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Facilitation of Sexual Behaviors in the Male Rat Associated With Intra-VTA Injections of Opiates

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MITCHELL, J. B. AND J. STEWART. *Facilitation of sexual behaviors in the male rat associated with intra-VTA injections of opiates*. PHARMACOL BIOCHEM BEHAV **35**(3) 643–650, 1990.—Male rats were tested for sexual behaviors after bilateral injections of morphine sulfate or dynorphin$_{1-13}$ into the ventral tegmental area. Both morphine and dynorphin$_{1-13}$ increased, in a dose-orderly manner, the number of males that mounted, and the display of female-directed behavior. Repeated administration of morphine, but not dynorphin$_{1-13}$, into the region of the ventral tegmental area increased dopamine (DA) metabolism in the nucleus accumbens, a terminal field of the mesolimbic DA system. These results suggest that activation of elements within the region of the VTA activated by mu and kappa selective agonists are able to facilitate some aspects of sexual behavior, but that only morphine appears to activate dopaminergic elements within the VTA.

Ventral tegmental area Dopamine Morphine Dynorphin Sexual behavior

DATA from a variety of sources suggest that common neural mechanisms may underlie at least some aspects of all appetitively motivated behaviors (52). Exploration, feeding, drinking, copulation and predation can all be elicited by electrical stimulation within the medial forebrain bundle (14), and there is considerable evidence that the appetitive properties of drugs of abuse are mediated by components within the same system (60). Evidence from several sources suggests that activation of the mesolimbic dopamine (DA) system is involved in the arousal of male sexual behavior. The initiation of copulation of castrated males can be facilitated by treatment with DA agonists and the DA antagonist, pimozide, can block these effects (34–36). Intraventricular infusions of 6-hydroxydopamine that lesion mesencephalic catecholamine cells, including mesolimbic DA cells, result in deficits in male sexual behaviors (6). Bilateral lesions of the medial forebrain bundle interrupt projections from the ventral tegmental area (VTA) and abolish pursuit of the female and mount attempts (20), as well as copulation itself (4,22). Furthermore, electrical brain stimulation in the medial forebrain bundle that could transsynaptically activate the mesolimbic DA system (60) has been shown to induce stimulation-bound copulation (3, 5, 7, 11). Electrical stimulation of the VTA itself has also been reported to facilitate sexual behaviors (11).

The VTA has a high concentration of both enkephalinergic terminals (51,59) and opiate receptors (16, 23, 51), suggesting that endogenously released opioids might influence the activity of the DA cells. Indeed, peripheral and local injections of morphine and mu-receptor specific analogues of enkephalin peptides into the VTA alter the firing frequency of a population of neurons in the VTA (17), increase DA metabolism in mesolimbic terminal fields (29), and produce a dose-dependent increase in locomotor activity that is blocked by DA antagonists (28, 29, 54).

Dynorphin is thought to be the endogenous ligand for the kappa opioid binding site (8). Dynorphin-like immunoreactivity is found in the VTA (12), as are kappa opioid binding sites (37). Both morphine and dynorphin injected into the VTA elicit feeding in satiated rats (18,19), and similarly placed injections of both morphine and the kappa receptor agonist (U-50,488H), as well as the delta receptor agonist, [D-Pen^2,D-Pen^5] enkephalin, DPDPE, facilitate lateral hypothalamic electrical stimulation-induced feeding (27). Interestingly, although both morphine and DPDPE facilitate the effects of rewarding brain stimulation at the same sites, U-50,488H did not (26). Taken together, these findings suggest that endogenously released opioids might influence the activity of cells within the region of the VTA, and thereby influence motivated behaviors such as sexual behavior. Furthermore, these data suggest that although endogenous opioids with affinity for mu, delta, and kappa receptor subtypes may all play a role in the mediation of appetitively motivated behaviors, there is probably anatomical separation of the neural elements in the VTA upon which they act.

We were interested, therefore, in determining whether intra-

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VTA morphine and dynorphin might facilitate the expression of behaviors directed toward a different but primary incentive object, the estrous female. Male rats were tested for sexual behaviors after direct application of opioids to the region of the VTA to investigate the effects on sexual behaviors, particularly behaviors such as initiation latencies and pursuit and manipulation of the female, that have been associated with sexual arousal or motivation. Baseline sexual activity was reduced and stabilized by castrating the males and then maintaining them on behaviorally subthreshold doses of testosterone (10). The doses of morphine and dynorphin$_{1-13}$ used were selected on the basis of their efficacy in eliciting feeding (18, 19, 21, 62) and from a pilot study of male sexual behavior. As discussed earlier, morphine is known to increase activity of dopaminergic cells, but the involvement of DA in mediating the effects of dynorphin is not clear; intraventricular administration of dynorphin, however, has no effect on nigrostriatal DA metabolism, and does not alter morphine-induced increases in nigrostriatal DA metabolism (63). Changes in mesolimbic DA metabolism after central injections of dynorphin have not been reported. Therefore, we investigated whether repeated dynorphin administration, directly to the VTA, would affect mesolimbic DA metabolism.

METHOD

Subjects

Male Long-Evans rats (Charles River Canada Ltd.) weighing 280–300 g were used. Subjects used in the tests for sexual behaviors after drug infusion were screened for sexual activity. Males were bilaterally castrated via a single incision along the midline of the scrotum, and received daily injections of 5 μg testosterone propionate (Sigma, St. Louis, MO), SC, in peanut oil vehicle throughout the experiment. Surgery was performed under methoxyflurane anesthetic (Metofane, Pitman-Moore Ltd./M.T.C. Pharmaceuticals, Mississauga, Canada). Males used for the measurement of mesolimbic DA metabolism after drug infusion were sexually naive and gonadally intact.

Target females were ovariectomized under methoxyflurane anesthesia. Sexual receptivity was induced by injections of 10 μg estradiol benzoate, SC (Sigma), in 0.1 ml peanut oil 72 and 24 hr before use, and 0.5 mg progesterone (Sigma) in 0.2 ml peanut oil 4 to 6 hr before use. Female sexual receptivity was verified by placing a female with a vigorous copulator just prior to use with an experimental male.

All animals were housed in standard wire mesh cages with Purina Rat Chow and water available ad lib. The animal colony was maintained on a 12-hr light:12-hr dark reverse light cycle with lights off at 0930 hr. All testing occurred during the animals' dark cycle, between 1200 and 1700 hr.

Stereotaxic Surgery

Animals were injected in 0.1 ml atropine sulfate, SC (Glaxo Laboratories, Montreal, Canada), and anesthetized with sodium pentobarbital, IP (0.85 ml/kg Somnotol, M.T.C. Pharmaceuticals Ltd.). Subjects were stereotaxically implanted with chronic bilateral guide cannulae (22 gauge, Plastic Products, Roanoke, VA) aimed at the VTA or substantia nigra. Blocker and injection cannulae (28 gauge, Plastic Products) extended 1 mm beyond the guide cannulae. The VTA coordinates were: A/P −3.6, L ±0.6, and D/V −8.9 from skull (49). The guide cannulae were implanted at 16 degrees to the vertical to avoid the periventricular gray (PVG) and penetration of the cerebral aqueduct. The substantia nigra coordinates were: A/P −3.8, L ±2.5, and D/V −8.9 (49). The substantia nigra cannulae were implanted at 8 degrees to the vertical, permitting the use of Plastic Products blocker cannulae. Guide cannulae were secured by dental cement molded around 4–5 stainless steel screws imbedded in the skull. Animals were allowed 10–14 days to recover from surgery.

Apparatus

Subjects were screened for sexual behavior in semicircular boxes, 61 cm diameter × 36 cm deep, in a room dimly lit by four, 40-watt red light bulbs. Tests for sexual behavior were conducted in Plexiglas-fronted boxes, 36 × 50 × 28 cm, individually lit by a 7-W red light bulb. A red-light sensitive camera (Panasonic CCTV camera, model WV-1460), and a video cassette recorder (Sony Betamax VCR, model SLO-420 or SL-HFR30) were used to record the sessions for future scoring.

Drug Infusions

Morphine sulfate (BDH Chemicals, Toronto, Canada) and dynorphin$_{1-13}$ (Sigma) were dissolved in sterile 0.9% saline. All drug doses were given in a volume of 0.5 μl/side and were injected by hand over 45 sec using 28 gauge injection cannulae connected by polyethylene tubing to 1 μl microsyringes (Hamilton, Reno, NV). The injections were made in unrestrained animals, and by taping two syringes together, the plungers could be moved smoothly and simultaneously to the two sides. Seventy-five seconds after the end of the injection, the injection cannulae were removed, obturators replaced, and the animal immediately placed in a mating arena. Groups of 6–8 males were tested concurrently. Tests were conducted every 2–3 days.

Procedure

Animals with VTA cannulae were randomly assigned to one of two groups. One group of 10 animals received bilateral infusions of 0.1, 1, 10 and 30 nmol morphine, and the other group received bilateral infusions of 0.03, 0.1, 0.3 and 3 pmol of dynorphin$_{1-13}$; both groups also received a vehicle injection. Dose order was randomized with the restriction that some animals in each group received the vehicle injection on the first, third and fifth test. Three days after the dose-response investigation was completed, a test for naloxone antagonism was conducted; each animal received an IP injection of 1 mg/kg naloxone HCl (Endo Laboratories Inc., Garden City, NY) prior to a VTA infusion of either 10 nmol morphine or 0.3 pmol dynorphin$_{1-13}$ and were tested for sexual behavior.

To assess the anatomical specificity of the injections, animals with substantia nigra cannulae were tested for sexual behavior after injection with vehicle, 10 nmol morphine, and 0.3 pmol dynorphin$_{1-13}$, in randomized order.

After completion of the experiment, all subjects were deeply anesthetized and perfused transcardially with saline and 10% formalin (Fisher), and the brains stored for 7–10 days in 10% formalin. Histological verification of cannulae tip placements were made on 40 μm thionin stained coronal sections.

Tests for Sexual Behaviors

Males were placed individually in the mating arenas, and 5 min later a sexually receptive female was introduced. Tests lasted 30 min from the time of the introduction of the female.

After the female had been placed in the mating arena, sexual behaviors were scored using the following categories (50): *Mounts:* Identified by the male mounting the female from the rear and displaying a number of rapid, shallow pelvic thrusts. *Intromissions:* Similar to a mount, but included a long, deep thrust after the

rapid shallow thrusts, a rapid kick with one hindleg, and a rapid short-stepped withdrawal from the female. *Ejaculatory pattern:* Identified by a final pelvic thrust that was slower and deeper than of an intromission, a lateral removal of the forelimbs from the female that was held momentarily at the apex, and an absence of back-stepping before genital grooming. Where appropriate, six other measures were taken. These included: *Mount latency:* The latency from the introduction of the female to the first mount. *Intromission latency:* The latency from the introduction of the female to the first intromission. *Ejaculation latency:* the length of time from the first intromission to the first ejaculation. *Postejaculatory interval:* the time between ejaculation and the first intromission of the next copulatory series. *Interintromission interval:* the average number of intromissions per min to the first ejaculation. *Intromission ratio:* the ratio of intromissions to mounts plus intromissions.

The videotapes were scored for female-directed behavior using a time sampling procedure. Female-directed behavior was defined as activities directed toward the female that commonly precede and accompany copulation. These included: anogenital exploration, pursuing, sniffing, grooming, and climbing over the female, and manipulating the female's flanks (33,40). During the 30-min test, each male was observed for 2–3 sec every 30 sec and the predominant behavior noted, providing 60 observations per animal in each test. An animal's overall score was expressed as the percent of observations in which female-directed behavior occurred. Interrater reliability was >0.9 for all measures.

Dopamine Concentrations and Metabolism

To assess the effect of drug infusions on DA metabolism, different groups of animals received intra-VTA infusions of 0.9% saline, 0.3 pmol dynorphin$_{1-13}$, or 10 nmol morphine every other day. On the day of the fifth drug infusion, animals were sacrificed 1 hr after infusion. The brains were rapidly removed and placed on an ice-cold glass plate. Each brain was bisected coronally 2–3 mm anterior to the cannulae holes. The anterior section was immediately frozen on dry ice, and stored at −70 degrees C. It was later cut into 300 μm sections, and the nucleus accumbens and medial frontal cortex removed using the Palkovits punch technique (46,47). DA, dihydroxyphenylacetic acid (DOPAC), norepinephrine, serotonin, and 5-hydroxyindoleacetic acid were assayed using high performance liquid chromatography with electrochemical detection (HPLC-EC) as previously described (43). The posterior section was placed in 10% formalin and, 4–5 weeks later, cannulae tip placements were verified in 40 μm thionin stained sections.

Statistics

Measures of sexual behavior, and the results of the neurochemical assay were analysed by analysis of variance, and subsequent post hoc comparisons were made using Tukey's HSD. The proportion of animals in each group mounting, intromitting, or displaying the ejaculatory pattern were analysed by χ^2-tests; for conditions under which the obtained frequencies were 0, Yate's correction was applied (13).

RESULTS

The VTA cannulae placements were lateral of the interpeduncular nucleus and medial of the medial lemniscus (see Fig. 1); this area corresponds to the approximate location of the mesolimbic DA cell bodies (1,9). The data for two subjects in the dynorphin group and one in the morphine group were excluded because of inaccurate cannulae tip placements, and the data for a second morphine subject were dropped because the dental cement securing the guide cannulae became loose, precluding accurate histology. The substantia nigra injector cannulae tips were located in the substantia nigra for all but one subject; the data for this subject were excluded.

Sexual Behaviors After Morphine and Dynorphin$_{1-13}$

The frequency of female-directed behavior after morphine and dynorphin$_{1-13}$ infusions is shown in Fig. 2. There was an effect of dynorphin$_{1-13}$ on the frequency of female-directed behavior, $F(4,28) = 17.73$, $p<0.001$. Female-directed behavior was more frequent after infusions of 0.3 pmol of dynorphin$_{1-13}$ than after infusions of either saline or 0.03 pmol of dynorphin$_{1-13}$ (p's<0.05), and less frequent after 3 pmol than 0.1 or 0.3 pmol (p's<0.05). In morphine-treated animals, however, the mean frequency of female-directed behavior was high following vehicle and low dose infusions relative to the dynorphin-treated animals after corresponding infusions. Upon closer inspection of the data, it was noted that, in the morphine group, the frequency of female-directed behavior following a saline infusion increased from the first to the fifth trial; the means were: 23.3, 18.3, and 34.4 percent of observations for trials 1, 3, and 5, respectively. In the dynorphin group, on the other hand, the frequency of female-directed behavior after saline infusion did not vary as a function of trial; the means were: 23.9, 17.5, and 21.7 percent of observations for trials 1, 3, and 5, respectively. Therefore, for the morphine group the data from the fifth test were excluded from the analysis.

There was an effect of morphine infusions on frequency of female-directed behavior, $F(4,26) = 10.22$, $p<0.001$. Female-directed behavior was more frequent after infusions of 10 nmol of morphine than after saline ($p<0.05$), and less frequent after infusions of 30 nmol of morphine than after infusions of 0.1, 1, or 10 nmol of morphine (p's<0.05).

Figure 3 presents the proportion of animals in each group that mounted, intromitted or displayed the ejaculatory pattern after drug or vehicle infusions. There was a dose-related increase in the number of animals that mounted in both groups; at the highest doses of both morphine and dynorphin$_{1-13}$, however, the number of animals that mounted decreased. The number of animals that mounted differed significantly between infusions for both the morphine, $\chi^2(5) = 11.69$, $p<0.05$, and dynorphin$_{1-13}$, $\chi^2(5) = 11.23$, $p<0.05$, groups. Morphine did not affect the number of animals intromitting or displaying the ejaculatory pattern (p's>0.1); in the dynorphin group, there was a small effect on the occurrence of the ejaculatory pattern, $\chi^2(5) = 9.12$, $0.05<p<0.1$.

Naloxone Pretreatment

The frequency of female-directed behavior after naloxone pretreatment plus drug was compared to that seen after the same drug dose without naloxone pretreatment using t-tests for repeated measures (two-tailed). Naloxone decreased significantly the frequency of female-directed behavior observed after infusion of 10 nmol of morphine from 27.9 to 22.7 percent of observations, $t(7) = 2.67$, $p<0.05$, and after infusion of 0.3 pmol dynorphin$_{1-13}$ from 36.9 to 27.3 percent of observations, $t(7) = 3.41$, $p<0.05$. Naloxone pretreatment also blocked the facilitation of mounting previously seen after drug infusion. Seven animals mounted after infusions of 0.3 pmol of dynorphin$_{1-13}$, whereas only one animal mounted when the infusion of dynorphin$_{1-13}$ was preceded by naloxone, $\chi^2(1) = 9.0$, $p<0.01$; six animals mounted after infusions of 10 nmol of morphine, but none mounted if the same dose of morphine was preceded by naloxone, $\chi^2(1) = 7.84$, $p<0.01$.

Substantia Nigra Infusions

The frequency of female-directed behavior displayed after

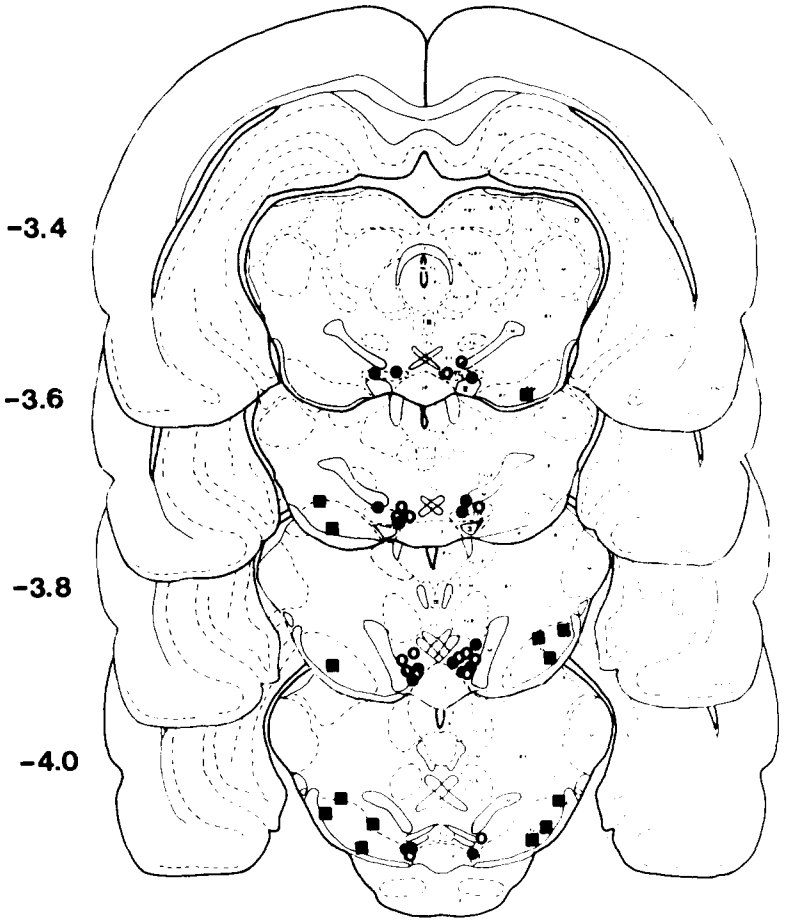

FIG. 1. Location of cannulae tips for animals that had received dynorphin$_{1-13}$ (filled circles), or morphine (open circles) into the region of the VTA, or both dynorphin$_{1-13}$ and morphine into the substantia nigra (filled squares). Adapted from (49).

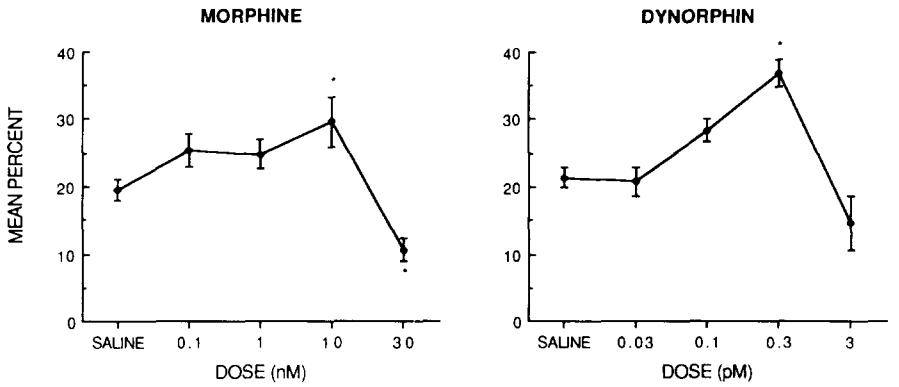

FIG. 2. Mean ($\pm$ 1 S.E.M.) percent of observations during which female-directed behavior was observed after different doses of morphine (left panel), and dynorphin$_{1-13}$ (right panel). *Significantly different from vehicle ($p<0.05$).

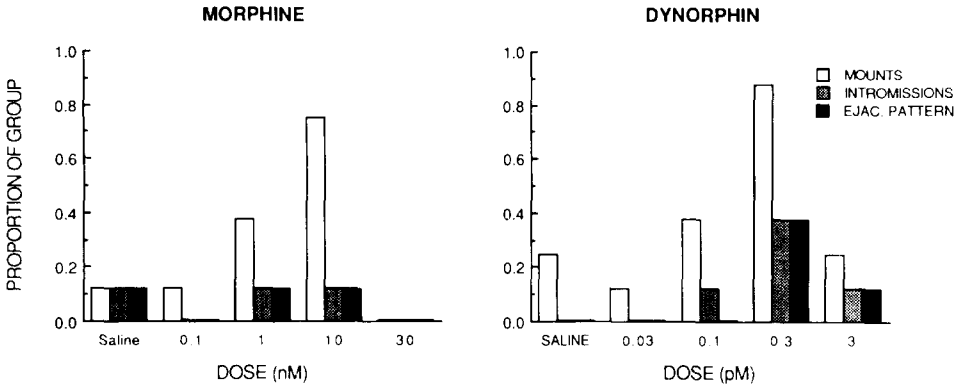

FIG. 3. Proportion of animals in each group that mounted, intromitted, or displayed the ejaculatory pattern after different doses of morphine (left panel) and dynorphin$_{1-13}$ (right panel).

infusions of vehicle, morphine or dynorphin$_{1-13}$ into the substantia nigra was analysed using a two-factor repeated measures analysis of variance (drug × time). Neither the drug effect nor the drug × time interaction was statistically significant (p's>0.1), although there was a significant time effect, $F(2,12)=64.29$, $p<0.01$, indicating that female-directed behavior decreased during the 30-min test. Virtually no copulation occurred after substantia nigra infusions; one animal mounted after a vehicle infusion, and no other copulatory behaviors were observed.

DA Metabolism

The mean concentrations of DA and DOPAC and the DOPAC/DA ratio for the nucleus accumbens are shown in Fig. 4. The three groups did not differ in DA concentrations ($p>0.1$). There were group effects for DOPAC concentrations, $F(2,8)=7.90$, $p<0.01$, and the DOPAC/DA ratio, $F(2,8)=14.19$, $p<0.01$. The morphine-treated animals had higher DOPAC concentrations than the saline controls, and higher DOPAC/DA ratios than either the saline- or dynorphin$_{1-13}$-treated animals (p's<0.05), suggesting increased DA metabolism in the nucleus accumbens after intra-VTA infusions of morphine relative to infusions of either saline or dynorphin$_{1-13}$.

DOPAC concentrations and the DOPAC/DA ratio in the medial frontal cortex exhibited a similar trend to that found in the nucleus accumbens, but the differences were not statistically significant (p's>0.1). Groups did not differ in norepinephrine, serotonin or 5-hydroxyindoleacetic acid concentrations in either the nucleus accumbens or the medial frontal cortex.

DISCUSSION

Both morphine and dynorphin$_{1-13}$ infused into the VTA produced dose-dependent, naloxone-sensitive increases in the display of female-directed behavior, and in the number of animals that mounted. Morphine or dynorphin$_{1-13}$ infusions into the substantia nigra had no effect on sexual behavior, suggesting that the facilitation of sexual behavior by morphine and dynorphin$_{1-13}$ was due to the drugs acting within the VTA. It should be noted that extremely small amounts of dynorphin were required to facilitate sexual behaviors, consistent with studies on dynorphin-induced feeding (18,19); indeed, the potency of dynorphin was apparent when it was initially sequenced (15).

At the highest doses of both morphine and dynorphin$_{1-13}$ tested, sexual behavior decreased. No obvious explanation for this reversal can be offered. Morphine-treated animals were observed to sit and sniff with occasional bursts of activity. Dynorphin-treated subjects were somewhat hypoactive, but otherwise ap-

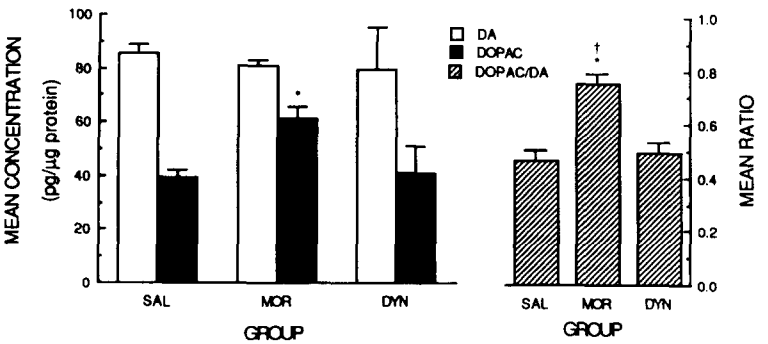

FIG. 4. Mean (+1 S.E.M.) concentrations of DA and DOPAC (left panel), and the DOPAC/DA ratio (right panel) in the nucleus accumbens for groups that had received repeated infusions of saline (SAL), morphine (MOR), or dynorphin$_{1-13}$ (DYN) into the VTA. *Significantly different from SAL ($p<0.05$), †significantly different from DYN ($p<0.05$).

peared normal. Motor suppression has been reported after intraventricular injections of dynorphin, although these effects were found following higher doses than those used here (53, 56, 57).

Repeated injections of morphine into the region of the VTA (54) and repeated systemic injections of morphine (55) have been found to result in an increase in activity when animals are tested with saline in the drug-associated environment. We have recently found that when animals are tested, drug-free, in an environment previously associated with morphine, sexual behavior is enhanced (42). In the experiments reported here, we attempted to minimize any conditioning to morphine and dynorphin. There was, however, some evidence that morphine-treated subjects displayed increased female-directed behavior after a saline injection when they had previously received morphine on several occasions in the mating arenas.

The doses of morphine that increased sexual behavior were also found to increase DA metabolism in the nucleus accumbens. Dynorphin$_{1-13}$, however, did not affect DA metabolism in the nucleus accumbens in the dose that facilitated sexual behavior, and that has been reported to elicit feeding (18,19), suggesting that these two opioid compounds mediate their effects on motivated behaviors via different systems. It is possible that the inability of dynorphin to influence DA metabolism, measured 1 hr after the last of a series of injections, is related to the shorter duration of action that would be expected based on the vulnerability of dynorphin to endogenous peptidases. In the present experiments, however, dynorphin had lasting behavioral effects [as long as 30 min; also, see (18,19)], suggesting that rapid clearance of dynorphin was not a problem. Evidence from other sources also suggest that dynorphin does not influence DA metabolism or utilization (58,63).

The differences between the effects of morphine and dynorphin in the VTA may reflect different affinities of these ligands for different opioid receptors. The existence of multiple opioid receptors is well documented (31,38). Morphine binds preferentially at the mu-binding site, whereas dynorphin binds preferentially at the kappa site (48), and is thought to be the endogenous kappa ligand (8). Although both mu and kappa agonists are analgesics (24), and when infused into the VTA both elicit feeding (18,19), differences between them have been reported. Infusion of the prototypical mu agonist, morphine, into the VTA elicits contraversive circling and facilitates brain stimulation reward, but the kappa agonist U-50,488H does not (25,26). Morphine and U-50,488H have been reported to have opposite effects on substantia nigra DA cell firing (58), and morphine, but not dynorphin, increases nigrostriatal DA metabolism (63).

These results suggest that opiates, likely via activation of dopaminergic cells, can increase motivated behaviors including sexual behavior, feeding and brain stimulation reward, but that other elements in the VTA, likely accessed via kappa opioid receptors, can activate sexual behaviors and feeding without the apparent involvement of the mesolimbic DA system. The neural elements that mediate dynorphin's action, and the functional heterogeneity of cells of the VTA clearly requires further investigation.

Both morphine and dynorphin$_{1-13}$ increased the frequency of female-directed behavior and the likelihood of mounting. The performance of copulation, itself, was not affected by intra-VTA infusions of the opiates. That is, the effects of the opiates were to facilitate approach to a sexually receptive female and the display of behaviors appropriate to a female conspecific. Consistent with these findings are those from a series of experiments by Leiblich *et al.* (30) and Miller and Baum (41) concerned with the possible role of endogenous opioids in the control of male sexual behavior. They found that naloxone, given two to three weeks following castration, further reduced ejaculation and mounting in rats and significantly inhibited the resumption of mating in sexually exhausted intact males. These results suggested to them that endogenous opioids acted to facilitate sexual behavior by enhancing the positive incentive properties of the female.

Finally, mention should be made of the fact that facilitation of sexual behaviors by morphine found in these experiments could appear to conflict with findings from previous studies of opiates and male sexual behavior. Systemic injections of morphine to gonadally intact or castrated, T-treated male rats has been reported to inhibit sexual behavior (32, 39, 45). It is important to note, however, that most studies of opiate agonist and antagonist effects on male sexual behavior have used either systemic or intraventricular injections. Opiates have a number of different effects mediated by interactions with opiate receptors at different brain, spinal, and peripheral sites, and some of these effects may be incompatible. It is well known, for example, that, given systemically, mu selective agonists such as morphine can produce conditioned place preferences, but paradoxically, conditioned taste aversions; kappa agonists, on the other hand, have been reported to have aversive effects in place preference tests, but to increase food intake (44). Injections of morphine into the periventricular gray area have sedative actions (2), whereas intra-VTA injections of morphine increase locomotor activity (28,54). Thus, in the case of sexual behavior, when given into the VTA, morphine may act to facilitate behavior, but when given systemically or intraventricularly concurrent incompatible actions at other sites may mask this facilitation.

The finding that both mu and kappa receptor selective agonists were able to facilitate sexual behaviors, but that only morphine appeared to activate DA systems might suggest that more than one type of endogenous opioid, released within the region of the VTA and acting upon different neural systems, is normally involved in sexual arousal and perhaps in the arousal of other motivated behavior patterns. A project for the future will be to determine whether mild stressors and conditioned stimuli known to facilitate sexual arousal have their effects via the concerted action of more than one type of endogenous opioid within these same neural systems.

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