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EDITORIAL

Vanadium: A Rather Unknown Trace Element of Our Body and a Possible Therapeutic Agent in the Future

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Vanadium is a transition metal with atomic number 23 and atomic mass 50.94, appearing in the 4th period and the 5th group of the periodic table of elements. It is the 21st most abundant element in earth's crust. The soil in volcanic areas as well as oil products are rather rich in vanadium. It is also the 2nd most abundant transition metal in seawater (30-35 nM), while in drinkable water its concentration is considerably lower (10 nM).[1] Vanadium is present in several foods, mainly mushrooms, shellfish, black pepper, certain herbs (e. g. parsley, dill), commodity groups (grains and grain products, sweeteners, infant cereals) as well as beer and wine. The usual daily intake of vanadium is estimated as 6-18 μg. Some food supplements contain vanadium, increasing its daily intake by nearly 9 μg.[2]

A major proportion of ingested vanadium is transformed by the alimentary tract enzymes to vanadium oxyhydroxide ($VO(OH)_2$) which has low water solubility and so is poorly absorbed. On the contrary, vanadate -the pentavalent vanadium ion- is much more absorbable from mucosal membranes of the alimentary and respiratory tract and so it may cause toxicity if present in the environment, as in some industrial working places or old houses with lead water pipe systems.[1] Burning fossil fuels (coal or oil) results in the production of vanadium oxides that can be absorbed to dust particles, enter the human respiratory tract and be harmful for the health. The concentration of vanadium in the air of urban areas is 2-3fold higher than in rural ones. In high concentrations (up to 35 mg/m^3) it is considered by the U.S. National Institute for Occupational Safety and Health as highly toxic or even lethal.[3]

In human blood, vanadium binds to serum proteins and is rapidly transferred to several organs, including the brain. It is mainly eliminated by the kidneys and, as expected, is accumulated in patients with renal failure.[4] As an atom, vanadium shares a few common characteristics with phosphorous, but there exists a surprising similarity in the structure of vanadate ion to that of phosphate. This similarity seems to explain their antagonism in several molecules and the ability of vanadate to substitute phosphate in various protein molecules, therefore modifying their function. Some characteristic examples of such a substitution are the apatite of the bones or some enzymes, including phosphatases or kinases. The result of phosphate substitution by vanadate is inhibition of these enzymes and this is a very important mechanism for its biological -therapeutic or toxic- effects.[2]

A physiological role of vanadium has been found in a restricted number of bacteria (e. g. some ocean algae) where it acts as an active center of some enzymes or as electron acceptor in respiration procedures.[2] Some interest in a possible pharmacological role of vanadium in humans has been raised since the end of the 19th century. Up-to-

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date it has been discussed as possibly effective against several metabolic, infectious or malignant diseases but it has not yet been approved in clinical practice.

The most promising field seems to be its possible anti-diabetic effect. Vanadium is believed to exert its action by interfering with the insulin receptor. This is a trans-membrane receptor consisting of two subunits, an extracellular (α) and an intracellular (β). Insulin is connected to the α subunit and this results in the phosphorylation of the tyrosine residues of the β subunit. This phosphorylation gives a signal to the glucose transporter GLUT4 and so glucose enters the cell. Whenever there is insulin insufficiency -either due to defective secretion by the pancreas or to insulin resistance- a protein tyrosine phosphatase present in the cytoplasm dephosphorylates the β subunit and so prevents the activation of GLUT4. Vanadate has the ability to be strongly attached to the protein tyrosine phosphatase molecule and inhibit its action. The result is an increased insulin effect on the cell.

The antidiabetic effect of vanadium was first shown in a study in rats with streptozotocin-induced diabetes which appeared in 1985.[5] Since then, a considerable number of experimental data has shown that vanadium compounds may increase insulin sensitivity, reduce serum glucose in diabetic animals, prevent cardiac complications and improve diabetic nephropathy. Several inorganic and organic vanadium compounds have been studied in order to achieve better bioavailability and less toxicity. Among them, two complex organic compounds, bis (maltolato) oxovanadium (IV) and bis (ethylmaltolato) oxovanadium (IV), seem to be very promising.[6]

One of the first clinical studies on the subject, published in 1996, concerned eight patients with non-insulin-dependent diabetes mellitus who received 50 mg of vanadyl sulfate twice daily for 4 weeks. The drug in this dose was well tolerated, except for temporary gastrointestinal symptoms. Its effect was estimated with several methods, including euglycemic-hyperinsulinemic clamps. There was a 20% decrease in fasting glucose concentration and a decrease in hepatic glucose output during hyperinsulinemia, indicating decreased hepatic insulin resistance.[7] More recent clinical trials in humans showed lower glucose and hemoglobin A_1c values in type 2 diabetic patients and decreased exogenous insulin demands both in type 1 and type 2 insulin-treated diabetics, without any hypoglycemic episodes.[6] It is interesting that such an effect was obtained without increasing C-peptide levels in type 1 diabetics, meaning that insulin excretion was not increased -a fact that would not be expected in these patients whose pancreatic beta cells function is seriously disturbed- but the action of the existing hormone was enhanced.[8] This finding is consistent with the aforementioned possible mode of action of vanadium at cellular level. However, all these studies were performed in limited numbers of patients and need to be further confirmed with more extended projects.

There are also some findings indicating a positive effect of vanadium products in lipid metabolism. In one study, serum cholesterol levels significantly decreased in type 2 diabetic patients by 24% after sodium metavanadate administration.[8] Another in vitro study has shown an insulin-like action of an organic vanadium compound in human adipocytes obtained from overweight women undergoing plastic surgery. It actually inhibited lipolysis and activated glucose transport, thus indicating a possible protective role against lipotoxicity in insulin resistant subjects.[9] An epidemiologic study from China, recruiting 533 vanadium exposed workers and 241 non-exposed workers from a Steel and Iron Group, showed significantly higher levels of HDL-cholesterol and apoprotein A-I as well as lower atherogenic indexes (total cholesterol/HDL-cholesterol, LDL-cholesterol/HDL-cholesterol, and apoprotein B/apoprotein A-I) in the former group. It was concluded that occupational vanadium exposure may offer an antiatherogenic protection.[10] Some other studies have also supported a beneficial effect of vanadium on lipid metabolism.[6]

Organic vanadium compounds have shown neuroprotective effects in several central nervous system injury models. In rats with experimentally induced cervical unilateral contusive spinal cord injury, administration of vanadium offered significant neuroprotection and clinical improvement which was attributed to reduced motor neuron death, increased tissue sparing, and minimized cavity formation.[11]

Several vanadium compounds have been discussed as possibly active against infectious agents. There is some evidence for their effectiveness in cases of parasitic (leishmaniasis, Chagas disease, amebiasis), bacterial (e. g. tuberculosis) and viral (e. g. AIDS) diseases. A suggested mode of action is through formation of radicals, such as superoxide and nitrous oxide. A limited number of studies has shown in vitro antineoplastic effects of complex vanadium compounds against cell cultures from osteosarcoma, renal and cervical cancer.[2]

Another point of interest on vanadium is connected to a possible anti-inflammatory action. The effect of some types of cytokines -which play a crucial role in immunological mechanisms- is dependent on phosphorylation procedures catalyzed by protein tyrosine phosphatases. Vanadium acts as a pan-inhibitor of this enzyme superfamily.[12] This effect might prove useful in preventing adipose tissue inflammation and development of type 2 diabetes in obese subjects. Through the same enzymic inhibition, a complex organic vanadium compound has also been found to inhibit in vitro the formation of d-dimers and prevent hypercoagulation states.[13] So, it has been suggested that because of a combination of antiviral, anti-inflammatory and anticoagulant properties some vanadium compounds should be tried as an additional treatment in patients with a COVID-19 infection.[6]

The introduction of vanadium products in clinical practice, however, has delayed due to references of more serious side

effects than the usual gastrointestinal symptoms, including hepatotoxicity, nephrotoxicity and neurotoxicity. There is a hope that some modifications in the structure of the vanadium compounds or the route of its administration (e.g. through nanoparticles) may significantly reduce its toxicity and permit a better utilization of its pharmacologic abilities.[6]

In conclusion, vanadium seems to have some biologically interesting properties that may prove useful in the future. The most promising fields are enhancement of insulin action and anti-inflammatory activity. The selection of most suitable vanadium compounds together with large and well-constructed clinical trials are the next necessary steps in that effort.

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