 0-4°C with increasing concentrations of GHB (10 μM to 10 mM). The incubation media were rapidly filtered at 4°C under suction and then were rinsed twice with 2 ml incubation buffer (50 mM Tris-citrate, pH 7.1, at 0°C).

Effects of antiabsence drugs on the conversion of [³H]-GHB to [³H]-GABA by rat brain membranes. Crude synaptic membranes were prepared according to Hill and Bowery (1981). These membranes were incubated at ambient temperature in 50 mM potassium phosphate buffer, pH 7.4, containing 200 μM [³H]-GHB (10 μCi/mmol) and 1.5 mM of either ethosuximide or valproate. The kinetics of the [³H]-GABA formed was monitored after separation from [³H]-GHB on a Dowex 50W-X8 column (0.5 × 3 cm, H⁺ form). Controls were carried out in the absence of antiepileptic drugs. Radioactive GABA eluted from the columns by 0.1 N NaOH was counted by means of a liquid scintillation counter (Vayer *et al.*, 1985).

In another set of experiments, various concentrations of valproate or ethosuximide (0-5 mM) were added to the medium and incubated for 20 min at ambient temperature in the presence of 200 μM [³H]-GHB (10 μCi/mmol). The [³H]-GABA formed at each inhibitor concentration was measured using the ion-exchange chromatographic protocol previously described. The K_i value for each inhibitor was determined by plotting 1/v = f([inhibitor]).

Measurement of [³H]-aminoacids formed from [³H]-GHB in the presence of rat brain crude synaptosomal membranes. Crude synaptosomal membranes were prepared from a whole rat brain according to the method of Hill and Bowery (1981). These membranes were incubated 20 min at ambient temperature with 1 ml of 50 mM Tris-HCl, pH 7.4, containing CaCl₂ (2.5 mM) and 200 μM [³H]-GHB (100 μCi/200 nmol). Perchloric acid (0.1 M, final concentration) was added to precipitate the proteins, which were removed by centrifugation. The amino acid content of the supernatant was determined by separation of the amino acids' o-phthalaldehyde derivatives by high-performance chromatography/fluorimetric detection, using a modification of the method of Allison *et al.* (1984). Briefly, all chromatographic separations were performed with a Nucleosil C 18 column (5 μm, 25 × 0.4 cm) with two Waters pumps 590 and a Waters Baseline 810 integrator. Detection was carried out with a Waters fluorimeter 470 (excitation: 345 nm, emission: 455 nm). The mobile phase was a binary gradient of solution A (0.1 M NaH₂PO₄, pH 6.0, containing 2% methanol, pH 6.0) and of solution B (40% 0.1 M NaH₂PO₄, pH 6.0, 30% methanol and 30% acetonitrile). Precolumn autoderivatization (2 min) and injection were achieved with a CMA 200 refrigerated Microsampler (Carnegie Medicine, Sweden) by adding to 20 μl of tissue extract 20 μl of the following derivatization mixture: 5 ml of 0.1 M sodium tetraborate, pH 9.5, containing 10 μl of 3-mercaptopropionic acid (Sigma, Aldrich Chimie, France) and 15 mg of o-phthalaldehyde (Sigma) in 500 μl of methanol. Elution was carried out at a rate of 0.8 ml/min and at a temperature of 35°C with the following steps: 0 min, 90% A/10% B; 15 min, 40% A/60% B (linear gradient); 16 min, 40% A/60% B (isocratic); 19 min, 100% B (isocratic); 24 min, 90% A/10% B (isocratic) until 29 min.

The different peaks of the amino acids derivatives were collected after chromatographic separation, and their radioactivities were determined by liquid scintillation spectrometry.

Statistical analysis. Nonlinear regression fitting and IC₅₀ calculations were performed using the Graphpad-Prism program. Comparison between regression curves was analyzed using the two-way ANOVA statistical test.

Results

Effects of GHB on GABA_B binding in the presence and absence of GHB dehydrogenase inhibitors. In a first set of experiments, GABA_B binding was carried out on rat brain crude synaptosomal membranes prepared according to the method of Bernasconi *et al.* (1992) or to that of Hill and Bowery (1981). The presence of 100 μM GHB in the incubation medium led to different percentages of displacement of radioactive GABA (from zero to a maximum of 37%.

in the amount of GABA formed from GHB in the different incubation media. However, when valproate (5 mM) was present in the medium, GHB was without effect on GABA_B binding no matter what technique was used for membrane preparation (table 1).

In a second set of experiments, displacement by GHB of GABA_B binding was studied in the presence and absence of concentrations of GHB dehydrogenase inhibitors (1.5 mM valproate or 1.5 mM ethosuximide) that blocked the conversion of GHB into SSA almost completely. Under these conditions, the IC₅₀ value for GHB ($23 \pm 0.66 \mu\text{M}$) was considerably increased, reaching $0.51 \pm 0.012 \text{ mM}$ in the presence of ethosuximide and $5.1 \pm 0.38 \text{ mM}$ in the presence of valproate (fig. 1A, B and C). To determine that GABA_B binding was not changed by the presence of the drugs used, we tested the displacement of [³H]-GABA by baclofen in the presence of 1.5 mM valproate (fig. 2). No effect was apparent, and an IC₅₀ value of 566 nM was calculated for baclofen in the absence of valproate, compared with an IC₅₀ value of 964 nM in the presence of valproate. Statistical comparison of the two displacement curves showed no significant difference between them ($P = .09$, two-way ANOVA, Graphpad-Prism program).

Effect of GHB on GABA_B binding when GHB degradation was blocked by GABA-T inhibitor. The degradation of GHB to GABA implies the presence in the brain membrane preparation of GABA-T, which is capable of converting SSA to GABA. To demonstrate the role of this GABA-T activity, GABA_B specific binding was measured in the presence of GHB alone (300 μM) or in the presence of GHB (300 μM) and aminooxyacetic acid (500 μM). The results of these experiments are shown in figure 3. GHB alone displaced specific GABA_B binding by about 35%, whereas the presence of aminooxyacetic acid completely blocked this effect of GHB. Compared with those in figure 1A, these results demonstrate that the ability of GHB to displace GABA_B binding is not uniform but depends on the batch of membranes used and their potency to convert GHB into GABA.

The apparent K_i value for aminooxyacetic acid inhibition of GHB conversion into GABA was measured under GABA_B binding conditions for various concentrations of inhibitor

(0–500 μM) for a fixed incubation time (20 min) and a fixed concentration of GHB (200 μM). The graphical representation of $1/v = f([\text{inhibitor}])$ gives a K_i value of 339 μM , and in the absence of inhibitor, 0.35% of GHB was converted into GABA (fig. 4).

Demonstration that GABA is formed from GHB in a standard incubation medium used for GABA_B binding assays. The formation of [³H]-GABA from [³H]-GHB was directly quantified in the medium incubated with the crude synaptosomal membranes under the conditions required for GABA_B binding. Membranes prepared from rat brain (method 1) were incubated for 20 min at room temperature with radioactive GHB. Chromatographic profiles revealed that all amino acids were present in significant amounts in the brain membrane extract, but only GABA was radioactive. That 0.36% of [³H]-GHB was converted into [³H]-GABA suggests a concentration of about 720 nM GABA in the medium.

In control experiments, GABA_B binding was tested in the presence of 200 μM GHB or 720 nM GABA. Under these conditions, GHB and GABA displaced [³H]-GABA by 58% and 63%, respectively (results not shown). These experiments showed that the concentration of GABA formed from GHB under GABA_B binding conditions was able to reproduce the GHB effect.

Effects of antiabsence drugs on [³H]-GHB transformation into [³H]-GABA by rat brain membranes. On incubation with crude brain synaptosomal membranes under the same conditions as for the GABA_B binding assay, [³H]-GHB was rapidly converted to [³H]-GABA. The kinetics of this conversion were followed for 30 min (fig. 5). Under control conditions, the reaction was linear for about 10 min, and the GABA formation was 18.7 pmol/min/mg protein. During a 20-min incubation, about 0.37% (0.32%–0.37%) of [³H]-GHB was converted. In the presence of 1.5 mM ethosuximide or 1.5 mM valproate, GABA synthesis from GHB was linear for 30 min, and the activity was reduced to 6.6 pmol/min/mg (35% of control activity) or to 1.7 pmol/min/mg (9% of control activity), respectively.

The K_i values for inhibition of [³H]-GHB conversion into [³H]-GABA were determined for valproate and ethosuximide.

TABLE 1

Effects of GHB on GABA_B binding in the presence and in the absence of valproate

Crude synaptosomal membranes were prepared according to Bernasconi *et al.* (1992) or Hill and Bowery (1981). Membranes were incubated in Tris-HCl 50 mM, CaCl₂ 2.5 mM, pH 7.4, containing 100 μM isoguvacine, [³H]GABA (25 nM, 74 Ci/mmol) and GHB 100 μM . In some experiments, valproate (5 mM) was added in order fully to inhibit GHB dehydrogenase. After a 15-min incubation at room temperature, bound [³H]GABA was separated from free [³H]GABA by rapid centrifugation at 40,000 $\times g$ for 30 min.

Crude Synaptosomal Membranes Prepared According to the Method of Bernasconi <i>et al.</i> (1992)	Crude Synaptosomal Membranes Prepared According to the Method of Hill and Bowery (1981)
Cerebellum	Cerebellum
Total binding: 5411 \pm 217 cpm	Total binding: 6329 \pm 256 cpm
Specific binding: 3390 cpm	Specific binding: 1827 cpm
Nonspecific binding: 2021 \pm 111 cpm	Nonspecific binding: 4502 \pm 318 cpm
GHB 100 μM : 1269 cpm displaced 37% of the specific binding	GHB 100 μM : 335 cpm displaced 18% of the specific binding
GHB 100 μM + valproate 5 mM: 0 cpm displaced	GHB 100 μM + valproate 5 mM: 0 cpm displaced
Cerebrum	Cerebrum
Total binding: 6922 \pm 312 cpm	Total binding: 7212 \pm 236 cpm
Specific binding: 3882 cpm	Specific binding: 2393 cpm
Nonspecific binding: 3040 \pm 52 cpm	Nonspecific binding: 4848 \pm 613 cpm
GHB 100 μM : 933 cpm displaced 24% of the specific binding	GHB 100 μM : 0 cpm displaced
GHB 100 μM + Valproate 5 mM:	GHB 100 μM + valproate 5 mM:

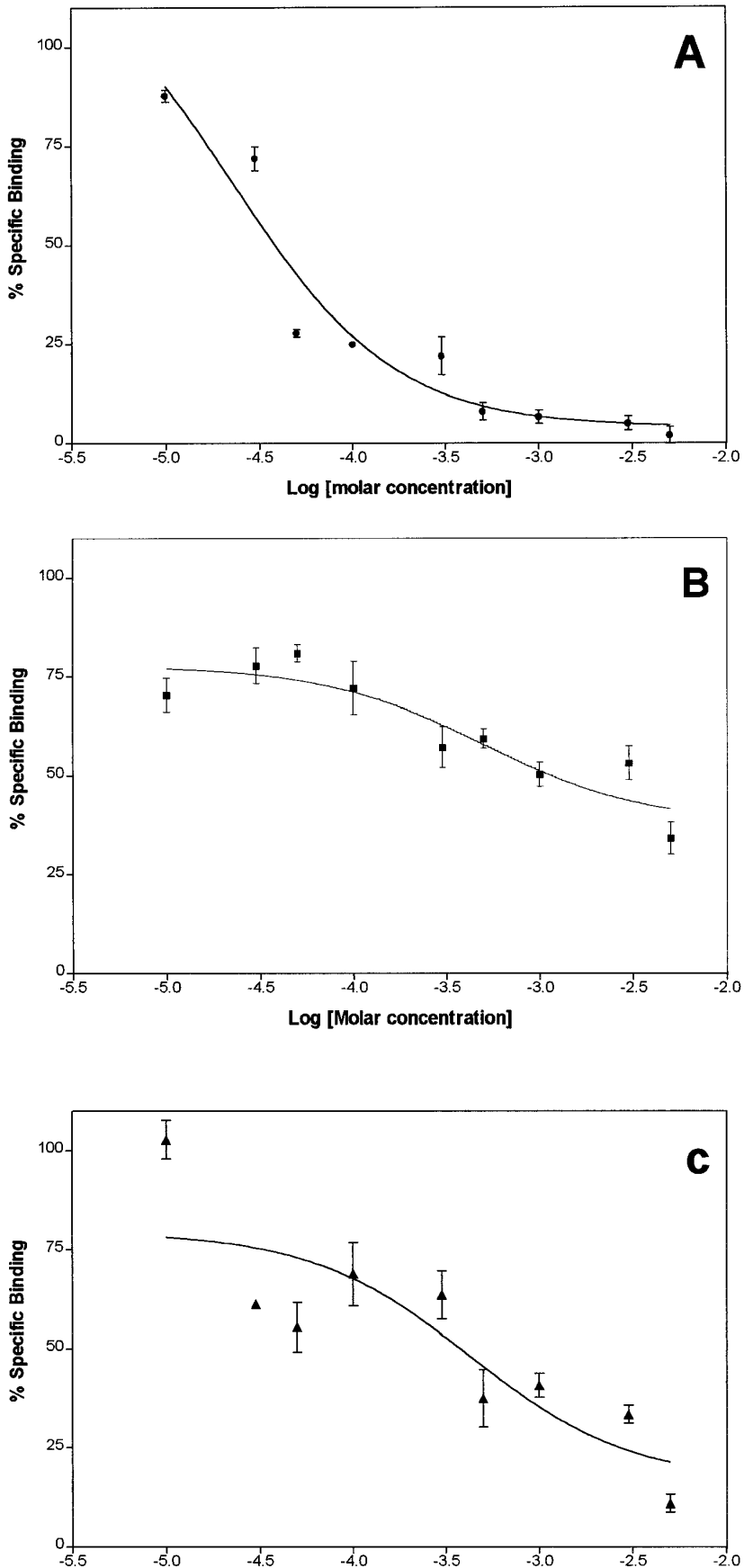


Fig. 1. GABA_B binding was carried out as described by Hill and Bowery (1981). Crude synaptic membranes were prepared from a whole rat brain P₂ fraction dispersed in distilled water and centrifuged at 8000 × *g* for 20 min. The supernatant was then centrifuged at 50,000 *g*, and the resulting pellet, after a second wash in distilled water, was re-centrifuged and stored at -20°C overnight. The pellet was then incubated and washed as indicated in the original protocol. Binding assays were performed in 50 mM Tris-HCl buffer, pH 7.4, containing 2.5 mM CaCl₂ at ambient temperature. Incubation media contained [³H]-GABA (25 nM) and 100 μM isoguvacine. Total reversible binding was measured in the presence of 100 μM baclofen. A) Displacement curve of GHB on GABA_B binding from rat brain crude synaptosomal membranes. Increasing concentrations of GHB displace [³H]-GABA in the presence of 100 μM isoguvacine with an IC₅₀ value of 23 ± 0.66 μM (nonlinear regression line, Graphpad-Prism program). B) Same experiment as in panel A, but all the incubation media contained 1.5 mM sodium valproate. IC₅₀ is increased to a value of 5.1 ± 0.38 mM. Under the same conditions, the activity of baclofen in displacing [³H]-GABA_B binding was not altered (nonlinear regression line, Graphpad Prism program). C) Same experiment as in panel A, but all the incubation media contained 1.5 mM ethosuximide. The potency of GHB in displacing GABA_B binding is greatly decreased (IC₅₀ = 0.51 ± 0.012 mM) (nonlinear regression line, Graphpad-Prism program).

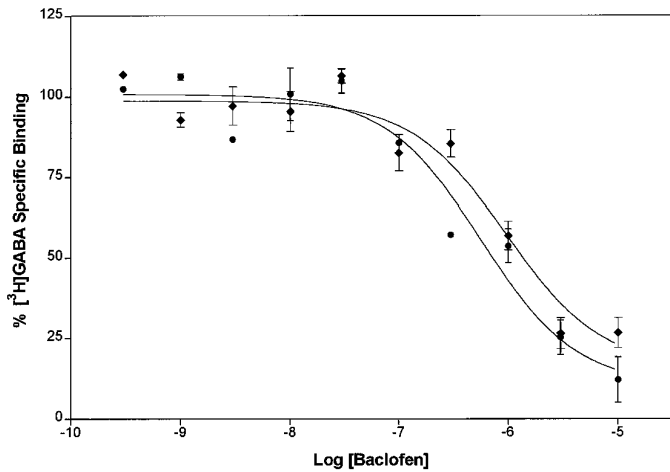


Fig. 2. Displacement curve of [³H]-GABA_B binding according to Hill and Bowery (1981) in the absence (◆) or presence (●) of 1.5 mM valproate. Binding was carried out in the presence of 100 μM isoguvacine, and nonspecific binding was determined with 100 μM baclofen. The differences between the two curves are not significant ($P = .09$, two-way ANOVA). Each data point is the mean of three separate determinations.

Under the GABA_B binding conditions (membrane preparation and incubation medium according to Hill and Bowery, 1981), valproate and ethosuximide inhibit GABA synthesis from GHB with K_i values of 1.0 mM ($r = 0.93$) and 2.0 mM ($r = 0.98$), respectively. GHB concentration was 200 μM in each case. In the absence of valproate and of ethosuximide, 0.55% and 0.51% of GHB, respectively, were converted into GABA after a 20-min incubation (fig. 6).

GABA_A binding in presence of GHB. Under the conditions described by Olsen *et al.* (1981) for GABA binding, [³H]-muscimol was displaced by GHB with an IC_{50} value of 4.6 ± 0.4 mM ($r = 0.91$). However, in the presence of 1.5 mM valproate, no significant [³H]-muscimol displacement was induced by GHB (fig. 7).

Discussion

Several authors have described the displacement of [³H]-GABA from GABA_B sites by GHB, but they have reported IC_{50} values varying from 150 μM (Bernasconi *et al.*, 1992), to 500 μM (Ito *et al.*, 1995) and 796 μM (Ishige *et al.*, 1996). Our own results have ranged from 23 μM (the present results) to about 520 μM (unpublished results) and largely depend on the batch of membranes and the protocol used for GABA_B binding. Using the conditions of Hill and Bowery (1981) or Bernasconi *et al.* (1992), such large variations suggest the degradation of GHB by the synaptosomal membranes, which can be modified by the methods used for preparing the membranes and/or the incubation conditions (time, temperature, pH and concentrations of GHB). GHB could be converted into GABA *in vitro* by the sequential action of GHB dehydrogenase, which oxidizes GHB to SSA, and then a GABA-T activity transaminating SSA to GABA. All the free amino acids that could be detected under the present conditions were identified in the extract of the synaptosomal/mitochondrial membranes, in concentrations of about 0.1 to 0.4 μM. This result suggests that the cofactors (glutamate, NADP and so on) necessary for the enzymatic conversion of GHB to GABA

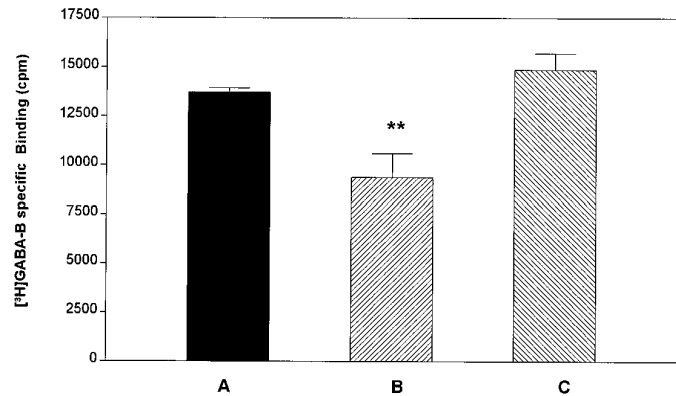


Fig. 3. Displacement of GABA_B binding by GHB in the presence or absence of a GABA-T inhibitor. Incubation conditions and GABA_B membranes were identical to those described in the protocol of Hill and Bowery (1987). Column A = control; specific GABA_B binding displaceable by 100 μM baclofen. Column B = specific GABA_B binding displaceable by 300 μM GHB (significantly different from column A, $P < .01$). Column C = specific GABA_B binding in the presence of 300 μM GHB and 500 μM aminooxyacetic acid. The inhibition of GABA-T from rat brain crude synaptosomal membranes blocks the synthesis of GABA from GHB and inhibits the effect of GHB on GABA_B binding. In this set of experiments, 300 μM GHB displaced [³H]-GABA_B binding by about 35%. Each data point is the mean of three separate determinations.

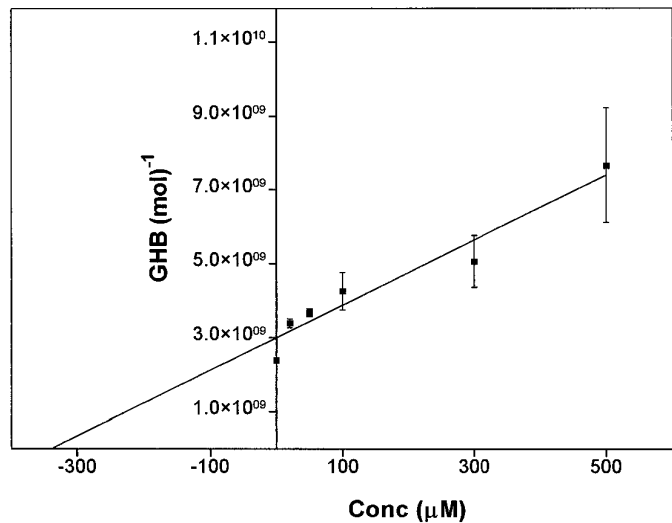


Fig. 4. Determination of the K_i value for aminooxyacetic acid (339 μM, $r = 0.81$). Ordinate = $1/\text{radioactive GABA produced from } 200 \mu\text{M GHB after a } 20\text{-min incubation}$, Abscissa = concentration of aminooxyacetic acid. Conditions were those described in the legend for figure 5.

membrane preparation used for GABA_B binding experiments.

Two types of enzymes in brain are able to catalyze the oxidation of GHB to SSA (Kaufman and Nelson, 1991). One of these enzymes is a cytosolic NADP⁺-dependent oxidoreductase, whereas the other is present in the mitochondrial fraction and does not require NAD⁺ or NADP⁺. The former enzyme, which has been named GHB dehydrogenase, is more likely to be the main route for GHB degradation in brain because its inhibition by valproate and other antiepileptic drugs (trimethadione, ethosuximide) leads to an accumulation of GHB in brain (Snead *et al.*, 1980). The mitochondrial enzyme is not sensitive to valproate. In the *in vitro* experi-

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.