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POST-EXERCISE KETOSIS IN POST-PRANDIAL EXERCISE: EFFECT OF GLUCOSE AND ALANINE INGESTION IN HUMANS

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SUMMARY

1. This study examined ketosis in response to 90 min of running before and after the ingestion of 50 g glucose or 50 g L-alanine in thirty-three athletes. Everyone ran 20 km at 07.30 h and then rested, while fasting, till 16.00 h.

2. There were four test groups: 'glucose-before', 'glucose-after', 'alanine-before' and 'alanine-after' according to whether glucose or alanine was ingested at 07.00 h, or 09.00 h. Controls did not ingest either test substance.

3. The control 3-hydroxybutyrate concentration rose from $0{\cdot}23 \pm 0{\cdot}03$ mmol/l (S.E. of mean) at 07.00 h to $0{\cdot}74 \pm 0{\cdot}27$ mmol/l at 12.00 h, and $0{\cdot}94 \pm 0{\cdot}33$ mmol/l at 16.00 h.

4. Glucose ingestion before or after exercise did not influence post-exercise ketosis significantly, despite high insulin:glucagon ratios, low free fatty acid concentrations and hyperglycaemia.

5. Alanine significantly lowered the 3-hydroxybutyrate levels, especially after exercise (to $0{\cdot}14 \pm 0{\cdot}07$ mmol/l at 12.00 h; $P < 0{\cdot}05$) despite reversed insulin:glucagon ratios.

6. This suggests that hepatic responsiveness to portal hyperglycaemia and the main hormones of metabolism is altered immediately after exercise, presumably to promote muscle glycogen synthesis in preference to liver glycogen synthesis.

INTRODUCTION

We have shown previously that post-exercise ketosis can be prevented by consuming a high carbohydrate diet for 2 days before exercise (Koeslag, Noakes & Sloan, 1980) or be abolished by the ingestion of glucose or alanine 2 h after exercise (Koeslag, Noakes & Sloan, 1982). But since the ingestion of glucose $\frac{1}{2}$–1 h before exercise, unlike the consumption of extra carbohydrate on the previous day (Jansson & Kaijser, 1982), frequently impairs performance and predisposes to hypoglycaemia (Ahlborg & Felig, 1977; Costill, Coyle, Dalsky, Evans, Fink & Hoopes, 1977; Foster, Costill & Fink, 1979; Koivisto, Karonen & Nikkilä, 1981; Nelson, Poussier, Marliss,

Albisser & Zinman, 1982), we were led to investigate the development of ketosis in post-prandial exercise, suspecting that glucose and alanine ingestion might not inhibit ketogenesis under these circumstances.

We also administered glucose and alanine immediately after exercise to ascertain whether the continued avidity of the exercised muscles for glucose during early recovery (Fell, Terblanche, Ivy, Young & Holloszy, 1982; Richter, Garetto, Goodman & Ruderman, 1982; Young, Garthwaite, Bryan, Cartier & Holloszy, 1983) might similarly affect the normally antiketogenic actions of glucose and alanine.

METHODS

Thirty-three highly trained, healthy, young, male, long-distance runners from Cape Town athletics clubs gave their informed consent to participate 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. Their ages, heights and weights are summarized in Table 1. No individual was more than 10% above or below his ideal mass, based on the 1959 Metropolitan Life Insurance Tables.

TABLE 1. Ages and physical characteristics of subjects

Group	Age (yr) Range	Height (cm) Mean ± S.D.	Weight (kg) Mean ± S.D.
Control ($n = 6$)	17–25	174 ± 9	65·7 ± 8·7
Glucose-before ($n = 7$)	21–27	184 ± 9	74·2 ± 8·5
Glucose-after ($n = 6$)	22–26	180 ± 4	68·5 ± 2·4
Alanine-before ($n = 7$)	20–26	184 ± 8	74·1 ± 4·1
Alanine-after ($n = 7$)	22–29	181 ± 1	64·8 ± 8·1

Procedure

To induce post-exercise ketosis (Koeslag, 1982), all the subjects ate a very low carbohydrate diet consisting of meat, fish, eggs, green vegetables and unsweetened dairy products, for 48 h before experimental days whilst continuing their training (running 15–20 km per day). On the experimental day they ate a standard breakfast (an egg, some cheese and a cup of milk) at 06.00 h, and then ran 20 km in exactly 1½ h (from 07.30 to 09.00 h) as previously described by Koeslag *et al.* (1980, 1982). To ensure that all the subjects ran at the same speed, they were paced by one of the investigators in a car, which also carried emergency equipment in case any one suffered from hypoglycaemia, nausea or extreme exhaustion (Hultman & Nilsson, 1971; Costill *et al.* 1977; Foster *et al.* 1979; Koivisto *et al.* 1981; Koeslag *et al.* 1982). The average outside air temperature at 08.00 h was 13 °C (range 12–14 °C), the humidity 93% (range 85–100%) and the wind light. The sky was overcast on each occasion. The rest of the day was spent indoors, watching video films.

At 07.00 h on the experimental day the subjects were randomly assigned to a 'control', and four experimental groups. These were called the 'glucose-before', 'glucose-after', 'alanine-before' and 'alanine-after' groups according to whether they were given 50 g D(+)-glucose or 50 g L-alanine to ingest before or after the exercise. The glucose and alanine were dissolved in the 400 ml of 'Diet Pepsi' which everyone, including the controls, had to drink at 07.00 h and again at 09.00 h. Thereafter none of the subjects had anything further to eat or to drink, except water, till the end of the observation period at 16.00 h. 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 07.00 h and 09.00 h (in both cases before drinking the Diet Pepsi), and then at hourly intervals till 16.00 h, to determine the D-3-hydroxybutyrate, long chain free fatty acid (FFA), glucose, immunoreactive insulin (IRI) and immunoreactive glucagon (IRG) concentrations. In addition, each subject was asked to rate the perceived exertion of the test exercise privately in terms of his previous experience of the run on a scale from 0 to 10. A rating of 5 indicated that it had been no more exhausting than usual. A rating of zero meant that the subject had been unable to complete the course, and 10 that the 20 km run had never been easier.

Analytical procedures

A portion of the venous blood was deproteinated in ice-cold 0·6 M-perchloric acid, and the precipitated protein was removed by centrifugation. The neutralized supernatant was used for the measurement of the D-3-hydroxybutyrate concentration (Williamson, Mellanby & Krebs, 1962), using 3-hydroxybutyrate dehydrogenase obtained from Boehringer Mannheim GmbH. Some of the remaining venous blood was allowed to clot at 0 °C and serum glucose concentrations were measured by the Beckman Glucose Analyser, using glucose oxidase obtained from Boehringer Mannheim GmbH. Serum long chain free fatty acid levels were determined in triplicate by the method of Dole & Meinertz (1960). IRI concentrations were measured using the Sorin Biomedica IRI kit (INSIK-1). For measurement of the plasma glucagon concentration, 2·5 ml blood was mixed with 0·25 ml aprotinin solution (Midran, 10000 kallidinogenase inhibitor units per millilitre, Novo Industries) and 50 i.u. heparin. This was stirred by shaking and immediately chilled to 0 °C before centrifugation to remove the red blood cells. Plasma IRG concentrations were determined by radioimmunoassay, using pancreatic specific antibody 30K obtained from Dr Roger H. Unger, University of Texas, South Western Medical School, Dallas.

Statistics

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

RESULTS

General observations

None of the subjects experienced abdominal discomfort or nausea as a result of the ingestion of glucose or alanine (Koeslag *et al.* 1982) when these substances were dissolved in Diet Pepsi. There were no symptoms of hypoglycaemia during or after exercise, and no one rated the 20 km run on the experimental day at less than 3 or more than 7. The 'glucose-before' group rated the perceived exertion at 4·0 ± 0·3 units, which was significantly lower ($P < 0·05$) than the average rating by those who had drunk only Diet Pepsi before exercise (4·8 ± 0·2). The 'alanine-before' group perceived the exertion at 4·8 ± 0·5 units.

3-Hydroxybutyrate

The mean blood 3-hydroxybutyrate concentration of all the subjects was 0·23 ± 0·03 mmol/l at 07.00 h on test days (Fig. 1). This level rose to 0·35 ± 0·04 mmol/l after 90 min of exercise ($P < 0·001$), except in the subjects who had ingested 50 g alanine before the run, in whom the 3-hydroxybutyrate concentration fell to 0·19 ± 0·05 mmol/l with exercise ($P < 0·05$).

The mean blood 3-hydroxybutyrate concentration in the control group continued to rise after exercise, reaching 0·94 ± 0·33 mmol/l at 16.00 h. The ingestion of glucose before or after exercise did not have a statistically significant effect on post-exercise ketosis. The ingestion of alanine after exercise significantly suppressed post-exercise 3-hydroxybutyrate levels, which reached a nadir at 12.00 h ($P < 0·05$); but there were no significant differences between the mean blood 3-hydroxybutyrate concentrations of any of the groups at 16.00 h.

The wide range of individual variations in the results can probably be ascribed to the fact that we were unable to supervise the diet and training during the vital 48 h preceding experimental days.

Glucose

The mean serum glucose concentration at 07.00 h was 4·98±0·17 mmol/l. This level did not change significantly with exercise in any of the groups, but showed thereafter 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 10.00 h ($P < 0·001$) in the subjects who ingested glucose after exercise, and to 5·09±0·38 mmol/l at 12.00 h ($P < 0·05$) in those who ingested alanine after exercise. There were no statistically significant differences between the glucose concentrations of any of the groups at 16.00 h. The average level at 16.00 h (4·19±0·12 mmol/l) was significantly lower than that at 07.00 h ($P < 0·001$).

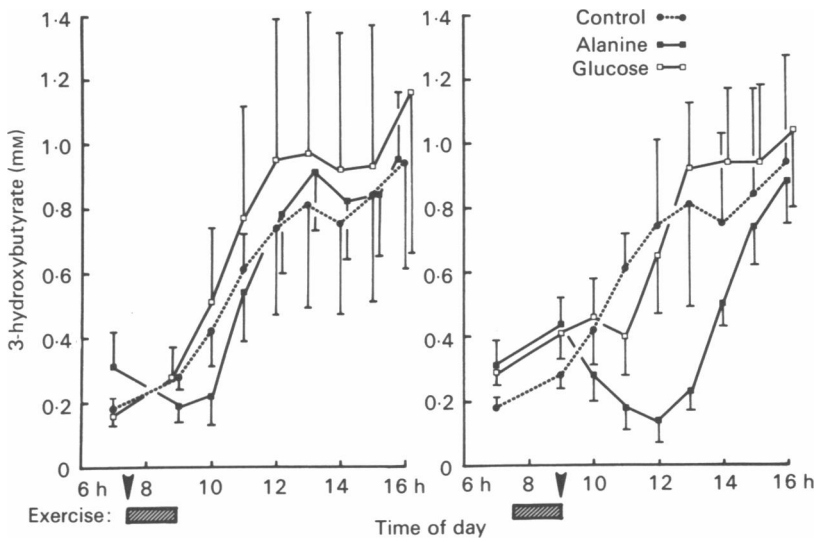

Fig. 1. The blood 3-hydroxybutyrate concentrations (mean±S.E. of mean) of trained athletes who ran 20 km at 07.30–09.00 h, following a 48 h low carbohydrate diet. The control group ($n = 6$), whose results are shown in both graphs, fasted during the observation period, except for the consumption of 400 ml 'Diet Pepsi' at 07.00 h and again at 09.00 h. The other groups had 50 g glucose or 50 g L-alanine dissolved in the 'Diet Pepsi' before (left) or after (right) exercise as indicated by the arrows.

Long-chain free fatty acids

Exercise in carbohydrate-starved athletes who did not ingest alanine or glucose at 07.00 h, caused the mean plasma FFA concentration to rise from 0·73±0·04 to 1·95±0·12 mmol/l ($P < 0·001$). The ingestion of glucose before exercise caused the FFA level immediately after exercise (1·32±0·17 mmol/l) to be significantly lower than the control level ($P < 0·02$). The ingestion of glucose after exercise had a similar effect on the 10.00 h FFA levels (0·77±0·20 mmol/l). Alanine had no effect on serum FFA concentrations before or after exercise. There were no stastically significant differences between the serum FFA levels of any of the groups at 16.00 h.

Insulin

The mean serum IRI level at 07.00 h was 163 ± 26 μu./ml (Fig. 2). Exercise caused a highly significant reduction in the IRI concentration to 79 ± 20 μu./ml at 09.00 h ($P < 0{\cdot}005$) 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 IRI concentration continued to fall to 40 ± 11 μu./ml ($P < 0{\cdot}02$) at 10.00 h in the subjects who had only Diet Pepsi to drink after exercise, but rose significantly in the 'glucose-after' group to 437 ± 99 μu./ml at 10.00 h ($P < 0{\cdot}005$). Alanine did not significantly influence the serum IRI concentration during or after exercise.

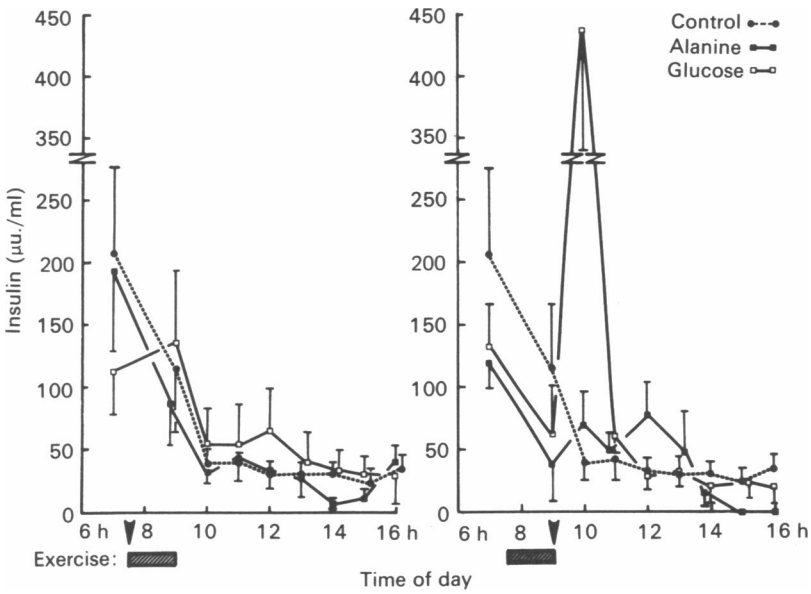

Fig. 2. Serum immunoreactive insulin concentrations (mean $\pm$ S.E. of mean) of trained athletes who ran 20 km at 07.30–09.00 h, after eating very little carbohydrate for 48 h. The experimental conditions and symbols are explained in Fig. 1.

The mean 16.00 h serum IRI concentration of the control group did not differ statistically from the 10.00 h level, nor were there significant differences between the groups at 16.00 h.

Glucagon

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

The ingestion of glucose after exercise caused a significant decrease ($P < 0{\cdot}05$), and alanine a significant increase ($P < 0{\cdot}02$), in the mean plasma IRG concentration at 10.00 h. From 13.00 h there were no significant differences between any of the groups.

DISCUSSION

The development of post-exercise ketosis could not be prevented by the ingestion of 50 g glucose 30 min before exercise, despite higher than normal insulin:glucagon ratios in the blood during exercise (Figs. 2 and 3). 50 g glucose taken immediately after exercise also failed to inhibit the development of post-exercise ketosis, despite its ability to bring about a prompt reduction in ketonaemia if taken 2 h later (Koeslag *et al.* 1982). Alanine, on the other hand, retains its antiketogenic properties regardless of when it is ingested in relationship exercise.

When glucose is ingested $\frac{1}{2}$–1 h before exercise less than half of the load is effectively retained in the splanchnic bed (Felig, Wahren & Hendler, 1975; Maehlum, Jervell & Pruett, 1976; Ahlborg & Felig, 1976, 1977), compared with 60–85% at rest (Felig *et al.* 1975; Ahlborg & Felig, 1976, 1977; Maehlum *et al.* 1976). Much of this, in both cases, however, represents a saving in the consumption of gluconeogenic precursors, so that the gain in hepatic carbohydrate content is only about 10% of the glucose load at rest (Maehlum *et al.* 1976; Radziuk, McDonald, Rubenstein & Dupre, 1978), and probably not markedly different, in absolute terms, during exercise (Maehlum *et al.* 1976). That ketogenesis is not suppressed during post-prandial exercise, therefore, supports the notion already known from the pathophysiology of diabetes mellitus, that portal hyperglycaemia itself has little effect on hepatic ketogenesis *in vivo*, either as a precursor for malonyl-CoA production (Foster & McGarry, 1982), or through its binding to glycogen phosphorylase *a* (Hers, 1976; Madsen, Kasvinsky & Fletterick, 1978; Cohen, 1979). In contrast to the diabetic situation however, our results show that portal hyperglycaemia can fail to inhibit hepatic ketogenesis even in the presence of a favourable hormonal milieu (a high insulin:glucagon ratio).

Post-exercise ketosis characteristically develops during the first hour or two of recovery (Koeslag, 1982) (Fig. 1), whereas the exercise period itself (despite its low insulin:glucagon ratios) is usually comparatively antiketogenic (Drury, Wick & MacKay, 1941; Johnson & Passmore, 1960; Houghton, Hawkins, Williamson & Krebs, 1971; Balasse, Fèry & Neef, 1978). This would suggest that post-exercise ketosis is due to a legacy of the increased muscular activity: perhaps a post-exercise maldistribution of fuel (Koeslag *et al.* 1980). The significance of our results is therefore not so much that glucose has no effect on hepatic ketogenesis during exercise, but rather that its ingestion before or immediately after exercise has no influence on hepatic fuel metabolism during early recovery: rapid muscle glycogen resynthesis occurs during the first 60 min of recovery (Maehlum, Felig & Wahren, 1978; Ivy & Holloszy, 1981; Fell *et al.* 1982; Richter *et al.* 1982) even in fasting subjects (Maehlum & Hermansen, 1978; Maehlum, Felig & Wahren, 1978; Fell, McLane, Winder & Holloszy, 1980), and much of the body's mobilizable carbohydrate is probably diverted to this purpose (Wahren, Felig, Hendler & Ahlborg, 1973; Maehlum, Felig & Wahren, 1978; Fell *et al.* 1980). Thus, splanchnic glucose production remains elevated for about an hour after exercise (Zinman, Murray, Vranic, Albisser, Leibel, MacClean & Marliss, 1977; Vranic & Kawamori, 1979; Young *et al.* 1983) and any gain or saving there might therefore have been in liver glycogen content on cessation of post-prandial exercise is probably forfeited during this redistribution of depot carbohydrate, setting the stage for increased hepatic ketogenesis despite post-exercise

hyperinsulinaemia, with (Fig. 2) or without (Oseid & Hermansen, 1971; Böttger, Schlein, Faloona, Knochel & Unger, 1972; Wahren *et al.* 1973; Vranic & Kawamori, 1979; Chisholm, Jenkins, James & Kraegen, 1982) glucose ingestion.

Alanine lowers the blood ketone body concentration in a wide variety of conditions (see Koeslag *et al.* 1982), in the presence of reversed insulin:glucagon ratios

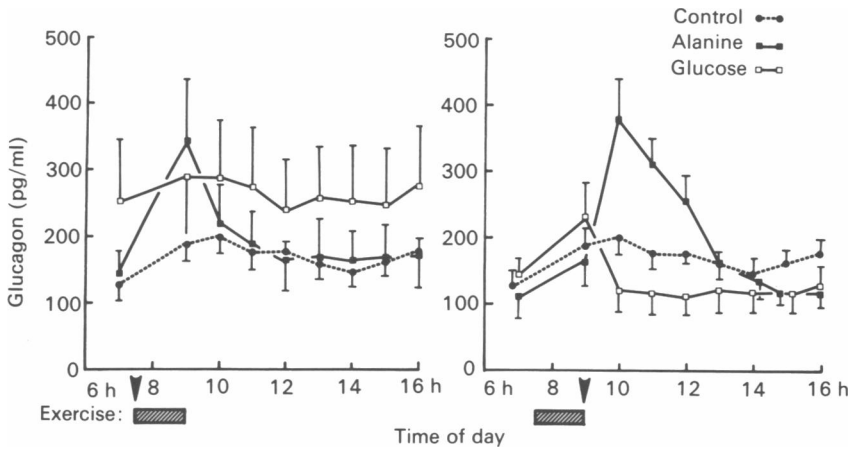

Fig. 3. Plasma immunoreactive glucagon concentrations (mean ± S.E. of mean) of endurance athletes who ran 20 km at the time indicated, after eating very little carbohydrate for 2 days. The experimental conditions and symbols are explained in Fig. 1.

(Figs. 2 and 3), without influencing ketone body utilization (Nosadini, Datta, Hodson & Alberti, 1980). It is an effective antiketogenic agent even when the peripheral disposal of ketone bodies is inhibited by dichloroacetate (Ozand, Girard, Hawkins, Collins, Reed, Tildon & Cornblath, 1976), which suggests that alanine acts specifically on hepatic ketogenesis, presumably by increasing the mitochondrial supply of oxaloacetate (Nosadini *et al.* 1980; Sugden & Watts, 1982). Since post-exercise ketosis can thus be counteracted solely by inhibiting ketone body production indicates therefore, that glucose's ineffectiveness cannot be ascribed to a post-exercise alteration in peripheral ketone body metabolism (Fèry & Balasse, 1983) on which its ingestion might not have had any effect. The refractoriness of post-exercise ketosis to glucose ingestion must therefore be the result of an altered hepatic responsiveness to portal hyperglycaemia, and, more importantly, to the main hormones of fuel metabolism immediately after exercise. The precise neural, hormonal or chemical factors responsible for the altered responsiveness of the liver during post-exercise recovery remain to be established.

In conclusion, our results confirm that glucose ingestion immediately before exercise has some unexpected metabolic results, which manifest themselves to the runner as impaired performance (see 'General observations') and to the exercise physiologist as post-exercise ketosis. However, abolition of the ketosis by means of alanine ingestion before or after exercise produced no subjective benefits to any of the runners.

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