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Opiatergic Modulation of Preparatory and Consummatory Components of Feeding and Drinking

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NENCINI, P. AND M. GRAZIANI. *Opiatergic modulation of preparatory and consummatory components of feeding and drinking.* PHARMACOL BIOCHEM BEHAV 37(3) 531–537, 1990.—We present data here indicating that stimulation of kappa but not mu opiate receptors influences motivational and consummatory aspects of feeding and drinking. To differentiate mu and kappa mechanisms controlling preparatory (appetitive) and consummatory components of ingestive behavior, the effects of morphine (MORPH), compound U50488H (U50) and naloxone (NAL) were studied in rats trained to negotiate a straight runway using food or water as a reinforcer. At doses that increase feeding and drinking in conditions of free access to food and water (i.e., 1–2 mg/kg IP), MORPH affected neither food- nor water-maintained runway performance. Since 1 mg/kg of NAL is also devoid of effects, mu-opiate mechanisms are probably not involved in food- or water-maintained behavior. Pharmacological manipulation of kappa-opiate mechanisms had complex effects. At 5 mg/kg, NAL accelerated satiation, depressing food intake, without affecting running. U50 did not increase food intake, but accelerated running for food, an effect that was antagonized by a high dose of NAL (5 mg/kg). These findings suggest that motivational and consummatory components of food-maintained runway performance are both activated by kappa-opiate mechanisms. NAL also reduced water intake but had minimal influences on running. In contrast, U50 depressed both water intake and runway performance; rather than being antagonized, these effects were slightly enhanced by NAL. The combined antidipsic and diuretic effects of U50 suggest that kappa-opiate mechanisms play a dissipatory role in water balance. However, the similar antidipsic effects of U50 and NAL, and the fact that NAL did not antagonize the antidipsic effects of U50, suggest that U50 may reduce drinking by mechanisms other than kappa-opiate agonism.

Drinking Feeding Runway Naloxone Morphine U50488H Rat

SINCE the discovery of the anorectic effect of NAL (11), extensive studies of the opiatergic control of ingestive behavior, performed under different experimental conditions, have shown that opiate antagonists suppress both feeding (6,24) and drinking (7). This suggests that the physiological functions of the endogenous opiate system include the activation of ingestive behavior. However, part of the data obtained with agonists at opiate receptors indicates that this suggestion needs further resolution in terms of opiate receptor subtypes (6, 7, 24). Stimulation of feeding, for instance, usually occurs only when drugs with opiate agonist properties are administered to satiated animals having free access to food. By contrast, when food is presented to food-deprived animals these agonists have inhibitory effects (23,33). Studies of drinking have provided similar results (7, 33, 34, 37, 41). In food- or water-deprived animals, an unusual situation therefore occurs, in which feeding or drinking is inhibited both by opiate agonists and by antagonists. This suggests that ingestive behavior is promoted or suppressed by divergent opiate mechanisms.

In contrast, other evidence suggests that different opiate mechanisms converge in the control of ingestive behavior. Thus, feeding in satiated animals is promoted by agents acting as agonists at mu, or delta, or kappa receptors (6,24). Particularly surprising is the finding that the prototypical mu agonist MORPH and the selective kappa agonist U50 both stimulate feeding. MORPH and U50 are thought to have opposite effects on several behavioral functions involved in the expression of ingestive behavior: MORPH stimulates (1, 2, 42) and U50 inhibits locomotion (8,44); MORPH has rewarding effects (3) and U50 is aversive (25,38). In addition, MORPH stimulates and U50 inhibits dopamine release in brain areas involved in reward-motivated behaviors, such as the nucleus accumbens (8). In this context, it is interesting to observe that an increase in the feeding response to both U50 and MORPH was obtained in rats treated repeatedly with amphetamine (27,28), a condition probably involving sensitization of the mesolimbic reward system (31).

Convergence and divergence in the overall effect of opiates on food and water intakes may be the result of the different actions these drugs exert on the behavioral repertoire that terminates with ingestion. An effective tool for analyzing various components of this repertoire is the runway procedure, as adapted to the study of anorectic drugs (40). In this version of the runway method, rats trained to negotiate a straight runway for food or water receive test sessions consisting of 15 trials, that is, an exposure which is extensive enough to produce an asymptotic decline in rat performance, including food or water intake (15, 29, 40). Such a procedure has been used for differentiating the anorectic effects of drugs like amphetamine, fenfluramine and NAL or naltrexone

(15,40). In particular, it has been shown that NAL and naltrexone do not block the initiation of feeding but do advance eating termination (16); this suggests that opiate control is exerted more on the consummatory than on the preparatory (appetitive) components of the repertoire. In the present study, we used the runway procedure to differentiate mu- and kappa-opiate mechanisms which control preparatory and consummatory components of alimentary behavior in rats, evaluating the effects of MORPH, U50 and NAL on feeding or drinking.

GENERAL METHOD

Animals

The subjects were 16 male Sprague-Dawley rats (Morini, San Polo d'Enza, RE) initially weighing 300–350 g. They were individually housed in the laboratory in which the experiment was performed and where temperature was maintained at 23°C with a light-dark cycle of 12 hr (0700–1900).

Apparatus

The runway apparatus, already described in detail (29), consisted of a 1.8 m long alley that connected a start box to a goal box, each box measuring 35 cm long × 16 wide × 16 high. The internal surface of the starting box and alley were black, the inside of the goal box was white. A hand-operated wooden guillotine gate controlled access to the alley from the start box. Two sets of infrared photocells were inserted in the walls of the runway, 20 cm from the gate and 5 cm from the goal-box entrance. The photocells allowed running time to be measured by an electronic timer. Latencies to leave the start box and to eat (or drink) on reaching the goal box were measured by two hand-operated stop watches. When feeding was studied, a plastic box containing food (75 mg pellets, Piccioni, Milan) was put into the goal-box, close to the wall facing the alley. When drinking was studied, a 200-ml water bottle was positioned on the outside of the goal box, with a 1-cm drinking spout protruding into the box, 6 cm above the floor.

Drugs

MORPH hydrochloride (SIFAC, Confienza, Italy), NAL hydrochloride (Sigma Chemical Company) and U50 [trans-(±)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl)]-benzene-acetamide methane sulfonate (Upjohn Company)] were freshly dissolved in distilled water to a final volume of 1 ml/kg.

EXPERIMENT 1

FOOD-REINFORCED BEHAVIOR

Training

Eight rats were chosen at random prior to the start of training. To compromise between the need to maintain motivation for food and that of avoiding extreme starvation, rats received enough food to maintain a body weight of about 85% of their previous ad lib level. When training and testing in the runway began, rats received food supplements 1 hr after the session.

Once 85% body weight had been attained, animals were trained to obtain food in the runway, as previously described (15,40). During the first 5 days, for 10 min each day, the rats were given access to all the compartments of the runway, including the goal box where food was available. During the next 10 days, each rat was submitted to a daily training session consisting of 3 trials. On each trial, the rat was placed in the starting box and after 10 sec the gate was opened. Once the rat had reached the goal box, the animal was allowed 30 sec to eat. Trials were separated by 5 min. On the last 3 days of training, the rats were sham-injected before the session according to the time schedule of treatments described below. After this training period, 6 rats were selected for their consistent starting and running speeds.

Test Procedure

The test procedure differed from training in that rats were given 15 consecutive trials. In each trial, the rats were kept for 30 sec in the start box before the gate was opened and were allowed 2 min to eat after they entered the goal box. If they failed to leave the start box within 30 sec from gate opening, they were placed in the goal box by the experimenter and left there for 2 min. Sessions were conducted 6 days/week (Monday through Saturday). Tests were performed twice a week, on Tuesday and Friday.

On each test session, 15 min before the test each rat was sequentially injected (intraperitoneally: IP) with either water and U50 (4 or 8 mg/kg), MORPH (1 or 2 mg/kg), or NAL (1 or 5 mg/kg); or with NAL (1 or 5 mg/kg) and U50 (4 mg/kg). Each animal received all 9 possible treatments according to a random sequence which was determined separately for each animal.

Data Analysis

On each trial the following measures were taken: time to leave the start box; time to traverse the runway; interval between entering the goal box and eating; and amount of food ingested. To normalize the data, starting times and latencies to eat were transformed into their reciprocal, while running time was transformed into running speed (m/sec).

A mixed-model analysis of variance (ANOVA) with subjects as blocks (random variable) was performed for each parameter (analysis of variance and covariance with repeated measures, Copyright: Regents of University of California; BMDP Statistical Software, Inc., Los Angeles, CA; Program Version: 1987). The fixed variables were treatments within subjects and repeated measures within subjects and treatments (five trial blocks, each of three trials; the presence of this variable led to the use of the Greenhouse-Geisser probability correction). Subsequent comparisons within logical sets of means were made using Tukey's test. In all cases but one (water intake; see Experiment 2 below) the treatment × repeated measures interaction failed to reach statistical significance; therefore, except in the case just mentioned, multiple comparisons used overall treatment means. In some instances, it seemed justified to complement the overall ANOVA so far described by additional ANOVA on data from single trial blocks followed by appropriate Tukey's tests (see the Results section).

RESULTS

Starting Speed, Running Speed and Speed to Eat

Figures 1 and 2 show the data for each measure. As expected, repeated measures showed highly significant changes in starting speed, $F(4,20) = 14.01$, $p<0.001$, running speed, $F(4,20) = 22.91$, $p<0.001$, and speed to eat, $F(4,20) = 7.31$, $p<0.05$, through trial blocks. When saline-injected, rats showed a biphasic trend in starting speed: they left the starting box faster in the second than in the first trial block, whereas the response declined asymptotically in the last 3 trial blocks. The curve representing running speed was shallow, but similar in shape to that representing starting speed. Finally, speed to eat increased up to the third trial block and then decreased on blocks 4 and 5.

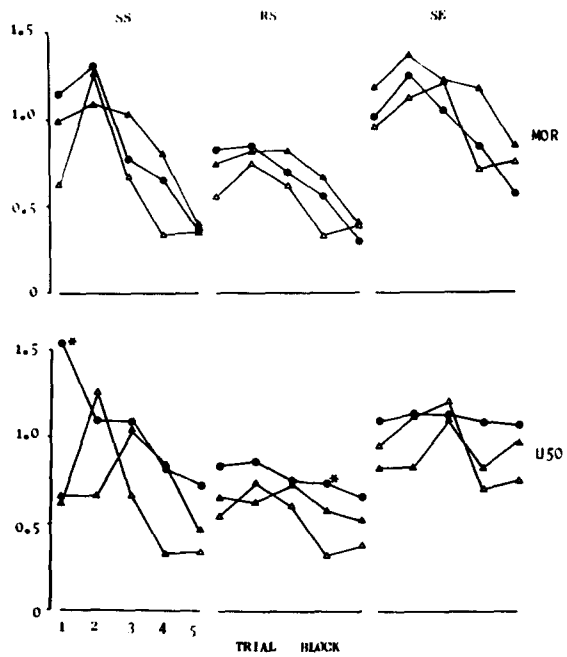

FIG. 1. Food-reinforced behavior. Effects of MOR (upper panel; ●: 1 mg/kg; ▲: 2 mg/kg) and of U50 (lower panel; ●: 4 mg/kg; ▲: 8 mg/kg) on starting speed (SS, sec^{-1}), running speed (RS, m/sec) and speed to eat (SE, sec^{-1}). Control values (△: water 1 ml/kg IP) are replicated in all panels. Each of the six rats received all the treatments shown in this and in the following figure in a random sequence and each point shows the mean of three trials. *$p<0.05$ vs. saline (Tukey's test).

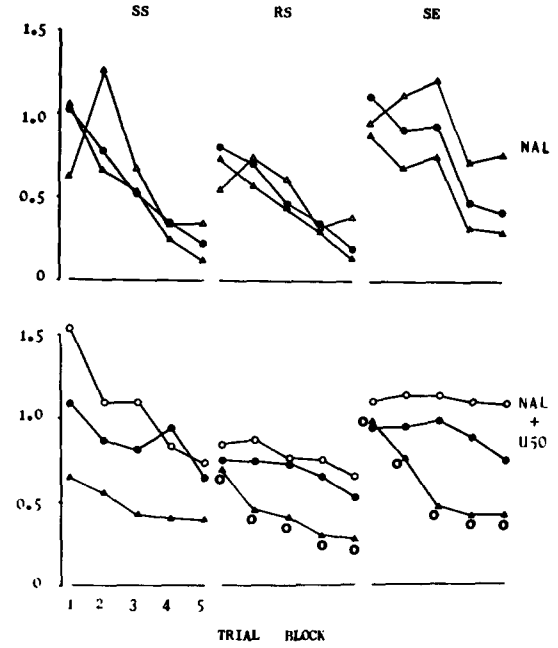

FIG. 2. Food-reinforced behavior. Effects of NAL (●: 1 mg/kg; ▲: 5 mg/kg) given alone (upper panel) or in combination with U50 4 mg/kg (lower panel) on starting speed (SS, sec^{-1}), running speed (RS, m/sec) and speed to eat (SE, sec^{-1}). Each of the six rats received all the treatments shown in this and in the previous figure in a random sequence and each point shows the mean of three trials. Results obtained in control condition (△) or after U50 4 mg/kg treatment (○) are shown in the upper and lower panels, respectively. ○: $p<0.05$ vs. U50 4 mg/kg (Tukey's test).

In the overall ANOVA, drug treatments did not exert a statistically significant effect on starting speed. However, a Tukey's test based on an ANOVA limited to the first trial block showed that U50, at the dose of 4 mg/kg, significantly increased starting speed. A significant drug effect was found in the overall ANOVA concerning running speed, $F(8,40)=3.32$, $p<0.05$, and speed to eat, $F(8,40)=4.10$, $p<0.05$. Tukey's test showed that this effect was due to the inhibition of U50 response produced by NAL, at a dose of 5 mg/kg. Additional tests based on separate ANOVA's for the fourth and the fifth trial blocks gave some evidence for a higher running speed in the U50 than in the control condition ($p<0.05$ in the fourth block).

Food Intake

In basal conditions (i.e., after IP water administration), rats ingested 12.1 ± 0.6 g (mean ± SEM) of food in 30 min. As is shown in Fig. 3, food intake was progressively reduced in successive trials, $F(4,20)=60.02$, $p<0.001$, and was significantly affected by drug treatments, $F(8,40)=10.39$, $p<0.001$. A Tukey's test showed that 5 mg/kg NAL significantly reduced food intake both in the absence and in the presence of U50 4 mg/kg.

EXPERIMENT 2

WATER-REINFORCED BEHAVIOR

Training and Test Procedure

Eight rats were water restricted throughout the study by reducing daily access to water to a 20-min period. Together with water, the rats were given approximately 25 g of food. This regimen allowed the body weight of the animals to be maintained at about 85% of the previous ad lib level. When training in the runway began, water and food were given 1 hr after the end of the session.

Training and testing were performed as described for food-reinforced behavior, water being available in the goal box instead of food. At the end of the training period, the six rats with the most consistent starting and running speeds were selected for testing. Treatments and data analyses were as in food-maintained behavior.

RESULTS

Starting Speed, Running Speed and Speed to Drink

As expected, running for water in basal conditions declined markedly across the test [starting speed: $F(4,20)=16.42$, $p<0.01$; running speed: $F(4,20)=28.41$, $p<0.01$; speed to drink: $F(4,20)=35.05$, $p<0.001$] (Figs. 4 and 5). In the case of starting speed, this trend was not significantly affected by drug treatment. By contrast, drug treatment significantly affected both running speed, $F(4,80)=3.88$, $p<0.05$, and speed to drink, $F(4,80)=4.69$, $p<0.02$. This effect was due to the depression produced by U50 when given alone ($p<0.05$). In fact, neither MORPH nor NAL, given alone or in combination with U50 4 mg/kg, were able to affect running for water.

Water Intake

In basal conditions, rats ingested 18.8 ± 1.3 g (mean ± SEM) of

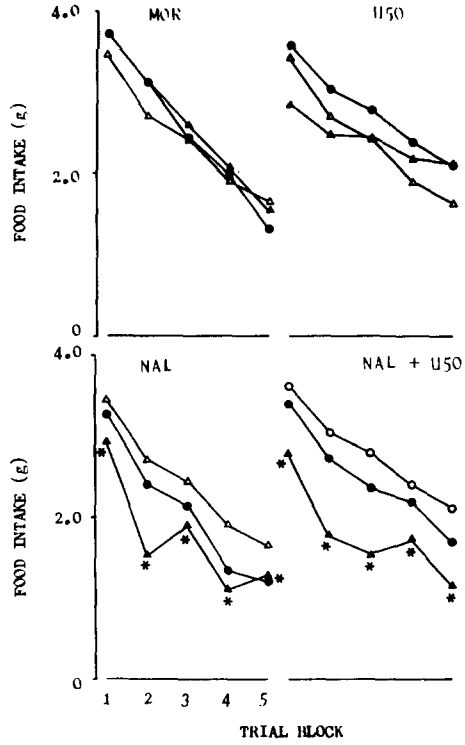

FIG. 3. Food-reinforced behavior. Effects on food intake of MOR (upper left panel; ●: 1 mg/kg; ▲: 2 mg/kg), U50 (upper right panel; ●: 4 mg/kg; ▲: 8 mg/kg), and NAL given either alone (lower left panel; ●: 1 mg/kg; ▲: 5 mg/kg) or in combination with U50 4 mg/kg (lower right panel; ○: U50 alone). Control values (△: water 1 ml/kg IP) are replicated in all panels. Each point represents the sum of the amounts of food consumed in the 3 corresponding trials. *$p<0.05$ vs. saline (Tukey's test).

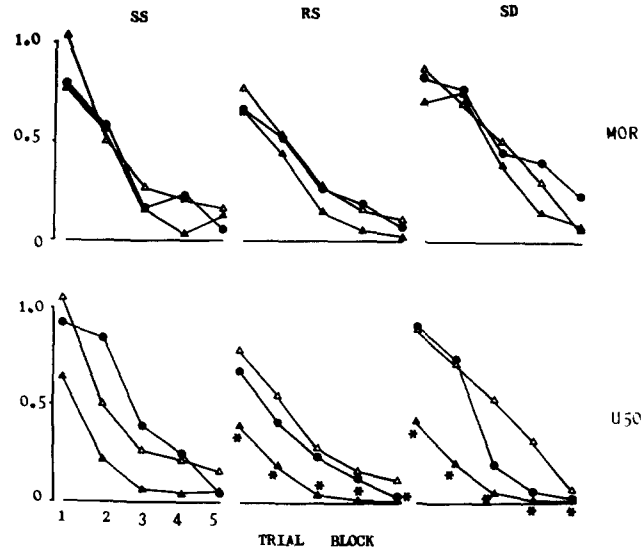

FIG. 4. Water-reinforced behavior. Effects of MOR (upper panel; ●: 1 mg/kg; ▲: 2 mg/kg) and of U50 (lower panel; ●: 4 mg/kg; ▲: 8 mg/kg) on starting speed (SS, sec^{-1}), running speed (RS, m/sec) and speed to drink (SD, sec^{-1}). Control values (△: water 1 ml/kg IP) are replicated in all panels. Each of the six rats received all the treatments shown in this and in the following figure in a random sequence and each point shows the mean of three trials. *$p<0.05$ vs. saline (Tukey's test).

water in 30 min. Water intake showed a linear decline across the test and during the last block very little water was ingested, $F(4,20)=133.92$, $p<0.001$ (Fig. 6). The analysis of variance disclosed a significant effect of treatments, $F(4,80)=13.09$, $p<0.001$, and a significant interaction between treatments and blocks, $F(32,160)=3.16$, $p<0.05$. Tukey's test showed that U50, given alone or in combination with NAL, and the highest dose of NAL (5 mg/kg) reduced water intake except in the later phases of the test when control values were at a low level.

DISCUSSION

Feeding Behavior

The present results confirm that the runway method is a sensitive procedure for assessing treatments which can modify preparatory (appetitive) and consummatory components of eating and drinking by different mechanisms (15,40). In particular, the selective inhibition of food intake that we obtained with a dose of 5 mg/kg of NAL is essentially in agreement with the previous findings that NAL reduces food intake before it affects running speed, an effect which has been ascribed to an acceleration of the physiological process of satiation (15,16).

By contrast, we found that 1 mg/kg of NAL was completely ineffective. Since moving from 1 to 5 mg/kg of the drug means passing from a dose effective on mu-opiate receptors alone to a dose that is also effective on kappa receptors (46), the satiation produced by NAL is probably due to the blockade of kappa receptors. If this is the case, stimulation of kappa receptors should delay the satiation process, an assumption supported by findings that U50 reinstates motivation in presatiated rats consuming a

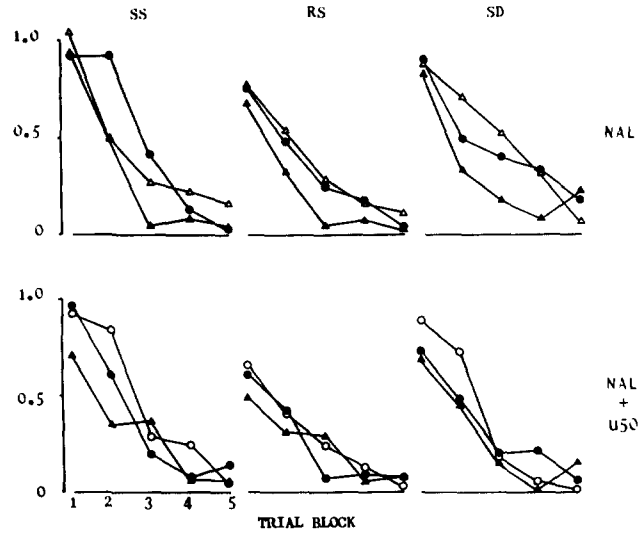

FIG. 5. Water-reinforced behavior. Effects of NAL (●: 1 mg/kg; ▲: 5 mg/kg) given alone (upper panel) or in combination with U50 4 mg/kg (lower panel) on starting speed (SS, sec^{-1}), running speed (RS, m/sec) and speed to drink (SD, sec^{-1}). Each of the six rats received all the treatments shown in this and in the previous figure in a random sequence and each point shows the mean of three trials. Results obtained in control condition (△) or after U50 4 mg/kg treatment (○) are shown in the upper and lower panels, respectively.

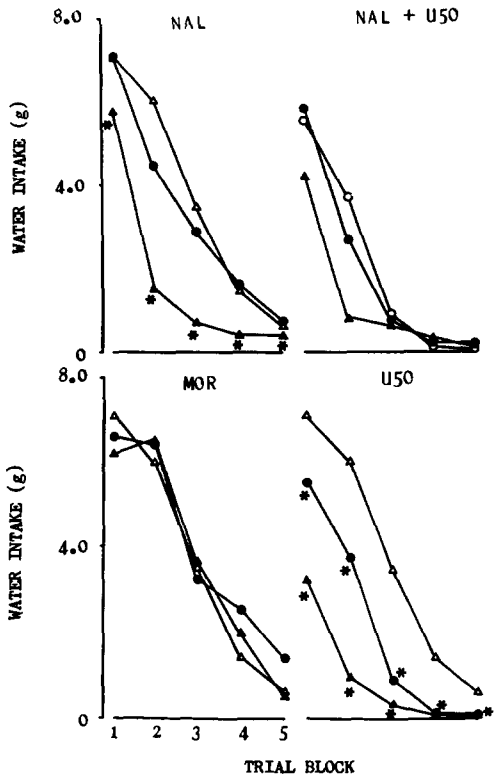

FIG. 6. Water-reinforced behavior. Effects on water intake of MOR (lower left panel; ●: 1 mg/kg; ▲: 2 mg/kg), U50 (lower right panel; ●: 4 mg/kg; ▲: 8 mg/kg), and NAL given either alone (upper left panel; ●: 1 mg/kg; ▲: 5 mg/kg) or in combination with U50 4 mg/kg (upper right panel; ○: U50 alone). Control values (△: water 1 ml/kg IP) are replicated in all panels. Each point represents the sum of the amounts of water consumed in the 3 corresponding trials. *$p<0.05$ vs. saline (Tukey's test).

sweet palatable food (12). In our runway experiments, the small increase in food intake produced by U50 was not statistically significant; the drug, however, produced an immediate speeding in the exit from the start box and then prevented the decline in running for food that occurred across the test under control conditions. Thus, U50 seemed to increase and maintain motivation for food independently from the actual amount of food ingested.

One can also account for the apparent contradiction between the effects of U50, which suggest a role of kappa-opiate receptors mainly in the appetitive components of the feeding repertoire, and those of NAL, which suggest that the same receptors are involved mainly in the modulation of consummatory components. In the condition of mild food deprivation in which our rats were maintained, kappa-receptor-mediated control of consummatory behavior, but not of appetitive behavior (as reflected by running speed), may have been almost fully expressed. This may explain why the administration of U50 resulted only in an increase of running for food, bringing both the runway performance and food ingestion to a ceiling level. Although speculative, the suggestion that these ceiling effects were due to the activation of kappa-opiate mechanisms is supported by the fact that they were prevented by the administration of a NAL dose active at kappa-opiate receptors (i.e., 5 mg/kg). Overall, our data seem to indicate that kappa-opiate mechanisms control both the appetitive and the consummatory aspects of feeding.

Mu-opiate mechanisms have been thought to exert an important role in the control of feeding behavior (22, 39, 45). Besides orectic effects in free-feeding conditions (28, 34, 39, 45), MORPH also produces anorectic responses, particularly in food-deprived animals (21, 23, 33). Such opposite effects are probably mediated by different brain structures; this is suggested by studies in which feeding activation was obtained by injecting MORPH into the hypothalamic paraventricular nucleus (45) and in the nucleus accumbens or in the ventral tegmental area (13,26), whereas MORPH injected into the periaqueductal grey inhibited feeding (13). In the present experiment, we used MORPH doses that produce a significant increase in feeding in conditions of free access to food (28,34). However, MORPH did not affect either runway performance or food intake. Since 1 mg/kg NAL was also unable to depress runway performance and food intake, it is unlikely that the absence of MORPH effects was due to a maximal activation of mu-receptor-mediated mechanisms in basal conditions.

The most plausible explanation is that in rats negotiating a runway for food, mu-opiate mechanisms activating food intake are functionally inactive. Since the prophagic effects of MORPH are usually observed when baseline food intake is low, the lack of MORPH effects in the present study may be due to the high response level in the runway. On the other hand, the anorectic effects of MORPH are usually obtained with doses much higher than those used in our study (10–15 mg/kg) (21, 23, 34).

In conclusion, our results suggest that the runway performance maintained by food presentation is under the control of activatory kappa, but not mu, opiate mechanisms. This is not what we would expect if we consider that running for food in a straight runway is a typical example of approach behavior, that is, of a response which together with locomotion, feeding and reinforcement, is deemed to be mainly under the control of the mesolimbic reward system (43). MORPH injection in the ventral tegmental area increases dopamine release in the nucleus accumbens, has rewarding effects, stimulates locomotor activity and, as expected, increases food intake [for a review, see (3)]. In contrast, kappa opiates seem to play an inhibitory role on the mesolimbic reward system; U50, in particular, inhibits dopamine release in the nucleus accumbens (8), reduces spontaneous activity (8) and has aversive properties (25,38). Moreover, when injected in the ventral tegmental area, U50 stimulates feeding (13). Therefore, our results confirm the atypical profile of U50 which in spite of its aversive properties is able to cause desatiation and to increase motivation for food.

Drinking Behavior

As in the case of feeding, opiate antagonists have been found to inhibit water intake under a variety of experimental conditions (7). Our study shows that the suppressant effect of NAL on drinking rate is also reproducible in the runway situation; therefore, all available data point to an effect on satiation mechanisms, as in the case of feeding. This suggestion is fully consistent with other studies adopting different schedules of water presentation (4, 5, 35). NAL inhibition of drinking became apparent at the same dose that produced food satiation, i.e., 5 mg/kg, while MORPH was devoid of effects on both runway performance and drinking rate. Therefore, neither water-, nor food-maintained runway performance appears to be under the control of mu-opiate mechanisms. Also in this case, the baseline level of ingestion was probably too high to disclose activatory effects of MORPH and MORPH doses were too low to produce inhibitory effects. This is supported by the results of a recent study showing that the intrahypothalamic administration of a selective mu-opiate agonist (DAGO) tends to increase drinking in nondeprived rats, but suppresses it in dehydrated animals (41).

The results so far discussed tempt us to conclude that there are no major differences in the way opiates control either water- or food-maintained runway performance. In particular, the finding that a high dose of NAL inhibited the consummatory component of the drinking repertoire suggests that kappa-opiate mechanisms have a role in the activation of such a response. However, the results obtained with U50 do not fit in with this hypothesis, since this agent produced a dose-related inhibition of running for water and of drinking. Several studies report an inhibitory effect of kappa-opiate agonists on drinking (7) and our data are consistent with the observation that intracerebroventricular administration of U50 reduces water intake by affecting the latency to drink (36). The lack of effects of U50 on running, when the performance was maintained by food, ruled out the possibility that suppression of drinking was the result of a motor impairment. The inhibitory effect of U50 therefore appears to be selective for the consummatory component of the drinking behavior and seems to consist of an acceleration of the satiation process. The antidipsic effect of U50 makes sense if we consider that agonists at kappa-opiate receptors also produce diuresis (18–20). Altogether, these data suggest that kappa-opiate mechanisms serve a dissipative role in the organism's water balance, a hypothesis that is taking ground (7).

It remains to be explained why U50 and NAL produced similar effects on water ingestion. Recent reports suggest that there are two or more subtypes of kappa receptors (30, 32, 47). It is interesting that U50 has a low affinity for the so-called K_2 sites, that is, on the subtype which predominates in rat brain (47). Therefore, the data seem to challenge the initial assumption that the pharmacological effects of U50 are mediated by the activation of kappa-opiate receptors. Moreover, they indirectly support the view that kappa-opiate agonists act via an antagonistic effect at mu-opiate receptors (9, 10, 14). In other words, both NAL and U50 may reduce drinking by similar mechanisms, that is, by blocking mu-opiate receptors.

CONCLUSIONS

It appears at this point that the runway paradigm may be useful in further drug studies aimed at separating the mechanisms responsible for preparatory and consummatory activations with the same or with different reinforcements [see, particularly, (17)]. For example, U50 and NAL have different effects on running for water but similar effects on drinking. This makes it necessary to postulate at least a partial nonoverlap of the mechanisms underlying the two components of the repertoire. More generally, it appears that considerable caution is needed when comparing effects on consummatory responses assessed in different situations, that is, without or with the requirement to perform a preparatory sequence prior to feeding or drinking.

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