Review

Insulin and hypertension: a causal relationship?

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1. Introduction

The association between insulin and hypertension has been extensively explored during the past decade and remains an area of intense discussion and debate. Interest in the link between insulin and high blood pressure was fueled by two distinct observations: (i) the lack of effective antihypertensive drugs to reduce the increased risk of coronary artery disease in hypertensive subjects [1-4] and (ii) the realization that essential hypertension per se is frequently associated with insulin resistance (resistance to the glucoregulatory effects of insulin) and hyperinsulinemia [5,6]. These two observations led to the so-called “insulin hypothesis” of hypertension where it was postulated that insulin resistance and/or hyperinsulinemia may be causally related to the development of hypertension [7,8]. This was an attractive proposition which could help explain the apparent inability of conventional antihypertensive drugs (thiazides, beta blockers) to decrease the incidence of coronary ischemic events, since these drugs did not improve but rather worsened insulin action [9-11].

Subsequent studies revealed that these defects in glucose metabolism are associated with an atherogenic risk profile and may play a role in the development of hypertension, dyslipidemia, atherosclerosis and coronary artery disease [12-19]. Recent reports clearly indicate that insulin resistance and hyperinsulinemia occur not only in untreated human hypertensives [24,25] but also in several rodent models of hypertension [12,26,27] strengthens the contention that these abnormalities are intrinsically linked with hypertension and are not mere coincidental findings. Studies indicate that hyperinsulinemia is an independent risk factor for coronary artery disease [28,29] and that even a small degree of glucose intolerance significantly increases the risk of developing coronary heart disease [30]. Another finding that strongly supports this intriguing association is that patients with hypertension who have microvascular angina are insulin-resistant and hyperinsulinemic when compared to hypertensive subjects without ischemic heart disease [31-33]. The intent of this review is to summarize the current evidence linking insulin to hypertension, an issue that still attracts considerable controversy and dispute. Specifically, the proposition that these metabolic abnormalities may be causally related to hypertension will be discussed.

2. Insulin and hypertension: epidemiology

Welborn et al. were the first to demonstrate higher fasting and postprandial insulin levels in both treated and untreated hypertensive patients when compared to control, normotensive subjects [34]. This initial finding was subsequently confirmed in several large epidemiological studies. Berglund et al. screened middle aged Swedish hypertensive men who had no other clinical disease and who were not taking any antihypertensive medication [35]. They reported that both fasting insulin and glucose concentrations were higher in hypertensive patients as compared to their normotensive controls. These results were confirmed in another extensive study from Israel, which demonstrated that hypertensive patients exhibited fasting and postprandial hyperinsulinemia independent of obesity, age or magnitude of glucose tolerance [36]. This observation has since...
been confirmed by several epidemiological and clinical studies [37–39] which have documented the presence of irregularities in carbohydrate metabolism in young, non-obese subjects with untreated, uncomplicated essential hypertension. In a different approach, Singer et al. compared the day-long insulin and glucose profiles in response to standard meals in untreated hypertensive patients and found that the insulin response after each meal was markedly increased in hypertensive patients [40]. Results from their study indicated that essential hypertensive subjects not only had an increased insulin response to a glucose challenge but that this exaggerated insulin response occurred after every meal that they consumed.

Not all hypertensive patients are hyperinsulinemic and several studies demonstrate a weak correlation between insulin and high BP [41,42]. In addition, it was reported that insulinemia was not related to the prevalence of hypertension in Pima Indians after controlling for obesity and drug treatment [43]. Mbanya et al. demonstrated that plasma insulin levels were similar between hypertensive and normotensive subjects and that insulin levels were increased only in those hypertensive patients who also had NIDDM [44]. In an attempt to resolve the conflicting results from a virtual flurly of reports examining the relationship between insulin and hypertension, Denker and Pollock performed a meta-analysis on the various studies reported between the years 1983 and 1991 [45]. They included only those studies that were conducted in untreated hypertensives or in which an adequate washout period was included as part of the study protocol and in which the subjects were neither glucose intolerant or diabetic. The results of their meta-analysis indicated that fasting serum insulin concentration was strongly correlated with both systolic and diastolic BP when data from all the studies were pooled together to yield a statistically meaningful result.

Despite the dispute that exists due to the disparate results of almost 50 different studies reported in the last 10 years, several consistencies have emerged regarding this association. First, as many as 50% of hypertensive patients appear to be insulin-resistant and hyperinsulinemic when compared to age- and weight-matched normotensive controls [45,46]. There is ethnic variation in this relationship such that significant correlations between these metabolic defects and hypertension exist in Caucasian, Hispanic White and Japanese populations but not in Afro-Americans or Pima Indians [47,48]. However, a lack of correlation in an epidemiological study does not rule out a role of insulin in the development of hypertension in that population. For example, although a correlation between insulin concentration and hypertension was not found in Afro-Americans, subsequent studies demonstrated that hypertensive Afro-Americans were both insulin-resistant and hyperinsulinemic when compared with normotensive controls [49,50].

Second, it was reported in several studies that the correlation between insulin and BP became weak or even non-significant after accounting for obesity. This led some investigators to propose that obesity may be the primary factor that causes or modulates insulin resistance in hypertensive subjects. Although several studies had indicated that insulin resistance was present even in lean, untreated hypertensive patients, the role of hypertension in modulating insulin resistance in obese subjects remained undefined. It was not clear whether the insulin resistance observed in obese, hypertensive subjects was due to obesity per se or high BP or both. The answer to this dilemma came from a recent study in which insulin resistance was quantified in 5 different groups of subjects: normotensive-obese, normotensive-nonobese, hypertensive-obese, hypertensive-nonobese and hypertensive-obese with NIDDM [51]. The results unequivocally demonstrated that the effects of obesity, hypertension and NIDDM on insulin resistance are additive and that each one of these diseases independently contributes towards resistance to insulin’s glucoregulatory effects. Taken together, current evidence indicates that insulin resistance and hyperinsulinemia are present in a substantial proportion of hypertensive patients. Furthermore, this relationship is stronger among some ethnic groups than in others and is independent of age, obesity or drug treatment.

3. Prospective studies in normotensive offspring of hypertensive subjects

Although insulin resistance and hyperinsulinemia correlated positively with high BP in a considerable proportion of hypertensive patients, it was not clear whether these defects were primary or whether they were a consequence of hypertension. In the first report that dealt with this issue, insulin sensitivity and plasma insulin levels in normotensive offsprings of essential hypertensive parents were compared with those obtained from age- and weight-matched normotensive subjects with no parental history of hypertension [52]. It was found that young, lean, normotensive adults (mean age about 24 years) who had a positive family history of hypertension were insulin-resistant and hyperinsulinemic when compared to normotensive controls without a hypertensive parent. Insulin sensitivity was decreased by about 28% and insulin levels were increased by about 15% in subjects with a parental history of hypertension, which indicated that these defects antedate the increase in BP and are not secondary to hypertension. Almost identical results were reported by Facchini et al. one year later, in their study the majority of subjects were female as opposed to the study by Ferrari et al. in which the subjects were predominantly male [53]. These results indicated that the link between insulin and hypertension had a genetic basis that was independent of age, gender or body weight.

Subsequent studies extended these observations and demonstrated that the reduced insulin sensitivity that ante-
dated the increase in BP in normotensive adults with a positive family history of hypertension was also accompanied by a higher intracellular calcium concentration [54]. This suggested that disturbed intracellular calcium metabolism was also an inherited trait and raised the possibility that this intracellular defect could be a link between insulin and hypertension. However, it was not clear whether the abnormal calcium metabolism was a cause or consequence of insulin resistance, a question that remains unanswered to date. A recent study demonstrated that hyperinsulinemia was present even in young children (mean age about 14 years) who were normotensive, normolipidemic but had a positive family history of hypertension, which strongly suggests that defects in insulin action antedate most of the metabolic and hemodynamic abnormalities seen in hypertensive subjects [22]. The observation that insulin resistance can be modified by environmental influences such as body weight or physical exercise [13] suggests that the final phenotypic expression of these defects is probably a combination of both genetic and acquired influences. Nevertheless, the studies discussed above clearly indicate that insulin resistance is a genetically inherited trait and is not simply a consequence of increased BP.

4. Insulin and hypertension: experimental evidence

4.1. Human studies

Ferrannini et al. provided the first direct evidence that essential hypertensive patients are insulin-resistant [24]. By employing the euglycemic hyperinsulinemic clamp technique, they studied insulin sensitivity in young, lean, untreated hypertensive subjects and found that insulin sensitivity was markedly decreased (about 40%) in hypertensive patients when compared to age- and weight-matched controls [24]. Furthermore, they also demonstrated that the insulin resistance was tissue specific in that it occurred mainly in the skeletal muscle and that insulin-induced suppression of hepatic glucose production was normal in hypertensive subjects. Another interesting observation that stemmed from their elegant study was that almost the entire reduction in insulin sensitivity could be accounted for by a decrease in nonoxidative glucose disposal (glycogen synthesis) whereas glucose oxidation and suppression of lipolysis were unaltered in hypertensive patients. This observation has subsequently been confirmed by several investigators [55–57].

Other studies have unequivocally demonstrated that not only is insulin resistance present in hypertensive subjects but that it is not improved by lowering BP with antihypertensive drugs [9–11]. On the contrary, several studies indicate that antihypertensive therapy worsens insulin resistance and hyperinsulinemia in essential hypertensives [9,25]. The view that insulin resistance is not secondary to an increase in BP is further supported by studies indicating that insulin-mediated glucose utilization and glucose-stimulated insulin secretion is normal in patients with secondary hypertension such as renovascular hypertension and primary hyperaldosteronism [23]. More direct evidence for such a link has come from studies where it was observed that physical training lowered BP in obese patients without any change in body weight, but only in those patients who were hyperinsulinemic before the start of the training [58].

However, it is important to remember that insulin resistance is not always associated with hypertension and vice versa. As was discussed earlier, there is ethnic variability in this relationship such that the link appears stronger in Caucasians and Hispanic Whites. Two other arguments that have been frequently cited as evidence against the insulin-hypothesis of hypertension deserve mention. First, insulin when administered acutely is a vasodilator and does not cause an increase in BP [59]. The inability of insulin to increase BP acutely does not go against the view that insulin may modulate BP chronically. It rather suggests that if insulin is a vasoactive hormone, then resistance to its vasodilatory effects may result in an increase in peripheral vascular resistance and a consequent rise in BP. The finding that BP falls when the dose of insulin is decreased in obese, hypertensive patients with NIDDM [60] and that an increase in BP occurs when insulin treatment is started in NIDDM patients [61] strengthens the contention that chronic insulin therapy may exert pressor effects in humans. This view is further supported by a recent study indicating that troglitazone, a drug that improved insulin sensitivity, also lowered BP in essential hypertensive patients with diabetes mellitus [62].

The second argument that is often advanced against the view that insulin modulates BP is that patients with insulinoma who are hyperinsulinemic are generally not hypertensive [63]. What is overlooked while advancing this argument is that patients with insulinoma do not have primary insulin resistance, since hyperinsulinemia in such patients is accompanied by marked hormonal counter-regulatory responses. In addition, patients with insulinoma lack the substrate for insulin (i.e. glucose), which is necessary for insulin’s effects on vascular smooth muscle responses [64]. Finally, in the study that addressed this issue [63], hyperinsulinemia was present for a relatively short period (about 18 months) as opposed to the increased levels of insulin that are present throughout the life span of hypertensive patients.

In summary, current evidence indicates that insulin resistance in hypertension is a primary defect (independent of obesity, diabetes or drug treatment) and is tissue specific (resides primarily in skeletal muscle) and pathway specific (involves glycogen synthesis). This defect in insulin-mediated glucose uptake may play a role in the development of hypertension or may chronically predis-
pose a certain proportion of subjects with a specific neurohumoral phenotype towards an increase in BP.

4.2. Animal studies

The association between insulin and hypertension has also been documented in several models of rodent hypertension. These include the Dahl rat [26], the spontaneously hypertensive rat [8,12,27], the Milan hypertensive rat [65] and the fructose-hypertensive rat [66]. All of these hypertensive rat models, although unrelated to each other, exhibit common defects in glucose metabolism. In Dahl rats, insulin resistance and hyperinsulinemia occur in salt-sensitive as well as salt-resistant animals and are independent of the salt content of the diet [72]. In spontaneously hypertensive rats, hyperinsulinemia precedes the development of hypertension [67]; however, the presence of insulin resistance in this rat strain remains controversial [68-71]. Some very pertinent findings have emerged from studies in which insulin resistance and hyperinsulinemia were induced in normotensive Sprague Dawley rats by giving them a high fructose diet [66]. Induction of these metabolic defects was associated with a concomitant increase in blood pressure in these rats. Furthermore, exercise training (which resulted in improved insulin sensitivity) and somatostatin administration (which decreased hyperinsulinemia) to the fructose-fed rats attenuated the fructose-induced increase in BP in the animals [20,73]. Although these findings do not establish causality, they do support such a link.

In a series of experiments, we recently examined the proposition that insulin resistance and hyperinsulinemia contribute causally to the development of high BP. Essentially, if these metabolic abnormalities were responsible for an increase in BP, then drugs that improve these metabolic defects should also attenuate hypertension. We, therefore, examined the effects of drugs that are known to improve insulin sensitivity on BP in SHR and fructose-hypertensive rats. We found that chemically diverse drugs that have the common property of attenuating hyperinsulinemia also lower BP in both the SHR [74-76] and fructose-hypertensive rats [77,78]. These drugs included compounds of the trace element vanadium [74,75], the antihyperglycemic agent metformin [76,78] and pioglitazone [79,80], a thiazolidinedione compound that improves peripheral insulin sensitivity. All of the drugs not only caused sustained reductions in plasma insulin concentration and BP in the rats, but the antihypertensive effects of the drugs could be reversed by simply restoring plasma insulin levels in the drug-treated rats to those that existed before treatment. Similar results have been reported by other laboratories [81-83] and indicate that there exists a strong and close association between hyperinsulinemia and hypertension in rodent models of hypertension.

Results obtained from studies conducted in dogs are in contrast to those reported in rats. Acute insulin infusion in dogs did not raise BP [84], whereas it led to a dose-dependent increase in BP in rats [85]. Furthermore, chronic insulin infusion in dogs for up to 4 weeks did not cause hypertension [86]. When experiments were repeated in dogs made susceptible to hypertension by partial nephrectomy coupled with a high salt intake, insulin still did not cause an increase in BP [87]. In contrast, a chronic, physiological increase in plasma insulin concentration increased BP in rats [88]. Interestingly, when dogs were fed a high fat or a high fructose diet, they became insulin-resistant, hyperinsulinemic and hypertensive [89]. Thus there are species differences with regard to the effects of insulin on BP, which may be a result of differential effects of insulin on the sympathetic, renal or cardiovascular systems. These disparate results between dog and rodent studies support the notion that hyperinsulinemia may increase BP only in conjunction with the contribution of other pressor systems and may have a different phenotypic expression in different animal species. Taken together, although results from animal studies appear contradictory, there is sufficient evidence to suggest that the link between insulin and hypertension is more than coincidental and that insulin may cause hypertension in certain animal species. The obvious issue that then needs consideration pertains to the possible mechanisms linking insulin to an increase in BP, which is addressed in the next section.

5. Insulin and hypertension: the possible links

5.1. Insulin-induced antinatriuresis

DeFronzo et al. were the first to demonstrate a direct sodium-retaining effect of insulin in healthy humans. They performed euglycemic insulin clamps in young subjects and found that urinary sodium excretion decreased within 30-60 minutes of a physiological increment in plasma insulin concentration and gradually reached a minimum, which was 50% lower than the basal rate [90]. This observation has been subsequently confirmed in humans [91], dogs [92] and rats [93]. The hypothesis that hyperinsulinemia leads to renal sodium and fluid retention is based on the assumption that the kidneys of hypertensive patients maintain normal sensitivity to the antinatriuretic effect of insulin, in contrast to the peripheral tissues which are resistant to insulin’s glucoregulatory effects. This premise has been directly confirmed in essential hypertensive patients, where it was demonstrated that although insulin mediated glucose uptake was markedly lower in hypertensives, insulin-induced sodium retention was maintained when compared to normotensive controls [94]. In addition, it was recently reported that in hypertensive patients, insulin directly increased sodium reabsorption in the proximal and distal tubules [95,96].

These reports raise the possibility that insulin may cause sodium and volume overload in hypertensive pa-
tients, which could lead to hypertension. A recent study demonstrated for the first time that although the sodium-retaining effect of insulin was maintained in hypertensive patients, they were resistant to the natriuretic effects of atrial natriuretic peptide [97]. This novel finding raises the possibility that resistance to the natriuretic effects of atrial natriuretic peptide may be one of the mechanisms underlying the insulin-induced increase in BP. However, young subjects with essential hypertension do not have an increased body sodium content or an increased plasma volume or a reduced plasma renin concentration [98], indicating that these acute effects may not be sustained or may be compensated for over a longer period of time.

5.2. Insulin and the sympathetic nervous system

Rowe et al. reported that elevations in plasma insulin levels caused a dose-dependent increase in plasma catecholamine levels and a concurrent increase in pulse and BP [99]. However, they observed this effect only at pharmacological concentrations of insulin, which casts doubt with regard to the physiological relevance of their findings [99]. Other studies have documented that fasting decreased catecholamine levels whereas feeding led to an increase in plasma norepinephrine levels [100–102]. This increase in sympathetic activity would be expected to cause an increase in cardiac output, peripheral vasoconstriction and a consequent increase in BP. However, studies have demonstrated that although a physiological increase in insulin concentration causes an increase in muscle sympathetic activity and nerve firing rate, it results in a decrease in vascular resistance and either no change or a paradoxical decrease in BP [103,104]. In a series of elegant experiments, Baron et al. demonstrated that insulin caused a rightward shift in the norepinephrine dose–response curve and that this effect was more pronounced in lean as compared to obese subjects [105]. They also found that insulin caused a 25% increase in the metabolic clearance of norepinephrine and that this effect was also blunted in obese, insulin-resistant subjects. Finally, they reported that obese subjects were more susceptible to the pressor effects of insulin than lean insulin-sensitive humans. The reason why insulin does not increase BP, despite stimulation of the sympathetic nervous system, is that insulin causes preferential vasoconstriction in the skeletal muscle vasculature and thereby leads to a redistribution of cardiac output to skeletal muscle [106]. Thus, the vasoconstrictory effects of insulin offset the increase in cardiac output, an issue that will be addressed in detail in one of the subsequent sections.

5.3. Trophic effects of insulin

It has been reported that insulin, via its action on insulin-like growth factor receptors, causes an increase in vascular smooth muscle cell growth in vitro [107,108]. Furthermore, it has been demonstrated that insulin stimulates DNA synthesis in fibroblasts and vascular smooth muscle cells [109,110]. One of the primary events in atherosclerotic plaque formation involves migration and proliferation of smooth muscle cells from the tunica media to the intimal layer in the smaller arteries and arterioles. Insulin, either directly or via its effects on other growth factors such as IGF-I, has been shown to affect smooth muscle cell migration and proliferation [111,112]. Although arterial smooth muscle cells express both insulin and IGF-I receptors [108,113], recent reports suggest that the atherogenic effects of insulin may be mediated primarily via its stimulatory effects on IGF-I production and the subsequent growth promoting effects of IGF-I [111,115]. Lending further support to this notion are observations that insulin stimulates the transcription as well as secretion of IGF-I in vascular smooth muscle cells [114]. IGF-I has been shown to be a potent chemotactic hormone which has the ability to cause smooth muscle cell migration in both neonatal and adult smooth muscle cells; furthermore, insulin (at high concentrations) can stimulate smooth muscle cell migration by acting through the IGF-I receptor [111]. Therefore, chronic hyperinsulinemia in hypertensive patients could not only affect vascular smooth muscle proliferation but also has the potential to stimulate chemotaxis and cell migration, which are hallmarks of the early atherosclerotic process. Cruz et al. reported that chronic insulin infusion into one femoral artery in the dog caused vascular hypertrophy only on the ipsilateral side [116]. Therefore, it is possible that chronic hyperinsulinemia may cause vascular hypertrophy and lead to narrowing of the lumen of resistance vessels, consequently raising vascular resistance and BP. Although this hypothesis has not been validated, it is important to mention that the hypertrophic effects of insulin have been observed only at supraphysiological concentrations and that the possibility of insulin exerting trophic effects at physiological concentrations remains to be determined. However, it is possible that insulin may have synergistic effects with other growth factors such as IGF-I, which may contribute towards accelerated atherogenesis in hyperinsulinemic, hypertensive subjects.

5.4. Hemodynamic effects of insulin

The hemodynamic effects of insulin have been extensively investigated over the last 3 years and results indicate that not only does insulin exert a variety of metabolic effects but that it is also a powerful vasoactive hormone [106]. Although some early reports had suggested that insulin exerted cardiovascular effects, most of the effects were observed at pharmacological insulin concentrations [99]. This led to the suggestion that insulin did not modulate vascular smooth muscle activity under normal physiological conditions, a notion that has been proven incorrect in recent years. The first study that examined this issue in
detail was that of Laakso et al. who reported that insulin, when infused intravenously, caused a dose-dependent increase in leg blood flow in humans and that this effect was independent of plasma glucose concentration [117]. Subsequently, it was demonstrated that in lean, insulin-sensitive subjects, acute insulin infusion causes a rise in peripheral blood flow with an EC₅₀ of about 40 μU/ml [118]. This indicates that insulin exerts potent vasodilator effects at physiological concentrations. Furthermore, it was demonstrated that insulin also caused significant increases in cardiac output with an EC₅₀ of about 70 μU/ml [119]. Studies revealed that although insulin caused both systemic and peripheral vasodilation, the increase in skeletal muscle blood flow far exceeded the increment at the systemic level [119]. Thus insulin, by preferentially increasing skeletal muscle blood flow, may redistribute the cardiac output to skeletal muscle (the major site of glucose utilization). This also explains why the insulin-induced increase in cardiac output and sympathetic activity do not cause a resultant increase in BP.

Even more fascinating are findings indicating that these vasodilator effects of insulin are markedly impaired in insulin-resistant states such as obesity and diabetes mellitus [106]. In obese subjects, the EC₅₀ of the dose–response curve to insulin’s vasodilator actions was about 3-fold higher than that in lean controls. In NIDDM patients, the EC₅₀ was about 17-fold higher, indicating a marked resistance to the vasodilator effects of insulin [118]. The compelling question that then comes to mind is whether resistance to insulin’s vasodilator effects also occurs in hypertensive patients. Indeed, it was recently demonstrated that insulin-induced vasodilation in pre-constricted dorsal hand veins was impaired in essential hypertensive patients [120]. The mechanism/s underlying insulin-mediated vasodilation remain to be determined and may include both systemic and local effects [59]. Several recent reports suggest that insulin may alter vascular tone via direct effects on intracellular calcium concentration in vascular smooth muscle cells [121,122]. Insulin has also been shown to attenuate the contractile responses of vascular smooth muscle to vasoactive amines, probably by causing changes in intracellular calcium [123,124]. Other reports strongly suggest a role for endothelium-derived nitric oxide in the insulin-induced vasodilation [125], since infusion of a nitric oxide synthase inhibitor completely prevented the increase in insulin-mediated leg blood flow. Furthermore, methylene blue, a guanylate cyclase inhibitor, also abolished insulin-mediated venodilation, suggesting that insulin’s effects are cGMP dependent [126].

If the insulin-mediated decrease in vascular tone were impaired in insulin-resistant states, it could cause a resultant increase in the pressor response to various neurohumoral factors, thus increasing vascular resistance and BP. Lending support to this hypothesis are findings that obese, insulin-resistant subjects have a greater sensitivity to the pressor effects of norepinephrine when compared with lean, insulin-sensitive controls [105]. Insulin resistance at the vascular level could, therefore, tip the balance in favor of the pressor forces and therefore predispose an individual towards hypertension [119]. Whether such an effect occurs in essential hypertension remains to be elucidated, but current evidence strongly suggests such a possibility.

5.5. Insulin and the intracellular cation transport systems

It was initially postulated that insulin may regulate the activity of Na⁺–K⁺-ATPase, an important cellular enzyme that extrudes sodium in exchange for potassium and is responsible for maintaining the normal resting potential in cells. This hypothesis stemmed from observations that the activity of this pump (which is insulin regulated) was reduced in essential hypertensive subjects as well as in experimental models of hypertension [127-129]. Such a reduction in Na⁺–K⁺-ATPase activity could lead to increased intracellular sodium levels, which could sensitize the arteriolar smooth muscle cells to the pressor effects of catecholamines and angiotensin II. Although this is an attractive hypothesis, evidence suggests that such an abnormality is unlikely to be the cause underlying the increase in BP in hypertensive subjects. For example, it has been demonstrated that insulin-stimulated potassium uptake (a reflection of Na⁺–K⁺-ATPase activity) is unrelated to insulin’s stimulatory effect on glucose metabolism [130]. Furthermore, insulin can promote cellular potassium uptake normally in hypertensive patients [10]. Therefore, it does not seem that resistance to insulin’s glucoregulatory effects also extends to its effects on the Na⁺–K⁺-ATPase enzyme.

Another cation pump that has been examined is the Na⁺–H⁺-antiporter, which is responsible for maintaining intracellular sodium concentration as well as intracellular pH. Increased activity of this pump in response to increased levels of insulin has been observed in various cell types in hypertensive subjects [131-133]. Overactivity of this pump could result in increased sodium levels inside the cell, which would sensitize vascular smooth muscle cells to the effects of various pressor amines. In addition, increased sodium levels could result in an indirect increase in intracellular calcium concentration, which would also cause an increase in vascular tone. Finally, an increase in the activity of this proton pump would lead to intracellular alkalinization, which is a stimulus for vascular smooth muscle growth [134]. Probably the most important observation that may explain the direct vasodilatory effects of insulin is that insulin has marked effects on intracellular calcium concentration [121]. It has been reported that insulin attenuates vascular smooth muscle calcium influx through both receptor and voltage-operated calcium channels. In addition, insulin also modulates the activity of Ca²⁺-ATPase, which is responsible for the extrusion of calcium from cells [122]. Resistance to these effects of insulin would cause an increase in intracellular calcium...
levels and a consequent enhancement of vascular tone and BP. Thus, insulin has the ability to directly modulate several intracellular ionic pumps and thereby alter vascular tone and BP.

6. Summary

Although considerable evidence lends credence to the association between insulin and hypertension, the precise nature of this link remains elusive. Recent observations indicating that insulin may modulate vascular smooth muscle contractility have given yet another interesting twist to this intriguing association. The finding that insulin can directly alter smooth muscle calcium transients as well as attenuate the effect of other vasoconstrictor amines suggests that this metabolic hormone may also play an important hemodynamic role under pathophysiologic conditions. However, the independent contribution of insulin resistance toward an increase in BP is probably smaller and more complex than is often emphasized and to assume that insulin is directly linked to a rise in BP in hypertensive subjects is perhaps oversimplistic and incorrect. Future research efforts should be targeted at examining the effects of insulin on vascular smooth muscle contractility in hypertensive subjects and the interaction of insulin with other vasoactive peptides.

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