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Differential Effects of Intrahypothalamic Administration of Opioids on Food Intake in Naive and Tolerant Rats

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GULATI, K. *Differential effects of intrahypothalamic administration of opioids on food intake in naive and tolerant rats.* PHARMACOL BIOCHEM BEHAV **52**(4) 689–694, 1995.—We investigated the effects of intrahypothalamic administrations of the opioid agonists morphine (MOR) and ketocyclazocine (KCZ) and antagonists naltrexone (NALTX) and Mr2266 on food intake (FI) during light and dark phases of the diurnal cycle, after acute or chronic administration in rats. Acute intralateral hypothalamic (LH) administration of MOR or KCZ (1 μg/rat) enhanced FI during dark and light phases, respectively, whereas intraventromedial hypothalamic (VMH) injections resulted in moderate hyperphagia during dark phases by both μ and κ agonists. The receptor specificity was evident from blockade of the responses to MOR or KCZ by the respective antagonists NALTX and Mr2266. After repeated administrations of MOR and KCZ, FI responses to the test dose of these agonists injected in LH were modulated in opposite directions. However, the adaptative changes in FI after intra-VMH injection of KCZ were similar to those seen with MOR. These results are discussed in light of a differential opioid receptor involvement and their possible functional interactions within the hypothalamus during food intake.

Morphine Ketocyclazocine Lateral hypothalamus Ventromedial hypothalamus Food intake

INITIALLY known for their classical role in the control and regulation of pain sensitivity, the opioid peptides are now known to be involved in autonomic, neuroendocrinal, and behavioral regulation (10,14,17); and the demonstration of several systems with specific receptors and ligands has helped to explain the complexities of opiate neurobiology. The crucial role of opioid peptides in the control of ingestive behaviour has also been widely speculated (6,16). Most studies have measured acute effects, and long-term and/or specific receptor-mediated effects have not been extensively evaluated. Thus, the exact nature, sites, and receptor(s) involved in the opioidergic regulation of food intake (FI) remain to be clearly elucidated.

Normal eating patterns in rats follow a rhythm directed by diurnal cyclicity (i.e., increased FI during the night and reduced FI during the light phase of the cycle). Furthermore, the concentrations of endogenous opioids in several areas of the brain have been found to change with circadian diurnal rhythms of feeding (13,19). Although such variations suggest differential endopioidergic involvement in the regulation of FI, the effects of exogenous opioids, which would authenticate such a modulatory role of these peptides in ingestive behaviour, have not been extensively examined.

Both central and peripheral mechanisms are involved in FI regulation, and the hypothalamus has a crucial role in this phenomenon. It receives inputs from metabolic, hormonal, neurogenic, thermal, and cortical stimuli related to the nutritional status of the organism. The major regulating areas for appetite have been described in hypothalamus—the ventromedial hypothalamus (VMH) responsible for producing the sensation of fullness, and the lateral hypothalamus (LH), which initiates feeding. The link between these two hypothalamic areas is bidirectional (i.e., activation of one inhibits the other and damage to one disinhibits the other) (18). However, the differential role of these two hypothalamic areas in the opioidergic regulation of FI has not been studied. The present study was thus designed to critically evaluate the effects of μ and κ opioid agonists and antagonists on FI during light or dark phases after acute or chronic administration in the lateral and ventromedial hypothalamus of rats.

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EXPERIMENT 1

The lateral hypothalamus, periventricular, and perifornical regions have been demonstrated to contain endorphinergic neurons, with the notable exceptions of the ventromedial nucleus and mammillary bodies (4). Moreover, some hypothalamic nuclei such as the dorsomedial, ventromedial, paraventricular, and suprachiasmatic nuclei have relatively high concentrations of dynorphin-like peptides (3). Furthermore, intrahypothalamic injections of opioidergic drugs have also been shown to modulate ingestive behavior (14,22). However, the exact site and receptors involved in such responses are not clearly defined. In view of the high concentration of endogenous opioids in hypothalamic nuclei (which are crucial for FI), the present study was designed to investigate the possible role of intrahypothalamic opioidergic mechanisms in the regulation of FI after the acute administration of μ- and κ-opioid receptor agonists and antagonists into the LH and VMH in rats.

Methods

Male Wistar rats (250–300 g), maintained under standard lighting conditions of 18 D : 6 L (lights on from 0900–1500 h), were used for the study. They were housed individually and randomly allocated to different groups of seven to 10 rats each, and were given food and water ad lib.

After habituation in this vivarium for 3 days and standardization and stabilization of FI, the rats were administered with vehicle or drugs at 900 h, and 6 h thereafter. The drugs administered intra-LH and intra-VMH were saline, MOR (1 μg/rat), NALTX (5 μg/rat), and NALTX + MOR, in separate groups. Similar experiments were done by replacing the NALTX with Mr2266 (0.3 μg/rat) and KCZ (1 μg/rat) in the place of MOR. The antagonists were administered 10 min before agonists. The doses of agonists were selected after a pilot study with various doses (1–10 μg/rat). Thus, the experiment was done in four sets to handle the rats individually and to monitor the FI accurately. Drugs or saline injections were made in a volume of 2 μl slowly over a period of 1 min with a 5μl Hamilton syringe. The injection cannula attached to the syringe with microbore polyethylene tubing was allowed to remain in the guide cannula for an additional 2-min period, to allow diffusion of the injected solution into the brain tissue. After 10 min administration of drugs, preweighed food pellets were placed in the cage and the quantity of food consumed was measured during light (0–6 h) and dark (6–24 h) phases. All significant spillage was collected and deducted from the amount consumed.

For surgery, the rats were anesthetised with pentobarbitone sodium (35 mg/kg, IP) and secured on a stereotaxic instrument. A midsagittal incision was made on the scalp from the eyes to the centre between the ears to expose the bregma. Using the coordinates of Konig and Klippel (12), cannulae were implanted in VMH (2.6 P to bregma, 0.5 L to sagittal suture, 9.0 V to the surface of skull) or LH (2.6 P to bregma, 1.6 L to sagittal suture, 8.0 V to the surface of the skull). At these sites marked in individual rats for VMH or LH, respectively, a small hole was made with the help of a suitable stainless-steel dental burr. We secured a 23-gauge guide cannula (Plastic Products, Roanoke, VA) in position and anchored it to the skull by screws and dental acrylic. The cannula tip rested 2.0 mm above the target site, and the injection cannula with a preset length reached the site only during the delivery of the drug. The cannula was closed with a steel wire stopper that was put back every time the injections were given. The cannula thus implanted was functional for a minimum period of 1 mo. The animals were allowed a 1-week recovery period.

At the conclusion of the study, the rats were given a intracardiac perfusion of 0.9% saline and 10% formalin. Their brains were extracted from their skulls, embedded in paraffin, and sectioned at 15 μm to locate the track of the cannula and ensure its correct position. The data obtained from the rats with placement of the cannula at sites other than LH or VMH were discarded.

The results of FI were expressed as mean (weight in grams for food) $\pm$SEM. Statistical analysis of data was done by factorial analysis of variance (ANOVA), followed by post hoc Tukey's test. A p value of at least 0.05 was chosen as the level of significance in all tests. When necessary, data were transformed as a percent of control values to achieve homogeneity of variance and to simplify the comparisons.

Results and Discussion

As shown in Table 1, a single injection of MOR (1 μg/rat) into the LH produced no significant changes in food consumption during the light phase (0–6 h); however, the dark phase (6–24 h) FI was increased by about 35% ($p < 0.05$). This selective action of MOR in the dark phase may have been due to the levels of opiate peptides, which showed a circadian rhythmicity. However, these results contrast with those observed by Stanley et al. (22), who demonstrated enhanced feeding responses to MOR (25 nmol or 17 μg) during the light phase when applied in LH. This discrepancy may have resulted from differences in the drug dose or duration of measurement of FI as compared to the present experiments. However, prior treatment with NALTX attenuated the hyperphagic effect of MOR during the dark phase (6–24 h). The increase in FI in the MOR group (by 33%) was significantly antagonized after NALTX pretreatment: The increase in FI in the NALTX + MOR group was 16%; i.e., a twofold reduction was seen. The μ-antagonist NALTX, per se, produced no significant change in FI, thus indicating the lack of a tonic regulatory role of μ-receptors in LH. Woods and Leibowitz (25) also reported that some sites in the brain were refractory to naloxone, which failed to affect a feeding response after injection into the dorsomedial nucleus of hypothalamus, striatum, and lateral hypothalamus.

Intra-VMH administration of MOR (1 μg/rat) produced no significant changes in FI during the light or dark phases as compared to vehicle-treated rats (Table 1). NALTX (5 μg/rat, VMH) produced no changes in response to MOR during the light phase but blocked the marginal hyperphagic response to MOR during the dark phase. The results are similar to those by Woods and Leibowitz (25), who demonstrated VMH to be unresponsive to MOR but sensitive to naloxone administration, and suggested that opiate receptors affecting eating behaviour either are less dense or have variable responsiveness within the VMH. Contrary to this, Richard et al. (20) demonstrated that the anorexic effect of naloxone remained intact in VMH-lesioned rats, thus suggesting that opiate receptors in VMH are not essential for naloxone-induced suppresion of feeding.

As shown in Table 1, intra-LH administration of KCZ enhanced FI during 0–6 h by 30% ($p < 0.05$). The dark-phase FI was not influenced by KCZ. Mr2266 (0.3 μg/rat, LH), per se, reduced FI during the light phase and did not affect it during the dark phase. Pretreatment with Mr2266 blocked the hyperphagic effect of KCZ during the light phase (Table 1).

TABLE 1

EFFECTS OF INTRAHYPOTHALAMIC ADMINISTRATION OF MORPHINE (MOR) AND KETOCYCLAZOCINE (KCZ) ON FOOD INTAKE AND THEIR INTERACTION WITH NALTREXONE (NALTX) AND Mr2266

	Mean Food Intake (g) ± SE			
	Lateral Hypothalamus		Ventromedial Hypothalamus	
Treatment (μg/rat)	0–6 h	6–24 h	0–6 h	6–24 h
Vehicle	10.17 ± 0.5	18.23 ± 8.93	3.96 ± 0.35	10.66 ± 0.56
MOR(1)	9.73 ± 0.42	24.07 ± 1.86*	3.85 ± 0.11	12.25 ± 1.05
NALTX (5)	9.65 ± 0.67	15.40 ± 1.26	2.53 ± 0.22*	9.10 ± 0.60
NALTX + MOR	10.48 ± 0.38	20.91 ± 1.20	3.92 ± 0.26	10.65 ± 0.61
Vehicle	9.46 ± 0.49	21.73 ± 0.84	5.33 ± 0.41	10.25 ± 0.52
KCZ (1)	12.28 ± 0.41*	22.40 ± 1.04	5.08 ± 0.31	12.20 ± 0.67
Mr2266 (0.3)	7.45 ± 0.53*	19.86 ± 0.95	5.25 ± 0.63	10.75 ± 0.75
Mr2266 + KCZ	9.85 ± 1.05	22.96 ± 1.05	4.97 ± 0.40	12.3 ± 0.69

*$p < 0.05$ compared to respective vehicle treated groups.

The increase of 30% in FI in the KCZ group was reduced to 9% in the Mr2266 + KCZ group.

Intra-VMH administration of KCZ produced no significant changes in FI during either the light or dark phases, although the FI was enhanced by approximately 20% during the dark phase as compared to vehicle-treated rats (Table 1). Mr2266 per se was also ineffective in modifying food consumption. In addition, combined treatment with Mr2266 + KCZ, produced no change in the FI as compared to that in control rats. This suggests that κ-receptors in VMH are probably not, or are less involved in the regulation of ingestive behaviour. Studies related with neuroanatomic localization of the endogenous opioids and their receptors in rat brain areas that may be potentially important in the modulation of appetite have shown a relative absence of dynorphin, an endogenous κ ligand, in VMH (16).

The intra-LH administration of MOR or KCZ (1 μg/rat) enhanced FI during the dark and light phases, respectively, whereas intra-VMH injections resulted in moderate hyperphagia (20%) during the dark phase by both μ and κ agonists. The involvement of specific μ and κ receptors in the hyperphagic effect is evident from blockade of the responses by the respective antagonists NALTX and Mr2266. Although Mr2266 has affinity for both μ and κ receptors, a dose of 0.3 μg/rat is relatively specific for κ-receptor blockade (2). These findings are in line with others who have suggested the role of both μ and κ receptors in ingestive behaviour (15,16,24).

EXPERIMENT 2

The chronic administration of opioid agonists is known to produce tolerance to some of their effects, such as analgesia and euphoria (11,21). However, such tolerance has not been reported for the FI response. We thus investigated and compared the acute and chronic effects of intra-LH and VMH administration of μ- and κ-receptor agonists on food intake in rats during the light (0–6 h) and dark (6–24 h) phases of the diurnal cycle.

Methods

Rats used for cannulation of the LH or VMH were kept in the same vivarium as in Experiment 1. They were randomly allocated to four groups of seven to 10 rats each (two groups with cannulae placed in LH and two groups with cannulae in VMH). After the stabilization of basal FI, they were administered saline or MOR (1 μg/rat) in separate groups. Tolerance was induced by peripheral injections of escalating doses of these agonists after completing acute studies. We continued to inject the same group of animals for 7 days, with saline or escalating doses of MOR ranging from 5–35 mg/kg, IP, with an incremental rise of 5 mg/kg per day. A similar set of experiments was done by replacing KCZ for MOR in separate groups of rats. The same groups were continued for 8 days with saline or escalating doses of KCZ ranging from 1–8 mg/kg/day, IP, doubling the dose every 3rd day. After a withdrawal period of 36 h the rats were given intrahypothalamic (LH or VMH) injections of saline or a test dose of MOR (1 μg/rat) or KCZ (1 μg/rat) in separate groups, and FI was measured as in Experiment 1.

The statistical methods employed were similar to those used for analysing the data of Experiment 1.

Results and Discussion

As already observed in Experiment 1, a single injection of MOR (1 μg/rat, LH) produced no significant effect on FI during the light phase and enhanced food consumption by approximately 35% during the dark phase (i.e., 6–24 h) (Table 2). The results are in line with those of our earlier reports with systemic or intraventricular injections (8,9). After chronic administration with escalating doses of MOR (peripheral), the test dose (1 μg/rat, LH) did not enhance FI during the dark phase (i.e., tolerance developed to the response) (Fig. 1). This may be due to the subsensitization of μ receptors; MOR becomes relatively ineffective in its orexic effect when applied repeatedly in LH. Alternatively, the site responsible for FI regulation and its modulation after repeated exposure is not accessible after LH injections. Thus, the role of LH is seemingly questionable as far as the long-term regulation of ingestive behaviour by MOR is concerned.

As shown in Table 2, MOR (1 μg/rat, VMH) produced a 24% reduction in FI during the light phase and an enhancement of 22% during the dark phase, but neither attained a level of statistical significance (Fig. 2). Our findings differ from those of earlier studies (5,23), which reported a significant stimulation of FI in response to MOR injections into the

TABLE 2

EFFECT OF INTRAHYPOTHALAMIC ADMINISTRATION OF MORPHINE (MOR, 1μg/RAT) ON FOOD INTAKE IN NAIVE AND TOLERANT RATS

	Mean Food Intake (g) ± SE			
	Lateral Hypothalamus		Ventromedial Hypothalamus	
Treatment	0-6 h	6-24 h	0-6 h	6-24 h
Naive rats				
Vehicle	10.60 ± 1.29	12.20 ± 1.33	3.15 ± 0.29	9.97 ± 0.90
MOR	9.93 ± 0.65	16.50 ± 0.83*	2.40 ± 0.39	12.17 ± 1.25
Tolerant rats				
Vehicle	10.55 ± 0.94	11.40 ± 0.67	2.92 ± 0.64	10.32 ± 0.53
MOR	11.71 ± 0.65	11.24 ± 0.60†	4.08 ± 0.55	8.48 ± 0.57†

*$p < 0.05$ compared to respective vehicle treated groups.
†$p < 0.05$ compared to respective naive groups.

VMH. In addition, they also reported that the response was gradual following MOR, suggesting that MOR triggers some other neurotransmitter systems or endopioidergic system to produce the effect. The variation in our results could be due to higher doses of MOR or a different duration of measurement in the experimental procedures. After chronic administration with escalating doses of MOR (peripheral), the test dose 1 μg/rat (VMH) of MOR showed a significant ($p < 0.05$) enhancement (by 40%) of FI during the light phase as compared to that in vehicle-treated rats. In contrast, the FI during the dark phase was reduced by approximately 20% as compared to that in control rats (i.e., marginal hyperphagia produced by MOR in naive rats was reversed in tolerant rats) (Table 2 and Fig. 2). Thus, there was: a) an induction of hyperphagia during the light phase, and b) a reduction of FI during the dark phase.

As already shown in Experiment 1, injection of KCZ (1 μg/rat, LH) significantly ($p < 0.05$) enhanced FI compiled together for 0-6 h, whereas the FI during the dark phase was not affected as compared to control animals (Table 3). After the chronic administration of KCZ, tolerance developed to the hyperphagic effect seen during 0-6 h, whereas the dark-phase FI was accentuated as compared to that in naive rats. The results are similar to those observed earlier using systemic or intraventricular injections (8,9)—that is: a) development of tolerance to the hyperphagic effect during the light phase, and b) augmentation of the response during the dark phase. This suggests that LH may be a probable site of action for mediating the response, also observed by peripheral or ICV routes of administration.

On the other hand, a single microinjection of KCZ (1 μg/rat) in the VMH reduced FI during 0-6 h by approximately 20% as compared to that in control animals (Table 3). However, there was an increase of 25% in food consumption during the dark phase ($p > 0.05$) as compared to controls. Following chronic administration with escalating doses of KCZ, the test dose produced an increment in FI by 26% ($p < 0.05$) during 0-6 h over that seen in control rats (Fig. 2). In addition, the hyperphagic response seen during the dark phase in the naive, KCZ-treated group was completely blocked. That is, after chronic administration with KCZ, the test dose: a) induced hyperphagia during the light phase, and b) reduced the orexic effect seen during the dark phase after a single administration. The modulation of responses during the light and dark phases was similar to that observed with MOR when injected into VMH (the same area). It is possible that the

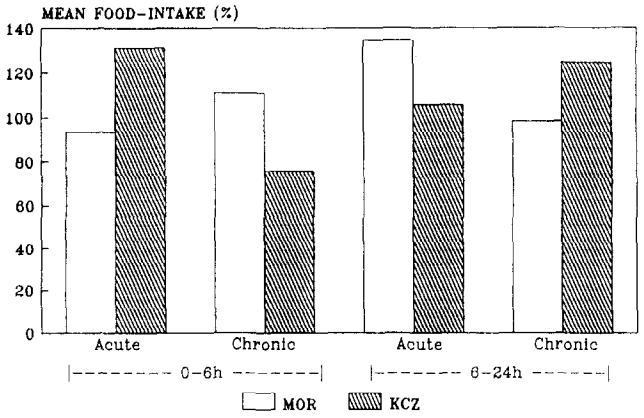

FIG. 1. Mean changes (%) in food intake after intra-LH administrations of morphine (MOR) and ketocyclazocine (KCZ) during light (0-6 h) and dark (6-24 h) phases after acute and chronic treatments.

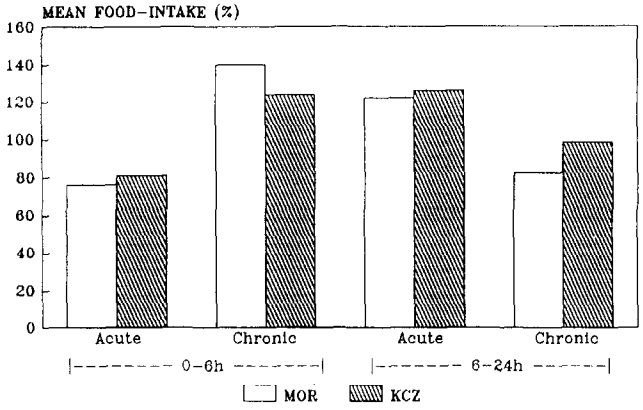

FIG. 2. Mean changes (%) in food intake after intra-VMH administrations of morphine (MOR) and ketocyclazocine (KCZ) during light (0-6 h) and dark (6-24 h) phases after acute and chronic treatments.

TABLE 3

EFFECTS OF INTRAHYPOTHALAMIC ADMINISTRATION OF KETOCYCLAZOCINE (KCZ, 1 μg/RAT) ON FOOD INTAKE IN NAIVE AND TOLERANT RATS

	Mean Food Intake (g) ± SE			
	Lateral Hypothalamus		Ventromedial Hypothalamus	
Treatment	0-6 h	6-24 h	0-6 h	6-24 h
Naive rats				
Vehicle	9.89 ± 0.99	18.00 ± 1.35	5.40 ± 0.59	10.57 ± 0.53
KCZ	13.00 ± 0.54*	19.11 ± 1.43	4.38 ± 0.47	13.15 ± 1.05
Tolerant rats				
Vehicle	9.91 ± 0.92	18.76 ± 1.58	5.45 ± 0.31	9.87 ± 0.90
KCZ	7.49 ± 0.80†	23.44 ± 1.58†	6.87 ± 0.46†	9.72 ± 0.44†

*$p < 0.05$ compared to respective vehicle treated groups.
†$p < 0.05$ compared to respective naive groups.

responses to KCZ may have been mediated through μ receptors or a subtype of κ receptor (probably κ_3, which has a similar pharmacology as μ receptors). Moreover, Tepperman and Hirst (23) also proposed that opioid receptors in VMH are responsive to μ but not κ or σ agonist. This could be explained on the basis of the involvement of different receptor subtypes or differential adaptation after chronic opiate treatment in different parts of the CNS. Bhargava et al. (1) also reported that daily administration of the κ agonist U 50488 produced downregulation of the κ receptors in pons, medulla, midbrain, cortex, and spinal cord, but upregulation of those receptors in corpus striatum, and no effect in many brain regions tested.

GENERAL DISCUSSION

The present study compares the effects of intra-LH and -VMH administrations of μ- and κ-receptor agonists and antagonists on FI during the light and dark phases of the diurnal cycle in both naive and tolerant rats. It was generally observed that control and baseline FI values of VMH-injected rats were appreciably lower than their corresponding LH-injected counterparts. This may have resulted from stimulation of the VMH as a result of cannula implantation. Most notable among the present findings was that after the repeated administration of MOR and KCZ, the consummatory responses to the test dose of these agonists in LH were modulated in opposite directions. For example, reverse tolerance developed to FI response to MOR during the light phase, whereas tolerance developed to that of KCZ. On the other hand, during the dark phase, tolerance developed to the FI response to MOR and reverse tolerance developed to that of KCZ. Similar results were obtained by peripheral administration in our earlier studies (8). This suggests that the hypothalamus may be the site mediating these changes in FI in tolerant rats. However, the adaptative changes in FI after intra-VMH administration of KCZ were similar to those seen with MOR, which indicates some overlapping in their functions or receptors in this area. In conclusion, it appears that complex mechanisms are involved in the modulation of FI by various opioidergic agents, and factors such as time of measurement, receptor specificity, and site of administration are crucial in determining the response. Furthermore, it seems that μ and κ agonists have differential roles in the regulation of FI at the level of hypothalamus. LH seems to be more important in mediating the responses to κ receptors and VMH more important for μ agonists. It appears that ingestive behaviour is controlled by multiple receptors, each perhaps relating to a different aspect of feeding, which are probably found in different nuclei of the hypothalamus.

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