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Metallokinetic Study of Zinc in the Blood of Normal Rats Given Insulinomimetic Zinc(II) Complexes and Improvement of Diabetes Mellitus in Type 2 Diabetic GK Rats by their Oral Administration

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Summary: In order to understand the insulinomimetic activity of zinc(II) complexes, we studied the metallokinetic features of zinc in the blood of normal rats given the zinc complexes, bis(maltolato)zinc(II) (Zn(mal)$_2$) and bis(6-methylpicolinato)zinc(II) (Zn(6mpa)$_2$) by comparing each of them with an ionic form of zinc chloride (ZnCl$_2$). The bioavailability of the zinc(II) complexes following oral administration was enhanced to 1.4–1.5-fold that of ZnCl$_2$ with respect to zinc level. Based on the results of a metallokinetic analysis and administration method in normal rats, we examined the antidiabetic ability of the zinc(II) complexes in GK rats, a model animal of type 2 diabetes mellitus. High blood glucose levels of GK rats were normalized following intraperitoneal injections and oral administration of the zinc(II) complexes, in which the Zn(6mpa)$_2$ complex was found to be more effective than Zn(mal)$_2$. The present results are noteworthy, not only due to their potential relevance for clinical application, but also for the development of new zinc(II) complexes.

Key words: zinc; pharmacokinetic study; GK rat; type 2 diabetes mellitus

Introduction

A new concept for treating diabetes mellitus has been developed that involves the use of metal complexes such as vanadium,$^1$ manganese,$^2$ cobalt,$^3$ and selenium,$^4$ in place of insulin injection and synthetic therapeutics for type 1 (insulin-dependent diabetes mellitus; IDDM) and type 2 (non-insulin-dependent diabetes mellitus; NIDDM) diabetes mellitus. Recently, we proposed another candidate, a group of zinc(II) complexes, including bis(maltolato)zinc(II) (Zn(mal)$_2$),$^5$ bis(amino acid)zinc(II) (Zn(aa)$_2$),$^6$ and bis(picolinato)zinc(II) (Zn(pic)$_2$),$^7$ as well as an analogue of the latter, the bis(6-methylpicolinato)zinc(II) (Zn(6mpa)$_2$) complex. These candidates were chosen on the basis of the results of their in vitro insulinomimetic activities in isolated rat adipocytes and in vivo hypoglycemic potential in type 2 diabetic model KK-A$^v$ mice that had been administered the complexes daily via intraperitoneal injections. To develop clinically useful insulinomimetic zinc(II) complexes, demonstration of the effectiveness of oral administration will be necessary, as well clarification of the pharmacokinetic features of the complexes.

Recently, it was reported that vanadyl sulfate (VOSO$_4$; VS) was shown to be effective in treating subjects with type 2 diabetes mellitus when they were given an oral daily dose of 150 mg for 6 weeks.$^8$ In that study, plasma vanadium concentrations were below 10 mg/L before treatment, whereas after treatment, an increase to 104 ± 18 mg/L after 6 weeks of VS administration was observed. This result indicated that control of the plasma glucose concentration can be achieved by VS treatment and that the monitoring of vanadium concentrations in the blood of the subjects is necessary with such treatment. We then analyzed the pharmacokinetic feature of VS and found that the bioavailability of VS is very low (4.8%) on oral administration but can be enhanced to approximately 10–13% via jejunal and ileal administration.$^9$ Based on these results, we proposed the administration to diabetic patients of a
capsule containing VS that had been coated such that it would ensure vanadium absorption at the jejunum and ileum. Furthermore, we indicated the usefulness of pharmacokinetic study for the development of therapeutic agents.

Using zinc(II) complexes, we examined the pharmacokinetic features of zinc in the blood of normal rats given zinc(II) ion and zinc(II) complexes. On the basis of the obtained pharmacokinetic parameters, we tested the in vivo hypoglycemic activity of the zinc(II) complexes following oral administration in GK rats, a reliable animal model of type 2 diabetes with low insulin secretion, non-obesity, and modest hyperglycemia.

On the basis of the results of pharmacokinetic study, the present results demonstrated for the first time that the zinc(II) complexes Zn(mal)\(_2\) and Zn(6mpa)\(_2\) are effective for the treatment of diabetes in a rat model when orally administered.

Materials and Methods

Materials: Zinc chloride (ZnCl\(_2\)), nitric acid (HNO\(_3\)) for the detection of poisonous metals), perchloric acid (HClO\(_4\)) for the detection of poisonous metals) and hydrogen peroxide (H\(_2\)O\(_2\)) for the atomic absorption in the spectrochemical analysis for wet digestion, and standard solutions of Zn for the atomic absorption spectrometry (AAS) measurements were all purchased from Wako Pure Chemicals (Osaka, Japan). Pentobarbital (50 mg/mL), sodium heparin, and Aron Alpha (an instant adhesive for surgery) were purchased from Dainabot Co. (Osaka, Japan), Shimizu Co. (Osaka, Japan), and Sankyo Co. (Tokyo, Japan), respectively. Cyclodextrin was obtained from Tokyo Kasei Organic Chemicals (Tokyo, Japan). All other compounds used were of analytical reagent grade. Bis(maltolato)zinc(II) (Zn(mal)\(_2\)) and bis(6-methylpicolinato)zinc(II) (Zn(6mpa)\(_2\)) were synthesized by previously reported methods.

Animals: Normal male Wistar rats (8 weeks old, 240–250 g) and GK rats (4 weeks old, 70–80 g) were purchased from Shimizu Experimental Material Co. (Kyoto, Japan) and CLEA Japan Inc. (Tokyo, Japan), respectively. Before both single and chronic administration, rats were housed in a temperature-controlled room at 23 ± 1°C on a 12 h light/12 h dark cycle. Rats were fed a standard laboratory diet (MF Oriental Yeast Co., Tokyo) and were given tap water ad libitum. Normal rats were fasted overnight for 12 h before single administration. ZnCl\(_2\) was dissolved in a physiological saline (0.9% NaCl) for the administration. Zn(mal)\(_2\) and Zn(6mpa)\(_2\) were suspended in 13% \(\gamma\)-cyclocelotin solution for the injection and the oral administration. All animal experiments were approved by the Experimental Animal Research Committee of Kyoto Pharmaceutical University and were performed according to the Guide-
AAS were as follows: drying, 90°C for 10 sec; ashing, 300°C for 30 sec; and atomizing, 1500°C for 4 sec.

**Pharmacokinetic analyses of the blood**

The time course of zinc concentrations in the blood, in which zinc concentrations in the blood at each sampling time after the administration of saline (0.9% NaCl) alone were subtracted from those at each sampling time after the administration of the zinc complexes dissolved in physiological saline (0.9% NaCl), was evaluated on the basis of non-compartment pharmacokinetic analysis (moment analysis).

The area under the zinc concentration in the blood-time curve (AUC), maximal zinc concentration ($C_{max}$), mean residence time (MRT) of zinc, and time required to attain $C_{max}$ ($T_{max}$) were estimated model-independently. Bioavailability (Fa) in each group was calculated by the following equation: $Fa = (AUC_{p.o.} \cdot \text{Dose}_{p.o.})/(AUC_{i.v.} \cdot \text{Dose}_{i.v.})$.

**Chronic administration of Zn(mal)$_2$ and Zn(6mpa)$_2$ to GK rats:** GK rats were allowed free access to standard solid food and tap water for one month (4 weeks) from the purchase before chronic administration of zinc compounds. The body weight of GK rats and the intake of solid food and drinking water in each rat were measured daily during the experiments. GK rats (n = 8) were given Zn(mal)$_2$, intraperitoneally at a dose of 62 μmol (4 mg) zinc/kg body weight for 30 days. Another group of GK rats (n = 10) was administered Zn(6mpa)$_2$, intraperitoneally at a dose of 62 μmol (4 mg) zinc/kg body weight for the first 16 days, at a dose of 8 μmol (0.5 mg) for 6 days, and then at a dose of 31 μmol (2 mg) for another 23 days. These zinc complexes were also administered to GK rats by oral administration. Zn(mal)$_2$ was given orally to GK rats (n = 6) at doses of 462 μmol (30 mg) zinc/kg body weight for 15 days and then 308 μmol (20 mg) for another 15 days. Zn(6mpa)$_2$ was given orally at doses of 462 μmol (30 mg) zinc/kg body weight for the first 16 days, then 77 μmol (5 mg) for 6 days, and 231 μmol (15 mg) for another 23 days (n = 10). During the administration period, blood glucose levels were measured daily using Fuji Dri-Chem Slide and Fuji Dri-Chem 1000 (Fuji Film Med. Co., Tokyo, Japan).

**Oral glucose tolerance tests:** Before and after the administration of the zinc complexes to GK rats, 40% glucose solution (2 g/kg body weight) was intragastrically administered to the rats in the fasting state (12 h). Blood samples were obtained from the tail vein at 0, 15, 30, 60, 90, 120, 180, and 240 min after administration. Blood glucose levels were determined using Fuji Dri-Chem Slide and Fuji Dri-Chem 1000 (Fuji Film Med. Co., Tokyo, Japan).

**Measurement of serum parameters and HbA$_1c$:** Serum parameters and HbA$_1c$ were determined before and after the administration of zinc complexes. Serum glucose levels (GLU), blood urea nitrogen (BUN), glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT), total cholesterol (TCHO), and triglyceride (TG) were determined with Fuji Dri-Chem 3000 (Fuji Film Med. Co., Tokyo, Japan). Serum insulin was measured by GLAZYME insulin-EIA test (Wako Pure Chemicals). HbA$_1c$ was measured by a DCA 2000 system (Bayer Co., Tokyo, Japan).

**Statistical analyses:** All experiments results were expressed as the arithmetic mean and standard deviation (s.d.) of measurements. Statistical analysis was performed using analysis of variance at a 5% (P < 0.05) or 1% (P < 0.01) significance level.

**Results**

**Metallokinetic analysis:** ZnCl$_2$, Zn(mal)$_2$ or Zn(6mpa)$_2$ was given to normal rats by intravenous (i.v.) injection (15 μmol/kg body weight), oral administration (154 μmol/kg body weight), and intraduodenal (i.d.) administration (154 μmol/kg body weight), and the zinc concentration in the blood was measured. The time course of zinc concentrations in the blood of rats and the calculated metallokinetic parameters are summarized in Fig. 1–3 and Table 1, respectively. Although the mean endogenous zinc concentration in the blood of rats was 100 nmol/mL, the zinc concentration in the blood of rats given the vehicle (0.9% NaCl) alone changed at each sampling time. Therefore, in calculation of metallokinetic parameters, the zinc concentration in the blood due to the administration of zinc complexes was obtained from the zinc concentration after administration of zinc compounds by subtracting the concentration in the blood of rats given the vehicle alone at each sampling time. No significant differences in the metallokinetic parameters in rats given the zinc compounds by i.v. administration were observed. $CL_{tot}$ values obtained for the data by i.v. administration were used for calculating the Fa value on the assumption of a linear condition, which is defined as bioavailability from the non-intravenous administration sites.

To evaluate the intestinal absorption of the zinc compounds, the three zinc compounds were given to rats by oral and i.d. administration. The Fa values of rats received oral Zn(mal)$_2$ and Zn(6mpa)$_2$ (37.3% and 32.6%, respectively) were higher than that of rats given ZnCl$_2$ (23.6%). The $C_{max}$ values for the three compounds given by oral administration were almost unchanged.

**Administration of zinc complexes to GK rats:** Because the bioavailability in terms of zinc concentration in the blood was found to enhance on oral administration of the zinc(II) complexes in normal rats by metallokinetic analysis, Zn(mal)$_2$ or Zn(6mpa)$_2$ were given to GK rats by daily oral administration for 30 or 45 days, in which the data were compared with those for intraperitoneal (i.p.) injection. Blood glucose levels
Fig. 1. Time course of zinc concentration in the blood of normal rats after intravenous injection (i.v., ○), oral (p.o., ▲) administration, and intraduodenal (i.d., □) administration of ZnCl₂. Rats were given ZnCl₂ at doses of 1 mg (i.v.) and 10 mg (p.o. and i.d.) Zn/kg body weight. Each symbol represents the mean ± s.d., n = 3–5. Solid and dotted lines represent zinc concentration after administration of ZnCl₂ and the vehicle alone, respectively.

Fig. 2. Time course of zinc concentration in the blood of normal rats after intravenous injection (i.v., ○), oral (p.o., ▲) administration, and intraduodenal (i.d., □) administration of Zn(mal)₂. Rats were given Zn(mal)₂ at doses of 1 mg (i.v.) and 10 mg (p.o. and i.d.) Zn/kg body weight. Each symbol represents the mean ± s.d., n = 3–5. Solid and dotted lines represent zinc concentration after administration of Zn(mal)₂ and the vehicle alone, respectively.
Fig. 3. Time course of zinc concentration in the blood of normal rats after intravenous injection (i.v., ◆), oral administration (p.o., ▲), and intraduodenal (i.d., ⬤) administration of Zn(6mpa)2. Rats were given Zn(6mpa)2 at doses of 1 mg (i.v.) and 10 mg (p.o. or i.d.) Zn/kg body weight. Each symbol represents the mean ± s.d., n = 3–5. Solid and dotted lines represent zinc concentration after administration of Zn(6mpa)2 and the vehicle alone, respectively.

Table 1. Metallokinetic parameters in the absorption and elimination processes of ZnCl2, Zn(6mpa)2 or Zn(mal)2 after intravenous injection (i.v.), and oral (p.o.) and intraduodenal (i.d.) administrations

<table>
<thead>
<tr>
<th>Compound</th>
<th>Adm. site</th>
<th>Dose (mg Zn/kg)</th>
<th>AUC (nmol-hr/mL)</th>
<th>Cmax (nmol/mL)</th>
<th>MRT (hr)</th>
<th>Tmax (hr)</th>
<th>CLtot (mL/hr/kg)</th>
<th>Vd (mL/kg)</th>
<th>Fa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZnCl2</td>
<td>i.v.</td>
<td>1</td>
<td>158 ± 9</td>
<td>157 ± 22</td>
<td>0.73 ± 0.02</td>
<td>0.58 ± 0.14</td>
<td>97.4 ± 5.5</td>
<td>72.2 ± 8.4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>p.o.</td>
<td>10</td>
<td>373 ± 34</td>
<td>103 ± 12</td>
<td>2.89 ± 0.08</td>
<td>2.00 ± 0.71</td>
<td>150.4 ± 59.7</td>
<td>112.3 ± 47.4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>i.d.</td>
<td>10</td>
<td>461 ± 50</td>
<td>167 ± 45</td>
<td>2.76 ± 0.17</td>
<td>1.60 ± 0.22</td>
<td>23.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zn(mal)2</td>
<td>i.v.</td>
<td>1</td>
<td>114 ± 45</td>
<td>180 ± 34</td>
<td>0.63 ± 0.30</td>
<td>0.58 ± 0.14</td>
<td>150.4 ± 59.7</td>
<td>112.3 ± 47.4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>p.o.</td>
<td>10</td>
<td>425 ± 48</td>
<td>115 ± 15</td>
<td>3.01 ± 0.28</td>
<td>2.00 ± 0.61</td>
<td>37.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>i.d.</td>
<td>10</td>
<td>291 ± 24</td>
<td>146 ± 13</td>
<td>2.46 ± 0.16</td>
<td>1.00 ± 0.00c</td>
<td>25.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zn(6mpa)2</td>
<td>i.v.</td>
<td>1</td>
<td>135 ± 5</td>
<td>206 ± 21</td>
<td>0.66 ± 0.12</td>
<td>0.58 ± 0.14</td>
<td>113.8 ± 4.0</td>
<td>84.2 ± 6.4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>p.o.</td>
<td>10</td>
<td>440 ± 45</td>
<td>106 ± 10</td>
<td>2.96 ± 0.03a</td>
<td>2.00 ± 0.45</td>
<td>32.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>i.d.</td>
<td>10</td>
<td>416 ± 81</td>
<td>136 ± 25c</td>
<td>2.69 ± 0.22d</td>
<td>1.67 ± 0.29</td>
<td>30.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations are as follows: AUC: area under the zinc concentration in the blood time curve; Cmax: maximal zinc concentration; MRT: mean residence time of zinc; Tmax: time required to attain Cmax; Fa: absorption ratio.

Data are shown as the mean values ± s.d. for 3–5 rats.

Fa = \( \frac{\text{AUC}_{(p.o. or i.d.,)} \cdot \text{D}_{\text{i.v.}}}{\text{AUC}_{\text{i.v.}} \cdot \text{D}_{(p.o. or i.d.,)}} \times 100 \).

Significance level: a: P < 0.05, b: P < 0.01 vs. ZnCl2 at the same administration site, c: P < 0.05, d: P < 0.01 vs. p.o. at the same compound.

significantly decreased by oral administration and i.p. injection of the zinc complexes (Fig. 4). Then we evaluated whether or not the diabetes in GK rats were improved by the glucose tolerance test using oral 2 g glucose/kg body weight (Fig. 5). The fasting blood glucose levels in the GK rats given zinc complexes were not significantly different from those in the untreated GK rats. However, the maximum level of blood glucose in GK rats treated orally with Zn(6mpa)2 was significantly lower than that in the untreated GK rats.

The serum parameters in GK rats treated with the zinc complexes by i.p. injection and oral administration are summarized in Table 2. The serum glucose levels decreased upon i.p. administration of the two zinc complexes and on oral administration of Zn(6mpa)2. HbAic level of GK rats was lower than that of the untreated GK rats when Zn(mal)2 was administered by intraperitoneal injection. Insulin levels were improved in the GK rats
Fig. 4. Changes in blood glucose levels after intraperitoneal injection (i.p.) (open column) and oral (p.o.) (closed column) administration of Zn(mal)$_2$ (A) or Zn(6mpa)$_2$ (B) to GK rats. GK rats received Zn(mal)$_2$ at doses of 4 mg (i.p.) or 20–30 mg (p.o.) Zn/kg body weight, and Zn(6mpa)$_2$ at doses of 0.5–4 mg (i.p.) or 5–30 mg (p.o.) Zn/kg body weight. Each column represents the mean ± s.d., n = 3–4. Significance level: *P < 0.01 vs. 0 day, **P < 0.01 vs. 14 days.

Fig. 5. Changes in blood glucose levels after oral glucose loading (2 g/kg body weight) to GK rats treated with Zn(mal)$_2$ (A) or Zn(6mpa)$_2$ (B). GK rats were untreated (△) or treated by intraperitoneal injection (○) for 30 and 45 days and oral (■) administration for 30 and 45 days of zinc complexes. GK rats received Zn(mal)$_2$ at doses of 4 mg (i.p.) or 20–30 mg (p.o.) Zn/kg body weight, and Zn(6mpa)$_2$ at doses of 0.5–4 mg (i.p.) or 5–30 mg (p.o.) Zn/kg body weight. Each symbol represents the mean ± s.d., n = 3–4. Significance level: *P < 0.05 vs. untreated rats.

given the zinc complexes compared with those of the untreated rats. BUN levels decreased after i.p. administration of the two zinc complexes and after oral administration of Zn(6mpa)$_2$. GPT levels were unchanged by administration of the zinc complexes. GOT levels decreased by i.p. administration of Zn(mal)$_2$ and on oral administration of the two zinc complexes. TCHO levels decreased by i.p. injection and by oral administration of Zn(6mpa)$_2$. TG levels decreased after i.p. administration of the two zinc complexes, as well as following oral administration of Zn(6mpa)$_2$.

Discussion

Diabetes mellitus (DM) is a metabolic disease which causes hyperglycemia and many other complications.15) Recently, it was reported that a variety of metal ions
Table 2. Serum parameters in GK rats treated with Zn(mal)₂ or Zn(6mpa)₂

<table>
<thead>
<tr>
<th>Adm. method</th>
<th>Dose (mg Zn/kg)</th>
<th>Age (week)</th>
<th>GLU (mg/dL)</th>
<th>HbA₁c (%)</th>
<th>Insulin (mU/mL)</th>
<th>BUN (mg/dL)</th>
<th>GPT (U/L)</th>
<th>GOT (U/L)</th>
<th>TCHO (mg/dL)</th>
<th>TG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i.p.</td>
<td>4</td>
<td>10</td>
<td>368 ± 17</td>
<td>3.2 ± 0.2</td>
<td>18.3 ± 3.6</td>
<td>15.7 ± 0.6</td>
<td>35 ± 5</td>
<td>72 ± 11</td>
<td>109 ± 12</td>
<td>71 ± 12</td>
</tr>
<tr>
<td>p.o.</td>
<td>20–30</td>
<td>14</td>
<td>259 ± 16</td>
<td>2.8 ± 0.4</td>
<td>15.5 ± 1.5</td>
<td>12.4 ± 3.5</td>
<td>30 ± 9</td>
<td>45 ± 11</td>
<td>114 ± 18</td>
<td>59 ± 6‡</td>
</tr>
<tr>
<td>Zn(6mpa)₂</td>
<td>i.p.</td>
<td>0.5–4</td>
<td>240 ± 63</td>
<td>3.4 ± 0.3</td>
<td>10.2 ± 1.5‡</td>
<td>11.8 ± 1.2</td>
<td>19 ± 5</td>
<td>73 ± 8</td>
<td>71 ± 15b</td>
<td>51 ± 11b</td>
</tr>
<tr>
<td>p.o.</td>
<td>5–30</td>
<td>16</td>
<td>200 ± 11b</td>
<td>3.7 ± 0.1</td>
<td>10.2 ± 1.5‡</td>
<td>11.8 ± 1.2</td>
<td>19 ± 5</td>
<td>73 ± 8</td>
<td>71 ± 15b</td>
<td>51 ± 11b</td>
</tr>
</tbody>
</table>

Abbreviations are as follows: GLU: serum glucose level; BUN: blood urea nitrogen; GPT: glutamic pyruvic transaminase; GOT: glutamic oxaloacetic transaminase; TCHO: total cholesterol; TG: triglyceride.
Data are shown as the mean values ± s.d. for 3–5 rats.
Significance level; a: P < 0.05, b: P < 0.01 vs. no treatment.

have insulinomimetic activity.¹⁶⁻¹⁸) Coulston and Dandona found that zinc, which is one of the essential elements in animals and humans, stimulates lipogenesis in rat adipocytes, which is similar to the action of insulin.¹⁹) Furthermore, previous studies have demonstrated that zinc acts on adipocytes and promotes the induction of leptin; it also acts on the pancreas, and therefore helps insulin to bind with the insulin receptor, resulting in improvement of the conditions of type 2 DM.²⁰)

Generally, it is known that the complexation of free metal ions lowers the toxicity of metal ions and promotes their absorption into the blood.²¹,²²) We indicated that vanadyl (IV) complexes with picolinate and 6-methyl-picolinate exhibit high insulinomimetic activity²³,²⁴) and that they increase the bioavailability of vanadyl species.⁹) Therefore, we first investigated the absorption processes of two zinc(II) complexes, bis(maltolato)zinc(II) (Zn(mal)₂) and bis(6-methyl-picolinato)zinc(II) (Zn(6mpa)₂), by comparing them with that of an ionic form of zinc chloride (ZnCl₂).

From the results, the Fa values of two zinc(II) complexes after oral administration were found to be 1.4–1.5-fold higher than that of ZnCl₂ (Table 1), similarly to enhancement of the absorption of the vanadyl complexes.⁹,¹⁰)

The bioavailability of BioZn-AAS, a zinc gluconate stabilized with glycine, was reported as being 25–28%.²³) In the present study, ZnCl₂ was found to be absorbed to the same extent (23.6%) (Table 1). However, the zinc complexes were found to be enhanced after their oral administration.

On the basis of the metallokinetic analysis of zinc compounds in normal rats, we examined whether or not the zinc complexes exhibit hypoglycemic activity on oral administration in GK rat, type 2 DM model animal. Previously, Zn(mal)₂ and Zn(6mpa)₂ given by i.p. injection were both found to show hypoglycemic activity in KK-A⁻ mice, a type 2 DM model.²⁵) The GK rat is one of the most reliable models for type 2 diabetes because of the many primary features manifested, including fasting hyperglycemia, impaired insulin response to glucose, hepatic and peripheral insulin resistance, and typical complications.¹¹)

The treatment with Zn(mal)₂ and Zn(6mpa)₂ lowered the blood glucose levels in GK rats (Fig. 4). HbA₁c level, which indicates average blood glucose levels over a long period, is known to increase with aging of diabetic states. In the present study, however, HbA₁c levels were unchanged by Zn(II) complexes. Insulin levels of GK rats were significantly decreased by treatment of Zn(II) complexes. Type 2 DM is resulted from a relative lack of insulin secretion or the decline of insulin sensitivity in targeting organs. From the decrease of insulin levels of GK rats in the present study, insulin sensitivity was thought to enhance by treatment of zinc(II) complexes, suggesting zinc(II) complexes improve the insulin resistance of type 2 DM. BUN, GPT, GOT, TCHO and TG levels were unchanged or decreased in zinc(II) complexes treated GK rats, suggesting that zinc(II) complexes appear to be non-toxic to the renal and hepatic functions, and to improve the hyperlipidemia in diabetes mellitus.

Conclusion

On the basis of the results of the metallokinetic study in normal rats receiving two zinc(II) complexes, the present study revealed for the first time that oral administration of either of Zn(mal)₂ and Zn(6mpa)₂, lowered the blood glucose levels in GK rats with type 2 DM. These results will be useful not only for clinical application in the future but also for developing new and more effective zinc(II) complexes.

References

Improvement of Type 2 Diabetes Mellitus by Zinc Complexes


