

Mechanism of action of VVP808: A novel insulin sensitising agent

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Background: We used gene expression signature technology to identify a family of compounds with insulin sensitising activity. The aim of these studies was to characterise the effects of these compounds in animal models of insulin resistance and diabetes, and to investigate the molecular mechanism of action of these compounds.

Methods: The VVP800 family of compounds was tested in diet induced obese (DIO) mice, db/db mice and STZ rats. The lead compound, VVP808, was administered by single daily oral gavage to animals for 12-40 days at a range of doses, and efficacy was assessed by measuring body weight, blood glucose, insulin and HbA1c concentrations, and by conducting hyperinsulinemic-euglycemic clamps.

Results: VVP808 reduced fasting blood glucose concentration ($p=0.00004$) and HbA1c levels ($p=0.04$) in db/db mice, and improved glucose tolerance in diet-induced obese (DIO) mice ($p<0.05$). VVP808 also reduced body weight by up to 14% ($p<0.01$) and epididymal fat pad weight by up to 48% ($p=0.01$) in DIO mice. In STZ diabetic rats, VVP808 (50 mg/kg/d for 12 days) had no effect on fasting blood glucose concentration. However, VVP808 significantly enhanced the glucose-lowering effects of exogenous insulin (0.5U/kg) in an insulin tolerance test (by 2.2-fold after 30 min ($p=0.045$) and by 2.4-fold after 60 min ($p=0.038$)). Data from hyperinsulinemic-euglycemic clamp studies in DIO mice showed that treatment with VVP808 (50 mg/kg/d for 14 days) increased the glucose infusion rate by 27% ($p=0.005$), and this was associated with a 23% decrease in endogenous glucose production ($p=0.04$). We are currently conducting a range of studies to identify the molecular mechanism of action of VVP808 including ligand capture affinity chromatography studies using analogues of VVP808 and protein lysates extracted from livers of mice treated with VVP808, and microarray pathway analysis studies in tissues of animals treated with VVP808.

Conclusion: VVP808 is a novel insulin sensitising agent that acts primarily on the liver to suppress endogenous glucose production.