Pharmacology Biochemistry & Behavior, Vol. 33, pp. 197–203. © Maxwell Pergamon Macmillan plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

The Actions of Nicotine and Cocaine in a Mouse Model of Anxiety

BRENDA COSTALL, M. ELIZABETH KELLY, ROBERT J. NAYLOR[1] AND EMMANUEL S. ONAIVI

Postgraduate School of Studies in Pharmacology
University of Bradford, Bradford, BD7 1DP, England

Received 4 March 1988

COSTALL, B., M. E. KELLY, R. J. NAYLOR AND E. S. ONAIVI. *The actions of nicotine and cocaine in a mouse model of anxiety*. PHARMACOL BIOCHEM BEHAV **33**(1) 197–203, 1989.—The acute administration of nicotine (0.01–1.0 mg/kg IP) to the mouse increased the time spent and rearings and line crossings in the aversive brightly illuminated white area of a two compartment white/black test box, with a corresponding decrease in the black. This profile of change was maintained during twice daily administration (0.1 mg/kg IP) for 14 days. Eight to 96 hr following withdrawal of nicotine (14-day treatment), the behavioural profile was reversed to a preference for the black area: by 240 hr values had returned to control levels. In contrast to the effects of nicotine, an acute injection of cocaine (0.1–10 mg/kg IP) exacerbated the aversive response to the white area. However, similarly to nicotine, the administration of cocaine (1.0 mg/kg IP) twice daily for 14 days reduced the aversion to the white area and exacerbated the response following cocaine withdrawal. The effects of nicotine and cocaine to reduce and enhance responsiveness to the aversive properties of the white area are discussed in terms of an anxiolytic and anxiogenic response and the possibility of a serotonergic involvement.

Mouse Black and white test box Nicotine Cocaine Anxiolytic/anxiogenic-5-HT

THE withdrawal of drugs of abuse in man is associated with a wide range of adverse effects including increased irritability, anxiety, depression, dysphoria, difficulty with concentration, craving and somatic changes. The precise nature and intensity of response is in most cases related to the drug used, e.g., alcohol, narcotic agents, caffeine, nicotine, benzodiazepines, or cocaine, and the degree of abuse. Thus increased anxiety is one of the major manifestations of benzodiazepine withdrawal (27,31), although this is frequently ignored or considered of little consequence in assessments of the principle components of other drug-induced withdrawal states (32). Furthermore, the possibility that chronic drug administrations in animals can induce an anxiogenic response on withdrawal has received little attention, even for the benzodiazepines themselves. Using the rat, Emmett-Oglesby and colleagues (17) have reported that the withdrawal effects of diazepam discriminated with the effects of pentylenetetrazol, an anxiogenic agent. In a quite different model using the elevated plus-maze, rats subject to long-term treatment with chlordiazepoxide followed by withdrawal showed behaviour believed to be predictive for increased anxiety states in man (18). Such findings are in agreement with our own observations where mouse behaviour in a black and white test box is changed to indicate an anxiogenic response following diazepam withdrawal (2). Alcohol withdrawal also caused an anxiogenic response in the mouse model (11), indicating that anxiogenesis may be a common feature of withdrawal from drugs of abuse. The purpose of the present study was to test this hypothesis by studying the effects of an administration and withdrawal of nicotine and cocaine in a mouse model of anxiety.

METHOD

Experimental Animals

Male albino BKW mice (Bradford strain) 25–30 g were used throughout the studies. Mice were housed in groups of 10 in conditions of constant temperature (21°C) and controlled lighting (dark period 07.00–19.00 hr) and fed ad lib on a standard laboratory chow.

Behavioural Tests

Tests were conducted between 13.00 and 18.00 hr in a quiet darkened room illuminated with a red light. Mice were taken from a dark holding room in a dark container to the dark testing room where, after a 1-hour period of adaptation to the new environment, they were placed into the test box. The metal test box (45 × 27 × 27 cm high) was positioned on a bench 1 m above floor level. The box was open-topped and the base lined into 9-cm squares, two-fifths painted black and illuminated by red light (1 × 60 W, 0 Lux) and partitioned from the remainder of the box which was painted white and brightly illuminated with a 1 × 60 W (400 Lux)

[1]Requests for reprints should be addressed to Robert J. Naylor.

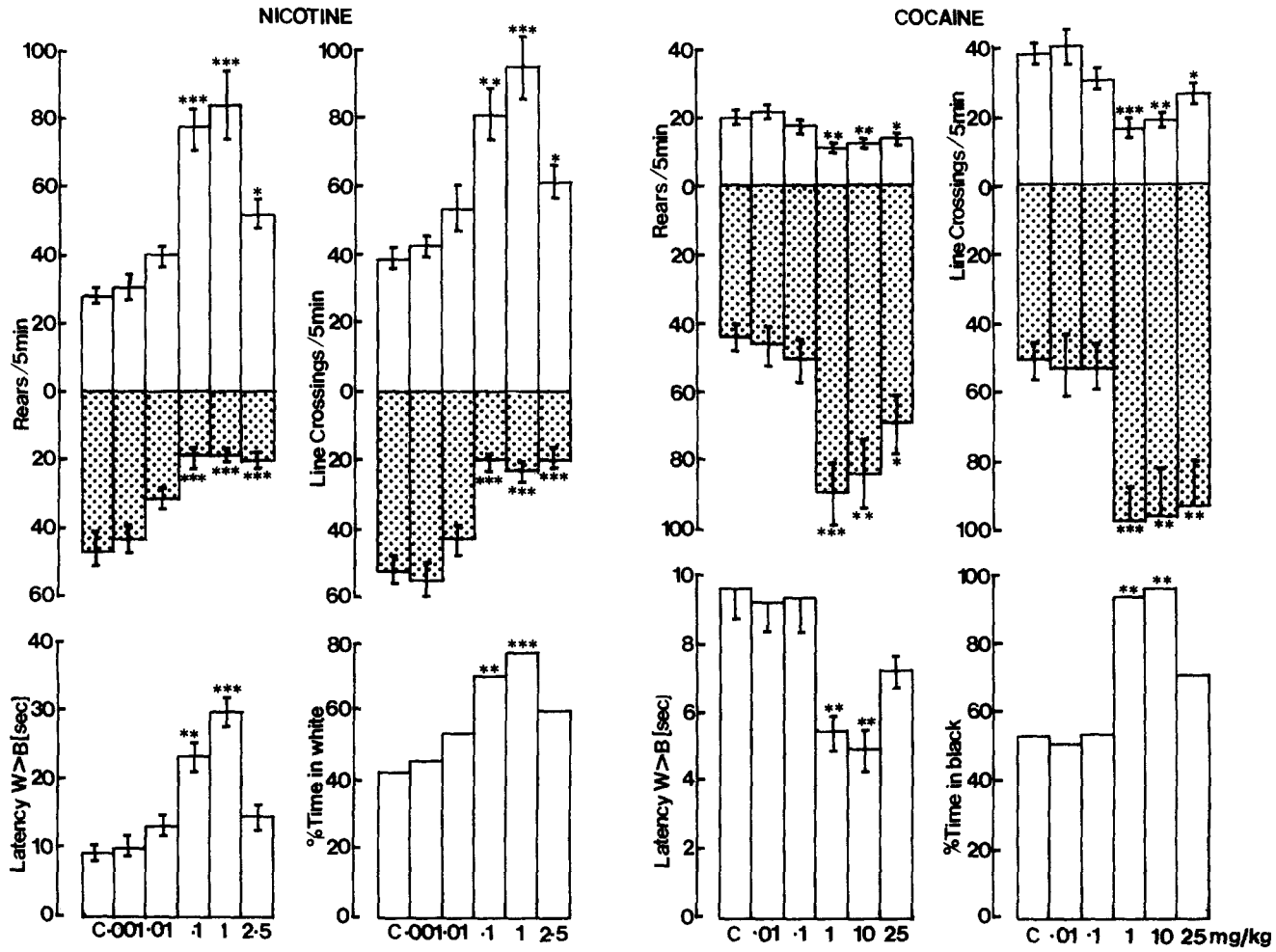

FIG. 1. Effects of nicotine and cocaine in the light/dark discrimination test in the mouse. Mice were tested singly in an open-topped box, three-fifths painted white and brightly illuminated (white section) and partitioned from the remainder of the box which was painted black and illuminated with red light (dark section). The compartments were connected by an opening located at floor level in the centre of the partition. The floor of each section was lined into 9-cm squares. Behavioural changes in rearing (rears), line crossings, latency of movement from the white (W) to the black (B) section (after first placement into the white area) and % time spent in the white or black area is shown. In the upper set of histograms, stippled columns indicate data for the dark area, open columns for the light area. Data obtained from control (C) and drug-treated mice were analysed using single factor Analysis of Variance, and Dunnett's test. Significant increases/decreases in responding are indicated as $*p<0.05$, $**p<0.01$ and $***p<0.001$. n=5. Vertical bars indicate S.E.M.s; S.E.M.s were less than 12% (nicotine) and 9% (cocaine) on the original data for calculation of the % time in the white (nicotine) and black (cocaine) sections.

light source, the red and white lights being located 17 cm above the box. The compartments were connected by an opening 7.5 × 7.5 cm located at floor level in the centre of the partition. Mice were placed into the centre of the white, brightly lit area and the operator withdrew from the room. The mice were observed by remote video recording over a 5-min period and five behaviours were noted: (a) the number of exploratory rearings in the white and black sections, (b) the number of line crossings in the white and black sections, (c) the number of transitions between the two compartments, (d) the time spent in the white and black areas and (e) the latency of the initial movement from the white to the black area.

Experimental Design

Animals were used once only in treatment groups of 5 and vehicle-treated mice and nontreated mice were used as control animals on each day of testing. Results were analysed using Single-Factor Analysis of Variance and where appropriate followed by Dunnett's procedure for comparing all treatments with control.

Treatment Groups

Acute treatments. Mice received a single IP injection of nicotine (0.001–5.0 mg/kg), cocaine (0.01–100 mg/kg) or vehicle and were tested after 40 min, preliminary experiments demonstrating a maximal drug induced effect at this time.

Chronic treatments. Eight groups of mice received a twice daily IP injection with nicotine (0.1 mg/kg, 07.30 and 19.30 hr) or cocaine (1.0 mg/kg, 07.30 and 19.30 hr) or vehicle for 1, 3, 7 and 14 days and were tested on these days and 8, 48, 96 and 240 hr

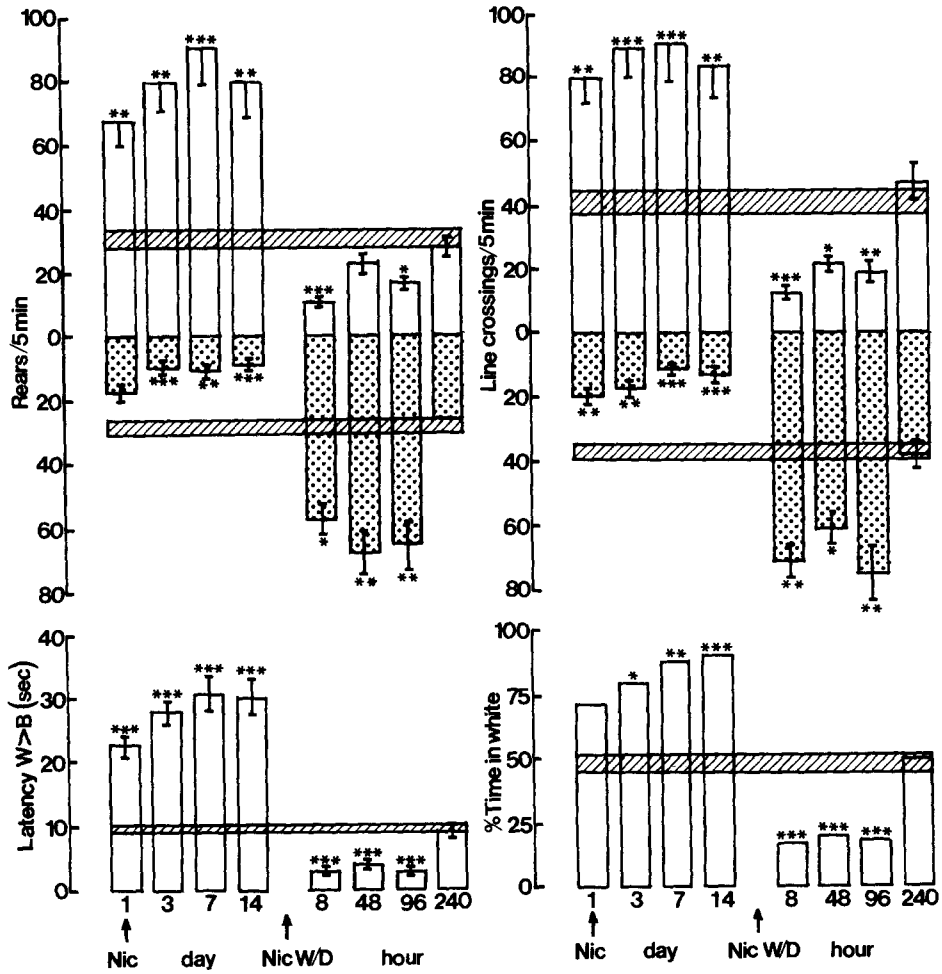

FIG. 2. Effects of nicotine administration and withdrawal in the light/dark discrimination test in the mouse. Mice were tested singly in an open-topped box, three-fifths painted white and brightly illuminated (white section) and partitioned from the remainder of the box which was painted black and illuminated with red light (dark section). The compartments were connected by an opening located at floor level in the centre of the partition. The floor of each section was lined into 9-cm squares. Behavioural changes in rearing (rears), line crossings, latency of movement from the white (W) to the black (B) section (after first placement into the white area) and % time spent in the white area were recorded over a 5-min period. In the upper set of histograms, stippled columns indicate data for the dark area, open columns for the light area. Mice received nicotine (Nic.) administered twice daily (0.1 mg/kg, IP) for 1, 3, 7 or 14 days and were tested on the days of treatment and 8, 48, 96 and 240 hr following nicotine (14-day treatment) withdrawal (Nic. W/D). The data obtained for each treatment was obtained from different groups of mice (n=5). Control data obtained for each treatment was indistinguishable and indicated by the hatched horizontal bars (mean ± S.E.M.). Data obtained from control and drug-treated mice were analysed using single factor Analysis of Variance, and Dunnett's *t*-test. Significant increases/decreases in responding are indicated as $*p<0.05$, $**p<0.01$ and $***p<0.001$. Vertical bars indicate S.E.M.s; S.E.M.s were less than 11% on the original data for calculation of the % time in white section.

following a 14-day treatment.

It is emphasised that drug-treated animals and their respective vehicle controls were used on a single occasion only, to ensure the use of naive animals in each experimental group.

Drugs

Nicotine hydrogen tartrate and cocaine hydrochloride (B.D.H.) were prepared daily in distilled water. Doses are expressed as the base and were administered in a volume of 1 ml/100 g body weight.

RESULTS

General Observations

Vehicle-treated control mice displayed the same characteristic behavioural profile in the black and white test box throughout the duration of the studies. It should be noted that given the relative

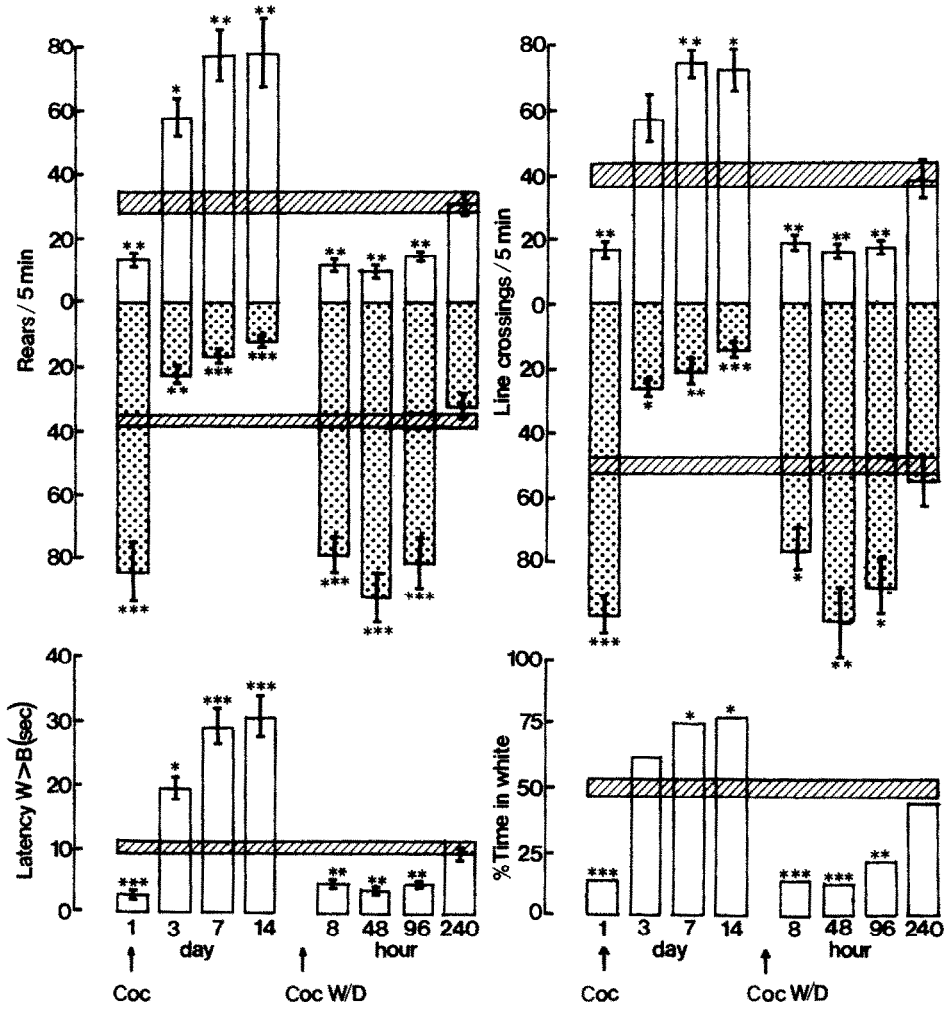

FIG. 3. Effects of cocaine administration and withdrawal in the light/dark discrimination test in the mouse. Mice were tested singly in an open-topped box, three-fifths painted white and brightly illuminated (white section) and partitioned (with an interconnecting door) from the remainder of the box which was painted black and illuminated with red light (dark section). The compartments were connected by an opening located at floor level in the centre of the partition. The floor of each section was lined into 9-cm squares. Behavioural changes in rearing (rears), line crossings, latency of movement from the white (W) to the black (B) section (after first placement into the white area) and % time spent in the white area were recorded over a 5-min period. In the upper set of histograms, stippled columns indicated data for the dark area, open columns for the light area. Mice received cocaine (Coc.) administered twice daily (1.0 mg/kg, IP) for 1, 3, 7 or 14 days and were tested on the days of treatment and 8, 48, 96 and 240 hr following cocaine (14-day treatment) withdrawal (Coc. W/D). The data obtained for each treatment was obtained from different groups of mice (n=5). Control data obtained for each treatment group was indistinguishable and indicated by the hatched horizontal bars (mean ± S.E.M.). Data obtained from control and drug-treated mice were analysed using single factor Analysis of Variance, and Dunnett's *t*-test. Significant increases/decreases in responding are indicated as $*p<0.05$, $**p<0.01$ and $***p<0.001$. Vertical bars indicate S.E.M.; S.E.M.s were less than 13% on the original data for calculation of the % time in white section.

size of the two compartments, two-fifths black and three-fifths white, a preference for the black section was shown by the approximately equal time spent and line crossings in the two areas and, in some experiments, a trend to an increase in rearings in the black section. The initial latency of movement from the white to the black section was consistently in the range of 9.5–12 sec and the transition rate between the two areas was in the order of 18 to 24 transitions in a 5-min period.

Similar profiles of activity can be observed from the control data presented on Figs. 1, 2 and 3, a preference for exploratory behaviour in the black area possibly being induced by the aversive properties of the brightly-lit section. Since the response of vehicle-treated mice was not significantly different from nontreated animals, only the responses obtained from vehicle-treated animals are given as control data in the following results. Also, the transition rate between the two areas was not modified by any

treatment and such data is not presented.

Modification of Behaviour in the Black and White Test Box Following Acute Administration of Nicotine and Cocaine

Nicotine- (0.1–1.0 mg/kg) treated mice showed a significant increase in rearings (to 303%) and line crossings (to 247%) in the white area with a decrease in such activities in the black. The changes in rearings and line crossings in the white section occurred concomitant to an increase in time spent (to 180%) in the white section, indicating that a proportion only of the increase in rearings and line crossings could be attributed to this factor. The initial movement of the mouse form the white to the black area was also significantly delayed by 330% in nicotine-treated animals. Therefore, the overall effect of nicotine in doses up to 1.0 mg/kg is to increase behaviour in the normally aversive white area of the test box (Fig. 1). The use of a higher dose of 2.5 mg/kg was associated with seizure activity which obscured a meaningful measurement of behavioural changes and doses higher than 2.5 mg/kg caused death.

Cocaine caused effects opposite to those induced by nicotine. Thus, cocaine (1.0 and 10.0 mg/kg) significantly increased the incidence of rearings (to 440%) and line crossings (to 252%) in the black area and decreased such activities in the white area. On placement into the white area the mice showed a reduced latency to move into the black area (from 9/10 to 4/6 sec) where they spent a greater proportion of their time (to 190%). Therefore, the effect of cocaine was to increase the aversion to the white area of the test box (Fig. 1). The use of higher doses of cocaine (25.0 mg/kg) was associated with an uncoordinated motor activity which interfered with the development of normal behaviours. The use of 50.0 mg/kg was associated with seizures and 100.0 mg/kg caused death.

Modification of Behaviour in the Black and White Test Box Following Repeated Treatment With Nicotine and Cocaine

A dose of 0.1 mg/kg nicotine was selected as causing a marked behavioural change on acute administration and was administered twice daily in the experiments involving repeated treatment. The twice daily injection of nicotine for 1, 3, 7 or 14 days caused an identical profile of behavioural change to that observed using a single administration, i.e., an increase in rearing (to 296%) and line crossings (to 220%) in the white section with a reduction in the black area (by 72%), a greater proportion of time spent in the white area (to 185%) and an increased latency of the first movement from the white to the black section (from 9/11 to 29/32 sec). The effect of a repeated twice daily treatment with nicotine clearly maintained an ability to reduce the aversive response to the white area (Fig. 2).

A reversal of this response was shown within 8 hr of withdrawal from a 14-day treatment with nicotine. Thus, rearings and line crossings increased in the black area by 279 and 197% respectively to control values, and by some 700% relative to the values obtained during treatment with nicotine. At the same time rearings and line crossings were decreased in the white section. The latency of movement of the mice from the white to the dark area was also markedly decreased (from 9/10 to 2/4 sec), as was the time spent in the white section (by 67%) (Fig. 2). The effects of nicotine withdrawal were still fully present after 96 hr, but by 240 hr the behaviour of the mice was indistinguishable from controls.

A dose of 1 mg/kg cocaine was selected as causing a maximal behavioural change on acute injection and a twice daily administration for 1 day caused the same behavioural change as observed to a single treatment, i.e., a significant decrease in rearing and line crossings in the white area and increased in the black area, mice moving more quickly into the black area and spending less time in the white (Fig. 3). However, on the 3rd day of twice daily dosing, the profile of behavioural change was reversed to an increased incidence of rearings and line crossings in the white area and decreased in the black area, a delay in movement from the white to the black area, and a trend to an increased time spent in the white area. These behavioural changes had maximised by the 7th day of treatment (rearings and line crossings increased to 248 and 195% respectively, latency of movement from the white to the black area increased form 10/12 to 28/31 sec, time spent in the white section increased to 152%) and were maintained at this level during the 14-day treatment (Fig. 3). Eight hr following withdrawal from the latter treatment, the behavioural change was reversed to a profile of increased behaviour in the black area, similar to that observed on the first day of cocaine treatment. This reversal was maintained 48 and 96 hr after withdrawal but the behaviour of mice had returned to control values 240 hr after cocaine withdrawal (Fig. 3).

DISCUSSION

It was the aim of the present study to determine whether nicotine and cocaine as drugs of abuse could induce a spectrum of behaviours indicative of anxiolytic and anxiogenic action during and following withdrawal, similar to that reported for ethanol and diazepam in the mouse black and white test box model (2,11). The model was designed around the technique developed by Crawley and colleagues (14,15) and is based on the natural tendency of mice to explore a novel environment balanced against the aversive properties of a brightly-lit open field (8). Thus, if mice are taken from a dark holding room and placed into a black and white test box where both areas are illuminated with red light, they will distribute their behaviour in proportion to the sizes of the two areas of the box (10). However, illuminating the white area with a bright light creates an aversive environment and mice will redistribute their behaviour, decreasing their behaviour, e.g., rearing and line crossings and time spent in the white area, with increasing activity in the black area. Under such conditions mice placed into the white section also move more quickly into the black area (10). The aversive behaviour is antagonised by anxiolytic agents such as the benzodiazepines and buspirone (2, 12, 15) and intensified by the anxiogenic agents FG7142 and methyl-β-carboline-3-carboxylate (3, 10, 38). Therefore, the antagonism or exacerbation of the aversive response, i.e., to respectively increase or decrease behaviour in the white area, has been taken to reflect an anxiolytic and anxiogenic response and this profile of change is not obtained using other types of psychopharmacological agents, e.g., antidepressants, stimulants or neuroleptics (10,14).

The administration and withdrawal of nicotine was shown to have a profile of action comparable to that of ethanol (11) and diazepam (2), i.e., an anxiolytic action during an acute or chronic treatment and an anxiogenic effect following withdrawal. The study used doses chosen to avoid any seizure potential or indiscriminate ability to increase locomotor activity. The behavioural profile of the mouse in the black and white test box was modified by cocaine in a similar manner to that induced by alcohol or nicotine, with one notable exception. The administration of an acute one or two dose treatment with cocaine failed to cause an anxiolytic response. Indeed, the treatment induced a profile indicative of anxiogenesis, i.e., a markedly reduced behaviour in

the white area and enhanced in the black area. It may be relevant to such observations that the acute administration of cocaine to man is also reported to induce anxiety (9, 36, 40). However, a continued treatment with cocaine was found to induce an anxiolytic profile on the 3rd day of assessment and this was maintained for the 14-day duration of the experiment. As recorded using ethanol and nicotine, the withdrawal from a cocaine treatment was followed by an anxiogenic response persisting for at least 96 hr after withdrawal, values having returned to control levels by 240 hr. The result is supportive of a previous finding in the rat that withdrawal of cocaine can substitute for pentylenetetrazol in a drug discrimination test where the effectiveness of the substitution was most obvious 120 hours after the last injection of cocaine (41).

It is also noteworthy that within the 14-day period of the experiment, and the dose regimens employed, tolerance did not develop to the actions of nicotine and cocaine to modify anxiety. This has previously been noted for other actions of cocaine, e.g., the ability to modify self-stimulation train duration thresholds (21) and nicotine, e.g., the ability to modify accoustic startle and crosses and rears in the Y-maze test (6). It remains an interesting observation that in the latter study cross tolerance was observed between nicotine and ethanol.

With the exception of the acute anxiogenic response to cocaine, the profiles and intensity of anxiolytic and anxiogenic response during and following withdrawal were similar to those reported for nicotine, diazepam (2) and ethanol (11). The results indicate that the four different classes of drugs have a similar profile of action to modify anxiety responding in a mouse model. A key issue is whether four such diverse chemical entities mediate their effects on anxiety via a common pathway. The mechanism of action of diazepam is most likely to involve an action at the benzodiazepine-GABA-receptor-chloride channel complex (24), and ethanol may also exert some effects at this site (39). Thus, the anxiolytic effects of ethanol in the mouse black and white test box are attenuated by Ro15-4513, a partial inverse agonist acting on the benzodiazepine receptor (33). It would be instructive to assess the actions of Ro15-4513 to modify the anxiolytic effects of nicotine and cocaine. But at the present time, there is no evidence that nicotine or cocaine can directly interact at the benzodiazepine receptor complex and attempts to provide a neurochemical basis for their actions have frequently focused on monoaminergic transmitter systems.

There is an extensive literature that cocaine can modify monoamine transmission in the brain by blocking reuptake processes and perhaps by causing transmitter release [see reviews by Lakoski and Cunningham (16, 25, 30, 35)]. It is unlikely that an action of cocaine on catecholamine transmitter function can modify anxiety responding since catecholamine receptor antagonists have no profile of anxiolytic or anxiogenic action in the mouse black and white test box (10). However, in their review of the electrophysiological approach to elucidate cocaine interaction with monoaminergic systems, Lakoski and Cunningham (30) report that the most striking effect of cocaine on monoaminergic neurons has been identified from extracellular recordings of 5-HT-containing cells in the dorsal raphe nucleus (DRN). Thus, a complete inhibition of the spontaneous firing of these cells is observed following the intravenous administration of cocaine, and microiontophoretic application will depress the firing of such cells and potentiate the inhibitory effects of 5-HT [see (30)]. Lakoski and Cunningham concluded that the depressant effects of 5-HT may result from a localised autoinhibition of 5-HT neuronal activity resulting from reuptake inhibition.

It should be noted that the doses of peripherally administered cocaine causing such changes are in the range causing changes in anxious-like behaviour in the mouse model and that there is considerable evidence for a 5-hydroxytryptamine (5-HT) involvement in anxiety [see reviews by Gardener (23) and Chopin and Briley (7)]. In particular, a number of studies have investigated the involvement of 5-HT in the raphe nuclei with anxiety responding and it has been shown that (a) lesion of the DRN increases social interaction in the rat (19), (b) the injection of benzodiazepines into the DRN of the rat or mouse will release behaviour suppressed by punishment (37) and attenuate an aversive response in the mouse black and white test box (13), whereas the injection of the inverse benzodiazepine receptor agonist methyl-β-carboline-carboxylate has the opposite effect (26,28), (c) the administration of diazepam enhances the inhibition of firing of 5-HT cells in the raphe nucleus induced by GABA (22) and (d) 5-HT_3 receptor antagonists injected into the DRN will reduce the aversive response in the mouse black and white test box, whereas the 5-HT_3 receptor agonist 2-methyl-5HT has the opposite effect (13).The sum total of such evidence is to suggest that a 5-HT agonist/antagonist interaction in the DRN may act to regulate activity in the ascending 5-HT projection, where a reduced 5-HT function may predispose to an anxiolytic aciton.

Therefore, the effect of cocaine to reduce 5-HT cell firing in the DRN may contribute significantly to an anxiolytic potential, although this does not exclude a possible action of cocaine on 5-HT mechanisms in the amygdala or other limbic brain areas involved in anxiety [see review by Kuhar (13,29)]. Whilst the effect of cocaine to modify catecholamine-induced depression of cell firing (30) may be important for its action in self-stimulation and administration experiments (25), the relevance of such effects to an anxiolytic potential remains to be shown.

There is no direct evidence to link an anxiolytic action of nicotine in the mouse black and white test box or in a Montgomery Y-maze (33) to an effect on 5-HT or other transmitter systems. Whilst many studies have reported that nicotine can modify the turnover and/or release of catecholamines and acetylcholine, few have investigated an effect on 5-HT mechanisms. Nevertheless, nicotine is reported to cause a selective reduction in the concentration and biosynthesis of 5-HT in the rat hippocampus (14,15) and depletion of whole brain 5-HT by parachlorophenylalanine reduces nicotine-induced hyperactivity (20).

In summary, we have shown that cocaine and nicotine can induce an anxiolytic profile of action in the mouse black and white test box followed by an anxiogenic response on drug withdrawal. We have hypothesised that the anxiolytic actions of cocaine and, more speculatively, nicotine may reflect a decreased 5-HT function in the ascending projection from the DRN. It would be of particular interest to further investigate the behavioural, biochemical and electrophysiological actions of nicotine and cocaine within the DRN to substantiate or disprove the hypothesis, and whether the anxiogenesis of drug withdrawal is associated with an increased 5-HT function.

REFERENCES

1. Balfour, D. J. K.; Graham, C. A.; Vale, A. L. Studies on the possible role of brain 5-HT systems and adrenocortical activity in behavioural responses to nicotine and diazepam in an elevated X-maze. Psychopharmacology (Berlin) 90:528–532; 1986.

2. Barry, J. M.; Costall, B.; Kelly, M. E.; Naylor, R. J. Withdrawal syndrome following subchronic treatment with anxiolytic agents. Pharmacol. Biochem. Behav. 27:239–245; 1987.
3. Belzung, C.; Misslin, R.; Vogel, E. The benzodiazepine receptor inverse agonists β-CCM and Ro15-3505 both reverse the anxiolytic effects of ethanol in mice. Life Sci. 42:1765–1772; 1988.
4. Benwell, M. E. M.; Balfour, D. J. K. Effects of chronic nicotine administration on the response and adaptation to stress. Psychopharmacology (Berlin) 76:160–162; 1982.
5. Benwell, M. E. M.; Balfour, D. J. K. The effects of nicotine administration on 5-HT uptake and biosynthesis in rat brain. Eur. J. Pharmacol. 84:71–77; 1982.
6. Burch, J. B.; de Fiebre, C. M.; Marks, M. J.; Collins, A. C. Chronic ethanol or nicotine treatment results in partial cross-tolerance between these agents. Psychopharmacology (Berlin) 95:452–538; 1988.
7. Chopin, P.; Briley, M. Animal models of anxiety: the effect of compounds that modify 5-HT neurotransmission. Trends Pharmacol. Sci. 8:383–388; 1987.
8. Christmas, A. G.; Maxwell, D. R. A comparison of the effects of some benzodiazepines and other drugs on aggressive and exploratory behaviour in mice and rats. Neuropharmacology 9:17–29; 1970.
9. Cohen, S. Cocaine. JAMA 231:74–75; 1975.
10. Costall, B.; Jones, B. J.; Kelly, M. E.; Naylor, R. J.; Tomkins, D. M. Exploration of mice in black and white test box: Validation as a model of anxiety. Pharmacol. Biochem. Behav. 32(3): 777–785; 1989.
11. Costall, B.; Kelly, M. E.; Naylor, R. J. The anxiolytic and anxiogenic actions of ethanol in a mouse model. J. Pharm. Pharmacol. 49: 197–202; 1988.
12. Costall, B.; Kelly, M. E.; Naylor, R. J.; Onaivi, E. S. Actions of buspirone in a putative model of anxiety in the mouse. J. Pharm. Pharmacol. 40:494–500; 1988.
13. Costall, B.; Kelly, M. E.; Naylor, R. J.; Onaivi, E. S.; Tyers, M. B. Neuroanatomical sites of action of 5-HT_3 receptor antagonists to alter aversive behaviour in the mouse. Br. J. Pharmacol. 96:325–332; 1989.
14. Crawley, J. N. Neuropharmacologic specificity of a simple animal model for the behavioural actions of benzodiazepines. Pharmacol. Biochem. Behav. 13:695–699; 1981.
15. Crawley, J. N.; Goodwin, F. K. Preliminary report of a simple animal behaviour model for the anxiolytic effects of benzodiazepines. Pharmacol. Biochem. Behav. 13:167–170; 1980.
16. Dwoskin, L. P.; Peris, J.; Yasuda, R. P.; Philpott, K.; Zahniser, N. R. Repeated cocaine administration results in supersensitivity of striatal D-2 dopamine autoreceptors to pergolide. Life Sci. 42:255–262; 1988.
17. Emmett-Oglesby, M.; Spencer, D.; Lewis, M. W.; Elmesallamy, F.; Lal, H. Anxiogenic aspects of diazepam withdrawal can be detected in animals. Eur. J. Pharmacol. 92:127–130; 1983.
18. File, S. E.; Baldwin, H. A.; Aranko, K. Anxiogenic effects in benzodiazepine withdrawal are linked to the development of tolerance. Brain Res. Bull. 19:607–610; 1987.
19. File, S. E.; Hyde, J. R. G.; Macleod, N. K. 5,7-dihydroxytryptamine lesions of dorsal and median raphe nuclei and performance in the social interaction test of anxiety and in a home-cage aggression test. J. Affect. Disord. 1:115–122; 1979.
20. Fitzgerald, R. E.; Oettinger, R.; Battig, K. Reduction of nicotine-induced hyperactivity by pPCA. Pharmacol. Biochem. Behav. 23: 279–284; 1985.
21. Frank, R. A.; Martz, S.; Pommering, T. The effect of chronic cocaine on self-stimulation train-duration thresholds. Pharmacol. Biochem. Behav. 29:755–758; 1988.
22. Gallagher, D. W. Benzodiazepines: potentiation of a gaba inhibitory response in the dorsal raphe nucleus. Eur. J. Pharmacol. 49:133–143; 1978.
23. Gardener, C. R. Pharmacological studies of the role of serotonin in animal models of anxiety. In: Green, A. R., ed. Neuropharmacology of serotonin. Oxford: Oxford University Press; 1985:281–325.
24. Haefley, W. The biological basis of benzodiazepine actions. J. Psychoactive Drugs 15:19–39; 1983.
25. Hernandez, L.; Hockel, B. G. Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. Life Sci. 42:1705–1712; 1988.
26. Hindley, S. W.; Hobbs, A.; Paterson, I. A.; Roberts, M. H. T. The effects of methyl-β-carboline-3-carboxylate on social interaction and locomotor activity when microinjected into the nucleus raphe dorsalis of the rat. Br. J. Pharmacol. 86:753–761; 1985.
27. Hollister, L. E.; Motzenbecker, F. P.; Degan, R. O. Withdrawal reactions from chlordiazepoxide (librium). Psychopharmacologia 2: 63–68; 1961.
28. Jones, B. J.; Paterson, I. A.; Roberts, M. H. T. Microinjections of methyl-β-carboline-3-carboxylate into the dorsal raphe nucleus: Behavioural consequences. Pharmacol. Biochem. Behav. 24:1487–1489; 1986.
29. Kuher, M. J. Neuroanatomical substrates of anxiety: a brief survey. Trends Pharmacol. Sci. July:307–311; 1986.
30. Lakoski, J. M.; Cunningham, K. A. Cocaine interaction with central monoaminergic systems: electrophysiological approaches. Trends Pharmacol. Sci. 9:177–180; 1988.
31. Lodewig, D. Dependence liability of the benzodiazepines. Drug Alcohol Depend. 13:139–149; 1984.
32. McNeill, A. D.; West, R. J.; Jarvis, M.; Jackson, P.; Bryant, A. Cigarette withdrawal symptoms in adolescent smokers. Psychopharmacology (Berlin) 90:533–536; 1986.
33. Misslin, R.; Belzung, C.; Vogel, E. Interaction of Ro15-4513 and ethanol on the behaviour of mice: antagonistic or addicitve effects? Psychopharmacology (Berlin) 94:392–396; 1988.
34. Morrison, C. E.; Stephenson, J. A. Drug effects on a measure of unconditional avoidance in the rat. Psychopharmacologia 18:133–143; 1970.
35. Pitts, D. K.; Marwah, J. Cocaine modulation of central monoaminergic neurotransmission. Pharmacol. Biochem. Behav. 26:453–461; 1987.
36. Resnick, R. B.; Kestenbaum, R. S.; Schwartz, L. K. Acute systemic effects of cocaine in man: a controlled study of intranasal and intravenous routes of administration. In: Ellinwood, E. H.; Kilbey, M. M., eds. Cocaine and other stimulants. New York: Plenum Press; 1977:615–628. (Adv. Behav. Biol., vol. 21.)
37. Thiebot, M. H.; Hamon, M.; Soubrie, P. Attenuation of induced-anxiety in rats by chlordiazepoxide: role of the raphe dorsalis benzodiazepine binding sites serotonergic on neurones. Neuroscience 7:2287–2294; 1982.
38. Thiebot, M-H.; Soubrie, P.; Sanger, D. Anxiogenic properties of beta-CCE and FG7142: a review of promises and pitfalls. Psychopharmacology (Berlin) 94:452–463; 1988.
39. Ticku, M. K. Benzodiazepine-GABA-receptor ionophore complex. Current concepts. Neuropharmacology 22:1459–1490; 1983.
40. Wesson, M. C.; Smith, D. E. In: Petersen, R.; Stillman, R., eds. Cocaine 1977. Washington, DC: U.S. Government Printing Office, 1977:137–152.
41. Wood, D. M.; Lal, H. Anxiogenic properties of cocaine withdrawal. Life Sci. 41:1431–1436; 1987.