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BRIEF COMMUNICATION

Cocaine-Induced Conditioned Taste Aversions in Rats

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GOUDIE, A. J., D. W. DICKINS AND E. W. THORNTON. *Cocaine-induced conditioned taste aversions in rats.* PHARMAC. BIOCHEM. BEHAV. 8(6) 757–761, 1978. – In two separate studies cocaine hydrochloride at doses between 10–36 mg/kg was found to induce a dose-related conditioned taste aversion (C.T.A.) to saccharin, and to be an effective conditioning agent even when injections of the drug were delayed 90 min after saccharin intake. These data contrast with an earlier report [3] which suggested that cocaine was totally devoid of aversive properties. However, they do indicate that cocaine is only a weak aversion-inducing agent. In contrast to other drugs, the doses of cocaine which are required to induce a C.T.A. are very large relative to those commonly employed in behavioural studies. The weak potency of cocaine in inducing C.T.A. may be related to the drug's marked potency in the self-administration paradigm. Some possible determinants of cocaine's weak effects are discussed.

Conditioned taste aversion Cocaine Self-administration Toxicity

MOST psychoactive agents induce conditioned taste aversions (C.T.A.s) when administered after ingestion of a novel tasting fluid [2, 3, 6, 8, 10–13, 20, 24]. However, remarkably little research has been directed at determining which features of drug action are responsible for conditioning taste aversions [2,3]. One way of examining this problem is by considering the profiles of pharmacological actions shown both by agents which do and by agents which do not condition aversions [15,19]. Paradoxically, amongst the very few agents which have been reported to fail to induce C.T.A.s are the drugs strychnine, cyanide and gallamine [15,19]. Since these drugs are generally considered amongst the most toxic of agents, it is clear that the ability of a drug to induce a C.T.A. is not indicative of the drug having a toxic effect. This conclusion is supported by the data of D'Mello *et al.* [6] who reported that a dose of d-amphetamine as low as 0.1 mg/kg was effective as a taste aversion conditioning agent in rats; such doses can hardly be considered toxic. Since toxicity is not an adequate explanation of C.T.A. induction it is necessary to look elsewhere to account for the reported profile of successes and failures in C.T.A. studies. Furthermore, since failures in C.T.A. studies with psychotropic agents have been far less common than successes [10], it is clear that the study of agents which fail to induce C.T.A.s may shed some light on the nature of the effective stimulus in aversive conditioning [10,22]. Cappell and Le Blanc [2,3] have reported that it is impossible to condition aversions in rats with doses of cocaine hydrochloride as great as 36 mg/kg. This report is particularly surprising when viewed in conjunction with reports of the marked potency of amphetamine at very low doses in C.T.A. studies [6], since cocaine and amphetamine share many common behavioural and pharmacological properties. For example, they are both self-administered [23], show reverse tolerance [16], interact paradoxically with sedatives [4], induce stereotyped behaviour [9] and have similar stimulus properties in discrimination learning tasks [5]. The contrast between the reported efficacy of amphetamine at low doses in C.T.A. studies [6], and the absence of effective conditioning with very high doses of cocaine [2,3] was therefore remarkable. The work reported here was designed to investigate further the possible aversive properties of cocaine.

EXPERIMENT 1

In this study the aversive properties of cocaine at doses of 5, 10, 20 and 36 mg/kg were assessed over repeated taste aversion conditioning trials. The last dose was included to make the results directly comparable with those of Cappell and Le Blanc [2,3].

Method

Animals. Animals were 45 female albino rats. At the start of the study body weights varied between 195 and 285 g. Animals were housed individually at 70 (± 2°) F in a 12 hr light/dark cycle, and allocated to one of five groups (n = 9), consisting of the four drugged groups described above, and a saline control group. Groups were matched approximately for mean and variance of body weight. Throughout the study food was available ad lib.

Procedure. Following habituation to individual housing, animals were water deprived at 1100 hr (Day 0). For the next five days they received water at 1100–1130 hr only. On Day 5 the amount of water drunk was recorded for each animal to the nearest 0.1 g. On Day 6 conditioning trial 1 was initiated at 1100 hr. Animals received 30 min access to 0.1% sodium saccharin solution, followed within 10 min of the end of the drinking period by the relevant injection. Cocaine hydrochloride was made up as the salt in 0.9%

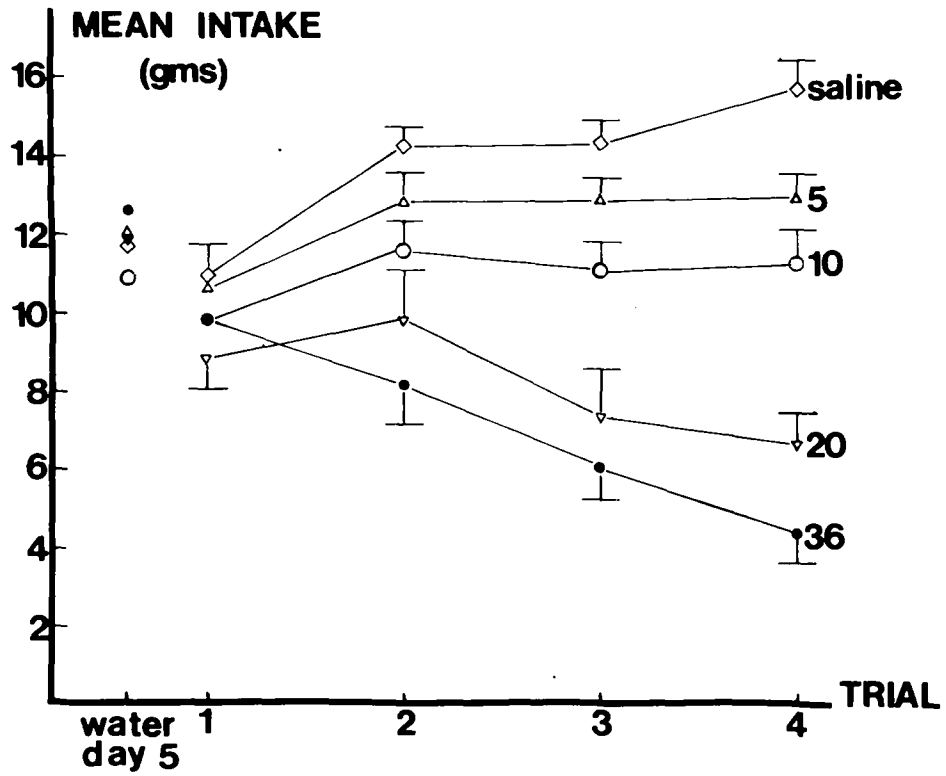

FIG. 1. Mean (± SE) amounts of saccharin consumed by four cocaine treated groups (5–36 mg/kg), and by saline control group over repeated trials. Preconditioning (Day 5) water baseline intakes are also shown. (Some standard errors are omitted for clarity).

saline and injected IP at 2 ml/kg body weight. On all conditioning trials amounts of saccharin consumed by each animal were recorded to the nearest 0.1 g. On Days 7 and 8 animals received access to water for 30 min at 1100 hr, followed on Day 9 by conditioning trial 2. This procedure of aversive conditioning trials separated by two days of water access has been described elsewhere [2, 11, 13]. The cycle was repeated three times, the experiment being terminated on Day 15 by trial 4.

Results

Figure 1 shows the mean amounts of water consumed on Day 5 by animals in each group, and the mean amounts of 0.1% saccharin consumed on succeeding conditioning trials.

Analysis of variance revealed no groups effect in Day 5 baseline water intakes, $F(4,40) = 0.53$. On first exposure to saccharin on trial 1 (Day 6) animals drank significantly less fluid (correlated $t(44) = 3.73$, $p<0.001$), showing a typical neophobic response to a novel taste [11,13]. This neophobic effect dissipated with saccharin experience so that the aversive effects of cocaine are evaluated against a baseline of increasing saccharin intake, as previously reported [11,13].

Analysis of saccharin intakes with a two factor (5 groups × 4 trials) ANOVA, with repeated measures over trials, revealed significant group, $F(4,40) = 17.52$, $p<0.001$, and trials, $F(3,120) = 5.59$, $p<0.001$, effects, and a significant interaction, $F(12,120) = 9.47$, $p<0.001$. Further analysis with Dunnett's test [18] revealed that no group differed significantly ($\alpha = 0.01$) from controls on trial 1 before drug treatment. The 5 mg/kg treated group showed no significant aversion on any trial. The 10 mg/kg showed a significant aversion on trials 3 and 4, whilst both the 20 and 36 mg/kg groups showed significant aversions on trials 2 through 4.

Discussion

These data demonstrate that cocaine is an effective conditioning agent at doses between 10 and 36 mg/kg, although the potency of the drug in inducing C.T.A. is weak. Only doses with extensive behavioural effects were effective in conditioning aversions, and even high doses were only effective in producing relatively limited suppression of intake, in contrast to the almost complete suppression of intake commonly reported with other psychoactive agents at relatively low doses [2, 3, 6, 10, 11–13, 24]. Since the data reported above conflict with the earlier reports of Cappell and Le Blanc [2,3], and since the reported negative findings with cocaine have been considered to be of considerable importance for theoretical expositions of the nature of the UCS in the C.T.A. paradigm [10,22], the contrasting positive results reported above appeared to require further validation. Consequently, a further study was conducted to replicate some of the findings reported above, and to attempt to extend the conditions under which cocaine could be shown to be an effective C.T.A. inducing agent.

EXPERIMENT 2

In conventional C.T.A. studies the introduction of a

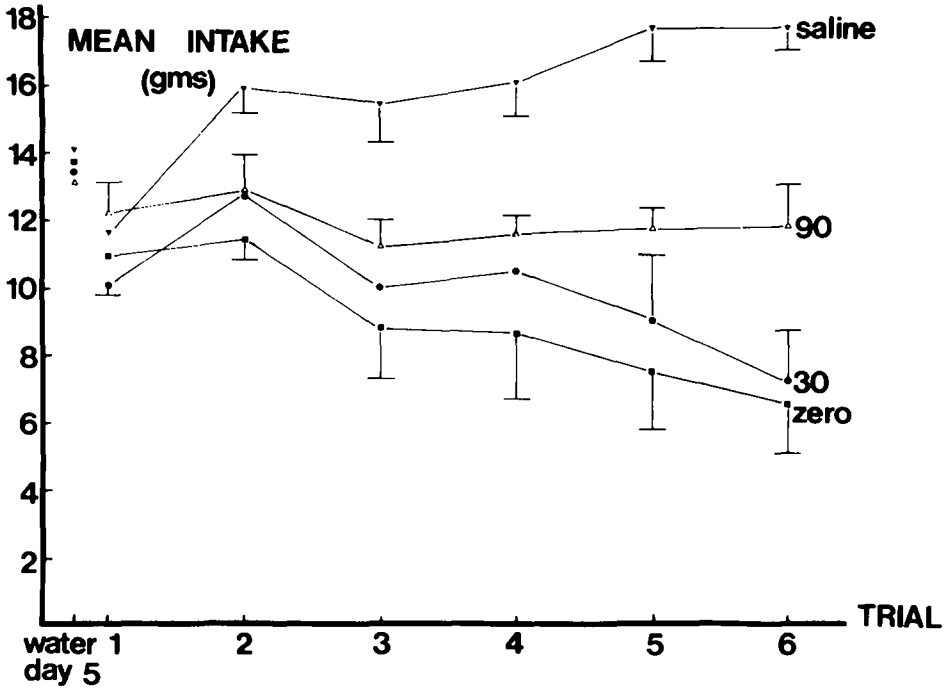

FIG. 2. Mean (± SE) amounts of saccharin consumed by three experimental groups and saline control over repeated trials. Drug treated groups received injections of cocaine (20 mg/kg) at 0, 30 and 90 min respectively after saccharin ingestion. Preconditioning (Day 5) water baseline intakes are also shown. (Some standard errors are omitted for clarity).

delay between the CS and the UCS is generally found to weaken aversive conditioning [7]. In Experiment 2 the aversive effects of delayed cocaine injections were studied to determing whether a gradient of aversive conditioning related to the CS-UCS interval would be observed.

Method

Animals. Animals were female albino rats, derived from the same stock as those used in Experiment 1. At the start of the study body weights varied between 210 and 311 g. Animals were housed as described in Experiment 1, they were allocated to four groups (n = 8) made up of one control group and three drug treated groups, with differing CS-UCS delays consisting of zero (i.e. less than 10 min, as in Experiment 1), 30 and 90 min. Groups were matched approximately for mean and variance of body weight.

Procedure. Following habituation to individual housing, animals were water deprived at 1200 hr (Day 0). For the next five days they received water at 1200–1230 hr only. On Day 5 water intakes in the 30 min access period were recorded for each animal to the nearest 0.1 g. On Day 6 conditioning trial 1 was initiated, animals received access to 0.1% saccharin for 30 min at 1200 hr followed by injections with the relevant delays. Cocaine hydrochloride was administered at a dose of 20 mg/kg, this dose being chosen on the basis of the results of Experiment 1. Drug injection parameters were exactly as described in Experiment 1. On all trials saccharin intakes were recorded to the nearest 0.1 g. On Days 7 and 8 animals received access to water from 1200–1230, a second conditioning trial followed on Day 9. This cycle of conditioning trials separated by two days of water access was repeated five times, the study being terminated on Day 21 by trial 6.

Results

Figure 2 shows the mean amounts of water consumed on Day 5, and the mean amounts of 0.1% saccharin consumed on succeeding trials.

Analysis of variance revealed no group differences in baseline water intakes on Day 5, $F(3,28) = 0.30$. On first exposure to saccharin (Day 6) animals showed the characteristic neophobic response to saccharin, drinking less fluid than on the previous day (correlated $t(31) = 5.29$, $p<0.001$). The observed pattern of neophobia and its dissipation with trials is as described in Experiment 1.

Analysis of the saccharin intake data with a two factor (4 groups × 6 trials) ANOVA with repeated measures over trials revealed significant group, $F(3,28) = 9.44$, $p<0.001$, and trials, $F(5,140) = 4.28$, $p<0.001$, effects, as well as a significant interaction, $F(15,140) = 5.32$, $p<0.001$. The effects of UCS delay were evaluated by a lower level ANOVA on the three drug treated groups, the saccharin intake data being subjected to a 2 factor (3 delay conditions × 6 trials) ANOVA with repeated measures over trials. This analysis indicated that there was a significant trials effect, $F(5,105) = 7.76$, $p<0.001$; and, more importantly, a significant trials × delay interaction, $F(10,105) = 2.52$, $p<0.01$. Analysis of trial 6 intakes indicated that animals receiving cocaine injections delayed 90 min drank significantly less than control animals, $t(14) = 4.25$, $p<0.001$ two tailed; but significantly more than animals receiving immediate injections of cocaine, $t(14) = 2.81$, $p<0.02$ two tailed.

Discussion

Some of the findings of Experiment 2 constitute

systematic replications of those of Experiment 1. Cocaine at 20 mg/kg induced a C.T.A., although the conditioned aversion was again relatively weak. The results demonstrate that cocaine is also an effective conditioning agent even when CS-UCS delays as great as 90 min are introduced, and that as a UCS cocaine acts like conventional UCSs in promoting less conditioning when CS-UCS delay is introduced [7].

GENERAL DISCUSSION

These studies clearly demonstrate that cocaine at doses between 10–36 mg/kg induces a C.T.A. These findings contrast with the data of Cappell and Le Blanc [2,3] who failed to condition an aversion to saccharin with doses as great as 36 mg/kg. Cappell (personal communication, 1977) could detect no sign of aversive conditioning in any animals treated with cocaine, so that the results reported appear to be genuinely discordant with those of Cappell and Le Blanc [2,3]. The reasons for this apparent discrepancy are not obvious. Strain differences in C.T.A. studies have been reported [1], as have age-related differences in the duration of action of cocaine [21]. Furthermore, the data of Cappell and Le Blanc [2,3] were obtained in studies with male rats, in contrast to the female rats used in the work reported here. Any of these factors could account for the discrepant findings. Alternatively, the discrepancy might be attributable to relatively subtle differences between laboratories in routine procedures of handling, injection and maintenance which could modify the actions of cocaine. Definitive statements about the discrepancy between these data and those of Cappell and Le Blanc are clearly precluded.

Although the data do contrast with earlier reports, it is clear that cocaine-induced C.T.A.s are very weak. The lowest dose of cocaine which will induce an aversion is one which has very marked behavioural effects, inducing vigorous stereotyped behaviour. This is not true of amphetamine, which induces a C.T.A. at a dose (0.1 mg/kg) which has minimal stimulant effects [6]. Whilst cocaine and amphetamine show a number of behavioural and pharmacological similarities, they appear to differ to a remarkable extent in their aversive properties.

A potential explanation of this difference lies in the different temporal profiles of the action of amphetamine and cocaine. For example, a comparison in drug-naive rats between the effects of doses of the two drugs which had the same peak behavioural effects [16] indicates that the drugs can be differentiated in terms of latency of onset of peak behavioural effects (15 and 60 min for cocaine and d-amphetamine respectively at the doses studied) and in terms of duration of action (150 and 300 min respectively). Thus it is possible that the difference between cocaine and amphetamine in potency in the C.T.A. paradigm may be attributable to differences in the temporal profiles of the two drugs' actions. Cappell and Le Blanc [2,3] originally attributed their negative findings with cocaine to the drug's short duration of action. The data reported here are clearly not inconsistent with this hypothesis, although they provide no direct empirical support for it. Other lines of evidence also indicate that the temporal features of the UCS in C.T.A. studies may be important determinants of potency of conditioning [2, 10, 11, 14, 17, 20, 22]. It is of course possible that the weak potency of cocaine in C.T.A. studies is not due simply to its specific temporal profile of action, and that some other factor, such as action, or lack of action, on a specific neurochemical or physiological system is the critical factor. The reason why cocaine is such a weak agent in C.T.A. studies would seem to merit further study since it is possible that the very weak potency of the drug in aversive conditioning studies may explain why the drug is a very potent reinforcing agent in self-administration studies, being effective in rats at doses below 0.64 mg/kg IV [23]. Research is currently in progress in this laboratory which attempts to define why cocaine is a weak aversive conditioning agent.

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NOTE ADDED IN PROOF

In a recent independent study, Booth, D. A., C. W. T. Pilcher, G. D. D'Mello and I. P. Stolerman. Comparative potencies of amphetamine, fenfluramine and related compounds in taste aversion experiments in rats. (*Br. J. Pharmac.* **61**: 669–677, 1977) have shown that cocaine is an effective agent in inducing weak conditioned aversions, in confirmation of the results reported above.

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