Blood and Liver Lipid Concentrations in EDS Shrews Exhibiting Spontaneous Non-Insulin Dependent Diabetes Mellitus (NIDDM)

Tamio OHNO1), Fumihiko HORIO2), Junzoh KITOH3), Shin TANAKA4), Masahiko NISHIMURA1), and Takao NAMIKAWA5)

1) Institute for Laboratory Animal Research, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, 2) Division of Biomodeling, Graduate School of Bioagricultural Sciences, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8601, 3) Emeritus Professor of Nagoya University, 4) National Institute of Longevity Sciences, National Chubu Hospital, 36–3 Gengo Morioka-cho, Ohbu, Aichi, 474-8522, and 5) Laboratory of Animal Genetics, Graduate School of Bioagricultural Sciences, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan

Abstract: The EDS (early-onset diabetes in suncus) colony was developed as a new laboratory colony of the musk shrew and is characterized by a high incidence of early-onset spontaneous non-insulin dependent diabetes mellitus (NIDDM). We examined blood lipid (triglyceride [TG], total cholesterol [TC], phospholipid [PL], free fatty acid [FFA]) and liver lipid (TG, TC, PL) concentrations to investigate the features of lipid metabolism in these animals. All lipid concentrations examined both in blood and liver of the diabetic shrews had a tendency toward higher values than those in non-diabetic shrews. The PL concentration was the only parameter that barely showed a significant difference. Values for all blood lipid concentrations in diabetic shrews at 7–9 months tended to be higher than those of 2-month-old diabetic shrews, although the difference was not significant. These findings indicate that diabetic EDS shrews exhibit a much milder defect of lipid metabolism induced by NIDDM than other rodent models.

Key words: lipid, non-insulin dependent diabetes mellitus (NIDDM), suncus

Non-insulin dependent diabetes mellitus (NIDDM) is a common metabolic disorder with complex forms caused by genetic and environmental factors in humans. Many rodent models have been developed for analysis of the etiology and pathophysiology of this disease [9]. However, they may have some different species-specific biological features due to their phylogenetic distance from humans. To make up for the biological disparity between humans and rodents, it is important to develop many models in various mammalian species and compare their characteristic features. The musk shrew (Suncus murinus, Insectivora), which is not a rodent, has been developed and utilized as a new laboratory animal [4]. This animal may have some interesting character...
istics that are not observed in rodent models for diabetic research. We developed an EDS colony of musk shrews that is characterized by a high incidence of spontaneous early-onset NIDDM without obesity [7, 8]. For this paper, we investigated blood and liver lipid concentrations in EDS shrews to accumulate basic data on the only spontaneous NIDDM model among Insectivora.

Male shrews of the EDS colony, which is maintained at the Laboratory of Animal Genetics, Graduate School of Bioagricultural Sciences, Nagoya University, were used in this study. Only male shrews were used because gender differences in the incidence of diabetes and blood lipids concentrations were observed in many rodent animal models [5, 9]. They were kept in a conventionally conditioned animal room: 23–27°C, no humidity control and 14L10D light, and were supplied commercial trout pellets containing 45.0% protein, 3.5% fat, 3.0% fiber, 13.0% ash and 26.2% complex carbohydrate (No. 7P pellets, Nippon Haigou Shiryou, Tokyo, Japan) and water ad libitum. To determine the blood glucose concentration, blood samples were taken from tail tips and assayed with the Glutest E analyzer (Kyoto Daiichi Kagaku, Kyoto, Japan). Shrews were defined as diabetic when blood glucose concentrations exceeded 200 mg/dl. Blood samples were collected from the right atrium for measurement of blood immunoreactive insulin (IRI), triglyceride (TG), total cholesterol (TC), phospholipid (PL) and free fatty acid (FFA) concentrations. The blood IRI concentration was determined by a double-antibody radioimmunoassay using the ShionoRIA Insulin kit (Shionogi, Osaka, Japan) in which rat insulin was used as the standard. Blood lipid (TG, TC, PL and FFA) concentrations were measured by a Cobas Mira Plus auto-analyzer (Nippon Roche, Tokyo, Japan). After collecting blood samples, shrews were sacrificed and their livers immediately removed and stored at –80°C. Part of the liver was homogenized in 50 ml of chloroform:methanol (2:1). Liver lipids were extracted according to the method of Folch et al [1]. Hepatic TG, TC and PL contents were measured by enzymatic colorimetric methods using Monotest Cholesterol (Boehringer Mannheim GmbH, Mannheim, Germany), Trigly Color III BMY (Boehringer Mannheim GmbH, Mannheim, Germany), and Phospholipid C-Test Wako (Wako, Osaka, Japan), respectively.

Table 1 shows blood glucose, insulin and lipid (TG, TC, PL NEFA) concentrations (Mean ± SEM) in EDS shrews in non-fasting state.

<table>
<thead>
<tr>
<th>Animals</th>
<th>Age (months)</th>
<th>n</th>
<th>BG (mg/dl)</th>
<th>IRI (ng/dl)</th>
<th>TG (mg/dl)</th>
<th>TC (mg/dl)</th>
<th>PL (mg/dl)</th>
<th>NEFA (µEq/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-DM</td>
<td>2</td>
<td>7</td>
<td>74 ± 6</td>
<td>7.6 ± 2.0</td>
<td>20.4 ± 1.2</td>
<td>10.2 ± 1.6</td>
<td>46.3 ± 4.6</td>
<td>76.7 ± 11.5</td>
</tr>
<tr>
<td></td>
<td>7–9</td>
<td>9</td>
<td>102 ± 12</td>
<td>3.7 ± 1.1</td>
<td>22.2 ± 1.7</td>
<td>12.8 ± 1.2</td>
<td>51.3 ± 2.9</td>
<td>128.1 ± 18.7</td>
</tr>
<tr>
<td>DM</td>
<td>2</td>
<td>7</td>
<td>364 ± 23*</td>
<td>4.3 ± 1.0</td>
<td>27.0 ± 7.3</td>
<td>15.3 ± 2.8</td>
<td>64.3 ± 6.3*</td>
<td>174.3 ± 51.0</td>
</tr>
<tr>
<td></td>
<td>7–9</td>
<td>10</td>
<td>383 ± 30*</td>
<td>3.0 ± 0.8</td>
<td>32.9 ± 4.7</td>
<td>20.6 ± 2.0</td>
<td>78.0 ± 4.7*</td>
<td>214.0 ± 31.2</td>
</tr>
</tbody>
</table>

*: P<0.05 vs Non-DM of the same age.
as well as in humans [2], with hypertriglyceremia being characteristic of the hyperlipidemia associated with NIDDM [2]. However, there was no significant difference in the TG concentration between diabetic and non-diabetic EDS shrews, although a significant difference was found in the PL concentration between the two groups in both the blood and liver. We do not know the reason for this finding. It may be a peculiarity of lipid metabolism of suncus. Rodent NIDDM models can be roughly divided into two types according to the onset of hyperlipidemia which often depends on the onset of hyperglycosuria: 1) early-onset type represented by Lepob/Lepob, Leprdb/Leprdb and tub/tub mice [5] and 2) late-onset type such as the OLETF rat [3]. Interestingly, diabetic EDS shrews did not exhibit a significant increase in blood lipid concentrations even when the hyperglycemic condition persisted for more than 6 months. EDS shrews do not belong to either of the aforementioned two types of rodent models. This indicates that the EDS shrew is resistant to hyperlipidemia induced by NIDDM in comparison with other rodent models.

We previously reported fatty liver (severe TG accumulation) and hyperlipidemia in shrews with severe insulin-dependent diabetes mellitus (IDDM) that was induced by the administration of a large dose of streptozotocin (STZ) [6] and concluded that severe hypoinsulinaemia had an important role in these metabolic defects [6]. On the other hand, the spontaneously diabetic EDS shrew did not exhibit fatty liver and manifested very mild increases in blood lipid concentrations compared with STZ-induced IDDM shrews, although blood glucose concentrations were nearly the same in both groups of animals. It was suggested that the nearly normal levels of blood insulin prevented severe defects in lipid metabolism in the spontaneously diabetic EDS shrews.

Further investigation of EDS shrews should be undertaken to reveal new characteristic features not present in current rodent NIDDM models. Such findings may elevate the value of this novel NIDDM model from the viewpoint of comparative biology.

Acknowledgment

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References


Table 2. Liver lipid (TG, TC, PL) levels (Mean ± SEM) in EDS shrews at 2 months of age in non-fasting state

<table>
<thead>
<tr>
<th>Animals</th>
<th>n</th>
<th>TG (mg/g liver)</th>
<th>TC (mg/g liver)</th>
<th>PL (mg/g liver)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-DM</td>
<td>7</td>
<td>11.75 ± 0.27</td>
<td>0.79 ± 0.05</td>
<td>12.85 ± 0.59</td>
</tr>
<tr>
<td>DM</td>
<td>7</td>
<td>12.75 ± 0.56</td>
<td>0.94 ± 0.06</td>
<td>14.54 ± 0.48*</td>
</tr>
</tbody>
</table>

*: P<0.05.