Insulin-mimetic property of vanadium compounds

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Received: February 26, 2016
Accepted: March 3, 2016

Key words: vanadium, diabetes mellitus, insulin

Abbreviations: GLUT4 - glucose transporter type 4; GSK-3 - glycogen synthase kinase-3; IGF-1R - insulin-like growth factor 1 receptor; IGF-1 - insulin-like growth factor 1; LDL - low-density lipoprotein; PI3K - phosphatidylinositol-3-kinase; PKB - protein kinase B; PTEN - phosphatase and tensin homolog; PTP - protein tyrosine phosphatase; PTP-1B - protein tyrosine phosphatase 1B

ABSTRACT

Vanadium is a transition metal which creates a number of inorganic and organic derivatives with various organic substances. Some of these compounds have pharmaceutical significance, e.g. vanadyl cation, vanadate and bis(maltolato) oxovanadium(IV). Vanadium compounds are competence inhibitors of protein tyrosine phosphatases (PTP). They have anti-tumor properties, capable of inhibiting cell proliferation at the concentrations of several micromoles. They also display insulin-mimetic and hypoglycemic properties. As they can increase the activity of the insulin-like growth factor I receptor, they stimulate glycogen synthesis, increase the number of GLUT-4 transporters in the cell membrane and impair glucose genesis. In addition to their effects on sugar metabolism, vanadium compounds increase the synthesis of fatty acids, reducing the concentration of glucose in the blood. Thanks to their mitotic properties, low concentrations of vanadium compounds are also able to induce β cell regeneration. Clinical tests have shown that vanadium compounds may be used as antidiabetic drugs with low toxicity. However, the range of therapeutic concentrations is very narrow; at concentrations as low a several micromoles vanadium compounds inhibit cell proliferation and cause apoptosis, necrosis and inflammation.

INTRODUCTION

Vanadium is a transition metal with atomic number 23 and atomic mass 50.9 g/mol. It is used in industry as an important steel dope to increase the hardness and strength of a supplemented alloy [1]. The name of vanadium stems from the Norse mythology and refers to a goddess, whose attributes include beauty and fertility [2,3]. In the environment vanadium can be found in some minerals and igneous or clay rocks [3,4]. In biological conditions vanadium occurs in a form of inorganic salts in an oxidation state of +4 and +5 (Fig. 1). In an oxidation state of +2 and +3 is unstable and is converted to its more stable form at a higher oxidation state [1]. The most important, with regard to a biochemical meaning, inorganic compounds of vanadium are the following substances.

Vanadates (V) are major inorganic compounds of vanadium occurring in aqueous solutions. In cell, this form of vanadium is bound to proteins. The vanadates include sodium orthovanadate (Na₃VO₄) and sodium metavanadate (NaVO₃), in which vanadium occurs in an oxidation state of +5. At higher concentrations vanadium forms condensates of polivanadates - cyclical tetravanadate and pentavanadate, or non-cyclic tetravanadate and divanadate [5]. In acidic environment in mitochondria prevails a form of decavanadate, containing 10 atoms of vanadium [V₁₀O₃₈]⁶⁻ [6,7].

![Figure 1. Inorganic compounds of vanadium. Vanadium forms inorganic salts, in which occurs in an oxidation state of +4 and +5. The most important inorganic compounds with vanadium on the oxidation state of +4 is vanadyl cation (IV). Vanadium in an oxidation state of +5 forms vanadates, including sodium orthovanadate.](image-url)
Vanadyl cation (IV) is a very often occurring, reduced by intracellular antioxidants, form of vanadate, with vanadium in an oxidation state of +4. VO$^{2+}$ is a predominant form of vanadium in cytoplasm [5]. Vanadium (V) oxide, V$_2$O$_5$, is formed during a combustion of fossil fuels containing vanadium. It contributes to anthropogenic pollution of large urban centers and industrial centers that utilize fossil fuels. In particular V$_2$O$_5$ is emitted by combustion of oil and certain types of coal [8]. Exposure to V$_2$O$_5$ may cause inflammatory response or even respiratory system cancers [9,10].

In addition to inorganic compounds, vanadium also forms a number of complexes with organic substances (Fig. 2). In early 1990’s, the first synthesized organic derivatives of vanadium, in the early 90’s, were BMOV and naglivan. Since then, still new organic derivatives of vanadium have been synthesized.

All organic derivatives of vanadium, vanadate, or vanadyl cation due to their properties are significant as potential drugs. All of the above mentioned vanadium compounds are known as competence inhibitors of protein tyrosine phosphatases (PTP) [18-20]. It is possible thanks to a structural similarity of PTP and orthophosphate anions [19]. Vanadium compounds in the reaction with H$_2$O$_2$ may oxidize free cysteine residues [19,21], such as those contained within the PTP active site and, therefore, irreversibly inactivate the enzyme [22-24].

Vanadium compounds reveal anti-tumor properties. It has been reported that at micromolar concentrations they inhibit cell proliferation in vitro [25-28]. Also in vivo experiments on animals confirm the anti-tumor properties of vanadium compounds [29]. Nevertheless, these compounds have been not currently tested clinically as potential anticancer drugs. Though, much more advanced have been studies on clinical trials of vanadium compounds as promising anti-diabetic agents [30]. This is due to their insulin-mimetic and hypoglycemic properties.

**SIGNAL TRANSDUCTION FROM INSULIN RECEPTOR**

Insulin receptor plays a key role in glucose metabolism [31-33]. After insulin binding to the receptor the following signaling pathways are triggered. Main pathways include ERK MAPK cascade and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB) pathway [34-35]. Signal transduction from the insulin receptor by ERK MAPK pathway involves mitogen signal and cell differentiation, and only to a minor extent affects sugar and lipid metabolism [36]. In contrast, PI3K-PKB is mainly responsible for the metabolism of sugar and lipids. After insulin receptor a sequential activation of PI3K and PKB is initiated. The process of PKB activation requires a second messenger, phosphatidylinositol (3,4,5)-trisphosphate, which is then degraded by phosphatase and tensin homolog (PTEN). The activated PKB phosphorylates a variety of proteins, in particular, FOXO1 transcription factor, which diminishes the expression of enzymes involved in gluconeogenesis. Additionally, PKB phosphorylates gly-
cogen synthase kinase-3 (GSK-3), which inhibits its activity and thereby increases glycogen synthesis. Moreover, PKB activation increases the level of glucose transporter type 4 (GLUT4) in a cell membrane which transfers glucose in the cytoplasm of adipocytes or muscle cells. Beside the sugar metabolism, signal transduction from the insulin receptor to PKB stimulates also mTOR kinases. This, in turn, increases fatty acids synthesis and decreases acetyl-CoA level, derived from glucose, in blood system.

INSULIN-MIMETIC PROPERTIES OF VANADIUM COMPLEXES

As PTP inhibitors, vanadium compounds affect the activity of a number of receptors. After entering a cell, vanadium complexes together with organic substances are degraded and vanadyl cation is oxidized to vanadium in an oxidation state of +5, which competitively inhibits PTP [19,20,37]. The orthovanadate inhibition constant for protein tyrosine phosphatase-1B (PTP-1B) equals 0.38 ± 0.02 µM [19]. It may seem that the inhibition of PTP-1B phosphatase by vanadium compounds will promote signaling from insulin receptor, since PTB-1B is known to inactivate the receptor. However, other research proved that vanadium compounds do not affect the process of signal transmitting from the insulin receptor alone, but require additional factors [38].

Vanadium compounds owe their insulin-like properties to an activated insulin-like growth factor I receptor (IGF-IR), as confirmed by studies on animal models with induced diabetes [53,58]. IGF-IR activation stimulates PI3K which increases the PIP3 level. PIP3 level is also increased by vanadium compounds through their inhibitory impact on PTEN. In addition to the effect on the receptor-to-cell signal transmission, vanadium compounds directly hinder the activity of gluconeogenesis enzymes.

Figure 3. Effect of vanadium compounds on signal transduction from the insulin receptor. By activation of the IGF-IR, vanadium compounds enhance the activity of PI3K, which increases the PIP3 level. PIP3 level is also increased by vanadium compounds through their inhibitory impact on PTEN. In addition to the effect on the receptor-to-cell signal transmission, vanadium compounds directly hinder the activity of gluconeogenesis enzymes.

The hypoglycemic mechanism is the same. Vanadium compounds act on glucose metabolism in liver, kidney-cortex, muscles, adipose tissue, and contribute to pancreatic β-cell regeneration (Fig. 4).

The liver is essential for sugar and lipid metabolism. There are intensively produced fatty acids, as well as glucose, in the process of gluconeogenesis. Glucose is stored in liver in a form of glycogen. In diabetes, vanadium complexes normalize an increased synthesis and activity of gluconeogenesis enzymes [46-51] and the synthesis of glycolysis enzymes [47,48,54]. It has been reported that vanadium complexes also increase glycogen accumulation in liver in animals with induced diabetes [54]. Apart from sugar metabolism, vanadium compounds decrease HMG-CoA reductase level in liver, which is an enzyme crucial for ketogenesis [48]. Moreover, they elevate fatty acids synthesis [9], and reveal a protective properties toward toxic effects of increased blood glucose [57].

In addition to the liver, kidney-cortex also performs gluconeogenesis upon which glucose is produced. In diabetes, vanadium compounds stabilize the elevated level of gluconeogenesis by decreasing the synthesis and activity of gluconeogenesis enzymes [41,51].

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Muscles, as well as a liver, store glucose in a form of glycogen. By synthesis and degradation of glycogen deposit, muscles may directly, as a liver, or indirectly, as muscles, regulate glucose level in blood system. Vanadium compounds reduce blood glucose level by increasing the GLUT4 expression and inducing glycogen synthesis in muscles in animals with induced diabetes [53,58].

IMPACT OF VANADIUM COMPLEXES ON ENERGY METABOLISM IN ANIMALS

A number of in vivo studies on animal models with induced diabetes have demonstrated that both vanadium inorganic compounds and vanadium organic derivatives normalize blood glucose level [41,46-56]. What is more, they lower total cholesterol and LDL level in plasma [52]. Due to the conversion of vanadium complexes in the cytoplasm, and the observed similar effect of all vanadium complexes,
Adipose tissue is highly important in lipid metabolism. Vanadium compounds increase the fatty acids synthesis in this tissue by elevating the expression and activity of enzymes responsible for their synthesis [49]. Also GLUT4 expression is upregulated by vanadium complexes, that at the same time do not affect the location of the transporter in a cell [38,59]. This increases the uptake of glucose and lipids accumulation in adipose tissue.

Furthermore, the latest research on vanadium complexes, apart from their impact of on the sugar and lipid metabolism, mediate regeneration of pancreatic β-cells and thus, increase the insulin production [56,60,61]. Vanadium compounds, in addition to hypoglycemic properties, reveal a mitogenic character. They stimulate cells to proliferate. This effect is an important aspect, as up to now a standard anti-diabetic therapy is symptomatic - reduces blood glucose level without eliminating the cause of diabetes [62]. Vanadium compounds promote pancreatic β cells to regenerate. This can significantly influence the course of diabetes, providing early diagnosis and the use of vanadium compounds as drugs [56,60,61].

**VANADIUM COMPLEXES AS NON-TOXIC HYPOGLYCEMIC DRUGS**

The obtained up to now results of in vivo experiments performed on animals with induced diabetes suggest that vanadium compounds possess anti-diabetic properties. Also, clinical trials indicate the therapeutic and non-toxic effects of inorganic vanadium compounds. In all tests, patients with diabetes type 1 or type 2 received vanadyl sulphate. In clinical trials with type 2 diabetes, vanadyl sulphate was dosed at a concentration of 100-300 mg per day and, depending on the experiment, from 3 to 6 weeks [63-67]. In clinical studies on type 1 diabetes, patients were treated with the same vanadium compound in a dosage of 225-300 mg per day for 2.5 years [30]. In all clinical studies, reductions in blood glucose level and glycosylated hemoglobin level were observed, as well as lipid metabolism was reported to improve. After therapy patients exhibited decreased levels of free fatty acids, total cholesterol or HDL in blood system [65,66]. Moreover, the tissue sensitivity on insulin was strengthened [63,66]. Clinical studies have also shown that vanadyl sulphate at the predetermined dosages was non-toxic to humans, though at the beginning of the treatment the tested compound caused diarrhea and a mild pain [30,66], which resolved in the course of its further application. However, it did not reveal any toxicity to liver or kidneys. This indicates that vanadyl sulphate at a predetermined safe dose can be incorporated into a standard antidiabetic therapy [30].

**TOXICITY OF VANADIUM COMPOUNDS**

Vanadium compounds at low concentrations successfully lower blood glucose level. This fact has been confirmed by clinical studies, in which patients were treated with 100-300 mg dosages of vanadyl sulphate per day [30,63,67]. Such a dose results in low micromolar traces of vanadium in the blood system [64,66]. Nevertheless, the therapeutic effect of vanadium compounds is very narrow. At a concentration of 30 µM vanadyl sulphate is cytotoxic and inhibits proliferation of both cancer and normal cells [26], and causes cell apoptosis and necrosis [26]. At a concentration of 10 µM, vanadium compounds may promote inflammation, by increasing the cPLA2 activity and then PGE2 synthesis [68]. This shows that vanadium compounds, when considered as putative therapeutics, should be dosed very strictly.

**REFERENCES**

Insulino-mimetyczne właściwości związków wanadu

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Słowa kluczowe: wanad, cukrzyca, insulina

STRESZCZENIE