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Reciprocal cross-sensitization between amphetamine and salt appetite

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Abstract

Previous work in our laboratory has demonstrated a potentiation of the psychomotor effects of amphetamine in animals with a history of sodium depletion, a process referred to as cross-sensitization. The present studies were done to further develop this finding by assessing multiple effects of amphetamine in rats with and without a history of sodium depletion. For Experiments 1–3, rats were depleted of sodium twice then subjected to one of three experimental procedures [open-field activity, conditioned place preference (CPP) and conditioned taste aversion (CTA)]. A history of depletion produced an elevation in the psychomotor effects of amphetamine. CPP, used to assess the rewarding properties of amphetamine, developed in rats with a history of depletion but not in controls. The aversive component of amphetamine as measured by CTA was unaffected by previous experience with sodium depletion. Finally, acute salt appetite after depletion was assessed in rats exposed to a sensitizing regimen of amphetamine. Animals with a drug history demonstrated a significant elevation in NaCl solution intake after depletion in comparison to controls. Together, the data provide strong evidence for the reciprocal cross-sensitization of salt appetite and response to amphetamine.

Keywords: Cross-sensitization; Amphetamine; Salt appetite; Conditioned place preference

1. Introduction

Sensitization is defined as an enduring increase in the response to drugs as a consequence of repeated exposure (Stewart and Badiani, 1993). In the case of psychostimulants, such as cocaine and amphetamine, sensitization is characterized by progressive increases in the locomotor response with repeated drug administrations. Behavioral sensitization appears to result, at least in part, from experience-induced plasticity in brain regions thought to be important in mediating motivation for drugs of abuse and natural rewards—the mesolimbic dopamine system. For example, repeated treatment with amphetamine has been found to lead to modifications in the dendritic arbors of medium spiny neurons in the nucleus accumbens (Robinson and Kolb, 1997).

To address whether similar changes in dendritic morphology occur after repeated exposures to a natural challenge, induction of a salt appetite was used as a model system (Roitman et al., 2002). Sodium depletion is a strong homeostatic challenge that is ultimately balanced by the ingestion of salt. Rats depleted of sodium display a strong salt appetite. Concentrated NaCl solutions that are otherwise avoided are eagerly sought and ingested by depleted animals. There is also evidence of sensitization of salt appetite in that rats respond more strongly to depletion if they have had previous experience (Sakai et al., 1987). Roitman et al. found morphological alterations in nucleus accumbens (e.g., increases in dendritic length and branching) in animals with a history of sodium depletions. These changes were strikingly similar to those that had previously been described after sensitizing treatment with amphetamine.

The general issue of comparing effects of drug and natural challenges on neural and behavioral outcome measures is compelling for a number of reasons. For one, it is presumed that the neural systems that are targeted by drugs of abuse did not evolve to mediate drug effects. Rather, drugs are thought to exploit circuitry involved in mediating responses to natural stimuli necessary for survival (Kelley and Berridge, 2002). Secondly, it is important to understand the degree to which prior experience with homeostatic challenges, such as food deprivation (Cabib et al., 2000) or sodium depletion, might alter an individual's response to drugs of abuse.

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Cross-sensitization, the process whereby one type of treatment may potentiate the response to another, has been demonstrated not only between classes of drugs (Robinson and Berridge, 1993) but also between drugs of abuse and natural rewards (Fiorino and Phillips, 1999; Nocjar and Panksepp,2002; Vitale et al., 2003). Based on these observations and the similar morphological alterations (Robinson and Kolb, 1997; Roitman et al., 2002), it was predicted that a history of sodium depletion might produce cross-sensitization to the locomotor activational effects of amphetamine. Indeed, a history of sodium depletion produced an increase in some of the activating effects of amphetamine. The present experiments expand upon this initial observation.

The first experiment replicated Roitman et al.'s (2002) observation that rats with a history of sodium depletion show significant sensitization to the psychomotor activating effects of amphetamine. In that study, sensitization was seen with rearing after amphetamine but not with horizontal locomotion. To confirm that finding and assess whether the dissociation between effects on rearing and locomotion was limited to the single dose tested, two challenge doses were tested.

Amphetamine sensitization can be expressed not only by an increase in its activating effects but also by its rewarding effects. Therefore, the second experiment examined whether a history of sodium depletion sensitizes rats to the rewarding effects of amphetamine using a conditioned place preference (CPP) paradigm to address this (Tzschentke, 1998). Drugs of abuse, such as amphetamine, have aversive as well as rewarding effects. For example, amphetamine can support a conditioned taste aversion (CTA) when paired with tastants, such as saccharin (Hunt and Amit, 1987). The third experiment used a CTA paradigm to ask whether the sensitization to amphetamine, produced by a history of sodium depletion, increases the aversive as well as rewarding effects of the drug.

The final experiment addressed whether effects of drug and depletion treatments were reciprocal. In other words, rats subjected to a sensitizing regimen with amphetamine were assessed to determine whether they would display a stronger (sensitized) salt appetite than those without prior amphetamine exposure.

2. Methods

2.1. General

For all experiments, male Long–Evans rats weighing between 300 and 350 g were housed individually on a 12-h light/dark cycle. Prior to the start of experiments, animals were maintained with access to water and Teklad Rodent Chow (Madison, WI) ad libitum. Animals were then split into two groups, history (depleted) and no history (sham). To induce salt appetite, animals in the history group were depleted of sodium using a procedure modified from Wolf (1982). Food and water were removed from all cages. Depletion treatment consisted of an injection of the diuretic/natriuretic Furosemide (10 mg/kg sc), while controls were injected with an identical volume of isotonic saline. To confirm diuresis, animals were weighed before and 3 h after injection to assess weight loss. Depleted animals were then given sodium deficient chow (ICN Nutritional Biochemicals, Cleveland, OH) and distilled water while standard chow and water were returned to control animals. Twenty-four hours later, food and water were removed from all cages and animals were offered a 3% NaCl solution for 1 h. Standard chow and water were returned to all animals after testing. The depletion procedure and testing were repeated 1 week later. All procedures were done in accordance with Institutional Animal Care and Use Committee standards at the University of Washington.

2.2. Experiment 1: amphetamine induced locomotor activation in animals with and without a history of sodium depletions

Twenty-four male Long–Evans rats, history ($n=12$) and no history ($n=12$), were given two depletion or sham treatments according to the methods described above. One week after the second depletion, all animals received two habituation sessions (30 min each) to a novel, open field (Truscan photobeam chamber $40.6 \times 40.6 \times 40.6$ cm, Coulbourn Instruments, Allentown, PA). One day later, all animals were tested for psychomotor activation by amphetamine in the same open field. Animals were placed in the chamber for a 30-min baseline activity period, removed, injected with amphetamine (D-amphetamine sulfate; Sigma, St. Louis, MO), and then returned to the chamber for 30 min. Half of the animals were injected with 1 mg/kg ip and half were injected with 2 mg/kg ip. Activity during the 1-h test period was monitored by photobeams mounted on the walls of the chamber. Briefly, x–y coordinates were obtained at a sample rate of 1/s by two rings of photobeams. Coordinates obtained by the ring in the horizontal plane were used to calculate distance traveled. Coordinates obtained in the vertical plane (ring placed 17.8 cm above the floor) were used to calculate discrete rearing events. The final 10 min of the preinjection period was used as a baseline and the subsequent 30-min test was divided into 3- to 10-min bins for analysis.

A mixed-factor ANOVA was used to compare within-group differences from baseline and to analyze overall between-group differences. t Tests were used to compare between-group differences at appropriate time points.

2.3. Experiment 2: amphetamine induced CPP in animals with and without a history of sodium depletions

Twenty-four male Long–Evans rats, history ($n=12$) and no history ($n=12$), were given two depletion or sham

treatments. One week after the second depletion, animals began CPP training using a procedure developed by Cunningham et al. (1999, 2000) and Bormann and Cunningham (1997). Place conditioning boxes were made of black acrylic (51 × 20 × 30 cm). The floors were composed of interchangeable halves of two types, grid and hole. The "grid" floor consisted of 2.3-mm stainless steel rods mounted 13 mm apart in an acrylic frame. The "hole" floor was made of perforated stainless steel with 13-mm round holes on 19-mm staggered centers. Type of flooring served as the CS+ and CS − for conditioning. Training and testing consisted of three phases: pretest, conditioning and posttest. On Day 1, animals were placed in the conditioning boxes with both floor types in place. This 20-min pretest was videotaped and scored to assess each animal's initial floor preference. Animals displaying an initial preference of greater than 65% were dropped from further study ($n = 4$). For the next 6 days, animals were exposed to a differential Pavlovian conditioning procedure consisting of three 30-min CS+ pairings and three 30-min CS − pairings. For each animal, the CS+ (flooring paired with amphetamine) was its initially less preferred type. CS+ pairings and CS − pairings were alternated and order of presentation was counterbalanced within conditioning groups. During conditioning, animals had access to the entire box with both halves of the floor being either hole or grid. Initial pilot work with this training protocol indicated that a significant CPP developed with 1.0 mg/kg in control animals; after CPP training, animals spent 63% of their time on the CS+ (amphetamine-paired) side relative to 47% in saline-treated controls. A lower dose was used in the present experiment to determine whether cross-sensitization could yield a significant CPP at a dose which was marginal in animals without a depletion history. Animals received D-amphetamine sulfate (0.5 mg/kg ip) paired with CS+ flooring and saline paired with CS − flooring. Saline controls received saline paired with both floor types. On Day 8, animals were placed in the boxes with both CS+ and CS − flooring types for a 20-min drug-free posttest. This session was videotaped and scored to assess time spent on each side. Change in the amount of time spent on the CS+ flooring from pre- to posttest was the measure of CPP.

All data were analyzed with planned contrasts of pretest and posttest times on the CS+ flooring for each group (history–amphetamine, no history–amphetamine and saline).

2.4. Experiment 3: amphetamine induced CTA in animals with and without a history of sodium depletions

Twenty-four male Long–Evans rats, history ($n = 12$) and no history ($n = 12$), received two depletion or sham treatments. One week after the second depletion, rats began water restriction training with access to water for 30 min in the morning (8:30–9:00 a.m.) and again in the afternoon (1:00–1:30 p.m.). Those with and without a history of depletion were then assigned to matched conditioning and control groups that received saccharin paired with amphetamine or saline. The conditioning procedure consisted of allowing animals access to saccharin (0.15%) for 30 min and then injecting them with either D-amphetamine sulfate (0.5 mg/kg ip) or saline. Three daily conditioning trials were run, with saccharin intake measured. One day after the last conditioning trial, animals received two-bottle testing with water and saccharin. Preference scores were calculated by dividing the amount of saccharin consumed by the total amount of fluid consumed (water + saccharin) during the 30-min test.

Data were analyzed with ANOVA and Tukey's post hoc comparisons.

2.5. Experiment 4: NaCl intake after acute depletion in animals with and without a history of amphetamine exposure

Twelve male Long–Evans rats received daily injections of amphetamine, treatment group ($n = 6$), or saline, sham group ($n = 6$). Rats were given 1 mg/kg amphetamine ip for 5 days and then, 1 week later, they were given 2 mg/kg amphetamine ip for an additional 5 days. One week after the final injection, animals were depleted of sodium and tested for salt appetite in accordance with the methods described above.

Independent samples t tests were used to compare mean NaCl intake between groups.

3. Results

3.1. Experiment 1: sodium depletion cross-sensitizes locomotor activity after acute amphetamine challenge

Animals in both groups showed a significant elevation relative to baseline in number of rears and distance traveled after either 2 or 1 mg/kg amphetamine. The number of rears in animals with a history of sodium depletions was significantly elevated above controls at the higher dose. Psychomotor activation (distance traveled and rearing) after amphetamine in rats with and without a history of sodium depletions is depicted in Figs. 1 and 2. Effects of the high dose (2 mg/kg; Fig. 1) show elevations above baseline in distance traveled but no significant group difference. Mixed-factor ANOVA revealed a significant increase in distance traveled relative to baseline [$F(3,27) = 53.96$, $P < .001$]. Rearing also significantly increased relative to baseline [$F(3,27) = 16.04$, $P < .001$]. In addition, there was a significant repeated Factor × Group interaction [$F(3,27) = 4.13$, $P < .05$]. Direct comparison revealed a significant elevation in number of rears for depleted animals relative to controls at 10 min postinjection [$t(9) = 2.87$, $P = .019$]. These results replicate previous

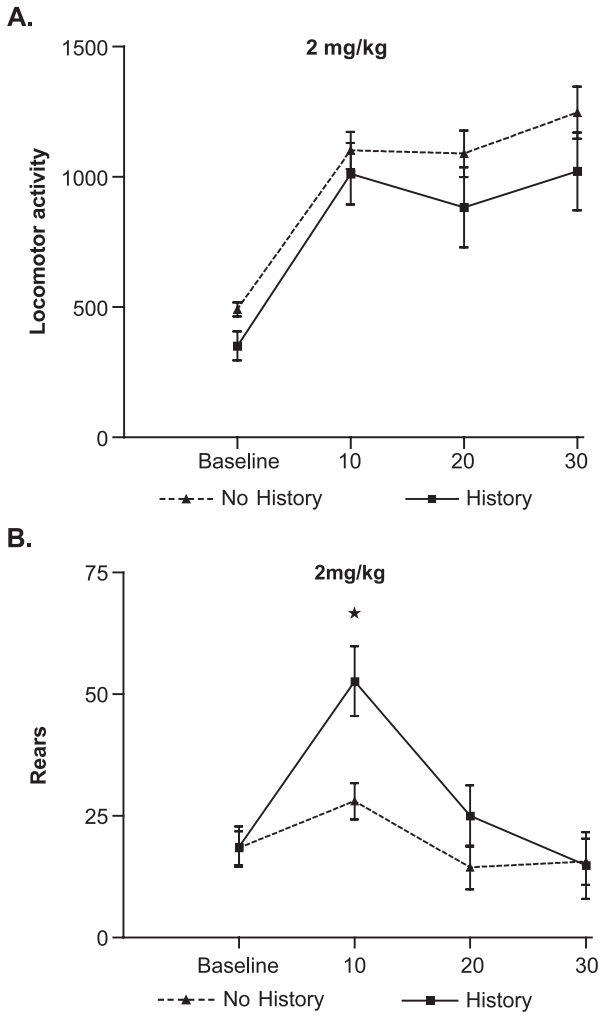

Fig. 1. Activity in the open-field chamber during the initial 10-min period (baseline) and each subsequent 10-min period postinjection with 2 mg/kg amphetamine. Mean distance traveled ± S.E.M. (A). Mean number of rears ± S.E.M. (B). * $P < .05$ history vs. no history at the first time point postinjection.

published work from this laboratory and provide further support for a potentiation of the psychostimulant effects of amphetamine in animals with a history of sodium depletion.

Effects of the low dose (1 mg/kg; Fig. 2) show elevations above baseline in distance traveled and rearing but no significant group differences. Mixed-factor ANOVA revealed a significant increase in distance traveled [$F(3, 30) = 99.70$, $P < .001$] and number of rears [$F(3,30) = 14.88$, $P < .001$] relative to baseline. No group differences in distance traveled or rears were found, although there appeared to be a trend toward more rearing in the history group at 20 and 30 min postdrug.

NaCl intake increased from 4.2 ml after the first depletion to 7.2 ml after the second depletion in depleted animals and from 0.6 to 1.8 ml in control animals. Paired sample t tests confirmed this difference to be significant in depleted [$t(11) = 4.45$, $P < .001$] but not in control animals. NaCl intake was significantly correlated with number of rears postinjection ($r = .45$, $P < .05$; $n = 22$) but not with distance traveled.

3.2. Experiment 2: amphetamine-induced CPP in animals with and without a history of sodium depletion

A low dose (0.5 mg/kg) of amphetamine yielded a significant place preference in animals with a history of sodium depletions that was not seen in controls. Mean pre- and posttest time on the CS+ flooring for the history group ($n = 6$), no-history group ($n = 6$) and the saline–saline group ($n = 8$) are shown in Fig. 3. Planned contrasts revealed a significant increase in time spent on the CS+ flooring only in the history group ($P < .05$). This dose of amphetamine is at the low end of a range of doses that produce place preferences and was chosen to avoid ceiling effects (Bardo et al., 1995). The finding that this dose (0.5 mg/kg) was able

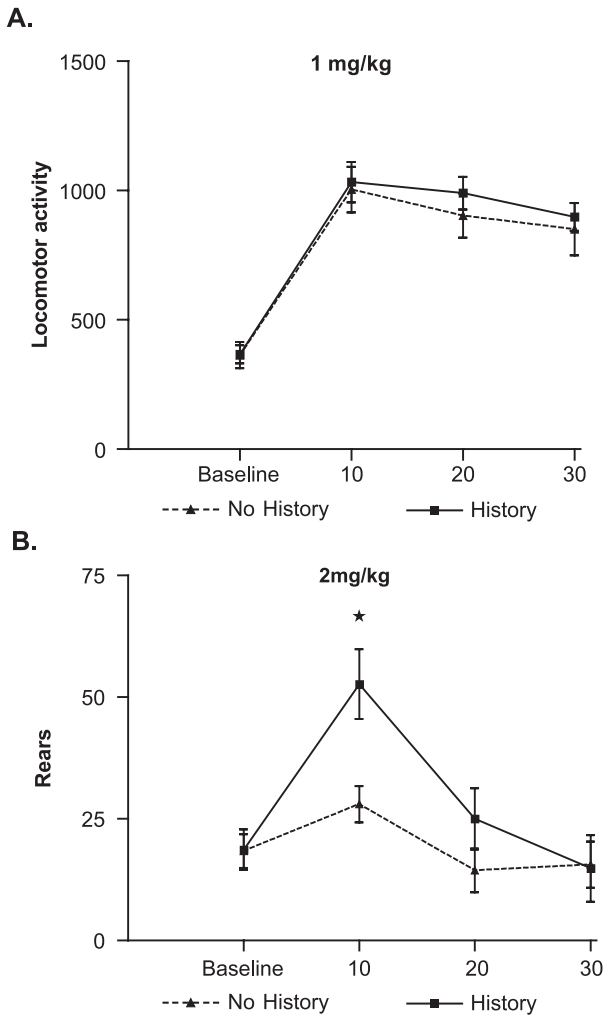

Fig. 2. Activity in the open-field chamber during the initial 10-min period (baseline) and each subsequent 10-min period postinjection with 1 mg/kg amphetamine. Mean distance traveled ± S.E.M. (A). Mean number of rears ± S.E.M. (B).

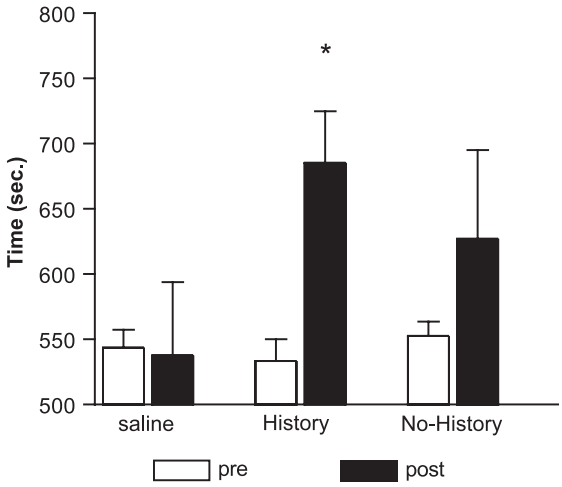

Fig. 3. Mean time ± S.E.M. spent on the CS+ flooring on the pre- and posttest for each group. * $P<.05$ pre- vs. posttime.

to support a place preference in animals with a history of sodium depletions but not in animals with no such history suggests that a history of sodium depletion enhances sensitivity to the rewarding effects of amphetamine.

NaCl intake increased from 6.5 ml after the first depletion to 8.4 ml after the second depletion in depleted animals and from 0.4 to 0.5 ml in control animals. Paired sample *t* tests confirmed this difference to be significant in depleted [$t(9)=2.35$, $P<.05$] but not in control animals. Additionally, NaCl intake was correlated with preference for CS+ side ($r=.41$, $P<.05$; $n=20$).

3.3. Experiment 3: sodium depletion fails to sensitize an amphetamine-induced CTA

Amphetamine treatment produced a significant CTA in both groups, but did not affect them differentially. Mean intake for each group across trials is shown in Fig. 4A. Mean preference scores from the two-bottle test are shown in Fig. 4B. ANOVA revealed a significant difference between groups [$F(3,22)=5.94$, $P<.01$]. Post hoc comparisons revealed a lower preference score for amphetamine groups than saline groups (history $P<.01$, no history $P<.01$), indicating significant CTAs for both groups receiving amphetamine. However, there were no differences between the history and no-history conditions. In contrast to the influence of depletion history on amphetamine reward as measured by CPP, there was no effect of the treatment on amphetamine CTA. This is particularly striking given that the dose and number of exposures were identical in both experiments.

NaCl intake increased from 5.9 ml after the first depletion to 8.2 ml after the second depletion in depleted animals and from 1.2 to 2.2 ml in control animals. Paired sample *t* tests confirmed this difference to be significant in depleted [$t(10)=3.45$, $P<.01$] but not in control animals. NaCl intake was not correlated with preference scores.

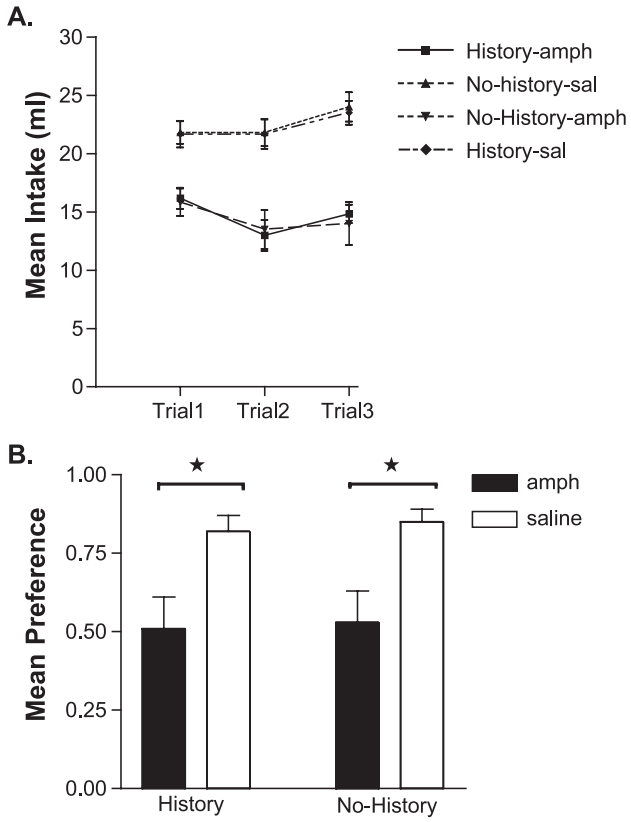

Fig. 4. Mean intake (ml) ± S.E.M. of 0.15% saccharin solution for each group across trials (A). Mean preference scores ± S.E.M. for all four groups on the two-bottle test (B). * $P<.05$ amphetamine vs. saline.

3.4. Experiment 4: amphetamine treatments cross-sensitize salt appetite

Intake of 3% NaCl solution in sodium-depleted animals was elevated by prior amphetamine experience. Mean intake of NaCl solution after depletion for the history and control groups is shown in Fig. 5. Intake in animals with a history of amphetamine exposure was double that of control animals. Independent samples *t* test confirmed this difference to be statistically significant [$t(10)=3.09$, $P=.011$].

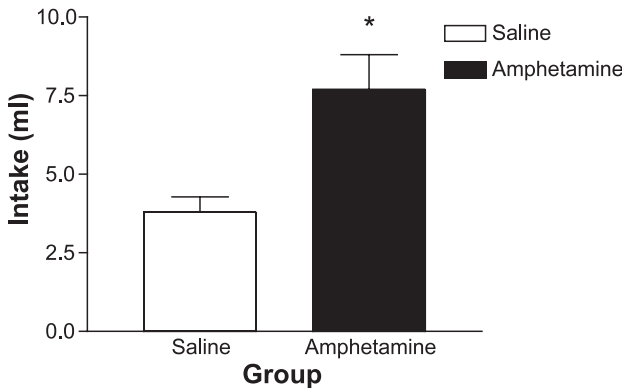

Fig. 5. Mean intake of 3% NaCl solution (± S.E.M.) in amphetamine and saline pretreated animals. * $P<.05$ amphetamine vs. saline group.

Previous research has demonstrated the sensitization of salt appetite in animals with prior depletion experience (Sakai et al., 1987). This finding was confirmed in Experiments 1–3, with intake of NaCl solution increasing by almost 50% from the first to the second depletion. Interestingly, the average intake after the second depletion in Experiments 1–3 was 7.9 ml, which is quite similar to the 7.7 ml consumed after the first depletion in animals with a history of amphetamine exposure. Thus, prior experience with amphetamine potentiated the acute salt appetite induced by sodium depletion, suggesting reciprocal cross-sensitization between the two treatments, amphetamine and sodium depletion.

4. Discussion

The present studies examined cross-sensitization between drug and natural challenges. The provocation of a salt appetite, followed by ingestion of NaCl, was used as a model of a strong, natural motivational state. Prior work in this laboratory had shown that this challenge led to alterations in neural and behavioral outcome measures (alterations in dendritic morphology in nucleus accumbens; sensitization to the stimulant effects of amphetamine) that were very similar to those seen after sensitization to amphetamine (Roitman et al., 2002). The findings presented here replicate the prior behavioral work and extend it. Prior experience with salt appetite led to cross-sensitization to the effects of amphetamine. This was manifested in significant elevations in psychostimulant effects of amphetamine and greater positive effects of a low dose of the drug, as manifested by a significant amphetamine-based CPP at a dose which was ineffective in controls. Aversive effects of amphetamine did not appear to be sensitized, as indicated by comparable conditioned aversions to a taste paired with amphetamine in animals with and without a history of sodium depletions. Finally, the cross-sensitizing effects of drug and depletion treatments appear to be reciprocal. When rats exposed to a sensitizing regimen of amphetamine were tested for salt appetite, they displayed a stronger appetite than animals without prior amphetamine experience.

In the first experiment, psychomotor stimulant effects of two doses of amphetamine were assessed in animals with and without a history of sodium depletions. Findings replicated our previous report that a history of sodium depletions significantly enhances the stimulant effects of amphetamine (2 mg/kg) on rearing but not horizontal movement. The inclusion of a lower dose (1 mg/kg) allowed us to assess whether the selective effect on rearing but not horizontal movements was due to a ceiling effect (on horizontal movements) at the higher dose. Administering a low dose did not eliminate the dissociation; marginal effects on rearing were seen in animals given the lower dose (P=.053 and P=.069 for group difference at the 20- and 30-min time points, respectively) and no effect at all on horizontal movements. Interestingly, most behavioral assessments of the stimulant effect of amphetamine find similar patterns for rearing and horizontal locomotion. Nonetheless, there is some evidence emerging that these two behavioral measures may involve different neural circuits and that rearing may be more dependent on dopamine–opioid interaction (Balcells-Olivero and Vezina, 1997). Furthermore, Muschamp and Siviy (2002) recently reported that repeated treatment with the CB_1 agonist WIN 55,212-2 produced cross-sensitization to amphetamine as measured by rearing but not locomotor activity so the pattern reported here is not without precedent. It remains to be determined whether this dissociation between rearing and locomotion qualitatively distinguishes different sensitization models and the mechanisms that underlie them.

In addition to sensitization of stimulant effects of amphetamine, drug exposure can sensitize animals to the rewarding effects of amphetamine, as measured by CPP (Lett, 1989; Shippenberg and Heidbreder, 1995). Indeed, in Experiment 2, animals with a history of sodium depletions demonstrated a significant CPP at a dose that did not support such learning in controls. This observation provides intriguing evidence that exposure to strong, natural motivational challenges can cross-sensitize individuals to the rewarding effects of a drug. Both the enhanced psychostimulant effects and rewarding effects of amphetamine in animals subjected to prior sodium depletions are similar to recent reports that an episode of food restriction and weight loss can produce enduring changes in the response to addictive drugs in at least one mouse strain (Cabib et al., 2000). We believe it is important to distinguish between these protocols and those which find alterations in drug response while animals are chronically food restricted (Carr, 2002). The distinction between studies which test animals when they are deprived and studies which test drug responses after the animals have been allowed sufficient time to recover from their physiological need (for energy or sodium) may be important with regard to underlying mechanism.

The behavioral and physiological response to amphetamine appears to be complex, and includes both positive and aversive components. While a CPP paradigm is a useful way to assess rewarding or positive effects, a CTA paradigm detects aversive or unpleasant effects of the drug (but see Grigson and Freet, 2000). If sensitization in effect increases the overall physiological effect of a given dose of drug, then one might predict that cross-sensitization would increase both the pleasant and aversive effects of amphetamine. Therefore, CTAs might be expected to be more severe in cross-sensitized animals. Results of Experiment 3 do not support this prediction. Rather, CTAs were virtually identical in groups with and without a history of sodium depletion when they received a series of conditioning trials in which saccharin was paired with 0.5 mg/kg amphetamine. That effects of depletion history are restricted to stimulant and rewarding effects of the drug is consistent with the notion that changes in the mesolimbic dopamine system, such as

the dendritic restructuring observed by Roitman et al. (2002), were responsible for these effects and that CTAs rely on amphetamine acting on some other pathway. This is perhaps not surprising, except that Grigson et al. have suggested that the paradoxical finding that "rewarding" drugs produce CTAs is not due to aversive effects. Rather she argues that CTAs are due to rewarding effects of drugs and that animals avoid tastes, like saccharin solution, in anticipation of the more rewarding drug (Grigson and Freet, 2000). Clearly, our data do not support this prediction. According to this view, the potentiation of the rewarding effects of the drug (demonstrated in Experiment 2) should have produced a stronger CTA in Experiment 3.

The final study demonstrated that cross-sensitization effects of amphetamine and sodium depletion are reciprocal, a prediction which would follow from the presumption that both treatments affect the same circuits in much the same way. In Experiment 4, rats were subjected to an amphetamine-sensitizing regimen and then tested for salt appetite after sodium depletion. The elevated salt intake is similar to that seen when salt appetite is sensitized by prior depletions, but in this case, animals were not subjected to sodium depletion challenges. Rather, we believe that the neural plasticity seen after amphetamine exposure (Robinson and Kolb, 1997) and salt appetite induction (Roitman et al., 2002) may underlie sensitization effects and our final experiment suggests that these effects are reciprocal.

One interpretation of the present findings is that neural systems, which respond to motivational challenges, whether those challenges involve the administration of addictive drugs or the imposition of a strong physiological need, overlap significantly. Furthermore, when subjected to frequent challenges, these common systems show persistent alterations that provide a mechanism for an enhanced behavioral response to subsequent exposure to such challenges.

An alternative explanation for these results is that sodium depletion acted as a nonspecific stressor. Cross-sensitization between acute stressors and psychostimulants is a well-established phenomenon (Marinelli and Piazza, 2002). At the present time, we favor the view that the critical feature of our depletion treatment is the imposition of strong homeostatic challenge. One reason for this is the finding that this sodium depletion protocol was not associated with elevated glucocorticoids (e.g., corticosterone; Roitman et al., 1999). Elevations in glucocorticoids are generally taken as an indicator of significant stress. However, we acknowledge that there is no complete agreement as to the defining features of significant stress and that additional work is clearly needed to identify the conditions that are both necessary and sufficient for this cross-sensitization effect.

Acknowledgements

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