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Repeated exposures intensify rather than diminish the rewarding effects of amphetamine, morphine, and cocaine

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Abstract. It is commonly believed that repeated exposures diminish the pleasurable effects of drugs and hence that pleasure must have only a minor role in addiction. In six experiments with rats, repeated exposures to amphetamine, morphine, or cocaine were found to enhance the drug-induced rewarding effect as measured by conditioned place preference. Thus, sensitization to the rewarding effect, rather than tolerance, was obtained. Also, cross-sensitization was obtained; exposures to amphetamine enhanced the rewarding effect of morphine and vice versa; similarly, exposures to morphine enhanced the rewarding effect of cocaine. These findings support a new theory: drugs of abuse are addictive because repeated exposures sensitize the central reward mechanism so that drug taking produces a progressively greater reinforcing effect each time it occurs.

Key words: Sensitization to drug reward – Amphetamine – Morphine – Cocaine – Tolerance – Drug addiction

The prevailing theory of addiction, called the withdrawal theory (Lindesmith 1968; Wikler 1973), holds that repeated drug exposures produce tolerance to the rewarding effect. Thus, contrary to evidence marshalled most notably by Stewart, de Wit, and Eikelboom (1984), the withdrawal theory assumes that drug-induced pleasure must play only a minor role in causing and maintaining addiction. Since tolerance to the rewarding effect is a central assumption of the withdrawal theory, it is surprising that there is little experimental evidence for such tolerance (Falk et al. 1983). Moreover, there is a substantial body of indirect evidence that repeated exposures to drugs with a rewarding effect such as amphetamine or morphine might actually produce the opposite of tolerance: sensitization. That is, repeated exposures may increase, rather than decrease, the capacity of these drugs to function as rewards.

The possibility of sensitization to the rewarding effect is suggested by the many findings that repeated exposures to rewarding drugs such as amphetamine and morphine enhance the behavioral activation also produced by these drugs (Segal and Mandell 1974; Joyce and Iversen 1979; Vezina and Stewart 1984). These activating effects are presumed to be mediated by a mesolimbic dopaminergic neural system (Joyce and Iversen 1979; Joyce and Koob 1981; Vezina and Stewart 1984), as are the rewarding effects (Wise 1978; Phillips et al. 1983; Stewart et al. 1984; Bozarth 1986). Indeed, Wise and Bozarth (1987) have argued that the rewarding and the activating effects are mediated by a common mechanism. Thus, it is conceivable that repeated exposures to amphetamine or morphine augment the drug-induced rewarding effect just as they enhance the drug-induced activation of locomotor and stereotypic behaviors.

The present experiments were designed to test the prediction that repeated exposures produce sensitization to the rewarding effect of amphetamine, morphine, and cocaine. The same general plan, shown in Table 1, was used in each of six experiments. During phase 1, the experimental rats (Group Sen in Table 1) were given repeated drug exposures to sensitize the dopaminergic reward mechanism. One control group (Group No Sen) received saline injections. Half of the rats in a second control group (Group Base) were treated like those in Group Sen and half like those in Group No Sen. Then in phase 2, the rewarding effect produced by the drug was measured using the technique of conditioned place preference (CPP). To produce a CPP, each rat in Groups Sen and No Sen was confined in a distinctive chamber while under the influence of the rewarding drug. Those in Group Base received exposures to the distinctive chamber unpaired with the drug and thus provided a baseline against which to assess CPP in Groups Sen and No Sen. Later, the rats were given a choice between the drug-paired chamber and an adjacent, neutral chamber. If repeated exposures produce sensitization to the drug's rewarding effect, Group Sen should show stronger CPP than Group No Sen.

Experiments A–A, M–M, A–M, and M–A. Experiments A–A and M–M studied sensitization to the rewarding effect produced by repeated exposures to amphetamine (A) and morphine (M), respectively. There is a considerable body of evidence that the rewarding effects of these drugs are mediated by the same central reward mechanism (e.g., Wise 1978, 1987; Wise and Bozarth 1987). Thus, experiments A–M, and M–A studied cross-sensitization produced by these drugs.

Table 1. The treatments given to different groups during phases 1 and 2 in each of six experiments

Group	Phase 1	Phase 2
Sen	Drug injections	Place-drug pairings
No Sen	Saline injections	Place-drug pairings
Base	Drug or saline	Place unpaired with drug

Amphetamine and morphine not only have a rewarding effect that can be measured with the technique of CPP but also an aversive effect (Reicher and Holman 1977) that can be readily detected with the method of conditioned taste aversion (CTA). Since the aversive, CTA-inducing effect of other drugs such as lithium chloride can be used to induce a conditioned place aversion (Mucha et al. 1982), pairings of place with amphetamine or morphine might also be expected to produce some conditioning of place aversion as well as place preference. Although the place aversion induced by a drug with a strong rewarding effect would be masked by the place preference, it should detract from the apparent strength of the CPP (Lett 1988). Thus, any procedure that attenuates the aversive effect of amphetamine or morphine should enhance CPP. Repeated drug exposures produce tolerance to the aversive effect as measured by CTA (Braveman 1975; Vogel and Nathan 1976) and could, therefore, enhance CPP by attenuating the place aversion produced during CPP training rather than by increasing the drug's rewarding effect. To circumvent this problem, a special procedure was added to those outlined in Table 1.

The purpose of this special procedure was to minimize the extent to which the aversive effect could affect the strength of the CPP displayed by Groups Sen and No Sen so that any difference between these groups could be clearly attributed to a change in the strength of the rewarding effect. On two occasions prior to phase 1, each rat in every experiment was given saccharin solution and was then injected with lithium chloride to produce an association between saccharin and the aversive effect of lithium. The saccharin taste was later used to block (Kamin 1969) the association between place and the aversive effect of amphetamine or morphine. During CPP training in phase 2, prior to each place-drug pairing, each rat was forced to taste a small amount of saccharin solution. Since the saccharin taste was previously established as a signal for the aversive, CTA-inducing effect of lithium, it was expected to block the conditioning of the place aversion produced by place-amphetamine or place-morphine pairings. This procedure has been shown to block the association between place and the aversive effect of amphetamine as measured by the resulting enhancement of CPP in experimental rats relative to appropriate controls (Lett 1988). Also, exposures to the aversive, CTA-inducing effect of lithium should produce cross-tolerance to the aversive effects of amphetamine (Ford and Riley 1984) and morphine. In any case, the special blocking procedure should not by itself produce any differences between groups, since it was administered to every rat in all groups in the same way during experiments A–A, M–M, M–A, and A–M.

Experiments C–C and M–C. Experiment C–C studied sensitization produced by repeated exposures to cocaine (C). Since there is evidence suggesting that the rewarding effect of cocaine is mediated by the same central reward system that mediates those of amphetamine and morphine (Roberts et al. 1977; Stewart 1984), experiment M–C tested whether repeated exposures to morphine would result in cross-sensitization to the rewarding effect of cocaine.

Relatively weak aversive effects seem to accompany the rewarding effect of cocaine since it, unlike amphetamine and morphine, appears to produce little CTA at dosages that produce CPP. For example, 5 mg/kg cocaine do not produce a detectable CTA (Goudie et al. 1978) but this dose and even smaller ones produce CPP (Spyracki et al. 1982a). Thus, it was possible to use a very low dose of cocaine, 2.5 mg/kg, that should be nearly free of an aversive effect to induce CPP in these two experiments. This should virtually eliminate any possibility that the repeated drug exposures given in phase 1 could enhance CPP by causing tolerance to the aversive effect of cocaine rather than sensitization to its rewarding effect. For this reason, the blocking procedure described earlier was omitted, but otherwise the procedures of experiments C–C and M–C were similar to those of experiments A–A, M–M, M–A, and A–M.

Method

Subjects. In each of experiments A–A and M–A, the subjects were 30 male Sprague-Dawley rats; in experiments M–M and A–M, they were 30 and 32, respectively, female Sprague-Dawley rats; in each of experiments C–C and M–C, there were 30 male Sprague-Dawley rats. The mean weights at the beginning of each experiment were 171 g, 196 g, 198 g, 184 g, 212 g, and 204 g, respectively. All the rats were obtained from Canadian Hybrid Farms in Centreville, Nova Scotia.

Drugs. d-Amphetamine sulfate, morphine sulfate, and cocaine hydrochloride were dissolved in isotonic saline at concentrations that permitted an injection volume of 1 ml/kg. The dose of amphetamine used to produce sensitization (experiment A–A) or cross-sensitization (experiment A–M) to the rewarding effect was 1.5 mg/kg. In experiment C-C, the dose of cocaine used to produce sensitization was 20 mg/kg. Repeated exposures to these doses of amphetamine (Segal and Mandell 1974) and cocaine (Kilbey and Ellinwood 1977) should produce sensitization to their activating effects. When morphine was used as the sensitizing agent (experiments M–M and M–C), the dose was 5 mg/kg.

The dose of amphetamine used to induce CPP (experiments A–A and M–A) was 1.5 mg/kg. In experiment M–M, the morphine dose used to induce CPP with one place-drug pairing was 5 mg/kg. These doses of amphetamine and morphine should be maximally effective in producing CPP (Spyracki et al. 1982b; Mucha and Iversen 1984). In experiment A–M, the dose of morphine used to induce CPP with three place-drug pairings was 1 mg/kg; this dose should be close to the minimum dose that will produce CPP (Mucha and Herz 1985; Mucha and Iversen 1984). In experiments C–C and M–C, the dose of cocaine used to induce CPP was 2.5 mg/kg; this dose should be slightly above the minimum effective dose (Spyracki et al. 1982a).

A 0.15 M solution of lithium chloride was used to produce CTA. When amphetamine was used to induce CPP (experiments A–A and M–A), the dose of lithium paired with saccharin to produce CTA was 63.6 mg/kg. When morphine was used to induce CPP (experiments M–M and A–M), the dose of lithium was reduced to 31.8 mg/kg since morphine at the present doses should produce relatively weak taste aversions (Riley et al. 1978). Amphetamine, cocaine, and lithium chloride were always injected intraperitoneally and morphine was always injected subcutaneously.

Apparatus. CPP training was given in a shuttlebox consisting of two adjoining, wooden chambers, each $33 \times 12.5 \times 15$ cm. One chamber was painted white and had

a solid floor; the other was painted black and had a wire mesh floor; each chamber was covered by a transparent plastic lid. A metal partition was used to confine the rat to a particular chamber during CPP training and was removed during the CPP test.

Procedure. The same general plan, shown in Table 1, was used in each of the six experiments. In the first four experiments, A–A, M–M, M–A, and A–M, the blocking procedure discussed above was added to the treatments outlined in Table 1; not so, for experiments C–C and M–C. Thus, the procedures of the first four experiments will be described together, followed by a separate description of the remaining two experiments.

Experiments A–A, M–M, M–A, and A–M. Prior to phase 1, all rats in these experiments were trained to have a conditioned saccharin aversion. The rats were first habituated to receiving water twice a day, during a 15-min period followed 3 h later by an additional 30-min period. On two training occasions each separated by 2 days, every rat was given 0.1% w/v saccharin solution during the 15-min drinking period and then injected with lithium chloride. Thereafter, the 15-min drinking period was omitted and on weekdays the rats received water during the 30-min period only; on weekends the animals were usually given free access to water for 24 h and then returned to their usual drinking schedule.

Several days after the last saccharin-lithium pairing, phase 1 of the experiment proper began. In each experiment, the rats were divided into three groups equated as to mean body weights: Group Sen, Group No Sen, and Group Base. In experiments A–A, M–M, and M–A, there were always ten rats per group. In experiment A–M, Groups Sen and No Sen each contained 11 rats while Group Base had 10.

During phase 1, the rats in Group Sen were injected with the designated drug to produce sensitization. In experiments A–A and A–M, these rats were injected with amphetamine on six occasions separated by 24–72 h. In experiment M–M, the rats received five injections of morphine spaced 24 h apart; and in experiment M–A, they received six injections of morphine separated by 24–72 h. In all of these experiments, Group No Sen received equivalent injections of physiological saline on these occasions. In Group Base, half the rats received the drug and half received saline.

Several days after the last injection, CPP training was administered. In all four of these experiments, every rat received a taste of saccharin solution at the beginning of each CPP training trial. As explained earlier, the saccharin taste had previously been established as a signal for the aversive, CTA-inducing effect of lithium chloride and was expected therefore to block (Kamin 1969) the association between place and the aversive effect of amphetamine or morphine. The rat was held in one hand by the experimenter; the tip of a syringe (with needle removed) was put into one side of the rat's mouth and 2 ml of solution were delivered. Typically, the rat drank little but instead let the solution drip out of its mouth. Then the rat was put back into its home cage.

In each of the four experiments, 4–8 min after the brief exposure to the saccharin solution, the rats in Groups Sen and No Sen were injected with amphetamine (experiments A–A and M–A) or morphine (experiments M–M and A–M) and immediately placed in the white chamber of the black-white shuttlebox for 25 min. The rats in Group Base received exposures to the white chamber without the drug. In experiment A–A, saline was injected instead of the drug prior to the rat's placement in the white chamber. In the remaining three experiments, each rat in Group Base was injected with the drug but not until at least 30 min after its removal from the white chamber.

In each experiment, the rats were also habituated to the black chamber to minimize any neophobic tendencies during the CPP test. On these occasions, the rat was simply confined to the black chamber for 25 min; no sacharin solution or injections were administered.

In experiments A–A and A–M, the rats were exposed to the white chamber on three occasions spaced 2 days apart and to the black chamber on the 2 intervening days. In experiment M–M, one exposure each to the white and black chambers was given. In experiment M–A, there were two training trials in white and two in the black chamber. The minor differences in procedure were due in part to the exploratory nature of these experiments and the constraints of the laboratory schedule. Another consideration was to arrange conditions (i.e., dosage and/or number of place-drug pairings) that would result in a low level of CPP in Group No Sen so as to make sensitization easy to detect in Group Sen. Table 2 shows a summary of the main procedural details of these experiments.

Several days after the last place-drug pairing, each rat was given free access to both chambers for 10 min. At the start of the test, the rat was placed in the white chamber with its head pointing away from the black chamber. The rat was considered to be in the white chamber until all four of its feet were in the black chamber. Then it was considered to be in the black chamber until all four feet were in the white chamber and so on. The amount of time spent in the white chamber was measured.

Experiments C–C and M–C. In each experiment, 30 rats were assigned in equal numbers to the three groups shown in Table 1; however, one rat from Group Base in experiment M–C died before the experiment was completed. In both experiments, the rats had free access to food and water in the home cage. During phase 1, as in the preceding experiments, Group Sen and half of Group-Base were injected with the drug while Group No Sen and the remainder of

Table 2. Summary of the main procedural details of phases 1 and 2 in experiments A–A, M–M, A–M, M–A, C–C, and M–C. The first letter tells which drug, amphetamine (A), morphine (M), or cocaine (C), was injected during phase 1 to produce sensitization; the second letter tells which drug was used to produce CPP in phase 2

	Experiment					
	A–A	M–M	A–M	M–A	C–C	M–C
Phase 1						
Number of injections	6	5	6	6	10	8
Dose injected (mg/kg)	1.5	5.0	1.5	5.0	20.0	5.0
Phase 2						
Number of CPP pairings	3	1	3	2	3	3
Dose (mg/kg)	1.5	5.0	1.0	1.5	2.5	2.5

Group Base received equivalent injections of saline. As shown in Table 2, ten injections of cocaine were administered during phase 1 in experiment C–C and there were eight injections of morphine in experiment M–C. These were spaced 24–72 h apart.

During phase 2, Groups Sen and No Sen were given CPP training similar to that administered in the preceding experiments. On three occasions spaced 48 h apart, these rats were injected with cocaine, then immediately placed in the white chamber of the shuttlebox, and confined there for 15 min in experiment C–C or for 30 min in experiment M–C. Group Base received unpaired exposures to the white chamber and cocaine. At least 30 min separated removal from the white chamber and the injection of cocaine. As in the preceding experiments, each rat was also habituated to the black chamber. On the 2 days intervening between the 3 training days, the rats were simply placed in the black chamber for 15 min in experiment C–C or for 30 min in experiment M–C.

Several days after the last place-drug pairing, the rats were tested in the manner described above. As before, the amount of time spent in the white chamber was measured during a 10-min test.

Data analysis. In all experiments, statistical reliability was assessed by means of planned comparisons based on the *t*-test. Sensitization of the central reward system produced by repeated drug exposures during phase 1 was inferred from a particular pattern of results: Group Sen should spend more time in the drug-paired, white chamber during the test than either Group Base or Group No Sen. The first difference would indicate that Group Sen showed CPP while the second would indicate that Group Sen showed stronger CPP than Group No Sen. Group No Sen was not required to show CPP, since the procedures were generally set to ensure a low level of conditioning in that group so as to maximize the probability of detecting sensitization in Group Sen. The reported *P* values are two-tailed.

Results

Table 3 shows the percentage of time spent in the drug-paired chamber by each group during the CPP test in each of the six experiments. Although the details of the procedures differed somewhat, the same pattern of results was found in each experiment. Group Sen spent reliably more time in the drug-paired chamber than did Group No Sen ($t(18)=3.73$, $P<0.01$ in experiment A–A; $t(18)=6.38$, $P<0.001$ in experiment M–M; $t(20)=6.58$, $P<0.001$ in experiment A–M; $t(18)=3.07$, $P<0.01$ in experiment M–A; $t(18)=6.73$, $P<0.001$ in experiment C–C; $t(18)=3.06$, $P<0.01$ in experiment M–C). In every experiment, Group Sen also showed reliable CPP relative to Group Base ($P<0.01$ in experiment M–C; $Ps<0.001$ in all other experiments). These findings indicate that sensitization and cross-sensitization were obtained.

Group No Sen showed reliable CPP in every experiment except experiment M–M ($Ps<0.001$ in experiments A–A, M–A, and C–C, $P<0.01$ in experiment M–C; $P<0.05$ in experiment A–M). The failure of Group No Sen to exhibit CPP in experiment M–M is probably attributable to the use of only one CPP pairing.

Table 3. Percentage of time spent in the drug-paired chamber by each group during the CPP test in experiments A–A, M–M, C–C, M–A, A–M, and M–C. The first letter tells whether amphetamine (A), morphine (M), or cocaine (C) was used to sensitize; the second letter indicates whether A, M, or C was used to produce CPP. SEMs are given in parentheses

Experiment	Group Sen % Time (SEM)	Group No Sen % Time (SEM)	Group Base % Time (SEM)
A–A	58.4 (1.3)	48.3 (2.3)	22.3 (1.3)
M–M	57.3 (1.8)	39.4 (2.1)	37.9 (2.4)
C–C	59.2 (2.0)	41.6 (1.7)	30.1 (3.2)
M–A	58.1 (2.1)	49.1 (2.0)	35.6 (2.5)
A–M	63.8 (2.6)	45.6 (0.8)	40.2 (2.4)
M–C	52.1 (3.2)	41.4 (1.4)	33.5 (3.6)

Discussion

Proponents of the withdrawal theory (e.g., Wikler 1973) assume that repeated drug exposures not only attenuate the rewarding effect but, more importantly, they also produce physical dependence. Once physical dependence develops, the absence of the drug is assumed to result in an aversive withdrawal syndrome that can be alleviated or prevented by an administration of the drug. After tolerance to the drug-induced rewarding effect occurs, administrations of the drug were presumed to be rewarding mainly because they alleviate or prevent the distress of withdrawal.

The present findings are difficult for the withdrawal theory to explain. It would have to be assumed that the five to ten low-dosage drug exposures given prior to CPP training in the present experiments produced some degree of physical dependence while producing little tolerance to the rewarding effect. Then it could be argued that the observed enhancement of CPP was due to an increase in the total amount of reward produced by each drug injection that results from adding the reward value of alleviating withdrawal symptoms to that of the drug itself. Even so, this explanation would still be incomplete, since there is no cross-dependence between amphetamine and morphine or between morphine and cocaine (Wise and Bozarth 1987). That is, amphetamine would not alleviate the symptoms produced by withdrawal from morphine or vice versa; neither would cocaine alleviate the symptoms produced by withdrawal from morphine. Hence, no alleviation of withdrawal symptoms should have been possible in experiments A–M, M–A, and M–C in which pretraining exposures to one drug enhanced the CPP induced by a different drug.

In contrast to this lack of an empirical or theoretical basis for cross-dependence (Wise and Bozarth 1987), there are reasons for expecting cross-sensitization to the rewarding effect. First, cross-sensitization to the activating effect occurs between amphetamine and morphine (Stewart and Vezina 1987) and also between amphetamine and enkephalin (Kalivas 1985). More importantly, as noted earlier, there is a substantial body of evidence (e.g., Wise 1978; Wise and Bozarth 1987) that a common neural mechanism mediates the rewarding effect of amphetamine, morphine, and cocaine. Thus, the present findings provide strong evidence that repeated drug exposures produce sensitization to the rewarding effect.

Other evidence for sensitization to the rewarding effect has been obtained in rhesus monkeys that were trained to press a lever to obtain an intravenous infusion of metham-

phetamine (Woolverton et al. 1984). A low dose of methamphetamine with minimal motoric side-effects supported lever pressing after, but not before, chronic exposures were given. Thus, chronic exposures lowered the threshold dose of methamphetamine that maintained lever pressing. This reduction in threshold cannot reasonably be attributed to tolerance to the aversive effect, since the monkeys had received extensive exposures to the drug prior to the first determination of threshold. Neither is it readily attributable to an alleviation of withdrawal symptoms, since the monkeys were tested after a lengthy period of abstinence. Hence, this finding, like those of the present experiments, shows that repeated drug exposures produce sensitization to the rewarding effect.

Evidence from human addicts suggests, however, that tolerance to the rewarding effect does occur (e.g., Haertzen and Hooks 1969) although such tolerance may be far from complete after many years of heavy drug use (McAuliffe and Gordon 1974). The discrepancy between the present findings of sensitization in rats and those indicating tolerance in human addicts is not readily attributable to a species difference, since there is evidence, as discussed above, that sensitization also occurs in rhesus monkeys (Woolverton et al. 1984). Another explanation is that sensitization to the rewarding effect develops more rapidly than tolerance. That is, the predominant effect of initial drug exposures is sensitization, but eventually, after many exposures, tolerance becomes predominant. This implies that sensitization may be more important in the causing of an addiction than in the maintenance of an already established one.

Sensitization could be important in explaining addiction to the extent that it continues past the relatively few exposures given in the present experiments and also persists for a substantial length of time. There is evidence, both direct and indirect, that sensitization to the rewarding effect continues to increase with many more than the five to ten exposures given in the present experiments and also that it is a long lasting effect. The less direct evidence is that sensitization to the activating effect has been shown to increase progressively over many more drug exposures than those given in the present experiments and to be a long lasting effect (Robinson and Becker 1986). More direct evidence can be obtained from the experiment by Woolverton et al. (1984) described above, in which rhesus monkeys showed sensitization to the rewarding effect of methamphetamine even though the sensitizing exposures were not given until the monkeys had had extensive experience with the drug. The monkey were first trained to press a lever for an intravenous injection of methamphetamine. Then over several sessions, they were trained to respond on a fixed-ratio 30 schedule. After stabilization of fixed-ratio performance, dose response relationships were determined; next, the effect of methamphetamine on food-maintained responding was studied. Then the monkeys were chronically exposed to high doses of methamphetamine for 14 days. Before the effect of the chronic drug treatment was tested, the monkeys were allowed a minimum of 1 month to recover their normal body weights. The finding of sensitization under these conditions indicates that sensitization to the rewarding effect continues to increase with many more exposures than the first few. Also, it shows that sensitization to the rewarding effect, like that to the excitatory effect, is long lasting, since a month or more of abstinence intervened between the sensitizing exposures and the test.

A detailed theory of addiction would require an examination of how sensitization of the central reward mechanism would amplify the conditioned and unconditioned incentive properties of drugs (Stewart et al. 1984). This is beyond the scope of the present paper. As a beginning, however, the present proposal is as follows. With repeated exposures, the probability of addiction increases because drug taking produces a progressively greater reinforcing effect each time it occurs.

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