

Abstract

This study was conducted to establish the role of nitric oxide as an etiological factor in the pathogenesis of type II diabetes mellitus. An animal model of type II diabetes was developed by injecting adult Wistar rats, weighing between 120 and 300 g, with 65 mg/kg body weight of streptozotocin in conjunction with 180 mg/kg body weight nicotinamide. The non-fasting plasma insulin concentration in the diabetic rats was measured 4 wks after drug administration using a radioimmunoassay, and found to be significantly lower in the diabetic rats ($119.83 \pm 0.62 \mu\text{IU/ml}$) than the levels in the controls ($249.00 \pm 7.56 \mu\text{IU/ml}$); $P < 0.05$. This was accompanied by significant hyperglycaemia in the diabetic rats ($15.44 \pm 0.84 \text{ mmol/L}$) compared to the controls ($5.22 \pm 0.23 \text{ mmol/L}$); $P < 0.05$. The fasting insulin concentration was not significantly different in the diabetic and control rats.

The specific alkaline phosphodiesterase activity of PC-1 was determined using an enzymatic assay that measured the rate at which thymidine 5'-monophosphate p-nitrophenyl ester (PNTP) was hydrolysed in cytosol-enriched fractions of skeletal muscle and adipose tissue. The specific activity was significantly elevated in the adipose tissue of the diabetic rats ($0.54 \pm 0.083 \text{ nmol of PNTP hydrolysed/mg/min}$; $P = 0.013$), but significantly decreased in the skeletal muscle ($3.43 \pm 0.28 \text{ nmol of PNTP hydrolysed/mg/min}$; $P = 0.032$).

Measurement of the specific activity of GAPDH in the liver and skeletal muscle from control and diabetic rats showed a significant decrease in the specific activity of the enzyme in the skeletal muscle of the diabetic rats ($0.064 \pm 0.006 \mu\text{mol/mg/min}$; $P = 0.002$) compared to the controls. The activity of the enzyme in the liver was not significantly different in the control and diabetic rats.

Glucose transport was measured in the diabetic and control rats by measuring the rate at which D-glucose-[1- $^3\text{H}(\text{N})$] was taken up into adipocytes and myocytes of these rats. In the absence of insulin, glucose uptake was not significantly different in the adipocytes of control and diabetic rats. Upon stimulation by insulin (100 nM), glucose uptake was significantly lower in the diabetic rats ($1.26 \times 10^{-8} \pm 3.47 \times 10^{-9} \mu\text{mol/mg/min}$) compared to the controls ($4.17 \times 10^{-8} \pm 1.28 \times 10^{-8} \mu\text{mol/mg/min}$); $P = 0.045$. In the skeletal muscle, however, the rate of glucose uptake in the absence of insulin was significantly higher in the diabetic rats ($5.81 \times 10^{-8} \pm 4.70 \times 10^{-11} \mu\text{mol/mg/min}$) than in the controls ($2.93 \times 10^{-10} \pm 8.84 \times 10^{-11} \mu\text{mol/mg/min}$); $P = 0.028$. Insulin stimulation resulted in an increase in the rate of uptake in both the control and diabetic rats, with a greater increase seen in the myocytes of the diabetic rats.

These results suggest that type II diabetes is caused by a combination of defects at different levels of glucose metabolism, in different tissues, and that the NO-releasing drug might have a role in causing these defects. Care should be taken when prescribing NO-releasing drugs for patients, especially those

who are overweight or obese, since the drug seems to have a greater effect on the adipose tissue.