IV. 5. Effects of Hyperglycemia on Myocardial FDG Uptake

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PET using 2-deoxy-2-[18F]fluoro-D-glucose (FDG) has become a valuable method for the evaluation of various myocardial diseases\(^1\). In myocardial imaging with FDG, the increase in myocardial uptake of FDG after glucose loading has been well known. After glucose loading, the increase in insulin levels coupled with the decrease in FFA shifted the metabolic fuel of myocardium from fatty acid to glucose, resulting in an increase in FDG uptake\(^1-3\). Under fasting, distribution of FDG in myocardium is not uniform, that becomes homogeneous after glucose loading\(^4\). However, under severe hyperglycemia in diabetic patients, a defect in myocardial glucose utilization and non-uniformity of FDG distribution has been reported\(^5\). Exact correlation of myocardial FDG uptake and hyperglycemia is not clear. In order to study the effects of hyperglycemia on myocardial FDG uptake in vivo, FDG uptake in vivo was studied using rats under various pre-treatments which induce hyperglycemia.

Materials and methods

The experimental protocol was approved by the Laboratory Animal Care and Use Committee of Tohoku University.

Young male Donryu rats weighing (140-180g) were used for radioisotope study after various pre-treatments which may be expected to modify the blood glucose level. The control rats (n=48) were fasted for 12 hr. The glucose loading group (n=42) was given an oral ingestion of 0.6 ml of 50% glucose 15 min before the radioisotope injection. Also 8 other treatments were performed as shown in Table 1. Stereoptozotocin (Szi) and dehydroascorbic acid have been known to induce experimental diabetes\(^6\). Dexamethasone (Dex), triiodothyronine and epinephrine have been known to induce hyperglycemia clinically. Ascorbic acid as the comparison to the dehydroascorbic acid, and dipyridamole as a popular coronary dilator were also included.

After various hyperglycemic treatments, rats were intravenously injected of 1.11MBq of FDG and killed 1hr later. Blood samples, myocardium, and skeletal muscle from thigh
were excised, weighed and radioactivity was measured using an automated gamma counter. Serum samples were separated and stored at -20 °C. The glucose level was measured by glucose oxidase method using an autoanalyzer. FDG uptake was expressed as differential uptake ratio (DUR)

\[
\text{DUR} = \frac{\text{Sample radioactivity/Sample weight}}{\text{Injection dose/Body weight}}
\]

Results

Table 1 shows the effects of pre-treatments on the blood glucose level. Treatments of ascorbic acid and dipyridamole showed no significant differences from the control. Glucose loading, dehydroascorbic acid, triiodothyronine, epinephrine and Szt-2 induced moderate level of hyperglycemia (significantly higher than the control, p<0.001). Szt-1 and Dex induced severe hyperglycemia (significantly higher than the glucose loading, p<0.001).

Figure 1 shows FDG uptake and serum glucose level. Myocardial uptake of FDG increased along the increase in serum glucose level from about 100mg/dl until about 200mg/dl. Thereafter, myocardial FDG uptake dropped suddenly and became almost constant irrespective of the serum glucose level. Skeletal muscle uptake of FDG also showed the same pattern, blood level of FDG was almost constant.

Discussion

At the moderate level of hyperglycemia (lower than 200 mg/dl), myocardial uptake of FDG was increased along the increase of glucose level. Dehydroascorbic acid has been known to induce hyperglycemia in vivo\(^6\) and to inhibit brain uptake of glucose\(^7\). It increased FDG uptake by myocardium. Enhanced cardiac glucose utilization under hyperthyroidism has been induced by the secondary changes in glucose-lipid interaction at the tissue level rather than the changes in glucose transporter expression\(^8\). In this study, triiodothyronine induced moderate hyperglycemia and increased FDG uptake by myocardium in vivo. Epinephrine stimulated translocation of glucose transporter into plasma membrane of muscle\(^9\). In this study, moderate hyperglycemia and increased FDG uptake by myocardium was induced by epinephrine the same as that by glucose loading. Each treatment has been reported to induce hyperglycemia by each different mechanism. However, considering the effects of these treatments on the myocardial uptake of FDG, FDG uptake is simply increased along the increase in blood level of glucose.

In severe hyperglycemia, myocardial FDG uptake was dropped and became almost constant around 1.8-0.7 (DUR) independent of the glucose level. There must exist some specific change of glucose metabolism or transport at the level of 200 mg/dl. A shift of metabolic fuel from glucose to fatty acid, or impairment of glucose metabolism or transport may explain this low FDG uptake of myocardium under severe hyperglycemia.
Glucocorticoid suppressed myocardial glucose extraction in vivo\textsuperscript{10}, and Dex reduced skeletal muscle glucose uptake\textsuperscript{11}. Dex-induced insulin resistance in rat skeletal muscle was not due to suppression of glucose transporter gene expression, and possible failure of translocation of glucose transporter-4 (GLUT4) containing intracellular vesicles to plasma membrane was suggested\textsuperscript{11}. Szt is known to induce experimental diabetes due to selective destruction of the pancreatic $\beta$ cells\textsuperscript{6}. Several studies indicated that glucose uptake in heart and skeletal muscle was reduced in Szt-induced diabetes\textsuperscript{12}. Recently, a dissociation of reduced glucose uptake rates and unaltered levels of GLUT 4 at early stage (7 days) of the Szt diabetes has been observed and impaired glucose transporter translocation or activity was suggested\textsuperscript{13}. The reduced FDG uptake by myocardium and skeletal muscle under severe hyperglycemia induced by Dex or Szt treatments might be explained by reduced transport of glucose.

Irrespective to its mechanisms, our observation that myocardial FDG uptake showed two-phase correlation to the blood glucose level seems to be useful knowledge for FDG-PET imaging of myocardium under various disease or medication which may alter blood glucose level.

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References

Table 1  Effects of treatments on serum glucose.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of rats</th>
<th>Glucose (mg/dl) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>48</td>
<td>105±13</td>
</tr>
<tr>
<td>Glucose loading</td>
<td>50%, 0.6 ml p.o.</td>
<td>42</td>
</tr>
<tr>
<td>Dehydroascorbic ac.</td>
<td>100mg i.p.</td>
<td>5</td>
</tr>
<tr>
<td>Ascorbic ac.</td>
<td>100mg i.p.</td>
<td>7</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>3mg i.p.</td>
<td>7</td>
</tr>
<tr>
<td>Streptozotocin-1</td>
<td>6mg i.v.</td>
<td>6</td>
</tr>
<tr>
<td>Streptozotocin-2</td>
<td>4mg i.v.</td>
<td>10</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1mg s.c.×6</td>
<td>34</td>
</tr>
<tr>
<td>Triiodothyronine</td>
<td>10μg p.o.×3</td>
<td>7</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>50μg i.p.</td>
<td>7</td>
</tr>
</tbody>
</table>

*: Mean±SD.
†: p<0.001 compared to the control (Student’s t-test).
$: p<0.001 compared to the Glucose loading and the Dehydroascorbic acid.
Fig. 1 FDG uptake by myocardium (A), and by skeletal muscle from thigh (B) correlated with the serum glucose level. Blood level of FDG (C) was almost constant. Each point represent mean and SD of $5 \sim 8$ rats data. Data were obtained 60 min after injection of FDG, after various pre-treatments listed in Table 1.