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Withdrawal Syndrome Following Subchronic Treatment With Anxiolytic Agents

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BARRY, J. M., B. COSTALL, M. E. KELLY AND R. J. NAYLOR. *Withdrawal syndrome following subchronic treatment with anxiolytic agents.* PHARMACOL BIOCHEM BEHAV 27(2) 239–245, 1987.—The acute administration of diazepam (0.1–2.5 mg/kg IP), sulpiride (0.5–20 mg/kg IP) and tiapride (0.5–40 mg/kg IP) to the mouse enhanced exploratory activity (rearings/line crossings) in the brightly illuminated white area of a two compartment white/black anxiety test box, with a corresponding decrease in the black, indicating an anxiolytic action. This profile of change was maintained during a twice daily administration for 7 days with diazepam (2.5 and 10 mg/kg), sulpiride (5 and 20 mg/kg) and tiapride (10 and 40 mg/kg). However, 8 and 48 hr following withdrawal of diazepam, the profile of exploratory behaviour was reversed to a preference for the black area: by 96 hr values for behaviour had returned to control levels. In contrast, an anxiolytic profile of action was maintained 8 and 48 hr following the withdrawal of sulpiride and tiapride, the values returning to control levels after 96 hr. It is concluded that a sub-chronic treatment with diazepam, sulpiride and tiapride induces an anxiolytic profile of action in the mouse model, that an anxiogenic profile follows the abrupt withdrawal of diazepam but that this is not recorded following the abrupt withdrawal of sulpiride and tiapride.

Benzodiazepine Substituted benzamides Subchronic treatment Anxiety Withdrawal anxiogenesis

THE benzodiazepines possess anxiolytic activity in man which is detectable in animal models [10,11] and there is some evidence that the substituted benzamide derivatives sulpiride and tiapride have similar activity [3, 9, 18]. Although such compounds may be used clinically for prolonged periods of time, the profiles of anxiolytic potential established in animal models generally relate to acute drug administrations, and the consequence of chronic treatments, either the effects during administration or following its withdrawal, remain uncertain. Thus, there are no reports on the anxiolytic activities of chronic treatments with the substituted benzamides in animal models, and the literature on the benzodiazepines attests to a complex situation. It is widely held that the anxiolytic effects of the benzodiazepines persist on chronic treatment [16], although tolerance is reported to the anxiolytic effects of diazepam in the rat [12,21]. The present study was designed to further investigate the effects of diazepam, sulpiride and tiapride both during and following a subchronic treatment in a mouse model of anxiety. Since the withdrawal of the benzodiazepines may be associated with increased anxiety [1], the animal model used was appropriate for detecting the withdrawal syndrome.

METHOD

Experimental Animals

Naive male albino BKW mice, 25–30 g, were used in all experiments. Ten mice were normally housed in each cage with free access to food and water. The mice were kept on a 12 hr light-dark cycle with lights off at 10.00 hr.

Assessment of Anxiety Responding

Animals were taken in a dark container from a dark holding room to the dimly lit testing room where the experiments were conducted between 13.00 and 18.00 hr. The apparatus used for the detection of changes in anxiety consisted of an open-topped box (45×27×27 cm high) having a smaller portion painted black (40% of area) and illuminated under a dim red light (1×60 W) and partitioned from the remainder of the box which was painted white and brightly illuminated with a 100 W light source located 17 cm above the box. The floor area was lined into 9 cm squares. Access between these areas was enabled by means of a 7.5×7.5 cm opening located at floor level in the centre of the partition. Animals that had received drug or vehicle injections were placed individually into the centre of the white area and their behaviour observed over a 5 min period by remote video recording. An increased exploratory activity in the brightly-lit environment is taken as an index of anxiolytic action when a dark environment is simultaneously available. Four behavioural parameters were noted every min, the number of exploratory rearings in the white and black areas, the number of line crossings in the white and black areas, the number of transitions between the white and black or black and white areas, and the time spent in the white and black areas. Experi-

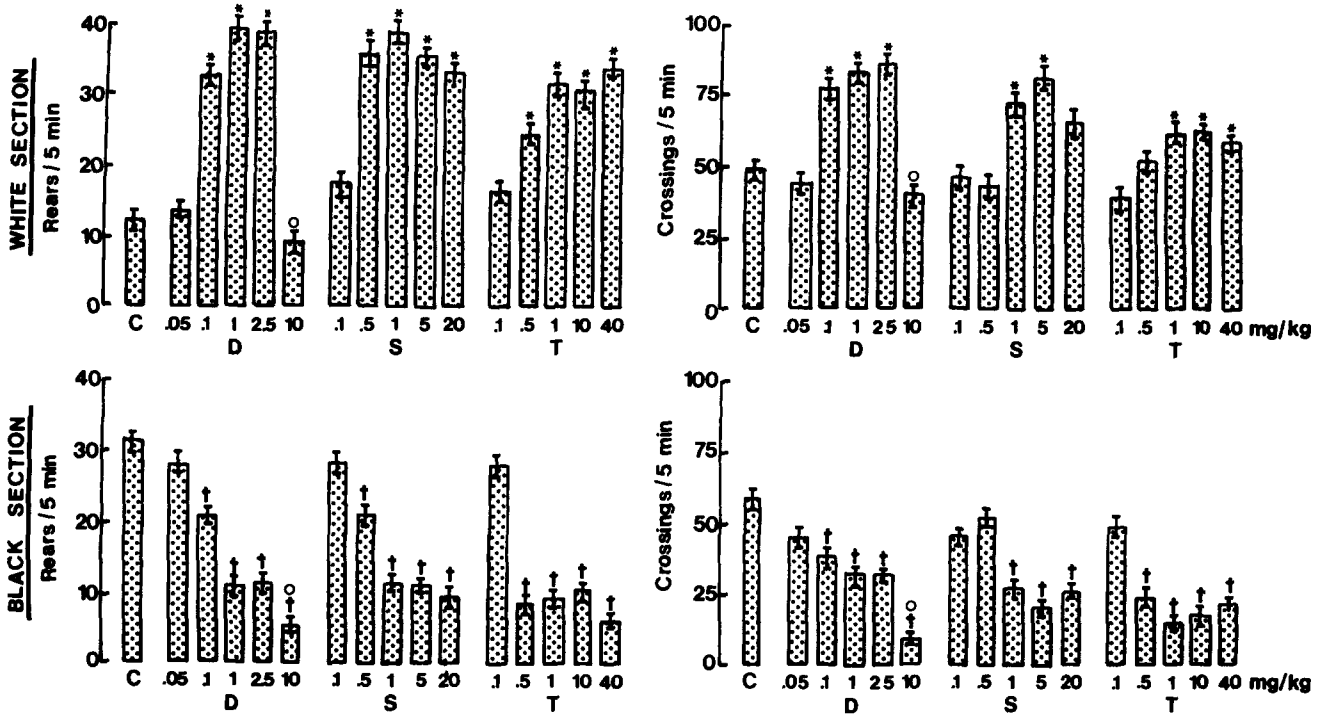

FIG. 1. Effects of diazepam (D, 0.05–10 mg/kg IP), sulpiride (S, 0.1–20 mg/kg IP) and tiapride (T, 0.1–40 mg/kg IP) administered as 45 min pretreatments on rearing behaviour and line crossings in the white and black sections of a box separated into light (white illumination) and dark (red illumination) compartments having an interconnecting 'door.' Measurements were made from remote video recordings every min and were cumulated over a 5 min period. C indicates the response of vehicle treated, control animals (n=10). S.E.M.s given. Significant increases in responding are indicated as $*p<0.001$, significant decreases as $\dagger p<0.05$–<0.001 (one-way ANOVA followed by Dunnett's t-test). °Sedation.

menters remained blind to drug treatment throughout, with the code only being broken after analysis was complete.

Experimental Design

Animals were used on a single occasion only, thus different naive animals were used in each experimental group. Different groups of mice (n=5 or 10) were tested for changes in anxiety during and after drug (or vehicle) administration. Vehicle treated controls were run on each day of testing, i.e., acute (45 min) and chronic (7 days) treatment and 8, 48 and 96 hr after drug withdrawal. Since the effect of the vehicle treatment was indistinguishable when assessed on the 5 occasions, only a single mean control value is given for clarity of presentation in the figures.

Drugs

Sulpiride (SESIF) was prepared in a minimum quantity of HCl made up to volume with distilled water, tiapride · HCl (SESIF) was prepared in distilled water and diazepam (Roche) in the minimum quantity of polyethylene glycol made up to volume with distilled water. Doses are expressed as the base and were administered in a volume of 1 ml/100 g body weight by the intraperitoneal route. Pretreatment times and dose schedules are indicated in the Results section.

RESULTS

General Observations

Throughout the period of experimentation control non-treated and vehicle treated animals displayed the same characteristic behavioural profile in the black and white test box situation. Example control data for vehicle treated animals as shown in Fig. 1 indicates a marked increase in rearing in the black section (31.9±1.8 rears/5 min) as compared to the white area (12.6±1.7 rears/5 min) and a trend to an increased incidence of line crossings in the black area (61.3±5.0 crosses/5 min) as compared to the white area (50.1±4.2 crosses/5 min). Given that the black area is smaller in size than the white area, it is clear that mice demonstrate a preference for both exploratory rearings and line crossings in the black area. Similar profiles of activity can be observed on Figs. 2 to 4 from the data obtained in other vehicle treated control mice. The vehicle treated control animals spent an approximately equal time in each section of the test area with a transition rate between the two areas in the order of 17 to 23/5 min.

The data indicate that under the present test conditions 'normal' mice demonstrate a preference for exploratory behaviour in the black area induced by the aversive properties of the brightly-lit white painted area. As preference for the black section is most clearly demonstrated by measures of locomotion and rearing, transition data and findings concerning proportion of time spent in each section have not been presented in the interests of brevity. Since the responses of vehicle treated animals were not significantly different from those of non-treated animals only the responses obtained from vehicle-treated animals were given as control data in the following results section.

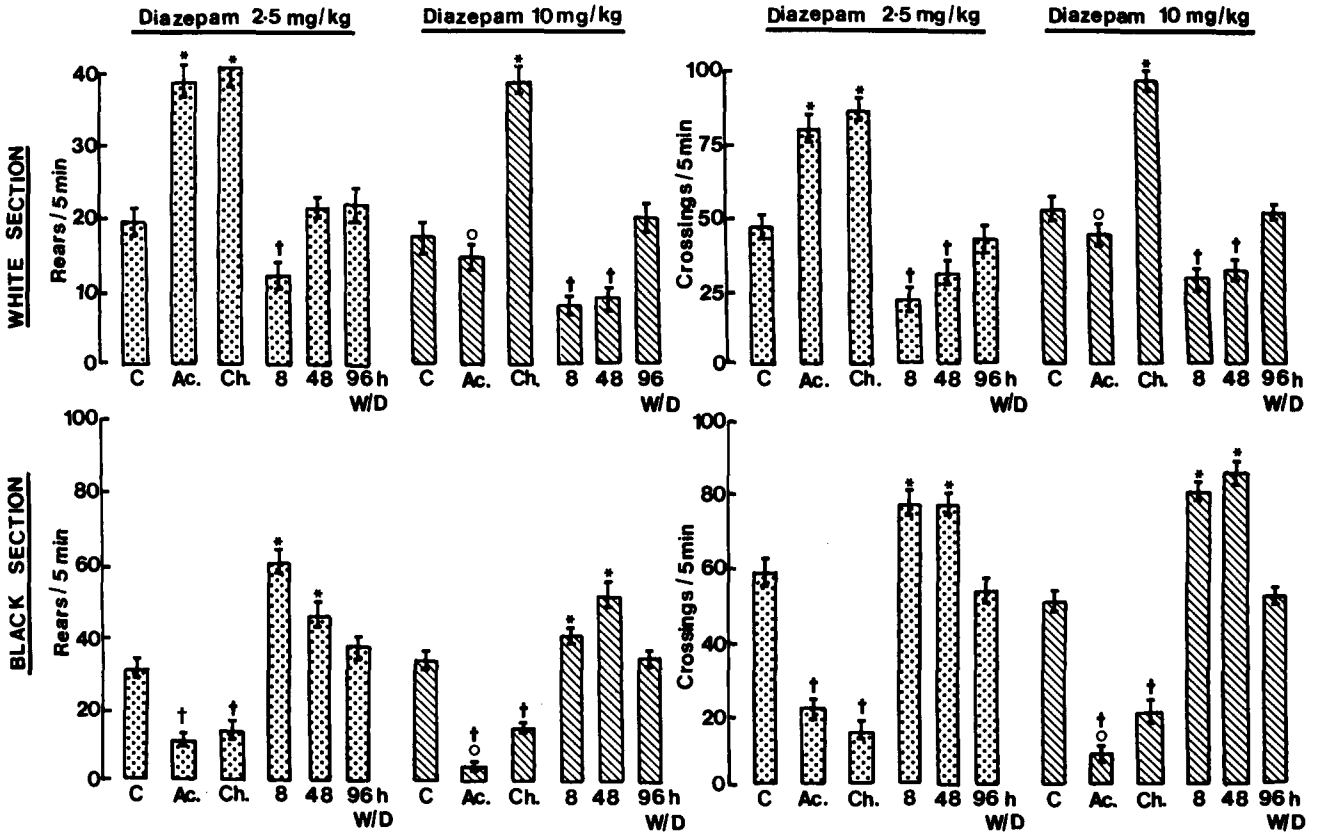

FIG. 2. Effects of a sub-chronic administration of diazepam (2.5 and 10 mg/kg IP b.i.d. for 7 days) on rearing behaviour and line crossings in the white and black sections of a box separated into light (white illumination) and dark (red illumination) compartments having an interconnecting 'door.' Measurements were made on the first day of treatment (i.e., on 'acute' treatment, Ac, 45 min after injection), on the 7th day of treatment (i.e., a 'chronic' treatment, Ch, 45 min after injection) and at 8, 48 and 96 hr after drug withdrawal (W/D). Measurements were made by remote video recordings every min and were cumulated over a 5 min period. Different groups of mice (n=5) were used to assess the effect of each of the 5 treatments and control mice (n=5) injected with vehicle were run with each treatment group. The control values were indistinguishable and C indicates the mean response of vehicle treated animals (n=25). S.E.M.s given. Significant increases in responding are indicated *$p<0.01-<0.001$, significant decreases as †$p<0.01-<0.001$ (Student's t-test). °Sedation.

Modification of Exploratory Behaviour Following Acute Administration of Diazepam, Sulpiride or Tiapride

Anxiolytic activity, characterised by increased behaviour in the white section of the test box and correspondingly decreased activity in the black, could be detected at doses of diazepam, sulpiride and tiapride as low as 0.1, 0.5 and 0.5 mg/kg IP respectively. Steep dose-response curves were obtained and anxiolytic activity was maintained across wide dose-ranges, up to 2.5 mg/kg IP diazepam, 20 mg/kg sulpiride and 40 mg/kg tiapride (Fig. 1). Sedation was observed at the high dose of 10 mg/kg IP diazepam (Fig. 1). In order to determine whether anxiolytic activity could be maintained during repeated treatments, and particularly to determine whether withdrawal changes in anxiety responding occurred on abrupt cessation of drug treatment, moderate to high doses of each agent (two of each) were selected for further study, to be given twice daily for 7 days.

Anxiety Responding During and Following Abrupt Withdrawal From 7 Days Treatment With Diazepam, Sulpiride or Tiapride

Repeated diazepam treatment and withdrawal. Diazepam given repeatedly at a dose of 2.5 mg/kg IP b.i.d., and tested on the 7th day, allowed maintenance of an anxiolytic response at the same level as recorded following a single, acute challenge with the same dose. Again, this anxiolytic action was exemplified by increased rearings and line crossings in the white section with corresponding decreases in the black. Eight hr following discontinuation of the 7 day treatment with diazepam, the profile of behavioural responding was reversed to that of anxiogenic responding characterised by decreased rearings and line crossings in the white area, correspondingly increased in the black. The same anxiogenic profile was also established 48 hr after withdrawing the diazepam treatment, but by 96 hr the distribution of behaviour between the white and black sections had generally returned to control values (at this time only rearing in the black area remained significantly above control levels).

The acute administration of a higher dose of 10 mg/kg IP diazepam caused sedation characterised by reduced exploratory activity in both areas of the test box. On repeated treatment with this dose of diazepam, tolerance developed to the sedation which was undetectable by the third day of continued treatment when a full anxiolytic profile was recorded (increased activity in the white with correlating decreased activity in the black): this maximal anxiolytic profile was maintained to the 7th day of treatment when drug was with-

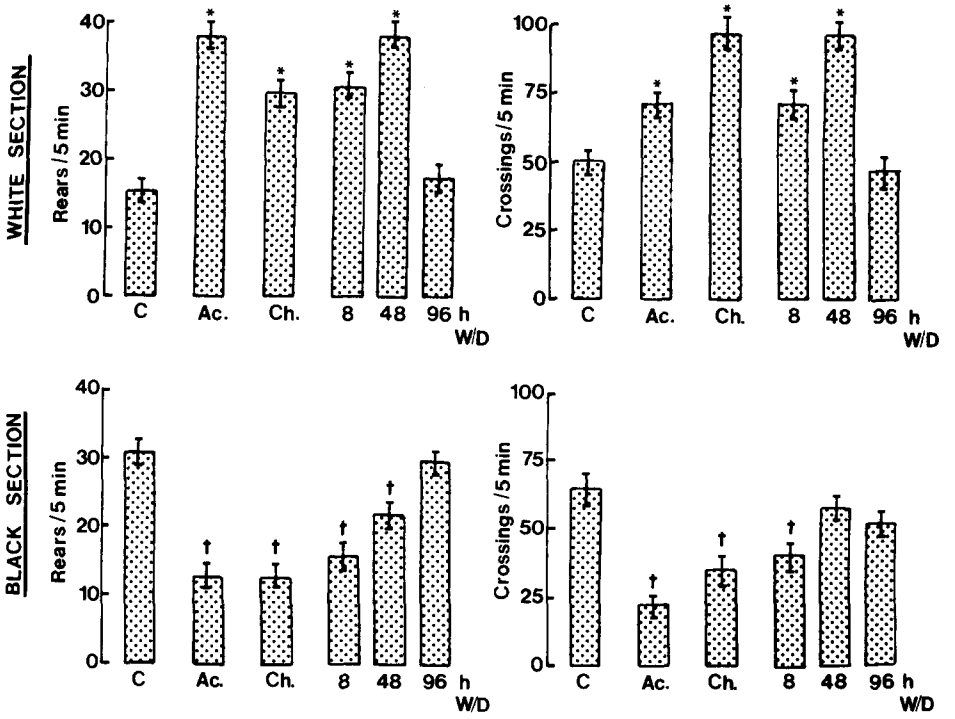

FIG. 3. Effects of a sub-chronic administration of sulpiride (5 mg/kg IP b.i.d. for 7 days) on rearing behaviour and line crossings in the white and black sections of a box separated into light (white illumination) and dark (red illumination) compartments having an interconnecting 'door.' Measurements were made on the first day of treatment (i.e., on 'acute' treatment, Ac, 45 min after injection), on the 7th day of treatment (i.e., a 'chronic' treatment, Ch, 45 min after injection) and at 8, 48 and 96 hr after drug withdrawal (W/D). Measurements were made by remote video recordings every min and were cumulated over a 5 min period. Different groups of mice (n=5) were used to assess the effect of each of the 5 treatments and control mice (n=5) injected with vehicle were run with each treatment group. The control values were indistinguishable and C indicates the mean response of vehicle treated animals (n=25). S.E.M.s given. Significant increases in responding are indicated $*p<0.01-<0.001$, significant decreases as $\dagger p<0.01-<0.001$ (Student's t-test).

drawn. As observed following withdrawal of the lower dose of diazepam, anxiogenesis was marked during the 8–48 hr withdrawal period, with characteristic increased behavioural responding (rearings and line crossings) in the black, decreased in the white section. Again, by 96 hr this withdrawal anxiogenesis had subsided and values obtained for behavioural responding in the black:white box were indistinguishable from those of control vehicle-treated animals (Fig. 2).

Repeated sulpiride treatment and withdrawal. The anxiolytic activity of a single acute administration of sulpiride, 5 mg/kg IP, was maintained when the same dose was given twice daily for 7 days, i.e., there were comparable increases in rearings and line crossings in the white section, decreased in the black. This anxiolytic profile generally persisted even after withdrawal of the chronic sulpiride treatment, for 8–48 hr, with just a tendency for a return of the reduced line crossings in the dark area to control values. By 96 hr following withdrawal of sulpiride treatment all behavioural parameters had returned to control levels (Fig. 3). When a higher dose of 20 mg/kg IP sulpiride was given twice daily for 7 days again a maximal anxiolytic profile was maintained throughout treatment and for up to 48 hr following withdrawal, with return to control responding by 96 hr of withdrawal (data not shown). The data obtained using 20 mg/kg sulpiride (a non-sedative dose) was thus indistinguishable from that obtained using the lower dose.

Repeated tiapride treatment and withdrawal. As recorded for both diazepam and sulpiride, a repeated treatment with tiapride (10 mg/kg IP b.i.d.) allowed maintenance of the maximal anxiolytic activity recorded using a single acute challenge, with rearings and line crossings maximally elevated in the white section of the test box, and correspondingly decreased in the black. Such anxiolytic responding persisted for 8 hr after withdrawing the tiapride treatment, and rearings/line crossings remained elevated in the white section for 48 hr after withdrawal, although at this time the reductions in rearings/line crossings in the black area had returned to control levels. By 96 hr following withdrawal the responses of the mice given tiapride were indistinguishable from those of control, vehicle-treated animals, i.e., there was no indication of withdrawal anxiogenesis (Fig. 4). Also, the profile of change in exploratory activity during and following a 7 day treatment with a higher dose of 40 mg/kg b.i.d. tiapride (a non-sedative dose) was identical to that observed using the smaller dose of 10 mg/kg (data not shown).

DISCUSSION

The present study used a two compartment black and

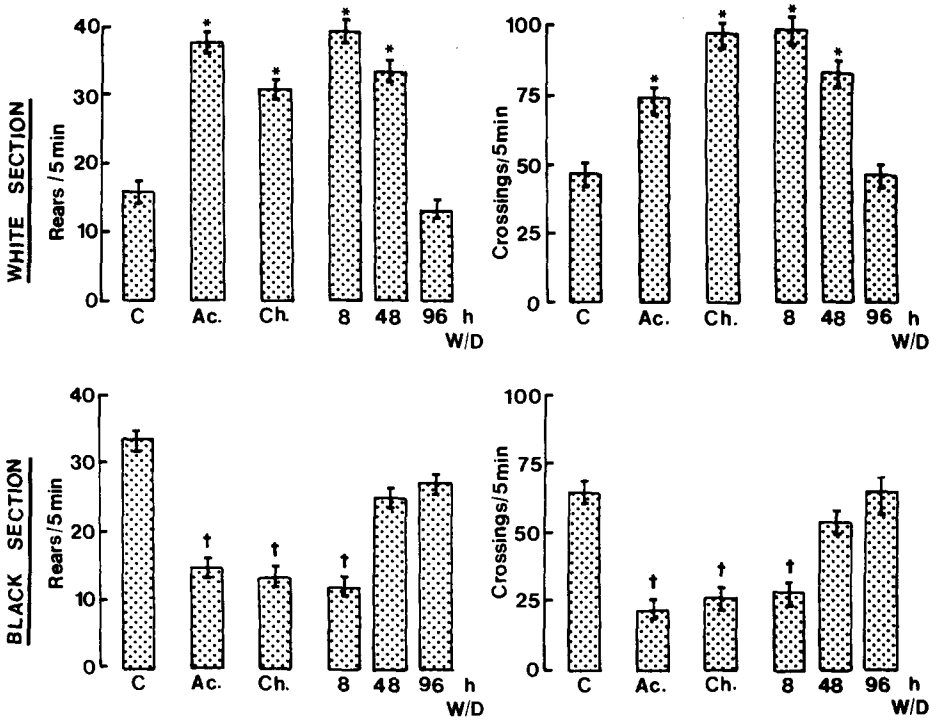

FIG. 4. Effects of a sub-chronic administration of tiapride (10 mg/kg IP b.i.d. for 7 days) on rearing behaviour and line crossings in the white and black section of a box separated into light (white illumination) and dark (red illumination) compartments having an interconnecting 'door.' Measurements were made on the first day of treatment (i.e., on 'acute' treatment, Ac, 45 min after injection), on the 7th day of treatment (i.e., a 'chronic' treatment, Ch, 45 min after injection) and at 8, 48 and 96 hr after drug withdrawal (W/D). Measurements were made by remote video recordings every min and were cumulated over a 5 min period. Different groups of mice (n=5) were used to assess the effect of each of the 5 treatments and control mice (n=5) injected with vehicle were run with each treatment group. The control values were indistinguishable and C indicates the mean response of vehicle treated animals (n=25). S.E.M.s given. Significant increases in responding are indicated as $*p<0.01-<0.001$, significant decreases as $\dagger p<0.01-<0.001$ (Student's t-test).

white test box system to assess anxiety responding in mice. The model was initially designed around the technique described by Crawley and colleagues and is based on the observation that open fields appear to have aversive properties which inhibit rodent exploratory behaviour [6,11]. Thus, naive mice taken from a dark home environment and placed into the white and black system show a preference for the darkly illuminated black area. In a systematic series of experiments Crawley and colleagues have shown that anxiolytic agents increase the rate of transition between the black and white areas (for references see [7]). In our experimental protocol rearings and line crossings in the white and black compartments were shown to be the measurements most indicative of changes in anxiety responding [3].

As reported previously, the present experiments showed that the exploratory activity of mice, taken from the dark, was preferentially exhibited in the black compartment. This preference for exploratory activity in the dark environment was abolished by diazepam, sulpiride and tiapride (see below) and exploration was correspondingly enhanced in the white area. It is interesting to note that the strain of mice used in the present studies did not reflect anxiolytic drug treatment as changes in transitions between the two compartments. The differences in transition rates reported by Crawley and Davis [5] following diazepam treatment, but not observed in the present studies, may reflect strain and methodological differences [3, 5, 15] and it is misleading to attempt close comparisons. The important concept is that in the test system described in the present studies the measurement of rearings and line crossings gave consistent indices of changed anxiety responding, and the measurement of line crossings provided a further valuable measure of changes in locomotor activity to indicate sedation.

The acute injections of diazepam, sulpiride and tiapride were shown to increase exploratory responses of rearings and line crossings in the white area with corresponding decreases in the black area. Both diazepam and sulpiride in low doses are reported to increase rodent locomotor activity [2,8] and it has been suggested that such changes may compromise an interpretation of the changes in exploratory activity in terms of an anxiolytic effect [8]. However, whilst changes in locomotor activity can obviously contribute to changes in exploratory behaviour, it is unlikely that such changes are the determining factor in the white and black test box system. Firstly, whilst sulpiride, tiapride and diazepam all increased line crossings (i.e., locomotor activity) in the white area, all three agents caused marked decreases in line crossings in the black area. Such changes are inconsistent

with the concept that an anxiolytic action reflects a general increase in locomotor activity. Secondly, low doses of tiapride fail to increase locomotor activity in the rodent and yet retain the ability to enhance line crossings in the white area as effectively as sulpiride and diazepam. Thirdly, the mouse model has demonstrated pharmacological specificity to the anxiolytic agents; the acute administration of stimulants, antidepressants, sedatives and other agents all fail to produce the characteristic profile of change to a preferential exploration in the normally aversive environment (see [3,7], Costall and colleagues, unpublished observations).

This profile of anxiolytic activity was fully maintained when diazepam, sulpiride or tiapride were given continuously over a 7 day period. The activities of sulpiride and tiapride were not complicated by sedation, but this was marked during the first two to three days of treatment with diazepam, after which time tolerance developed and there was subsequently no apparent impairment of locomotor activity responding. It was an interesting observation, however, that whilst tolerance developed to the sedative effects of diazepam, which is a well documented phenomenon [17], the anxiolytic action was maintained. Also, in animal conflict models an anti-punishment action of the benzodiazepines develops or is enhanced as the sedative properties decline [13, 16, 17]. However, other workers have indicated that tolerance may develop to the anxiolytic action of the benzodiazepines in rat models [19–21] and this is discussed below.

Whilst diazepam, sulpiride and tiapride all maintained a profile of anxiolytic action on repeated daily treatment, differences between diazepam and the substituted benzamides were apparent on drug withdrawal. Thus, eight hours after administration of the last dose of diazepam, exploratory behaviour in the white area was decreased, indeed, the rearings and line crossings were reduced to below control values in the white area and enhanced above control values in the black area. This reversal of the anxiolytic profile of action of diazepam to a preference for exploratory behaviour in the dark section has been observed using the anxiogenic agent ethyl-β-carboline-3-carboxylate (Costall and colleagues, unpublished data). Thus, an abrupt withdrawal from treatment with high doses of diazepam is associated with an anxiogenic response in the mouse model, and can also be observed in man (see review by Ayd, [1]). It is interesting to speculate that in studies which have reported that tolerance develops to the anxiolytic effect of benzodiazepines, and which have employed a drug withdrawal regimen [19], that the apparent reduction in anxiolytic action may partly reflect an attempt to overcome the anxiogenic response. There is also evidence that the development of tolerance to the anxiolytic actions of diazepam may be dependent on the intensity of the aversive stimuli [20] which can vary between studies. Further, differences in the duration of the 'chronic' treatments employed in various experiments is a factor worthy of more detailed consideration.

In contrast to the anxiogenic response which followed the abrupt withdrawal of diazepam treatment, withdrawal from continued sulpiride and tiapride treatments was followed not by anxiogenesis, but by a slow waning of anxiolytic activity over a period of approximately 2 days. This may reflect a residual presence of drug within body tissues and was not observed after 4 days, the behavioural profile then being indistinguishable from that of control animals. However, at no time did the withdrawal of sulpiride and tiapride cause any change in behaviour in the mouse model consistent with an anxiogenic potential. It may be relevant to such findings that the clinical use of the substituted benzamides and their withdrawal is not associated with anxiogenesis.

The present study has shown that diazepam, sulpiride and tiapride exert anxiolytic action in a mouse model during both acute and sub-chronic administration. The substituted benzamides can be distinguished from diazepam by their failure to cause withdrawal anxiogenesis. Further comparative studies on the mechanisms of action of benzodiazepines and substituted benzamides may provide clues to the disturbances of neurotransmitter function in neuropathological or drug-induced anxiety states, and so aid the development of new therapeutic approaches.

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REFERENCES

1. Ayd, F. J. Benzodiazepine dependency and withdrawal. In: *Pharmacology of Benzodiazepines*, edited by E. Usdin, P. Skolnick J. F. Tallman, D. Greenblatt and S. M. Paul. London: Macmillan Press Ltd., 1982, pp. 593–600.
2. Costall, B., A. M. Domeney and R. J. Naylor. Stimulation of rat spontaneous locomotion by low doses of haloperidol and (−)sulpiride: importance of animal selection and measurement technique. *Eur J Pharmacol* **90:** 307–314, 1983.
3. Costall, B., C. A. Hendrie, M. E. Kelly and R. J. Naylor. Actions of sulpiride and tiapride in a simple model of anxiety in mice. *Neuropharmacology* **26:** 195–200, 1987.
4. Crawley, J. N. Neuropharmacologic specificity of a simple animal model for the behavioural actions of benzodiazepines. *Pharmacol Biochem Behav* **13:** 695–699, 1981.
5. Crawley, J. N. and L. G. Davis. Baseline exploratory activity predicts anxiolytic responsiveness to diazepam in five mouse strains. *Brain Res Bull* **8:** 609–612, 1982.
6. Crawley, J. N. and F. K. Goodwin. Preliminary report of a simple animal behaviour model for the anxiolytic effects of benzodiazepines. *Pharmacol Biochem Behav* **13:** 167–170, 1980.
7. Crawley, J. N., P. Skolnick and S. M. Paul. Absence of intrinsic antagonists of benzodiazepine antagonists on an exploratory model of anxiety in the mouse. *Neuropharmacology* **23:** 531–537, 1984.
8. File, S. E. Models of anxiety. *Br J Clin Pract* **38:** 15–20, 1985.
9. Hasegawa, K., T. Nishimura, M. Miyasaka, H. Ishino, M. Yamada, U. Shimizu, M. Kameyama and H. Itoh. A double blind study of tiapride comparing with chlorpromazine in patients with psychiatric disorders of the aged in multi-centre cooperation. 14eme CINP Florence, p. 809, 19–23rd June, 1984.
10. Hollister, L. E. Pharmacology and clinical use of benzodiazepines. In: *Pharmacology of Benzodiazepines*, edited by E. Usdin, P. Skolnick, J. F. Tallman, D. Greenblatt and S. M. Paul. London: Macmillan Press Ltd., 1982, pp. 29–35.
11. Lal, H. and M. W. Emmett-Oglesby. Behavioural analogues of anxiety. *Neuropharmacology* **22:** 1423–1441, 1983.
12. Lister, R. G., S. E. File and D. J. Greenblatt. Functional tolerance to lorazepam in the rat. *Psychopharmacology (Berlin)* **81:** 292–294, 1983.
13. Margules, D. L. and L. Stein. Increase of anti-anxiety activity and tolerance of behavioural depression during chronic administration of oxazepam. *Psychopharmacologia* **13:** 74–80, 1968.

14. Ryan, G. and N. Boisse. Experimental induction of benzodiazepine tolerance and physical dependence. *J Pharmacol Exp Ther* **226:** 100–107, 1983.
15. Schweri, M., M. Cain, J. Cook, S. Paul and P. Skolnick. Blockade of 3-carbomethoxy-β-carboline induced seizures by diazepam and the benzodiazepine antagonists, Ro 15-1788 and CGS 8216. *Pharmacol Biochem Behav* **19:** 951–955, 1983.
16. Sepinwell, J. and L. Cook. Mechanism of action of the benzodiazepines: behavioural aspects. *Fed Proc* **39:** 3024–3031, 1980.
17. Sepinwall, J., F. S. Grodsky and L. Cook. Conflict behaviour in the squirrel monkey: effects of chordiazepoxide, diazepam and N-desmethyldiazepam. *J Pharmacol Exp Ther* **204:** 88–102, 1978.
18. Standish-Barry, H. M. A. S., N. Bouras, P. K. Bridges and J. P. Watson. A randomised double blind group comparative study of sulpiride and amitriptyline in affective disorders. *Psychopharmacology (Berlin)* **81:** 258–260, 1983.
19. Stephens, D. N. and H. H. Schneider. Tolerance to the benzodiazepine diazepam in an animal model of anxiolytic action. *Psychopharmacology (Berlin)* **87:** 322–327, 1985.
20. Treit, D. Evidence that tolerance develops to the anxiolytic effect of diazepam in rats. *Pharmacol Biochem Behav* **22:** 383–387, 1985.
21. Velluci, S. and S. E. File. Chlordiazepoxide loses its anxiolytic action with long-term treatment. *Psychopharmacologia* **21:** 1–7, 1979.