Effect of Vanadium on Insulin Sensitivity and Appetite

Jian Wang, Violet G. Yuen, and John H. McNeill

Vanadium, a potent nonselective inhibitor of protein tyrosine phosphatases, has been shown to mimic many of the metabolic actions of insulin both in vivo and in vitro. The mechanism(s) of the effect of vanadium on the decrease in appetite and body weight in Zucker fa/fa rats, an insulin-resistant model, is still unclear. Because insulin may inhibit hypothalamic neuropeptide Y (NPY), which is known to be related to appetite, and increase leptin secretion in adipose tissue, we studied the possibility that the changes in appetite produced by vanadium may be linked to altered NPY levels in the hypothalamus. We also examined effects of vanadium on leptin. Zucker lean and fatty rats were chronically treated with bis(maltolato)oxovanadium(IV) (BMOV), an organic vanadium compound, in the drinking water. Plasma and adipose tissue leptin levels were measured using radiommunoassay and immunoblotting, respectively. Hypothalamic NPY mRNA and peptide levels were measured using in situ hybridization and immunocytochemistry, respectively. BMOV treatment significantly reduced food intake, body fat, body weight, plasma insulin levels, and glucose levels in fatty Zucker rats. Fifteen minutes after insulin injection (5 U/kg, intravenous [IV]), circulating leptin levels (+100%) and adipose leptin levels (+60%) were elevated in BMOV-treated fatty rats, although these effects were not observed in untreated fatty rats. NPY mRNA levels in the arcuate nucleus (ARC) (-29%), NPY peptide levels in ARC (-31%), as well as in the paraventricular nucleus (PVN) (-37%) were decreased with BMOV treatment in these fatty rats. These data indicate that BMOV may increase insulin sensitivity in adipose tissue and decrease appetite and body fat by decreasing NPY levels in the hypothalamus. BMOV-induced reduction in appetite and weight gain along with normalized insulin levels in models of obesity, suggest its possible use as a therapeutic agent in obesity.

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MATERIALS AND METHODS

Animals

Experiment 1 (n = 78). Male fa/fa fatty Zucker rats and their lean littermates were obtained at 7 weeks of age from the breeding colony in the Department of Physiology, University of British Columbia, Vancouver, BC and randomly divided into untreated and treated groups. Beginning at 8 to 9 weeks of age, BMOV was administered in the drinking water at an initial concentration of 0.2 mg/mL and increased to a maximum concentration of 0.8 mg/mL. Animals were

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treated for 3 weeks. Body weight, food, and fluid intake were measured 3 times per week.

At termination, animals were fasted overnight (16 hours), and pentobarbital (65 mg/mL) was administered by intraperitoneal injection. Before euthanization, some animals received an injection of insulin 5 U/kg intravenously (IV). Blood was collected by cardiac puncture for analysis of plasma leptin, insulin, and glucose in non-insulin-injected animals. Inguinal (ING), retroperitoneal (RP), epididymal (EPI), and mesenteric (MES) fat depots were dissected out and weighed. The fat depots were dissected from each animal according to defined anatomic landmarks. The ING fat depot was composed of all subcutaneous fat between the lower part of the rib cage and midhigh. The RP fat depot was taken from around the kidney. Fat found along the mesentery starting at the lesser curvature of the stomach and ending at the sigmoid colon was considered to be the MES fat depot. Total dissected body fat is the sum of ING + RP + EPI + MES fat depots. Brains were removed and fixed in 4% paraformaldehyde in 0.1 mol/L phosphate buffer (pH 7.4) for 2 days. The brains were stored at −70°C until used for in situ hybridization and immunocytochemistry.

Experiment 2 (n = 56). Rats were obtained from the same source as experiment 1 at 12 weeks of age. Animals were randomly divided into untreated and BMOV-treated groups. BMOV was administered in the drinking water as in experiment 1. The total duration of the treatment was 10 weeks. Animals received a single IV injection of saline or insulin (5 U/kg) 15 minutes before termination. Animals were killed as described previously and blood was collected by cardiac puncture for analysis of plasma leptin and insulin. EPI fat depots were removed and immediately frozen in liquid nitrogen and stored at −70°C before determination of adipose tissue leptin levels. Adipose tissue was homogenized with a polystyrene in cold 3-[N-morpholino]propanesulfonic acid (MOPS) buffer (25 mmol/L, pH 7.2) containing 5 mmol/L EGTA, 2 mmol/L EDTA, 75 mmol/L N-β-glycerophosphate, 2 mmol/L dithiothreitol (DTT), and various protease inhibitors (1 mmol/L phenylmethylsulfonyl fluoride, 3 mmol/L benzamidine, 5 μmol/L pepstatin A, 10 μmol/L leupeptin, and 200 μg/mL trypsin inhibitor). The crude homogenate was centrifuged at 10,000 × g for 15 min at 4°C. The supernatant was centrifuged at 100,000 × g for 45 minutes at 4°C. The resultant supernatant was stored at −70°C for measurement of leptin levels by immunoblotting analysis. Protein content was determined using a Bio-Rad kit (Bio-Rad Laboratories, Hercules, CA).

Measurement of plasma leptin, plasma insulin, and plasma glucose. Plasma leptin and insulin were measured by radioimmunoassay with commercially available kits from Linco Research, St Louis, MO. Plasma glucose was determined by the glucose oxidase method using a commercially available kit (Boehringer Mannheim, Laval, Quebec).

Measurement of adipose tissue leptin by immunoblotting. The adipose tissue homogenate (200 μg protein) was separated on a 10% sodium dodecyl sulfate (SDS) polyacrylamide gel. Gel electrophoresis was performed at 10 mA/igel overnight, and the proteins were transferred to nitrocellulose membranes at 50 mA for 3 hours. The membrane was blocked for 2 hours with 5% skim milk Tris-buffered saline solution containing 0.1% Tween 20 (TBST). Leptin antibody (1:500 dilution; Linco Research) was added to the blots and incubated overnight at 4°C with gentle rocking. The membrane was then washed with TBST and incubated for another hour with goat antirabbit immunoglobulin G (IgG) horseradish peroxidase conjugate. After washing with TBST buffer, the immunoreactive proteins were visualized with the enhanced chemiluminescence (ECL) detection system. Leptin bands were quantitated by densitometry.

Measurement of NPY mRNA by in situ hybridization. Antisense cRNA probes labeled with digoxigenin were prepared by in vitro transcription. Briefly, a 511-bp EcoR fragment of the rat NPY cDNA was subcloned into a modified plasmid containing a T7 promoter. The NPY plasmid was linearized with EcoR and transcribed in the presence of digoxigenin-11-UTP (Boehringer Mannheim) as previously described.19 The brains were cut into 30-μm thick sections with a cryostat. Coronal sections were treated with proteinase K (0.001% proteinase K in 50 mmol/L tris-HCl, 5 mmol EDTA) for 10 minutes and fixed with 4% paraformaldehyde. After dehydronation, sections were incubated in hybridization buffer (50% formamide, 1x Denhardt’s solution, 10% dextran sulfate) containing digoxigenin-labeled NPY at 55°C for 20 hours. Between each step sections were rinsed twice in 0.1 mol/L phosphate buffer (PB, pH 7.2) for 5 minutes. Sections were then treated with the following: 5xSSC (NaCl, 0.73 mol/L, Na-citrate, 0.073 mol/L, pH 7) wash at 60°C for 20 minutes and a stringent wash in 50% formamide for 30 minutes at 60°C. Finally, sections were incubated with sheep antidigoxigenin antibody conjugated to alkaline phosphatase (antidig-AP, Fab fragments, 1:1,000; Boehringer Mannheim) for 24 hours at room temperature. The developer was freshly prepared by the addition of 50 μL of 4-nitroblue tetrazolium chloride solution (NBT; Boehringer Mannheim) and 37.5 μL of 5-bromo-4-chloro-3-indolyl phosphate solution (BCIP, X-phosphate; Boehringer Mannheim) in 10 mL Tris buffer (100 mmol/L Tris-HCl, 100 mmol/L NaCl, 50 mmol/L NaCl2, pH 9.5) at room temperature in the dark for 6 hours. Lastly, the sections were mounted on slides, treated for 10 minutes with 4% paraformaldehyde, and dehydrated using a graded series of ethanol and xylene and coverslipped.

Measurement of NPY peptide by immunocytochemistry. The brains were cut as described above for in situ hybridization. The tissue sections were placed in an 80% methanol phosphate-buffered saline (PBS) solution containing 0.3% H2O2 for 30 minutes. The sections were then incubated with normal goat serum (1:10 dilution in PBS with 0.5% Triton X-100) for 30 minutes before being incubated with NPY primary antibody (1:1,000 dilution, Peninsula, Belmont, CA) at room temperature for 24 hours. The tissues were exposed to secondary antiserum, biotinylated antirabbit IgG (Vectorstain Elite Kit, Vector, Burlington, Canada) for 1 hour. The sections were processed further using standard Vectorstain ABC techniques with 0.01% 3,3’-diaminobenzidine tetrahydrochloride (Sigma, St Louis, MO) as the substrate. Between each step the sections were rinsed twice with 0.1 mol/L PBS (pH 7.4). The sections were mounted on slides, dehydrated with graded series of ethanol and xylene, and coverslipped.

Quantification of in situ hybridization and immunoreactivity. Using a rat brain atlas and a digital imaging system, NPY was quantified in rat brain tissue. Different hypothalamic and extrahypothalamic areas were examined on 2 levels: (1) PVN (Bregma 1.8 mm) and (2) ARC, median eminence (ME), frontal cortex (FC) and central nucleus of the amygdala (CNA) (Bregma 2.8 mm). The densities of cells or fibers in 2 to 3 sections at the same level were measured for each rat. A Nikon microscope was used with a 4 x illumination objective when focused on the cells and 10 x when focused on the fibers. A video camera was connected to an IBM computer with Northern Eclipse Software (Empix Imaging, Mississauga, Canada) and converted the microscopic field to a digital image, with a grey value ranging from 0 to 255. To count the number of black pixels, we established a threshold above which pixels were counted. The threshold was the same for all sections counted.

Statistical Analysis

Values are expressed as means ± SEM. Statistical significance was determined by a 2-way analysis of variance (ANOVA) followed by the Newman-Keuls test. The level of statistical significance was set at P < .05.
RESULTS

Experiment 1

Food and fluid intake, body weight, body fat, plasma glucose, and hormones. After 3 weeks of BMOV treatment, food intake was significantly decreased in both lean and fatty rats: -10% in lean rats and -13% in fatty rats compared with the corresponding untreated rats (Table 1). Both body weight and body fat in the BMOV-treated fatty rats were significantly decreased compared with the untreated fatty rats. Body fat was decreased from all areas with the greatest decrease in the inguinal area (data not shown). Therefore, the results were pooled. Body weight and body fat of BMOV-treated lean rats were not significantly different from untreated lean rats. Fluid intake was only different between fatty and lean-treated groups. That is, there was no significant difference produced by vanadium treatment.

Fatty rats exhibited both hyperinsulinemia and hyperleptinemia compared with lean rats. The decrease in body fat was accompanied by a decline in leptin (-25%) and insulin (-68%) levels in treated fatty rats compared with the untreated group (Table 1). There were no differences in leptin and insulin levels between untreated and treated lean rats.

Compared with lean rats, fatty rats were mildly hyperglycemic, which was partially corrected after BMOV treatment. In the lean groups, BMOV treatment did not affect plasma glucose levels (Table 1). The dose of vanadium for each group was: lean-treated, 0.2 ± 0.02 mmol/kg/d and fatty-treated, 0.18 ± 0.02 mmol/kg/d.

NPY mRNA and content in hypothalamic nuclei. The hypothalamic NPY mRNA and peptide-immunoreactivity (IR), examined by in situ hybridization and immunocytochemistry, were similarly decreased in the BMOV-treated groups in both lean and fatty rats compared with corresponding untreated groups (Fig 1). Using a precise anatomical analysis, 2 specific areas were distinguished by their response to vanadium. One was a specific area of ARC, which has a dense cluster of NPY-synthesizing neurons, and the other was the PVN. A sample photo of ARC was a pictorial representation of BMOV-effects on NPY (Fig 2).

Fatty rats exhibit high levels of NPY mRNA and peptide-IR fibers in ARC compared to lean rats. In the lean animals, BMOV treatment significantly lowered mRNA (-20%) (Figs 1A and 2) and peptide-IR fibers (-30%) (Fig 1B) in ARC.

![NPY mRNA levels in ARC](A)

![NPY peptide-IR in ARC](B)

![NPY peptide-IR in PVN](C)

Fig 1. Effect of 3-week BMOV treatment on NPY mRNA in the ARC (A), NPY peptide IR in the ARC (B), and NPY peptide IR in the PVN (C). L, untreated lean; LT, BMOV-treated lean; F, untreated fatty; FT, BMOV-treated fatty (n = 5/group). Statistical analysis was performed by 2-way ANOVA followed by a Newman-Keuls test, P < .05. Shared letters refer to groups that are not significantly different at P < .05.

Table 1. General Characteristics of the Animals After a 3-Week Treatment With BMOV

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Lean</th>
<th>Lean-Treated</th>
<th>Fatty</th>
<th>Fatty-Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food intake (g/d)</td>
<td>24 ± 0.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22 ± 0.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>40 ± 0.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35 ± 1.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fluid intake (mL/d)</td>
<td>42 ± 2&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>32 ± 3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>47 ± 4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>39 ± 3&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>324 ± 14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>289 ± 10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>486 ± 23&lt;sup&gt;b&lt;/sup&gt;</td>
<td>428 ± 18&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Body fat (g)</td>
<td>9.4 ± 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.1 ± 0.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>70 ± 6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>58 ± 5&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma insulin (ng/mL)</td>
<td>2.6 ± 0.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.3 ± 0.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.6 ± 0.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.1 ± 0.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma leptin (ng/mL)</td>
<td>1.46 ± 0.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.9 ± 0.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>47 ± 6.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>35 ± 4.0&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>6.6 ± 0.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.4 ± 0.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.2 ± 0.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8.0 ± 0.3&lt;sup&gt;c&lt;/sup&gt;</td>
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</table>

NOTE. The 4 experimental groups were lean (n = 19), lean-treated (n = 18), fatty (n = 18), and fatty-treated (n = 18). Values are mean ± SEM. Statistical analysis was performed by ANOVA followed by a Newman-Keuls test, P < .05. Shared letters refer to groups that are not significantly different, at P < .05.
similarly in PVN, BMOV decreased NPY peptide (-27%) (Fig 1C). In the fatty groups, NPY mRNA (Figs 1A and 2) and peptide IR levels in the ARC (Fig 1B) were significantly decreased by 29% and 31%, respectively; NPY peptide IR level in the PVN was also decreased by 37% (Fig 1C). In contrast to the ARC, NPY mRNA expressing neurons in the FC and the CNA did not show significant changes between treated and untreated rats in either the lean or fatty groups (data not shown).

Experiment 2

Food intake, body weight, body fat, plasma insulin, and glucose. Food intake and body weight were significantly decreased in both lean and fatty BMOV-treated rats as compared with untreated rats (Table 2). Compared with untreated fatty rats, plasma insulin and glucose in BMOV-treated fatty rats were decreased by 63% and 9.5%, respectively. There were no differences in insulin and glucose levels between untreated and treated lean rats (Table 2).

Plasma Leptin

There were no significant differences in leptin levels among any of the lean groups (Fig 3A). In fatty groups, leptin levels in non–insulin-injected BMOV-treated fatty rats decreased by 27% as compared with untreated fatty rats. Insulin injection elevated (+100%, P < .001) circulating leptin levels in BMOV-treated fatty rats, although this effect was not observed in untreated fatty rats (Fig 3B).

Adipose Tissue Leptin

Leptin protein expression in lean groups was not detectable by this method. Compared with untreated fatty rats, leptin protein expression in adipose tissue in non–insulin-injected BMOV-treated rats was significantly decreased (40%). Insulin administration increased (60%) leptin protein expression in adipose tissue in BMOV-treated fatty rats (Fig 4).

DISCUSSION

In agreement with previous studies,7,8 the present results show that vanadium treatment significantly reduced food intake and body weight in both lean and fatty rats. Moreover, the data also show that BMOV decreased hypothalamic NPY levels in both lean and fatty rats and suggest that the effect of BMOV on food intake may be linked to its action on NPY in the hypothalamus. It has been shown that vanadium either injected into the lateral cerebral ventricle or administered orally via the drinking water not only suppressed food intake, but also enhanced glucose utilization in brain tissue.7,31 It appears that orally administered vanadium can both enter and produce effects on the brain. Our results showed that BMOV decreased NPY in ARC and PVN, but not in other areas of the brain. NPY in both ARC and PVN has been shown to play an important role in food intake regulation.10,11 Collectively, the results suggest that BMOV in the hypothalamus leads to a decrease in NPY levels and sends a signal that can suppress food intake. Vanadium treatment at this dose did not decrease fluid intake, and animals showed no sign of toxicity. The decrease in food intake does not appear to be a toxic effect.
Mechanism(s) underlying the effect of BMOV on NPY are unclear. Previous studies have shown that vanadium is capable of mimicking insulin’s actions in different tissues.6-9 It has been shown that insulin can also decrease food intake, body weight, and NPY in the hypothalamus after intracerebroventricular injection in rats.19,32 Thus, vanadium appears to mimic insulin action in the brain, as well. The actions of BMOV on hypothalamic NPY appear to have site-specificity. BMOV produced effects similar to those of intracerebroventricular insulin injection.19 Specifically, BMOV decreased NPY levels in the ARC-PVN system, but did not affect NPY neurons in the FC and NPY levels in the hypothalamus via an insulin postreceptor-intracellular signaling pathway, and that this effect decreases food intake. In the only other study on the effects of vanadium on NPY, Malabu et al33 did not find a decrease in NPY levels in STZ-diabetic rats treated with a very low dose of sodium metavanadate (0.03 mmol/kg/d). The difference in the result is likely due to a dose difference, as well as the different animal model.

Metabolic abnormalities such as glucose intolerance, hyperlipidemia, hyperinsulinemia, hyperleptinemia, insulin resistance, and leptin resistance are found in both human and animal obesity.8,27 Compared with Zucker lean rats, the fatty Zucker (fa/fa) rats appear to have a decreased response to insulin, with no response to intracerebroventricular insulin administration in terms of food intake, body weight, and NPY levels in the brain.20,36 Hardie et al37 also showed no change in leptin levels in fa/fa Zucker rats 4 hours after administration of insulin (10 U/kg). However, they did find that this dose of insulin significantly increased plasma leptin in lean rats. The increase in leptin following insulin in lean animals in the present study was significant using a t test, but not by ANOVA. The low amount of leptin in lean animals due to the relative lack of fat contributed to this result, and the lack of effect of vanadium treatment may be due to the relative low amount of leptin. The unaltered leptin levels after insulin administration in untreated fatty Zucker rats shown in our study is likely due to insulin resistance in these rats. Leptin levels are related to the amount of body fat and with decreased body fat, the hyperleptinemia in BMOV-treated obese rats was decreased compared with untreated obese rats. However, 15 minutes after a single IV administration of insulin (5 U/kg) to BMOV-treated fatty Zucker rats, plasma leptin levels were significantly increased. These results suggest insulin may increase leptin levels due to increased insulin sensitivity in the adipose tissue of BMOV-treated obese rats. Other evidence showing an improvement in insulin sensitivity in fatty rats is the decrease of plasma insulin and glucose levels after BMOV treatment. The data suggest that an increase in insulin sensitivity in the brain of fatty rats, as in adipose tissue, may enhance inhibition of insulin on NPY and appetite. This hypothesis will be the subject of further studies.

In several studies, protein-tyrosine phosphatase (PTPases) has been found to be involved in insulin signal transduction.38-40 Some PTPases, such as PTP-1B, may also be involved in the regulation of body weight and to insulin resistance.41,42 Ahmad and Goldstein43 found that the increases in activity of PTPases and the amount of PTP-1B in skeletal muscle were associated with severe insulin resistance in the Zucker obese and Zucker diabetic fatty rats. PTP-1B-/- mice showed increased phosphorylation of the insulin receptor after insulin injection and enhanced insulin sensitivity as compared with PTP-1B+/+ (wild-type) mice.41 After 10 weeks of treatment with a high-fat diet, the PTP-B-/- mice were resistant to weight gain and remained insulin sensitive, whereas the PTP1B+/+ mice rapidly gained weight and were insulin resistant.41 Vanadium is a potent nonselective PTP inhibitor in vivo and in vitro.43-46 We recently found BMOV inhibits PTP-1B in vivo

Table 2. General Characteristics of Animals After a 10-Week Treatment With BMOV

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Lean</th>
<th>Lean-Treated</th>
<th>Fatty</th>
<th>Fatty-Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food intake (g/d)</td>
<td>31 ± 1*a</td>
<td>27 ± 1*b</td>
<td>34 ± 1*c</td>
<td>28 ± 1*b</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>418 ± 8*a</td>
<td>387 ± 5*b</td>
<td>565 ± 10*c</td>
<td>522 ± 13*d</td>
</tr>
<tr>
<td>Plasma insulin (ng/mL)</td>
<td>0.8 ± 0.04*a</td>
<td>0.7 ± 0.07*b</td>
<td>7.2 ± 0.73*b</td>
<td>2.7 ± 0.48*c</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>5.9 ± 0.2*a</td>
<td>5.9 ± 0.1*a</td>
<td>7.7 ± 0.2*b</td>
<td>7.1 ± 0.4*d</td>
</tr>
</tbody>
</table>

NOTE. The 4 experimental groups were lean (n = 14), lean-treated (n = 14), fatty (n = 15), and fatty-treated (n = 14). Values are mean ± SEM. Statistical analysis was performed by ANOVA followed by a Newman-Keuls test, P < .05. Shared letters refer to groups that are not significantly different, at P > .05.
and in vitro (data not shown), thus there may be a link between BMOV effects on PTPases and body weight.

In summary, the fatty Zucker rat is characterized by hyperinsulinemia, high NPY levels, and hyperphagia. Chronic BMOV treatment decreased food intake, body fat, plasma insulin levels, and NPY levels in the hypothalamus and, as well, increased insulin sensitivity. These data support the concept that vanadium compounds, as potent insulin-enhancing agents, may prove to be useful in treating obesity, and that the decrease in food intake is a specific effect of vanadium in this animal model.

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