# Insulin-Mimetic Vanadium IV/V Complexes

Natasha H. Yeung Inorganic Literature Seminar October 21, 2004

Diabetes mellitus is a disease where the body either does not produce insulin (Type I diabetes) or the body cannot use insulin properly (Type II diabetes). Insulin is a hormone that signals the cellular uptake of glucose for metabolism. Since 1899, vanadium salts have been used to treat diabetes. However, it was not until 1980 that the insulin-mimetic effect of vanadium was discovered.[1,2]

The insulin-mimetic effect of vanadium compounds refers to the ability of vanadium salts and vanadium complexes to lower blood glucose levels by activating glucose uptake by cells for metabolism. Although simple vanadium salts such as $NaVO_3$ and $VOSO_4$ can lower blood glucose levels in rats and humans, numerous studies have shown that organic vanadium complexes are less toxic and several times more effective in lowering blood glucose levels.[2] As such, much research has gone into studying the active form of insulin-mimetic vanadium complexes, their pharmacological properties and their transport to target sites in the body by the blood stream.

Both V(IV) and V(V) complexes show insulin-mimetic effects. Vanadium(V) oxoanions and complexes are known to inhibit protein tyrosine phosphatases (PTPs).[3] Inhibition of PTPs keeps the insulin receptor phosphorylated, allowing glucose transport into the cell (Figure 1). Under physiological conditions, vanadium complexes can interconvert between V(IV) and V(V), and V(V) can inhibit PTPs.[4] Moreover, V(IV) can activate the recruitment of glucose transporters to the cell membrane, thereby increasing glucose cell uptake and lowering blood glucose levels.[5]

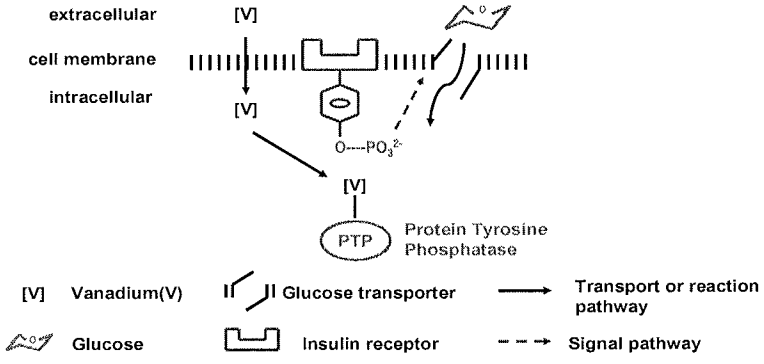


**Figure 1:** Proposed mechanism of vanadate insulin-mimetic activity. Phosphorylation of tyrosine on the insulin receptor signals cellular glucose uptake by glucose transporters, lowering blood glucose levels. Phosphoester bond cleavage by PTP shuts down glucose uptake. Vanadium(V) can inhibit PTP. Adapted from ref 4.

Insulin-mimetic vanadium complexes contain a variety of coordination modes. The most effective insulin-mimetic vanadium complexes are neutral V(IV) compounds of

the general formula $VO[L_2]^0$, where L represents a ligand such as maltolate, aminothiophenolate and acetylacetonate (Figure 2). Vanadium(V) complexes usually exist as tridentate complex anions (eg. VO[dipic]$^-$, dipic=dipicolinate, Figure 2).[6]

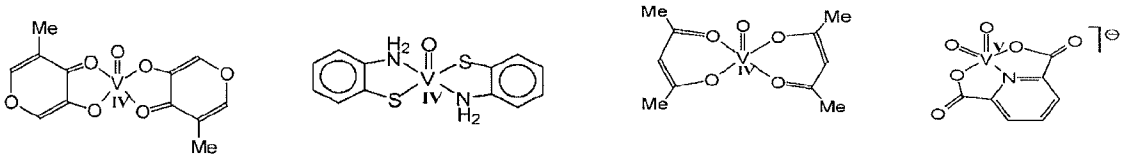


**Figure 2:** Insulin-mimetic V(IV) and V(V) complexes.

Peters *et al.*[7] used X-ray crystallography to show that administration of the V(IV) complex $VO(malto)_2$ yielded unchelated vanadate $[VO_4]^{3-}$ in the active site of a PTP, supporting PTP inhibition by vanadate as the mechanism of insulin-mimetic activity. Administration of [ethyl-1-$^{14}$C]$VO(malto)_2$ *in vivo* resulted in a vanadium uptake curve that did not coincide with $^{14}$C uptake.[8] Both of these observations provide evidence of vanadium complex ligand dissociation during transport to target cells.

The pharmacological properties of forty-one different vanadium complexes with different coordination modes and oxidation states were studied by Rehder and coworkers.[6] Uncomplexed vanadate and sulfur coordination modes were the most toxic. While ON ligation seemed to afford the most efficient glucose uptake in cells, there was no striking correlation between the ligand system and insulin-mimetic potency.

Vanadium complex transport into red blood cell (RBC) membranes was studied by Yang *et al.*[9] Oxidation of the neutral V(IV) complexes $VO(acac)_2$ and $VO(malto)_2$ to vanadate anions inhibited vanadium accumulation in RBCs in the presence of the anion channel blocker DIDS (4,4'-diisothiocyano-2,2'stilbene disulphonate). Interaction of $VO(acac)_2$ and $VO(malto)_2$ with cell membranes stabilized the V(IV) oxidation state.

The mode of vanadium complex transport through the blood stream was studied by EPR binding studies of $VOSO_4$ and $VO(malto)_2$ with blood serum proteins immunoglobulin (IgG)[10], transferrin (Tf)[11] and human serum albumin (HSA).[11] No binding was observed between $VOSO_4$ or $VO(malto)_2$ and IgG. The $VOSO_4$-Tf binding product is identical to the $VO(malto)_2$-Tf binding product, suggesting that ligand dissociation of $VO(malto)_2$ occurs before binding to Tf. The protein complex formed between $VOSO_4$ and HSA is different from that formed by $VO(malto)_2$ and HSA. Therefore, HSA and Tf can transport vanadium compounds to target sites.

Thus, continued advances in the field of insulin-mimetic vanadium IV/V complexes and their chemistry will hopefully lead to their use in the treatment of diabetes.

## References

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