Pharmacology Biochemistry & Behavior, Vol. 16, pp. 1013–1015, 1982. Printed in the U.S.A.

A Comparison of the Effects of Opiate Antagonists on Operant and Ingestive Behavior

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Received 24 October 1981

SANGER, D. J. AND P. S. McCARTHY. *A comparison of the effects of opiate antagonists on operant and ingestive behavior.* PHARMAC. BIOCHEM. BEHAV. 16(6), 1013–1015, 1982.—Previous studies have found that naloxone and other opiate antagonists will decrease the food and water intake of experimental animals. The present study investigated the possibility that these effects may be due to a generalized action of opiate antagonists to block an endogenous reward system. A direct comparison was made between the effects of naloxone and naltrexone on FR responding maintained by small quantities of milk and on the consumption of milk when it was freely available. Both drugs reduced milk consumption at all doses (0.3–30 mg/kg) but produced only small decreases in FR response rates at the highest doses. These results do not support the view that the actions of opiate antagonists on eating and drinking represent an inhibitory action on central reward mechanisms.

Naloxone Naltrexone Food reward

A NUMBER of recent studies have demonstrated that food and water intake in experimental animals can be markedly attenuated by administration of naloxone [10]. Similar effects are shown by several other drugs believed to act by blocking opiate receptors [2] and it has also been found that the reductions in food and water intake are produced by the (−) but not (+) enantiomers of these drugs [2,11]. These results indicate that the effects of naloxone and similar drugs are mediated through receptor mechanisms (presumably opiate receptors). It would thus appear that endogenous opiates are important in the physiological systems mediating food and water intake.

The specific opiate mechanisms involved in controlling ingestive behavior could, however, take a variety of forms. One explanation for the actions of opiate antagonists on food and water intake favored by some researchers is that the drug effects represent an action on a general opiate reward system (e.g., [7,9]). Blockade of such a system would be expected to reduce the effectiveness of a variety of rewarding stimuli including food and water. Belluzzi and Stein [1,12] suggested that endogenous opiate peptides may have an important role in the physiological substrate of reward. This hypothesis was based on several areas of evidence including the observation that rats would self-administer methionine - and leucine - enkephalin into the cerebral ventricles and the finding that naloxone reduced rates of bar pressing for electrical stimulation of the brain. In order for the hypothesis relating endogenous opiate activity to a physiological reward system to be tenable it is necessary to show that operant responding maintained by a variety of rewarding events is similarly attenuated by opiate antagonists. In particular, in the present context it would be necessary to demonstrate that operant responding maintained by food and water is reduced to the same extent as is eating and drinking in animals with food and water freely available.

METHOD

Subjects

Ten male Sprague-Dawley rats weighing between 260–280 g were used. They were individually housed and maintained at approximately 85% of their freely-feeding weights by giving them food supplements after the daily sessions.

Apparatus

The apparatus consisted of a standard LVE operant test chamber equipped with a lever and a liquid dipper. Reinforcers were 0.01 ml deliveries of sweetened condensed milk (Fussell's) diluted 50% with tap water.

Procedure

Five of the 10 rats were trained to press the bar in the operant test chamber to obtain milk deliveries. After training on a continuous reinforcement schedule the response requirement was gradually increased until the animals were required to press the bar 20 times to obtain each reinforcer (FR 20). Daily sessions were 60 min in duration. At the same time as each animal was tested in the chamber a second (untrained) rat was given a bottle containing sweetened milk for 60 min. Thus the experiment consisted of two groups of rats maintained under similar conditions, one group being

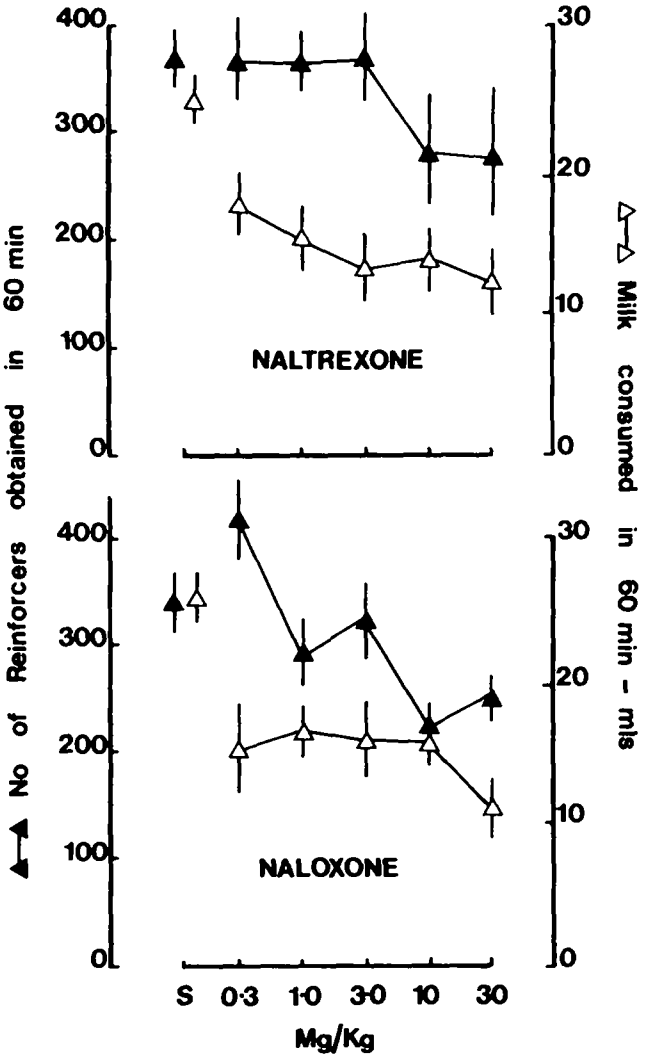

FIG. 1. The effects of naloxone and naltrexone on the number of reinforcers (0.01 ml of sweetened milk) obtained during 60 min sessions of FR 20 bar pressing and on the quantities of milk consumed when a bottle of milk was put into the animal's home cage. Five rats were tested under each condition and each animal received every drug dose. The points at S show the means ± SE of values taken from the days immediately preceding drug injection days.

required to obtain milk deliveries according to a FR 20 schedule and the other obtaining milk freely from a bottle.

When daily response rates and levels of milk consumption were relatively steady drug administration was begun. Each animal received SC injections of several doses of naloxone and naltrexone (0.3, 1.0, 3.0, 10, 30 mg/kg as base) 5 min before an experimental session. Both members of each pair of rats were injected with the same dose on the same day. Drugs and doses were given in a mixed order and only one drug injection was given in any one week. Saline (1 ml/kg) was injected on non-drug days. The effects of the drugs were assessed by analysis of covariance in which the quantity of milk consumed or number of reinforcers obtained after each dose was covaried against the corresponding value on the immediately preceding day.

RESULTS

The effects of naloxone and naltrexone on milk consumption and on numbers of milk rewards obtained on the FR 20 schedule are presented in Fig. 1. The control data shown in the figure are taken from the sessions immediately preceding drug sessions. The figure shows that the five animals on the FR schedule obtained on average about 360 milk deliveries each session giving approximately 3.6 ml of milk. The five rats which had a bottle of milk freely available for 60 min consumed an average of about 25 ml each day.

The difference between the effects of the drugs on bar pressing and on milk consumption are shown quite clearly in the figure. Every dose of naloxone and naltrexone produced a reduction in milk consumption in all five rats obtaining milk freely from the bottles. In contrast, the lower doses (0.3–3.0 mg/) of both drugs had no consistent effects on FR bar pressing. The higher doses (10, 30 mg/kg) appeared to produce small reductions in numbers of milk rewards obtained but this effect varied between individual animals. One rat showed substantial decreases in response rates (<10% of control values) after 10 and 30 mg/kg of naltrexone but other animals were unaffected by any dose of either drug. The statistical analysis showed that the effect of naloxone on number of milk rewards obtained just reached an acceptable level of statistical significance ($p=0.045$) while the effect of naltrexone on this measure did not.

DISCUSSION

The results of this study demonstrate that the opiate antagonists naloxone and naltrexone can produce reductions in the milk consumption of food-deprived rats. These drugs do not, however, produce substantial reductions in rates of bar pressing when rats maintained under similar conditions are required to obtain small portions of milk according to an FR 20 schedule. These findings have significance for possible explanations of the actions of opiate antagonists on ingestive behavior.

The first hypothesis which may be questioned on the basis of these results is the possibility that opiate antagonists reduce food and water intake by inducing general motor debilitation. As rats continue to bar press at relatively high rates after doses of naloxone and naltrexone which substantially reduce food, water and milk consumption, it is unlikely that the animals are physically unable to continue eating and drinking. Recently Carey *et al.* [4] came to a similar conclusion on the basis of a study which showed that a dose of naloxone (10 mg/kg) which reduced food and water intake in rats had no effect on wheel running in the same animals. The demonstration [3] that schedule-induced drinking is unaffected by naloxone is also consistent with this view.

A second explanation of the effects of opiate antagonists on ingestive behavior which appears inconsistent with the present results concerns the possible involvement of endogenous opiate mechanisms in the hypothesized neural substrate of reward. If, as has been suggested [1,12], naloxone and other opiate antagonists produce a blockade of activity in an endogenous reward system then behavior maintained by a variety of rewarding events would be expected to be attenuated to similar extents. However, the present finding that bar pressing for small milk portions is unaffected by drug doses which reduce milk intake seems to rule out a simple explanation in terms of disrupted reward mechanisms. Other recent data also appear inconsistent with the existence of an opiate reward system. For example, although

this hypothesis would presumably predict that sexual behavior would be attenuated by opiate antagonists it has been reported that such behavior can be facilitated by naloxone [8]. Also, not all researchers have been able to observe clear attenuating effects of naloxone on behavior rewarded by electrical stimulation of the brain [6,13].

In the present study there are several factors which distinguish the two experimental conditions and which may account for the different effects of the drugs on operant responding and on ingestive behavior. The factor most likely perhaps to provide an explanation is the difference in the quantities of milk which could be obtained by the animals in the different conditions. Because of the schedule of reinforcement and the small reinforcement magnitude the rats bar pressing for milk obtained only an average of 3.6 ml of milk during each session. In experiments concerned with consummatory, rather than operant, behavior, animals usually are presented with large quantities of food and water and in the present experiment the rats consumed an average of 25 ml of milk under control conditions. It is thus possible that opiate antagonists may attenuate food and water intake by bringing forward satiety. Thus the drugs would not be expected to reduce food reinforced operant responding until large numbers of reinforcers had been obtained. Other researchers have also proposed that naloxone may act through satiety mechanisms [5] and this hypothesis is supported by the observation that this drug does not completely suppress food and water intake even at relatively high doses [10]. However, neither the present study nor previous experiments have been specifically designed to test this hypothesis and it is therefore for future research to determine the role of satiety in the actions of opiate antagonists.

ACKNOWLEDGEMENTS

The naloxone and naltrexone used in this study were generously supplied by Endo Laboratories.

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