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Editorial

Hyperglycaemia as an inducer as well as a consequence of impaired islet cell function and insulin resistance: implications for the management of diabetes

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Summary. It is postulated that hyperglycaemia influences the natural history of Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetes mellitus. Hyperglycaemia, even when mild, can attenuate the secretory response of pancreatic β and α cells to increments in glucose and can impair insulin-mediated glucose transport, thus impeding its own correction and initiating a cycle of progressive self-exacerbation and metabolic deterioration. Both reduced islet function and insulin action may be the consequence of a generalized down-regulation and/or occupation of glucose transporters by hyperglycaemia so that the islets respond less to further increments in glycaemia. The postulated hyperglycaemic cycle can be initiated by any environmental perturbation that increases insulin demand in previously normoglycaemic patients in whom insulin secretion has already reached a maximum level of compensation for peripheral insulin resistance (as in obese pre-Type 2 diabetes) or for a reduced β-cell mass (as in pre-Type 1 diabetes). Elimination of hyperglycaemia by any means can halt this cycle of progressive metabolic deterioration and may restore transiently metabolic recompensation both in Type 1 and Type 2 diabetes. There is experimental evidence that long-standing severe hyperglycaemia may irreversibly damage β cells.

Key words: Hyperglycaemia, islet cell function, insulin, glucagon, diabetic remissions, Type 1 diabetes, Type 2 diabetes.

The hyperglycaemia hypothesis

It is postulated that hyperglycaemia, by directly attenuating responses of the pancreatic islets to increments in blood glucose concentration and reducing insulin-mediated glucose transport in peripheral tissues, influences the natural history of diabetes mellitus. Hyperglycaemia may be provoked by an environmental perturbation that increases insulin demand and/or decreases insulin supply in a previously normoglycaemic individual whose β cells are already secreting at a maximal level to compensate for a reduction in β-cell mass or insulin resistance. By reducing the responses that prevent more severe hyperglycaemia, an initially mild hyperglycaemic state may launch a self-exacerbating cycle of metabolic deterioration (Fig. 1). Any intervention that abolishes the hyperglycaemia may restore both islet cell function and glucose transport towards normal and thus re-establish a metabolically compensated state.

Evidence that hyperglycaemia impairs islet cell function

Acute insulin response to intravenously injected glucose is impaired in subjects with fasting plasma glucose levels > 6.4 mmol/l [1]. Although functional loss is initially restricted to glucose, when the fasting plasma glucose level exceeds 11.1 mmol/l β cells become unresponsive to other secretagogues [1]. This glucose-restricted loss of the insulin response to intravenous glucose is observed in pre-overt Type 1 diabetes as well as in Type 2 diabetes [2]. Loss of the α cell response to glucose [3] parallels the glucose unresponsiveness of β cells [4] and both are restored to normal by eliminating the hyperglycaemia whether by diet, sulphonylureas, insulin or phloridzin glucuresis [5–10]. This raises the possibility that the defect is secondary to a hyperglycaemia-induced reduction in available glucose transporters similar to that induced by hyperglycaemia in adipocytes [11] and at the blood-brain barrier [12, 13].

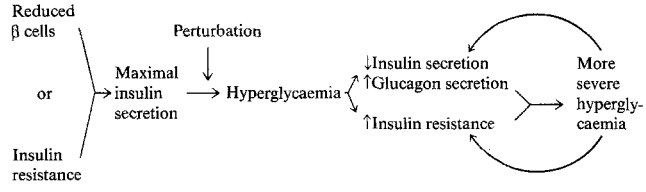

Fig. 1. Initiation of hyperglycaemia and the cycle of self-exacerbation. "Perturbation" refers to any environmental factor, illness, weight gain or carbohydrate excess that would unfavourably alter the balance between insulin production and insulin need

It is reported that high glucose levels ultimately may cause irreversible damage to β cells both in vivo [14] and in vitro [15]. Damage in vivo is prevented by reduction in hyperglycaemia [16].

Evidence that hyperglycaemia causes insulin resistance

Insulin resistance unrelated to obesity occurs in various hyperglycaemic states [17–19] and is corrected by elimination of the hyperglycaemia with insulin [19, 20]. Since the resistance seems restricted to insulin-mediated effects on glucose transport [21], it could reflect depletion of intracellular glucose transport systems in insulin-requiring tissues [11–13], which would produce a "post-receptor" form of insulin resistance [22, 23].

Role of hyperglycaemia in the natural history of diabetes

Type 1 diabetes

During the pre-hyperglycaemic phase of β-cell destruction in patients destined to develop Type 1 diabetes, the production of insulin keeps pace with insulin demand through compensatory hypersecretion by the surviving β cells. However, once compensatory insulin secretion has reached its maximum level, a further increase in insulin demand consequent to stressful illness, weight gain or high carbohydrate intake would initiate hyperglycaemia and begin the cycle of progressive metabolic deterioration. Aggressive insulin therapy early on can induce a remission in over 70% of such patients [24] by interrupting and reversing the cycle, thus restoring compensation until a new perturbation or further immunological damage supervenes.

Type 2 diabetes

In many patients destined to develop Type 2 diabetes, compensated obesity-related insulin resistance may precede hyperglycaemia. Although the β cells may be numerically normal [25], they must hypersecrete to maintain normoglycaemia in the face of insulin resistance. When compensatory insulin secretion has reached a maximum level, a further increase in insulin demand due to stressful illness, weight gain or dietary excess may initiate a hyperglycaemic state and begin a gradual cycle of progressive but reversible metabolic deterioration by reducing islet responses and insulin effectiveness. Thus, hyperglycaemia may be the long-sought link between pre-existing peripheral insulin resistance and the hitherto unexplained failure of islet cells to maintain full compensation [26–28], so-called "exhaustion".

Therapeutic and prophylactic implications

The hyperglycaemia hypothesis provides a novel rationale for meticulous control of glycaemia, namely induction and maintenance of a metabolic remission through improved islet cell responses to glucose and reduced hyperglycaemia-related insulin resistance. In the compensated pre-hyperglycaemic phase of diabetes, measures that prevent hyperglycaemia might postpone decompensation to the overt diabetic state. Avoidance of perturbations that increase insulin demand together with pharmacological enhancement of insulin production (sulphonylureas reportedly reduce the 10-year incidence of overt Type 2 diabetes in individuals with impaired glucose tolerance [29]), may deserve careful evaluation. In established Type 2 diabetes, the possibility that aggressive short-term correction of hyperglycaemia may induce a worthwhile remission beyond the 2 weeks already reported also warrants consideration.

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