Pharmacology Biochemistry & Behavior, Vol. 15, pp. 65–70, 1981. Printed in the U.S.A.

Behavioral Effects of Phenylpiperidine Narcotic Antagonists

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Received 9 December 1980

LEANDER, J. D. *Behavioral effects of phenylpiperidine narcotic antagonists.* PHARMAC. BIOCHEM. BEHAV. 15(1) 65–70, 1981.—The effects of three phenylpiperidines were studied in pigeons responding under a multiple fixed-ratio 30-response, fixed-interval 5-minute schedule of grain presentation. The first one studied was LY-27372 which has narcotic agonist analgesic effects but not antagonist activity. It decreased responding in both components and was not antagonized by naloxone. The two other drugs, LY-88329 and LY-99335, are tri-alkyl-4-phenylpiperidines which have narcotic antagonist activity. They decreased responding at doses of 5 and 40 mg/kg, respectively, when administered alone. When administered in combination with 20 mg/kg of morphine, they antagonized morphine's effects at 0.16 and 0.08 mg/kg respectively. A 10 mg/kg dose of pentobarbital attenuated the behavioral suppressant effects of 40 mg/kg of LY-99335, but not the suppressant effects of 5 mg/kg of LY-88329 or of 10 mg/kg of LY-27372. The data show that LY-99335 has a large separation between the doses which antagonize morphine and those which alone produce behavioral suppression by a proconvulsant effect at higher doses.

Narcotic antagonism Phenylpiperidine Schedule-controlled responding Pigeons

CHANGING the N-methyl substitution of morphine to an N-allyl group produces the narcotic antagonist, nalorphine [19]. Likewise, substitution of N-allyl for the N-methyl group on levorphanol and oxymorphone produces the narcotic antagonists levallorphan and naloxone, respectively [19]. In the 4-phenylpiperidine series of narcotic analgesics (meperidine, as an example; Fig. 1), substituting an N-allyl group for the N-methyl group on an agonist, however, does not produce a narcotic antagonist [8].

Recently, narcotic antagonist activity has been reported for several drugs in the 4-phenylpiperidine series [20]. Apparently, a 3-methyl substitution was the important determinant in producing narcotic antagonists in the phenylpiperidine series, since even compounds with N-methyl substitutions produced narcotic antagonist effects. The purpose of the present research was to study on schedule-controlled responding the narcotic antagonist effect of 2 members of the 1,3,4-trialkyl-4-phenylpiperidine series and compare their effects to an analogue lacking the antagonist effects. The first compound selected for study was LY-27372 (Fig. 1; compound VIIm in [16]). LY-27372 lacks the 3-methyl substitution and exhibits no morphine antagonist effects in mice and rats (D. M. Zimmerman, 1980, personal communication). However, it is a fairly potent narcotic agonist [16]. LY-27372 was studied alone and in the presence of naloxone to determine if the effects produced by LY-27372 on schedule-controlled responding could be antagonized by naloxone. Previous work has shown that the effects of meperidine, normeperidine, and several other phenylpiperidines on schedule-controlled behavior are not antagonized by narcotic antagonists [10, 11, 12, 14, 15], whereas the effects of morphine, methadone, etonitazene, fentanyl, and other narcotic agonists are readily antagonized [4, 6, 10, 14, 15, 18].

The other two compounds studies were LY-88329 and LY-99335 (Fig. 1; compounds V and I in [20]). These drugs were studied alone and in the presence of a behavior suppressing dose of morphine to determine over what range of doses these drugs would antagonize the effects of morphine on schedule-controlled responding. Both of these agents have been shown to be antagonists of morphine's effects in mice and rats without any sign of narcotic agonist effects [20]. LY-99335 has a methyl in place of the propyl group in LY-27372 as well as a 3-methyl on the piperidine ring which results in narcotic antagonist properties. LY-88329 is the most potent racemic compound in the series reported, having an antagonist potency similar to naloxone [20]. LY-99335 and LY-88329 have been reported to be without narcotic agonist activity in the mouse writhing test when administered at a dose of 100 mg/kg, subcutaneously [20]. Due to this lack of effect in an analgesic test which is sensitive to mixed narcotic agonist/antagonists such as pentazocine and nalorphine, LY-88329 and LY-99335 have been called "pure" narcotic antagonists [20].

A dose of each of these meperidine analogues was administered simultaneously with a 10 mg/kg dose of pentobarbital in order to determine if the behavioral suppressing effects of these drugs could be attenuated by pentobarbital.

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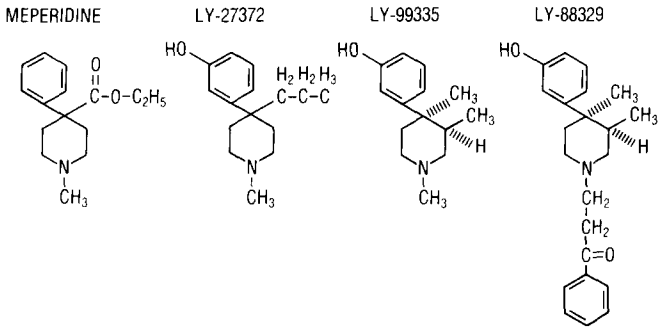

FIG. 1. Structural formulas of the three agents used in the present study and, for comparison, meperidine.

The behavioral suppressing effects of meperidine, normeperidine, and related phenylpiperidine analogues have been shown to be attenuated by 10 mg/kg of pentobarbital, suggesting that the behavioral suppression is due to proconvulsive effects of these agents [12,13].

METHOD

Animals

Seven male White Carneaux pigeons from the Palmetto Pigeon Plant (Sumter, SC) were housed in individual wire mesh cages and maintained at 80% of their free-feeding weight by pigeon grain presented during experimental sessions and by postsession supplemental feedings. Water and oyster shell grit were continuously available in the home cages of the birds, and water was available in the test chamber during experimental sessions. The three birds (2248,4513, and 4632) used for the majority of the study had extensive and varied histories of responding under multiple schedules of food presentation and with injections of diverse psychoactive drugs prior to the initiation this study. The four birds studied with the drugs in combination with pentobarbital were relatively drug naive compared to the other three birds.

Apparatus

The experimental chambers were sound-attenuating and ventilated [5]. The experimental space was 29 cm high×27 cm wide×29 cm long. A translucent plastic response key, 2 cm in diameter, was mounted in the center of a wall inside the chamber, 22 cm above the wire mesh floor. The response key could be transilluminated by red or blue lights. A peck with a minimal force of 0.15 N operated the key and defined a response. Below the response key was a rectangular opening through which the pigeon could be given access to mixed grain. The experimental space was illuminated by a 7.5 watt bulb. During the 4-sec grain presentation cycle, all lights in the test chamber were off except one illuminating the grain. Relay programming and recording equipment in an adjacent room controlled events and recorded the data.

Procedure

The multiple fixed-ratio 30-response, fixed-interval 5-min schedule (mult FR-30, FI-5) can be described in the following manner [5]. When a blue light transilluminated the response key, the 30th response produced the 4-sec grain presentation (FR-30). When a red light transilluminated the response key, the first response to occur after 5 min elapsed produced grain presentation (FI-5). A 40-sec limited hold was in effect in both components; i.e., in the FR component, the bird had 40 sec to emit the 30 responses, and in the FI component, the bird had up to 40 sec after 5 min had elapsed to respond and produce grain presentation. Schedule components alternated after each grain presentation or when the limited hold elapsed. Sessions were conducted Monday through Friday for 1 hr each day, and began in the FR component.

Administration of Drugs

The drugs used and the form in which doses were calculated are morphine sulfate, sodium pentobarbital, meperidine hydrochloride (donated by Sterling-Winthrop Research Institute, Rensselaer, NY), naloxone hydrochloride (donated by Endo Laboratories, Inc., Garden City, NY), LY-88329: (±)-3-4β-(m-hydroxyphenyl)-3β,4α-dimethylpiperidine propiophenone maleic acid, LY-99335: (±)-m(1,3α, 4α-trimethyl-4β-piperidyl)phenol hydrochloride, and LY-27372: 4-(m-hydroxyphenyl)-4-propyl-1-methylpiperidine hydrochloride. LY-88329, LY-99335 and LY-27372 were graciously supplied by D. Zimmerman of Lilly Research Laboratories, Indianapolis, Indiana 46206. All drugs except LY-88329 were dissolved in distilled water, and distilled water was used for control injections. LY-88329 was dissolved in dilute hydrochloric acid with warming. All injections were administered in the breast muscle usually in a volume of 1 ml/kg, 10 min before the 60-min test sessions began. Doses of LY-88329 above 1.25 mg/kg were given by using a 1.25 mg/ml solution and increasing the volume injected to obtain the desired dose. When the interactions of two drugs were studied, injections of each drug were administered within 15 sec of each other in no systemaic order in opposite sides of the breast muscle. Injections of drugs were administered no more frequently than twice a week (usually on Tuesdays and Fridays). One or two injections of distilled water were given on Thursdays of each week, and the data obtained on Thursdays served as nondrug control data.

Measurement of Drug Effects

Average rates of responding for each individual bird during the FR and FI components were computed in responses per second from digital counters and elapsed-time meters. Drug effects were then calculated as a percent of the mean control values obtained on sessions when distilled water was injected as the vehicle control (usually Thursdays). The responses within successive tenths of the FI-5 were used to calculate a quarter-life value, a statistic that is independent of response rate and is used to describe quantitatively the positively accelerated pattern of responding that occurs during the FI schedule. The quarter-life value is defined as the percentage of the FI required for 25% of the total responses to be emitted [7,9].

RESULTS AND DISCUSSION

The average non-drug rates of responding under the FR component of the multiple schedule were quite high (ranging from 2.4 to 3.5 responses/sec in individual birds) as compared to the average non-drug rates of responding maintained by the FI component of the multiple schedule (ranging from 0.65 to 1.5 responses/sec in individual birds). The non-

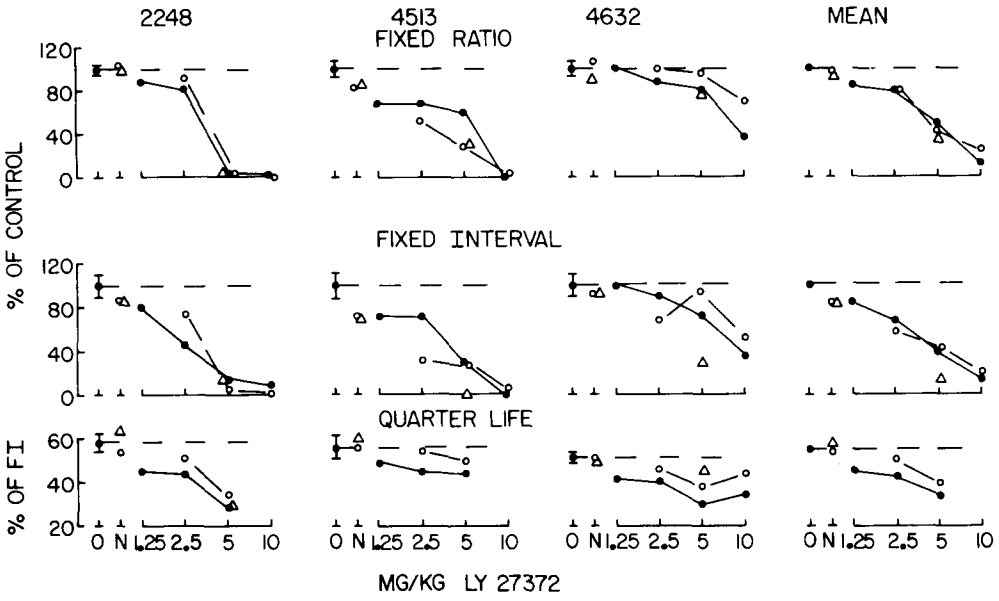

FIG. 2. Effects of LY-27372 alone (●) and in combination with 1 (○) or 10 (△) mg/kg of naloxone on the rates of responding within the fixed-ratio component (top row) and fixed-interval component (middle row) and on the fixed-interval quarter-life value (bottom row) for each of the 3 birds and the mean values. Abscissa: dose of LY-27372, log scale; Ordinate: rates of responding as percent of control rates (top and middle rows) for fixed-ratio and fixed-interval components, respectively, and quarter-life (bottom row) as percent of the fixed-interval. The points and dashed lines above 0 indicate the control means ± the standard deviation of all control sessions (6 or more) for each bird during the testing of this drug. The points above N indicate the effects of 1 mg/kg (○) and 10 mg/kg (△) of naloxone alone. The data points for LY-27372 alone are usually the mean of two determinations, LY-27372 in combination with naloxone are usually from single determinations. Quarter-life values were not calculated if FI response rates were below 0.1 response/sec since such a low response output would make calculation of the quarter-life unreliable. The average non-drug control values (data from Thursdays) across all 3 birds were 2.91 responses/sec for the FR component, 1.02 responses/sec for the FI component, and 55% of the FI for the quarter-life value.

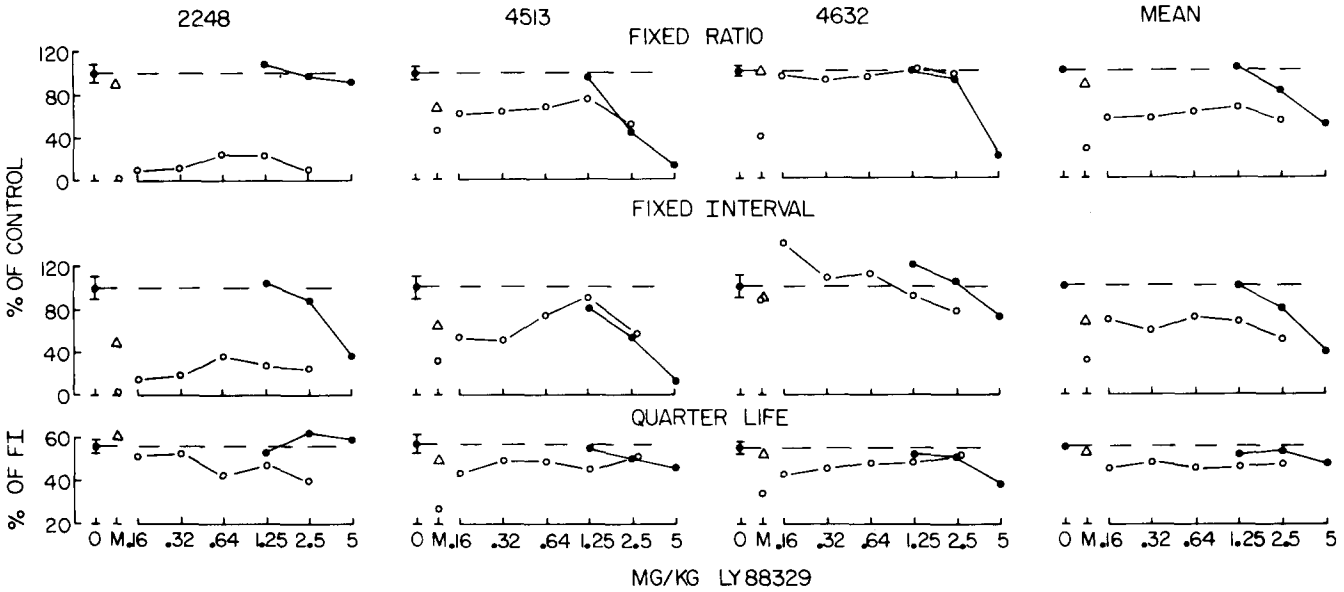

FIG. 3. Effects of LY-88329 alone (●) and in combination with 20 mg/kg of morphine (○). The unfilled circle above M indicates the effects of 20 mg/kg of morphine alone, whereas the unfilled triangle indicates the effects of 20 mg/kg of morphine in combination with 1 mg/kg of naloxone. Data points are one determination in each bird, except the data points for 20 mg/kg morphine alone which are the mean of 3 determinations in each bird. Other details as with Fig. 2. The average non-drug control values were 2.75 responses/sec for the FR component, 0.98 response/sec for the FI component, and 56% of the FI for the quarter-life value.

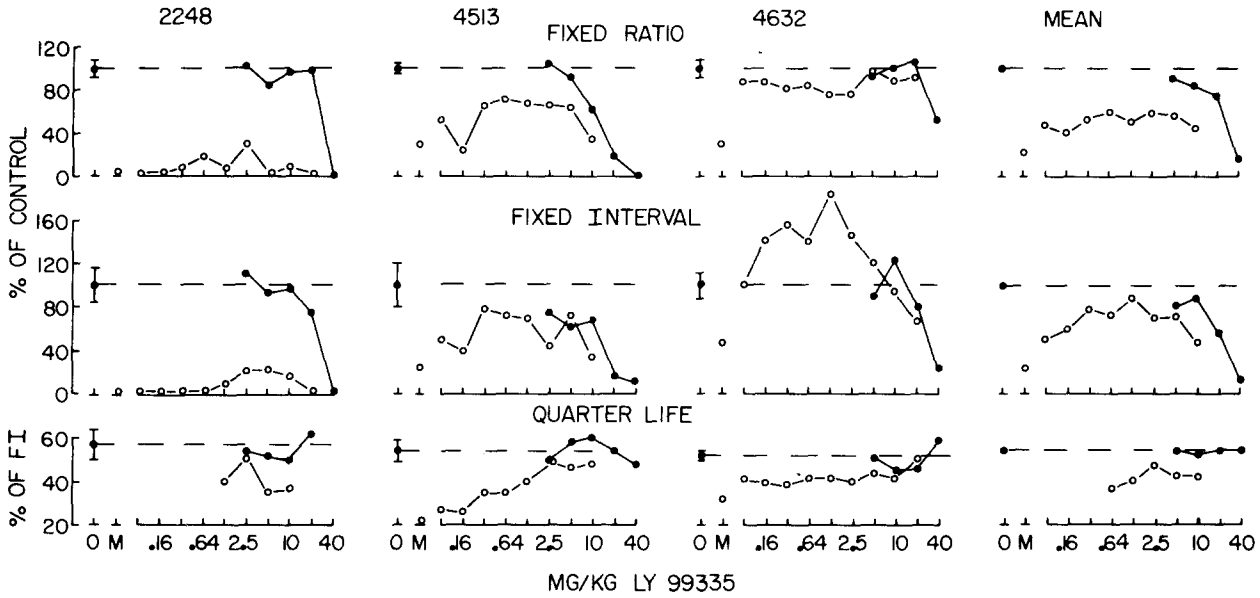

FIG. 4. Effects of LY-99335 alone (●) and in combination with 20 mg/kg of morphine (○). The average non-drug control values were 2.70 responses/sec for the FR component, 1.0 response/sec for the FI and 54% of the FI for the quarter-life value. Other details as with Fig. 3.

drug quarter-life values (ranging from 52 to 58% of the FI in individual birds) indicated that the typical, positively accelerated pattern of responding was generated by the FI schedule. This pattern is characterized by a very low rate of responding early in the FI component, followed by a transition period, which is then followed by a fairly high rate of responding just prior to the end of the FI component and the subsequent grain presentation. These control performances are similar to those previously reported for pigeons, rats, monkeys, and other animals, responding under similar schedules [2, 5, 11, 17].

Figure 2 shows the effects of LY-27372 in each of the three birds and the mean data. Increasing doses of LY-27372 produced dose-related decreases in the rates of responding in both components of the multiple schedule along with decreases in the FI quarter-life value (as shown by the filled circles in Fig. 2). These effects were not antagonized reliably by either 1 mg/kg (unfilled circles) or 10 mg/kg (unfilled triangles) of naloxone. Generally, the effects of 1 and 10 mg/kg of naloxone administered alone were only slight. A 20 mg/kg dose of morphine produced an average decrease in responding in both the FR and FI components to approximately 22–24% of control which was not antagonized by the minimally-effective agonist dose (1.25 mg/kg) of LY-27372 (data not shown).

Like previous reports of meperidine [14,15], and various related analogues [10, 11, 12], the agonist effects of LY-27372 on schedule-controlled responding were not antagonized by naloxone in spite of the fact that it produces narcotic-like analgesic effects [16]. Thus the behavioral suppressing effects of LY-27372 are probably not mediated by an interaction with a narcotic receptor, since naloxone readily and completely antagonizes the behavioral suppressing effects of morphine, fentanyl, and other narcotic agonists [4, 6, 10, 14, 18]. Consistent with observations in rats and mice (Zimmerman, 1980, personal communication), LY-27372 did not antagonize the effect of morphine in the pigeon.

Figure 3 shows the effects of LY-88329 alone (filled circles) and in combination with 20 mg/kg of morphine (unfilled circles). A dose of 1.25 mg/kg of LY-88329 alone was generally without effect on responding, whereas higher doses produced a dose-related decrease in responding. The 20 mg/kg dose of morphine alone decreased responding in both the FR and FI components to varying extents in the different birds. This dose of morphine also decreased the quarter-life value in birds 4513 and 4632 (bird 2248 did not emit enough responses in the FI component after 20 mg/kg of morphine to calculate a quarter-life value). Doses of LY-88329 from 0.16 to 2.5 mg/kg produced some antagonism of the effects of 20 mg/kg of morphine, bringing suppressed rates of responding back towards the 100% of control level and reversing the morphine-induced decrease in quarter-life value in birds 4513 and 4632. The antagonism produced by LY-88329 was generally comparable to that produced by 1 mg/kg of naloxone (unfilled triangles in Fig. 3) which is an optimal dose for antagonizing the behavioral suppressing effects of narcotic agonists [4, 6, 10, 18]. The only exception was bird 2248, which was most sensitive to the behavioral suppressing effect of morphine, and exhibited less antagonism by LY-88329 as compared to 1 mg/kg of naloxone.

Figure 4 shows the effects of LY-99335 alone (filled circles) and in combination with 20 mg/kg of morphine (unfilled circles). Higher doses of LY-99335 alone decreased responding in both components of the multiple schedule. As with LY-88329, there was large between bird variability in the antagonism of the effect of 20 mg/kg of morphine; however, at doses of 0.32 mg/kg to 10 mg/kg of LY-99335, the effects of morphine were antagonized to some extent in all three birds. Reliable morphine antagonism was evident after 0.08 mg/kg of LY-99335 in bird 4632.

As with LY-88329, the clearest evidence for narcotic an-

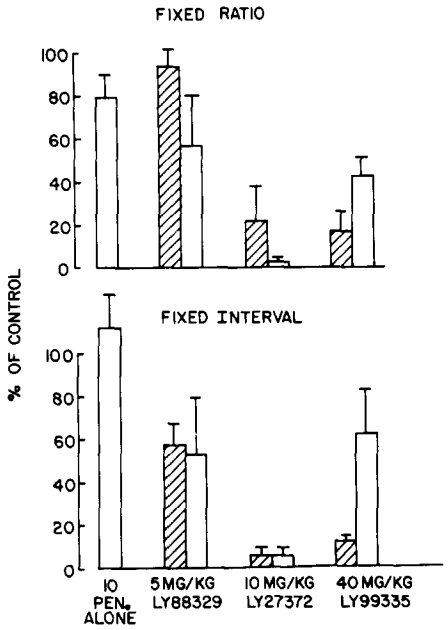

FIG. 5. Mean (±S.E., N=4) effects of 10 mg/kg of pentobarbital alone and in combination with 5 mg/kg of LY-88329, 10 mg/kg of LY-27372, and 40 mg/kg of LY-99335. Open bars indicate the effects with pentobarbital, whereas the filled bars indicate the effects with LY compounds alone. Top frame shows the effects on the FR component; lower frame shows the effects on the FI component.

tagonism by LY-99335 is provided by the quarter-life value approaching the non-drug control mean in birds 4513 and 4632 after doses of LY-99335 in combination with 20 mg/kg of morphine. As previously shown, the narcotic antagonists naloxone and naltrexone antagonize not only the effect of morphine on mean response rate, but also antagonize the effect of morphine on response patterning [3,18]. In contrast, pentobarbital attenuates the rate-decreasing effect of meperidine and normeperidine, but does not attenuate meperidine's and normeperidine's disruptive effects on response patterning [13]. Thus the antagonism of morphine's effect on the quarter-life value by LY-99335 and LY-88329 is good evidence for the specificity of the narcotic antagonism.

Figure 5 shows the average effects of 10 mg/kg of pentobarbital alone and in combination with either 5 mg/kg of LY-88329, 10 mg/kg of LY-27372, or 40 mg/kg LY-99335 in four birds which were not subjects in the previous manipulations. These doses of the LY compounds were chosen on the basis of the earlier studies to produce reliable, but not complete behavioral suppression. The 10 mg/kg dose of pentobarbital alone slightly decreased FR rates but not FI rates from control values. The 5 mg/kg dose of LY-88329 alone did not decrease FR rates, but decreased FI rates to 57% of control. The effect of pentobarbital in combination with 5 mg/kg of LY-88329 was to slightly decrease FR rate, but pentobarbital did not affect the LY-88329-induced decrease in the FI component. Likewise, with LY-27372, the pentobarbital further decreased the LY-27372-induced effect on FR response rates. The FI rates were markedly decreased by LY-27372 alone and in combination with pentobarbital. The 40 mg/kg dose of LY-99335 markedly decreased responding in both the FR and FI components, and pentobarbital attenuted the rate-decreases in all four birds under both schedule components. Moreover, naloxone (1 mg/kg) did not antagonize or attenuate the behavioral suppression produced by 40 mg/kg LY-99335 (mean FR rates=10±10%; FI=33+33%). These results with pentobarbital suggest that the behavioral suppressing effects of LY-99335 are similar to those of meperidine and related analogues as previously reported [12,13] and that LY-99335 might produce similar proconvulsive effects as these agents do [1]. In contrast, the fact that the behavioral effects of LY-27372 or LY-88329 were not attenuated by pentobarbital suggests that these agents produce their effects on schedule-controlled responding by a different mechanism than the proconvulsive action of most phenylpiperidines, including LY-99335.

The two phenylpiperidines tested which are narcotic antagonists, LY-88329 and LY-99335, exhibited antagonist activity well below doses which suppressed schedule-controlled behavior by themselves. For LY-99335, there was approximately a 500-fold difference in dose, and for LY-88329, a 32-fold difference in dose between the minimal dose for antagonist activity and for suppression of schedule-controlled behavior. Thus LY-99335 compares favorably with naloxone as being a relatively "pure" narcotic antagonist [6, 18, 20]. It is interesting to note that high doses of naloxone (30 and 56 mg/kg) produce suppression of schedule-controlled responding in the pigeon which is attenuated by pentobarbital (unpublished data from this laboratory) similarly to the effect shown by LY-99335 in the present study. Thus in terms of their ratio between behavioral suppressing doses and morphine antagonizing doses, and in terms of pentobarbital attenuation of the behavioral suppressing effects, LY-99335 and naloxone are very similar in effect.

ACKNOWLEDGEMENTS

I would like to thank Dr. Zimmerman of Lilly Research Laboratories for supplying the Lilly compounds, the drugs companies which donated the other drugs, and Ms. C. Edwards and Ms. B. Gau for their technical help. Supported by DA-017111.

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