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Short communication

Oral self-administration of γ-hydroxybutyric acid in the rat

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Abstract

The present study describes the induction of γ-hydroxybutyric acid (GHB) preference over water in rats. GHB solution (1% w/v in water) was initially offered as the sole fluid available for 14 consecutive days. Subsequently, rats were given a free choice of GHB solution and tap water for 20 consecutive weeks. Under the free-choice regimen, all rats showed periods of preference for GHB solution over water and periods of voluntary abstinence from GHB. On GHB-preference days, GHB was ingested at pharmacologically relevant doses. GHB intake occurred in 2–3 discrete episodes during the nocturnal phase. The development of an animal model of GHB self-administration may constitute a useful tool in the investigation of the neurobiological substrates of GHB-reinforcing properties.

Keywords: GBH (γ-hydroxybutyric acid); Voluntary γ-hydroxybutyric acid intake; Alcoholism; (Rat)

1. Introduction

Administration of γ-hydroxybutyric acid (GHB), a putative neurotransmitter or neuromodulator found in mammalian brain, has been reported to produce a number of neuropharmacological effects both in laboratory animals and humans (see Cash, 1994). GHB has been clinically used as a general anaesthetic and hypnotic agent (Laborit et al., 1962) and in the treatment of narcolepsy (Lammers et al., 1993). More recently, GHB has been proposed as an effective agent in the pharmacotherapy of alcoholism and opiate addiction. Indeed, GHB reduces alcohol craving and consumption (Gallimberti et al., 1992) and ameliorates symptoms of alcohol (Gallimberti et al., 1989) and heroin (Gallimberti et al., 1993) withdrawal syndrome.

However, recent papers (Auerbach, 1990; Chin et al., 1992) and warning reports by U.S. agencies (Food and Drug Administration, 1991; Krawczeniuk, 1993) suggest a potential abuse liability of GHB. Administration of GHB allegedly produces subjective feelings of being 'high' and euphoria, rendering the drug compelling. More recently, Martellotta et al. (1995) found that GHB is able to induce conditioned place preference in rats, indicating that it possesses reinforcing properties.

The present study describes the development of an animal model of GHB self-administration, which might constitute a useful experimental paradigm in the search of the biological basis of GHB-reinforcing effects.

2. Materials and methods

2.1. Animals

Twenty male Wistar rats (Charles River, Calco, CO, Italy), weighing 400–500 g and aged 4 months at the start of the study, were used. The rats were singly housed in standard plastic cages with wood chip bedding under a 12-h artificial light-dark cycle (lights on at 7:00 p.m.), at constant temperature of 22 ± 2°C and relative humidity of 60%. Standard laboratory rat chow (MIL Morini, San Polo d'Enza, RE, Italy) was pro-

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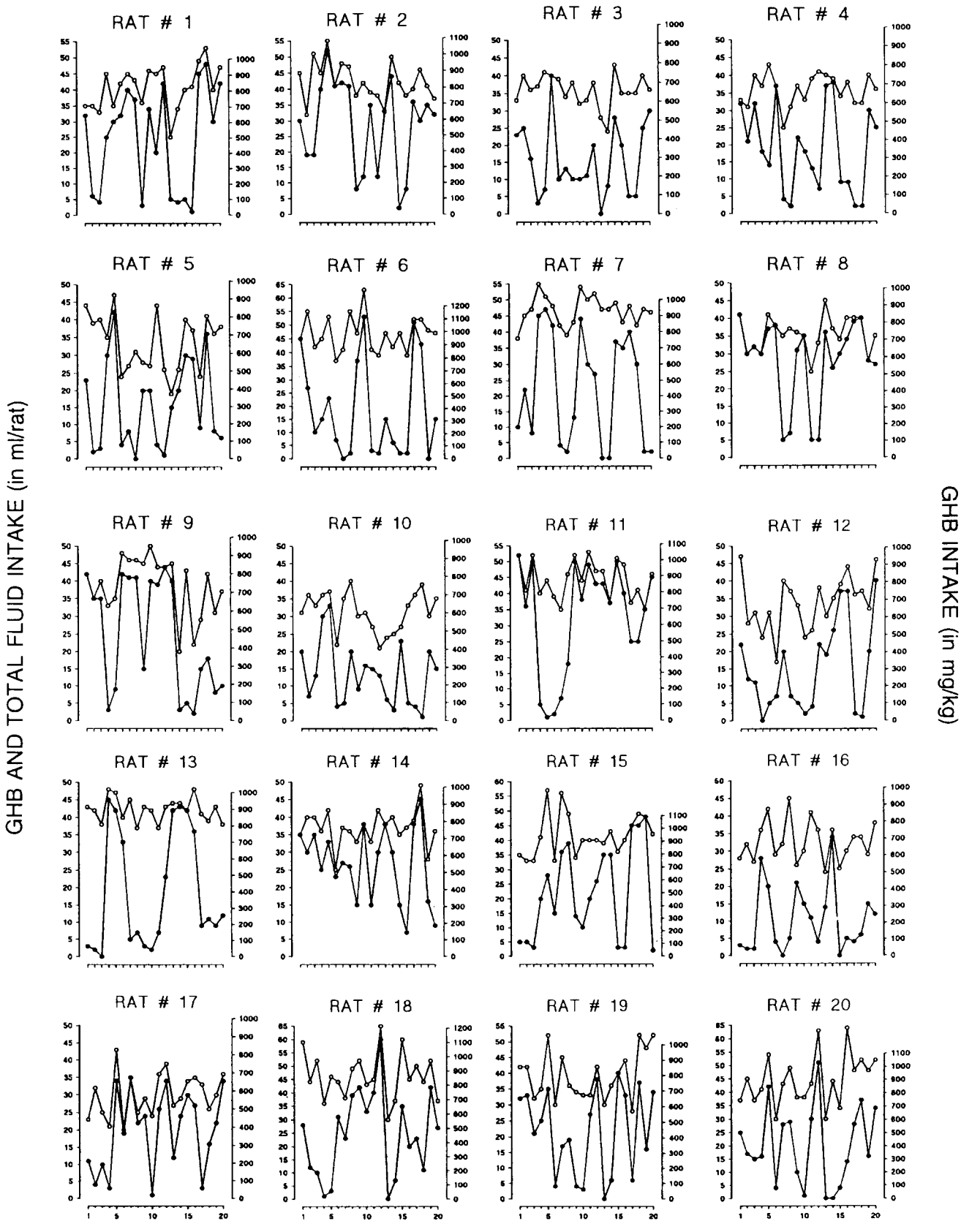
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GHB AND TOTAL FLUID INTAKE (in ml/rat)
GHB INTAKE (in mg/kg)
DAYS

vided ad libitum to the rats throughout the experimental period. Rat body weights were monitored weekly.

2.2. Induction of GHB preference

The rats were initially forced to drink 1% (w/v) GHB (sodium salt, from Sigma, St. Louis, MO, USA) in water, this being the sole drinking fluid available for 14 consecutive days. GHB intake was recorded daily at the beginning of the dark period (7:00 a.m.). On the fifteenth day, the rats were changed to a free-choice regimen. Two graduated bottles, containing tap water and 1% (w/v) GHB in water, respectively, were continuously offered for 20 consecutive weeks. GHB and water intakes were monitored daily at 7:00 a.m. Bottles were refilled every day with fresh solution and their position was reversed at random to avoid development of position habit. The criterion of preference for GHB was defined as a daily intake of GHB solution greater than 50% of the total fluid intake (GHB-preference day).

3. Results

During the 14 days of the no-choice period, the rats showed a stable intake of GHB, ranging 800–1200 mg/kg/day.

Once GHB and water were offered under the free-choice procedure, preference for GHB was established in all rats and persisted for the entire experimental period. However, in order to simplify data layout, only the results of the first 20 consecutive days of the free-choice regimen are reported in detail.

Fig. 1 shows the pattern of GHB and water intake on the first 20 consecutive days of the free-choice regimen by all rats used in the present study.

All rats alternated periods of high daily intake of GHB with temporarily self-imposed cessation of GHB intake. A virtually equal number of GHB-preference days (10.15 ± 0.7 (mean ± S.E.M.)) and water-preference days (9.85 ± 0.7 (mean ± S.E.M.)) was recorded. However, a large individual variability (with respect to other rats and by the same rat) in the duration of the GHB- and water-preference day sequences was observed. Indeed, GHB- and water-preference periods ranged from 1 to 12 (2.6 ± 0.2 (mean ± S.E.M.)) and 1 to 11 (2.7 ± 0.2 (mean ± S.E.M.)) consecutive days, respectively. On GHB-preference days, GHB consumption averaged 666.3 ± 13.2 (mean ± S.E.M.) mg/kg/day. On water-preference days, a compensatory increase in water consumption took place, so that the daily total fluid intake in each rat did not significantly change. No difference in the amount of food intake was observed between GHB-preference and water-preference days. No signs of a withdrawal syndrome were observed on the water-preference days.

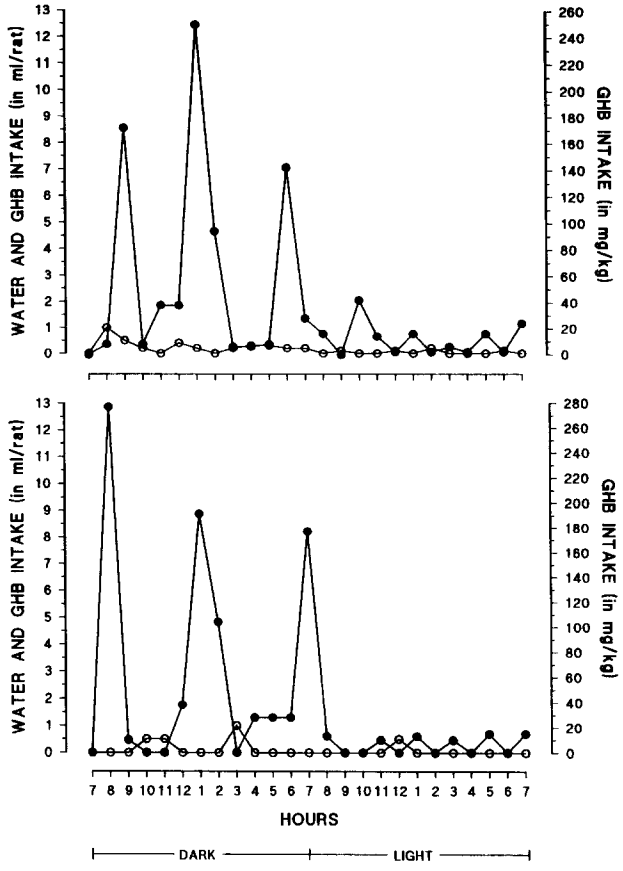

Fig. 2. Illustrative patterns of GHB (1% w/v) and total fluid intakes for 24 consecutive hours by rat No. 7 (top panel) and rat No. 13 (bottom panel) on day 5 and day 4, respectively, of the free-choice period. The hourly intake of GHB (●) is expressed on the left ordinate as milliliters of solution consumed by the rat and on the right ordinate as mg/kg. Water (○) intake is expressed on the left ordinate as milliliters consumed by the rat.

Fig. 2 illustrates the one-day pattern of GHB and water intake by two rats on a GHB-preference day (rat No. 7 on day 5 (top panel) and rat No. 13 on day 4 (bottom panel), respectively). In agreement with the well-characterized drinking pattern of rats, GHB and

Fig. 1. Individual patterns of GHB (1% w/v) and total fluid intakes on 20 consecutive days during the free-choice period by all the rats (n = 20) tested in the present study. The daily intake of GHB (●) is expressed on the left ordinate as milliliters of solution consumed by the rat, and on the right ordinate as mg/kg. Total fluid intake (○) is expressed on the left ordinate as the sum of milliliters of GHB solution and tap water consumed by the rat.

water intake took place predominantly during the nocturnal phase of the light-dark cycle. In both the above rats, about 75% of GHB consumption occurred in three separate binges evenly distributed over the 12-h dark period.

Both the pattern of alternatively preferring GHB or water and the amount of GHB consumed did not vary during the remaining 17 weeks of monitoring. No rat showed any sign of withdrawal when GHB was finally removed at the end of the 20-week period.

4. Discussion

In a previous experiment, we failed to establish GHB preference in GHB-naive rats offered 1% (w/v) GHB and water in a two-bottle free-choice paradigm. In contrast, the 14-day no-choice period described in the present study resulted in the induction of GHB preference over water in all the rats tested, as shown in Fig. 1 by the occurrence of daily intakes of GHB largely exceeding the amount of consumed water. The reason for this discrepancy between the two experiments might be the unpleasant taste of GHB (presented as sodium salt), which would prevent the rats from discovering its reinforcing properties. In the present study, these effects were revealed during the period of forced GHB intake.

Voluntary intake of GHB occurred under a fluctuating pattern, showing a sequence of GHB-preference days followed by a sequence of water-preference days. Periods of GHB- and water-preference days alternated during the entire experimental period in each rat. Voluntary and temporary discontinuation of drug intake has been reported to occur in monkeys self-administering amphetamine, cocaine and ethanol (see Meisch and Stewart, 1994). Thus, although the alternation between GHB- and water-preference periods observed in the present study is not a unique and peculiar characteristic of voluntary GHB intake, at present the reason for this phenomenon escapes our understanding. It might be hypothesized that prolonged GHB consumption induces noxious and aversive effects that mask the reinforcing properties of the drug and lead the rats to temporarily avoid GHB. The accumulation of a product of GHB catabolism might be responsible for the toxic effects. Further studies are needed to verify this hypothesis.

On the GHB-preference days, GHB consumption took place in distinct binges, interspaced by 3–5 h, during the dark phase of the light-dark cycle. In each binge, GHB intake occurred at pharmacologically relevant doses (100–300 mg/kg), well within the dose range reported to produce anxiolytic (Kršiak et al., 1974) and discriminable (Colombo et al., 1995) effects, and establish place preference (Martellotta et al., 1995) in the rat. Moreover, the 3–5 h interval between GHB binges is consistent with the pharmacokinetic characteristics of oral GHB in the rat (Lettieri and Fung, 1979), indicating a self-controlled adjustment of GHB dose by the rat over the 24-h cycle.

In conclusion, these results (a) indicate that GHB can be voluntarily ingested by the rat after a period of forced GHB drinking, and (b) confirm that GHB possesses reinforcing properties. Indeed, it has recently been demonstrated by Martellotta et al. (1995) that GHB is capable of inducing place preference in rats. Future studies will address whether the reinforcing properties of GHB can give rise to potential abuse liability.

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