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Review

Vanadium and proteins: Uptake, transport, structure, activity and function

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ABSTRACT

Vanadium is an element ubiquitously present in our planet's crust and thus there are several organisms that use vanadium for activity or function of proteins. Examples are the vanadium-dependent haloperoxidases and the vanadium-containing nitrogenases. Some organisms that use vanadium have extremely efficient and selective protein-dependent systems for uptake and transport of vanadium and are able to accumulate high levels of vanadium from seawater, vanabins being a unique family of vanadium binding proteins found in ascidians involved in this process. For all of the systems a discussion regarding the role of the V-containing proteins is provided, mostly centered on structural aspects of the vanadium site and, when possible or relevant, relating this to the mechanisms operating. Phosphate is very important in biological systems and is involved in an extensive number of biological recognition and bio-catalytic systems. Vanadate(V) is able to inhibit many of the enzymes involved in these processes, such as ATPases, phosphatases, ribonucleases, phosphodiesterases, phosphoglucomutase and glucose-6-phosphatase, and it appears clear that this is closely related to the analogous physicochemical properties of vanadate and phosphate. The ability of vanadium to interfere with the metabolic processes involving Ca^{2+} and Mg^{2+}, connected with its versatility to undergo changes in coordination geometry, allow V to influence the function of a large variety of phosphate-metabolizing enzymes and vanadate(V) salts and compounds have been frequently used either as inhibitors of these enzymes, or as probes to study the mechanisms of their reactions and catalytic cycle. In this review we give an overview of the many examples so far reported, also disclosing that vanadate(IV) may also have an equally efficient inhibiting effect. The prospective application of vanadium compounds as therapeutics has also been an important topic of research. How vanadium may be transported in blood and up-taken by cells are particularly relevant issues, this being mainly dependent on transferrin (and albumin) present in blood plasma. The thousands of studies reported on the effects of vanadium compounds reflect the complexity of the interactions occurring. Although it is not easy to anticipate/determine if a particular effect observed in a test tube or *in vitro* is also going to take place *in vivo*, it is clear that vanadium ions may interfere with many metabolic processes at many distinct levels. Emphasis is given on structural and functional aspects of vanadium–protein interactions relevant for vanadium binding and/or for clarification of role of the metal center in the reaction mechanisms. The additional knowledge that the presence of vanadium can change the action of a protein, other than simply inhibiting it, may also be important to understand how vanadium affects biological systems. This possibility, together with the vanadate–phosphate analogy further potentiates the belief that vanadium probably has relevant functions in living beings, which may involve interaction or incorporation of the metal ion and/or its compounds with several proteins.

1. Introduction

Many metal ions have a general tendency to interact with biomolecules, therefore it is not surprising that natural evolution has incorporated some of them into performing a wide variety of tasks and playing crucial roles in organisms [1,2]. Vanadium is a transition metal that is widely distributed in soil, crude oil, water and air and its compounds may have oxidation states ranging from −3 to +5. Being ubiquitously present in our planet's crust it is thus not surprising that it also found roles in biological systems namely as an essential element for many living beings.

Only V^{III}-, V^{IV}- and V^{V}-species are of biological relevance and nature has evolved several enzymatic systems using vanadium in their active sites as relevant components for their function including vanadium-dependent haloperoxidases, nitrogenases and vanabins.

1.1. Vanadate(V)-phosphate analogy

Phosphate is very important in biological systems and is involved in an extensive number of biological recognition and bio-catalytic systems. It is known that vanadate(V) and phosphate participate in similar reactions. Vanadium inhibits several ATPases with different efficiency [3]. Moreover, vanadium and vanadium compounds also inhibit different proteins such as phosphatases (alkaline phosphatases, acid phosphatases and tyrosine-protein phosphatases) [4,5], ribonucleases, phosphodiesterases, phosphoglucomutase and glucose-6-phosphatase [5]. Inhibition can be very strong and the enzyme-inhibitor constant (K_i) values range from 10^{-5} to 10^{-7} M [6]. The ability of vanadium to inhibit these enzymes is closely related to the physicochemical properties of vanadate(V) and phosphate (see below), with vanadate(V) showing a greater flexibility in this coordination geometry.

In most cases, enzyme activation by vanadium follows indirect mechanisms. Vanadium can stimulate the enzyme activity through the formation of complexes with ligands that resemble the structure of physiological substrates. For instance, the glucose-6-phosphate dehydrogenase is activated by vanadate(V). Another mechanism of activation or inhibition involves the phosphorylation of tyrosine residues. Vanadate(V) also forms esters with Tyr residues mimicking their phosphorylation process, with a great impact in several biological events and similar actions have been proposed also for $V^{IV}O^{2+}$.

Monovanadate(V) and phosphate are structural analogues (see Fig. 1). Besides monovanadate(V) being structurally similar to phosphate, the acid–base equilibria operating and other types of reactions (*e.g.* V and/or P 'ester' formation) are also comparable. Nevertheless, there are some structural and pK_a differences, namely the relative stability of 5-coordinate trigonal–bipyramidal structures or intermediates, bound in protein active sites, differs for vanadate and phosphate [5].

From a geometrical point of view, the two anions are not much different and vanadate(V) is a competitor in sites commonly occupied by phosphate. However, there are also significant differences: