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GLUCOSE TOLERANCE

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Normal glucose tolerance is dependent on satisfactory pancreatic beta cell function and is characterised by very rapid gut hormone-enhanced insulin secretion after carbohydrate ingestion together with a normal tissue response to insulin.

Epidemiological studies have consistently found associations between insulin resistance and hyperlipidaemia, hypertension and cardiovascular disease even when hyperglycaemia is absent and insulin resistance is hypothesised to be the underlying metabolic abnormality. The aetiology of insulin resistance is complex. Rare mutations of enzymes affecting insulin secretion (eg. Glucokinase) or of the insulin receptor (or other molecules in the insulin signalling pathway) can cause abnormal glucose tolerance or diabetes via selective defects in insulin secretion or insulin action. However the common form(s) of impaired glucose tolerance or type 2 diabetes in the community results from a combination of impaired insulin action and a relative decrease in insulin secretion. The molecular mechanisms involved are still poorly understood, but in the pathogenic process insulin resistance generally appears first and is closely related to excessive central abdominal fat and intramyocellular triglyceride. Disturbances in lipid metabolism are known to contribute to insulin resistance. For example, fatty acid availability plays an important role in generating insulin resistance. This is supported by the effectiveness of the thiazolidinedione group of drugs which stimulate the PPAR γ receptor with a differentiation and synthetic effect in peripheral fat cells - causing fatty acids to be "sequestered" in peripheral rather than central fat. Conversely in various lipodystrophies (including those due to HIV protease inhibitors) fatty acids cannot be stored in peripheral fat and appear to be in excess supply in liver and muscle.

Progression from insulin resistance to impaired glucose tolerance or frank hyperglycaemia results from deteriorating pancreatic beta cell function which is not well understood. Hypotheses as to the mechanism include impairment of function due to excess fatty acid availability ("lipotoxicity"), damage from excess amylin secretion from the beta cell which accompanies the hyperinsulinaemia, or a genetic beta cell defect. Whatever the reason for impairment of beta cell function, the advent of hyperglycaemia causes a further deterioration ("glucotoxicity") which often causes a rapid progression to symptomatic hyperglycaemia.

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