Pancreatic polypeptide response to exercise

Effect of alanine and glucose ingestion in carbohydrate-starved athletes

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Summary

Human pancreatic polypeptide (hPP) secretion in response to 90 minutes of exercise before and after the ingestion of 50 g glucose or 50 g L-alanine in 33 carbohydrate-starved athletes was examined. There was a very marked increase in plasma hPP concentration with exercise under these circumstances, despite previous reports that the hPP response to exercise is eliminated by training. Glucose and alanine ingestion had no effect on hPP either before or after exercise. This differentiates hPP from other hormones in which secretion is increased by exercise in carbohydrate-depleted subjects.

Pancreatic polypeptide was accidentally discovered in 1968 by Kimmel et al., as a contaminant of chicken insulin. Subsequently Lin and Chance identified similar peptides in bovine, porcine, sheep and human pancreas; in the latter it has been associated with the F cells scattered throughout the organ.

The ingestion of food (particularly protein), hypoglycaemia, fasting and exercise serve as the main stimuli for the release of pancreatic polypeptide, in which respect its behaviour is very similar to that of glucagon and growth hormone, although it has not been demonstrated to have any metabolic actions similar to those of glucagon or growth hormone in mammals. The parallelism between pancreatic polypeptide and glucagon secretion, as described above, may therefore be fortuitous. To investigate this possibility we measured the plasma human pancreatic polypeptide (hPP) and glucagon response to a number of hitherto untried circumstances, namely glucose and alanine ingestion immediately before and after exercise in carbohydrate-starved athletes.

Carbohydrate depletion exaggerates the normal hormone response to exercise in athletes and non-athletes, and therefore provides a useful scenario in which the endocrinology of exercise can be studied. Glucose ingestion counteracts the hormone response to exercise, but alanine, being a powerful glucagon and growth hormone secretagogue, enhances it. This investigation was undertaken to ascertain whether the hPP response to exercise could be similarly manipulated by glucose and alanine ingestion.

Subjects and methods

Thirty-three highly trained, healthy young (17 - 29 years) male long-distance runners from Cape Town athletics clubs gave their informed consent to participation in the study, which was approved by the Ethical Committee of the Faculty of Medicine, University of Cape Town. None was on medication or smoked cigarettes. No individual was more than 10% above or below his ideal mass, based on the 1959 Metropolitan Life Insurance Tables.

Procedure

All the subjects ate a diet very low in carbohydrate, consisting of meat, fish, eggs, green vegetables and unsweetened dairy products, for 48 hours before experiment days. On the day of the experiment they had a standard breakfast (an egg, some cheese and a cup of milk) at 06h00, and then ran 20 km in 1 1/2 hours (from 07h30 to 09h00). During the run they were paced by one of the investigators in a car, carrying emergency equipment in case any of the runners suffered from hypoglycaemia, nausea or extreme exhaustion. The average outside air temperature at 08h00 was 13°C (range 12 - 14°C), the humidity was 93% (range 85 - 100%) and the wind was light. The sky was overcast on each of the experiment days on which the study was conducted. The rest of the day was spent indoors watching video films.

At 07h00 on the day of the experiment the subjects were randomly assigned to a control group (6 subjects) and four experimental groups. The latter were called the 'glucose-before' (7 subjects), the 'glucose-after' (6 subjects), the 'alanine-before' (7 subjects) and the 'alanine-after' (7 subjects) groups, according to whether the participants were given 50 g D(+) glucose or 50 g L-alanine to ingest before or after exercise. There were no statistically significant differences as regards height, weight or age in any of the groups. The glucose and alanine were dissolved in the 400 ml of Diet Pepsi which everyone, including the controls, had to drink at 07h00 and again at 09h00. Thereafter none of the subjects had anything further to eat or to drink except water until the end of the observation period at 16h00. The controls therefore differed from the others only in that they did not, at any stage, ingest either test substance.

Venous blood was taken from an arm vein at 07h00 and 09h00 (before the Diet Pepsi was drunk), and then at hourly intervals until 16h00, for determination of the blood glucose, immunoreactive insulin (IRI), immunoreactive glucagon (IRG) and hPP concentrations.

Analytical procedures

A portion of the venous blood was allowed to clot at 0°C and serum glucose concentrations were measured by the Beckman glucose analyser, using glucose oxidase (Boehringer Mannheim). IRI concentrations were measured using the
Sorin Biomedica IRI kit. For measurement of the plasma glucagon concentration, 2,5 ml blood was mixed with 0,25 ml aprotinin solution (Midran; 10 000 kallidinogenase-inhibitor units/ml; Novo Industries) and 50 IU heparin. This was shaken and immediately chilled to 0°C before centrifugation to remove the red blood cells. Plasma IRG concentrations were determined by radio-immunoassay17 using pancreatic specific antibody 30K obtained from Dr Roger H. Unger, University of Texas, South Western Medical School, Dallas. Plasma hPP was measured by the method of Sive et al.16 using reagents kindly supplied by Dr R. Chance, Lilly Research Laboratories, Indianapolis.

Statistics

Results are expressed as mean ± standard error of the mean (SEM). Student's two-tailed t-test for paired (intragroup comparisons) and unpaired (intergroup comparisons) data was used to determine statistical significance.

Results

None of the subjects experienced abdominal discomfort or nausea as a result of the ingestion of glucose or alanine18 when these substances were dissolved in Diet Pepsi, and no symptoms of hypoglycaemia occurred during or after exercise.

Glucose

The mean serum glucose concentration in all subjects at 07h00 was 4,98 ± 0,17 mmol/l (Fig. 1). This level did not change significantly with exercise in any of the groups, but thereafter showed a slow but steady fall in all but the ‘glucose-after’ and ‘alanine-after’ groups. The mean serum glucose concentration rose to 6,80 ± 0,38 mmol/l at 10h00 (P < 0,01) in those who ingested glucose after exercise, and to 5,09 ± 0,38 mmol/l at 12h00 (P < 0,05) in those who ingested alanine after exercise. There were no statistically significant differences between the glucose concentrations in any of the groups at 16h00. The average level at 16h00 (4,19 ± 0,12 mmol/l) was significantly lower than that at 07h00 (P < 0,001).

Fig. 1. The blood glucose concentrations (mean ± SEM) of 33 highly trained athletes who ran 20 km from 07h30 to 09h00 after a 48-hour low-carbohydrate diet. The control group (6 subjects), whose results are shown in both graphs, fasted during the entire observation period. The other groups ingested 50 g glucose or 50 g-l-alanine before (left) or after (right) exercise, as indicated by the arrows.

The lowest individual blood glucose concentration (2,80 mmol/l) was recorded at 10h00 in a subject who had ingested glucose before exercise. However, this was not accompanied by any untoward symptoms.

Insulin

The mean serum IRG level in all subjects at 07h00 was 163 ± 26 mU/l (Fig. 2). Exercise caused a highly significant reduction in the IRG concentration to 79 ± 20 mU/l at 09h00 (26 subjects; P < 0,005) in all subjects except those who had ingested 50 g glucose before the run, in whom the insulin level did not change significantly. The mean serum IRG concentration continued to fall to 40 ± 11 mU/l (P < 0,02) at 10h00 in the subjects who had only Diet Pepsi to drink after exercise, but rose significantly in the ‘glucose-after’ group to 437 ± 99 mU/l at 10h00 (P < 0,005). Alanine did not significantly influence the serum IRG concentration during or after exercise.

Fig. 2. Serum IRG concentrations (mean ± SEM) of trained athletes who ran 20 km from 07h30 to 09h00 after eating very little carbohydrate for 48 hours. (The experimental conditions and symbols are the same as in Fig. 1.)

The mean serum IRG concentration of the control group at 16h00 did not differ statistically from the level at 10h00, nor were there significant differences between the groups at 16h00.

Glucagon

Exercise caused a marked increase in the mean plasma IRG concentration from 124 ± 15 pg/ml to 181 ± 25 pg/ml in subjects who had only Diet Pepsi to drink before exercise (19 subjects; P < 0,02). The ingestion of alanine before exercise caused a significantly greater increase in the plasma IRG concentration with exercise to 342 ± 92 pg/ml (P < 0,05), whereas glucose had no effect (Fig. 3).

The ingestion of glucose after exercise caused a significant decrease (P < 0,05) and alanine a significant increase (P < 0,02) in the mean plasma IRG concentration at 10h00. From 13h00 there were no significant differences between any of the groups.

Pancreatic polypeptide

The mean plasma hPP concentration at 07h00 was 220 ± 25 pg/ml in all the carbohydrate-depleted athletes (Fig. 4). In the 19 subjects who did not ingest glucose or alanine before exercise the hPP concentration rose to 552 ± 82 pg/ml after
exercise during postprandial exercise is, however, matched by a greater contribution from the hepatic stores. In the present study, the two to three times increased splanchnic glucose output during postprandial exercise is, however, matched by an even greater rate of glucose consumption, so that the arterial blood glucose concentration commonly falls below that of controls, causing increased muscle glycogen utilization and early fatigue. The ingestion of glucose immediately before exercise therefore has little influence on either liver or muscle glucose levels, and any reflex based on them, rather than on the blood glucose concentration, would not be activated under these circumstances. Might low tissue glycogen levels therefore be the primary stimulus for hPP secretion? The major portion of a post-exercise oral glucose load also escapes hepatic retention, allowing muscle glycogen repletion to take precedence over hepatic glycogen repletion. The increment in muscle glycogen content caused by a 50 g glucose load would, however, not be as great as the increment in blood glucose concentration (Fig. 1), a difference that would be reflected between the response of any hormone (e.g. hPP) concerned primarily with tissue glucose homeostasis and those concerned primarily with blood glucose homeostasis (e.g. glucagon and insulin).

Fig. 3. Plasma IRG concentrations (mean ± SEM) of trained athletes who ran 20 km at the time indicated after eating very little carbohydrate for 2 days. (The experimental conditions and symbols are explained in Fig. 1.)

Fig. 4. Plasma hPP concentrations (mean ± SEM) of trained athletes who ran 20 km at the time indicated after a 48-hour low-carbohydrate diet. (The experimental conditions and symbols are the same as in Fig. 1.)

Discussion

Gingerich et al.'s trained subjects after comparable exercise. This suggests that there is a qualitative, if not quantitative, similarity between the hPP and the glucagon, growth hormone and catecholamine responses to carbohydrate depletion and exercise. But whereas the blood concentrations of the latter hormones can be suppressed by the ingestion of glucose before (or during) exercise (Fig. 3),11-14 hPP appears not to be influenced by such short-term changes in carbohydrate status (Fig. 4).

When glucose is ingested 50 minutes before exercise little of it is retained in the splanchnic bed,13 compared with 60 - 85% at rest.23 The two to three times increased splanchnic glucose output during postprandial exercise is, however, matched by an even greater rate of glucose consumption, so that the arterial blood glucose concentration commonly falls below that of controls, causing increased muscle glycogen utilization and early fatigue.24-28 The ingestion of glucose immediately before exercise therefore has little influence on either liver or muscle glucose levels, and any reflex based on them, rather than on the blood glucose concentration, would not be activated under these circumstances. Might low tissue glycogen levels therefore be the primary stimulus for hPP secretion?

The major portion of a post-exercise oral glucose load also escapes hepatic retention, allowing muscle glycogen repletion to take precedence over hepatic glycogen repletion. The increment in muscle glycogen content caused by a 50 g glucose load would, however, not be as great as the increment in blood glucose concentration (Fig. 1), a difference that would be reflected between the response of any hormone (e.g. hPP) concerned primarily with tissue glycogen homeostasis and those concerned primarily with blood glucose homeostasis (e.g. glucagon and insulin).

Alanine is a primary substrate for hepatic gluconeogenesis.29 It is also a powerful glucagon secretagogue,27,30 the glycemic response to alanine ingestion being proportional to the IRG surge. Glucagon does not, however, affect the uptake of alanine by the liver, but rather its conversion to free glucose.32-34 The marked hyperglucagonaemia found in the subjects in this study would therefore suggest that a substantial portion of the alanine ingestion causes the reverse of the glucose-induced insulin : glucagon response, its effect on the body's carbohydrate status is probably very similar. The non-responsiveness of hPP to alanine ingestion is therefore not out of keeping with the other findings in this study.

Although the physiological functions of hPP are uncertain, its impressive increase during exercise in carbohydrate-starved athletes suggests that it may be an important hormone in fuel metabolism, but its failure to respond to glucose and alanine ingestion before and after exercise very definitely sets it aside from the more familiar hormones of glucose homeostasis.

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REFERENCES

Detection of breast cancer metastases

The presence or absence of metastases in patients with carcinoma of the breast has a direct bearing on the subsequent management of the case. Detection of metastases has until now largely depended on the skill of the clinician and the thoroughness with which the physical examination is conducted. Even in meticulous hands, it is easy for small metastases to be missed, and the development of a reliable technique to detect these lesions has been greatly needed. It now looks as though such a technique may have been developed (Thompson et al., Lancet 1984; ii: 1245). A radio-labelled human monoclonal antibody which reacts strongly with the membrane and cytoplasm of breast carcinoma and the luminal membrane of normal breast tissue was injected into the web membrane of normal breast tissue was injected into the web of the antibody; previous results when it was given intravenously were not particularly good, probably because a large quantity remained in circulation and little was detected in the tumour even by subtraction analysis. The authors stress that these are preliminary results and that further trials are now necessary.