SCIENTIFIC VERSES

Vanadate Complexes: The next generation of insulin mimetics

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Diabetes mellitus (DM) is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels or hyperglycemia. Diabetes develops due to a diminished production of insulin (in Type 1; Insulin Dependent Diabetes Mellitus; IDDM) or resistance to its effects (in Type 2; Non-insulin Dependent Diabetes Mellitus (NIDDM) and gestational). Both lead to hyperglycemia, which largely causes the acute signs of diabetes: excessive urine production, resulting compensatory thirst and increased fluid intake, blurred vision, unexplained weight loss, lethargy, and changes in energy metabolism. It also results in many serious secondary complications such as atherosclerosis, microangiopathy, renal dysfunction and failure, cardiac abnormality, diabetic retinopathy and ocular disorders. DM has been stated as the 'most common non-communicable diseases' globally. At present India tops the list as the 'diabetic capital' of the world with 35.5 million people afflicted with the disease.

Treatment of this metabolic disorder is dated back to the discovery of insulin by Banting and Best. Management of Type 1 DM still involves administration of insulin as subcutaneous (s.c.) injections. Considerable research has been carried out in the development of new insulin analogues with higher therapeutic duration with structural stability. Type 2 involves reduced insulin sensitivity with lessened insulin secretion. Treatment of Type 2 DM typically involves therapeutic agents such as organic molecules of the classes of sulfonyl ureas, thiazolidine diones, alphaglucosidase inhibitors and peptides. Since the discovery of glucose lowering activity of vanadates in 1980, the development of vanadium complexes as insulin mimetics has been under investigation.

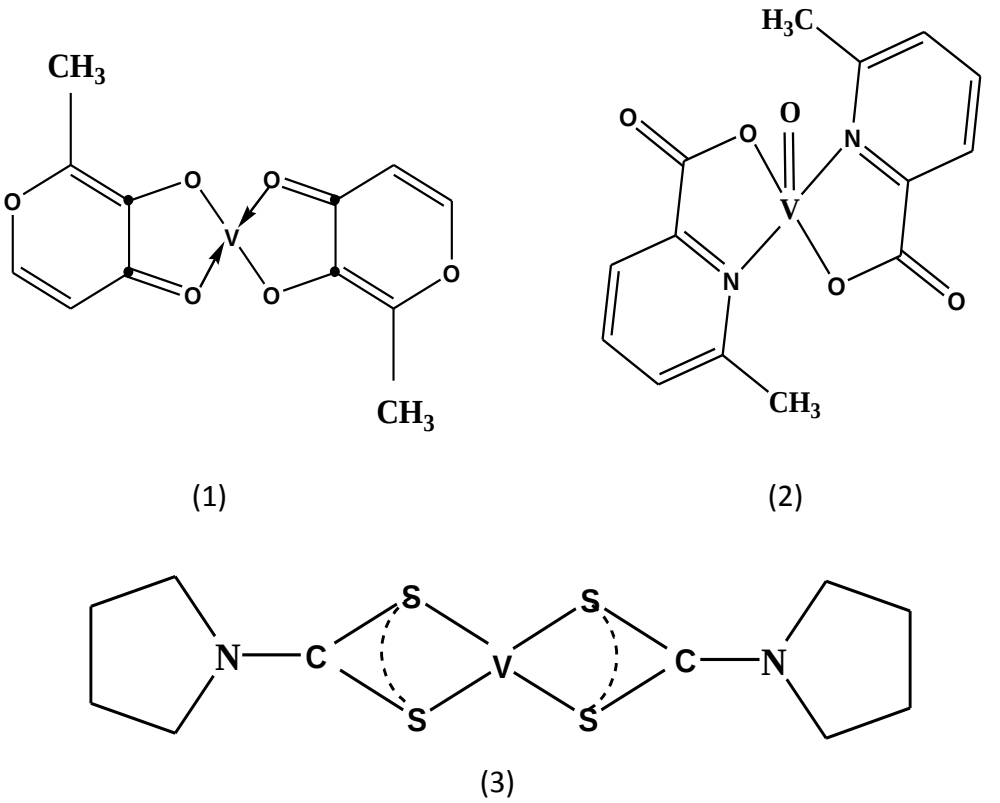

Fig 1. Vanadium (IV) complexes with reduced toxicity.

Vanadium has 4 oxidation states of which vanadium (IV) and (V) occur commonly in biological systems while vanadium (III) has been identified only in tunicates. Vanadate is easily reduced to the (IV) state by common reducing agents under physiological conditions. In aqueous solutions, most of the reduced vanadium species are found to exist as vanadyl $[VO_4]^{2+}$ which forms strong complexes with a variety of ligands such as proteins.

Quite a few physiological effects of vanadium are mainly attributed to the Structural Similarity of vanadate(V) and phosphate ions. The ability of vanadium to adopt higher coordination numbers makes it a useful tool for structural characterization of phosphate metabolizing enzymes. One Important example is the inhibitory action of vanadate on phosphotyrosine phosphatase, an enzyme of the insulin receptor system. Unlike insulin, vanadate does not seem to stimulate the autophosphorylation and endogenous tyrosine phosphorylation of insulin receptor kinase or other intracellular proteins either directly or by virtue of its known inhibitory effect on protein phosphotyrosine phosphatase. Results from many studies support a model in which vanadate activates glucose metabolism by either utilizing an alternative (Insulin-independent)

cascade or bypassing the early events of the Insulin-dependent cascade. Both these possibilities are of clinical importance because early insulin events may become defective as a result of severe hyperinsulinemia and may contribute to insulin resistance. Alternative pathways by which vanadate may stimulate glucose metabolism, include increasing intracellular Ca^{2+} levels and/or regulating intracellular and intra-vesicular pH. In addition, vanadate restores tissue responsiveness to insulin and hepatic glycogen levels and activates new synthesis of key enzymes for carbohydrate metabolism. It was also found to affect lipid synthesis and stimulate glycogen synthase as well as mitogenic activities like cell replication and DNA and protein synthesis.

Vanadate ions were found to mimic most of the rapid actions of insulin in various cell types. The complete mechanism by which vanadate mimics the actions of insulin is still obscure. The most extensively characterized of these effects is the potent inhibitory action of vanadate on the (Na^+/K^+) ATPase activity (EC 3.6.1.4) in both purified enzyme preparations and intact cells. Several of the observed pharmacologic effects of vanadate, including its natriuretic action and its antagonistic action on the short circuit current across epithelial tissue, have been attributed to a vanadate-induced inhibition of the (Na^+-K^+) ATPase. Studies on bone cells have also shown regulation of alkaline phosphatase activity and stimulation of Na^+/K^+ pump and glucose transport similar to insulin.

Various vanadium complexes have been synthesized with different organic species since the establishment of its anti-diabetic potential to reduce the toxicity associated with the metal. The most successful vanadium complexes contain organic ligands that are reasonably soluble in both organic and aqueous environments and therefore, easily uptaken by cells and are compatible with human metabolism. Most of the compounds reported contain bidentate ligands and have a 1:2 metal-to-ligand stoichiometry. The maltol ligand (3-hydroxy-2-methyl-4-pyrone) is particularly desirable because, in addition to its favorable chemical properties, it is already an approved food additive. Bis(maltolato)oxovanadium(IV) (1) was successful in lowering blood glucose in diabetic animals with no evidence of toxicity for over 6-month administration. Picolinic acid (2-pyridinecarboxylic acid) is another important ligand because it alone has a low level of insulin-like properties and is formed in the body as an intermediate in the tryptophan degradation pathway. Recent organic vanadium complexes have been designed as polydentate ligands with 1:1 stoichiometry, which should reduce the potential for side product formation. One successful ligand is dipicolinic acid because of its low toxicity and its amphophilic nature. 3-Pyridinecarboxylic acid (commonly known as niacin or vitamin B_3), which is closely related to dipicolinic acid, is a precursor for the coenzyme NAD and is an essential dietary component. Dipicolinic acid (2,6-pyridinedicarbo-xylic acid) is furthermore related to 2,3-pyridinedicarboxylic acid (quinol-inic acid), which is also an inter-mediate in the tryptophan degradat-ion pathway and is a precursor for NAD. A number of other vanadium (+4 oxidation state) derivatives have been prepared due to its reduced toxicity in comparison to (+5) compounds. Bis(methylpicolinato)oxovanadium (IV) (2) showed a dose dependent decrease in FFA synthesis. Glucose lowering was found to be maintained during oral administration for 14 days and extended for a period of 30 days post-feeding with gain in body weight. A number of thiolated ligands have also been tested for their insulin mimetic potential. One of the tested compounds is a sulphur ligand-vanadyl complex, vanadyl-cysteine methyl ester. Among the various vanadyl complexes with –O, –N and –S coordination modes, the bis(pyrrolidine-N-carbodithiato)oxovanadium(IV) complex (3) was found to show the strongest insulin-mimetic activity. Significant mortality was observed at doses 10 times that needed for glucose lowering in this series in vivo. Of all the compounds tested the maltol derivative (1) showed a maximum lowering in glucose levels on oral administration with least toxicity.

To conclude, from a clinical perspective, evidences are required to evaluate the potential of vanadate complexes for prolonged treatment of DM. This includes searching new agents that potentiate its insulin mimetic actions in vitro and in vivo with better physico-chemical properties and physiological stability along with reduced toxicity. Long-term toxicity studies in experimental animals are also crucial for the further development of these agents.

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