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Effects of LY150720 (Picenadol), A Novel Mixed-Action Opioid, on Schedule-Controlled Responding in the Squirrel Monkey[1]

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CARTER, R. B. AND L. A. DYKSTRA. *Effects of LY150720 (picenadol), a novel mixed-action opioid, on schedule-controlled responding in the squirrel monkey.* PHARMACOL BIOCHEM BEHAV **21**(5) 779–786, 1984.—The opioid LY150720 is a racemic mixture whose resolution results in a highly stereospecific separation of agonist and antagonist activity. The effects of LY150720 (0.3–3.0 mg/kg), its agonist (dextro) isomer LY136596 (0.3–1.7 mg/kg) and morphine (0.03–1.0 mg/kg) were studied alone and in combination with naloxone (0.001–1.0 mg/kg) in squirrel monkeys whose responding was maintained under a multiple fixed-ratio 30-response fixed-interval 5-minute (mult FR-30 FI 5-min) schedule of food presentation. LY150720, LY136596 and morphine generally decreased responding under both schedule components, although in several instances increases in responding under the FI component were noted, particularly following LY150720 and LY136596. Naloxone (0.1–3.0 mg/kg) generally had little effect on responding, whereas the antagonist (levo) isomer LY136595 (0.3–10.0 mg/kg) decreased responding under both schedule components. The rate-decreasing effects of morphine, LY150720 and LY136596 were reversed by naloxone; doses of naloxone required to reverse the effects of all three drugs were comparable. When combined with morphine, naloxone restored rates and patterns of responding to control values, whereas combinations of LY150720 or LY136596 and naloxone increased responding under the FI component in excess of control values. These increases appear to be due to anticholinergic actions of LY150720 and LY136596, as they are reversed by physostigmine (0.01 mg/kg) and similar increases are produced by scopolamine (0.01–0.1 mg/kg).

LY150720 (picenadol) Mixed agonist-antagonist Phenylpiperidine Opioid Schedule-controlled behavior Squirrel monkey

OPIOIDS that possess both agonist and antagonist properties are of considerable interest as potential analgesics. Many opioids with this dual capacity have been synthesized in hopes that they would retain agonist properties sufficient to provide effective pain relief, but antagonist properties that would preclude the development of physical dependence and abuse [17,29]. Of these, several such as pentazocine, nalbuphine and butorphanol have found their way into clinical use [14].

Recently, a phenylpiperidine derivative possessing both opioid agonist and antagonist activity was described that may be distinctly different from other mixed-action opioids. LY150720 (picenadol) is a unique racemic mixture whose resolution results in a highly stereospecific separation of opioid agonist and antagonist activity [16, 25, 37]. Its opioid properties appear to arise from strong *mu* agonist actions of the *d*-isomer and weak *mu* competitive antagonist actions of the *l*-isomer. LY150720 also differs from previously described opioids in that it exhibits an unprecedented affinity for *delta* opioid binding sites with a *mu/delta* binding ratio of 1 for the *d*-isomer and 0.5 for the *l*-isomer [16].

LY150720 has been shown to possess antinociceptive activity in a number of analgesiometric assays, including: mouse acetic-acid writhing, rat tail-jerk, mouse hot-plate, mouse phenylquinone-writhing, and squirrel monkey electric shock titration tests [1, 3, 16, 37], although it is inactive in the mouse tail-flick test [1]. Primary dependence and drug self-administration studies suggest that LY150720 possesses low physical dependence and abuse liabilities ([1,36], Woods, personal communication).

The purpose of the present experiment was to compare the effects of LY150720 and its isomers on schedule-controlled responding in the squirrel monkey. The effects of a wide variety of opioid compounds have been studied on

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behavior maintained under multiple fixed-ratio fixed-interval (mult FR FI) schedules of food presentation [4, 7–9, 21–24, 26, 27, 32, 33, 35]. Extensive use of this type of schedule-controlled performance to characterize the behavioral effects of opioids makes it well suited for collecting data on a new compound such as LY150720, since comparisons to a wide variety of opioid agonists and antagonists can be easily made. In the present study, the effects of LY150720, its agonist isomer (LY136596) and morphine were studied alone and in combination with naloxone. The effects of the antagonist isomer (LY136595) and naloxone were also compared. During the course of these studies, it appeared that these compounds possessed anticholinergic properties. Thus, the effects of scopolamine were examined for comparison. In addition, the effects of selected doses of these compounds were determined in combination with physostigmine.

METHOD

Animals

Three adult male squirrel monkeys (*Saimiri sciureus*) were individually housed in a room of constant temperature (75°F) with a 12-hr day-night cycle (0700–1900 hr light). Two monkeys had previous experimental histories which consisted of exposure to morphine, naloxone and scopolamine while responding under a discrete-trial auditory discrimination, whereas one monkey was experimentally naive (S-845). Monkeys were maintained at approximately 80% of their free-feeding weights (760–820 g) by food presented during the experimental session (Noyes banana pellets) and by postsession and weekend supplemental feedings consisting of Purina Monkey Chow and a vitamin C tablet. Their diet was also supplemented with fresh fruit. Water was freely available in the home cage.

Behavioral Test Apparatus

A small primate test chair (model 142-11, BRS/LVE, Beltsville, MD) maintained in a sound- and light-attenuating ventilated enclosure in an isolated room was used. Monkeys were restrained in the seated position by a waist lock. A response lever (BRS/LVE model 121-05) was mounted in the center of the front wall, 8.5 cm below a recessed circular light panel. The panel was illuminated by light from two GE 1820 lamps passed through either clear or red Kodak Wratten gelatin filters. A lever press with a minimum force of 30 g defined the measured response and produced an audible click within the test chamber. A food cup was located directly below the lever into which 190 mg Noyes banana pellets were dispensed. Continuous white noise was present inside the chamber to mask extraneous sounds. Programming and recording equipment was located in an adjacent room.

Behavioral Test Procedure

The multiple fixed-ratio 30-response fixed-interval 5-minute (mult FR-30 FI 5-min) schedule used in the present experiment may be described as follows. When the FR-30 component was in effect, the light panel was illuminated by a white stimulus light and the 30th lever press produced a banana pellet. When the FI 5-min component was in effect, the light panel was illuminated by a red stimulus light and the first response after 5 min had elapsed produced a banana pellet. Components were separated by a 30 sec time-out period during which all lights were extinguished and responding had no programmed consequence. During each component a 60-sec limited hold was programmed This means that during the FR-30 component the animal had 60 sec to make the required thirty responses and receive a banana pellet, whereas during the FI 5-min component the animal had 60 sec after 5 min had elapsed to make a response and obtain a banana pellet. Schedule components alternated after each pellet presentation or after the limited hold elapsed in a component. Sessions always started with the FR-30 component and terminated after 24 components had been presented. Sessions were conducted Monday through Friday at approximately the same time each day.

Pharmacological Procedure

The drugs used and the forms in which the doses were calculated were as follows: LY150720 (*d,l-m*-(1,3-dimethyl-4-propyl-4-piperdyl) phenol hydrochloride:Picenadol), LY136595 (*l-m*-(1,3-dimethyl-4-propyl-4-piperdyl) phenol hydrochloride), LY136596 (*d-m*-(1,3-dimethyl-4-propyl-4-piperdyl) phenol hydrochloride) (gifts from Eli Lilly and Company, Indianapolis, IN), morphine sulfate (provided by the National Institute on Drug Abuse, Rockville, MD) naloxone hydrochloride (gift from Endo Laboratories, Garden City, NJ), (−)-scopolamine hydrochloride and physostigmine sulfate (purchased from Sigma Chemical Company, St. Louis, MO). All drugs were dissolved in distilled water and distilled water was used for control injections. Injections were made into the thigh muscle in a volume of 0.5 ml/kg of body weight, 10 min prior to the start of the session. When two injections were given, one injection was given into the right thigh muscle and the other injection was given into the left thigh muscle, with injections no more than 5 sec apart. Except as otherwise noted, drug injections were given no more than twice a week (usually on Tuesdays and Fridays). Injections of distilled water were given on Thursdays of each week with the data obtained serving as non-drug-injection control data. Dose-response functions were determined once in each monkey with some doses repeated; doses were administered in mixed order.

Data Analysis

Average rates of responding in FR and FI components were computed in responses per second. Data from distilled water injection days that occurred during the determination of a particular dose-response curve served as control data for that drug. Rates of responding on drug days were divided by the mean control response rate and multiplied by 100 to obtain drug effects as percent of control responding in individual monkeys. Cumulated responses within successive tenths of the FI were used to calculate a quarter-life value, a statistic that is independent of response rate and which is used to describe quantitatively the pattern of positively accelerated responding that occurs within the interreinforcement interval of the FI. The quarter-life value is defined as the proportion of the FI required for the animal to emit 25% of the total responses in the FI [10,12]. In addition, a cumulative record was obtained which shows responding as a function of time.

RESULTS

Control Performance

Mean rates of responding after control injections for FR and FI components of the multiple schedule and quarter-life

TABLE 1
CONTROL RATES OF RESPONSE

Monkey	FR Rate*	Fl Rate	Quarter Life†
S-875	2.28 (1.84–2.81)	0.08 (0.05–0.11)	0.73 (0.65 ± 0.78)
S-845	1.34 (1.11–1.53)	0.36 (0.27–0.42)	0.64 (0.58–0.70)
S-872	0.96 (0.85–1.11)	0.26 (0.22–0.31)	0.64 (0.57–0.72)

*Mean response(s)/second (range).
†Mean proportion of FI (range).

values are shown in Table 1 for individual monkeys. Control performances were similar to those previously reported for squirrel monkeys responding under mult FR FI schedules of food presentation [4, 8, 9, 18, 33]. Responding under the FR component was characterized by a brief pause followed by a high steady rate of responding which persisted until food was presented. Responding under the FI component was comprised of an initial period of little or no responding followed by a gradual positive acceleration in responding which continued until food presentation. Quarter-life values indicate that 75% of the total responses emitted in the FI occurred during the last one-third to one-quarter of the interval. Responding seldom occurred during the 30-sec time-out period that separated each alternation of schedule components.

Effects of Opioid Agonists Under the Multiple Schedule

The effects of morphine, LY150720 and LY136596 on rates of responding and quarter-life values are shown in Fig. 1. Morphine generally produced only dose-related decreases in responding in both FR and FI components as a function of increasing dose. Whereas a dose of 0.03 mg/kg of morphine generally had no effect on responding, doses of 0.3–1.0 mg/kg produced marked suppression of both FR and FI responding in all three monkeys. In two monkeys, decreases in rates of responding following morphine were similar under both FR and FI components of the multiple schedule; however, in monkey S-845, responding was decreased to a greater extent in the FI component than in the FR component. Slight increases in FI rates of responding after morphine occurred in monkey S-872.

Under the FR component increasing doses of LY150720 produced only dose-related decreases in rates of responding in all three monkeys. The effects of LY150720 on FI responding differed among the three monkeys. In monkey S-845, LY150720 produced only dose-related decreases in responding under the FI component, whereas in monkeys S-875 and S-872, LY150720 increased rates of responding in the FI component at doses that did not affect decreased FR response rates. LY150720-induced increases in rates of responding under the FI component were much greater and occurred over a broader dose range in monkey S-872 than in S-875. LY150720 also produced a dose-related decrease in quarter-life values in all three monkeys.

The effects of LY136596 on mult FR FI responding were qualitatively similar to those observed with LY150720. In

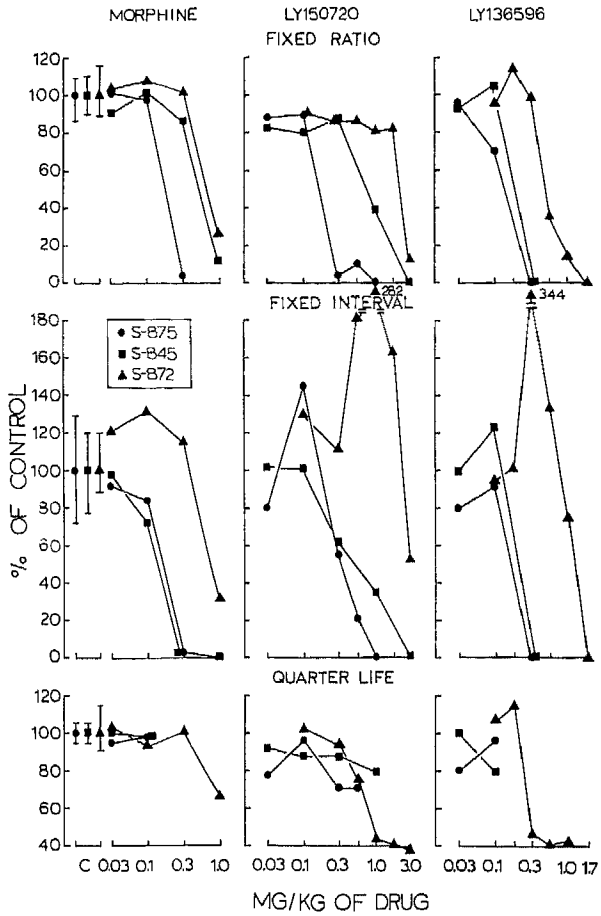

FIG. 1. Effects of morphine, LY150720 and LY136596 on responding under the FR-30 schedule component (top), the FI 5-min schedule component (middle) and on the quarter-life value for the FI 5-min component (bottom) in individual monkeys. Ordinate: rates of responding and quarter life as percent of control values after water injection. Abscissa: dose of drug in milligrams per kilogram of body weight. The brackets above C represent the range of control values following water injection in each individual monkey. Quarter-life values were not calculated for determinations with FI rates below 0.001 response/second.

monkeys S-875 and S-845, LY136596 produced only dose-related decreases in responding under both FR and FI components as a function of increasing dose; decreases were similar under both components. In monkey S-872, LY136596 increased rates of responding in the FI component at doses that did not affect FR response rates, whereas higher doses decreased rates of responding under both FR and FI components. The effects of LY136596 on quarter life were inconsistent except in monkey S-872, in which a marked dose-dependent decrease in quarter-life values was observed.

Effects of Opioid Antagonists Under the Multiple Schedule

The effects of naloxone and LY136595 on rates of responding and quarter-life values are shown in Fig. 2. Monkeys exhibited differential sensitivity to naloxone's effects. In monkey S-872, naloxone (1.0–10.0 mg/kg) produced marked dose-related decreases in responding under both FR and FI components as a function of increasing dose; responding was

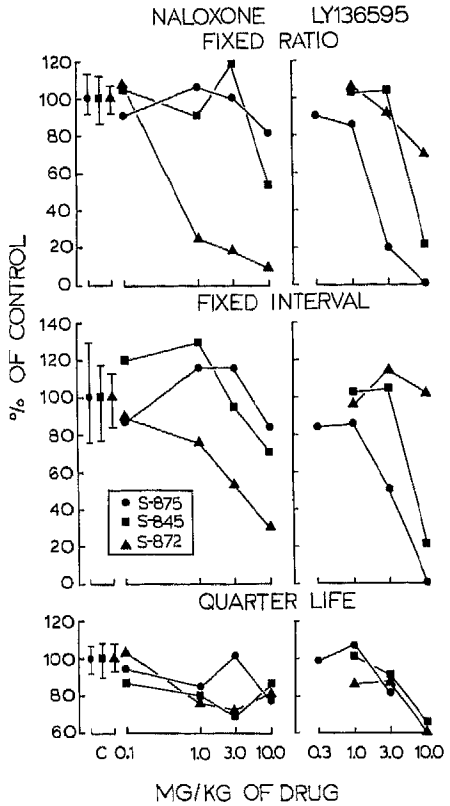

FIG. 2. Effects of naloxone and LY136595 on responding under the multiple FR-30 FI 5-min schedule in individual monkeys. Details are as in Fig. 1.

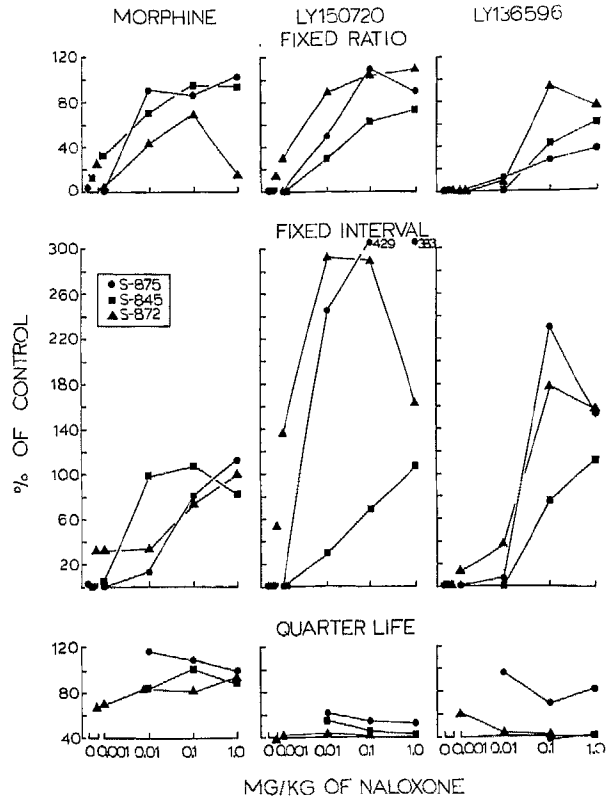

FIG. 3. Effects of naloxone in combination with a high dose of morphine, LY150720 or LY136596 on responding under the multiple FR-30 FI 5-min schedule in individual monkeys. The points above 0 represent the effect of each agonist administered alone in each individual monkey. Doses used were: 0.3, 1.0 and 1.0 mg/kg morphine; 1.0, 3.0 and 3.0 mg/kg LY150720; and 0.3, 0.3 and 1.7 mg/kg LY136596 for monkeys S-875, S-845 and S-872, respectively. Other details are as in Fig. 1.

decreased to a greater extent in the FR component than in the FI component. In monkeys S-875 and S-845, naloxone did not consistently affect responding in the FR component at doses up to 3.0 mg/kg. A dose of 10.0 mg/kg naloxone did, however, decrease FR responding in both monkeys. Under the FI component, naloxone (0.1–1.0 mg/kg) produced a slight increase in responding in monkey S-845, whereas FI responding was slightly decreased at a dose of 10.0 mg/kg. Decreases in quarter-life were noted in some monkeys at some doses.

LY136595 produced only dose-related decreases in responding under both FR and FI components. Again, monkey S-872 differed from the other two monkeys. Whereas LY136595 markedly decreased FR rates of responding in monkeys S-875 and S-845, it only slightly decreased FR rates in monkey S-872. Responding under the FI component in monkey S-872 was not affected by any dose of LY136595, whereas marked decreases were observed in monkeys S-875 and S-845. Dose-dependent decreases in quarter-life values, however, occurred in all three monkeys.

Effects of Opioid Agonists in Combination With Naloxone Under the Multiple Schedule

Naloxone was studied in combination with the dose of morphine, LY150720 or LY136596 that produced the greatest effect on mult FR FI responding in each individual monkey (see Fig. 1). These effects are shown in Fig. 3. Naloxone antagonized the rate-decreasing effects of a high dose of morphine at doses far below those that affected responding when administered alone. Whereas a dose of 0.001 mg/kg of naloxone produced little if any reversal of morphine's effects, doses of 0.01 to 1.0 mg/kg restored responding under both FR and FI components towards control levels. At the highest doses of naloxone (0.1–1.0 mg/kg), antagonism was complete in monkeys S-875 and S-845 (i.e., rates of responding were restored to control levels), but was not complete in monkey S-872. Since S-872 was particularly sensitive to the rate-decreasing effects of naloxone. naloxone's own rate-decreasing effects may have interfered with its ability to reverse morphine's effects completely in this monkey [8,18].

The effects of a high dose of LY150720 on FR responding were also reversed in a dose-dependent fashion by doses of naloxone far below those that affected responding when given alone (0.01–1.0 mg/kg). Complete reversal was obtained in two of three monkeys. The effects of naloxone in combination with LY150720 under the FI component differed among monkeys. In monkey S-845, naloxone produced a dose-dependent antagonism of LY150720's effects, whereas in S-872 and S-875 combinations of naloxone and LY150720 increased rates of responding under the FI component well above control levels. Indeed, these increases were in excess of those previously observed following ad-

ministration of LY150720 alone. Quarter-life values were decreased in all three monkeys.

When administered in combination with LY136596, naloxone produced effects similar to those observed when it was given in combination with LY150720. Naloxone antagonized the effects of a high dose of LY136596 on responding under the FR component in a dose-dependent manner. Complete reversal was obtained in one of three monkeys under the FR component and in all three monkeys under the FI. Under the FI component, monkeys differed in their response to combinations of naloxone and LY136596. In monkey S-845 naloxone produced a dose-dependent reversal of the effects of a high dose of LY136596. In monkeys S-872 and S-875, naloxone-LY136596 combinations increased FI rates of responding in excess of control levels. Although these increases were not as large as those obtained with naloxone-LY150720 combinations, they occurred in the same two monkeys. Quarter-life values were also decreased in all three monkeys.

Effects of Scopolamine Under the Multiple Schedule

The effects of scopolamine on rates of responding and quarter-life values are shown in Fig. 4. Under the FR component scopolamine decreased rates of responding in all three monkeys. The effects of scopolamine on responding under the FI component differed among the three monkeys. In monkey S-845, scopolamine produced only dose-related decreases in FI responding, whereas in monkeys S-875 and S-872, scopolamine increased rates of responding in the FI component at doses that did not affect FR response rates. These two monkeys differed in their response to a given dose of scopolamine. For example, whereas a dose of 0.056 mg/kg of scopolamine completely suppressed FI responding in monkey S-875, this dose increased responding 118% of control in monkey S-872. It is important to note that these are the same two monkeys in which FI rate increases occurred previously following LY150720 and LY136596 alone and in combination with naloxone. Quarter-life values were decreased in two of three monkeys.

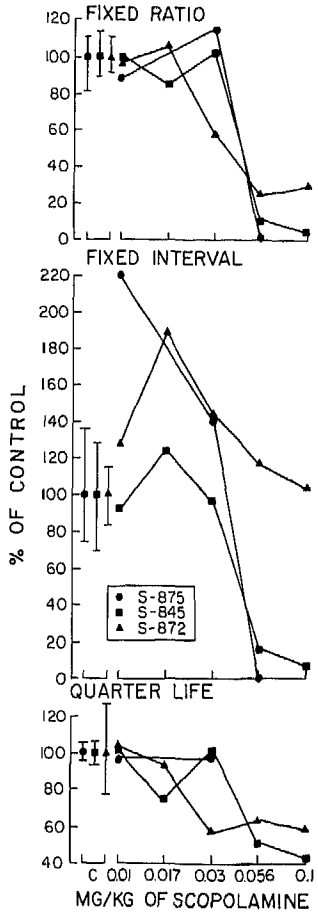

FIG. 4. Effects of scopolamine on responding under the multiple FR-30 FI 5-min schedule in individual monkeys. Details are as in Fig. 1.

Effect of Physostigmine on Rate Increases Under the FI Component

To examine further the increases in FI rates of responding that occurred in monkeys S-872 and S-875, the effects of 0.01 mg/kg of physostigmine were studied in combination with doses of LY150720 or LY136596 that either alone or in combination with naloxone produced maximal increases in FI response rates. Results of these combinations are shown in Table 2. Rate increases produced by LY150720 or LY136596 alone or in combination with naloxone were reversed by a dose of physostigmine that did not affect responding when given alone. The dose of 0.01 mg/kg physostigmine was selected on the basis of dose-response determinations which showed it to be just below threshold for producing effects when given alone (data not shown).

DISCUSSION

The results show that morphine, LY150720 and LY136596 generally decreased responding under both components of a mult FR FI schedule, although in several instances increases in rates of responding under the FI component were noted, particularly following LY150720 and LY136596. These results are similar to those previously reported for morphine in squirrel monkeys responding under mult FR FI schedules of food presentation [8,9]. These results differ, however, from those shown previously for LY150720 and LY136596 in pigeons responding under a mult FR FI schedule of food presentation [27]. Increases in FI rates of responding following LY150720 and LY136596 were not reported in that study. The reason for this discrepancy may lie in the species used, as the effects of phenlypiperidine opioid agonists have previously been shown to differ in these two species. For example, although meperidine often increases responding maintained under FI schedules in pigeons [26], increases typically do not occur in squirrel monkeys [35]. Moreover, whereas the rate-decreasing effects of meperidine on FI responding in squirrel monkeys are reversed by naloxone [35], they are not in pigeons [26].

Naloxone generally had little effect on responding under either component of the multiple schedule, although marked decreases in rates of responding under both components were noted in one monkey. In contrast, LY136595 generally decreased responding under both components of the multiple schedule, although again differences in sensitivity occurred between monkeys. These results are similar to those previously reported for naloxone in squirrel monkeys responding under mult FR FI schedules of food presentation [8, 9, 18].

TABLE 2
MAXIMUM INCREASE IN FI RESPONDING*

Monkey	LY150720	LY136596	Naloxone/ LY150720	Naloxone/ LY136596
S-872	282	344	290	179
+Physostigmine†	101	105	148	121
S-875	144		429	230
+Physostigmine†	97			109

*Expressed as percent of control response rate.
†0.01 mg/kg.

These results are also consistent with those reported for the effects of LY136595 on mult FR FI responding in pigeons [27].

Naloxone effectively antagonized the rate-decreasing effects of morphine, LY150720 and LY136596 under both components of the multiple schedule. Moreover, the dose of naloxone required to reverse the effects of each of these drugs was roughly comparable. These doses (0.1–1.0 mg/kg) correspond to doses of naloxone required to antagonize the effects of morphine in squirrel monkeys responding under schedules of food presentation [8, 9, 35], electric shock presentation [2,35], shock avoidance [13] and shock titration [6]. These doses stand in contrast, however, to the larger doses of naloxone required to reverse the effects of ethylketazocine in squirrel monkeys responding under schedules of food presentation [33] and electric shock titration [5].

The ability of naloxone to antagonize the effects of opioids purported to exert their actions through different opioid receptors varies considerably. Thus, the dose of naloxone required to reverse the effects of opioids that act on *kappa* or *sigma* receptors is greater than that required to reverse the effects of opioids that exert their effects through activation of *mu* receptors [11, 15, 19, 24, 30, 34]. The doses of naloxone that reversed the effects of morphine, LY150720 and LY136596 in the present study were found to be similar. Therefore, the present data are consistent with the notion that the rate-decreasing effects of LY150720 and LY136596 in squirrel monkeys responding under a multiple schedule of food presentation are, like those of the prototypic *mu* agonist morphine, mediated by *mu* opioid receptors. This finding is consistent with previous reports which indicate that LY150720 and LY136596 produce their effects by actions at the *mu* opioid receptor [16,37] and do not possess significant *kappa* or *sigma* receptor activity [20, 27, 28].

Whereas the rate-decreasing effects of morphine, LY150720 and LY136596 were reversed by similar doses of naloxone, the effects of LY150720 and LY136596 combined with naloxone differed from those of morphine combined with naloxone. In two monkeys, combinations of LY150720 or LY136596 and naloxone increased rates of responding under the FI component in excess of control levels. In contrast, when combined with morphine, naloxone restored rates and patterns of responding to control values. These results are similar to those previously reported for combinations of meperidine or normeperidine and naloxone on FI responding in squirrel monkeys [35]. These results differ, however, from those shown previously for combinations of LY150720 or LY136596 and naloxone in pigeons [27]. Although the rate-decreasing effects of LY150720 and LY136596 on FI responding in squirrel monkeys were reversed by naloxone, they are not in pigeons. In general, the effects of phenylpiperidine opioids on schedule-controlled behavior in pigeons have been reported to be non-naloxone reversible [21, 22, 26]. Inability to reverse effects of phenylpiperidine opioids on schedule-controlled responding with naloxone has also been reported in rats [23]. Inasmuch as the rate-decreasing effects of LY150720 and LY136596 in the present study and of meperidine and normeperidine in the study by Witkin *et al.* [35] were reversed by naloxone, a species difference in response to phenylpiperidine opioids is suggested. These results are consistent with the more general finding that phenylpiperidine opioids possess, in addition to their morphine-like properties, activity that is distinctly unlike that of morphine [21–23, 26, 27].

Whereas combinations of LY150720 or LY136596 and naloxone produced marked increases in FI responding, increases were also sometimes observed following LY150720 and LY136596 alone. Although the response to a given drug or drug combination varied markedly across monkeys, increases occurred in a systematic fashion within individual monkeys. For example, one monkey (S-872) exhibited marked increases following LY150720 and LY136596 administered alone or in combination with naloxone. Another monkey (S-875) exhibited marginal increases following combinations of LY150720 or LY136596 and naloxone. Conversely, the third monkey (S-845) failed to exhibit increases in excess of control levels under any condition. That increases following combinations of LY150720 or LY136596 and naloxone did not occur in all monkeys and that increases sometimes occured following LY150720 or LY136596 alone, distinguishes these results from those obtained previously for meperidine and normeperidine in squirrel monkeys and suggests possible differences in the pharmacologic basis for the increases observed in these two studies. In this regard, it is of interest that similar patterns of individual sensitivity to the rate-increasing effects of drugs in squirrel monkeys responding under FI schedules of food presentation have previously been reported to occur with compounds that possess anticholinergic activity [31]. Both LY150720 and LY136596 possess significant anticholinergic properties as demonstrated by their ability to antagonize the behavioral effects of oxotremorine and displace [^{3}H]-QNB from muscarinic binding sites [27]. The notion that FI rate increases observed in the present study were due to the anticholinergic properties of LY150720 and LY136596 is supported by the finding that scopolamine increased FI rates in the same two monkeys in which increases previously occurred and failed to increase rates in the one monkey in which FI rate increases did not

previously occur. This notion is further supported by data demonstrating that increases produced by LY150720 or LY136596 either alone or in combination with naloxone were reversed by physostigmine.

In summary, the effects of LY150720 and LY136596 in squirrel monkeys responding under a multiple schedule of food presentation were found to be similar in many respects to those of morphine. The rate-decreasing effects of LY150720, LY136596 and morphine under this baseline appear to be due largely to the action of these drugs at the *mu* opioid receptor. The effects of LY150720 and LY136596 were found to differ in several respects from those of morphine. These differences appear to be due to anticholinergic properties of LY150720 and LY136596 and perhaps also to nonopioid effects peculiar to opioids possessing the phenylpiperidine structure.

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