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Ability of Baclofen in Reducing Alcohol Intake and Withdrawal Severity: I—Preclinical Evidence

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Background: The similarities between the pharmacological effects of the γ-aminobutyric acid receptor agonist, baclofen, and the alcohol-substituting agent, γ-hydroxybutyric acid, led us to investigate whether baclofen was capable of reducing (a) ethanol withdrawal syndrome in ethanol-dependent rats and (b) voluntary ethanol intake in ethanol-preferring rats.

Methods: In experiment 1, Wistar rats were rendered physically dependent on ethanol by the repeated administration of intoxicating doses of ethanol for 6 consecutive days. Baclofen was acutely administered intraperitoneally at doses of 10, 20, and 40 mg/kg. In experiment 2, baclofen (0, 2.5, 5, and 10 mg/kg, intraperitoneally) was administered once a day for 14 consecutive days to ethanol-preferring sP rats that had continuous access to ethanol (10%, v/v) and water under the two-bottle free choice regimen.

Results: In experiment 1, baclofen dose-dependently decreased the intensity of ethanol withdrawal signs; furthermore, 20 mg/kg of baclofen protected from audiogenic seizures in ethanol-withdrawn rats. In experiment 2, baclofen selectively and dose-dependently reduced voluntary ethanol intake; a compensatory increase in water intake left total fluid intake virtually unchanged.

Conclusions: These results are in close agreement with those of a preliminary clinical study and suggest that baclofen may constitute a novel therapeutic agent for alcoholism.

Key Words: Baclofen, $GABA_B$ receptor, Ethanol Withdrawal Syndrome, Voluntary Ethanol Intake, Sardinian Alcohol-Preferring (sP) Rats.

SEVERAL LINES OF experimental evidence suggest that the γ-aminobutyric acid ($GABA_B$) receptor agonist, baclofen, and the alcohol-substituting agent, γ-hydroxybutyric acid (GHB), share different pharmacological properties. For instance, both drugs produce muscle relaxation (Hudgson and Weighman, 1971; Laborit, 1973), hypomotility (Agabio et al., 1998; Nissbrandt and Engberg, 1996), anxiolysis (Agabio et al., 1998; Andrews and File, 1993b; Breslow et al., 1989; Ketelaars et al., 1988; Kršiak et al., 1974; Schmidt-Mutter et al., 1998; Shephard et al., 1992), amnesia (DeSousa et al., 1994; Grove-White and Kelman, 1971; McNamara and Skelton, 1996; Stackman and Walsh, 1994), catalepsy (Kasture et al., 1996; Navarro et al., 1996), and generalized absence seizures (Crunelli and Leresche, 1991; Snead, 1996a). Spontaneous firing rates of dopaminergic neurons (Engberg and Nissbrandt, 1993; Engberg et al., 1993) and dopamine metabolism (Cott et al., 1976; Da Prada and Keller, 1976; Gessa et al., 1968; Nissbrandt and Engberg, 1996; Waldmeier, 1991) in the rat striatum and mesolimbic system are similarly affected by baclofen and GHB. Finally, drug discrimination studies have shown that baclofen elicits discriminative stimulus effects (i.e., the animal correlate of the human subjective feelings perceived after intake of a psychoactive drug) similar to those produced by GHB (Colombo et al., 1998a; Winter, 1981). Although GHB possesses a negligible affinity for the $GABA_B$ receptor (Snead, 1996b), several pharmacological effects of GHB, including the discriminative stimulus effects, are blocked by $GABA_B$ antagonists (Colombo et al., 1998a; Engberg and Nissbrandt, 1993; Ito et al., 1995; Nissbrandt and Engberg, 1996; Snead, 1996a; Waldmeier, 1991; Williams et al., 1995; Xie and Smart, 1992). It has been proposed that the $GABA_B$-like effects of GHB may be due to the conversion of GHB into GABA, which, in turn, binds to $GABA_B$ receptors (Hechler et al., 1997). Alternatively, these GHB effects may be secondary to activation of a GHB recognition site related to, although separate from, a $GABA_B$ receptor, which forms a presynaptic $GABA_B$/GHB receptor complex that regulates neurotransmitter release (Snead, 1996a).

The beneficial role of GHB in the treatment of alcohol-

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ism has been documented in both laboratory rodents and humans. GHB administration has been reported to markedly reduce (a) ethanol intake in ethanol-preferring rats (Agabio et al., 1998; Gessa et al., 1999; June et al., 1995) and alcoholics (Addolorato et al., 1996, 1998; Gallimberti et al., 1992), and (b) intensity of ethanol withdrawal syndrome in rats made physically dependent on ethanol (Fadda et al., 1989; Gessa et al., 1999) and alcoholics (Addolorato et al., 1999; Gallimberti et al., 1989; Nimmerrichter et al., 1997). It has been proposed that GHB exerts its reducing effects on ethanol craving, consumption, and withdrawal syndrome by mimicking ethanol actions in the central nervous system (Colombo et al., 1995a; Gessa et al., 1999).

The similarities between the pharmacological effects of baclofen and GHB would predict that ethanol self-administration and withdrawal syndrome may also be altered by baclofen. However, the existing preclinical literature on this issue reports inconsistent results. Administration of a low dose of baclofen initially was found to selectively reduce daily ethanol intake in Long-Evans rats (Daoust et al., 1987). However, subsequent studies reported that a higher dose of baclofen stimulated daily ethanol intake during both acquisition (Smith et al., 1992) and maintenance (Smith et al., 1999) phases of ethanol drinking behavior in Long-Evans rats. Finally, central administration of baclofen failed to alter ethanol intake in Wistar rats (Tomkins and Fletcher, 1996). In regard to ethanol withdrawal syndrome, File and colleagues (1991) reported that small doses of baclofen reversed the anxiety-like behaviors and tremors associated with ethanol withdrawal syndrome in ethanol-dependent rats; however, no effects of baclofen administration on ethanol withdrawal tremors were observed in mice (Humeniuk et al., 1994) and rhesus monkeys (Tarika and Winger, 1980).

The present study was designed to reexamine this issue. Experiment 1 tested the ability of baclofen to reduce the intensity of ethanol withdrawal syndrome in Wistar rats rendered physically dependent on ethanol by the repeated administration of intoxicating doses of ethanol. Experiment 2 assessed the effect of baclofen on voluntary ethanol intake in Sardinian alcohol-preferring (sP) rats, selectively bred in this laboratory for high ethanol preference and consumption.

METHODS

Experiment 1: Effect of Baclofen on Ethanol Withdrawal Syndrome

Animals. Male Wistar rats (Charles River, Calco, CO, Italy) weighing 275 to 300 g at the start of the experiment were used. After delivery to our facilities, rats were left undisturbed for 7 days to acclimatize to new housing conditions. Animals were housed five per cage with wood chip bedding under an artificial light-dark cycle of 12/12 hr (light on at 700 hr), at a constant temperature of 22 ± 2°C and relative humidity of 60%. Rats were given free access to water and standard laboratory food (MIL Morini, San Polo d'Enza, RE, Italy) throughout the entire experimental period.

Intoxication Procedure. Rats were rendered physically dependent on ethanol by the method of Majchrowicz (1975). This consisted of four daily administrations of ethanol solution (20% w/v, in tap water) by intragastric gavage for 6 consecutive days, to maintain constant blood ethanol concentrations. Animals were treated at 600, 1200, 1800, and 2400 hr. At the very first administration of the treatment, 4 g/kg of ethanol was given to all rats. Subsequent doses were individually assessed for each rat at the previously mentioned administration times on the basis of the observed degree of intoxication, by using the intoxication-dose relationship conceived by Majchrowicz (1975). Six successive stages of intoxication were defined: neutrality, sedation, ataxia 1, 2, and 3, loss of righting reflex. Ethanol doses, ranging from 0 to 5 g/kg, were inversely related to the degree of intoxication. Assessment of the degree of intoxication and of the ethanol dose was made by operators trained for the same evaluation criteria.

Rats were weighed once a day (at 900 hr). During chronic ethanol treatment, rats spent most of the time in a severe state of intoxication, unable to eat by themselves. Therefore, the loss in body weight was partially compensated by the daily oral administration (at 900 hr) of 20 g/kg of liquid diet (Isomil, M&R, Zwolle, The Netherlands).

Withdrawal Assessment. Intensity of ethanol withdrawal signs was evaluated in each rat by scoring 11 separate items. We used a 4-point scale (0 to 3, paralleling increased frequency of occurrence and degree of severity of items), modified from a scale described by Lal et al. (1988). Some items (general activity, shakes, jerks, head tremors, bracing posture, and spontaneous convulsions) were rated before the rat was touched, whereas assessment of other items required palpation (namely, general tremors, tail tremors, rigidity of muscle tone, and tail rigidity) or handling stimulation (vocalization). The sum of the 11 values was the total score assigned to each rat on each observation. Scores of 8 to 9 indicated a neutrality state, corresponding to healthy and undrugged rats. Observation and scoring were carried out on a blind basis. Between observations, rats were left undisturbed in their home cages.

Experimental Design. Observations and scoring were carried out every hour for 11 consecutive hours starting at 15 hr after the last ethanol administration. Before we began the observation and scoring, rats were randomly assigned to four groups of eight subjects each. Animals that convulsed before drug administration were excluded from the study. Baclofen [(±)-baclofen; Sigma Chemical Co., St. Louis, MO] was dissolved in saline (with a few drops of 0.1N HCl solution) and injected intraperitoneally at the doses of 0, 10, 20, and 40 mg/kg (injection volume: 10 ml/kg) immediately after the 15 hr observation.

Two separate groups of rats received 0 (n = 8) and 20 (n = 9) mg/kg of baclofen, dissolved and injected as previously described, 16 hr after the last ethanol administration. One hour later, these rats were tested for susceptibility to audiogenic seizures, being placed in a cylindrical box of 60 cm diameter and exposed to 30 sec key shaking.

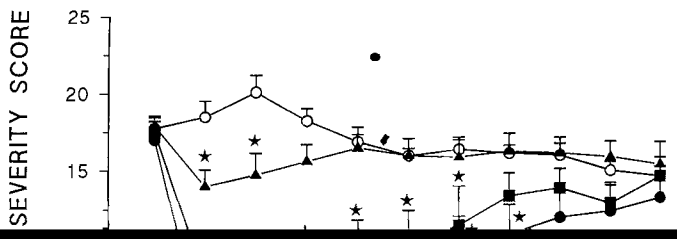
Statistical Analyses. Statistical evaluation of the daily amount of ethanol administered and the loss of rat body weight in each rat group was performed by one-way ANOVAs in the study testing the effect of baclofen on intensity of withdrawal signs, and by Mann-Whitney U tests in the study testing the effects of baclofen on susceptibility to audiogenic seizures. Data on the effects of baclofen on the intensity of ethanol withdrawal signs—both (a) sum of the 11 total items and (b) some selected items (namely, tremors, rigidity, posture, and vocalization)—were analyzed by a two-way (baclofen dose × time interval) ANOVA with repeated measures on time intervals, followed by the Newman-Keuls test to test group differences. Occurrence of audiogenic seizures was evaluated by the Fisher exact test for a 2 × 2 table [treatment (vehicle, baclofen) × seizure (presence, absence)].

Experiment 2: Effect of Baclofen on Voluntary Ethanol Intake

Animals. Male sP rats, from the 42nd generation and approximately 6 months old, were used. Rat body weight ranged between 450 and 600 g. Rats were individually housed in standard plastic cages with wood chip bedding. The animal facility was under a reverse, artificial 12/12 hr light-

dark cycle (light on at 2100 hr), at a constant temperature of 22 ± 2°C and relative humidity of 60%. Food pellets (MIL Morini, San Polo d'Enza, RE, Italy) were always available.

Ethanol Drinking Procedure. Ethanol (10% v/v, in tap water) and tap water were offered under the two-bottle free choice regimen with unlimited access 24 hr/day. Bottles were refilled every day with fresh solution and their positions interchanged at random to avoid development of position preference. Ethanol and water intakes were recorded daily, immediately before lights off. All rats used in the present study fulfilled the



	10
3	5.75 ± 0.31
5	6.00 ± 0.71
0	5.25 ± 0.70
0	4.88 ± 0.87
6	4.00 ± 0.19
3	3.75 ± 0.45
7	3.88 ± 0.52
5*	2.63 ± 0.53*
7	1.13 ± 0.23
6	1.50 ± 0.19
7	1.13 ± 0.35
6	1.88 ± 0.35
8	1.63 ± 0.18
6	2.13 ± 0.23
6	2.25 ± 0.16
5	1.75 ± 0.31

f ethanol withdrawal
e the sum of scores
< 0.05 in comparison

rats [$F_{dose}(3,312) = 6.20$, $p < 0.005$] (Fig. 2A). The magnitude of the reduction, compared to saline-treated rats and calculated over the entire treatment period, averaged approximately 10, 20, and 30% in the 2.5, 5, and 10 mg/kg baclofen-dosed rats. Baclofen efficacy was maximal over the first 2 to 5 days of treatment and then tended to reduce

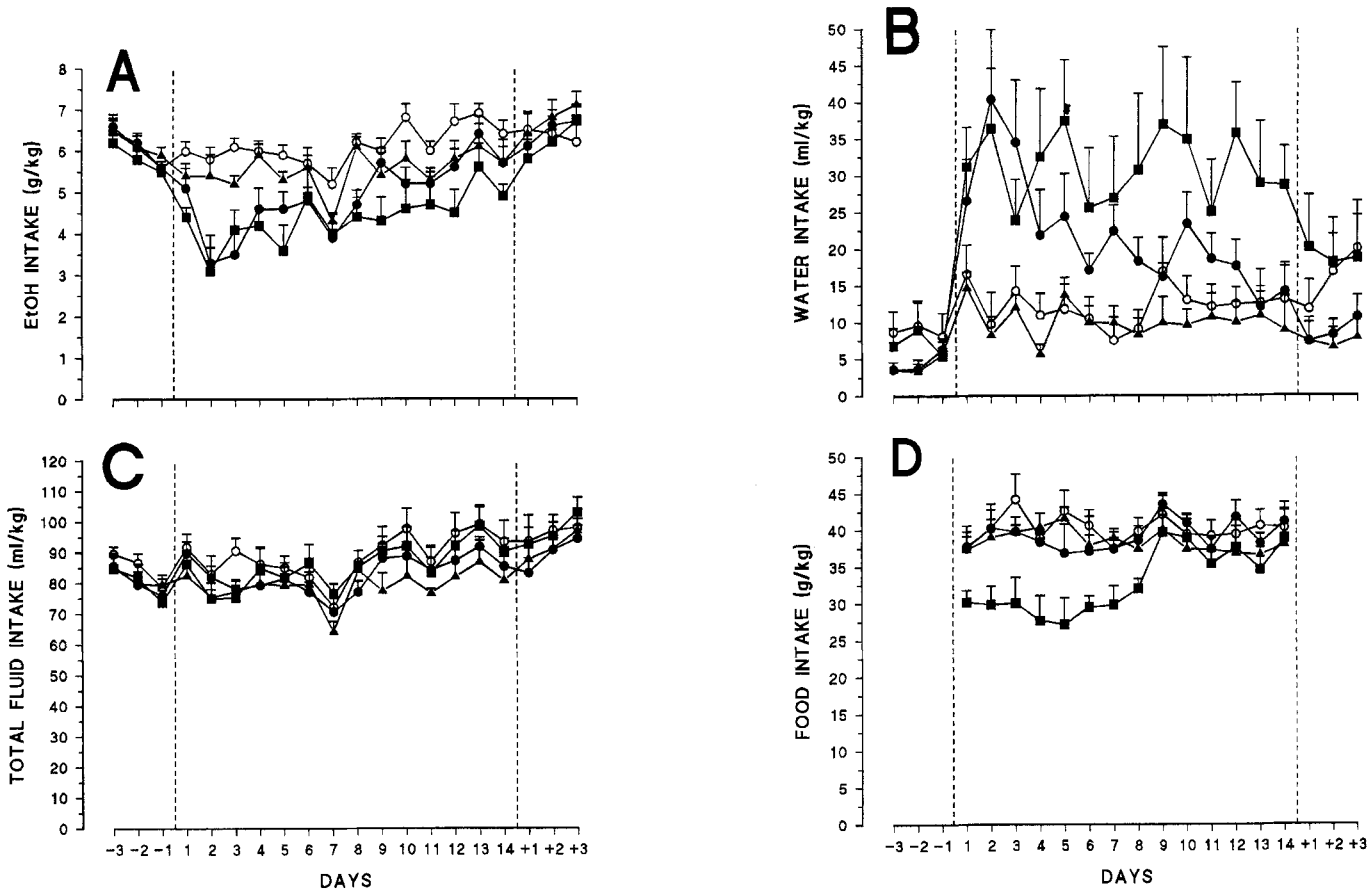


Fig. 2. Effect of baclofen on ethanol drinking behavior in ethanol-preferring sP rats. Baclofen [0 (open circles), 2.5 (triangles), 5 (closed circles), and 10 (squares) mg/kg] was administered intraperitoneally once a day (20 to 30 min prior to light off) for 14 consecutive days. Rats had continuous access to ethanol (10% v/v) and water under the two-bottle free choice regimen. Ethanol, water, and food intake were recorded daily. Each point is the mean ± SEM of $n = 7$.

more, in the studies by File et al. (1991) and Humeniuk et al. (1994), animals were made physically dependent on ethanol by the liquid diet method, whereas in the present study we used the intoxicating procedure conceived by Majchrowicz (1975), which, to our knowledge, yields the most severe withdrawal signs.

Also, the anticonvulsant activity of baclofen observed in the present study seems puzzling and difficult to reconcile with part of the existing literature. Indeed, although Humeniuk and co-workers (1994) indicated that baclofen exerted a proconvulsant effect in ethanol-withdrawn mice, Frye and colleagues (1986) reported that the microinjection of baclofen into the inferior colliculus suppressed withdrawal (Frye et al., 1986; present study), baclofen has been described as abolishing the incidence of audiogenic seizures in barbital-abstinent rats (Benedito and Leite, 1981).

The results of experiment 2 indicate the capability of baclofen to reduce voluntary ethanol intake in selectively bred, ethanol-preferring sP rats. The magnitude of this change was dose-dependent. The decrease in ethanol intake was compensated by an increase in water consumption; subsequently, total fluid intake (i.e., the sum of ethanol solution and water consumed) was unaffected, and the preference ratio (i.e., ratio between ethanol solution consumed over total fluid intake) was significantly reduced

(Daoust et al., 1987) or increased (Smith et al., 1992, 1999) voluntary ethanol intake in Long-Evans rats. All four studies (Daoust et al., 1987; Smith et al., 1992, 1999; present study) employed comparable doses of baclofen (2.5–10 mg/kg range), and rats had unlimited access to ethanol and water under the two-bottle free choice regimen.

Despite the contradictory results reported in the preclinical literature, a recently completed open trial demonstrated that the repeated oral administration of baclofen suppressed alcohol craving and induced sobriety in human alcoholics (Addolorato et al., 2000).

The mechanism by which baclofen exerts its anti-alcohol effects is not known. Little is known about the role of $GABA_B$ receptors in mediating the central effects of ethanol. In vitro studies indicated that presynaptic (Ticku, 1990) and postsynaptic (Frye and Fincher, 1996) $GABA_B$ receptors were insensitive to the acute application of pharmacologically relevant concentrations of ethanol. Furthermore, in vitro studies showed that the $GABA_B$ receptor function was not altered after chronic ethanol treatment and withdrawal from ethanol (Frye and Fincher, 1996; Molleman and Little, 1995).

The $GABA_B$ receptor system is believed to exert an inhibitory action in the brain, regulating the release of excitatory amino acids (e.g., glutamate) via stimulation of presynaptic $GABA_B$ receptors, and hyperpolarizing the postsynaptic neuron via stimulation of postsynaptic $GABA_B$ receptors (see Misgeld et al., 1995). Several lines of evidence indicate that ethanol withdrawal hyperexcitability is associated with an increased function of the *N*-methyl-D-aspartic acid (NMDA) subtype of glutamate receptor; for instance, NMDA receptors are up-regulated when ethanol withdrawal states appear (Follesox and Ticku, 1996; Grant et al., 1990, 1992; Gulya et al., 1991; Iorio et al., 1992; Sanna et al., 1993; Snell et al., 1993; Trevisan et al., 1994; Valverius et al., 1990), and adminis-

erties of the drug (see Wise and Bozarth, 1987), and because voluntarily consumed ethanol stimulated locomotor activity in sP rats (Colombo et al., 1998b). Activation of the mesolimbic dopamine system is the likely neural substrate that mediates both phenomena (see Wise and Bozarth, 1987). Consistently, microinjection of baclofen in the ventral tegmental area (VTA) (the site where cell bodies of dopamine neurons that project to the nucleus accumbens are located) has been reported to decrease dopamine release in the nucleus accumbens in rats (Yoshida et al., 1994). Thus, the ability of baclofen to reduce voluntary ethanol intake in sP rats might result from its ability to diminish the reinforcing properties of ethanol by inhibiting ethanol-stimulated dopamine release in the mesolimbic system. In this regard, it may be noteworthy that parenteral administration as well as intra-VTA injection of baclofen in rats selectively reduced self-administration of cocaine (Campbell et al., 1999; Roberts and Andrews, 1997; Roberts et al., 1996; Shoaib et al., 1998) and heroin (Xi and Stein, 1999), the reinforcing properties of which are mediated, at least in part, by enhanced dopamine function in the mesolimbic system (see Koob, 1992). Consistently, systemic administration of baclofen decreased heroin-induced release of dopamine in the rat nucleus accumbens (Xi and Stein, 1999). In a recent clinical survey, baclofen administration decreased cocaine craving and use (Ling et al., 1998), proving to be a promising candidate for treating cocaine abuse. Furthermore, stimulation of $GABA_B$ receptors by baclofen in the rat VTA reduced the rewarding properties of midbrain self-stimulation, a phenomenon closely associated with activation of dopamine neurons in the VTA, as suggested by the observed increase in current threshold for self-stimulation (Willick and Kokkinidis, 1995).

Alternatively, the reported anxiolytic effect of baclofen (Andrews and File, 1993b; Breslow et al., 1989; Kataloars et

baclofen shares with GHB, beside other pharmacological effects, the ability to reduce the severity of ethanol withdrawal syndrome and voluntary ethanol intake in rats (see the introductory section for references on GHB). The results of the current study may shed light on the molecular mechanism by which GHB exerts its alcohol-substituting effects. Taking for granted that the effects of baclofen on ethanol withdrawal syndrome and ethanol intake are secondary to the drug's capability of activating $GABA_B$ receptors, the question arises whether the reducing effect of GHB on ethanol withdrawal signs and ethanol consumption is mediated by the $GABA_B$ receptor, possibly via its conversion into GABA (Hechler et al., 1997) or activation of its own binding site being part of a $GABA_B$/GHB receptor complex (Snead III, 1996a). Further studies that employ selective $GABA_B$ and GHB receptor antagonists are needed to address this issue.

In conclusion, results of the present study suggest that baclofen alleviated ethanol withdrawal syndrome and decreased volitional consumption of ethanol in two animal models of alcoholism: rats made physically dependent by

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