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Stress and Sucrose Hyperphagia: Role of Endogenous Opiates

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BERTIERE, M. C., T. M. SY, F. BAIGTS, A. MANDENOFF AND M. APFELBAUM. *Stress and sucrose hyperphagia: Role of endogenous opiates.* PHARMACOL BIOCHEM BEHAV 20(5) 675–679, 1984.—Two experimental situations induce hyperphagia in the rat: the cafeteria model and the tail-pinching model. In non-deprived rats which are offered for one hour a choice of 3 liquid cafeteria items in addition to ordinary chow and water, mild tail-pinching results in a preferential sucrose hyperphagia; naltrexone (2.5 mg/kg IP) suppresses this stress-induced hyperphagia; β-endorphin (3 μg ICV) has the same effect. This apparent discrepancy is discussed: the antagonist may suppress the hyperphagia because it suppresses the reward provoked by the sucrose, the agonist because it makes it unnecessary.

Endogenous opiates Food intake Highly palatable diet Stress Rat

COMMON sense as well as clinical observation lead to the consensus that some forms of eating behavior which do not imply any feeling of hunger, such as nibbling, especially sweets, can be related to the non specific stressors of every day life. This relationship cannot be objectively studied in man, since these two features—nibbling and stressors—are not easily quantified. In the rat, however, two experimental models can be considered relevant to these human situations:—in the cafeteria model, animals are offered a large choice of highly palatable foods, and an hyperphagia occurs [28,30]—in the tail-pinching model, animals are submitted to a moderate unavoidable stressor [3] and they react by overeating whatever food is available (laboratory chow [3], sweetened milk [13], sweetened water [13], or chocolate cookies [26]). In both these models, it has been suggested that the endogenous opiates are involved, as shown by experiments using antagonists and agonists.

Naloxone, the best documented opiate antagonist, when injected to non stressed rats, decreases intake of chow [9], sweetened water [18], sweetened milk [21], or water sweetened with saccharin [23]. When a rat is given a choice (chow and chocolate chips), naloxone decreases the intake of chow and totally suppresses consumption of chips [10]. Using naltrexone, another albeit long-acting opiate antagonist, we have shown that an acute injection in cafeteria fed rats results in a disappearance of hyperphagia for a few hours, corresponding to the drug's bio-availability [5]; the chronic administration of naloxone zinc tannate, a salt characterized by a slow release of naloxone over several days, prevents the occurrence of cafeteria-induced obesity [11]. With tail-pinching only naloxone has been investigated: two studies [14,26] concluded that it reduces stress-induced hyperphagia, but this result was not confirmed in a third work [4] (see discussion).

Since antagonists are reported to decrease food intake and to suppress or reduce both stress and cafeteria-induced hyperphagias, it might be expected that agonists would have opposite effects. In fact morphine injected at small doses peripherally [29] or intraventricularly [6] increases the consumption of food by rats fed ad lib; however injected at high doses, it has the unexpected effect of a reduction in intake. Dynorphin injected intraventricularly at small doses enhances food intake [16] as does d-ala^2-methionine-enkephalin [6]. β-Endorphin does not affect feeding when injected peripherally [22] but it seems that it does not cross the blood-brain barrier (or fails to cross it in an intact form or in amounts sufficient to exert centrally mediated effects) since intravenous injections exert no analgesic action [19]. When β-endorphin is injected in the ventromedial hypothalamic nucleus, it increases the intake of ordinary chow [20]; in the lateral ventricle, it increases the intake of chow (in a dose dependent manner) [32] and of sweetened milk (but only at one dose) [27]. In the cafeteria model, there are no data concerning the effects of opiate agonists. In the tail-pinching model, injections of d-ala^2-methionine-enkephalin reestablish the stress-induced hyperphagia previously suppressed by anorectic factors, such as bombesin, CCK, haloperidol, histidyl-proline-diketopiperazine [15,17].

Thus, data on the relationship between food intake and opiate agonists and antagonists are not fully consistent. These discrepancies could be related to experimental condi-

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tions: the strains studied, the nutritional status, the type of food given, the drug and the dose used. In the present work, we have combined the two experimental models (cafeteria and tail-pinching) and the action of an opiate antagonist and an agonist in a series of homogeneous experiments.

METHOD

Animals

Subjects in all experiments were naive male Wistar rats, weighing about 200 g. They were housed individually at 24°C with lights on between 7.30 a.m. and 7.30 p.m.

Tail-Pinching

Mild tail-pinch was administered as described by Antelman [3] with a plastic-tipped hand-held hemostat. Each session lasted one hour, each rat being pinched three times for two minutes, at 20 min intervals. Twenty-one rats were selected as "good responders" to tail-pinching (a good responder being defined as an animal which reacted to the pinch with permanent or quasi permanent licking of liquid diet. Two trials of one hour were performed for this selection).

Liquid Cafeteria Diet

Between two test sessions, animals had free access to laboratory chow and water. During the sessions, a choice of food was offered in plastic feeding bottles. The choice included: whole milk (2.5 Kilojoules/ml) (Kj/ml), partially skimmed milk containing 20 g of fat per liter (/l) and sweetened with 150 g of sucrose/l, (4.6 Kj/ml), water sweetened with 300 g of sucrose/l (5.01 Kj/ml), laboratory chow (14.25 Kj/g), and plain water. Items were measured or weighed before and after each session, i.e., during the 1 hour experiment including 3 T.P periods and intervals.

Experimental Schedule

All tests were conducted toward the beginning of the dark period, from 8.30 to 9.30 p.m. when rats, if undisturbed, are actively eating. The sessions (with and without pinch, with and without drug) took place in higher individual cages (measuring 30 cm in diameter and 40 cm in height); one can consider that the new environment does not bias the results since the study followed a cross-over design.

Experiment 1: tail-pinch and naltrexone. Four test sessions (one per day) were performed on 12 "good responders," at an interval of 2 days. Each rat was pinched during 2 sessions out of 4 but received half an hour before each session an intraperitoneal (IP) injection of 1 ml/kg of body weight of 9‰ NaCl solution or of 2.5 mg/kg of naltrexone (it was previously shown that this dose of 2.5 mg/kg in the same strain does not modify the ingestive behavior when only laboratory chow and water are available [5]). The experiment was designed according to a latin square, in such a way that each rat served as its own control for the 2 parameters: pinch and naltrexone. Thus 4 situations are defined:—"Basal": no tail-pinch + NaCl injection.—"Naltrexone": no tail-pinch + naltrexone injection.—"T.P": tail-pinch + NaCl injection.—"T.P + naltrexone": tail-pinch + naltrexone injection.

Experiment 2: tail-pinching and β-endorphin. Nine "good responders" were anaesthetized with Nembutal (IP 30 mg/kg) and stainless steel cannula (made from a hypodermic needle, 0.6 mm diam, 17 mm long) was chronically implanted in the ventral third ventricle using the stereotaxic coordinates of Albe-Fessard's atlas [1], (from Lambda anterior=+6, depth=−7.5, lateral=0). The implantation in the 3rd ventricle was checked by the pulsations of the cerebrospinal fluid inside the cannula and was further confirmed at the end of the experiment by systematic examination of histological sections of the brain. The cannula was secured to the skull with dental cement, and protected by a soft polyethylene cap. The animals were allowed to recover from surgery for over a week, until they returned to their preoperative weight.

Four test sessions were performed at an interval of 2 days: each rat was pinched during 2 sessions out of 4, but received half an hour before each session an intracerebroventricular (ICV) injection of 10 μl of 9‰ NaCl solution or of 3 μg of human β-endorphin (Beckman Geneve), in 10 μl of 9‰ NaCl solution. The dose-response curve of ICV β-endorphin on food intake was previously tested in rats synchronized on a 3 hour a day meal schedule; when only laboratory chow and water was available, doses of 1, 3, 5 and 10 μg had not modified the size of the meal. Since cases of catalepsy were observed for doses starting from 5 μg, the maximal tolerable dose of 3 μg was retained for this experiment. The experiment was also designed according to a latin square; four situations are defined as in Experiment 1.

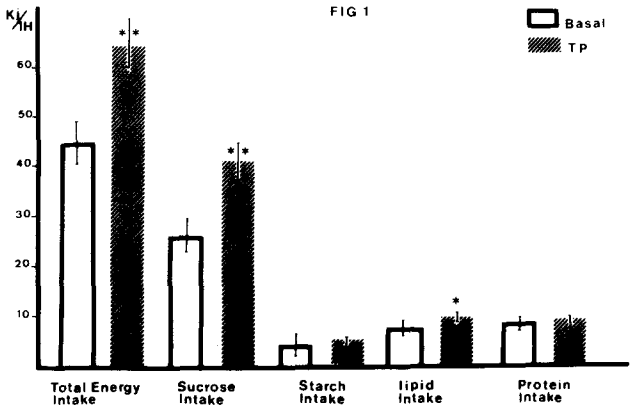

FIG. 1. Effect of tail-pinch on food intake of liquid cafeteria-fed-rats. Intakes of different items are expressed in Kilojoules/1 hour, mean±SEM; data are analyzed with paired *t*-test. $*p<0.05$; $**p<0.01$ (vs. basal).

Statistical Tests

Data concerning the effect of tail-pinch on food intake (Fig. 1) were analyzed using *t*-paired test; all other data were evaluated by analysis of variance.

RESULTS

Effects of Tail-Pinching and Naltrexone on Liquid Cafeteria Fed Rats

Table 1 shows the effects of tail-pinch, naltrexone, and tail-pinch + naltrexone on the intake of each item presented. Tail-pinch results in an increase of total energy intake from 44.8 to 63.9 Kilojoules (Kj) ($p<0.01$). Intakes of sweetened milk and sweetened water are increased; intakes of ordinary

TABLE 1

TAIL-PINCH, NALTREXONE AND TAIL-PINCH + NALTREXONE IN CAFETERIA FED-RATS: INTAKES OF DIFFERENT ITEMS ARE EXPRESSED IN ml/1 hour, OR grams/1 hour, MEAN ± SEM; DATA ARE TESTED WITH ANALYSIS OF VARIANCE

	Basal Intake (BI)	BI. vs. T.P	Tail-Pinch (T.P)	p T.P vs. T.P + N	Tail-Pinch + Naltrexone (T.P + N)	p T.P +N vs. N	Naltrexone (N)
Sweetened Milk (ml)	5 ± 1.2	$p<0.05$	7.6 ± 0.8	$p<0.01$	2.8 ± 0.3	NS	3 ± 0.7
Sweetened Water (ml)	0.8 ± 0.2	$p<0.01$	3 ± 0.7	$p<0.01$	0.7 ± 0.3	NS	0.6 ± 0.2
Regular Milk (ml)	2.8 ± 1	NS	2.7 ± 0.3	$p<0.05$	1 ± 0.3	NS	0.7 ± 0.2
Water (ml)	4.8 ± 1.1	NS	5 ± 0.7	$p<0.05$	2.3 ± 1.8	NS	2.1 ± 0.3
Total Water (ml)	13.3 ± 1.6	$p<0.005$	18.4 ± 1.7	$p<0.001$	6.9 ± 0.8	NS	6.5 ± 0.9
Chow (g)	0.79 ± 0.3	NS	0.74 ± 0.1	$p<0.01$	0.24 ± 0.1	NS	0.18 ± 0.1

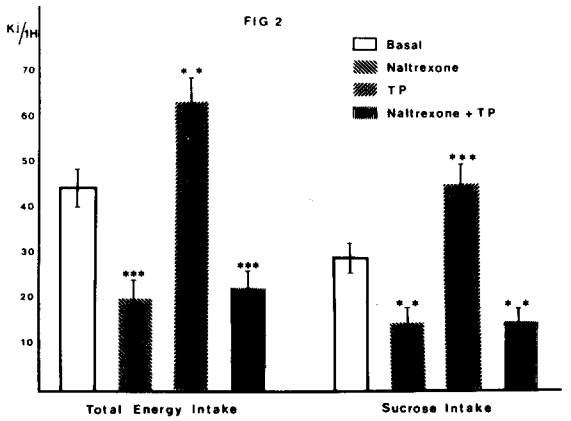

FIG. 2. Effect of naltrexone and tail-pinch on food intake of liquid cafeteria-fed-rats. Intakes of different items are expressed in Kilojoules/1 hour, mean±SEM; data are tested with analysis of variance. $^{**}p<0.01$; $^{***}p<0.001$ (vs. basal).

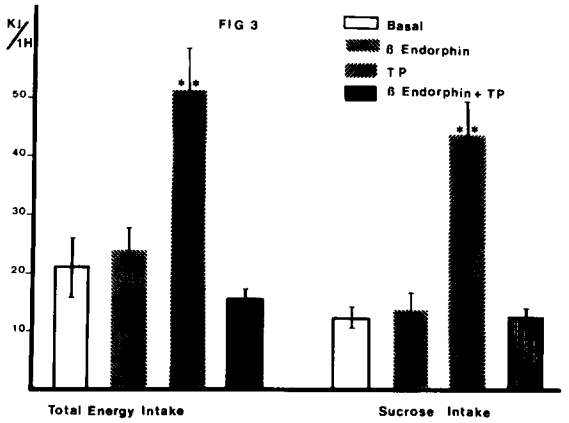

FIG. 3. Effect of β-endorphin and tail-pinch on food intake of liquid cafeteria-fed-rats. Intakes of different items are expressed in Kilojoules/1 hour, mean±SEM; data are tested with analysis of variance. $^{**}p<0.01$ (vs. basal).

chow and regular milk, already eaten in small amount in the cafeteria situation without stress, are not significantly modified. Total water intake (defined as the sum of pure water + volume of the three liquid formulas, considering that the change in volume introduced by dissolved solids is trivial), is increased, due exclusively to the over-consumption of the two sweetened solutions.

Since the sessions took place during night time, precise collection of behavioral data was rendered difficult; as far as semi-obscurity allowed it, the observation was made that during the tail-pinch itself (the 2 minute pinches) all animals ate (that is why they were selected as good responders) and that this instantaneous intake was mainly of sucrose solutions.

Figure 1 represents the effect of tail-pinch on food intake expressed in term of nutrients: protein and starch intakes remain unchanged. Lipid intake is moderately enhanced (by 27%), related exclusively to sweetened milk. The main change is in sucrose intake (+55.7%).

Figure 2 shows the comparison of energy and sucrose intakes measured in the 4 experimental situations. Injection of naltrexone reduces the energy intake from 44.8 to 20.7 Kj ($p<0.001$) by diminishing consumption of all items (as shown in the table). Moreover it suppresses the tail-pinch-induced hyperphagia: there is no difference in the cafeteria intake of pinched vs. non-pinched animals treated with naltrexone, either in terms of energy or in terms of amount of food consumed; in other words the effect of pinch is completely prevented. Sucrose is the main nutrient affected in this experiment. Tail-pinch increases sucrose intake from 25.6 to 40.8 Kj, and naltrexone reduces it to 15.9 Kj, which is not different from the 14.9 Kj obtained with naltrexone alone (without pinch).

Effects of β-Endorphin and Tail-Pinching on Food Intake of Liquid Cafeteria Fed Rats

An intracerebroventricular injection of β-endorphin does

not modify the energy intake or the sucrose preference of control rats (Fig. 3). Combined with cafeteria choice and tail-pinch however, this injection suppresses tail-pinch-induced hyperphagia. Energy and sucrose intakes of the control rats (21.1 Kj and 16.3 Kj respectively) and those of both the "β-endorphin" rats (23.4 Kj and 17.6 Kj) and the "T.P−β-endorphin" rats (15.2 Kj and 12.7 Kj) are not significantly different. Neither β-endorphin nor tail-pinching affect water intake ("basal" intake: 3.2 ml, with β-endorphin: 2.6 ml, with tail-pinch: 3.3 ml and 2.5 ml for T.P+β-endorphin).

DISCUSSION

A rat submitted to an unavoidable stressor and offered a choice between several foods, reacts by eating more sweet foods. Both naltrexone and β-endorphin were shown to suppress this hyperphagia.

Tail-Pinching and Preferential Intake of Sucrose

When an acute stressor as tail-pinch is applied to rats which are offered a choice of foods: they do not modify their intake of pure water and whole milk; they increase their intake of sweetened formulas, both sucrose solution and sweetened milk; the increase in intake of total water is entirely related to the amount of water contained in these sweetened solutions. Therefore tail-pinching acts primarily on the food intake, especially sucrose intake, and not on the water intake.

It was reported [33] that rats submitted to a severe stress—12 hour food and water deprivation + 10 minutes swimming in cold water—reacted, when only one kind of diet was offered, by a bigger intake of hyperlipidic diet than of hyperproteic or hyperglucidic diet (it seems that the hyperglucidic diet included no sucrose but starch).

Differences between this experiment and our experiment are numerous: nature of stress, timing of experiment, absence of choice, carbohydrates as starch. It was recently reported [7] that each of these factors can modify data on self-selection. For instance, the choice of food by a rat placed in a situation of acute stressor is obviously quite different from that of an undisturbed rat: in the stress situation, the rat selects sucrose preferentially; in the cafeteria situation it selects a hyperlipidic diet [12]. Both these behaviors and the discrepancy between them, seem to be relevant to human situations: the overabundance of palatable foods in Western countries results in a high lipid intake, and stresssors often induce a behavior of nibbling, especially sweets.

Suppression of Stress-Induced Sucrose Hyperphagia by Naltrexone in Liquid Cafeteria Fed-Rats

Antelman [3] demonstrated that tail-pinching induces hyperphagia in rats fed with ordinary laboratory chow; Morley and Levine [14] confirmed this observation as did Lowy using chocolate cookies [26] and they showed that this hyperphagia was suppressed by naloxone [14,26]. But Antelman failed to confirm this latter result [4] and suggested that it could be due to a lowering of the nociceptive threshold by naloxone, in such a way that pressures which ordinarily are compatible with eating during tail-pinching may become painful and produce gnawing without ingestion of solid food, and that the results obtained by Morley and Levine and Lowy, could be related to a confusion between gnawing and eating. We attempted to circumvent this controversy by using a liquid cafeteria diet in which licking itself necessarily provokes ingestion.

At this point, a new question arises: is the effect of naltrexone on feeding related to its effect on drinking or is it an independant one?

Naltrexone alone decreases pure water intake by 56%, which is consistent with previous studies [8, 13, 18]. Tail-pinch does not modify pure water intake, and tail-pinch + naltrexone results in a decrease not different from that provoked by naltrexone alone. Tail-pinch increases the consumption of both sucrose solution and sweetened milk; the T.P + naltrexone pattern suppresses entirely this increase in such a way that naltrexone totally inhibits the effect of tail-pinch. Thus this double comparison allows to conclude that the preference for sucrose provoked by the T.P is suppressed by naltrexone independently of the effect of naltrexone on drinking.

Suppression of Stress-Induced Sucrose Hyperphagia by β-Endorphin in Liquid Cafeteria-Fed-Rats

In control rats, ICV injection of 3 μg of β-endorphin modified neither energy nor sucrose intake. It has been reported that β-endorphin does increase the intake of ordinary chow [20,32]. However, when the injection is performed in the ventromedial hypothalamic nucleus [20] there is a possible overlap between the effect of the localization and the effect of the drug itself. Concerning injections in the lateral ventricle, no details on the technical conditions have been reported [32]. Our results are not inconsistent with those of Mac Kay *et al.* [27] who found that an intraventricular injection of β-endorphin enhanced the intake of sweetened milk in starved animals, but only at a small dose of 200 ng; lower or higher doses were ineffective; Mac Kay did not test the dose of 3 μg and we did not test doses below 1 μg.

Nevertheless, while a 3 μg injection of β-endorphin has no effect on the undisturbed rats, it has a clearcut effect when they are stressed: the sucrose hyperphagia induced by tail-pinching is totally suppressed by β-endorphin. The question arises as to whether this effect is specific or whether it is relayed through side effect(s) such as hyperglycemia or analgesia.

It is known that stressors induce hyperglycemia [2] and that hyperglycemia (when glucose levels rise above 150 mg/dl) can suppress the tail-pinch-induced eating [24]. It was reported in severely hyperglycemic mice (with streptozotocine-induced diabetes) that the hyperglycemia results in a decreased response to morphine [31] and in an increased response to naloxone [25]. In our model, two parameters may induce hyperglycemia: the stressor and the cafeteria diet.

In our experimental series blood glucose levels were not measured (since animals participated in several tests and blood puncture would induce another stress which could constitute a bias). However in an independent group of 18 Wistar rats, blood glucose was measured after decapitation immediately at the end of the experiment, performed in the same conditions as in the main studies. Blood glucose was (mean±SEM): 134±1 mg/dl in a subgroup (n=6) which received the cafeteria diet, and 137±3 in a subgroup (n=6) which was submitted to T.P in presence of cafeteria diet; in a third subgroup receiving only lab chow and water, glycemia was 129±2 mg/dl. Thus increases in blood glucose induced by cafeteria diet and stress are trivial and the hyperglycemia hypothesis receives little support.

β-Endorphin has analgesic properties [19], while stress can induce hyperphagia, presumably because of the unpleasant sensation it produces. One might hypothesize that β-endorphin enhances the nociceptive threshold and thus suppresses hyperphagia. In that case, naltrexone would be expected to increase hyperphagia; this does not occur, since the food intake of "naltrexone-rats" is not different from that of "T.P +naltrexone" animals.

Therefore another explanation is needed since an opiate agonist and an opiate antagonist both result in the same disappearance of stress-induced sucrose hyperphagia. Our hypothesis is that the secretion of hypoalgesic endogenous opiates by pinch-stress may be insufficient to protect the animal against the stimulation. In this case, the ingestion of sweets may be particularly adaptative since a possible secretion of endorphins provoked by sucrose is diverted from the pleasure of gluttony to be used as an additional hypoalgesic treatment; thus the injection of an opiate antagonist would suppress gluttony because it is no longer efficient, while the injection of an agonist would also suppress it, because it is no longer necessary.

In conclusion, when a rat is placed in a situation which experimentally caricatures our every day life—a large choice of palatable foods and small, unavoidable and repeated stress—it reacts in the same way many of us do: it nibbles on sucrose rich foods. Injections of an opiate agonist or an opiate antagonist both result in a total suppression of this sucrose hyperphagia. This does not imply that the endogenous opiate system is necessarily active in the control of food intake but it certainly suggests that it is involved in what are usually designated as eating disorders.

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