Metabolic effects of vanadyl sulfate in humans with non-insulin-dependent diabetes mellitus: in vivo and in vitro studies

Alternative Medicine Review, Oct, 2000

Metabolic effects of vanadyl sulfate in humans with non-insulin-dependent diabetes mellitus: in vivo and in vitro studies. Goldfine AB, Patti ME, Zuberi L, et al. Metabolism 2000;49:400-410.

To investigate the efficacy and mechanism of action of vanadium salts as oral hypoglycemic agents, 16 type 2 diabetic patients were studied before and after 6 weeks of vanadyl sulfate (VOSO4) treatment at three doses. Glucose metabolism during a euglycemic insulin clamp did not increase at 75 mg/d, but improved in 3 of 5 subjects receiving 150 mg VOSO4 and 4 of 8 subjects receiving 300 mg VOSO4. Basal hepatic glucose production (HGP) and suppression of HGP by insulin were unchanged at all doses. Fasting glucose and hemoglobin A1c (HbA1c) decreased significantly in the 150- and 300-mg VOSO4 groups. At the highest dose, total cholesterol decreased, associated with a decrease in high-density lipoprotein (HDL). There was no change in systolic, diastolic, or mean arterial blood pressure on 24-hour ambulatory monitors at any dose. There was no apparent correlation between the clinical response and peak serum level of vanadium. The 150- and 300-mg vanadyl doses caused some gastrointestinal intolerance but did not increase tissue oxidative stress as assessed by thiobarbituric acid-reactive substances (TBARS). In muscle obtained during clamp studies prior to vanadium therapy, insulin stimulated the tyrosine phosphorylation of the insulin receptor, insulin receptor substrate-1 (IRS-1), and Shc proteins by 2- to 3-fold, while phosphatidylinositol 3-kinase (PI 3-kinase) activity associated with IRS-1 increased 4.7-fold during insulin stimulation (P = .02). Following vanadium, there was a consistent trend for increased basal levels of insulin receptor, Shc, and IRS-1 protein tyrosine phosphorylation and IRS-1-associated PI 3-kinase, but no further increase with insulin. There was no discernible correlation between tyrosine phosphorylation patterns and glucose disposal responses to vanadyl. While glycogen synthase fractional activity increased 1.5-fold following insulin infusion, there was no change in basal or insulin-stimulated activity after vanadyl. There was no increase in the protein phosphatase activity of muscle homogenates to exogenous substrate after vanadyl. Vanadyl sulfate appears safe at these doses for 6 weeks, but at the tolerated doses, it does not dramatically improve insulin sensitivity or glycemic control. Vanadyl modifies proteins in human skeletal muscle involved in early insulin signaling, including basal insulin receptor and substrate tyrosine phosphorylation and activation of PI 3-kinase, and is not additive or synergistic with insulin at these steps. Vanadyl sulfate does not modify the action of insulin to stimulate glycogen synthesis. Since glucose utilization is improved in some patients, vanadyl must also act at

Vanadyl sulfate inhibits NO production via threonine phosphorylation of eNOS - Research

Environmental Health Perspectives, Feb, 2004 by Zhuowei Li, Jacqueline D. Carter, Lisa A. Dailey, Yuh-Chin T. Huang

Exposure to excessive vanadium occurs in some occupations and with consumption of some dietary regimens for weight reduction and body building. Because vanadium is vasoactive, individuals exposed to excessive vanadium may develop adverse vascular effects. We have previously shown that vanadyl sulfate causes acute pulmonary vasoconstriction, which could be attributed in part to inhibition of nitric oxide production. In the present study we investigated whether NO inhibition was related to phosphorylation of endothelial nitric oxide synthase (eNOS). VOS[O.sub.4] produced dose-dependent constriction of pulmonary arteries in isolated perfused lungs and pulmonary arterial rings and a right shift of the acetylcholine-dependent vasorelaxation curve. VOS[O.sub.4] inhibited constitutive as well as A23187-stimulated NO production. Constitutive NO inhibition was accompanied by increased [Thr.sup.495] (threonine at codon 495) phosphorylation of eNOS, which would inhibit eNOS activity. [Thr.sup.495] phosphorylation of eNOS and inhibition of NO were partially reversed by pretreatment with calphostin C, a protein kinase C (PKC) inhibitor. There were no changes in [Ser.sup.1177] (serine at codon 1177) or tyrosine phosphorylation of eNOS. These results indicate that VOS[O.sub.4] induced acute pulmonary vasoconstriction that was mediated in part by the inhibition of endothelial NO production via PKC-dependent phosphorylation of [Thr.sup.495] of eNOS. Exposure to excessive vanadium may contribute to pulmonary vascular diseases. Key words: boilermakers, protein kinase C, pulmonary hypertension, vanadium. Environ Health Perspect 112:201-206 (2004). doi:10.1289/ehp.6477 available via http://dx.doi.org/ [Online 22 October 2003]

1: Eksp Klin Farmakol. 2004 May-Jun;67(3):42-4.

[Comparative assessment of the cell mechanisms of antidiabetic action of a new organic derivative of vanadium(IV) oxide and vanadyl sulfate]

[Article in Russian]

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The antidiabetic effect of a new organic derivative of vanadium(IV) oxide with isonicotinic acid hydrazide (compound no. 8), as manifested by the action upon the alpha and beta cell populations in Langerhans islands of the pancreas, was studied in rats with alloxane diabetes model in comparison to the analogous effect of the inorganic drug vanadyl sulfate. The hypoglycemic activity of compound no. 8 was comparable with that of vanadyl sulfate. The results of immunohistochemical and morphometric investigation showed that both preparations produced a reliable increase in the population of insulin-producing cells and a decrease in the (alloxane-enhanced) population of [alpha] cells in the pancreatic islands.

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1: Clin Biochem. 2004 Aug;37(8):694-7.

Vanadyl sulfate ameliorates insulin resistance and restores plasma dehydroepiandrosterone-sulfate levels in fructose-fed, insulin-resistant rats.

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OBJECTIVES: To elucidate whether vanadyl sulfate ameliorates the decreased dehydroepiandrosterone sulfate (DHEAS) in hyperinsulinemic rats, we evaluated plasma DHEAS, insulin and triglyceride (TG) levels in fructose-induced, insulin-resistant rats. DESIGN AND METHODS: Animals were divided into three groups: control (C), fructose fed (F-F), and vanadyl-treated fructose fed (F-T). Control animals were fed with standard chow; F-F and F-T groups fed with 66% fructose diet. F-F and C groups received tap water; F-T group received water supplemented with 0.2 mg/ml vanadyl sulfate. RESULTS: Fasting plasma glucose levels of three groups were comparable. Vanadyl treatment prevented the increase in plasma insulin and TG in the F-T group ($P < 0.001$) compared with the F-F group. Fructose feeding led to a decrease in plasma DHEAS in the F-F group ($P < 0.001$) compared with the C group. Vanadyl treatment prevented the decrease in plasma DHEAS in the F-T group ($P < 0.001$) compared with the F-F group. CONCLUSIONS: Our results indicated that the hyperinsulinemia in fructose-fed, insulin-resistant rats is associated with low levels of DHEAS. Vanadyl sulfate probably restores plasma DHEAS, due to the improved insulin action.

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Insulin-Mimetic Vanadyl(IV) Complexes as Evaluated by Both Glucose-Uptake and Inhibition of Free Fatty Acids (FFA)-Release in Isolated Rat Adipocytes

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We have recently proposed the existence of some potent vanadyl complexes with blood glucose-lowering activity in experimental diabetic animals based on the results of an *in vitro* FFA (free fatty acids)-release assay in isolated rat adipocytes treated with epinephrine and evidence of an *in vivo* blood glucose lowering effect in experimental diabetic animals. However, the FFA assay depends indirectly on the glucose-uptake of vanadyl complexes in adipocytes. It is therefore necessary to develop a more reliable *in vitro* glucose-uptake assay, in place of the glucose uptake method using radioactive compounds such as ^{14}C-glucose, to identify insulin-mimetic vanadyl complexes. In the present study, we proposed a combined *in vitro* assay by using the conventional glucose oxidase method for glucose-uptake and FFA assay in isolated rat adipocytes. Insulin, vanadyl sulfate ($VOSO_4$), bis(picolinato)vanadyl ($VO(pa)_2$), and bis(6-methylpicolinato)vanadyl ($VO(6mpa)_2$) complexes exhibited concentration-dependent uptake of (+)-D-glucose and inhibition of FFA release in the adipocytes treated with epinephrine. Vanadyl complexes were found to accelerate glucose-uptake at lower concentrations than $VOSO_4$. *In vitro* high insulin-mimetic activity of $VO(pa)_2$ and $VO(6mpa)_2$ were thus indicated by both glucose-uptake and FFA-release, with the insulin-mimetic activity of $VO(6mpa)_2$ being higher than that of $VO(pa)_2$, as suggested by the partition coefficient (0.330 for $VO(pa)_2$ and 0.595 for $VO(6mpa)_2$). The proposed assay provides a more reliable method than each single method for the evaluation of *in vitro* insulin-mimetic activity of compounds.

Key words vanadyl compound; glucose-uptake assay; free fatty acids (FFA)-release assay; insulin-mimetic effect; adipocyte

The number of patients suffering from diabetes mellitus (DM) is increasing throughout the world, as it becomes the most significant disease of the 21st century.[1—4] However, no agents other than insulin have been developed for the treatment of either type 1 DM or serious type 2 DM. As such, there is an urgent need for developing new types of therapeutic agents for the treatment of diabetes.

Since the discovery of the insulin-mimetic effects of vanadate(V) compounds in adipocytes in 1980,[5,6] the effects of vanadium compounds have attracted many researchers. Among the several oxidation states of vanadium from II to V, this metal ion in living systems is considered to exist exclusively as vanadyl(IV) cation (VO^{2+}) and a small amount of vanadate(V) anion (VO_4^{3-}).[7] In experimental diabetic animals, both vanadyl and vanadate ions have been found to have an insulin-mimetic effect on glucose metabolism.[8—14] Interestingly, both compounds have been proposed to partially improve human DM.[15—24] However, the vanadyl ion is less toxic than the vanadate ion, as judged by the LD_{50} values in several animals,[25,26], and most vanadium in normal rats treated with vanadate exists in the vanadyl form.[7,27] Based on these findings, vanadyl(IV) complexes with low molecular weight organic ligands have recently been prepared to provide more effective insulin-mimetic compounds than vanadyl sulfate ($VOSO_4$). In recent decades, some vanadyl complexes with several types of organic ligands have been proposed by many research groups for clinical use in humans.[28—34]

To evaluate the insulin-mimetic vanadyl complexes, glucose-uptake in cells or tissues has been monitored, which requires radioisotope (RI) reagents.[5,6,27] In 1995, we proposed a new *in vitro* assay, based on the inhibition of FFA (free fatty acids)-release from isolated rat adipocytes treated with epinephrine (adrenalin), which is simple and convenient compared with the use of RI reagents.[35] By this *in vitro* assay, we have evaluated some insulin-mimetic activities of vanadyl complexes with different chemical structures and coordination modes such as $VO(O_4)$,[36] $VO(N_2O_2)$,[37—43] $VO(S_2N_2)$,[36] $VO(S_2O_2)$,[44,45] $VO(N_3O)$,[39] and $VO(N_4)$.[28] Our results indicate that the complexes with a strong ability to inhibit FFA-release from adipocytes lowered the high blood glucose levels in type 1 and 2 diabetic animals more effectively than $VOSO_4$. However, this method evaluates the glucose-uptake in the cells indirectly. We therefore attempted to develop a more reliable method than the FFA-release assay to evaluate the insulin-mimetic activity of vanadyl complexes.

We propose herein the usefulness of simultaneous evaluations of both FFA-release and glucose-uptake based on a conventional glucose oxidase method in isolated rat adipocytes in identifying insulin-mimetic compounds.

Experimental

Materials Vanadyl sulfate ($VOSO_4 \cdot 2.8H_2O$, VS) was purchased from Wako Pure Chemicals (Osaka). The purity of $VOSO_4 \cdot 2.8H_2O$ was determined by chelatometry using an indicator, Cu-Pan (Cu-1-(2-pyridylazo-2-naphthol)) (Dojindo, Kumamoto). Bis(picolinato)vanadyl ($VO(pa)_2$), and bis(6-methylpicolinato)vanadyl ($VO(6mpa)_2$) complexes were prepared as described.[37,38] Collagenase (Type II), bovine serum albumin (BSA; fraction V), and (±)-epinephrine hydrochloride (adrenaline) were obtained from Sigma Chemical (St. Louis, MO, U.S.A.). Insulin was purchased from Novo Nordisk Pharma. (Tokyo). (+)-D-Glucose was purchased from Nacalai Tesque, Inc. (Kyoto). Other reagents were of the highest purity commercially available.

Animals Male Wistar rats (7—8 weeks old) weighing 200—250 g were obtained from Shimizu Experimental Material Co. (Kyoto). Animals were maintained in a 12-h light/dark cycle in our central animal facility, and were allowed free access to solid food (MF, Oriental Yeast Co. Tokyo) and tap water. Animal experiments were approved by the Experimental Animal Research Committee of Kyoto Pharmaceutical University (KPU) and were per-

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1: Biol Trace Elem Res. 2003 Oct;95(1):73-85.

Effects of vanadyl sulfate on kidney in experimental diabetes.

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The aim of this work was to investigate the biochemical and histological effects of vanadyl sulfate on blood glucose, urea, and creatinine in serum and nonenzymatic glycosylation and glutathione levels in kidney tissue of normal and streptozotocin (65 mg/kg) diabetic rats. Vanadyl sulfate was administered by gavage at a dose of 100 mg/kg. After 60 d of treatment, serum urea, creatinine, and blood glucose levels significantly increased in the diabetic group but not so in the vanadyl sulfate, which showed significantly reduced serum urea and blood glucose levels and a nonsignificant reduction of serum creatinine levels. Nonenzymatic glycosylation was increased and the glutathione level was decreased in the kidney tissue of diabetic rats. Treatment with vanadyl sulfate reversed these effects. Degenerative changes were detected in diabetic animals by electron and light microscopy. Although there are individual differences in diabetic animals given vanadium, some reduction of degenerative changes were observed.

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1: Arch Toxicol. 2004 Jan;78(1):7-15. Epub 2003 Sep 10.

Vanadyl sulfate can differentially damage DNA in human lymphocytes and HeLa cells.

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Using the comet assay, we showed that vanadyl sulfate induced DNA damage in human normal lymphocytes and in HeLa cells. Vanadyl at 0.5 and 1 mM produced DNA single- and double-strand breaks (SSBs and DSBs) in lymphocytes, whereas in HeLa cells we observed only SSBs. Post-treatment of vanadyl-damaged DNA from lymphocytes with formamidopyrimidine-DNA glycosylase (Fpg), an enzyme recognizing oxidized purines, gave rise to a significant increase in the extent of DNA damage. A similar effect was observed in HeLa cells, but, using endonuclease III, we also detected oxidized pyrimidines in DNA of these cells. There were no differences in the extent of DNA damage in the lymphocytes and HeLa cells in the pH >13 and pH 12.1 conditions of the comet assay, which indicates that strand breaks, and not alkali-labile sites, contributed to the measured DNA damage. Study of DNA repair, determined in the comet assay as an ability of cells to decrease of DNA damage, revealed that HeLa cells retained the ability to repair vanadyl-damaged DNA induced at a ten-fold higher concentration than that in lymphocytes. Incubation of the cells with nitrone spin traps DMPO, POBN and PBN decreased the extent of DNA damage, which might follow from the production of free radicals by vanadyl sulfate. The presence of vitamins A, C or E caused an increase of DNA damage in HeLa cells whereas in lymphocytes such an increase was observed only for vitamin C. Our data indicate that vanadyl sulfate can be genotoxic for normal and cancer cells. It seems to have a higher genotoxic potential for cancer cells than for normal lymphocytes. Vitamins A, C and E can increase this potential.

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1: Int J Sport Nutr Exerc Metab. 2002 Dec;12(4):470-9.

Effect of acute and short-term administration of vanadyl sulphate on insulin sensitivity in healthy active humans.

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Vanadium compounds have been shown to have insulin-like properties in rats and non-insulin-dependent diabetic humans. The purpose of the present study was to examine whether the effects of acute and short-term administration of vanadyl sulfate (VA) on insulin sensitivity also exist in healthy active individuals. Five male and two female participants (age: 24.9 +/- 1.5 years; height: 176.1 +/- 2.9 cm; body mass: 70.1 +/- 2.9 kg) underwent 3 oral glucose tolerance tests (OGTT). The first OGTT was performed to obtain a baseline index of insulin sensitivity (ISI). On the night preceding the second OGTT, participants ingested 100 mg of VS, and the acute effects of VS on ISI were examined. For the next 6 days, participants were instructed to ingest 50 mg of VS twice daily, and a final OGTT was performed on day 7 to determine the short-term effects of VS on ISI. No differences were found in fasting plasma glucose and insulin concentrations after VS administration. Furthermore, ISI after 1 day and 7 days of VS administration was not different compared with baseline ISI (4.8 +/- 0.1 vs. 4.7 +/- 0.1 vs. 4.7 +/- 0.1, respectively). These results demonstrate that there are no acute and short-term effects of VS administration on insulin sensitivity in healthy humans.

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1: Chem Rec. 2002;2(4):237-48.

A new concept: the use of vanadium complexes in the treatment of diabetes mellitus.

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In the 21st century, patients suffering from diabetes mellitus (DM), a lifestyle-related disease, will increase more than in the 20th century. DM is threatening because of the development of many severe secondary complications, including atherosclerosis, microangiopathy, renal dysfunction and failure, cardiac abnormalities, diabetic retinopathy, and ocular disorders. Generally, DM is classified as either insulin-dependent type 1 or noninsulin-dependent type 2 DM. Type 1 DM is treated only by daily insulin injections; type 2 DM is treated by several types of synthetic therapeutic substances together with a controlled diet and physical exercise. Even with these measures, the daily necessity for several insulin injections can be painful both physically and mentally, whereas the synthetic therapeutic substances used over the long term often have side effects. For those reasons, the creation and development of a new class of pharmaceuticals for treatment of DM in the 21st century would be extremely desirable. In the last half of the 20th century, investigations of the relationships among diseases and micronutrients, such as iron, copper, zinc, and selenium, have been numerous. Research into the development of metallopharmaceuticals involving the platinum-containing anticancer drug, cisplatin, and the gold-containing rheumatoid arthritis drug, auranofin, has also been widespread. Such important findings prompted us to develop therapeutic reagents based on a new concept to replace either insulin injections or the use of synthetic drugs. After many trials, we noticed that vanadium might be very useful in the treatment of DM. Before the discovery of insulin by Banting and Best in 1921 and its clinical trial for treating DM, the findings in 1899, in which orally administered sodium vanadate (NaVO(3)) was reported to improve human DM, gave us the idea to use vanadium to treat DM. However, it has taken a long time to obtain a scientific explanation as to why the metal ion exhibits insulin-mimetic or blood-glucose lowering effects in in vitro and in vivo experiments. After investigations from many perspectives involving biochemistry and bioinorganic chemistry, vanadyl sulfate (VOSO(4)) and its complexes with several types of ligands have been proposed as useful for treating DM in experimental diabetic animals. On the basis of a mechanistic study, this article reports on recent progress regarding the development of antidiabetic vanadyl complexes, emphasizing that the vanadyl ion and its complexes are effective not only in treating or relieving both types of DM but also in preventing the onset of DM.

Publication Types:
Review
Review, Tutorial

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1: J Med. 2000;31(5-6):227-46.

Effects of niacin-bound chromium and grape seed proanthocyanidin extract on the lipid profile of hypercholesterolemic subjects: a pilot study.

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Hypercholesterolemia, a significant cardiovascular risk factor, is prevalent in the American population. Many drugs lower circulating cholesterol levels, but they are not infrequently associated with severe side effects. Accordingly, natural means to lower cholesterol levels safely would be welcomed. We examined 40 hypercholesterolemic subjects (total cholesterol 210-300 mg/dL) in a randomized, double-blind, placebo-controlled study. The four groups of ten subjects received either placebo bid, chromium polynicotinate (Cr) 200 microg bid, grape seed extract (GSE) 100 mg bid, or a combination of Cr and GSE at the same dosage bid. Over two months, the average percent change +/- SEM in the total cholesterol from baseline among groups was: placebo -3.5% +/- 4, GSE -2.5% +/- 2, Cr -10% +/- 5, and combination -16.5% +/- 3. The decrease in the last group was significantly different from placebo ($p < 0.01$). The major decrease in cholesterol concentration was in the LDL levels: placebo -3.0% +/- 4, GSE -1.0% +/- 2.0, Cr -14% +/- 4.0, and the combination -20% +/- 6.0. Again, the combination of Cr and GSE significantly decreased LDL when compared to placebo ($p<0.01$). HDL levels essentially did not change among the groups. Also, there was no significant difference in the triglyceride concentrations among the groups; and no statistically significant differences were seen in the levels of autoantibodies to oxidized LDL (Ox-LDL). However, the trend was for the two groups receiving GSE to have greater decreases in the latter parameter, i.e., -30.7% and -44.0% in the GSE and combined groups in contrast to -17.3% and -10.4% in the placebo and chromium groups. We determined the number of subjects in each group who decreased autoantibodies to oxidized LDL greater than 50% over eight weeks and found these ratios among groups: placebo = 2/9, Cr = 1/10, GSE = 6/10, and combined = 3/8. Thus, 50% of subjects (9/18) receiving GSE had a greater than 50% decrease in autoantibodies compared to 16% (3/19) in the two groups not receiving GSE. No significant changes occurred in the levels of circulating homocysteine and blood pressure among the four groups. We conclude that a combination of Cr and GSE can decrease total cholesterol and LDL levels significantly. Furthermore, there was a trend to decrease the circulating autoantibodies to oxidized LDL in the two groups receiving GSE.

Publication Types:
Clinical Trial
Randomized Controlled Trial

PMID: 11508317 [PubMed - indexed for MEDLINE]

1: Eur J Intern Med. 2002 Dec;13(8):518-520.

Chromium-induced toxic hepatitis.

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A clinical case of acute hepatitis in a patient undergoing an alternative medicine weight-reduction regimen is reported. Chromium polynicotinate had been ingested in combination with vegetable extracts over a 5-month period. Liver biopsy was compatible with toxic hepatitis and greatly elevated hepatic chromium levels were found (>10x normal). The clinical picture regressed following suspension of the medication.

PMID: 12446198 [PubMed - as supplied by publisher]