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Effects of Acute and Chronic Morphine on Food Intake in Rats: Modulation by Oxytocin and Vasopressin

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GULATI, K., A. RAY AND K. K. SHARMA. *Effects of acute and chronic morphine on food intake in rats: Modulation by oxytocin and vasopressin.* PHARMACOL BIOCHEM BEHAV **40**(1) 27–32, 1991.—The effects of acute and chronic morphine administration and the interaction with oxytocin and vasopressin on food intake response were investigated at various intervals during a 24-h schedule in rats. Acute morphine (5 mg/kg, IP) produced a generalized hyperphagic effect in both light (0–6 h) and dark (6–24 h) phases, the most marked effects being at 0–1 h, 1–3 h and 6–24 h. Chronic morphine (7 days) in an escalating dose schedule (5–35 mg/kg/day) produced (a) an enhancement of the hyperphagic effect in the light phase and (b) an attenuation of the food intake response during the dark phase. Neither oxytocin nor vasopressin had any significant influence on food intake, per se, after either acute or chronic administrations. However, both OXY and AVP reduced the hyperphagic response to acute morphine throughout the 24-h observation period. Further, on chronic administration, both neurohypophyseal peptides blocked the enhancements of morphine-induced hyperphagia (reverse tolerance) during light phase, whereas only vasopressin was effective in attenuating the reduction of hyperphagia (tolerance) during dark phase. These results are discussed in light of complex opiate-oxytocin/vasopressin interactions in the regulation of food intake.

Morphine Oxytocin Vasopressin Food intake

ENDOGENOUS opioids play a crucial role in the regulation of food intake and several lines of experimental data have shown stimulation of food intake by opioid agonists (8, 9, 29, 32) and inhibition by antagonists (5, 26, 37). However, though most studies were directed at investigating the mechanisms involved in the mediation of feeding after acute (single) drug administration, the influence of chronic treatment with opioidergic drugs on this phenomenon are less extensively studied, and the data available are equivocal. For example, Jaloweic (13) reported no changes in the otherwise hyperphagic effects in spite of repeated morphine (MOR) injections for 8 days. On the other hand, Morley et al. (29) demonstrated an enhancement in the food incrementing effects of opioids after similar duration of treatment. In both these studies, food intake was measured cumulatively for 4 hours/day during the light phase. Similar enhancements in the feeding response after repeated administrations of other opioid agonists have also been reported (41,42). Interestingly, a recent study (24) showed a triphasic effect on food intake after a single injection of MOR, suggesting that cumulative measurements of food intake do not give the correct index or help in adequately explaining the temporal changes in this phenomenon in response to MOR.

In view of the above, the present study was designed to critically evaluate the effects of acute and chronic administrations of MOR on food intake at various time intervals during a 24-h schedule. Several neuropeptides are known to interact with endogenous opioids in the CNS (20, 23, 44). Some nonopioids like oxytocin (OXY) and vasopressin (AVP) reportedly alter acute and long-term effects of opioids like analgesia (20,23) and reinforcing behavioural paradigms (43). Therefore, the possible influence of these two neurohypophyseal peptides on the modulatory effects of MOR on food intake were also investigated.

EXPERIMENT 1

Chronic administration of MOR is known to result in tolerance/adaptation to some of its acute effects (12, 17, 30, 46). However, such tolerance has not been reported for the food intake response. We thus investigated the effects of long-term MOR administration and compared them with acute (single) MOR treatment on feeding behaviour at various time intervals during 24 h in rats.

Method

Male Wistar rats (180–220 g), maintained under standard lighting conditions of 16:8 h (lights on from 0900 to 1700 h), were used. They were housed individually and randomly allocated to three groups of 10 rats each and were given food ad lib. After habituation in this vivarium for three days and stabili-

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TABLE 1

EFFECTS OF ACUTE AND CHRONIC MORPHINE (MOR, 5 mg/kg, IP) ON FOOD INTAKE

	Mean Food Intake (g) ± S.E.									
	0–1 h		1–3 h		3–6 h		0–6 h		6–24 h	
Treatment	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
Vehicle	1.23 ±0.3	1.25 ±0.4	1.12 ±0.2	0.85 ±0.4	1.9 ±0.3	1.44 ±0.3	4.2 ±0.3	3.5 ±0.3	11.84 ±0.9	12.8 ±1.4
MOR	2.1 ±0.3*	3.57 ±0.5†	2.01 ±0.3*	1.93 ±0.3†	1.06 ±0.3	2.27 ±0.3	5.1 ±0.3*	7.7 ±0.4†	15.27 ±1.2*	11.22 ±0.8

*$p<0.05$; †$p<0.01$; Compared to respective vehicle controls (Mann-Whitney U-test).

zation of basal food intake, they were treated with escalating doses of MOR, from 5 to 35 mg/kg IP, twice daily at 0900 and 1700 h, with an increment of 5 mg/kg/day for seven days. After 15 min of administration of vehicle or drug, preweighed food pellets (Hindustan Lever, Bombay) were placed in the cage and quantity of food consumed was measured at 1, 3, 6 and 24 h from the time the experiment was commenced. All significant spillage was collected and deducted from the amount consumed. The experiment was started during the light phase as it has been shown that maximal effect of opioid agonists on feeding is seen within 2 h of the onset of this phase (28). Food intake in response to test dose (a single 5 mg/kg injection) was measured on the first day and after seven days of escalating doses of MOR.

The data of acute study was analysed by Mann-Whitney U-test (two-tailed). Wilcoxon's rank test was used to compare the food intake responses after acute and chronic drug administrations in the same group of animals.

Results and Discussion

Acute treatment with MOR (5 mg/kg, IP) resulted in differential, time-dependent changes in feeding behaviour. In general, there was a 20% increase in food intake during both light (0–6 h) and dark (6–24 h) phases (Fig. 1). As shown in Table 1, MOR significantly enhanced the food intake during 0–1 h, 1–3 h and 6–24 h ($p<0.05$). On the other hand, food intake tended to be reduced at 3–6 h, which, however, did not attain levels of statistical significance ($p>0.05$). This response is in contrast to the triphasic response reported earlier by Lesham (24), i.e., a brief suppression (1 h) followed by hyperphagia (3 h) and then a mild yet persistent (4–24 h) hypophagia. The difference could be due to different doses, routes and satiety states of rats used. The absence of initial hypophagic effect seen in our study may be due to lack of sedative effects of MOR at the doses used (5 mg/kg, IP). This indicates that the general behavioural depressant effect of MOR was probably contributing to its hypophagic effects in the earlier study.

After seven days of escalating dose treatment with MOR, a test dose of 5 mg/kg of this drug produced a marked overall increase in the food intake during the light phase (Fig. 1). As shown in Table 1, the effects at 0–1 h and 1–3 h were clearly significant ($p<0.01$, in each case). The results show that when compared to hyperphagia after acute administration, chronic MOR treatment (a) enhanced the response during light phase (0–6 h), whereas (b) food intake was reduced during the dark phase (6–24 h). Opiates are well known to produce both depressant and stimulant effects on CNS and tolerance usually develops to the depressant, but not the stimulant effects. For example, tolerance is known to develop to analgesia and other CNS depressant effects (20, 22, 23, 44), whereas most investigators report either no change or sensitization (an enhanced response) to effects like lowering of self-stimulation threshold, hypothermia and hyperactivity (1, 11, 34, 35). An enhancement in the hyperphagic response during the light phase after chronic MOR is in line with the lack/opposite of tolerance mentioned earlier for some effects of MOR. In fact, a similar phenomenon was observed earlier and termed as "reverse tolerance" by Morley et al. (29). This could be due to the following reasons: (a) Tolerance development to sedative effects; but in our study, no sedation was observed with acute MOR (5 mg/kg), thus suggesting that this enhanced response was not due to any tolerance to the depressant (sedative) effect. (b) Involvement of different types/subtypes of receptors and/or central sites in the mediation of this response, distinct from those involved in other responses like analgesia (33). For example, no correlation was found between antagonist potency for reducing eating and blocking analgesia. Tolerance to various behaviours is shown to develop at different times depending on the involvement of various receptors and

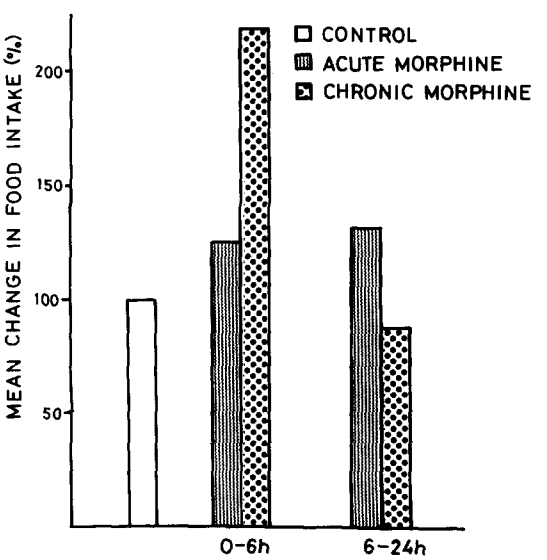

FIG. 1. Changes in food intake during light (0–6 h) and dark (6–24 h) phases after acute and chronic morphine (MOR, 5 mg/kg, IP) treatment in rats.

TABLE 2

EFFECTS OF ACUTE AND CHRONIC MORPHINE (MOR, 5 mg/kg, IP) AND ITS INTERACTION WITH OXYTOCIN (OXY, 10 μg/kg, SC) ON FOOD INTAKE

	Mean Food Intake (g) ± S.E.									
	0–1 h		1–3 h		3–6 h		0–6 h		6–24 h	
Treatment	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
Vehicle	0.74 ±0.3	1.10 ±0.4	1.19 ±0.2	0.94 ±0.5	1.53 ±0.3	1.10 ±0.3	3.46 ±0.3	3.14 ±0.4	11.8 ±1.2	12.3 ±1.4
MOR	1.67 ±0.2*	3.58 ±0.7§	2.11 ±0.4†	2.0 ±0.4	0.81 ±0.3	1.80 ±0.4§	4.59 ±0.3*	7.38 ±0.6§	14.94 ±1.4*	12.34 ±0.8‡
OXY	0.53 ±0.2	1.93 ±0.7	0.91 ±0.3	1.8 ±0.9	1.9 ±0.4	1.98 ±1.2	3.34 ±0.3	5.71 ±1.0*	12.70 ±1.3	11.64 ±0.8
OXY + MOR	0.99 ±0.2	1.39 ±0.2	1.83 ±0.3	1.61 ±0.4	0.9 ±0.2	1.7 ±0.3‡	3.72 ±0.3	4.7 ±0.4	12.5 ±0.7	10.1 ±0.7

*$p<0.05$; †$p<0.002$; Compared to respective vehicle controls (Mann-Whitney U-test).
‡$p<0.05$; §$p<0.01$; Compared to appropriate acute group (Wilcoxon's test).

central sites. (c) Sensitization of receptors mediating excitatory responses on chronic administration. Recent reports indicate that the excitatory responses to opiates are mediated through activation of a subpopulation of cell bodies in ventral tegmental area via the mesolimbic dopaminergic pathways (15,38). Sensitization of these receptors occurs on repeated exposure. However, the mechanisms involved in such sensitization remain to be elucidated. This observation is also consistent with the report of enhanced prolongation of action potential of dorsal root ganglion neurons after chronic exposure to opioids (4).

MOR seems to reverse the normal physiological food intake rhythm by increasing food intake during light phase and reducing it during dark phase. This may be due to modulation in levels of endogenous opioids, which are governed by diurnal rhythmicity. High concentrations of β-endorphin are reported in neurointermediate pituitary, pons, medulla, cerebellum and septum during the middle of dark phase of diurnal cycle (7), whereas reduced levels are observed at the onset of light cycle. Thus, daily administration of MOR, through a negative feedback, may be reducing the nocturnal (high) levels of opioids, i.e., pharmacological redundancy of these neurons. This in turn could lead to tolerance to food intake behaviour during the dark phase. Gianoulakis et al. (6) also reported reduced endorphin concentrations and rate of synthesis in rats made tolerant to MOR. Alternatively, this reduction could also be a compensatory response to increased daytime food intake, thus resulting in tolerance to the response.

EXPERIMENT 2

A number of studies have suggested complex interactions between opioids and OXY and AVP (20, 23, 44). Krivoy et al. (23) demonstrated that desglycinamide-arginine-vasopressin facilitated the rate of development of tolerance to MOR-induced analgesia in mice. On the other hand, Van Ree (45) reported the attenuation of heroin addiction as evidenced by the decreased amount of methadone required to suppress withdrawal reactions in heroin addicts. Both peripheral (SC) and central injections of OXY attenuated the development of tolerance to MOR (20). Van Ree and De Wied (44) reported an enhancement in the rate of tolerance development to analgesic action of opiates. However, such opioid-OXY/AVP interactions during food intake are not well documented. Since neurohypophyseal peptides play an important role in adaptation and learning processes (19,40), this study was designed to investigate the effects of OXY and AVP on food intake in response to acute and chronic administration of MOR in free-fed rats.

Method

Male Wistar rats were randomly allocated to four groups of 8–10 rats each and maintained as in Experiment 1. After stabilization of basal food intake, they were administered saline, MOR (5 mg/kg, IP, b.i.d.), OXY (10 μg/kg, SC) or OXY+MOR in separate groups, and food intake was measured as before. After completion of the acute study, the same groups of animals were continued for seven days with escalating doses of MOR (as in Experiment 1) ranging from 5 mg/kg to 35 mg/kg, IP with an increment of 5 mg/kg/day. OXY, per se, was administered daily for 7 days. In the interaction studies, OXY was injected prior to each dose of MOR during the 7-day treatment schedule. A similar set of experiments was done to study AVP (10 μg/kg, SC) and MOR interactions. OXY and AVP were given in doses which reportedly reach the CNS after systemic injection (27).

The results were analysed using the Mann-Whitney U-test (two-tailed) for comparing food intake in response to drug treatments with vehicle controls. Food intake after chronic administration was compared with the acute (single) administration data using the Wilcoxon test for paired samples.

Results and Discussion

As seen in Experiment 1, MOR (5 mg/kg, IP) produced a generalized hyperphagia at most time intervals during the light phase (0–6 h). Similarly, chronic administration of MOR, in escalating doses for 7 days resulted in (a) a potentiation of hyperphagia in the light phase (0–6 h) and (b) a reduction in the food intake during the dark phase (6–24 h) (Tables 2 and 3).

OXY, per se, had no significant effect on food intake on acute administration (Table 2). However, OXY pretreatment clearly attenuated the hyperphagic effects of MOR during the light phase (0–6 h), as well as dark phase (6–24 h) (Fig. 2). As seen in Table 2, this acute OXY-MOR interaction was more pronounced at 0–1 h and 1–3 h of the light phase and throughout the dark phase. When OXY was administered chronically along with MOR, it significantly attenuated the enhancement of hyperphagia only during the light phase (mostly at 0–1 h), in

TABLE 3

EFFECTS OF ACUTE AND CHRONIC MORPHINE (MOR, 5 mg/kg, IP) AND ITS INTERACTION WITH VASOPRESSIN (AVP, 10 μg/kg, SC) ON FOOD INTAKE

	Mean Food Intake (g) ± S.E.									
	0–1 h		1–3 h		3–6 h		0–6 h		6–24 h	
Treatment	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
Vehicle	1.72 ±0.3	1.40 ±0.4	1.06 ±0.3	0.76 ±0.3	2.28 ±0.3	1.78 ±0.3	5.06 ±0.3	3.94 ±0.3	11.86 ±0.6	13.3 ±1.4
MOR	2.53 ±0.3*	3.56 ±0.4#	1.91 ±0.3*	1.86 ±0.3	1.32 ±0.3	2.75 ±0.2‡	5.76 ±0.3	8.17 ±0.4	15.6 ±0.9*	10.1 ±0.8‡
AVP	1.26 ±0.2	1.67 ±0.6	0.64 ±0.3	0.82 ±0.2	2.6 ±0.4	2.32 ±0.2	4.5 ±0.4	4.81 ±0.3	11.4 ±1.2	14.1 ±1.9
AVP + MOR	1.96 ±0.3	1.98 ±0.2	1.29 ±0.2	1.08 ±0.3	0.65 ±0.2†	1.3 ±0.2‡	3.9 ±0.2	4.36 ±0.2	13.1 ±0.5	13.98 ±1.1

*$p<0.05$; †$p<0.01$; Compared to respective vehicle controls (Mann-Whitney U-test).
‡$p<0.05$; Compared to appropriate acute group (Wilcoxon's test).

response to MOR, whereas tolerance to the dark phase food intake was not much affected.

Acute administration of OXY along with MOR marginally reduced the latter's hyperphagic effect (Fig. 2), whereas chronic administration attenuated the development of "reverse tolerance" during the light phase (Fig. 3). No reports are available regarding the interaction of OXY with MOR on feeding behaviour. Similar interactions of OXY with MOR are, however, reported with analgesic response where no modification of either the magnitude or the duration of analgesia was seen after the first MOR challenge in drug-naive animals (20). These findings indicate that OXY probably interfered with the development of "adaptive tolerance" rather than with dispositional factors or the opiate receptors themselves. There is little effect of OXY on tolerance to dark phase food intake in response to MOR. Moreover, acute administration of MOR is demonstrated to enhance OXY levels in limbic areas like hippocampus, amygdala, etc., which come back to normal or are even further reduced to chronic treatment (22).

AVP, on the other hand, per se, only partially reduced the food intake as compared to saline-treated animals during both light and dark phases (Table 3). However, this did not attain levels of statistical significance in both acute as well as chronic studies. There was no appreciable difference between reduction in food intake after single or repeated exposure to AVP. When AVP was administered prior to MOR, it significantly reduced the hyperphagic effect of MOR during the light phase (mostly at 0–1 h and 1–3 h). The food intake during the dark phase (6–24 h) was, however, reduced to a lesser extent (Fig. 2). Chronic administration of AVP along with MOR attenuated the development of (a) "reverse tolerance" to the food intake response during the light phase and (b) tolerance development to the hyperphagic effect of MOR during the dark phase (Fig. 3).

AVP, per se, reduced the food intake on acute as well as

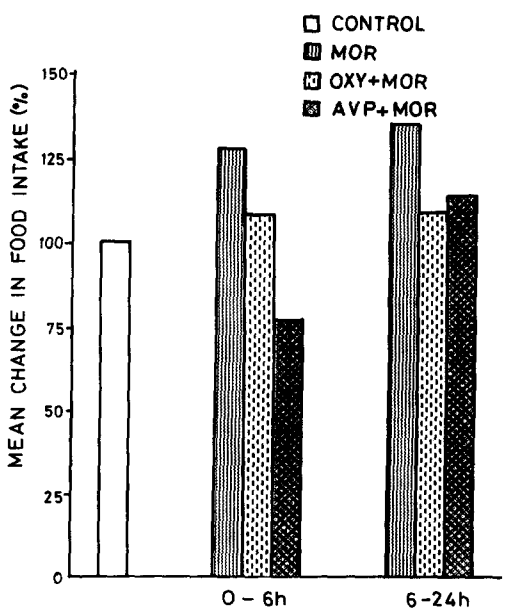

FIG. 2. Influence of oxytocin (OXY, 10 μg/kg, SC) and vasopressin (AVP, 10 μg/kg, SC) on food intake during light (0–6 h) and dark (6–24 h) phases after acute morphine (MOR, 5 mg/kg, IP) treatment in rats.

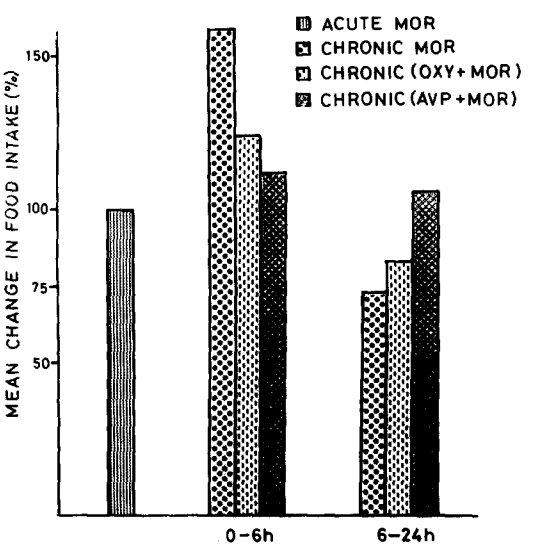

FIG. 3. Influence of oxytocin (OXY, 10 μg/kg, SC) and vasopressin (AVP, 10 μg/kg, SC) on food intake during light (0–6 h) and dark (6–24 h) phases after chronic morphine (MOR, 5 mg/kg, IP, escalating doses) treatment in rats.

chronic administration. This observation is consistent with an earlier report of anorectic effect of AVP (3). Stable hypophagic effect to AVP on continued administration indicates lack of tolerance development to the effect in this low dose, i.e., 10 μg/kg, SC. Acute administration of AVP prior to MOR reduced the hyperphagic effect of MOR during 0–6 h, as well as during 6–24 h. The reduction in response may simply be due to opposite effects of AVP and MOR. Similar modification of biphasic effect of MOR on body temperature by AVP has been reported by Ritzman et al. (31). Chronic administration of AVP along with MOR attenuated the enhancement of food intake during the light phase which may be because of direct suppression of hyperphagia by the continued hypophagic effect of AVP, per se. A number of reports are available to indicate the role of AVP in adaptation and learning resulting in tolerance/reverse tolerance (43–45). Diurnal variations are reported in the levels of AVP in different brain regions mediating food intake. This may explain the differential role of the peptide on "reverse tolerance" and "tolerance" to MOR during light and dark phases respectively. Interestingly, Kasting et al. (14) showed that AVP lowers seizure threshold in rats. Since the results from several studies have indicated that seizures disrupt tolerance to a number of drugs including ethanol and MOR (16,39), this effect of AVP on seizure threshold could account for the influence of AVP on MOR tolerance. Blockade of tolerance to the hyperphagic effects of MOR by AVP, during the dark phase, is consonant with the attenuation of tolerance development to other effects, like self-administration of heroin (44). The complex/differential modification of MOR effects can also be due to the variable effects of MOR on AVP release. At least two central sites, both of which are naloxone sensitive, are involved, one increasing AVP release and the other decreasing it (25). The net result may have influenced the responses to exogenous administration of the drugs.

The development of tolerance to MOR is also associated with changes in other neurotransmitters, e.g., DA (2) and 5-HT (10). There is evidence that both OXY and AVP exert regional effects on the NA, DA and 5-HT levels (19,40) and their receptors (21). Thus such neuropeptide-biogenic amine interactions may also play a modulatory/regulatory role on chronic actions of opiates.

GENERAL DISCUSSION

Most notable amongst our findings is that MOR differentially affects food intake after acute and chronic administration in free-fed rats. After acute treatment, a generalized hyperphagic effect is seen during both light (0–6 h) and dark phases (6–24 h). After repeated administration with escalating doses, "reverse tolerance" developed to food intake during light phase, whereas tolerance developed to dark phase (Fig. 1). Such differential effects of morphine on food intake during light and dark phases have not been reported earlier. The discrepancy in these "adaptive" responses could have been due to diurnal variations in the endogenous opioid levels [vide supra, (7)].

Neuropeptides are reported to interact with each other during the expression of several centrally mediated behavioural paradigms (20, 23, 43). The hypothalamus, which is crucial for physiological regulation of food intake, is rich in both opioidergic and oxytocinergic/vasopressinergic nerve terminals. Further, colocalization of endogenous opioids and OXY/AVP in the same terminal is also reported, suggesting that the regulation of release/effect of one by the other is possible (36). Our results show that both OXY and AVP were effective in attenuating MOR-induced food intake responses during the light and dark phases, after both acute and chronic administration, AVP being generally more effective. This could be because of the reported differential regulation of OXY and AVP by endogenous opioids under different experimental conditions (36). Further, both endogenous opioids and neurohypophyseal peptides are known to interact with classical neurotransmitters like DA, NA, 5-HT, etc. (2, 10, 19, 40), and the net outcome of such interactions could have contributed to the present results. These findings are also particularly significant in view of the fact that both OXY and AVP play a crucial role in "adaptive mechanisms" (42–44).

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