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Antihypertensive effects of vanadium compounds in hyperinsulinemic, hypertensive rats

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Abstract

Although considerable evidence lends credence to the association between insulin resistance, hyperinsulinemia and essential hypertension, the precise nature of this relationship remains unexplained. In the present investigation, we examined the proposition that these metabolic defects contribute causally to the development of high blood pressure. If these metabolic abnormalities were responsible for the development of hypertension, then drug interventions that improve these defects should also decrease high blood pressure. Since previous studies have demonstrated that vanadium compounds enhance insulin action and lower plasma insulin levels in nondiabetic rats, we examined the effects of these compounds on insulin sensitivity, plasma insulin concentration and blood pressure in two hyperinsulinemic models of experimental hypertension. The animal models studied were the genetically predisposed spontaneously hypertensive rat and the fructose-hypertensive rat, where hypertension is induced in normotensive rats by feeding them a high fructose diet. Vanadium compounds caused marked and sustained decreases in plasma insulin concentration and blood pressure in both the animal models studied. Furthermore, the effect of the drugs on blood pressure was reversed by restoring plasma insulin levels in the drug-treated rats to those observed in their untreated counterparts. These data suggest that either hyperinsulinemia contributes to the development of hypertension in both the spontaneously hypertensive and the fructose-hypertensive rats or that the underlying mechanism is closely related to the expression of both these disorders. (Mol Cell Biochem **153:** 205–209, 1995)

Key words: hyperinsulinemia; insulin resistance; hypertension; vanadium compounds

Overview

Considerable epidemiological, clinical and experimental data lend credence to the association between essential hypertension and abnormalities in carbohydrate and lipid metabolism [1, 2]. Of these metabolic defects, two that seem to be frequently associated with hypertension are insulin resistance (or resistance to the glucoregulatory effects of insulin) and hyperinsulinemia [1–5]. These defects in glucose metabolism are associated with a highly atherogenic risk profile and a good deal of evidence now suggests that they may play a central role in the development of hypertension, dyslipidemia and atherosclerosis [4–7]. The presence of insulin resistance and hyperinsulinemia in young, non obese subjects with untreated, uncomplicated hypertension strengthens the contention that there may exist an intrinsic link between these metabolic abnormalities and an increase in blood pressure [8]. However, an important limitation of studies linking insulin resistance and hyperinsulinemia to hypertension is that they do not establish causality. Although associations and correlations favor such a link, this issue requires further experimental evaluation. Essentially, if these metabolic abnormalities were responsible for the development of hypertension, then drug interventions that improve these defects may also decrease high blood pressure.

One such class of drugs that has been of particular interest to us includes the inorganic and organic derivatives of the trace element vanadium. Recently discovered, and of particular interest in diabetic research, are the insulin-mimetic effects of vanadium, which include increased glucose uptake in rat diaphragm, liver and fat cells [9], enhanced glucose transport and oxidation in rat adipocytes and skeletal muscle [10, 11,12] as well as inhibition of lipolysis [13] and activation of lipogenesis [14]. Recent work from our laboratory

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has shown the effectiveness of oral vanadyl sulfate in correcting various abnormalities in the heart and adipose tissue in streptozotocin-diabetic rats and in enhancing the effects of insulin *in vivo* [15, 16]. An early observation that surfaced from our studies was that vanadyl treatment not only decreased plasma glucose levels in diabetic rats (without an increase in plasma insulin) but that it also reduced insulin levels in control, non-diabetic rats [16, 17]. These findings suggested that vanadyl either potentiated or replaced the glucose-lowering effects of endogenous insulin, leading to a decreased requirement of insulin in non-diabetic rats.

We recently initiated a series of experiments in which we employed vanadium compounds as a tool to elucidate the relationship between insulin resistance, hyperinsulinemia and hypertension. In an effort to broaden the nature of our enquiry, we used both a genetic and an acquired model of experimental hypertension in our studies. These are the spontaneously hypertensive rat, which is thought to closely resemble human essential hypertension [18] and the fructose hypertensive model, where hypertension is induced in normotensive rats by feeding them a high fructose diet [19]. The intent of this review is to summarize and discuss the results obtained from these studies in context to the general hypothesis under study.

Specific research problem and research strategy

One of the major issues that requires resolution is to determine whether the insulin resistance and hyperinsulinemia associated with hypertension are a cause or an effect of the 'hypertensive syndrome.' It has been documented that epinephrine, acting primarily through the beta adrenergic receptor, markedly impairs hepatic as well as peripheral tissue sensitivity to increments in plasma insulin [20]. It could, therefore, be argued that a primary increase in sympathetic activity (increases in plasma catecholamines) may antagonize insulin action and lead to secondary insulin resistance. However, decreasing blood pressure with most antihypertensive drugs does not improve insulin sensitivity or decrease plasma insulin levels [21, 22], which suggests that these metabolic defects are not secondary to hypertension. Resolution of this issue requires more direct and specific experimental interventions, which were attempted in the experiments described below. We examined the hypothesis that insulin resistance and hyperinsulinemia are causally related to hypertension by attempting to improve the defects in glucose metabolism (with vanadium compounds) and studying the consequent changes in blood pressure. We reasoned that if insulin resistance and hyperinsulinemia played a role in the development of hypertension, then such metabolic improvements would lead to a decrease in high blood pressure. However, if these metabolic defects were not causally related to hypertension, or were secondary to it, then specific improvements in these abnormalities should not cause any resultant change in blood pressure.

Effects of vanadium compounds in spontaneously hypertensive rats

Spontaneously hypertensive rats (SHR) exhibit a genetic propensity for hypertension and have been shown to be hyperinsulinemic as compared to their controls, the Wistar Kyoto (WKY) strain [18, 23]. In addition, the SHR exhibit a decreased insulin clearance, which may also result in higher circulating insulin levels [24]. Recent studies have demonstrated that SHR exhibit postabsorptive hyperinsulinemia as compared to their Wistar Kyoto (WKY) controls [25]. The primary reason for postabsorptive hyperinsulinemia in the SHR appears to be 'an enhanced pancreatic beta-cell responsiveness', which results in hypersecretion of insulin in response to a glucose load [26]. It has been proposed that hyperinsulinemia may contribute causally towards the development of high blood pressure in the SHR.

(A) Studies with vanadyl sulfate

In the initial series of experiments, the effects of chronic vanadyl sulfate treatment in the SHR were tested in two stages: a prevention study, where the drug treatment was initiated when the SHR were only 6 weeks of age and a reversal study, where it was given after the SHR were fully hypertensive (11 weeks of age). Vanadyl sulfate, in doses of 0.4–0.6 mmol/kg/day markedly attenuated the increase in both plasma insulin and systolic BP in the SHR when it was given before the SHR were fully hypertensive (Table 1, [27]). When vanadyl was given after the SHR became fully hypertensive, it again caused significant and sustained decreases in plasma insulin and blood pressure. Vanadyl treatment did not affect plasma glucose levels in either the SHR or the WKY (Table 1). No changes in BP or plasma insulin were seen in the normotensive WKY. Since vanadyl sulfate decreased food/fluid consumption and body weight in the treated rats, a separate study was initiated in which one group of rats (SHR as well as WKY) was pair-fed with the corresponding vanadyl treated group, but was not given vanadyl. This was done to observe if a decrease in food and fluid intake per se caused a lowering of plasma insulin levels and thereby contributed towards the amelioration of hypertension in the vanadyl treated rats. We observed that the pair-fed SHR remained as hypertensive as the untreated rats, thereby excluding any contribution of weight loss towards the antihypertensive effects observed with vanadyl (Table 1). Ten weeks of vanadyl sulfate treatment had no effect on plasma GOT (glutamic oxaloacetic transaminase), GPT (glutamic pyruvic transaminase) or urea levels [27], indicating that vanadyl did not affect hepatic or renal function in the SHR and WKY.

Table 1. Various parameters from the experimental groups in the vanadyl sulfate studies

Rats	B.P. (mmHg)	Insulin (pmol/L)	Glucose (mmol/L)
SHR	189 ± 3	336 ± 12	6.7 ± 0.1
SHRV	158 ± 2†	252 ± 22†	6.8 ± 0.2
SHRP	193 ± 4	293 ± 18'†	6.9 ± 0.2
WKY	135 ± 1†	264 ± 22†	6.7 ± 0.1
WKYV	127 ± 12†	262 ± 12†	6.6 ± 0.3
WKYP*	138 ± 2†	270 ± 18†	7.0 ± 0.3

*SHR (untreated, n = 15); SHRV (vanadyl treated, n = 8); SHRP (pair-fed, n = 7); WKY (untreated, n = 12); WKYV (vanadyl treated, n = 6) and WKYP (pair-fed, n = 8). Values are mean ± SE.†p < 0.001, different from SHR. Calculated in part from: reference [27]; Bhanot, S and McNeill, J.H.: Hypertension, 1994.

(B) Studies with bis(maltolato)oxovanadium(IV)

Vanadyl sulfate is poorly absorbed from the gastrointestinal tract (absorption ranges from 1–10%) and also causes some gastrointestinal side effects [28, 29]. In an effort to increase the absorption of vanadyl from the gut and to decrease its gastrointestinal toxicity, an organic vanadium complex, bis(maltolato)oxovanadium(IV) (BMOV), was synthesized by complexing one molecule of vanadyl with two molecules of the common food additive maltol [30]. We speculated that an organic compound would be more lipophilic than its inorganic counterpart and may, therefore, be better absorbed from the GI tract. Preliminary studies indicated that BMOV also exhibited insulin enhancing effects and that besides lowering plasma glucose levels in diabetic rats, it also decreased insulin levels in non-diabetic rats [30]. In addition, BMOV also had a lesser negative effect on weight gain in rats as compared with vanadyl sulfate [30]. Furthermore, in the previous experiments, we had not examined the effect of vanadyl on insulin sensitivity in the SHR. Although euglycemic clamp studies conducted in anesthetized SHR demonstrate that they are insulin resistant, recent studies done in conscious SHR have challenged this notion. These investigators have proposed that the SHR are more responsive to stress (anesthesia or restraint) as compared to the WKY [25]. Consequently, there may be a greater release of endogenous catecholamines in the SHR, which may in turn antagonize insulin action and lead to secondary insulin resistance in the anesthetized SHR. Their studies done in conscious, minimally restrained rats showed no difference in insulin sensitivity in the SHR as compared to the WKY. However, the presence of hyperinsulinemia in the SHR was confirmed even in those studies [25, 26] and it was proposed that increased insulin levels may contribute to the development of high BP in the SHR.

Therefore, we initiated chronic BMOV treatment in the SHR with the following aims: (a) to assess insulin sensitivity in SHR and WKY by performing euglycemic hyperinsulinemic clamps in conscious, minimally restrained rats

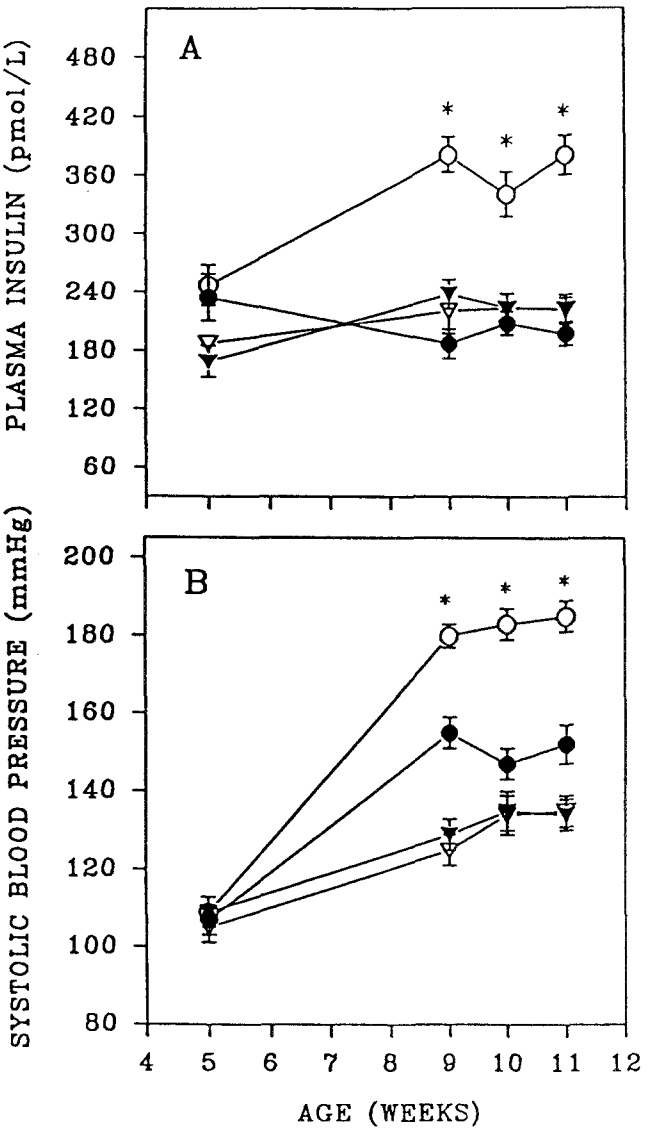

Fig. 1. (A) Plasma insulin levels and (B) Systolic blood pressure in the four groups: O SHR (untreated, n = 9), ■ SHR BMOV treated (n = 11), ▽ WKY (untreated, n = 11) and ▼ WKY BMOV treated, n = 9). Values are means ± SE. *p < 0.0001, SHR different from the other 3 groups.

and (b) to examine the effects of the drug on insulin sensitivity, plasma insulin levels and systolic blood pressure. BMOV (0.35–0.45 mmol/kg/day) caused a marked reduction in plasma insulin levels in the hyperinsulinemic SHR (Fig. 1A, [31]); the average percentage decrease ranged from 30–35% (5 h fasted values). BMOV also lead to a marked reduction in systolic BP (30–35 mmHg) in the SHR (Fig. 1B). No effect on insulin or BP was observed in the WKY rats. BMOV caused no reduction in food intake or body weight in either the SHR or the WKY until 11 weeks of age [31]. Euglycemic, hyperinsulinemic clamps conducted in conscious, minimally restrained rats indicated that the SHR were not insulin resistant as compared to the WKY and that

BMOV caused a further increase in insulin sensitivity in the SHR [31].

(C) Insulin implant studies

Vanadium compounds have been shown to affect other enzyme systems such as the Na-K-ATPase [32]. It may, therefore, be argued that vanadyl may also affect factors other than insulin; ie, it may lower blood pressure independent of its effects on insulin action. In order to further examine this issue, we decided to examine the effect of restoration of plasma insulin levels in the vanadyl-treated rats to those that existed in the untreated SHR. In a separate study, we administered exogenous insulin (14000 pmol/kg/day given as a subcutaneous insulin implant) to the vanadyl-treated rats and observed that restoration of insulin levels in the drug-treated group reversed the effects of the drug on blood pressure [27]. Reversal of blood pressure was independent of any change in plasma glucose or body weight [27], which indicated that whatever the precise mechanism of vanadyl might be, the anti-hypertensive effects of the drug could be reversed simply by raising plasma insulin levels to those seen in the untreated SHR. Taken together, these data suggest that either hyperinsulinemia may contribute towards the increase in blood pressure in the SHR or that the underlying mechanism is very closely linked to the expression of both the disorders.

Effects of vanadyl sulfate in fructose hypertensive rats

The fructose rat model represents an acquired form of systolic hypertension, where the rise in blood pressure is not genetically determined but is diet induced [19, 33]. Some very interesting findings have emerged from studies in which insulin resistance and hyperinsulinemia were induced in normotensive Sprague Dawley rats by giving them a fructose enriched diet [33]. Induction of these metabolic defects was associated with a concomitant increase in blood pressure in these rats [19, 33]. 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 blood pressure in the animals [34, 35]. Although the precise mechanism of fructose-induced hypertension has not been elucidated, it has been suggested that the rise in blood pressure is secondary to the development of insulin resistance and hyperinsulinemia [34]. In order to determine if these metabolic defects were causally related to the fructose induced increase in blood pressure, we initiated chronic vanadyl sulfate treatment in the fructose-fed rats and examined the resultant changes in plasma insulin levels and blood pressure. Furthermore, we studied the effects of vanadyl treatment on insulin sensitivity by conducting euglycemic clamps in the rats. We observed that fructose feeding caused a marked impairment in insulin sensitivity (an 80% decrease as compared to control untreated rats). Vanadyl treatment completely prevented this decrease in insulin sensitivity in the fructose-fed rats [36]. In addition, vanadyl completely prevented the fructose induced increases in plasma insulin and blood pressure. Once again, restoration of plasma insulin levels in the fructose-vanadyl-treated rats to pre-treatment levels reversed the anti-hypertensive effects of vanadyl. Reversal of vanadyl's antihypertensive effects was independent of any change in plasma glucose or body weight. These results are consistent with the hypothesis that hyperinsulinemia may contribute causally towards the development of fructose induced increases in blood pressure.

Since our initial demonstration of the anti-diabetic effects of vanadium compounds *in vivo* [15], impressive advances have been made in understanding the glucose lowering properties and the mechanism of action of these compounds. We believe that our studies are the first to demonstrate that these compounds also exhibit antihypertensive effects in two well established models of experimental hypertension. Further studies are needed to examine the effects of these compounds on specific organ systems and to elucidate the mechanism/s of action underlying their anti-hypertensive properties.

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