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Effects of a Low Dose of Naltrexone on Glucose-Induced Allesthesia and Hunger in Humans

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MELCHIOR, J.-C., M. FANTINO, R. ROZEN, L. IGOIN, D. RIGAUD AND M. APFELBAUM. *Effects of a low dose of naltrexone on glucose-induced allesthesia and hunger in humans.* PHARMACOL BIOCHEM BEHAV 32(1) 117–121, 1989.—In order to study the effects of a low dose of the opioid antagonist naltrexone on ingestive behavior for sucrose in humans, preference for sucrose solutions and feelings of hunger were scored on visual analogical scale by 14 healthy subjects with or without naltrexone. Effects of intragastric glucose load or water, and naltrexone (25 mg) or placebo were tested. At this low dose, naltrexone alone had a slight effect on allesthesia, and it produced a strong potentiation of glucose-induced allesthesia.

Allesthesia Sweet preference Hunger Human Opioid system Ingestive behavior

THE opioid system is involved in the control of food intake in animals and humans as indicated by the action of both opiate agonists and antagonists (1, 7, 24, 26, 28, 29). In animals, high doses of exogenous opiates depress food intake by their general depressant action (18,20), but administration at low doses increases food intake (25,30).

Naloxone and naltrexone, predominantly mu antagonists, abolish the hyperphagic effects of endogenous opiates (27) and also abolish or decrease other nutritionally- or pharmacologically-induced hyperphagias (1, 3, 7, 14, 17, 21, 26, 28, 31). In contrast to these clear-cut results, the reported effects of opiate antagonists on food intake in humans are confusing: Atkinson *et al.* (2), Maggio *et al.* (22) and Malcolm *et al.* (23) did not find any long-term effect of naltrexone in obese patients. However, Cohen *et al.* (13) and Trenchard and Silverstone (32) reported a decrease in food intake during a meal immediately after naloxone had been given to normal subjects. But, the spontaneous ingestive behavior in humans is frequently modified when it is monitored.

A different approach, measuring not the food intake itself but the hedonic rating of food, was proposed by Cabanac (8–10, 15). Previously we used it to test the effects of naltrexone. At the dose we used (60 mg), naltrexone provoked a negative allesthesia for sweetened solutions significantly greater than that induced by a massive glucose load alone (16); combined with glucose load, naltrexone did not further enhance this response. However the 100 g glucose load is considered to have maximal effect (12). Since the 60 mg naltrexone effect was greater, one can hypothesize that it was itself maximal, obscuring additivity of effects.

Thus, the aim of the present study is to determine whether a lower dose of naltrexone, which has itself little or no effect on preference for sucrose, could potentiate the allesthesia provoked by a glucose load.

METHOD

Subjects

Subjects were fourteen healthy adults (eleven men and three women) with a mean age of 22.93 years (range: 20–25 years). Their body weight was within normal range for their height, BMI=21.36±1.3 (mean±SD) and had not changed by more than 1.0 kg during the six months preceding the study. A previous study ascertained that all subjects had a significant allesthetic response to a gastric glucose load. The protocol was approved by the Ethic Committee and informed consent was obtained for each subject.

Gustatory Stimuli

The affective component of the subjects' sensations was explored in ten successive series of tests. Each series was composed of five gustatory stimuli. These sweet tests were 25 ml sucrose solutions at concentrations: 1 M, 0.5 M, 0.25 M, 0.125 M, 0.06 M, maintained at ambient temperature (20°C). Gustatory stimuli were not swallowed but spit out after being tested for 20 seconds, and then subjects rinsed

their mouth with tepid tap water. Stimuli were given to subjects at 3 minute intervals. Each series of five stimuli was tested within fifteen minutes. During each series, 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. Positive values represented pleasant sensations and negative values unpleasant ones.

Hunger Rating

Another visual 100 mm analogical scale measuring hunger sensation was used at 15 min intervals, before, between and after each series of stimuli. Moreover, hunger sensation was rated immediately before and immediately after gastric load (120 min), resulting in double ratings at this time (see below).

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 0900 and 1200 in the morning, after an overnight fast. All subjects first received two identical series of 5 stimuli. The first series was designed to help the subjects learn to scan the stimuli. The responses obtained were disregarded. The second series provided baseline reference values. At the end of this second series, subjects consumed 25 mg of naltrexone or placebo in a double-blind manner. Then they waited for 45 min to allow intestinal absorption of the drug. After three series of stimuli designed to evaluate the action of naltrexone in fasted subjects, the subjects inserted a nasogastric tube and received in a double-blind manner a 200 ml intragastric load of water or 2.8 M glucose solution (100 g). Then the tube was withdrawn and five series of stimuli were successively presented at 15 min intervals. The total duration of each experimental session was 195 min. No side effects were observed. Subjects participated in four experimental sessions over a period of four weeks, with varied crossover 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.* (8,11), as the algebraic difference between the total of the hedonic ratings for the five stimuli or a series after and before administration of placebo, naltrexone and/or water or glucose. Results were expressed as means±S.E.M. of individual allesthesias observed in the fourteen subjects for each series of stimuli tested after naltrexone or placebo intake and after the loads. Total maximal allesthesia was expressed as the mean of individual maximal allesthesia in each session.

Statistical Analysis

All results are expressed as mean±S.E.M.

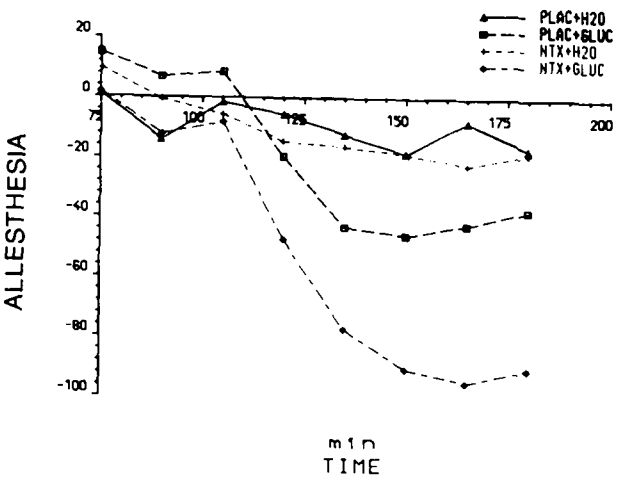

FIG. 1. Naltrexone potentiates glucose-induced allesthesia (mean of individual data for each experimental session). Glucose versus placebo or naltrexone: $p<0.01$; naltrexone plus glucose versus placebo or naltrexone: $p<0.001$; naltrexone plus glucose versus glucose: $p<0.05$.

Intragroups comparison. In each session, means of allesthesia and hunger ratings were compared by analysis of variance. Post hoc comparison was performed with Newman-Keuls test ($p<0.05$).

Intergroups comparison. Allesthesia and hunger ratings between different sessions were compared by two-way analysis of variance for repeated measures. Post hoc comparison was performed with Newman-Keuls test ($p<0.05$).

RESULTS

Allesthesia

The evolution of mean allesthesia is presented in Fig. 1 (and Table 1 which includes S.E.M.). In the session without naltrexone, the glucose load was followed by a significant ($p<0.001$) negative allesthesia; values at 135, 150, 165 and 180 min were significantly lower than the basal value (75 min). After water load, no modification of hedonic rating was found.

In the naltrexone sessions, naltrexone alone was followed by a slight but significant decrease in affective rating ($p<0.05$); values at 165 and 180 min were different from the basal value ($p<0.05$). When associated with glucose load, naltrexone produced a dramatic decrease in hedonic rating ($p<0.001$); values at 120, 135, 150, 165 and 180 min were statistically different from the basal value (75 min) ($p<0.05$). The effect of the addition of naltrexone to glucose load was significantly greater than that of glucose load alone ($p<0.05$). A similar potentiation was found when considering the maximal allesthesia response ($p<0.05$) (Fig. 2).

Hunger

The evolution of hunger ratings over time is presented on Fig. 3 (and Table 2 which includes S.E.M.).

In all sessions a transient but not significant decrease in hunger ratings was observed just after the gastric load, probably due to the introduction of the nasogastric tube.

TABLE 1

EVOLUTION OF ALLESTHESIA*

	Time (min) 75	90	105	120	135	150	165	180
Plac + H_2O	1	−14.3	− 1.6	− 5.7	−12.3	−18.6	− 7.8	−17
	±7.7	± 9.6	± 9.8	±11	±10	±10	±13	±13
Plac + Gluc	15	6.8	8.5	−19.7	−43	−46	−43	−37.8
	±6	± 5	± 9.6	±11	±14	±15.8	±14.7	±16
NTX + H_2O	9.5	− 1	− 5.8	−14.7	−16	−12.8	−22.4	−18.6
	±9.6	± 9	± 7.2	± 8.2	± 8.5	± 9	±12	±16
NTX + Gluc	1.7	−12.3	− 8	−47.7	−77.7	−90.0	−95.4	−91.4
	±5	± 9.8	±12	±13	±20	±19	±22	±23

*Results are expressed as mean ± S.E.M.

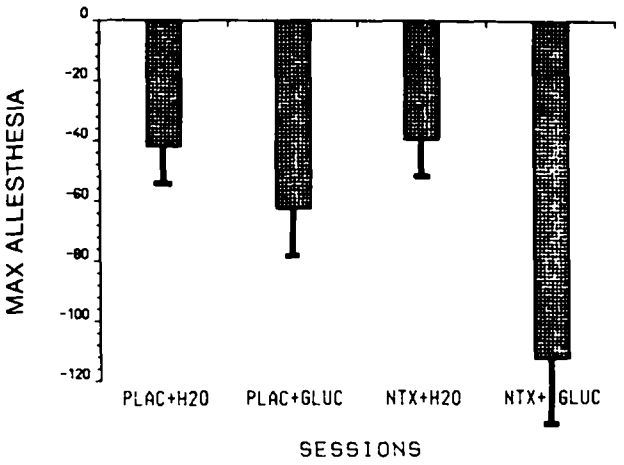

FIG. 2. Naltrexone potentiates also the maximal glucose-induced allesthesia (values are expressed as mean±SEM).

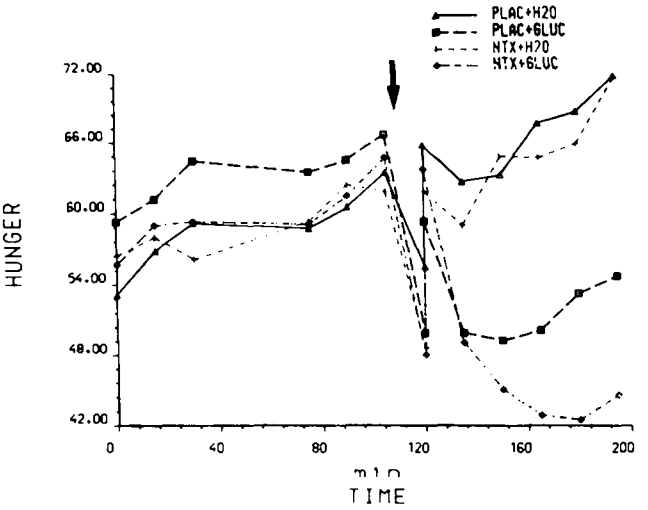

FIG. 3. Mean of individual self ratings of hunger for each experimental session. The gastric load (arrow) provokes a transient decrease. Naltrexone versus placebo: N.S.; glucose versus placebo or naltrexone: $p<0.01$; naltrexone plus glucose versus placebo: $p<0.001$; naltrexone plus glucose versus glucose: $p<0.05$.

TABLE 2

EVOLUTION OF HUNGER SELF-RATING*

	Time (min) 0	15	30	75	90	105	120	120	135	150	165	180	195
Plac +	53	57	59	58.5	60.4	63.3	65.4	55.4	62.4	63	67	68	71
H_2O	±7.4	±7.2	±7.2	±6.4	±6.7	±6	±7	±5.8	±6	±6	±5.7	±5.3	±6.3
Plac +	59	61	64	63	64	66.5	59	49.8	49.8	49	50	53	54.6
Gluc	±7.6	±7.9	±7.9	±6.7	±6.6	±6.7	±7.7	±7.5	±7.2	±7.2	±7.7	±7.9	±7.6
NTX +	56.5	58	56	59.3	62.3	61.7	61.7	48.6	58.8	64.5	64.4	65.6	71.2
H_2O	±6.3	±6.4	±7.4	±7	±7.1	±6.6	±7.1	±6.3	±5.9	±6.1	±6.2	±6.3	±6.5
NTX +	55.7	59	59.3	59	61.3	64.5	63.5	48	49	45	42.8	42.5	44.5
Gluc	±8	±8	±7.7	±7.9	±7.1	±6.4	±6.9	±6.8	±7.5	±8	±8	±8.8	±8.8

*Results are expressed as mean ± S.E.M.

In the control session with placebo and water load, there was an increase in hunger rating over time ($p<0.001$). This increase was of similar magnitude as with naltrexone.

In the session with glucose load and placebo, a global decrease in hunger was observed ($p<0.01$). Glucose plus naltrexone also resulted in a significant decrease in hunger ($p<0.001$) that was slightly greater than that of glucose load alone ($p<0.05$).

DISCUSSION

Allesthesia

At 25 mg, naltrexone alone had a slight effect on allesthesia. These results are consistent with those obtained previously with a dose of 60 mg (16). In combination with glucose, the 25 mg dose of naltrexone provoked a strong potentiation on glucose-induced allesthesia, whereas the 60 mg dose did not. An explanation for such a discrepancy has already been proposed; 60 mg of naltrexone may induce a maximal allesthetic effect for naltrexone which cannot be further increased by the glucose load (12). When one uses a dose of naltrexone resulting in a moderate affect, the potentiation can occur.

Dissociation Hunger-Allesthesia

In fasting subjects, a feeling of hunger was not modified by either 25 mg or 60 mg naltrexone (16). Thus, there is an apparent dissociation between hunger and pleasure for alimentary stimuli. Four studies provide indirect arguments consistent with this observation. In animals, a dose of naltrexone which did not effect food intake of control, chow-fed rats (hunger?), reduces the hyperphagia induced by a highly palatable diet (allesthesia?) and brings the intake back to that of the control rats (1). In humans, Trenchard *et al.* (32) and Cohen *et al.* (13), giving 1.6 mg and 2 mg/kg of naloxone respectively to normal subjects, reported decreases in food intake without changes in the perception of hunger. Another study showed that aspartame provokes a negative allesthesia without changing the feeling of hunger (4). One the other hand, d-fenfluramine, an anorectic drug, induces a decrease in hunger feeling, without effecting hedonic sensation (5).

The effect of naltrexone plus glucose on hunger feeling is not clear-cut. The slight difference observed between glucose alone and naltrexone plus glucose suggests that naltrexone could potentiate the glucose-induced decrease in hunger (6). Three hypotheses could explain this slight potentiation.

First, we cannot exclude an artefact. Nevertheless, in our previous study, we also found a slight (but nonsignificant) difference between the effects of glucose alone on hunger and glucose plus 60 mg of naltrexone. Secondly, in the paradigm of two distinct mechanisms of food intake control in humans, one acting on the pleasure from alimentary stimuli, the other on hunger, these two mechanisms could be linked. Thirdly, during the fast, hunger feeling depends on interprandial satiety on which naltrexone could be ineffective. On the other hand, after a glucose load, hunger could depend on earlier postprandial satiation on which naltrexone could have an effect.

In terms of regulation, this study provides a strong argument for the action of naltrexone on the pleasure of eating, both by a decrease in hedonic rating for sweetened solutions, and by a strong potentiation of glucose-induced allesthesia. Thus, the dose of 25 mg resulting in clear-cut but not maximal effects seems to be more appropriated than the previous dose of 60 mg in order to test responsiveness in pathological situations.

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REFERENCES

1. Apfelbaum, M.; Mandenoff, A. Naltrexone suppresses hyperphagia induced in the rat by a highly palatable diet. Pharmacol. Biochem. Behav. 15:89–91; 1981.
2. Atkinson, R. L.; Berke, L. K.; Drake, M. L.; Bibbs, M. L.; Williams, F. L.; Kaiser, D. L. Effects of long term therapy with naltrexone on body weight in obesity. Clin. Pharmacol. Ther. 38:419–422; 1985.
3. Bertière, M. C.; Mame Sy, T.; Baigts, F.; Mandenoff, A.; Apfelbaum, M. Stress and sucrose hyperphagia: Role of endogenous opiates. Pharmacol. Biochem. Behav. 20:675–679; 1984.
4. Blundell, J. E.; Hill, A. J. Paradoxical effects of an intense sweetner (Aspartame) on appetite. Lancet 5:1092–1093; 1986.
5. Blundell, J. E.; Hill, A. J. Effect of d-fenfluramine on satiety mechanisms in lean and obese subjects. Collegium International Neuro-Psychopharmacologium. Dec. 14–17, Puerto Rico, 1986.
6. Booth, D. A.; Campbell, A. T.; Chase, M. Temporal bounds of post-ingestive glucose induced satiety in man. Nature 228:1104–1105; 1970.
7. Brands, B.; Thornhill, J. A.; Hirts, M.; Gowdey, C. W. Suppression of food intake and body weight gain by naloxone in rats. Life Sci. 24:1773–1778; 1979.
8. Cabanac, M. Physiological role of pleasure. Science 173:1103–1107; 1971.
9. Cabanac, M. Preferring for pleasure. Am. J. Clin. Nutr. 42:1151–1155; 1985.
10. Cabanac, M. Sensory pleasure. Q. Rev. Biol. 54:1–29; 1979.
11. Cabanac, M.; Duclaux, R.; Spector, N. H. Sensory feedback in regulation of body weight: is there a ponderostat? Nature 229:125–127; 1971.
12. Cabanac, M.; Fantino, M. Origin of olfactogustatory allesthesia: Intestinal sensitivity to carbohydrate concentration. Physiol. Behav. 18:1039–1045; 1977.
13. Cohen, M. R.; Cohen, R. M.; Pickard, D.; Murphy, D. L. Naloxone reduces food intake in humans. Psychosom. Med. 47(2):132–138; 1985.
14. Cooper, S. J. Benzodiazepine-opiate antagonist interactions in relation to feeding and drinking behavior. Life Sci. 32:1043–1051; 1983.
15. Duclaux, R.; Feisthauer, J.; Cabanac, M. Effets du repas sur l'agrément d'odeurs alimentaires et non alimentaires chez l'homme. Physiol. Behav. 10:1029–1033; 1973.
16. Fantino, M.; Hossotte, J.; Apfelbaum, M. Opioid antagonist, naltrexone, reduces the preference for sucrose in man. Am. J. Physiol. 251:R91–R96; 1986.
17. King, B. M.; Castellanos, F. X.; Kastin, A. J.; Berzas, M. D.; Olson, G. A.; Olson, R. D. Naltrexone-induced suppression of food intake in normal and hypothalamic obese rats. Pharmacol. Biochem. Behav. 11:729–732; 1979.
18. Kumar, R.; Mitchell, E.; Stolerman, I. P. Disturbed patterns of behavior in morphine tolerant and abstinent rats. Br. J. Pharmacol. 42:473–484; 1971.

19. Le Magnen, J. La satiété induite par les stimulus sucrés chez le rat blanc. C R Soc. Biol. (Paris) 148:1339–1342; 1955.
20. Leshem, M. Morphine-induced anorexia in lateral hypothalamic rats. Psychopharmacology (Berlin) 75:48–53; 1981.
21. Lowy, M. T.; Maickel, R. P.; Yim, G. K. W. Naloxone reduction of stress-related feeding. Life Sci. 26:2113–2118; 1980.
22. Maggio, C. A.; Presta, E.; Bracco, E. F.; Vasselli, J. R.; Kissileff, H. R.; Pfohl, D. N.; Hashim, S. A. Naltrexone and human eating behavior: A dose-ranging inpatient trial in moderately obese men. Brain Res. Bull. 14:657–661; 1985.
23. Malcolm, R.; O'Neil, P. M.; Sexaver, J. D.; Riodle, E.; Currey, H. S.; Counts, C. A controlled trial of naltrexone in obese humans. Int. J. Obes. 9:347–353: 1985.
24. Mandenoff, A.; Fumeron, F.; Apfelbaum, M.; Margules, D. L. Endogenous opiates and energy balance. Science 215:1536–1538; 1982.
25. Morley, J. E.; Levine, A. S. Dynorphin-(1–13) induces spontaneous feeding in rats. Life Sci. 29:1901–1903; 1981.
26. Morley, J. E.; Levine, A. S. Stress-induced eating is mediated through endogenous opiates. Science 209:1259–1261; 1980.
27. Morley, J. E.; Levine, A. S.; Gosnell, B. A.; Billington, C. J. Which opioid receptor mechanism modulates feeding? Appetite 5:61–68; 1984.
28. Morley, J. E.; Levine, A. S.; Yim, G. K. W.; Lowy, M. T. Opioid modulation of appetite. Neurosci. Biobehav. Rev. 7:281–305; 1983.
29. Sanger, D. J. Endorphinergic mechanisms in the control of food and water intake. Appetite 2:193–208; 1981.
30. Sanger, D. J.; McCarty, P. S. Increased food and water intake produced in rats by opiate receptor agoinsts. Psychopharmacology (Berlin) 74:217–220; 1981.
31. Sewell, R. D. E.; Jawaharlal, K. Antagonism of 2-deoxy-D-glucose induced hyperphagia by naloxone. Possible involvement of endorphins. J. Pharm. Pharmacol. 32:148–149; 1980.
32. Trenchard, E.; Silverstone, T. Naloxone reduces the food intake of normal human volunteers. Appetite 4:43–50; 1983.