Intra-Accumbal Injection of CART (Cocaine-Amphetamine Regulated Transcript) Peptide Reduces Cocaine-Induced Locomotor Activity

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ABSTRACT
Evidence suggests that CART (cocaine-amphetamine regulated transcript) peptides are mediators or modulators of the actions of psychostimulant drugs. In this study, the effects of intra-accumbal injections of rat long form (rl) CART 55-102 were examined. Injection of the peptide alone had no effect, but pretreatment with the peptide blunted or reduced the locomotor-inducing effects of cocaine after an i.p. injection. This effect was dose related and time limited, as expected. rlCART 1-27, a CART peptide fragment not active in other studies, was without effect on cocaine-induced locomotor activity. Because the actions of cocaine involve dopamine, the effect of rlCART 55-102 on dopamine-induced locomotor activity was examined. Intra-accumbal injection of dopamine produced a dose-related and time-limited increase in locomotor activity, as expected. Coinjection of rlCART 55-102 with dopamine blunted the effect. In summary, these data suggest that CART peptides in the nucleus accumbens would tend to oppose the actions of cocaine.

Cocaine- and amphetamine-regulated transcript (CART) peptides are neurotransmitters that appear to be involved in feeding and satiety, stress, endocrine control, sensory processing, autonomic control, and other functions (Thim et al., 1998a; Adams et al., 1999; Couceyro and Lambert, 1999; Hurd et al., 1999; Kuhar and Dall Vechia, 1999; Kuhar et al., 2000). Evidence for a possible role in the action of psychostimulants has been presented. CART mRNA was found elevated in the rat striatum after acute administration of cocaine or amphetamine (Douglass et al., 1995). This finding has been reproduced in the striatum and amygdala (Fagergren and Hurd, 1999; Brenz Verca et al., 2001) but has been challenged by Vrang et al. (2002). Evidence for a possible role in the action of psychostimulants has been presented. CART mRNA was found elevated in the rat striatum after acute administration of cocaine or amphetamine (Douglass et al., 1995). This finding has been reproduced in the striatum and amygdala (Fagergren and Hurd, 1999; Brenz Verca et al., 2001) but has been challenged by Vrang et al. (2002). Also, injections of CART peptide into the ventral tegmental area (VTA) also produce a conditioned place preference (Kimmel et al., 2000), suggesting that CART peptide can be reinforcing. Behavioral studies with CART suggest some psychostimulant-like effects. Direct injection of rat long form (rl)CART 55-102 (see Kuhar et al., 2000 for nomenclature) into the VTA causes a dose-dependent and time-limited increase in locomotor activity that is blocked by haloperidol, a dopaminergic antagonist (Kimmel et al., 2000).

Further, the anatomic localization of the peptide is suggestive of an interaction with mesolimbic dopamine. They are concentrated throughout the VTA in fibers and varicosities, where they impinge on dopamine (DA) neurons and GABAergic interneurons (Dallvechia-Adams et al., 2001). Thus, CART could either directly affect the activity of DA neurons or indirectly affect them by disinhibiting GABAergic interneurons, for example. The peptides are also found colocalized with GABA in accumbal medium spiny output neurons and in many fibers and terminals throughout the nucleus accumbens (Smith et al., 1997, 1999; Koylu et al., 1998). Taken together, these findings in the VTA indicate that these peptides may mediate or modulate the action of psychostimulant drugs.

Although effects of injections of rlCART 55-102 into the VTA have supported the hypothesis that they are involved in the modulation of locomotor activity, no experiments have examined the effects of these peptides in the nucleus accumbens. In this study, the effects of intra-accumbal injection of CART peptides on locomotor activity are examined. The potential involvement of dopamine in the effects of CART is examined as well.

Materials and Methods

Animals. Male Sprague-Dawley rats (Charles River Laboratories, Inc., Wilmington, MA) weighing between 340 and 560 g were used. The rats were group housed prior to surgery and individually housed thereafter. Food and water were available ad libitum, and the rats

ABBREVIATIONS: CART, cocaine-amphetamine regulated transcript; CART, CART peptide, or CART 55-102, the peptide rlCART 55-102; LMA, locomotor activity; rl, rat long form; VTA, ventral tegmental area; DA, dopamine; ANOVA, analysis of variance.
were maintained on a 12-h light/dark cycle (lights on at 7:00 AM). All experiments were carried out according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Surgical and Infusion Procedures. At least 1 week after arrival, rats were anesthetized with ketamine HCl (75 mg/kg i.p.; Henry Schein, Inc., Melville, NY) and medetomidine HCl (0.5 mg/kg i.p.; Pfizer Inc., New York, NY). A bilateral stainless steel guide cannula assembly (22-gauge; Plastics One, Roanoke, VA) was implanted above the nucleus accumbens using a stereotaxic frame. Target coordinates relative to bregma were A/P +1.6, L/M ±1.5, and D/V –5.7 (Paxinos and Watson, 1986). Guide cannulae were anchored in place using dental acrylic and two stainless steel screws into the skull. Dummy cannulae extending 0.5 mm past the tip of the cannulae were inserted to prevent blockage, and a dust cap was attached to the top of the cannula assembly. The rats were allowed to recover from surgery for at least 10 days before the start of the experiments.

Stainless steel injector cannulae (28-gauge; Plastics One), which projected 2 mm past the tip of the guide cannulae, were used for infusions. These cannulae were connected to 25-μl syringes (Hamilton Co., Reno, NV) via polyethylene-10 tubing. Infusion pumps (Harvard Apparatus Inc., Holliston, MA) were used for fluid delivery. For each infusion, rats were confined to a small polyethylene box. Bilateral infusions into the nucleus accumbens were given in a 0.5 μl volume per side over a 30-s duration. After the infusion, the injector cannulae were left in place for an additional 30 s, the injector cannulae were removed, the dummy cannulae was put back in place, and the dust cap was secured.

All of the experiments were done in a randomized, balanced repeated-measures design, such that each rat received all of the treatments for each experiment. A separate group of rats was used for each experiment. Each treatment day was followed by at least 3 days of no testing. Thus, each rat in Fig. 2 received four bilateral accumbal infusions (saline, 1 and 2.5 μg/side CART 55-102 in a random order over 3 separate treatment days, followed by 7.5 μg/side amphetamine on the final treatment day as a positive control). Each rat in Fig. 3 received three bilateral accumbal infusions (saline, 2.5 μg/side CART 1-27 and 2.5 μg/side CART 55-102 in a random order over 3 treatment days), each immediately followed with an i.p. injection of 10 mg/kg cocaine. Each rat in Fig. 4 received five bilateral accumbal infusions (two saline infusions, 0.25, 1, and 2.5 μg/side CART 55-102 in a random order over 5 treatment days). One of the saline infusions was immediately followed with i.p. saline, whereas the other infusions were followed by (i.p.) 10 mg/kg cocaine. Each rat in Fig. 5 received five bilateral accumbal infusions (two saline infusions, 0.25, 1, and 2.5 μg/side CART 1-27 in a random order over 5 treatment days). One of the saline infusions was immediately followed with i.p. saline, whereas the other infusions were followed by (i.p.) 10 mg/kg cocaine. Each rat in Fig. 6 received six bilateral accumbal infusions (three each of saline and 2.5 μg/side CART 55-102) paired with (i.p.) saline, 5 or 20 mg/kg cocaine in a random order over six treatment days. Each rat in Fig. 7 received three bilateral accumbal infusions (saline, 15 and 40 μg/side dopamine in a random order over 3 treatment days). Each rat in Fig. 8 received four bilateral accumbal infusions (saline, 15 μg/side dopamine, 15 μg/side dopamine + 0.75 μg/side CART 55-102, or 15 μg/side dopamine + 2.5 μg/side CART 55-102 in a random order over 4 treatment days).

Measurement of Locomotor Activity (LMA). LMA was measured in a photocell cage (Omnitech Electronics, Columbus, OH) measuring 40 × 40 × 30 cm. The cages were equipped with 32 photoembs (16 front to back and 16 side to side, every 2.4 cm) located 5 cm above the floor to measure LMA. Each cage was placed within a separate isolated stainless steel box equipped with an exhaust fan, a 10-W light, and an eyehole to allow the experimenter to observe the rats during testing. Experimental data were collected using an IBM computer equipped with software (Digipro; Omnitech Electronics) to monitor LMA.

The rats were habituated to the testing chambers prior to the experiments by receiving sham infusions daily for 3 days prior to the experiments. For each habituation, the rats were placed into the testing chambers for 1 h, given a sham infusion (an identical procedure of actual infusions), and were placed back into the chambers for an additional hour. On treatment days, the rats were placed into the testing chambers for an hour, given an infusion of the test compound, and returned to the chambers for 90 min. After each treatment, the rats were returned to their home cage for a minimum of 72 h before the next testing period.

Statistics. The temporal data of distance traveled were analyzed by a two-way ANOVA with repeated measures on drug treatment and time. A significant drug × time interaction was followed by a Tukey’s post hoc test. Each total measure of distance traveled (summed across time) was subjected to a one-way ANOVA with repeated measures on treatment, followed by a Student’s t test or Tukey’s post hoc test. Statistics were significant at P < 0.05.

CART Peptides and Nomenclature. In general, the phrase “CART peptides” refers to rlCART 55-102 and/or rlCART 62-102, both of which have been shown to be active (Thim et al., 1998b; Bannon et al., 2001; Kimmel et al., 2002). Only rlCART 55-102 (American Peptide Co., Inc., Sunnyvale, CA and Peptides International, Louisville, KY) and rlCART 1-27 (Neuromics, San Diego, CA) were used in this study. The peptides were dissolved in sterile 0.9% saline. Aliquots of two batches of rlCART 55-102 used in this study were tested for biological activity prior to these experiments by examining their effects on LMA after injection into the VTA. Both batches of rlCART 55-102 significantly increased LMA in a nearly identical manner to that previously reported (Kimmel et al., 2000).

The assignment of numbers to CART amino acid sequences has varied in the literature. The numbering used in this study corresponds to the rat long form of pro-CART protein having 102 amino acids (Kuhar and Dall Vechia, 1999). rlCART 55-102 peptide begins with the amino acids IPIYE and continues to the terminal leucine. Unless specified otherwise, the use of the acronym CART, CART peptide, or CART 55-102 in this paper refers to the peptide rlCART 55-102.

Histology. After completion of the experiments, each rat was given chloral hydrate (400 mg/rat) and decapitated. After each brain was removed, it was either immediately frozen for slicing on a cryostat or fixed in 30% sucrose formalin for slicing on a microtome. In both cases, each brain was mounted along the plane of the atlas by Paxinos and Watson (1986) and sliced in 50-μm-thick sections through the area of the target nuclei. The glass slides were then mounted onto slides, stained with toluidine blue, and examined under a microscope to localize the tip of the injector cannula.

Results

Animals were prepared for accumbal injections as described under Materials and Methods. Following testing, the brains were removed, and the location of the injector tip was determined histologically. The locations of all 47 cannulae in this study are graphed in Fig. 1; not all are visible due to overlap. For clarity, the location of only one side of each bilateral cannulae is shown. All injections were found in the accumbal area at or near the core/shell junction as desired, and no animals were eliminated based on improper injector location.

The effect of injecting rlCART 55-102 alone at either 1.0 or 2.5 μg per side was tested (Fig. 2). To be sure that the injection sites were involved in LMA as presupposed, amphetamine injection (7.5 μg per side) was carried out as a positive control, since amphetamine is known to increase LMA after injection into nucleus accumbens (Pijnenburg et al., 1976). The time course data in Fig. 2A were analyzed by
a two-way ANOVA with repeated measures on treatment (drug dose) and time. There was a significant effect of treatment \(F(3,306) = 12.10, P < 0.0001\) and time \(F(17,306) = 25.56, P < 0.0001\) as well as a significant treatment \times time\) interaction \(F(51,306) = 12.97, P < 0.0001\). However, although amphetamine (7.5 \(\mu g\) per side) increased LMA over time significantly more than saline \(F(1,17) = 170.8, P < 0.0001\) (Fig. 2A), as expected, neither dose of CART peptide had an effect significantly different from that for saline. The total distance traveled after these various injections is shown in Fig. 2B. After an overall effect of treatment was found with a one-way ANOVA \(F(3,27) = 29.71, P < 0.0001\), Tukey’s post hoc testing revealed a significant increase in LMA (over saline) for amphetamine but not for either dose of CART peptide. The amphetamine results indicate that the injections were properly located in the accumbens, as the histology also confirmed.

The effect of intra-accumbal rLCART 55-102 pretreatment (2.5 \(\mu g\) per side) on LMA induced by 10 mg/kg (i.p.) cocaine was tested (Fig. 3). Pretreatment with 2.5 \(\mu g\) per side with rLCART 1-27, an inactive peptide in other measures (Kimmel et al., 2000), was also tested. These time course data were analyzed by a two-way ANOVA with repeated measures on pretreatment (CART dose) and time. There was a significant effect of pretreatment \(F(2,170) = 6.280, P < 0.05\) and time \(F(17,170) = 16.589, P < 0.0001\) as well as a significant pretreatment \times time\) interaction \(F(34,170) = 3.209, P < 0.001\). Pretreatment with rLCART 55-102 peptide inhibited cocaine-induced LMA (Fig. 3A) \(F(1,90) = 142.74\) versus saline pretreatment, \(P < 0.0001\), whereas rLCART 1-27, an inactive peptide, did not. The total activity measures for this experiment are shown in Fig. 3B. Following an overall effect...
of pretreatment \( F(2,17) = 6.280, P < 0.05 \) determined by a one-way ANOVA, Tukey’s post hoc testing revealed a significant effect of rlCART 55-102 versus saline but no effect of rlCART 1-27. Thus, rlCART 55-102 blunted the cocaine effect, but the inactive CART 1-27 did not. Activity was found only with the peptide that is also active in other tests (Kimmel et al., 2000, 2002).

Dose-response data obtained with rlCART 55-102 (Fig. 4) and rlCART 1-27 (Fig. 5) supported the initial findings where the two peptides were compared in the same experiment. The time course data in Fig. 4A were analyzed by a two-way ANOVA with repeated measures on treatment (CART 55-102 dose) and time. The data from the animals that received saline instead of (i.p.) cocaine (the solid bar) were not included in the analysis. There was a significant effect of time \( F(17,255) = 10.38, P < 0.0001 \), treatment \( F(3,255) = 11.22, P < 0.0001 \), and treatment \( \times \) time interaction \( F(51,255) = 8.32, P < 0.0001 \). Follow-up analysis indicated a significant effect for both 1 and 2.5 \( \mu \)g/side CART (versus 0 \( \mu \)g/side CART) \( F(1,90) = 16.04, P < 0.05 \) and \( F(1,90) = 26.78, P = 0.0001 \), respectively.

The total locomotor data collapsed across time shown in Fig. 4B were analyzed by a one-way ANOVA. The data from the animals that received saline instead of (i.p.) cocaine (the solid bar) were not included in the analysis. There was a significant difference in total locomotion between the groups \( F(3,15) = 13.37, P < 0.0001 \). Tukey’s post hoc testing indicated a significant decrease in locomotion for 2.5 \( \mu \)g/side CART 55-102 versus 0 \( \mu \)g/side CART 55-102.

The time course data in Fig. 5A were analyzed by a two-way ANOVA with repeated measures on treatment (CART 1-27 dose) and time. The data from the animals that received saline instead of (i.p.) cocaine (the solid bar) were not included in the analysis. There was a significant effect of time \( F(17,255) = 8.32, P < 0.0001 \) but not treatment \( F(3,255) = 2.38, P > 0.05 \) or treatment \( \times \) time interaction \( F(51,255) = 1.33, P > 0.05 \).

The total locomotor data collapsed across time shown in Fig. 5B were analyzed by a one-way ANOVA. The data from the animals that received saline instead of (i.p.) cocaine (the solid bar) were not included in the analysis. There was no difference in total locomotion between the groups \( F(3,15) = 0.86, P > 0.05 \).

To extend the data in Fig. 3, the effect of rlCART 55-102 (2.5 \( \mu \)g/side) on locomotion produced by additional doses of cocaine (0, 5, and 20 mg/kg i.p.) was tested. Pretreatment with rlCART 55-102 significantly decreased the response to 5 and 20 mg/kg cocaine over the duration of the cocaine time courses (data not shown). The data collapsed across time are shown in Fig. 6. There was a significant effect of CART \( F(1,12) = 5.12, P < 0.05 \) and cocaine \( F(2,12) = 15.89, P < 0.01 \), but there was not a significant CART \( \times \) cocaine interaction \( (P = 0.085) \). Tukey’s post hoc testing revealed a significant effect of CART pretreatment at the dose of 20 mg/kg cocaine but not 0 or 5 mg/kg cocaine.

To explore the mechanism of the rlCART 55-102 effect on the actions of cocaine, the effect of the peptide on DA-induced LMA was examined. This would test for possible effects of the peptide on DA-receptive neurons or on downstream events in the accumbens. DA (15 and 40 \( \mu \)g/side) injection into the accumbens increased LMA in a dose-dependent fashion, as expected (Pijnenburg et al., 1976; Kalivas et al., 1984; Swan-son et al., 1997) (Fig. 7). The time course data (Fig. 7A) were analyzed by a two-way ANOVA with repeated measures on
Fig. 6. Effect of intra-accumbal CART 55-102 (2.5 μg/side) on LMA (distance traveled, mean ± S.E.M.) produced by a range of doses of cocaine. Each rat (n = 5) received six treatments in a counterbalanced order over 6 treatment days (0, 5, and 20 mg/kg cocaine, each paired with saline and CART intra-accumbal injections). * indicates difference from saline pretreatment at that dose of cocaine. See text for details. Note the different scale of the y-axis for this figure versus the other figures.

Fig. 7. Effect of intra-accumbal DA on LMA. Each rat (n = 5) received intra-accumbal injections of saline and DA (15 and 40 μg/side) in a counterbalanced order over 3 treatment days. Locomotion (distance traveled, mean ± S.E.M.) was measured for 90 min after bilateral injections. The time course data (A) and cumulative values (B) over 90 min are shown. * indicates a significant difference compared with saline. Distance traveled for the 15-μg dose had a P value of 0.06. See text for additional details.

Fig. 8. Effect of CART 55-102 on DA-induced LMA. Each rat (n = 8) received intra-accumbal injections of saline, 15 μg/side dopamine alone, 15 μg/side dopamine + 0.75 μg/side CART peptide, and 15 μg/side dopamine + 2.5 μg/side CART peptide in a counterbalanced order over 4 treatment days, and LMA was measured. Time course data (A) and cumulative data (B) over 60 min are shown. * indicates significant difference from saline, and + indicates significant difference from DA alone. See text for additional details.

A significant effect of treatment [F(3,357) = 4.56, P < 0.05], time [F(17,357) = 6.77, P < 0.001], and treatment × time interaction [F(51,357) = 7.44, P < 0.001] was found. The total LMA measures for the DA and CART coinjection experiment are shown in Fig. 8B. After an overall effect of treatment was found [F(3,21) = 5.056, P < 0.01], Tukey's post hoc testing revealed that DA injection significantly increased locomotion over saline injection and that coinjection of DA and CART peptide (2.5 μg/side) produced significantly less locomotion than injection of DA alone.

**Discussion**

A reasonable hypothesis is that CART peptides are involved in reward and reinforcement associated with food and with psychostimulant drugs (Thim et al., 1998a; Adams et al., 1999; Couceyro and Lambert, 1999; Hurd et al., 1999; Kuhar and Dall Vechia, 1999; Kuhar et al., 2000). Evidence for involvement with psychostimulants is that CART peptides are found in relevant brain regions such as the VTA and nucleus accumbens, and mRNA levels are altered by these drugs (for a review, see Jaworski et al., 2003). Also, injection of rCART 55-102 into the VTA results in psychostimulant-like effects, i.e., an increase in LMA and a conditioned place preference (Kimmel et al., 2000). The increase in LMA is inhibited by DA receptor blockers (Kimmel et al., 2000), suggesting the involvement of DA and that the increased LMA is due to activation of DA-containing neurons. In this study, the effect of CART peptide injection into the nucleus accumbens, another region important for the action of psychostimulants, was examined.

After intra-accumbal injection, rCART 55-102 had no significant effects by itself. However, CART peptide inhibited cocaine-induced (i.p. injection) LMA. This effect on the action of cocaine was dose responsive and time limited, as expected.
An inactive CART peptide, rCART 1-27, had no effect in the same experiments. Thus, although rCART 55-102 had a significant effect, the effect after accumbal injection was quite different from the effects after intra-VTA injection (Kimmel et al., 2000). Intra-VTA injection of rCART 55-102 alone caused an increase in LMA, whereas intra-accumbal injection did not. Furthermore, intra-accumbal injection of rCART 55-102 blunted cocaine-induced LMA, whereas intra-VTA injection of CART peptide produced similar effects to cocaine (Kimmel et al., 2000) in an additive or possibly subadditive manner with cocaine (unpublished data).

The ability of CART peptide to inhibit cocaine- or dopamine-induced LMA is not due to giving supramaximal stimulant doses or to producing additive effects related to an inverted “U” dose-response curve. In Fig. 4, locomotion caused by 10 mg/kg cocaine was either not affected or was decreased by all the doses of CART peptide, despite the fact that this dose of cocaine is clearly not at the peak of the cocaine dose-response curve. Additionally, in these experiments, CART peptide reduced locomotor activity caused by all doses of cocaine, even the low doses (Figs. 3 and 6). If CART 55-102 was an agonist and “pushed” the effects of cocaine higher and “over the top of the inverted U”, then we would see CART potentiating cocaine at lower doses, but we do not. This can also be approached by considering theoretical dose-response curves. If CART 55-102 were an agonist, then it would shift the dose-response curve of cocaine to the left, and low doses of CART would potentiate cocaine. However, this is not seen with submaximal doses of cocaine and with very low doses of CART 55-102. It is not seen under any conditions either with cocaine or dopamine. It should also be noted that qualitatively, these animals did not ever appear to have received “supramaximal” stimulant doses. At the end of the time courses, there was not a “rebound” locomotor activity, which would be expected if the animals were on the descending limb of the dose-response curve, and no overt stereotypic behaviors were observed with CART administration alone and paired with cocaine (data not shown).

Because cocaine induces LMA by potentiating dopaminergic transmission (Kuhar et al., 1991), the effect of rCART 55-102 on DA-induced LMA was examined in this study. Intra-accumbal injection of DA produced a dose-responsive and time-limited increase in LMA, as expected (Piñenberg et al., 1976; Kalivas et al., 1984; Swanson et al., 1997). However, coinjection of CART peptide with DA blunted the DA-induced increase in LMA, just as it did for the cocaine-induced increase. Therefore, the effects of CART can be explained by considering released DA rather than stored DA, and the data suggest a post- rather than presynaptic effect of CART relative to the dopaminergic nerve terminal. Because CART peptide has been reported to inhibit release of DA from hypothalamic nerve terminals (Brunetti et al., 2000), some effect on release cannot be ruled out. However, an effect on release has not been demonstrated in the accumbens. Because rCART 55-102 has similar effects on DA-induced and cocaine-induced LMA, the same mechanism is likely to be involved in both cases, but this needs to be explored further.

Additional evidence for the mechanism of rCART 55-102 in these experiments can be had from anatomical studies. CART peptide and mRNA were found in the nucleus accumbens, shell, and core in both cell bodies and neuronal processes (Smith et al., 1997, 1999; Koylu et al., 1998), and in our experiments, injected CART peptide is likely to affect both shell and core. CART immunoreactivity in neuronal cell bodies was in medium spiny projection neurons that are GABAergic, and thus CART peptides coexist with GABA (Smith et al., 1999). CART-containing neurons in the core project to the substantia nigra (Dalley et al., 2001), and some nerve terminals in the VTA derive from the CART-containing neurons in the shell (unpublished data). In the accumbens shell, CART is found in nerve terminals that appose both CART-positive and CART-negative neurons and dendrites, and some of these neurons and dendrites have apposing tyrosine hydroxylase-positive boutons as well (Smith et al., 1999). Thus, the effects of CART in the accumbens are likely due to an action at neuronal cell bodies and their processes that have a DA input where the functional result of CART is that the action of dopamine is opposed. This also suggests that the action of CART in the accumbens is homeostatic and tends to reverse or limit the effects of high levels of DA caused by cocaine. A similar role has been suggested for other peptides in the striatum (Steiner and Gerfen, 1998).

Although the CART receptor has not been identified, and although rCART 55-102 does not appear to affect GABA receptor binding at the TBOB (t-[3H]butylbicycloorthobenzoate) site (Jaworski et al., 2003), the CART receptor seems likely to occur in the accumbens. The behavioral effects demonstrated here and the presence of CART peptide at synapses in this region (Smith et al., 1997, 1999) indicate the presence of some type of receptor in this region.

Although many peptides, including rCART 55-102, produce increased LMA after injection into the VTA (Kalivas, 1985; Kelley and Cador, 1988; Kimmel et al., 2000), not many have been found to limit the action of cocaine after injection into the accumbens. For example, neurotensin injections do limit cocaine-induced LMA, presumably through interactions with DA (Ervin et al., 1981; Kalivas et al., 1983; Wagstaff et al., 1996; Hanson and Keefe, 1999; Boules et al., 2001), but neuromedin N is much less potent in this regard (Kalivas et al., 1986). Furthermore, substance P has the opposite effect on cocaine-induced LMA (Kalivas and Miller, 1984), and TRH and LHRH have no effect under similar conditions (Ervin et al., 1981; Kalivas et al., 1984). Thus, the actions of CART in this brain region could not have been easily anticipated.

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References


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