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Effects of Methamphetamine on Atropine-Induced Conditioned Gustatory Avoidance[1]

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PRESTON, K. L., G. C. WAGNER, L. S. SEIDEN AND C. R. SCHUSTER. *Effects of methamphetamine on atropine-induced conditioned gustatory avoidance*. PHARMACOL BIOCHEM BEHAV **20**(4) 601–607, 1984.—The repeated administration of high doses of methamphetamine (MA) has been shown to cause monoaminergic damage in rhesus monkeys and rats. In view of the purported interaction between central cholinergic and monoaminergic systems, rhesus monkeys and rats previously exposed to high doses of MA were tested in conditioned gustatory avoidance studies with atropine (a muscarinic blocker) as the unconditioned stimulus. It was observed that both rhesus monkeys and rats previously exposed to high doses of MA exhibited less of an atropine-induced avoidance than control monkeys and rats. To control for the nonspecific effects of prior exposure to stimulants, an additional group of rats previously exposed to high doses of methylphenidate (a stimulant shown to not cause catecholaminergic damage) was tested in the same paradigm. The methylphenidate treated rats showed no change in sensitivity to atropine in the conditioned gustatory avoidance paradigm as compared to control rats which indicated that prior exposure to the nonspecific effects of a stimulant without monoaminergic alterations does not alter the sensitivity of atropine's avoidance-inducing properties. The results of these experiments imply that atropine's avoidance-inducing properties may in part be mediated through the monoaminergic system.

Conditioned gustatory avoidance Atropine Methamphetamine Methylphenidate

REPEATED high dose administration of methamphetamine (MA) or amphetamine (AMPH) has been shown to cause long-lasting neuronal alterations in the dopaminergic and serotonergic nervous systems in various species. These include decreased DA and/or serotonin (5-HT) levels in various regions of the brain [10, 19, 23, 38, 41, 44, 47, 48, 49], decreased tyrosine hydroxylase and tryptophan hydroxylase activity [19,45], decreased DA and 5-HT high-affinity uptake sites [33, 41, 47, 48], an increase in transmitter turnover [33], and terminal degeneration [28,32]. Behavioral studies have shown that animals with MA-induced decreases in DA brain levels show decreased sensitivity to the effects of MA and apomorphine and increased sensitivity to the effects of haloperidol on performance on a differential

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reinforcement of low rates schedule [8,9], force lever performance [21], and on locomotor activity [29]. The purpose of the present study was to determine whether animals treated with repeated high dose administration of MA might also have altered sensitivity to agents acting on neurotransmitters other than dopamine. Because of the purported interaction between central cholinergic and dopaminergic neurons, drugs acting on cholinergic neurons were studied.

There is a great deal of evidence, both biochemical and behavioral, indicating an interaction between central cholinergic and dopaminergic systems. Dopamine (DA) antagonists generally increase ACh release and turnover and decrease ACh levels whereas DA agonists generally decrease ACh release and turnover and increase levels [17, 22, 30, 39, 40, 43]. Conversely, cholinergic agonists increase DA release and turnover [2, 3, 11, 18] whereas cholinergic antagonists decrease DA turnover, and block haloperidol- and ACh-induced increases in DA turnover [1,18]. In addition, anticholinergic agents have been shown to enhance the behavioral effects of DA agonists [37], and reverse the effects of DA antagonists [31] while cholinergic agonists inhibit the effects of DA agonists [7] and are inhibited by DA antagonists [42]. Finally, a serotonergic modulation of cholinergic neurons has also been suggested [6,36] as well as cholinergic modulation of serotonergic neurons [18].

The ability of AMPH and MA to induce gustatory avoidance has been shown to be sensitive to changes in the dopaminergic nervous system. That is, the ability of AMPH and MA, administered following the consumption of a novel substance, to decrease intake of that substance on its subsequent presentation can be attenuated by pretreatment with pimozide [16], alpha-methylparatyrosine [14], or intraventricular 6-hydroxydopamine [25, 45, 46]. The conditioned gustatory avoidance paradigm was, therefore, chosen to determine whether long-term changes in the monoaminergic systems induced by MA cause a change in sensitivity to the behavioral effects of atropine sulfate, a muscarinic antagonist. Accordingly, the ability of atropine to produce gustatory avoidance was compared in MA-treated and control rats. Since prior exposure to MA or AMPH attenuates gustatory avoidance induced by these agents [5, 13, 15], a second experiment was conducted in which methylphenidate, a stimulant similar to MA but shown not to produce catecholamine damage [47], was substituted for the MA as a pretreatment. A third study was conducted in which atropine's ability to induce gustatory avoidance was compared in rhesus monkeys previously treated with high dose regimen of MA and control animals.

The results of these studies indicates that, following high dose administration of MA (which caused decreases in brain DA and 5-HT levels), rats and monkeys demonstrated a lowered sensitivity to the gustatory avoidance inducing properties of atropine sulfate. However, rats previously treated with high doses of methylphenidate (which did not produce changes in brain DA levels) showed no change in sensitivity to atropine sulfate. Therefore, the change in sensitivity appears to be the result of neuronal alterations induced by MA.

EXPERIMENT 1

METHOD

Subjects and Housing

Male Sprague-Dawley rats (Holtzman Co., Madison, WI) weighing approximately 250 grams were housed individually with free access to food (Teklad Co., Winfield, OH) and water. Colony room lights were automatically turned on at 0600 and off at 1900. The temperature was maintained at 21°C. Rats were injected subcutaneously at 0800 and 1700 for four days with either physiological saline (2 ml/kg) or 50 mg/kg of methamphetamine HCl as described by Wagner *et al.* [48].

Training and Apparatus

Four weeks after the last saline or MA injection, 48 rats (24 saline treated and 24 MA-treated) were water deprived for 24 hours. Water was then presented for a 15-minute session at 0800 for 8 daily sessions. All fluid was presented in bottles modified from calibrated 50 ml syringes, attached to the front of each cage. Rats were weighed each day of the experiment 30 minutes prior to the presentation of water. Baseline intake was determined for the last 3 days of training. At the end of the training period, the rats were randomly divided into groups of 6 rats each, 4 groups of control and 4 groups of MA-treated rats, and testing was begun.

Testing

On the first and third test days, all rats received a bottle of sweetened condensed milk (Borden Co., Columbus, OH, diluted 2 parts water to 1 part milk) at room temperature for 15 minutes, in place of water. Fifteen minutes after the milk was removed, groups of rats received IP injections of atropine sulfate 2.5 mg/kg, 5.0 mg/kg or 10.0 mg/kg, or physiological saline 1.0 ml/kg. On test days 2 and 4 water was presented without injections. On day 5, milk was again presented; however, no injections were given after this session. Following the last milk presentation, rats were given free access to food and water.

Drugs

Methamphetamine HCl (National Institute on Drug Abuse) was administered in a concentration of 25 mg/ml in physiological saline. Atropine SO_4 (Aldrich, Milwaukee, WI) was given in a concentration of 2.5, 5.0, or 10.0 mg/ml in physiological saline. All doses are expressed as the salt.

Neurochemistry

Two weeks after the last milk presentation, rats were killed by decapitation; their brains removed quickly and dissected. A transverse cut was made posterior to the olfactory bulbs and another cut was made anterior to the optic chiasm. From this slice the anterior striatum was dissected from the cortex and septum to provide the caudate sample. Dopamine and serotonin levels were determined by high performance liquid chromatography with electrochemical detection. A 1 m×2.0 mm column packed with DuPont Zipax SCX strong cation exchange resin was used. Samples were homogenized in 0.3 ml 0.4 N perchloric acid of which 20 μl were injected into the column. The mobile phase was an acetate-citrate buffer (pH 5.2). Flow rate was 0.5 ml/min and dopamine and serotonin were oxidized by a potential of 0.72 mV. Quantitation of dopamine and serotonin was done by measuring peak heights on a Heath Servo recorder.

Statistics

The results of the milk drinking study are expressed as intake in milliliters per kilogram (ml/kg). Statistical analysis

was performed using a two factor ANOVA and post hoc Newman-Keuls test where appropriate for the fifth test day milk drinking data and 2-tailed students t-test for the baseline milk drinking data and chemical data. Significance was taken at the $p<0.05$ level.

RESULTS

The MA treatment was effective in inducing long-lasting decreases in brain DA and 5-HT levels. Caudate DA and 5-HT levels were significantly ($p<0.05$) reduced to about 70% of controls. DA levels were 14.3 μg/g (S.E. 0.67) of tissue for controls and 9.92 μg/g (S.E. 0.70) for MA-treated rats. 5-HT levels were 0.47 μg/g (S.E. 0.03) of tissue for controls and 0.32 μg/g (S.E. 0.04) for experimentals.

There were no significant differences between the MA-treated rats and saline-treated rats in terms of their baseline water intake [48 (S.E. 5.5) vs. 50 (S.E. 7.9) ml/kg] (Fig. 1). Analysis of the milk drinking data for the fifth test day by a two-factor ANOVA indicated that there were significant effects of methamphetamine vs. saline pretreatment, $F(1,40)=6.09$, $p<0.025$, and significant effects of atropine dose, $F(3,40)=23.30$, $p<0.001$. Newman Keul's tests revealed that milk intake was significantly reduced in all saline-treated rats receiving post session atropine (Fig. 1) relative to rats receiving post-session saline ($p<0.05$). In addition, MA-treated rats which received atropine 5.0 or 10.0 mg/kg post session drank significantly less milk on the third presentation of milk than MA-treated rats receiving post session saline ($p<0.05$). Milk intake was not significantly decreased in MA-treated rats treated post session with atropine 2.5 mg/kg compared to MA-treated or saline-treated rats given saline post session (Fig. 1).

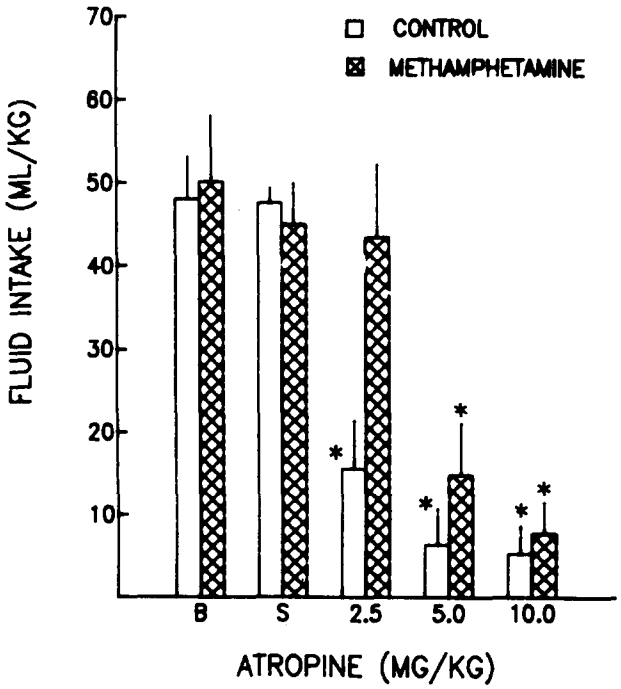

FIG. 1. Fluid intake for control and methamphetamine-treated rats following exposure to atropine. Baseline water intake is the mean of the last 3 days of training (B). Mean intake on the third presentation of milk in groups of control (open bars) and methamphetamine-treated (cross-hatched bars) rats treated with saline or atropine 2.5, 5.0, or 10.0 mg/kg. Vertical lines represent the standard deviation of the means. *Represents a significant difference from the respective saline-treated control groups at $p<0.05$, Mann Whitney U test.

EXPERIMENT 2

METHOD

Subjects and Housing

Subjects and housing were similar to those in Experiment 1. Rats were injected subcutaneously at 0800 and 1700 for one day with 50 mg/kg and 3 days with 100 mg/kg of methylphenidate HCl (Ciba, Summit, NJ). Control rats received saline injections on all four days.

Training and Testing

There were 4 groups of 6 rats [24] each treated with saline and 4 groups of 6 [24] rats each treated with methylphenidate. Training, apparatus, and testing were identical to that used in Experiment 1.

Neurochemistry

Two weeks after the last milk presentation, 12 experimental and 12 control rats were randomly selected for monoamine brain level determination. Rats were killed by decapitation, and their brains were removed and dissected as described in Experiment 1. The rest of the brain was further dissected according to the method of Glowinski and Iverson [12] to yield portions of the pons-medulla, midbrain, hypothalamus, and telencephalon. DA levels were determined as in Experiment 1. NE levels were determined by high performance liquid chromatography with electrochemical detection using a 0.5 m×2.1 mm column packed with Vydac CX, a cation exchange resin. The mobile phase was a 0.04 M phosphate buffer (pH 2.6). Flow rate was approximately 0.4 ml/min, and NE was oxidized by a potential of 0.72 mV.

Statistics

The statistical tests used were the same as those described in Experiment 1.

RESULTS

No changes in monoamine levels were found in the hypothalamus, telencephalon, pons-medulla, or midbrain nor in caudate DA. NE was not measured in the caudate because of the limited quantity of sample.

There were no significant differences between the methylphenidate-treated and control rats in terms of their baseline water intake [56 (S.E. 7) vs. 51 (S.E. 8) ml/kg, Fig. 2]. Analysis of the milk drinking data for the fifth test day by a two factor ANOVA indicated that there was a significant effect of atropine dose, $F(3,40)=9.93$, $p<0.001$, but no significant effect of methylphenidate vs. saline pretreatment, $F(1,40)=0.70$. Newman Keul's tests reveal that post-session treatment with all three doses of atropine (Fig. 2) significantly decreased milk intake on the third exposure in control and methylphenidate-treated rats compared to saline treatment ($p<0.05$).

EXPERIMENT 3

METHOD

Subjects and Housing

Eighteen adult rhesus monkeys (8 female and 10 male) were housed individually in standard cages with free access

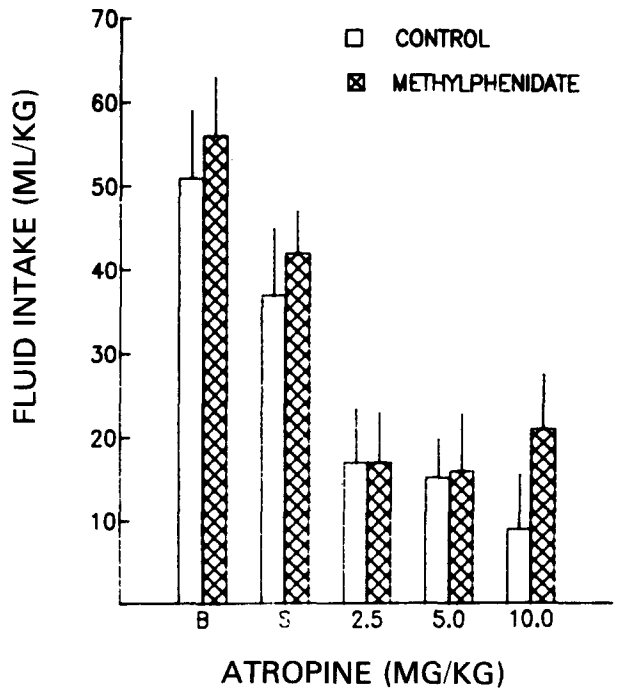

FIG. 2. Fluid intake for control and methylphenidate-treated rats following exposure to atropine. Baseline water intake is the mean of the last 3 days of training (B). Mean intake on the third presentation of milk in groups of control (open bars) and methylphenidate-treated (cross-hatched bars) rats treated with saline (S) or atropine 2.5, 5.0, or 10.0 mg/kg. Vertical lines represent the standard deviations of the means.

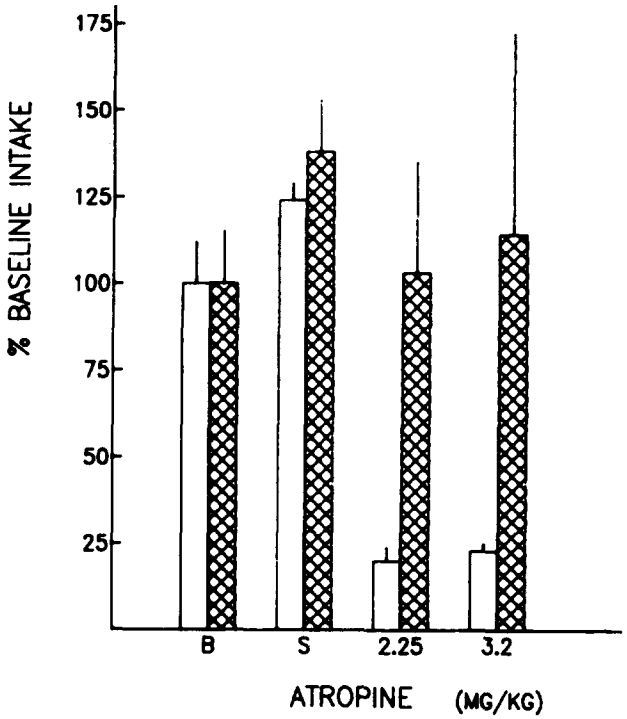

FIG. 3. Fluid intake for control and methamphetamine-treated monkeys following exposure to atropine. Mean percent of water baseline intake (B) on the third presentation of orange drink in groups of control (open bars) and methamphetamine-treated (cross-hatched bars) monkeys treated with saline (S) or atropine 2.25 or 3.2 mg/kg. Vertical lines represent the standard deviations of the means.

to Purina Monkey Chow (St. Louis, MO). All monkeys had had experience in behavioral and/or pharmacological studies. Four months to 2 years prior to this experiment, nine of the monkeys had received repeated high dose administration of MA which has previously been shown to cause decreases in brain DA and 5-HT levels ([8,38], Preston in preparation). All MA-treated subjects were in ongoing experiments but had not participated nor received any drugs for 2 or more weeks prior to beginning this study. All MA-treated monkeys had been shown to have decreased sensitivity to MA in either a force lever task [20] or differential reinforcement of low rates of responding schedule (DRL 40 sec) [8]. Control monkeys had not been in any experiment nor received any drug for at least 2 weeks prior to this experiment.

Training and Apparatus

Monkeys were water deprived for 24 hours after which water was presented for 15 min at 0800 daily for 7 or more sessions until water intake became stable. All fluid was presented in one quart glass water bottles attached to the front of each monkey's home cage. Metal pans were placed beneath the cages to collect any fluid which spilled from the bottles during the sessions. A graduated cylinder was used to measure fluid before and after the session. Baseline intake was determined from the last 3 sessions of training.

Testing

On the first and fourth test days each monkey received a bottle of orange flavored drink (Tang Instant Breakfast Drink, General Foods Corp., White Plains, NY: mixed according to package directions) at room temperature for 15 min in place of water. Fifteen min after the orange drink was removed, each monkey received an intramuscular injection of atropine sulfate 2.5 mg/kg or 3.2 mg/kg (1/2 log unit higher) of physiological saline. Three control and three MA-treated monkeys received each treatment. On days 2, 3, 5, and 6 (that is, for 2 days after each orange drink presentation) water was presented without injections. On day 7 of testing, orange drink was again presented as on day 1; however, no injections were given following this session.

Drugs

Atropine SO_4 (Aldrich, Milwaukee, WI) was given in a concentration of 22.5 or 32.0 mg/ml in physiologial saline. Control subjects received 0.1 ml/kg of physiological saline. All doses are expressed as the salt.

Statistics

Due to individual differences in intake between monkeys of different size and sex, results are expressed as percent of baseline water intake. For statistical analysis, the intake of orange drink (during its third presentation) by control and MA-treated monkeys assigned to post session saline group was combined. Similarly, the intake of orange drink (during its third presentation) by control monkeys assigned to post session atropine 2.5 or 3.2 mg/kg groups was combined to form one atropine-treated control group. MA-treated monkeys which received atropine 2.5 or 3.2 mg/kg post session

were also combined into one atropine treated MA-treated monkey group.

Statistical analysis was performed using the Mann-Whitney U test for the fluid intake data. Significance was taken at the $p<0.05$ level.

RESULTS

The results from Experiment 3 are shown in Fig. 3. No significant differences between MA-treated and control monkeys were found in the baseline water intake [48 (S.E. 7) vs. 38 (S.E. 5) ml/kg, respectively]. The orange drink intake on the first presentation was significantly lower than baseline water intake in the control group [25 (S.E. 4) vs. 38 (S.E. 5) ml/kg; $U(9,9)=12.5$]. In MA-treated monkeys, orange drink intake on the first presentation was not significantly different from baseline fluid intake [54 (S.E. 10) vs. 48 (S.E. 7) ml/kg].

The statistical analysis of the combined data showed that atropine-treated control monkeys drank significantly less orange drink during its third presentation compared to saline-treated control and MA-treated control monkeys [21% (S.E. 2) vs. 131% (S.E. 8); $U(6,6)=0$]. In contrast the orange drink intake on its third presentation to atropine-treated MA monkeys was not significantly different from the orange drink intake of saline-treated control and MA monkeys [108% (S.E. 30) vs. 131% (S.E. 8)].

GENERAL DISCUSSION

The results of the first experiment indicate that pretreatment of rats with repeated high dose administration of MA caused a decreased sensitivity to atropine in the conditioned gustatory avoidance paradigm. The MA-treated rats were subsequently shown to have decreased caudate DA and 5HT levels. Although only one brain region was assayed in this study, the findings of other studies using a similar treatment regimen [33] would indicate that MA also causes decreases in these transmitter levels in other brain regions. Therefore, the available data do not identify a specific brain region involved in this change in sensitivity to atropine.

It has been demonstrated that previous experience with a specific drug attenuates its ability to induce an avoidance in a gustatory avoidance paradigm. This phenomenon is not necessarily the result of tolerance since experience with any one of a variety of drugs across pharmacological classes may also decrease the ability of a drug to induce a gustatory avoidance [4]. These findings suggest that the change in sensitivity to atropine seen in this experiment might be attributable to the exposure to the MA regimen. This, however, does not appear to be the case since pre-exposure to methylphenidate at doses which produce comparable behavioral effects, i.e., stereotypy and stimulation, to that of the MA regimen in Experiment 2 did not alter the sensitivity of treated rats to any dose of atropine given. It is possible that the differences between the results of pretreatment with methylphenidate and methamphetamine are due to a difference between the potency of the two drugs to induce conditioned gustatory avoidance. This appears to be unlikely, however, since the doses of both agents used in the present study are well above the doses of each agent necessary to produce a maximum avoidance response [34,46].

The third study showed that the decreased sensitivity to atropine in inducing gustatory avoidance also occurred in rhesus monkeys which had received a high dose regimen of MA. Although brain transmitter levels have not yet been measured in all of these monkeys, the neurochemistry has been completed in selected subjects. These monkeys were shown to have decreased DA and 5-HT in various brain regions (Preston *et al.*, in preparation). Furthermore, all of the monkeys had shown decreased sensitivity to the effects of MA on an operant behavior (Preston *et al.*, in preparation; Ando *et al.*, in preparation). Because of the varied but extensive experimental histories of the monkeys, the interpretation of the results of this study must be made with caution. However, the fact that two studies, using both the rat and the monkey, showed decreased sensitivity in MA-treated animals to the effects of atropine strongly favors the validity of these conclusions.

It is not possible to determine from the present studies whether the decrease in DA or in 5-HT levels, or, perhaps, the decrease in both transmitters is necessary for the change in sensitivity since both have been shown to be involved in mediating cholinergic activity. However, several studies have been reported in which electrolytic or 5,7-dihydroxytryptamine lesions of the midbrain raphe nuclei decreased brain 5-HT levels and potentiated the gustatory avoidance induced by LiCl [26,27] and fenfluramine [24]. These data suggest that the decreased sensitivity to atropine induced by MA is not due to decreased 5-HT brain levels.

The mechanism for the decrease in sensitivity to the gustatory avoidance-inducing properties of atropine in MA-treated rats and monkeys is not clear. If this phenomenon were due to specific disruption of a cholinergic-dopaminergic balance resulting from MA-induced neuronal alterations, one might expect an increase in sensitivity to the effects of a muscarinic agonist in MA-treated animals in a gustatory paradigm. If, on the other hand, the decrease in sensitivity to atropine is due to a more generalized deficit in the ability of MA-treated animals to form a gustatory avoidance the effects of a muscarinic agonist would be expected to be decreased. Further experiments exploring changes in sensitivity in MA-treated animals to dopaminergic and other cholinergic agents are indicated.

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