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Interaction Between Opioid Agonists or Naloxone and 5-HTP on Feeding Behavior in Food-Deprived Rats

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FERNANDEZ-TOME, M. P., Y. GONZALEZ AND J. DEL RIO. *Interaction between opioid agonists or naloxone and 5-HTP on feeding behavior in food-deprived rats.* PHARMACOL BIOCHEM BEHAV **29**(2) 387–392, 1988.—Morphine and the enkephalin analogs DAME, DADLE and FK-33824, as well as the opioid antagonist naloxone, decrease feeding in food-deprived rats after intraventricular or subcutaneous administration, FK-33824 being by far the most potent drug tested. The administration of subeffective doses of either morphine or naloxone given by the subcutaneous route induces anorexia when given in combination with a subeffective dose of 5-HTP whereas the treatment with subeffective intraventricular doses of any of the opioids or naloxone fails to potentiate 5-HTP. Similarly, the anorexia induced by FK-33824 is blocked by either morphine or naloxone given subcutaneously but not by intraventricular administration of the same two drugs. The results appear to suggest that central or peripheral opioid receptors differentially affect feeding behavior in the rat and, on the other hand, that the interaction of opiates with the serotonergic system appears to occur preferentially in the periphery.

Anorexia Feeding behavior Opioids Naloxone 5-Hydroxy-tryptophan Serotonin

THE opioid system seems to play a complex role in feeding behavior (see reviews in [30, 33, 40]). Opioid peptides such as beta-endorphin [19,27], dynorphin [31] or the enkephalin analog DADLE [43] may increase food ingestion in free-feeding rats after intracerebroventricular or intrahypothalamic injection. Morphine reduces food intake in food-deprived animals but may increase the small amount of food consumed by non-deprived animals [41]. The opiate antagonist naloxone consistently reduces food consumption both in food-deprived and in free-feeding animals [4, 14, 24–26] and this effect is found after either central or peripheral administration of the drug [44]. Other studies point to the importance of opioid receptors situated outside the central nervous system in the control of eating (see review in [40]).

The evidence favoring a role for serotonergic mechanisms in the regulation of food intake is probably more widely documented [2, 23, 39]. The intrahypothalamic [17] or peripheral [36] injection of 5-HT reduces feeding. The 5-HT precursor 5-hydroxy-tryptophan (5-HTP) or the 5-HT releasing agent fenfluramine also reduce food intake both in sated and in fasted animals [3, 11, 35]. Conversely, serotonergic blockers such as methergoline or cinanserin [13] or the serotonergic neurotoxin 5,7-dihydroxytryptamine [38] or the inhibitor of 5-HT synthesis p-chlorophenylalanine [6] have generally been reported to induce hyperphagia.

Multiple interactions between opiates or opioid peptides and the serotonergic system have been described both in the peripheral [10] and in the central nervous system (see review in [5]). For example, administration of opiates has been reported to stimulate the turnover rate of brain 5-HT [18] and some effects of opiates such as hypothermia or catalepsy appear to be mediated by an increase in serotonin function [5]. Serotonergic agonists increase plasma levels of beta-endorphin [9] and the repeated administration of fenfluramine, an anorexic drug which releases 5-HT, increases the hypothalamic content of met-enkephalin and beta-endorphin [21,22].

The aim of the present study was to determine the effect of different drugs acting on opioid receptors on feeding behavior in food-deprived rats as well as their interactions with the serotonin precursor 5-HTP. In addition to morphine and naloxone, the synthetic enkephalin analogs DADLE, DAME and FK-33824 were used. FK-33824 is a preferential agonist towards opioid μ receptors, whereas DAME and especially DADLE are preferential agonists of opioid δ receptors [12,45]. Both intraventricular and systemic administration of drugs was used in an attempt to establish the central or peripheral origin of the interaction. Locomotor activity was also measured in some instances as a control for sedation of the animals.

METHOD

Animals

Male Wistar rats weighing 200–250 g before initiating the

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TABLE 1

DECREASE IN FOOD INTAKE INDUCED BY ICV INJECTION OF OPIOID AGONISTS OR NALOXONE IN FOOD-DEPRIVED RATS

Drug	Dose μg/rat	Food Intake (g)
Saline	—	6.15 ± 0.82
Morphine	0.5	5.25 ± 0.94
Morphine	1	4.31 ± 1.22
Morphine	5	3.26 ± 0.50*
Morphine	10	1.72 ± 0.34*
Morphine + NX, 1	5	5.94 ± 1.05†
DAME	0.5	6.04 ± 0.73
DAME	1	6.38 ± 1.57
DAME	2	5.63 ± 1.38
DAME	5	1.27 ± 0.62*
DAME + NX, 1	5	5.11 ± 0.82†
DADLE	0.5	6.20 ± 1.34
DADLE	1	5.83 ± 0.90
DADLE	2	0.35 ± 0.11*
DADLE + NX, 2	2	5.10 ± 0.61†
FK-33824	0.0001	5.55 ± 0.86
FK-33824	0.005	5.16 ± 1.09
FK-33824	0.001	3.52 ± 0.60*
FK-33824	0.01	1.60 ± 0.43*
FK-33824 + NX, 1	0.001	4.98 ± 0.51†
Naloxone	2	5.32 ± 1.06
Naloxone	5	4.05 ± 0.71*
Naloxone	10	3.78 ± 0.62*

Shown are the means ± SEM of 7–12 rats. Opioid agonists or naloxone were given ICV 10 min before the animals had access to food. In combined treatments, naloxone (NX, mg/kg SC) given 5 min before the opioid injection. Food intake was measured in the first 30 min. Molar equivalence: 1 mol FK-33824=1.03 DAME = 1.06 DADLE = 1.66 Naloxone = 1.87 Morphine.

*Significant decrease ($p<0.05$ or better, Student's t-test).

†Significant difference vs. rats receiving only the corresponding dose of the opioid.

TABLE 2

DECREASE IN FOOD INTAKE INDUCED BY SC INJECTION OF OPIOID AGONISTS OR NALOXONE IN FOOD-DEPRIVED RATS

Drug	Dose (mg/kg)	Food Intake (g)
Saline	—	5.74 ± 0.64
Morphine	2	5.35 ± 0.56
Morphine	5	4.05 ± 0.60*
Morphine	10	0.95 ± 0.23*
Morphine + + Naloxone	5 + 1	5.97 ± 0.88†
DAME	0.05	6.02 ± 0.95
DADLE	0.05	5.44 ± 1.02
FK-33824	0.0025	6.10 ± 0.71
FK-33824	0.005	4.98 ± 0.87
FK-33824	0.01	2.43 ± 0.32*
FK-33824 + Naloxone	0.01 + 1	4.79 ± 0.74†
Naloxone	0.5	5.42 ± 1.10
Naloxone	1	5.60 ± 0.82
Naloxone	2	4.87 ± 0.97
Naloxone	5	3.53 ± 0.60*
Naloxone	10	1.38 ± 0.53*
Naltrexone-MeBr	10	5.00 ± 1.05
Naltrexone-MeBr	20	5.24 ± 0.62
Naltrexone-MeBr	80	4.68 ± 0.75

Shown are means ± SEM of 7–12 rats. Drugs given 15 min before the animals had access to food. Food intake was measured in the first 30 min.

*Significant decrease ($p<0.05$ or better, Student's t-test).

†Significant difference vs. rats receiving only the corresponding dose of the opioid.

experiments were used throughout. The animals were individually housed in transparent plastic cages. Water was available ad lib.

Food Consumption

The rats were maintained on a deprivation schedule which allowed free access to the usual dry pellet diet for 2.5 hr a day (10.30 to 13 hr). The food consumed was measured daily 30, 60 and 150 min after the animals had access to the diet. It was considered that the rats were habituated to this feeding schedule when the change in the amount of food consumed was less than 10% in five consecutive days. This habituation period took approximately 2 weeks. The amount of food consumed was in the range of 5–6. 5 g in the first 30 min, 1.5–3 g in the 30–60 min interval and 3–7 g in the last 90 min. The first 30 min of the feeding period yielded the most reproducible results so this time interval was selected for the studies with drugs. The rats were frequently handled and received saline injections in preliminary sessions to habituate them to the experimental procedure. Each rat received, on the average, 3–4 drug treatments spaced at least 2 weeks apart. When a rat did not return within 2–3 days after drug treatment to its basal food intake values, the animal was discarded.

Locomotor Activity

Locomotion was measured by means of a battery of 4-photocell circular activity cages with 50 cm outer diameter and a central light source. In these cages, two or more consecutive interruptions of the same photocell beam resulted in only one count [15]. In this way only locomotor activity was measured and repeated sniffing, licking or biting on a given photocell did not yield a false index of locomotion.

Intraventricular Injections

For intraventricular injections, cannulae were permanently implanted into the left lateral ventricle (coordinates: 1 mm posterior bregma, 1.5 mm lateral bregma and 3.5 mm below the surface of the skull). A constant volume of 10 μl was used for ICV injections. After testing had been com-

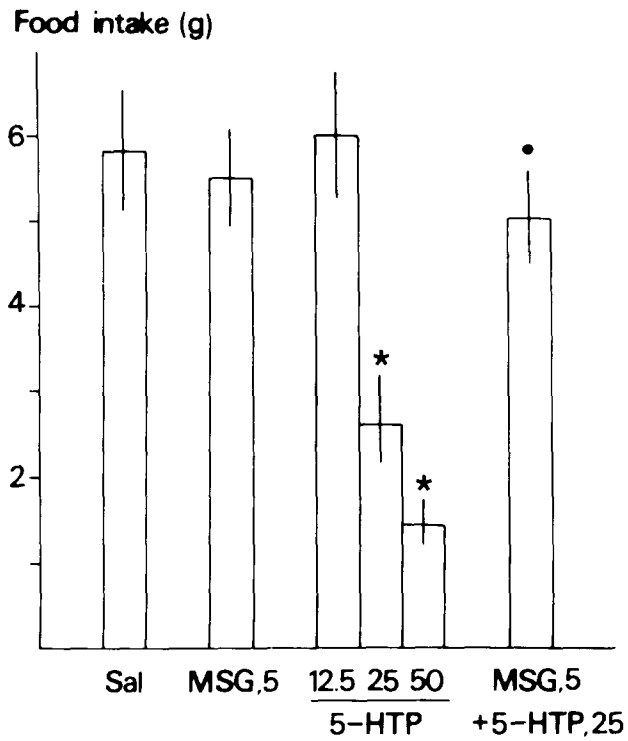

FIG. 1. Antagonism by methysergide (MSG, mg/kg IP) of the anorexic effect of 5 hydroxy-tryptophan (5-HTP, mg/kg IP) in food deprived rats (groups of 6–8 animals). MSG and 5-HTP given respectively 45 and 30 min before the rats had access to food. Food intake measured in the first 30 min. *Significant change ($p<0.01$, Student's t-test). •Significant difference ($p<0.01$) vs. rats receiving only the corresponding dose of 5-HTP.

pleted the correct placement of the cannulae was confirmed by injection of bromophenol blue into the ventricles.

Drugs

The drugs used were: 5-hydroxy-DL-tryptophan (Sigma), methysergide dimaleate (Sandoz), naloxone hydrochloride (Endo), naltrexone methylbromide (Boehringer Ingelheim), morphine hydrochloride (Hoffman-La Roche), (D-Ala^2, Me Phe^4, Met (O)^5-ol)-enkephalin (FK-33824, Sandoz), (D-Ala^2), Met^5-enkephalinamide (DAME, Biosearch) and (D-Ala^2, D-Leu^5) enkephalin (DADLE, Biosearch).

RESULTS

In rats habituated to the present experimental procedure ICV or SC injections of saline did not modify the normal amount of food consumed (Tables 1 and 2). Food intake was decreased in a dose-related manner by ICV injection of naloxone or of the opioid agonists morphine, DAME, DADLE or FK-33824 (Table 1). On a molar basis, this last enkephalin analog was approximately 200–400 fold more potent than the two other synthetic enkephalins and about one-thousand fold more potent than either morphine or naloxone. Much higher SC doses of either naloxone or morphine were necessary to decrease feeding and FK-33824 was again much more potent than either morphine or naloxone (Table 2). Food intake was not significantly modified by the quaternary narcotic antagonist naltrexone methylbromide, at doses up to 80 mg/kg or by SC injections of either DAME or

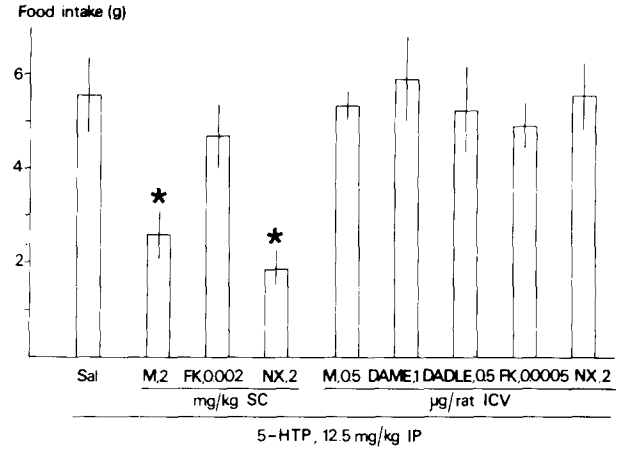

FIG. 2. Effect of the combined treatment of 5-hydroxy-tryptophan (12.5 mg/kg IP) and opioid agonists (M: morphine; FK: FK-33824, DAME or DADLE) or naloxone (NX) on food intake by food-deprived rats (groups of 8–9 animals). ICV, SC and IP injections given respectively 10, 15 and 30 min before the animals had access to food. Food intake measured for 30 min. *Significant difference ($p<0.01$) vs. rats receiving only 5-HTP.

DADLE at doses up to 50 μg/kg (Table 2). The anorexic effect of morphine or opioid agonists was significantly prevented by prior SC injection of naloxone, at a dose (1 mg/kg) without intrinsic effects on feeding behavior (Tables 1 and 2). This dose of naloxone did not prevent DADLE anorexia but a significant antagonism was also observed after doubling the dose (Table 1).

The IP administration of 5-HTP (12.5–50 mg/kg) produced a dose-dependent decrease in food intake in fasted rats, the decrease being prevented by prior administration of the serotonergic antagonist methysergide (Fig. 1).

When a low, ineffective dose of 5-HTP (12.5 mg/kg) was given in combination with an also ineffective dose of either morphine or naloxone, given by the SC route, a significant decrease in food intake was observed (Fig. 2). An ineffective SC dose of FK-33824 did not however potentiate the 5-HTP effect. The same lack of interaction was also observed after the combined treatment of low, subeffective doses of naloxone or any of the opioid agonists, given by the ICV route, and 5-HTP (Fig. 2).

In view of the differential effect of naloxone in the above experiment, it appeared of interest to determine whether the anorexic effect of the most potent opioid agonist used in the present study, FK-33824, would be blocked not only by peripheral naloxone (cf. Tables 1 and 2) but also by the opioid antagonist given into a lateral ventricle at an approximately equipotent dose. However, no antagonism of the anorexic effect of FK-33824 was found (Table 3) and, likewise, morphine was able to antagonize the effect of the enkephalin analog when given SC but not ICV (Table 3).

The potentiation of 5-HTP by peripheral morphine or naloxone could be conceivably due to the sedation produced by the combined treatments. A final experiment was consequently planned in which the locomotor activity of fasted rats was measured giving the same doses of 5-HTP and naloxone and using the same time intervals. A control group of sated rats was included in this experiment as to check the possibility of a more pronounced effect of the drugs on food-deprived animals. Actually, the sedating effect of either

TABLE 3

ANTAGONISM OF THE ANOREXIC EFFECT OF FK-33824 BY MORPHINE OR NALOXONE IN FOOD-DEPRIVED RATS

1st Treatment	Dose	2nd Treatment	Dose	Food Intake (g)
Saline (ICV)	—	Saline (ICV)	—	5.38 ± 0.70
FK-33824	1 ng/rat ICV	Saline (SC)	—	2.80 ± 0.56
FK-33824	1 ng/rat ICV	Morphine	0.5 μg/rat ICV	3.65 ± 0.86
FK-33824	1 ng/rat ICV	Naloxone	2.0 μg/rat ICV	2.91 ± 0.30
FK-33824	1 ng/rat ICV	Morphine	2.0 mg/kg SC	5.32 ± 0.95*
FK-33824	1 ng/rat ICV	Naloxone	2.0 mg/kg SC	6.05 ± 1.07*
FK-33824	10 μg/kg SC	Saline (ICV)	—	2.05 ± 0.35
FK-33824	10 μg/kg SC	Morphine	0.5 μg/rat ICV	2.03 ± 0.47
FK-33824	10 μg/kg SC	Naloxone	2.0 μg/rat ICV	1.88 ± 0.50
FK-33824	10 μg/kg SC	Morphine	2.0 mg/kg SC	5.87 ± 0.64*
FK-33824	10 μg/kg SC	Naloxone	2.0 mg/kg SC	5.40 ± 0.88*

The data are the means ± SEM of 6–9 rats. Subcutaneous and intraventricular injections were given respectively 15 and 10 min before the animals had access to the food. Food intake measured in the first 30 min.

*Significant difference vs. rats treated with FK-33824 alone ($p<0.01$, Student's t-test).

5-HTP or naloxone tended towards significance in fasted rats and not in sated animals. However, no further decrease in locomotion was found when the combined treatment of 5-HTP and naloxone was given to the food-deprived animals (Fig. 3).

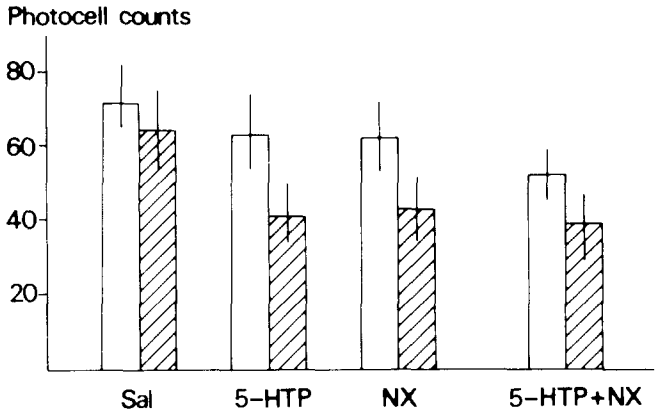

FIG. 3. Effect of 5-hydroxy-tryptophan (5-HTP, 12.5 mg/kg IP) and naloxone (NX, 2 mg/kg SC) on the locomotor activity (counts in 30 min) of sated (white columns) and food-deprived (hatched columns) rats. The data shown are the means±SEM of 6–8 rats.

DISCUSSION

The results of the present study indicate that both the opioid antagonist naloxone and morphine or the enkephalin analogs DAME, DADLE or FK-33824 decrease feeding in food-deprived rats, FK-33824 being by far the most potent drug after either peripheral or central administration. When these compounds were given at subeffective doses in combination with an also subeffective dose of 5-HTP, only peripheral morphine or naloxone were able to potentiate 5-HTP anorexia.

The ability of both naloxone and morphine to suppress feeding in food-deprived rats is certainly surprising but this is not a new finding. In fact, naloxone decreases feeding in rats under a variety of conditions including sated or fasted rats, stress-induced feeding or feeding induced by different drugs (see review in [32]). The effect of morphine has been less thoroughly analyzed but it is known that morphine consistently reduces food intake in food-deprived rats [40] whereas the much smaller amounts of food consumed by non-deprived animals are increased by the drug [41]. The enkephalin analogs used at about the same doses that induce analgesia [16, 34, 37] also reduce feeding on ICV administration, FK-33824 also being very active after peripheral administration as could be expected from its high metabolic stability [37]. Naloxone, given at the moderate dose of 1–2 mg/kg SC, generally used for antagonizing an opioid effect, prevents the effect of opioid agonists and higher doses (5–10 mg/kg SC), perhaps acting on other neurotransmission systems, are necessary to reduce food intake. Very high SC doses of the quaternary narcotic antagonist naltrexone methylbromide, which does not cross the blood-brain barrier [7], did not modify at all the ingestive behavior, indicating that a blockade of peripheral opioid receptors does not affect by itself food intake. The apparent agonist activity of naloxone in a variety of behavioral and *in vitro* test systems has been reviewed [42] and this could be perhaps another example of naloxone being an opioid antagonist at low doses and acting like opioids at higher doses. On the other hand, if the different affinity of naloxone towards the multiple opioid receptors is considered [12] it could be perhaps speculated that low doses of naloxone only exert an antagonistic effect on a hypothetical anorectic μ receptor [33] whereas higher doses block the κ receptor which may be involved in the initiation of feeding [33].

For the interaction of opioid agonists or naloxone with 5-HTP, the highest dose of each drug without any deleterious effect on food intake was used. Neither naloxone nor the opioid peptides given ICV potentiated the 5-HTP effect, a potentiation being observed only after SC administration of

either morphine or naloxone. Even though the much lower ICV doses which reduce food intake (cf. Table 1) would indicate that central opioid receptors are primarily involved in this effect, the results of these combined treatments suggest a peripheral interaction between the serotonergic and the opioid system. It is known in this regard that the peripheral administration of 5-HT suppresses feeding [36], that both central and peripheral naloxone reduce feeding [44] and that morphine enhances the release of 5-HT from the perfused dog intestine [10]. Opioid receptors have been described in rat small intestine [28] but the functional roles of the different types of receptors remain to be elucidated. The lack of potentiation by the μ-agonist FK-33824 of 5-HTP suggests, on the other hand, that opioid μ receptors are not involved in the modulation of serotonergic systems. Obviously, it is not known if the dose used of FK-33824 is low enough to stimulate selectively opioid μ receptors. Otherwise, δ receptors would be also activated [45] and it is known that opioid receptors of the μ- or δ-type can be involved in opposite regulatory mechanisms [20,29].

The importance of peripheral opioid receptors was again inferred from the inability of ICV naloxone to antagonize the anorexic effect of FK-33824, a finding in sharp contrast with the antagonism by a moderate SC dose of naloxone of the anorexic effect of all the opioid agonists considered in this study (Tables 1 and 2). In a like fashion, peripheral morphine, a much weaker anorexic drug than FK-33824, probably acting as a partial agonist, antagonized the decrease in food intake induced by FK-33824 whereas the ICV injection was ineffective. The results of this study thus tend to support the hypothesis of the predominant aversive effects derived of the stimulation of opioid receptors located in the periphery [1].

The issue of sedation or behavioral debilitation (cf. [8]) in the interpretation of the decrease in food intake induced by single or combined treatments was finally considered. Since a marked supraadditive effect on feeding was found after the peripheral administration of naloxone and 5-HTP, the effect of the same combined treatment on locomotor activity was also studied. It was found that single treatments with either naloxone or 5-HTP tended to decrease the locomotor activity of rats but no further decrease was found after the combined treatment. It is obvious that the decrease in locomotion may not be an adequate behavioral control for decreased feeding but the present experiment may indicate at least that the sedation was not too pronounced.

In summary, the results of the present study suggest that central or peripheral opioid receptors may affect differentially feeding behavior in the rat and that the interaction of opioids with the serotonergic system in regard to this behavior appears to occur preferentially in the peripheral and not in the central nervous system.

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