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PCP, THC, Ethanol, and Morphine and Consumption of Palatable Solutions

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MILANO, W. C., K. D. WILD, Y. HUI, C. L. HUBBELL AND L. D. REID. *PCP, THC, ethanol, and morphine and consumption of palatable solutions.* PHARMACOL BIOCHEM BEHAV 31(4) 893–897, 1988.—Water-deprived rats were given daily opportunities (2.0-hr sessions) to take water or a sweet solution (20% or 24% sugar-water). After stable intakes of each fluid were achieved, the effects of phencyclidine hydrochloride (PCP), delta-9-tetrahydrocannabinol (THC), ethanol (E), and morphine (M) on intakes were tested. PCP, THC, and M all enhanced intake of the sweet solution, while E produced varying effects across doses tested. With other rats, nearly the same procedure was used except that the test solution presented with water was 0.9% sodium chloride. Doses of PCP enhanced intake of the salty solution. These data, combined with the data from similar studies of the effects of opioids and benzodiazepines, indicate that a wide variety of agents that are self-administered also modify intake of ingesta.

Phencyclidine Tetrahydrocannabinol Ethanol Ingestion Palatable solutions Morphine

THERE are two general, but vague and unsystematized, notions concerning the nature of addictions. The first centers about the notion that addictive agents are drive-reducing. There are two variants of the drive-reduction hypothesis. One focuses on tolerance and withdrawal and suggests that use of the addictive agent creates a new drive for which subsequent administration of the agent reduces. The other variant is that addictive agents reduce extant motivations, such as fear, hunger, and sexuality, in either a general way (a calming agent) or specifically by reducing one or two drives.

The second general notion centers about the idea that addictive agents are acting as "false transmitters" in the neural circuitry for reward. From this perspective, no particular drive needs to be "satisfied," but nevertheless one would expect to see some systematic effects of drugs of addiction on responding for rewards.

Neither of these two general notions deals adequately with many features of addiction, but they do lead to different predictions concerning responding for ordinary reinforcers. Variants of the drive-reduction hypothesis predict reduced responding for rewards, whereas alternatives predict either no effect or increments in responding. Large doses of addictive agents often do reduce instances of responding for ordinary rewards, but the interest is with doses that are apt to be self-administered. Given that only a few addictive agents have been assessed at these smaller dose ranges with respect to their effects on motivated responding, we now extend those assessments across some other drugs taken recreationally by people, namely phencyclidine (PCP), delta-9-tetrahydrocannabinol (THC), and ethanol (E) while again assessing morphine's (M) effects on intake of palatable solutions.

GENERAL METHOD

Subjects

Male, Sprague-Dawley rats were purchased from Taconic Farms (Germantown, NY) when they weighed about 200 g. Upon arrival, the rats were individually housed in standard hanging cages in a colony room maintained at 24°C. The windowless colony room had 12 hr of artificial light a day, beginning at 0800 hr. Food was always available. Water was always available except as specified.

Solutions and Drugs

The salty solution was 0.9% saline, i.e., 0.9 g of NaCl plus tap-water to yield 100 g of solution, a concentration known to be palatable to rats. The sweet solution was either 24% sugar, i.e., 24 g of table-sugar containing sucrose and dextrose plus tap-water to yield 100 g of solution (Experiments 1 and 2), or 20% sucrose solution, i.e., 20 g sucrose in tap-water resulting in 100 g of solution (Experiments 3 and 4). Solutions were presented in glass bottles equipped with ball-point sipping tubes.

PCP-hydrochloride was tested at doses of 0.5, 1.0, and 1.25 mg/kg. Placebo injections were physiological saline, the vehicle of PCP. All PCP and PCP-placebo injections were given subcutaneously, 1.0 ml/kg. THC was administered in a dose of 1.0 mg/kg. Placebo for THC was a solution of 2% Tween 80 and 3.7% absolute E in saline, the vehicle of THC.

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THC and its placebo were administered by oral gavage in a volume of 4.0 ml/kg. The doses of E tested were 0.09, 0.16, 0.3, 0.55 and 1.0 g/kg. All E injections were given intraperitoneally, 10.0 ml/kg. When M-sulfate, 1.0 mg/kg, was administered, it was injected sucutaneously, 1.0 ml/kg. The vehicle for E and M was physiological saline, and served as placebo for both. When the placebo injections were given, they were administered in the same manner as the respective drug injection.

Procedure

Formal procedures began by placing the subjects on a daily regimen involving 22 hr of water deprivation followed by the presentation of water and test solution for 2 hr. This daily regimen of deprivation and presentation of fluids was used in all procedures.

Measures and Statistics

Subjects' body weights and intake of water and test solution were tabulated daily to the nearest 0.1 g. The intake scores were corrected for spillage (14,21). Total fluid intake is the amount of water plus the amount of test solution taken. Preference ratios were also calculated (amount of test solution taken/total amount of fluid taken). In Experiments 1 and 3, the data associated with these measures were analysed by way of analyses of variance (ANOVAs) having repeated measures with factors associated with doses and placebo versus drug. When reliable interactions were revealed, further analysis was by way of appropriate Student's *t*-tests. The data obtained in Experiments 2 and 4 were analysed by way of Student's *t*-tests for dependent measures.

EXPERIMENT 1

PCP is self-administered by rats (5,7). Studies testing various doses of PCP in food-deprived animals have usually found little or no effect on intake of ingesta using low doses, i.e., 0.15 to 2.0 mg/kg and significant decreases in consumption with higher doses (26,27). Also, PCP administered intracranially into the ventromedial hypothalamus led to a decrease in consumption among nondeprived rats (25). Here, we show that small doses of PCP will enhance intake of solutions containing sugar or salt in a testing procedure involving water deprivation and palatable ingesta.

METHOD

Subjects

The subjects were 60 rats weighing a mean of 317.6 g at the start of these procedures. Prior to these procedures, some subjects had previously received 4 administrations of PCP in another test which ended 10 days before these procedures. The others had received saline injections. Since we could discern no effects of previous history of drug administration on the outcome of these tests, history of drug administration was ignored in the final analyses of the data.

Procedure

Two test solutions were presented, one salty and one sweet. Injections were given 15 min before fluid presentation which began at 1200 hr each day. The test solution for half of the rats was the salty solution, while for the other half it was the 24% sugar solution.

The rats to receive either the salty or sweet solutions were, in turn, randomly divided into 3 equally sized groups.

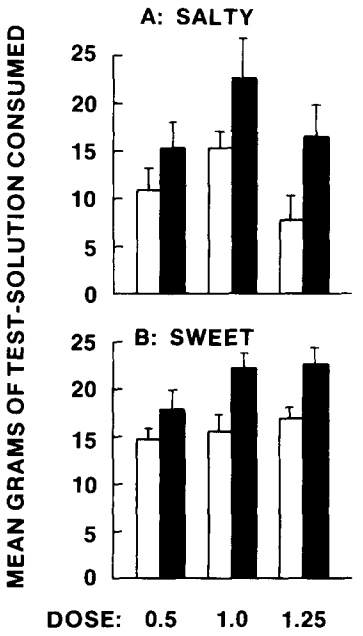

FIG. 1. Depicted are mean grams of test solution consumed by rats after a placebo injection (open bars) and after one of 3 doses (mg/kg) of phencyclidine (PCP). Panel A (SALTY) depicts the effects of PCP on rats' intake of 0.9% NaCl solution. The 0.5, 1.0, and 1.25 mg/kg doses all reliably increased rats' intake of the salty solution compared to placebo, $t(8)=2.6$, $p<0.04$, $t(8)=2.28$, $p=0.052$, and $t(8)=4.5$, $p<0.01$, respectively. Panel B (SWEET) depicts the effects of PCP on rats' intake of a sweet solution. The 0.5, 1.0, and 1.25 doses all reliably increased rats' intake of the sweet solution, $t(8)=2.25$, $p<0.055$, $t(8)=5.7$, $p<0.001$, and $t(8)=4.3$, $p<0.01$, respectively. All *t*-values are for dependent measures. The bars indicate the standard errors of the means.

Each group would eventually receive one of the doses of PCP. Stable intakes of fluids were achieved after one week of the daily regimen and on Day 8 all rats received a placebo injection. On the following day, they received an injection of PCP. After 3 days they received another placebo injection, followed the next day by the same dose of PCP that they had received previously.

Data Reduction and Statistics

The data from the two placebo days and the two drug days were averaged so that each rat had one placebo score and one drug score for each measure. Therefore, the data conform to a 3 by 2 ANOVA having repeated measures with factors associated with Dose and PCP versus placebo, respectively.

RESULTS AND DISCUSSION

The effects of PCP on intake of the salty solution are depicted in Fig. 1A. PCP reliably increased rats' intake of the salty solution, $F(1,24)=24.6$, $p<0.0001$, but had no reliable effects on water intake, $ps>0.05$. Since PCP increased intake of the salty solution and had no effect on water intake, there were reliable increases in both total fluid intake, $F(1,24)=32.4$, $p<0.0001$, and preference ratios, $F(1,24)=15.3$, $p<0.001$. The effects were not dose-related as indicated by unreliable Dose by Drug-placebo interactions.

As depicted in Fig. 1B, PCP reliably increased rats' intake of the sweet solution, $F(1,24)=47.3$, $p<0.0001$. Water intake was modified differentially by PCP, as revealed by the reliable PCP-placebo by Dose interaction, $F(2,24)=4.2$, $p<0.03$. Inspection of the mean difference scores for water intake (drug score minus placebo score) revealed the source of the interaction. The rats which received 0.5 mg/kg PCP took a mean of 2.4 g more water on the drug day than on the placebo day, while the groups which received 1.0 and 1.25 mg/kg PCP decreased their water intake by a mean of 0.4 g and 0.8 g, respectively. PCP reliably increased total fluid intake, $F(1,24)=54.4$, $p<0.0001$. PCP also increased preference ratios reliably, $F(1,24)=16.7$, $p<0.001$, and did so differentially as revealed by the reliable Drug-placebo by Dose interaction, $F(2,24)=4.5$, $p<0.03$. The 1.0 and 1.25 mg/kg doses of PCP reliably increased rats' preference ratios, $t(8)=3.6$, and $t(8)=5.2$, respectively (for dependent measures), $ps<0.01$. The 0.5 mg/kg dose did not reliably modify rats' preference ratios.

These results are not in agreement with previous studies (25–27). However, these procedures used water deprivation and assessed palatable solution intake, whereas previous research employed food deprivation and assessed either food or solution intake. Of these studies, one (27) showed a nonsignificant increase in intake of a sweetened, condensed milk solution using doses of 1.0 and 2.0 mg/kg. In summary, PCP increased rats' intake of palatable salty and sweet solutions, while having little effect on their water intake.

EXPERIMENT 2

It is part of the folklore surrounding use of marijuana that it induces the "munchies," i.e., binge eating episodes subsequent to administration. This has been supported by research in humans (13). Some researchers have found that low doses of THC initially increase intake of a variety of ingesta in deprived and nondeprived rats (3, 18, 26), but later suppress intakes (3, 11, 18). Other researchers, using high doses of THC, have reported suppression of ingestive behavior at all times after administration (10,19). Here, we show that a low dose of THC enhances intake of a sweet solution among rats across 2-hr opportunities.

METHOD

Twelve experimentally naive rats were the subjects of these procedures. At the start of these procedures the rats weighed a mean of 379.5 g.

The test solution was the 24% sugar solution. The rats were presented with water and test solution each day at 1400 hr. After the rats' daily intake of test solution became stable, a series of administrations of placebo and THC began. All rats received placebo on the same day, and THC on the next. Three days later, all rats received placebo again, followed by THC on the next day. The scores of the two placebo days and the two drug days were averaged so that each rat had one placebo score and one drug score.

RESULTS AND DISCUSSION

As depicted in Fig. 2, THC, 1.0 mg/kg, reliably increased rats' intake of the sweet solution, $t(11)=7.3$, $p<0.0001$, while having no reliable effect on water intake. As a result, total fluid intake and preference ratios were reliably increased, $t(11)=7.6$, $p<0.0001$, and $t(11)=3.8$, $p<0.01$, respectively. The data support the idea that the active ingredient of marijuana, THC, produces an enhanced avidity for sweets.

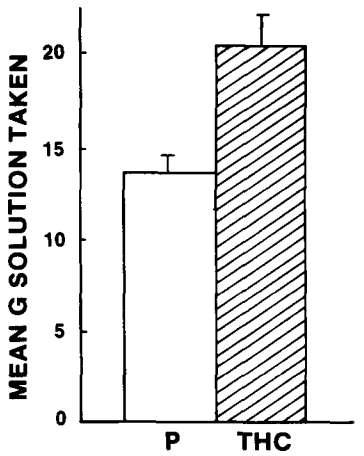

FIG. 2. Mean grams of sweet solution consumed by rats after placebo and THC administration is depicted. THC, 1.0 mg/kg, reliably increased rats' intake of the sweet solution compared to placebo, $t(11)$, for dependent measures, $=7.3$, $p<0.0001$. The bars indicate the standard errors of the means.

EXPERIMENT 3

Drinks containing E are often used by people as an *apertif*. Closer observations, however, do not lead to the conclusion that E is a powerful stimulant of appetite in humans (13). Here, we test the effects of injections of 5 doses of E on the intake of a sucrose solution among rats.

METHOD

The subjects of this experiment were 12 rats weighing a mean of 417.2 g at the beginning of these procedures. Each day at 1130 hr, the rats were presented with water and sucrose solution. The daily regimen was performed for 10 days before any injections were given, after which time the rats' intakes of water and the 20% sucrose solution were stable. All injections were given immediately before presentations of fluids.

Across Days 11 to 38, all doses of E were tested. After receiving a dose of E, another dose was not tested until intake of water and sucrose solution returned to baseline levels, which typically occurred the day after a drug injection. Tests were, however, usually separated by more than one day. When rats were tested with a particular dose of E, they all received a placebo injection on the days before and after the day of E administration. Effects that might be associated with a particular day were controlled by beginning a series of injections for half of the rats a day after the other half. The data obtained for each measure, therefore, conform to a 5 by 2 ANOVA having repeated measures with factors associated with Dose of E and E versus placebo, respectively.

RESULTS AND DISCUSSION

The overall ANOVAs yielded reliable interactions for each of the measures, all $ps<0.03$. Further analyses revealed that the 0.09 and 0.16 g/kg doses did not reliably modify any of the measures as compared to placebo, all $ps>0.1$.

The 0.3 and 0.55 g/kg doses did not reliably modify sucrose intake, while 1.0 g/kg reliably decreased it, $t(11)=2.6$,

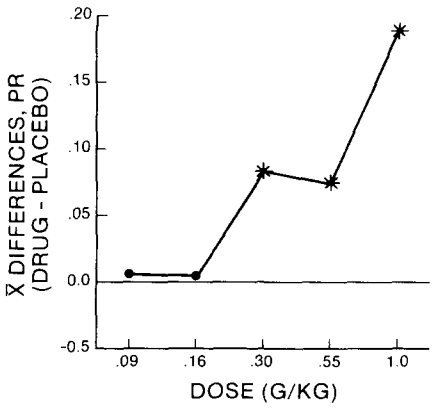

FIG. 3. Mean difference scores (drug minus placebo) in preference ratios (PRs) under 5 doses of ethanol (E) are depicted. The 0.09 and 0.16 g/kg doses did not reliably modify rats' PRs, $ps>0.6$. The 0.3, 0.55, and 1.0 g/kg doses all reliably increased rats' PRs, $t(11)=4.7$, $p<0.001$, $t(11)=2.3$, $p<0.04$, and $t(11)=7.3$, $p<0.0001$, respectively. Asterisks indicate these reliable increases. All t-values are for dependent measures.

$p<0.03$. Water intake was reliably decreased by the 0.3 and 1.0 g/kg doses, $ps<0.01$. The 0.55 g/kg dose also decreased water intake, but the effect was not reliable, $p=0.059$. Total fluid intake was unaffected by 0.3 g/kg and 0.55 g/kg ($p=0.056$ and >0.7, respectively), but reliably decreased by 1.0 g/kg, $t(11)=9.0$, $p<0.0001$. Figure 3 depicts the effects of E on rats' preference ratios. As depicted, E dose-relatedly increased rats' preference ratios. Specifically, the 0.3, 0.55 and 1.0 g/kg doses all reliably increased preference ratios as compared to placebos.

In summary, E produced weak effects on rats' intake of sucrose solution. Although some doses reliably increased preference ratios, these increases were primarily a function of decreased water intake, rather than of increased intake of sucrose solution.

EXPERIMENT 4

Although small doses of M had been shown to increase intake of solutions of saccharin (4,17), a study (23) of M's effects on intake of sucrose solutions failed to show any such effect. Further study, however, indicated that M did increment intakes of sucrose solutions and indicated why the earlier study failed to find an effect. Small doses of M increment intake when the testing sessions are longer. The initial study (23) used 30-min sessions while the subsequent one (9) showed that in sessions longer than 1.5 hr, M incremented intakes. Here, we show again that M increases intake of sucrose solution when testing sessions are longer.

METHOD

The subjects of this experiment were those that had participated in Experiment 3 and were maintained on the daily regimen of limited opportunity to take fluids. All rats had returned to baseline levels of consumption before injections were begun. They all received placebo on the same day and M on the next.

RESULTS AND DISCUSSION

M, 1.0 mg/kg, reliably increased rats' a) intake of sucrose solution, $t(11)=6.8$, $p<0.0001$, b) total fluid intake, $t(11)=3.6$, $p<0.01$, and c) preference ratios, $t(11)=5.7$, $p=0.0001$. M reliably decreased rats' water intake, $t(11)=3.2$, $p<0.01$. These results replicate and confirm previous findings which demonstrate that a small dose of M increases rats' intake of sucrose solution (9) when testing sessions are on the order of 1.5 to 2.0 hr. M, therefore, seems to extend the bout of ingestion. It is also interesting to note that naloxone, the classic opioid antagonist, seems to shorten bouts of ingestion (24).

GENERAL DISCUSSION

Injections of M, PCP, and THC in small doses enhance intake of sweet solutions. The effects of E on intake of a sucrose solution indicate a weak effect toward increasing preference ratios. PCP (this paper) and M (2) increase intakes of palatable salty solutions. Other drugs frequently used by people, such as benzodiazepines (8,15) and amphetamines (12, 16, 20), also modify rats intake of ingesta. Opioids (9) and benzodiazepines (8,15) have both been shown to increase rats' intake of ingesta and, although early research with amphetamine showed decreases in ingestion (16), more recent research with low doses of amphetamine (and other dopamine agonists) has also reported significant increases in food intake (12,20). In addition, naloxone (9,28), the classic antagonist at opioid receptors as well as antagonists at dopamine receptors (i.e., haloperidol) (20) have previously been shown to decrease intake of ingesta. Furthermore, manipulations modifying ingestion (e.g., deprivation of nutrients) also modify self-administration of drugs [for a review, see (6)].

The general idea that drugs of addiction produce satiation of drive (one or all) and, therefore, achieve their capacity to be reinforcing is not supported by findings such as those reported here. Drugs of addiction, in doses that are apt to be self-administered, often increase behavior that has been established by systematically providing a palatable ingesta. The drive-reduction notion can hardly be a complete explanation of addiction when we observe a considerable number of addictive agents enhancing intake of palatable ingesta.

One need not show that all drugs of addiction increment intake of ingesta to seriously question the broadest concept of drive-reduction as an explanation of addiction. Some agents might enhance motivations other than those of ingestion. Nevertheless, even agents that are supposedly anorectic and addictive, such as amphetamine, may at smaller doses increment intake of ingesta (12,20).

Given the apparent relationship between some drugs used recreationally by people and these drugs' tendency to modify intakes of palatable ingesta by rats, it seems reasonable to suppose that one side-effect of recreational drug use among people may be the distrubance of mechanisms that are involved with the regulation of ingestion.

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