Leading Article

Insulin resistance and hypertension – implications for treatment

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Introduction

It is now well established by numerous clinical trials that the treatment of hypertension reduces the risk of stroke.\(^1\) However, these trials have generally failed to demonstrate a significant reduction in the incidence of myocardial infarction. The likely explanation for this is that whereas hypertension is the major risk factor for stroke and cholesterol is of less importance,\(^2\) other risk factors, including plasma lipids, are of equal or greater importance than hypertension in the genesis of coronary artery disease. Lowering blood pressure cannot therefore be expected to reduce the risk attributable to these other risk factors and any positive effect in lowering that part of the risk due to hypertension may be offset by the increase in serum cholesterol which is often observed in treated hypertensives.\(^3\) Any benefit from control of blood pressure in reducing myocardial infarction will therefore be smaller than that in stroke and the trials conducted to date may have been too short in duration or too limited in size to demonstrate significant benefit from treatment.

Because of the increasing awareness of the role of hyperlipidaemia in the pathogenesis of vascular disease, concern has grown in recent years that treatment with the conventional first line drugs, thiazide diuretics and beta-adrenergic blockers, may worsen plasma lipids and that this may explain their failure to reduce myocardial infarction rates.

Anxiety over the possible adverse effects of the older antihypertensive agents has been heightened since it has been suggested that insulin resistance with hyperinsulinaemia, glucose intolerance and hyperlipidaemia may be the primary abnormality in essential hypertension.\(^4\) Both beta-blockers and thiazide diuretics cause increased insulin resistance\(^5\)\^-\(^8\) and may therefore worsen already adverse risk factor patterns. In contrast, calcium antagonists do not influence insulin sensitivity\(^9\) and angiotensin converting enzyme (ACE) inhibitors may even increase insulin sensitivity.\(^1\)

These observations have led to controversy over the choice of first line drug treatment for hypertension. One camp favours the beta-blockers and thiazides, proven to be of benefit in clinical trials, and, incidentally, much cheaper,\(^10\)\(^,\)\(^11\) whereas others are persuaded by the superior biochemical side effect profile of the calcium antagonists and ACE-inhibitors despite the lack of clinical trial evidence of benefit.\(^12\) Before considering these arguments further it is worthwhile to re-examine the role that has been suggested for insulin resistance in the pathogenesis of essential hypertension.

The concept of insulin resistance

In 1939 Himsworth and Kerr\(^13\) showed that, in response to an oral glucose load combined with intravenous insulin, some patients maintained normal plasma glucose whereas others were insulin insensitive (resistant) and plasma glucose increased. When radioimmunoassay made the measurement of plasma insulin widely available it became clear that, in some individuals, a normal glucose tolerance curve was achieved with higher than normal insulin levels, indicating insulin resistance.\(^4\) The ratio of blood glucose to plasma insulin goes some way to quantifying insulin resistance and can be used in comparing various pathological conditions.

A more precise, but perhaps less physiological, quantitation of insulin resistance has been sought using the euglycaemic hyper-insulinaemic clamp. In this technique subjects are infused with insulin at a predetermined rate and sufficient glucose is infused to maintain blood glucose at the pre-infusion concentration.\(^14\)\(^,\)\(^15\) The rate of glucose

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infusion is then a measure of the net effect of insulin in reducing hepatic glucose production and increasing peripheral glucose utilization.

There are, however, some problems in interpreting the results of this test. The clamp technique measures largely the non-oxidative disposal of glucose by skeletal muscle\(^{16}\) rather than the full range of physiological insulin action which includes a major action on the liver in controlling glucose delivery to the periphery.\(^{17}\) Thus insulin resistance measured in this way is largely an abnormality of skeletal muscle, and other tissues cannot be assumed to show similar resistance to insulin action. There are, in addition, methodological pitfalls with the technique and ideally insulin sensitivity should be assessed using a series of clamps at different insulin infusion rates.\(^{18,19}\) This has not been done in studies of hypertensive patients.

**Do patients with essential hypertension exhibit insulin resistance?**

Glucose intolerance in patients with hypertension was described by Harris in 1949\(^{20}\) and confirmed in studies incorporating formal oral glucose tolerance tests in the 1970s.\(^{21,22}\) As early as 1966 Welborn and his colleagues\(^{23}\) had described hyperinsulinaemia in essential hypertensives but this was not pursued until the mid 1980s when Singer et al. reported post-prandial hyperinsulinaemia in these patients.\(^{24}\) The possible role of hyperinsulinaemia in hypertension was further supported by the observations that obesity is often accompanied by hypertension and hyperinsulinaemia and that a significant correlation has been demonstrated between systolic blood pressure and plasma insulin levels after an oral glucose load in obese subjects.\(^{25-27}\)

Ferranini and his colleagues,\(^{28}\) using the euglycaemic insulin clamp, found increased insulin resistance in non-obese essential hypertensives with a positive correlation between the level of blood pressure and the defect in whole body glucose utilization thus strongly suggesting that hypertension itself was associated with insulin resistance independently of obesity. However, the sensitivity to insulin is reduced to a much lesser extent in non-obese (14\%) than in obese (39\%) hypertensives.\(^{29}\) These observations do, however, appear to provide quite strong support for the presence of insulin resistance in essential hypertension and they have been confirmed in other studies.\(^{30,31}\)

There are, however, reservations in relating insulin resistance to hypertension. The mechanism of insulin resistance in non-insulin dependent diabetics (NIDDM) on the one hand and in obesity, and therefore potentially in essential hypertension on the other, appears to be different. In NIDDM, hepatic and adipose tissue insulin receptor tyrosine kinase activity is lower than in obese insulin resistant subjects,\(^{32,33}\) whereas the enzyme activity in skeletal muscle is equally reduced in both NIDDM and obese subjects.\(^{34}\) A difference in the loss of glucose transporters in the two conditions has also been reported with equal reductions being observed in skeletal muscle but a greater reduction in adipose tissue in NIDDM than in obesity.\(^{35}\) In Ferranini’s studies\(^{28}\) the characteristics of the resistance to insulin action in non-obese essential hypertensives, that is, reduced non-oxidative glucose disposal in peripheral tissues, also differed from those in patients with obesity or non-insulin-dependent diabetes\(^{35}\) in whom there were in addition defects in lipid and glucose oxidation and reduced potassium uptake. Thus, although there is a clinical overlap between obesity, diabetes and hypertension,\(^{36}\) hyperinsulinaemia may not necessarily play an aetiological role in non-obese hypertensives. In particular the tissue differences indicate that it cannot be assumed that all tissues will show the same resistance to the action of insulin as does skeletal muscle.

Other factors besides obesity may influence insulin resistance and in particular the state of physical fitness, which has been shown to have very significant effects on sensitivity to insulin.\(^{37}\) was not taken into account by Ferranini’s group.\(^{28}\) Some studies of obese and lean hypertensive patients\(^{38,39}\) have found no independent correlation between serum insulin levels and blood pressure.

Our own studies using the glucose : insulin ratio as a measure of insulin resistance, rather than the less physiological euglycaemic hyperinsulinaemic clamp, revealed no evidence of insulin resistance in non-obese essential hypertensives, although we did confirm insulin resistance in non-insulin dependent diabetics (NIDDM).\(^{40}\) Furthermore, many patients with NIDDM are normotensive despite pronounced hyperinsulinaemia.

There is therefore evidence of glucose intolerance and of hyperinsulinaemia in patients with essential hypertension. These patients also probably have resistance to the action of insulin which is not fully explained by obesity, although an effect of lack of physical fitness has not been excluded. However, there is some uncertainty as to the interpretation of the euglycaemic hyperinsulinaemic clamp and the more physiological assessment of insulin sensitivity using the glucose insulin ratio has failed to confirm insulin resistance. Although the question of insulin resistance in uncomplicated essential hypertension remains ‘not completely proven’, there is sufficient evidence of hyperinsulinaemia to go on to consider its possible role in the pathogenesis of raised blood pressure.
The effect of hyperinsulinaemia on blood pressure

Insulin resistance in hypertension may be the primary event leading to the increase in blood pressure or may be secondary to the events accompanying hypertension. For example insulin receptor binding is pH sensitive and blood pH is slightly increased in hypertension. There are also lipid abnormalities in association with hypertension and, as well as possibly arising as a result of insulin resistance, could affect the cellular response to insulin by changing the cell membrane receptor. However, a recent longitudinal study over 18 years showed that glucose intolerance preceded the development of hypertension, suggesting that the change in insulin sensitivity may be the primary event.

Direct effects of insulin

Insulin has both hypotensive and hypertensive actions. At the cellular level insulin blocks calcium currents and would therefore be expected to lower blood pressure and in patients with autonomic failure it has in fact been shown to do so. In addition, insulin appears to antagonize the cardiovascular effects of circulating catecholamines. These observations led Resnick to suggest that the hypertension which accompanies insulin-resistant states might be due to resistance to the hypotensive effects of insulin as well as to its metabolic effects. However, hyperinsulinaemia may also directly raise blood pressure through its other actions on membrane transport and on the sympathetic nervous system.

Stimulation of the sympathetic nervous system

The infusion of insulin in high dose stimulates the sympathetic nervous system (SNS) although tachyphylaxis may develop and lower doses giving plasma levels in the physiological range do not do so. However, the hyperinsulinaemia seen in obese subjects is accompanied by increased plasma noradrenaline levels and insulin may be responsible for this increased activity of the SNS. The hyperinsulinaemia which occurs in some patients with hypertension may therefore also result in stimulation of the SNS.

There is evidence of stimulation of the SNS at least in some hypertensives. Plasma noradrenaline (PNA) is increased in obese hypertensives and there is parallel fall in blood pressure and PNA with weight reduction. In addition to the increase in PNA an increased sensitivity of sympathetic receptors to stimulation in essential hypertension has been described although this has not been confirmed by others. Increased sensitivity to alpha-adrenergic stimulation may only develop after medial hypertrophy of resistance vessels has occurred but the hyper-responsiveness does seem to be specific since in studies infusing noradrenaline and angiotensin II into the forearm in hypertensives the vasoconstrictive response to the former was greater.

In early or 'borderline' hypertension, heart rate and stroke volume are increased, indicating increased cardiac sympathetic drive and there is a failure of peripheral vascular resistance to fall appropriately in the face of increased tissue oxygen consumption again suggesting increased sympathetic drive. In approximately 30% of 'borderline' hypertensives plasma renin activity and plasma noradrenaline are increased indicating increased sympathetic activity. In these, pharmacological blockade of the autonomic nervous system with a combination of alpha and beta-blockers and atropine resulted in correction of the hypertension suggesting that the hypertension was neurogenic in these cases. Lund-Johansen has shown in longitudinal studies over 17 years that neurogenic borderline hypertension does, in fact, progress to established hypertension.

The obstacle to accepting the importance of increased sympathetic activity in the pathogenesis of essential hypertension has been the normality of cardiac output and of plasma noradrenaline in established hypertension. Julius has suggested that cardiac output returns to normal from high levels in the early stages because of reduced responsiveness of beta-adrenergic receptors following prolonged stimulation. Cardiac output may also fall because of reduced cardiac compliance due to ventricular hypertrophy. The fall in plasma noradrenaline may be explained by the increased sensitivity of resistance vessels if it is assumed that the sympathetic drive is controlled by feedback based on the blood pressure level achieved.

There does seem, therefore, to be good evidence for the role of the sympathetic nervous system in the pathogenesis of some cases of essential hypertension and perhaps weaker evidence that the increase in sympathetic activity is due to hyperinsulinaemia.

Hyperinsulinaemia, sodium balance and hypertension

Insulin stimulates sodium potassium ATPase activity directly and may augment the action of aldosterone on this membrane pump. Insulin receptors have been demonstrated along the distal convoluted tubule and, in keeping with these observations, the infusion of insulin leads to an increase in distal tubular sodium reabsorption.
Insulin also stimulates the sodium hydrogen antiporter which is the rate-limiting step for sodium reabsorption in the proximal tubule. Insulin receptors have been demonstrated in the proximal tubule and insulin increases proximal sodium reabsorption in isolated rabbit tubules. There has been controversy on the exact site of increased sodium reabsorption in response to hyperinsulinaemia with de Franzó finding it to be from the distal tubule and Hannedouche, ourselves and Trevisan from the proximal tubule. The last three studies were in diabetics and, although glucose control was good, part of the increased proximal sodium reabsorption may have been due to stimulation by glucose of the glucose sodium co-transporter. There is resistance to the effect of insulin on erythrocyte sodium potassium ATPase in hypertension as well as to the metabolic effects of insulin and it is not certain whether this resistance extends to the renal tubular cells. However, insulin infusion does reduce urinary sodium excretion in obese adolescents despite their metabolic insulin resistance and plasma potassium is reduced to the same degree by insulin infusions in essential hypertensives and normal controls, suggesting normal renal and tissue sodium potassium ATPase responsiveness to insulin despite the resistance of the erythrocytes. The effect of hyperinsulinaemia in essential hypertension in leading to sodium retention is therefore at least plausible.

The increased sympathetic activity in essential hypertension may also contribute to sodium retention by redistribution of blood flow to sodium conserving nephrons, stimulation of renin release and by a direct effect on tubular reabsorption of sodium.

In keeping with the sodium retaining role in insulin, sodium retention has been demonstrated in both insulin-dependent and non-insulin-dependent diabetics. Unfortunately for the theory that hyperinsulinaemia may be responsible for the raised blood pressure in essential hypertensives through sodium retention, most studies have shown no evidence of sodium retention in essential hypertension. Bianchi showed an initial sodium retention in some hypertensives and Weder found an increase in proximal tubular sodium reabsorption in essential hypertensives. However, others have been unable to confirm the increased proximal sodium reabsorption and plasma volume and whole body exchangeable sodium have usually been found to be normal or even decreased in essential hypertension, whether in the early or established stage, and in the normotensive children of hypertensive parents.

Thus, although there is good evidence that insulin stimulates sodium reabsorption in the kidney and may lead to volume expansion in diabetics, there is little evidence of sodium retention in essential hypertension. The absence of sodium retention in hypertensives may be due to the balancing effect of pressure natriuresis or it may reflect a resistance to the effect of insulin on membrane cation transport as well as to its metabolic effects. Whatever the explanation for the absence of hypervolaemia it is difficult to attribute the raised blood pressure in essential hypertension to insulin-induced sodium retention.

The effect of insulin on intracellular cations and on smooth muscle hypertrophy

Insulin stimulates sodium-hydrogen exchange and increased sodium influx into the cell in turn stimulates sodium potassium pump activity. Stimulation of sodium potassium ATPase may also be mediated by an increase in intracellular magnesium which is increased following a glucose load and during hyperinsulinaemic clamping. This increase in intracellular magnesium is attenuated in patients with essential hypertension or NIDDM and this may explain the reduced activity of the sodium pump in these conditions. It has, of course, been suggested that there may be a circulating inhibitor of the sodium pump in essential hypertension. The combined effects of increased sodium hydrogen exchange, driven by hyperinsulinaemia and inhibition of sodium potassium ATPase are postulated to result in an increase in intracellular sodium. This results in an increased intracellular calcium due to reduction in the sodium gradient driving the calcium sodium antiporter. The activity of this antiporter is also stimulated by insulin and may be further reduced in essential hypertension if it shares a general resistance to insulin. The increase in intracellular calcium in smooth muscle cells of resistance vessels leads to contraction with increased peripheral resistance and hypertension. However, there are conflicting reports on the relationship of intracellular sodium to hypertension since erythrocytes may not be representative of other cells and studies on leucocytes and smooth muscle cells are more difficult and have not confirmed the increase in sodium concentration reported in erythrocytes.

Insulin is a growth factor and has been shown to promote the growth of vascular smooth muscle in culture. If this occurs in vivo and the response does not share the resistance to insulin observed in relation to glucose uptake in hyperinsulinaemia, then the resulting increase in thickness and possibly noradrenaline responsiveness in resistance vessels may contribute to the development of hypertension.
How well established is the role of insulin resistance in essential hypertension?

There seems little doubt that there is resistance to some of the actions of insulin in patients with essential hypertension but it differs in some respects from that in NIDDM. Furthermore, it is not yet certain that it is not explicable by obesity, hyperlipidaemia and lack of physical fitness, which often accompany hypertension, rather than the hypertension itself. However, the observation that a tendency to hyperglycaemia precedes hypertension by many years does suggest a primary relationship. Further larger scale studies in essential hypertension with carefully matched controls and family studies are required to firmly establish that essential hypertension per se is associated with insulin resistance. Hyperinsulinaemia is a credible candidate for a role in the pathogenesis of essential hypertension. Insulin probably stimulates the sympathetic nervous system at the levels which are found in essential hypertension and there is evidence of increased sympathetic activity in hypertension. Any effect of insulin in raising blood pressure through sodium retention is less well established since, although insulin undoubtedly stimulates renal sodium retention, there is no evidence of sodium retention in established essential hypertension. The role of hyperinsulinaemia in the intracellular cation changes, seen in essential hypertension, and as a growth factor for smooth muscle, has not yet been fully established.

Implications for management

Since the role of hyperinsulinaemia and insulin resistance in essential hypertension is not yet established it would be premature to base clinical decisions on choice of drug therapy for hypertension on a particular drug’s effect on insulin resistance. It seems prudent to depend on the results of clinical trials and to continue to use beta blocking drugs and diuretics as first line drugs. In patients who have hyperlipidaemia, or who develop it during treatment, and in whom plasma lipids do not return to normal with dietary measures it seems reasonable to change to a drug without adverse effects of lipids or insulin resistance. Calcium antagonists and ACE-inhibitors are ‘lipid neutral’ and have no adverse effect on insulin resistance. Indeed, in the case of captopril, insulin resistance may even be reduced, and either would be a reasonable choice. Alpha-one adrenergic blocking drugs such as prazosin have a favourable effect on lipids and are also a reasonable choice in hyperlipidaemic patients.

The selection of drug treatment on the basis of a theoretical concept rather than clinical trial led to a great enthusiasm for ACE-inhibitors in diabetes as renoprotective agents. Experience has shown that, although they are, of course, very useful in the treatment of hypertension in diabetics, they are no more effective than calcium antagonists in protecting the kidney.91

We should not go beyond hard evidence in recommending a change in treatment strategy in hypertension especially in view of the cost implications of a widespread movement away from diuretics and beta blockers. It is likely, however, that the threshold for changing from the established first line drugs to the newer drugs will gradually fall as their safety and efficacy become better established and perhaps prices fall.

References


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