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Involvement of Dopamine in the Aversive Stimulus Properties of Cocaine in Rats

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HUNT, T., L. SWITZMAN AND Z. AMIT. *Involvement of dopamine in the aversive stimulus properties of cocaine in rats.* PHARMACOL BIOCHEM BEHAV 22(6) 945–948, 1985.—Previous studies of cocaine self-administration have demonstrated central dopaminergic involvement in cocaine's positive reinforcing properties. The present study reports the ability of pimozide, a dopamine receptor antagonist, to attenuate a conditioned taste aversion induced by repeated injections of cocaine. Rats placed on a daily water deprivation schedule were subsequently presented with a novel saccharin taste in their drinking fluid immediately followed by administration of four 9 mg/kg injections of cocaine spaced at 20 min intervals. These animals exhibited a reduction in saccharin intake on subsequent presentations. Animals pretreated with pimozide 90 min prior to the saccharin-cocaine pairings failed to show this reduction. In a second experiment using an identical procedure, repeated injections of lithium chloride were shown to induce a CTA both in pimozide-pretreated and control animals. The results of these two experiments are consistent with the notion that a functional relationship may exist between neurochemical mechanisms underlying both the aversive (CTA-inducing) and positive reinforcing properties of self-administered drugs such as cocaine.

Conditioned taste aversion Dopamine Cocaine Self-administration

THE capacity to induce conditioned taste aversion (CTA) has been demonstrated across a wide range of drugs [22]. Of particular interest to psychopharmacologists is the induction of CTA by psychoactive drugs which are also self-administered by animals [12]. Drugs such as morphine and amphetamine are known to induce CTA in rats [1, 3, 17], and are also self-administered within a similar dose range [19,29]. Moreover, using a straight runway paradigm, the same morphine injection has been shown to act simultaneously both as an aversive (CTA-inducing) and positive reinforcing agent [28]. Other researchers have reported both amphetamine CTA and amphetamine place preference when drug treatment was given just prior to exposure to distinctive environmental stimuli and a novel tasting solution [21]. Pharmacological manipulations which disrupt self-administration of morphine or ethanol are also found to disrupt CTA induced by these drugs [25]. Pimozide, a dopamine receptor antagonist, is found to block both self-administration of amphetamine [30], and to block amphetamine CTA [16]. Thus, the neurochemical mechanisms mediating the positive reinforcing and CTA-inducing properties of these drugs may be the same or at least be functionally related.

One of the very few psychoactive drugs which does not readily induce a CTA in rats is cocaine [1, 2, 14]. For instance, in comparison to amphetamine, which is reported to induce CTA at doses as low as 0.1 mg/kg [7], cocaine induced only a moderate CTA even at high doses [1,14]. In one study examining the relative CTA-inducing potency of these drugs [1], a 1.0 mg/kg dose of amphetamine was found to induce approximately an 80% reduction in fluid intake (seen after four conditioning trials), whereas a 36 mg/kg dose of cocaine induced only a 40% reduction under similar conditions. It has been hypothesized that cocaine's relatively short duration of action may underlie this drug's weak CTA-inducing properties [2]. Recently, it was reported that while a single intraperitoneal infusion of 36 mg/kg cocaine failed to induce a CTA in rats, four infusions of 9 mg/kg, spaced 15 min apart, successfully induced a CTA [9]. In contrast to these findings, evidence has also been presented which fails to support the notion of the importance of duration of action in determining cocaine's capacity to induce CTA. In two studies, a longer lasting metabolite of cocaine (WIN 35,428) was found to be no more potent than cocaine in inducing a CTA [5,6]. In addition, it was found that while inhibition of drug metabolism with Proadifen (SKF 525A) served to potentiate amphetamine CTA, no such enhancement was found for a cocaine CTA [13].

It has also been proposed that cocaine may be a weak CTA-inducing agent due to this drug's strong efficacy as a positive reinforcer [14]. Cocaine is a notorious drug of abuse, which has been well established to have potent positive reinforcing properties in self-administration studies using both monkeys [11] and rats [20]. However, some apparently paradoxical findings have also been reported. In a study using a two-lever operant paradigm, it was demonstrated that monkeys self-administering cocaine will also respond on a second lever to terminate the availability of the self-administered drug [26]. These data may be taken to suggest

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that cocaine can act both as a positive reinforcer and as a negative reinforcer. It would seem of particular relevance, therefore, to examine the neurochemical mechanisms which may underlie cocaine's potentially aversive (CTA-inducing) stimulus properties. As mentioned earlier, there is evidence to suggest that a significant functional relationship may exist between neurochemical mechanisms mediating the positive reinforcing and aversive (CTA-inducing) properties of self-administered drugs such as morphine [25,28], ethanol [25], and amphetamine [16,30]. Disruption of cocaine self-administration is found following destruction of central dopaminergic mechanisms by 6-hydroxydopamine lesions of the ventral tegmental area [23] and nucleus accumbens [24]. Self-administration of cocaine into the medial prefrontal cortex of rats is attenuated by microinjection of the dopamine antagonist, sulpiride [10]. Pimozide also attenuated intravenous self-administration of cocaine in rats [4].

Inconsistent with these data, failure of pimozide pretreatment to alter cocaine-induced place preference has recently been reported [27]. Interpretation of this finding with regard to dopaminergic involvement in cocaine reinforcement, however, presently remains unclear.

The first experiment of the present investigation, therefore, examines the capacity of pimozide, a dopamine receptor antagonist, to attenuate a CTA induced by repeated injections of cocaine. In a second experiment, a similar pimozide pretreatment was evaluated for its capacity to alter a CTA induced by lithium chloride (LiCl), a non self-administered, emetic drug.

EXPERIMENT 1

Pimozide pretreatment is known to block cocaine self-administration [4]. Pharmacological manipulations known to disrupt self-administration of several psychoactive drugs also attenuate CTAs induced by these drugs [16, 25, 30]. Accordingly, it was hypothesized in the present experiment that pretreatment with pimozide should similarly alter a CTA induced by repeated injections of cocaine.

METHOD

Animals

The animals were 40 experimentally naive, male Wistar rats, (Canadian Breeding Farms and Laboratories Ltd.) weighing 280–340 g at the start of the experiment. The rats were individually housed in stainless steel cages with standard laboratory chow and tap water available ad lib prior to initiating the experimental procedure.

Drugs

Pimozide (Janssen Pharmaceutica) was first dissolved in 100 μl of glacial acetic acid, and mixed in a 5% sucrose solution to yield a final suspension with a pH of 4.5, at a concentration of 1 mg/ml.

Cocaine hydrochloride (May and Baker Can. Ltd.) was dissolved in physiological saline (Abbott Laboratories Ltd.).

Procedure

Following a period of at least one week to allow for adaptation to laboratory housing conditions, the animals were placed on a 23 hr 30 min water deprivation schedule. Subsequently, fluid intake of each animal during each daily 30 min drinking period was measured to the nearest ml. For the initial 6 consecutive days, tap water was presented to the animals in stoppered plastic tubes fitted with stainless steel ball-bearing spouts which were inserted through the front of each rat's home cage. The animals were then randomly assigned to treatment groups. On day 7, half of the rats received intraperitoneal (IP) injections of pimozide (1 mg/kg) while the remaining rats received injections of the pimozide vehicle 90 min prior to presentation of a novel 0.1% (w/v) saccharin solution, given in place of the normal drinking water. Immediately following this 30 min exposure to the saccharin solution, half of the animals receiving pimozide pretreatment (n=10) and half of the animals receiving the pimozide vehicle (n=10) were given four IP injections of cocaine (9 mg/kg per injection) spaced at 20 min intervals. The remaining animals in the pimozide (n=10) or pimozide vehicle (n=10) pretreatment groups were given four identically spaced injections of saline vehicle. The injection volume for these injections was 1 ml/kg body weight. On subsequent days the animals were maintained on the water deprivation schedule, as before, and the above conditioning procedure was repeated on days 10 and 13. On day 16, a final test presentation of the saccharin solution was given without drug treatment.

RESULTS AND DISCUSSION

A three-way ANOVA conducted on the data revealed a significant interaction between pimozide pretreatment and post-saccharin drug conditions, $F(1,36)=20.99$, $p<0.01$. Main effects of days, $F(3,108)=18.26$, $p<0.01$, of cocaine $F(1,36)=30.31$, $p<0.01$, and of pimozide, $F(1,36)=28.82$, $p<0.01$, were also statistically significant. The main effect of pimozide, reflecting an unconditioned suppression of fluid (saccharin) intake has previously been reported [15]. As can be observed in Fig. 1a, (triangles, T4) when no pimozide pretreatment was given on the final test day, this suppressive effect of pimozide was not evident.

In animals pretreated with pimozide vehicle, post-hoc Tukey tests, $Q(4,36)=4.75$, $p=0.01$, revealed that rats exposed to cocaine following saccharin exposure (solid circles, Fig. 1a) subsequently exhibit reduced saccharin intake ($p<0.01$) relative to saline controls (open circles, Fig. 1a). This reduction in saccharin consumption, then, is indicative of the development of a cocaine CTA, confirming earlier reports [1, 9, 14]. In contrast, rats pretreated with pimozide, displayed no overall difference in saccharin intake between animals given cocaine (solid triangles, Fig. 1a) and saline (open triangles, Fig. 1a) following saccharin presentation. As can be seen in Fig. 1a, no differences were apparent between these groups over the three pairing days. While such a difference was observed on the test day (T4, $p<0.05$) the magnitude of this difference is clearly much less than that observed between cocaine and saline groups in the vehicle pretreated rats. Thus, the pimozide pretreatment served to disrupt the cocaine CTA otherwise observed in the vehicle pretreated rats. In Experiment 2, the question of whether pimozide pretreatment would also disrupt a CTA induced by repeated LiCl injections was addressed.

EXPERIMENT 2

Lithium chloride, an emetic agent widely used in CTA studies [22], is an effective CTA-inducing drug [18]. Repeated injections of this drug following novel taste exposure were reported to increase the magnitude of the CTA subsequently observed [8], in a manner similar to that reported

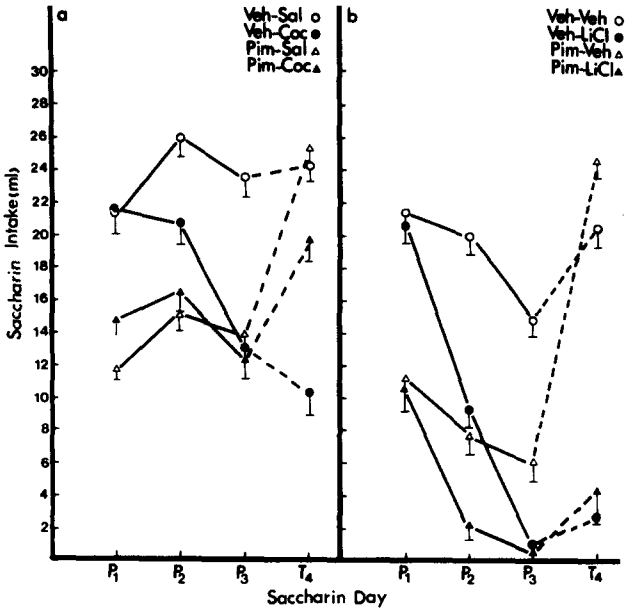

FIG. 1. Mean (±SEM) saccharin fluid consumption over three pairing days and a final drug-free test day of animals pretreated with pimozide or vehicle solution and (a) conditioned with cocaine or saline, or (b) conditioned with lithium chloride or vehicle.

for repeated cocaine injections [9]. The capacity of pimozide pretreatment to alter a CTA induced by repeated LiCl injections was investigated below.

METHOD

Animals

Forty experimentally naive, male Wistar rats weighing 280–340 g at the start of the experiment were used. Housing conditions were the same as in Experiment 1.

Drugs

Pimozide was prepared as in the previous experiment. Lithium chloride (Abbott Laboratories Ltd.) was dissolved in distilled water to make a 0.15 M solution.

Procedure

The procedure was identical to that used in the first experiment. After adaptation to the water deprivation schedule, on day 7, pimozide or vehicle pretreatment was administered 90 min prior to saccharin presentation. Immediately following this presentation, four injections (IP) of LiCl or equivalent volumes of vehicle were given, spaced at 20 min intervals. The dose per injection of LiCl was 0.45 mEq/kg (3 ml/kg of a 0.15 M solution). This procedure was repeated on days 10 and 13, with a final saccharin presentation on day 16.

RESULTS AND DISCUSSION

A three-way ANOVA was conducted on the data revealing a significant pimozide × conditioning drug interaction, $F(1,35)=7.83$, $p<0.01$. As in Experiment 1, a significant unconditioned effect of pimozide to suppress saccharin fluid consumption was evident, $F(1,35)=110.65$, $p<0.01$, an effect previously established [15]. Post-hoc Tukey tests, $Q(4,35)=4.75$, $p=0.01$, indicated that in both pimozide and vehicle pretreatment groups, those rats exposed to LiCl following saccharin presentation significantly decreased their saccharin intake relative to vehicle-treated rats (see Fig. 1b). Thus, pimozide pretreatment was ineffectual in disrupting a LiCl CTA.

GENERAL DISCUSSION

The results of the present study demonstrated that pretreatment with pimozide, a dopamine receptor blocker, serves to attenuate a CTA induced by repeated cocaine injections, but does not alter a CTA induced by repeated LiCl injections. Central dopaminergic systems would therefore appear to be critically involved in cocaine's aversive (CTA-inducing) properties. A similar involvement of dopamine in cocaine self-administration has been previously established [4, 10, 23, 24]. The present findings lend further support to the notion that the neurochemical mechanisms mediating the CTA-inducing and positive reinforcing properties of psychoactive drugs may be the same or be at least functionally related [11, 25, 28]. Continued investigation of the neurochemical mechanisms underlying induction of CTA by self-administered drugs such as cocaine, constitutes an important area of inquiry within animal drug research. For instance, more specific information could be gained using a CTA paradigm to examine the effects of intracranial pretreatment with various antagonists aimed at different brain regions. Such a methodology has recently been successfully used in an investigation of cocaine's positive reinforcing properties [10]. It would be of great interest, then, to compare the results of such studies in order to evaluate what role specific neural systems may play in determining the positive reinforcing and/or aversive stimulus properties of drugs such as cocaine. When considered in parallel to self-administration studies, such CTA studies may lead to valuable insight into processes underlying the complex motivational stimulus properties of these drugs. The potential involvement of the same neurotransmitter systems in what would commonly be considered to be two behaviorally distinct and opposing motivational processes underscores the complex nature of the discriminative and motivational properties of self-administered, psychoactive drugs such as cocaine.

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