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BRIEF COMMUNICATION

Direct Evidence for Mediation of an Anticonflict Effect of Baclofen by GABAb Receptors

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SHEPHARD, R. A., P. WEDLOCK AND N. E. WILSON. *Direct evidence for mediation of an anticonflict effect of baclofen by GABAb receptors.* PHARMACOL BIOCHEM BEHAV 41(3) 651–653, 1992.—The present article reports an experiment on the effects of baclofen (0, 0.5, 1.0, and 2.0 mg/kg) on punished drinking in rats and the modification of these by delta-amino-*n*-valeric acid (DANVA) (0 and 10.0 mg/kg). Baclofen significantly enhanced punished drinking and this increase was abolished by DANVA, which had no intrinsic anxiogenic activity. It is concluded that GABAb receptors probably mediate this effect of baclofen and that such receptors may be a potential site of anxiolytic drug action.

Baclofen Delta-amino-*n*-valeric acid GABA Conflict behavior

IT is generally believed that GABA systems have a role in anxiety [e.g., (2,7)]. In recent years, attention in behavioural pharmacology has focussed primarily on drugs acting at the GABAa receptor subtype because of the well-known association between these and the benzodiazepine receptor. However, there is hardly any evidence that GABAa agonists such as muscimol can reproduce behavioural effects of benzodiazepines and evidence for opposite effects of GABAa antagonists such as bicuculline is, although more complex and difficult to interpret, far from conclusive [see (6,8,9) for reviews].

Baclofen, generally thought to be an agonist at GABAb receptors, has been shown to enhance punished drinking, a well-known animal model of anxiety (3). No effect on unpunished drinking has been noted (3,4) and it was concluded that this action of baclofen was probably mediated by GABAb receptors rather than the GABAa/benzodiazepine receptor complex (3).

In the present study, we attempted to replicate the enhancement of punished drinking with baclofen and also to determine whether such action would be modified by delta-amino-*n*-valeric acid (DANVA), a drug that functions as an antagonist at GABAb receptors (5). Thus, baclofen (0, 0.5, 1.0, and 2.0 mg/kg) and DANVA (0 and 10.0 mg/kg) were assessed in a 4 × 2 design that also tested the effect of DANVA alone.

METHOD

Subjects

Subjects were 10 adult, male Sprague-Dawley rats, bred in our laboratory, caged individually, and weighing 276–417 g throughout the study. They were maintained on a 12 L:12 D cycle at 18–22°C.

Apparatus

Tests were conducted in five identical boxes measuring 45 × 24 × 18 cm with electrical connections to the drinking spout and cage floor (Anxiometer, Columbus Instruments, Inc.). When subjects completed the circuit by touching both spout and floor, a lick count of seven licks per s was generated by the drinkometer. During shock trials, every twentieth lick resulted in an 0.8-mA shock being generated at the drinking spout by constant-current shock generators (Campden Instru-

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ments Ltd). Duration of the shock was preset at 2 s, but was only experienced by the animal for as long as it remained in contact with the tube.

Procedure

Subjects were thoroughly acclimatised to presentation of water for 1 h daily sessions and their weight stabilised. Water was freely available at this time and food at all times except during the test session. They were then acclimatised to all aspects of the experimental apparatus and procedure, including handling, IP saline injections in a volume of 1 ml/kg 30 min before placement in test box, and 10-min sessions in the test boxes with no shock. For the last 3 days of this phase, unpunished licks were recorded and the mean of these observations calculated. Punished trials with control injections ensued for 2 days with 10-min sessions and 0.8-mA shocks. Animals that licked at more than 50% of their mean preshock rate or that took only a single shock in these sessions were discarded from further analysis, leaving the 10 subjects described above. Drug testing then began with each 10-min test session being separated by at least one control day on which subjects were tested following saline. Stable and high levels of suppression always resulted on such days. Shock level was maintained at 0.8 mA throughout.

Drug Administrations

Drugs used were (+/−) baclofen (Research Biochemicals Inc.) and DANVA hydrochloride (Sigma Co Ltd.). These were dissolved in 0.85% saline for injection in a volume of 1 ml/kg. Each subject received all eight possible combinations of baclofen (0, 0.5, 1.0, and 2.0 mg/kg) with DANVA (0 and 10.0 mg/kg) by IP injection 30 min pretest for baclofen and 20 min pretest for DANVA. Order of treatments was randomised for each subject. Doses were chosen on the basis of pilot and published studies and are expressed as salt.

Data Analysis

Because of interanimal variation in the extent of suppression, nonparametric techniques are more powerful. Friedman's analysis of variance (ANOVA) by ranks was used to test overall variation between drug conditions. Further analysis was by one-tailed sign tests in accordance with the predictions that punished drinking would be enhanced by baclofen and these increases would be attenuated by DANVA. In the sign tests, X = the number of subjects conforming to the predictions and N = the number of comparisons (ties are disregarded).

RESULTS

Results of this study are shown in Fig. 1. Friedman's test confirmed highly significant variation between the drug conditions ($\chi^2_r = 96.13$, $df = 7$, $p < 0.001$). In the absence of DANVA, punished drinking was significantly elevated by baclofen at 0.5 and 2.0 mg/kg ($X = 9$, $N = 10$, $p = 0.011$ in both cases) but the effect of 1.0 mg/kg was not significant ($X = 7$, $N = 10$, $p = 0.172$). In the presence of DANVA (10 mg/kg), no dose of baclofen affected punished drinking as shown in Fig. 1 and confirmed by nonsignificant sign tests. Increases in punished drinking induced by 0.5 and 2.0 mg/kg baclofen were significantly attenuated by DANVA ($X = 8$, $N = 10$, $p = 0.050$ in both cases), but DANVA did not reduce punished drinking in the presence of 0 or 1.0 mg/kg baclofen ($X = 3$, $N = 10$; $X = 6$, $N = 10$), respectively.

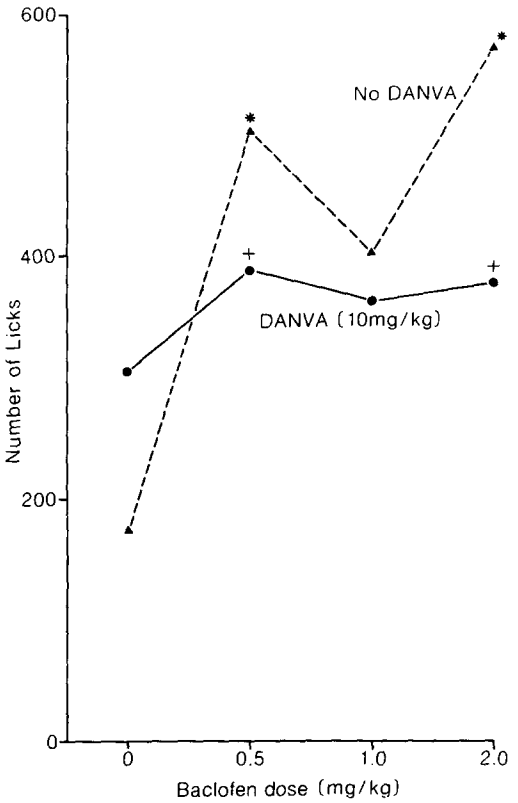

FIG. 1. Enhancement of punished drinking by baclofen and the abolition of this effect by DANVA. All values shown are means of 10 observations on different rats, control sessions being incorporated in the experimental design described in the text. The average standard error was 101.2 s. *significantly different from control ($p = 0.011$); +significantly different from baclofen only ($p = 0.050$).

DISCUSSION

The present study confirms the capacity of baclofen to enhance punished drinking (3), an anticonflict effect characteristic of benzodiazepines and related drugs. The lack of formal significance for the 1 mg/kg dose in the present study can probably be regarded as a statistical anomaly as this dose has previously been reported to be effective (3); furthermore, it increases punished drinking even when mild shock is used and the extent of behavioural suppression is small (Wilson and Shephard, unpublished data). The efficacy of baclofen in enhancing punished drinking contrasts with its reported failure to enhance punished operant behaviour (1) or alleviate conditioned suppression (9). However, it should be noted that these studies only report ineffectiveness of baclofen at a single dose (1 mg/kg) and it may be that further investigations would reveal anticonflict effects of baclofen in other anxiety paradigms.

Abolition of the effect of baclofen by DANVA (10 mg/kg) provides direct support for the previous suggestion that anticonflict effects of baclofen are mediated by GABAb receptors (3). It would be interesting to determine whether higher doses of baclofen would surmount the antagonism by DANVA. The lack of intrinsic anxiogenic action of DANVA, together with its inability to reverse reductions in conditioned suppression induced by valproate (9) or chlordiazepoxide (10),

are evidence for its specificity in preventing baclofen action in the present study. Moreover, DANVA (10 or 20 mg/kg) does not attenuate effects of chlordiazepoxide (5 or 10 mg/kg) on punishing drinking (Wedlock and Shephard, unpublished data). Further research on these matters is indicated, but it is clear that drugs acting at the GABAb receptor can modify punished drinking and it could be a potentially useful site of anxiolytic drug action.

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