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# Naltrexone Suppresses Hyperphagia Induced in the Rat by a Highly Palatable Diet

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APFELBAUM, M. AND A. MANDENOFF. *Naltrexone suppresses hyperphagia induced in the rat by a highly palatable diet.* PHARMAC. BIOCHEM. BEHAV. **15**(1) 89–91, 1981.—A highly palatable diet (ordinary chow supplemented with 4 highly palatable items changed every day) (HPD) provokes hyperphagia and overweight in the rat. After 17 weeks of such a diet, naltrexone (0.5 or 2.5 mg/kg IP) an opiate antagonist, was injected at the beginning of the dark period, and a food intake test was performed during the 3 following hours. Naltrexone does not modify the energy intake in control rats receiving ordinary chow but suppresses HPD induced hyperphagia. The involvement of the β-endorphin system in this type of hyperphagia is discussed.

Naltrexone Hyperphagia Energy intake Endorphin-antagonist Dietary obesity Highly palatable diet

A large choice of highly palatable items, varied everyday, provokes in the rat hyperphagia, overweight, and an enlargement of adipose tissue [13, 14, 16, 18]. In other models of hyperphagia β-endorphin is involved: in genetically obese rodents naloxone, an opiate antagonist suppresses hyperphagia and the amount of β-endorphin in the pituitary gland is very high [11]. Naloxone also suppresses hyperphagia induced by 2-deoxyglucose [19], by diazepam [20] and by lesions of the ventromedial nucleus of the hypothalamus [9].

On the other hand, β-endorphin injected into the ventromedial nucleus of the hypothalamus provokes a complementary food intake in satiated rats and this effect is suppressed by naltrexone, another opiate antagonist [5]. The present experiment was designed to check whether naltrexone can also suppress dietary hyperphagia.

## METHOD

### *Animals*

40 male Wistar rats (commentry), weighing between 100 and 120 g, were housed in groups of 3 during 10 weeks and in individual cages thereafter. They were maintained at 24°C with a 12 hour light/dark cycle. They were divided into two experimental groups. The first group, "control," received ordinary chow (extralabo M25) ad lib; the second group "high palatability" (HP) was given 4 palatable foods in addition to the chow. The 4 supplementary items were changed each day on a week rotation. The list of palatable items was previously tested and includes such delicacies as ham, salami, smoked fish, tuna, potato chips, lard, marshmallows, cheeses, cookies, breakfast cereals, bread, pop corn, noodles and a large choice of penny candies and chocolate bars.

Animals were weighed regularly. By week 17, the mean weight of the HP group was 546.8±11.6 g (SEM) versus 453±10.6 for the control group. On Wednesday of week 17 at 20.00 hr, the end of the light period, both groups were divided into two randomized subgroups of 10 rats each:

(1) Ten control and ten HP animals received an intraperitoneal injection of 1 ml/kg of body weight of 9% solution of NaCl;

(2) The other ten control and ten HP animals received an intraperitoneal injection of 0.5 mg/kg of body weight of naltrexone.

### *Food Intake*

Food intake tests were then conducted over a period of 3 hours. At the start of the test session, rats were placed in individual cages, where a fresh choice of preweighed foods (lard, noodles, cakes, chocolate, and chow) was presented to the HP rats, and preweighed chow was given to the control rats. At the end of the test period, all rats were returned to their home cages. Unconsumed palatable food and chow were collected and the food intake was calculated as the difference between the weight of the food prior the testing and the amount of food recovered subsequent to the test session. The energy content of each item consumed was calculated according to tables [21].

During the following week, the animals continued to have free access to their respective diets. At week 18 the same experiment following the same schedule was performed again, but this time using 2.5 mg/kg of naltrexone.

TABLE 1

EFFECTS OF NALTREXONE ON FOOD INTAKE OF HP AND CONTROL RATS

| | | NaCl N=20* | Naltrexone 0.5† N=10 | Naltrexone 2.5† N=10 |
|---|---|---|---|---|
| Control | kJ/Rat‡ | 51.0 ± 6.3 | 54.0 ± 5.8 | 38.6 ± 6.3 |
| | kJ/kg B.W.‡ | 111.7 ± 12.9 | 123.2 ± 16.0 | 86.8 ± 15.5 |
| Cafeteria | kJ/Rat‡ | 140.8 ± 13.4 | 67.9 ± 11.1 | 36.0 ± 8.8 |
| | kJ/kg B.W.‡ | 251.3 ± 23.1 | 125.5 ± 21.5 | 67.4 ± 16.2 |

*Food intakes after NaCl injection in 0.5 mg and 2.5 mg experiments are the same for chow group and for HP group, therefore these control values were pooled.

†Doses of naltrexone are expressed in mg/kg of body weight.

‡Food intakes are expressed in kJoules/rat/3 hours of darkness and in kJoules/kg of body weight/3 hours of darkness (mean ± SEM).

*Statistical Analysis*

The parameter studied was the energy intake after administration of naltrexone compared to intake after administration of NaCl, expressed in kJoules/animal/first 3 hours of darkness and in kJoules/kg/of body weight/first 3 hours of darkness. The data were analyzed using the variance analysis; F values reported in the text correspond to energy intake per animals.

## RESULTS

The food intake of HP rats injected with NaCl is significantly higher than that of control NaCl, $F=84.6$; $p<0.05$. Naltrexone does not modify the caloric intake of control rats either at 0.5 mg or at 2.5 mg. However, in the HP rats, naltrexone results in a highly significant decrease in food intake: the decrease with 0.5 mg is from 140.8 to 67.9 kJoule/animal, $F=55.85$; $p<0.05$, and with 2.5 mg is from 140.8 to 36.0, $F=115.48$; $p<0.05$. The intake with 2.5 mg is significantly lower than that obtained with 0.5 mg, $F=10.71$; $p<0.05$. With both doses the food intake decreases so dramatically that it is no longer significantly different from that of controls. Thus naltrexone suppresses dietary induced hyperphagia.

## DISCUSSION

*Control Rats*

In this experiment the tested drug was naltrexone rather than the usual opiate antagonist naloxone, because the duration of its effect is twice as long [6]. We did not find any reports in the literature about the effects of naltrexone on eating behavior; however there are several studies on those of naloxone. At a 0.25 mg/kg of body weight naloxone does not modify food itnake in normal rats [11]; at a 1 mg/kg dose it does not suppress the operant behavior learned in order to obtain food in chronically food restricted rats [4]. Results of a high dose of 10 mg are controversial—Brands [1] found a decrease in food intake and Stapleton [20] did not find any effect—but such a dose provokes sickness [12], thus making difficult to discriminate a possible specific effect from the others. As a whole, it appears that endogenous opiates have little or no involvement in the control of food intake in normal rats fed with laboratory chow.

*HP Rats*

Hyperphagia is not due to an inability of the rat to recognize the amount of energy contained in the various items, since it is classically demonstrated that the rat adapts its food intake accurately whether the animal is given concentrated or diluted food as well as when it is fed with a choice of elemental nutrients. On the other hand, effects of naltrexone are not that of an anorectic agent since only hyperphagia has been suppressed. Thus, it can be hypothesized that the $\beta$-endorphin system may constitute a trigger of HP hyperphagia independent from the hunger-satiation loop. This hypothesis is consistent with $\beta$-endorphin's role in two other experimental situations which also result in hyperphagia: stress and fast.

A stress like tail-pinching induces a range of inappropriate responses such as motor hyperactivity, sexual hyperactivity or hyperphagia [17]; the level of $\beta$-endorphin is increased in plasma [15] and in brain [10].

A 24 hour fast increases the algesic threshold and is followed by a compensatory overeating. Naloxone tends to normalize the threshold [9] and to reduce the overeating [2,7].

Thus in the rat the endogenous opiate system is not indispensable for an adequate control of food intake in a stress-shielded environment including the availability of monotonous food; however, it is involved in hyperphagia provoked by either stressors or overabundance of palatable foods, when these events are unavoidable, whatever the behavior of the rat.

Both these situations are prevalent in modern societies. Thus it could be of interest to test whether human hyperphagia can also be suppressed by antagonists of endogenous opiates.

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