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FAILURE OF THERMOREGULATION IN THE COLD DURING HYPOGLYCAEMIA INDUCED BY EXERCISE AND ETHANOL

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SUMMARY

1. After young men had exercised for approximately 2 hr at 70% maximum O_2 uptake, and taken 28 ml. ethanol by mouth, their mean blood glucose fell to 2·17 mM. It fell further to 1·77 mM during a 30 min exposure to air at 14·5° C. Plasma lactate, glycerol, β-hydroxybutyrate and free fatty acid concentrations increased.

2. Rectal temperature fell to reach a mean level of 34·49° C by the end of the cold exposure; oesophageal temperature fell to as low as 33·00° C in one case.

3. Virtually no increase in metabolic rate and no visible shivering occurred during the cold exposure.

4. Administration of glucose (mean 60·4 g) prevented the falls in temperature, and restored metabolic response to the cold to the size found in control experiments without exercise or ethanol.

5. Neither exercise without ethanol or ethanol without exercise significantly lowered the blood glucose or impaired the maintenance of body temperature in the cold.

6. One obese subject showed almost as great a fall in blood glucose and depression of metabolic response to cold as the thinner men, but no fall in body temperature.

INTRODUCTION

Experiments described in the previous paper (Haight & Keatinge, 1973) showed that body temperature was regulated at a higher level than normal after 8–10 hr moderate exertion, probably because the exercise had liberated small amounts of endogenous pyrogen. There was no hypoglycaemia and the metabolic response to cold was not impaired.

The present study was designed to see whether more severe exertion

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with or without the consumption of small quantities of ethanol would produce sufficient hypoglycaemia to impair body temperature regulation. Blood glucose concentration sometimes falls during severe exercise (Saltin & Hermansen, 1967). It seemed likely that ethanol, apart from any direct effects it might have on temperature regulation, would increase the frequency and degree of hypoglycaemia since it impedes gluconeogenesis in the liver (Krebs, Freedland, Hems & Stubbs, 1969). A large enough fall in blood glucose might interfere with temperature maintenance in the cold in man, since insulin-induced hypoglycaemia abolishes visible shivering in cold-exposed cats and dogs (Cassidy, Dworkin & Finney, 1925) and low body temperatures have been recorded in patients with both spontaneous (Stenström, 1926) and insulin-induced (Kedes & Field, 1964) hypoglycaemia.

In the present study rectal and oesophageal temperature and metabolic rate were measured in volunteers who had exercised to exhaustion and in some cases had taken ethanol. Determinations were made of blood ethanol and glucose, as well as plasma lactate, β-hydroxybutyrate and free fatty acids, important substrates for gluconeogenesis or skeletal muscle, which can at high concentrations be metabolized by the brain. Plasma glycerol was also measured to give some indication of the rate of lipolysis in adipose tissue.

METHODS

Subjects and general procedure

The subjects were fourteen male volunteers aged 19–27 yr. Routine medical examination revealed no cardiovascular or respiratory disease. Most of them played energetic games such as Rugby football once or twice weekly; only subjects 10, 11 and 13, who each regularly ran 100 km per week, were in a higher state of physical training. All of them understood and consented to the experiments.

The subjects were divided into three groups. Those of the first group (nos. 1–6) were subjected to a standard cold stress once without preliminary treatment; once after exercise to exhaustion; and once after similar exercise with glucose. The three experiments were performed at intervals of 3–4 weeks, and their order was varied in different subjects to minimize any distortion of results due to adaptation. Those of the second group (nos. 7–13) were subjected to the same three experiments with the addition that they were given ethanol in each experiment, after the exercise or control rest period and before the cold exposure. The third series of experiments was carried out on one obese subject (no. 14); the procedure was the same as for the second group.

All subjects fasted throughout the day that each experiment started and continued until observations were complete, except subjects 12 and 13 who were given breakfast of four slices of bread, butter and jam 30 min before the exercise or control rest period of each experiment. They were all allowed unlimited water, and up to 14 g salt, to replace losses in sweat. They ate normally before experiments except that subjects 1–6 and 14 were asked to avoid foods rich in carbohydrate for 3 days.

Details of procedure and measurements

Preliminary measurements. Height, weight and skinfold thicknesses at triceps, subscapular, subcostal and abdominal sites were measured as described in the previous paper (Haight & Keatinge, 1973). Each subject then pedalled at 60 c/min on a bicycle ergometer (Elema-Shonander AM368) for successive 4 min periods at increasing work loads until the maximum work load that he could sustain for this time was found. Air expired during the 4th min of each period of exercise was collected, measured and analysed as described in the previous paper.

Exercise. In the 'exercise' experiments each subject pedalled the ergometer at the load which the preliminary experiments showed would require $70 \pm 7\%$ of the subject's maximum O_2 uptake; metabolic rate during this was determined as in the previous paper. The subjects rested for 5 min after the first 30 min of exercise, and after successively shorter periods of exertion as they became tired. Exercise was stopped when they were unable to exercise for 5 consecutive minutes. On the control day, on which the subjects did not exercise, they sat quietly during the time corresponding to the exercise.

In warm room after exercise or rest period ('before cold exposure'). After the exercise or control rest period the subject entered a warm room ($19{\cdot}5 \pm 2{\cdot}5°$ C) wearing shorts, socks, gymshoes and a blanket. In the 'exercise with glucose' experiment subjects of the first group then took 51–65 g (mean 57·9) glucose, and those of the second and third groups 50–88 g (mean 60·4) glucose; usually the glucose was given orally with water, but subjects 7, 11 and 13 were given part of it (56 ml. of 2·8 M glucose solution each) I.V. to ensure high blood levels in spite of interference with glucose absorption by ethanol (Tuovinen, 1931). At this point subjects of the second and third group drank ethanol diluted with 500 ml. water in every experiment. To compensate for interference with ethanol absorption by glucose, they took 30–50 ml. (mean 38·9) ethanol in the 'exercise with glucose', compared with 25–32 ml. (mean 29·1) in the 'exercise without glucose' experiments and 27–33 ml. (mean 29·4) in the control study (no exercise or glucose).

Metabolic rate was then determined from a 10 min expired air collection started 5 min after the end of exercise, with the subjects seated in a chair. A venous blood sample was taken from the left antecubital vein after the arm had been immersed in water at 40–43° C for 5 min to increase blood flow. Rectal temperature was measured by thermocouple as described in the previous paper. In subjects 9, 11 and 12 an oesophageal thermocouple (Ellab Type TE3) was inserted through a nostril to a depth assessed by external measurement to take the tip to the level of the midpoint of the sternum. It was held in position by a firm noseclip.

In cold room. After 30–50 min in the warm room the subject entered the cold room ($14{\cdot}5 \pm 0{\cdot}4°$ C) and sat there for 30 min wearing only shorts in an airflow of $15{\cdot}3 \pm 0{\cdot}8$ km/hr. All air expired during this time was collected for a metabolic rate determination, and rectal and oesophageal temperature was noted at 10 min intervals.

In warm room after cold exposure. The subject then sat for 15 min in the warm room, wrapped in a blanket, his left arm immersed in water at 40–43° C, before a final venous blood sample was taken from the arm.

Biochemical determinations

Blood obtained by venepuncture (10–20 ml.) was put immediately into heparin tubes and these were inverted. Blood (1 ml.) was mixed with 1 ml. 86 mM saline and with 0·5 ml. 2 M perchlorate to precipitate protein. This mixture and the heparin tubes were both centrifuged, and the supernatants removed and deep frozen at $-20°$ C. Within 3 months they were thawed in lukewarm water and analysed;

reanalysis of other samples after freezing for 1 yr showed no appreciable change in the results. Before analysis the plasma samples were deproteinized as described for blood, and the deproteinized samples were adjusted to a pH of approximately 7·5 by KOH solution, using phenol red as an indicator.

Glucose was determined with glucose oxidase (Bergmeyer & Bernt, 1963), lactate with lactate dehydrogenase (Hohorst, 1963) and ethanol with ethanol dehydrogenase (Krebs, Freedland, Hems & Stubbs, 1969) in deproteinized blood. Glycerol was determined with glycerokinase (Wieland, 1963) and β-hydroxybutyrate with β-hydroxybutyrate dehydrogenase (Williamson, Mellanby & Krebs, 1962), in deproteinized plasma. Long chain free fatty acids in plasma were determined by a calorimetric method (Itaya & Ui, 1965). Oxidation and reduction of nicotinamide adenine dinucleotide, and change of dye intensity, in these tests were measured on a Zeiss PMQ II Spectrophotometer.

Statistics. Comparisons were made by the paired Student t test.

TABLE 1. Physical characteristics of the subjects, and the exercise performed by them

	Height (cm)	Weight (kg)	Skinfold thickness* (mm)	O_2 consumption during exercise, (l./min)		Duration of exercise (hr and min)	
				Exercise without glucose expt.	Exercise and glucose expt.	Without glucose expt.	With glucose expt.
First group (subjects 1–6)	178 ± 1·5	66·8 ± 1·3	7·6 ± 0·5	2·3 ± 0·1	2·3 ± 0·1	1:15 ± 0:05	1:10 ± 0:10
Second group (subjects 7–13)	176 ± 1·9	67·3 ± 2·3	7·3 ± 0·3	2·2 ± 0·1	2·2 ± 0·1	2:15 ± 0:18	1:57 ± 0:15
Subject 14	173	73·9	22·8	2·4	2·5	2:06	1:53

Values for first group and second group are means ± S.E.

* Mean of readings from triceps, subscapular, subcostal and abdominal sites.

RESULTS

The subjects. Table 1 shows that the heights, weights and skinfold thicknesses of subjects of the first and second groups were very similar. They indicate a normal degree of fatness, the weights being close to the standard value of 69·1 kg (Brozek & Keys, 1951) and the skinfolds close to the standard value of 7·6 mm (Hammond, 1955) for men aged 19–20. Subject 14 was much fatter, with a skinfold thickness three times the standard value. O_2 consumption during exercise was similar in all subjects; the first group of subjects, who had been on a reduced carbohydrate diet, were able to exercise for a rather shorter time than the second group.

Results of first group of experiments (without ethanol). No important disturbances of temperature regulation were observed after exercise without ethanol, whether or not glucose was given.

Table 2 shows that in air at 19·5° C, 30–50 min after the end of exercise, rectal temperature was at least as high after exercise, with or without glucose, as on the control day. It did not fall significantly after any of the three treatments during the subsequent 30 min exposure to cold. Metabolic rate in the warm was also at least as high after the exercise experiments as in the control, and increased greatly during the cold exposures

TABLE 2. Results from first group of subjects (nos. 1–6, all without ethanol)

	Before cold exposure			After cold exposure (during it for metabolic rate)		
	No exercise or glucose Col. 1	Exercise without glucose Col. 2	Exercise and glucose Col. 3	No exercise or glucose Col. 1	Exercise without glucose Col. 2	Exercise and glucose Col. 3
Rectal temp. (° C)	36·60 ± 0·09	36·79 ± 0·18	36·71 ± 0·27	36·67 ± 0·13	36·63 ± 0·12	36·71 ± 0·19
Met. rate ($kcal.m^{-2}.hr^{-1}$)	40·9 ± 1·4	55·2* ± 3·3	58·4* ± 3·0	78·5 ± 8·2	81·8 ± 10·6	90·0 ± 10·2
Blood glucose (mM)	3·40 ± 0·04	3·40 ± 0·13	4·24*† ± 0·08	3·47 ± 0·14	3·14 ± 0·09	6·25*† ± 0·62
Blood lactate (mM)	0·66 ± 0·12	1·41* ± 0·18	1·33* ± 0·20	0·86 ± 0·11	1·62* ± 0·09	1·41* ± 0·15
Plasma glycerol (mM)	0·16 ± 0·01	0·43* ± 0·04	0·31*† ± 0·02	0·22 ± 0·03	0·35 ± 0·05	0·22 ± 0·02
Plasma free fatty acid (mM)	0·76 ± 0·09	2·47* ± 0·22	1·86*† ± 0·22	1·09 ± 0·11	1·75* ± 0·22	0·98† ± 0·12
Plasma β-hydroxybutyrate (mM)	0·60 ± 0·18	1·71* ± 0·25	1·58* ± 0·22	0·83 ± 0·19	2·08* ± 0·08	1·32† ± 0·21

* Differs from Col. 1, $P < 0·05$; † differs from Col. 2, $P < 0·05$. Values are means ± S.E. of six experiments; statistical comparisons are on paired basis.

to reach similar levels in each of the experiments. Blood glucose was not significantly lowered by exercise; it was greatly increased by administration of oral glucose. Blood lactate and plasma glycerol, free fatty acid, and β-hydroxybutyrate were raised after exercise, and these increases were reduced by the administration of glucose.

Results of second group of experiments (with ethanol). After exercise and ethanol all subjects appeared confused and unsteady but after ethanol

alone, or exercise, ethanol and glucose there was no confusion or unsteadiness. None of the subjects shivered visibly during cold exposure after exercise and ethanol, but they did shiver during cold exposure in the other two experiments.

Table 3 shows that after exercise and ethanol mean rectal temperature fell to 35·52° C even during the 30–50 min spent in the warm room, and to 34·49° C during the subsequent 30 min exposure to cold. Table 3 shows that there was no comparable fall after ethanol alone, or after exercise, ethanol and glucose; rectal temperature then remained close to the values (see Table 2) recorded in corresponding experiments without ethanol.

TABLE 3. Results from second group of subjects (nos. 7–13, all with ethanol)

	Before cold exposure			After cold exposure (during it for metabolic rate)		
	No exercise or glucose Col. 1	Exercise without glucose Col. 2	Exercise and glucose Col. 3	No exercise or glucose Col. 1	Exercise without glucose Col. 2	Exercise and glucose Col. 3
Rectal temp. (° C)	36·89 ± 0·12	35·52* ± 0·25	36·88† ± 0·18	36·82 ± 0·14	34·49* ± 0·34	36·94† ± 0·14
Met. rate ($kcal.m^{-2}.hr^{-1}$)	45·6 ± 1·1	65·7* ± 2·7	65·2* ± 1·7	76·1 ± 7·7	45·0* ± 2·9	91·0† ± 10·4
Blood glucose (mM)	3·71 ± 0·13	2·17* ± 0·18	5·17*† ± 0·49	2·82 ± 0·17	1·77* ± 0·20	4·96*† ± 0·61
Blood lactate (mM)	1·16 ± 0·14	2·20* ± 0·28	1·69* ± 0·16	1·29 ± 0·22	2·65* ± 0·11	1·89† ± 0·12
Plasma glycerol (mM)	0·16 ± 0·03	0·48* ± 0·06	0·26† ± 0·07	0·20 ± 0·04	0·70* ± 0·18	0·20 ± 0·02
Plasma free fatty acid (mM)	0·58 ± 0·12	2·01* ± 0·18	1·04*† ± 0·12	0·94 ± 0·16	2·16* ± 0·31	0·86† ± 0·11
Plasma β-hydroxybutyrate (mM)	0·22 ± 0·08	1·56* ± 0·38	0·78 ± 0·22	0·18 ± 0·04	1·74* ± 0·44	0·34† ± 0·11
Blood ethanol (mM)	5·36 ± 0·32	5·23 ± 0·52	4·83 ± 0·78	5·12 ± 0·18	5·11 ± 0·29	5·80 ± 0·74

* Differs from Col. 1, $P < 0·05$; † differs from Col. 2, $P < 0·05$. Values are means ± S.E. of seven experiments except Cols. 2 and 3 of metabolic rate before cold exposure which are from six subjects only; statistical comparisons are on paired basis.

Oesophageal temperature, which is not shown in the tables, fell more than rectal temperature but showed similar differences between the experiments in the three subjects (9, 11 and 12) in whom it was measured.

By the end of the cold exposure it was 33·00, 34·40 and 34·90° C in the exercise and ethanol experiment; 35·85, 36·30 and 36·20° C in the ethanol experiment; and 36·45, 35·40 and 36·10° C in the exercise, ethanol and glucose experiment.

It can be seen from Table 3 that exercise and ethanol depressed the metabolic response to cold, while ethanol alone, or exercise, ethanol and glucose, did not. In the warm room metabolic rate after each of these treatments was much the same as in corresponding experiments without ethanol. After exercise and ethanol metabolic rate failed to increase at all in the cold. After ethanol alone, or exercise, ethanol and glucose, metabolic rate rose in the cold to about the same extent during cold exposure as it had done in corresponding experiments without ethanol. Blood glucose was greatly reduced after ethanol and exercise, falling to a mean value of 1·77 mM by the end of the cold exposure (Table 3). Blood glucose did not fall below normal values after ethanol alone, and was maintained well above control levels after exercise, ethanol and glucose. Individual values for blood glucose, which are not given in the table, show that after exercise and ethanol the lowest value reached at the end of the cold exposure was 0·97 mM (subject 7); blood glucose fell in this experiment to 2·01, 1·61 and 2·14 mM even in the fit subjects 10, 11 and 13, and to 2·46 mM in subject 12, who like subject 13, had eaten a large carbohydrate meal before exercising.

TABLE 4. Results from one fat subject (no. 14, with ethanol)

	Before cold exposure			After cold exposure (during it for metabolic rate)		
	No exercise or glucose	Exercise without glucose	Exercise and glucose	No exercise or glucose	Exercise without glucose	Exercise and glucose
Rectal temp. (° C)	36·80	36·80	37·00	36·80	36·80	37·25
Metabolic rate ($kcal.m^{-2}.hr^{-1}$)	44·9	—	—	109·6	65·7	104·2
Blood glucose (mM)	3·85	2·24	3·80	3·61	2·46	8·00
Plasma β-hydroxybutyrate (mM)	0·82	4·80	0·93	1·58	5·25	1·02
Blood ethanol (mM)	6·47	7·01	4·32	2·75	4·04	5·69

Table 3 also shows that blood lactate and plasma glycerol, free fatty acid and β-hydroxybutyrate concentrations during these experiments were comparable with those in the corresponding experiments without

ethanol (Table 2). Again the levels of these metabolites were all considerably increased after exercise, and less so after glucose than without it. Blood ethanol concentration was similar in all three experiments.

Results from one fat subject (with ethanol). Table 4 shows that after ethanol and exercise subject 14 maintained his rectal temperature both before and during cold exposure. His metabolic rate rose a little in the cold and his blood glucose fell only moderately below normal values. However, both his metabolic rate in the cold and blood glucose were substantially lower in that experiment than after ethanol alone, or with the combination of exercise, ethanol and glucose. His plasma β-hydroxybutyrate after exercise and ethanol rose to very high levels which were in fact greater than any individual value recorded in the thinner subjects. Blood ethanol levels were comparable with those of men in the second group.

DISCUSSION

The two most important findings were: firstly, that ethanol taken by mouth after about 2 hr hard exercise consistently produced profound falls in blood glucose; secondly, that this was associated with a failure of metabolic response to cold and a rapid fall in body temperature in cold air.

Ethanol presumably lowered the blood glucose after exercise by impairing hepatic gluconeogenesis at a time when liver glycogen reserves are depleted, as it does after starvation (Freinkel, Singer, Arky, Bleicher, Anderson & Silbert, 1963). Ethanol impairs gluconeogenesis, probably because it reduces the formation of pyruvate from lactate sufficiently to limit pyruvate carboxylation (Krebs *et al.* 1969). In the rat liver 60% inhibition of gluconeogenesis is produced by ethanol concentrations of only 5 mM (Krebs *et al.* 1969), approximately the blood ethanol concentration in the present experiments. Insulin release is not likely to have contributed to the hypoglycaemia since plasma insulin falls after exercise with ethanol (Haight, 1971).

Neither a high degree of previous athletic training, a carbohydrate meal before the exercise, or moderate obesity, completely prevented hypoglycaemia after exercise and ethanol. The last is of particular interest since Arky, Abramson & Freinkel (1968) have shown that ethanol does not lower the blood glucose of grossly obese people even after starvation for 3 days.

The failure of metabolic response to cold after exercise and ethanol might explain why body temperature fell in the cold, but does not explain why it fell in the warm; increased heat loss caused by vasodilatation must then have been responsible. Limb blood flow is known to increase during hypoglycaemia induced by insulin (Abramson, Schkloven, Margolis & Mirsky, 1939–40; Allwood, Ginsburg & Paton, 1957). Neither the failure of

shivering nor the vasodilatation were due in any important degree to a direct action of ethanol on the temperature regulating mechanisms, since they did not occur in subjects given glucose as well as ethanol after exercise. Ethanol, in amounts comparable to those used in the present study, is known to cause only slight vasodilatation and impairment of shivering (Keatinge & Evans, 1960; Andersen, Hellstrøm & Lorentzen, 1963). The fact that glucose restored normal temperature regulation strongly suggests that the failure of the thermoregulatory responses after exercise with ethanol was due to the hypoglycaemia rather than to any coincidental metabolic disturbance. Glucose is known to restore shivering after administration of insulin to rabbits (Laufberger, 1926), and abolishes insulin-induced vasodilatation in man (Abramson *et al.* 1939–40).

The hypoglycaemia is unlikely to have caused thermoregulatory failure by blocking peripheral effector organs. In particular the failure of metabolic response cannot have been due to failure in the skeletal muscles or motor neurones since the subjects were able to walk. The changes taken together are most easily explained by hypoglycaemia producing a substrate deficiency within, and so inhibiting, the hypothalamic centre that activates the mechanisms for heat conservation and heat production. The central nervous system can metabolize not only glucose but also β-hydroxybutyrate (Owen, Morgan, Kemp, Sullivan, Herrera & Cahill, 1967) and perhaps lactate (Ide, Steinke & Cahill, 1969) and free fatty acids (Volk, Millington & Weinhouse, 1952; Vignais, Gallagher & Zabin, 1958). The plasma concentrations of all these substances increased after exercise with ethanol in the present experiments but none reached levels at which it might have been expected to substitute for glucose in the central nervous system. Ethanol itself is not metabolized to any important extent by the brain, or indeed by any tissue except the liver (Schmidt & Schmidt, 1960).

Exercise without ethanol did not lower plasma glucose significantly. However, occasional blood glucose concentrations as low as those produced by exercise with ethanol in the present experiments have been recorded without ethanol after marathon races (Levine, Gordon & Derick, 1924; Best & Partridge, 1929–30; Matthies, 1931) and even after exercise comparable with that used in the present experiments (Saltin & Hermansen, 1967). Exercise alone may therefore be expected occasionally to cause enough hypoglycaemia to impair body temperature maintenance.

From the practical point of view the present findings imply that the casual hill-walker who stops in the open to drink spirits, without taking carbohydrate as well, runs a serious risk of developing an incapacitating degree of hypoglycaemia which is liable to be followed by death from hypothermia. Consumption of alcoholic drink has been reported to precede some cases of death from exposure in the mountains (Strang, 1969).

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