Preexposure to, but Not Cotreatment with, the Neurotensin Antagonist SR 48692 Delays the Development of Cocaine Sensitization

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This study examined the role of neurotensin (NT) in the development of cocaine sensitization using the novel nonpeptide NT antagonist SR 48692. Male Sprague-Dawley rats received five daily administrations of SR 48692 (80 µg/kg, IP or PO) or vehicle. Following a 7 day drug-free period, cocaine-induced (15 mg/kg, IP) locomotor activity was assessed. Subsequent cocaine tests occurred every other day. No differences were observed between groups during the first day of cocaine testing. Sensitization to the locomotor activating effects of cocaine occurred rapidly in the controls reaching peak effects by the third cocaine challenge injection. By contrast, subjects preexposed to SR 48692 IP were delayed in the development of cocaine sensitization maintaining significantly lower cocaine-induced activity counts relative to controls until the sixth cocaine challenge injection. Preexposure to SR 48692 PO also produced an attenuating effect on the development of cocaine sensitization. The decreased cocaine-induced activity in

SR 48692-preexposed subjects did not appear to be the result of a locomotor deficit as SR 48692-preexposed subjects exhibited increased activity rates following a high dose (30 mg/kg, IP) cocaine challenge injection. In an additional experiment, the effect of cotreatment with SR 48692 on the development of cocaine sensitization was assessed. Subjects were cotreated with SR 48692 (80 µg/kg, IP) or vehicle 60 minutes prior to each of two cocaine (15 mg/kg, IP) or saline preexposure injections. Following a drug-free day, subjects were tested for cocaine-induced (15 mg/kg, IP) locomotor activation. SR 48692 cotreatment had no effect on the development of sensitization to cocaine. These data suggest that chronic preexposure to SR 48692 produces lasting effects rendering subjects resistant to the development of sensitization to the activating effects of cocaine. Further, these data provide direct evidence for a role of NT in the development of cocaine sensitization.
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Repeated exposure to a psychostimulant, such as cocaine, produces an augmentation of its behavioral activating effects (Tatum and Seevers 1929; Post and Rose

1976; Shuster et al. 1977). Behavioral sensitization is accompanied by an enhanced ability of cocaine to elevate extracellular levels of dopamine (DA) in the ventral striatum (VS) (Kalivas and Duffy 1990a). This hypersensitivity of midbrain DA systems has led some to propose behavioral sensitization as a model for amphetamine psychosis and schizophrenia (Robinson and Becker 1986; Robinson 1991; Sato et al. 1992).

Recently the tridecapeptide neurotensin (NT) has been postulated to have a role in stimulant-induced sensitization. NT administered into the ventral tegmental area (VTA) produces stimulant-like behavioral activating effects such as increased locomotor activity and rear-

ing (Kalivas et al. 1983; Cador et al. 1985; Elliot and Nemeroff 1986). In addition, intra-VTA infusions of NT increase extracellular levels of DA in the VS (Laitinen et al. 1990; Kalivas and Duffy 1990b). With repeated exposures, the locomotor activating effects of VTA-administered NT become augmented (Kalivas and Taylor 1985; Elliot and Nemeroff 1986; Kalivas and Duffy 1990b). This increase in NT's behavioral effects is accompanied by an enhanced ability of intra-VTA NT to elevate extracellular levels of DA in the VS (Kalivas and Duffy 1990b).

In vitro and in vivo electrophysiological studies have indicated that NT modulates mesencephalic DA cell firing (Seutin et al. 1989; Shi and Bunney 1990). When applied alone into the VTA, NT excited relatively few DA cells except at high currents. Yet, in a majority of these cells, NT attenuated quinpirole-induced autoreceptor inhibition (Shi and Bunney 1991). This effect could have been due to a neuromodulatory effect on D2 receptor binding as low nanomolar concentrations of NT have been shown to reduce the affinity of D2 receptors for agonists without affecting antagonist binding (Euler 1991; Euler et al. 1991).

The VTA has been implicated as a critical site in the development of behavioral sensitization to cocaine. Repeated injections of amphetamine into the VTA, but not the VS, produce a sensitized locomotor activating response to a subsequent systemic cocaine challenge (Kalivas and Weber 1987; Hooks et al. 1992). Recently, we have found that an acute systemic injection of cocaine results in an increase in NT-like immunoreactivity in samples recovered from the VTA using in vivo microdialysis (Roth et al. 1993). Thus, it is possible that NT in the VTA could have a role in the development of cocaine sensitization.

Recently, a selective NT receptor antagonist has become available (SR 48692). This nonpeptide bioavailable compound has been characterized as a potent and selective antagonist for the NT receptor that readily crosses the blood brain barrier (Gulley et al. 1993). A low dose of SR 48692 administered systemically has been shown to block the behavioral activating effects of centrally administered NT. Thus, SR 48692 has potential as a valuable pharmacological tool for investigating the actions of central NT. The present set of experiments uses SR 48692 to investigate the role of NT in the development of cocaine sensitization.

METHODS

Subjects

Male Sprague-Dawley rats purchased from CAMM (Wayne, NJ) at a weight of 225 g to 250 g were used as subjects for each experiment. The colony room was on a 12 hour light/dark schedule and temperature con-

trolled to 21°C. The animals were housed two per cage with free access to laboratory chow and water. All subjects were housed in the colony room for at least 5 days before beginning their respective procedures.

Drugs

SR 48692 (courtesy of Sanofi Recherche, Montpellier, France) was administered at a dose of 80 μg/kg either intraperitoneally (IP) or perorally (PO). This dose has previously been shown to block the activating effects of centrally-administered NT (Gulley et al. 1993). For IP injections, SR 48692 was solubilized in dimethyl sulfoxide (DMSO) by warming and diluted with deionized water. The final concentration of DMSO was 37% of the vehicle in an injection volume of 1 ml/kg. SR 48692 was administered PO via oral gavage in 0.5% methylcellulose (in deionized water) in an injection volume of 3 ml/kg. Cocaine HCl (Sigma, St. Louis, MO) was dissolved in physiological saline and administered in an injection volume of 1 ml/kg. All cocaine injections in Experiment I and Experiment II were administered IP at a dose of 15 mg/kg (salt weight). In Experiment III, cocaine-induced locomotor activity was assessed at a dosage of 30 mg/kg (salt weight).

Apparatus

Locomotor activity was measured using the automated Omnitech (Columbus, OH) Digiscan Micro-monitor system equipped with 16 photocells. Movement within the test cage produced interruptions of the photocell beams. The number of interruptions (activity counts) was recorded in 10 minute intervals. The same type of Plexiglass cage used to house the subjects in the colony room was used as the test cage. This kept conditioning cues between home cage cocaine injections (Experiment II) and testing for cocaine-induced locomotor activation relatively constant (see Post et al. 1981). Prior to each test session, the activity test cages were cleaned with 70% ethanol. The test cages were located inside a sound attenuated chamber equipped with a white noise generator. The testing chamber was illuminated with red light.

Experiment 1: Effects of SR 48692 Preexposure on the Development of Cocaine Sensitization

Subjects were preexposed to SR 48692 or vehicle daily for 5 days. SR 48692 or vehicle was administered either IP or PO in the home cage. Following the fifth SR 48692 or vehicle administration there was a 7-day drug-free interval. Subsequently, cocaine-induced locomotor activity testing began. On test days, the animals were placed in the activity monitor test cages for 60 minutes prior to cocaine administration and activity counts were

recorded. This procedure served to habituate subjects and to establish preinjection baseline activity levels. Following the baseline period, subjects were given a cocaine injection and tested for an additional 60 minutes. Cocaine-induced locomotor activity was assessed every other day.

Experiment 2: Effects of SR 48692 Cotreatment on the Development of Cocaine Sensitization

In contrast to the preexposure design of Experiment 1, subjects in the present experiment were cotreated with SR 48692 prior to each of two cocaine preexposure injections. Subjects received an IP injection of SR 48692 or vehicle 60 minutes prior to a cocaine or saline injection in the home cage. This procedure was repeated again following one drug-free day. The treatment groups formed were: (1) SR 48692/cocaine, (2) vehicle/cocaine, (3) SR 48692/saline, and (4) vehicle/saline.

Following an additional drug-free day all subjects were tested for cocaine-induced locomotor activation. Subsequent to a 60-minute baseline period, subjects were given a single cocaine injection and tested for cocaine-induced locomotor activity for an additional 60 minutes. Data from this procedure was equivalent to that obtained on cocaine challenge day 3 in Experiment 1.

In this procedure, cocaine-induced locomotor activity was assessed 48 hours after the last SR 48692 cotreatment injection. Whereas the effects of SR 48692 have been shown to be relatively long lasting (Gulley et al. 1993), pilot data indicated that SR 48692 (80 μg/kg, IP) pretreatment 1 hour prior to a cocaine injection (15 mg/kg, IP) does not affect cocaine's ability to produce locomotor activation (unpublished observations). Thus, if residual SR 48692 were present after 2 days, it should not have affected the assessment of cocaine-induced locomotor activation.
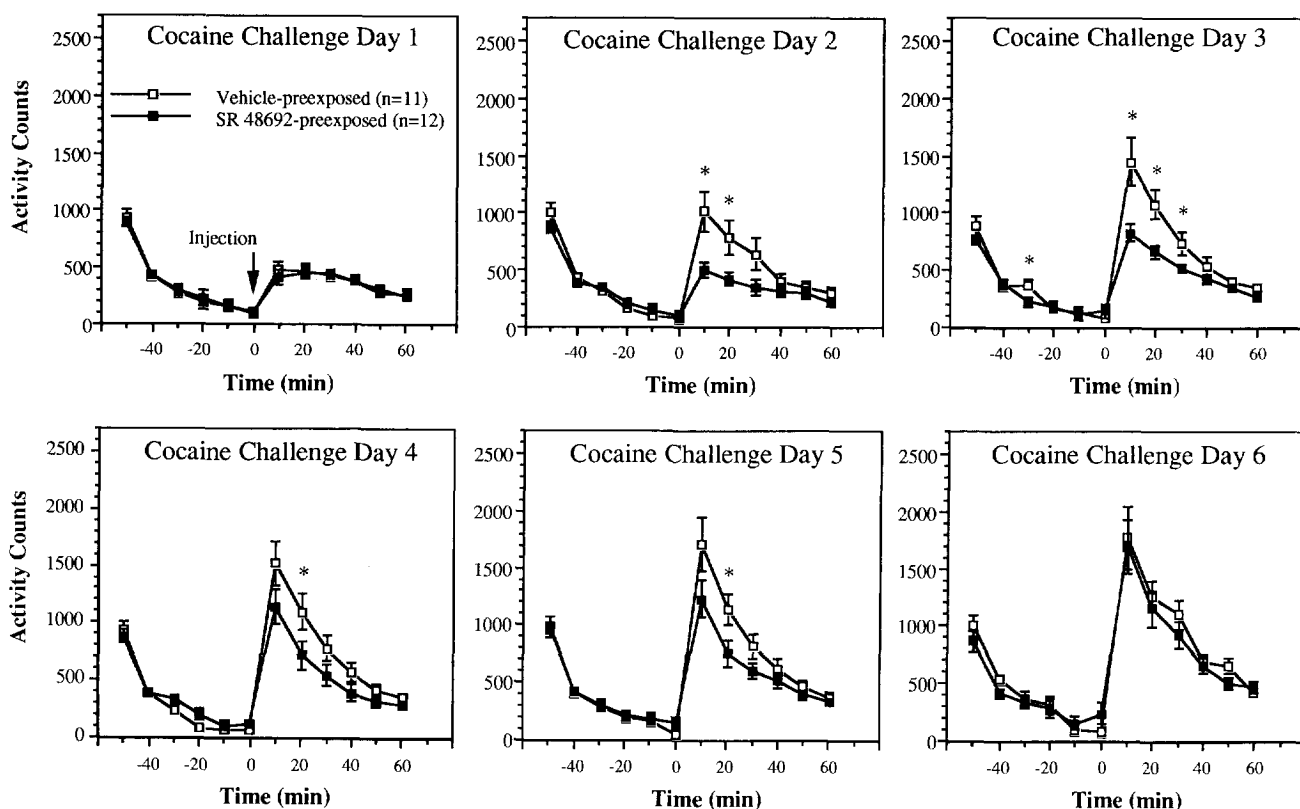
Figure 1. Intraperitoneal preexposure to SR 48692. Mean (± SEM) activity counts 60 minutes prior to and following each of six cocaine (15 mg/kg, IP) injections in subjects preexposed to SR 48692 (80 μg/kg, IP) or vehicle for 5 days. The first cocaine challenge was administered 7 days after the last SR 48692 or vehicle preexposure injection. Subsequent challenges were conducted every other day. Individual 2-way (Preexposure × Time) ANOVAs conducted on each cocaine challenge day revealed a significant interaction on cocaine challenge day 2 through day 5 [F(11,231) = 35.43, $p < .0001$; 5.21, $p < .0001$; 3.14, $p < .001$; 3.03, $p < .001$; respectively] and a significant effect of Preexposure on cocaine challenge day 3 [F(1,21) = 6.77, $p < .05$]. Significant differences as determined by Scheffe's posthoc analyses are indicated with an asterisk ($p < .05$). The number of subjects tested on each cocaine challenge were as indicated in the figure legend except cocaine challenge day 6 in which the number of subjects were 6 and 8 in vehicle-preexposed groups and SR 48692-preexposed groups, respectively.

Experiment 3: Ability of Subjects to Engage in High Rates of Locomotor Activity Following Preexposure to SR 48692

To assess the effects of repeated exposure to SR 48692 on high rates of activity, locomotor activity was assessed following a larger dose of cocaine. Subjects daily received five IP injections of SR 48692, or vehicle in the home cage as described in Experiment 1. Seven days after the last preexposure injection subjects were tested for cocaine-induced locomotor activity. Following a 60 minute baseline period, subjects received a cocaine (30 mg/kg, IP) injection. Locomotor activity was then recorded for an additional 60 minutes.

RESULTS

Experiment 1: Preexposure to SR 48692 Retards the Development of Cocaine Sensitization

Figure 1 depicts activity counts on each cocaine challenge day in subjects that had received IP preexposure injections of SR 48692 or vehicle. There were no sig-

nificant differences between vehicle-preexposed and SR 48692-preexposed subjects in activity counts produced by an acute cocaine exposure (cocaine challenge day 1). Following the second cocaine exposure, vehicle-preexposed controls exhibited a sensitized response relative to the SR 48692-preexposed subjects. Controls approached peak activating effects by cocaine challenge day 3. In contrast, activity counts in the SR 48692-preexposed subjects remained significantly lower until cocaine challenge day 6.

Similar effects were observed in subjects preexposed to SR 48692 via PO administration. As depicted in Figure 2, sensitization occurred more rapidly in the vehicle-preexposed controls relative to the SR 48692-preexposed (PO) subjects. However, the attenuating effect on the development of cocaine sensitization following PO preexposure to SR 48692 was not as robust relative to that produced by IP preexposure (Figure 1). Activity counts in the SR 48692-preexposed (PO) subjects were significantly reduced on cocaine challenge day 3 only.

To confirm that sensitization had indeed occurred in both SR 48692-preexposed and vehicle-preexposed
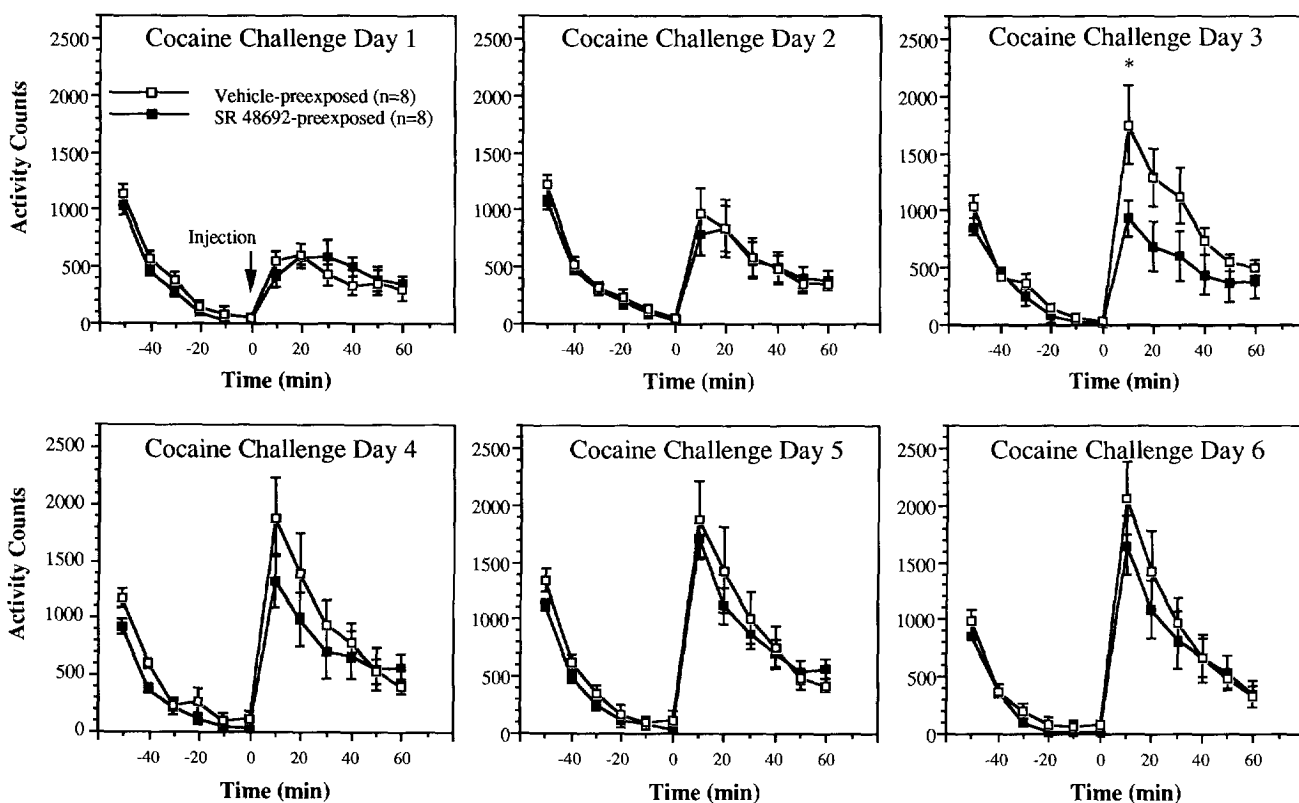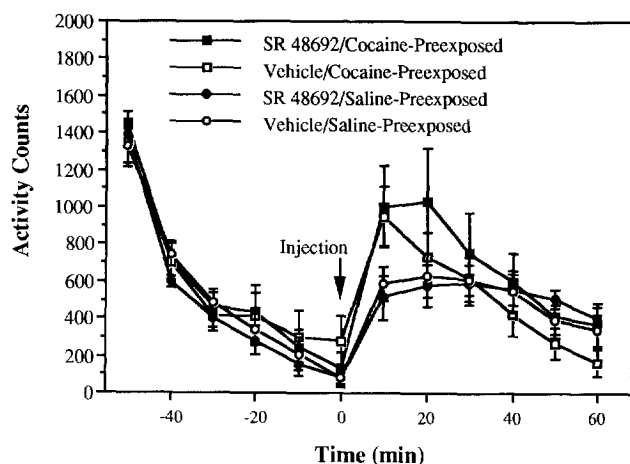

Figure 2. Peroral preexposure to SR 48692. Mean (± SEM) activity counts 60 minutes prior to and following each of six cocaine (15 mg/kg, IP) injections in subjects preexposed to SR 48692 (80 µg/kg, PO), or vehicle for 5 days. The first cocaine challenge was administered 7 days after the last SR 48692 or vehicle preexposure administration. Subsequent challenges were conducted every other day. Individual 2-way (Preexposure × Time) ANOVAs revealed a significant interaction on cocaine challenge day 3 [F(11,154) = 2.67, $p < .01$]. Significant differences as determined by Scheffe's posthoc analyses are indicated with an asterisk ($p < .05$).

groups by the sixth cocaine injection, activity counts on cocaine challenge day 1 and day 6 were compared. A 3-way (Preexposure × Challenge × Time) ANOVA of total activity counts postinjection revealed a significant effect of Challenge for both IP-preexposed subjects [F(1,20) = 28.15, $p < .0001$] and PO-preexposed [F(1,28) = 10.49, $p < .01$] subjects (data not shown). The lack of a significant Preexposure × Challenge interaction for both IP-preexposed groups and PO-preexposed groups suggested that SR 48692-preexposed subjects and vehicle-preexposed subjects were sensitized to a similar degree by cocaine challenge day 6.

Experiment 2: Cotreatment with SR 48692 Does Not Affect the Development of Cocaine Sensitization

Sensitization to the locomotor activating effects of cocaine developed regardless of whether the subjects were cotreated with SR 48692 or with vehicle. As depicted in Figure 3, cocaine-preexposed subjects (Vehicle/Cocaine and SR 48692/Cocaine groups) exhibited increased activity counts in the first 10 minute period after the cocaine challenge injection relative to the saline-preexposed controls (Vehicle/Saline and SR 48692/Saline groups). SR 48692 co-treatment did not alter activity
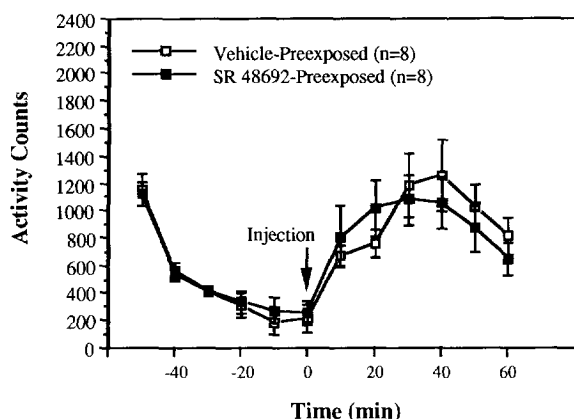
counts exhibited by subjects preexposed to cocaine or saline. Thus, cotreatment with SR 48692 60 minutes prior to cocaine preexposure injections did not attenuate the development of cocaine sensitization.

Experiment 3: Lack of a Locomotor Deficit Following Repeated Exposure to SR 48692

Both SR 48692-preexposed subjects and vehicle-preexposed subjects demonstrated high rates of activity counts following a 30 mg/kg cocaine injection. As depicted in Figure 4, no significant differences in activity counts were observed between groups. Notably, peak activating effects did not occur until 40 minutes postinjection. Most likely this was due to the induction of stereotypy during the peak effects of this high dose of cocaine, although subjects were not observed for stereotypy to confirm this. Nevertheless, locomotor activity did eventually exceed the sensitized rates of locomotor activity produced by vehicle-preexposed subjects on cocaine challenge day 2 and approached rates observed on day 3 (Figure 1).

DISCUSSION

Preexposure to the NT antagonist SR 48692 produced a significant delay in the development of sensitization to the locomotor activating effects of cocaine. In contrast, co-treatment with SR 48692 1 hour before two daily cocaine injections failed to produce an antagonistic effect on the development of cocaine sensitization. Thus, chronic exposure to SR 48692 followed by a

Figure 3. SR 48692 cotreatment. Mean (± SEM) activity counts 60 minutes before and after a cocaine (15 mg/kg, IP) injection. Subjects had received two cotreatment injections of either SR 48692 (80 μg/kg, IP) or vehicle 60 minutes prior to a cocaine (15 mg/kg, IP) or saline injection ($n = 8$ in each group). Cotreatment injections were administered in the home cage 2 and 4 days prior to testing for cocaine-induced locomotor activity. A 3-way (SR 48692 Preexposure × Cocaine Preexposure × Time) ANOVA revealed a significant interaction between the Cocaine Preexposure and Time variables only [F(11,308) = 2.94, $p < .001$] with no significant treatment effects. Analyses of simple main effects indicated that subjects preexposed to cocaine exhibited significantly higher activity counts above that of saline-preexposed subjects in the first 10 minute postinjection time point only ($p < .01$).

Figure 4. Thirty mg/kg cocaine challenge. Mean (± SEM) activity counts 60 minutes prior and subsequent to a high dose (30 mg/kg, IP) cocaine challenge injection in subjects preexposed to SR 48692 (80 μg/kg, IP) or vehicle for 5 days. Cocaine-induced locomotor activity was assessed 7 days after the last SR 48692, or vehicle preexposure injection. A 2-way (Preexposure × Time) ANOVA failed to indicate a significant interaction [F(11,154) = 0.70, NS] or Preexposure effect [F(1,14) = 0.01, NS].

1-week drug-free interval produced long lasting effects resulting in subjects being more resistant to the development of cocaine sensitization.

It is unlikely that SR 48692 preexposure interfered with the ability of the subjects to engage in locomotor activity. Chronic preexposure to SR 48692 did not interfere with the acute activating effects of cocaine as demonstrated by the lack of significant differences between groups on cocaine challenge day 1 (Figures 1 and 2). In addition, SR 48692-preexposed subjects eventually exhibited the same high rates of locomotor activity as that observed in the vehicle-preexposed controls. The possibility that chronic SR 48692 preexposure could have produced a transient locomotor deficit rendering the rats incapable of locomoting at high rates until after the third cocaine challenge injection (11 days post-preexposure) is unlikely. Subjects preexposed to SR 48692 and challenged with a high dose of cocaine demonstrated higher rates of activity counts with no significant differences relative to the vehicle-preexposed controls (Figure 4). Locomotor activity in the SR 48692-preexposed subjects exceeded the rates produced by the sensitized vehicle-preexposed subjects on cocaine challenge day 2 and approached rates observed on cocaine challenge day 3 (Figure 1). These data suggest that the reduced activating response of cocaine in the SR 48692-preexposed subjects (Figures 1 and 2) was not the result of a locomotor deficit. Rather, chronic exposure to SR 48692 appears to produce a relatively long-lasting attenuating effect specific to the development of cocaine sensitization.

The mechanism by which SR 48692 preexposure exerts its effects on the development of cocaine sensitization is unclear. Using in vivo microdialysis, we have observed increases in extracellular levels of NT in the VTA following an acute cocaine injection (Roth et al. 1993). The hypothesis that cocaine sensitization is dependent upon an elevation of extracellular NT in the VTA would predict that preexposure to SR 48692 attenuates the NT increases that occur with repeated cocaine administration. Future investigations will explore this as a possible mechanism by which SR 48692 preexposure antagonizes the development of behavioral sensitization to cocaine.

Preliminary data suggest that chronic exposure to SR 48692 increases NT mRNA receptor levels in the VTA (Bolden-Watson et al. 1993). An upregulation of NT receptors in the VTA would be expected to result in an augmentation of NT's neuromodulatory effects at this site. Although this may be predicted to produce a sensitized effect rather than a blockade of cocaine sensitization, we have only a fragmentary understanding of the mechanisms by which NT affects DA cell activity. It should be considered, for example, that different subtypes of NT receptors have been characterized (Schotte et al. 1986), the function of which remains unknown.

The selectivity of SR 48692 for these subtypes has yet to be determined. Whereas a majority of NT receptors in the VTA seem to be located on DA cells (Szigethy and Beaudet 1989), few of these receptors are proximal to NT containing axon terminals. Less than 10% of NT immunoreactive axons in the VTA are in direct apposition with tyrosine hydroxylase immunoreactive elements, whereas many appositions occur between NT-positive varicosities and nonlabeled elements (Woulfe and Beaudet 1989, 1992); thus, it is possible that SR 48692 is not selective for the NT receptor subtype(s) that has a direct neuromodulatory influence on DA cell function.

Although sensitization to the behavioral and neurochemical effects of cocaine has been increasingly characterized, the mechanisms responsible for its development have remained elusive. NT has been postulated to have a role in the development of sensitization due to the induction of stimulant-like behavioral sensitization upon repeated administration of NT into the VTA. The present data demonstrate that preexposure to SR 48692 attenuates the development of cocaine sensitization and provide compelling evidence for a role of NT in stimulant-induced sensitization.

The development of cocaine sensitization has been shown to be blocked by co-treatment with glutamate and dopamine receptor antagonists (Karler et al. 1989, 1990; Karler and Calder 1992; Wolf and Jeziorski 1993). In these studies, MK–801 or haloperidol were administered prior to each cocaine preexposure injection. SR 48692 appears to act uniquely in that administration does not have to immediately precede cocaine exposure. In fact, the attenuating effects of SR 48692 preexposure on the development of cocaine sensitization appear to be relatively long lasting.

Sensitization to the locomotor activating effects of cocaine can also be induced by preexposure to other stimulants or stress (Shuster et al. 1977; Sorg and Kalivas 1991). It would be of interest to determine whether preexposure to SR 48692 retards the development of sensitization induced by these procedures as well. Behavioral sensitization has been proposed as a model for schizophrenia and amphetamine psychosis (Robinson and Becker 1986; Robinson 1991; Sato et al. 1992). In this regard, identification of the mechanisms by which SR 48692 preexposure produces lasting attenuating effects on the development of cocaine sensitization may lead to increased understanding of the etiology of these disorders and aid in the development of rational therapeutic strategies for their treatment.

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