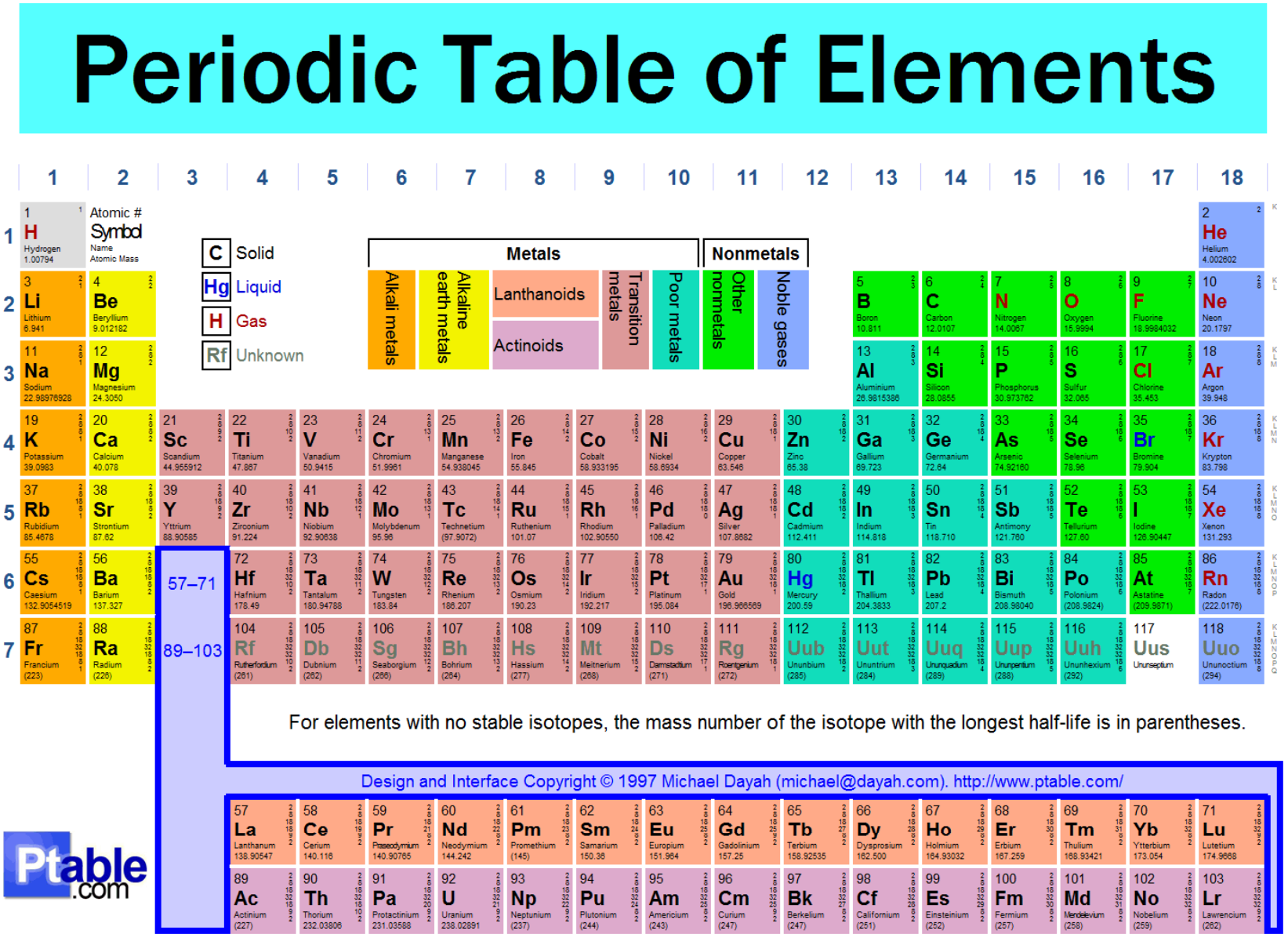
Vanadium Compounds as Possible Insulin Modifiers…



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: $<10^{-8}$M

In Man body pool: 100µg

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 $[HVO_4]^{2-}$ and $[H_2VO_4]^-$).

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

$$[PO_4]^{3-} \equiv [VO_4]^{3-}$$

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.

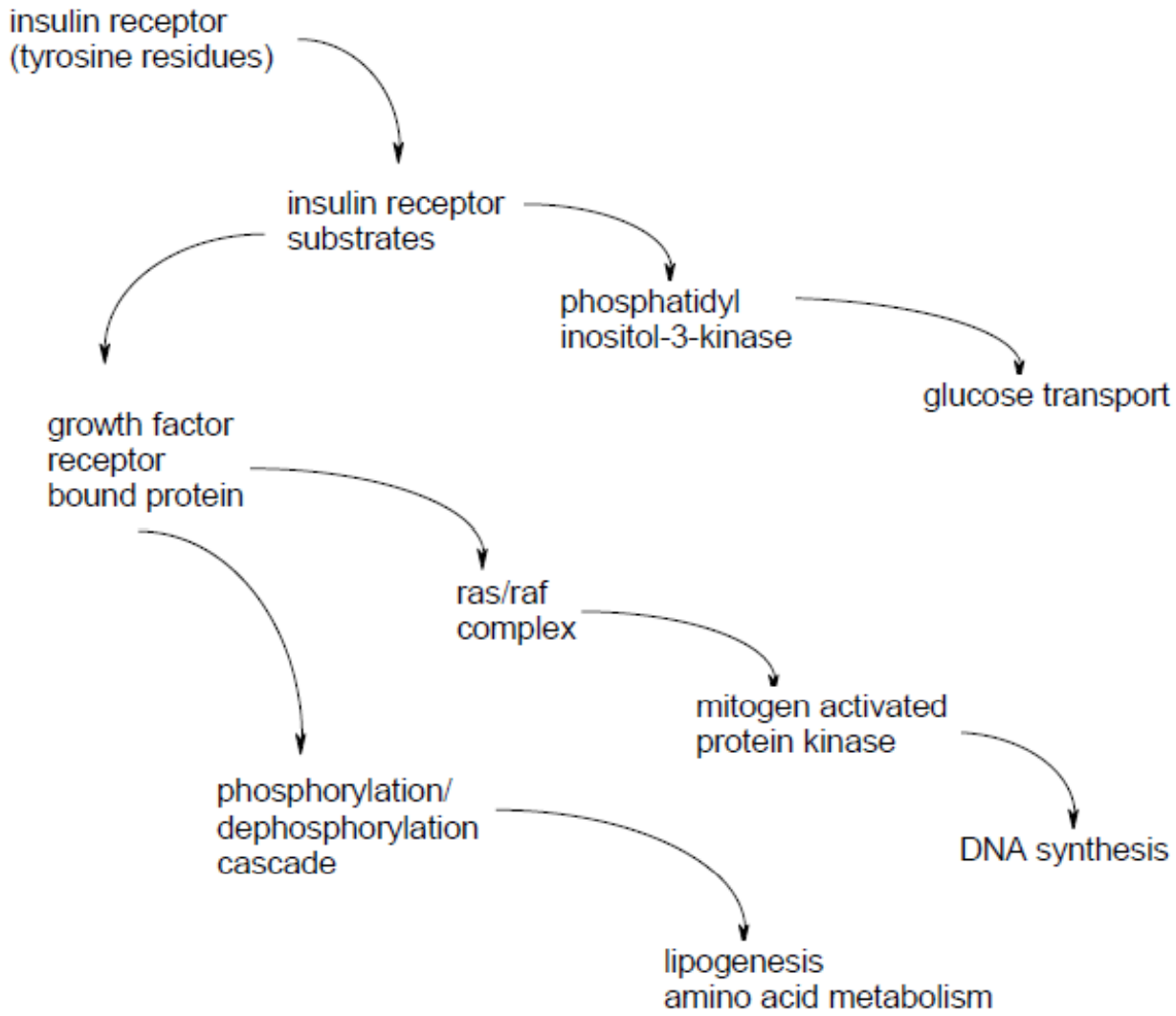
Insulin mimetics

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.

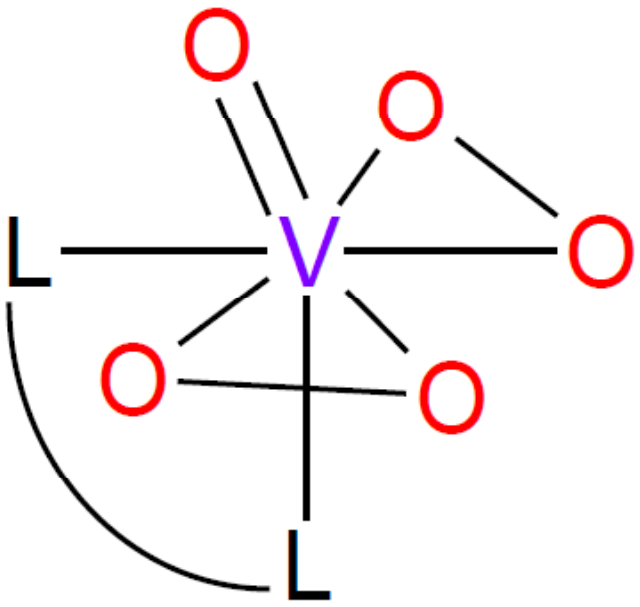
These results were from sodium vanadate as the drug.

3 categories:

V(V) compounds

vanadate and peroxide

V(IV)



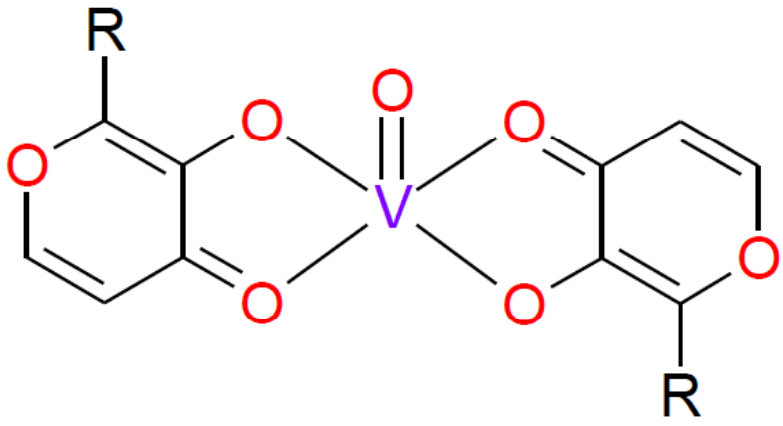
McNeill found vanadate had gastro-intestinal tract toxicity, therefore V(IV) was considered.

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

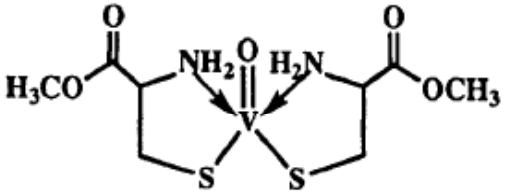
The type of toxicity most often associated with oral vanadium treatment is gastrointestinal, indicated by diarrhea and subsequent dehydration. It has been suggested that vanadate is perhaps not as well tolerated as vanadyl; however, differences may be slight.

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

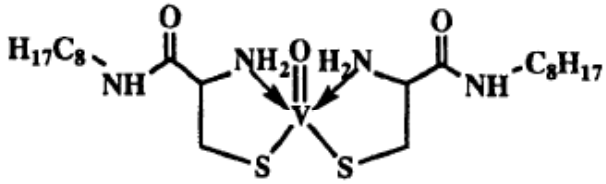
...BUT...

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.

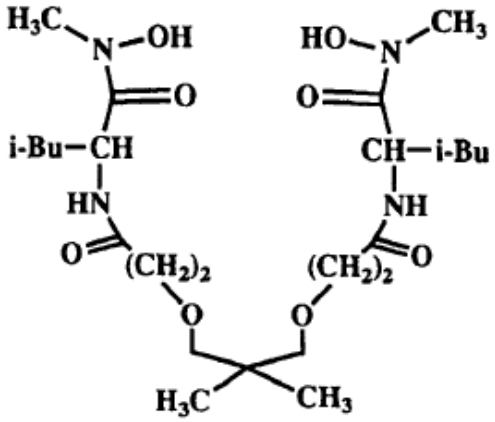
Overall, mortality was 19% in the vanadyl-treated diabetic rats, compared with 60% in the untreated diabetic rats.



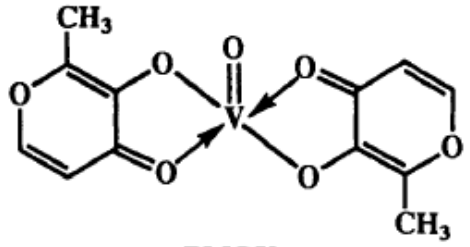
Vanadyl cysteine methyl ester



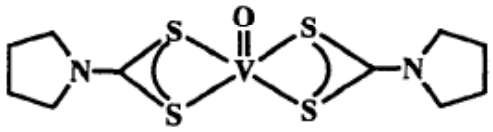
Naglivan



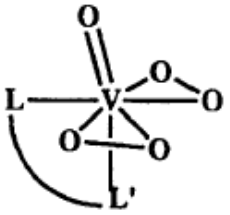
RL-252



BMOV

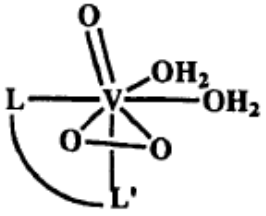


V-P



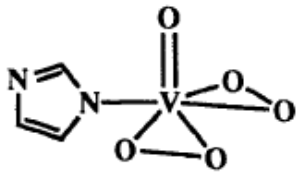
$[VO(O_2)_2(L\text{–}L')]^{n-}$

Ligandoxobis(peroxo)-vanadate(V)



$[VO(O_2)(H_2O)_2(L\text{–}L')]^{n-}$

Ligandoxoperoxo-vanadium(V)



$[VO(O_2)_2(im)]^-$

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.