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Food Hoarding and Ingestion in the Deer Mouse, *Peromyscus maniculatus*: Selective Responses to Mu and Kappa Opiate Agonists

MARTIN KAVALIERS*†[1] AND MAURICE HIRST‡

**Department of Zoology and †Division of Oral Biology, Faculty of Dentistry*
‡Department of Pharmacology and Toxicology, University of Western Ontario
London, Ontario, Canada N6A 5C1

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KAVALIERS, M. AND M. HIRST. *Food hoarding and ingestion in the deer mouse,* Peromyscus maniculatus: *Selective responses to mu and kappa opiate agonists.* PHARMACOL BIOCHEM BEHAV **25**(3) 543–548, 1986.—The feeding behavior of the deer mouse, *Peromyscus maniculatus*, includes food hoarding as well as ingestion. Administration of the prototypical mu opiate agonist, morphine sulfate, 1–20 mg/kg, produced over three hours a significant dose-dependent stimulation of hoarding by free feeding deer mice. The specific kappa opiate agonist, U-50,488H, 0.10–10 mg/kg, markedly increased ingestion without having any augmentatory effects on hoarding. The mixed mu and kappa opiate agonist, ketocyclazocine hydrochloride, 1–10 mg/kg, as well as various combinations of morphine sulfate and U-50,488H, augmented both hoarding and ingestion. Food restriction for 24 hr caused a significant, naloxone (1.0 mg/kg) reversible, increase in food intake. Food deprivation also modified the hoarding and ingestion responses of the deer mice to the mu and kappa opiate agonists, reducing the relative amounts of food that were hoarded. These results indicate that mu and kappa opioid systems are differentially involved in the mediation of various aspects of feeding. This also suggests that environmental factors, such as food restriction, can modify the relative roles of mu and kappa opioid systems in the expression of feeding behavior.

Deer mice *Peromyscus maniculatus* Feeding Food hoarding Mu opioid Kappa opioid
Morphine Ketocyclazocine U-50,488H · Naloxone Food restriction

THERE is substantial evidence for the hypothesis that endogenous opioid peptides participate in the regulation of feeding [8, 20, 30, 31, 35, 43]. Administrations of opiate agonists have been shown to have both qualitative and quantitative influences on ingestive behaviors [8, 14–21, 23, 29–31, 37, 38, 43]. With the recognition of the existence of multiple opioid peptides and differing opioid receptors [24], there is evidence to suggest that several opioid systems may modulate feeding behavior [30,31]. The results of several investigations indicate that dynorphins, and the kappa opioid receptor on which they act, may have specific roles in the determination of mammalian food intake [8, 11, 16, 23, 26, 28, 29, 35]. Additionally, several other studies suggest that mu opioid receptors are also involved in the mediation of feeding [14, 30, 31, 37, 38]. Relatively little is known, however, about the influences of opioid systems on the various components of the natural feeding behavior of mammals. The existence of differing receptor species and multiple endogenous opioid peptides [24], has raised the possibility that distinct aspects of feeding behavior may be variably influenced by differing opioid mechanisms [17, 20, 30, 31]. This consideration has been supported by recent findings in the deer mouse, *Peromyscus maniculatus*, which indicate that mu and kappa opioid systems may differentially mediate primary components of feeding behavior [15,19].

The deer mouse displays, in the field and in the laboratory, a variety of behaviors associated with feeding. These include searching for food, foraging, transporting and handling of food, hoarding-caching of food, and food ingestion [3, 9, 10, 15, 34, 40–42]. Results of initial studies with this rodent suggested that mu and kappa opiate agonists selectively influence hoarding and ingestion, respectively [15]. In the present study the effects of the prototypic mu opiate agonist morphine [24], the highly selective kappa opiate agonist, U50,488H, [trans-3,4-dichloro-N-methyl-N-2-(1-pyrrolidinyl)-cyclohexyl-benzeneac-etamide methanesulfonate hydrate) 45], the preferential kappa-mu opiate agonist, ketocyclazocine [24,26], as well as combinations of morphine and U-50,488H, on hoarding and ingestion by deer mice are described in detail. In addition, the effects of 24 hr food deprivation on food ingestion and hoarding by deer mice, as well as their responses to the mu and kappa opiate agonists, are presented. The results show that selective administrations of mu and kappa opiate agonists systematically

[1]Requests for reprints should be addressed to Martin Kavaliers, Division of Oral Biology, Faculty of Dentistry, University of Western Ontario, London, Ontario N6A 5C1.

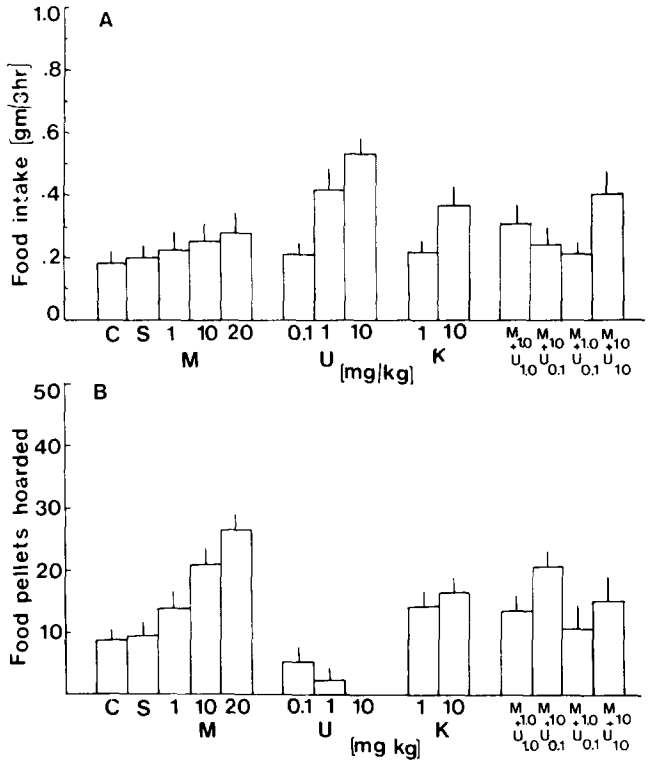

FIG. 1. A–B. Effects of intraperitoneal (IP) administrations of morphine sulfate (M, 1.0, 10 and 20 mg/kg), U-50,488H (U, 0.10, 1.0, 10 mg/kg), ketocyclazocine hydrochloride (K, 1.0, 10 mg/kg) and various combinations of morphine (1.0, 10 mg/kg) and U-50,488H (0.10, 1.0, 10 mg/kg) (M+U) on (A) the food intakes of individual deer mice over 3 hr and (B) the number of pellets hoarded by individual deer mice over 3 hr. Saline injected (S, 10 ml/kg) mice served as a control for handling. Untreated mice (C) were used as an additional control. N=10 for all treatments. Vertical lines denote two standard errors of the mean.

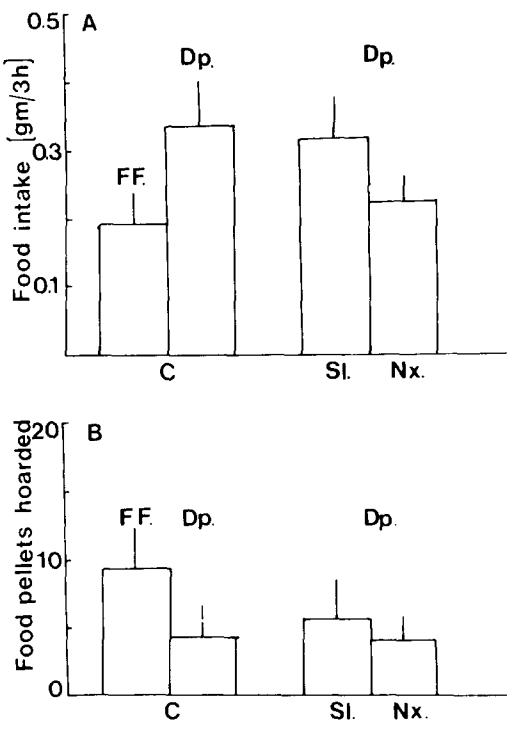

FIG. 2. A–B. Effects of mid-light naloxone hydrochloride (Nx., 1.0 mg/kg) pretreatment on (A) the food intakes and (B) the number of pellets hoarded over 3 hr by 24 hr food deprived mice (Dp.). Saline (Sl, 10 ml/kg) injected mice served as a control. The 3 hr food intakes and hoarding rates of control untreated (C) food deprived and free feeding (FF) mice are also provided. N=10 in all cases. Vertical lines denote two standard errors of the mean.

affect the feeding behavior of deer mice, and modulate the relative amounts of food hoarded and ingested. Additionally, it was identified that food deprivation differentially alters the responses of deer mice to the mu and kappa opiate agonists, and the proportions of food hoarded and ingested.

METHOD

Animals

Sexually mature male deer mice (*Peromyscus maniculatus nebrascensis* (Coues)), 20–25 g and 1–2 months of age were, prior to experimentation, housed in groups of 5 in polyethylene cages at 20±1°C under a 10 hour light:14 hour dark cycle (light 0800–1800 hr at 25 μw/cm^2 provided with hardwood sawdust and cotton bedding. Food (Purina mouse chow 5015, 3% water content and an energy value of 18.8 KJ/g) and water were provided ad lib. Mice were eighth laboratory generation, derived from a population trapped in a semi-arid grassland habitat in southeastern Alberta (49°N, 111°W). Characteristics of these wild and laboratory populations are provided by Millar [25].

Experimental Procedures

Food intake determinations. Deer mice were housed individually in elevated 20 cm diameter (7 cm high) clear plastic small rodent metabolism units that had a wire mesh floor (E-1100 Econo-Metabolism Unit, Maryland Plastics, NY). Cotton bedding was provided for the animals in the feeding units. A short (3 cm) aluminum tunnel provided access to a food hopper in which powdered food (Purina mouse chow 5015) was placed. An aluminum ring in front of the hopper restricted entry to only the head and prevented the animals from placing their paws in the food. The animals readily consumed the powdered food by licking. Water was provided in a plastic, graduated tube which was placed directly across the unit from the food hopper.

After three days of habituation, the animals were provided with pre-measured amounts of food (2.0–2.5 g) in a plastic tray placed in the food hopper. The amounts eaten by licking were determined by weighing the residual powder to the nearest 0.01 g at hourly intervals. Food that was lost by scatter or spillage (0.01–0.03 g) was collected and weighed. Determinations were made of the amounts of food ingested hourly in three hour blocks in the light period (1300–1600 hr) following intraperitoneal (IP) injections of either morphine sulfate ((mu agonist) 1.0, 10 and 20 mg/kg, B.D.H., Toronto), ketocyclazocine hydrochloride ((mixed mu-kappa agonist) 1.0 and 10 mg/kg, Sterling-Winthrop, NY), U-50,488H ((kappa agonist) 0.10, 1.0 and 10 mg/kg, Upjohn Kalamazoo), combinations of morphine sulfate and U-50,488H as identified later (Fig. 1), or the saline vehicle (10 ml/kg), which was given as a control. Different groups of

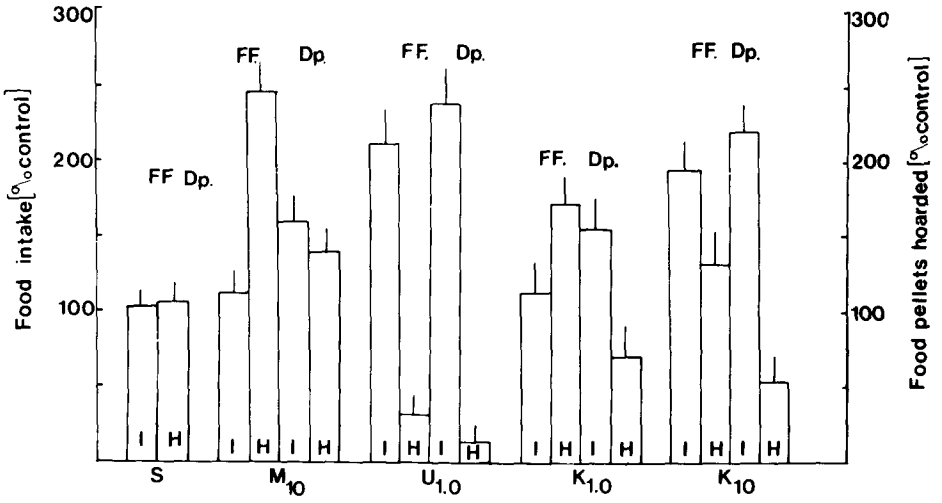

FIG. 3. Comparisons of the effects of mid-light intraperitoneal administrations of saline (S, 10 ml/kg), morphine sulfate (M_{10}, 10 mg/kg), U-50,488H ($U_{1.0}$, 1.0 mg/kg) ketocyclazocine hydrochloride ($K_{1.0}$, K_{10}, 1.0 and 10 mg/kg, respectively) on the amounts of food ingested (I) and hoarded (H) by individual free feeding (FF) and 24 hr food deprived (Dp.) deer mice. Food intakes and numbers of food pellets hoarded over 3 hr are expressed as a percentage of the feeding and hoarding rates, respectively, of control untreated free feeding and food deprived mice. N=10, in all cases. Vertical lines denote two standard errors of the mean.

mice (n=10, in all cases) were used for each drug and dose or vehicle determination. Additional groups of mice (n=10) were used as a further control for the handling and injection procedures.

Food hoarding determinations. Hoarding by individual deer mice was monitored by measuring the amounts of food (0.2–0.3 g pellets, Martin Feed Mills, Elmira, Ontario), of the same composition and nutrient value as the powdered food, removed from a source and cached in a new location. Mice were acclimated in cages (18×30×13 cm) which had a black polyethylene U-shaped tunnel (8.5 cm total length) attached to one end. A black polyethylene tube (5.0 cm length, 3.5 cm dia.) was placed inside the other end of the cage. Hoarding was measured by the number of pellets that were removed from a pre-determined amount placed in the removable bottom of the tunnel and hoarded in the tube. The animals readily learned to cache pellets in the tube, with minimal scatter in the rest of the cage.

The animals remained undisturbed for five days and, on the sixth day, determinations were made of the amounts of food hoarded, each hour over three hours, in the light period (1300–1600 hr) following IP administrations of either morphine sulfate (0.10, 1.0, 10 mg/kg), ketocyclazocine hydrochloride (1.0 and 10 mg/kg), U-50,488H (0.10, 1.0, 10 mg/kg), combinations of morphine sulfate and U-50,488H as described later (Fig. 1), or the saline (10 ml/kg) vehicle. Uninjected handled animals were used as an additional control. Different groups of mice (n=10, in all cases) were used for each of these determinations.

The hoarding behavior of U-50,488H (1.0 mg/kg), morphine sulfate (10 mg/kg) and saline (10 ml/kg) treated mice was also examined with a non-food item (n=5, in all cases). Small, calcium carbonate chips of the same mass and shape as the food pellets were used. In addition, the hoarding behaviors of injected mice were examined when both powdered and pelleted food was present in the hoarding units.

Food deprivation. Deer mice that had been habituated to the feeding and hoarding units were deprived of food for 24 hr. After this period they received IP injections of either morphine sulfate (10 mg/kg), ketocyclazocine hydrochloride (1.0, 10 mg/kg), U-50,488H (1.0 mg/kg), or the saline vehicle (10 ml/kg), and the amounts of powdered food ingested and numbers of pellets hoarded over 3 hours were recorded. Uninjected animals were used as an additional control for handling procedures. In addition, determinations were made of the effects of 30 min pre-treatment with either naloxone hydrochloride (1.0 mg/kg, Sigma, St. Louis) or the saline vehicle (10 ml/kg), on the ingestive and hoarding responses of the food-deprived animals. Different groups of mice (N=5) were used for each of these determinations.

Data were analysed by analysis of variance and the Student-Newman-Keuls test was used for post-hoc comparisons. In the following section the doses given refer to the salt forms of the drugs.

RESULTS

Food Ingestion

Deer mice receiving U-50,488H displayed a significant ($p<0.01$ for 1.0 mg/kg, 240% increase) dose-dependent enhancement of food intake over three hours as compared to either the saline treated or uninjected animals (Figs. 1A, 3). Ketocyclazocine at 1.0 mg/kg had no significant effect on food intake, while treatment with 10 mg/kg of ketocyclazocine led to an appreciable increase ($p<0.01$, 160%) in food intake over that of saline treated animals (Figs. 1A, 3). This latter increase in food intake was, however, significantly less ($p<0.05$) than that obtained with 10 mg/kg of U-50,488H. Morphine (1–20 mg/kg) had no significant effects on the food intake of free feeding deer mice (Figs. 1A, 3). The combination of morphine (1.0 mg/kg) and U-50,488H (1.0 mg/kg), as well as the combination of morphine (10 mg/kg) and U-50,488H (10 mg/kg), caused a significant increase ($p<0.05$) in food intake (Fig. 1A). The food intake

obtained after injection with the latter combinations of morphine and U-50,488H was, however, significantly less ($p<0.05$) than that observed after treatment with U-50,488H (10 mg/kg) by itself. There were no significant differences in the amounts of food ingested by saline injected and control uninjected deer mice.

Food Hoarding

The control, saline injected and untreated mice displayed similar low levels of food hoarding. Morphine caused a significant ($p<0.01$, for 1.0 mg/kg) dose-dependent increase in hoarding over 3 hours (Fig. 1B). Administration of 10 mg/kg of morphine led to a large (250%) increase in the hoarding rate of the deer mice (Fig. 3). The deer mice given morphine did not hoard the calcium carbonate or wood chips that were comparable in size and shape to the food pellets. Additionally, equivalent levels of morphine-induced hoarding occurred in either the presence or absence of the powdered food.

Ketocyclazocine (1.0 mg/kg) also significantly increased ($p<0.01$) the number of pellets hoarded (Figs. 1B, 3). This increase (175%) in hoarding levels (Fig. 3) was equivalent to that observed after treatment with morphine (1.0 mg/kg). Ketocyclazocine (10 mg/kg) did not cause any further enhancement in the quantity of pellets hoarded. The number of pellets hoarded following administration of ketocyclazocine (10 mg/kg) was significantly less ($p<0.05$) than that obtained with morphine (10 mg/kg).

U-50,488H significantly suppressed ($p<0.05$ for 1.0 mg/kg) food hoarding (Fig. 1B), with the animals partially ingesting the food pellets. There was a complete absence of hoarding by animals treated with U-50,488H (1.0 and 10 mg/kg) during the second and third hours after administration of the drug. The total number of pellets hoarded over 3 hours by deer mice treated with U-50,488H (1.0 mg/kg) was one-quarter of that of the control mice (Fig. 3). When powdered food was also available, the deer mice equally consumed both foods.

Treatment with combinations of morphine (1.0 mg/kg) and U-50,488H (1.0 mg/kg) led to a significant increase ($p<0.05$) in the number of pellets hoarded (Fig. 1B). Administration of morphine (10 mg/kg) and U-50,488H (0.10 mg/kg) also significantly increased ($p<0.05$) hoarding to a level similar to that observed after injection with 1.0 mg/kg of morphine. Morphine (1.0 mg/kg) and U-50,488H (10 mg/kg) led to a slightly lower, but still significant ($p<0.05$), increase over the control level in the number of pellets hoarded.

Food Deprivation

Food deprivation for 24 hr significantly increased ($p<0.05$) ingestion during 3 hr, while significantly reducing ($p<0.05$) the number of pellets hoarded by control, saline treated and uninjected mice (Figs. 2A, 3). The deer mice ingested the pellets rather than hoarding them. Pre-treatment with naloxone (1.0 mg/kg) significantly reduced ($p<0.05$), but did not block the deprivation-induced feeding (Fig. 2B). Naloxone had no significant effect on hoarding responses of the food-deprived animals (Fig. 2B). Results of previous investigations [15] had shown that naloxone (1.0 mg/kg) had no significant effects on the basal food intakes or hoarding rates of free feeding deer mice. Saline pre-treatment also had no significant effects on either the ingestive or hoarding behaviors of the food deprived animals. Administration of morphine (10 mg/kg) to food deprived deer mice led to a significant increase ($p<0.05$) in the number of pellets hoarded. The increase (150%) in hoarding was, however, significantly lower ($p<0.05$) than that (250%) obtained in free feeding animals treated with morphine. In contrast to that of free feeding animals, morphine also induced a significant ($p<0.05$), increase in the amount of food ingested by the deprived animals.

Ketocyclazocine (1.0 mg/kg) significantly increased ($p<0.05$) food ingestion (175% of the levels of saline treated or uninjected animals) and significantly reduced ($p<0.05$) the number of pellets hoarded (60% of the levels of saline treated or uninjected animals) by the food deprived animals. These effects of ketocyclazocine (1.0 mg/kg) on hoarding and ingestion were both significantly different ($p<0.05$) from those observed in free feeding deer mice. Ketocyclazocine (10 mg/kg) had similar significant ($p<0.05$) ingestive effects in food-deprived and free-feeding deer mice. It significantly reduced ($p<0.05$) the number of pellets hoarded (60% of control untreated animals) in the food deprived mice. U-50,488H had equivalent, significant ($p<0.01$) ingestive effects in the food deprived and free feeding deer mice.

DISCUSSION

The present results show that, in the deer mouse, activation of mu and kappa opioid receptors has distinct effects on the components of feeding behavior related to the acquisition and ingestion of food, respectively. They further demonstrate that the relative levels of these feeding associated behaviors can be systematically varied by differential applications of kappa and mu opiate agonists. The present results also show that food deprivation can significantly modify the food hoarding and ingestion responses of the deer mice to the mu and kappa opiate agonists. These findings confirm and extend previous observations that mu and kappa opiate receptors selectively mediate food hoarding and ingestion by deer mice [15]. These results are also consistent with the results of earlier investigations with laboratory mice and rats [8, 11, 16, 28, 29, 31], as well as invertebrates [17, 20, 21], which suggest that kappa opioid systems are associated with the initiation of feeding, while mu systems affected other aspects of feeding. Moreover, the present results indicate that the expression of natural feeding behavior, in the deer mouse, involves the concurrent and differential activation of at least the mu and kappa opioid systems.

The marked ingestive effects of the highly specific kappa opiate agonist, U-50,488H [45], in deer mice, agree with previous findings from laboratory mice and rats [8, 16, 28, 29]. The dose-dependent increases in food consumption, time-courses of response, as well as the partial suppression by naloxone of feeding in deer mice induced by U-50,488H [15], are analogous to the responses obtained from laboratory mice and rats [16, 28, 29]. Additionally, U-50,488H was more potent in inducing food ingestion in both the deer mice and laboratory rodents than was the mixed mu-kappa opiate agonist, ketocyclazocine [8, 14, 16] which augmented both the hoarding and ingestive components of feeding behavior.

Peak nocturnal values in central levels of dynorphins, a family of peptides considered to be the endogenous ligands for the kappa opioid receptor [12,35] have, in rats and mice, been correlated with augmented night-time levels of food intake [8, 16, 30]. In addition, intracerebroventricular administrations of dynorphins have marked ingestive effects in rats [26,28]. Substantial levels of immunoreactive dynorphin have been reported from a variety of other mammals, includ-

ing species such as hamsters, whose feeding mechanisms and responses to morphine are reported to be different from those of rats and mice [4]. Whether or not significant levels of dynorphins are present in deer mice remains to be determined.

The prototypic mu opiate agonist, morphine, failed to have any significant ingestive effects in free feeding deer mice. A similar lack of sensitivity of food intake to morphine has been reported in hamsters [4]. There are also data to indicate that, in certain cases, morphine may have no effect, or reduce the food intake of satiated rats [31, 37, 38]. In hamsters, the lack of sensitivity to morphine has been attributed to modifications in their opioid systems that may arise from and/or be associated with the ability to undergo torpor and hibernation [4]. Deer mice can also undergo torpor that is antagonized by high doses of naloxone [34]. Morphine does have, however, significant analgesic and locomotory effects in deer mice (in preparation), indicating the presence of morphine sensitive opioid systems in these animals.

Although the ingestive responses of deer mice were unaffected by morphine, their food hoarding behavior was markedly sensitive to this mu agonist. Peripheral administration of morphine caused a significant, dose dependent, and naloxone reversible induction of hoarding by free feeding deer mice. The mixed mu-kappa opiate agonist, ketocyclazocine, also caused a significant increase in the food hoarding behavior of deer mice. These responses were not due to a non-specific activation of locomotor, handling or related behaviors, as the morphine-treated deer mice did not hoard or cache comparable, non-food items.

In previous observations it had been shown that neither naloxone, nor naltrexone, had any significant effects on the basal hoarding of free-feeding deer mice [15,42]. This parallels the general lack of effectiveness of naloxone on the basal food intakes of other free feeding rodents, including laboratory mice [16,30]. It should also be noted that naloxone did decrease the ingestive responses of food deprived deer mice, in a manner similar to that observed in other, fasted, laboratory rodents [6, 7, 15, 27, 30].

As noted earlier, morphine has significant locomotory and analgesic effects in free feeding deer mice that are similar to those obtained from laboratory mice and rats [13,24]. Morphine also had significant ingestive effects in food deprived deer mice. This effect may, however, reflect the actions of morphine at other opioid receptors sites, it having been hypothesized that stress may induce allosteric changes in opioid receptors [1, 2, 32]. It is possible that this may involve modifications in the actions of morphine at delta opioid receptors and/or relative effects at mu and mu subtypes [15,33]. The locomotory effects of morphine may be a component of, or indicative of food searching of foraging behaviors which precede and accompany hoarding [22,36]. Whether or not morphine has similar effects on food searching, foraging and hoarding in other species of mammals remains to be determined. Results of studies with a variety of species of invertebrates have, however, raised the possibility that morphine may initiate, under the appropriate environmental circumstances, food searching and foraging behaviors [17,20]. These results further reinforce the necessity of considering the behavioral ecology and natural feeding habits of animals when examining central controls of feeding [39, 40, 44]. In this context, it should be noted that since deer mice are primarily crepuscular the relative roles of mu and kappa opioid systems in the mediation of feeding and hoarding need to be also examined at night. This is especially important in view of the diel variations in the analgesic and ingestive effects of opiate agonists in laboratory mice [13, 14, 16].

Food deprived deer mice displayed enhanced levels of food intake that could be partially antagonized by naloxone. This is similar to the food deprivation induced activation of endogenous opioid activity reported for laboratory mice and rats [27, 30, 31]. However, the amounts of food ingested by the fasted deer mice were proportionately lower than those reported for laboratory mice. The lower food intake of the deer mice may arise from reduction in their body temperature and energy requirements that are suggested to accompany food restriction [34]. The kappa agonist had a relatively greater ingestive effect in the food-deprived, while the mu agonist induced a proportionally lower level of hoarding behavior than in free feeding animals. These effects may be indicative of an enhanced sensitivity and/or activity of kappa opioid systems in food deprived deer mice. It has been considered that the maintenance of dynophinergic and kappa opiate control of feeding behavior weakens as satiation proceeds [8]. As mentioned earlier, the altered sensitivity to the kappa agonist may also arise from and involve either stress-induced changes in opiate sensitivity, and/or allosteric changes in opioid receptors [5]. A variety of physical stressors have been shown to enhance the analgesic and hypothermic effect of systemically administered morphine in laboratory mice and rats [1, 2, 32]. Little is known, however, about possible stress-induced effects, including that of food-deprivation, on other opioid systems.

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