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Increased potency of vanadium using organic ligands

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Abstract

The *in vivo* glucose lowering effect of orally administered inorganic vanadium compounds in diabetes was first reported in our laboratory in 1985. While both vanadate and vanadyl forms of vanadium are orally active, they are still not well absorbed. We have synthesized several organic vanadium compounds and one compound, bis(maltolato)oxovanadium(IV) or BMOV, has been extensively investigated. BMOV proved effective in lowering plasma glucose and lipids in STZ-diabetic rats when administered in drinking water over a 25 week period. The maintenance dose (0.18 mmol/kg/day) was approximately 50% of that required for vanadyl sulfate (VS). Secondary complications of diabetes were prevented by BMOV and no marked toxicity was noted. Oral gavage of STZ-diabetic rats with BMOV also reduced blood glucose levels. The ED_{50} for BMOV was 0.5 mmol/kg, while for VS the estimated ED_{50} was 0.9 mmol/kg. BMOV was also effective by the intraperitoneal route in STZ-diabetic rats. The ED_{50} was 0.08 mmol/kg compared to 0.22 mmol/kg for VS. Some animals treated p.o. or i.p. remained euglycemic for up to 14 weeks. An i.v. infusion of BMOV of 0.05 mmol/kg over a 30 min period reduced plasma glucose levels by 50% while VS was not effective. (Supported by the CDA). (Mol Cell Biochem **153**: 175–180, 1995)

Key words: Vanadium, diabetes, insulin-mimetic, hypertension

Introduction

Vanadium is a Group V transition element that exists in many oxidation states and is ubiquitous in nature. First discovered by Nils Sefstrom in 1831, vanadium was named after the Norse goddess Vanadis because of its crystalline beauty. Vanadium was used at the turn of the century by a French physician to treat a number of disease states including diabetes [1]. However, it was not until the 1970's that the current interest in vanadium was revived with the discovery that vanadate was a potent phosphatase inhibitor when used *in vitro* [2, 3].

A large body of *in vitro* experimental work exists that demonstrates the insulin-mimetic actions of vanadium. In both the vanadate (+5 oxidation state) and vanadyl (+4 oxidation state) forms, vanadium mimics the actions of insulin on carbohydrate and fat metabolism. In carbohydrate metabolism vanadium stimulates hexose transport, glucose transporter expression, glucose oxidation and glycogen synthesis in a number of tissues [4–7]. At the cellular level, vanadium has been shown not to bind directly to the insulin receptor but it does increase the autophosphorylation of the β subunit of the receptor, tyrosine kinase activity and phosphorylation of substrates [8–12]. Given the reported insulin-mimetic properties of vanadium *in vitro*. the possible *in vivo* insulin-like effects of vanadium were tested in animal models of diabetes mellitus.

There are a number of animal models of diabetes available for the examination of drug effects on the diabetic condition. Alloxan and streptozotocin (STZ) injection chemically induce a model of Type I diabetes mellitus in which the animal is hyperglycemic, hypoinsulinemic, hyperlipidemic, hyperphagic and polydipsic; however, insulin treatment is not always required to maintain these animals since the severity of the diabetic state depends on the dose of the drug used [13]. Another method of producing a hypoinsulinemic model of diabetes mellitus is to partially pancreatectomize rats by the removal of approximately 90% of the pancreas [14]. BB Wistar rats are a commercially

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available strain of rats that are genetically prone to the development of insulin-dependent Type I diabetes [15, 16]. In these models vanadium has been shown to be effective in reducing plasma glucose levels to normal or near normal, in restoring altered plasma lipid levels and improving the glucose response to an oral or intravenous glucose tolerance test [17–20].

Type I diabetes mellitus is not the only diabetic state in which vanadium has been shown to be effective. There are several animal models of Type II diabetes characterized by mild to marked hyperglycemia, hyperinsulinemia, obesity and glucose intolerance. These models include the STZ-injected neonatal rat, ob/ob mice and the fa/fa Zucker rat. Vanadium has improved peripheral glucose utilization, hepatic glycogen content and tolerance to oral glucose [21–23].

Inorganic vanadium *in vivo*

The first evidence for the *in vivo* insulin-mimetic actions of vanadium were demonstrated by Heyliger *et al* in 1985. Sodium metavanadate was administered at a maximal concentration of 0.8 mg/mL in 0.9% NaCI drinking water to both control and STZ-diabetic rats. Vanadate treatment decreased food and fluid intake in the diabetic treated group and fluid intake in control treated animals. Plasma glucose levels in diabetic treated rats were restored to within normal parameters without an increase in circulating plasma insulin levels. It was also observed that vanadium treatment decreased plasma insulin levels in control treated animals without altering plasma glucose values. In addition, the isolated working heart preparation, done at the termination of the experiment to evaluate the effect of vanadium on the impaired heart function observed in diabetes, showed that vanadium restored heart function to normal. Vanadate treatment did not affect the body weight gain in the diabetic treated animals but did significantly reduce weight gain in the control treated animals and in both groups of animals problems with diarrhea and dehydration were noted [24].

Since a review of the literature suggested that vanadyl was less toxic than vanadate [25], the insulin-mimetic effects of vanadyl were subsequently examined. Vanadyl was administered in the drinking water at concentrations ranging from 0.25–1 mg/mL. There was a dose dependent increase in the number of animals that responded with improved plasma glucose levels following treatment. Ramanadham *et al* showed that 63 days of treatment with vanadyl normalized plasma glucose, triglyceride, T_4 and creatinine levels, and restored heart function in STZ-diabetic animals. However, the slowed body weight gain observed in control animals treated with vanadate was not improved with vanadyl treatment [17].

One question that was raised was whether vanadium treatment would be effective if the start of therapy was delayed. Cam *et al* administered vanadyl sulfate in the drinking water starting 3, 10 and 17 days after STZ injection. The time of onset of treatment did not alter the glucose lowering properties of vanadyl [20].

Removal of vanadyl treatment for 13 weeks after an initial 3 week period of treatment showed that plasma glucose, lipid and thyroid hormone levels and heart function in STZ-diabetic treated animals were still normalized [26]. An oral glucose tolerance test showed an improved glucose response without a concomitant increase in circulating plasma insulin levels. The maintenance effects following withdrawal of vanadium therapy have subsequently been repeated in a number of experiments [27, 28]. The mechanism of action for the sustained euglycemia observed following withdrawal of vanadium therapy is not known.

A one year toxicity study has shown that vanadyl sulfate treatment improved or prevented the tissue damage seen in the kidney of diabetic animals. Vanadyl treatment normalized serum transaminases and urea nitrogen and creatinine levels in diabetic treated animals. Cataract formation, a common secondary characteristic in diabetes, was prevented with vanadium therapy [29, 30].

Because the STZ model of diabetes is not completely insulin deficient, a question arose concerning the effectiveness of vanadium in controlling elevated glucose levels in the BB Wistar rat model. BB rats were stabilized on exogenous insulin prior to the start of vanadyl treatment. Vanadyl sulfate was administered in the drinking water at a maximal concentration of 0.75 mg/mL for 6 months. It was found that the dose of exogenous insulin required could be significantly reduced with vanadium treatment. However, when exogenous insulin levels were reduced by greater than 50% there was a crossover point at which the beneficial effects of vanadium and insulin in combination were diminished and there was a detrimental effect on body weight gain. This suggests that vanadyl was not effective in mimicking the anabolic effects of insulin [19].

A current hypothesis in hypertension research is that insulin resistance and hyperinsulinemia may indirectly play a role in the development of elevated blood pressure (Fig. 1; [31]) thus a drug intervention which can reduce plasma insulin levels may be effective in lowering blood pressure.

Since treatment with either vanadate and vanadyl results in a significant reduction in circulating plasma insulin levels in control treated animals, a number of experiments were done to examine the hypertension/insulin resistance hypothesis. Spontaneously hypertensive rats (SHR) are a genetic strain of animals that develop essential hypertension starting at 8 weeks of age. While this model is hyperinsulinemic, there is some controversy as to whether SHR are insulin resistant [32–35]. Bhanot *et al* showed that treatment of SHR with vanadyl sulfate in the drinking water could prevent the

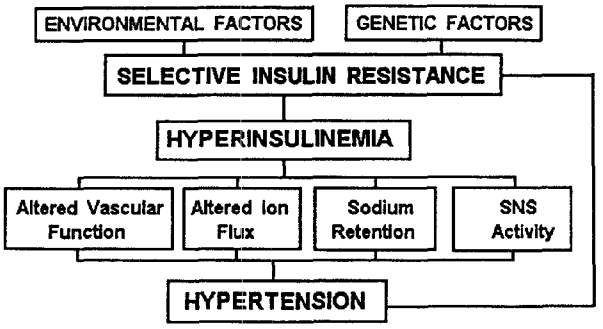


Fig. 1. Schematic representation of the possible inter-relationship between hypertension and insulin resistance and hyperinsulinemia. (Modified from Rocchini, 1992).

development of hypertension and reduce plasma insulin levels to normal. Secondly, a group of SHR were allowed to develop hypertension and then vanadium treatment was initiated; it was found that plasma insulin levels were restored to normal and high blood pressure was reduced by approximately 50% of untreated animals. Hyperinsulinemia and insulin resistance may contribute to the etiology of hypertension [35].

The fructose animal model represents an acquired form of systolic hypertension where the increased blood pressure is diet induced [36]. Similar effects of vanadium treatment on elevated blood pressure and plasma insulin levels have been shown in the fructose-induced hypertensive rat [37].

Organic vanadium *in vivo*

While a reduced food intake and a slowed body weight gain in control treated animals have been attributed to vanadium treatment, pair fed studies conducted in this laboratory and others have shown that the insulin-mimetic actions of vanadium cannot be attributed to the redudion in food intake [21, 35]. Therefore since inorganic vanadium is poorly absorbed from the gastrointestinal (Gl) tract and [38, 39] some Gl difficulties have been reported with both vanadyl and vanadate, our laboratory and others have synthesized a number of organic vanadium compounds.

The first compound manufactured for our laboratory was a cysteine/vanadyl complex, naglivan (Fig. 2). Naglivan was synthesized in France and was investigated in collaboration with Dr. G. Cros, Montpellier, France. Naglivan is water insoluble and therefore it was administered as a suspension by oral gavage. Treatment with naglivan alone was not initially effective in reducing plasma glucose to normal and thus it was administered in combination with insulin. The combination therapy was effective in reducing plasma glucose levels, restoring elevated plasma lipid levels and heart function in STZ-diabetic rats. The reduction in body weight gain observed in non-diabetic animals with inorganic vanadium was not seen with naglivan over an 8 week treatment period. After a 3 week combination therapy regime insulin was withdrawn and diabetic animals that continued to receive naglivan alone demonstrated an improved glucose control. A subsequent experiment showed that diabetic animals could be euglycemic with naglivan alone when the dose of naglivan was increased [40].

Bis(maltolato)oxovanadium(IV) (BMOV) (Fig. 3), a maltol/vanadyl compound, was developed in a collaboration with Dr. C. Orvig in the Department of Chemistry at the University of British Columbia [41]. BMOV is a potent example of a series of compounds designed to be orally absorbed by passive diffusion as a result of their properties of water solubility, electrical neutrality and low molecular weight. BMOV was administered to STZ-diabetic rats in the drinking water at a maximal concentration of 0.75 mg/mL for 6 months. BMOV restored plasma glucose levels to normal in 8/12 animals and restored elevated plasma lipid parameters and heart function in all diabetic treated rats. There was a strong correlation between improved heart function and long term glucose control. However unlike vanadyl, BMOV treatment did not result in the sustained euglycemic response observed following withdrawal of treatment [42].

There was no effect of BMOV therapy on body weight gain in control treated animals for the first 10 weeks of treatment as compared to inorganic vanadium therapy which reduced body weight gain within 1–2 weeks of treatment initiation.

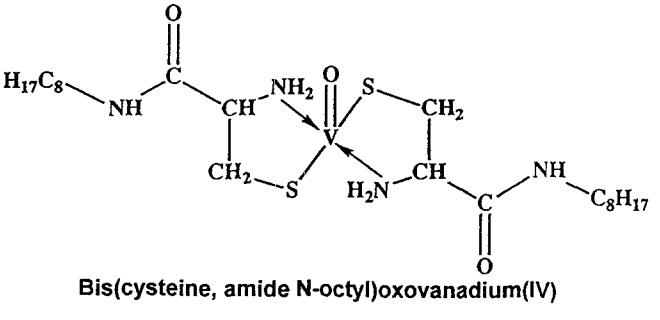


Fig. 2. Bis(N-octylcysteinamide)oxovanadium(IV) – Naglivan.

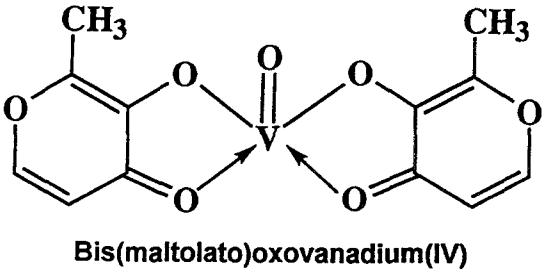


Fig. 3. Bis(maltolato)oxovanadium(IV) – BMOV.

However, the reduction in circulating plasma insulin levels in control treated animals was similar to that seen with vanadyl. Chronic BMOV treatment was effective in ameliorating the pathological abnormalities associated with STZ-induced diabetes mellitus [43].

It was observed that the diabetic treated group could be subdivided based on the glucose response to BMOV with 4/12 diabetic treated animals never demonstrating stable glucose control. There was no difference in the dose of vanadium administered between control and euglycemic diabetic treated animals whereas the uncontrolled diabetic animals had significantly elevated and highly variable levels of vanadium intake. Figure 4 shows the dose of BMOV required to maintain the euglycemic effect. This dose was 2–3 times lower than that required with either vanadate or vanadyl; 0.18 mmol/kg/day for BMOV as compared to 0.4–0.6 mmol/kg/day for vanadate or vanadyl [44].

A number of acute experiment were conducted to compare the glucose lowering properties of BMOV and vanadyl sulfate. BMOV and vanadyl sulfate were administered by oral gavage at a concentration of 175 mg/kg (0.55 and 0.82 mmol/kg, respectively) or by intraperitoneal injection at a concentration of 20 mg/kg (0.063 and 0.091 mmol/kg, respectively). BMOV was found to be 2–3 times as potent as vanadyl sulfate by either route of administration. An euglycemic response to both organic and inorganic vanadium could be observed within hours of administration. The lower plasma glucose levels were sustained with BMOV in 15–20% of animals for up to 14 weeks following a single administration. Intravenous administration of vanadium produced a plasma glucose lowering effect only when given by infusion over an extended period of time. A bolus or slow bolus injection of vanadium into the tail vein did not lower plasma glucose levels. A determination of plasma vanadium levels following a slow bolus injection (Fig. 5) suggested that the

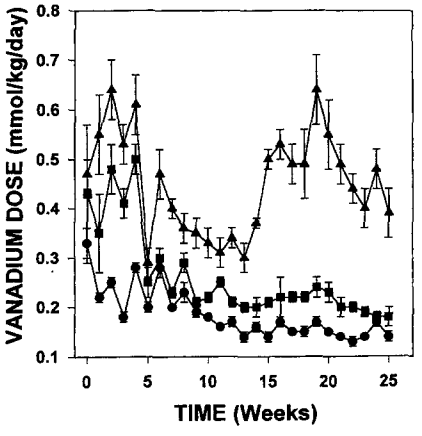


Fig. 4. The vanadium dose for control-treated (●, n = 8), diabetic-treated responders (■, n = 8) and diabetic-treated partial responders (▲, n = 4) for 25 weeks of treatment with BMOV.

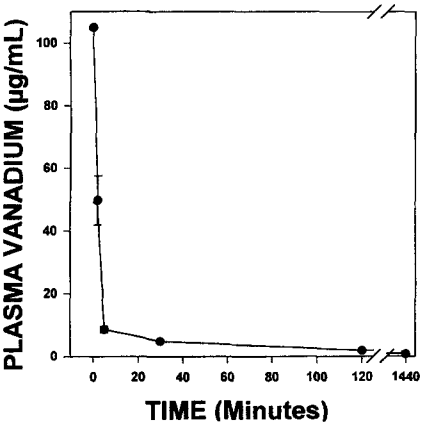


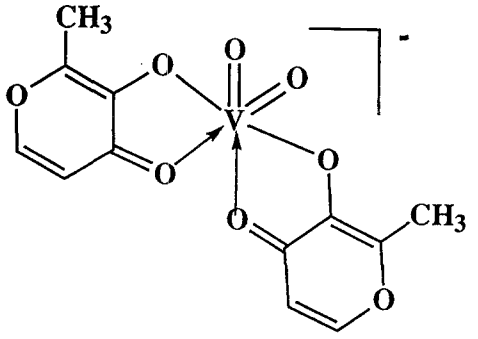
Fig. 5. Plasma vanadium levels following slow i.v. bolus administration of BMOV 32 µmol/kg over 7 to 10 minutes.

vanadium was cleared from the circulation, either by redistribution to tissues or by excretion from the body, before it could affect glucose levels [45].

Both oral dose response and intraperitoneal dose response curves have been done to compare the effectiveness of BMOV and vanadyl sulfate following administration of a single dose. At the highest doses administered BMOV produced an euglycemic response in 100% of animals treated as compared to 80% to 90% with vanadyl sulfate. The ED_{50} following oral administration indicated that BMOV was 2 times as potent as vanadyl sulfate; 0.5 mmol/kg for BMOV as compared to 0.92 mmol/kg for vanadyl sulfate. Similarly, BMOV was 3 times as potent by intraperitoneal injection [45].

BMOV administration to SHR animals had similar effects on elevated blood pressure and hyperinsulinemia as was seen with inorganic vanadium. The dose required to produce this reduction in blood pressure was 0.35–0.45 mmol/kg/day of BMOV as compared to 0.4–0.6 mmol/kg/day of vanadyl sulfate [46].

BMOV has also been used in fa/fa (fatty) Zucker rats to examine the effectiveness of organic vanadium in Type II diabetes. BMOV at a maximal concentration of 0.5 mg/mL for 14 weeks of treatment reduced plasma insulin levels from 180 µU/mL to normal (50 µU/mL) by 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 effect 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 to140 µU/mL. An oral glucose tolerance test showed an improved glucose tolerance in fatty treated animals regardless of the con-



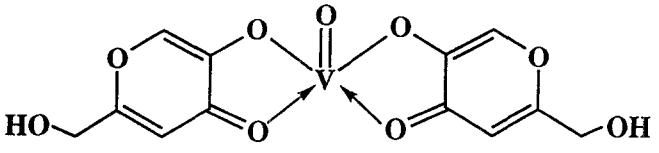
Bis(maltolato)dioxovanadate(V)

Fig. 6. Bis(maltolato)dioxovanadate(V)–BMO2V.

centration of BMOV.(unpublished observations)

Bis(maltolato)dioxovanadate(V) (BMO2V) is an anionic vanadium (V) analog of BMOV prepared in Dr. Orvig's laboratory (Fig. 6). Chronic oral administration of BMO2V in the drinking water was found to be less effective than BMOV and required higher doses of vanadium to obtain the plasma glucose lowering effects. Acute administration of BMO2V was as effective as BMOV in reducing plasma glucose levels but was not as well tolerated. All animals treated acutely with BMO2V had severe diarrhea that lasted for at least 12 h.(unpublished observations)

Bis(kojato)oxovanadium(IV) (BKOV) is a kojic acid/vanadyl complex directly analogous to BMOV that was more soluble in water than BMOV (Fig. 7). BKOV was less effective than BMOV in lowering plasma glucose levels both



Bis(kojato)oxovanadium(IV)

Fig. 7. Bis(kojato)oxovanadium(IV)–BKOV.

chronically and acutely. Chronic administration of BKOV in the drinking water required higher doses of vanadium than those used in the BMOV studies in order to lower blood glucose.(unpublished observations)

Summary

Both organic and inorganic vanadium are effective compounds in the treatment of hyperglycemia in diabetes mellitus and the prevention of the secondary complications associated with this disease state. Organically chelated vanadium complexes appear to be as effective insulin-mimetic agents at significantly lower doses. These compounds reduced the gastrointestinal side effects of vanadium treatment and did not effect body weight gain and food and fluid intake in control treated animals. As reported elsewhere in this same volume, early trials with vanadyl in diabetic human volunteers have shown positive findings which are consistent with the results obtained in animal studies discussed in this and other papers. There is a possible role for the use of these compounds in the treatment of diabetes mellitus, either alone or as an adjunct therapy along with insulin.

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