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INSULIN RESISTANCE - MODELLING STUDIES

I.F. GODSLAND, C. WALTON, D. CROOK and V. WYNN

Wynn Institute for Metabolic Research - 21 Wellington Road - London NW8 9SQ - U.K.

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Elevated insulin concentrations are independent predictors of coronary heart disease (CHD) and are related to high blood pressure, low serum HDL-cholesterol and elevated serum triglyceride. Insulin resistance is a major determinant of the plasma insulin concentration. Computer modelling of plasma glucose, insulin and C-peptide concentrations during an intravenous glucose tolerance test enables quantification of the determinants of plasma insulin concentration. The association between risk markers of CHD and model-derived measures of determinants of plasma insulin concentration in a group of healthy males has been investigated. In univariate linear regression analysis of the glucose, insulin and C-peptide data, the incremental insulin area during the second phase (10-180 min.) was found to be the strongest predictor of lipid, lipoprotein and blood pressure variables. Variations in insulin sensitivity and hepatic insulin throughput contribute to variation in the insulin response and may be secondary correlates of lipids, lipoproteins and blood pressure.

INTRODUCTION

Elevated insulin concentrations have been shown in prospective epidemiological studies to be independent predictors of coronary heart disease (2, 7) and there is evidence that insulin could have a direct role in atherogenesis (8). Elevated insulin concentrations are also related to adverse changes in other risk factors, including high blood pressure (4, 6), reduced serum high-density lipoprotein cholesterol and elevated serum triglyceride concentrations (12, 13).

Insulin resistance is a major determinant of the plasma insulin concentration, and other factors may also be important, including the responsiveness of pancreatic insulin secretion to glucose, the insulin half-life and hepatic uptake of newly secreted insulin as it passes from the hepatic portal vein into the general circulation. Computer modelling of plasma glucose, insulin and C-peptide concentrations during an intravenous glucose tolerance test (IVGTT) enables quantification of these determinants of plasma insulin concentration without the need for complex and invasive experimental procedures.

[1] Corresponding author.

METHODS

We investigated the association between established risk markers for coronary heart disease and model-derived measures of determinants of the plasma insulin concentration in a group of 182 healthy males aged 19-75 years and with body mass index range 18-41 kg/m^{-2}. Plasma glucose, insulin and C-peptide concentrations were measured in the fasting state and 3, 5, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150 and 180 minutes following a 0.5g/kg intravenous glucose load. Areas under the IVGTT concentration profiles were calculated, and the incremental area, between the fasting level and the profile, taken as the summary estimate of concentration response. Active and resting diastolic and systolic blood pressure, fasting serum cholesterol, triglycerides, low-density lipoproteins (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and HDL cholesterol subfractions 2 and 3 (HDL2 and HDL3) were measured.

Three models were applied in the analysis of the IVGTT concentration profiles:

Model 1 - the minimal model of glucose

disappearance (1). Using a curve fitting and integrating program, model equation parameters are determined which enable the prediction of the glucose concentration profile from the insulin profile. Model parameters thus obtained include measures of insulin sensitivity (inversely proportional to insulin resistance), and non-insulin dependent glucose uptake.

Model 2 - the minimal model of post-hepatic insulin delivery (9). Model equation parameters are determined which enable prediction of the insulin concentration profile from the glucose profile. Model parameters include measures of the sensitivity of first and second phase post-hepatic insulin delivery to glucose and the fractional insulin elimination rate (inversely proportional to the insulin half-life).

Model 3 - the pancreatic insulin secretion model (10, 11). Model equation parameters are determined which enable the simultaneous prediction of the insulin and C-peptide concentration profiles from the model parameters. Measures include net basal, first phase and second phase pancreatic insulin secretion during the IVGTT, insulin and C-peptide fractional elimination rates and hepatic insulin throughput.

In a preliminary analysis of this study, univariate relationships between glucose, insulin and C-peptide incremental areas and lipid, lipoprotein and blood pressure variables were explored. The ability of selected combinations of model-derived measures to predict the insulin concentration response was then determined and the univariate relationship between model-derived measures and lipid, lipoprotein and blood pressures evaluated.

RESULTS

In univariate linear regression analysis of the glucose, insulin and C-peptide data, the incremental insulin area during the second phase (10 - 180 minutes) was found to be the strongest predictor of lipid, lipoprotein and blood pressure variables (triglycerides $r = 0.43$ $p < 0.001$, HDL cholesterol $r = -0.27$ $p < 0.01$, HDL2 cholesterol $r = -0.28$ $p < 0.001$, active systolic blood pressure $r = 0.37$ $p < 0.001$, resting systolic blood pressure $r = 0.29$ $p < 0.001$, active diastolic blood pressure $r = 0.28$ $p < 0.01$, resting diastolic blood pressure $r = -0.26$ $p < 0.01$). Strong associations were also seen with the fasting insulin concentration.

In multiple linear regression analysis, 90% of the variation in second-phase insulin area was accounted for by parameters describing pancreatic insulin delivery (Model 3: net second-phase pancreatic insulin secretion, fractional insulin elimination rate and hepatic insulin throughput index). In a secod analysis, parameters describing the posthepatic insulin/glucose feedback loop (Model 1: the insulin sensitivity index and insulin independent glucose elimination. Model 2: the sensitivity of second-phase post-hepatic insulin delivery to glucose and the fractional insulin elimination rate) accounted for 67% of the variation in second-phase insulin area. In univariate analysis there were few associations between pancreatic insulin secretion parameters and lipid, lipoprotein and blood pressure variables, despite their strong association with plasma insulin concentrations. In contrast, there were a number of relationships with parameters describing the post-hepatic insulin/glucose feedback loop. The insulin sensitivity index showed significant association with triglycerides ($r = -0.35$ $p < 0.001$), HDL cholesterol ($r = 0.19$ $p < 0.05$), HDL2 cholesterol ($r = 0.23$ $p < 0.01$), active systolic blood pressure ($r = -0.30$ $p < 0.01$), resting systolic blood pressure ($r = -0.24$ $p < 0.01$) and active diastolic blood pressure ($r = -0.21$ $p < 0.05$). Additionally, the sensitivity of second-phase post-hepatic insulin delivery to glucose showed significant associations with triglycerides ($r = 0.33$ $p < 0.001$), HDL cholesterol (-0.18 $p < 0.05$) and HDL2 cholesterol ($r = -0.27$ $p < 0.01$). Since at least 50% of newly secreted insulin is taken up by the liver on first-pass from the hepatic portal vein to the general circulation, this latter parameter, as well as being dependent on pancreatic insulin secretion, is also dependent on hepatic insulin throughput. It is noteworthy that the hepatic insulin throughput index from Model 3 showed a significant association with HDL cholesterol ($r = 0.19$ $p < 0.05$) and a borderline association with triglycerides ($r = 0.16$ $p = 0.052$).

CONCLUSIONS

Correlations between lipid, lipoprotein and blood pressure variables and second-phase incremental insulin area were stronger than those for determinants of the insulin response. This suggests that the second phase insulin response to glucose is primarily responsible for the association between carbohydrate metabolism and lipid, lipoprotein and blood pressure variables. Variation in insulin sensitivity and hepatic insulin throughput contribute to variation in the insulin response and are thus secondary correlates of lipids, lipoproteins and blood pressure. However, net second-phase pancreatic insulin secretion and the fractional insulin elimination rate were also important determinants of the plasma insulin response, more so than parameters related to hepatic insulin uptake but, in contrast, showed few associations with lipids or lipoproteins. This suggests that, as well as determining variation in plasma insulin concentrations, hepatic insulin uptake may have direct effects on lipid and lipoprotein risk factors. This may also be the case for insulin sensitivity since two previously published studies demonstrate a lack of association between variation in insulin concentrations and lipid and lipoprotein variables, but did suggest that insulin sensitivity was important (3, 5).

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