Effect of Exogenous Insulin on Blood Pressure Regulation in Healthy and Diabetic Subjects

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SUMMARY To define the role of insulin in blood pressure regulation, the hormone’s action on renal sodium handling, potassium balance, pressor reactivity, and the release of catecholamines and aldosterone are summarized. Insulin-stimulated renal sodium reabsorption induces expansion of the extracellular volume, increase in cardiac output, and ultimately, hypertension. On the other hand, the insulin-induced shift of potassium into the cell interior is transient and appears to be of little consequence for long-term blood pressure control. Although the release of norepinephrine is stimulated by insulin, a norepinephrine-mediated pressor effect is prevented in healthy men by a simultaneous norepinephrine-antagonistic action of insulin. The latter causes the fall in blood pressure seen after intravenous insulin in patients with autonomic dysfunction who lack the rise in norepinephrine release. Both in healthy and in diabetic men, exogenous insulin does not modify the pressor effect of angiotensin II, although it impairs the secretion of aldosterone during stimulation by supraphysiological doses of angiotensin II. (Hypertension 7 [Suppl II]: II-49-II-53, 1985)

KEY WORDS • sodium • potassium • pressor reactivity • aldosterone

BLOOD pressure is controlled in humans by a variety of hemodynamic, metabolic, and endocrine variables that are constantly reacting to each other and with exogenous stimuli. Thus abnormal behavior of one regulatory mechanism is bound to induce additional derangements of other mechanisms. Consequently, where this cybernetic system is reset to maintain blood pressure at an elevated level, hypertension has been defined as a “disease of regulation.”

With regard to the high prevalence of hypertension among patients with diabetes mellitus, some attention has been given to the possible role of insulin within the complex interactions of blood pressure-regulating mechanisms. Insulin-induced decrease in blood glucose concentrations even in the physiological range provokes a rise in plasma epinephrine and other insulin-counteracting hormones, thus indirectly affecting the cardiovascular system. In addition, insulin may directly interfere with blood pressure control by its influence on renal sodium handling, potassium balance, pressor reactivity, and the release and/or actions of catecholamines, renin, and aldosterone. This review summarizes the available evidence concerning these direct actions of insulin and defines their actual importance for blood pressure regulation in healthy men and in patients with diabetes mellitus.

Insulin and Sodium Metabolism

Increases in plasma insulin concentrations in the physiological range directly stimulate sodium reabsorption by the distal nephron. Thus a sodium-retaining effect of acutely administered insulin is seen in diabetics with previous poor metabolic control. In patients with type II diabetes and/or obesity, insulin resistance with respect to glucose metabolism induces hyperinsulinemia. The latter may in turn stimulate sodium absorption by the kidney, ultimately leading to an increase in exchangeable sodium and to expanded extracellular volume. Endogenous hyperinsulinemia in insulin-resistant patients may explain why no difference has been observed in exchangeable sodium between insulin-treated and untreated diabetics, whereas exchangeable sodium is increased by about 10% in diabetic subjects as compared to healthy age- and weight-matched controls.

Continued expansion of the extracellular volume by sodium retention increases cardiac output, enhances pressor responsiveness to angiotensin II and norepinephrine, and eventually results in hypertension. The antinatriuretic effect of insulin is finally overcome by a rise in renal perfusion pressure, and a new equilibrium
is established. 1 If, on the other hand, obese subjects are treated with a hypocaloric diet, plasma insulin falls and the ensuing negative sodium balance lowers blood pressure. These assumptions help to explain the effect of weight reduction on blood pressure control in patients with obesity and type II diabetes.

**Insulin and Potassium Metabolism**

Insulin profoundly influences the distribution of potassium between extracellular and intracellular fluid compartments. 9 On the other hand, experimental evidence indicates that the secretion of insulin is altered by changes in the concentrations of potassium, 9, 10 although there is little evidence that changes in plasma potassium concentrations in the physiological range indeed influence peripheral insulin levels in humans. 11, 12

The reactivity of vascular smooth muscle depends on extracellular potassium concentrations during brief periods of exposure and during steady-state conditions. 13, 14 Both long-term depletion and supplementation of potassium decrease vascular pressor responsiveness to angiotensin II in the rat, 15, 16 and a potassium-enriched diet exerts a hypotensive effect in humans. 17, 18 For these reasons, the effect of insulin on potassium balance might be considered as yet another potential point of action on blood pressure regulation in humans.

The decrease of serum potassium concentrations induced by insulin does not affect total body potassium content, however, since it depends exclusively on extrarenal mechanisms, 19 that is, on an influx of potassium into the cell interior of both splanchnic and peripheral tissues. It is of interest in this context that patients with type II diabetes exhibit relative end-organ resistance to insulin-stimulated potassium transport. 20 Furthermore, during experiments using the euglycemic-clamp technique, an effective counterregulatory mechanism to prevent hypokalemia in fact resulted in a rise in serum potassium concentrations during prolonged infusions of insulin. 21 Thus the insulin-induced shift of potassium into the cell interior appears to be transient. For these reasons, insulin is not likely to influence blood pressure regulation in humans by changes in potassium homeostasis.

**Insulin and Catecholamine Release**

In subjects with an intact autonomic nervous system, intravenous insulin induces a rise in plasma norepinephrine even when blood glucose concentrations are kept constant. Concentrations of epinephrine remain unchanged. 22, 23 It has been argued that an acute insulin-induced decrease in plasma volume is counterbalanced by a rise in sympathetic nervous system activity in order to maintain blood pressure at normal levels at the expense of an increase in heart rate. 24, 25 This acute fall in plasma volume after administration of insulin seems to be catecholamine mediated, however, since it is not seen in sympathectomized individuals. 26, 27 Therefore it is assumed at present that in healthy subjects, an initial insulin-induced rise in plasma norepinephrine results in venous constriction, a rise in capillary pressure, and thus in a reduction of plasma volume. 28

Since the plasma clearance of norepinephrine does not change after intravenous insulin 22, 28 and since the rise in norepinephrine after intravenous insulin apparently reflects an increase in sympathetic nervous activity, the administration of insulin should induce a rise in blood pressure. This has indeed been shown in the dog, 29 where the rise in blood pressure during a euglycemic-clamp study depended on alpha-adrenergically mediated vasoconstriction. Simultaneously, however, insulin exerts a vasodilator effect in the skeletal muscle that appears to be independent of the sympathetic nervous system. 30 This vasodilator activity of insulin, which has yet to be confirmed in humans 28 might help to resolve the hitherto puzzling question of how insulin increases the release and at the same time antagonizes the actions of norepinephrine. It then would be understandable why only a small rise in blood pressure results from the opposing actions of insulin after its acute administration in healthy humans. 30 In sympathectomized individuals, insulin failed to induce a rise in norepinephrine and these patients consequently demonstrated an attenuated vasoconstrictor activity and a fall in blood pressure after insulin administration. 31 Similar observations were reported in diabetics with autonomous dysfunction. 32, 33 The behavior of pulse rate with intravenous insulin was quite variable in this group of patients, but blood pressure decreased even in those in whom tachycardia was seen, suggesting that the apparent lack of vasoconstriction was the decisive factor for the inability of these patients to maintain blood pressure. 33

Unfortunately, blood glucose concentrations were not kept constant during these early human experiments, thus leaving unsolved the question of whether the observed changes in blood pressure had been due to insulin per se or due to the metabolic effects of insulin-induced hypoglycemia, that is, due to epinephrine-induced vasodilatation. 34

**Insulin and Pressor Reactivity**

In the isolated perfused tails of male rats (a model without interference of changing blood glucose concentrations) an attenuated pressor responsiveness to norepinephrine was induced by supraphysiological doses of insulin. 34 Although some effect of insulin was seen at a concentration of 150 μU/ml, it was clearly more marked at a concentration of 120 μU/ml, a dose far beyond physiological levels. For unexplained reasons, the effect was absent in female animals.

A reduction in the response to vasoconstrictor stimuli in the nondiabetic rat was also seen after long-term insulin therapy. 35 In comparison to healthy animals, however, alloxan-diabetic insulin-deficient rats exhibited reduced responses to several vasoconstrictor stimuli. Insulin replacement abolishes this abnormality and restores pressor responsiveness. To resolve this apparent discrepancy, it was suggested that hyperglycemia and/or hyperglucagonemia may be largely responsible for the impaired pressor responsiveness in this animal model. Normalization of these metabolic derange-
ments by insulin replacement in turn caused a normalization of vascular function. Thus insulin exerts a dual effect in the alloxan-diabetic rat: While directly inhibiting vascular reactivity it simultaneously improves pressor responsiveness indirectly by correcting metabolic derangements.

In humans, the available evidence of the role of insulin on vasoreactivity is based on observations made when plasma insulin concentrations are acutely raised into the pharmacological range. In insulin-dependent diabetics who are regularly confronted with this situation, this approach at least bears resemblance to their clinical situation, although the acute effects of insulin may well be altered by long-term insulin therapy, endogenous hyperinsulinemia, or the metabolic abnormalities that are by definition present in these patients. Concerning healthy humans, the possible impact of changes in plasma insulin within the physiological range on vascular reactivity can hardly be inferred by extrapolation of results obtained during the acute administration of large doses of insulin.

Bearing these limitations in mind, we studied the effect of a pharmacological dose of insulin on pressor reactivity to angiotensin II in healthy men and in patients with insulin-dependent diabetes. Euglycemia was maintained by adequate administration of dextrose.

To induce a comparable state of insulinemia in the diabetic group, each patient was given his last dose of intermediate-acting insulin 24 hours prior to the test, followed by a constant infusion of 0.75 U of rapidly acting insulin/m² body surface/hr for 12 hours prior to the experiment. Two consecutive angiotensin II-infusion tests were performed with an equilibration period of 120 minutes between them. Sixty minutes before the beginning of the second angiotensin II infusion, a continuous infusion of regular insulin was begun in healthy individuals (2.5 U/m²/hr). In diabetics the dose of intravenous insulin was increased to 7.5 U/m²/hr. Plasma concentrations of potassium (diabetics: 4.1 ± 0.4 mmol/L; healthy individuals: 4.2 ± 0.2 mmol/L) were found to be unchanged after the first infusion of angiotensin II (diabetics: 3.9 ± 0.3 mmol/L; healthy men: 4.3 ± 0.2 mmol/L). Sixty minutes after the onset of induced hyperinsulinemia, however, plasma potassium fell to 3.5 ± 0.3 mmol/L (p < 0.05) in diabetics and to 3.6 ± 0.2 mmol/L (p < 0.005) in healthy individuals and remained at this level until the end of the second infusion (diabetics: 3.3 ± 0.3 mmol/L; healthy men: 3.6 ± 0.2 mmol/L). In both groups, basal blood pressure was similar at the beginning of either infusion of angiotensin II (Table 1) and the pressor response to angiotensin II was unchanged by hyperinsulinemia (Figure 1). These results did not support the notion that an altered vascular reactivity to angiotensin II contributes to the hemodynamic effect of insulin in healthy and in diabetic men. It remains to be determined whether insulin affects the response to other pressor agents in a different way and whether chronic effects of insulin therapy (notably sodium retention) contribute to the increased pressor responsiveness seen in diabetic patients compared to healthy controls.

**Table 1. Effect of Hyperinsulinemia on Serum Concentrations of Potassium and Sodium and on Basal Mean Blood Pressure in Six Healthy Men and Six Insulin-Dependent Diabetic Patients (mean ± sd)**

<table>
<thead>
<tr>
<th></th>
<th>Healthy men</th>
<th>IDD patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Hyperinsulinemia</td>
</tr>
<tr>
<td>K⁺ (mmol/L)</td>
<td>4.2 ± 0.2</td>
<td>3.6 ± 0.2*</td>
</tr>
<tr>
<td>Na⁺ (mmol/L)</td>
<td>142 ± 2</td>
<td>140 ± 4</td>
</tr>
<tr>
<td>mBP (mm Hg)</td>
<td>94 ± 11</td>
<td>95 ± 12</td>
</tr>
<tr>
<td>BG (mmol/L)</td>
<td>4.3 ± 0.4</td>
<td>5.4 ± 1.2*</td>
</tr>
</tbody>
</table>

Concentrations of blood glucose (BG) were maintained at euglycemic levels by intravenous dextrose.

*p < 0.05, compared with control group by Student’s two-tailed t test for matched pairs.

**Figure 1. Effect of induced hyperinsulinemia (••••••) on the pressor action of angiotensin II (5, 10, and 20 ng·kg⁻¹·min⁻¹) in healthy men and in insulin-dependent diabetic men as compared with a control experiment without hyperinsulinemia (○○○○○) (BPₘ = mean blood pressure).**
Insulin and the Secretion of Renin

Insulin-induced hypoglycemia stimulated renin secretion in intact animals and in humans. This increase in renin secretion may represent a response to the counterregulatory rise in catecholamines and not to insulin itself. In the isolated, perfused rat kidney, insulin exerted a dose-dependent, calcium-mediated suppression of renin release. The significance of this finding for the regulation of blood pressure in humans has yet to be determined.

Insulin and the Secretion of Aldosterone

Changes in extracellular and/or intracellular concentrations of potassium profoundly influence the regulation of aldosterone biosynthesis and serve to explain the acute effects of insulin on aldosterone secretion in humans. Both in healthy men and in anephric patients, basal plasma aldosterone concentrations decreased during hyperinsulinemia. This led to the assumption that either the glomerulosa cells may not share the influx of potassium during hyperinsulinemia and/or that extracellular rather than intracellular concentrations of potassium regulate human aldosterone secretion. After a slight decrease in basal plasma aldosterone, however, we observed increased angiotensin II-induced aldosterone secretion during euglycemic hyperinsulinemia in healthy men (Table 2). This could indicate that intracellular potassium content of glomerulosa cells was augmented to an extent to interfere with dynamic changes in aldosterone secretion induced by supraphysiological doses of angiotensin II. The above-mentioned end-organ resistance against insulin-mediated potassium transport could explain why this effect was not seen in diabetic patients (Table 2).

As pointed out previously, insulin does not influence external potassium balance and its impact on internal potassium balance is transient. Furthermore, in diabetics without hyporeninemic hypoaldosteronism (i.e., with a normal concentration of renin), the increase of 18-hydroxycorticosterone and of aldosterone in response to sodium depletion, upright posture, and angiotensin II was similar to that seen in healthy controls. Excessive production of aldosterone is obviously not the cause of diabetes-associated hypertension. On the basis of the data available at present, insulin apparently does not exert its effect on blood pressure by an action on aldosterone secretion.

Conclusions

Exogenous insulin influences blood pressure regulation in humans both indirectly by its effect on carbohydrate metabolism and by several direct actions that are of either immediate or long-term importance for specific blood pressure-regulating mechanisms. Since these direct actions were studied under experimental conditions where other variables were kept constant, it is difficult to evaluate their actual importance in vivo, where blood pressure is determined by mutual interactions between a large number of agonistic and antagonistic mechanisms.

At present, it appears that insulin influences blood pressure regulation in humans primarily by its antinatriuretic action, which contributes to hypertension by an increase in extracellular volume. The insulin-induced decrease in vasoreactivity is of practical importance in patients with autonomic dysfunction, in whom intravenous insulin induces orthostatic hypotension.

References


Table 2. Effect of Hyperinsulinemia on Basal and Angiotensin II-Stimulated Plasma Concentrations of Aldosterone in Six Healthy Men and Six Insulin-Dependent Diabetic Patients (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Plasma aldosterone (ng/dl)</th>
<th>Rise above basal concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Hyperinsulinemia</td>
</tr>
<tr>
<td>Healthy men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>6.3±2.2</td>
<td>5.0±1.2</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 ng·kg⁻¹·min⁻¹</td>
<td>8.0±1.3</td>
<td>7.0±2.2</td>
</tr>
<tr>
<td>10 ng·kg⁻¹·min⁻¹</td>
<td>13.7±4.7</td>
<td>14.1±6.4</td>
</tr>
<tr>
<td>20 ng·kg⁻¹·min⁻¹</td>
<td>14.7±8.6</td>
<td>21.4±9.6</td>
</tr>
<tr>
<td>Insulin-dependent diabetic men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>4.2±1.6</td>
<td>4.8±2.6</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 ng·kg⁻¹·min⁻¹</td>
<td>5.8±1.6</td>
<td>5.7±3.5</td>
</tr>
<tr>
<td>10 ng·kg⁻¹·min⁻¹</td>
<td>9.8±4.7</td>
<td>9.7±6.6</td>
</tr>
<tr>
<td>20 ng·kg⁻¹·min⁻¹</td>
<td>12.9±7.6</td>
<td>12.2±7.4</td>
</tr>
</tbody>
</table>

Each dose of angiotensin II was infused for 15 minutes. Values of aldosterone represent the mean of three determinations at 5-minute intervals. *p < 0.05, compared with control group by Student’s two-tailed t test for matched pairs.
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