CURRENT TOPICS IN CLINICAL AND EXPERIMENTAL ASPECTS OF DIABETES MELLITUS

Editors:

Nobuo SAKAMOTO, H. K. MIN
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Current topics in clinical and experimental aspects of diabetes mellitus

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A session of the 'Human Insulin Symposium'

Speakers D.R. Owens, T. Kuzuya, T. Kaneko, T. Toyota

Chairmen J.S. Skyler and K. Kosaka

Welcoming party. Steamed rice is pound into a cake.

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Dr. N. Sakamoto, President of the Symposium, presenting a letter of thanks to all the guest speakers.

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Place of the meeting in the 'Seiun' room of Hotel Nagoya Castle

Luncheon lecture

Current topics in clinical and experimental aspects of diabetes mellitus
N. Sakamoto, H. K. Min and S. Baba, editors

Hyperglycemia and hyperinsulinemia as causes of diabetic angiopathy

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Hyperglycemia is the most characteristic feature in diabetes mellitus. It is now well recognized that the long-standing hyperglycemia results in damages of various tissues such as nerves, blood vessels, lens, kidney, blood cells and others. Especially, generalized vascular disease is the most important factor predisposing to mortality in diabetics. However, the direct relationship between hyperglycemia and diabetic late complications has not been clearly demonstrated despite intensive efforts.

The angiopathies which develop in diabetes mellitus are usually classified in two categories, i.e. macroangiopathy and microangiopathy.

The causes responsible for the development of each angiopathy are thought to be different, and the microangiopathy is considered to be diabetes-specific, whereas the macroangiopathy is considered to be non-specific for diabetes.

Recent evidences suggest that the increase in polyol pathway activity provides a model for the biochemical mechanism by which hyperglycemia may induce the metabolic derangements in a number of tissues (1).

The polyol pathway reaction catalyses the mutual conversion of glucose and fructose, and produces sorbitol as an intermediate.

In vivo, the reaction is preferentially directed to the production of fructose from glucose. The rate-limiting step of the pathway is believed to be the aldose reductase (AR) reaction, which catalyses the conversion of glucose to sorbitol.

It should be noted that the high activity of the polyol pathway is found mainly in such tissues as blood vessel wall, lens, nerves, retina, kidney, liver, seminal gland and pancreatic islet, all of which are involved in diabetic late complications. In these tissues, the glucose transport is not subject to insulin regulation and the activity of the polyol pathway appears to be regulated mainly by intracellular glucose concentration.

It is also known that the Km (Michaelis constant) of aldose reductase for glucose is very high. Therefore, the activity of the AR is negligible under the condition of euglycemia, but when the blood glucose level rises, the activity of AR rapidly increases and a large amount of glucose is converted to sorbitol.

It is calculated that only less than 3% of glucose taken up by the cell flows into the polyol pathway in euglycemic state, whereas much more than 13% of glucose is metabolized through the polyol pathway in hyperglycemic state. In the latter case, sorbitol and fructose are accumulated within the cell, since the turnover rate of both substances is very slow. The accumulation of polyols would injure the cell through its osmotic effect. The increase in osmotic pressure due to the accumulation of sorbitol and fructose accelerates the inflow of water from the extracellular space, and brings about the cell swelling, which would inhibit severely the cell functions.

Dr. Hotta, a co-worker of the author, succeeded to provide an excellent model for the study of diabetic angiopathies and neuropathy in the rats by way of which the streptozotocin-diabetic rats were fed the fructose-rich diet for 1 to 10 months. In these rats the various tissue damages were observed, which are quite resembling the microangiopathy and neuropathy in human diabetics (2).

If the increased activity of the polyol pathway is involved in the development of the diabetic complications, then the treatment with the AR inhibitor should be effective for the protection and/or improvement of the diabetic complications.

As expected, the administration of AR inhibitor to the streptozotocin-fructose fed rats resulted in showing a marked preventive effect on the development of retinopathy and neuropathy. For example, the treatment with AR-inhibitor prevented the impairment of motor nerve conduction velocity (MNCV) of diabetic rats maintained on a fructose-rich diet. This effectiveness on MNCV is comparable to the insulin effect which is apparently exerted through normalizing the blood glucose level (3).

The clinical trial with AR inhibitor in human diabetics with retinopathy and neuropathy is now in progress, and it is expected that excellent effectiveness will be confirmed also in human diabetics.

These results obtained from experimental and clinical research suggest clearly that the increase in polyol pathway activity would be at least one of the most potent causes involved in the development of diabetic microangiopathy and neuropathy.

On the other hand, the cause of the macroangiopathy is even now relatively unclear. Among the various factors which have been claimed as a risk for diabetic macroangiopathy, hyperinsulinemia is now regarded as the most potential factor or rather cause of macroangiopathy. Metabolic derangements seen in diabetes mellitus are generally explained as the results of deficiency of insulin. However, the diabetic patients who are treated with insulin or sulfonylurea show frequently hyperinsulinemia in the peripheral blood.

What does it mean that after the introduction of insulin to clinical practice, the incidence of macroangiopathy has been surprisingly increasing? In the insulin-dependent diabetic subjects, not only microangiopathy but also