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Negative Allesthesia and Decreased Endogenous Opiate System Activity in Anorexia Nervosa

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MELCHIOR, J.-C., D. RIGAUD, N. COLAS-LINHART, R. ROZEN, M. FANTINO AND M. APFELBAUM. *Negative allesthesia and decreased endogenous opiate system activity in anorexia nervosa.* PHARMACOL BIOCHEM BEHAV **35**(4) 885–888, 1990.—The combined effects of an intragastric load of glucose compared to water and of naltrexone compared to placebo were tested on preference for sucrose in six anorectic patients. While in normal subjects, glucose-induced negative allesthesia is known to disappear upon loss of weight, it persisted in anorexia nervosa (AN) despite a major weight loss; furthermore, in contrast with its effects in normoponderal subjects, naltrexone at the dose of 25 mg did not decrease the preference for sucrose nor did it enhance glucose-induced allesthesia. Basal plasma beta endorphin level determined by radioimmunoassay was higher in AN than in normal subjects (75 ± 6.1 pmoles/l vs. 13 ± 3.8 pmoles/l) ($p<0.001$). It is suggested that a decrease in endogenous system opiate activity might be associated with food refusal and body weight loss in anorexia nervosa.

Negative allesthesia Opiate system Anorexia nervosa

A gastric caloric load of glucose reduces the pleasure related to alimentary stimuli and thereby has a negative effect on food intake (4,5). This impact of a strictly caloric intake on the hedonic response was first described by Cabanac, and was termed negative allesthesia. Aside from this acute effect, the energetic status of the subjects seems to modulate some mechanism of food intake control in the long term, since weight loss, even moderate (3 to 5 kg), leads to the disappearance of negative allesthesia both in normal subjects and in obese patients during slimming (4,5).

The return to initial body weight reestablishes allesthesia (4). In the short-term regulation of food intake, the endogenous opiate system (EOS) might be involved since we have shown in normal subjects that naltrexone, an opiate antagonist, at the dose of 60 mg, induced a stronger negative allesthesia than glucose itself (8), and, at a lower dose of 25 mg, was able to potentiate the negative allesthesia induced by glucose (16).

Little is known of the regulation of food intake in eating disorders and especially in anorexia nervosa (AN). This condition is characterized by an important decrease in food intake which induces a major weight loss greater than 20% of ideal body weight (9). In this condition, two factors could alter the phenomenon of glucose-induced negative allesthesia for sucrose: in the short term, the EOS since several hypothalamic-pituitary dysfunctions including abnormalities in the EOS (11,15) have been described in AN; in the long term, the major body weight loss which is a constant feature.

Thus, the aim of the present study was to determine the relation between allesthesia and body weight in underweight anorectic patients and to assess the sensitivity of the opiate system by testing the effect of 25 mg of naltrexone on allesthesia in AN.

METHOD

Subjects

Six patients who fulfilled the diagnostic criteria for anorexia nervosa (1) were hospitalized in order to be refed. All patients were only food restricted and did not vomit, and no change in body weight was reported during the month preceding hospitalization. The mean age was 21 years (range: 15–29) and the body weight at the beginning of the study was 35.3 ± 5.9 kg (mean $\pm$ SD). The protocol was approved by the Ethics Committee for Human Investigations and informed consent was obtained from each subject.

Gustatory Stimuli

The affective component of the subjects' sensations was

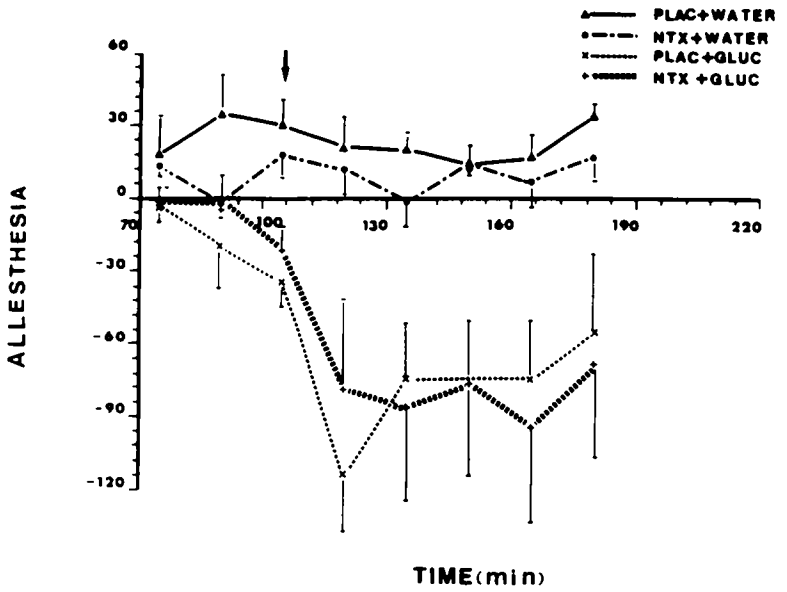

FIG. 1. Allesthesia: results are expressed as mean ± SEM. Glucose versus placebo or naltrexone: $p<0.05$. Naltrexone plus glucose versus placebo or naltrexone: $p<0.05$.

explored in ten successive series of tests. Each series was composed of five gustatory stimuli: these sweet tests were 25 ml sucrose solutions from 0.06 M to 1 M. Gustatory stimuli were not swallowed, but spit out after being tested for 20 seconds, after which the subjects rinsed their mouths with tepid tap water. Each series of five stimuli was tested within fifteen minutes. Stimuli were presented in a random order which changed from series to series and from subject to subject.

Hedonic Rating

The subjects evaluated their hedonic response immediately after receiving a stimulus by placing a stroke on a vertical visual analogical scale of 100 mm. This scale was anchored at each end with "maximal pleasure" at the top, "maximal displeasure" at the bottom and "indifference" in the middle. Hedonic response was calculated as the algebraic length between the stroke and the middle of the scale.

Hunger Rating

Another visual analogical scale measuring hunger sensation was used at 15-min intervals, before, between and after each series of stimuli. Moreover, at 120 min, hunger sensation was rated immediately before and after a gastric load (120 min) resulting in double ratings at this time.

Experimental Procedure

Subjects underwent four similar experimental sessions defined by the tablet ingested (placebo or naltrexone) and the gastric load (glucose or water). Sessions took place between 9:00 and 12:00 a.m. after an overnight fast. A naso-gastric tube was placed at the beginning of the hospitalization, but enteral nutrition was started only after this study.

All subjects first received two identical series of 5 stimuli: the first series was designed to help them learn to score the stimuli and the responses obtained were disregarded. The second series provided baseline reference values. At the end of this second series, the subjects ingested either 25 mg of naltrexone or placebo in a double-blind pattern. After a 45-min delay to allow intestinal absorption of the drug, three series of stimuli were performed to evaluate the action of naltrexone in fasted subjects. The subjects then received, still in double-blind, a 200 ml intragastric load of water or of a 2.8 M glucose solution (100 g). The five series of stimuli were then again successively presented at 15-min intervals. Each experimental session was performed within 195 min. No side effects were observed. Subjects participated in four experimental sessions over a period of ten days with varied cross-over administrations of naltrexone and glucose: placebo with water load, placebo with glucose load, naltrexone with water load and naltrexone with glucose load.

Allesthesia: Analysis of Results

Allesthesia was assessed, according to Cabanac *et al.* (4,7), as the algebraic difference between the total of the hedonic ratings for the five stimuli of a series tested either after or before administration of a placebo, or of naltrexone together with either water or glucose. Results were expressed as means ± SEM of individual allesthesia in the fourteen subjects, for each series of stimuli tested after naltrexone or placebo intake and after the gastric loads.

Statistical Analysis

All results are expressed as mean ± SEM. In each group, means of allesthesia and hunger ratings were compared by nonparametric analysis of variance.

Intergroup comparison. The area under the curve for allesthesia and hunger were compared between different sessions with Wilcoxon's matched pairs signed ranks tests.

Plasma Beta Endorphin Determination

Morning plasma beta endorphin concentration was determined in the six patients at the beginning of the hospitalisation and compared with those of twenty normal weight control subjects. Blood samples were drawn at 8:00 a.m. after an overnight fast.

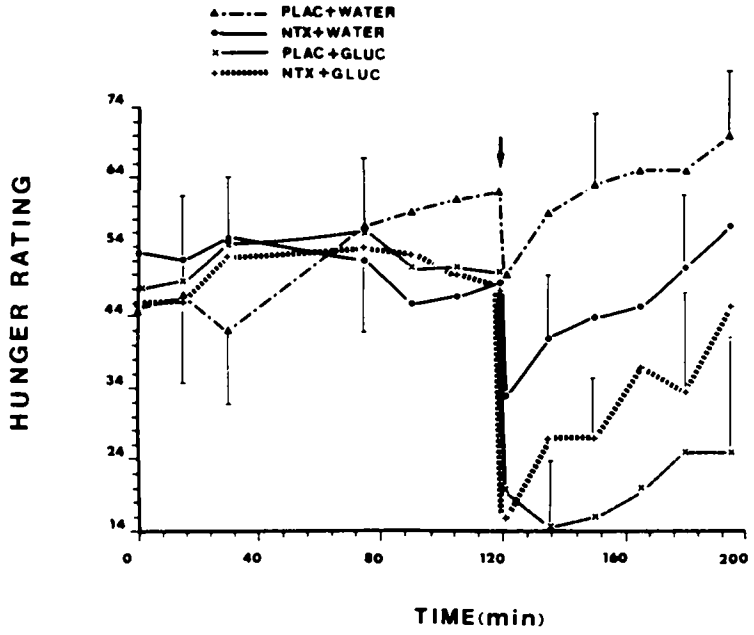

FIG. 2. Hunger rating: results are expressed as mean ± SEM. Decrease in self rating of hunger after glucose load, both with and without naltrexone versus water load, as well as with placebo or naltrexone ($p<0.05$).

After acidification, the plasma was separated and frozen at −80°C until assayed. Plasma concentrations were determined by a radioimmunoassay technique recently developed in our laboratory (8). The method makes use of an antibody which reacts 100% with human beta endorphin, but demonstrates less than 20% cross reactivity with beta lipotropin. The assay is sensitive (limit of detection = 5 pmoles/l) and reproducible (the intra- and interassay coefficients of variations are 5 and 6% respectively).

RESULTS

The time course of allesthesia is presented in Fig. 1. When the subjects received the placebo and the gastric water load, no change was observed in the affective response. In the glucose session (placebo and gastric glucose load) a clear decrease in the affective response, i.e., a negative allesthesia, was observed ($p<0.05$). Naltrexone, at the dose of 25 mg, had no effect on the absence of affective response given with the gastric water load, nor did it alter the negative allesthesia induced by glucose (no statistical difference between the 2 sessions).

The time course of the subjects' self ratings of hunger is presented in Fig. 2. In tests with water, after an early and transient, but nonsignificant decrease, the hunger ratings slowly increased with time (nonsignificant) whether placebo or naltrexone was given. After the glucose load, the decrease in hunger ratings was statistically significant both with placebo ($p<0.05$) and with naltrexone ($p<0.05$) with significant difference between placebo and naltrexone. Basal concentrations of beta endorphin were significantly higher in the anorectic patients (75 ± 6.1 pmoles/l) than in the control group (13 ± 3.8 pmoles/l) ($p<0.001$) (Fig. 3).

DISCUSSION

In this study, the phenomenon of glucose-induced allesthesia described in normal subjects was found to persist in AN despite a major weight loss; however, in contrast to what has been observed in normal subjects, naltrexone did not alter the preference for sucrose nor did it enhance glucose-induced allesthesia.

In normal subjects, a gastric glucose load induces a decrease in

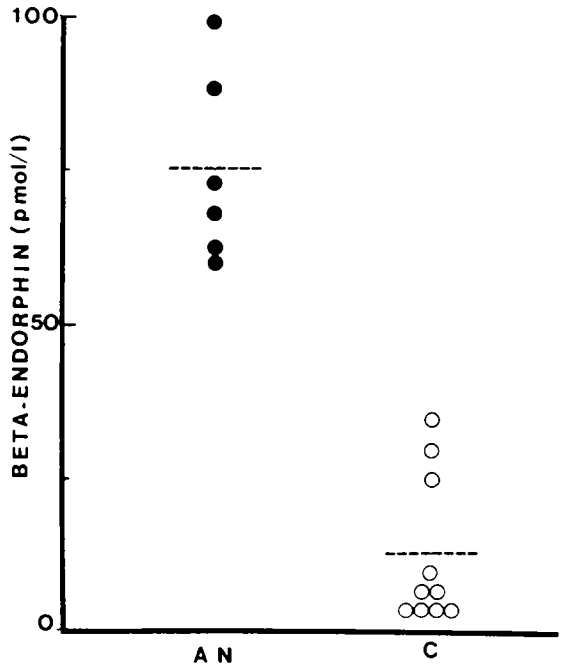

FIG. 3. Basal plasma level of beta endorphin in 6 anorectic patients compared with 20 normal control subjects ($p<0.001$). ●: Anorectic patients; ○: Control subjects. Dotted line indicates the mean value of the group.

the hedonic ratings for sucrose solutions (4). This effect is dose related and is maximal for a 100 g load (7). In the anorectic patients of the present study, despite a huge weight loss (over 10 kg), negative allesthesia induced by glucose was on the same order to that of normal subjects (4). This was not expected, since Cabanac *et al.* had evidenced the disappearance of this physiological phenomenon after a moderate weight loss (10%) in normal or in obese subjects (4). It had been hypothesised that the disappearance of the negative allesthesia after slimming participated in reestablishing body weight (4) by decreasing (or abolishing) the negative feedback exerted by food intake on the pleasure related to gustative stimuli. A further argument for this hypothesis was that the return to regular body weight caused the reappearance of negative allesthesia (4). The mechanism which allows negative allesthesia to persist in AN after weight loss remains unclear. The hypothesis that 100 g glucose was relatively a bigger load in anorectic patients than in normal subjects is unlikely since the intensity of negative allesthesia is not related to blood glucose concentration, but seems to be mainly dependent on gastroduodenal glucose concentrations (6). In fact, in normal subjects, a 100 g glucose load induces a maximal negative allesthesia response for glucose (7). Furthermore, while the intensity of glucose-induced negative allesthesia is known to be of the same amplitude in obese than in normal subjects (4), it was much greater in AN, reaching, with glucose alone, a degree similar to that observed in normal subjects after a naltrexone potentiated glucose ingestion (16).

Moreover, in six anorectic patients, 25 mg of naltrexone (a large dose considering their body weight) did not depress the hedonic preference for sweetened solutions nor did it enhance glucose-induced negative allesthesia, suggesting that the maximal effect was already reached with glucose alone in contrast to what we have described in normal subjects (8,16). The persistence of negative allesthesia combined with the inefficacy of naltrexone provides a strong argument in favor of the hypothesis of a decreased EOS activity in underweight anorectic patients. Abnormalities in EOS have been previously reported in several eating disorders including obesity and bulimia nervosa (2, 3, 11, 12, 14, 21). However, the basal plasma level of beta endorphin was strikingly higher in the anorectic group than in the control group as also reported by Müller *et al.* (19). By contrast, Germer *et al.* did not find any difference in cerebrospinal fluid beta endorphin immunoreactivity between anorectic and normal subjects (13), while Kaye *et al.* reported a decrease (15). The latter hypothesized that reduced central beta endorphin concentrations could be relevant to the symptom of food refusal in AN. Since opiate agonists are known to stimulate food intake (18,20), the association of food refusal with high plasma levels of beta endorphin in AN implies an impairment in the activity of the EOS, although it has been suggested that central (CSF) and peripheral (plasma) concentration of beta endorphin might sometimes be dissociated (22). Further studies are needed to determine whether these impaired physiological mechanisms related to eating are primary or secondary to malnutrition.

In summary, the present study suggests that in underweight anorectic patients, the persistence of negative allesthesia induced by glucose contributes to reset and/or to maintain the body weight at a lower level than in normal subjects. The mechanisms of this disregulation are unclear, but may involve a decrease of the EOS activity.

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