Thesis Title Effects of Antidiabetic Agents on Hepatic Drug-Metabolizing Enzymes in Chemical Diabetic Rats

Name Thiraporn Poopat

Degree Master of Science (Pharmacology)

Thesis Supervisory Committee

Amnuay Thithapandha, Ph.D.

Krongtong Yoovathaworn, Ph.D.

Kittima Sriwatanakul, Ph.D.

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ABSTRACT

The effects of antidiabetic agents on hepatic drug metabolism were studied in male Wistar rats over a period of 2 weeks. Fasting the animals for 24 hr before and 6 hr after alloxan (120 mg/kg, SC) was the optimum condition for the induction of chemical diabetic state. Under this condition, the rats given alloxan displayed about 4-5 fold increase in blood glucose level and body weight loss as compared with control.

The activity of aniline hydroxylase in alloxan-diabetic rats was significantly increased within 2 days after the drug treatment and still increased during day 2 to day 6. Then, the enzymatic activity began to decline and returned to normal on day 12, followed by a tendency to decrease though without any statistical significance. A significant increase in activity of p-nitroanisole O-demethylase was also increased

in these chemical diabetes over a period of 2 weeks after the induction of diabetic state. In contrast, the activity of aminopyrine N-demethylase was significant decreased in the animals treated with alloxan, though the significant reduction was rather transient and was observed only on day 4.

The stimulatory effect of alloxan on the metabolism of aniline and p-nitroanisole was most likely due to new synthesis of the enzymes. inasmuch as this effect was completely blocked by pretreatment of actinomycin D (0.1 mg/kg, IP). In kinetic studies, the Eadie-Hofstee plots of aniline hydroxylase activity from control and chemical diabetic rats gave essentially the same Km value, supporting the concept that the changes in enzymatic activity was quantitative rather than qualitative.

Furthermore, the changes in body weight, blood glucose and the activity of three hepatic drug-metabolizing enzymes of chemical diabetic animals were prevented by insulin supplement (NPH insulin 20 U/kg, SC, once daily for 3 days). However, the liver weight of insulin-treated diabetic rats was significantly greater than that of the controls. Orally administrations of tolbutamide (100, 500 or 1000 mg/kg), or glibenclamide (15, 30 or 60 mg/kg) or metformin (100, 500 or 800 mg/kg), twice daily for 3 days were ineffective in lowering the hyperglycemia and had no effect on body weight or liver weight of alloxan-diabetic rats. Moreover, these oral hypoglycemic drugs also had no effect upon the alteration of hepatic drug-metabolizing enzyme activities in chemical diabetic rats.