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Phosphodiesterase Inhibitors Potentiate Opiate-Antagonist Discrimination by Morphine-Dependent Rats

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HOLTZMAN, S. G. *Phosphodiesterase inhibitors potentiate opiate-antagonist discrimination by morphine-dependent rats.* PHARMACOL BIOCHEM BEHAV **33**(4) 875–879, 1989.—This study was performed to examine the relevance of the quasi-withdrawal syndrome in nondependent rats to the syndrome precipitated by naltrexone in rats physically dependent upon morphine. Morphine-dependent rats trained to discriminate between SC injections of naltrexone (0.1 mg/kg) and saline were pretreated with 10 mg/kg of a phosphodiesterase inhibitor: 3-isobutyl-1-methylxanthine (IBMX), Ro 20-1724, or papaverine. The naltrexone stimulus-generalization curve and dose-response curve for loss of body weight were shifted to the left by IBMX and Ro 20-1724, which produce quasi-withdrawal, but not by papaverine, which does not. IBMX also potentiated the naltrexone-like discriminative effects and loss of body weight induced by cyclazocine, an opioid agonist-antagonist. Butorphanol, another agonist-antagonist, occasioned choice responding appropriate for saline when tested alone but engendered more than 50% naltrexone-appropriate choice responses in rats pretreated with IBMX. Thus, phosphodiesterase inhibitors that produce an opiate quasi-withdrawal syndrome potentiate interoceptive stimuli and weight loss associated with the withdrawal syndrome precipitated by naltrexone in morphine-dependent rats. Furthermore, they appear to enhance the opiate-antagonist activity of opioids with mixed agonist and antagonist properties.

Drug discrimination Morphine dependence Naltrexone Opiate withdrawal syndrome Opioid antagonist Phosphodiesterase inhibitor Quasi-withdrawal syndrome

INHIBITORS of cyclic nucleotide phosphodiesterase, such as 3-isobutyl-1-methylxanthine (IBMX) and theophylline, can produce behavioral changes in opiate-naive rats that resemble the changes that occur in morphine-dependent rats during withdrawal from morphine (5,6). The opiate "quasi-withdrawal syndrome," like the true opiate withdrawal syndrome, is potentiated by the administration of an opiate antagonist. For example, rats injected with 10 mg/kg of IBMX followed 1 hr later by 1.0 mg/kg of naloxone exhibited a behavioral syndrome that was comparable qualitatively and quantitatively to the syndrome produced when that same dose of naloxone was given to rats treated 24 hr earlier with 150 mg/kg of morphine in a sustained release preparation (9). The withdrawal syndrome precipitated by naloxone in morphine-dependent rats also was potentiated by 1-hr pretreatment with 10 mg/kg of IBMX (9). It has been suggested that the syndrome produced in the rat by the sequential administration of a phosphodiesterase inhibitor and an opiate antagonist can provide a model for studying the cellular bases of opiate dependence and withdrawal (4,8). Indeed, the relative potency order of phosphodiesterase inhibitors for inducing the opiate quasi-withdrawal syndrome correlated significantly with their relative potency for inhibiting low km cyclic AMP phosphodiesterase in rat brain homogenates (2,8).

The purpose of the present study was to examine further the relevance of the behavioral state produced by phosphodiesterase inhibitors in the rat to the state of morphine withdrawal. Rats and pigeons treated chronically with morphine can be trained to discriminate between injections of saline and low doses of an opiate antagonist (7, 11, 15, 23). Stimulus control of behavior by naltrexone in morphine-dependent subjects derives from stimuli that appear to be uniquely associated with and fundamental to the state of opiate withdrawal (15). Because such stimulus control of behavior remains stable and reproducible over many months of testing (11), it is amenable to systematic study. Therefore, phosphodiesterase inhibitors were tested for their ability to potentiate the discriminative stimulus effects of naltrexone and the naltrexone-induced loss of body weight in the morphine-dependent rat. IBMX, a methylxanthine derivative, and Ro 20-1724, a nonxanthine phosphodiesterase inhibitor, were tested at a dosage level effective in producing the opiate quasi-withdrawal syndrome (8); papaverine, a potent phosphodiesterase inhibitor that does not produce the quasi-withdrawal syndrome (8), also was tested. In order to assess the pharmacologic generality of interactions between phosphodiesterase inhibitors and naltrexone, observations were extended to opioids that have agonist as well as antagonist components of action. IBMX was tested in combination with each of two mixed agonist-antagonist opioids, cyclazocine and butorphanol.

METHOD

Subjects

The subjects were nine male rats of Sprague-Dawley descent.

They had been tested with various opiate and nonopiate drugs in an investigation of the discriminative stimulus properties of naltrexone (15) that was completed two weeks before the start of the current study. All of the rats had been receiving morphine on a daily basis for at least four months.

The rats were housed singly in cages that were kept in a closed cabinet that was designed to permit control over the access of each animal to its water bottle (10). The water bottles were fitted with a metal drinking spout that was inserted into the cage for 10 min every six hr, at 5:00 a.m., 11:00 a.m., 5:00 p.m., and 11:00 p.m., every day during the study. The bottles contained a solution of morphine sulfate in a concentration of 0.05% (morphine base content). Daily intake of morphine was determined by weighing the water bottles after the 11:00 a.m. access period on successive days. It was assumed that a change in weight of 1.0 g represented the consumption of 1.0 ml of drug solution. Food was available continuously in the home cage. The cabinet holding the cages was ventilated and was maintained on a 12-hr light:dark cycle.

Discrimination Training and Testing

The rats had been trained to discriminate between injections of saline and 0.1 mg/kg of naltrexone in a two-choice discrete-trial avoidance procedure (19) as described previously (11,15). Sessions were conducted in an operant chamber that contained three response levers. The beginning of a trial was signaled by illumination of the houselight and presentation of white noise. Beginning 5.0 sec later an electric current of constant intensity (1.0–1.3 mA) was delivered to the grid floor of the chamber in 1.0-sec pulses every 3.0 sec. In order to terminate a trial the rat was required to complete a two-response chain. This consisted of depressing the single lever ("observing" lever) mounted in one wall of the chamber and then pressing one of the two levers ("choice" levers) mounted in the opposite wall. The first response on the observing lever turned off the white noise. During test sessions the first response on either choice lever after an observing response extinguished the houselight and ended the trial. During training sessions a trial was terminated only if the rat pressed the choice lever that was appropriate for its current drug state. Although a rat could avoid receiving shocks by completing a trial within 5.0 sec, trials were usually completed only after shock delivery had begun. The interval between trials was 50 sec during which the chamber was illuminated dimly with red light. A session ended after twenty trials or 30 min, whichever came first.

Training sessions were conducted at least three days per week: saline was injected SC 30 min before the training session on Mondays and Thursdays; 0.1 mg/kg of naltrexone was injected 30 min before the training session on Wednesdays. Tests of generalization to novel drug conditions were conducted on Tuesdays and Fridays provided the animal had completed at least 18 out of 20 trials on the choice lever appropriate for its drug state in the preceding three training sessions.

The different drugs were tested in a nonsystematic order. However, the various doses of each drug and the relevant control injections were administered to the subjects in a random sequence. Each of the phosphodiesterase inhibitors or their vehicle was administered 60 min before a session; naltrexone, cyclazocine, butorphanol, or their vehicle was administered 30 min before a session. All training sessions and test sessions took place between 12:00 noon and 4:00 p.m., 1 to 5 hr after a period of access to the morphine drinking solution.

Drugs

The following drugs were used: naltrexone hydrochloride (National Institute on Drug Abuse, Rockville, MD); cyclazocine base (Sterling Winthrop Research Institute, Rensselaer, NY); butorphanol tartrate (Bristol Laboratories, Syracuse, NY); 3-isobutyl-1-methylxanthine (IBMX), papaverine hydrochloride (Sigma Chemical Company, St. Louis, MO); 4-(3-butoxy-4-methoxybenzyl)-2-imidazol-idinone (Ro 20-1724; Roche Laboratories, Nutley, NJ). Cyclazocine and Ro 20-1724 were dissolved in three parts 8.5% lactic acid and 2 parts 1.0 N sodium hydroxide, IBMX was dissolved in 0.1 N sodium hydroxide and 0.9% saline, and the other drugs were dissolved in 0.9% saline. Drug solutions were injected SC in a volume of 1.0 ml/kg of body weight. Doses are expressed in terms of the free base or acid.

Data

The drug discrimination data are presented as the mean number of trials completed in the naltrexone-appropriate choice lever in a 20-trial session. The remaining trials of the session were always completed on the saline-appropriate lever. Change in body weight was determined for the interval from 30 min before a test session to the end of the session, which averaged 50–55 min. The data are shown as percent loss of body weight (mean ± S.E.M.). Dose-response curves were compared to one another in two ways. A relative potency analysis (22) was performed on the ascending limb of dose-response curves for lever selection and percent loss of body weight; potency ratios are presented with their 95% confidence limits. In addition, dose-response curves for percent loss of body weight were evaluated by two-factor analysis of variance for repeated measures (22). The effects of individual pretreatments on body weight were evaluated by a *t*-test for paired observations. *p*-Values of less than 0.05 were considered to be statistically significant.

RESULTS

The daily intake of morphine by the nine rats used in this study averaged 44 ± 2 mg/kg, with the average drug consumption of individual subjects ranging from 33 ± 2 to 50 ± 3 mg/kg. These values are based upon ten observations per animal made periodically over the course of the study. They are similar to values reported in other studies in which morphine was administered by scheduled access to water bottles containing drug solution (1,15).

The rats completed almost every trial on the lever appropriate for the saline condition in test sessions that followed an injection of saline or other drug vehicle; average loss of body weight for the group ranged from 1.8 ± 0.2 to 2.5 ± 0.3% in the vehicle control sessions of the various drug series.

Naltrexone (0.001–0.3 mg/kg) produced orderly dose-dependent increases in trials completed on the naltrexone-appropriate choice lever and in loss of body weight (Fig. 1). At 0.1 and 0.3 mg/kg of naltrexone the group completed an average of 19.0 and 18.7 trials, respectively, on the drug-appropriate lever and lost an average of 7.2 ± 0.6 and 7.9 ± 0.2 of body weight. Pretreatment with 10 mg/kg of either IBMX or Ro 20-1724 shifted the naltrexone stimulus-generalization curve to the left by 3- to 4-fold (Fig. 1). Drug-appropriate responding after 10 mg/kg of IBMX alone was at the upper end of the range seen with vehicle injections, averaging 2.0 trials for the group. Drug appropriate responding after 10 mg/kg of Ro 20-1724 alone, which averaged 3.8 trials, was higher than the level seen in vehicle test sessions.

Dose-response curves for naltrexone-induced loss of body weight also were shifted to the left, by 4- to 6-fold, in rats pretreated with 10 mg/kg of IBMX or Ro 20-1724 (Fig. 1). Analyses of variance revealed significant differences between the curves for naltrexone (0.001–0.03 mg/kg) alone and IBMX +

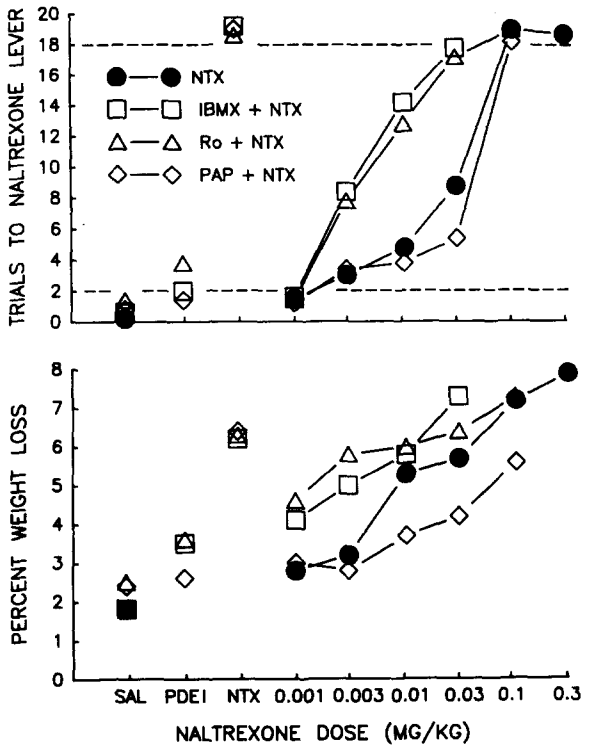

FIG. 1. The phosphodiesterase inhibitors IBMX and Ro 20-1724 (Ro), but not papaverine (PAP), potentiate the discriminative effects of naltrexone (NTX, upper panel) and naltrexone-induced loss of body weight (lower panel) in morphine-dependent rats trained to discriminate between 0.1 mg/kg of naltrexone and saline. Each point in the upper panel is the mean number of trials completed on the naltrexone-appropriate choice lever in a 20-trial session; the remaining trials of the session were completed on the choice lever appropriate for saline. The upper and lower horizontal dashed lines indicate the minimum levels at which the discrimination performance of the animals was maintained in training sessions with naltrexone (0.1 mg/kg) and saline, respectively. Each point in the lower panel is the mean percent loss of body weight during the test sessions. Means are based upon one observation in each of five or six rats. Points above SAL, PDEI and NTX represent data from sessions that followed the administration of saline, 10 mg/kg of a phosphodiesterase inhibitor or 0.1 mg/kg of naltrexone, respectively. Phosphodiesterase inhibitors (10 mg/kg) were administered SC, 60 min before a test session; saline or naltrexone were administered SC, 30 min before a session. The potency of naltrexone after pretreatment with IBMX, Ro 20-1724 or papaverine relative to naltrexone alone is 4.4 (1.8–11.9), 3.0 (1.1–10.2), and 0.7 (0.1–4.4), respectively, for choice lever selection, and 3.9 (1.9–8.4), 5.8 (2.5–16.7), and 0.3 (0.1–0.7) for percent loss of body weight.

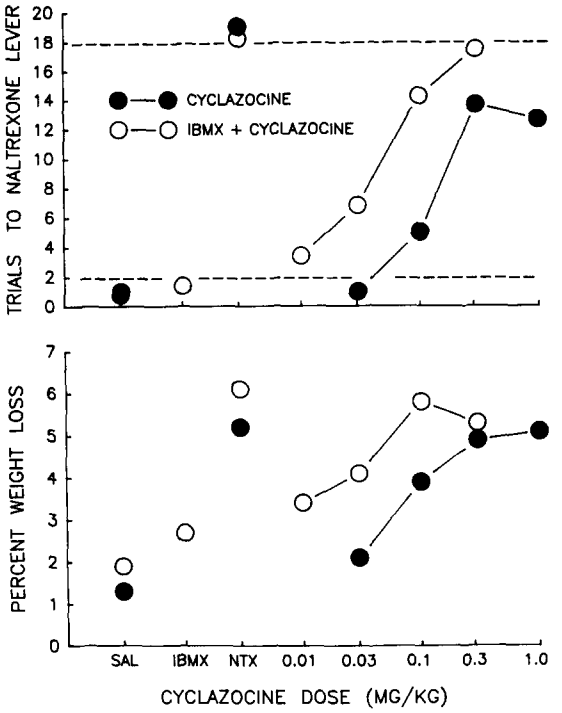

FIG. 2. Pretreatment with 10 mg/kg of IBMX potentiates the naltrexone-like discriminative effects of cyclazocine (upper panel) and cyclazocine-induced loss of body weight (lower panel) in morphine-dependent rats trained to discriminate between 0.1 mg/kg of naltrexone and saline. Other details as in Fig. 1. The potency of cyclazocine after pretreatment with IBMX relative to cyclazocine alone is 4.3 (1.6–14.7) for naltrexone-appropriate lever selection and 6.2 (3.0–16.2) for percent loss of body weight.

naltrexone ($p<0.001$) and for naltrexone (0.001–0.1 mg/kg) alone and Ro 20-1724 + naltrexone ($p<0.005$). There was not a significant pretreatment × naltrexone interaction in either case. IBMX (10 mg/kg) alone increased loss of body weight to $3.5\pm0.3\%$ from $1.8\pm0.1\%$ after vehicle ($p<0.05$). However, Ro 20-1724 (10 mg/kg) did not modify significantly body weight loss relative to its vehicle control: 3.6 ± 0.05 vs. $2.5\pm0.3\%$ ($p>0.1$).

Pretreatment with 10 mg/kg of papaverine did not affect the stimulus generalization curve for naltrexone (0.01–0.1 mg/kg), but attenuated the loss of body weight induced by the antagonist by a factor of almost six (Fig. 1). The difference between the two dose-response curves was highly significant ($p<0.005$). Papaverine (10 mg/kg) alone had no significant affect on either choice-lever selection or weight loss.

Cyclazocine (0.03–1.0 mg/kg) occasioned a dose-dependent increase in trials completed on the naltrexone-appropriate choice lever, which reached a peak of 13.6 trials at 0.3 mg/kg; increasing the dose of cyclazocine to 1.0 mg/kg did not produce a further increase in naltrexone-appropriate responding (Fig. 2). Cyclazocine also produced a dose-dependent loss of body weight, which reached an average of $5.1\pm0.4\%$ at 1.0 mg/kg (Fig. 2). Pretreatment with 10 mg/kg of IBMX shifted the cyclazocine stimulus-generalization curve to the left by a factor of four and increased the maximum number of trials completed on the naltrexone-appropriate lever to an average of 17.4 at 0.3 mg/kg of cyclazocine (Fig. 2). The curve for cyclazocine-induced loss of body weight was shifted to the left by a factor of six in the presence of IBMX (Fig. 2). Analysis of variance performed on the doses of cyclazocine common to both curves, 0.03–0.3 mg/kg, indicated that the curves differed from each other significantly ($p<0.025$). IBMX (10 mg/kg) alone had no affect either on lever selection (1.4 trials to the naltrexone lever vs. 1.0 trials after saline) or on loss of body weight ($2.7\pm0.3\%$ vs. $1.9\pm0.1\%$ after saline; $p>0.05$).

Butorphanol (0.03–3.0 mg/kg) occasioned responding almost exclusively on the lever appropriate for saline over the range of doses examined (Fig. 3). The curve for loss of body weight was biphasic, peaking at $4.5\pm0.7\%$ at 1.0 mg/kg of butorphanol and declining to $3.6\pm0.8\%$ at 3.0 mg/kg (Fig. 3). In animals pretreated with 10 mg/kg of IBMX, those same doses of butorphanol occasioned orderly increases in trials completed on the naltrexone-appropriate lever, which reached an average of 11.2 trials at 1.0 mg/kg (Fig. 3). The ascending limb of the butorphanol

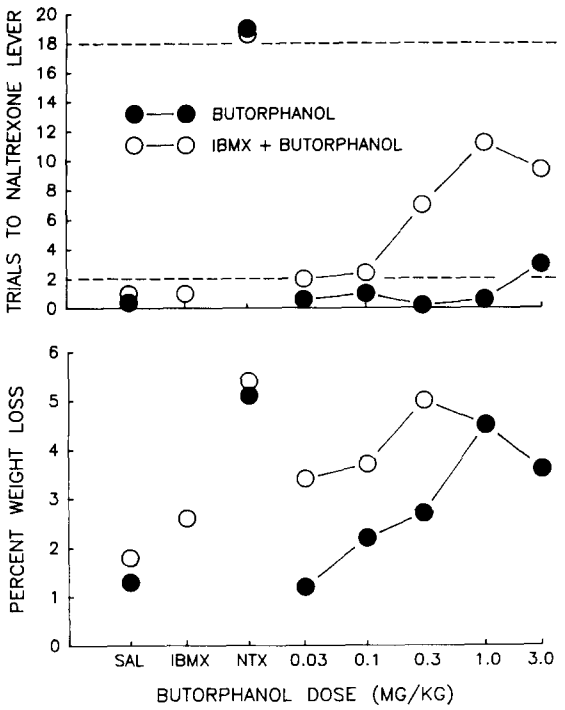

FIG. 3. Pretreatment with 10 mg/kg of IBMX enhances the naltrexone-like discriminative effects of butorphanol (upper panel) and butorphanol-induced loss of body weight (lower panel) in morphine-dependent rats trained to discriminate between 0.1 mg/kg of naltrexone and saline. Other details as in Fig. 1. The potency of butorphanol after pretreatment with IBMX relative to butorphanol alone is 20.8 (4.0–47.9) for percent loss of body weight.

curve for loss of body weight was shifted to the left by a factor of 20 in the presence of IBMX, whereas the descending limb of the curve was largely unaffected (Fig. 3). The two dose-response curves for butorphanol (0.03–3.0 mg/kg) differ from each other significantly ($p<0.025$). Neither of the dependent measures, lever selection and weight loss, was affected by 10 mg/kg of IBMX alone (Fig. 3).

DISCUSSION

IBMX and Ro 20-1724, phosphodiesterase inhibitors that induce a quasi-withdrawal syndrome in opiate-naive rats, potentiated the discriminative stimulus effects of naltrexone in morphine-dependent rats trained to discriminate between injections of naltrexone and saline. The discriminative effects of naltrexone under these conditions derive from interoceptive stimuli arising from the state of antagonist-precipitated morphine withdrawal (15). Loss of body weight, a reliable component of the morphine withdrawal syndrome in the rat (12), also was greater for a given dose of naltrexone in rats pretreated with IBMX or Ro 20-1724 than in unpretreated animals. Weight loss is a measure that is independent of choice lever selection but has been shown to correlate closely with it (11,15). Collectively, these results indicate that certain inhibitors of phosphodiesterase can increase the intensity of the morphine withdrawal syndrome precipitated by naltrexone.

Papaverine, also a potent inhibitor of phosphodiesterase, does not elicit a quasi-withdrawal syndrome (8) and did not potentiate the discriminative effects of naltrexone. The reason for these differences among phosphodiesterases is not clear. However, there exist numerous molecular forms of phosphodiesterase that are differentially sensitive to drugs (21,24). IBMX and Ro 20-1724 may be more effective than papaverine in inhibiting an isozyme involved in the expression of the opiate withdrawal syndrome. Papaverine is particularly effective in relaxing smooth muscle (24). This action of papaverine may account for its ability to attenuate the loss of body weight induced by naltrexone. Weight loss during antagonist-precipitated opiate withdrawal is due primarily to diarrhea (13), which in turn is a function of the smooth muscle tone of the gastrointestinal tract.

IBMX potentiated not only the discriminative effects of naltrexone but also the naltrexone-like discriminative effects of the mixed agonist-antagonist opioids, cyclazocine and butorphanol. Although cyclazocine is an effective morphine antagonist, generalization from naltrexone to cyclazocine appears to be constrained by the agonist activity of the drug (11). In the morphine-dependent rat, IBMX appeared to enhance selectively the antagonist component of action of cyclazocine.

Butorphanol has prominent agonist activity but relatively weak opiate-antagonist activity in rodents (16). In contrast, it is approximately one-tenth as potent as naloxone in precipitating withdrawal in human subjects physically dependent upon methadone (17). Butorphanol alone occasioned responding almost exclusively on the choice lever appropriate for saline. However, pretreatment with IBMX appeared to enhance selectively the antagonist activity of butorphanol, as it had done for cyclazocine, resulting in partial generalization. Weight loss seemed to be a particularly sensitive index of the antagonist actions of butorphanol.

IBMX and Ro 20-1724 inhibit multiple cyclic nucleotide phosphodiesterases. Consequently, it is not possible to ascribe their activity in the discrimination procedure to an effect on a single enzyme or to changes in the intracellular concentration of a particular cyclic nucleotide. However, the findings of this study are consistent with reports that levels of cyclic AMP in neuronal tissue are elevated during opiate withdrawal (18,20), and that injections of cyclic AMP increase the intensity of naloxone-precipitated jumping and weight loss in morphine-dependent mice (14).

Collier and his colleagues suggested that the opiate quasi-withdrawal syndrome could afford a model for studying the cellular mechanisms that underlie the states of opiate dependence and withdrawal (3, 4, 8). The present findings support that suggestion by showing that drugs that produce the quasi-withdrawal syndrome increase the intensity of interoceptive stimuli associated with the withdrawal syndrome in morphine-dependent subjects.

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