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Butorphanol's Efficacy at Mu and Kappa Opioid Receptors: Inferences Based on the Schedule-Controlled Behavior of Nontolerant and Morphine-Tolerant Rats and on the Responding of Rats Under a Drug Discrimination Procedure

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PICKER, M. J., S. S. NEGUS AND R. M. CRAFT. *Butorphanol's efficacy at mu and kappa opioid receptors: Inferences based on the schedule-controlled behavior of nontolerant and morphine-tolerant rats and on the responding of rats under a drug discrimination procedure.* PHARMACOL BIOCHEM BEHAV **36**(3) 563–568, 1990.—The purpose of the present investigation was to characterize the mu agonist and kappa antagonist effects of the mixed opioid agonist/antagonist butorphanol. To this end, the effects of butorphanol were examined: 1) alone and in combination with the kappa agonist bremazocine in nontolerant and morphine-tolerant rats responding under a fixed-ratio 30 (FR30) schedule of food presentation, and 2) in rats trained to discriminate 10 mg/kg morphine from saline. Prior to the induction of morphine tolerance, morphine, bremazocine and butorphanol produced dose-dependent decreases in rate of responding under the FR30. In these nontolerant rats, butorphanol failed to antagonize bremazocine's rate-decreasing effects. During the chronic morphine regimen, the dose-effect curve for morphine was shifted to the right of its prechronic position by approximately 0.9 log units, whereas the bremazocine curve was not altered substantially. The butorphanol dose-effect curve, in contrast, was shifted to the right and flattened such that doses which eliminated responding in nontolerant rats, as well as doses approximately 1.0 log unit higher, had no effect on responding. In these morphine-tolerant rats, butorphanol produced a dose-dependent antagonism of bremazocine's rate-decreasing effects. In rats trained to discriminate morphine from saline, butorphanol substituted completely for the morphine stimulus. Unlike morphine, which produced its stimulus effects only at doses that decreased rate of responding, butorphanol substituted for the morphine stimulus at doses that had little or no effect on rate of responding. The present investigation indicates that butorphanol acts as a kappa antagonist in the morphine-tolerant rat, an effect that is masked by butorphanol's rate-decreasing effects in the nontolerant rat. In addition, the profound degree of cross-tolerance conferred to butorphanol in morphine-tolerant rats and the finding that butorphanol substituted for the morphine stimulus at doses that had no effect on rate of responding suggest that butorphanol is an agonist at the mu receptor with intermediate efficacy.

Rats Butorphanol Morphine Bremazocine Morphine-tolerance Fixed-ratio Kappa antagonist Drug discrimination Cross-tolerance Opioids

BUTORPHANOL is a synthetic morphinan with structural characteristics similar to the opioid antagonist naloxone and the mixed opioid agonist/antagonist nalbuphine. In vitro butorphanol binds nonselectively to mu and kappa opioid receptors (10,30), whereas in vivo butorphanol acts as an agonist or an antagonist at both mu and kappa opioid receptors depending upon the assay and the parameters employed. Butorphanol's characterization as a mu agonist with intermediate efficacy is based on the findings that it produces partial to complete substitution for mu agonists in drug discrimination procedures (19, 23, 25, 29), is self-administered at rates lower than those maintained by the mu agonist codeine (31,33), yet precipitates withdrawal in morphine-dependent animals (9, 21, 31) and antagonizes the effects of high efficacy mu agonists in assays of antinociception (5). That butorphanol increases urinary output to a lesser extent than bremazocine and other high-efficacy kappa agonists, produces a kappa agonist-like dependence profile (31), and antagonizes the urinary output (11,12) and antinociceptive effects (5,21) produced by high-efficacy kappa agonists suggests that butorphanol also acts as a kappa agonist with intermediate efficacy.

Although it is well established that under certain circumstances drugs with low to intermediate efficacy at both mu and kappa

receptors can antagonize the effects of high-efficacy mu and kappa agonists [e.g., (5, 12, 14)], their antagonist effects can be limited by a number of factors (7, 15, 34). For example, we reported recently that buprenorphine displayed kappa antagonist effects in rats rendered tolerant to buprenorphine's mu agonist-mediated response rate-decreasing effects but not in nontolerant rats (15). Interestingly, in that study the chronic morphine regimen used to induce tolerance to buprenorphine's rate-decreasing effects engendered a greater degree of tolerance to buprenorphine than that reported with morphine and other high-efficacy mu agonists (15,20). Like butorphanol, buprenorphine is considered an intermediate efficacy mu agonist, yet substitutes completely for morphine and fentanyl in the drug discrimination procedure (16, 19, 24). Given that butorphanol and buprenorphine share many characteristics, including their intermediate efficacy actions at both mu and kappa receptors, we were interested in determining if butorphanol would display a similar profile. In addition, analysis of the effects of opioids characterized as intermediate efficacy agonists in tolerance and drug discrimination procedures may provide ways of further differentiating their behavioral actions from those produced by high-efficacy mu agonists. Thus, we examined butorphanol's mu agonist effects under two conditions: 1) in rats responding under a fixed ratio 30 (FR30) schedule of food presentation before and during a dosing regimen known to induce morphine tolerance (1,2) and, thus, cross-tolerance to other mu agonists, and 2) in rats trained to discriminate morphine (10 mg/kg) from saline. To determine whether butorphanol's kappa antagonist effects would be revealed in rats rendered tolerant to butorphanol's rate-decreasing effects, we examined its effects when administered in combination with the kappa agonist bremazocine in nontolerant and morphine-tolerant rats responding under the FR30 schedule.

METHOD

Subjects

Male Long-Evans hooded rats were fed a restricted diet that maintained them at approximately 80–85% of their free-feeding body weights (range across rats 300–340 g). Each rat was housed individually with unlimited access to water in a colony maintained on a 12-hr light-dark cycle.

Apparatus

Four plastic and aluminum operant conditioning chambers measuring 25 cm long, 31 cm high, and 25 cm wide were used. Each chamber was equipped with two centrally mounted 5 cm long response levers located 9 cm above the chamber floor and 2.5 cm from the side walls. When operated, a pellet dispenser could deliver a 45 mg Noyes food pellet (P.J. Noyes Co., Lancaster, NH) into a pellet trough, which was mounted under the two levers and approximately 1 cm above the chamber floor. Located 5 cm above each response lever were three stimulus lights. A white houselight was centrally mounted on the front wall, approximately 1 cm below the ceiling. Each chamber was equipped with an exhaust fan which supplied ventilation and white noise to mask extraneous sounds. Scheduling of experimental events and data collection were accomplished through the use of a TRS model IV microcomputer.

Schedule-controlled behavior. All rats used in this group were experimentally naive at the start of this experiment. After preliminary lever-press training, rats were exposed to successive trials in which a 5-min FR component alternated with a 5-min timeout period. During each FR component, the houselight and stimulus lights located above the left response lever were illuminated and 10 reinforcers could be earned under an FR30 schedule. During the timeout period, all stimulus lights were darkened and responses had no programmed consequences. Each session began with the FR component, followed by the timeout period, and alternated thereafter until five FR components were completed. Sessions were conducted 5–7 days per week at about the same time each day.

After rates of responding stabilized under the FR30 schedule, dose-effect curves were determined for morphine, bremazocine and butorphanol, and for butorphanol in combination with bremazocine. All dose-effect curves were determined using a cumulative dosing procedure. Briefly, 10 min prior to the session, rats were administered a single dose of the test drug. A sufficient quantity of drug was then administered at the start of each successive timeout period, which was increased from 5 to 10 min, to increase the total cumulative dose by 0.25 to 0.5 log units. During tests of antagonism, a single dose of butorphanol was administered at the beginning of the session immediately before the first dose of bremazocine; increasing doses of bremazocine were then administered at the start of each timeout until responding for an individual rat was eliminated. During each phase of testing, drugs were given on Tuesday and Friday, whereas saline was administered on Thursday with the data obtained during these sessions serving as the nondrug control data. All injections were administered SC at a volume of 0.5–1.0 ml/kg.

Following the completion of the dose-effect determinations for each of the test drugs, rats were exposed to a chronic dosing regimen which consisted of 24-hour access to drinking water adulterated with 0.1 mg/ml morphine. Over the next 2–3 weeks, the concentration of morphine was gradually increased to 0.5 mg/ml. Due to increases in motor activity and unstable rates of responding, the concentration of morphine for one rat was subsequently decreased to 0.4 mg/ml; for this rat, all testing occurred at this dose of morphine. After rates of responding stabilized at the 0.4 and 0.5 mg/ml concentrations, dose-effect curves for morphine, butorphanol and bremazocine alone as well as for butorphanol in combination with bremazocine were redetermined as described for the prechronic phase.

At the completion of this phase of testing, access to the morphine-adulterated drinking water was suspended. Between 4 and 8 weeks after the termination of the chronic morphine regimen, dose-effect curves for each of the test drugs were redetermined. Drug testing procedures were identical to those described for the prechronic phase of testing.

Discrimination training. All rats had previous experience discriminating 10 mg/kg morphine from saline [see (18)]. Briefly, during training sessions the lights over both response levers were illuminated and the rats received IP injections of either 1.0 ml/kg saline or 10.0 mg/kg morphine, 30 min prior to the start of the session. A random sequence was used to determine which injection was administered, with the restriction that the same injection was not given on more than two consecutive sessions and that the number of saline and morphine injections were approximately equal. When saline was administered, 20 responses on one lever resulted in food delivery (45 mg Noyes pellet), whereas 20 responses on the other lever resulted in food delivery when morphine was administered. Although recorded, lever press responses that were not injection-appropriate had no programmed consequences. Sessions were 20 min in duration and were conducted 5 days per week.

During substitution tests, which were conducted with morphine, butorphanol and bremazocine, doses of each drug were administered IP, 30 min prior to the test session in a volume of 0.5–1.0 ml/kg. All doses of each drug were administered in an irregular order that varied across rats. During these tests, conditions were identical to those described above for discrimination training sessions with the exception that 20 responses on either

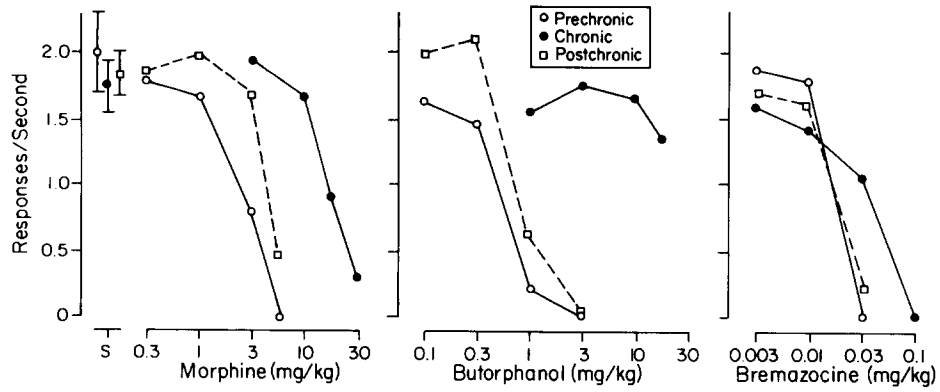

FIG. 1. Effects of morphine, butorphanol and bremazocine on response rates in rats (n = 4) responding under an FR30 schedule of food presentation before (prechronic), during (chronic) and after (postchronic) exposure to a regimen of chronic morphine administration. Abscissae: doses expressed in mg/kg. Ordinate: response rates expressed as responses per second. Values above "S" represent the mean response rates during control sessions for each phase of the experiment; vertical lines represent the S.E.

response lever were followed by food delivery. Substitution tests were conducted on Tuesday and Friday, whereas training sessions were continued on Monday, Wednesday and Thursday. A test drug was considered to produce stimulus effects similar to morphine if the drug produced at least 80% responding on the morphine-appropriate lever prior to the completion of 20 responses on either lever. Only data prior to the completion of 20 responses on either lever were used in the calculation of percent drug-appropriate responding, whereas rates of responding were calculated on the basis of the total number of responses emitted during the entire session.

Drugs

Morphine sulfate (provided by the National Institute on Drug Abuse), bremazocine methanesulfonate (Sandoz Ltd., Basel, Switzerland) and butorphanol tartrate (Bristol-Myers, Wallingford, CT) were dissolved in saline. Doses for all drugs are expressed in terms of the forms described above.

RESULTS

The mean overall rate of responding under the FR30 schedule was 2.02 ± 0.37, 1.74 ± 0.20 and 1.83 ± 0.18 responses/sec during the prechronic, chronic and postchronic phases, respectively (see control data in Fig. 1). Before initiation of the chronic morphine regimen, the average daily consumption of water was 31.4 ± 1.1 ml. Daily water intake decreased slightly following the introduction of 0.1 mg/ml morphine, then increased over the next few days. This pattern was repeated each time the dose of morphine was increased. At the highest morphine concentration, 0.5 mg/ml in three rats and 0.4 mg/ml in one rat, the average daily intake was 30.5 ± 1.3 ml. Based on individual body weights, the average daily dose of morphine was 49.6 ± 3.4 mg/kg with a range across rats of 44.1 to 55.3 mg/kg.

Figure 1 shows the effects of morphine, butorphanol and bremazocine when administered alone during the prechronic, chronic and postchronic phases in rats responding under the FR30. During the prechronic phase, each of these drugs decreased rate of responding in a dose-dependent manner. Based on the dose required to decrease rate to 50% of control levels (i.e., ED_{50}), the dose-effect curves obtained for morphine and bremazocine during the chronic phase were shifted to the right of their prechronic positions by 0.9 and 0.3 log units, respectively. In these morphine-tolerant rats, the dose-effect curve for butorphanol was shifted to the right and flattened such that doses which eliminated responding in the nontolerant rat, as well as doses approximately 1.0 log unit higher, had no effect in the morphine-tolerant rat. Using the highest dose tested (17.5 mg/kg) as the estimate of the ED_{50}, the butorphanol dose-effect curve was shifted at least 1.5 log units to the right of its prechronic position. Following termination of the chronic morphine regimen (i.e., postchronic phase), the ED_{50} doses for morphine, butorphanol and bremazocine returned to within 0.3 log units of their prechronic values.

Figure 2 shows the effects of bremazocine in combination with various doses of butorphanol in nontolerant and morphine-tolerant rats responding under the FR30. In the nontolerant rats, butorphanol produced leftward shifts in the bremazocine dose-effect curve; thus, across the dose range examined, butorphanol did not antagonize the rate-decreasing effects produced by bremazocine. In contrast, in the morphine-tolerant rat butorphanol produced dose-dependent rightward shifts in the bremazocine dose-effect curve. The lowest dose of butorphanol tested (1.0 mg/kg) produced an approximately 0.4 log unit shift in the bremazocine dose-effect curve and the highest dose tested (10 mg/kg) produced a 0.9 log unit shift.

In rats trained to discriminate 10 mg/kg morphine from saline, the administration of the training dose of morphine produced greater than 90% morphine-appropriate responding, whereas the administration of saline produced less than 10% morphine appropriate-responding (see control data in Fig. 3). During morphine training sessions, rates of responding were 53% of those obtained during saline training sessions. When morphine and butorphanol were administered during substitution tests, these drugs produced dose-related increases in morphine-appropriate responding. In contrast to the relatively steep slope characteristic of the morphine dose-effect curve, the butorphanol dose-effect curve was relatively shallow with 88, 66 and 76% morphine-appropriate responding obtained at the 1.0, 3.0 and 10.0 mg/kg doses, respectively. Across the range of doses evaluated, morphine, but not butorphanol, decreased responding in a dose-related fashion. Up to and including doses that decreased rate of responding, bremazocine produced predominantly saline-appropriate responding.

DISCUSSION

The present investigation examined the mu agonist and kappa antagonist effects of butorphanol in rats before and during a

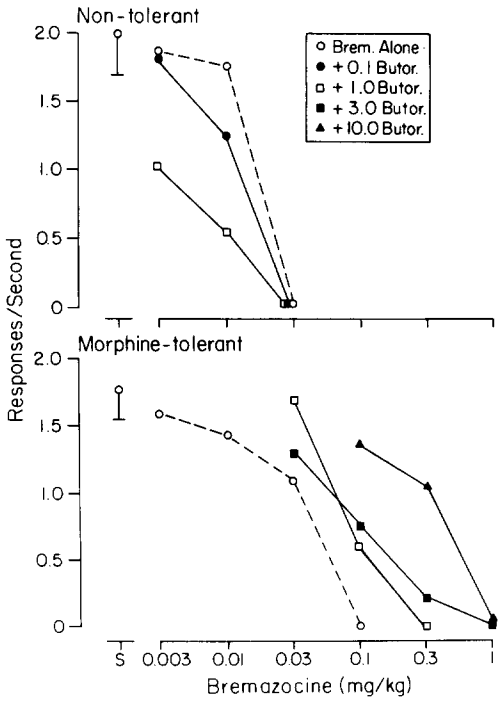

FIG. 2. Effects of butorphanol on the bremazocine dose-effect curve in rats (n = 4) responding under an FR30 schedule of food presentation before (nontolerant) and during (morphine-tolerant) exposure to a regimen of chronic morphine administration. Abscissae: dose of bremazocine expressed in mg/kg. Ordinate: response rates expressed as responses per second. Values above "S" represent the mean response rates during control sessions for each phase of the experiment; vertical lines represent the S.E.

regimen of chronic morphine administration as well as butorphanol's mu agonist effects in rats trained to discriminate morphine (10 mg/kg) from saline. The results of this investigation yielded three important findings. First, the chronic administration of morphine produced tolerance to the rate-decreasing effects of morphine and butorphanol. Such findings are consistent with butorphanol's mu agonist effects reported in other investigations (19, 21, 25); however, in the present investigation butorphanol and morphine could be distinguished on the basis of the extent to which tolerance developed to their rate-decreasing effects. Indeed, during the chronic morphine regimen, the dose-effect curve for morphine was shifted to the right of its prechronic position by approximately 0.9 log units, whereas a conservative estimate of the shift in the butorphanol dose-effect curve was at least 1.5 log units. This rightward shift obtained with butorphanol was considerably larger than those reported previously in the rat for the high efficacy mu agonists fentanyl and *l*-methadone (13,20), but comparable to that reported with the intermediate efficacy mu agonist buprenorphine (15). Taken together, these data suggest that the profound degree of cross-tolerance observed with butorphanol in morphine-tolerant rats is a characteristic effect of an intermediate efficacy mu agonist. Such an interpretation is consistent with receptor theory which predicts that the magnitude of tolerance that develops to a drug's effects should be inversely related to its efficacy, with rightward shifts in the dose-effect curves produced by intermediate efficacy agonists being larger than those produced by high-efficacy agonists [for discussion and example, see (28)].

That morphine-tolerant rats were cross-tolerant to butorphanol is somewhat surprising, however, given the finding that butorphanol, like other compounds that display mu antagonist effects (i.e., low- and intermediate-efficacy mu agonists), can precipitate withdrawal in mu agonist-dependent rhesus monkeys (9,31), mice (21) and humans (22). Indeed, in contrast to the decrease in relative potency obtained for butorphanol's rate-decreasing effects in the present investigation, the potency of opioids with mu antagonist effects typically increase in morphine-dependent animals (1, 17, 20, 32). Although the variables that account for these discrepant findings remain unclear, recent investigations in our laboratory and others suggest that species plays an important role in determining if the relative potency for an opioid's rate-decreasing effects increases or decreases during chronic exposure to morphine. In contrast to butorphanol's effects reported here with rats, butorphanol's relative potency for decreasing rate of responding increases in the morphine-tolerant squirrel monkeys (17), but is unchanged in morphine-tolerant pigeons (unpublished observation). Since the regimens used to induce tolerance in these species resulted in similar degrees of morphine tolerance and enhanced sensitivity to opioid antagonists, it is unlikely that these species-dependent effects obtained with butorphanol reflect differences in the chronic dosing regimens.

Like butorphanol, drugs with agonist effects at more than one opioid receptor have been reported to produce differential effects in morphine-tolerant animals. For example, recent investigations indicate that the relative potency of the mixed mu/kappa agonist ethylketocyclazocine's rate-decreasing effects decreases in morphine-tolerant pigeons, increases in morphine-tolerant squirrel monkeys and mice, and is unchanged in morphine-tolerant rats (3, 4, 20, 27). In contrast to these species-dependent changes in potency for drugs with low selectivity, only decreases in relative potency have been reported in morphine-tolerant animals for highly selective and efficacious mu agonists (3, 4, 20, 27). These data suggest that when efficacy at the mu receptor is inferred from cross-tolerance data, species differences are most evident for opioids with low selectivity, (e.g., butorphanol, ethylketocyclazocine) and least evident for opioids with high selectivity (e.g., morphine, fentanyl).

A second important result obtained in the present investigation was that prior to the induction of morphine tolerance, butorphanol failed to antagonize the response rate-decreasing effects produced by the kappa agonist bremazocine. However, during the chronic morphine regimen, which resulted in an attenuation of butorphanol's mu agonist-mediated rate-decreasing effects, doses of butorphanol that substantially reduced or eliminated responding in nontolerant rats produced a dose-dependent antagonism of bremazocine's rate-decreasing effects. Thus, the present findings extend previous reports which describe the kappa antagonist effects of butorphanol in assays of urinary output (12) and antinociception (5). In addition, these findings suggest further that the kappa antagonist effects of certain opioids can be masked by their own rate-decreasing effects (7,34), and can be revealed in procedures in which the opioid's mu agonist-mediated rate-decreasing effects are attenuated.

A third important result obtained in the present investigation was that butorphanol produced effects similar to high efficacy mu agonists in the drug discrimination procedure insofar as it substituted completely for the morphine stimulus. Complete substitution between butorphanol and various mu agonists has been reported previously in rats (25), pigeons (19) and macaque monkeys (33). While some agonists with low or intermediate efficacy at the mu receptor (e.g., nalbuphine, ethylketocyclazocine) have been shown to substitute for low but not high training doses of morphine (18,26), this would not account for the substitution patterns obtained with butorphanol in the present investigation where a

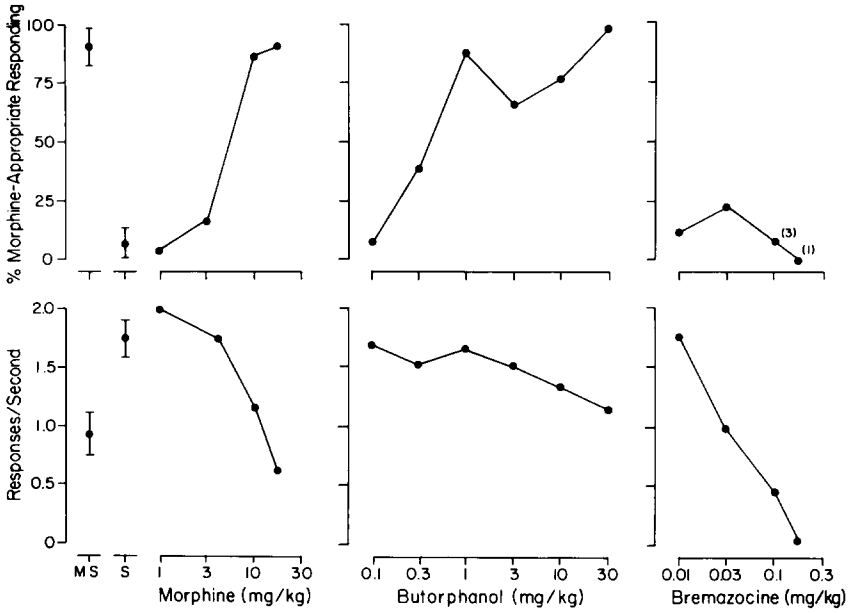

FIG. 3. Effects of morphine (n=5), butorphanol (n=4) and bremazocine (n=4) on percent morphine-appropriate responding and response rates in rats trained to discriminate 10 mg/kg morphine from saline. Abscissae: doses expressed in mg/kg. Ordinate: for top panel, percent morphine-appropriate responding, and for bottom panel, response rates expressed as responses per second. The data for percent morphine-appropriate responding were based only on responses emitted prior to the delivery of the first reinforcer. For these data, the number indicated in parentheses represents the number of rats that completed at least 20 responses on either response lever during the test session; when not indicated a data point was based on all rats tested. The calculation of responses per second were based on responses emitted during the entire 20-min session. The values above "MS" and "S" represent the mean percent morphine-appropriate responding and responses per sec obtained during training sessions in which the training dose of morphine or saline was administered; vertical lines represent the S.E.

relatively high training dose was used to establish the discrimination (18).

Although butorphanol and morphine produced similar discriminative stimulus effects in the drug discrimination procedure, their effects could be distinguished on the basis of their relative potency for producing morphine-like stimulus effects and decreasing rate of responding. Whereas the lowest dose of morphine (i.e., the training dose) that produced at least 80% morphine-appropriate responding substantially decreased rate of responding, butorphanol substituted for the morphine stimulus at doses that had little or no effect on rate. The differential potencies obtained in the present investigation with butorphanol are in agreement with those reported previously for butorphanol (19,25) and buprenorphine (6, 8, 16, 19, 24) in pigeons and rats trained to discriminate morphine or fentanyl from saline. In contrast to the findings obtained with these opioids, the high-efficacy mu agonists morphine, fentanyl, levorphanol and *l*-methadone produce their mu-like stimulus effects only at doses that decrease rate of responding (8, 19, 25). These findings, along with those reported here indicate that a distinguishing characteristic of an intermediate efficacy mu agonist is its differential in potency for producing mu-like stimulus effects and decreasing rate of responding.

An alternative, although not mutually exclusive, explanation of these differences in relative potency is the extent to which tolerance develops selectively to the rate-decreasing effects of intermediate efficacy mu agonists under drug discrimination procedures. This effect was evident in the present investigation when the potency of butorphanol's rate-decreasing effects under the drug discrimination procedure was compared to that under the FR30 schedule. In nontolerant rats responding under the FR30, for example, a dose of 1.0 mg/kg butorphanol virtually eliminated responding, whereas even a dose as high as 30 mg/kg had little effect on rate under the drug discrimination procedure. The extent to which butorphanol's potency for decreasing rates differed between these two procedures was comparable to that reported in rats for buprenorphine (15,16) but considerably greater than that for morphine and fentanyl [(18,20), present investigation]. Taken together, these data indicate that even the intermittent (but not chronic) exposure to high doses of morphine in the drug discrimination procedure was capable of producing a profound degree of tolerance to the rate-decreasing effects of mu agonists with intermediate efficacy.

In summary, the present findings indicate that butorphanol has kappa antagonist effects in morphine-tolerant rats, an effect that is masked in nontolerant rats by butorphanol's rate-decreasing effects. In addition, the profound degree of cross-tolerance conferred to butorphanol in morphine-tolerant rats and the finding that butorphanol substituted for the morphine stimulus at doses that had no effect on rate of responding indicate that in rats butorphanol also acts as a mu agonist with intermediate efficacy.

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