Cardiovascular responses to insulin in the absence of hypoglycemia

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Cardiovascular responses to intravenous administration of insulin were studied in lightly anesthetized dogs treated with a neuromuscular blocking agent. An early transient pressor response was observed. This abrupt increase in arterial pressure appeared 2–9 min after insulin was given. It was accompanied by increases in cardiac output and right atrial pressure. It occurred in the presence of hyperglycemia and in the absence of hypoglycemia. It was not altered by glucagon but it could be antagonized by ganglionic and adrenergic blocking drugs and by pentobarbital. The response could be produced when insulin was given in the carotid artery in doses that caused no effect when injected in a systemic vein. The experiments suggest that insulin may have a direct action on the brain.

The cardiovascular responses reportedly associated with intravenous administration of insulin include gradual increases in blood pressure, heart rate, and cardiac output (1–6). These changes begin 20–45 min after the insulin is given and only after blood sugar has fallen to a critical level (2, 7–9). They appear to result from hypoglycemic stimulation of the hypothalamus with excitation of sympathetic nerves and release of catecholamines (2, 7, 8, 10–17). The hemodynamic changes regress promptly, and the secretion rate of catecholamines is reduced when the hypoglycemia is corrected with intravenous glucose (8, 13, 17).

We observed fortuitously that a sharp transient increase in arterial pressure occurred 2–9 min after insulin was given to dogs treated with gallamine. To our knowledge, no such response had been observed previously. Preliminary experiments suggested that it was not the result of hypoglycemia. This report concerns our efforts to determine the mechanism or mechanisms responsible for this early increase in pressure.

METHODS

Mongrel dogs weighing 0.5–25.0 kg were fasted for 48 hr before study. They were lightly anesthetized with small doses of thiopental, treated with gallamine, and ventilated through a cuffed endotracheal tube connected to a fixed-volume respiratory pump. The rate and depth of ventilation were adjusted initially so that end-expiratory CO2 concentration was approximately 4%.

Cardiac output was measured by the indicator dilution method with injections of indocyanine green dye in the pulmonary artery through an intracardiac catheter. Dyed blood was sampled from the carotid artery through the cuvette of a Gilford densitometer. Blood pressures were measured with Statham strain gauges connected to the catheter through which the dye was injected, to a second catheter, the tip of which lay in the right atrium, and to a needle in the femoral artery. Dye curves and blood pressures were recorded with a Sanborn direct-writing oscillograph. Drugs were injected through a cannula into the femoral vein.

Regular insulin (2–3 u/kg, with or without glucagon) was injected intravenously. Cardiac output was determined before and at frequent intervals after each dose of insulin, and blood pressures were recorded continuously. Blood glucose concentration was determined according to Somogyi's modification (18) of Nelson's method (19). The measurements were made on venous blood samples obtained at intervals of 30 sec to 1 min for 5–10 min after the injection of the insulin and at intervals of 15 min thereafter.

The systemic pressor effects of intravenous injections of regular insulin with glucagon (3 u/kg) were studied also under the following conditions: 1) in the presence of hyperglycemia induced by continuous intravenous
FIG. 1. Acute changes in end-expiratory CO₂ concentration (EEC0₂), mean right atrial pressure (RAP), pulmonary arterial pressure (PAP), systemic arterial pressure (SAP), and dye curves (DC) recorded 5 min after intravenous injection of insulin (3 u/kg). A and B indicate dye injections.

FIG. 2. Changes in mean systemic arterial pressure (B.P.), cardiac output (C.O.), and peripheral resistance (R) observed in a representative experiment before and during a period of 90 min after intravenous insulin. After acute pressor response, blood pressure remained elevated above control level. This prolonged elevation corresponds to delayed pressor response described previously in association with hypoglycemia.

FIG. 3. Early pressor response occurred during initial increase in blood glucose (B.G.), which followed injection of insulin containing glucagon. Hypoglycemia followed this initial increase in blood sugar.

FIG. 4. Early pressor response observed after injection of insulin containing glucagon in presence of hyperglycemia produced by infusion of 10% dextrose in water.

**RESULTS**

Early hemodynamic responses to intravenous insulin, 2–3 u/kg. A sharp increase in systemic arterial pressure was seen in each of five dogs 1.5–5 min after the insulin injections (Fig. 1). The peak response was reached within 15–30 sec, and the pressure began to return toward the control level within 3 min. It remained above the control level, however, for about 1.2 hr (Fig. 2).

Table I shows the increases in cardiac output, peripheral
TABLE 1. Early hemodynamic responses to intravenous insulin

<table>
<thead>
<tr>
<th>Dog</th>
<th>Wt, kg</th>
<th>SAm, mm Hg</th>
<th>KAm, mm Hg</th>
<th>PAm, mm Hg</th>
<th>HR, beats/min</th>
<th>CO, liters/min</th>
<th>R, units</th>
<th>SV, ml</th>
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<td></td>
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<td>P</td>
<td>C</td>
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<td>2</td>
<td>16.4</td>
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<td>211</td>
<td>1.8</td>
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<tr>
<td>Mean</td>
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<td>2.9</td>
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<td>11</td>
<td>0.9</td>
<td>10</td>
<td>3</td>
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<tr>
<td>SE</td>
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<td>1.54</td>
<td>13.2</td>
<td>0.34</td>
<td>8.1</td>
<td>1.4</td>
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<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>&gt;0.2</td>
<td>&gt;0.05</td>
<td>&gt;0.2</td>
<td>&gt;0.05</td>
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</tr>
</tbody>
</table>

SAm is systemic arterial mean pressure; RAm is right atrial mean pressure; PAm is pulmonary arterial mean pressure; HR is heart rate; CO is cardiac output; R is peripheral resistance; SV is stroke volume; C is for measurements made before the administration of insulin; P is for measurements made during the pressor response. * Peak SAm pressures after insulin; these values were not used for calculating R since dye curves obtained during pressor response did not always coincide with peak pressure (Fig. 1).

The results indicate that the early pressor response to insulin is the result of active vasoconstriction and increased cardiac output. The vasocostriction is not caused by a direct action of insulin on the blood vessels. The changes appear to be brought about by sympathetic impulses which originate in the central nervous system. The blood glucose level at the time of the peak responses averaged 80.4 mg/100 ml. Hypoglycemia was observed only after the pressor response subsided.

In five other dogs similar pressor responses were observed (Table 2) when blood sugar was maintained at hyperglycemia levels averaging 293 mg/100 ml by intravenous infusion of 10% glucose in water (Fig. 4).

Effect of ganglionic and adrenergic blockade and pentobarbital on early pressor response to insulin. Table 2 shows that the increase in arterial pressure after 3 u/kg of regular insulin was smaller in animals which had received a ganglionic blocking drug (P < 0.05) and in those which had received an adrenergic blocking drug (P < 0.01) than in untreated animals. Treatment with pentobarbital practically abolished the pressor response (P > 0.05).

Pressor response to intracarotid injections of small doses of insulin. In four dogs intravenous administration of 0.025-0.1 u/kg of insulin with or without glucagon produced no pressor effect. The subsequent administration of the same doses of the same preparation of insulin in the carotid artery caused the characteristic acute pressor response observed with the larger intravenous doses. The average increase in pressure was 76.8 mm Hg (P < 0.01). The pressor response to intracarotid injection occurred with insulin containing glucagon as well as with the glucagon free preparation.

Intra-arterial injection of insulin. In five dogs the injection of 0.1-3.0 units of insulin in the constantly perfused brachial artery produced no change in perfusion pressure.
occurring in the absence of a fall in blood sugar. It may be that failure of others to observe similar early responses is related to the use of drugs that depress the central nervous system as anesthetic agents in animals and the uncommon use of the intravenous route of administration in normal, conscious human subjects. Our animals received only small doses of thiopental, and adequate time was allowed for nearly complete disappearance of the effects of this agent before the insulin was given (24, 25).

Another consideration is the role of gallamine in our preparation. This substance is a neuromuscular blocking agent similar to curare (1). It has no known effects on the central nervous system but it does have a selective vagal blocking action. It may be that this property made the vascular system of our animals more sensitive to a sympathetic discharge which might otherwise be masked by the antagonistic effect of coincidental parasympathetic impulses. Nevertheless, the results of these experiments lend support to the notion that insulin has a direct action on the cells of the central nervous system.

REFERENCES