

**P001** Role of translocation of PKC $\zeta$  in the development of insulin resistance and Type II diabetes in a rat model using continuous glucose infusion

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We investigated the molecular mechanisms of hyperglycemia-induced insulin resistance and diabetes in rats receiving a continuous glucose infusion. Rats accommodated systemic glucose oversupply and developed insulin resistance on day five (normoglycemia/hyperinsulinemia) and Type II diabetes on day 15 (hyperglycemia/normoinsulinemia). Protein and activity of phosphatidylinositol (PI) 3-kinase and protein kinase B (PKB) in skeletal muscle in the insulin resistant state was unchanged compared with controls. The effect of glucose infusion on protein kinase C $\zeta$  (PKC $\zeta$ ) activity was independent of changes in PI 3-kinase activity, and occurred in parallel with an increase in phosphatidylinositol-dependent kinase 1 (PDK1) activity. Activated PKC $\zeta$  was mainly located in the cytosol of muscles in glucose-infused rats after five days and contributed to the translocation of GLUT4 to the plasma membrane (PM), which maintained normoglycemia. After 15 days of glucose infusion, PKC $\zeta$  was found to move from the cytosol to the PM with a concomitant decrease in PDK1 activity. This led to an increase in the association between PKC $\zeta$  and PKB and a decrease in PDK1-PKB reactions in the PM, which inhibited PKB activity. The activity of PKC $\zeta$  was also compromised. The reduced activity of PKC $\zeta$  and PKB resulted in blunted translocation of GLUT4, which eventually led to hyperglycemia and diabetes. Thus, translocation of PKC $\zeta$  may play a central role in the development of insulin resistance and diabetes.