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Glucagon and insulin response to meals in non-obese and obese Dutch women

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Summary

Many digestive complaints are associated with abnormalities in gastrointestinal peptide hormone function. To investigate the effect of obesity on the release of pancreatic peptide hormones, we have compared the release of insulin and glucagon in non-obese–obese Dutch women in response to isocaloric mixed meals and to Naloxone, an opioid antagonist.

Healthy premenopausal women who were separated into three groups based on body mass index (BMI < 23; 23–27, > 28), were fed 600-calorie breakfasts. Higher fasting levels of plasma insulin and glucagon occurred in obese (BMI > 28) than lean (BMI < 23) women, while glucagon and insulin release after a high fat meal occurred in obese women. Naloxone administration in obese women decreased plasma insulin and glucagon, but in lean women, naloxone increased plasma glucagon but did not alter plasma insulin levels. Results indicate differences in opiate effects on pancreatic function in non-obese–obese women.

Introduction

A high incidence of diseases related to abnormalities in eating behaviour and digestion occur in Western societies. Two major factors, body weight and stress alter the physiological and biochemical control of digestion.

Gastric emptying is faster in the obese [1] and slower emptying occurs in patients with Anorexia Nervosa [2]. Gastric emptying time is also modified by age, meal composition [3], liquids vs. solids, and sex [4]. Stress modifies gastrointestinal transit

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time [5], while emotional events alter eating patterns and body mass index [6].

While the etiology of obesity remains unclear, differences in eating patterns [7], or specific cravings [8] reflect changes in the gut-CNS peptide hormones which control the absorption of nutrients. Composition of luminal nutrients per se alter absorption [9] and the release of gut-pancreatic peptide hormones [10]. Administration of glucagon causes gastric dysrhythmia [11] and decreases the secretion of gastric acid [12], while administration of B-endorphin has been reported to release insulin and glucagon from the pancreas [13] and inhibit colonic motility. Opioid peptides has been reported to increase food intake [14] while higher plasma levels have been reported in obese versus lean women [15].

Accordingly, we have studied the pancreatic peptide hormone response to isocaloric mixed-meals, and naloxone administration, an opiate antagonist, in healthy non-obese and obese Dutch women to determine whether differences occur in these women.

Materials and methods

Healthy menstruating Dutch women with regular bowel movements and free from overt digestive problems, allergies, constipation, diarrhea or endocrine dysfunction, hyperthyroid or diabetes mellitus were selected. Regular daily users of laxatives, aspirins, or ant-acid compounds or current use of medication including oral contraceptives were excluded. All studies were carried out on days 5–10 of the menstrual cycles.

The women were separated into three groups based on body mass index. Group I body mass index (BMI) < 23, mean 21 ± 0.3; Group II BMI 23–27, mean 25 ± 0.2; Group III BMI > 28, mean 31 ± 0.6. The mean age of the three groups was Group I 45.7 ± 0.7, Group II 47.5 ± 0.6, Group III 47.1 ± 0.8. The minimum number in any group was eight women.

Women were fed standardized isocaloric carbohydrate and high-fat breakfasts providing 600 calories per meal. After an overnight fast, an indwelling catheter was placed in the anticubital vein and the first blood sample taken 15 min later. The meal was then fed and the women allowed 15 min to eat the meal. Serial blood samples were taken during and after the meals.

Naloxone was administered as 5 mg i.v. bolus 15 min before the meals and was infused at 5 mg per hour for two hours starting with the meal. Naloxone studies were carried out only in women with BMI < 23 and BMI > 28.

Breakfast were prepared by the dietitian using customary Dutch food. The high fat breakfast, for example, consisted of bread with butter, cheese, and coffee with whole cream. The protocol was approved by the ethics committee, while informed consent was obtained.

Plasma assays

Insulin was determined by RIA using the MRC 66/217 preparation as the reference standard [16] while pancreatic glucagon was determined using a RIA provided by Novo Research Institute, Bagsverd, Denmark. The inter- and intra-as-

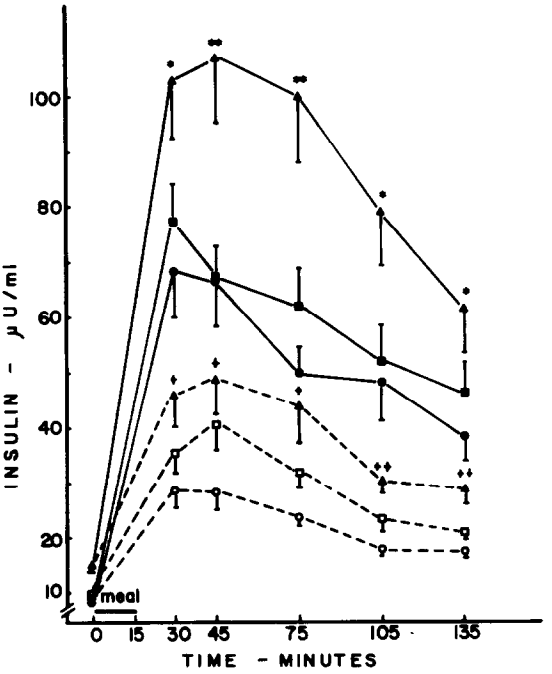

Fig. 1. Insulin response to high fat breakfast (— — —) or a high carbohydrate breakfast (———) in lean BMI < 23 (○, ●) $n = 12$; BMI 23–27 (□, ■) $n = 15$; obese women BMI > 28 (△, ▲) $n = 13$. Results given as mean ± SE $*p < 0.05$ $**p < 0.01$ significantly greater in BMI > 28 than BMI 23–27 carbohydrate breakfast or BMI > 28 than BMI < 23 high fat breakfast, respectively.

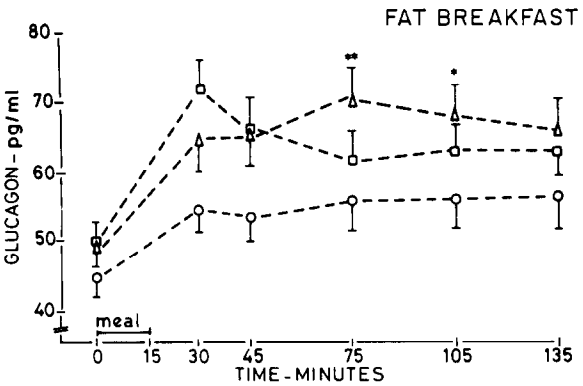

Fig. 2. Glucagon response to a high fat breakfast in women with increasing body weight. Glucagon release significantly greater in women BMI > 28 (△) compared to women BMI < 23 (○). No. per group as in Fig. 1.

say coefficients of variation (CVs) were 7.0% and 4.3% and 12.7% and 11.5%, respectively. B-Endorphin, was determined by RIA using an antibody with a 1% cross reactivity with B-lipotropin (Immunonuclear Corp., Stillwater, MN, USA). The inter- and intra-assay CVs were 14.5% and 6.4%, respectively, with a recovery of 88% at 5 pmol/l. Basal endorphin levels obtained in 4 different days in 12 women showed a high correlation ($r^2 = 0.83$) indicating that basal levels were highly reproducible in the same individual.

Statistical analysis

Comparison between studies of individual women was carried out using Student's paired '*t*' test while responses to meals and Naloxone administration between groups was determined by comparison of the integrated area under the curves.

Results

As shown in Fig. 1, the carbohydrate breakfast released more insulin than the isocaloric fat breakfast. Although the increase in insulin correlated with increasing BMI for the carbohydrate meal, a comparable release of insulin occurred in women BMI < 23 and 23–27.

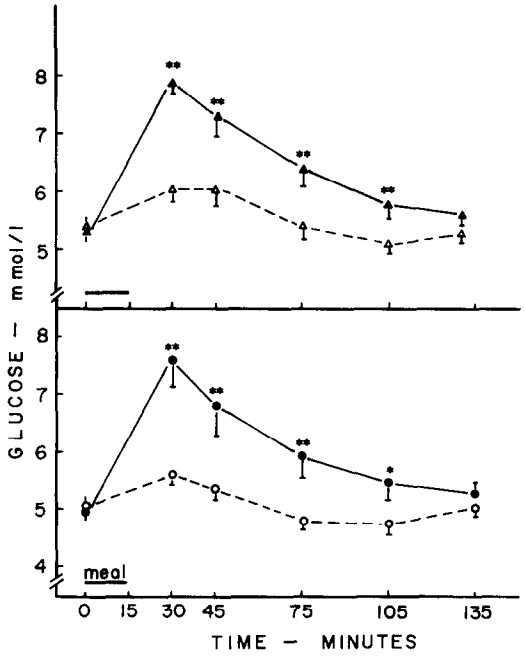

Fig. 3. Glucose response to a high fat breakfast (— — —) or a high carbohydrate breakfast (———) in lean BMI < 23 (○, ●) and obese BMI > 28 (△, ▲). Significantly higher on carbohydrate breakfast. $p \leq 0.01$.

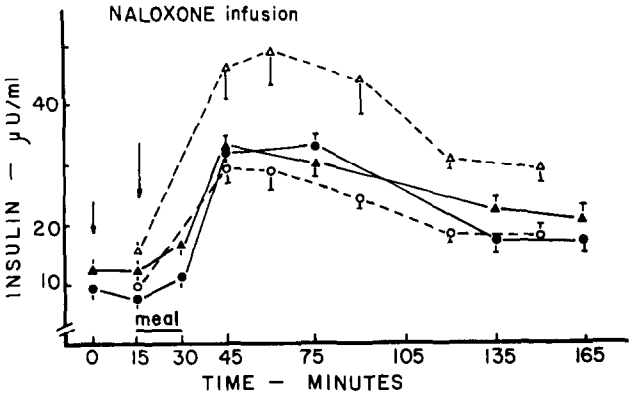

Fig. 4. Insulin response to intravenous infusion of Naloxone, 5 mg bolus 15 min before the meal and infused for 2 h starting with the meal, in lean (BMI < 23; [●]; $n = 6$) and obese (BMI > 28; [▲]; $n = 6$) women fed a high fat breakfast. Results given as mean ± SE. Insulin release in obese women significantly reduced by naloxone infusion $**p \leqslant 0.01$, area under curve.

The high-fat breakfast caused a greater and more prolonged release of glucagon in women BMI > 28 (Fig. II). The increase in plasma glucose was significantly higher with the carbohydrate breakfast, but the increase in glucose levels after the high fat meal was similar in obese (BMI > 28) than lean (BMI < 23) women (Fig. 3).

To prevent overlapping of pancreatic response to meals in the intermediate group of women (BMI 23–27), Naloxone infusion was given only to lean (BMI < 23) and

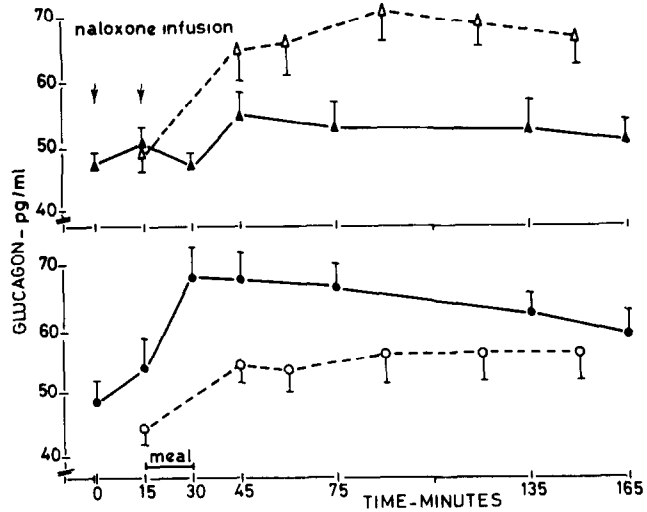

Fig. 5. Glucagon response to intravenous infusion of naloxone as described in Fig. 4. Glucagon release in women BMI > 28 significantly decreased by naloxone following a high fat breakfast, while in women BMI < 23 glucagon release was significanlty increased as determined by area under curve. $p \leqslant 0.01$.

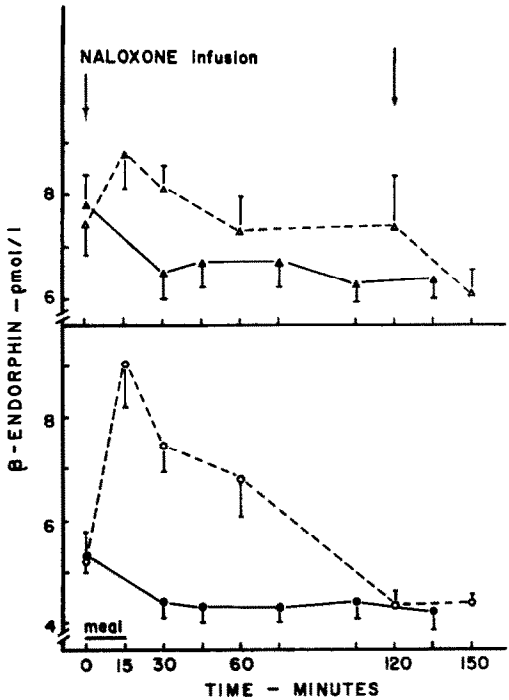

Fig. 6. Effect of Naxolone administration on plasma B-endorphin in lean, BMI 23 and obese, BMI 28 women fed a high fat breakfast. A significant increase in plasma-endorphin occurred in the lean women administered Naxolone. $p \leqslant 0.01$ area under curve details Fig. 4.

obese (BMI > 28) women. Naloxone administration decreased plasma insulin only in obese women (BMI > 28) (Fig. 4), while plasma glucagon levels were decreased in obese women but increased in lean (BMI < 23) women (Fig. 5). Naloxone infusion delayed, for 30 min, the increase in plasma glucose after a high fat breakfast in lean and obese women.

As previously reported plasma B-endorphin levels were higher in obese versus lean women, while neither the high fat or carbohydrate breakfast altered plasma B-endorphin levels.

Infusion of Naloxone caused a significant increase in plasma B-endorphin in lean (BMI < 23) but not obese (BMI > 28) women (Fig. 6).

Discussion

Although the increase in plasma insulin was less after a high fat versus a high carbohydrate breakfast, an increased release of insulin occurred with both breakfasts with increasing body mass index. Similarly, a greater increase in plasma glucagon levels occurred in obese vs. lean women. Interestingly an increase in plasma B-endorphin levels occurred only in obese women administered naloxone and fed a high-fat meal.

Since insulin induced hypoglycemia is associated with an increase of glucagon and as oral glucose administration decreases glucagon, Hatfield et al [17] suggested that the balance between alpha and beta cell activity in the pancreas was related to carbohydrate intake with a preference for insulin rather than glucagon release. Furthermore, insulin–glucagon activity is affected by meal composition [10] while in the obese, glucagon may depend on the interaction of luminal protein and glucose with a loss of insulin control of free fatty acid metabolism [18].

High-plasma levels of glucagon in obese compared with lean women have been reported previously by some [19,20] but not all studies [21,22], while Alford et al [19] have reported a greater release of glucagon in obese women after oral glucose administration.

Regarding the relationship of opioid peptides and the release of pancreatic glucagon and insulin, B-endorphin administration have been reported to release insulin and glucagon [13,23], although Naloxone administration failed to block insulin secretion [24].

It should be noted that B-endorphin has been reported in D-cells of the pancreas [25,26] while glucagon and endorphin immunoreactivity have been reported in alpha cells of the pancreas [27].

In obese women, Naloxone administration significantly decreased the secretion of insulin and glucagon, while in lean women fed a high-fat breakfast, glucagon secretion increased but insulin secretion was unaltered.

While all the lean women in this study menstruated regularly, it has been reported that in patients with Anorexia Nervosa that Naloxone increased plasma glucagon levels and did not alter plasma insulin levels [28]. Lower plasma levels of B-endorphin have also been reported in Anoretic patients.

Lower plasma levels of B-endorphin in lean (BMI < 23) women and the significant increase in plasma B-endorphin in lean women fed a high fat breakfast and administered Naloxone suggests that in lean women B-endorphin or mu receptors are not implicated in insulin release, as reported by Morley et al [24].

Alternatively, in lean women fed a high fat meal and administered Naloxone the increased glucagon release implies an inhibitory role of opioid peptides.

Opioid peptide control of food intake [14] and carbohydrate craving by the obese [8] form part of the eating patterns in obese subjects; patterns which are also modulated by cephalic–vagal stimulation involving insulin secretion in the obese [29].

In the obese, the prolonged higher plasma glucagon levels and greater glucagon response to a high fat meal may lead to a higher incidence of gastric dysrhythmias and/or higher gastric acid secretion. This study clearly indicates the importance of mixed meals on the pancreatic release of peptide hormones and the interaction with body weight and their possible relationship with digestive dysfunction.

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