Coordination Chemistry Reviews 255 (2011) 2178–2192

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

How environment affects drug activity: Localization, compartmentalization and reactions of a vanadium insulin-enhancing compound, dipicolinatooxovanadium(V)

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ARTICLE INFO

Article history:
Received 3 November 2010
Accepted 19 January 2011
Available online 27 January 2011

Keywords:
Vanadium
Membrane interactions
Compartmentalization
Oxidation by vanadium complexes
Drug uptake
Insulin-enhancing
Toxicology
Mode of action
Intermembrane space
Chemical and biological transformations
Environmental effects
Hydrophobic environment
Oxovanadium(V) dipicolinate
Vanadate
Dipicolinic acid
2,6-Pyridinedicarboxylic acid

ABSTRACT

The chemical and biological properties of a simple and traditional V(5+) coordination complex, dipicolinatooxovanadium(V) (abbreviated $[VO_2dipic]^-$), are described in order to present a hypothesis for a novel mode of action wherein a hydrophobic membrane environment plays a key role. Specifically, we propose that the compartmentalization and both chemical and biological transformations of vanadium-complexes direct whether beneficial or toxic effects will be observed with this class of compounds. This concept is based on the formation of high levels of uncontrollable reactive oxygen species (ROS) from one-electron reactions or alternative events possibly initiated by a two-electron reaction which may be directly or indirectly beneficial by reducing the high levels of ROS. The properties of dipicolinatooxovanadium(V) compounds in aqueous solution (D.C. Crans, et al., Inorg. Chem. 39 (2000) 4409–4416) are very different from those in organic solvents (S.K. Hanson, et al., J. Am. Chem. Soc. 131 (2009) 428–429) and these differences may be key for their mode of action. Since other vanadium complexes are known to hydrolyze upon administration, the low stability of the aqueous complex requires entrapment in hydrophobic environments for such a complex to exist sufficiently long to have an effect. The suggestion that the environment changes the reactivity of the compounds is consistent with the very different modes of action by which one complex act. In short, a novel hypothesis is presented for a mode of action of vanadium compounds based on differences in properties resulting from environmental conditions. These considerations are supported by recent evidence supporting a role for membranes and signal transduction events (D.A. Roess, et al. Chem. Biodivers. 5 (2008) 1558–1570) of the insulin-enhancing properties of these compounds.

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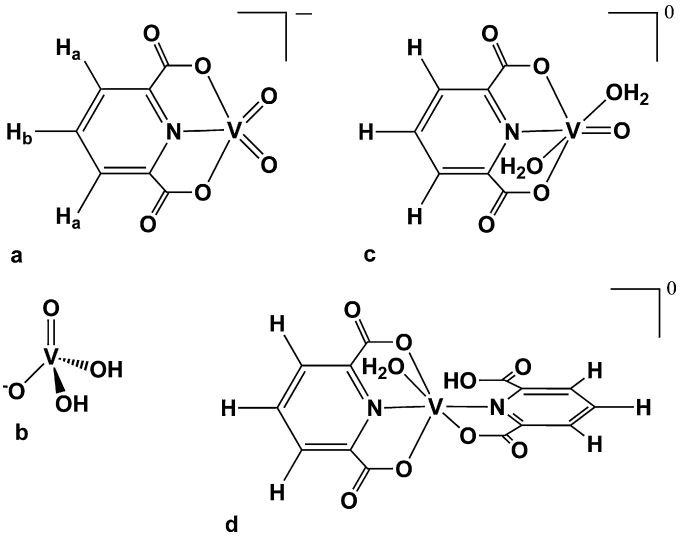
doi:10.1016/j.ccr.2011.01.032

1. The action of vanadium compounds can be beneficial and malicious; could chemical and biological transformation be related to function?

Design, efficacy, and mode of action are defining properties of all drugs, including metal-containing drugs [1,2]. Drug efficacy is dependent on absorption, distribution, metabolism and excretion, properties that are disease- and organism-specific, and ultimately dictate mechanism of action. The action of a drug generally describes how the product impacts cellular function resulting in the reduction of a disease state. Drug design is often linked to its function and cellular uptake mechanism to facilitate efficacy. Pharmacokinetic studies characterize distribution and transformations that occur during drug function. Since the success of a drug is often a balance between beneficial and toxic concentrations, the greater the difference between therapeutic and toxic levels, the better. Targeting improves the benefit of a drug due to the inherent reduction in risk of toxicities in a host (i.e. by lowering potential systemic levels and the attainment of toxic levels) while still achieving therapeutic results. Therefore, for the successful development and administration of any drug, detailed information on its transformation and localization *in situ* is critical. Herein, we review available evidence regarding the biotransformation [3–9], localization [4,5,8,10–15], and toxicity [8,16,17] of one vanadium(V)-containing insulin-enhancing agent, 2,6-pyridinedicarboxylato-oxovanadium(V) ($[VO_2dipic]^-$; Scheme 1) [3–7,9,12,18–23], reconciling its beneficial and malevolent effects in cells and in diabetic animals with its chemical properties.

Vanadium (abbreviated as V) compounds, where salts are considered charged complexes, are particularly sensitive to their environment [24–27]. Importantly, various forms of V exert different biological activities [24,28–31]. It is well known that V salts and compounds undergo biotransformations (summarized in Fig. 1). Undoubtedly, the degree to which pentavalent V(5+) is reduced to tetravalent V(4+) is an important factor influencing how much metal/agent is transported into/out of cells, the magnitude of detoxification reactions initiated, how extensively superoxide



Scheme 1. The structures of the (a) oxovanadium(V) dipicolinate ($[VO_2dipic]^-$) (b) vanadate, the V(5+) salt diprotonated anion, $H_2VO_4^-$ (c) oxovanadium(IV) dipicolinate $[VOdipic(H_2O)_2]$ (d) hydrogen bis(dipicolinato)vanadium(III) $H[V(dipic)_2H_2O]$.

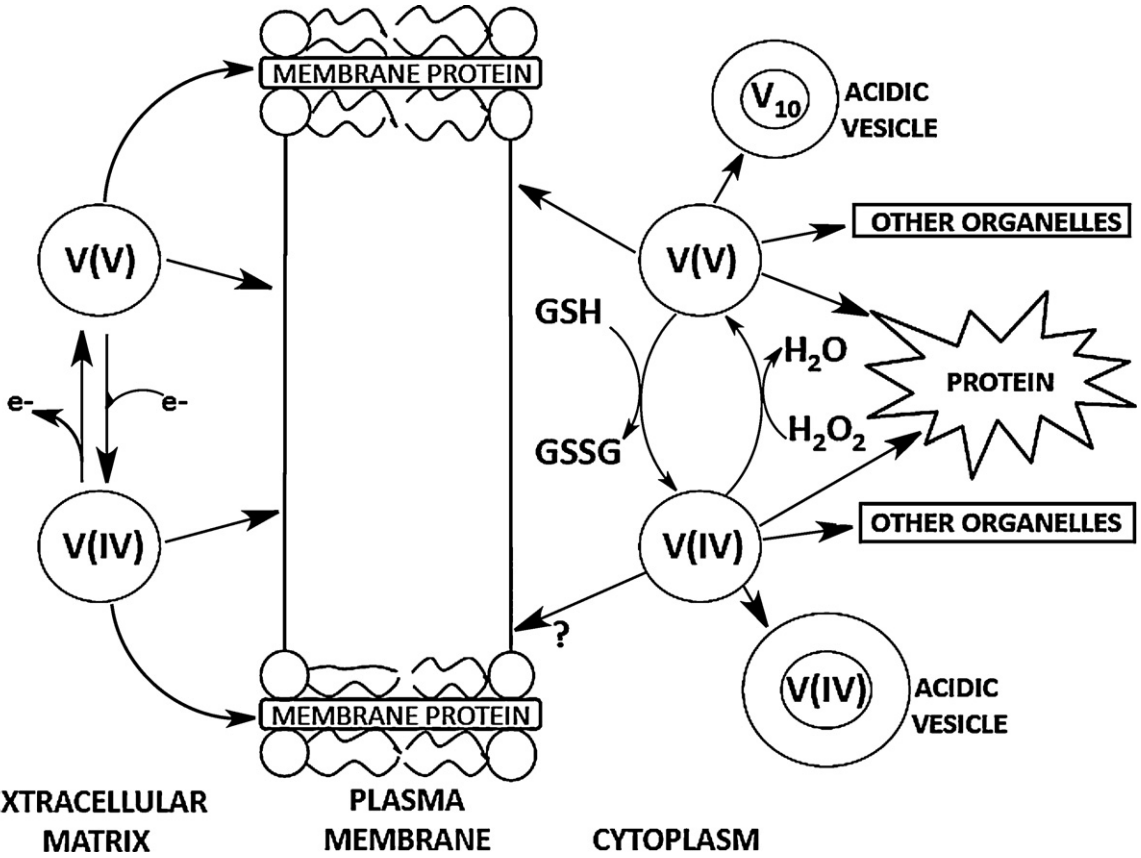


Fig. 1. An illustration of the current reported vanadium interactions in biological systems, with one electron V(4+/5+) redox chemistry occuring in the extracellular matrix (ECM). Membrane interactions are shown occuring via either passive diffusion of membrane protein interaction mechanisms. Upon entry into the cytoplasm V(4+) and (5+) affect cellular components in many ways.