TODC31 5/17/02 1:30 PM Page 1

Chapter 31 Metabolic disturbances in diabetes mellitus

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Summary

- Type 1 diabetes is an immune-mediated disorder that leads to destruction of the islets of Langerhans causing profound insulin deficiency.
- The pathogenesis of type 2 diabetes mellitus is complex and incompletely understood. It appears to be caused by an interaction of genetic and environmental factors that lead to defects in insulin secretion, insulin action and glucose effectiveness.

Type 1 diabetes mellitus

- Absolute insulin deficiency is accompanied by abnormal concentrations of counter-regulatory hormones (glucagon, growth hormone, catecholamines) which lead to multiple metabolic abnormalities. Most of these abnormalities may be corrected by physiological insulin replacement.
- Insufficient insulin is frequently accompanied by impaired insulin action. The defect in insulin action can be wholly or partially reversed by improved glycaemic control.
- Insulin is the main hormonal regulator of lipolysis. The absence of insulin-induced suppression of lipolysis leads to higher concentrations of free fatty acids (FFAs). Elevated FFAs may impair insulin-induced suppression of hepatic glucose production and stimulation of glucose disposal.
- Poorly controlled type 1 diabetes mellitus is characterized by a negative nitrogen balance and muscle wasting indicative of protein catabolism. The resultant increase in circulating amino acids may be utilized for gluconeogenesis.
- Diabetic ketoacidosis is the result of unrestrained tissue lipolysis and the synthesis of ketone bodies by the liver. These are osmotically active and can lead to an osmotic diuresis. Ketone bodies are organic acids and can lower blood pH leading to dysfunction of many enzymatic processes and organs.

Type 2 diabetes mellitus

- People with type 2 diabetes mellitus exhibit fasting and postprandial hyperglycaemia. Insulin secretion in response to meal ingestion is decreased and delayed. Glucagon concentrations are inappropriately elevated and glucose effectiveness and insulin action are impaired. Together, these abnormalities cause fasting and postprandial hyperglycaemia in people with type 2 diabetes mellitus.
- A generalized impairment of insulin-induced suppression of lipolysis is present in people with type 2 diabetes. The resulting increase in FFA concentrations may explain some of the metabolic abnormalities seen in type 2 diabetes.
- In most cases, circulating insulin concentrations in type 2 diabetes are well above the threshold necessary to prevent proteolysis so that tissue catabolism and muscle wasting does not occur.

Hyperglycaemia or abnormal glucose tolerance is one of the many metabolic abnormalities present in diabetes that has been used to define the presence of this disease. Diabetes comprises a heterogeneous group of disorders, all characterized by hyperglycaemia, though the underlying pathogenesis differs amongst subgroups.

Broadly speaking, diabetes mellitus can be divided into two categories based on the severity of insulin deficiency present. Type 1 diabetes is characterized by absolute insulin deficiency—insufficient to prevent unrestrained lipolysis during systemic illness or severe physical stress. On the other hand, some degree of insulin secretion is preserved in type 2 diabetes although it is inappropriate for the prevailing glucose concentration. This relative or absolute deficiency of insulin together with poor diet, obesity, lack of exercise and elevated counter-regulatory hormones (glucagon, epinephrine (adrenaline), growth hormone and cortisol) lead to the various metabolic abnormalities observed in diabetes.

The regulation of carbohydrate, fat and protein metabolism in non-diabetic humans (see also Chapter 9)

In non-diabetic humans, glucose concentrations average 4.5–5.5 mmol/L following a 6–12 h overnight fast. At this time, the rate of entry of glucose into the circulation

TODC31 5/17/02 1:30 PM Page 2

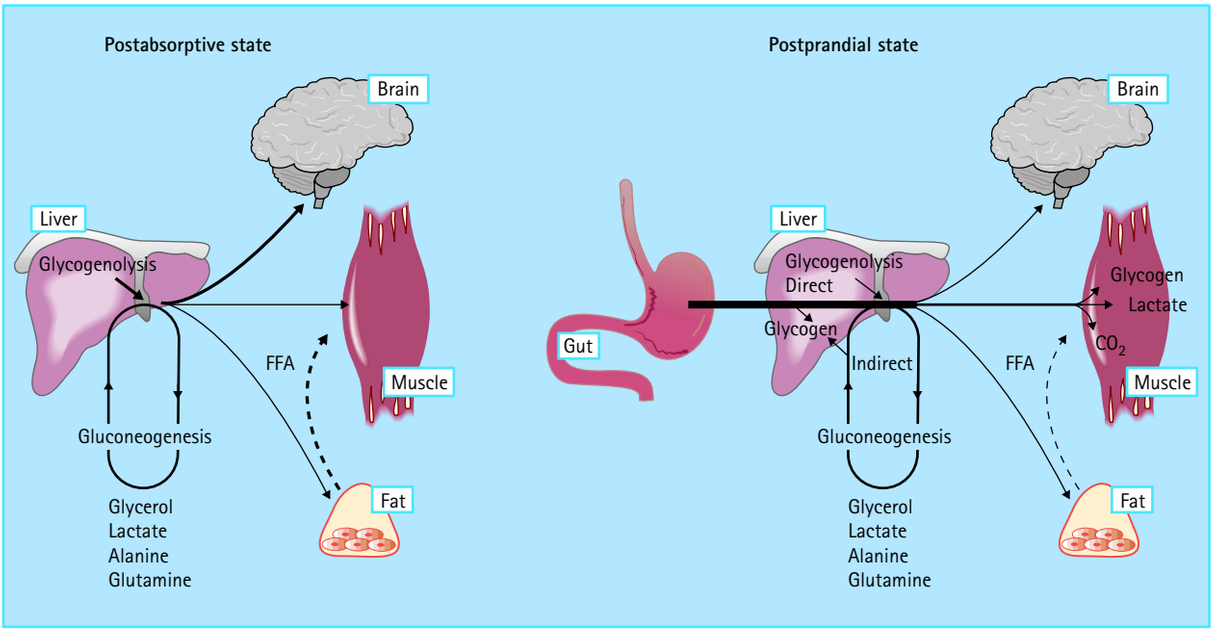

Fig. 31.1 Major sites of glucose metabolism in the postabsorptive and postprandial states. After meal ingestion, the primary site of glucose uptake shifts from insulin-independent organs (e.g. brain) to insulin-dependent tissues (e.g. liver, muscle, adipose tissue). Gluconeogenic substrates are derived predominantly from peripheral tissues. Hepatic glycogen synthesis may occur via the direct or indirect (gluconeogenesis) pathways. FFA, free fatty acids. Adapted with permission from [1].

(glucose production) approximates the rate of removal (glucose utilization). Within 5–6 h after a meal (i.e. in the fasting state), essentially all glucose entering the circulation comes from the liver and is derived from glycogenolysis and gluconeogenesis [1]. Gluconeogenesis is responsible for ~50–60% of endogenous glucose production following an overnight fast, with the proportion increasing with increasing duration of the fast [2]. Gluconeogenesis utilizes three-carbon precursors to synthesize glucose molecules; these substrates include lactate, alanine and glycerol (Fig. 31.1).

Following an overnight fast, approximately 80% of glucose disposal is insulin independent and occurs in the brain, splanchnic tissues and erythrocytes [3]. The majority of insulin-mediated glucose disposal occurs in muscle [4], but since insulin levels are low in the postabsorptive state, muscle predominantly uses free fatty acids (FFAs) for fuel [5]. In the presence of low insulin concentrations, glucose taken up by tissues predominantly is oxidized or undergoes glycolysis to release alanine and lactate (which can be reutilized by the liver for gluconeogenesis) [6].

Sensitivity to insulin varies amongst tissues. Low concentrations of insulin limit lipolysis and prevent unrestrained breakdown of fat. However, the insulin concentrations sufficient to prevent lipolysis are insufficient to stimulate significant muscle glucose uptake.

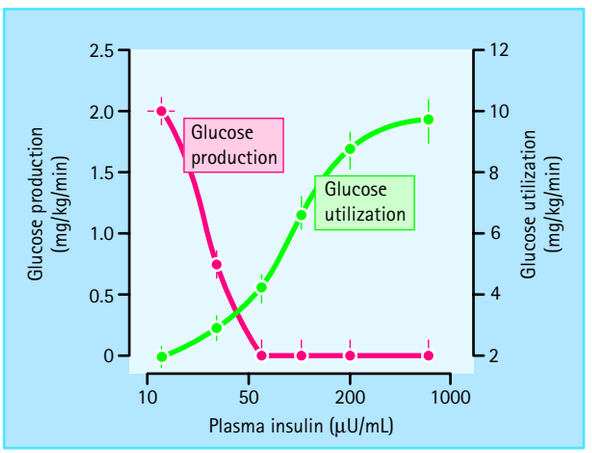

Fig. 31.2 Insulin dose–response curves for glucose production and utilization in non-diabetic subjects. Adapted with permission from [7].

Whereas maximal suppression of endogenous glucose production occurs at insulin concentrations of ~250 pmol/L (42 μU/mL), these concentrations result in only half maximal stimulation of glucose uptake [7] (Fig. 31.2).

Increases in plasma glucose (which occur within 5–10 min after eating) stimulate insulin secretion and

TODC75 5/17/02 1:31 PM Page 1

Chapter 75 Stem cell therapy in diabetes

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Summary

- Stem cells are self-renewing cells that possess the ability to generate daughter cells that produce large numbers of differentiated progeny. They can be divided into two broad categories: embryonic stem cells and adult stem cells.
- Embryonic stem cells are derived from the inner cell mass of mammalian blastocysts and can give rise to all of the differentiated tissues of the embryo proper, including the β cells of the pancreas.
- Adult stem cells have been identified in many organs, where they participate in tissue repair and homeostasis. However, no definitively identified stem cell population in the pancreas has yet been described.
- Experiments conducted in animal models of regenerating pancreata suggest that an adult stem cell compartment may exist. In addition, a number of tissue culture experiments have demonstrated that heterogeneous populations of cells derived from the adult pancreas can grow and differentiate *in vitro* to produce insulin-expressing cells.
- Mouse and human embryonic stem cells have been shown to produce insulin-positive cells *in vitro.* However, the similarity of these cells to mature β cells with respect to both physiology and gene expression is unclear.
- In general, the characterization of pancreatic stem cells and the insulin-expressing cells derived from them is incomplete. In particular, these cells have yet to be compared to β cells using a broad array of transcriptional markers instead of relying on the expression of one or a few genes. Furthermore, detailed physiological assays of glucose responsiveness and insulin secretion are lacking.

The aim of stem cell therapy in the treatment of type 1 diabetes mellitus is to provide a source of cells that are identical or nearly identical to β cells. Stem cells by definition are self-renewing, and in some cases they can be propagated clonally from a single cell. These properties allow a degree of reproducibility that is unusual for a cell-based therapeutic vehicle. It may be possible to engineer stem cells to evade immune recognition, or to use syngeneic stem cell therapy to avoid allograft rejection. However, the identity of adult pancreatic stem cells and the signals that allow for their production, proliferation and differentiation remain obscure. Similarly, the ability to produce β cells from embryonic stem cells has been hampered by an incomplete understanding of the developmental processes involved in the differentiation of the mature mammalian β cell.

General definitions: adult and embryonic stem cells

Stem cells are defined functionally. They are capable of self-renewal and possess the ability to generate daughter cells that produce large numbers of differentiated progeny [1]. They can be divided into two broad categories: embryonic stem cells and adult stem cells. Embryonic stem cells are derived from the inner cell mass of the mammalian blastocyst (Fig. 75.1) and are said to be pluripotent, because they give rise to all of

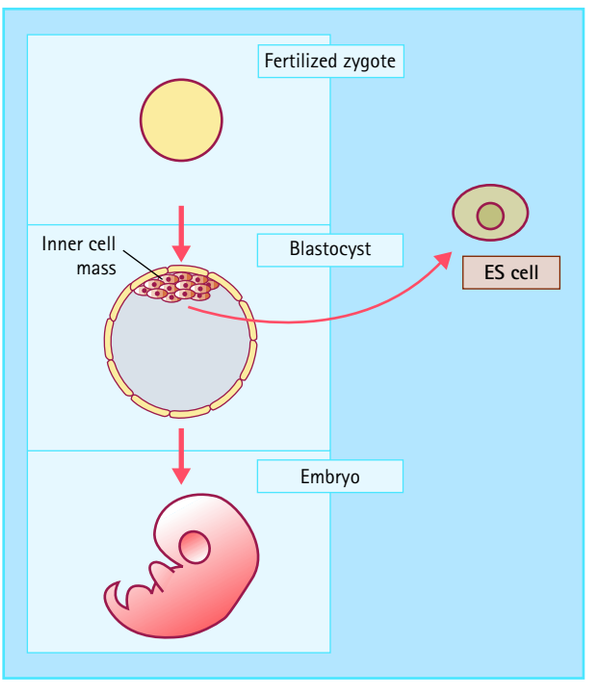

Fig. 75.1 Derivation of embryonic stem cells. After fertilization, the single-cell human or mouse zygote undergoes cleavage to produce a multicellular blastocyst. The blastocyst stage of mammalian development occurs well before cytodifferentiation and organogenesis. Cells from the inner cell mass, which normally give rise to the tissues of the embryo proper, can be cultured *in vitro* to produce embryonic stem cells. ES, embryonic stem.

TODC75 5/17/02 1:31 PM Page 2

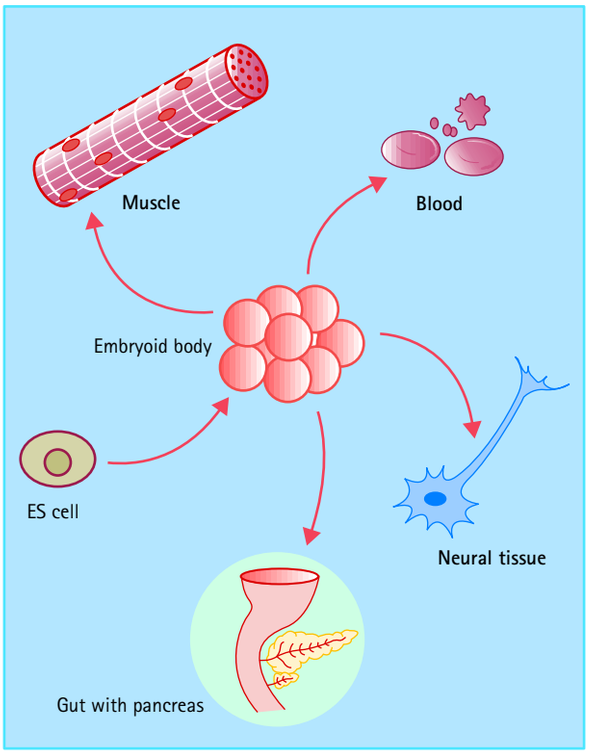

Fig. 75.2 The pluripotent nature of embryonic stem (ES) cells. Embryonic stem cells can be cultured *in vitro* indefinitely. When allowed to aggregate in suspension culture, forming embryoid bodies, they differentiate into derivatives of all three embryonic germ layers. This includes ectodermal tissues such as neurones, mesodermal tissues such as muscle cells and blood, and endodermal tissues such as β cells. Although there are many cell types in embryoid bodies, they are often disorganized and do not adopt the same patterned structure found in mature embryos and adults (for example, actual muscle, ganglia, gut or islets).

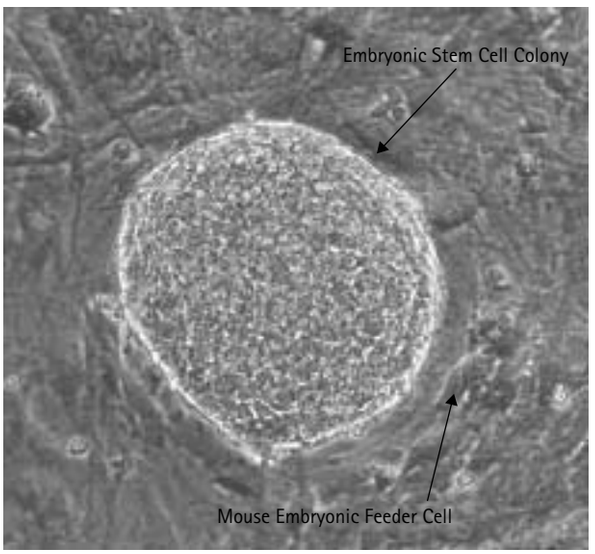

Fig. 75.3 A human embryonic stem cell colony is composed of hundreds to thousands of homogeneous cells grown in a Petri dish along with hundreds of other similar stem cell colonies. One colony is shown here. These colonies are grown on mouse embryonic fibroblasts, which provide signals preventing embryonic stem cell differentiation. This allows repeated, near-indefinite subculture of embryonic stem cells. When removed from the murine feeder layer, the stem cells spontaneously differentiate into a wide variety of cell types (not shown).

the fully differentiated tissues of the embryo proper, including the products of all three embryonic germ layers and thus the β cells of the pancreas (Fig. 75.2) [2–5]. Fortunately, conditions have been described that permit the long-term culture of these cells *in vitro* without chromosomal aberration or loss of potency to form diverse tissues (Fig. 75.3) [2–6]. Indeed, cell lines can be created by the propagation of a single cell, ensuring homogeneous cell populations that can subsequently be used as starting material for β-cell differentiation experiments.

Adult stem cells are thought to be rare cells and are known to participate in the repair or regeneration of certain tissues, most notably in the bone marrow [7,8]. Stem cell populations are also involved in the tissue homeostasis of the liver, the brain, the skeletal muscle and the skin [9–13]. Adult stem cells, like their embryonic counterparts, are capable of self-renewal and retain the ability to generate large numbers of differentiated progeny, but they are traditionally thought to produce a more limited number of cell types. Although there is some evidence to suggest the existence of a pancreatic stem cell function, no one cell type or marker of such a putative cell has been identified. In fact, it is unclear whether the concept of an adult stem cell represents a single well-defined cell type or a common property of a heterogeneous population of different cells [1]. Recently, a number of studies have suggested that stem cells once thought to be specific for a single organ are able to generate differentiated cells from other tissues. For example, bone marrow stem cells have been shown to differentiate into cells typical of other organs, including the liver, muscle, brain and heart [14–17]. In these and other cases, adult stem cells from one germ layer produce differentiated cells of all three primary embryonic germ layers, suggesting a heretofore unimagined plasticity. This raises the possibility that stem cells derived from adult organs other than the pancreas may be capable of producing β cells (Fig. 75.4).