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Effect of Naltrexone on Food Intake and Hoarding in White-Footed Mice *(Peromyscus)*

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TANNENBAUM, M. G. AND E. B. PIVORUN. *Effect of naltrexone on food intake and hoarding in white-footed mice* (Peromyscus). PHARMACOL BIOCHEM BEHAV 20(1) 35–37, 1984.—Increases in food consumption and hoarding in mammals have been shown to be immediate and preparative adjustments to the energetic stresses of temperate winters. The sensitivity of these behaviors to the opiate antagonist naltrexone was tested in non-deprived white-footed mice *(Peromyscus leucopus)*. Mice received naltrexone hydrochloride intraperitoneally (10 mg/kg in saline vehicle) once daily for four consecutive days subsequent to an equivalent period of injection with saline as control. Daily food intake was significantly ($p<0.05$) lower after naltrexone treatment. Hoarding, as assessed by logarithmic hoarding scores and the weight of cached food, was not affected by administration of this drug at this dosage. These results suggest that hoarding, a complex behavioral pattern that does not immediately affect internal energy stores, may not fall within the opiate regulatory scheme.

White-footed mice Naltrexone Feeding behavior Hoarding *Peromyscus*

DURING the late fall and early winter, many small mammals must increase their intake of food in order to meet the metabolic demands of lower environmental temperatures. Paradoxically, this is the time of year when naturally occurring food supplies are likely to become depleted. The resultant problem of supply and demand is often overcome by the initiation of food hoarding in the late summer and early fall, when food is more plentiful. In many small rodents, the onset of such caching behavior is cued by changes in photoperiod and/or ambient temperature [1, 3, 21].

A recent hypothesis [15] postulates that the endorphins and enkephalins may be responsible for the activation of physiological and behavioral mechanisms that serve to direct the conservation of energy and bodily resources. For example, the induction and maintenance of hibernation, a state of reduced metabolic demand, may be opiate dependent [16]. Another example of a system under endorphinergic regulation is that of consummatory behavior. In laboratory mice and rats, administration of beta-endorphin stimulates food intake [9,17]. Moreover, these rodents consume less food [2,5] when given naloxone, an opiate antagonist. In light of the involvement of the opiates with physiological energy balance mechanisms, the suite of autumnal behaviors (nest building, den construction, food hoarding, etc.) displayed by rodents in preparation for winter may also be modulated by the endogenous opiates.

The sensitivity of one of these behaviors (food hoarding) to the administration of naltrexone, a long-acting opiate antagonist, was tested in the white-footed mouse, *Peromyscus leucopus*. This wide-ranging [10] species exhibits a high propensity towards hoarding [25]. Changes in food consumption in association with naltrexone treatment were also assessed to determine if opiate involvement in consummatory behavior in free-living species is qualitatively similar to the results obtained with traditional laboratory animals.

METHOD

Seven white-footed mice *(Peromyscus leucopus)* that had displayed a high proclivity for hoarding in a previous experiment were utilized for the food hoarding and consumption experiments. These mice (4 females and 3 males) were chosen from among a genetically heterogeneous group of first- and second-generation offspring of mice trapped around Clemson, SC. All mice had been conceived, born, and raised to weaning in a breeding colony at room (20–22°C) temperature under a photoperiod of 12L:12D. Upon weaning, they were transferred to a cold (5°C) room with a winter lighting schedule (9L:15D), were caged individually in 29×18×12 cm cages, and were given food and water ad lib. After an acclimation period of at least five months, seven to 12 month old mice were introduced into individual test cages and were allowed a three day habituation period before hoarding tendency was measured. Although hoarding in the wild most often occurs during the autumn, white-footed mice that were long-term residents of this cold room continued to display elevated hoarding tendencies under the winter temperature and photoperiod regime (manuscript in preparation).

These test cages were identical to the cages in which the mice had been held prior to the test, with the exception of an attached hardware cloth runway (50 cm long, 5 cm diameter) that allowed access to a hardware cloth food hopper (15×10×10 cm). Nesting material was supplied to the home cages, and 25 preweighed (±0.1 g) Purina Rat Chow pellets

TABLE 1

HOARDING SCORES, HOARDING WEIGHTS, AND FOOD INTAKE IN *PEROMYSCUS LEUCOPUS* UNDER CONTROL (SALINE) AND EXPERIMENTAL (NALTREXONE) CONDITIONS

Animal	Sex	Treatment	Hoarding Score (±1 SE)	Hoarding Weight (g, ±1 SE)	Food Intake (g, ±1 SE)
1	F	Saline	3.19 ± 0.01	92.4 ± 1.4	8.0 ± 0.3
		Naltrexone	3.23 ± 0.02	89.3 ± 2.7	7.4 ± 1.2
2	M	Saline	2.18 ± 0.28	31.3 ± 9.0	5.0 ± 0.6
		Naltrexone	2.47 ± 0.10	35.7 ± 7.1	4.6 ± 0.5
3	F	Saline	1.04 ± 0.20	5.9 ± 2.4	6.9 ± 1.3
		Naltrexone	1.42 ± 0.31	13.6 ± 4.9	3.4 ± 0.9
4	F	Saline	1.64 ± 0.12	13.6 ± 2.8	3.5 ± 0.4
		Naltrexone	2.52 ± 0.28	43.0 ± 11.3	2.4 ± 0.7
5	M	Saline	0.17 ± 0.17	0.8 ± 0.8	8.8 ± 0.4
		Naltrexone	0	0	7.2 ± 0.7
6	M	Saline	3.16 ± 0.07	86.0 ± 7.5	5.4 ± 0.6
		Naltrexone	3.24 ± 0.01	88.3 ± 2.2	4.9 ± 1.8
7	F	Saline	1.33 ± 0.69	25.8 ± 21.5	5.5 ± 0.4
		Naltrexone	0	0	5.3 ± 0.5
Mean		Saline	1.81 ± 0.22	36.5 ± 7.4	6.2 ± 0.4*
		Naltrexone	1.91 ± 0.25	40.0 ± 7.1	5.0 ± 0.5*

*$p<0.05$.

were placed into the food hopper. Each day, within the hour following the onset of light in the cold room, the pellets remaining in the food hopper, as well as those that had been transported by the mice into the home cage, were counted and weighed. After this weighing procedure, all food was removed from the home cage and the supply of pellets in the food hopper was replenished. The difference between the total weight of food present on successive days, minus any spillage, was recorded as daily food consumption. Mice were allowed full access to food and water throughout the experiment. Two measures of hoarding, weight and number of pellets, were also recorded for each mouse. A hoarding score (log of the number of pellets hoarded plus 1) was then assigned to each mouse for each day [18].

In order to minimize disturbance to the animals, naltrexone or saline injections were administered at the same time that hoarding and food intake was measured. Each mouse received a single intraperitoneal injection of 0.9% physiological saline (0.25 ml per mouse) for four successive days, followed by four consecutive days of 0.25 ml injections of naltrexone hydrochloride (10 mg per kg) in an identical saline vehicle. Use of this long-acting opiate antagonist was prompted by findings that naloxone at doses of 10 and 20 mg/kg significantly altered patterns of daily torpor bouts in a closely related species, *P. maniculatus* [23]. Moreover, use of naltrexone, as opposed to naloxone, seemed justified in light of the fact that both hoarding and feeding were assessed over a 24-hour test period.

Each individual served as its own control, a condition necessitated by the great variation in the tendency to hoard seen among individuals of this species. Data were subjected to a paired *t*-test and analysis of variance.

RESULTS AND DISCUSSION

Intraperitoneal injection of naltrexone (10 mg/kg) significantly ($p<0.05$) reduced mean food consumption in nondeprived *Peromyscus leucopus*, the white-footed mouse. In contrast to consummatory behavior, hoarding, as assessed by hoarding score and the weight of cached food, was not significantly altered by naltrexone (Table 1). Naltrexone administration abolished the hoarding response in two individuals; however, mean hoarding scores for the other five mice were slightly (but non-significantly) increased by this opiate antagonist. Furthermore, in four of the latter five animals, the mean weight of cached food was also increased by drug treatment. There was no significant day-to-day variation in either hoarding score ($F=0.02$, $p<0.99$) or hoarding weight ($F=0.06$, $p<0.98$). Similarly, food consumption did not vary significantly among the four successive days within each treatment.

These results are consistent with those of other studies in which peripherally administered naloxone [4, 11, 26] at doses of 0.5–10 mg/kg and naltrexone [13,24] at doses of 0.3–30 mg/kg suppressed food intake in rats. Although a paucity of data exists for wild mammals, there presumably exists a common mechanism for opiate modulation of feeding among both wild and domesticated species. A recent study [19] demonstrated naloxone's suppression of feeding in wolves at concentrations of 1 and 5 mg/kg. Lowy and Kim [14], however, have shown that hamster feeding behavior is "opiate-insensitive" compared to rats.

As has been stressed in other reports, reduced feeding in response to opiate antagonist injection may not be a reflection of direct action on a central site mediating energy bal-

ance, but rather may be due to non-specific effects such as taste aversion [8] or changes in emotional tone [12]. Such effects may become increasingly important at high doses [7] such as used in this study.

Fantino and Cabanac [6] have shown that the amount of food hoarded by deprived rats was proportional to their body weight decrease, or energy deficit. The amount of food hoarded and eaten by wild rodents is higher during autumn, when the body weight set-point may be elevated [20,22]. It is therefore surprising that hoarding is not as susceptible to modulation by opiate antagonists as is food intake, since augmentation of both behaviors would serve to increase and maintain body weight. A single, large, systemic dose of naltrexone did not elicit lower hoarding scores in white-footed mice; a dose-response curve is necessary to fully determine the involvement of the opiates with hoarding behavior. Alternatively, central, as opposed to peripheral, administration of opiate antagonists may have resulted in the attenuation of hoarding. It is also possible that not all of the multiple causes underlying this complex behavioral pattern fall within the opiate regulatory scheme. Furthermore, the differential sensitivity of food hoarding and eating to naltrexone injections may arise from the former only indirectly affecting energy balance.

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