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Parker and Radow Test of Drug Withdrawal Aversion: Opposite Effect in Rats Chronically Infused With Sufentanil or Amphetamine

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MUCHA, R. F., M. J. K. WALKER AND F. F. FASSOS. *Parker and Radow Test of drug withdrawal aversion: Opposite effect in rats chronically infused with sufentanil or amphetamine.* PHARMACOL BIOCHEM BEHAV **35**(1) 219–224, 1990.—In rats, cessation of periodic injections of morphine reduces a preference for a palatable saccharin solution presented in a choice with water, and this has been interpreted to reflect withdrawal malaise. We confirmed and examined this "Parker and Radow Model" using subcutaneously implanted osmotic minipumps as the means of drug delivery and the opiate, sufentanil, and the psychostimulant, amphetamine, as the treatment drugs; surgical removal of the pumps was used to initiate withdrawal. Thus, rats withdrawn after 2 weeks exposure to a sufentanil-delivering pump (0.25 μg/hr) showed a decreased preference for the saccharin and animals exposed to an amphetamine pump (68 μg/hr) showed an increased preference, as compared to placebo-exposed controls. This pattern of effects was systematically replicated in new subjects using 4 weeks of treatment and 136 μg/hr amphetamine. Since the locomotor increasing and body weight decreasing effects of amphetamine were also demonstrated and the doses of amphetamine and sufentanil were in comparable dose ranges, it was concluded that the Parker and Radow procedure may be a reliable measure of opiate withdrawal, but under similar test and treatment conditions other processes may be operative in amphetamine-treated animals. Problems of measuring motivation of withdrawal, particularly of spontaneous withdrawal, were noted.

Opiate Sufentanil Amphetamine Withdrawal Alzet minipumps Saccharin intake Motivation Taste aversion Body weight Rat

IT has long been accepted from clinical reports that the withdrawal from chronic drug exposure in the addict may play some role in the maintenance of drug intake or in the relapse of addicts long after a successful detoxification. Much controversy exists on this question [e.g., (28)] and it may reflect the fact that the traditional literature has concentrated on the study of somatic signs as an intermediary for the production of the aversive property of withdrawal. A large literature has evolved on many aspects of the withdrawal signs, but recent examination has suggested that these signs may not be reliable predictors of the aversive effects of withdrawal (16).

For the important problem of spontaneous withdrawal this is particularly troublesome, as there are few simple effects that can be used to directly address and systematically examine the issue of motivation produced by it. Spontaneous withdrawal remains the clinically relevant condition, not precipitated withdrawal which can be readily studied in the laboratory. Moreover, the study of precipitated withdrawal often is not possible. Conditioned aversions produced by antagonists, for example, have been applied as an efficient means for examining opiate withdrawal motivation (16,20), but this has been only permitted by the existence of good antagonists. There are a variety of abused substances, like the psychostimulants, that do not have such a range of antagonists.

A number of years ago Parker and Radow (22) reported an effect that may be useful for analyzing the motivational consequences of spontaneous drug withdrawal. Following a baseline preference test between water and saccharin, rats were exposed to a 28-day regimen of morphine injections. Upon abrupt cessation of the injections, there was reduced preference for the saccharin solution when given in a choice with water and this was correlated with withdrawal-produced body weight loss. Although this pattern of effect was consistent with a withdrawal-produced conditioned aversion and it was proposed that this test could be used as a measure of the drug's propensity for "causing physical dependence" (22), this phenomenon has not received any systematic attention in the literature.

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Accordingly, the present work was designed to replicate, extend, and critically evaluate this phenomenon from the perspective of its value as a measure of the motivating effect of drug withdrawal. Three problems were singled out for further investigation. First, the previous work involved only daily systemic injections (22). However, in the last few years it has become clear that such drug administration regimens can have powerful influences on behavior. For example, cues predicting opiate injections are known to acquire secondary reinforcing properties (17, 19, 28) and, since Parker and Radow (22) did not continue their injections into the withdrawal period, the observed decrease in saccharin preference may be due to the absence of these reinforcing effects, rather than due to a discomfort of drug removal. Therefore, a major purpose of this report was to test the Parker and Radow model in animals treated without cues predictive of opiate effect, using constant drug infusions with chronically implanted osmotic minipumps.

Second, morphine was the only treatment that was used previously (22). This drug, unfortunately, readily produces taste aversion itself (17). A possible explanation of the effect reported by Parker and Radow may involve a backward association between flavor and drug effect which is possible between the end of the baseline preference test and the start of treatment. The opiate, sufentanil, does not produce taste aversion (17); therefore, a second important purpose here was to report data on sufentanil as the treatment drug.

A final problem addressed here was whether any findings on opiates and the interpretation of these effects can be generalized to other drug classes. It is now well-known that opiate withdrawal is aversive, and this is consistent with the effect of morphine withdrawal on saccharin consumption seen by Parker and Radow (22). Recent work indicates that cessation of amphetamine and cocaine treatment produce a suppression of barpressing in rats (3, 13, 14, 26), as seen in morphine withdrawal (23). Therefore, an additional purpose of this report was to describe the effect of using amphetamine as a drug of treatment.

The treatment drug dosings used here were carefully determined to allow comparison of the sufentanil and amphetamine results. For sufentanil the dosing was 0.25 μg/hr. When expressed according to body weight per hr for our typical 330 g rat, 0.75 μg/kg, the dose was just below the dose (1 μg/kg) that produced place preference conditioning using a 1-hr session and just above the dose (0.5 μg/kg) that produced taste preference conditioning (17). The amphetamine dosings were 68 and 136 μg/hr, and were equivalent to 0.2 and 0.4 mg/kg/hr. The equivalent doses of amphetamine needed for place and taste conditioning are between 0.1 and 0.5 mg/kg (2,4) and were, therefore, considered analogous to that of the sufentanil. It was further considered that an infusion rate of 8 mg/kg/day amphetamine produced anorexia and tolerance to this effect (12). Finally, both the sufentanil and the high infusion rate of amphetamine used here were just below those reported to produce unacceptable adverse effects in rats: self-injury was seen with amphetamine at infusion rates of as low as 0.47 mg/kg/hr (21) and deaths were noted in a small porportion of subjects with 0.5 μg/hr sufentanil (24).

METHOD

Animals

Adult male Sprague-Dawley rats purchased from Charles River Canada Inc. (St. Constant, Quebec), at an initial weight of 180–200 g, were used. The rats weighed approximately 310–350 g at the start of the drug treatments. They were housed individually in stainless steel cages fitted with two Richter tubes, one containing water and the other water or a saccharin solution. In the home room the lights were on from 1900 to 0800 hr; maintenance and experimental manipulations were carried out between 0900 and 1800 hr. Normal rat chow was provided ad lib. Each rat was exposed to two or three surgical procedures, carried out under halothane anaesthesia, for the implantation and/or removal of osmotic pumps or placebo pumps. A single incision in the loose skin on the rat's back was used and each pump or placebo was placed into a new pocket in the subcutanium.

Drugs and Flavored Solutions

Solutions of the experimental drugs, sufentanil citrate (Janssen Pharmaceuticals) and d-amphetamine hydrochloride (BDH Chemicals, Toronto), were prepared with 0.9% saline and the doses were expressed as the free base. They were administered subcutaneously using ALZET mini-osmotic pumps (model No. 2002). Drug concentrations were prepared so that the delivery during treatment from each pump was either 68 μg/hr of d-amphetamine, or 0.25 μg/hr of sufentanil. Placebo pumps were pieces of Teflon machined to the size of the Alzet pumps. The test solution comprised 0.1% (w/v) sodium saccharin (Sigma Chemical Co., St. Louis, MO) mixed with fresh Toronto tap water.

General Procedures

Approximately 1.5 weeks after arrival in the laboratory the subjects were given a 1- or 2-day saccharin preference test: Richter tubes were fitted on the home cage, one tube with water and the other saccharin; during the 2-day test, the position of the tubes were reversed on the second day. Five days after the preference test, the rats were implanted with pumps delivering drug or placebo and then returned to their home cage for 14 days. At approximately 0900 hr of this day, all the rats were reanesthetized and the pumps were removed; some animals were then sutured and allowed to recover (Study 1), others were reimplanted with pumps for another two weeks after which the pumps were then removed (Study 2). In Study 1 only, it was considered necessary to test some of the rats for locomotor effects of the drug treatment. This was done with a minimum of disturbance on days 1, 2, 3, 6, after surgery, and every second day thereafter to Day 12, by placing the rats for 1 hr into a clear $30 \times 42 \times 30$ cm ($l \times h \times w$) stainless-steel and Plexiglas box located in a quiet area of the vivarium. They were observed over the last 30 min through a closed circuit television for the number of times that the midpoint between the rats's ears crossed lines dividing the floor into equal quadrants.

The taste preference testing always commenced 6 hr after the final removal of the pumps. All animals were again given free access to two Richter tubes; one containing tap water and the other containing saccharin solution. Every 24 hr the position of the tubes was reversed and the tubes were refilled.

Experimental Designs, Data, and Statistical Analyses

The first of the two studies was actually carried out in two separate parts. This was deemed necessary to confirm the suitability of using osmotic minipumps to treat animals chronically with an opiate before going on to test with amphetamine. Thus, an initial group of 18 rats was started with sufentanil as a test drug; a second group of 12 rats was used to test for amphetamine effects. Each of these two groups of animals was divided in half; one-half were implanted with a single pump delivering drug and a second group was implanted with a placebo. All the subjects were assigned to the respective groups randomly. Also, to confirm that the amphetamine was having an effect in the present rats, these animals and their controls were tested for locomotor activity

during the treatment phase. This was not done in any of the other groups of animals.

The second study was carried out in 18 different, identically handled rats to determine the effect of a higher dose of amphetamine and a longer treatment period on saccharin preferences and to compare any effects to that of the sufentanil dosing. These animals were given a 2-day test for baseline consumption of the test fluids and divided up into three equal-sized groups matched according to body weights. The subjects were then implanted with a placebo, a pump delivering amphetamine, or a pump delivering sufentanil. Following two weeks these were removed and the animals were treated for an additional two weeks before testing. The sufentanil rats were reimplanted as initially with a single pump delivering sufentanil. The amphetamine animals were implanted with two pumps delivering a total dose of 136 μg/hr amphetamine.

The main data collected and analyzed in both experiments were the amounts of saccharin and water consumed over a 24-hr period by each rat during the fluid choice tests before and after surgery; body weights of the animals taken during the second study were also used. Saccharin preference ratios were calculated by first determining the difference between the amount of saccharin and water consumed over a 24-hr period and then dividing this by the total amount of fluid taken in.

The results were evaluated according to the methods of Kirk (10) using a priori and a posteriori statistical tests. In the first study, where no hypotheses were advanced for the preference effects, the data were analyzed with overall analyses of variance for unbalanced data followed by analyses of simple main effects. The data were then subjected to pairwise comparisons using the Tukey A-test. In the second study, Dunn's test was used for pairwise comparisons. The preference ratios were subjected to arcsine transformations prior to any statistical analyses. Estimates of the slopes of weight gains in various groups of rats were made using least-square methods of fitting a regression line through the relevant data; all available weight data were used for this analysis except those taken within one day after surgery. The locomotor activity data of Study 1 were analyzed parametrically. Any means in the text were presented as ±SEM. Tests were carried out using a criterion for significance of $p<0.05$, two-tailed.

RESULTS

Study 1: Effect of Two Weeks Treatment With Sufentanil or Amphetamine

During the implantation one subject in the placebo group of the sufentanil part of the study died from an overdose of the anaesthetic and its data were dropped from the study. Therefore, completing the study were eight animals in the sufentanil condition, six in the amphetamine, and 13 in the placebo.

On the pretest it was clear that the saccharin solution was preferred by all animals. The consumption of water and saccharin for individual rats ranged from 0 to 47 ml and 39 to 100 ml, respectively, with all but three rats drinking 10 ml or less water. Analyses of all the data revealed no significant baseline differences among the three groups for saccharin or for water intake (Kruskal-Wallis tests); the highest and lowest means on these measures were 58.6±5.4 (n=13) and 83.6±8.5 (n=8) ml for saccharin and 2.6±1.6 (n=8) and 9.5±4.5 (n=13) ml for water. However, the total fluid intakes tended towards a difference, $F(2,26)=2.98$, $p<0.1$, although the magnitude did not reach our criterion of significance; the mean total fluid intake on the baseline test ranged from 68.1±6.2 ml (n=13) to 87.5±3.7 (n=6) ml.

Accordingly, the remaining preference data were evaluated in terms of a score which is not sensitive to differences in absolute levels of consumption. These data, summarized in Fig. 1, also indicate the initial high preferences for saccharin and the lack of significant baseline differences in the three groups, $F(2,26)=0.77$. However, shortly after the removal of the pumps, the pattern of consumption of the subjects diverged from these initially similar levels of preference for the saccharin solution. For example, on Day 2 the mean scores were −0.70±0.19 for the sufentanil group, 0.25±0.07 for the placebo, and 0.95±0.01 for the amphetamine. The effects noted were confirmed by a significant group by days interaction, $F(16,192)=3.3$, in the preference scores measured over the withdrawal period. In addition, the analyses of simple group effects were significant on Days 2 to Day 5 [all between $F(1,216)=11.1$ and 19.5], and examinations of the data with a multiple comparison test indicated that the scores of the sufentanil animals were significantly lower and those of the amphetamine animals were significantly higher than those of the controls on Days 2 to 5 (all Tukey A-tests). This was also seen in measures of absolute consumption: On the third withdrawal day, for example, the consumption of the saccharin and water in the control group was 31.6±7.2 and 17.6±5.5 ml, respectively. In the amphetamine group, these respective scores were 66.8±5.2 and 2.2±1.0 ml, while in the sufentanil groups they were 12.3±8.1 and 35.0±9.6 ml. Inspection of the data also revealed a significant simple main effects of time in the sufentanil-, $F(1,192)=111.3$, and saline-treated groups, $F(1,192)=32$.

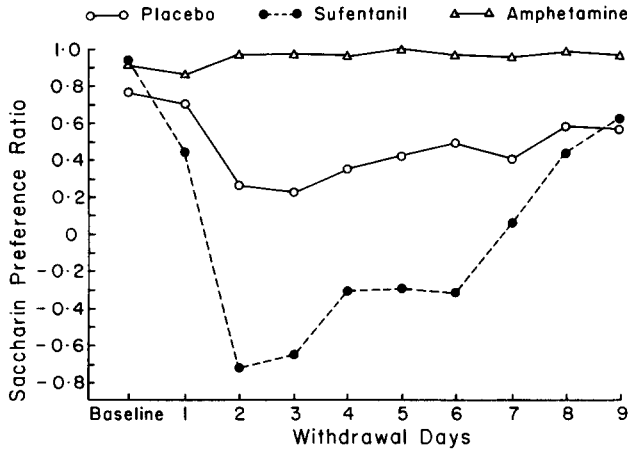

FIG. 1. Mean daily preference ratios for a saccharin solution in a choice with normal water before and after 2 weeks of sufentanil infusion, amphetamine infusion, or no infusion.

From the locomotor activity measures taken from the 12 animals in the amphetamine part of the study, there was evidence of amphetamine-produced increase in activity. Twenty-four hr after the implantation the number of lines crossed by the six amphetamine animals (86±6) was in every case greater than these seen in the six controls (23±4). This pattern was still present 3 days after surgery, with the respective means of 47±4 and 12±2 lines crossed. However, by the end of the infusion period, there was evidence for tolerance to this effect; on day 12, for example, the means were 18±5 and 11±5, respectively. Analysis of variance indicated significant group, $F(1,10)=24$, $p<0.001$, and days by group effects, $F(7,70)=24$, $p<0.001$.

Study 2: Effect of Four Weeks Treatment With Sufentanil or Amphetamine

In this experiment one animal in the control condition died

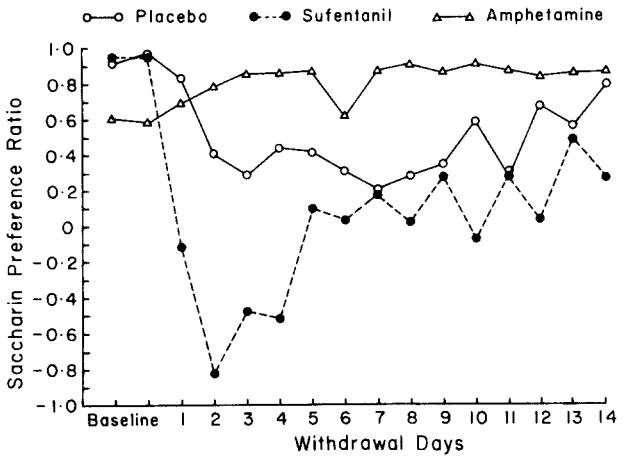

FIG. 2. Mean daily preference ratios for a saccharin solution in a choice with normal water before and after 4 weeks of sufentanil infusion, amphetamine infusion, or no infusion.

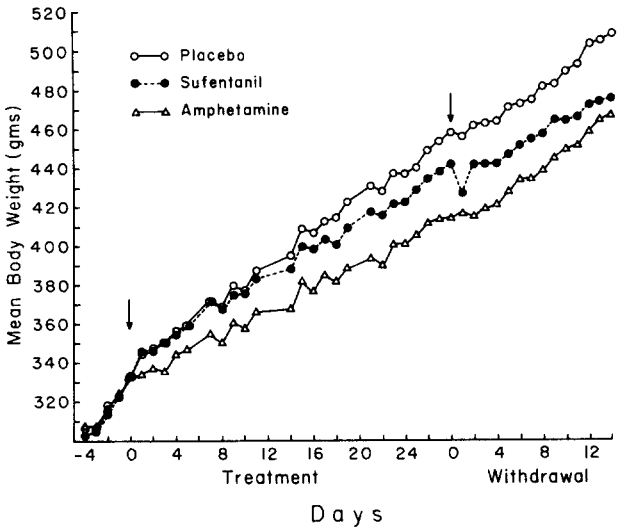

FIG. 3. Mean body weights of rats depicted in Fig. 2 before, during, and after treatment. The first arrow represents the implantation of osmotic pumps or placebos and the second arrow when they were finally removed.

during the second surgery and its data were dropped from the study. The results were again expressed as preference scores (Fig. 2), and they confirmed the results of the previous study. Analyses of the data from the two baseline days indicated no appreciable differences between the three experimental groups, $F(2,14) = 1.3$. However, after removal of the pumps, the groups diverged in a pattern seen in the first study. An analysis of preference data collected over the first three days of the withdrawal period revealed a highly significant groups effect, $F(1,14) = 14.6$, but by the end of the test period the differences between the groups had subsided. An analysis of the data on the last three days of the test indicated that the group difference no longer reached our criterion of significance, $F(2,14) = 3.37$. There were significant mean differences beween the controls and the sufentanil animals on the second and third days (Dunn's tests). Differences between the amphetamine and control groups were confirmed by a significant group by day interaction in data collected over the entire test period, $F(13,117) = 2.55$.

Analyses of the body weight data, summarized in Fig. 3, confirmed with another measure that the drug treatments and the cessation of drug treatments effected a number of changes in the subjects. From almost identical mean body weights on the 4 baseline days, there was a gradual and progressive separation of the groups after the pump implantation. Therefore, by the final day of the treatment period, the amphetamine animals (413 ± 12 g) were significantly smaller, $F(1,14) = 5.2$, than those of the control group (453 ± 10 g). This was also reflected in significantly different slopes of the regression lines of the body weights, $t(236) = 13.4$. They reflected weight gains of 4.2 ± 0.2 g/day in the controls and 3.0 ± 0.2 g/day in the amphetamine animals. During the period after recovery from the removal of the pump the daily weight of the amphetamine animals was 4.4 ± 0.9 g per day, contrasting significantly with the value taken in this group over the treatment period, $t(206) = 2.00$. However, this increased weight gain was not significantly different from that (4.2 ± 0.7 g/day) of the control group during the withdrawal period. Over the 24 hr after removal of the pumps it was noted that significant body weight loss was seen in the sufentanil group (-15.3 ± 2.2 g), but not the control (-2.5 ± 3.4 g) or the amphetamine groups (2.8 ± 3.6 g); the sufentanil animals were also significantly different from the other two groups (both t-tests).

DISCUSSION

Rats withdrawn from chronic sufentanil exposure by the removal of an osmotic minipump delivering the opiate showed a decreased preference for a saccharin solution when given in a choice with normal water. This replicated an effect initially described by Parker and Radow (22), and ruled out any explanation of their observed decreased consumption of saccharin that may be based on the use of only morphine as the treatment drug and periodic administration by the experimenter of drug as the mode of treatment. Sufentanil, for example, does not readily produce conditioned taste aversion, as seen with morphine. This may be important since a notion of backward conditioning and aversive properties of the treatment drug may account for some of Parker and Radow's effects (see Introduction). Also, with the continuous infusion methodology used here, it is not possible to argue that a loss of secondary reinforcing properties associated with cessation of the injections could account for an aversive effect of the withdrawal period as seen with Parker and Radow (see Introduction).

Parker and Radow (22) viewed the decrease in the saccharin preference to be due to a conditioned aversion produced by the malaise associated with opiate withdrawal. Consistent with this, the major effect of opiate withdrawal on the saccharin preference was not seen until a day after the start of the withdrawal, which would be expected if time is required for an association between the saccharin and the malaise. Also, body weight losses seen in opiate withdrawal indicated that the treatments gave rise to withdrawal signs.

Therefore, it was concluded that the decreased preference seen on tests in the withdrawal period is likely a general feature of opiate treatment, regardless of the particular compound used or the nature of the drug administration employed. The data further support a view that the decrease in preference reflects the aversive effect of opiate withdrawal. Accordingly, this further indicates that the protocol of Parker and Radow may be an important and neglected tool for the modelling of the clinically important motivational properties of opiate withdrawal. Since it reflects spontaneous withdrawal, rather than precipitated, it may add important capabilities to a number of other simple models in this area; these are based largely on conditioned aversions precipitated by naloxone in morphine dependent animals [e.g., (16,20)].

A more pressing application of the present test model stems

from the paucity of ways to study withdrawal aversive effects associated with other classes of abused drugs, particularly those that do not have a wide range of competitive antagonists as is the case for the opiates. For this reason, in parallel with the present sufentanil rats, a number of subjects were tested in withdrawal from chronic infusion with amphetamine. As compared to the control subjects, a clear effect was seen in the amphetamine animals, but it was opposite to that seen with sufentanil. Instead of a reduction in saccharin preference, the amphetamine animals showed increased preference.

These findings were unexpected, as withdrawal from amphetamine and related psychostimulants, such as cocaine, produced a suppression of barpressing for various reinforcers (3, 13, 14, 26), as is seen with withdrawal from morphine (23). Interestingly, in one study, barpressing for sweetened fluid (glucose/saccharin solution) was reduced in cocaine withdrawal (3), and it seems reasonable to expect that a related psychostimulant, amphetamine, should produce a similar effect on the present baseline of saccharin intake. Whereas the full explanation of the present and previous findings likely requires further work, there are several points worthy of consideration.

First, the increased saccharin preference produced by amphetamine was seen here in two different studies, and differences between them offered a systematic replication (25) over a range of treatment doses and duration of treatments. Therefore, the effect appears to be reliable and not specific to a narrow set of treatment conditions.

Second, it is further unlikely that the present amphetamine dose range is not relevant for the previous literature, as may be implied by a comparison of the present daily dose (0.4 mg/kg/day) to the 36 mg/kg/day and 10 mg/kg/day used by Leith and Barrett (14) and Kokkinidis *et al.* (13) to demonstrate a withdrawal produced decrease of self-stimulation induced operant responding. These authors, however, used injections and not chronic implanted drug delivery systems to chronically treat their animals, and it is easily ascertained from the morphine dependence literature that these two means for treating chronically do not permit a comparison of doses: For example, a withdrawal syndrome with wet shakes, jumping, and writhing requiring several weeks of injection with doses up to 240 mg/kg morphine (18) can be produced by implanting 75 mg morphine as a pellet for 4 days (16). What may be more worthy of consideration is that the present amphetamine treatments have been reported to produce anorexia and tolerance to this effect (12). Consistent with this, decreases in body weight gain normally associated with amphetamine [e.g., (29)] were noted in the present animals. Increases in locomotor activity were also produced by the present drug dosings and we noted that tolerance develops to this effect. Also, upon cessation of the drug treatment there was renewed weight gain, confirming that the cessation of the amphetamine indeed had some effect on a measure other than preference. It can further be noted that osmotic minipumps have been used to deliver amphetamine dosings in the present dose range to produce changes in the responses of substantia nigra neurons to apomorphine (5).

Third, one may also want to argue that a decrease in saccharin preference as seen with sufentanil may be produced by amphetamine, but in a different dose range; however, this may not be simple. Since a significant increase in preference was seen in the present study, this would imply that amphetamine has a biphasic effect that spans a rather wide dose range. Whereas the present data cannot rule this out, it should be emphasized that Parker and Radow (22) used a broad range of morphine doses and saw no evidence of a biphasic relation between the intensity of treatment and the effect of withdrawal on the saccharin preference. It may also be difficult to suggest that the 28 days of amphetamine treatment was not long enough to give rise to withdrawal aversions. Consistent with the view that the treatment period was too short, Green and Garcia saw increased preference for a distinctive flavor in the withdrawal phase after a single high dose of apomorphine (7) and, given that amphetamine has potent and long-lasting acute aversive effects (1,4), then an increased preference will be expected with short durations of treatment. In addition, to the extent that tolerance and physical dependence may be related (9), the treatment period was not sufficient for tolerance to develop to the weight decreasing effects of amphetamine, although it was expected (29). However, tolerance did develop to the locomotor activity effects of amphetamine and long treatment intervals do not seem to be important for sufentanil to decrease saccharin preference.

Accordingly, it was concluded that the increased preference seen here with amphetamine may be a reliable and general phenomenon, occurring in treatment situations normally studied in the context of the behavioral effects of amphetamine. However, if we accept that the motivational processes operating in the withdrawal from opiate treatment are reflected in the decreased saccharin preference of the Parker and Radow effect, then different processes may be involved with amphetamine treatment. This raises several questions for future research and for understanding the literature that gave rise to the present study.

The first concerns the fact that both withdrawal from opiates and from amphetamine treatment result in suppression of operant responding and suggests that the suppressions may be for different reasons. The effect of the opiate withdrawal is probably due to withdrawal malaise, but other explanations for the effect in amphetamine withdrawal now seem reasonable. For example, chronic methamphetamine and its withdrawal causes a disruption in circadian rhythms, and this could be disruptive in certain operant responding testing situations, such as those that are short and at specific times of the day, as used by Leith and Barrett (14). That test demands are important for the disruptive effect of amphetamine withdrawal can be noted from work by Kokkinidis *et al.* (13). A second question directs itself at the fact that in previous studies (3, 13, 14, 26) the subjects received their drug during periodic experimenter or self administration sessions. It may be that the decreases in operant responding may reflect loss of the stimuli associated with the drug administration when it is stopped: One possibility could involve secondary reinforcing effects of these stimuli (see Introduction). This may not be required for opiates to show a decrease in effect on a behavioral baseline, but it may be instructive to examine this more closely for the psychostimulants. A third possibility is that amphetamine and opiates interact differently with regard to the nutritive content of the reinforcer. Saccharin is a nonnutritive and, work by Evans (6) suggest that amphetamine not morphine acutely affects reinforcement produced by sweet tastes by themselves. The present protocol should be examined using a palatable, but not sweet flavor, such as a MSG/citric acid solution (17). A final question is whether a component of the present effect reflects the signficant withdrawal-days effect seen in the control groups of this study. It is known that surgery itself may have serious physiological consequences (8,27), and it may be that opiate and amphetamine treatment differentially interact with this. It can be noted that amphetamine has been reported to stimulate processes dealing with the effects of surgery whereas narcotics appear to have the opposite effect (11).

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