Review Article

Nutritional Factors that Can Favorably Influence the Glucose/Insulin System: Vanadium

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A growing body of experimental and clinical research indicates that the trace element, vanadium, exerts potent insulin-mimetic effects in vitro and in vivo when used in pharmacological doses. Since our first demonstration of the anti-diabetic and cardioprotective effects of vanadium in vivo, impressive advances have been made in our understanding of its mechanism of action, pharmacokinetics and pharmacodynamics. A major advance in the use of vanadium as an insulin-mimetic has been the development of organic vanadium complexes which are 2 to 3 times as potent as inorganic vanadium and have been extensively studied in our laboratory. There is an emerging role for the use of vanadium in human diabetes and the recently conducted clinical trials support this contention. The present review summarizes some of the key aspects of vanadium biology which exemplify the potent insulin-mimetic, anti-diabetic and antihypertensive effects of this intriguing trace element.

Key teaching points:

- Vanadium is a Group V transition element that exists in many oxidation states and is ubiquitous in nature
- A large body of in vitro and in vivo evidence exists that demonstrate the potent insulin-mimetic actions of vanadium.
- Long-term vanadium treatment causes marked and sustained decreases in plasma glucose, triglyceride and cholesterol levels. Chronic treatment also ameliorates secondary complications of diabetes including cardiomyopathy, vascular hyperactivity and cataract formation.
- In an effort to improve bioavailability, we have synthesized several organic vanadium compounds, noteworthy among which is bis(maltolato)oxovanadium(IV) (BMOV). BMOV is 2 to 3 times more potent than inorganic vanadium.
- Vanadium compounds exhibit antihypertensive effects via their ability to counter insulin resistance and attenuate hyperinsulinemia.
- The exact cellular mechanism of action of vanadium appears to involve a combination of several post-receptor events in the insulin-signaling cascade.
- Recent clinical trials with vanadium have yielded positive effects.

INTRODUCTION

The field of diabetes research has progressed exponentially over the last two decades and has contributed volumes to our understanding of the complex inter-relationship between insulin action, insulin resistance, lipid and carbohydrate metabolism. Amidst this surge of diabetes research, one singular observation has been the intriguing discovery that the element, vanadium, with a molecular weight of 51, can mimic or enhance the actions of the main glucoregulatory peptide insulin. The first demonstration of the in vivo insulin-mimetic effects of pharmacological doses of vanadium in experimental models of diabetes [1] to the current data demonstrating its benefits in human diabetes leads to the question of whether vanadium can be successfully utilized as a treatment for diabetes. We herein review some of the key aspects of vanadium biology in relation to the insulin-mimetic, antihyperglycemic, and antihypertensive effects of this unique trace element.

BACKGROUND

Vanadium was first discovered in 1813 by the Spanish mineralogist del Rio, who gave it the name panchromium

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because of its color changes when passing through various oxidation states. It was rediscovered in 1831 by the Swedish chemist Nils Gabriel Sefstrom, who named the compound Vanadis, a nickname of the Germanic goddess of beauty. In humans, the total body pool of vanadium is estimated to be around 100 to 200 μg [2]. In common with most transitional metals, vanadium exists in several valence states (-3, -1, 0, $+1$ to $+5$) and the expression of a given form is highly pH dependent. In biological systems vanadium is found predominantly as vanadate ($+5$) and vanadyl ($+4$) forms. In the plasma, vanadium exists in both oxidation states. Approximately 90% is bound to proteins, predominantly transferrin [3]. Most ingested vanadium is transformed in the stomach to VO^{+2} and remains in this form as it passes through the duodenum. Vanadium is preferentially distributed in the bone, kidney and liver following i.p. injection; the bone representing the main storage depot for vanadium [4].

IN VITRO INSULIN-MIMETIC ACTIONS OF VANADIUM

Vanadium affects various aspects of carbohydrate metabolism including glucose transport, glucose transporter translocation, glycolysis and glycolytic enzymes, glucose oxidation, glucose output and glycogen synthesis [5–11]. The insulin-like effects of vanadium also extend to the lipid metabolic pathways and on protein metabolism and mitogenesis [12–16].

IN VIVO INSULIN MIMETIC ACTIONS OF VANADIUM

Heyliger et al [1] were the first report to describe the in vivo insulin-mimetic and anti-diabetic actions of vanadium. In this study, chronic treatment of streptozotocin (STZ) diabetic rats with sodium orthovanadate (100 mg/kg) normalized hyperglycemia and improved cardiac function independent of changes in plasma insulin levels. The ability of vanadium to cause euglycemia without increases in plasma insulin levels is indicative of its ability to improve insulin sensitivity; we have recently demonstrated that vanadium counters insulin resistance when assessed using the euglycemic hyperinsulinemic clamp [17]. In 1987, Meyerovitch et al demonstrated that chronic sodium metavanadate administration also lowered plasma glucose levels and enhanced basal hexose transport in both liver and muscle [18]. Subsequently, the dose-response relationship between vanadate and its glucose lowering effects was described by Brichard et al in 1988 [19]. Some of the well described in vivo effects of vanadium administration in STZ-diabetic rats are listed in Table 1.

Table 1. In Vivo Effects of Vanadium in STZ-Diabetes

Amelioration of insulin resistance reflected by a greater glucose-lowering effect of vanadium-treated rats to insulin [20]
Normalization of both basal and stimulated hepatic glucose production by chronic vanadium administration [21,22]
Enhanced insulin sensitivity in vanadium treated rats correlates with restoration of insulin stimulated MAP and S6 kinase activities in skeletal muscle [23]
Chronic vanadium treatment corrects abnormalities in glycolytic enzymes i.e. phosphofructokinase-2 and glucokinase [24]
Restoration of glycogen synthase and phosphorylase activities [25]
Aberrations in the tissue-specific expression of two isoforms of glucose transporter in STZ-diabetes are normalized by vanadium treatment [26]
Amelioration of oxidative stress [27]

Subsequent to our demonstration of the in vivo antihyperglycemic effects of vanadate, work in our laboratory and that by others revealed that high concentrations of vanadate used in the drinking water was accompanied by adverse effects including diarrhea and death because of dehydration. Based on observations indicating that the LD_{50} of sodium orthovanadate was 6 to 10 times lower than vanadyl sulfate [28–29], we hypothesized that the vanadyl rather than the vanadate form may be more appropriate for in vivo administration. In 1990 we reported that STZ-diabetic rats treated with vanadyl sulfate exhibited normal plasma levels of glucose, lipids, creatinine and thyroid hormone levels [32]. In addition, abnormalities in isolated working heart function and glycerol output from adipose tissue of diabetic animals were also corrected after vanadyl sulfate treatment. These results indicated that vanadium when used in the vanadyl form was effective in ameliorating the diabetic state by either replacing insulin or enhancing the effects of insulin towards whole body glucose uptake.

An interesting observation on the effects of vanadyl sulfate was made in the study by Ramanadham et al demonstrating the sustained prevention of myocardial and metabolic aberrations in diabetic rats following withdrawal from vanadyl sulfate treatment [30]. In this study, after 3 weeks of treatment with vanadyl sulfate followed by 13 weeks of withdrawal, plasma concentrations of glucose, insulin, lipids and thyroid hormones in the STZ-treated animals returned to control levels. Myocardial dysfunction and increased glycerol output from adipose tissue in untreated diabetic rats was also found to be normalized in the STZ-treated group. Furthermore, there was no evidence of cataracts in these animals compared with untreated diabetic rats. These findings indicated the novel ability of vanadium to ameliorate the diabetic state following withdrawal from treatment and revealed for the first time the long-term effectiveness of short-term treatment of diabetic rats with oral vanadyl sulfate.

To examine whether the anti-diabetic effects of vanadyl sulfate were attributable to a prevention of the cytotoxic destruction of the pancreatic β cells by STZ, Cam et al examined the effectiveness of vanadyl sulfate when administration was delayed from the time of induction of diabetes [31]. Vanadyl sulfate was administered in the drinking water (0.75 mg/ml) from 3, 10 and 17 days after STZ injection and treatment was

then maintained for 5 months. Glucose tolerance and adipose tissue function was normalized in vanadyl treated diabetic rats irrespective of whether treatment was initiated 3, 10 or 17 days after induction of diabetes thus supporting the concept that the efficacy of vanadyl sulfate as an insulin-mimetic is not secondary to a protection of the pancreatic β cells from the cytotoxic effects of STZ.

In an attempt to examine the concentration-dependent effects of oral vanadyl treatment and possible in vivo interaction of vanadyl with insulin in diabetic rats, Ramanadham et al examined the effects of vanadyl sulfate treatment in the spontaneous BB rat (a model of absolute insulin deficiency) [20]. Chronic vanadyl sulfate treatment reduced the exogenous insulin required to prevent glycosuria in BB diabetic rats. This effect was dose-dependent and vanadium treatment reduced the required insulin dose to maintain normoglycemia by up to two-thirds. The beneficial effects of vanadium have also been demonstrated in other models of Type I and Type II diabetes (Table 2).

THE USE OF ORGANIC VANADIUM COMPLEXES TO INCREASE POTENCY

Since inorganic vanadium is poorly absorbed from the gastrointestinal (GI) tract and some GI difficulties have been reported with both vanadyl and vanadate, our laboratory and others have synthesized a number of organic vanadium compounds.

Bis(maltolato)oxovanadium(VI) (BMOV) (Fig. 1, a maltol/vanadyl compound, was developed in collaboration with Dr. C. Orvig in the Department of Chemistry at the University of British Columbia, Vancouver, Canada [37]. BMOV is a potent example of a series of compounds designed specifically to be orally absorbed by passive diffusion as a result of their properties of water solubility, electrical neutrality and low molecular weight [10,40]. Both oral and i.p. dose response curves

Table 2. In Vivo Effects of Vanadium in Other Models of Diabetes

Spontaneously diabetic BB rat
Reduces the dose of insulin required to maintain glycosuria [20]
Partially pancreatectomized rats
Improves insulin-sensitivity towards peripheral glucose uptake in 90% pancreatectomized rats predominantly through correction of muscle glycogen synthesis [33]
Neonatal STZ-diabetic rats
Vanadium treatment corrects basal and stimulated hepatic glucose production and peripheral glucose utilization [34]
Genetically obese fa/fa
Attenuates hyperinsulinemia and impaired glucose tolerance [35]
Obese ob/ob mice
Attenuates hyperglycemia, improves glucose tolerance and hepatic glycogen content. Prevents pancreatic exhaustion of insulin [36]

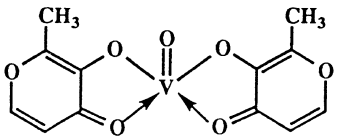

Fig. 1. Bis(maltolato)oxovanadiumIV (BMOV). An organic vanadium compound with improved bioavailability, low molecular weight, electrical neutrality and potency exceeding inorganic vanadium by two to three fold.

have been conducted to compare the effectiveness of BMOV and vanadyl sulfate following administration of a single dose [38]. At the highest doses, administered BMOV produced euglycemia in 100% of animals treated as compared to 80 to 90% with vanadyl sulfate. The ED_{50} following oral administration indicated that BMOV was two times as potent as vanadyl sulfate (ED_{50}: 0.5 mmol/kg for BMOV vs. 0.92 mmol/kg for vanadyl sulfate). Similarly, BMOV was three times as potent via i.p. injection than vanadyl sulfate.

BMOV was administered to STZ-diabetic rats in drinking water at a concentration of 0.75 mg/ml for 6 months. BMOV restored plasma glucose levels to normal in 8/12 animals and restored heart function in all diabetic treated rats. There was a strong correlation between improved heart function and long-term glucose control [38]. Compared to inorganic vanadium, BMOV administration did not affect body weight gain in control rats during the initial 10-week treatment period. However, the reduction in circulating plasma insulin levels in control-treated animals was similar to that seen with vanadyl [38]. Dai et al evaluated the effects of long-term BMOV treatment on several pathological determinants of STZ-induced diabetes [39]. Chronic BMOV treatment completely prevented elevations in plasma urea, creatinine, alanine aminotransferase (ALT) and improved histological abnormalities in the kidney and liver from STZ-diabetic rats.

We have recently examined the effects of chronic BMOV administration on vascular reactivity in STZ-diabetic rats (S. Verma, Ismail Laher, Linfu Yao, unpublished observations). Aortae isolated from STZ-diabetic rats exhibited an increased reactivity to norephinephrine which was normalized by BMOV treatment. By contrast, endothelium-dependent relaxation to acetylcholine (ACh) was not different between control and diabetic mesenteric arteries ($68\pm3\%$ vs. $65\pm4\%$). Intriguingly, chronic BMOV treatment enhanced ACh-induced relaxation in both control and diabetic arteries (control-treated: 95 ± 2 vs. control, $p<0.05$ and diabetic-treated 96 ± 3 vs. diabetic, $p<0.05$). Although the exact physiological relevance of this observation remains elusive, the potential interaction between BMOV and the endothelium-derived nitric oxide system warrants further investigation. What perhaps is more important is the observation that BMOV prevents diabetes induced norepinephrine hyperactivity suggesting a vascular protective effect of this compound.

BMOV has also been used in fa/fa (fatty) Zucker rats to

examine the effectiveness of organic vanadium in Type II diabetes [41]. BMOV at a maximal concentration of 0.5 mg/ml for 14 weeks of treatment reduced plasma insulin levels from 180 uU/ml to normal in week 4. At these concentrations, BMOV did not affect body weight gain in lean controls but did significantly reduce body weight in the fatty treated group. BMOV administration at a maximal concentration of 0.2 mg/ml did not affect food and fluid intake, body weight gain or plasma cholesterol levels in fatty treated animals. At the lower concentration, BMOV did significantly reduce plasma glucose and triglyceride levels. Fed plasma insulin levels were significantly reduced from 260 to 140 uU/ml. An oral glucose tolerance test showed an improved glucose tolerance in fatty untreated animals regardless of the concentration of BMOV.

VANADIUM COMPOUNDS AMELIORATE INSULIN RESISTANCE, HYPERINSULINEMIA AND HYPERTENSION

Considerable epidemiological, clinical and experimental data lend credence to the association between essential hypertension and abnormalities in carbohydrate and lipid metabolism [42–44]. Of these metabolic defects, two that seem to be frequently associated with hypertension are insulin resistance and hyperinsulinemia. These defects in glucose metabolism are associated with a highly atherogeneic risk profile and a good deal of evidence suggests that they may play a central role in the development of hypertension, dyslipidemia and atherosclerosis. Essentially, if these metabolic defects were responsible for the development of hypertension, then drug interventions that improve these defects may also decrease blood pressure. In a series of experiments, we employed vanadium (both vanadyl sulfate and BMOV) to examine the relationship between hyperinsulinemia, insulin resistance and hypertension [17,45–47]. In an effort to broaden the nature of our inquiry, we used both a genetic and an acquired model of hypertension. These were the spontaneously hypertensive rat (SHR) and the fructose-hypertensive rat. Vanadium compounds caused marked and sustained decreases in plasma insulin concentration and blood pressure in both animals models studied. Furthermore, the effect of the drugs on blood pressure were reversed by restoring plasma insulin levels in the drug treated rats to those observed in their untreated counterparts. These data reinforce accumulating evidence linking hyperinsulinemia and insulin resistance to hypertension and demonstrate the potent antihypertensive effects of vanadium in vivo.

MECHANISM/S OF ACTION

The mechanism/s of the antidiabetic effects of vanadium in-vivo are a subject of much current interest. Although vanadium has been demonstrated to affect various aspects of the insulin signaling pathway in vitro (Table 3), the exact in vivo mechanism(s) remains elusive.

A postulated mechanism of vanadium's insulin-mimetic effects is that vanadium behaves as a phosphate analog and stimulates protein-tyrosine phosphorylation by virtue of its inhibitory actions on phosphatases (PTPase) [48,49]. Early studies suggested that vanadium activated autophosphorylation of solubilized insulin receptors (IR) but not serine or threonine residues of the receptors, in a fashion analogous to insulin [9,50,51]. Vanadium also stimulated tyrosine kinase activity of the IR β subunit [50,52]. Subsequently, it was found that vanadium was equally effective in stimulating glucose metabolism in rat fat cells when half the IRs had been inactivated by insulin overstimulation [53]. In addition, oral vanadium treatment failed to change IR kinase activity while exerting glucose lowering effects [54]. Accumulating evidence suggests that vanadium's insulin-mimetic effects may be mediated via some post-receptor event in the insulin-signaling cascade [55,56]. As intracellular vanadium appears to exist in the vanadyl form (which is not a potent PTPase inhibitor) it is reasonable to speculate that additional mechanism/s, at a later point in the insulin-signaling pathway may be the site of vanadium action. It is important to note that the effects of vanadium on intracellular calcium influx as well as intracellular and intravesicular pH modification have not been ruled as potential sites of vanadium's insulin-mimetic effects.

Vanadium has been shown to mimic several insulin-like effects in rat adipocytes via a staurosporine sensitive cytosolic protein tyrosine kinase (CytPTK), distinct from the IR tyrosine kinase [57]. Activation of CytPTK in intact rat adipocytes appears to be highly selective for vanadium as neither insulin, isoproterenol, dibutryryl cAMP, okadaic acid, hydrogen peroxide nor phorbol ester TPA affect CytPTK activity. Inhibition of CytPTK but not of IR tyrosine kinase blocked the effects of vanadate on glucose oxidation and lipid synthesis in rat adipocytes but had no effect on glucose uptake and inhibition of lipolysis, suggesting a selective role for CytPTK in some of the post-IR mechanisms of vanadium. Like vanadium, other PTPase inhibitors have also been shown to activate CytPTK in adipocytes. However, it is important to note that the insulin-mimetic effects of vanadium on hexose uptake and inhibition of lipolysis are not blocked by staurosporine (a blocker of

Table 3. Effects of Vanadium on Insulin-Signalling Pathways In Vitro*

Stimulates autophosphorylation of insulin receptors
Increases insulin receptor tyrosine kinase activity
Stimulates down-regulation of insulin receptors
Increases insulin receptor binding
Increases protein tyrosine kinase activity
Increases Ser/Thr protein kinase activity
Inhibits phosphotyrosine phosphotase activity

* From reference [64].

CtyPTK) indicating that this pathway may not represent the only site of action of vanadium (for review see [57]).

The post-receptor pathways of insulin signal transmission appear to be mediated through complicated cascades of reversible protein phosphorylation and dephosphorylation. A central component in one such cascade is the MAP kinase [58]; we have previously demonstrated defects in both basal and insulin-induced activation of MAP and S6 kinases in STZ-diabetic rats [23]. Using the same model, we have found that insulin-induced activation of MAP and S6 kinases is corrected by chronic vanadium treatment suggesting that insulin resistance associated with long-term diabetes may be linked with depressed signaling through these kinases and that this can be rectified by vanadium [23].

As alluded to earlier, the observation that short term treatment of diabetic rats with vanadium provides sustained euglycemic effects for up to 20 weeks post-withdrawal has added yet another twist to our current hypotheses. As the animals appear to maintain a chronic euglycemic state despite only minor improvements in pancreatic secretory function, it is reasonable to speculate that the treated rats had sustained an increased sensitivity to circulating insulin after vanadium treatment was withdrawn. Alternatively, tissue vanadium stores could be released and continue to exert antihyperglycemic effects. A detailed study by Cam et al [59] recently addressed this issue and suggest that vanadium-induced amelioration of the diabetic state appears to be secondary to the preservation of a functional portion of the pancreatic β-cells which initially survived STZ-toxicity. This partial preservation of β-cells, although small in proportion to the total insulin store is both critical and sufficient for a chronic reversal of the diabetic state. Thus, a modest pancreatic preservation can have profound consequences on glucose homeostasis and may underlie the insulin-mimetic effects of vanadium in vivo [59].

CLINICAL STUDIES WITH VANADIUM

Goldfine et al examined the effects of 2-week sodium orthovanadate administration in both Type I and Type II diabetic patients [60]. Treatment with sodium orthovanadate (125 mg daily in divided doses) lowered insulin requirements but had no effect on basal or C-peptide levels. Two of the five Type I diabetic patients showed improvements in glucose utilization. More dramatic improvements were observed in Type II diabetic patients which displayed an improved insulin sensitivity attributed to an enhancement of non-oxidative glucose disposal rates. Vanadium treatment did not affect hepatic glucose production. Furthermore, basal MAP and S6 kinases were significantly activated in monocytes. The main side effects observed were GI in nature.

Cohen et al evaluated the effects of vanadyl sulfate (100 mg/day) for 3 weeks in six Type II diabetic subjects [61]. Treatment resulted in a reduction in fasting plasma glucose and HbA_{1c} without changes in plasma insulin levels. Of particular interest was the observation that the beneficial effects on insulin-sensitivity persisted for up to 2 weeks following cessation of treatment; the latter observation is consistent with experimental studies described earlier.

THE GLUCOSE LOWERING EFFECTS OF VANADIUM ARE DISTINCT FROM FOOD RESTRICTION

In association with the insulin-mimetic effects, vanadium and vanadium compounds have been shown to normalize hyperphagia associated with experimental diabetes. This normalization of food intake has led repeatedly to the issue of the effects of dietary restriction on glycemic responses after vanadium administration. In 1994, Malabu et al claimed that the decreases in plasma glucose levels observed after administration of vanadate were entirely attributable to a reduction in food intake [62]. Yuen et al recently conducted a detailed study to clarify the effects of vanadium vs. food restriction on metabolic aberrations in diabetic rats [63]. BMOV was administered daily to STZ-diabetic rats for 6 weeks. Pair-fed groups were fed based on the intake for their respective counterparts from the previous day. BMOV reduced plasma glucose (diabetic=31.2±1.9, diabetic-treated=10.2±1.8 and diabetic-pair fed=34.2±1.1 mM), triglyceride and cholesterol levels without affecting plasma insulin levels. Their was no body weight gain in the diabetic-pair group compared with all other groups. BMOV but not pair feeding was effective in preventing the decreased cardiac function observed in STZ-diabetic rats. These data clearly indicate that the effects of vanadium are independent of the effects on dietary restriction. Although in the study by Malabu et al the authors state that daily, fluid and weight measurements were done daily at 0900, they do not specify the frequency of feeding, time of feeding or the relationship of feeding to the time of blood collection. Furthermore, a possible period of prolonged fasting due to rapid consumption of daily food rations is not discussed. This factor is crucial, since the reduction in plasma glucose levels in their study for the pair-fed diabetic groups were similar to that observed after prolonged periods of fasting.

CONCLUSIONS

Since our initial demonstration of the anti-diabetic effects of vanadium in vivo, impressive advances have been made in understanding the glucose lowering properties and the mechanism of action of these compounds. Although the exact cellular mechanism/s and/or mediators involved in vanadium's action remain elusive, it appears that the final action of vanadium may be mediated by a synergy between several post-receptor events

in the insulin-signaling cascade. An important advance in the use of vanadium compounds as insulin mimics has been the development of various ligands in order to improve the absorption, tissue uptake and intracellular mobility of vanadium. BMOV exemplifies one such organically chelated complex that appears to be a potent insulin-mimetic at significantly lower doses than inorganic vanadium. Notably, these compounds reduce the GI side effects of vanadium treatment and do not affect body weight gain and food and fluid intake in control-treated rats. Another significant advance in vanadium research have been studies demonstrating the antihypertensive effects of this insulin-sensitizer in hyperinsulinemic and insulin resistant models of hypertension. There is thus a potential role for the use of vanadium, particularly organic vanadium compounds, in the treatment of diabetes mellitus, and early trials with vanadyl in diabetic human volunteers have shown very promising results which are consistent with experimental studies reported in this paper. Clearly, further studies are warranted to define the exact role of this compound in clinical diabetes.

It should be emphasized that the total body store of vanadium is about 100 μg and that the average daily intake of vanadium is less than 50 μg/day [65]. The essentiality of vanadium in humans have never been established [65]. The amounts required for the biological effects of vanadium in animals (500 to 1000 mg/kg of vanadium salt) and in man (100 to 125 mg vanadium salt) obviously greatly exceed amounts that can be consumed in the diet since the amount of vanadium in any food is quite small. The biological effects of vanadium are thus pharmacological and vanadium should be considered as a drug rather than a supplement, although it is currently sold as such in the United States.

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