Summary

Insulin-induced hypoglycemia has been shown to produce an increase in plasma renin activity (PRA) in dogs and in normal human subjects. This response in PRA is inhibited by β-adrenergic blockade; insulin-induced hypoglycemia thus appears to provide an endogenous β-adrenergic stimulus to renin release.

The change in PRA is abnormally low in response to various stimuli in a distinct subgroup of the population with essential hypertension, and this group has been referred to as having low renin essential hypertension. In an effort to gain insight into the mechanism(s) under which various stimuli in a distinct subgroup of the population with normal renin essential hypertension but failed to do so in a group of six patients with low renin essential hypertension. In both groups, plasma cyclic adenosine 3',5'-monophosphate (cyclic AMP; cAMP) increased more than 2-fold during hypoglycemia, but the response in the low renin group was significantly less than that previously observed in normal subjects under the same conditions. Plasma cortisol increased to an equal extent in both groups of hypertensive patients during hypoglycemia. Infusion of the phosphodiesterase inhibitor, theophylline, resulted in definite increases of PRA in patients with normal renin hypertension but not in patients with low renin hypertension. Because changes in the level of plasma cAMP during hypoglycemia have been thought to reflect adrenal catecholamine release, our finding of a blunted increase in plasma cAMP during hypoglycemia in patients with low renin hypertension may suggest that there is a generalized alteration in adrenergic responsiveness in this condition.

Methods

Eleven hypertensive patients, studied as outpatients, were separated into two groups on the basis of their PRA responses to the dual stimulus of orally administered furosemide and 3 hours of upright posture, in accordance with a previously standardized procedure. While on a ad lib diet, patients received 40-mg oral doses of furosemide at 6 p.m., midnight, and 6 a.m., and were upright from 6 a.m. until blood samples for PRA were drawn at 9 a.m. The six patients in whom stimulated PRA was less than 1.67 ng/ml/hr were classified as low renin hypertensives, and the remaining five patients were considered normal renin hypertensives. Known causes of hypertension were excluded on the basis of a careful history and physical examination: normal renal function; measurement of serum potassium, urinary vanillylmandelic acid or catecholamines, and urinary aldosterone excretion rates; intravenous pyelography; and (in all but one case) renal arteriography. In one normal renin subject fasting blood sugar was marginally elevated; values for fasting blood glucose were within the normal range for all other patients. After completion of the studies described above the blood pressure of each of the six low renin patients was shown to be responsive to therapy with the mineralocorticoid antagonist, spironolactone.

After the patients had been selected for the study, they were hospitalized on a metabolic ward under informed consent and in accordance with institutional requirements for human investigation. All antihypertensive therapy had been stopped at least 2 weeks prior to admission. All patients received a diet containing 100 mEq of sodium and 60 mEq of potassium per day, and remained fasting and recumbent from midnight until completion of the test period at noon. Blood was withdrawn from an indwelling polyethylene venous catheter at -15 minutes and at zero minutes, at which time the stimulus was administered; subsequent blood
samples were obtained every 30 minutes for 3 hours (i.e., at 30, 60, 90, 120, 150, and 180 minutes). The catheter was kept open between samplings by infusion of isotonic saline. Samples were assayed for glucose, cortisol, PRA, and cAMP.

Blood for plasma renin determination was collected on ice in tubes prepared with 0.3 ml of 10% liquid ethylenediaminetetraacetic acid (EDTA) and centrifuged at 4°C; the plasma was separated immediately and frozen. For radioimmunoassay for angiotensin I, we used a modification of the technique described by Haber et al. Serum glucose was measured by the colorimetric autoanalyzer technique. Plasma cortisol was determined by a fluorometric method. Blood for cAMP was drawn in prechilled tubes containing 15 mg of EDTA and immediately centrifuged at 4°C; the plasma then was separated and frozen. Plasma cAMP was measured by the protein-binding method of Gilman after purification.*

Regular insulin was administered intravenously in a dose intended to produce hypoglycemic symptoms and a decrease of at least 50% in serum glucose, preferably to less than 50 mg/100 ml. The dose usually was 0.15 to 0.20 units/kg.* On a subsequent day theophylline was administered in the form of aminophylline, 500 mg, by intravenous drip over a period of 10–20 minutes. Statistical evaluation was accomplished by randomized blocks analysis of variance.

**Results**

**INSULIN-INDUCED HYPOGLYCEMIA**

PRA (Fig. 1). In patients with normal renin essential hypertension increases in PRA were statistically significant (P < 0.001) and comparable to those previously described for normal subjects. In contrast, there were no significant changes in PRA in the low renin patients despite a serum glucose nadir virtually identical to that of the normal renin group.

Cyclic AMP (Fig. 2). Plasma cAMP increased significantly (P < 0.005) during hypoglycemia in both groups, although the response of the low renin patients was significantly lower (P < 0.01) than that previously described for a group of normal subjects under the same conditions.*

Cortisol. Plasma cortisol increased promptly in response to hypoglycemia in all low renin and normal renin hypertensive patients, so that no significant difference in responsiveness between groups could be detected (Table 1). Peak values were observed 60–90 minutes after the injection of insulin.

**THEOPHYLLINE INFUSION**

The infusion of theophylline caused increases in PRA in all patients with normal renin hypertension (P < 0.001) in a manner very similar to that previously described for normal

*One obese low renin patient and two obese normal renin patients received additional dosages of insulin because of lack of appropriate hypoglycemia and hypoglycemic symptoms following the initial dose. Accordingly, data from these patients have not been included in the figures depicting chronological changes in glucose, PRA, and cAMP, although changes in all parameters were comparable to those observed in other members of their respective groups, and their data were included for purposes of statistical analysis.

**TABLE 1 Cortisol Response to Hypoglycemia**

<table>
<thead>
<tr>
<th>Group</th>
<th>Plasma cortisol (μg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>15.8 ± 3.3</td>
</tr>
<tr>
<td>Insulin</td>
<td>34.2 ± 7.4</td>
</tr>
<tr>
<td>Normal renin (5 patients)</td>
<td>17.5 ± 2.7</td>
</tr>
<tr>
<td>Low renin (6 patients)</td>
<td>33.3 ± 2.1</td>
</tr>
</tbody>
</table>

Mean peak plasma cortisol ± SE (μg/100 ml) after insulin-induced hypoglycemia, as compared to mean control values ± SE, in patients with low renin and normal renin essential hypertension.
Discussion

It is well known that a sizable group of patients with essential hypertension can be distinguished by the blunted responsiveness of plasma renin to sodium depletion, upright posture, diuretics, and other pharmacological agents. These patients may or may not represent a homogeneous group, but when defined as having a low PRA and high blood pressure which can be easily lowered by the administration of the mineralocorticoid antagonist spironolactone, our present group of six such patients may be considered typical. If so, it appears that low renin essential hypertension is a condition in which renin hypo responsiveness persists even during the acutely stressful condition of hypoglycemia, a circumstance normally associated with elevations in PRA. Since the increase in PRA during hypoglycemia can be inhibited by propranolol, endogenous \( \beta \)-adrenergic stimulation appears to be the mechanism by which the juxtaglomerular cell is stimulated under these conditions. Adenyl cyclase activity is enhanced by \( \beta \)-adrenergic stimulation, and it has been asserted that cyclic nucleotides are important in the renin-release mechanism. Thus, in low renin hypertension the unresponsiveness of renin could be attributable to any “defect” in the sequence: (1) evocation of the adrenergic stimulus, (2) integrity of the \( \beta \)-receptor, (3) responsiveness of the adenylate cyclase-cAMP-phosphodiesterase system, or (4) responsiveness of the intracellular machinery “distal” to cAMP (protein kinase activity, protein synthetic capacity, renin-releasing capability, etc.). Although some investigators have reported abnormalities in catecholamines and \( \alpha \)-adrenergic responsiveness in low renin essential hypertension, consistent abnormalities have not been found. The finding by Jose and co-workers that PRA was unresponsive to the infusion of pressor doses of norepinephrine in a group of low renin hypertensive patients suggests that altered adrenal catecholamine release is not, by itself, a sufficient explanation for the unresponsiveness.

Our finding that the change in cAMP level in response to hypoglycemia was blunted in these patients (Fig. 2) could be interpreted as indicative of a generalized “defect” in their responsiveness to adrenergic stimuli, since we have previously demonstrated that changes in plasma cAMP during hypoglycemia are a reflection of \( \beta \)-adrenergic stimulation. Our data comparing plasma cAMP in normal subjects and hypertensive patients during hypoglycemia should perhaps be viewed with caution because the number of subjects is relatively small and the subjects were not matched for age, sex, or race; nevertheless, an additional observation which points to abnormal metabolic control mechanisms in our low renin hypertensive patients is the slower return toward baseline of blood glucose, despite an insulin-induced nadir which was virtually identical to that produced in the normal renin group (Fig. 1). Although not carefully quantitated, the degree and duration of diaphoresis, tachycardia, and systolic blood pressure elevation in the two groups were not appreciably different.

In our study theophylline increased PRA in patients with normal renin but not low renin hypertension. Theophylline is a phosphodiesterase inhibitor, and its pharmacological effects often have been ascribed to an increase in tissue cAMP levels. Accordingly, an argument could be made that, since our hypertensive patients with low renin showed little or no PRA response to theophylline (Fig. 3), renin suppression must have been operative at some point “distal” to intracellular cAMP, so that the postulated increases in the latter were without effect. The data are indeed consistent with this concept, but several other interpretations are equally tenable.

To begin with, the plasma levels of theophylline which can be achieved by administration of conventional doses to man may be lower than those needed to inhibit phosphodiesterase. Also, it is likely that extracellular cAMP is not always a good indicator of intracellular events in all tissues, and the finding of increased plasma cAMP in our low renin patients during hypoglycemia therefore might not be paralleled by increases of cAMP in the renal juxtaglomerular cell. That this may be true is suggested by the finding, under certain conditions, of a dissociation between changes in PRA and levels of plasma cAMP. For example, we have found previously that in normal subjects PRA rose in response to theophylline infusion, and that theophylline potentiated the PRA response to hypoglycemia but did not potentiate the effects of hypoglycemia on plasma cAMP and did not elevate as appreciably the plasma level of cAMP when it was infused in the absence of hypoglycemia (unpublished results). Moreover, hypoglycemia alone did not cause a rise of plasma cAMP in adrenalectomized patients, although PRA was increased under those conditions.

Thus, changes in plasma cAMP cannot necessarily be expected to predict changes in PRA, even though the
changes in peripheral PRA might, themselves, be closely related to events involving cAMP within the juxtaglomerular cell. Since we were unable to directly measure cAMP within the juxtaglomerular cell, it cannot be ascertained whether theophylline elevated PRA in our normal renin subjects through its effects on phosphodiesterase, by its stimulating effects on the adrenergic and central nervous systems, or by its effects on mechanisms perhaps entirely unrelated to cAMP. Similarly, the lack of a means to measure intracellular cAMP in the low renin group during insulin and theophylline infusions prevents distinction between (1) possible juxtaglomerular cell unresponsiveness to cAMP and (2) juxtaglomerular unresponsiveness "proximal" to cAMP (e.g., at the β-receptor-adenylate cyclase level).

In summary, we have found that PRA in patients with low renin essential hypertension does not respond to insulin-induced hypoglycemia or to theophylline. The finding of a blunted increase in plasma cAMP during hypoglycemia may point to a generalized alteration in adrenergic responsiveness in these patients. The possible relation of a defect in the autonomic nervous system and the suspected mineralocorticoid excess in this condition remains to be evaluated. The lack of response of PRA to theophylline in low renin essential hypertension is consistent with the view that juxtaglomerular cell cAMP is either low or lacking in effect in these patients, and underlines the need for more direct, in vitro studies on the intracellular interaction of renin, cAMP, phosphodiesterase and the β-receptor in essential hypertension.

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References


Contrasting effects of hypoglycemia on plasma renin activity and cyclic adenosine 3',5'-monophosphate (cyclic AMP) in low renin and normal renin essential hypertension.

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