Pharmacology Biochemistry & Behavior, Vol. 14, pp. 419–421. Printed in the U.S.A.

Naloxone Suppresses Food/Water Consumption in the Deprived Cat

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Received 13 March 1980

FOSTER, J. A., M. MORRISON, S. J. DEAN, M. HILL AND H. FRENK. *Naloxone suppresses food/water consumption in the deprived rat.* PHARMAC. BIOCHEM. BEHAV. 14(3) 419–421, 1981.—Intraperitoneal administration of the opiate antagonist, naloxone hydrochloride, resulted in decreased food and water consumption in drug-naive cats. In a cross-over Latin Square design, food consumed by six cats in a one hour period following 23 hours of deprivation, was decreased significantly below control ($p<0.05$) in linear relation to increasing dose (1 mg/kg and 10 mg/kg) of naloxone. Non-linear and time/order effects were not significant. Water consumption was decreased below control in a linear relation to increasing dose (1 and 10 mg/kg) for 5 of 6 cats at the 0.05 significance level. Non-linear and time/order effects on water consumption were not statistically significant for the same 5 cats. These results, and behavioral signs (i.e., vomiting, persistant vocalization, heavy salivation, mydriasis, moderate catatonia, and hissing) occasionally exhibited by four of the six cats in a 1-hr period following injection of the high dose, suggest a malaise-effect of naloxone.

Naloxone Narcotic antagonist Cats Food intake Food deprivation Water intake Water deprivation

OPIATE antagonists have been reported to suppress food and water intake in deprived rats [3, 6, 7, 11, 12, 13, 16] and in deprived male mice [3]. Mice appear to be less susceptible than rats to the suppressant effects of naloxone [3]. The question arises as to what extent these suppressant effects of naloxone on appetitive behavior may be generalized to other species. It has been known for many years that opiates administered to mice and cats in intermediate doses produce excitation while in rats sedation results. Thus, one might expect to see some differences in behavior in response to naloxone. The present investigation evaluates the effect of naloxone on the consumption of food and water by the deprived cat.

METHOD

Adult cats (four sexually-intact females and two castrated males) were individually housed in cat cages in one room in an Animal Research Facility. All procedures were conducted in that room. The animals were maintained on Purina Cat Chow (starfish-shaped pellet) and tap water presented in stainless steel bowls attached to the inside face of a feeding door. Bowls were weighed to the nearest gram before and after the 1-hr presentation period. The cats were subdivided into two groups of three with one male in each group. One group was conditioned to a 23-hr food deprivation schedule and the other to a 23-hr water deprivation schedule. During the conditioning period and throughout the test program, both groups received daily IP injections 15 minutes prior to the mid-morning 1 hr food/water presentation period. Test trials were started following stabilization of food and water intake. The control injections consisted of 1 cc of 0.9% sodium chloride acidified to match the pH of naloxone hydrochloride. Test doses consisted of control, and 1 and 10 mg/kg naloxone hydrochloride (donated by Endo Laboratories) dissolved in 1 cc of injectable distilled water. Test days were separated by at least 72 hours to permit clearance of naloxone [17]. The order of test dose administration to individual cats was established by a 3×3 Latin square design (Fig. 1). Persons administering the test substances were blind to dose-cat pairing. Upon completion of three Latin Squares (9 test days) the two groups were crossed-over for food/water deprivation and resubmitted to the test procedure.

The data for each cat were analyzed separately, i.e., each cat served as its own control. Orthogonal contrasts [5,21] were used to test linear, non-linear, and time/order effects. The linear and nonlinear contrasts assess the effect of dose level on food/water consumption while the time/order contrast tests changes in consumption over the time course of the nine experiments. Each contrast sum of squares was divided by the error variance, the result being an analysis of variance F-statistic with one and five degrees of freedom. The data were not normalized for body weight of cat because of the with-in subject experimental design.

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TEST DAY SEQUENCE

CAT	1	2	3	4	5	6	7	8	9
#21	C	1	10	1	10	C	10	C	1
#17	10	C	1	C	1	10	1	10	C
#20	1	10	C	10	C	1	C	1	10

FIG. 1. Latin square experimental design (C=control; 1=1 mg naloxone/kg body weight; 10=10 mg naloxone/kg body weight).

RESULTS

Naloxone, administered intraperitoneally, decreased food consumption linearly with increasing dose for the six cats (Table 1). Because of multiple tests the reader should be aware that these statistics have the same denominator. Therefore, the significance should not be read too precisely. Clearly, however, the linear contrasts for cats 17, 20, 24 and 25 are highly significant with F-values of 61.0, 102.0, 94.8 and 37.6, respectively. Since the three contrasts for each cat represent a partitioning of the total variation in food consumption over the 9 experiments, it is important to note that the linear effect for each of the 6 cats is much larger than either the nonlinear or the time/order effects. For all six cats, the nonlinear and time/order effects on food consumption are not statistically significant.

Five out of the six cats showed a significant linear decrease of water consumption with increasing naloxone dose (Table 1). No explanation could be formed as to why the water consumption of cat 16 was unrelated to dose. A significant nonlinear effect with dose and a significant time/order effect were exhibited by cat 24, but, the linear effect was much greater than either of the other two.

Qualitative observations made on test days showed that, apart from the diminished food or water intake in response to naloxone, other behaviors were present which were not observed on control days. In the one-hour period following IP injection of 10 mg/kg naloxone, behaviors such as vomiting, persistent and distressful vocalization, excessive salivation, mydriasis and moderate catatonia, and unusual hostility and hissing were noted at different times for 4 of the 6 cats in the study. Though dose-cat pairing was blind, the persons giving the injections could reliably predict, toward the end of the extensive series of experiments, which cats received the high-dose naloxone. During and immediately after the high-dose injection, the recipient cats would struggle and resist restraint. This behavior was never observed with the lower doses nor with the daily control injections.

DISCUSSION

The present results clearly demonstrate that naloxone suppresses food and water consumption in deprived cats in a dose-related fashion. Thus, this behavioral effect is not limited to rats, genetically obese mice [15] nor male mice [3].

Belluzzi and Stein [1] have proposed that endogenous opioids may mediate drive-reduction reward. An implication of this hypothesis would be that specific opiate receptors might mediate drive-reducing behaviors, such as food or water intake, in deprived animals. The stereospecificity of appetitive suppression by naloxone [19] supports this hypothesis. Whereas results obtained from rats tend to support this hypothesis [6], the finding that naloxone induces conditioned taste aversion in rats [6, 14, 19, 22, 23] and in cats (J. Foster *et al.*, unpublished observations) does allow the alternative hypothesis that naloxone may exert its food/water suppressant effects through nonspecific malaise mechanisms. The qualitative behavioral observations in these experiments support this alternative hypothesis. The quantitative observations reported here are consistent with one report on the rat [19] but not with another [22]. An hypothesis of IP naloxone in cat antagonizing a "normal" antiemetic tone provided by an endogenous morphine-like factor and thereby producing emesis through a release mechanism has been proposed [4]. The experiments giving rise to that hypothesis support the premise that the mechanisms underlying emesis include, or are influenced by, opioid receptors. Thus, not all malaise mechanisms can be classified as "nonspecific".

TABLE 1

F-STATISTIC VALUES
$F(1,5)=6.61$, $p<0.05$
$F(1,5)=16.3$, $p<0.01$

	Cat					
Deprivation Contrasts	Female 17	Castrated Male 20	Female 21	Female 16	Castrated Male 24	Female 25
Food						
Linear	61.0	102.0	11.1	10.7	94.8	37.6
Non-linear	2.3	0.2	0.1	1.2	1.4	2.5
Time/order	1.1	0.4	1.1	0.8	0.8	0.1
Mean	236.0	273.0	28.4	102.0	569.0	127.0
Water						
Linear	23.1	8.6	15.8	0.2	78.6	17.6†
Non-linear	1.6	0	5.7	1.3	9.8	*
Time/order	0.1	0.8	1.3	0.2	12.3	0.3†
Mean	225.0	30.2	145.0	108.0	146.0	28.9†

*Removed from last latin square because of bowel impaction.
†$F(1,3)=10.1$, $p<0.05$.

The excitatory response of cats to intermediate doses of opiates in contrast to sedation for rats raises the possibility of a differential response to naloxone. Presumably, the "endorphinergic systems" differ between the species to produce this contrast in behavioral response. However, the appetitive behavior of cat explored in this report reflects no observed differences. This experiment and recent reports [3, 6, 19, 22] indicate that rats, cats and mice *all* respond to naloxone with suppression of consummatory behavior. Perhaps another choice of cat behavior can discriminate the underlying differences and reveal further insights into functional mechanisms.

The evidence increase ([2, 8, 9, 10, 14, 18] and the results reported here) that the pharmacologic profile of naloxone includes many effects. The question of whether all of these effects are mediated by specific endorphinergic mechanisms remains to be determined.

ACKNOWLEDGEMENTS

This work was sponsored by the Veterans Administration Medical Service. Credit for the experimental design is given to Wilfrid J. Dixon and Maryann Hill, Statistical Research Unit, VAMC Brentwood. The authors thank John C. Liebeskind for helpful suggestions on the work.

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