STUDIES OF THE PERIPHERAL VASODILATOR RESPONSE TO ACUTE INSULIN-INDUCED HYPOGLYCAEMIA IN MAN

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SUMMARY

1. The response of hand blood flow to acute insulin-induced hypoglycaemia was measured in normal subjects in whom vasomotor tone had been released physiologically by body heating, anatomically by unilateral nerve block and pharmacologically by unilateral intra-arterial infusion of bretylium tosylate or phenoxybenzamine. Five patients who had undergone unilateral cervical sympathectomy were also studied.

2. Under these conditions the usual increase in hand blood flow associated with acute hypoglycaemia was converted into a decrease except during complete unilateral $\alpha$-adrenergic blockade when hypoglycaemia produced no change in hand blood flow.

3. The possible mechanisms responsible for the vasodilatation associated with hypoglycaemia are discussed.

4. The results suggest that release of vasoconstrictor tone, rather than activation of specific vasodilator mechanisms (neurogenic or humoral), is the principal means whereby acute hypoglycaemia produces increased blood flow in the hand.

Key words: insulin, hypoglycaemia, hand blood flow.

The catecholamine response to acute insulin-induced hypoglycaemia is well established (Holzbauer & Vogt, 1954; Goldfein, Moore, Zileli, Havers, Boling & Thorn, 1961; Wallace & Harlan, 1965) and it is frequently stated that many of the clinical features of acute hypoglycaemia are due to the release of adrenaline. However, French & Kilpatrick (1955) concluded that only a minority of the features of the hypoglycaemic reaction can be attributed to adrenaline release. The purpose of this investigation was to determine the mechanism whereby many subjects during insulin hypoglycaemia feel warm, become flushed and develop an increase in skin blood flow in contrast to the known effects of adrenaline, namely pallor and a decrease in skin blood flow.

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METHODS

The subjects were normal healthy volunteers, apart from five patients who had undergone unilateral cervical sympathectomy. Informed consent was obtained from all patients and volunteers.

The subjects were fasted overnight and hypoglycaemia was induced by giving an intravenous dose of soluble insulin (0·15 unit/kg body wt.). Hand blood flow (HBF) was measured with a water-filled plethysmograph (water temperature 33°C). The plethysmograph was supported above heart level with the subject supine and hand blood flow was measured at 1–2 min intervals before and during hypoglycaemia at an occlusion pressure of 60 mmHg. Pulse rate was also recorded at minute intervals. An abrupt rise in pulse rate 25–30 min after the injection of insulin coincided within a minute or so with the first complaint of symptoms and other objective signs including blood pressure change, the onset of sweating and the rise in HBF. The rise in pulse rate was taken as marking the onset of the hypoglycaemic reaction. On completion of each experiment the subjects were given a snack with sweet coffee. Coma never occurred and none of the subjects required intravenous glucose.

Interruption of vasoconstrictor tone was produced by physiological, anatomical and pharmacological approaches. In all experiments, except where the physiological approach was applied, simultaneous measurement of blood flow through the untreated hand acted as a control for the treated hand.

Physiological

In four normal subjects vasodilatation in the arms was induced by heating the rest of the body, except the head, hands and arms. HBF measurements were begun only after heavy sweating was observed and body heating was maintained throughout the experiment. The HBF responses during hypoglycaemia under these conditions were compared with the responses obtained when the same subjects were studied on another day under standard environmental conditions.

Anatomical

Peripheral nerve block. In three normal subjects this was achieved by local anaesthetic block (with 2% xylocaine) of the ulnar, radial and median nerves on the left arm before the injection of insulin.

Unilateral cervical sympathectomy. Five patients who had undergone unilateral cervical sympathectomy for ischaemia of fingers due to Raynaud’s phenomenon (three), ulnar artery occlusion (one) and causalgia (one) were studied several months post-operatively; one of these patients was also studied on the day after the operation.

Pharmacological

Bretylium tosylate. Bretylium tosylate, 24·2–36·3 μmol (10–15 mg) was infused into the right brachial artery of three subjects over 15–40 min before the injection of insulin.

Phenoxybenzamine. In three experiments, phenoxybenzamine, 8·8–14·7 μmol (3–5 mg) was infused at a rate of 1·5 μmol (500 μg)/min into the left brachial artery via an indwelling intra-arterial catheter. In two of these experiments a brief intra-arterial infusion of noradrenaline, 3·0 μmol (0·5 μg)/min, was then given through the same catheter to test whether α-adrenergic
blockade was complete. In both experiments the blockade was incomplete and a further 5.9 μmol (2 mg) of phenoxybenzamine was then infused. A subsequent brief intra-arterial infusion of noradrenaline caused no vasoconstriction. At that point insulin was given intravenously. During the infusion of phenoxybenzamine venous return from the treated arm was obstructed at 60 mmHg in an attempt to minimize entry of the drug into the general circulation. At the same time the circulation to the other arm was occluded to protect it from any phenoxybenzamine that may have reached the general circulation.

RESULTS

Physiological approach

Fig. 1 shows the effect of insulin hypoglycaemia on HBF in a normal subject at normal room temperature. When the same subject was heated, it can be seen from Fig. 2 that there was a transient vasoconstriction at the onset of the hypoglycaemic reaction. Similar responses were obtained in three other subjects in whom a vasodilator response had occurred at room temperature (20°C).

Anatomical approach

Peripheral nerve block. Table 1 shows that high basal HBF values were obtained on the
FIG. 2. Hand blood flow and pulse rate in the same subject as Fig. 1 after intravenous injection of 15 units of insulin (at the arrow) during body heating.

blocked side. With the onset of the hypoglycaemic reaction vasoconstriction occurred in contrast to vasodilatation on the control side.

**Unilateral cervical sympathectomy.** Five patients were studied several months after the operation when basal HBF on the denervated side was either similar to or only slightly higher than basal HBF on the control side. As shown in Table 2, HBF increased on the control side and simultaneously decreased on the sympathectomized side in all five patients. Fig. 3(a) illustrates

**TABLE 1. Response of hand blood flow to hypoglycaemia in normal subjects with unilateral upper limb nerve blockade**

Average values for hand blood flow (ml min\(^{-1}\) 100 ml\(^{-1}\)) responses to hypoglycaemia are shown.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control arm</th>
<th>Block arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before reaction</td>
<td>After reaction</td>
<td>Change</td>
</tr>
<tr>
<td>J.B.</td>
<td>4.1</td>
<td>12.0</td>
</tr>
<tr>
<td>F.A.</td>
<td>7.9</td>
<td>10.6</td>
</tr>
<tr>
<td>E.C.</td>
<td>8.4</td>
<td>18.5</td>
</tr>
</tbody>
</table>
Vasodilatation during acute hypoglycaemia

Fig. 3. Pulse rate and hand blood flows after intravenous injection of 10 units of insulin (at the arrow) in patient M.B., who had undergone right pre-ganglionic cervical sympathectomy: (a) 6 months after sympathectomy and (b) 1 day after sympathectomy.
TABLE 2. Response of hand blood flow to hypoglycaemia in patients with unilateral cervical sympathectomy
Average hand blood flow (ml min⁻¹ 100 ml⁻¹) responses to hypoglycaemia are shown.

(a) Control arm

<table>
<thead>
<tr>
<th>Subject</th>
<th>Before reaction</th>
<th>After reaction</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.B.</td>
<td>2.5</td>
<td>13.6</td>
<td>+11.1</td>
</tr>
<tr>
<td>J.H.</td>
<td>6.4</td>
<td>14.6</td>
<td>+8.2</td>
</tr>
<tr>
<td>M.H.</td>
<td>5.7</td>
<td>15.5</td>
<td>+9.8</td>
</tr>
<tr>
<td>W.S.</td>
<td>1.3</td>
<td>14.8</td>
<td>+13.5</td>
</tr>
<tr>
<td>M.P.</td>
<td>3.2</td>
<td>5.3</td>
<td>+2.1</td>
</tr>
</tbody>
</table>

(b) Sympathectomized arm

<table>
<thead>
<tr>
<th>Subject</th>
<th>Before reaction</th>
<th>After reaction</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.B.</td>
<td>5.4</td>
<td>2.5</td>
<td>-2.9</td>
</tr>
<tr>
<td>J.H.</td>
<td>5.6</td>
<td>2.5</td>
<td>-3.1</td>
</tr>
<tr>
<td>M.H.</td>
<td>7.7</td>
<td>2.8</td>
<td>-4.9</td>
</tr>
<tr>
<td>W.S.</td>
<td>4.4</td>
<td>2.4</td>
<td>-2.0</td>
</tr>
<tr>
<td>M.P.</td>
<td>2.5</td>
<td>2.2</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

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these responses in patient M.B. 6 months after the operation. A similar study was made on this patient on the first post-operative day (Fig. 3b). It can be seen that the control hand behaved similarly whereas on the sympathectomized side HBF was high and did not show any definite change after hypoglycaemia.

Pharmacological approach

Intra-arterial bretylium. The hypoglycaemic reaction was associated with vasoconstriction on the treated side compared with vasodilatation on the control side in all three subjects (Table 3). This is well illustrated by subject E.B.F. (Fig. 4).

TABLE 3. Response of hand blood flow to hypoglycaemia in normal subjects after intra-arterial infusion of bretylium tosylate
Average hand blood flow (ml min⁻¹ 100 ml⁻¹) responses to hypoglycaemia are shown.

(a) Control arm

<table>
<thead>
<tr>
<th>Subject</th>
<th>Before reaction</th>
<th>After reaction</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.F.</td>
<td>4.4</td>
<td>14.7</td>
<td>+10.3</td>
</tr>
<tr>
<td>J.B.</td>
<td>18.5</td>
<td>22.5</td>
<td>+4.0</td>
</tr>
<tr>
<td>P.H.</td>
<td>7.7</td>
<td>15.0</td>
<td>+7.3</td>
</tr>
</tbody>
</table>

(b) Arm treated with bretylium

<table>
<thead>
<tr>
<th>Subject</th>
<th>Before reaction</th>
<th>After reaction</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.F.</td>
<td>25.0</td>
<td>21.0</td>
<td>-4.0</td>
</tr>
<tr>
<td>J.B.</td>
<td>30.3</td>
<td>20.8</td>
<td>-9.5</td>
</tr>
<tr>
<td>P.H.</td>
<td>22.6</td>
<td>14.6</td>
<td>-8.0</td>
</tr>
</tbody>
</table>

Intra-arterial phenoxybenzamine. Fig. 5 shows the effect of insulin hypoglycaemia on HBF when complete unilateral α-adrenergic blockade has been achieved. During a 25 min period before and after the hypoglycaemic reaction, the average HBF remained unchanged at 31.5 and 32.0 ml min⁻¹ 100 ml⁻¹ respectively on the blocked side in contrast to the vasodilator response on the control side. In a repeat experiment on the same subject and in a similar experiment on another normal subject vasodilatation occurred at the time of the reaction on the control side and a transient vasoconstriction was exhibited by the experimental hand, suggesting that the α-adrenergic blockade was incomplete on these occasions by the time the reaction occurred.
Fig. 4. Hand blood flows after intravenous injection of 15 units of insulin (at the arrow) in a normal subject (E.B.F.), after infusion of 36·3 μmol of bretylium tosylate into the left brachial artery over 40 min.

Fig. 5. Hand blood flows after intravenous injection of 14 units of insulin (at the arrow) in a normal subject (E.B.F.), after infusion of phenoxybenzamine into the left brachial artery.
DISCUSSION

In most normal subjects, acute insulin-induced hypoglycaemia is followed by an increase in hand blood flow (French & Kilpatrick, 1955; Allwood, Ginsburg & Paton, 1957). Furthermore, when the adrenaline response to hypoglycaemia is eliminated, e.g. in patients who have had bilateral thoracolumbar sympathectomy (French & Kilpatrick, 1955) or bilateral adrenalectomy (Ginsburg & Paton, 1956), there is a consistent increase in HBF at the onset of the hypoglycaemic reaction. The exact mechanism of this vasodilatation is still debated (Abramson, 1967) and the principal hypotheses are activation of vasodilator nerve fibres, release of vasodilator substances into the circulation and inhibition of vasoconstrictor tone. Considering in sequence these possibilities, we believe that the first two had been eliminated by previous work for the following reasons.

Activation of specific vasodilator fibres

The reflex vasodilator response of the skin blood vessels of the hand during body heating has been studied extensively before and after peripheral nerve block; specific vasodilator fibres have never convincingly been shown to play a role (Arnott & Macfie, 1948; Gaskell, 1956; Roddie, Shepherd & Whelan, 1957). Furthermore, Allwood & Ginsburg (1959) studied the effect of unilateral intra-arterial atropine on HBF during insulin hypoglycaemia and showed that there was no significant difference between the HBF response on the atropinized and control sides. By contrast, the same authors concluded that cholinergic sympathetic vasodilator fibres to skeletal muscle probably play a part in the increased forearm blood flow during hypoglycaemia because the forearm vasodilator response to hypoglycaemia was significantly reduced on the atropinized side.

Release of vasodilator peptides

Release of the vasodilator peptides kallidin and bradykinin as a consequence of sweat gland activation is considered to play a role in the vasodilator response to body heating (Fox & Hilton, 1958). However, atropinization of one limb failed to alter significantly the hand blood flow response to hypoglycaemia even though sweat gland activity was abolished (Allwood & Ginsburg, 1959). This suggests that sweat gland release of vasodilator peptides is not a major factor in causing vasodilatation in hypoglycaemia. In animal studies large amounts of free kinin have been detected in venous blood after infusions of adrenaline (I. J. Zeitlin, personal communication). The contribution which this may make during hypoglycaemia in man must be small as vasodilatation is preserved in patients who have had bilateral adrenalectomy and therefore do not release adrenaline (Ginsburg & Paton, 1956). The observation by Allwood & Needham (1971) that no rise in venous blood bradykinin could be detected in six normal individuals subjected to acute insulin-induced hypoglycaemia is also against the theory that bradykinin is involved.

Release of vasoconstrictor tone

When vasoconstrictor tone is abolished by cervical sympathectomy, acute insulin-induced hypoglycaemia is accompanied by a decrease in HBF (Allwood et al., 1957). This vasoconstriction is presumably the consequence of increased amounts of circulating adrenaline and our experiments on sympathectomized patients show similar responses (Table 2). This effect is more
obvious after the return of vessel tone (Barcroft, 1952) and the development of hypersensitivity to adrenaline (Duff, 1955), as shown by the experiments performed on subject M.B. (Figs. 3a and 3b). We do not know why vasoconstriction did not occur on the first post-operative day. However, the irregularity of blood flows on the operated side may have been due to difficulty in drawing accurate slopes at high rates of flow or perhaps the results were influenced by post-operative discomfort. The unusual rise in pulse rate before the hypoglycaemic reaction lends some support to the latter possibility.

Our experiments, with the exception of the \( \alpha \)-adrenergic blockade studies, show that irrespective of the manner in which vasoconstrictor tone is interrupted the usual hand blood flow vasodilatation during hypoglycaemia is converted to vasoconstriction. Although these observations suggest that release of vasoconstrictor tone is the principal mechanism whereby hypoglycaemia causes vasodilatation, they are not wholly conclusive since measures such as sympathectomy and nerve block may also interrupt, if they exist, the alternative autonomic vasodilator mechanisms discussed above, namely specific vasodilator fibres and bradykinin release.

For this reason we completed the study by examining the response to hypoglycaemia under conditions of local \( \alpha \)-adrenergic blockade, as this manoeuvre releases vasoconstrictor tone but preserves the integrity of other autonomic mechanisms operating in the upper limb. \( \alpha \)-Adrenergic blockade has the added advantage of allowing us to study the HBF response uncomplicated by the vasoconstrictor component due to the circulating adrenaline. If a specific vasodilator mechanism, either neurogenic or humoral, was operating, one would expect a further increase in HBF during hypoglycaemia under these conditions. From our observation that insulin hypoglycaemia causes no change in hand blood flow during complete \( \alpha \)-adrenergic blockade (Fig. 5) and only transient vasoconstriction when the blockade is partial, we conclude that release of vasoconstrictor tone is the only significant mechanism whereby hypoglycaemia causes peripheral vasodilatation. It could still be argued that this does not exclude entirely the possibility of vasodilator substances being involved, because any further vasodilatation mediated by such substances may not be demonstrable under conditions of complete vasomotor release with its inevitably high basal blood flows. It should be noted, however, that in the patients studied several months after cervical sympathectomy the basal hand blood flows were almost back to normal and yet in each case the usual vasodilator response was absent and replaced by vasoconstriction.

On the present evidence it seems reasonable to conclude that the increased hand blood flow associated with hypoglycaemia is neither mediated by a specific vasodilator pathway nor by circulating vasodilator substances. Our results support the view that release of vasoconstrictor tone is the principal means whereby acute hypoglycaemia brings about a vasodilatation in the hand which usually obscures some simultaneous vasoconstriction caused by release of adrenaline.

ACKNOWLEDGMENTS

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REFERENCES


