Pharmacology Biochemistry & Behavior, Vol. 26, pp. 191–193, 1987. © Pergamon Journals Ltd., 1987. Printed in the U.S.A. 0091-3057/87 $3.00 + .00

BRIEF COMMUNICATION

Naloxone Sensitivity in Squirrel Monkeys Under a Schedule of Shock Titration[1]

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Received 19 June 1986

OLIVETO, A. H. AND L. A. DYKSTRA. *Naloxone sensitivity in squirrel monkeys under a schedule of shock titration.* PHARMACOL BIOCHEM BEHAV **26**(1) 191–193, 1987.—In order to explore the conditions under which sensitivity to naloxone develops, naloxone's effects were examined in squirrel monkeys responding under a discrete trial schedule of shock titration. Naloxone's effects were examined prior to and following a chronic naloxone regimen in which 10 mg/kg of naloxone was administered daily for at least 21 days. The level at which monkeys maintained the shock and rates of responding were recorded. Prior to chronic administration, selective doses (1.0, 3.0 mg/kg) of naloxone decreased shock levels slightly. These decreases were accompanied by increases in response rates. Subsequent to chronic administration, shock levels were unaltered; however, rates of responding showed greater increases. These results suggest that, following chronic naloxone exposure, animals responding under a schedule of shock titration became more sensitive to the rate-increasing effects of naloxone, but not to naloxone's effects on shock intensity.

Naloxone sensitivity Opioid antagonist Shock titration Naloxone

RECENTLY, much interest has focused on the development of increased sensitivity to the behavioral effects of opioid antagonists upon frequent exposure to these compounds. For instance, it has been widely observed that monkeys responding under schedules of food presentation become increasingly sensitive to the rate-decreasing effects of naloxone or naltrexone following chronic administration of the respective compound (e.g., [3, 5, 6, 8, 9]). Nevertheless, increased sensitivity to opioid antagonists does not develop under all conditions. For instance, it has been reported that squirrel monkeys responding under a fixed-ratio schedule of stimulus-shock termination did not become more sensitive to the effects of naltrexone following a chronic regimen of naltrexone administration [2]. In addition, food-deprived rats performing under a schedule of shock avoidance did not develop an increased sensitivity to the behavioral effects of naloxone after several administrations of the compound, while free-fed rats developed a strong sensitivity to naloxone [7]. Thus, the conditions under which sensitivity to opioid antagonists occurs are not well-established.

Since increased sensitivity to naloxone has not been observed to develop consistently under procedures involving electric shock, one factor which might determine whether sensitivity develops to an opioid antagonist is the event that maintains responding (i.e., food vs. shock). Therefore, we examined the effects of chronic administration of naloxone under a discrete trial schedule of shock titration. In the shock titration procedure, the intensity of an electric shock automatically increases every 15 sec, but decreases whenever the response requirement is completed. The effects of naloxone were first examined prior to a chronic naloxone regimen in which naloxone was administered daily for at least 21 days. Naloxone's effects were then redetermined subsequent to the chronic regimen.

METHOD

Three individually housed, adult male squirrel monkeys (*Saimiri sciureus*) were used. Weights were maintained with a diet consisting of 10 Purina Monkey Chow pellets and

[1]This work was supported by U.S. Public Service Grants DA 02749 from the Natl. Inst. on Drug Abuse. A preliminary report of this work was presented at the 1986 Convention of the American Psychological Association.

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TABLE 1

CONTROL PERFORMANCE OF SQUIRREL MONKEYS RESPONDING UNDER A SCHEDULE OF SHOCK TITRATION PRIOR TO AND FOLLOWING CHRONIC NALOXONE

	Pre-Chronic	Post-Chronic
Median Shock Intensity* (mA)	0.09 (0.03)	0.07 (0.02)
Resp/Sec* During Shock	0.29 (0.001)	0.30 (0.009)
Resp/Sec* During Time Out	0.21 (0.025)	0.24 (0.034)

*Data represent the mean (±s.e.) performance of three monkeys.

supplements of fresh fruit. Water was freely available in the home cage. All monkeys had extensive drug histories.

Each monkey was restrained in the seated position [4] and electric current was delivered to its tail, according to the shock titration procedure described previously [1]. Briefly, the shock increased from 0 to 5.5 mA in 30 steps with smaller increments occurring at the lower end of the shock range. During an experimental session, monkeys received continuous shock for 15 sec periods. If the monkeys did not complete a fixed-ratio requirement of 5 responses during the shock period, the shock remained on for the duration of the shock period, and increased by one increment for the next 15 sec shock period. If, however, five responses were made during the shock period, the shock was immediately terminated for 15 sec (time-out). After the 15-sec time-out period, the shock resumed at the next lower intensity. If the shock rose to its peak intensity (5.5 mA) and the five-response requirement was not met in any of ten consecutive 15-sec shock periods, the session automatically terminated. Experimental sessions lasted one hour and were conducted five times a week.

Dose-effect curves were determined for naloxone (1.0–10.0 mg/kg) prior to and following a chronic regimen in which 10.0 mg/kg of naloxone was administered daily for at least 21 days. Naloxone (Endo Laboratories) was dissolved in distilled water, doses being expressed as the salt. Injections were administered intramuscularly into the thigh in a volume of 0.5 ml/kg 10 min before the experimental session; during the chronic regimen injections were administered 10 min before the session during the week and around noon on weekends. During dose-effect curve determinations, naloxone was administered on Tuesdays and Fridays. Data from Thursday sessions were used as non-injection control values.

Rates of responding in the presence of shock were measured separately from rates of responding in the absence of shock (i.e., during time-out). The number of times the five-response requirement was completed was recorded as a function of shock intensity at which the response requirement was completed. Median shock levels (the shock intensity below which the shock was kept 50% of the time) were derived from these data (see [1]).

RESULTS

Table 1 compares the control median shock levels and rates of responding obtained prior to and following chronic naloxone administration. Performance during control sessions was similar to that reported previously [1] and did not change significantly following the chronic regimen.

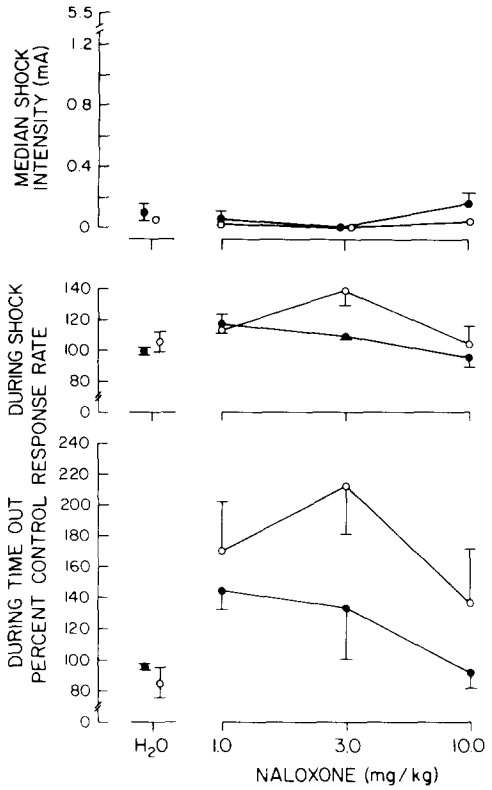

FIG. 1. The effects of naloxone alone on median shock level performance (top), and rates of responding during shock (middle) and time-out periods (bottom) under a schedule of shock titration. Two curves represent naloxone's effects prior to (●) and following (○) chronic naloxone. Ordinate: top—median shock intensity in milliamperes; middle, bottom—rates of responding as a percent of control rates obtained from the Thursday control session. Abscissa: dose of drug in milligrams per kilogram of body weight. Each point represents the mean±s.e. of three monkeys.

Figure 1 shows the effects of naloxone on median shock level performance (top graph), as well as on rates of responding during shock (middle graph) and time-out (bottom graph) periods. Prior to chronic naloxone administration, median shock levels were decreased slightly at doses of 1.0 and 3.0 mg/kg of naloxone, although at the 1.0 mg/kg dose, median shock levels were still within the range of the water control performance. Decreases in median shock level were accompanied by increases in rates of responding during both shock and time-out periods.

During the chronic regimen (data not shown) median shock intensities decreased and response rates increased in two monkeys. In the third monkey no consistent changes in performance were observed during the chronic naloxone regimen, even when it was extended 15 days beyond the original 21-day regimen. After the chronic regimen was terminated, performance returned to previous control levels within 2 to 3 weeks and the dose-effect curve for naloxone alone was redetermined.

Figure 1 also shows the effects of naloxone on perform-

ance subsequent to the chronic naloxone regimen. It can be seen that the chronic naloxone regimen did not alter naloxone's effect on median shock level; however, naloxone-induced increases in rates of responding were greater following the chronic regimen. These increases in rates of responding were greatest at 3.0 mg/kg of naloxone, the dose which decreased the median shock level to the greatest extent.

DISCUSSION

In the present study, naloxone initially decreased the intensity at which monkeys maintained shock, and this effect was not altered following chronic exposure to naloxone. It is unclear why there were no changes in the effect of naloxone on median shock level following the chronic naloxone regimen. This may have been due to the fact that baseline median shock levels were already very low; therefore, consistent decreases in median shock level performance were difficult to discern. On the other hand, naloxone-induced increases in rates of responding were enhanced following chronic exposure to naloxone. These results suggest that monkeys develop an increased sensitivity to the rate-increasing effects of naloxone under a schedule of shock titration, but not to naloxone's effects on shock intensity.

These results extend the conditions under which sensitivity develops to naloxone's effects. Previous studies [3, 5, 6] have shown that naloxone's rate-decreasing effects are enhanced following a chronic naloxone regimen similar to that used here. Sensitivity has not been observed, however, under conditions in which naloxone increased rates of responding. In addition, the results suggest that naloxone sensitivity can develop in situations where shock is the event which maintains behavior.

It is interesting that chronic exposure to naloxone enhanced its rate-increasing effects under a schedule of shock titration, whereas a previous study indicated that chronic exposure to naltrexone did not produce sensitivity to naltrexone's effects in squirrel monkeys responding under a schedule of shock termination [2]. It is important to note, however, that these opioid antagonists produced different effects under the two schedules. Moreover, the consequences of these effects were different. Under the stimulus-shock termination schedule, naltrexone only decreased rates of responding, an effect which produced an increase in shock frequency. Under the shock titration procedure, naloxone only increased rates of responding, an effect which either decreased or did not alter shock intensity. Thus, the development of opioid antagonist sensitivity may be dependent upon the nature of the response contingency, as well as the event which maintains responding. Further work is necessary to more clearly define the conditions that are important in the occurrence of this phenomenon.

ACKNOWLEDGEMENTS

The authors wish to express their appreciation to Vicki Fowler for her assistance on the preparation of the manuscript.

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