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Pharmacology, Biochemistry and Behavior 75 (2003) 173–179
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Dimenhydrinate produces a conditioned place preference in rats

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Received 14 October 2002; received in revised form 1 March 2003; accepted 4 March 2003

Abstract

Dimenhydrinate (DMH; trade names Gravol and Dramamine) is a compound of diphenhydramine (DP) and 8-chlorotheophylline in equimolar ratios. DMH has been reported to be abused by humans for its euphoric and hallucinogenic properties but few studies have evaluated its reinforcing effects in animals. To evaluate the hypothesis that DMH and its constituents DP and 8-chlorotheophylline are rewarding in animals, rats were tested for conditioned place preference (CPP). The paradigm consisted of pre-exposure (three 15-min sessions of access to both sides of the chamber), conditioning [eight 30-min pairings of one side with drug (four sessions) and, on alternate days, the other side with vehicle (four sessions)] and test phases (three 15-min sessions of access to both sides of the chamber). Significant preferences for the drug-paired location were found on test session one after conditioning with 60.0, but not 25.0, 40.0 or 50.0 mg/kg of DMH, and after conditioning with 37.8 but not 27.0 or 32.4 mg/kg of DP. No preference was found after conditioning with 23.0, 27.6 or 32.2 mg/kg of 8-chlorotheophylline. All three drugs stimulated locomotor activity during conditioning sessions and DMH and DP showed sensitization over conditioning sessions. DMH doses that showed sensitization (25.0 and 40.0 mg/kg) were lower than the dose (60.0 mg/kg) that produced a CPP revealing a dissociation of locomotor stimulating versus rewarding effects. Results reveal that DMH and DP have rewarding properties, although the molar equivalent dose–response curve for DP appeared to be further to the right than that for DMH. Future investigations into the neurotransmitter systems modulating this effect are awaited.

Keywords: 8-Chlorotheophylline; Conditioned place preference; Dimenhydrinate; Diphenhydramine; Dramamine; Gravol; Locomotor activity; Reward; Sensitization

1. Introduction

Dimenhydrinate (DMH), an over-the-counter antiemetic known by the trade names Gravol or Dramamine, has been reported to be abused by humans. For example, street drug users will self-administer 750–1250 mg (15–25 tablets) of DMH to experience euphoria and hallucinations (Brown and Sigmundson, 1969; Malcolm and Miller, 1972; Rowe et al., 1997). Psychiatric patients will tolerate up to 5000 mg (100 tablets) in a single dosage to experience the drug's antidepressant, anxiolytic or locomotor-activating effects (Craig and Mellor, 1990; Gardner and Kutcher, 1993; Oliver and Stenn, 1993). Thus, there is considerable evidence suggesting that DMH has rewarding effects in humans.

DMH is composed of the antihistaminergic agent diphenhydramine (DP), sold under the trade name Benadryl, plus the methylxanthine 8-chlorotheophylline in equimolar ratios (Gardner and Kutcher, 1993; Gutner et al., 1951). The subjective effects of large doses of DMH are believed to be due to its antihistaminergic component (Manning et al., 1992). Animal behavioral paradigms such as self-administration (Bergman and Spealman, 1986) and conditioned place preference (CPP) (Zimmerman et al., 1999) suggest that antihistamines are rewarding in animals (review: Halpert et al., 2002). Although DP acts at the H1 receptor (Babe and Serafiin, 1996), the antidepressant, anxiolytic or euphoric effects seen after its administration suggest that it may interact, either directly or indirectly, with other neurotransmitter systems as well. Specifically, DP may antagonize muscarinic receptors (Craig and Mellor, 1990), modulate serotonin functioning (Coyle and Snyder, 1969), potentiate the noradrenergic system (Horn et al., 1970), enhance dopamine levels (Suzuki et al., 1991) or interact with opioid receptors (Su, 1983). Thus, the rewarding effects of DMH

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0091-3057/03/$ – see front matter © 2003 Elsevier Science Inc. All rights reserved.
doi:10.1016/S0091-3057(03)00068-6

administration may be attributable to the action of its antihistaminergic constituent, DP.

The other component of DMH, 8-chlorotheophylline, is an adenosine antagonist. Adenosine has a general inhibitory effect on neuronal activity and when adenosine activity is diminished, there is a resultant increase in neurotransmission. Thus, psychomotor stimulant effects are seen following theophylline administration both in mice (Snyder et al., 1981) and squirrel monkeys (Spealman, 1988). While the amount of theophylline present in a standard dose of DMH does not have stimulatory effects in humans (Wendt et al., 1962), the behavioral effects induced by higher doses of this agent are poorly understood.

There are several possible neuropharmacological mechanisms underlying the behavioral effects following DMH administration. Whether the behavioral effects are due to the antihistaminergic actions of DP, the stimulant actions of 8-chlorotheophylline or a synergism of the two have yet to be determined.

The notion that DMH has abuse liability is supported both by human case studies and by animal experimentation (review: Halpert et al., 2002). The goal of the present research was to determine whether DMH, or either of its components DP and 8-chlorotheophylline, has rewarding value in the rat, assessed by the CPP paradigm. It was hypothesized that a dose-dependent preference for the drug-paired location would be found for DMH.

2. Method

2.1. Subjects

Male Wistar rats ($N = 120$) weighing from 250 to 350 g were housed in pairs and had water and food freely available in their home cages. They were kept on a reversed 12-h light–dark schedule and were tested in the dark portion of the cycle. Handling of the animals occurred daily for 5 days immediately prior to the commencement of each experiment. The rats were treated according to the regulations of the Canadian Council on Animal Care and the experimental protocol was approved by the Queen's University Animal Care Committee.

2.2. Apparatus

The CPP apparatus consisted of four chambers, each with two distinct compartments ($38 \times 27 \times 36$ cm) and a connecting tunnel ($8 \times 8 \times 8$ cm). One compartment had urethane-sealed walls and the other had 1.0-cm-wide black-and-white vertical stripes. The floors of the compartments were also distinct: one had steel mesh flooring and the other had stainless steel rods. The mesh floor was in the right compartment in two of the chambers and in the left in the others. Similarly, the stripes were in the right compartment in two of the chambers and in the left in the others. The floors and walls were arranged so that the configuration was different for each of the four chambers. Two Plexiglas guillotine doors could be used to close the tunnel off from the separate compartments and a Plexiglas lid covered each chamber. Six photocells were located in each chamber: two (height 5 cm) trisected each compartment into equal sections and two (height 3 cm) similarly trisected the tunnel. An 80C188EB-based Experiment Control Board using custom-made software written in ECBASIC used information from these photocells to record the amount of time spent in each compartment, as well as the number of beam breaks created by each rat. The chambers were indirectly lit by 7.5-W light bulbs, ventilated with a small fan and housed in wooden boxes that were insulated with sound-attenuating Styrofoam (for further details of the apparatus, see Brockwell et al., 1996).

2.3. Drugs

DMH, DP and 8-chlorotheophylline (Sigma-Aldrich Canada, Oakville, ON) each were dissolved in dimethylsulfoxide (DMSO). DMH was tested at 25.0, 40.0, 50.0, and 60.0 mg/kg. Due to the appearance of side effects such as convulsions, higher DMH doses were not tested. The doses of DP and 8-chlorotheophylline were selected to correspond with the amount of each component present in 50.0, 60.0 and 70.0 mg/kg of DMH. Thus, DP was tested at 27.0, 32.4 and 37.8 mg/kg and 8-chlorotheophylline was tested at 23.0, 27.6 and 32.2 mg/kg. On drug conditioning days, rats were administered the appropriate drug and dose plus DMSO solution. On the vehicle days, the rats were given DMSO alone. All drugs were injected intraperitoneally with 1.0 ml/kg of body weight.

2.4. Procedure

All experiments were conducted between 0900 and 1900 h. Each dose of DMH, DP or 8-chlorotheophylline was evaluated in the CPP using a group of 12 randomly assigned experimentally naïve rats. The experiment consisted of three phases, a pre-exposure phase of three sessions, a conditioning phase of eight sessions and a test phase of three sessions; sessions were separated by 24 h.

During the 15-min pre-exposure sessions the tunnel was open. The compartment into which a rat was placed to begin a session was constant for all pre-exposure sessions for each rat but counterbalanced among the rats, so that in each group six rats began in the left compartment and six in the right. No drugs were administered during this phase.

On conditioning sessions 1, 3, 5 and 7, rats were injected with their respective drug 15 min prior to being placed into one compartment of the chambers for 30 min and on conditioning sessions 2, 4, 6 and 8, they were injected with the vehicle solution and placed into the other compartment. The compartments were separated from each other and from the tunnel with the use of the guillotine doors during the conditioning sessions. The drug-paired compartments were

counterbalanced across rats so that the start compartment was the drug-paired compartment for half the rats and the vehicle-paired compartment for the other half. Activity was assessed during conditioning sessions.

The 15-min test sessions followed. The rats were placed into the start compartments used in the pre-exposure sessions. The amount of time spent in each compartment was measured for the pre-exposure sessions and the test sessions.

2.5. Data analyses

An alpha level of .05 was used for all statistical tests. Preference for the drug-paired compartment was assessed by comparing the amount of time in this location during the first test session to the amount of time spent in this compartment over the average of the three pre-exposure days. Each dose for each drug tested served as an individual experiment and was evaluated with a planned paired *t* test. For each compound tested, a three-variable mixed-design analysis of variance (ANOVA), with sessions and phases as within factors and dose as a between factor, was also conducted to evaluate the possible decay of the CPP effect over test sessions and to test for a dose effect.

Activity data consisted of total counts for each of eight conditioning sessions, four with drug and four without. For each compound, these data were analyzed using a three-variable mixed-design ANOVA with repeated measures on day and condition (drug vs. vehicle) and independent groups. Significant main effects or interactions were followed by tests of simple effects and pairwise comparisons where appropriate.

3. Results

3.1. Location preference

On average, rats spent approximately half of the session time on the drug-paired side during pre-exposure, showing no significant bias towards either side. For example, the DMH 25.0 mg/kg group spent a mean time of 414.3 s on the to-be-drug-paired side and 428.6 s on the to-be-vehicle-paired side during the average of the pre-exposure sessions; these values did not differ significantly. Tunnel time from the pre-exposure phase for each drug and dose was compared to the tunnel time for the relevant first test sessions and no differences were found. For example, for the 25.0-mg/kg DMH group, respective mean tunnel times were 57.1 and 59.2 s. Thus, observed differences in time spent in the drug-paired side from pre-exposure to test were not affected by changes in tunnel time.

Fig. 1 shows the differences in time spent on the drug-paired side between the pre-exposure and the first test session for each dose of DMH, DP and 8-chlorotheophylline. After conditioning with DMH, increases in time spent on the drug-paired side were seen for all doses, ranging between 10 and 90 s (Fig. 1A). The change in time was significant at 60.0 mg/kg [$t(11) = 2.57$, $P < .05$], but not at 25.0 mg/kg [$t(11) < 1.00$, $P > .05$], 40.0 mg/kg [$t(11) = 2.13$, $P > .05$] or 50.0 mg/kg [$t(11) = 1.23$, $P > .05$]. The Session × Phase × Dose ANOVA yielded only a significant phase effect [$F(1,44) = 10.98$, $P < .05$], indicating that for all doses combined more time was spent on the drug-paired side after conditioning (the data for the individual pre-exposure sessions and for test sessions 2 and 3 are not shown).

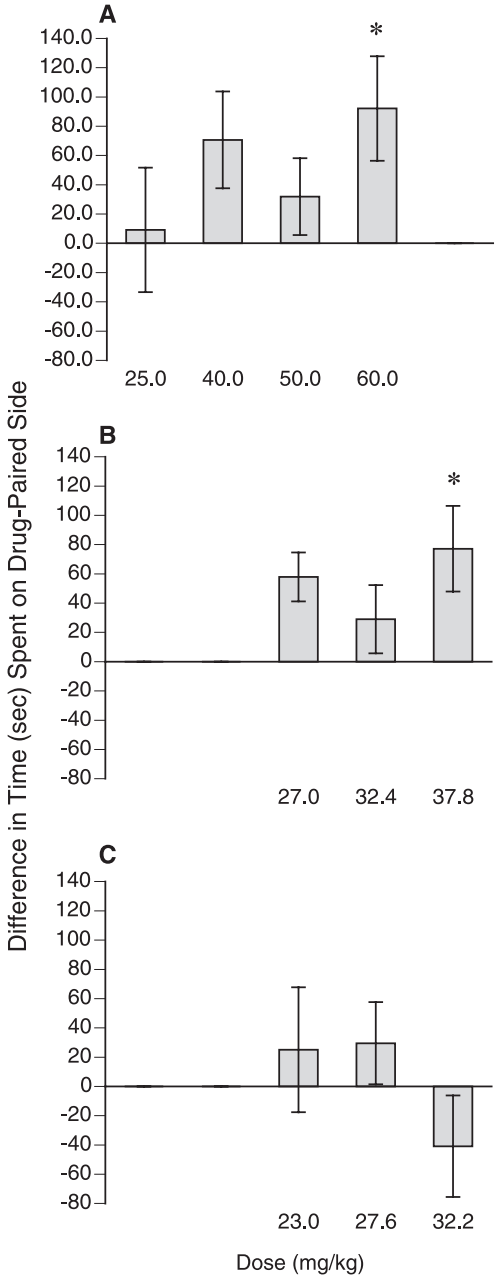

Fig. 1. Mean (± S.E.M.) difference in time (s) spent on the drug-paired side from the average of the three pre-exposure sessions to the first test session for groups treated with DMH (A), DP (B) or 8-chlorotheophylline (C) during conditioning. * Significant ($P < .05$) change in time spent on the drug-paired side by *t* test.

Conditioning with DP yielded increases in time spent in the drug-paired location that ranged between 29 and 77 s (Fig. 1B). While the change in time spent on the drug-paired side was not significant for the 27.0 mg/kg [$t(11) = 1.48$, $P > .05$], or 32.4 mg/kg doses [$t(11) = 1.24$, $P > .05$], 37.8 mg/kg showed a significant effect [$t(11) = 2.63$, $P < .05$]. The doses used were equivalent to the amount of DP found in 50.0, 60.0 and 70.0 mg/kg DMH, respectively. The three-way Session × Phase × Dose ANOVA for the experiments with DP revealed a significant phase effect [$F(1,44) = 10.98$, $P < .05$]; thus, overall the rats preferred the drug-paired compartment after conditioning with DP.

After administration of 8-chlorotheophylline, the changes in time spent on the drug-paired side ranged from a decrease of 41 s to an increase of 30 s (Fig. 1C). None of the effects was significant [t's(11) = 0.59, 1.04 and −1.18, all $P > .05$]. These doses were equivalent to the amount of 8-chlorotheophylline contained in 50.0, 60.0 and 70.0 mg/kg of DMH, respectively. There were no significant effects found in the three-way Session × Phase × Dose ANOVA.

In summary, preference for the drug-paired location was found after conditioning with 60.0 mg/kg of DMH. While location preference was also seen after testing with DP, the dose–response curve appeared to be shifted to the right; thus, a DP dose of 37.8 mg/kg, corresponding to the amount of DP found in 70 mg/kg of DMH, but not a DP dose of 32.4 mg/kg, corresponding to a DMH dose of 60.0 mg/kg, produced a CPP. No preference was recorded after conditioning with 8-chlorotheophylline.

3.2. Activity

DMH stimulated locomotor activity at lower doses but not at the highest dose (Fig. 2A). Increases were seen in later conditioning sessions suggesting that there was sensitization to the stimulant effects of DMH over the four conditioning sessions. Activity during vehicle sessions was similar in the different dose-groups and generally decreased across sessions.

The three-variable ANOVA revealed a significant three-way interaction of Day × Condition × Dose-group [$F(9,120) = 1.98$, $P < .05$], showing that the relationship among dose-groups differed across conditions and days. Tests of simple interaction effects for each condition revealed a significant Day × Dose-group interaction for the drug condition [$F(9,132) = 2.56$, $P < .01$], but not for the vehicle condition. For the vehicle condition, there was a significant effect of days [$F(3,120) = 10.33$, $P < .001$], showing that the decline in activity over days of the four dose-groups combined was significant.

Further analyses of the drug-condition data revealed a significant effect of days for the 25.0 mg/kg DMH group [$F(3,30) = 10.63$, $P < .001$]. The day effect was near significance for the 40.0-mg/kg group [$F(3,27) = 2.61$, $P = .072$], and not significant for the 50.0 and 60.0 mg/kg groups. Furthermore, in tests of simple main effects of groups at each day, dose-groups only differed significantly on Day 4 [$F(3,40) = 3.88$, $P < .02$]. Newman–Keuls post hoc comparisons of groups on Day 4 revealed that the 40.0 mg/kg dose-group differed from the 60.0 mg/kg dose-group ($P < .01$); the corresponding difference for the 25.0 versus 60.0-mg/kg dose-groups was near significance ($.05 < P < .06$). These analyses confirm that DMH stimulated locomotor activity during conditioning sessions at lower doses (25.0 and 40.0 mg/kg) but not at the higher doses (50.0 and 60.0 mg/kg) and that the stimulant effect was seen as a sensitization to the drug effect over the 4 days of conditioning.

The activity data for the groups conditioned with DP are shown in Fig. 2B. In general, activity was higher in the drug

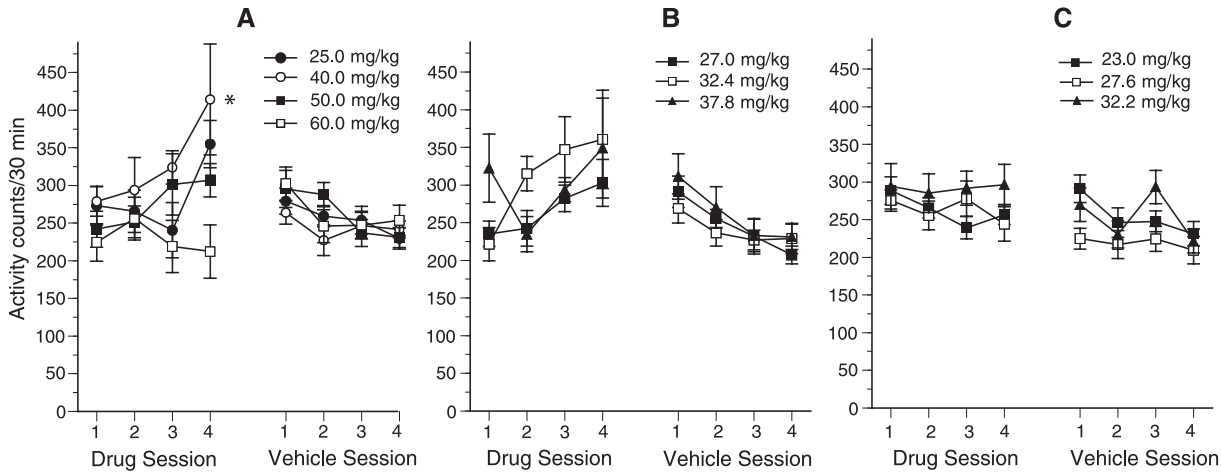

Fig. 2. Mean (±S.E.M.) activity counts (per 30 min) during each of the four conditioning sessions on the drug-paired side (left panels) and on the vehicle-paired side (right panels) for groups treated with DMH (A), DP (B) or 8-chlorotheophylline (C). ANOVA revealed significantly higher activity on the drug-paired side for each drug treatment. Groups treated with DMH or DP during conditioning also showed significant sensitization, motor activity increasing from session to session. * Significantly ($P < .05$) different from 60.0 mg/kg in Newman–Keuls post hoc test following significant simple main effect of groups on conditioning day 4 following significant interaction in ANOVA of groups over days of conditioning with drug.

condition than in the vehicle condition and the stimulant effect seemed to show sensitization like that seen in the DMH experiments, the highest levels of activity being seen on Drug Day 4 of the conditioning phase. In contrast, the vehicle-treated groups showed a gradual decrease in activity over days.

The three-variable ANOVA revealed a main effect of drug condition [$F(1,30) = 14.77$, $P < .001$], confirming that activity was higher on drug versus vehicle days. The ANOVA also yielded a significant Day × Condition interaction [$F(3,90) = 9.27$, $P < .001$]. This interaction occurs when dose-groups are combined and reflects the general increase in activity seen over drug days versus the general decrease in activity seen over vehicle days. Individual two-way ANOVA done separately on the drug and vehicle conditions both yielded only significant days effects [$F(3,90) = 3.72$, $P < .02$, and $F(3,90) = 11.13$, $P < .001$, respectively]. These analyses confirm that DP stimulated activity and that the stimulant effect showed sensitization over days; however, there were no significant effects of dose.

8-Chlorotheophylline also seemed to produce higher levels of activity than vehicle but there was no evidence of a sensitization effect such as that seen with DMH and DP (Fig. 2C). The three-variable ANOVA yielded main effects of days [$F(3,99) = 4.19$, $P < .01$], and condition [$F(1,33) = 18.75$, $P < .001$]. The days effect reflects the generally downward trend in activity over days in both conditions and the condition effect confirms that treatment with 8-chlorotheophylline enhanced locomotor activity. As was the case with DP, there were no significant effects of dose on activity.

In summary, DMH, DP and 8-chlorotheophylline enhanced locomotor activity. DMH and DP produced sensitization, the stimulant effect being apparent on the latter conditioning days. Differential dose effects were only seen with DMH; for DMH lower but not higher doses stimulated locomotor activity.

4. Discussion

The present study demonstrated that high doses of DMH and its component DP can produce a CPP, suggesting that they are rewarding. No preference was seen after conditioning with 8-chlorotheophylline. Activity counts were increased by lower doses of DMH and by DP and 8-chlorotheophylline. DMH (25.0 and 40.0 mg/kg) and DP produced sensitization, the locomotor stimulant effect increasing from session to session. For DMH, there was a dissociation between place conditioning and locomotor stimulation; the dose (60.0 mg/kg) that produced a CPP did not produce locomotor stimulation and the doses (25.0 and 40.0 mg/kg) that produced locomotor stimulation did not produce a CPP. Locomotor activity was also increased by DP and 8-chlorotheophylline but there was no significant effect of dose. In the case of 8-chlorotheophylline, this result further emphasizes the dissociation of locomotor and place conditioning effects.

A change in the amount of time spent in the tunnel between preconditioning and test days could alter the significance in the amount of time spent in the drug-paired location. Upon examination of tunnel times for all experiments, it was concluded that this variable did not significantly influence the place preference results. The vehicle, DMSO, can impair acquisition of conditioned autoshaped behavior in rats (Fossom et al., 1985). To control for possible behavioral effects of DMSO associated with a particular compartment, DMSO was administered on both drug and vehicle conditioning days. Neither a change in tunnel time nor possible behavioral effects of DMSO confounded the significant findings in the present study.

4.1. Location preference

The place preference induced by DMH supports the hypothesis that DMH has rewarding properties. This finding is consistent with case studies in which doses exceeding the recommended daily intake were self-administered to achieve a drug "high" (Brown and Sigmundson, 1969; Malcolm and Miller, 1972; Rowe et al., 1997). The CPP paradigm can be used to identify rewarding drug states, as has been shown in experiments using cocaine, morphine, amphetamine and a number of related compounds (Tzschentke, 1998). Therefore, the finding that DMH administration can induce a CPP suggests that DMH may have rewarding properties similar to those associated with other drugs of abuse.

The antihistaminergic component of DMH, DP, also produced a place preference, but at a higher dose (37.8 mg/kg) than that (32.4 mg/kg) found in the rewarding dose of DMH. Antihistamines have been shown to induce a CPP in both goldfish (Mattioli et al., 1998) and rats (Privou et al., 1998) and DP is self-administered when substituted for cocaine in drug substitution studies (Brown et al., 2001; Rumore and Schlichting, 1985). These reports, coupled with the present findings, suggest that DP, and antihistamines in general, have rewarding properties. The rewarding effects of DMH may reflect its antihistaminergic component.

8-Chlorotheophylline did not produce a place preference. Theophylline can increase schedule-controlled responding in operant conditioning experiments (McKim, 1980; Spealman, 1988), possibly reflecting its stimulant effects. On the other hand, methylxanthines, including 8-chlorotheophylline, produced dose-dependent *increases* in the reinforcement threshold in intracranial self-stimulation paradigms (Mumford and Holtzman, 1990); typically, rewarding compounds produce a decrease in threshold. 8-Chlorotheophylline alone does not seem to have rewarding properties.

Consideration of the CPP results for the three compounds together suggests that 8-chlorotheophylline may synergize with DP to enhance the rewarding properties of DP. Thus, the dose of DMH that was rewarding, 60.0 mg/kg, contained

32.8 mg/kg of DP. However, 32.8 mg/kg of DP alone did not produce a CPP although a higher dose, 37.8 mg/kg, did. A 60.0-mg/kg dose of DMH also contains 27.6 mg/kg of 8-chlorotheophylline. This dose of 8-chlorotheophylline did not produce a CPP. A DMH dose (60 mg/kg) that contained an ineffective rewarding dose of DP (32.4 mg/kg) and an ineffective rewarding dose of 8-chlorotheophylline (27.6 mg/kg) produced a significant rewarding effect in the CPP test. Thus, 8-chlorotheophylline and DP synergize in DMH to produce a rewarding effect.

The rewarding effects of DMH are likely due to the antihistaminergic actions of DP but may also be potentiated by the methylxanthine, 8-chlorotheophylline. Drugs of abuse are believed to induce their rewarding properties through actions on the mesolimbic DA system (Robinson and Berridge, 1993). This may indicate that the rewarding properties elicited by DMH and DP administration are due to either a direct or an indirect interaction with the DA system. Neurochemical evidence supports this notion; H1 antagonists can both inhibit DA reuptake in the striatum (Coyle and Snyder, 1969) and increase DA levels in the nucleus accumbens (Dringenberg et al., 1998). Other neurotransmitter systems, such as the cholinergic, serotonergic, adrenergic, opioid and adenosine systems are modulated by the administration of antihistamines, but whether these interactions influence the agent's rewarding capacity is undetermined. Rewarding effects of the antihistamines DMH and DP may be the result of their ability to stimulate mesolimbic DA activity.

Theophylline is an adenosine receptor antagonist. While modulation of this system is not generally associated with reward, there is evidence that adenosine A1 receptor antagonism will increase striatal extracellular DA levels (Okada et al., 1986) and A2 receptor antagonism will produce a place preference (Brockwell and Beninger, 1996). 8-Chlorotheophylline may indirectly potentiate the rewarding effect of DP through its interactions with the adenosine system. Therefore, rewarding properties observed after DMH administration may be due to the antihistamine-induced increases in DA transmission, which may be further potentiated by the methylxanthine's indirect influence on this neurotransmitter system. This notion is in line with the anecdotal evidence that DMH abuse is reported more often than DP abuse.

4.2. Activity

The agents evaluated in this experiment were all capable of eliciting motor effects. DMH increased activity at lower doses; DP and 8-chlorotheophylline also increased activity but statistical analyses revealed no significant differences among the doses tested. These results are in line with previous reports of the stimulating effects of antihistamines and methylxanthines. For example, antihistamine administration will induce motor excitation in monkeys (Evans and Johanson, 1989) and behavioral stimulation in squirrel monkeys (McKearney, 1982, 1985); this effect is probably due to histamine antagonism. Psychomotor stimulation is seen following theophylline administration, and correlates with the agent's ability to antagonize adenosine receptor sites (Snyder et al., 1981). DMH and both of its components, DP and 8-chlorotheophylline, have significant effects on locomotion.

Lower doses of DMH and DP (all doses combined) produced sensitization. Slight locomotor stimulation was produced by these compounds in the first conditioning session and generally greater effects were seen from session to session. Sensitization has been reported for a number of locomotor stimulants including amphetamine and cocaine (Lett, 1989) and doses that produce sensitization generally are rewarding (Koob and Le Moal, 1997). The present finding of a dissociation between DMH doses that produce sensitization of the locomotor response and those that produce a CPP suggests that the underlying mechanisms mediating the two processes may be different. Further studies are needed to characterize the nature of these putative mechanisms.

In the present experiment, the drug doses capable of eliciting a motor response did not correspond to the doses capable of producing rewarding effects. While the reinforcing properties of some drugs of abuse are related to their ability to stimulate locomotion (Wise and Bozarth, 1987), this was not the case for DMH, DP or 8-chlorotheophylline. This finding supports a previous experiment where doses of DP that substituted for amphetamine in pigeons did not produce stimulatory effects and doses of DP that produced convulsions in monkeys did not substitute for amphetamine (Evans and Johanson, 1989). Further studies are required to elucidate the neurochemical mechanisms responsible for these responses.

5. Conclusions

The present study confirmed the hypothesis that DMH has rewarding properties, like drugs of abuse. This appears to be due to the action of its antihistaminergic component, DP, though administration of DP alone had a dose–response curve that was shifted to the right. The abuse potential of DMH may be related to its influence on mesolimbic DA transmission; antihistamines directly increase DA levels in this system while methylxanthines indirectly enhance DA activity via adenosine antagonism. Thus, 8-chlorotheophylline may potentiate the rewarding effects of DP making DMH (a compound made up of DP and 8-chlorotheophylline) more rewarding than DP.

There was a dissociation between doses of DMH, DP and 8-chlorotheophylline that produced increased activity and those that produced reward. The stimulatory and rewarding effects of DMH and its components may be modulated through different neurotransmitter mechanisms and further studies are needed to elucidate these putative mechanisms.

While the present results confirm previous findings that antihistamines are rewarding, this is, to our knowledge, the

first experiment that has evaluated the rewarding effects of DMH specifically. DMH is available "over the counter," making it a cheap and accessible "high" for drug users. Future research in this field is necessary to establish the neuronal mechanisms underlying the observed rewarding properties of this drug.

Acknowledgements

Supported by grants from the Natural Sciences and Engineering Research Council of Canada to RJB and MCO.

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