Evidence for the Improvement of Noninsulin-Dependent Diabetes Mellitus in KKA\(^b\) Mice with Daily Oral Administration of Bis(6-methylpicolinato)oxovanadium(IV) Complex

Yae Fujisawa and Hiromu Sakurai\(^a\)

Department of Analytical and Bioorganic Chemistry, Kyoto Pharmaceutical University, 5 Nakauchi-cho, Misasagi, Yamashina-ku, Kyoto 607–8414, Japan.

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A vanadyl complex, bis(6-methylpicolinato)oxovanadium(IV), VO(6MPA), with VO(N\(_2\)O\(_2\)) coordination mode, was found to exhibit a normoglycemic effect on KKA\(^b\) mice with hereditary noninsulin-dependent diabetes mellitus with daily oral administration.

**Key words** vanadyl complex, insulinomimetic activity, oral administration, VO(N\(_2\)O\(_2\)) coordination, NIDDM

Recent intensive research has demonstrated that exogenous vanadyl (oxidation state +4) and vanadate (oxidation state +5) ions both mimic the biological actions of insulin in rat adipocytes in terms of hexose uptake, stimulation of glucose oxidation, and inhibition of lipolysis.\(^1\)–\(^4\) However, due to the low insulinomimetic activity of vanadyl (VO(SO\(_4\))\(_2\)) attributed to the solubility and stability of vanadyl ions at neutral pH values, and permeation into cell interior, vanadate ions were exclusively used in such experiments.\(^5\)–\(^7\) Vanadate ions administered orally (in drinking water) to streptozotocin (STZ)-induced hyperglycemic rats, a model of insulin-dependent diabetes mellitus (IDDM), have been demonstrated to reduce the high levels of circulating glucose levels to normal values.\(^5\)–\(^9\) Moreover, it was found that vanadate administration is also effective in experimental models of non-insulin-dependent diabetes mellitus (NIDDM). Oral vanadate therapy in db/db and ob/ob mice induced normoglycemia,\(^10\)

while oral administration of insulin failed to do so.\(^11\)

Attempts to use vanadyl ions have been made, because vanadate ions have the disadvantage of being 6- to 10-fold more toxic than vanadyl ions.\(^12\) To overcome the solubility of vanadyl ions, autoxidation of vanadyl ions to vanadate, and vanadate toxicity in animals, we have used vanadyl complexes with different coordination modes involving VO(O\(_2\)), VO(N\(_2\)O\(_2\)), VO(N\(_3\)S\(_2\)), and VO(S\(_2\))\(_5\).\(^11\)–\(^13\) In such systemic investigations, we first examined the complexes for the in vitro insulinomimetic activities such as potentiation of glucose incorporation in rat adipocytes and suppression of free fatty acid (FFA) release from adipocytes treated with epinephrine,\(^14\)–\(^15\) and then evaluated the in vivo insulinomimetic action in STZ-induced hyperglycemic rats (STZ rats) with IDDM by intraperitoneal (i.p.) injection or oral administration.\(^14\)–\(^18\) Among the complexes, we found that bis(6-methylpicolinato)oxovanadium(IV) (VO(6MPA)) complex is the most effective agent in treating the hyperglycemia of STZ rats in intraperitoneal injection as well as oral administration.\(^18\) On the basis of these observations and results, we further attempted to use VO(6MPA) to treat hyperglycemic animals with NIDDM.

To the authors' knowledge, this paper reports the first example of treating hyperglycemic KKA\(^b\) mice with NIDDM with the vanadyl complex VO(6MPA) given daily by oral administration.

VO(6MPA) was prepared in aqueous solution, pH 6–7, by mixing 6-methylpicolinic acid (Tokyo Kasei Organic Chemical, Tokyo, Japan) and VOS\(_4\) (VS) (Nakalai Tesque, Kyoto, Japan) in a molar ratio of 2:1, respectively, and washed with water, as reported previously.\(^18\)

KKA\(^b\) mice (Clea Japan, Tokyo, Japan) weighing 30–35 g were divided into 4 groups: 1) control group; 2) intraperitoneal injection VS-treated group; 3) intraperitoneal injection VO(6MPA)-treated group; and 4) oral VO(6MPA)-treated

![Fig. 1. Changes in Blood Glucose Level in KKA\(^b\) Mice Given VOSO\(_4\) or VO(6MPA) by Daily Injection (Left) (0.049 mmol/kg Weight i.p. for 12 d and Then No Treatment) and Oral Administration (Right) (0.098 mmol/kg Body Weight for the First 2 d and 0.196 mmol/kg for the Following 12 d and Then No Treatment)](image_url)

Each symbol represents the mean±S.D. for five mice. – - control mice, ■ - VO(6MPA)-treated mice by intraperitoneal injection, — - VOSO\(_4\)-treated mice by intraperitoneal injection, and — — VO(6MPA)-treated mice by oral administration.

* To whom correspondence should be addressed.

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Table 1. Serum parameters of KKA' Mice Treated with VO(6MPA) by Oral Administration for 14 d

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Glucose (mg/dl)</th>
<th>Insulin (mU/ml)</th>
<th>FFA (mEq/l)</th>
<th>BUN (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>578±50</td>
<td>310±35</td>
<td>0.89±0.15</td>
<td>32.4±6.5</td>
</tr>
<tr>
<td>VO(6MPA)</td>
<td>273±30*</td>
<td>236±39*</td>
<td>1.04±0.19</td>
<td>28.5±4.5</td>
</tr>
</tbody>
</table>

VO(6MPA) was given by daily oral administration to KKA' mice at doses of V 0.098 mmol/kg body weight for first 2 d and V 0.196 mmol/kg for the following 12 d. Data are expressed as the mean±S.D. for five mice. *: Significance p<0.01 vs. no treatment (Student's t-test).

The present study indicates that VO(6MPA) has a normoglycemic effect not only in IDDM model rats but also in NIDDM model mice. Moreover, the high glucose levels as well as high BUN levels observed in NIDDM mice were improved. Therefore VO(6MPA) is expected to be effective in treating milder forms of NIDDM such as in humans. Furthermore, it has recently been reported that oral vanadate and vanadyl ions both improve the insulin resistance and glucose tolerance that are characteristic of NIDDM patients.21,22 Thus the lipophilic vanadyl complex VO(6MPA)23 is a more potent oral therapeutic agent in treating both IDDM and NIDDM than vanadium ions. A more refined investigation involving the mechanism of action of VO(6MPA) is in progress.

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References and Notes
19) The body weights of the mice were measured daily during administration of the compounds. On days 0 and 12 of the experiments, the body weights of the control mice and those treated with intraperitoneal injection of V and VO(6MPA) were 36.7±1.8 g and 42.7±2.4 g, 34.8±1.2 g and 44.1±2.0 g, and 36.4±2.1 g and 44.2±2.9 g, respectively.
20) On days 0 and 14 of the experiments, the body weights of the mice treated with oral VO(6MPA) were 35.0±1.1 g and 37.4±0.9 g, respectively.
21) Li J., Elberg G., Crans D., Shechter Y., Biochemistry, 35, 8214—8318


