

Hypoglycaemia, hypothermia and shivering in man

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Summary

1. The present experiments were designed to elucidate the reasons for the fall in central body temperature during hypoglycaemia.

2. The first experiment was carried out at a room temperature of 25°C on 11 male subjects. Hypoglycaemia was induced by infusion of insulin. Heat production (calculated from respiratory gas exchange) rose from a baseline of 5.10 ± 0.13 kJ/min (mean \pm SEM) to a peak of 6.25 ± 0.21 kJ/min ($P < 0.001$), but core temperature fell concurrently by 0.51 ± 0.08 °C and skin temperature fell by 1.1 ± 0.2 °C. The net heat loss was due to peripheral vasodilatation and sweating.

3. To determine the effect of insulin-induced hypoglycaemia on thermoregulation in a cool environment, the experiment was repeated at a room temperature of 18–19°C on five of the subjects who had air blown over them until shivering was sustained. During this time heat production rose to 10.13 ± 1.67 kJ/min, but core temperature remained constant. Shivering stopped as plasma glucose fell below 2.5 mmol/l during insulin infusion and the subjects said they no longer felt cold.

4. During hypoglycaemia in the cold peripheral vasodilatation and sweating occurred, skin temperature fell by up to 0.8°C and core temperature fell below 35°C, so subjects had to be rewarmed.

5. Recovery of plasma glucose after hypo-

glycaemia in the cold was impaired at low body temperatures, but shivering was restored within seconds when glucose was given intravenously.

Key words: hypoglycaemia, hypothermia, insulin, shivering, thermoregulation.

Introduction

Hypothermia accompanies hypoglycaemia in conditions as diverse as hypopituitary coma [1], kwashiorkor [2], alcohol intoxication [3] and insulin-treated diabetes [4, 5]. Under experimental conditions body temperature falls when hypoglycaemia is induced with insulin [6] or alcohol [7], or when cerebral glucopenia is produced by infusing the glucose analogue 2-deoxy-D-glucose [8, 9]. A similar response to insulin-induced hypoglycaemia has been reported in several small mammalian species. It has been suggested that hypothermia may, by lowering overall energy requirements, help protect the brain from the harmful consequences of glucose deprivation [10], but the mechanism of the fall in temperature has not been established.

During thermal equilibrium, heat production equals heat loss. A fall in body temperature must mean that less heat is being generated or that more is being lost. The hypothermia of hypoglycaemia is thought to result from impaired heat production [6, 11], but there are reasons to doubt this. In the first place, hypoglycaemia stimulates the release of adrenaline and noradrenaline, which would normally promote thermogenesis. Secondly, hypoglycaemia causes peripheral vasodilatation and sweating, which would be expected to accelerate heat loss. We have studied the effect of insulin-induced hypoglycaemia on heat production, peripheral blood flow and body temperature in an attempt to resolve this problem.

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The normal response to a fall in core temperature is shivering, but Haight & Keatinge [12] found that volunteer subjects in whom hypoglycaemia had been induced by alcohol and exercise did not shiver when exposed to a room temperature of 14.5°C, although rectal temperature fell as low as 34.5°C. Animal experiments have shown that active shivering is suppressed during hypoglycaemia and restored with intravenous glucose [13]. For this reason we repeated the experiment in five volunteer subjects during active shivering.

Methods

Subjects

Eleven healthy male volunteer subjects (aged 25–35 years) took part in the initial experiment; five had additional studies. All subjects were non-obese as assessed by height and weight (ranges 1.65–1.82 m, 58–82 kg) and were medical students and staff members who gave informed written consent. The procedures used were approved by the Medical School Ethical Committee.

Experiment 1

The study consisted of a 30 min sodium chloride solution (150 mmol/l: saline) infusion, followed by a 40 min insulin infusion and a 50 min period of recovery. Room temperature was controlled at 25°C, relative humidity was 30–35%; the subjects wore shorts and were covered with a light blanket. A cannula in a left forearm vein was used for infusion and one in the right arm for blood sampling. Blood was taken at 10 min intervals during the experiment; blood glucose concentrations were measured with a Yellow Springs analyser. A plastic earpiece was placed in the outer ear and the thermistor probe protruded through this earpiece to a depth of 17 mm into the auditory canal. The outer ear was insulated with a large 2 cm thick foam pad and both pads were held in place with a bandage wrapped over the ears, the top of the head and under the chin. In our experience, after an initial 20 min warm-up period these thermistors give readings similar to those obtained with a zero-gradient aural thermometer [14] and also register identical changes in subjects exposed to whole-body cooling. In addition, in this experiment a heated-pad deep-body thermometer [15] was attached to the left side of the thorax of six of the subjects. Although the baseline 'core' temperature measured in this way was 0.4°C higher than with the auditory

canal thermistors, the temperature changes recorded during hypoglycaemia with both techniques were identical.

Skin temperature was recorded as the arithmetic mean of a total of eight thermistor probes taped on the ventral surface of the body on each shoulder, on the abdomen either side of the umbilicus in the mid-clavicular line, over the quadriceps femoris on each thigh and on each foot over the cuneiforms. The mean temperature was obtained with the eight thermistors connected in parallel into a single Wheatstone bridge circuit. The mean temperature obtained in this way is approximately 1.1°C lower than the weighted mean temperatures derived as described by Hardy & Dubois [16] or Ramanathan [17], but a fall in temperature of approximately 2°C produced by external cooling is recorded similarly with all three techniques. Core and skin temperatures were recorded every 2 min. The heart rate was taken from ECG electrodes sited on the chest. The left hand was placed in a water-filled plethysmograph maintained at 34°C for measurement of hand blood flow [18]. Venous occlusion plethysmography was used to measure calf blood flow, which was recorded with a mercury-in-rubber strain gauge [19]; forearm blood flow could not be measured because of the intravenous cannulae. Hand and calf blood flows were recorded at 10 min intervals with an SE oscillograph (S.E. Laboratories, Feltham, Middx., U.K.). Blood pressure was taken by auscultation at the same time. Mean blood pressure was calculated as: (systolic BP + 2 × diastolic BP)/3.

Hand and calf vascular resistances were calculated as: mean blood pressure/blood flow. In calculating calf vascular resistance we assumed that there would be no large differences between mean brachial and popliteal arterial pressures in young healthy supine subjects.

All subjects were trained previously in the use of valved mouthpieces, nose-clips and Douglas bags. At the start of each experiment, the subject breathed through the mouthpiece for 5 min before any collections were started. Afterwards, expired air was collected in Douglas bags for 4 min out of every 10 min for measurement of respiratory gas exchange. Total gas volume, oxygen and carbon dioxide content were determined with a dry-gas meter (DTM-115 R4, Singer), a paramagnetic oxygen analyser (Servomex OA 137) and an infrared carbon dioxide analyser (PK Morgan 901 Mk II). Heat production (energy expenditure) was calculated from the formula of Weir [20].

A slow saline infusion was given by syringe pump during the 30 min control period. Insulin

(Actrapid, Novo) was then given as a 4 unit bolus followed by a 40 min infusion at a rate of 6 units/h. The saline infusion continued during the 50 min recovery period. Sweating was observed but not measured quantitatively. All results have been expressed as means \pm 1 SEM. The significance of differences was tested with Student's paired *t*-test.

Experiment 2

Insulin hypoglycaemia was induced during shivering in five of the original subjects. The room temperature was set at 18–19°C and the volunteers lay uncovered on a couch wearing shorts only, while air was blown across them with a fan at a wind speed of 1.7 m/s. This continued until sustained shivering was observed for at least 10 min; this period was reached within 60–75 min of the start. The identical procedure was followed, with the addition that shivering was recorded with surface EMG electrodes attached over the left quadriceps muscle and monitored on a Grass recorder. Insulin hypoglycaemia was then induced as in the previous experiment.

Further studies

Experiment 2 was repeated in two subjects with the difference that hypoglycaemia was now reversed by a glucose injection in the face of continued insulin infusion. After 40 min of hypoglycaemia the first subject was given 25 g of intravenous glucose as 50% (w/v) glucose solution. The second subject received 10 g of glucose as 10% (w/v) glucose solution after 20 min of hypoglycaemia.

On another occasion the second subject repeated the procedure, with the addition that EMG electrodes were attached to both thighs and a cuff placed round the upper part of the left thigh was inflated to above arterial pressure 1 min before hypoglycaemia was reversed with intravenous glucose given into an arm vein.

Results

Experiment 1

Symptoms and signs of hypoglycaemia appeared within 20–30 min of starting the insulin infusion. Plasma glucose fell to a mean of 1 ± 0.1 mmol/l and remained below 2 mmol/l for at least 30 min (Fig. 1). Core temperature began to fall after 30 min, reaching a minimum 58–78 min after insulin was given. The mean maximal fall was $0.51 \pm 0.08^\circ\text{C}$ ($P < 0.001$) with a mean

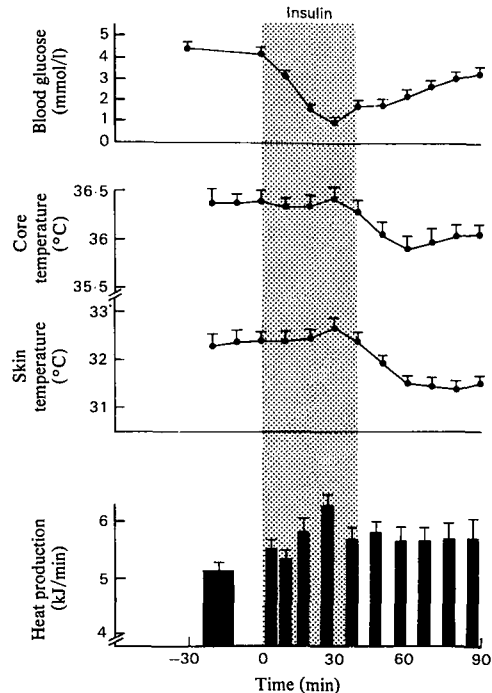


FIG. 1. Effect of insulin-induced hypoglycaemia on plasma glucose, core temperature and skin temperature in 11 normal volunteer subjects at an environmental temperature of 25°C; values are means \pm 1 SEM. Heat production rose but central temperature fell.

rate of fall of $1.2^\circ\text{C}/\text{h}$. Skin temperature rose at first, but fell after 30 min as sweating developed; the total fall was $1.1 \pm 0.2^\circ\text{C}$ (Fig. 1); differential changes on the limbs and trunk could not be determined with the recording system used.

Energy expenditure rose from 5.10 ± 0.13 kJ/min during the baseline period to a peak of 6.25 ± 0.21 kJ/min 30 min after the insulin infusion started ($P < 0.001$); it remained elevated throughout the experiment. Maximum increases in heart rate and systolic blood pressure were seen at 33 min and minimum diastolic pressure was reached at 43 min. Calf blood flow rose from 2.8 ± 0.4 to a peak of 5.4 ± 0.8 ml min^{-1} 100 ml $^{-1}$ of tissue at 33 min; hand blood flow rose from 10.3 ± 1.5 to 17.9 ± 2.8 ml min^{-1} 100 ml $^{-1}$ of tissue and was maximal at 43 min (Table 1).

Core temperature fell despite an increase in energy expenditure and this loss was associated with peripheral vasodilatation and sweating.

Experiment 2

Continuous shivering developed in all five subjects after 1 h of cold exposure and became

TABLE 1. Cardiovascular changes (mean \pm SEM) in the warm and in the cold
Results are maximum or minimum values observed during hypoglycaemia. Hand blood flow could not be measured during shivering (N.D.).

	Expt. 1 (25°C) (n = 11)		Expt. 2 (18–19°C) (n = 5)	
	Baseline	Hypoglycaemia	Pre-infusion	Hypoglycaemia
Plasma glucose (mmol/l)	4.4 \pm 0.2	1.0 \pm 0.1	4.3 \pm 0.2	1.2 \pm 0.1
Heart rate (beats/min)	61.0 \pm 2.0	78.0 \pm 3.0	59.0 \pm 4.0	71.0 \pm 6.0
Systolic BP (mmHg)	114.0 \pm 3.0	142.0 \pm 5.0	116.0 \pm 6.0	134.0 \pm 5.0
Diastolic BP (mmHg)	77.0 \pm 2.0	54.0 \pm 2.0	83.0 \pm 2.0	61.0 \pm 3.0
Calf blood flow (ml min ⁻¹ 100 ml ⁻¹ of tissue)	2.8 \pm 0.4	5.4 \pm 0.8	1.7 \pm 0.4	2.1 \pm 0.4
Calf vascular resistance (arbitrary units)	34.5 \pm 3.1	18.1 \pm 2.1	63.6 \pm 18.8	45.5 \pm 5.8
Hand blood flow (ml min ⁻¹ 100 ml ⁻¹ of tissue)	10.3 \pm 1.5	17.9 \pm 2.8	N.D.	12.8 \pm 3.0
Hand vascular resistance (arbitrary units)	12.7 \pm 4.1	5.9 \pm 1.5	N.D.	8.0 \pm 1.6

progressively more intense. Despite unaltered environmental conditions, shivering was completely suppressed within 8.5–15 min of infusing insulin. This occurred when plasma glucose was in the range 2.5–2.7 mmol/l. Cessation of shivering was confirmed by the EMG trace. There were no central effects during hypoglycaemia other than mild drowsiness and mental clarity was not affected, although this was not tested in any objective way. Notwithstanding, subjective awareness of cold discomfort virtually disappeared.

Energy expenditure doubled during shivering (Fig. 2), while core temperature remained constant. When shivering stopped energy expenditure fell rapidly and was below initial levels by the end of the experiment. Core temperature fell below 35°C in all five volunteer subjects and intervention became necessary. Skin temperature, already low at the start of the infusion, fell by up to 0.8°C thereafter. Maximal cardiovascular changes during hypoglycaemia are detailed in Table 1. Calf and hand blood flows were low during cold exposure, but showed a transient increase with hypoglycaemia; two subjects sweated visibly for a few minutes.

The minimum of plasma glucose was, at 1.2 mmol/l, higher than in Experiment 1, but the recovery of blood glucose was greatly impaired (Fig. 3). Plasma glucose did not begin to rise in any individual until active rewarming was started and shivering did not resume until oral glucose was given at the end of the experiment.

Further studies

Both subjects stopped shivering as hypoglycaemia developed. After intravenous glucose,

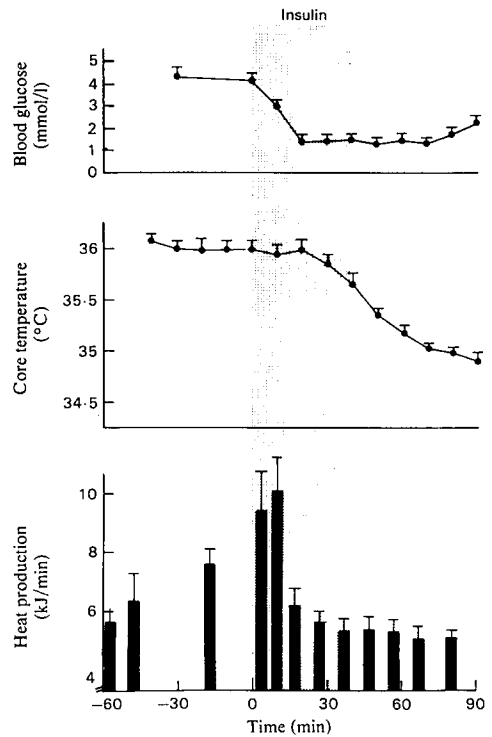


FIG. 2. Effect of insulin-induced hypoglycaemia on plasma glucose, core temperature and heat production in five volunteer subjects who were fanned with air at 18–19°C; values are means \pm 1 SEM. Heat production rises as shivering develops but returns to baseline as shivering is inhibited. Core temperature fell below 35°C in each subject.

shivering restarted within 40 s in both subjects. This is illustrated by the EMG trace from the first subject (Fig. 4). In the repeated experiment on the second subject, glucose injection restored shiver-

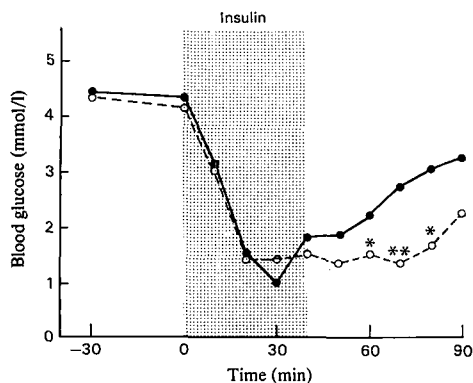


FIG. 3. Plasma glucose responses to insulin infusion. Expt. 1 (—) shows the response of five volunteer subjects at 25°C. Expt. 2 (---, 18–19°C) shows the same five subjects during cold exposure. Recovery of plasma glucose is impaired at low body temperature. Significance of differences: * $P < 0.05$; ** $P < 0.01$.

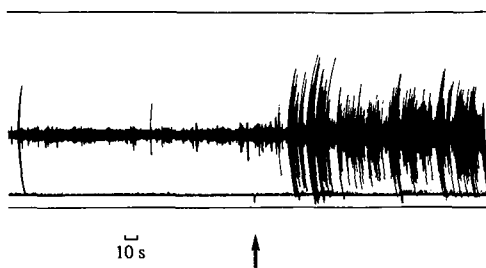


FIG. 4. EMG trace from the quadriceps muscle of a hypoglycaemic volunteer subject in a cold environment (tympanic temperature = 35.2°C). Glucose injection (indicated by arrow) restored shivering within 40 s.

ing in the arterially occluded leg at the same time as the other limb.

Discussion

The observation that body temperature falls during hypoglycaemia was made soon after insulin was introduced [21]. By 1930, the effect had been noted in cats, dogs [13], woodchucks [22] and hens [23], as well as in man [24]. In the present study temperature fell by 0.3–1.2°C in normal volunteer subjects in a warm environment. Although temperature fell during hypoglycaemia, heat production increased by a mean of 23% with a range of 14–37%. Studies by Thompson *et al.* [9] showed an increase in heat production in man after 2-deoxy-D-glucose infusion, but body temperature fell. We have shown that the increase in heat production in hypoglycaemia can be abolished by pretreatment with

propranolol [25], suggesting that it is due to catecholamines secreted in response to hypoglycaemia. The apparent paradox that body temperature falls at a time when heat production is increased implies rapid heat loss at the surface of the body.

Two main factors contribute to heat loss during hypoglycaemia: peripheral vasodilatation and sweating. The rate and depth of breathing increase with the onset of hypoglycaemia but, since this is transient, evaporative heat loss due to respiration is unlikely to be of major importance. In contrast, sweat evaporates during hypoglycaemia at an estimated rate of 2 g/min for 30 min [26]. The evaporation of 60 g of sweat uses 146 kJ of heat, sufficient to lower the temperature of a 70 kg man in previous thermal equilibrium by 0.5°C. Infusions of adrenaline or noradrenaline cause a relatively weak sweating response [27], thus activation of cholinergic sudomotor nerves probably contributes to the profuse sweating of hypoglycaemia. Local release of bradykinin may be involved in the skin vasodilatation and sweating seen during hypoglycaemia in a similar way to its involvement during heat vasodilatation [28]. Although Allwood & Needham [29] reported that forearm venous bradykinin was not increased during hypoglycaemic vasodilatation and sweating, it is possible that the bradykinin either remained in the tissue fluid or was secreted in the sweat as these authors also did not detect increased forearm venous bradykinin after heating.

Changes in skin temperature produce the greatest change in core temperature when cutaneous blood flow is high. For example, victims of heat stroke cool more rapidly when sprayed with water and warm air than with cold air, since the latter induces vasoconstriction in the skin, thus insulating it from the core [30]. Despite the clinical impression of generalized pallor, the onset of hypoglycaemia is associated with vasodilatation of skin as well as of muscle [31]. It will be noted that skin temperature rose in our subjects until sweating developed (Fig. 1), and that hand blood flow, most of which is to skin, nearly doubled (Table 1). This effect on hand blood flow, totally opposite to that of circulating adrenaline, is thought to be due to release of neurogenic vasoconstrictor tone [32]. Sympathectomy of a limb, surgical or pharmacological [33, 32], converts the response to a localized vasoconstriction during hypoglycaemia; the effect high circulating catecholamine levels would be expected to produce in cutaneous blood vessels. The combination of cutaneous vasodilatation with sweating ensures rapid cooling and explains

why body temperature falls during hypoglycaemia despite increased heat production.

In 1925 Cassidy *et al.* [13] reported that insulin-induced hypoglycaemia inhibited shivering in the cat and dog. Their observations were later extended to the woodchuck [22] and the domestic hen [23]. Profound hypothermia developed when the animals were immersed in cold water, yet they survived for many hours, leading the authors to believe that they had induced a state of artificial hibernation. Glucose infusions rapidly restored shivering, so that temperature rose back to normal.

Our study has shown a similar pattern of responses in man. Shivering was suppressed at blood glucose levels below 2.5 mmol/l. The result was that our subjects, drowsy but fully conscious, were unable to maintain body temperature when fanned with cool air. There was no resumption of shivering although core temperature fell below 35°C in every case. It was equally striking that perception of cold discomfort was greatly reduced as hypoglycaemia developed. Intravenous glucose restored shivering almost at once. The speed of response suggested that it was central, rather than peripheral, and this was confirmed when shivering resumed in a limb isolated from the circulation by an arterial occlusion cuff.

Spontaneous recovery of blood glucose was impaired at lowered body temperatures (Fig. 3). We are unable to explain this observation but a similar failure of recovery from hypoglycaemia was noted in cats and dogs, although at the much lower temperature of 25°C, in the experiments of Cassidy *et al.* [13].

Hypoglycaemia inhibited shivering, resulting in hypothermia. Since blood glucose recovery was impaired at low body temperature, a vicious circle had been established. It seems likely that our volunteer subjects would have progressed to severe hypothermia if the experiment had not been interrupted.

In summary, a fall in body temperature appears to be an integral part of the hypoglycaemic response. The ability to maintain a constant temperature is affected in three distinct ways: by sweating, peripheral vasodilatation and inhibition of shivering. Moreover, hypothermia occurs in species other than man. Anoxia causes a similar fall in temperature in experimental animals [10] and when mice were kept at 37°C, so that cooling was impossible, the mortality during anoxia rose from 8 to 90% [34]. These considerations suggest that hypothermia may have functional benefit during hypoglycaemia in some species, though not necessarily so in man.

The effect of hypoglycaemia on shivering is more difficult to interpret. It could be argued that the inhibition of shivering during hypoglycaemia is beneficial in that it reduces the demand for glucose in the peripheral tissues thus possibly making more glucose available to the central nervous system. Small animals tolerate hypothermia relatively well and might benefit from a response that in man appears to be vestigial and potentially harmful. Speculation aside, these observations help to explain the coincidence of hypoglycaemia and hypothermia in a variety of clinical disorders.

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