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β-CELL DYSFUNCTION AND CHRONIC HYPERGLYCAEMIA

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INTRODUCTION

Type 2 diabetes mellitus is a complex illness with both genetic and environmental pathogenic elements. Disturbed insulin secretion (β-cell dysfunction) and tissue insulin insensitivity (insulin resistance) are jointly found, and there is controversy as to which comes first, and how they interact to lead to diabetes mellitus. Studies in high risk populations for type 2 diabetes have delineated the natural history of type 2 diabetes mellitus (Figure 1): yet undefined genetic mutation(s) combine with metabolic and lifestyle factors to cause the diabetes phenotype. Insulin resistance and β-cell dysfunction are shown at the bottom of Figure 1: they are present to some degree before glucose intolerance is detectable. The environmental factors aggravate insulin resistance (obesity, inactivity, aging, and pregnancy) or the β-cell dysfunction (electrolyte abnormalities, several drugs, and malnutrition). However, the insulin resistance typically worsens little during the early stages of the disease, when glucose intolerance progresses to overt fasting hyperglycaemia. Instead, the factor determining whether diabetes occurs is β-cell function. As long as β-cells compensate for the insulin resistance through increased insulin secretion, glycaemia can be controlled. Frank diabetes is seen when the β-cell compensation is lost – i.e. β-cell failure (1-3).

An important observation made in the late 1970s was that a period of intensive glycaemic control improves insulin secretion in persons with type 2 diabetes (4,5). An active research field has evolved to investigate how the diabetes metabolic milieu negatively affects the β-cell - the term glucose toxicity was coined in reference to that concept (6,7). More recently, detrimental effects of elevated levels of free fatty acids on β-cell function have been studied - so-called lipotoxicity (8,9). Other potential explanations for the β-cell failure in diabetes are that islet amyloid deposits which are found in type 2 diabetes may lower the functional β-cell mass (10), and speculation that altered β-cell growth factors and/or apoptosis-induced β-cell death may cause the β-cell mass to decline (11). However, the latter two entail a loss of β-cells, which would not acutely reverse with intensive glycaemic control. To summarize, the basis for the β-cell failure in type 2 diabetes is presumed to be multifactorial.

Our laboratory investigates diabetic rodents to better understand the reversible component of β-cell failure. Rats share many features with human type 2 diabetes mellitus in terms of abnormal β-cell function, and make it possible to perform biochemical and molecular studies of isolated islets which is impossible in humans.
We summarize here a working model for the β-cell dysfunction, based on a concept of β-cell "overwork" or "exhaustion" (12).

**Figure 1. Schematic for the pathogenesis of type 2 diabetes.**

**90% PANCREATECTOMY RAT MODEL**

This chapter focuses on studies that we have performed in 90% pancreatectomy (Px) rats. Pancreatectomy is performed by abrading pancreatic tissue off the blood vessels using cotton applicators (13). The surgery is well tolerated - the rats grow normally on standard chow diets - and results in mild sustained hyperglycaemia of 1-2 mM above normal within a week of the surgery. A source of confusion has been that some groups report much higher levels of glycaemia in 90% Px rats, presumably because of removal of more than 90% of pancreatic tissue. In these latter situations, marked hyperglycaemia or other associated metabolic changes may alter β-cell function in ways other than with the mild hyperglycaemia we see. Our studies have been performed to investigate the β-cell failure that occurs during the transition from glucose intolerance to fasting hyperglycaemia; thus, it is crucial to use animals which present with a mild degree of hyperglycaemia.

**Natural History of Insulin Secretion in the 90% Pancreatectomy Rat Model**

Our initial studies mapped out the natural history of β-cell function in 90% Px rats in order to identify when β-cell failure occurs. Insulin secretion was studied using the in situ perfused pancreas (a standard organ perfusion system) at weekly intervals after the surgery. Figure 2 shows mean insulin levels in response to perfusion of 16.7 mM glucose or 16.7 mM glucose + 10 mM arginine. The latter combination mimics the nutrient-induced insulin secretion as occurs with meals - so-called glucose potentiation (data from references 14 and 15).

One-week post surgery, insulin responses after administration of both perfusates are normal when adjusted for the reduced β-cell mass (~20% of normal). Two weeks post surgery, the insulin responses are still relatively intact. By three weeks, the insulin response to 16.7 mM glucose falls by 80% as compared to the one-week post-pancreatectomy value, and glucose-potentiated insulin secretion is also reduced, (although the percentage of decline is somewhat less). The cause is not a loss of β-cells since β-cell mass is increasing during this time period (13).