Insulin-Like Actions of Vanadium: Potential as a Therapeutic Agent

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Vanadium compounds are glucose-lowering agents that are shown to mimic/enhance most of the metabolic actions of insulin both in vitro and in vivo. Several studies have demonstrated that vanadium treatment lowers plasma glucose levels in experimental models of type 1 diabetes and enhances insulin sensitivity in models of type 2 diabetes. Therefore, these compounds have gained attention as candidates for oral therapy in both types of diabetes. Despite numerous studies, the mechanism(s) by which vanadium mediates its metabolic effects in vivo are still not completely understood. The finding that most of the insulin-like effects of vanadium in vitro are observed in the presence of high concentrations of vanadium that are not usually achieved in vivo suggests that these effects of vanadium may not have therapeutic relevance. Also, a growing body of evidence from in vivo studies indicates that enhancing glucose disposal in the peripheral tissues is not an adequate explanation for the glucose lowering effects of vanadium in vivo. Accordingly, recent studies suggest that suppression of hepatic glucose production through inhibition of key gluconeogenic enzymes might have an important role in mediating the glucoregulatory effects of vanadium. Several potential sites in the insulin-signaling pathways, including both receptor and postreceptor mechanisms, have been proposed for the insulin-like effects of vanadium compounds. In this review, we have attempted to discuss the possible molecular mechanism(s) underlying the metabolic effects of vanadium in vivo. J. Trace Elem. Exp. Med. 16:253–267, 2003. © 2003 Wiley-Liss, Inc.

VANADIUM: CHEMICAL AND BIOLOGICAL CHARACTERISTICS

Vanadium is a group 5 transition element that exists in several oxidation states. Under physiological conditions, vanadium predominantly exists in either an anionic form (vanadate) or a cationic form (vanadyl) [1,2]. The predominant form of vanadium in plasma is vanadate, which is mainly bound to transferrin and to a lesser extent to albumin [2,3]. Vanadium ions enter cells via the anion transport system in a similar manner to phosphate [2]. In the cytosol, vanadate is reduced to vanadyl via a nonenzymatic reaction. Therefore, it is likely that, in vivo, vanadyl, which is the predominant intracellular form of vanadium, plays an important role in mediating its metabolic effects [4,5]. Most of the intracellular vanadium is bound to proteins especially glutathione, which prevents its oxidation and only less than 1% of intracellular vanadium exists in the free form.

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Received 22 May 2003; Accepted 16 July 2003

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The plasma concentration of vanadium is close to its physiological intracellular concentration (about 20 nM), and the total body pool of vanadium is estimated to be about 100–200 μg [1,6].

Several vanadium compounds have been developed and examined for their antidiabetic effects. Vanadium compounds in general fall into three major categories, including inorganic vanadium salts (vanadate and vanadyl), peroxovanadium complexes, and organic vanadium compounds [2]. For several years inorganic vanadium compounds, such as sodium orthovanadate and vanadyl sulfate, were used in both animal and human studies. Although these compounds were shown to be glucose-lowering agents, their side effects, mainly gastrointestinal discomfort, limited their use as therapeutic agents. The effective glucose-lowering doses of sodium orthovanadate and to a lesser extent vanadyl sulfate may produce diarrhea and dehydration [7–9]. Furthermore, inorganic vanadium compounds have a low rate of absorption. Hence, various organic compounds of vanadium were developed to enhance the bioavailability and reduce the side effects of inorganic compounds. Among them are bis(maltolato)oxovanadium(IV) (BMOV) and bis(ethylmaltolato)oxovanadium(IV) (BEOV), two vanadyl complexes with the VO(O₄) coordination mode, which are potent glucose-lowering agents. The advantages of these organic vanadium compounds over the inorganic compounds of vanadium include greater potency, lower toxicity, and improved tolerance [10,11]. Peroxovanadium complexes are of less interest because of their toxicity associated with the production of free radicals, which may increase oxidative stress in the cell [12].

**VANADIUM AND DIABETES**

Vanadium compounds are shown to have insulin mimetic/enhancing effects both in vitro and in vivo. Although the antidiabetic effect of vanadium was first reported by Lyonnet more than 100 years ago [13], its potential importance as an orally active insulin-mimetic agent was described several years later in 1985 [14]. This study and several subsequent reports showed that vanadium treatment decreases plasma glucose levels in different animal models of type 1 diabetes [12,14–16]. In type 2 diabetes and experimental models of insulin resistance, vanadium lowers plasma insulin levels and improves insulin sensitivity [17–19]. Hence, these compounds are potential candidates for oral therapy in both type 1 and type 2 diabetes. However, despite numerous studies during the past decade, the mechanism(s) by which vanadium mediates its in vivo antidiabetic effects are not well understood, and whether vanadium directly mimics or rather enhances insulin effects is still under investigation. Although several studies have shown that vanadium compounds mimic most of the metabolic actions of insulin in vitro, the finding that these insulin-like effects of vanadium in vitro are observed in the presence of high (millimolar) concentrations of vanadium that usually are not achieved in vivo suggests that these effects of vanadium may not have therapeutic relevance. Also, a growing body of evidence from in vivo studies indicates that enhancing glucose disposal in the peripheral tissues is not an adequate explanation for the glucose-lowering effects of vanadium in vivo. Accordingly, recent studies suggest that suppression of hepatic glucose output
through inhibition of key gluconeogenic enzymes may have an important role in mediating the glucoregulatory effects of vanadium [20–22]. The signal transduction pathways involved in mediating the metabolic effects of vanadium are still not completely understood but several enzymes in the insulin signaling pathways have been proposed to be potential targets for vanadium.

**VANADIUM AND TYPE 1 DIABETES**

Type 1 diabetes is characterized with hyperglycemia associated with progressive β-cell death and hypoinsulinemia [23,24]. Therefore, these patients require insulin therapy for their survival. Because of the potential problems associated with continuous insulin therapy, agents that could potentially be used as oral substitutes for insulin have been under intensive investigation for many years. Vanadium as an insulin mimetic/enhancing agent is one of the potential candidates for oral therapy in type 1 diabetes. Several studies have shown that chronic treatment with vanadium salts restores plasma glucose levels and corrects hyperlipidemia in different animal models of type 1 diabetes without any significant effect on plasma insulin levels [14,16,25–27]. Furthermore, vanadium has no (or minor) effects on plasma glucose and insulin levels in control animals [14,22]. Studies using the euglycemic hyperinsulinemic clamp technique have further demonstrated that improvement of metabolic state in diabetic animals after vanadium treatment was accompanied by a marked increase in the peripheral glucose utilization and complete normalization of elevated hepatic glucose output [15,28,29]. This improvement in peripheral glucose uptake was associated with the correction of low glucose transporter type 4 (GLUT4) mRNA and protein levels in both skeletal muscle and cardiac muscle [26,30,31]. GLUT 4 is the major glucose transporter in muscle that is regulated by insulin. Moreover, our laboratory has shown that treatment of streptozotocin (STZ)-diabetic rats with BMOV, an organic vanadium compound, in the drinking water for 8 weeks enhances insulin-induced GLUT4 translocation to the plasma membrane in the cardiac muscle [32].

In human patients clinical trials in type 1 diabetics have demonstrated that chronic treatment with vanadium significantly reduces insulin requirements. Interestingly, vanadium treatment in those patients had no effect on the plasma levels of C peptide [33]. This small peptide is cosecreted along with insulin in equimolar concentration from pancreatic β-cells and therefore this finding suggests that an increase in insulin secretion from pancreas could not explain the decrease in insulin requirements in those patients. Similarly, reduced insulin requirements were also reported in vanadium treated STZ-diabetic rats [27] and in spontaneously diabetic BB rats [34]. Taken together, several pieces of evidence from both human and animal studies suggest that vanadium compounds improve metabolic state and decrease insulin requirements in type 1 diabetes.

**VANADIUM AND TYPE 2 DIABETES**

Unlike type 1, type 2 diabetes is associated with progressive insulin resistance in peripheral tissues, and despite normal (or increased) plasma insulin levels,
these patients develop hyperglycemia [35]. Any approach that can improve insulin sensitivity and enhance response to insulin may therefore have important clinical significance in the treatment of type 2 diabetes. Hence, during the past decade vanadium compounds, because of their insulin mimetic/enhancing effects, have gained attention as candidates for treatment of type 2 diabetes. Accordingly, several vanadium compounds have been developed and examined for their antidiabetic effects. We and others have shown that treatment with both inorganic and organic compounds of vanadium significantly decreased plasma insulin levels and improved insulin sensitivity in several animal models of insulin resistance and type 2 diabetes [17,36–39]. Moreover, we have shown that in Zucker diabetic fatty rats, an animal model that closely resembles characteristics of type 2 diabetes in human, chronic treatment with vanadium reduced the elevated plasma glucose levels [40]. Because the glucoregulatory effects of insulin are mainly mediated by enhancing peripheral glucose uptake/utilization and suppression of hepatic glucose output, it is likely that vanadium improves insulin sensitivity by mimicking/enhancing the metabolic effects of insulin on these tissues. Studies using the euglycemic hyperinsulinemic clamp have demonstrated that improvement in glucose homeostasis in Zucker fatty rats (fa/fa) an animal model of prediabetic state of type 2 diabetes was not the result of a greater inhibition of hepatic glucose output but involved an increase in the insulin sensitivity in the peripheral tissues mainly skeletal muscle [41]. Similar observations have been reported from human studies with vanadyl sulfate [42]. However, because the increase in muscle glucose uptake was not associated with alterations in GLUT4 mRNA or protein expression in this tissue, the stimulatory effects of vanadium on glucose transport might be mediated by a more efficient translocation of GLUT4 or an increase in its intrinsic activity [38]. In addition to its effects on glucose uptake, vanadium restores the activity of key enzymes in glycogen metabolism (glycogen synthase α and phosphorylase α) and lipogenic enzymes (malic enzyme and glucose 6-phosphate dehydrogenase) in some animal models of insulin resistance [37,43,44]. Vanadium also enhances the effects of insulin in Zucker and Zucker diabetic fatty rats and effectively preserves pancreatic β-cell function [40,45]. Therefore, vanadium treatment may have clinical importance in preventing and/or delaying β-cell failure in type 2 diabetic patients.

In addition to its effects on the peripheral tissues, insulin regulates appetite and food intake by inhibition of hypothalamic neuropeptide Y (NPY), leading to an increase in leptin secretion from adipocytes, which has inhibitory effect on food intake. Because our previous studies have shown that treatment with BMOV reduces body weight and appetite in Zucker fatty rats, one proposed mechanism for vanadium action would be that vanadium mimics/enhances the effects of insulin on hypothalamus and that the changes observed on body weight and appetite after BMOV treatment may be linked to altered NPY levels in the hypothalamus. In fact, Wang et al. [46] recently showed that treatment with BMOV significantly reduced NPY mRNA levels and protein expression and enhanced the insulin-induced increase in plasma and adipose leptin levels, indicating that BMOV may increase insulin sensitivity in adipose tissue and decrease appetite and body fat by decreasing NPY levels in hypothalamus. Furthermore,
chronic treatment of Zucker diabetic fatty rats (9 weeks old) with bis(ethylmaltolato)oxovanadium(IV), an organic vanadium compound, significantly increased plasma leptin levels in parallel with plasma insulin levels [47], suggesting that the stimulatory effects of vanadium on leptin may also be mediated indirectly by improving β-cell function and subsequent increase in plasma insulin levels.

As with animal studies, human studies have shown that oral treatment with vanadium results in reduced fasting plasma glucose levels, suppression of hepatic glucose production, and improvement in insulin sensitivity in the skeletal muscle of type 2 diabetic patients [19,48,49]. The latter effect appears to be accounted for by an increase in nonoxidative glucose disposal [33,48]. Cusi et al. [49] have reported that treatment with a maximal tolerated dose (150 mg/day) for 6 weeks significantly reduced the elevated levels of endogenous glucose production, which was closely correlated with the reduction in fasting plasma glucose levels and also increased insulin-mediated glucose disposal. However, a few studies have reported an improvement in insulin sensitivity without any measurable effect on suppression of hepatic glucose production [42] or vice versa [50]. The discrepancy observed between the results of these studies is likely caused by different duration of treatment, type, and dose of vanadium compounds used in those studies. Interestingly, Jentjens et al. [51] recently showed that treatment with vanadyl sulfate had no effect on insulin sensitivity, fasting plasma glucose and insulin levels in healthy adults. This important finding which is also observed in several animal models [14,52], suggests that vanadium may have selective effects on the exaggerated metabolic pathways and does not affect normal pathways.

POSSIBLE MOLECULAR MECHANISMS FOR VANADIUM ACTION

Although antidiabetic effects of vanadium are well established, mechanism(s) by which vanadium mediates its metabolic effects are still not completely understood. The interesting finding that in diabetic animals vanadium lowers plasma glucose levels and restores diabetes-induced metabolic disorders without any significant effect on control animals suggests that vanadium has selective effects on the mechanisms responsible for exaggerated metabolic pathways during diabetes. This along with the finding that glucose-lowering effects of vanadium are dependent on the presence of endogenous insulin [5,34], supports the idea that tolerable therapeutic doses of vanadium may enhance rather than mimic the metabolic effects of insulin in vivo. It is worthwhile to emphasize that some, but not all, of the regulatory effects of insulin are mimicked/enhanced by vanadium compounds in vivo. An important exception would be that vanadium treatment is unable to reproduce the effects of insulin therapy on growth pattern in diabetic animals, which correlates with its lack of effects on amino acid uptake, protein synthesis and mitogenesis [53,54]. Hence, metabolic rather than mitogenic effects of insulin are mimicked/enhanced by vanadium. Because glucose homeostasis in the body depends largely on the balance between its formation by the liver and its use by peripheral tissues, the insulin-like effects of vanadium are likely mediated through these two pathways via insulin dependent and/or independent signaling cascades.
One of the important biological roles of insulin during absorptive state (after meals) is stimulation of glucose disposal in the peripheral tissues. This effect of insulin is mediated by both enhancing glucose uptake and stimulation of glycogen synthesis [55]. Among insulin sensitive tissues, skeletal muscle because of its mass, is the major target tissue for insulin-stimulated glucose disposal. The metabolic effects of insulin are initiated by activation of its receptor on the surface of the cell leading to the activation of two main signaling cascades referred to as phosphatidylinositol 3-kinase (PI3-K) pathway and mitogen-activated protein kinase (MAPK) pathway. It is believed that PI3-K pathway mediates most of the metabolic effects of insulin, whereas MAPK pathway is mainly involved in mediating the mitogenic effects of insulin [55]. Because vanadium mimics/enhances the metabolic rather than the mitogenic effects of insulin, in this review we have focused on the in vivo effects of vanadium on PI3-K signaling pathway. As with insulin, vanadium stimulates both glucose uptake and glycogen synthesis [53,56–58]; therefore, several insulin receptor and post receptor sites have been suggested as potential sites for vanadium action.

Vanadium is a nonspecific protein tyrosine phosphatase (PTPase) inhibitor [12]; therefore, one possible mechanism for vanadium action would be that vanadium enhances insulin receptor and/or insulin receptor substrate phosphorylation indirectly by inhibiting the dephosphorylation of these proteins [12,54]. In fact, recently our laboratory showed that the elevated activity of protein tyrosine phosphatase 1B, the enzyme that dephosphorylates the phosphotyrosine residues present on the insulin receptor, was restored in the skeletal muscle of Zucker fatty rats after chronic treatment with BMOV (0.18 mmol/kg/day for 3 weeks) [59]. Although inhibition of PTPases is important in mediating the metabolic effects of vanadium, current evidence suggests that inhibition of PTPases per se is not an adequate explanation. First, the intracellular form of vanadium (vanadyl) is not a potent protein phosphatase inhibitor [11]. Moreover, in vitro studies have demonstrated that effects of vanadium on glucose uptake and glycogen synthesis are independent of insulin receptor tyrosine kinase [56,60–62]. Accordingly, two nonreceptor protein tyrosine kinases, namely cytosolic [61,63] and membranous protein tyrosine kinases [64] were suggested to mediate some, but not all, of the insulin-like effects of vanadium [63,64].

It is believed that the stimulatory effects of insulin on glycogen synthesis are mediated via activation of PI3-K and its downstream enzyme protein kinase B (PKB) [65,66]. Therefore, a second possible mechanism for vanadium action would be regulation of activity and/or expression of these key enzymes. In fact, there is evidence from in vitro studies that vanadium in millimolar concentrations activates both PI3-K and PKB [62,67]. To examine whether these effects of vanadium could be reproduced by tolerable therapeutic doses of vanadium in vivo we treated STZ-diabetic rats with BMOV in the drinking water (0.75–1 mg/mL) for 3 weeks. BMOV treatment normalized fasting hyperglycemia in STZ-diabetic rats without any significant effect on the protein expression or activity of
IRS-1 associated PI3-K in skeletal muscle [68]. Moreover, vanadium had no effect on PKB protein expression and activity in the skeletal muscle and liver of STZ-diabetic rats [52]. Interestingly, further experiments with Zucker fatty rats, an animal model of prediabetic state type 2 diabetes, showed that BMOV treatment (0.75 mg/dL for 3 weeks) significantly lowered plasma insulin levels and improved insulin sensitivity but did not restore PI3-K and PKB activity in the skeletal muscle or liver of those animals [52,68]. These studies clearly showed that unlike insulin, the glucoregulatory effects of vanadium are mediated through a pathway(s) independent of PI3-K/PKB axis in vivo.

Activity of glycogen synthase, the key enzyme in glycogen synthesis, is regulated by both glycogen synthase kinase-3 (GSK-3), a downstream enzyme of PKB, which inactivates (phosphorylates) glycogen synthase and by protein phosphatase-1 (PP-1), which activates (dephosphorylates) the enzyme [69,70]. Therefore, GSK-3 and/or PP-1 are two potential targets for vanadium action. However, vanadium was unable to inhibit GSK-3 activity in either STZ-diabetic or Zucker fatty rats [71,72]. Interestingly, further studies with Zucker fatty rats demonstrated that the stimulatory effect of vanadium on glycogen synthase was mediated by enhancing the activity of PP-1 [71]. Overall, these findings suggest that, in vivo, BMOV modulates phosphorylation of insulin receptor and IRS proteins as well as glycogen synthase activity through its effects on the key regulatory phosphatases. Furthermore, vanadium has been shown to regulate glycogenolysis by normalization of phosphorylase a activity in vivo [37]. Unlike insulin, vanadium at therapeutic doses had no effect on the PI3-K, PKB, and GSK-3, three key enzymes mediating the stimulatory effects of insulin on glycogen synthesis.

Insulin regulates glucose uptake, the rate-limiting step in glucose utilization, through insulin-dependent GLUT4, the major form of glucose transporter in skeletal muscle and adipose tissue [55]. Therefore, vanadium might mediate its glucose lowering effects by enhancing glucose uptake in the insulin responsive tissues. Indeed, several in vivo studies have shown that vanadium restores the reduced levels of GLUT4 mRNA and protein expression [26,30,31] and enhances insulin-induced GLUT4 translocation from the intracellular pools to the plasma membrane in the muscle of diabetic animals [32]. Vanadium has no effect on GLUT4 expression or membrane translocation in control animals [32]. Again, emphasizing that vanadium restores diabetes-induced metabolic disorders but has no effect on normal metabolism. As with glycogen synthesis, the signaling pathway(s) involved in mediating the stimulatory effects of vanadium on GLUT4 translocation are not clear. Although in vitro studies have shown that vanadium stimulates glucose transport and GLUT4 translocation by both PI3-K-dependent and PI3-K-independent pathways in adipocytes and myotubes respectively [73,74], the finding that therapeutic doses of vanadium had no effect on PI3-K or PKB expression/activity in the skeletal muscle or liver of diabetic rats suggests that the effects of vanadium on GLUT4 membrane translocation are likely not mediated through PI3-K or PKB in vivo. Further investigations are required to identify the molecular mechanism(s) involved in mediating the effects of vanadium on glucose transport in vivo. Effects of vanadium on insulin signaling cascade are summarized in Figure 1.
Increased hepatic glucose production (HGP) is a major factor contributing to fasting hyperglycemia in both type 1 and type 2 diabetes [75]. Under normal conditions insulin secretion from \( \beta \)-cells inhibits gluconeogenesis in the liver; therefore, absolute (type 1) or relative (type 2) insulin deficiency leads to an increase in endogenous glucose production in the diabetic liver. This elevated HGP is associated with an increase in the expression and activity of phosphoe-
nolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G-6-Pase), two key gluconeogenic enzymes, in several animal models of diabetes [76,77].

The important finding that vanadium has a more profound effect on the plasma glucose levels in the fasted diabetic rats that have activated gluconeogenesis compared with the fed animals [22], led to the notion that vanadium may mediate its glucose lowering effects by inhibition of HGP. Several pieces of evidence support this idea: First, it has been shown that vanadium normalizes the glucagon-induced elevation in plasma glucose levels in control rats in vivo [78]. Second, the recent finding that vanadium had no effect on the key enzymes involved in mediating the effects of insulin on glucose uptake and glycogen synthesis, suggests that effects of vanadium on glucose utilization may not be the major mechanism for its anti-diabetic effects observed in vivo [52,68,72]. Third, in vivo studies from this and other laboratories have shown that vanadium compounds at doses sufficient to normalize plasma glucose levels are able to restore the elevated levels of PEPCK and G-6-Pase mRNA expression and activity in the liver of various animal models of diabetes [20–22,79].

The molecular mechanism(s) underlying the inhibitory effects of vanadium on PEPCK and G-6-Pase expression in the diabetic liver appears to be complex and involve several pathways. Because high glucose concentrations have been shown to increase G-6-Pase expression [80], it could be proposed that the inhibitory effects of vanadium on HGP might be secondary to the correction of hyperglycemia. However, we recently showed that correction of hyperglycemia with phlorizin, an antihyperglycemic agent that inhibits renal tubular glucose transport and blocks glucose reabsorption without any effect on gene expression, did not restore the elevated levels of PEPCK mRNA expression and only partially normalized G-6-Pase mRNA expression in the liver of STZ-diabetic rats in vivo [22]. These findings suggest that the inhibitory effects of vanadium on PEPCK might be mediated by direct effects on its gene expression, whereas suppression of G-6-Pase by vanadium involves both direct and indirect effects. Accordingly, a vanadium response region has been identified in the PEPCK gene promoter [81]. We previously had shown that vanadium did not have any effect on PI3-K or PKB protein expression/activity in liver of STZ-diabetic rats [52,68], therefore it seems that unlike insulin the inhibitory effects of vanadium on PEPCK and G-6-Pase are independent of PI3-K/PKB axis.

Vanadium also corrects the elevated levels of glucagon in STZ-diabetic rats [22]. Because glucagon stimulates gluconeogenesis in the liver, a second possible mechanism could be that vanadium inhibits HGP by correction of the diabetes-induced hyperglucagonemia. Although some of the effects of vanadium may be mediated indirectly through correction of hyperglucagonemia, it is unlikely that this is the major mechanism for vanadium action and the finding that vanadium inhibits both basal and cAMP-stimulated expression of PEPCK in hepatocytes in the absence of endogenous hormones speaks against this idea [81]. However, this does not rule out the possibility that vanadium may affect signaling pathways downstream of the glucagon receptor. Glucagon mediates its stimulatory effects on PEPCK and G-6-Pase by activation of its G-protein coupled receptor on the surface of the cell leading to the activation of adenylyl cyclase and an increase in intracellular cAMP levels, which in turn activates cAMP-dependent
protein kinase. Insulin may counteract these effects of glucagon by decreasing the levels of cAMP through activation of cAMP phosphodiesterase. Therefore, it could be suggested that vanadium might interfere with levels or actions of cAMP. This might involve G-proteins, adenylyl cyclase [82], cAMP phosphodiesterase [83], or cAMP-dependent protein kinase [84]. Potential sites of vanadium action on hepatic gluconeogenesis are summarized in Figure 2.

In summary, a growing body of evidence suggests that suppression of HGP through direct and/or indirect inhibition of PEPCK and G-6-Pase has an important role in mediating the glucose lowering effects of vanadium in vivo. However, these effects of vanadium might be mediated via pathway(s) distinct from insulin signaling pathways.

CONCLUSIONS

Vanadium compounds improve metabolic disorders in models of both type 1 and type 2 diabetes. In type 1 diabetes treatment with vanadium normalizes hyperglycemia, while in type 2 diabetes vanadium treatment lowers plasma insulin levels and enhances insulin sensitivity. Hence, these compounds are potential candidates for oral therapy in diabetes as substitutes for insulin or in
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combination with insulin therapy to reduce insulin requirements. Therefore, mechanisms by which vanadium mediates its glucose lowering effects have been under intensive investigation during the past decade. A growing body of evidence indicates that mechanism of action of vanadium in vivo is complex and vanadium may have several targets. Recent studies have shown that some of the insulin mimetic/enhancing effects of vanadium that were observed in vitro could not be reproduced with therapeutic doses of vanadium in vivo and therefore may not have clinical relevance. Also, the stimulatory effects of vanadium on glucose utilization are important but not enough to explain the glucose lowering effects of vanadium. Recent studies suggest that suppression of hepatic glucose output via inhibition of the key gluconeogenic enzymes might be an important mechanism involved in mediating the anti-diabetic effects of vanadium in vivo. Although vanadium mimics/enhances the effects of insulin on both glucose utilization and hepatic glucose production, it appears that these effects of vanadium and insulin might be mediated by distinct mechanisms. However, despite the great progress in this area several questions still remains to be answered and further investigations are required to identify the signaling pathways involved in mediating the glucoregulatory effects of vanadium in vivo.

ACKNOWLEDGMENTS

This work from our laboratory was supported by grants from The Canadian Institutes for Health Research (CIHR), The Canadian Diabetes Association (CDA), The National Sciences and Engineering Research Council of Canada (NSER), and Kinetek Pharmaceuticals Inc. L.M. was a recipient of the CIHR traineeship.

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