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Effects of Receptor-Selective Opioids on Operant Behavior in Morphine-Treated and Untreated Rats

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ADAMS, J. U. AND S. G. HOLTZMAN. *Effects of receptor-selective opioids on operant behavior in morphine-treated and untreated rats*. PHARMACOL BIOCHEM BEHAV **38**(1) 195–200, 1991.—Selective cross-tolerance is often used as evidence to differentiate opioid receptor subtypes. We used this strategy to study operant behavioral effects of the opioid peptides, [D-Ala^2, NMePhe^4, Gly-ol^5]enkephalin (DAGO), [D-Pen^{2,5}]-enkephalin (DPDPE) and dynorphin, agonists highly selective for μ, δ, and κ receptors, respectively. Food-deprived rats were trained to lever-press on a fixed-interval 3-min schedule of food-reinforcement. Time-effect and dose-effect curves were generated for each of the peptides, as well as for morphine, administered ICV, 5 min prior to the 1-h operant session. Experiments were performed on untreated subjects and on subjects receiving chronic infusion of morphine (10 mg/kg/day) from osmotic pumps. In untreated animals, morphine and the μ-selective peptide, DAGO, induced relatively long-lasting dose-related decreases in responding, whereas the non-μ agonists, DPDPE and dynorphin, induced only transient effects: response rates increased at low doses and decreased at high doses. Animals receiving chronic morphine infusion were tolerant to the rate-decreasing effects of morphine and DAGO; ED_{50}s increased by factors of 8 and 6, respectively. There was some evidence of cross-tolerance to DPDPE and of sensitization to dynorphin in the morphine-maintained animals.

Morphine Opioid peptides Cross-tolerance Operant behavior Opioid receptors

OPERANT responding provides a behavioral baseline with which to study drug effects and to quantify changes that occur with chronic drug administration. The effects of opioid drugs on operant behavior have been widely studied and have been shown to be mediated by at least two distinct opioid receptor types, μ and κ (6, 12, 26). Investigation with opioid peptides has indicated a possible role for the δ-opioid receptor, at least in a modulatory fashion (4,32). However, there are no reports on the effects of the opioid peptides, [D-Ala^2, NMePhe^4, Gly-ol^5]enkephalin (DAGO), [D-Pen^{2,5}]enkephalin (DPDPE) and dynorphin, agonists highly selective for μ, δ and κ receptors, respectively, on operant response rates. Thus the first goal of the present study was to characterize the effects of these peptides, as well as morphine, ICV, in rats responding on a fixed-interval 3-min schedule of food-reinforcement.

Selective cross-tolerance is one line of evidence that supports the differentiation of opioid receptors. Chronic administration of morphine, in addition to rendering animals tolerant to morphine, induces cross-tolerance to other μ-opioid agonists. There exist reports of cross-tolerance between morphine and ethylketocyclazocine (EKC), a κ-receptor agonist (7, 20, 31). However, with the development of the more selective κ agonist, U-50,488 (34), lack of cross-tolerance between μ- and κ-opioid receptor agonists has been the more common finding (5, 6, 10, 33). There has been only limited investigation on cross-tolerance to dynorphin (15,19), the putative endogenous ligand for the κ receptor (11). Attempts to differentiate μ- from δ-opioid receptors using the cross-tolerance strategy, on the other hand, have yielded less consistent results (24, 29, 31). Again, this may be due to the relatively low degree of selectivity of the drugs used; that is, the drugs may be acting on more than one receptor subtype. Still, one study showed that the effects of DAGO and [D-Ala^2-D-Leu^5]enkephalin (DADLE) on locomotor activity could not be differentiated with antagonists but could be in morphine-treated animals (16). More recently, compounds with greater selectivity for the δ receptor, e.g., DPDPE (18), have been developed and have been valuable in differentiating μ and δ receptors in cross-tolerance studies (21,22). However, investigation of this compound in morphine-treated animals has been limited to analgesic assays.

In situations where DPDPE or dynorphin have no direct effects, they often have the capacity to modulate the effects of morphine or other μ agonists (9, 21, 25, 32). Because of proposed interactions between opioid receptor types, it was of interest to test these drugs after functional down-regulation of μ receptors via chronic morphine administration, regardless of whether they had an effect in untreated animals. The second goal of the present study, then, was to assess the effects of ICV morphine, DAGO, DPDPE and dynorphin in morphine-treated animals. Morphine

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tolerance was induced and maintained by the continuous infusion of morphine from subcutaneously implanted osmotic pumps (1).

METHOD

Subjects

Animals used were male Sprague-Dawley-derived rats shipped from Charles River Laboratories (Raleigh, NC). They were housed singly and were food-deprived to approximately 80% of their free-feeding weight; rat chow (Purina Rat Chow; Purina Mills, Inc., St. Louis, MO) supplemented food earned during operant sessions (45 mg pellets; Bioserv Inc., Frenchtown, NJ). All rats were housed in laminar flow hoods in a temperature-controlled room with a 12/12-h light/dark cycle.

Surgery

Rats were anesthetized with 45–50 mg/kg pentobarbital, IP, and, if additional anesthetic was required, 25 mg/kg ketamine, IM. A 22-ga stainless steel guide cannula (Plastic Products, Inc., Roanoke, VA) was cut to a length of 5.5 mm and beveled and was surgically implanted into the lateral ventricle. Using a rat stereotaxic apparatus (David Kopf Instruments, Tujunga, CA) with the upper incisor bar set at 3.3 mm below horizontal zero, the cannula was placed at 0.8 mm posterior and 1.4 mm lateral relative to bregma, and 3.5 mm ventral to the skull, and was permanently secured with skull screws (No. $0.80 \times 3/32$ in.) and Cranioplastic cement (Plastic Products). A 28-ga dummy cannula (Plastic Products) was cut to protrude 0.5 mm beyond the tip of the guide cannula and was kept in the implanted cannula except during ICV injections.

Osmotic pumps (2ML4; Alza Corp., Palo Alto, CA) were filled with morphine solutions; the concentration of morphine ranged from 60–70 mg/ml, depending on the weight of the rat and pump flow rate, such that each pump delivered 10 mg/kg/day. Morphine solutions were warmed to 37°C to aid drug dissolution, and filled pumps were kept in 37°C saline until implantation. Rats were anesthetized with 25 mg/kg pentobarbital, IP (Nembutal; Abbott Laboratories, North Chicago, IL), and 50 mg/kg ketamine, IM (Ketaset; Bristol Laboratories, Syracuse, NY); a small incision was made in the interscapular region and morphine-filled pumps were implanted subcutaneously. Wounds were closed with wound clips (Clay Adams, Parsippany, NJ). At the end of four weeks, animals were anesthetized with half the doses cited above, old pumps were removed, and freshly filled pumps were implanted through a second incision.

Experimental Procedure

Experiments were held in standard operant chambers (Coulbourn Instruments, Lehigh Valley, PA), each housed in a ventilated, sound-attenuating cubicle. A single lever, a food receptacle, and a houselight were located on one wall. Session events and data collection were controlled by a Northstar Horizon computer.

Rats were shaped to press a lever for food reinforcement. The number of lever presses required for food presentation was gradually increased before a fixed-interval schedule was instated. The interval was gradually increased to 3 min (fixed-interval 3-min; FI-3) such that the first response made after 3 min had elapsed resulted in food reinforcement. The next interval began after a reinforced response or 10 s, whichever came first (i.e., 10-s limited hold). Operant sessions were one h in duration and animals were run five days per week.

Drug tests occurred not more often than twice a week when drug or vehicle was injected ICV 5 min prior to the start of the operant session. Injections were performed with a 28-ga internal cannula (Plastic Products), which was cut to protrude 0.5 mm beyond the tip of the guide cannula; the internal cannula was connected to a Hamilton syringe (Hamilton Co., Reno, NV) by polyethylene tubing (PE-20; Clay Adams). Injection volumes were usually kept to 2.0 μl; in some cases, larger volumes were necessary to deliver high doses (up to 10 μl). Rats were lightly restrained in a surgical towel to remove dummy cap and insert internal cannula, but were freely moving during injections, which were infused over 60 s. The internal cannula was kept in place for an additional 30–60 s after the injection was complete. Rats in the dependent groups were not tested with drug until they had received morphine infusion for at least two weeks.

Data Analysis

Operant responding data are expressed as percent of control, where control data were obtained by averaging values from three noninjection days preceding test days. Data from sessions following drug tests or surgery were not used. In addition to overall response rate, the temporal pattern of lever-pressing was expressed as quarter-life. This value represents the portion of the 3-min interval elapsed when the rat makes 25% of its total responses. Thus if the rat responded at a constant rate, the quarter-life would equal 0.25. Quarter-life values are also expressed as percent of the control value.

Means are shown with 1 SEM, except where noted otherwise. ED_{50} values were calculated for each animal by linear regression of the portion of the dose-effect curve that had a slope, then averaged for a group mean; confidence intervals were obtained using *t*-values (27). Dose-effect curves were subjected to one factor analysis of variance for repeated measures and Newman-Keuls post hoc tests where appropriate.

Drugs

Morphine sulfate (Penick Co., Nutley, NJ) was dissolved in 0.9% saline. [D-Ala^2,NMePhe^4,Gly-ol^5]enkephalin and dynorphin A (1–17) (both from Peninsula Laboratories, Inc., San Carlos, CA) were dissolved in sterile saline. [D-Pen^{2,5}]enkephalin (Peninsula Laboratories) was first dissolved in a few μl of 10 N acetic acid, and then brought up to volume with sterile water. All drug doses are reported as the free base. Dose ranges were chosen on the basis of published reports of these drugs, administered ICV, producing effects in other in vivo assays [e.g., (4, 14, 20)]. The upper range of DPDPE was limited by drug solubility, and the upper range of dynorphin was limited by the incidence of gross motor effects.

RESULTS

Untreated Subjects

Control rates averaged 21.3 responses/min (range: 10.6–49.4) for 20 rats used. Control quarter-life values averaged 0.62 (range: 0.52–0.70).

Morphine, administered ICV 5 min prior to the one-h operant session, produced dose-related decreases in response rate (Fig. 1; top panels). The rate-decreasing effects of morphine were relatively long-lasting as they persisted throughout the one-h session (Fig. 1A). Morphine selectively decreased overall rate, leaving the pattern of responding, as measured by quarter-life, unaffected (Fig. 1B). The ED_{50} of morphine for decreasing response rate was 2.9 μg (95% confidence limits: 0.92–9.1 μg) and the highest dose tested, 10 μg, virtually abolished responding in 4 out of 8 rats for an overall group average of $30.5 \pm 12.3\%$ of control in nondependent animals.

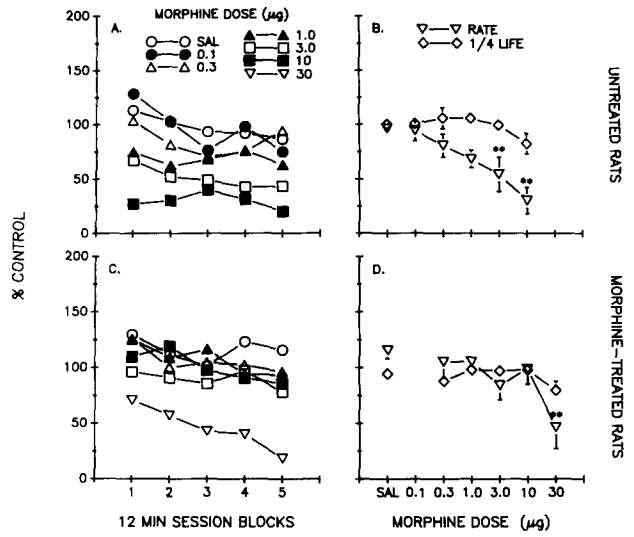

FIG. 1. Effects of ICV morphine, administered 5 min prior to the one-h session, in untreated (panels A and B) and morphine-treated (panels C and D) rats responding on a FI-3 min schedule of food reinforcement. (A and C) Rates of responding in each of 5 subdivisions of the 60-min operant session. Abscissae: Consecutive 12-min blocks. Ordinates: % of control response rate. (B and D) Dose-effect curves for response rate and quarter-life over the entire 60-min session. Abscissae: dose in μg. Ordinates: % of control values. Each point represents the mean of 8 rats except SAL where n = 5 and 0.3 μg where n = 7. Vertical lines in panels B and D represent 1 SEM or are absent if smaller than the radius of the point. *$p<0.05$ compared to saline value. **$p<0.01$ compared to saline value.

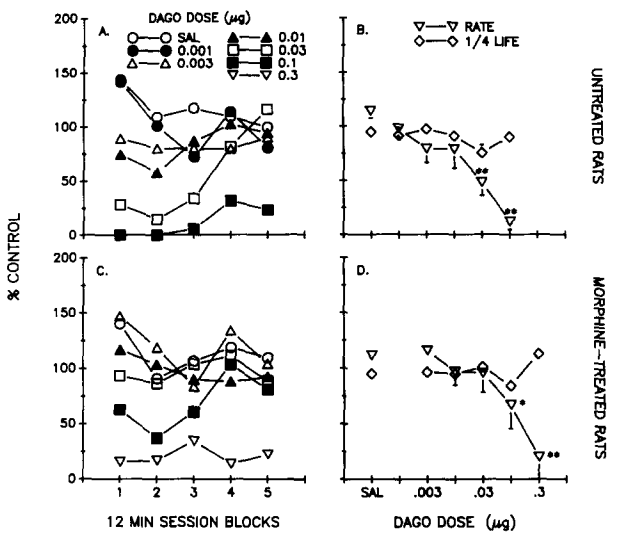

FIG. 2. Effects of ICV DAGO, administered 5 min prior to the one-h session, in untreated (A and B) and morphine-treated (C and D) rats responding on a FI-3 min schedule of food-reinforcement. Panels, axes and other details as in Fig. 1, except that the n ranged from 4–8 for individual doses in C and D.

The μ-selective opioid peptide, DAGO, also produced dose-related decreases in rates of operant responding (Fig. 2; top panels); the duration of rate-suppression was a function of dose as well (Fig. 2A). Thus 0.03 μg reduced rates to as low as 14.4 ± 9.8% of control in the second fifth of the session, but rates recovered to 115.8 ± 25.2 by the final 12-min block. A half log unit higher dose, 0.1 μg, produced rate-suppression throughout the one-h session, although a trend towards recovery can be seen in the later time blocks. Responding was abolished during the first 24 min, but 4 out of 8 rats were responding, albeit at reduced rates, by the end of the hour. Like morphine, DAGO selectively decreased response rate without affecting quarter-life (Fig. 2B). The ED_{50} for the rate-suppressing effect of DAGO was 0.021 μg (95% confidence limits: 0.008–0.054 μg) and the highest dose tested reduced rates to 11.0 ± 7.4% of control.

The δ-selective peptide, DPDPE, produced only modest effects on operant responding in the dose range tested (Fig. 3; top panels). The lowest dose, 0.3 μg, induced slight, but nonsignificant, increases in responding throughout the session (Fig. 3A), which translates to 122.4 ± 12.8% of control rate overall (Fig. 3B). The highest dose tested decreased response rates to 57.3 ± 16.0 and 65.9 ± 14.8 during the first two-fifths of the session; responding recovered later in the hour, and thus the overall decrease in rate did not reach statistical significance. There was no effect on quarter-life at any dose.

Like DPDPE, the κ-selective peptide, dynorphin produced only transient effects in nondependent animals (Fig. 4; top panels). Doses of 3.0 and 10 μg induced rate increases, particularly early in the session; for instance, rates were elevated to 201.1 ± 38.9% of control during the third session block approximately 30 min after 10 μg ICV dynorphin. The only rate decreases were seen during the first fifth of the session after a dose of 30 μg. Response rate not only recovered after this dose, but increased to 152.1 ± 27.4% of control by the fifth session block. The resultant dose-effect curve is a biphasic one (Fig. 4B). Again, there was no significant effect on quarter-life.

Morphine-Treated Subjects

Control rates averaged 14.2 responses/min (range: 5.9–25.2) during morphine treatment for 20 rats used. Control quarter-life values averaged 0.66 (range: 0.55–0.73). These values did not

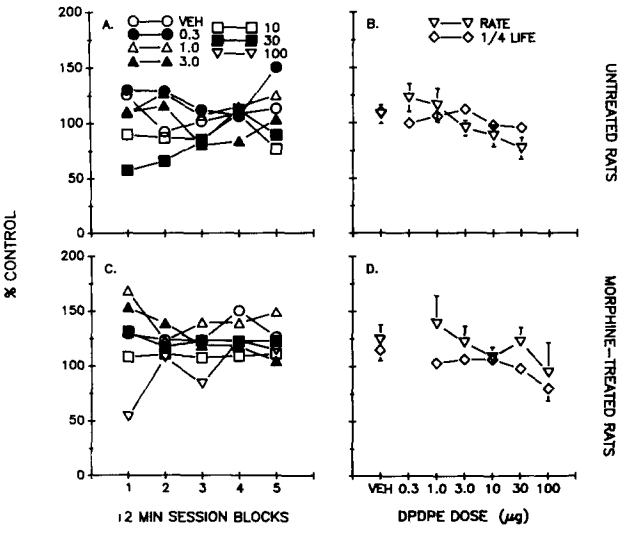

FIG. 3. Effects of ICV DPDPE, administered 5 min prior to the one-h session, in untreated (A and B) and morphine-treated (C and D) rats responding on a FI-3 min schedule of food-reinforcement. Panels, axes and other details as in Fig. 1, except 100 μg where n = 5.

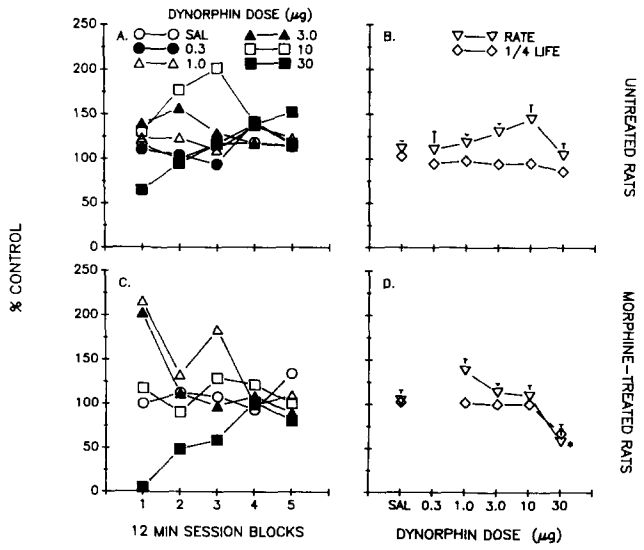

FIG. 4. Effects of ICV dynorphin, administered 5 min prior to the one-h session, in untreated (A and B) and morphine-treated (C and D) rats responding on a FI-3 min schedule of food-reinforcement. Panels, axes and other details as in Fig. 1, except in C and D, doses 1.0 and 3.0 μ where n=4 and 10 μg where n=7.

significantly differ from those obtained before implantation of osmotic pumps in this group of subjects; the average rate was 14.3 responses/min (range: 6.2–23.4) and the average quarter-life value was 0.65 (range: 0.47–0.71). The average duration of chronic morphine infusion was 2.8 months (range: 2–4).

Intracerebroventricular injection of morphine had no effect on operant responding in morphine-maintained rats except at the highest dose tested, 30 μg (Fig. 1; bottom panels). There was a gradual onset of the rate suppression, and the effect persisted throughout the one-h session (Fig. 1C). Overall, the response rate was 46.4 ± 19.4 after this dose (Fig. 1D). The ED_{50} for morphine in tolerant rats was 23 μg (95% confidence limits: 11–50 μg), or 8 times higher than in nontolerant animals.

DAGO produced primarily dose-related decreases in response rates in morphine-treated rats (Fig. 2; bottom panels). The lowest dose of DAGO tested produced slight increases in response rate; however, this was not significantly different than ICV saline injection in these animals. A dose of 0.1 μg produced marked rate suppression of short duration; rates recovered by the fourth session block (Fig. 2C). A half log unit higher dose of 0.3 μg markedly reduced rates throughout the session; 3 out of 4 rats tested with this dose did not respond at all. An ED_{50} of 0.12 μg (95% confidence limits: 0.049–0.28 μg) was calculated for the overall rate-decreasing effects of DAGO (Fig. 2D); this dose is 6 times greater than that required to suppress rates to 50% of control in nontolerant subjects.

DPDPE produced primarily rate increases in morphine-maintained rats (Fig. 3; bottom panels), although these were not significant. The largest effect was with a dose of 1.0 μg ICV DPDPE; rates were increased to 168.1 ± 11.4 during the first 12 min and remained increased throughout the one-h session (Fig. 3C). The only rate suppression observed was after a dose of 100 μg DPDPE; rates were reduced to 53.6 ± 27.4% of control during the first 12 min. Responding recovered to control levels after that, resulting in an overall effect equalling 94.3 ± 27.4% of control (Fig. 3D).

Dynorphin produced increases and decreases in rates of responding in morphine-treated animals (Fig. 4; bottom panels). Doses of 1.0 and 3.0 μg produced very large rate increases, particularly early in the first 12 min, where rates were increased to 215.3 ± 36.0 and 202.4 ± 40.3% of control, respectively (Fig. 4C). With 30 μg ICV dynorphin, rates were suppressed to 4.9 ± 2.1% of control during the first session block and gradually recovered to 102.0 ± 28.2% of control by the fourth block. The overall suppression was 57.6 ± 15.3% of control after 30 μg dynorphin, which was a greater effect than that seen in nontolerant animals (Fig. 4D).

DISCUSSION

Morphine, administered centrally, produced dose-related decreases in operant responding. The ED_{50} for the rate-decreasing effects of morphine administered ICV was 2.9 μg, or 8.3 μg/kg in these 350 g rats. This dose is approximately 200 times lower than the ED_{50} for morphine administered SC in rats that were tested under a similar procedure (1). This potency difference is comparable to other reports of centrally versus peripherally administered morphine doses, and suggests that the rate-decreasing effects of morphine are centrally mediated (4,8). The μ-selective peptide DAGO affected operant responding in a morphine-like manner; that is, dose-related decreases in responding that were relatively long lasting, without affecting the pattern of fixed-interval responding. No increases in response rates were observed at any dose of morphine or DAGO, in contrast to many reports of such an effect occurring at low doses of μ agonists (2, 4, 17).

The δ-selective peptide, DPDPE, had little effect on operant responding, whether using rate or quarter-life as a measure over the dose range tested. The highest dose tested, 30 μg, did induce transient rate-decreasing effects. The doses of DPDPE tested in the present study have been reported to be active in analgesic tests (21). To our knowledge, this is the first report on the effects of DPDPE in animals responding on a schedule of food reinforcement. One study tested the enkephalin analogs Leu- and Met-enkephalinamide and found biphasic effects on response rates, i.e., low doses increased rates and high doses decreased rates (4).

The κ-selective peptide, dynorphin, increased rates of responding at low doses, but had no consistent rate-decreasing effect. Increases in operant response rates are often seen with schedules of reinforcement that generate relatively low rates of responding, like the FI-3 min schedule used here (17, 23, 28). Again, we know of no reports on the effects of dynorphin in animals responding for food. In general, κ agonists, such as EKC and U-50,488, dose-dependently decrease rates of responding after systemic administration (5,26). Like DPDPE, the doses used have been reported to produce other pharmacologic effects, such as catalepsy, analgesia and hypothermia (15,19). The highest dose of dynorphin tested, 30 μg, produced only transient rate-decreasing effects. This short-lived effect may be the result of rapid metabolism of this naturally occurring peptide (14). Similar doses of dynorphin(1–13) have been reported to induce motor effects, the most distinctive being barrel-rolling but also including bizarre postures (15,19). Barrel-rolling was not seen, but some contorted postures were observed in the subjects in this study. A motor deficit could have been responsible for the transient rate disruption seen after 30 μg dynorphin.

Chronic administration of morphine via osmotic pumps induced tolerance to the rate-decreasing effects of centrally administered morphine. The degree of tolerance was approximately twice that seen with morphine administered systemically under conditions of chronic drug administration that were comparable to those of the present study: 8-fold versus 4-fold (1). Morphine-tolerant rats were also cross-tolerant to the rate-decreasing effects of the μ-selective peptide, DAGO; the apparent decrease in potency for DAGO was 6-fold. Cross-tolerance between morphine

and DAGO has been reported for other effects of μ opioids (35). While morphine-induced increases in response rates are often potentiated in morphine-tolerant animals (13), no rate-increasing effects were seen in the present study.

The non-μ agonists, DPDPE and dynorphin, had relatively modest effects on operant responding in the morphine-tolerant rats as well as in the nontolerant animals. Reports of cross-tolerance between agonists at δ and μ receptors have been inconsistent (24, 29, 31). For example, no change or increases in sensitivity were found for the enkephalin analogs, [D-Ala]Leu- and [D-Ala]Met-enkephalinamide, when tested for effects on operant responding in nontolerant and morphine-tolerant rats (4). The low degree of δ-receptor selectivity of the enkephalins may contribute to the variable findings of these cross-tolerance studies; even DADLE is only 4 times more selective for δ receptors than it is for μ (18). Studies using the highly selective δ-ligand DPDPE have found far less cross-tolerance in morphine-maintained rats (21,22). One study that tested the analgesic activity of both DADLE and DPDPE found a nonparallel shift of the DADLE dose-effect curve in morphine-tolerant rats. This resulted in a slope similar to that of the DPDPE dose-effect curve (which did not change with chronic morphine administration), as if the μ component of DADLE-induced analgesia had been removed (22). Although DPDPE did not have a large effect in the present experiments, there was some evidence of cross-tolerance: 100 μg in tolerant rats had less effect than 30 μg in nontolerant rats. Receptor selectivity may be compromised at these high doses; thus it is possible that the small depressant effect of these high doses of DPDPE was mediated by μ-opioid receptors.

Transient rate-decreasing effects were still evident after central administration of high doses of dynorphin; thus there was no cross-tolerance. In fact, the rate-decreasing effects of dynorphin were more prominent in morphine-tolerant than in nontolerant animals. Sensitization to the other effects of dynorphin in morphine-tolerant animals has been reported (15). Also, opposite effects of dynorphin on morphine analgesia in nontolerant versus morphine-tolerant mice have been found (30). Lack of cross-tolerance between μ and κ agonists is consistently reported (5, 6, 24, 33) particularly when selective agonists, such as U-50,488, are used. Thus the lack of cross-tolerance between morphine and the κ-selective peptide dynorphin in rats responding on a schedule of food-reinforcement is consistent with these data, as well as with the few reports on dynorphin tolerance and cross-tolerance in catalepsy and analgesia assays (15,29).

In summary, chronic morphine administration renders animals tolerant to centrally administered morphine and cross-tolerant to the μ-selective peptide, DAGO. There was some evidence of cross-tolerance to the δ-selective agonist, DPDPE, and of sensitization to the κ-selective agonist, dynorphin.

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