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Effects of Acute and Chronic Ketocyclazocine and Its Modulation by Oxytocin or Vasopressin on Food Intake in Rats

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GULATI, K., A. RAY AND K. K. SHARMA. *Effects of acute and chronic ketocyclazocine and its modulation by oxytocin or vasopressin on food intake in rats.* PHARMACOL BIOCHEM BEHAV **41**(1) 7–12, 1992.—The effects of acute and chronic ketocyclazocine (KCZ, a kappa receptor agonist) and its interactions with oxytocin (OXY) or vasopressin (AVP) were investigated on food intake in free-fed rats. Acute treatment with KCZ (1 mg/kg) produced a generalized hyperphagia during the light phase (0–6 h) without influencing dark phase (6–24 h) food intake. On chronic administration, tolerance developed to hyperphagic effect during light phase, whereas an enhancement in the food intake was seen during dark phase. OXY or AVP (both at 10 μg/kg) per se, did not affect the food intake response during either the light or the dark phase, after acute as well as chronic treatment. In the interaction studies, acute AVP or OXY attenuated the hyperphagia of KCZ during the light phase. On chronic treatment, both AVP and OXY blocked (a) the tolerance, and (b) the "reverse tolerance" to the food intake response to KCZ during light and dark phases, respectively. These results are discussed in light of complex opioid-OXY/AVP interactions during food intake in rats.

Ketocyclazocine Oxytocin Vasopressin Food intake

ENDOGENOUS opioids play an integral role in the regulation of food intake (9, 22, 29). Presently available studies provide evidence for the role of μ-, δ-, and κ-receptors in the modulation of feeding (7, 25, 35). However, a number of reports suggest a preferential role of κ-receptors in the maintenance of feeding behaviour (5, 21, 24). κ-Receptor agonists like bremazocine, U50-488H and tifluadom, have been shown to produce either enhancement of food consumption in free-fed rats (5) or no effect (27). Moreover, Morely (21) reported circadian variations in opiate (morphine, ethylketocyclazocine)-induced feeding when administered at different times of the day. However, most of the studies were directed at investigating the mechanisms involved in regulating food intake after acute drug administration. The influence of chronic treatment with opioidergic drugs on this phenomenon are less extensively studied. An earlier study reported enhancement of hyperphagic effect of KCZ when administered for 5 days (26). In general, enhancements of the feeding response after repeated administration of other opioid agonists have also been reported (36,37).

Several neuropeptides are known to interact with endogenous opioids in the CNS (14, 16, 39). Some nonopioid peptides like oxytocin (OXY) and arginine-vasopressin (AVP) reportedly alter acute and long-term effects of μ-, ε-, δ-receptor directed agents, e.g., analgesia (10, 14, 16) and reinforcing behavioural paradigms (40). To the best of our knowledge, no reports of such opioid-neurohypophyseal peptide interactions are available regarding modification of responses, more so on food intake behaviour to κ-agonists, even though Herkenham et al. (8) has suggested that opioid receptors in the neurohypophysis are most likely of κ-type. In view of the above, the present study was designed to critically evaluate the effect of acute and chronic administration of ketocyclazocine (KCZ) and its interactions with OXY/AVP during food intake at various time intervals during a 24-h schedule in rats.

EXPERIMENT 1

Chronic administration of κ-opioid agonists is known to produce tolerance to some of its effects like analgesia and aversion (20,31). Modulation of food intake in response to chronic administration of KCZ has not been studied in detail. A single report suggested an enhancement in the hyperphagic effect of KCZ (10 mg/kg, SC, during 4–6 h) on chronic (×5 days) treatment. This enhancement was suggested to be due to tolerance to the sedative effects of the opioid. We thus investigated the effects of acute and long-term KCZ administration on feeding behaviour, at various time intervals, during a 24-h schedule in rats.

METHOD

Male Wistar rats (180–220 g) maintained under standard lighting conditions of 16:8 h (lights on from 0900–1700 h) were used. They were housed individually and randomly allocated to three groups of 8–10 rats each and were given food ad lib. After habituation in this vivarium for three days and stabilization of basal food intake, they were treated with KCZ (Sterling Winthrop, Rensselaer, NY), 1 mg/kg, IP, dissolved in 1 drop of 0.1

TABLE 1

EFFECTS OF ACUTE AND CHRONIC KETOCYCLAZOCINE (KCZ, 1 mg/kg, IP) ON FOOD INTAKE IN RATS

Treatment	Food Intake (g) ± S.E. at different h									
	0–1 h		1–3 h		3–6 h		0–6 h		6–24 h	
	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
Vehicle	0.88 ± 0.2	1.00 ± 0.4	0.58 ± 0.2	0.58 ± 0.3	1.30 ± 0.3	0.95 ± 0.4	2.70 ± 0.4	2.50 ± 0.5	10.60 ± 0.5	11.00 ± 1.0
KCZ	2.75 ± 0.2†	1.65 ± 0.3*	0.80 ± 0.2*	0.38 ± 0.1	2.60 ± 0.2*	0.76 ± 0.1	6.00 ± 0.5†	3.00 ± 0.3	10.50 ± 0.2	13.70 ± 0.7*

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

N HCl and diluted with saline. After 15 minutes of administration of vehicle or drug, preweighed food pellets (Hindustan Levers, Bombay) were placed in the cage and the quantity of food consumed was measured at 1, 3, 6 and 24 h from the time of commencement of the experiment. All significant spillage was collected and deducted from the amount consumed. For studying the chronic effects of KCZ rats were administered with escalating doses of KCZ from 1 to 8 mg/kg, IP twice daily at 0900 and 1700 h. The dose was doubled every third day up to the eighth day. This was followed by a withdrawal period of 36 h. Food intake in response to a test dose (1 mg/kg, IP) was measured, as described earlier.

The data was analysed by Mann-Whitney U-test (two-tailed). A p value of at least 0.05 was considered as the level of significance in all statistical tests.

RESULTS AND DISCUSSIONS

As shown in Table 1, single injection of KCZ (1 mg/kg) significantly increased food intake during 0–1 h ($p<0.01$) and 1–3 h ($p<0.05$), i.e., induced generalized hyperphagia during light phase (0–6 h). The effect is in contrast to earlier observation where no change in food intake after administration of various κ-receptor agonists like bremazocine, tifluadom and U-50,488H was shown in free-fed rats (27). This difference could be due to differences in the κ-agonists, species, doses and routes used. However, Sanger and McCarthy (29) reported enhancement of food intake by KCZ in doses varying from 1–10 mg/kg. The dark phase (6–24 h) food consumption was not affected by acute administration of KCZ. This may be because of the already high basal levels of ingestion during the dark phase which masks the hyperphagic effect, if any. Moreover, diurnal variation in levels of endogenous κ-directed ligand, dynorphins in different brain regions have been reported (28). This may affect food intake in response to exogenous administration of κ-agonists, KCZ, differentially, during different phases of the diurnal cycle. This finding is in agreement with that of Morley (21) who reported no effect of KCZ during the nocturnal feeding (2000–0200 h).

Long-term treatment with escalating doses of KCZ, modulated the food intake response to test dose (1 mg/kg, IP) in a complex manner during different phases of the 24-h schedule. There was a significant reduction in the initial hyperphagic effect during 0–1 h ($p<0.01$) and 1–3 h ($p<0.05$). Taken together, the hyperphagia during the light phase (0–6 h) was significantly attenuated. However, an increase by 20% during dark phase (6–24 h) was observed as compared to that after single administration. A previous study reported an enhancement of the feeding response after repeated administration of KCZ (10 mg/kg, SC) for 5 days, with initiation of feeding occurring earlier (21). The enhancement of food intake termed as "reverse tolerance" has been suggested to be due to tolerance to sedative effect of opioids. This was unlikely in our experiments as no sedation was observed at the dose (1 mg/kg, IP) used. Our earlier studies along these lines have shown that food intake in response to morphine is enhanced during light phase and reduced in dark phase after chronic administration. Thus the finding suggests that interactions between κ- and μ-receptors are possible during food intake. In fact, Bhargava et al. (1) reported an up-regulation of brain and spinal cord κ-opioid receptors in rats tolerant to morphine with down-regulated μ-receptors.

Lee and Smith (19) also suggested a modulatory role for κ-ligands, dynorphin-(1–17) and dynorphin-(1–13) in brain, as they decrease opioid potency in morphine naive animals while increasing it in tolerant ones, thus holding opioid sensitivity within a fairly narrow range. The tolerance could also be attributable to lowered levels of endogenous κ-ligand, dynorphin, as κ-agonists act on autoreceptor and inhibit the release of dynorphin which plays an important role in enhancing food intake (19). The differential changes in food intake in response to chronic administration of KCZ during light and dark phases indicate the probable modulatory role of diurnal rhythmicity in levels of endogenous κ-directed ligands (28).

EXPERIMENT 2

Recent data indicate complex interaction between opioids and neurohypophyseal peptides (14, 16, 39). For example, OXY inhibits the development of tolerance to the analgesic effects of morphine, heroin, enkephalin and β-endorphin (10, 13, 30) which interact with μ-, δ- or ε-receptors respectively. Krivoy et al. (16) demonstrated that desglycinamide-AVP facilitated the rate at which tolerance to morphine-induced analgesia developed in mice. On the other hand, Van Ree (38) reported the attenuation of heroin addiction as evidenced by the decreased amount of methadone required to suppress withdrawal reactions in heroin addicts. However, no reports are available regarding such opioid-OXY/AVP interactions, particularly with κ-opiates. Moreover, acute and chronic morphine treatment in mice is reported to alter the endogenous VP and OXY content of the limbic areas in a complex manner (15). The effect of κ-opioids on the release/levels of AVP and OXY has not been examined in detail, though recently a few reports have indicated lowering of both OXY and AVP levels (3,18). Further, dynorphin A-(1–13) and other κ-agonists, ethylketocyclazocine and bremazocine are reported to increase VP release in a concentration dependent manner from cultured hypothalamo-neurohypophyseal system explants (32). In view of these data, the present study was designed to investigate the effects of OXY and AVP on food intake in response to acute and chronic administration of KCZ in free-fed rats.

METHOD

Male Wistar rats (180–220 g) were randomly allocated to four groups 5–8 rats each and maintained as in Experiment 1. After stabilization of basal food intake they were administered saline, KCZ, AVP (10 μg/kg, SC) or AVP + KCZ in separate groups. The same groups of animals were continued for eight days with escalating doses of KCZ ranging from 1 mg/kg to 8 mg/kg, doubling on every third day. After a withdrawal period of 36 h the saline-treated group was divided into four groups of 5–8 rats each and administered KCZ (1 mg/kg, IP), AVP (10 μg/kg, SC) or AVP + KCZ. Chronically treated rats also received the test dose of KCZ (1 mg/kg) after withdrawal period and the food intake was measured as in Experiment 1. In a separate group of rats, a similar set of experiments were performed using OXY in place of AVP and the interactions of OXY and KCZ were examined as before after both, acute and chronic drug administrations. OXY and AVP were purchased from Sigma Chemical Co., St. Louis, MO. They were dissolved in saline.

As in Experiment 1 the results were analysed using the Mann-Whitney U-test (two-tailed) for comparing food intake in response to various drug treatments.

RESULTS AND DISCUSSIONS

As in Experiment 1 the food intake in response to single treatment with KCZ was significantly increased during 0–1 h and 1–3 h; whereas the 6–24 h response was not affected (Tables 2, 3). Similarly, chronic administration of KCZ in escalating doses for 8 days resulted in (a) a reduction in the hyperphagia during the light phase and (b) an induction of hyperphagia during the dark phase (6–24 h), (Figs. 1, 2). AVP, per se, significantly reduced the food intake as compared to saline-treated rats during the 0–1 h and 1–3 h after acute as well as chronic administration. This observation is consistent with an earlier study where an anorectic effect of AVP was reported (4,17). There was no appreciable difference between reduction in food intake after single or repeated exposure to AVP, thus indicating a lack of tolerance development to the effect at this dose level, i.e., 10 μg/kg, SC. AVP when given prior to KCZ significantly reduced the hyperphagic effect of KCZ during 0–1 h only. This may simply be due to physiological antagonism as AVP, per se, has an anorectic effect. Chronic administration of AVP along with KCZ blocked both the reduction of hyperphagic effect (tolerance) during the light phase ($p<0.05$) and induction of hyperphagic effect (reverse tolerance) during the dark phase ($p<0.05$), Table 2. OXY, per se, did not affect the food intake on acute as well as chronic administration ($p>0.05$). Acute administration of OXY along with KCZ significantly reduced the hyperphagic effect of KCZ during the light phase (0–1 h) without affecting the dark phase food intake. Chronic administration of OXY along with KCZ blocked the reduction in hyperphagia in response to KCZ ($p<0.05$, Table 3), as well as induction of the hyperphagic effect.

Blockade of tolerance to hyperphagic effects of KCZ by AVP and OXY is parallel to the attenuation of tolerance development to other opioids effects like self-administration and analgesia (10,39). Thus both the peptides, OXY and AVP, affect the adaptative changes in food intake in response to repeated exposure to KCZ in the same manner. Some of the probable reasons for such interactions may be 1) AVP may affect opioid-receptors as is evident from blockade of acute effects of KCZ by AVP. 2) The exogeneous administration of the neurohypophyseal peptides in the study may be compensating for the reduced content of endogeneous peptide which may be one of the factors responsible for modulation of the κ-receptors mediating food intake. Dynorphin and κ-agonists are reported to inhibit the OXY secretion from isolated neurohypophysis (2) and isolated neurosecretory terminals (6) resulting in lowering of OXY levels (3). Moreover, the endogenous κ-ligand, dynorphin and VP are reported to colocalize in most neurones (32). κ-Agonists act on autoreceptors and inhibit the corelease of dynorphin and VP from neural lobe. Thus they may modulate each others release/levels to regulate various functions. 3) The reduction in hyperphagic effect of KCZ on chronic treatment can be considered as a learning process and the two peptides may be interacting to block the same. A number of reports suggest the role of AVP and OXY in adaptation and learning (38–40). 4) the development of tolerance to KCZ may be associated with changes in brain biogenic amines including DA (25,33). There is evidence that both OXY and AVP exert regional effects on these amines (11,34) and their receptors (12). Thus such complex neuropeptide-biogenic amine interactions may also contribute to the observed effects during food intake.

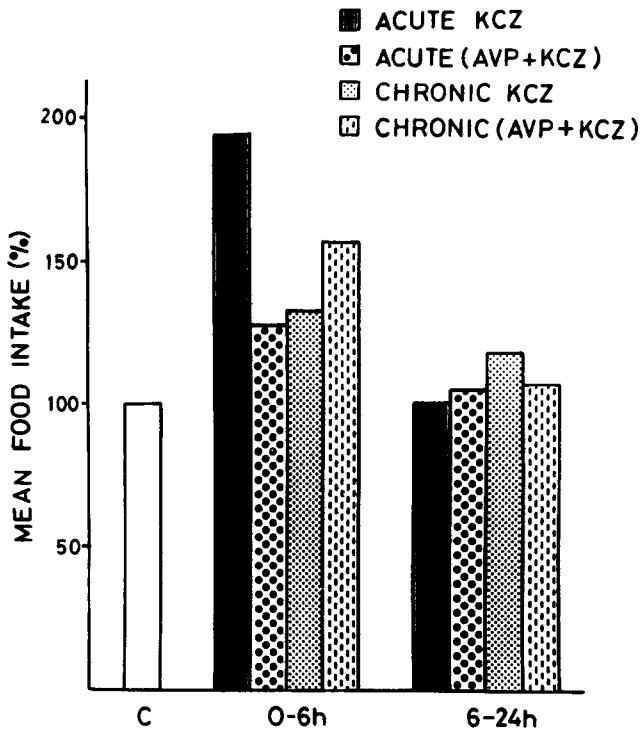

FIG. 1. Influence of arginine-vasopressin (AVP, 10 μg/kg, SC) on effects of ketocyclazocine (KCZ, 1 mg/kg, IP) on food intake during light (0–6 h) and dark (6–24 h) phases after acute or chronic administrations in rats. Data is expressed as percent of controls.

GENERAL DISCUSSION

The present results clearly show that the κ-agonist, ketocyclazocine produces differential effects on food intake after acute and chronic administration. Whereas, tolerance developed to the acute hyperphagic effects during the light phase (0–6 h), a marginal potentiation was seen in the dark phase (6–24 h) response. Earlier data from our laboratory has shown that diurnal rhythm and opioid receptor specificity are important for the regulation of food intake (unpublished observations), and present data with acute KCZ reaffirms our contention. However, long-term opiate effects on feeding behaviour are less extensively studied. Further, most studies have reported tolerance development to inhibitory/depressant (and not stimulatory) effects of exogenous opioids

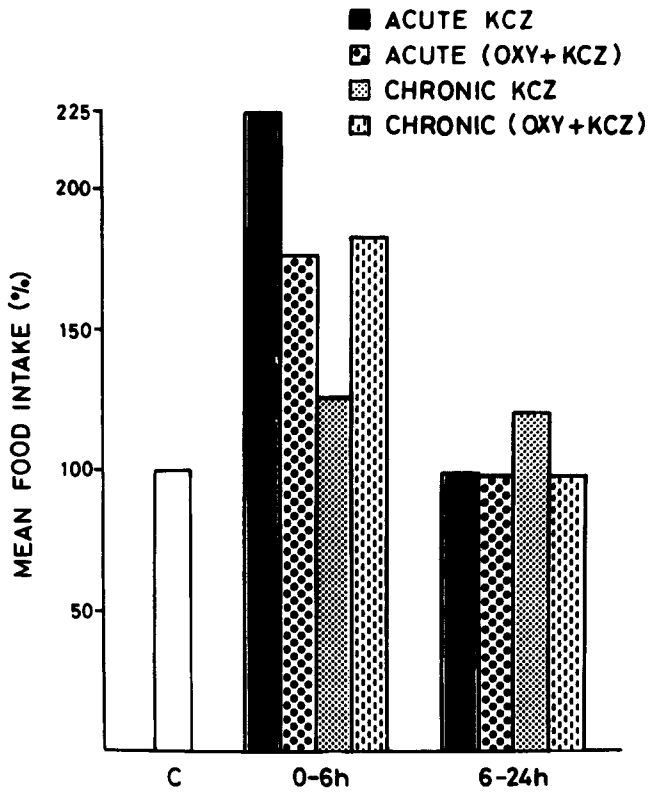

FIG. 2. Influence of oxytocin (OXY, 10 μg/kg, SC) on effects of ketocyclazocine (KCZ, 1 mg/kg, IP) on food intake during light (0–6 h) and dark (6–24 h) phases after acute or chronic administrations in rats. Data is expressed as percent of controls.

(10, 14, 16, 20, 31). Our data attempts to highlight these two effects in particular. Taken together it appears that dynorphinergic transmission and/or κ-receptor plasticity may play a crucial role in the regulation of food intake. The facilitation in the dark phase (6–24 h) food intake after chronic KCZ administration is interesting. Some reports have termed such trends as "reverse tolerance" (21,26). However, considering the quantum of change (20% increase) it is hard to label this marginal enhancement with this nomenclature. Nevertheless, it should not be totally overlooked as the neural mechanisms involved in the so called "reverse tolerance" are yet to be clearly defined.

Another notable aspect of our study is the complex interactions of KCZ with OXY or AVP during feeding behaviour. The (acute) hyperphagic effect of KCZ during the light phase (0–6 h) is markedly attenuated by both OXY and AVP. In addition both neurohypophyseal peptides prevented the tolerance development to the acute effects of KCZ (Fig. 2), the reversal being more consistent with OXY. This is not surprising as (a) neuropeptides are known to colocalize in the same area as well as in the same neurons (32) and, (b) modulation of one peptidergic circuit by the other is reported both at pre- and postsynaptic levels (2, 3, 6, 14). However, such interactions between endopioidergic and oxytocinergic/vasopressinergic neurotransmission during food intake are not reported and our preliminary data show that this may be a distinct possibility. The probable level of such interactions is hard to define on the basis of our present data. Nevertheless, the concept of such an interaction may be of some physiological significance particularly because both groups of neuropeptides are found in those areas of the CNS, like hypothalamus, amygdala, etc., which are seemingly crucial for feeding behaviour.

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TABLE 2

EFFECTS OF ACUTE AND CHRONIC KETOCYCLAZOCINE (KCZ, 1 mg/kg, IP) AND ITS INTERACTIONS WITH VASOPRESSIN (AVP, 10 μg/kg, SC) ON FOOD INTAKE IN RATS

	Food Intake (g) ± S.E. at Different h				
Treatment	0–1 h	1–3 h	3–6 h	0–6 h	6–24 h
Control	1.75 ± 0.4	0.50 ± 0.2	2.28 ± 0.7	4.52 ± 0.6	10.90 ± 0.6
Acute KCZ	5.00 ± 0.5†	0.93 ± 0.2*	2.86 ± 0.3	8.77 ± 0.4	10.63 ± 0.7
Acute AVP	1.06 ± 0.2*	0.30 ± 0.2	1.80 ± 0.4	3.15 ± 0.4	12.36 ± 0.8
Acute (AVP+KCZ)	2.31 ± 0.5§	0.90 ± 0.2	2.86 ± 0.4	5.80 ± 0.5‡	10.55 ± 0.8
Chronic KCZ	3.31 ± 0.6§	0.32 ± 0.1‡	2.48 ± 0.3	6.13 ± 0.3‡	12.96 ± 0.9‡
Chronic AVP	1.20 ± 0.3	0.35 ± 0.2	2.00 ± 0.6	3.50 ± 0.3	13.00 ± 0.7
Chronic (AVP+KCZ)	4.41 ± 0.3#	0.71 ± 0.2#	1.87 ± 0.2#	7.07 ± 0.4#	11.67 ± 0.85#

*$p<0.05$; †$p<0.01$; compared to respective vehicle controls (Mann-Whitney U-test); ‡$p<0.05$; §$p<0.01$; compared to respective acutely treated group (Mann-Whitney U-test); #$p<0.05$; compared to respective chronic KCZ-treated group (Mann-Whitney U-test).

TABLE 3

EFFECTS OF ACUTE AND CHRONIC KETOCYCLAZOCINE (KCZ, 1 mg/kg, IP) AND ITS INTERACTIONS WITH OXYTOCIN (OXY, 10 μg/kg, SC) ON FOOD INTAKE IN RATS

Treatment	Food Intake (g) ± S.E. at Different h				
	0–1 h	1–3 h	3–6 h	0–6 h	6–24 h
Control	1.00 ± 0.4	0.58 ± 0.2	1.30 ± 0.3	2.90 ± 0.6	10.60 ± 0.5
Acute KCZ	3.20 ± 0.2*	0.80 ± 0.2*	2.60 ± 0.2*	6.60 ± 0.4†	10.50 ± 0.2
Acute OXY	0.70 ± 0.3	0.60 ± 0.4	1.80 ± 0.3	3.20 ± 0.3	11.80 ± 0.3
Acute (OXY + KCZ)	2.10 ± 0.6‡	0.84 ± 0.3	2.20 ± 0.6	5.10 ± 0.7	10.40 ± 0.9
Chronic KCZ	2.60 ± 0.3‡	0.18 ± 0.1§	0.76 ± 0.1‡	3.65 ± 0.3‡	12.70 ± 0.7‡
Chronic OXY	0.90 ± 0.4	0.40 ± 0.2	1.10 ± 0.7	2.50 ± 0.4	12.30 ± 0.5
Chronic (OXY + KCZ)	2.90 ± 0.4	0.76 ± 0.2#	1.78 ± 0.3#	5.30 ± 0.4#	10.40 ± 0.70#

*$p<0.05$; †$p<0.01$; compared to respective vehicle controls (Mann-Whitney U-test); ‡$p<0.05$; §$p<0.01$; compared to respective acutely treated group (Mann-Whitney U-test); #$p<0.05$; compared to respective chronic KCZ-treated group (Mann-Whitney U-test).

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