

Effect of Low Doses of Gamma-Hydroxybutyric Acid on Serotonin, Noradrenaline, and Dopamine Concentrations in Rat Brain Areas

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The effects of intraperitoneal administration of gamma-hydroxybutyric acid (GHB) on biogenic amine levels in hemispheres, hypothalamus, midbrain, and medulla-pons, and on tryptophan in serum and brain, were studied. One hour after GHB administration (50 and 100 mg/kg) significant increases of dopamine concentration were observed in the hemispheres with both doses and in the hypothalamus with the higher dose, but a significant decrease of noradrenaline in the hypothalamus. No significant changes of serotonin metabolism were observed. These results indicate that low doses of GHB selectively affect the catecholaminergic neuronal activity.

KEY WORDS: GHB; biogenic amines; brain regions.

INTRODUCTION

Gamma-hydroxybutyric acid (GHB) is a metabolite found in the normal mammalian brain (5). Doherty et al. (4) suggested that GHB may develop its function independently of GABA. Maitre and Mandel (9) postulated a role of GHB as neurotransmitter in the central nervous system. GHB administration caused an increase of growth hormone levels (2), and alterations of brain dopamine (DA) (6), serotonin (5-HT) (14) and acetylcholine (13) have been reported after the administration of both non-anesthetic and anesthetic doses. In a previous work we have shown that the administration of non-anesthetic low doses of GHB produced significant changes in the levels of luteinizing hormone (10). This effect is assumed to be mediated by the action of GHB on the activity of certain neuronal systems.

In the present work, we have studied the effects

of low doses of GHB on biogenic amine levels in some brain regions.

EXPERIMENTAL PROCEDURE

Male Wistar rats, weighing 200–300 g, were used. They were kept under controlled conditions (light on from 08:00 to 22:00, at $22 \pm 2^\circ\text{C}$).

GHB (Sigma Chemical Co., St. Louis) was dissolved in 0.9% NaCl and administered intraperitoneally at doses of 50 and 100 mg/kg. Control groups received an equal volume of 0.9% NaCl.

One hour after GHB or saline injection, the animals were decapitated (which was always done at the same time of day in order to minimize variations due to the circadian rhythm). Blood was collected and free (ultrafiltrable) tryptophan was assayed after centrifugation of the serum through Centriflo CF 50 A filter cones (Amicon) at 800 g for 15 minutes at room temperature. Total tryptophan was assayed in unfiltered serum. Free and total serum tryptophan and brain tryptophan concentrations were determined by the fluorimetric method of Bloxam and Warren (1).

The brains were removed and dissected according to the technique of Miller et al. (11). 5-HT, NA, DA and 5-hydroxyindoleacetic acid (5-HIAA) levels were assayed in the rat brain regions using the method of Cox and Perhach (3). Significance of differences between means values obtained of controls and treated animals was calculated using Student's *t* test.

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RESULTS AND DISCUSSION

According to Gessa et al. (6) 1 and 2 g/kg doses of GHB caused an increase in DA levels in rat brain, whereas a dose of 500 mg/kg did not produce any changes. However, as appears from the results shown in Table I, doses of 50 and 100 mg/kg GHB are sufficient to produce a significant increase of DA levels in the hemispheres. These results are in agreement with the fact that a dose of 150 mg/kg inhibited about 50% of the dopaminergic cell activity and significantly reduced the DOPAC levels in the striatum (12). Based on these results, one may conclude that the increase of the DA levels in the hemispheres is associated with a reduction of DA release. The higher dose also produces significant concentration changes of DA in the hypothalamus (Table I).

A significant decrease of the hypothalamic NA was observed (Table II). However, Bluet-Pajot et al. (2) did not observe any variation of the NA levels in the hypothalamus after GHB administration (1 g/kg). Since the central noradrenergic system has a

stimulatory action on LH secretion (8) and since the reduction of hypothalamic NA levels is assumed to reflect an increase in the activity of noradrenergic neurons the increase in the concentration of serum LH induced by GHB (10) could be due to an action on the noradrenergic system in the hypothalamus.

The administration of a high dose of GHB (1 g/kg) did not cause significant alterations in the hypothalamic 5-HT concentration (2). However, Spano and Przegalinsky (14) demonstrated an increase of 5-HT synthesis and the turnover rate after administration of 4.8 mmol/kg, but significant changes of 5-HT levels were not found. Hedner and Lundborg (7) also found that the GHB (750 mg/kg) increased the rate of synthesis and degradation of 5-HT in the brain of young rats. However, as Table III and IV show that there were no changes of 5-HT and 5-HIAA concentrations, and we found that free, total, and cerebral levels of tryptophan did not exhibit any significant variations (Table V). Moreover, using the ratio 5-HIAA/5-HT as an index of serotonergic activity, it is clear that the function of the serotonergic neurons did not change at all under our experimental conditions. The discrepancies between our and previous findings are prob-

Table I. Dopamine Concentration in Different Brain Regions of Rats 1 Hour After Administration of Gamma-Hydroxybutyric Acid

Brain area	Control	GHB	
		50 mg/kg	100 mg/kg
Hypothalamus	0.80 ± 0.08	0.74 ± 0.07	0.56 ± 0.07*
Medulla-pons	0.23 ± 0.04	0.18 ± 0.03	0.19 ± 0.04
Midbrain	0.37 ± 0.03	0.32 ± 0.06	0.32 ± 0.04
Hemispheres	0.80 ± 0.09	1.00 ± 0.04	1.18 ± 0.05**

Values are the means (μg per g wet weight) \pm SEM of the results obtained from eight animals.

* $P < 0.05$; ** $P < 0.025$.

Table II. Noradrenaline Concentration in Different Brain Regions of Rats 1 Hour After Administration of Gamma-Hydroxybutyric Acid

Brain area	Control	GHB	
		50 mg/kg	100 mg/kg
Hypothalamus	1.92 ± 0.25	1.32 ± 0.08*	1.76 ± 0.17
Medulla-pons	0.47 ± 0.03	0.42 ± 0.05	0.53 ± 0.05
Midbrain	0.61 ± 0.04	0.50 ± 0.10	0.59 ± 0.04
Hemispheres	0.28 ± 0.03	0.33 ± 0.02	0.35 ± 0.03

Values are the means (μg per g wet weight) \pm SEM of the results obtained from eight animals.

* $P < 0.05$.

Table III. Serotonin Concentration in Different Brain Regions of Rats 1 Hour After Administration of Gamma-Hydroxybutyric Acid

Brain area	Control	GHB	
		50 mg/kg	100 mg/kg
Hypothalamus	1.16 ± 0.14	1.26 ± 0.13	1.16 ± 0.24
Medulla-pons	0.77 ± 0.12	0.76 ± 0.05	0.66 ± 0.03
Midbrain	1.01 ± 0.10	1.06 ± 0.07	0.90 ± 0.08
Hemispheres	0.53 ± 0.10	0.58 ± 0.05	0.45 ± 0.06

Values are the means (μg per g wet weight) \pm SEM of the results obtained from eight animals.

Table IV. 5-Hydroxyindoleacetic Acid Concentration in Different Brain Regions of Rats 1 Hour After Administration of Gamma-Hydroxybutyric Acid

Brain area	Control	GHB	
		50 mg/kg	100 mg/kg
Hypothalamus	0.69 ± 0.11	0.63 ± 0.13	0.93 ± 0.07
Medulla-pons	0.69 ± 0.06	0.75 ± 0.06	0.68 ± 0.05
Midbrain	1.05 ± 0.06	1.01 ± 0.05	0.85 ± 0.07
Hemispheres	0.40 ± 0.04	0.51 ± 0.05	0.36 ± 0.04

Values are the means (μg per g wet weight) \pm SEM of the results obtained from eight animals.

Table V. The Levels of Plasma and Brain Tryptophan in Control and Treated Rats

Substance	Control	Treated with GHB	
		50 mg/kg	100 mg/kg
Plasma total tryptophan ($\mu\text{g/ml}$)	14.93 \pm 1.02	13.94 \pm 1.28	15.36 \pm 0.52
Plasma free tryptophan ($\mu\text{g/ml}$)	0.83 \pm 0.13	0.69 \pm 0.11	0.94 \pm 0.14
Brain tryptophan ($\mu\text{g/g}$)	3.55 \pm 0.18	3.20 \pm 0.19	3.31 \pm 0.20

Values give in the table are the mean \pm S.E. of the results obtained from eight separate animals.

ably due to the use of different doses of GHB, indicating that the serotonergic activity changes only as very high doses of GHB.

In conclusion, we can note that low doses of GHB selectively alter the catecholaminergic activity.

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