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GABAergic Influences on Defensive Fighting in Rats

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RODGERS, R. J. AND A. DEPAULIS. *GABAergic influences on defensive fighting in rats*. PHARMAC. BIOCHEM. BEHAV. **17**(3) 451–456, 1982.—The involvement of GABAergic mechanisms in shock-induced defensive fighting in rats was investigated in a series of three experiments. In Experiment 1, sodium n-dipropylacetate (100–200 mg/kg) failed to produce significant behavioural change whilst γ-vinyl-GABA (100–200 mg/kg) induced a selective and dose-dependent reduction in fighting. In Experiment 2, although inconsistent behavioural effects were obtained with (+)-bicuculline (0.25–4 mg/kg), a biphasic influence on defensive fighting was observed with picrotoxin (0.125–2 mg/kg). The inhibitory effect on fighting, induced by the highest dose of picrotoxin, was related to motor impairment. In Experiment 3, muscimol reduced fighting at doses above 0.25 mg/kg with motor disruption evident only at the highest dose used (1 mg/kg). A dose-dependent inhibition of defensive fighting was observed with l-baclofen (0.15–1.2 mg/kg) which, at the highest dose tested, also impaired motor coordination. None of the compounds tested significantly altered shock thresholds. Results are discussed in relation to the hypothesized inhibitory role of GABA in the mediation of aggressive behaviours.

GABA Defensive fighting Shock thresholds nDPA GVG Picrotoxin Bicuculline Muscimol l-Baclofen Rats

γ-AMINOBUTYRIC acid (GABA) is believed to be a major inhibitory transmitter in the mammalian CNS [39]. Yet, whilst clinical observations have implicated GABAergic mechanisms in various neurological diseases (for review, see [14]) and biochemical/electrophysiological studies have drawn links between GABA receptor function and the action of benzodiazepines [6,43], our knowledge concerning the behavioural significance of this neurotransmitter is rather limited.

Recently, however, both biochemical and pharmacological studies have suggested that GABA may exert an important inhibitory influence on aggressive behaviour. For example, a correlation between aggression and GABA function is suggested by the findings that, compared to aggregated mice, isolated mice display lower GABA binding capacity in brain synaptosomal fractions [9] and lower brain activity of the GABA synthetic enzyme, glutamic acid decarboxylase [2]. Furthermore, whilst a poor correlation has been reported between whole brain GABA content and aggression [8], other studies have found that aggressive mice have lower regional GABA levels than their non-aggressive counterparts [13]. In rats, it has been reported that the GABA content of the olfactory bulbs is lower in killer (i.e., rats killing mice), than in non-killer, animals [30].

Pharmacological investigations have provided support for GABAergic inhibition of agonistic behaviour in mice and mouse-killing behaviour in rats. In mice, stimulation of GABA receptors or inhibition of GABA degradation results in a reduction in both isolation-induced fighting [8, 35, 36, 37] and shock-induced fighting [38]. Inhibition of GABA degradation also reduces attack shown by mice against lactating intruders [20]. Experiments with GABA antagonists have found facilitation of isolation-induced fighting [35] and shock-induced fighting [38] in this species. In rats, mouse-killing behaviour is decreased by systemic or intra-olfactory bulb administration of GABA agonists or inhibitors of GABA degradation [11, 12, 30].

Since GABAergic influences on attack behaviour in rats have only been studied in the mouse-killing paradigm, and since aggression is a non-unitary phenomenon [31], the current study employed the shock-induced fighting technique. Unlike shock-elicited behaviours in mice, which appear to be

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of an offensive nature [4,5], shocked rats display largely defensive fighting responses [1]. In accord with the recommendations of Roberts [39] and Enna [15], three pharmacological approaches have been used: Experiment 1 involved the use of inhibitors of GABA degradation, Experiment 2 examined the effects of GABA antagonists and Experiment 3 focused on the action of GABA agonists. Control tests for motor impairment and shock reactivity were also performed.

GENERAL METHOD

Animals

A total of 452 adult male Sprague-Dawley rats (250–350 g), from Bradford University colony, were used as subjects. Animals were group-housed (5/cage) with food and water available ad lib. They were maintained on a 12 hr light-dark cycle (lights on: 0900 hrs) in a temperature-controlled room (24±1°C). All testing was performed between 1300 and 1800 hrs.

Apparatus

Shock-induced fighting and shock threshold tests were carried out in a modified (manipulanda removed, flat interface) rat operant chamber, measuring 23.5×22×22 cm. The chamber was housed in a sound-attenuating enclosure and observations were made via a window in the front of the enclosure. An Aim Bioscience shock generator (model 507), controlled by relayed programming equipment, supplied scrambled electric shock of specified intensity, duration and frequency to the grid floor of the test chamber. Motor coordination was assessed using a rota-rod apparatus, consisting of a horizontally-positioned kymograph (CF Palmer). The central spindle of the kymograph was covered with wire mesh and rotation speed was fixed at 4 rpm.

Procedure

Twenty-four hours before experimentation, animals were tail-marked for individual identification and weight-matched to form pairs for the shock-induced fighting tests. Pairs were then assigned to the different experimental groups, ensuring that the mean group weights did not differ by more than 10 g.

On the test day, animals were transported to the laboratory three hours before testing and, following injection, treated animals were individually-housed until tested. Pairs of rats (one treated; one untreated opponent) were then placed into the test chamber and, after 60 sec habituation, were exposed to 10 min electric footshock (2 mA intensity, 0.5 sec duration), delivered at a frequency of 6/min. Responses of injected animals were scored as (1) no fight response (e.g., jump, escape, avoidance), (2) upright threat posture or (3) fight, consisting of directed striking or lunging at an opponent. These three response categories were used to facilitate distinctions between drug-induced alterations in fighting *per se* and changes in motor capability, escape or avoidance behaviours.

Immediately following this test, injected animals were individually placed on the rota-rod. A criterion of 60 sec on the rod was used and, where animals failed to reach this criterion, they were retested to a maximum of 3 trials (inter-trial interval=30 sec).

At least one week following the fighting test, uninjected opponents were weight-matched across experimental conditions and tested, in an order counter-balanced for condition, on a modified flinch-jump procedure [40]. Individual animals were placed in the test chamber where they received six series of electric shocks (0.5 sec duration), delivered at 15 sec intervals to the grid floor. Shock series were administered in alternating ascending and descending order, with intensities ranging between 0.05 and 1.3 mA in ten steps (inter-series interval=60 sec). Jump thresholds (the intensity at which the animals' hind feet left the grid floor) were determined for each series and an overall mean calculated to give an index of electric shock threshold for each animal.

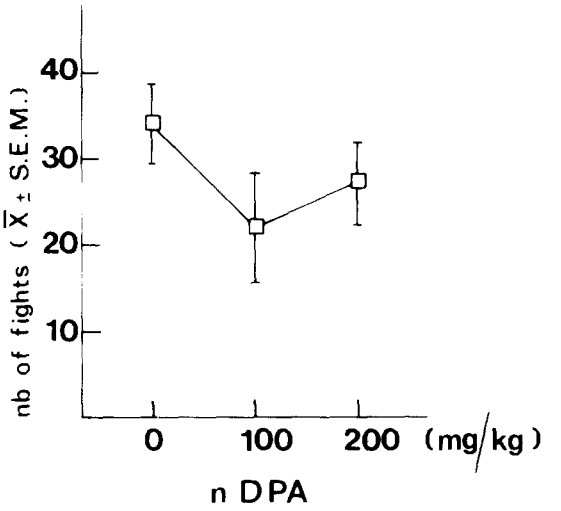

FIG. 1. The effects of sodium n-dipropylacetate (0–200 mg/kg) on shock-induced defensive fighting in rats. Data represent means (±SEM). Analysis failed to reveal a significant drug effect.

Drugs

The following compounds were tested: sodium n-dipropylacetate (nDPA; Labaz), gamma-vinyl-GABA (GVG; Merrel), picrotoxin (PX; Sigma), (+)-bicuculline (BIC; Sigma), muscimol (MUSC; Sigma) and l-baclofen (BACL; Ciba-Geigy). All drugs, with the exception of (+)-bicuculline, were dissolved in physiological saline (0.9%). Bicuculline was dissolved in acidified saline (1 drop 1 N HCl) and buffered to pH=4.5 with sodium hydroxide (0.1 N). Fresh drug solutions were prepared daily and administered intraperitoneally in a volume of 1 ml/kg. Contact times for the various compounds are indicated in the details for specific experiments.

Data Analysis

Results from the shock-induced fighting and shock threshold tests were initially subjected to analyses of variance (ANOVA), following which treatment and control means were compared using Dunnett's test. Data from the rota-rod test were of a non-parametric nature and, therefore, analyzed using Kruskal-Wallis and Mann-Whitney procedures.

EXPERIMENT 1

METHOD

In this experiment, two inhibitors of the GABA degrada-

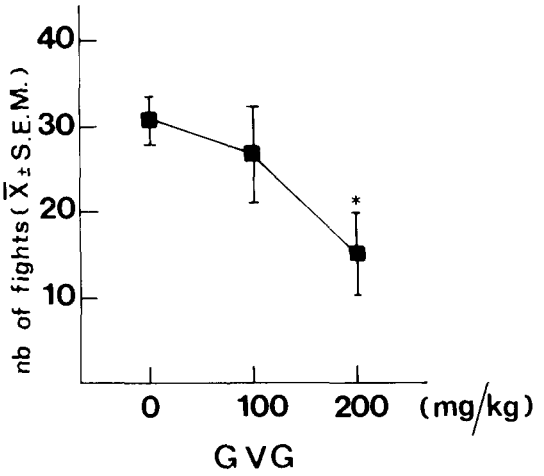

FIG. 2. The effects of gamma-vinyl-GABA (0–200 mg/kg) on shock-induced defensive fighting in rats. Data represent means (±SEM). Analysis revealed a significant reduction in fighting at 200 mg/kg (*$p<0.05$).

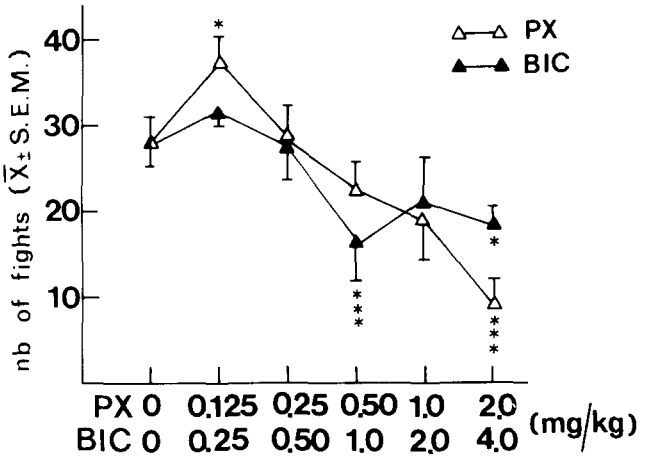

FIG. 3. The effects of picrotoxin (0–2 mg/kg) and bicuculline (0–4 mg/kg) on shock-induced defensive fighting in rats. Data represent means (±SEM). *$p<0.05$, ***$p<0.001$.

tive enzymes were used: (1) sodium n-dipropylacetate (nDPA), a reversible inhibitor of both GABA-transaminase (GABA-T; [18]) and succinic semialdehyde dehydrogenase (SSADH; [45]) and (2) γ-vinyl GABA (GVG), a more specific and irreversible inhibitor of GABA-T [23, 29, 33]. Both compounds have been shown to increase cerebral GABA levels, with maximum effect reached at 1 hr with nDPA [19,42] and at 4 hrs with GVG [23]. These injection-test latencies were used in the present study. Doses were determined with reference to biochemical data [19, 23, 42] and previous behavioural studies [12, 19, 20, 45, 46].

Ninety-six rats were weight-matched in pairs and assigned to the following experimental conditions (n pairs in each=8): saline, 100 or 200 mg/kg; nDPA: saline, 100 or 200 mg/kg GVG. Note that two control (saline) groups were used since the injection-test latencies for the two compounds were different (1 hr and 4 hrs, respectively).

RESULTS

In Fig. 1, it can be seen that nDPA failed to produce any significant effect on fighting behaviour, $F(2,21)=1.11$, ns. Analysis of threat, $F(2,21)=0.22$, ns, non-fight, $F(2,21)=0.63$, ns, and rota-rod ($H=0.76$) behaviours also failed to reveal any significant behavioural effects with this compound. Although ANOVA failed to yield a significant effect of GVG on fighting, $F(2,21)=2.20$, ns, threat, $F(2,21)=0.04$, ns, or non-fight, $F(2,21)=2.95$, ns, categories, examination of Fig. 2 suggests a dose-dependent inhibition of fighting. Comparison between treatment and control means, using Dunnett's test, revealed that 200 mg/kg GVG significantly reduced fighting ($p<0.05$) and increased non-fight behaviours ($p<0.05$). Control tests indicated that GVG was without effect on shock thresholds, $F(2,21)=0.83$, ns, or rota-rod performance ($H=0.01$, ns). Thus, GVG but not nDPA results in a selective inhibition of shock-induced defensive fighting in rats.

EXPERIMENT 2

METHOD

In this study, two GABA antagonists were used: (1) (+)-bicuculline (BIC) which is a competitive antagonist [7,32] and (2) picrotoxin (PX), a non-competitive antagonist which is believed to act on the chloride channel [16]. Since both compounds are potent convulsants, doses and injection latencies were determined with reference to EEG studies [25] and previous behavioural reports [24, 34, 35, 38, 46].

Two hundred sixteen rats were weight-matched and allocated to the following experimental conditions (n pairs=18 for saline and 9 for treatment groups): saline: 0.125, 0.25, 0.50, 1.00 or 2.00 mg/kg picrotoxin; 0.25, 0.50, 1.00, 2.00 or 4.00 mg/kg bicuculline. An injection-test interval of 30 min was used for both compounds and animals were tested in an order counterbalanced for drug condition.

RESULTS

Figure 3 summarizes the effects of both compounds on defensive fighting. ANOVA revealed a significant drug effect on fighting behaviour, $F(10,97)=5.85$, $p<0.01$, which upon further analysis was found to relate to enhanced fighting with picrotoxin at 0.125 mg/kg ($p<0.05$), and reduced fighting with 2 mg/kg picrotoxin ($p<0.001$) and bicuculline at 1 mg/kg ($p<0.001$) and 4 mg/kg ($p<0.05$). Threat behaviour was also significantly affected by drug treatment, $F(10,97)=2.41$, $p<0.05$, with inhibition observed at 0.50 ($p<0.05$), 1.00 ($p<0.025$) and 2.00 ($p<0.001$) mg/kg picrotoxin. Bicuculline treatment did not produce any significant alteration in threat. Non-fight behaviours were significantly affected by both drugs, $F(10,97)=7.10$, $p<0.01$, increases being observed with picrotoxin at 0.50 ($p<0.05$), 1.00 ($p<0.001$) and 2.00 ($p<0.001$) mg/kg and bicuculline 1 mg/kg ($p<0.01$) and 4 mg/kg ($p<0.025$).

Although ANOVA failed to show a significant drug effect on shock thresholds, $F(10,73)=0.55$, ns, the highest dose of picrotoxin (2 mg/kg) produced significant motor impairment on the rota-rod test ($p<0.02$). Together, these data indicate that whilst inconsistent effects on fighting were obtained with bicuculline, a dose-dependent biphasic influence was observed with picrotoxin.

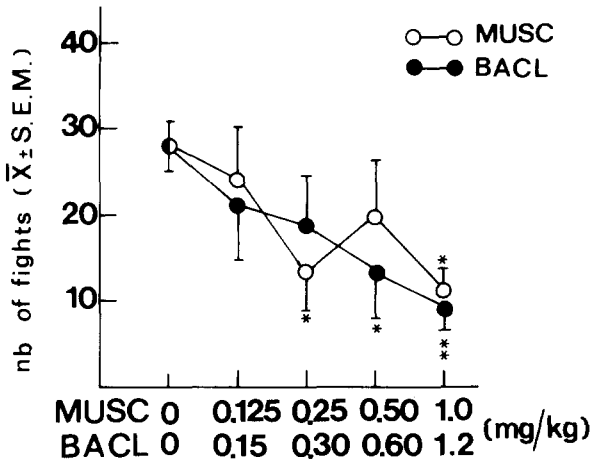

FIG. 4. The effects of muscimol (0–1 mg/kg) and l-baclofen (0–1.2 mg/kg) on shock-induced defensive fighting in rats. Data represent means (±SEM). *$p<0.05$, **$p<0.025$.

EXPERIMENT 3

METHOD

In the final experiment, two GABA agonists were used: (1) muscimol (MUSC) which is known to be a potent agonist of bicuculline-sensitive GABA receptors ($GABA_A$ agonist; [17,32]) and (2) the l-isomer of baclofen (BACL) which has potent effects upon bicuculline-insensitive GABA receptors ($GABA_B$ agonist; [3,21]). For muscimol, doses and injection-test latency were determined from the general behavioural literature [25,46] and previous studies on aggression [11, 30, 35, 36, 37]. Doses and injection-test latency for l-baclofen were derived from the literature [11,28] and checked by pilot experiment.

One hundred forty rats were weight-matched and assigned to the following experimental conditions (n pairs = 14 for saline and 7 for treatment groups): saline; 0.125, 0.25, 0.50 or 1.00 mg/kg muscimol; 0.15, 0.30, 0.60 or 1.20 mg/kg l-baclofen. Animals were tested in an order counterbalanced for drug condition and an injection-test latency of 30 min was employed for both compounds.

RESULTS

Drug effects on defensive fighting are summarized in Fig. 4. ANOVA revealed a significant drug effect on fighting, $F(8,61)=2.19$, $p<0.05$, which, upon further analysis, was found to relate to significant inhibition produced by 0.25 ($p<0.05$) and 1.00 ($p<0.05$) mg/kg muscimol and by 0.60 ($p<0.05$) and 1.20 ($p<0.025$) mg/kg l-baclofen. Neither compound significantly affected threat behaviours, $F(8,61)=0.84$, ns. However, non-fight behaviours were enhanced, $F(8,61)=2.12$, $p<0.05$, an effect attributable to muscimol 1 mg/kg ($p<0.05$) and l-baclofen 0.60 mg/kg ($p<0.05$) and 1.20 mg/kg ($p<0.025$). Neither drug produced consistent alterations in shock thresholds, $F(8,61)=1.13$, ns, although the highest dose of each compound impaired rota-rod performance (muscimol, $p<0.02$ and l-baclofen, $p<0.05$). Together, these data suggest a selective inhibition of fighting with muscimol (0.25 mg/kg) and a dose-dependent inhibition with l-baclofen which, at the highest dose tested, may relate to motor impairment.

GENERAL DISCUSSION

Data, from the three current experiments, suggest that GABAergic mechanisms may be involved in the inhibitory mediation of shock-induced defensive fighting in rats. Inhibition of GABA-T, following treatment with γ-vinyl-GABA, resulted in a dose-dependent reduction in fighting which could not be attributed to sedation, motor impairment or changes in shock thresholds (Experiment 1). Low doses of picrotoxin selectively increased fighting, whilst higher doses of both picrotoxin and bicuculline inhibited this behaviour (Experiment 2). Finally, intermediate doses of both muscimol and l-baclofen induced a specific inhibition of fighting behaviour, although higher doses of each drug resulted in a non-specific impairment of these responses (Experiment 3). These data are broadly consistent with previous reports concerning the involvement of GABA in various forms of aggression in rats [11, 12, 30] and mice [13, 20, 35, 36, 37, 38]. However, as certain aspects of our data are at variance with these previous reports, more detailed comment is warranted.

Firstly, although GVG produced a selective and dose-dependent inhibition of fighting in the current study, nDPA was without significant effect (Experiment 1). This result contrasts with earlier findings that nDPA, within a comparable dose range, is effective in reducing other forms of fighting behaviour [20, 36, 37, 38]. Although other workers have also reported behavioural differences between these two compounds [12,41], it might be argued that, in the present study, positive effects would have been obtained with higher doses of nDPA. Indeed, this would be consistent with the lower potency of nDPA compared to GVG [29]. However, in this context, it should be noted that doses of nDPA in excess of 200 mg/kg induce marked motor impairment [12,19] which would, of course, preclude selective effects of fighting. As the specificity of nDPA on GABAergic mechanisms has been challenged [27], and since it has been reported that GVG and nDPA exert different actions on the various GABA compartments in brain [22], we believe that our contrasting results may be explained in terms of biochemical differences between the compounds.

Secondly, rather different behavioural effects were observed with the two GABA antagonists employed in Experiment 2. Picrotoxin induced a biphasic influence on fighting whilst bicuculline treatment, over a wide dose range, resulted only in inhibitory effects. The enhancement of fighting, observed with the lowest dose of picrotoxin (0.125 mg/kg), could not be attributed to non-specific drug action and, therefore, is consistent with the hypothesis of GABAergic inhibition of fighting. In contrast, the inhibitory effects of high doses of each antagonist are less easy to interpret but may relate to the induction, in this dose range, of pre-convulsive EEG activity [25]. This interpretation, although consistent with the general behavioural disruption seen with 2 mg/kg picrotoxin, cannot account for the observed effects of bicuculline. This compound, at doses which did not impair either threat or rota-rod behaviours, significantly inhibited fighting. Although, on the basis of current data, we are unable to fully explain the differences in behavioural action of the two antagonists, it is known that they differ with respect to their mode of GABA antagonism [16,32].

Finally, both GABA agonists produced an inhibition of fighting which, at high doses only, could be related to motor impairment (Experiment 3). However, an interesting difference was apparent: l-baclofen (a $GABA_B$ agonist) induced a

dose-dependent inhibition of fighting whilst muscimol (a $GABA_a$ agonist) had a more complex effect, with low- and high-dose inhibition. Although the absence of a dose-related effect with muscimol is problematic, it should be noted that, over the same dose range, rather similar effects have been reported in a different behavioural context [46]. On the other hand, although muscimol is a potent GABA agonist, its sites of activity in brain appear to be more widespread than those of GABA [10] and interactions with other transmitter systems have been suggested [44]. The use of a more specific $GABA_a$ agonist, such as THIP [26], would seem warranted in future investigations. The general similarities in the effects of muscimol and l-baclofen (also noted in studies on mouse killing; [11]), do not allow any firm conclusions regarding receptor specificity of GABAergic effects on defensive fighting. This problem is compounded by the current lack of a specific $GABA_b$ antagonist and its solution must, therefore, await future developments.

In conclusion, our results (and those of previous studies) suggest that GABAergic mechanisms may be implicated in inhibitory processes underlying agonistic behaviour in rodents. Despite the non-unitary nature of agonistic phenomena, this inhibitory influence has been found in a variety of animal "models" of fighting behaviour (offensive and defensive). Whilst this general influence may reflect our lack of detailed knowledge on brain GABA systems, it might also relate to the ubiquitous distribution of GABAergic neurons in brain. In order to test the generality of our conclusions, studies are planned in which GABAergic influences on different aspects of agonistic behaviour will be assessed within the same test situation, i.e., a resident-intruder paradigm.

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