Psychopharmacology (1999) 145:412–417

ORIGINAL INVESTIGATION

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Manipulations of mu-opioid and nicotinic cholinergic receptors in the pontine tegmental region alter cocaine self-administration in rats

Received: 30 November 1998 / Final version: 25 March 1999

Abstract *Rationale:* The pedunculopontine tegmental nucleus (PPTg) has been implicated in drug reward, particularly in the development of dependence. However, little is known of the receptor systems within this nucleus which might be involved. Furthermore, some research suggests that the PPTg may also be part of the neuronal circuitry involved in established drug-taking behavior. *Objective:* The objective of these experiments was to examine the role of mu-opioid and nicotinic cholinergic mechanisms in the PPTg in cocaine self-administration. *Methods:* Microinfusions of mu-opioid and nicotinic receptor selective compounds were made into the PPTg of rats trained to self-administer cocaine intravenously, in the vicinity of cholinergic cells which are known to project to the midbrain dopamine neurons of the ventral tegmental area (VTA). *Results:* The mu-opioid selective agonist DAMGO, tested at doses of 0, 0.05 and 0.5 µg, produced a dose-related reduction in the number of cocaine infusions obtained during the 1-h self-administration sessions. The mu-selective antagonist CTOP (0–2 µg) and nicotine (0–10 µg) did not produce significant changes in cocaine self-administration. Microinfusions of the nicotinic antagonist dihydro-β-erythroidine (0–30 µg) produced a small but significant increase in cocaine-maintained responding. *Conclusions:* These data show that mu-opioid mechanisms in the PPTg can influence cocaine self-administration markedly. Moreover, the data demonstrate that PPTg circuitry can influence drug reward in already-established drug-reinforced behavior, as well as during the development of dependence (as shown by previous research).

Key words Drug reinforcement · Cocaine self-administration · Pedunculopontine tegmental nucleus · Mu opioid · Nicotinic cholinergic mechanisms

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Introduction

The pedunculopontine tegmental nucleus (PPTg) of the hindbrain has been implicated in a number of behavioral functions (see overviews in Mogenson et al. 1993; Inglis and Winn 1995; Winn et al. 1997), including reward and reinforcement. Regarding the latter effects, excitotoxin lesions of the PPTg have been shown to block the development of a conditioned place preference to environments paired with opioids, psychomotor stimulants and food (Bechara and van der Kooy 1989, 1992; Bechara et al. 1992; Olmstead and Franklin 1993, 1994), and to attenuate the reinforcing effects of heroin during acquisition (Olmstead et al. 1998). In some of these studies, descending non-cholinergic projections have been suggested to be the substrate involved. In contrast, muscarinic manipulations within the ventral tegmental area (VTA) have been shown to reduce hypothalamic self-stimulation, and ascending cholinergic fibers from the PPTg have been proposed to be constituents of the brain-stimulation pathway (Yeomans et al. 1993). In addition, we have shown that self-administered nicotine, which targets the mesolimbic dopamine system (Corrigall et al. 1992), does so through sites in the VTA that are blocked by the nicotinic cholinergic antagonist dihydro-β-erythroidine (DHβE) (Corrigall et al. 1994); this finding suggests that cholinergic input to the VTA should be capable of regulating dopamine-dependent drug reinforcement processes.

The most likely source of this input is also the population of cholinergic cells of the mesopontine region, that is, the PPTg and the nearby laterodorsal tegmental nucleus (LDTg). Recent work by Oakman and colleagues (1995) suggests that these cholinergic cells project topographically; in particular, VTA-projecting neurons are distributed primarily in the caudal compartment of the PPTg, and in the LDTg. Using this detailed anatomical localization as a guide, we have recently shown that selective lesions of the cholinergic cells of the caudal PPTg are sufficient to attenuate nicotine self-administration (Lança et al., unpublished observations). Furthermore, in non-lesioned animals, microinfusions of DHβE into the caudal PPTg reduce nicotine self-administration and attenuate nicotine-produced locomotor activity. It is clear, therefore, that cholinergic mechanisms in the caudal PPTg do play a role in drug reinforcement, at least for nicotine.

Little is known of other receptor systems within the PPTg that might regulate drug reinforcement, but one candidate is the mu-opioid site. For example, microinfusions of the mu-selective agonist DAMGO ([D-Ala2, *N*-Me-Phe4,Gly-ol5]-enkephalin) into the PPTg produce a dopamine-dependent elevation of locomotor activity (Klitenick and Kalivas 1994), suggesting that mu receptors in this area may influence other dopamine-dependent behaviors. It is possible that this, too, involves cholinergic PPTg neurons, since these cells are hyperpolarized by mu-selective agonists (Serafin et al. 1990).

The objective of the research described in this manuscript was to examine the role of nicotinic and opioid mechanisms in the caudal PPTg in drug reinforcement for a drug other than nicotine. To do so, we have taken the approach of making microinfusions of nicotinic- and mu-opiate-selective compounds into the caudal PPTg in animals trained to self-administer cocaine.

Materials and methods

General

Subjects were drug-naive, male, Long-Evans rats (Charles River, Lachine, Quebec). Animals were housed in a reversed light–dark cycle colony room (lights off between 0700 hours and 1900 hours). Animal care and experimental procedures were carried out in compliance with the guidelines of the Canadian Council on Animal Care. Prior to the start of experimental procedures, animals had ad libitum access to food and water and weighed approximately 300 g.

Drug self-administration techniques

Techniques for training and surgery were similar to those that we have used previously (Corrigall and Coen 1991; Corrigall et al. 1992). Animals were deprived of food for a short period (24 h), and trained to press a lever on a schedule in which each press resulted in the delivery of a 45-mg food pellet (continuous reinforcement, CRF). Once trained, each animal was surgically prepared with a chronic intravenous catheter implanted in the jugular vein; the catheter exited between the scapulae.

Surgery was performed under anesthesia induced by xylazine (10 mg/kg i.p.) and ketamine hydrochloride (90 mg/kg i.p.). Buprenorphine was given for post-operative analgesia (0.01 mg/kg s.c., administered once), and a single dose of penicillin (30,000 U i.m.) was administered at the completion of surgical procedures. Animals were allowed to recover for a period of 1 week before drug self-administration sessions were begun.

Drug self-administration was initiated on a CRF schedule with a 1-min signaled time-out (TO) period following each drug infusion. During the TO, responding was recorded but did not lead to drug delivery. Over an approximate 3-week period, the response requirements were increased to the final value of fixed-ratio 5 (i.e., five lever presses were required for each drug infusion, FR5); the TO remained at 1 min. There was no limit to the number of infusions that the animals could obtain other than the one imposed by the duration of the session and the TO. The unit dose of cocaine for acquisition was 0.3 mg/kg/infusion. Self-administered cocaine was delivered by a pneumatically driven microsyringe pump (Weeks 1981), resulting in infusion rates of 30 µl/s.

Self-administration sessions were carried out in experimental chambers equipped with two levers. Responding on one of the levers resulted in drug delivery when schedule requirements were met, while responding on the other lever was recorded but was never reinforced. Self-administration sessions were 60 min in duration and occurred once each weekday. Responding was deemed to be stable if the variation over the preceding week was less than 15% of the mean value.

Central nervous system manipulations and testing

Central nervous system (CNS) surgery was carried out when responding had stabilized at the FR5 schedule. Surgery to implant brain micro-cannulae was performed stereotaxically under the same regimen of anesthetics, analgesic and antibiotic described above. Brain micro-cannulae guides were prepared from 22-gauge stainless-steel needle tubing and fitted with a length of stainless-steel suture wire to restrict the entry of foreign material between brain infusions. Guide cannulae were positioned bilaterally to terminate above the histological boundary of the caudal PPTg; injection cannulae were cut to a longer length to reach the PPTg. Brain cannulae were anchored with dental acrylic to small screws threaded partially into the skull. Coordinates for the guide cannulae, relative to inter-aural zero, were as follows: AP +1.0 mm, L ±2.0 mm, DV 5.5 mm (Paxinos and Watson 1986). Injectors were cut to reach 1.7 mm beyond the guides (to reach coordinate +7.2 mm).

Experimental sessions were re-initiated after a 1-week recovery period. Following re-establishment of baseline responding, microinfusion tests were carried out on Tuesdays and Fridays. To do these microinfusions, animals were gently restrained manually, wire plugs were removed, and injection cannulae were inserted in the guides. Infusions were made over a 1-min period by means of a manually advanced microliter syringe. After the infusion was complete, the injection cannulae were left in place for an additional 1 min. When the injection cannulae were withdrawn, wire plugs were immediately re-introduced in the guide cannulae. Self-administration sessions began 10 min after brain microinfusions; during this 10-min interval, animals were housed temporarily in cages to permit observation for signs of behavioral effects resulting from the microinfusions.

Drugs and solutions

The following drugs were used: D-Phe-Cys-Try-D-Trp-Orn-Thr-Pen-Thr-NH_2 (CTOP), DAMGO, and DHβE (all obtained from RBI, Natick Mass.), and nicotine bitartrate (Sigma Chemical Co., St. Louis, Mo.).

Solution volumes for microinfusions were 0.5 µl/site, except for the highest dose of CTOP, which required a volume of 1 µl. Cocaine solutions for i.v. self-administration were prepared freshly each day and passed through a 0.22-µm filter to sterilize them

prior to use. The solution concentration was 3 mg/ml, delivered in a volume of 0.1 ml/kg to give a unit dose of 0.3 mg/kg/infusion. Values for doses and concentrations for all compounds (except anesthetics) refer to the base.

Histology-behavioral correlates

At the completion of the experiments, animals were anesthetized deeply with pentobarbital and perfused trans-cardially with isotonic saline followed by 10% formalin. Brains were removed and fixed for subsequent sectioning to determine the location of the cannulae tips. Frozen sections cut at 40-µm thickness were floated onto slides, and cresyl violet staining was performed as necessary to highlight cell bodies. Mounted sections were examined by means of light microscopy and the sites of the cannulae tips were located with respect to a standard stereotaxic atlas (Paxinos and Watson 1986). Acceptable histological placements were those that overlapped with the distribution of VTA-projecting cholinergic cells as described by Oakman et al. (1995).

The extent of effect with DAMGO was ranked by its magnitude, and each animal was designated as having a high, medium or low response to DAMGO based on this ranking. These response ratings were compared with the histological location of the cannulae tips.

Test design and statistical analysis

The experiments were done as within-group, repeated-measure designs in which each animal served as its own control (sample sizes are indicated in the respective figures). In each of these studies, analyses were carried out on the data from animals that received all experimental treatments in a given study, and for which histology was acceptable. Analysis of variance for a repeated measures design, or *t*-tests, were used as appropriate.

Agents for CNS microinfusions were delivered in a non-ordered fashion over successive treatment days. After a given treatment, a subsequent treatment was not given unless the baseline of self-administration, assessed on a case-by-case basis, had returned to within 10% of its pretreatment value. Typically this had occurred by the next day, but a minimum of two non-treatment days were interposed between treatments.

Results

The most pronounced effect on cocaine self-administration was produced by the mu agonist DAMGO (Fig. 1). A dose of DAMGO of 0.5 µg into the PPTg resulted in an almost-complete attenuation of responding for cocaine, whereas a dose tenfold lower reduced cocaine-maintained responding by approximately 50% from the baseline of vehicle treatment. This effect was obviously highly significant [$F2,22=36.56$, $P<0.0001$].

In contrast to DAMGO, the effects of the other agents tested were unremarkable. The mu-selective antagonist CTOP produced small increases in cocaine self-administration, which were not significant (Table 1; low dose: $t1,14=0.89$; high dose: $t1,19=0.96$). Microinfusions of nicotine into the caudal PPTg produced on average only small increases in cocaine self-administration which were also not statistically significant (Table 1; $F2,34=2.55$, $P=0.09$). However, microinfusions of the nicotinic antagonist DHβE into the same site produced small but significant increases in cocaine self-administration (Table 1; $F2,28=6.84$, $P<0.005$).

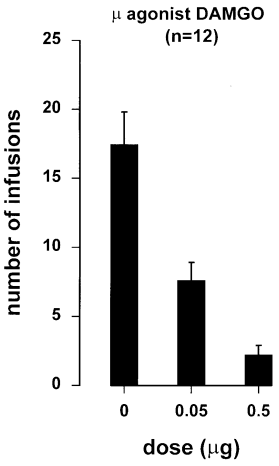

Fig. 1 Effects of microinfusions of the mu-selective opioid agonist DAMGO ([D-Ala2,*N*-Me-Phe4,Gly-ol5]-enkephalin) into the caudal pedunculopontine tegmental nucleus (PPTg) on cocaine self-administration. Data are presented as means of the number of cocaine infusions obtained during the 1-h experimental session. *Error bars* denote 1 standard error of the mean

Table 1 Cocaine self-administration after intra-pedunculopontine tegmental nucleus (PPTg) treatments. The values for cocaine self-administration are the mean numbers of infusions during the 1-h experimental session; values in parentheses are standard errors of the mean. As described in the text, a separate vehicle was used for each dose of CTOP (D-Phe-Cys-Try-D-Trp-Orn-Thr-Pen-Thr-NH_2) due to the larger volume required for the higher dose. *DHβE* dihydro-β-erythroidine

Compound microinfused	Dose (µg)	Number of cocaine infusions
CTOP (*n*=15)	0 (0.5 µl)	16.7 (2.0)
(*n*=15)	1 (0.5 µl)	18.2 (1.9)
(*n*=20)	0 (1 µl)	18.5 (1.2)
(*n*=20)	2 (1 µl)	20.4 (2.0)
Nicotine (*n*=18)	0	19.6 (0.8)
	4	20.9 (1.7)
	10	22.7 (1.6)
DHβE (*n*=15)	0	19.0 (0.9)
	17.8	23.9 (1.3)
	30	23.7 (1.6)

During the period of microinfusion and for the 10-min observation period thereafter, the only behavioral signs observed were in the animals treated with the 10-µg dose of nicotine. Of the 18 animals treated with this dose of nicotine, 7 became motorically tense during the microinfusion, while several other animals showed catatonic-like behavior, and several displayed bursts of activity. All of these unconditioned behavioral effects had waned by the time of testing.

It should be noted that this was not a response to the mechanical effects of the microinfusions, which were done slowly; these behavioral effects were also not observed in vehicle treatments, with the other dose of nicotine, or with other intra-PPTg drug treatments including DAMGO.

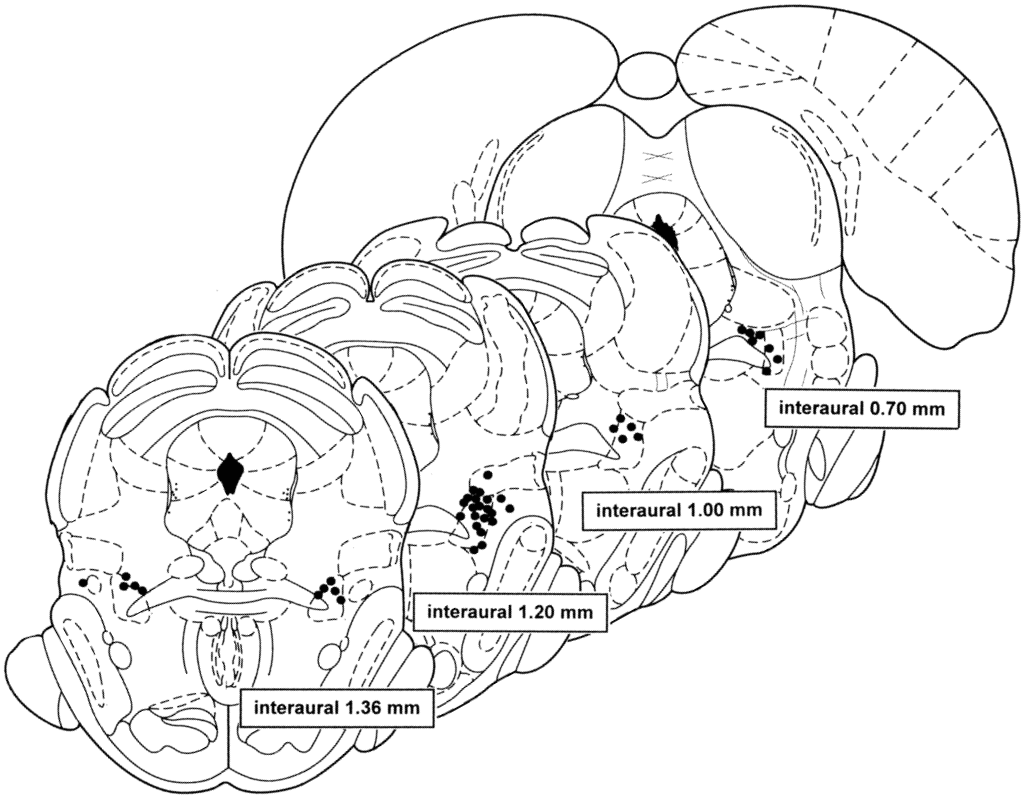

Fig. 2 Location of the tips of the microinjection cannulae located with respect to a standard stereotaxic atlas (Paxinos and Watson 1986). The range of these injection sites overlaps completely with the location of ventral tegmental area-projecting cholinergic neurons (Oakman et al. 1995)

Figure 2 shows the location of the microinjector cannulae tips with respect to a standard stereotaxic atlas (Paxinos and Watson 1986). The location of these microinjection sites, ranging in an anterior–posterior dimension between interaural 1.36 mm and interaural 0.70 mm, overlaps identically with the location of the majority of the VTA-projecting cholinergic cells of the caudal PPTg, as described by Oakman et al. (1995). Not included in this figure are data from four animals treated with DAMGO in which the cannulae tips were rated as being too deep with respect to the ventral extent of the population of cholinergic cells (placements for three animals at interaural plane 1.20 mm, for one animal at 0.70 mm). In these animals, there was a lesser effect of DAMGO than of vehicle, with average reductions in self-administration of 32% after treatment with the 0.05-µg dose, and of 65% after the 0.5-µg dose (compared with approximately 56% and 87%, respectively, in the group shown in Fig. 1).

Comparison of the extent of the DAMGO effect with the rostral-caudal distribution of the microinjection sites did not show any correlation. For example, two of the animals that were high-effect DAMGO had microinjection cannulae located in the 1.36-mm interaural plane, and an additional two were in the 0.70-mm plane. The placements for the subgroup with low-effect-size were distributed across 0.70–1.20 mm.

Discussion

The effect of intra-PPTg DAMGO on cocaine self-administration is consistent with the distribution of opioid receptors in the pontine mesencephalon (Mansour et al. 1987). Klitenick and Kalivas (1994) have shown that activation of mu receptors by means of DAMGO microinfusions into the PPTg produces an elevation of locomotor activity which appears to be both dopamine- and mesolimbic-dependent, since it is blocked by systemic haloperidol, attenuated by activation of γ-amino butyric acid (GABA) circuitry in the VTA (which inhibits dopamine cells), and associated with increases in dopamine and its metabolites in the nucleus accumbens. Since these data suggest that DAMGO may act to facilitate dopamine transmission in the mesolimbic system, one might speculate that the decrease in cocaine self-administration that we have observed following intra-PPTg DAMGO is due to an augmented dopamine signal, and a shift to the left in the cocaine dose–response curve, with an associated reduction in responding for doses of cocaine on the descending limb of the dose–effect curve for self-administration. For example, we have recently shown that DAMGO also alters cocaine self-administration when infused into the VTA (Corrigall et al. 1999). In the latter case, the dose effect curve for cocaine self-administration does appear to be shifted to the left. In the present case, further studies to examine the effects of intra-PPTg

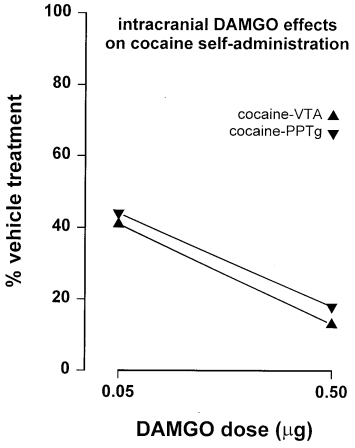

Fig. 3 Summary showing the effects of intracranial DAMGO ([D-Ala2,*N*-Me-Phe4,Gly-ol5]-enkephalin) microinjections into the pedunculopontine tegmental nucleus (PPTg) (this report) and the ventral tegmental area (VTA) (Corrigall et al. 1999) in cocaine self-administration. Data are plotted as a percentage of the vehicle treatment values

DAMGO on a range of cocaine doses, or with progressive ratio schedules of responding, will help to clarify the mechanism of the DAMGO effect.

The magnitude of the DAMGO effect in cocaine self-administration is similar in the VTA and the PPTg. In Fig. 3, we have summarized the data from these two sites as a percentage of the vehicle microinfusions. In both brain sites, the 0.05-μg dose of DAMGO produces an approximate 60% reduction in cocaine-maintained responding, while at the 0.5-μg dose, responding is reduced to about 20% of vehicle-treatment values. It is instructive to compare these values to work currently in progress, in which we have found that intra-VTA microinfusions of DAMGO are less effective when tested against nicotine self-administration and food-maintained responding. For example, at the lower dose of DAMGO (0.05 μg), nicotine self-administration is unaffected by intra-VTA DAMGO, and food-maintained responding is reduced by about 10%. At the higher dose of DAMGO, the effects are greater than at the lower dose, but still less than those observed in cocaine self-administration (reductions of about 50–60% compared with the approximate 80% reductions for cocaine). These comparisons thus suggest that there may be some specificity to the effect of DAMGO in cocaine reinforcement compared with its effect on other reinforcers, at least at low doses of the opioid. As we have noted elsewhere (Corrigall et al. 1999), the ability of DAMGO to alter cocaine self-administration at these sites may be one basic mechanism involved in the co-use of heroin and cocaine.

The effect of DAMGO is novel for two reasons. It is the first demonstration that mu-opioid receptors in the PPTg can influence cocaine self-administration. A second and particularly intriguing aspect of the finding is that it is the first demonstration of a role for the PPTg in drug reward which has already been established. Previous data regarding the role of the PPTg in drug reward have suggested that the nucleus is involved only when the subjects are not yet drug- or task experienced. For example, excitotoxin lesions of the PPTg block the acquisition of a conditioned preference for an environment paired with the presentation of a drug or food, but the lesions are not effective if they are made after the conditioning sessions or when the animals are drug experienced (Bechara et al. 1992; Bechara and van der Kooy 1989, 1992). Similarly, lesions of the PPTg are not effective in attenuating heroin self-administration if they are produced after the animals have learned the operant task, yet they can affect acquisition (Olmstead et al. 1998). With our current limited knowledge of the PPTg circuitry in drug reward, it is difficult to speculate about the reasons for the differences in these findings.

One element in the circuitry clearly requiring further investigation as a possible common component is the population of cholinergic cells in and around the caudal PPTg which are known to project to the VTA and which have been implicated in other reward functions. This population of cholinergic cells may be the substrate for the effect of DAMGO which we have observed. While we have not demonstrated this directly in the present study, several facts make this a likely identification. First and most importantly, the location of the injection sites within each rostral-caudal plane in this study falls within the distribution of the VTA-projecting cholinergic cells as described by Oakman and colleagues (1995). Data from the four animals with placements ventral to that population of cholinergic cells, in which the effects of DAMGO were smaller, strengthen the suggestion that it is important to target the locale of the cholinergic population. However, this was a small sample, with placements not substantially outside the relevant target area, and ventral to it. It is possible that even more definite boundaries exist than implied by the data from this small subset of animals, and these might have been revealed if cannulae tips had been displaced medio-laterally or dorsally from the cholinergic population such that the spread of DAMGO dorsally along the cannulae would be eliminated. Nevertheless, it does appear that there is a trend for a lesser effect of DAMGO as placements move away from the cholinergic cell population.

It is not surprising that there was no correlation between the anterior–posterior coordinates of the injection sites and the effect size for DAMGO, since we targeted the caudal PPTg, and throughout the anatomical range of our cannulae in Fig. 2 there are VTA-projecting cells (the PPTg extends almost another 1 mm rostrally).

Additional support for our suggestion that the effect of intra-PPTg DAMGO is mediated by the cholinergic cells of the caudal PPTg comes from other studies. Cholinergic cells from this area of the brain explanted in vitro have been shown to be directly influenced by mu agonists (Serafin et al. 1990). In addition, we have shown that selective lesions of these cholinergic cells, which spare other non-cholinergic cells in the PPTg, lead to a diminution of nicotine self-administration, a dopamine-dependent behavior (Lança et al., unpublished observa-

tions). Third, the ascending cholinergic projection from the PPTg to the VTA has been implicated in brain-stimulation reward (Yeomans et al. 1993; Yeomans and Baptista 1997).

In contrast to the effects of DAMGO, intra-PPTg microinfusions of nicotine were without significant effect on cocaine self-administration. However, during the microinfusions and for several minutes thereafter, a large fraction of the animals in this group did show behavioral consequences. It thus appears that nicotine did have effects, but that rapid desensitization of the nicotinic cholinergic receptors occurred (Pidoplichko et al. 1997). However, the nicotinic cholinergic antagonist DHβE did produce changes in cocaine self-administration, at the same doses that we have found to attenuate nicotine self-administration when delivered by microinfusion into the VTA (Corrigall et al. 1994) or PPTg (Lança et al. unpublished observations). If cholinergic cells in the PPTg are the substrate for the DAMGO effect, it is possible that they are influenced by cholinergic agents acting on a tonically active cholinergic signal to the PPTg or on autoreceptors, or both. However, at this time, there is a risk of over-interpreting the small, though significant, effects of DHβE on cocaine self-administration.

In summary, these data show that mu-opioid mechanisms in the caudal PPTg can influence dopamine-dependent reinforcement processes, and that they can do so when the behavior is already established. The fact that the mu-agonist is effective, but that the mu-antagonist CTOP is not, suggests that there is not a tonically-active opiate input to the PPTg. Further work should attempt to confirm that the substrate for this effect is in fact the cholinergic cells of the caudal PPTg. These data, considered in context with previous studies of the PPTg in rewarded behavior, suggest that the PPTg may play a complex role in drug dependence.

Acknowledgements This research was supported by a grant from the National Institute on Drug Abuse (DA09577) to WAC.

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