The effect of propranolol or metoprolol on thermoregulation during insulin-induced hypoglycaemia in man

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Summary
1. The effects of metoprolol and propranolol on heat production and body temperature have been studied in six male subjects during insulin-induced hypoglycaemia in a thermoneutral environment. Hypoglycaemia was induced by insulin infusion on three occasions in each subject, accompanied by the infusion of sodium chloride solution (154 mmol/l) (control), metoprolol ($\beta_1$-selective antagonist) or propranolol (non-selective antagonist).

2. During the period of hypoglycaemia in the control experiments mean heat production (calculated from respiratory gas exchange) increased by 1.07 ± 0.13 kJ/min and remained elevated for 30–40 min. This heat production response was reduced by metoprolol and abolished by propranolol. During the recovery period, heat production was significantly reduced in the presence of propranolol.

3. Skin and core temperatures fell during the period of hypoglycaemia in all three experiments. The fall in skin temperature was significantly greater in the presence of propranolol ($-2.51 \pm 0.47^\circ$C). The reductions in core temperature recorded during the three experiments were similar (control $-0.73 \pm 0.17$, metoprolol $-0.99 \pm 0.21$, propranolol $-0.88 \pm 0.22^\circ$C), but core temperature was still falling at the end of the propranolol experiment.

4. The cardiovascular responses to hypoglycaemia were similar in the control and metoprolol experiments but were substantially modified by propranolol. During the period of hypoglycaemia in the control experiments, plasma adrenaline levels rose to $7.78 \pm 1.79$ nmol/l; significantly higher levels were measured in the metoprolol ($10.11 \pm 1.64$) and propranolol ($22.76 \pm 7.02$) experiments. The very high adrenaline levels may have been responsible for the modified cardiovascular responses to hypoglycaemia observed in the propranolol experiment.

Key words: catecholamines, hypoglycaemia, insulin, metoprolol, propranolol, thermoregulation.

Introduction
Insulin-induced hypoglycaemia produces a rapid fall in body temperature both in diabetic [1, 2] and in non-diabetic subjects [3, 4]. This fall occurs despite an increase in resting heat production [4], and results from accelerated heat loss due to peripheral vasodilatation and sweating. Hypoglycaemia causes profound activation of the sympathoadrenal system [5, 6], and increased catecholamine levels can affect both heat production [7, 8] and heat loss (via sweating [9] and alterations in peripheral blood flow [10, 11]) and may influence body temperature.

Catecholamines increase heat production, most probably by acting upon both $\beta_1$- and $\beta_2$-adrenoceptors. We therefore examined the effects of selective ($\beta_1$) and non-selective ($\beta_1$ and $\beta_2$) adrenoceptor antagonists on heat production during insulin-induced hypoglycaemia. It was expected that one or both agents would prevent a rise in heat production during hypoglycaemia. If
so, the fall in body temperature should be greater than under control conditions, provided that there were no opposing effects upon heat loss. In this paper we report the effect of short term administration of propranolol or metoprolol upon body temperature, heat production, sweating and peripheral blood flow during insulin-induced hypoglycaemia in normal subjects.

Methods

Protocol

Six non-diabetic male volunteers aged 25–35 years took part in the study, which was approved by the Medical School Ethical Committee. None was obese. Each person was rendered hypoglycaemic on three occasions, while receiving, in random order, infusions of propranolol or metoprolol or sodium chloride solution (150 mmol/l: saline). At least 7 days were allowed to elapse between each experiment in each individual. The subjects fasted overnight for 12 h before the experiment, which was performed while they rested supine, wearing shorts only, on a mesh bed. Room temperature was maintained between 29° and 30°C; relative humidity varied from 18 to 30% throughout the series of experiments, but the greatest variation in relative humidity within a single experiment was 4%. Cannulae were inserted in veins in each forearm (see below). Blood was sampled at 10 min intervals from the right arm, and infusions were given in the left. Core temperature was measured from thermistors placed in each auditory canal, and the ears were insulated with foam pads [4]. Skin temperature was taken as the arithmetic mean recorded by eight thermistors taped to the ventral surface of the body [4]. The left hand was placed in a water-filled plethysmograph kept at 34°C [12] and a mercury-in-rubber strain-gauge [13] was attached to the right calf. The blood flows to hand and calf were determined at 10 min intervals throughout the experiment by venous occlusion plethysmography. Heart rate was monitored continuously from the ECG and both heart rate and blood flow were recorded on a U.V. recorder (S.E. Labs, Feltham, Middx., U.K.). Brachial arterial blood pressure was measured (with a sphygmomanometer) during each period of blood flow measurement.

All subjects were trained in the use of valved mouthpieces, nose-clips and Douglas bags and during experiments expired air was collected in Douglas bags for 4 min out of every 10 min. Gas composition and volume were measured as described previously [4] and from these measurements heat production was calculated by the method of Weir [14].

The rate of evaporation of sweat from the skin of the forehead, chest, abdomen, upper arm and thigh was measured with an evaporimeter (Servomex). Sweat evaporation rates were measured at 5 min intervals during each experiment.

Infusions

Each experiment started with a 30 min baseline period followed by a 25 min infusion of saline, propranolol or metoprolol before insulin was given. The infusions were as follows.

Control experiment. Saline (10 ml) was injected over 5 min followed by the infusion of 4 ml of saline/h.

Metoprolol experiment. Metoprolol tartrate (1 mg/ml) was injected intravenously (volume injected = 13 ml) over a period of 5 min, followed by an infusion of 4 mg (in 4 ml) of metoprolol/h for the remainder of the experiment. The dose ratio of 1:3:1 (metoprolol:propranolol, w/w), was chosen in the light of recent studies comparing the potency of the two agents, when administered intravenously, in reducing exercise-induced tachycardia [15].

Propranolol experiment. Propranolol hydrochloride (1 mg/ml) was injected intravenously (volume injected = 10 ml) over a period of 5 min, followed by an infusion of 3 mg (in 3 ml)/h, which was continued for the remainder of the experiment. The dose of propranolol chosen was previously found to abolish tachycardia during hypoglycaemia [16].

The variables listed were monitored during the first 25 min of saline, metoprolol or propranolol infusion (before insulin was given) and throughout the remainder of the experiment. Hypoglycaemia was induced by a bolus injection of 4 units of monocomponent insulin (Actrapid, Novo) followed by the infusion of a further 4 units over the next 40 min.

Blood samples

Whole blood (2 ml) was placed in tubes with fluoride/oxalate and centrifuged. The plasma was aspirated and frozen for later measurement of glucose concentration with an automated glucose oxidase assay (GOD-PAP, Boehringer) using a Technicon AA II autoanalyser.

Whole blood (5 ml) was placed in tubes with lithium/heparin and centrifuged at 4°C for 10 min. The plasma was added to 100 μl of EGTA/glutathione [17], and stored at −80°C.
until analysis of catecholamine content. The catecholamines were extracted from 1 ml of plasma by using alumina, separated by high performance liquid chromatography and measured with electrochemical detection by the procedures described by Hjemdahl et al. [18]. Each sample was assayed in duplicate, and the percentage recovery during the extraction of each sample was determined by addition of an internal standard (10 pmol of dopamine) to each extraction. A selection of samples was extracted with an alternative internal standard (dihydroxybenzylamine) and the dopamine content was found to be below the limit of detection of the assay (0.2 pmol/ml of plasma). The intraassay coefficient of variation (CV) for noradrenaline and adrenaline concentrations measured during hypoglycaemia is 4% in our laboratory and the interassay CV is 10%.

Results

Results are presented as mean values ± 1 SEM unless otherwise stated. Statistical significance of responses and differences between responses were assessed with a two-tailed Student's paired t-test or Wilcoxon matched pairs signed rank test. Since maximal responses to hypoglycaemia did not occur at the same time in all subjects, data were analysed not only as mean values at each time point but also as mean maximal responses.

Table 1 summarizes the results of the present experiments.

**Plasma glucose (Fig. 1)**

Plasma glucose was similar in all experiments during the baseline period (saline 5.08 ± 0.07, metoprolol 5.24 ± 0.08 and propranolol 5.01 ± 0.08 mmol/l), and fell rapidly and at an equal rate in response to insulin in all three experiments. Minimum plasma glucose concentrations were reached 20 or 30 min after the insulin infusion started. The group mean minimum values did not differ significantly (saline 1.44 ± 0.10, metoprolol 1.37 ± 0.10, propranolol 1.43 ± 0.10 mmol/l). Glucose recovery was not influenced by either β-adrenoceptor antagonist.

**Heat production (Fig. 2)**

Baseline heat production was not modified by saline, metoprolol or propranolol. In the control (saline) experiment, heat production rose significantly as hypoglycaemia developed, with a mean maximum increment of 1.07 ± 0.13 kJ/min (22%). Heat production remained significantly elevated for 20 min after the insulin infusion. A smaller, but otherwise similar, response occurred in the metoprolol experiment, with a mean maximum increment in heat production of 0.73 ± 0.14 kJ/min. Heat production returned to its baseline level 5 min after the insulin infusion stopped and showed no change thereafter.

In contrast there was no systematic increase in heat production in the presence of propranolol. The mean maximum increment was 0.46 ± 0.11 kJ/min. Although statistically significant, this 9.5% increase is small in relation to the 5% variation in the baseline observed in all experiments. Heat production was significantly and progressively depressed during the period of glucose recovery (Fig. 2).

**Skin temperature (Fig. 3)**

Skin temperature was similar at the start of insulin infusion in all experiments (saline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Maximum change during hypoglycaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Heat production (kJ)</td>
<td>+1.07 ± 0.13</td>
</tr>
<tr>
<td>Skin temperature (°C)</td>
<td>-1.75 ± 0.47</td>
</tr>
<tr>
<td>Core temperature (°C)</td>
<td>-0.73 ± 0.17</td>
</tr>
<tr>
<td>Hand blood flow (ml min⁻¹ 100 ml⁻¹ of limb)</td>
<td>+5.9 ± 1.35</td>
</tr>
<tr>
<td>Calf blood flow (ml min⁻¹ 100 ml⁻¹ of limb)</td>
<td>+2.4 ± 0.35</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>+15.0 ± 2.4</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>+30 ± 3.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>-10 ± 1.4</td>
</tr>
<tr>
<td>Plasma noradrenaline (nmol/l)</td>
<td>+2.97 ± 0.72</td>
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<tr>
<td>Plasma adrenaline (nmol/l)</td>
<td>+7.16 ± 1.76</td>
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</tbody>
</table>

Table 1. Summary of the physiological responses to hypoglycaemia and their modification by metoprolol and propranolol

Mean values ± SEM are shown.
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FIG. 1. Effect of β-adrenoceptor antagonists on the changes in plasma glucose produced by insulin infusion. The glucose curves are plotted from the mean of the four baseline values. Values are means ± 1 SEM. •, Control; Δ, metoprolol; □, propranolol. Neither antagonist affected the depth of hypoglycaemia or the first 60 min of glucose recovery.

33.15 ± 0.22°C, metoprolol 33.00 ± 0.17°C, propranolol 33.10 ± 0.30°C); changes during the insulin infusion and recovery periods are illustrated in Fig. 3. In every case, the fall in skin

FIG. 2. Effect of β-adrenoceptor antagonists on the heat production response to insulin-induced hypoglycaemia. Values are means ± 1 SEM. The response was reduced in both magnitude and duration by metoprolol and abolished by propranolol. Heat production was significantly reduced by propranolol in the recovery period after hypoglycaemia. Significance of differences from normoglycaemic values: *P < 0.05; **P < 0.01.

FIG. 3. Effect of β-adrenoceptor antagonists on the changes in skin and core temperature which occurred as a consequence of insulin-induced hypoglycaemia. Values are means ± 1 SEM. •, Saline; Δ, metoprolol; □, propranolol. Skin temperature fell in all three experiments; the decrease was significantly greater with propranolol. Core temperature fell by similar amounts in all three experiments but the fall was delayed in the propranolol experiment. Significance of differences of propranolol values from saline: *P < 0.05; **P < 0.01.
**Core temperature (Fig. 3)**

Core temperatures were similar at the start of insulin infusion in all experiments (saline 36.52 ± 0.09°C, metoprolol 36.50 ± 0.17°C, propranolol 36.57 ± 0.07°C). Subsequent changes are shown in Fig. 3.

Core temperature was stable during the first 30 min of insulin infusion in the saline and metoprolol experiments and then fell at a similar rate and to similar levels. The mean fall with saline (0.73 ± 0.17°C) was less than with metoprolol (0.99 ± 0.21°C) but not significantly so. Core temperature was returning towards baseline by the end of the recovery period (90 min) in the saline experiment but was at or near its minimum value in the metoprolol experiment.

In contrast, there was a small increase in core temperature at 30 and 40 min with propranolol (Fig. 3), followed by a fall at the end of the insulin infusion, which was slightly faster than with saline but not significantly so. The mean maximal fall in the propranolol experiment was 0.88 ± 0.22°C, and did not differ significantly from results in the other experiments. However, Fig. 3 suggests that core temperature was still falling at the end of the procedure, so that a longer experiment might have revealed a more striking effect upon core temperature.

**Peripheral blood flow (Fig. 4)**

Calf blood flow decreased slightly during the baseline period in all experiments, but this trend was not statistically significant. Calf blood flow was similar before the insulin infusion in the saline (3.57 ± 0.32 ml min⁻¹ 100 ml⁻¹ of limb) and propranolol (3.08 ± 0.34 experiments), but was significantly less with metoprolol (2.79 ± 0.37 ml min⁻¹ 100 ml⁻¹ of limb) than with saline (P < 0.01).

Hypoglycaemia was associated with a progressive increase in calf blood flow (Fig. 4) in the control experiment, with a mean maximum increase of 2.35 ± 0.35 ml min⁻¹ 100 ml⁻¹ of limb (P < 0.001) at either 30 or 40 min. The increase in calf blood flow of 1.24 ± 0.24 ml min⁻¹ 100 ml⁻¹ of limb seen with metoprolol was significant only at 30 min and was significantly less than that observed in the saline experiment. There was no significant change in the propranolol experiment.

Hand blood flow was similar and reasonably constant during the baseline period (saline 11.1 ± 1.8, metoprolol 10.0 ± 1.0 and propranolol 10.2 ± 0.9 ml min⁻¹ 100 ml⁻¹ of limb), and increased significantly during hypoglycaemia in both the saline and metoprolol

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**Table 2. Increase in sweat evaporation during hypoglycaemia**

<table>
<thead>
<tr>
<th>Values are means ± SEM, n = 6. *Significantly greater than saline, P &lt; 0.05, paired t-test.</th>
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<tr>
<th>Evaporation (g of water/m²)</th>
<th>Saline</th>
<th>Metoprolol</th>
<th>Propranolol</th>
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<tbody>
<tr>
<td><strong>Arm</strong></td>
<td>24.8 ± 1.2</td>
<td>34.4 ± 1.6</td>
<td>41.6 ± 1.9</td>
</tr>
<tr>
<td><strong>Thigh</strong></td>
<td>33.7 ± 1.3</td>
<td>33.5 ± 1.4</td>
<td>43.3 ± 2.4</td>
</tr>
<tr>
<td><strong>Chest</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Upper</strong></td>
<td>42.2 ± 1.9</td>
<td>45.4 ± 2.0</td>
<td>59.6 ± 3.1</td>
</tr>
<tr>
<td><strong>Lower</strong></td>
<td>34.7 ± 2.0</td>
<td>37.5 ± 2.1</td>
<td>48.5 ± 2.5</td>
</tr>
<tr>
<td><strong>Abdomen</strong></td>
<td>34.2 ± 2.1</td>
<td>37.5 ± 2.2</td>
<td>48.7 ± 2.6</td>
</tr>
<tr>
<td><strong>Forehead</strong></td>
<td>44.5 ± 2.5</td>
<td>69.1 ± 4.1</td>
<td>84.1 ± 6.3</td>
</tr>
</tbody>
</table>

Temperature coincided with an increase in sweat evaporation. Although the decline was similar in all three experiments during the insulin infusion period, skin temperature continued to fall in the propranolol experiment whereas some recovery occurred in the saline and metoprolol experiments. This is emphasized by the significantly greater (P < 0.05) mean maximum fall in skin temperature with propranolol: -2.51 ± 0.47°C compared with -1.75 ± 0.47°C with saline.

**Sweat evaporation (Table 2)**

During the baseline periods sweat evaporation rate was most rapid from the forehead (19.1 ± SD 1.4 g h⁻¹ m⁻²), with a mean value for the other sites of 8.0 ± SD 1.5 g h⁻¹ m⁻². Sweat evaporation increased markedly at all sites 20–30 min from the start of each insulin infusion. Peak evaporation rates varied between 100 and 150 g h⁻¹ m⁻² on the forehead, 75–140 g h⁻¹ m⁻² on the trunk and 50–125 g h⁻¹ m⁻² on the limbs. There were no significant differences in peak evaporation rates in the three experiments. The mean duration of increased sweat evaporation was 45 min in the saline experiment, 49.2 min with metoprolol and 56.7 min with propranolol, but none of the differences was significant. Total sweat evaporation during hypoglycaemia and the recovery period was estimated by integrating the area beneath the increase in sweat evaporation rate for each subject (Table 2). The mean values for the propranolol experiment were greater than the saline control at all sites but the difference was statistically significant only for the forehead. The increase observed with metoprolol was not significantly different from that with saline.
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Fig. 4. Effect of β-adrenoceptor antagonists on peripheral blood flow during insulin-induced hypoglycaemia. Values are means ± 1 SEM. ●, Saline; Δ, metoprolol; □, propranolol. Hand blood flow doubled during hypoglycaemia in the control and metoprolol experiments, calf blood flow doubled in the control experiment and increased slightly in the metoprolol experiment. With propranolol, calf blood flow did not change and hand blood flow fell during hypoglycaemia. Significance of the differences between the hypoglycaemic and the normoglycaemic values within each experiment: *P < 0.05; ***P < 0.001.

Experiments. The mean maximal increases did not differ significantly (saline +5.92 ± 1.35; metoprolol +8.8 ± 2.2 ml min⁻¹ 100 ml⁻¹ of limb). In contrast, hand blood flow decreased to a mean value of 6.0 ± 1.2 ml min⁻¹ 100 ml⁻¹ of limb (P < 0.05) in the propranolol experiment.

Heart rate and blood pressure

Both heart rate and blood pressure fell during infusion of metoprolol and propranolol in the baseline period. Before the insulin infusion, heart rate was 63 ± 3.5 beats/min in the saline experiment as against 55 ± 4.4 and 55 ± 3.0 in the metoprolol and propranolol experiments respectively. During insulin infusion there was an increase in heart rate in the saline (mean peak heart rate 78.0 ± 4.5 beats/min) and metoprolol (mean peak heart rate 69 ± 4.2 beats/min) experiments; the peak heart rate was recorded at either 30 or 40 min. In contrast, heart rate had fallen significantly in the propranolol experiment at 40 min and remained below baseline levels throughout the recovery period. The mean minimum heart rate during hypoglycaemia was 39 ± 1.6 beats/min in the propranolol experiment, and ECG changes with variable P-R intervals, ranging from normal down to zero, and prominent U waves appeared in all subjects. No changes occurred in the other experiments.

In the saline experiment, hypoglycaemia was associated with an increase in systolic blood pressure and decrease in diastolic blood pressure with no change in mean blood pressure. Systolic
blood pressure also rose during hypoglycaemia in the metoprolol experiment but there were no significant changes in either diastolic or mean blood pressure. Both systolic and diastolic blood pressure increased during hypoglycaemia in the propranolol experiment. In consequence, mean blood pressure rose from a baseline value of 92.3 ± 3.6 mmHg to a mean maximum of 115.2 ± 4.5.

**Plasma catecholamines (Fig. 5)**

Plasma concentrations of noradrenaline and adrenaline were similar in all experiments during the baseline period, were unaffected by propranolol or metoprolol, and remained at baseline levels for the first 20–30 min of insulin infusion. There was a rapid increase in plasma catecholamine concentrations (Fig. 5) as hypoglycaemia developed.

Plasma noradrenaline rose to a peak 30–40 min after the start of the insulin infusion (saline 4.15 ± 0.75, metoprolol 4.09 ± 0.61 and propranolol 5.13 ± 1.13 nmol/l). The peak concentrations and areas under the curves did not differ significantly between the three experiments.

In contrast, the rise in plasma adrenaline during hypoglycaemia was significantly potentiated by both β-adrenoceptor antagonists. The peak plasma adrenaline in the saline experiment (7.78 ± 1.79 nmol/l) was significantly (P < 0.05) lower than with metoprolol (10.11 ± 1.64 nmol/l) or propranolol (22.76 ± 7.02 nmol/l).

**Discussion**

Our main aim was to establish whether the increase in heat production during insulin-induced hypoglycaemia in non-diabetic subjects [4] is due to activation of β-adrenoceptor-mediated mechanisms. This was tested by observing the effects of a β₁-selective (metoprolol) and a non-selective (propranolol) adrenoceptor antagonist on the physiological responses to hypoglycaemia. Since the severity of hypoglycaemia and the rate of subsequent glucose recovery were not affected by
either agent, differences observed in the physiological response cannot be attributed to differences in the hypoglycaemic stimulus.

Table 1 summarizes the main findings. In the control experiment, resting heat production increased by 22%, and remained significantly elevated for 20 min after the insulin infusion. The magnitude and pattern of this response is similar to that in our earlier study [4] and is qualitatively similar to that seen after 2-deoxy-d-glucose-induced cerebral glucopenia [19]. There was a smaller, transient increase with metoprolol, and with propranolol there was a minimal increase in heat production during hypoglycaemia and a progressive fall during the recovery period.

The increase in heat production during hypoglycaemia thus results mainly from activation of /-adrenoceptor-mediated mechanisms, presumably leading to increased oxidation of circulating free fatty acids [7, 8] and lactate [8]. The free fatty acid response to hypoglycaemia is impaired both by metoprolol [20] and propranolol [21]. Corrall et al. [22] have recently shown that the lactate response to hypoglycaemia is prevented by propranolol but unaffected by metoprolol. However, in contrast to the results of Viberti et al. [20], it was found that the response of free fatty acids was impaired by propranolol but not by metoprolol [22].

Skin temperature falls during hypoglycaemia despite marked vasodilatation [4, 23] because of increased evaporative heat loss due to sweating. Several groups have reported that /-adrenoceptor antagonists increase hypoglycaemic sweating, but only Molnar & Read [24], who measured changes in body weight, have attempted to measure the response. They found that a small dose of propranolol (0.3 mg/kg body weight) doubled weight loss during hypoglycaemia. The evaporimeter which we used to measure sweating has recently been evaluated and found to underestimate sweat evaporation at high sweat rates (above 100 g h^{-1} m^{-2}) [25]. The instrument could not be calibrated under the conditions of this experiment and thus no correction factor could be introduced. It seems likely that the results we obtained during hypoglycaemic sweating underestimated the absolute rates of sweat evaporation but qualitative comparisons between experiments should be possible. Although the fall in skin temperature during hypoglycaemia was much greater in the presence of propranolol than with metoprolol or saline, in contrast to the findings of Molnar & Read [24], there was no statistically significant enhancement of sweat evaporation over the whole body. However, we are not sure to what extent this was a reflection of the technique used since the mean values for all sites were greater with propranolol than in the control experiment, but the difference was significant only for the forehead. This indicates that one should be cautious about estimates of hypoglycaemic sweating [20, 26, 27], which may place undue reliance on observation of the forehead.

Core temperature fell in the control experiment despite an increase in heat production during hypoglycaemia. Although this heat production response was abolished by propranolol and the fall in skin temperature was greater than in the control experiment, the fall in core temperature was not significantly greater than in the control experiment. A longer experiment might, however, have revealed a greater fall in temperature, since core temperature was rising at the end of the saline experiment but was still falling with propranolol. This continued fall in core temperature may partly have been due to the significant reduction in heat production during the recovery period in the presence of propranolol. However, the reason the fall in core temperature was not greater lies mainly in the markedly different peripheral blood flow changes which occurred with propranolol.

The peripheral vasodilatation which accompanies hypoglycaemia represents an expansion of the body core into the shell. Thus, when increased sweat evaporation from the shell surface (the skin) occurs, heat is lost from both the shell and core of the body. During hypoglycaemia core temperature falls despite an increase in heat production, due mainly to evaporative heat loss and peripheral vasodilatation. The absence of peripheral vasodilatation during hypoglycaemia in the propranolol experiment offsets the fall in core temperature which would otherwise have been expected as a consequence of sweat evaporation and decreased heat production. The decrease in hand blood flow, if representative of skin as a whole, represents increased insulation of the core from the environment. This would compensate for the lower heat production with propranolol, and the sweating response, whether normal or enhanced, would result in greater heat loss from peripheral tissues and hence a lower skin temperature than in the control experiment.

In the propranolol experiment, hypoglycaemia was associated with vasoconstriction, i.e. increased vascular resistance, in both the calf and the hand. This effect was less marked in the calf than in the hand. The vasoconstriction in the hand observed during hypoglycaemia in the presence of propranolol is likely to result from increased a-adrenoceptor activation by circulating catecholamines [28] or increased activity of...
the sympathetic nerves to the blood vessels in the hand or from inhibition of the $\beta$-adrenoceptor mediated dilatation of arteriovenous anastomoses in the fingers [29]. The vasculature of the calf is presumably like that of the forearm, containing both $\alpha$-adrenoceptors mediating vasoconstriction and $\beta$-adrenoceptors mediating vasodilatation [30, 31]. Thus the vasoconstriction observed in the calf during hypoglycaemia in the presence of propranolol is the result of the increased stimulation of $\alpha$-adrenoceptors and the inhibition of $\beta$-adrenoceptor activation.

Vasodilatation in the hand during hypoglycaemia is said to result from removal of sympathetic vasoconstrictor tone [32], which outweighs the $\alpha$-adrenoceptor mediated vasoconstrictor effect of elevated plasma adrenaline levels. However, the contribution of the $\beta$-adrenoceptor mediated vasodilator mechanism in the fingers [29] has not been established. It seems likely that the hand vasoconstrictor response seen during hypoglycaemia in the presence of propranolol is due to the enhanced plasma adrenaline response, although direct effects of propranolol on the vasomotor centre or the $\beta$-adrenoceptor mediated vasodilator mechanism in the finger cannot be excluded. The adrenaline response to hypoglycaemia was also enhanced by metoprolol although to a lesser extent than with propranolol. Since this did not prevent an increase in hand blood flow it is likely that only very high plasma adrenaline levels (above 10 nmol/l) are able to exert an $\alpha$-adrenoceptor mediated effect sufficient to overcome the release of vasoconstrictor tone which occurs during hypoglycaemia.

Adrenaline-induced muscle vasodilatation is thought to result from activation of $\beta_2$-adrenoceptors [30, 31], so it is interesting to note that the $\beta_2$-adrenoceptor antagonist metoprolol markedly reduced the calf blood flow response to hypoglycaemia, suggesting that metoprolol reduced the vasodilator effects of adrenaline. Selectivity of $\beta$-adrenoceptor antagonists is always relative, and at the doses used metoprolol may have affected both $\beta_1$- and $\beta_2$-receptors; but it is also possible that activation of $\beta_1$-receptors is responsible for some of the muscle vasodilatation produced by adrenaline.

An enhanced plasma adrenaline response to hypoglycaemia has been described after acute oral administration of propranolol [33] and chronic oral administration of both propranolol [34] and metoprolol [34, 35]. Adrenaline stimulates its own plasma metabolic clearance rate via a $\beta$-adrenoceptor mediated mechanism [36], and propranolol prevents this stimulation of metabolic clearance and so produces elevated plasma adrenaline levels [37]. Since plasma adrenaline levels were increased both with metoprolol and propranolol in our study, the adrenaline clearance mechanisms may involve activation of $\beta_1$-adrenoceptors.

Neither metoprolol nor propranolol affected the plasma glucose response to insulin or glucose recovery up to 50 min after the insulin infusion. This observation is in accord with most of the studies recently reviewed by Cryer [38]. Studies which report that propranolol impairs glucose recovery have usually shown this effect 90–120 min after the onset of hypoglycaemia [22, 26, 27], but Lilavivathana et al. [21] found lower blood glucose levels and immediate impairment of glucose recovery when propranolol was given together with an intravenous bolus of insulin. Delayed impairment of glucose recovery in the presence of propranolol [22, 26, 27] might be explained by a lower core temperature. We have shown that hypothermia leads to a marked impairment of glucose recovery [4], and core temperature was still falling at the end of the propranolol experiment in our present study.

Our observations on heart rate, blood pressure and the ECG during hypoglycaemia were similar to those of Davidson et al. [16] and Lloyd-Mostyn & Oram [39]. The profound bradycardia seen during hypoglycaemia in the presence of propranolol may be due to increased efferent vagal activity in response to hypoglycaemia or to a baroreflex response to the increased mean arterial blood pressure. This bradycardia is accompanied by abnormal P–R intervals on the ECG, which are probably a consequence of vagal inhibition of the sinuatrial node, resulting in pacemaker activity arising in other atrial cells.

In summary, we have shown that the heat production response to insulin-induced hypoglycaemia in a warm environment is reduced by metoprolol and inhibited by propranolol, suggesting that both $\beta_1$- and $\beta_2$-adrenoceptors are involved in the response. The inhibition of the response by propranolol did not lead to more severe hypothermia, mainly because cardiovascular responses to hypoglycaemia were also modified, but a longer experiment might have revealed a larger fall in core temperature. The combination of propranolol treatment and hypoglycaemia would have serious effects upon temperature regulation in a cold environment. Shivering would be abolished, glucose recovery impaired [4] and the rise in non-shivering heat production would also be inhibited. This possibility should be borne in mind for patients treated both with propranolol and insulin.
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