

Vanadium Compounds as Possible Insulin Modifiers...

Periodic Table of Elements

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18																												
1 H Hydrogen 1.00794	Atomic # Name Symbol Atomic Mass																2 He Helium 4.002602																												
3 Li Lithium 6.941	4 Be Beryllium 9.012182	<table border="1"> <tr> <td>C Solid</td> <td colspan="4">Metals</td> <td colspan="2">Nonmetals</td> </tr> <tr> <td>Hg Liquid</td> <td>Alkali metals</td> <td>Alkaline earth metals</td> <td>Lanthanoids</td> <td>Transition metals</td> <td>Poor metals</td> <td>Other nonmetals</td> </tr> <tr> <td>H Gas</td> <td></td> <td></td> <td>Actinoids</td> <td></td> <td></td> <td>Noble gases</td> </tr> <tr> <td>Rf Unknown</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>										C Solid	Metals				Nonmetals		Hg Liquid	Alkali metals	Alkaline earth metals	Lanthanoids	Transition metals	Poor metals	Other nonmetals	H Gas			Actinoids			Noble gases	Rf Unknown							5 B Boron 10.811	6 C Carbon 12.0107	7 N Nitrogen 14.0067	8 O Oxygen 15.9994	9 F Fluorine 18.9984032	10 Ne Neon 20.1797
C Solid	Metals				Nonmetals																																								
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11 Na Sodium 22.98976928	12 Mg Magnesium 24.3050	13 Al Aluminum 26.9815386	14 Si Silicon 28.0855	15 P Phosphorus 30.973762	16 S Sulfur 32.065	17 Cl Chlorine 35.453	18 Ar Argon 39.948																																						
19 K Potassium 39.0983	20 Ca Calcium 40.078	21 Sc Scandium 44.955912	22 Ti Titanium 47.887	23 V Vanadium 50.9415	24 Cr Chromium 51.9961	25 Mn Manganese 54.938045	26 Fe Iron 55.845	27 Co Cobalt 58.933195	28 Ni Nickel 58.6934	29 Cu Copper 63.546	30 Zn Zinc 65.38	31 Ga Gallium 69.723	32 Ge Germanium 72.64	33 As Arsenic 74.92160	34 Se Selenium 78.96	35 Br Bromine 79.904	36 Kr Krypton 83.798																												
37 Rb Rubidium 85.4678	38 Sr Strontium 87.62	39 Y Yttrium 88.90585	40 Zr Zirconium 91.224	41 Nb Niobium 92.90638	42 Mo Molybdenum 95.96	43 Tc Technetium (97.9072)	44 Ru Ruthenium 101.07	45 Rh Rhodium 102.90550	46 Pd Palladium 106.42	47 Ag Silver 107.8682	48 Cd Cadmium 112.411	49 In Indium 114.818	50 Sn Tin 118.710	51 Sb Antimony 121.760	52 Te Tellurium 127.60	53 I Iodine 126.90447	54 Xe Xenon 131.293																												
55 Cs Caesium 132.9054519	56 Ba Barium 137.327	57-71		72 Hf Hafnium 178.49	73 Ta Tantalum 180.94788	74 W Tungsten 183.84	75 Re Rhenium 186.207	76 Os Osmium 190.23	77 Ir Iridium 192.217	78 Pt Platinum 195.084	79 Au Gold 196.966569	80 Hg Mercury 200.59	81 Tl Thallium 204.3833	82 Pb Lead 207.2	83 Bi Bismuth 208.98040	84 Po Polonium (208.9824)	85 At Astatine (208.9871)	86 Rn Radon (222.0176)																											
87 Fr Francium (223)	88 Ra Radium (226)	89-103		104 Rf Rutherfordium (261)	105 Db Dubnium (262)	106 Sg Seaborgium (266)	107 Bh Bohrium (264)	108 Hs Hassium (277)	109 Mt Meitnerium (268)	110 Ds Darmstadtium (271)	111 Rg Roentgenium (272)	112 Uub Ununbium (285)	113 Uut Ununtrium (284)	114 Uuq Ununquadium (289)	115 Uup Ununpentium (288)	116 Uuh Ununhexium (292)	117 Uus Ununseptium	118 Uuo Ununoctium (294)																											

For elements with no stable isotopes, the mass number of the isotope with the longest half-life is in parentheses.

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57 La Lanthanum 138.90547	58 Ce Cerium 140.116	59 Pr Praseodymium 140.90765	60 Nd Neodymium 144.242	61 Pm Promethium (145)	62 Sm Samarium 150.36	63 Eu Europium 151.964	64 Gd Gadolinium 157.25	65 Tb Terbium 158.92535	66 Dy Dysprosium 162.500	67 Ho Holmium 164.93032	68 Er Erbium 167.259	69 Tm Thulium 168.93421	70 Yb Ytterbium 173.054	71 Lu Lutetium 174.9668
89 Ac Actinium (227)	90 Th Thorium 232.03806	91 Pa Protactinium 231.03588	92 U Uranium 238.02891	93 Np Neptunium (237)	94 Pu Plutonium (244)	95 Am Americium (243)	96 Cm Curium (247)	97 Bk Berkelium (247)	98 Cf Californium (251)	99 Es Einsteinium (252)	100 Fm Fermium (257)	101 Md Mendelevium (258)	102 No Nobelium (259)	103 Lr Lawrencium (262)

Vanadium in biology

- **Vanadium** is found as an ultratrace element although the biological role in higher organisms has not been well defined.
- Deficiency symptoms have not been described. (however **essential** to growth and development of some animals).

Concentration: $<10^{-8}\text{M}$

In Man body pool: $100\mu\text{g}$

Vanadium is multivalent but in physiological type environment (pH 3-7, aerobic, ambient temp.) +4 and +5 dominate.

Vanadium in blood plasma exists in both oxidation states, balanced by oxygen tension and the presence of endogenous reducing agents such as ascorbate and catecholamines. Physiological vanadium is largely protein bound (as are many other trace elements): **to transferrin in plasma**, to **hemoglobin in erythrocytes**, and to **glutathione** or other low-molecular-weight compounds intracellularly. The redox state of vanadium, whether **+ 4 as vanadyl**, or **+5 as vanadate**, depends on ligands, pH, and solute concentration. The majority of intracellular vanadium appears to be present as vanadyl, bound to small molecules or proteins, especially those containing thiol group

Vanadium (V): generally present as orthovanadate (mixture of $[\text{HVO}_4]^{2-}$ and $[\text{H}_2\text{VO}_4]^-$).

Vanadium(IV): present as vanadyl ion, VO^{2+} .

In blood plasma it exists in both oxidation states balanced by oxygen tension and reducing agents (e.g. catecholamine).

Diabetes

Type I: insulin production drops (usually seen in children)

Type II: tissue insensitivity to insulin leads to overproduction and requires insulin enhancing drugs.

Why vanadium?

Ortho-phosphate and ortho-vanadate are analogous



initially studied as a transition state analogue for kinases (which puts phosphates on to substrates)

Insulin mimetics

What does insulin do?

Insulin is a signaling hormone with numerous regulatory roles, including uptake of glucose, amino acids, and fatty acids for storage as, respectively, glycogen in muscle and liver, proteins in muscle, and triglycerides in adipose tissue. Insulin also serves to counteract catabolic hormones, whose function is the mobilization of these molecular forms of stored energy. Insulin is not orally active.

In diabetes, glucose uptake into peripheral tissues such as skeletal muscle and fat is impaired, and glucose utilization in the energy-dependent processes within cells is abnormal. The normal uptake and metabolism of glucose in nondiabetic individuals is initiated by a series of intracellular reactions known as the insulin signalling cascade.

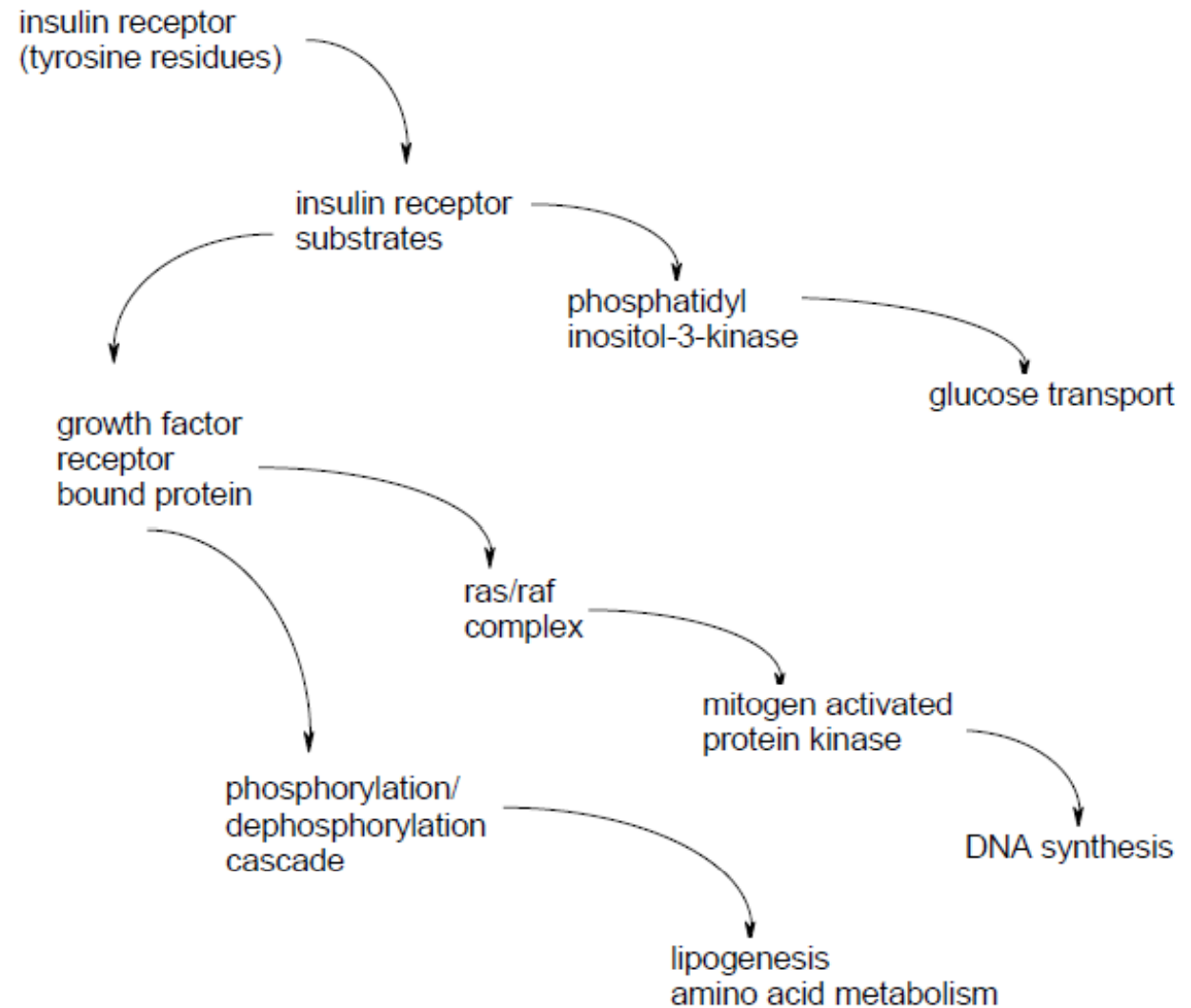
Insulin mimetics

What does insulin do?

Stimulates glucose uptake and oxidation,
and glycogen synthesis.

Vanadium compounds have been known to
mimic the above effects of insulin. They
can be orally active.

People with diabetes have impaired glucose uptake into peripheral tissues such as skeletal muscle and fat. Normal uptake and metabolism of glucose is initiated by a series of intracellular reactions known as the insulin cascade.



35 different insulin like effects can be ascribed, usually as vanadate, *in-vitro*.

The first *in-vivo* results:

McNeill, *Science* **1985**, 227, 1474.

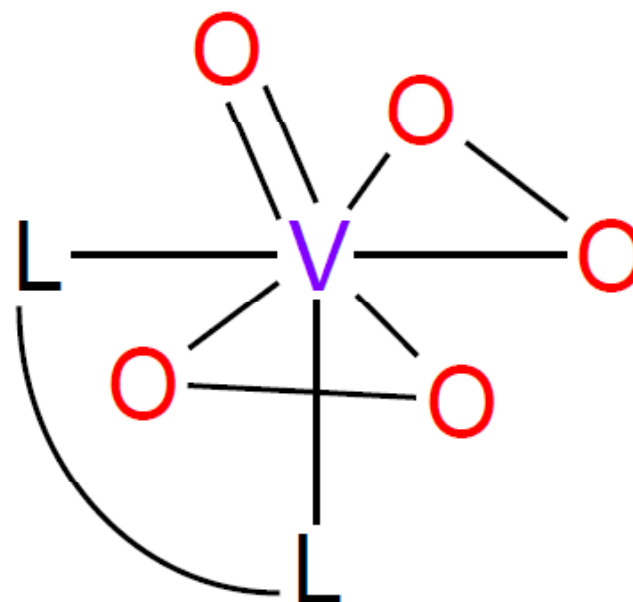
These results were from **sodium vanadate** as the drug.

3 categories:

V(V) compounds

vanadate and peroxide

V(IV)



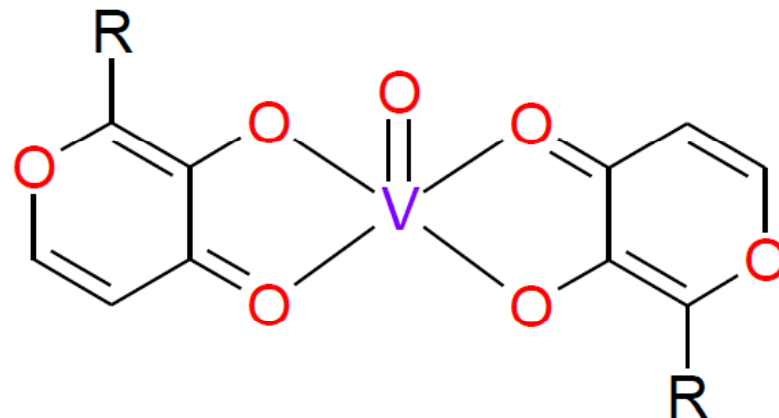
McNeill found vanadate had gastrointestinal tract toxicity, therefore V(IV) was considered.

Initially **vanadyl sulfate** was studied.

Vanadyl sulfate reacted with maltol gives **vanadyl maltolate** (Ken Raymond/ Chris Orvig):

a neutral compound with low molecular weight and high water solubility

- Structure: square pyramidal, oxygen rich for H-bonding to water



Animal model:

STZ diabetic rat- selectively destroys beta cell in the pancreas (gives glucose 2-4 times normal)

Plasma glucose levels were monitored and BMOV given in drinking water.... and it works.

Does it just stimulate insulin secretion?

Control animals had a lowering of insulin level.

Improvement over vanadyl sulfate:

2-3 times as potent.

Reaction chemistry: can oxidise to octahedral V(V) in water but these compounds show no activity.

Bidentate monoprotic ligands.

Methyl/ethyl maltol: food additives.

(Ethyl form is in clinical trials:
phase I and phase II)

What can be done to further determine the mechanism?

Diabetes is a disease of whole organisms, not like cancer and so you really have to work *in-vivo*.

^{48}V biodistribution studies.

Compare ^{48}V BMOV with ^{48}V vanadyl sulfate. [Same dose 2 to 3 times as much in to the animals (2 to 3 times more potent)]

The ligand is acting as a **delivery** vehicle.

Oral:

gastrointestinal tract, circulation

ligand and metal separate.

What happens to V?

Transferrin?

Bone uptake?

Hydroxy Storage or excretion?

Vanadyl transferrin: use EPR

Vanadyl/ +BMOV/+transferrin

(initial experiments suggest that vanadyl binds).

Toxicological Considerations

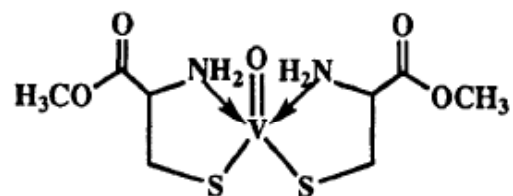
The type of toxicity most often associated with oral vanadium treatment is gastrointestinal, indicated by diarrhea and subsequent dehydration. It has been suggested that **vanadate is perhaps not as well tolerated as vanadyl**; however, differences may be slight.

A number of studies showed an unfavorable toxicological profile of vanadium regardless of the salt administered, whether sodium metavanadate, sodium orthovanadate or vanadyl sulfate, with an increased incidence of mortality and the accumulation of vanadium in tissue

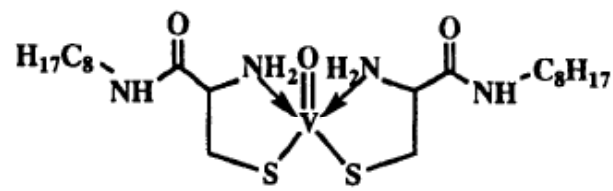
...BUT...

Intraperitoneal administration of the iron chelator tiron with oral vanadate in STZ-diabetic rats **lowered the accumulation of vanadium in several organs but did not diminish the anti-diabetic efficacy of vanadate**. However, a one-year toxicology study involving vanadyl sulfate at doses of 0.16-0.71 mmol kg⁻¹ day⁻¹ showed not only normalized plasma glucose and lipid levels in treated STZ-diabetic rats, but also no acceleration in the development of morphological abnormalities in a variety of organs (by histopathological tests) and no outstanding changes in hematological parameters.

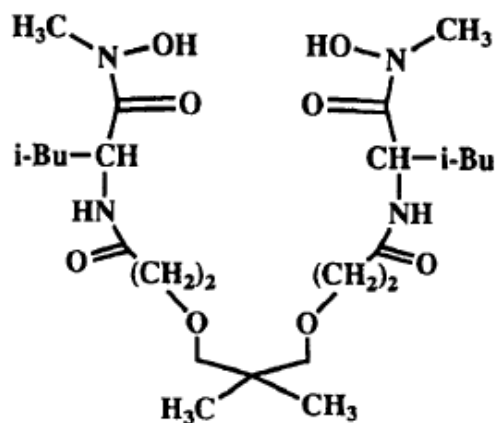
Overall, mortality was 19% in the vanadyl-treated diabetic rats, compared with 60% in the untreated diabetic rats.



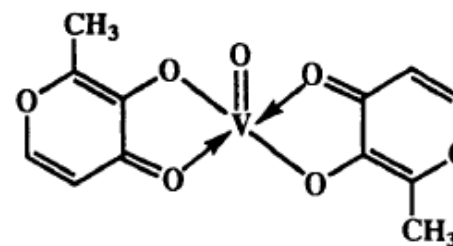
Vanadyl cysteine methyl ester



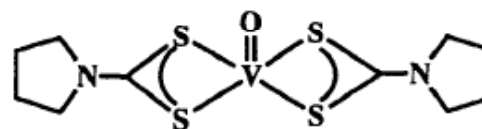
Naglivan



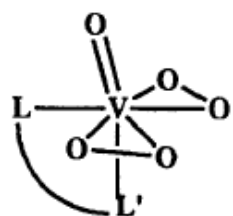
RL-252



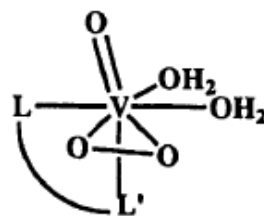
BMOV



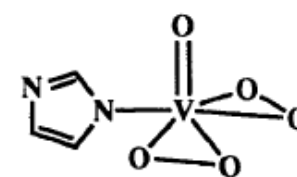
V-P



$[\text{VO}(\text{O}_2)_2(\text{L}-\text{L}')]\text{B}^-$
Ligandoxobis(peroxo)-
vanadate(V)



$[\text{VO}(\text{O}_2)(\text{H}_2\text{O})_2(\text{L}-\text{L}')]\text{B}^-$
Ligandoxoperoxo-
vanadium(V)



$[\text{VO}(\text{O}_2)_2(\text{im})]\text{B}^-$
Imidazoleoxobisperoxo-
vanadate(V)

Representative insulin-mimetic coordination complexes of vanadium(IV) and (V)

Future possibilities:

conjugate to known insulin enhancing drug.

Key point:

oral absorption can be improved
with the right kind of ligand.

...Diabetes is characterized by insulin deficiency or insulin resistance.

Because insulin cannot be absorbed intact following oral administration and must be administered parenterally, available therapies are cumbersome at best. Determining a therapeutic dosing regimen without significant toxicity for orally administered vanadium compounds would present a significant advance over currently available treatments.