

Thesis Title A Correlation between Morphological Changes
 in Liver Cells and Alterations of Hepatic Drug-
 Metabolizing Enzymes in Streptozotocin Diabetic
 Rats

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ABSTRACT

A correlation between the changes in the activities of hepatic drug-metabolizing enzymes and the ultrastructure of rat hepatocytes in streptozotocin-diabetic rats was studied. Fasting for 24 hr before and 6 hr after streptozotocin (65 mg/Kg, IP) was the optimum condition for the induction of chemical diabetic state in male Wistar rats. Under this condition, the rats given streptozotocin displayed about 4-5 fold increase in serum glucose level (25.35 ± 0.92 mmole/L) throughout 2 weeks' period. Polydipsia, polyuria, and loss in body weight gain as compared to that of the control were also observed.

The hepatic enzyme activities of aminopyrine N-demethylase (P450IIB and IIIA subfamilies) and 7-ethoxycoumarin O-deethylase (P450IIA and IIB subfamilies) in streptozotocin-induced diabetic rats were significantly decreased with the maximum reduction occurring at day 2 and day 8, respectively. The activity of aminopyrine N-demethylase was depressed over a period of 2 weeks whereas that of 7-ethoxycoumarin O-deethylase tended to be increased after day 8 but was still significantly lower than that of the control. In contrast, the activities of aniline hydroxylase (P450IIE1) and 7-ethoxyresorufin O-

deethylase (P450IA1) were significantly increased in chemical diabetic rats. The activity of aniline hydroxylase was significantly increased within 2 days and reached maximum induction on day 4; then it began to decline after day 6 and returned to normal at day 8, whereas that of 7-ethoxyresorufin O-deethylase was increased over a period of 10 days.

The stimulatory effect of streptozotocin-diabetes on the metabolism of aniline and 7-ethoxyresorufin was most likely due to new synthesis of the enzymes inasmuch as this effect was completely blocked by pretreatment of the animals with actinomycin D (0.1 mg/Kg, IP 1 hr before and 48 hr after streptozotocin). In kinetic studies, the Eadie-Hofstee plots of hepatic aniline hydroxylase and aminopyrine N-demethylase activities from control and chemical diabetic rats gave essentially the similar K_m values but the different V_{max} values, thus supporting the concept that the changes in enzyme activity was quantitative rather than qualitative.

The morphological alterations in rat hepatocytes were also studied. In streptozotocin-induced diabetic rats, the liver cells appeared to be more active; they revealed marked proliferation of the smooth endoplasmic reticulum (SER) and the irregular arrangement of dilated rough endoplasmic reticulum (RER). Insulin treatment (NPH insulin 20 U /Kg, SC, once daily) of streptozotocin-induced diabetic rats could correct the abnormalities of serum glucose level, body weight and other physical characteristics of the diabetic animals, though the hormone caused a significant increase in liver weight. The changes in hepatic drug-metabolizing enzyme activities were also restored to normal by insulin treatment. However, the morphology of hepatocytes of diabetic rats treated with insulin still showed some alterations as evidenced by proliferation of SER in certain cells.