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Suppression of Deprivation-Induced Food and Water Intake in Rats and Mice by Naloxone[1,2]

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BROWN, D. R. AND S. G. HOLTZMAN. *Suppression of deprivation-induced food and water intake in rats and mice by naloxone*. PHARMAC. BIOCHEM. BEHAV. 11(5) 567–573, 1979.—Naloxone, an opiate antagonist, was administered to male and female rats and male mice after periods of food or water deprivation ranging from 12 to 48 hr. Naloxone (0.01–10 mg/kg) reduced postdeprivational water intake in most groups of rats and mice in a dose-related manner. Naloxone suppression of water consumption appeared to be independent of sexual differences in rats, and phase of the diurnal cycle, and length of the deprivation interval in both rats and mice. Postdeprivational food intake in male rats and mice was also reduced by naloxone in a dose-dependent fashion. This naloxone effect was less pronounced than actions observed with water intake, and tended to diminish with lengthening food deprivation periods. In general, mice appeared to be less sensitive than rats to naloxone suppression of food and water intake. Naloxone appears to markedly reduce appetitive behavior, particularly water intake, following deprivation in both rats and mice. The fact that low doses of naloxone can elicit these effects suggests that the drug is acting at specific tissue sites, possibly endorphin receptors.

Naloxone Food intake Water intake Food deprivation Water deprivation Appetitive behavior Narcotic antagonist Endorphin

NALOXONE, a specific opiate antagonist, has long been considered to possess little intrinsic activity in most procedures [3,23]. However, in recent years, there have been numerous reports on effects of naloxone under a variety of conditions. For example, naloxone and other narcotic antagonists have been shown to reverse stress-induced increases in hotplate escape latency [1], to diminish the analgesic effects of acupuncture and focal brain stimulation [21, 29, 34], to produce hyperalgesia in response to the application of noxious stimuli [7, 11, 16, 22], to decrease diurnal variations in pain sensitivity [8], to antagonize conditioned hyperthermia [25], to reduce operant responding for electrical stimulation in the central gray region of the brain [2], to alter acoustic-evoked responses in several brain areas [6], to decrease serum prolactin and growth hormone levels [5], and to alter mood and sexual behavior [13,30]. These effects have been attributed to the antagonist properties of naloxone and are assumed to reflect perturbations in the activity of endogenous opioid (endorphin) systems [14]. Thus, naloxone has become a valuable pharmacological tool for elucidating the physiological roles of the recently discovered endorphins.

One consistent finding has been that relatively low doses of naloxone modify ingestive behavior. The excessive food consumption of genetically-obese strains of rats and mice is diminished by naloxone in a dose-dependent manner [28]. These particular rodent strains have abnormally high pituitary and plasma levels of endorphin, which is consistent with the view that opioid peptides are involved in the modulation of eating behavior [28]. Furthermore, β-endorphin injected intrahypothalamically in normal, satiated rats appears to stimulate food consumption [15]. Food and water intake in normal rats is also altered by the administration of naloxone. Reports from this and other laboratories have indicated that naloxone is capable of suppressing deprivation-induced food and water intake in male rats at doses ranging from 0.3–40 mg/kg [12, 18–20, 27, 35].

Despite the fact that many variables are known to influence appetitive behavior, these have received little consideration in previous studies. For example, naloxone-induced hyperalgesia in both mice and humans and sensitivity to painful stimuli in man appear to possess a circadian periodicity [8,11]. Consequently, it is conceivable that naloxone-mediated suppression of appetitive behavior might also manifest a circadian rhythmicity. Other potentially important variables include the gender of the animals and the length of the deprivation interval [31, 32, 37, 38].

This study was undertaken to confirm previous findings that naloxone reduces appetitive behavior in the rat, and to extend observations to the mouse. The effects of naloxone on food and water intake were evaluated in both rats and mice as a function of the length of the deprivation interval and as a function of the time of day during which the tests of food and water intake were conducted. Furthermore, the action of naloxone on water intake in rats was studied as a function of sex.

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METHOD

Animals

The subjects were 33 male and 16 female CFE rats and 80 male CF-1 mice (Charles River Breeding Laboratories, Wilmington, MA). The rats weighed 150–220 g and the mice weighed 20–40 g at the start of the experiment. All of the animals were housed 3–4 per cage in a large colony room with an average temperature of 72°F and constant illumination between 0700 and 1900 hr. Water and food (Rodent Laboratory Chow No. 5001, Ralston Purina Co., St. Louis, MO) were available in the home cages ad lib except for periods of controlled deprivation during experiments. The stage of the estrus cycle was not determined in experiments conducted with female rats.

Water Deprivation

Eight male and 8 female rats were assigned to each of two groups on which water intake tests were performed at 0800 or 2000 hr. Rats were deprived of water for 12 and 48 hr once a week or for 24 hr twice weekly prior to their assigned water intake test period. Food was always present throughout the periods of water deprivation. All animals underwent 2–3 trials to familiarize them with the deprivation and testing procedures prior to the beginning of drug testing. Thirty minutes prior to testing, rats were weighed and injected with naloxone or saline; 5 min before testing, animals were placed into individual plastic cages with no food present. Room lights were off during experiments conducted at 2000 hr. The subjects were allowed free access to water for 30 min from a 25 ml graduated cylinder fitted with a metal drinking spout. Water intake at the end of the period was measured to the nearest 0.2 ml. Following the test period, the animals were returned to their home cages where they again had free access to water until the next period of deprivation.

Thirty male mice were divided equally into 3 groups: one 12-hr water-deprived group that was tested at 0800 hr or two 24-hr water-deprived groups that were tested at 0800 or 2000 hr. Mice were deprived of water twice weekly for 12 or 24 hr prior to their assigned test time; food was present during the deprivation interval. Mice were weighed and pretreated with naloxone or saline 30 min before testing, and were placed into individual plastic cages containing no food at least 15 min prior to the start of the test session. Room lights were off during experiments performed at 2000 hr. Water intake was measured for 30 min from modified 10-ml Mohr pipets. The pipets were ground at the tapered end to an internal diameter of 4 mm and were fitted with a collar to facilitate positioning each pipet at a 40° angle through a slot in the metal top of the mouse testing cage. Prior to testing, pipets were filled to the zero mark and a 2-ml rubber bulb was placed over the end of opposite the taper to retain the water. Loss of water through spillage was negligible with these pipets. At the end of the test session, the mice were returned to their home cages where they were allowed continuous access to water and food. Water consumption was measured to the nearest 0.1 ml. Mice failing to consume at least 10 ml/kg of body weight of water following an injection of isotonic saline were removed from the study.

Food Deprivation

Ten male rats were assigned to each of two groups on which food intake tests were performed at 0800 or 2000 hr. Rats were subjected to food deprivation for 24 or 48 hr once weekly prior to their assigned food intake test session. Water continued to be available during the food deprivation period. All animals underwent at least 2 familiarization trials prior to drug testing. Rats were weighed and pretreated with naloxone or saline 30 min prior to testing. At 5–10 min before the test session, subjects were placed in individual cages containing absorbent paper taped to the floor. The rats were allowed access to a preweighed quantity of rodent chow (40–50 g) for 60 min; water was absent throughout the test session. Food intake tests at 2000 hr were conducted in darkness. At the end of the test period, the rats were returned to their home cages where they again had free access to food and water. Unconsumed food was carefully separated from non-food material and placed in tared 50 ml beakers; food was measured to the nearest 0.01 g. Food intake was calculated as the difference between the weight of the food prior to testing and the amount of food recovered subsequent to the test session.

Fifty male mice were divided into four groups: two groups of 15 mice were deprived of food for 24 hr prior to food intake testing at 0800 or 2000 hr, and two additional groups of 10 mice were subjected to food deprivation for 36 hr prior to testing at 0800 or 2000 hr. Food intake tests were conducted on a weekly basis. Water was available during all periods of food deprivation. Thirty minutes prior to testing, the mice were weighed and given naloxone or saline. Immediately after the injection, animals were placed in individual plastic cages containing absorbent paper taped to the floor. At the start of the test session, mice were given access to preweighed rodent chow for 60 min in the absence of water. The room lights were turned off during tests performed at 2000 hr. At the end of the test period, the mice were returned to their home cages where they again had free access to food and water. Unconsumed food was collected in tared 50 ml beakers and the amount of food consumed was determined in a manner similar to that described for rats. Data from animals that consumed less than 10 g/kg of body weight of food following saline administration were excluded from the data analysis.

Drugs

Naloxone hydrochloride was dissolved in 0.9% saline and injected subcutaneously in a volume of 1.0 ml/kg of body weight in the rats and 0.5 ml/100 g of body weight in the mice. In each series of experiments, various doses of naloxone (0.01–10 mg/kg) and saline were administered in a random sequence. All doses of naloxone are expressed in terms of the free base.

Data Analysis

Water intake data were converted to ml consumed per kg of body weight for both rats and mice. Similarly, food intake data were converted to g of food consumed per kg of body weight in both species. In order to facilitate comparisons among the different experimental groups, the data were further normalized by transformation to a percentage of the saline control values for each animal in each series of experiments. The transformed data were evaluated by analysis of variance for randomized groups, and comparisons of treatment means to that of the saline control were made by two-tailed paired and Dunnett's t-tests [9]. A p value of less than 0.05 was selected as the minimum level of statistical significance.

TABLE 1

CONTROL VALUES FOR DEPRIVATION-INDUCED FOOD AND WATER INTAKE*

Deprivation Interval	Time of Testing	Rat Male	Rat Female	Mouse Male
Water Intake				
12 hr	0800 hr	17.9 ± 1.2 (8)	26.9 ± 3.5 (8)	24.1 ± 4.2 (10)
	2000	7.3 ± 1.7 (8)	23.2 ± 3.0 (8)	— —
24 hr	0800	48.2 ± 3.8 (8)	51.4 ± 4.5 (8)	51.6 ± 5.8 (10)
	2000	45.2 ± 2.4 (8)	44.7 ± 2.1 (8)	44.5 ± 9.6 (10)
48 hr	0800	48.0 ± 2.3 (8)	65.3 ± 2.3 (8)	—
	2000	48.4 ± 3.4 (8)	62.3 ± 3.5 (8)	—
Food Intake				
24 hr	0800 hr	18.4 ± 1.5 (8)	—	16.9 ± 1.9 (10)
	2000	17.7 ± 1.6 (8)	—	19.0 ± 1.4 (14)
36 hr	0800	—	—	27.2 ± 3.2 (10)
	2000	—	—	22.9 ± 2.1 (9)
48 hr	0800	27.1 ± 1.9 (9)	—	—
	2000	21.7 ± 2.8 (7)	—	—

*Control values were determined in tests with saline that were randomly interspersed among the tests with naloxone in each series of experiments. Water intake is expressed as ml water consumed per kg of body weight, and food intake is expressed as g food consumed per kg of body weight. Each value is a mean ± S.E. based upon one observation in each of (n) subjects.

RESULTS

Water Intake

The absolute volumes of water consumed by the control groups under the various conditions of deprivation are presented in Table 1. In both male and female rats treated with saline, the magnitude of water intake subsequent to periods of water deprivation was directly related to the duration of the deprivation interval ($p<0.01$). Moreover, female rats consumed significantly more water than did their male counterparts after equivalent periods of water deprivation ($p<0.01$).

Naloxone (0.01–10 mg/kg) produced dose-related decreases in the deprivation-induced water consumption of rats which did not differ significantly in magnitude between the sexes, and which were essentially independent of both the degree of prior water deprivation and the time at which the tests of water intake were conducted (Fig. 1). In most experimental groups, naloxone significantly reduced water intake by as much as 30–50% at doses as low as 0.1–1.0 mg/kg ($0.01<p<0.05$). Among the 12 experimental groups whose data are depicted in Fig. 1, naloxone failed to suppress water intake only in male rats water-deprived for 12 hr and tested at 2000 hr; baseline water consumption in this group was considerably lower than that of the other experimental groups (Table 1). The low baseline water intake of this group probably reflects the fact that the interval of deprivation encompassed primarily a single period of the light cycle during which little drinking normally occurs [33].

Water intake in male mice deprived of water for 12 or 24 hr and tested at 0800 hr was also reduced by 0.01–10 mg/kg naloxone (Fig. 2). However, mice appeared less sensitive than rats to the suppressant effects of naloxone on water intake, and statistically significant reductions in water consumption occurred only at the highest dose of naloxone. Ten mg/kg of naloxone reduced water intake by 50% ($p<0.05$) in mice deprived of water for 12 hr, and by 30% in mice water-deprived for 24 hr ($p<0.05$) when both groups were tested at 0800 hr. Naloxone failed to decrease the volume of water consumed by mice deprived of water for 24 hr and tested at 2000 hr. In fact, a trend toward enhancement of water intake is evident in this group (Fig. 2).

The doses of naloxone employed did not appear to alter overt behavior of either the rats or mice.

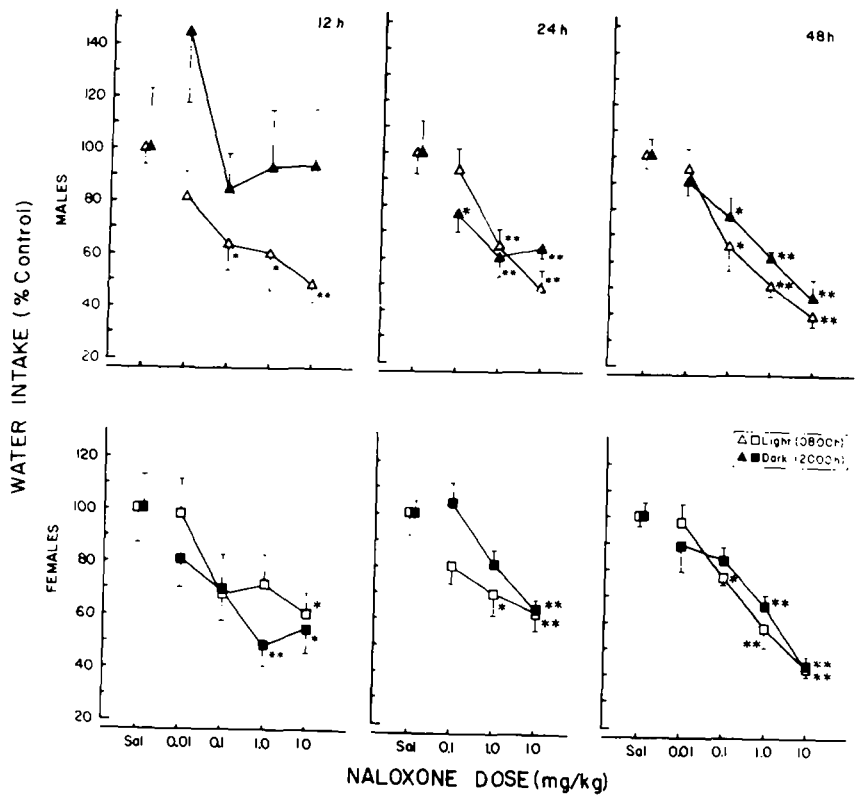

FIG. 1. Suppression of water intake by naloxone in the rat as a function of duration of deprivation (12, 24, or 48 hr), time of testing (0800 or 2000 hr), and sex. Each point represents the mean and SE of 8 observations. The absolute values obtained in tests with saline (points above Sal) are presented in Table 1. Significant differences between control and treatment means are indicated as: $*p<0.05$, and $**p<0.01$.

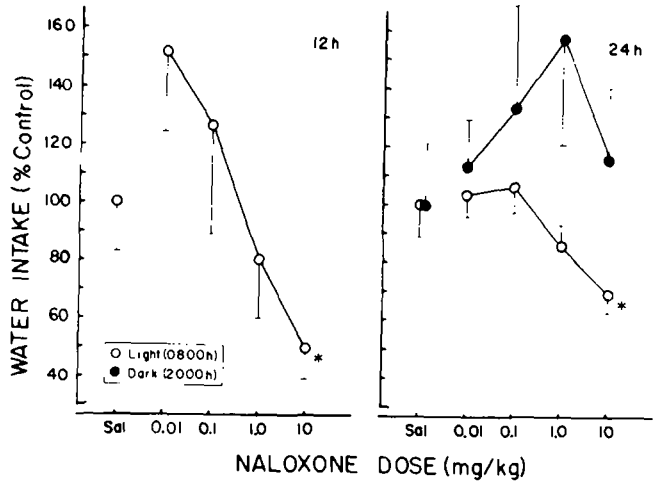

FIG. 2. Suppression of water intake by naloxone in male mice as a function of duration of deprivation (12 or 24 hr) and time of testing (0800 or 2000 hr). Each point represents the mean and SE of 10 observations. Absolute values obtained in tests with saline (points above Sal) are presented in Table 1. Significant differences between control and treatment means are indicated as: $*p<0.05$, and $**p<0.01$.

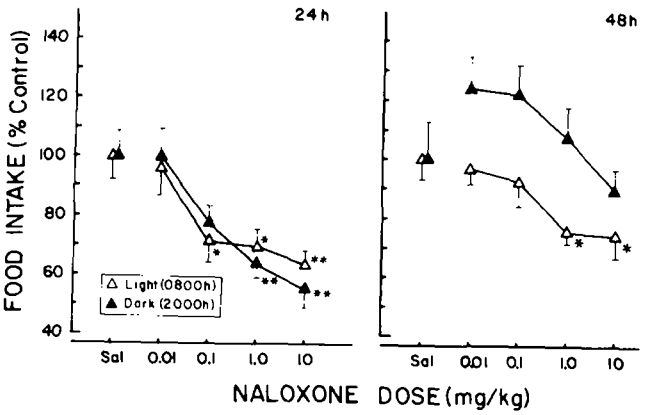

FIG. 3. Suppression of food intake by naloxone in male rats as a function of duration of deprivation (24 or 48 hr) and time of testing (0800 or 2000 hr). Each point represents the mean and SE of 7–9 observations. Absolute values obtained in tests with saline (points above Sal) are presented in Table 1. Significant differences between control and treatment means are indicated as: $*p<0.05$, and $**p<0.01$.

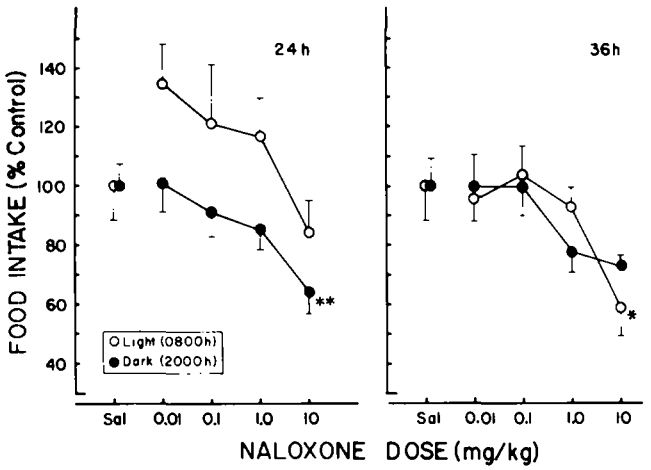

FIG. 4. Suppression of food intake by naloxone in male mice as a function of duration of deprivation (24 or 36 hr) and time of testing (0800 or 2000 hr). Each point represents the mean and SE of 9–14 observations. Absolute values obtained in tests with saline (points above Sal) are presented in Table 1. Significant differences between control and treatment means are indicated as: $*p<0.05$, and $**p<0.01$.

Food Intake

Male rats and mice were used in further studies of the effects of naloxone on food consumption following periods of food deprivation. Figure 3 demonstrates that, as in the case of water intake, food consumption in the rat was also reduced in a dose-related manner by 0.01–10 mg/kg of naloxone. At a dose of 1.0 mg/kg, naloxone reduced food intake to approximately 40% of the control value in male rats food-deprived for 24 hr and tested at either 0800 or 2000 hr. However, lengthening the deprivation interval reduced the sensitivity of the animals to the suppressant effects of naloxone. In rats deprived of food for 48 hr and tested at 0800 hr, a maximal reduction in food intake to 74% of control was observed following the administration of 10 mg/kg naloxone (Fig. 3). Naloxone had no significant effect on food intake at any dose in rats deprived of food for 48 hr and tested at 2000 hr (Fig. 3).

The effects of naloxone on food intake in male mice were also less prominent than its effects on water consumption in this species. Mice deprived of food for 24 hr exhibited a significant decrease ($p<0.01$) in food intake of 36% when tested at 2000 hr, but mice tested at 0800 hr did not show significant reductions in food consumption even at the 10 mg/kg dose of naloxone (Fig. 4). In mice food-deprived for 36 hr, naloxone significantly decreased food intake of those tested at 0800 hr only at the highest dose of 10 mg/kg ($p<0.05$), and failed to significantly affect food consumption in mice tested at 2000 hr (Fig. 4).

DISCUSSION

The results of this study confirm previous findings that naloxone suppresses appetitive behavior in a dose-related manner in male rats [12, 18–20, 27, 35] and further indicate that naloxone has similar effects in female rats and male mice.

In both rats and mice, water deprivation of increasing lengths was associated with correspondingly greater volumes of subsequent water intake. Baseline water consumption manifested some degree of circadian rhythmicity apparent after the 12 and 24 hr water deprivation periods. Subjects deprived of water during the light cycle and tested during the dark cycle (2000 hr) appeared to consume less water than subjects tested in the opposite fashion. Normal ingestive patterns of rats follow a diurnal periodicity with greatest food and water consumption occurring during the dark cycle [32, 33, 36]. Rats deprived of water for periods of 48 hr showed little or no circadian component in the amount of subsequent water intake. This disappearance of circadian expression in water intake has been reported to occur after deprivation periods exceeding 24 hr [32].

In the rat, the suppressant effects of naloxone on postdeprivational water intake appeared independent of sexual differences, the length of the deprivation interval, and the phase of the diurnal cycle in which water intake was measured. Naloxone generally reduced water intake to similar degrees across all experimental groups of male and female rats. Divergence of the naloxone suppressant effect from this general pattern, which occurred in male rats water-deprived for 12 hr and tested at 2000 hr, probably does not reflect variations in susceptibility to naloxone per se, but rather represents alterations in the water intake parameter due to circadian and deprivational factors.

Female rats displayed considerably higher baseline water intakes in comparison to males under most conditions. The greater water consumption of female rats may be the result of hormonal influences on ingestive behavior, innate qualities arising from sexual differentiation, or both. The estrus cycle of female rodents has been shown to alter food intake [31,37] and may influence water consumption as well, due to the close association of eating and drinking behaviors [10,32]. Sexual differentiation might also create disparities in water consumption between the sexes. Castrated female rats consume greater volumes of water than do castrated males in response to an injection of polyethylene glycol, an extracellular thirst stimulus [38]. Despite the sex-related differences in water intake baselines in the present study, naloxone reduced water intake in both male and female rats to comparable levels following equivalent periods of deprivation. Thus, the suppressant effects of naloxone on water intake appear to be independent of sexual differences.

Water intake following deprivation in male mice was also reduced in a dose-related fashion by naloxone. Mice appeared less sensitive to the effects of naloxone in comparison to the rat, indicating a possible species-dependent variation in susceptibility to naloxone actions. A trend toward decreasing naloxone effectiveness with lengthening periods of deprivation seems to exist. In contrast to the rat, naloxone was ineffective in reducing the water consumption of mice subjected to a 24 hr deprivation period and tested during the dark cycle.

Food intake in male rats and mice subsequent to periods of food deprivation was reduced by naloxone in a dose-dependent manner. In general, naloxone was less effective in suppressing food intake than it was in reducing water intake in both species. In male rats, an increase in the duration of the food deprivation period from 24 to 48 hr noticeably diminished naloxone suppressive effects on subsequent food intake. Thus, long periods of food deprivation appear to be capable of surmounting the anorexic effects of naloxone.

The postdeprivational food consumption of male mice was similarly reduced by naloxone, but significant decreases were observed only at the highest dose employed. This result

is contrary to a previous finding [18] in which naloxone appeared to have no effect on the food intake of mice. This discrepancy may stem from procedural differences between the two investigations: food intake measurements in the present study were conducted with individual mice familiarized to the protocol, whereas in the earlier experiment, food consumption was determined with grouped mice not previously exposed to the experimental conditions [18]. Nevertheless, it is evident that food consumption in deprived mice is less susceptible to the actions of naloxone than is water consumption.

Mechanisms governing food consumption may possess an endorphin component. Indeed, β-endorphin appears to stimulate food consumption when injected into the ventromedial hypothalamus of satiated rats [15]. Endorphin levels are elevated in the pituitaries of genetically-obese rats and mice, and the excessive food intake characteristic of both strains is partially reduced by low doses of naloxone [28]. Food and water deprivation may also be conceived as stressors, and as such, may play a role in some of the observed effects of naloxone. Both food and water deprivation are associated with elevations in serum corticosterone levels, an index of exposure to stress [24,26]. Short periods of food deprivation in the rat have been associated with the development of a transient analgesia [4] which may be related to the coupled release of adrenocorticotropin and β-endorphin occurring during stress exposure [17]. Other stressors, such as immobilization [1], also appear to produce an analgesic response which can be reduced or eliminated by naloxone, suggesting the presence of such an endorphin component. Stress-related endorphin mobilization and antagonism of its effects by naloxone may partly account for some of the observed actions of naloxone on deprivation-elicited ingestive behaviors.

It is not immediately clear why post-deprivational water intake is more susceptible to disruption by naloxone than is food consumption. Food deprivation might engender a stronger drive state in the animal to consume food than water deprivation can generate for water intake, and this may explain the differential sensitivity to naloxone of food vs water intake, and of rats vs mice. On the other hand, the effects of naloxone may not be related to the non-specific stress of food or water deprivation, but may be relatively specific for appetitive behaviors, especially drinking. Moreover, the implication of an endorphin component associated with naloxone effects on ingestive behavior is inferential at this point. More definitive studies are necessary to clarify the mechanisms by which naloxone, and possibly other narcotic antagonists, act to modify appetitive behavior.

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