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Opioid Agonists/Antagonists in Morphine-Tolerant Squirrel Monkeys

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DYKSTRA, L. A., M. J. PICKER AND K. R. POWELL. *Opioid agonists/antagonists in morphine-tolerant squirrel monkeys.* PHARMACOL BIOCHEM BEHAV **36**(3) 639–644, 1990.—The mu-opioid agonist morphine, the opioid antagonist naloxone and the isomers of the mixed action opioids, cyclazocine, n-allylnormetazocine, and pentazocine were examined in squirrel monkeys responding under a fixed-ratio 30 schedule of food presentation. Dose-effect curves for all drugs were obtained prior to, during, and following a chronic regimen in which monkeys received 6 mg/kg/day of morphine. When compared to the dose-effect curves obtained prior to the chronic regimen, the morphine dose-effect curve obtained during the chronic regimen was shifted to the right 0.5–1.0 log unit, whereas the naloxone dose-effect curve shifted over 3 log units to the left. No changes were observed between the prechronic and chronic dose-effect curves for (+)-cyclazocine, (+)-n-allylnormetazocine, and (+)- or (−)-pentazocine. The (−) isomers of n-allylnormetazocine and cyclazocine shifted 0.6–1.7 log units to the left. These results suggest that the (−) isomers of cyclazocine and n-allylnormetazocine have mu antagonist properties which are revealed during chronic morphine administration.

Opioid agonist/antagonists Morphine tolerance Stereospecificity Pentazocine Cyclazocine
n-Allylnormetazocine Naloxone Fixed-ratio schedule Squirrel monkey

PREVIOUS studies have shown that sensitivity develops to the effects of opioid antagonists following chronic morphine administration. For example, opioid antagonists such as naltrexone and naloxone produce behavioral effects in morphine-dependent animals at doses that produce no observable behavioral effects in nondependent animals (7, 8, 12, 18, 25). Recently, our laboratory has extended these observations by showing that morphine-maintained squirrel monkeys also become sensitive to the rate-decreasing effects of naloxone as well as to some mixed-action opioid agonist/antagonists, namely nalorphine and nalbuphine. Indeed, dose-effect curves obtained for naloxone, nalbuphine and nalorphine in morphine-tolerant squirrel monkeys were 2–3 log units left of those obtained in nontolerant monkeys (16). In contrast to the leftward shifts observed in the dose-effect curves for these drugs, the dose-effect curve for the mixed agonist/antagonist pentazocine was not altered in morphine-tolerant squirrel monkeys.

Given that morphine-tolerant animals are particularly sensitive to opioid antagonists, it is interesting that sensitivity did not develop to pentazocine since it has been shown to have some antagonist properties in other preparations (14,15). One possible reason that morphine-tolerant monkeys did not develop sensitivity to pentazocine may have been the fact that racemic pentazocine was used in these studies. Recent evidence suggests that pentazocine's activity, along with that of a number of other mixed action agonist/antagonists, differs markedly depending on the isomer being examined. For example, the (+) isomer of pentazocine does not have mu or kappa opioid-like activity in the pigeon (17). In contrast, the opioid-like effects of pentazocine are thought to reside in the (−) isomer (17,27). Similar differential profiles have been proposed for the isomers of cyclazocine and n-allylnormetazocine (11, 13, 17, 19, 22, 23, 27).

Given these reports of differential activity of the isomers of pentazocine, cyclazocine and n-allylnormetazocine, it is interesting to determine whether the (+) and (−) isomers of these compounds would be differentially altered in morphine-tolerant animals. We examined the effects of the (+) and (−) isomers of pentazocine, cyclazocine and n-allylnormetazocine in squirrel monkeys responding under a schedule of food presentation. Dose-effects curves were compared under three different conditions: prior to a regimen of chronic morphine, during the regimen and following termination of chronic morphine administration. For comparison, dose-effect curves were also obtained for morphine and naloxone during these conditions.

METHOD

Subjects

Two squirrel monkeys with a previous history of morphine administration were maintained at approximately 80% of free-feeding body weights (approx. 750 g). Monkeys were individually

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housed with continuous access to water in a colony maintained on a 12-hr light-dark cycle. They were fed Purina monkey chow and fresh fruit.

Apparatus

Two small primate cockpits (BRS/LVE 142-11) were used to hold the monkeys in the seated position during the experimental session. On the front wall of each chamber was a centrally mounted lever 2.75 cm long located 9.5 cm directly below a recessed stimulus light which was yellow when illuminated. When operated, a pellet dispenser could deliver a 90 mg banana-flavored Noyes food pellet (P. J. Noyes Co., Lancaster, NH) into a pellet trough located 7.5 cm directly below the response lever. The cockpit was enclosed in a ventilated chamber equipped with white masking noise and two houselights. When illuminated the houselights in one chamber were red and green and in the second chamber were red and blue. Scheduling of experimental events and data collection were controlled by a TRS model III microcomputer.

Behavioral Procedure

Monkeys were trained on a fixed ratio (FR) schedule of food presentation. Initially every response was followed by food presentation and then the response requirement was gradually increased until 30 responses were required for food (FR30). Each session consisted of four 15-min FR components. During each FR component, one stimulus light directly above the lever was illuminated. The component terminated when the monkey received 15 food pellets or after 15 min had elapsed. FR components were separated by 5-min timeout periods during which the stimulus light was extinguished and responding had no programmed consequences. The timeout period was lengthened to 15 min on test days to accommodate drug administration. Each session started with a FR component, followed by a timeout period, and alternated until four FR components were completed. Sessions were conducted 5 days per week at approximately the same time each day.

Pharmacological Procedure

Once each monkey was responding consistently under the FR 30 schedule of food presentation, dose-effect curves were determined for morphine, (+)- and (−)-n-allylnormetazocine, (+)- and (−)-cyclazocine, (+)- and (−)-pentazocine and naloxone using a cumulative dosing procedure. In this procedure, monkeys were administered a single dose of the test drug 15 min before the start of the session. At the beginning of each successive timeout period, a sufficient amount of the drug was administered to increase the total dose administered by ¼ to ½ log units. Dose-effect curves were determined on Tuesdays and Fridays, and four injections of saline were administered on Thursdays as a nondrug control. All drugs and saline were administered IM at an injection volume of 0.3–0.5 ml/kg.

Following determination of these initial dose-effect curves (prechronic condition), monkeys were started on a chronic regimen of morphine administration. Morphine was injected once daily at a dose of 1.0 mg/kg and gradually increased to 6.0 mg/kg. Eventually 3.0 mg/kg of morphine was administered twice daily (once 4 hours presession and once 7–8 hours later). After rates of responding stabilized under this regimen (at least 43 days), dose-effect curves for each of the test drugs were redetermined (chronic condition).

TABLE 1

MEAN RESPONSE RATES (RESPONSES/SEC) FOR INDIVIDUAL MONKEYS DURING CONTROL SESSIONS BEFORE (PRECHRONIC), DURING (CHRONIC) AND AFTER (POSTCHRONIC) EXPOSURE TO A REGIMEN OF CHRONIC MORPHINE ADMINISTRATION IN EACH OF THE FOUR COMPONENTS*

Subject No.	Component	Prechronic	Chronic	Postchronic
6-5	1	1.79 (0.08)	1.83 (0.07)	1.82 (0.06)
	2	1.94 (0.07)	1.73 (0.04)	1.80 (0.04)
	3	2.02 (0.08)	1.87 (0.06)	1.83 (0.07)
	4	1.98 (0.08)	1.89 (0.08)	1.93 (0.10)
	Mean	1.93 (0.06)	1.83 (0.04)	1.85 (0.03)
6-14	1	3.00 (0.11)	2.40 (0.11)	2.87 (0.08)
	2	3.13 (0.06)	2.38 (0.13)	2.99 (0.13)
	3	3.20 (0.10)	2.59 (0.10)	3.36 (0.15)
	4	3.29 (0.14)	2.73 (0.10)	3.22 (0.42)
	Mean	3.16 (0.07)	2.53 (0.06)	3.11 (0.13)

*All data are based on a mean of at least five observations; values in parentheses represent the S.E.

Following the completion of the dose-effect determinations during the chronic morphine condition, daily morphine was suspended. Three to four weeks later dose-effect curves for each of the test drugs were redetermined using procedures identical to those described under the prechronic testing phase (postchronic condition).

Data Analysis

Rates of responding were determined for each monkey by dividing the number of responses that occurred during each FR component by the time spent in that component. These were calculated for each of the 4 FR components and expressed as responses/second. Dose-effect curves were derived by expressing rates of responding following drug as a percent of the control rates of responding. For each dose-effect curve, the dose that reduced rates of responding to 50% of control rates was derived mathematically by log-linear interpolation using only those points on the dose-effect curve that were immediately above and below a 50% reduction in rate of responding.

Drugs

Morphine sulfate, (+)- and (−)-cyclazocine HCl, (+)- and (−)-n-allylnormetazocine HCl, (+)- and (−)-pentazocine succinate (all provided by National Institute on Drug Abuse, Rockville, MD) and naloxone HCl were dissolved in sterile 0.9% sodium chloride.

RESULTS

Control Performance

Table 1 shows mean rates of responding in individual monkeys for each of the 4 FR components within a daily experimental session. In general, mean rates of responding were consistent across the four components of the experimental session. Rates of responding in monkey 6-5 were similar during the prechronic, chronic and postchronic phases of the study, differing by no more than 10%. In monkey 6-14, rates of responding were approxi-

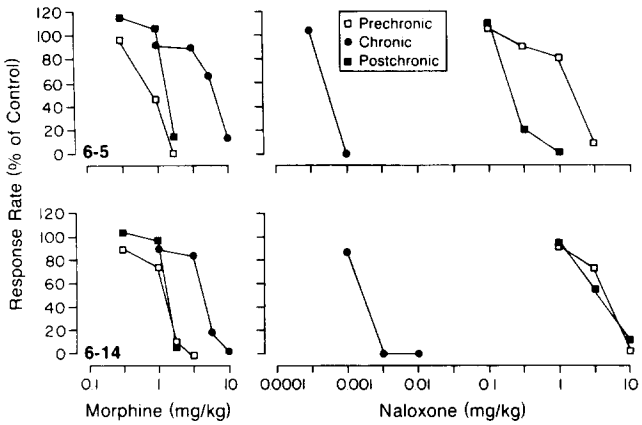

FIG. 1. The effects of morphine (left) and naloxone (right) on rates of responding in two squirrel monkeys under a fixed-ratio 30 schedule of food presentation. Dose-effect curves were determined prior to (□), during (●) and following (■) a regimen of chronic morphine administration. Ordinate: rates of responding expressed in terms of percent of control response rates. Abscissa: cumulative drug dose in milligrams per kilogram body weight. Top graphs represent data from monkey 6-5 and bottom graphs represent data from monkey 6-14.

mately 20% lower during the chronic phase of the study than during the prechronic or postchronic phases.

Morphine and Naloxone

Figure 1 shows the effects morphine and naloxone on response rate for each monkey during the prechronic, chronic and postchronic conditions. During prechronic conditions, morphine (0.3–3.0 mg/kg) produced dose-dependent decreases in rates of responding in both monkeys. Responding was virtually eliminated following the administration of 1.7 mg/kg in one monkey and 3.0 mg/kg in the other monkey.

During the chronic morphine condition, the morphine dose-effect curve shifted to the right in both monkeys. As seen in Fig. 1, a dose of 10.0 mg/kg of morphine was required to eliminate responding in both monkeys during the chronic morphine condition. When the morphine dose-effect curve was redetermined four to five weeks after the termination of the chronic condition, it had returned towards its prechronic position.

Table 2 shows the dose of morphine that reduced rates of responding by 50% in individual monkeys during each phase of the study (ED_{50}). The ED_{50}s for morphine obtained during the prechronic and postchronic conditions were very similar, whereas

TABLE 2

THE DOSE* (mg/kg) OF EACH COMPOUND THAT REDUCED RATES OF RESPONDING TO 50% OF CONTROL RATES DETERMINED FOR INDIVIDUAL MONKEYS (6-5 AND 6-14) DURING PRECHRONIC, CHRONIC AND POSTCHRONIC CONDITIONS

Drug	Prechronic	Chronic	Postchronic	Log Unit Difference Prechronic ⧫ Chronic
Morphine				
6-5	0.76	6.10	1.48	+0.91
6-14	0.95	3.40	1.16	+0.55
Naloxone				
6-5	1.28	0.0006	0.47	−3.37
6-14	4.05	0.0016	3.48	−3.40
n-Allylnormetazocine				
(−) isomer				
6-5	0.19	0.004	0.18	−1.70
6-14	0.27	0.034	0.16	−0.90
(+) isomer				
6-5	1.05	0.44	1.22	−0.38
6-14	1.21	1.19	0.93	−0.007
Cyclazocine				
(−) isomer				
6-5	0.006	0.0014	0.005	−0.63
6-14	0.021	0.0043	0.012	−0.69
(+) isomer				
6-5	1.30	1.38	1.33	+0.03
6-14	1.34	1.04	1.20	−0.11
Pentazocine				
(−) isomer				
6-5	0.63	0.51	1.31	−0.09
6-14	0.70	0.50	1.08	−0.15
(+) isomer				
6-5	6.41	4.56	4.54	−0.15
6-14	6.25	7.0	5.26	+0.05

*Dose estimates for each drug were derived mathematically by log-linear interpolation using only those points on the dose-effect curve that were immediately above and below the dose of each compound that reduced rates of responding to 50% of control rates.

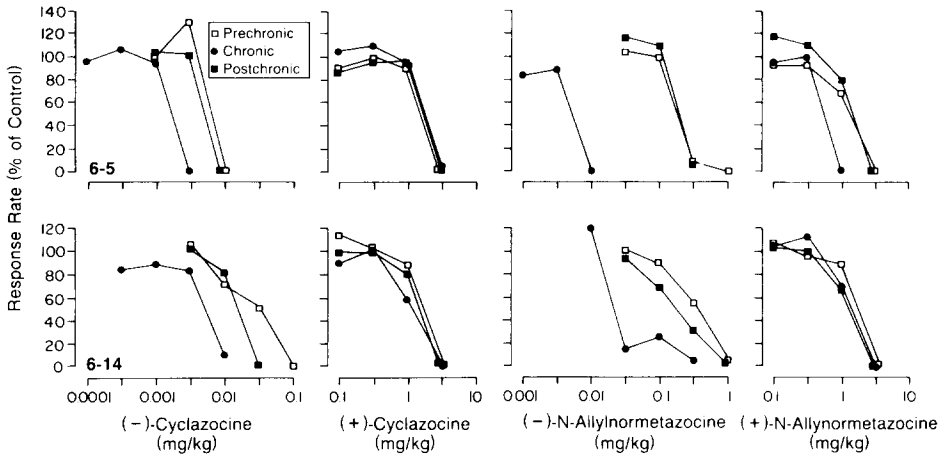

FIG. 2. Effects of (−)- and (+)-cyclazocine and (−)- and (+)-n-allylnormetazocine on rates of responding in two squirrel monkeys under a fixed-ratio 30 schedule of food presentation. Details as explained in Fig. 1.

the ED_{50} obtained for morphine during the chronic condition was approximately one-half log unit larger in monkey 6-14 and almost one log unit larger in monkey 6-5.

Figure 1 also shows the effects of naloxone (0.1–10.0 mg/kg) on rates of responding prior to, during and subsequent to the regimen of chronic morphine administration. During the prechronic condition, a dose of 3.0–10.0 mg/kg naloxone was required to eliminate responding; however, during chronic morphine administration, responding was eliminated by a dose as low as 0.0001–0.003 mg/kg of naloxone, representing more than a 3 log unit shift to the left in the naloxone dose-effect curves of both monkeys (see Table 2). As with morphine, when the naloxone dose-effect curves were redetermined subsequent to the chronic condition, they returned towards their prechronic positions.

Cyclazocine, n-Allylnormetazocine and Pentazocine

Figures 2 and 3 show the effects of the isomers of cyclazocine, n-allylnormetazocine and pentazocine on rates of responding prior to, during and subsequent to the regimen of chronic morphine administration. During the prechronic condition, the (−)isomer of each of these compounds was more potent than the (+) isomer in decreasing rates of responding. In the case of n-allylnormetazocine and pentazocine, the (−) isomer was 5–10 times more potent than the (+) isomer, whereas for cyclazocine the (−) isomer was over 60–200 times more potent than the (+) isomer.

In general, dose-effect curves for the (+) isomers of cyclazocine, n-allylnormetazocine and pentazocine did not change as the result of chronic morphine administration. Moreover, the dose-effect curve for the (−) isomer of pentazocine was not altered when the monkeys were morphine-tolerant. In contrast, dose-effect curves for the (−) isomers of both n-allylnormetazocine and cyclazocine were shifted to the left during the chronic condition and returned to their prechronic position during the postchronic condition. Table 2 shows the ED_{50}s obtained from the prechronic, chronic and postchronic dose-effect curves for each of these compounds. It can be seen that the (−)-cyclazocine dose-effect curve obtained during the chronic condition was shifted approximately 0.6 log units to the left of that obtained during the prechronic condition. For (−)-n-allylnormetazocine, the dose-effect curves obtained during the chronic condition were approximately one or more log units to the left of those obtained during the prechronic condition.

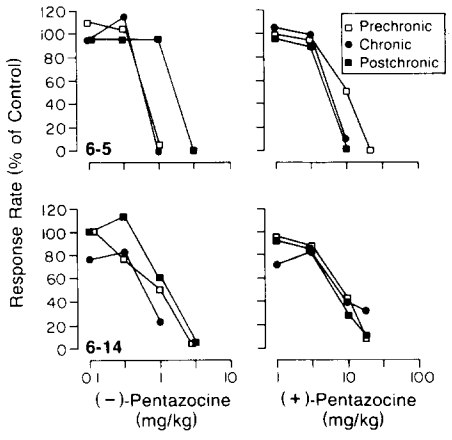

FIG. 3. Effects of (−)- and (+)-pentazocine on rates of responding in two squirrel monkeys under a fixed-ratio 30 schedule of food presentation. Details as explained in Fig. 1.

DISCUSSION

In squirrel monkeys responding under a schedule of food presentation, chronic administration of morphine differentially altered the effects of morphine, naloxone and the isomers of cyclazocine, n-allylnormetazocine and pentazocine. During the chronic morphine condition, the dose-effect curves for morphine shifted to the right, in a manner consistent with previous reports that squirrel monkeys develop tolerance to morphine's effect under these conditions (4,16). In contrast, dose-effect curves for naloxone and the (−) isomers of cyclazocine and n-allylnormetazocine shifted leftward when the monkeys were morphine-tolerant; chronic morphine did not alter the effects of the (+) isomers of cyclazocine, n-allylnormetazocine and pentazocine, nor of the (−) isomer of pentazocine.

The enhancement of naloxone's rate-decreasing effects during the chronic morphine condition is consistent with previous reports that morphine-maintained animals are more sensitive to the rate-decreasing effects of opioid antagonists such as naloxone and naltrexone (2, 6–8, 16, 18). For example, Oliveto and colleagues (16) reported leftward shifts in the naloxone dose-effect curve of 3

log units or more in squirrel monkeys maintained under chronic morphine conditions similar to those used in the present study. Moreover, leftward shifts such as these have been reported under a number of other conditions in which animals received morphine chronically and are generally thought to be a sensitive indicator of opioid antagonist activity (3, 9, 24, 26).

Given that morphine-induced sensitivity to a drug's rate-decreasing effects may reflect opioid antagonist activity, it is interesting that leftward shifts were also observed with the (−) isomers of n-allylnormetazocine and cyclazocine, however, the magnitude of these shifts was less than that observed with naloxone. Limited data are available about the antagonist activity of these compounds. (−)-Cyclazocine has been shown to be much more potent than (+)-cyclazocine as an antagonist of morphine's rate-decreasing effects in pigeons (14). Similarly (−)-n-allylnormetazocine, but not (+)-n-allylnormetazocine, has been shown to antagonize the rate-decreasing effects of morphine in both pigeons and squirrel monkeys (11) as well as the analgesic effects of morphine in squirrel monkeys (19). Thus, it appears that the present findings confirm previous observations that the (−) isomers of some benzomorphans have opioid antagonist effects (25).

The fact that dose-effect curves for the (−) isomer of pentazocine did not shift leftward suggests that (−)-pentazocine lacks antagonist activity in this preparation. This is in keeping with other reports indicating that although racemic pentazocine does have mu antagonist properties, these are very weak (5, 14, 15, 28). For example, racemic pentazocine either does not precipitate withdrawal in morphine-dependent monkeys, or only does so at very high doses (25,28). In addition, (−)-pentazocine does not antagonize the rate-decreasing effects of morphine in pigeons, whereas both (−)-cyclazocine and (−)-n-allylnormetazocine do (11,13).

Thus, given pentazocine's profile, it is not surprising that the (−)-pentazocine dose-effect curve did not shift leftward in morphine-tolerant squirrel monkeys. On the other hand, pentazocine also has opioid agonist activity and this activity is thought to reside in the (−) isomer (17,27). Thus, it is possible that the (−)-pentazocine dose-effect curve would shift rightward in morphine-tolerant squirrel monkeys as has been shown with other opioid agonists such as methadone (4,16). Indeed, the dose-effect curve for (−)-pentazocine shifts rightward in morphine-tolerant rats and pigeons (Picker, personal communication). On the other hand, it has been suggested that monkeys are less sensitive to the agonist actions of 6,7-benzomorphans than are other species (25).

Finally, it should be noted that the lack of shift in the dose-effect curves for (+)-cyclazocine, (+)-n-allylnormetazocine and (+)-pentazocine is in keeping with a number of studies which indicate that the (+)isomers of these compounds are not mediated by mu or kappa opioid receptors (1, 10, 20, 21, 23).

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