Adrenal Cortical and Medullary Responsiveness to Insulin-induced Hypoglycemia

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SHIBATA, O. Adrenal Cortical and Medullary Responsiveness to Insulin-induced Hypoglycemia. Tohoku J. exp. Med., 1971, 105 (1), 27-33 —— Experiments were done in dogs anesthetized with sodium pentobarbital. Adrenal venous blood was collected and analyzed for 17-hydroxycorticosteroids (17-OHCS), adrenaline and noradrenaline. The animals were injected intravenously with 1.0, 0.5, 0.1 and 0.05 U/kg of insulin. After injection of 0.1-1.0 U/kg of insulin the adrenal 17-OHCS and medullary secretion increased significantly. Following administration of 0.05 U/kg of insulin, however, no significant increases were observed. Thus, there was no definite difference in responsiveness to insulin-induced hypoglycemia between the adrenal cortex and medulla.

An increase in adrenal cortical (Goldfien et al. 1958, Kraicer and Logothetopoulos 1963, Suzuki et al. 1964, 1965b, Zukoski 1966, Matsui and Plager 1966) and medullary (Cannon et al. 1924, Yen et al. 1933, Goldfien et al. 1958, Cantu et al. 1963, Crone 1965, Ikeda 1968, Wurtman et al. 1968, Cantu et al. 1968) secretion in response to insulin-induced hypoglycemia has been firmly established. Dissociation of adrenal cortical and medullary response to E. coli endotoxin was found by Egdahl (1959). It was also demonstrated that there existed a differential response of the adrenal medulla and cortex to cyanide anoxia (Suzuki et al. 1965a) and muscular exercise (Ohukuzi 1966, Suzuki et al. 1967).

In the present studies, experiments were designed to compare the responsiveness of the adrenal cortex and medulla to insulin-induced hypoglycemia.

MATERIALS and METHODS

Adult mongrel dogs ranging in weight from 11 to 22 kg were used in these studies. Anesthesia was induced by an intravenous injection of sodium pentobarbital (Nembutal, Abbott) in a dose of 25 mg/kg. In order to collect the adrenal venous blood the left lumboadrenal vein was exposed and dissected free through the lumbar route (Satake et al. 1927), the side branches of the vein being ligated and cut. A small glass cannula attached to a short rubber tube was inserted into the vein lateral to the adrenal gland. The right saphenous vein was cannulated on the same day.

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On the following day the animals were re-anesthetized by an intravenous injection of sodium pentobarbital and heparinized for preventing blood coagulation. A saline infusion was done through the saphenous vein cannula to replace the blood loss due to adrenal venous blood sampling. Body temperature of the animals was always maintained throughout the experiment above 35°C by the use of external heat, when necessary. Various doses of insulin (Novo), i.e., 1.0, 0.5, 0.1 and 0.05 U/kg, were injected intravenously in 30 sec. Samples of adrenal venous blood were collected 30 and 10 min before and 10, 20, 40, 60, 90, 120 and 180 min after the injection of insulin.

Adrenal venous blood samples were promptly centrifuged. The plasma was analyzed for 17-OHCS by the method of Nelson and Samuels (1952) and for adrenaline and noradrenaline by a modification of the method of Euler and Lishajko (1959). In this paper the secretion rate of 17-OHCS is expressed in μg/kg/min and those of adrenaline and noradrenaline in μg/kg/min. The blood glucose concentration was determined by the iodometric method of Somogyi (1945).

RESULTS

Experiments were done in 17 dogs. Four dogs were injected with 1.0 U/kg, 4 dogs with 0.5 U/kg, 5 dogs with 0.1 U/kg and 4 dogs with 0.05 U/kg of insulin. The mean values of the adrenal 17-OHCS secretion rate, the adrenaline and noradrenaline secretion rates and the blood glucose concentration before and after injection of each dose of insulin are shown in Table 1.

Following injection of 1.0 U/kg of insulin the blood glucose concentration began to decrease within 10 min and was minimal from 60 to 180 min after the

<table>
<thead>
<tr>
<th>Dose of insulin (U/kg)</th>
<th>No. of dogs</th>
<th>Substance measured</th>
<th>Adrenal 17-OHCS secretion rate and blood glucose concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Min before injection of insulin</td>
</tr>
<tr>
<td>1.0</td>
<td>4</td>
<td>17-OHCS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ad.</td>
<td></td>
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<tr>
<td></td>
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<td>Norad.</td>
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<td>B. glucose</td>
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<tr>
<td>0.5</td>
<td>4</td>
<td>17-OHCS</td>
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<td></td>
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<td>Norad.</td>
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<td></td>
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<td>B. glucose</td>
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<tr>
<td>0.1</td>
<td>5</td>
<td>17-OHCS</td>
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<tr>
<td></td>
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<td>Ad.</td>
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<td>Norad.</td>
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<tr>
<td></td>
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<td>B. glucose</td>
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</tr>
</tbody>
</table>

Ad. = Adrenaline, Norad. = Noradrenaline
Adrenal Cortical and Medullary Responses to Insulin

There was significant increases in adrenal 17-OHCS and adrenal medullary secretion. The secretion rate of 17-OHCS attained the peak at 40 min after the injection of insulin. At 90 min it remained still at the maximal level and returned to the resting level after next 90 min. The adrenal medullary secretion attained the maximal increase within 40 min after the injection and it remained still at high level at 120 min.

After injection of 0.5 U/kg of insulin the blood glucose concentration began to decrease within 10 min and was minimal at 40 min. The adrenal 17-OHCS secretion and adrenal medullary secretion increased significantly after administration of insulin; the former attained the maximal level within 20 min while the latter at 40 min.

After the injection of 0.1 U/kg of insulin the blood glucose concentration decreased within 10 min and attained the lowest level at 20 min. The adrenal 17-OHCS and adrenomedullary secretion increased significantly. The maximal secretion rate of 17-OHCS was attained at 20 min and that of adrenal medullary secretion at 40 min after administration of insulin.

Following injection of 0.05 U/kg of insulin there was a significant hypoglycemic response. The blood glucose concentration was minimal at 20 min after the injection. There were, however, no significant increases in adrenal cortical and medullary secretion.

dogs in response to insulin-induced hypoglycemia

\[
\begin{array}{cccccc}
& 20 & 40 & 60 & 90 & 120 & 180 \\
\text{Blood glucose} & 0.87 \pm 0.23 & 0.80 \pm 0.19 & 0.84 \pm 0.13 & 0.58 \pm 0.048 & 0.59 \pm 0.032 & 0.59 \pm 0.032 \\
\text{Adrenaline secretion} & 53 \pm 28 & 98 \pm 31 & 104 \pm 20 & 71 \pm 15 & 79 \pm 22 & 29 \pm 9.5 \\
\text{Noradrenaline secretion} & 5.6 \pm 2.3 & 15 \pm 12 & 12 \pm 8.7 & 10 \pm 6.1 & 11 \pm 3.8 & 4.5 \pm 1.6 \\
\end{array}
\]

B. glucose = Blood glucose
DISCUSSION

In experiments of Zukoski (1966), 3 anesthetized dogs were administered with insulin in a dose of 0.1 U/kg. No significant decrease in blood glucose concentration and no significant increase in adrenal 17-OHCS secretion were observed. In the studies of Matsui and Plager (1966), 4 anesthetized dogs were injected with 0.1 U/kg of insulin. In 2 of 4 dogs, no changes in blood glucose concentration and adrenal 17-OHCS secretion were found and in the other 2 dogs a hypoglycemic response and a marked increase in adrenal 17-OHCS secretion were observed following administration of insulin. In the present studies a significant increase in adrenal 17-OHCS secretion could be observed after administration of 0.1 U/kg of insulin but not after injection of 0.05 U/kg of insulin. Thus, the minimal effective dose of insulin for causing elevation in adrenal 17-OHCS secretion was considered to be 0.1 U/kg.

As to the adrenal medullary secretion, it was increased by 0.1 U/kg of insulin but not by 0.05 U/kg of insulin in the present studies. Therefore, the minimal effective dose of insulin for causing an increase in adrenal medullary secretion was also considered to be 0.1 U/kg.

The increase in adrenal medullary secretion in response to insulin-induced hypoglycemia was found to be abolished by section of the splanchnic nerves and markedly reduced by transection of the spinal cord (Crone 1965, Ikeda 1968). Thus it was postulated that the adrenal medullary response to insulin was dependent on the central nervous system mechanism. The increase in adrenal 17-OHCS secretion in response to insulin-induced hypoglycemia was abolished by hypophysectomy (Matsui and Plager 1966), indicating that it was mediated through the release of ACTH from the anterior pituitary. The experimental results of the present studies indicated there was no definite difference in responsiveness to insulin between the pituitary-adrenocortical axis and the central nervous system center which controls the adrenal medullary secretion.

It was of interest to find that there was no differential responsiveness to insulin-induced hypoglycemia, since the differential response of the adrenal cortex and medulla to bacterial endotoxin intoxication (Egdahl 1959), cyanide anoxia (Suzuki et al. 1965) and muscular exercise (Ohukuzi 1966, Suzuki et al. 1967) had been reported. In the studies of Egdahl (1959), conscious dogs were injected with E. coli endotoxin. A marked increase in adrenal 17-OHCS secretion and rather infrequent increase in adrenal medullary secretion was produced by administration of a small dose (0.01 mg) of endotoxin. After administration of a large dose (0.2 mg) of endotoxin both adrenal 17-OHCS and medullary secretion increased markedly. They inferred that the pituitary-adrenal axis was more sensitive to bacterial endotoxin than the central nervous system center for the control of the adrenal medullary secretion. Suzuki et al. (1965a) studied the adrenal cortical and medullary secretion in response to various doses of potassium cyanide. Conscious dogs were injected subcutaneously with 1.0–4.0 mg/kg of potassium cyanide. After
administration of cyanide in doses of 1.0-3.0 mg/kg, a marked increase in adrenal 17-OHCS secretion was always observed, while the adrenal medullary secretion remained unchanged. After administration of cyanide in a dose of 4.0 mg/kg, a definite increase in adrenomedullary secretion as well as in adrenal 17-OHCS secretion occurred. Thus it was concluded by them that the adrenal cortical response to cyanide anoxia was more sensitive than the adrenomedullary response. It was found by Suzuki et al. (1967) that in unanesthetized dogs the adrenal 17-OHCS secretion increased definitely after exhausting exercise, whereas the adrenal medullary secretion was observed by Ohukuzi (1966) to increase only slightly even after the animals had been exhausted completely. Recently, Narita (1971) compared the adrenal cortical and medullary response to various doses of histamine in anesthetized dogs. Following intravenous injection of 0.01-0.02 mg/kg of histamine the adrenal medullary secretion increased significantly, while after the injection of 0.005 mg/kg of histamine no significant increase was observed. On the other hand, when the animals were injected intravenously with 0.002-0.005 mg/kg of histamine the adrenal 17-OHCS secretion increased significantly. No adrenal cortical response was observed after the injection of 0.001 mg/kg histamine. Thus the pituitary-adrenal axis was found in his experiments to respond to histamine more sensitively than the central nervous system mechanism for the control of the adrenomedullary hormone secretion.

Although no definite difference in responsiveness to insulin was found between the central nervous system center which controls the adrenal medullary secretion and the pituitary-adrenocortical axis, the time course of the adrenal 17-OHCS secretion in response to insulin induced-hypoglycemia was not wholly the same with that of the adrenal medullary secretion. In the present studies, after administration of 0.1 and 0.5 U/kg of insulin the adrenal 17-OHCS secretion reached the maximal rate at 20 min, while the adrenal medullary secretion at 40 min. Similar results were obtained by Goldfien et al. (1958). In their experiments, anesthetized dogs were injected with 1.0 U/kg of insulin. In 3 of 5 dogs a 30 mg/100 ml fall in blood glucose concentration was found to produce an increase in adrenal 17-OHCS secretion 20 min after injection of insulin at a time when no significant increase in adrenal medullary secretion had occurred. They inferred that the protective mechanism of the adrenal cortex was stimulated earlier than that of the adrenal medulla in the dog in response to insulin-induced hypoglycemia. The underlying mechanism of difference in time courses of the adrenal cortical and medullary secretion in response to insulin would be explained tentatively as follows. In experiments of Matsui and Plager (1966) it was found that the point at which the pituitary-adrenocortical axis responded to insulin-induced hypoglycemia correlated with the rate of blood glucose fall rather than the absolute blood glucose level. On the other hand it was observed by Sato et al. (1933) that a fall in blood glucose concentration to a certain level below normal was the primary determinant factor for causing the adrenal medullary activation in response to insulin-induced hypoglycemia rather than the velocity with which
the blood glucose concentration was reduced. Thus, when a moderate dose of insulin is administered there is a possibility that the adrenal cortical response will be manifested at the falling phase of the blood glucose level and then the adrenomedullary response will occur at the period of the lowest blood glucose level.

Acknowledgment

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References


