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Review

Growth hormone signaling in pancreatic β-cells—Calcium handling regulated by growth hormone

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ABSTRACT

Deficiency in insulin secretion is a fundamental part in the pathogenesis of all forms of diabetes, determined by impaired secretory function and inadequate β-cell mass. Growth hormone (GH) is a multifunctional hormone, involved in cellular metabolism, mitogenesis and differentiation. In pancreatic islets, GH is involved in maintaining β-cell mass, stimulating islet hormone production and insulin secretion, and, therefore, plays a role in maintaining normal insulin sensitivity and glucose homeostasis. The intracellular events that convey the GH signal into various cellular responses remain incompletely understood. In this review, we discuss GH signaling in the β-cells, with emphasis on Ca^{2+} handling and insulin secretion regulated by human GH (hGH). hGH-stimulated rise in $[Ca^{2+}]_i$ is dependent on extracellular Ca^{2+} and is mediated by Ca^{2+}-induced Ca^{2+} release (CICR) in the β-cell. This process is triggered by hGH-stimulated activation of the non-receptor tyrosine kinases JAK2 and c-Src, which causes tyrosine phosphorylation of RyRs, resulting in sensitization of CICR. The rise in $[Ca^{2+}]_i$ elicited by hGH is associated with an enhanced insulin secretion, effects that are mediated mainly through the prolactin receptor. These mechanisms indicate that a rise in $[Ca^{2+}]_i$ elicited by activation of PRLR is JAK2-dependent and is associated with enhanced insulin secretion. In contrast, GH receptor-mediated increase in $[Ca^{2+}]_i$ is JAK2-independent and is dissociated from insulin secretion.

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Pancreatic β-cells are unique in their ability to synthesize and secrete insulin, which keeps glucose levels within a physiological range. The capacity of the β-cells to respond to elevated blood glucose with increased insulin secretion depends on a sophistic regulation of the insulin secretory machinery by individual cells. Failure of the capacity of the β-cell is a fundamental part of the pathogenesis of all forms of diabetes. Although insulin resistance is one of the major contributors, diabetes develops only when β-cells fail to compensate for increased insulin demand (Weir et al., 2001). β-Cell dysfunction in diabetes involves a number of

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impairments, including decreased secretory response to glucose (Bell and Polonsky, 2001; Gloyn et al., 2003; Abdul-Ghani et al., 2006; Banhegyi et al., 2007; Goodarzi et al., 2007; Mizuno et al., 2007), impeded pulsatile insulin release (Porksen, 2002) and inefficient proinsulin processing to insulin (Kahn et al., 1995; Kahn and Halban, 1997; Loos et al., 2007).

Inadequacy of the pancreatic β-cell results from a combination of impaired secretory function and inadequate β-cell mass. The total β-cell mass is a major determinant of the amount of insulin that can be secreted by the pancreas, and might become rate limiting in long-term demand invoked on insulin secretion, such as in obesity and pregnancy. The amount of insulin secreted depends on long-term adaptations of the total β-cell mass, which is determined by a balance between islet β-cell neogenesis and apoptosis. The pancreatic β-cell has an estimated life span of approximately 60 days (Bonner-Weir, 2000a,b). A slow turnover of β-cells remains in adult life, and their proliferative activity decreases with increasing age when diabetes is also becoming more prevalent. About 0.5% of the adult β-cell population is undergoing replication, which is usually balanced by a small portion of β-cells entering into apoptosis (Bonner-Weir, 2000a,b). Adult β-cell proliferation can, however, be enhanced. Healthy β-cells undergo proliferation in response to increased demand, for example, in obesity or pregnancy (Bonner-Weir, 2000a,b; Lingohr et al., 2002). The ability of the pancreatic β-cell to expand its proliferative capacity in response to an increased insulin demand may be of critical regulatory significance for the development of diabetes. Diabetic patients, in particular those suffering from type 1 diabetes, but also type 2 diabetes, exhibit a reduced β-cell mass, possibly due to increased rates of apoptosis (Sjoholm, 1996; Pick et al., 1998; Lingohr et al., 2002; Sesti, 2002; Dickson and Rhodes, 2004). In different animal models, a defect in β-cell regeneration seems to be of central importance in the development of glucose intolerance (Sjoholm, 1996; Liu et al., 2004). Despite intensive studies, the molecular mechanisms causing the disorder still remain elusive. To achieve a more complete understanding of etiology and pathogenesis of diabetes, further elucidation of factors governing insulin production and proliferation of the β-cell is clearly warranted.

1. Growth hormone (GH) regulates proliferation and function of the pancreatic β-cell

GH is a multifunctional hormone, whose functions at the cellular level can be divided into three categories, *viz.* metabolism, mitogenesis and differentiation. GH levels in the blood rise during pregnancy and lactation, suggesting that elevated circulating levels of the hormone are associated with and responsible for the expansion of the β-cell mass that occurs under these conditions (Brelje and Sorenson, 1991).

Maintaining islet β-cell mass and adequate insulin secretion to meet metabolic demands is crucial to avoid glucose intolerance and the development of type 2 diabetes. GH is closely involved in maintaining pancreatic islet size, enhancing β-cell replication and differentiation, stimulating insulin gene expression and hormone production, insulin secretion and maintaining normal glucose homeostasis (Nielsen et al., 1989; Billestrup and Nielsen, 1991; Rhodes, 2000; Sjoholm et al., 2000; Fernandez et al., 2001; Nielsen et al., 2001; Okuda et al., 2001; Yakar et al., 2001; Lu et al., 2004). GH overexpression *in vivo* increased pancreatic islet number and volume in transgenic mice (Parsons et al., 1995), while disruption of GH signaling by knockout of the GH receptor gene ($GHR^{-/-}$) in mice resulted in hypoglycemia and hypoinsulinemia, associated with diminished pancreatic islet size and β-cell mass (Liu et al., 2004). The average size of the islets found in $GHR^{-/-}$ mice was only one-third of that in wild type littermates with 4.5-fold reduction in total β-cell mass (Liu et al., 2004). Adult $GHR^{-/-}$ mice exhibited significant decrease in glycemia and insulin levels, as well as β-cell insulin mRNA accumulation. Conversely, β-cell mass was substantially expanded in rats bearing GH-secreting tumors (Garay et al., 1971; Parsons et al., 1983). Interestingly, in this animal model, the increased β-cell mass occurred without concomitant hyperglycemia, suggesting a direct stimulatory effect of GH on β-cell mitogenesis. Similarly, β-cell growth is enhanced in patients with acromegaly (Hellman and Angervall, 1961), an influence that may be due to a combination of direct β-cell trophic effects and compensatory growth of the β-cell to meet an increased insulin demand due to insulin resistance under the circumstances.

GH and the biologically related lactogenic peptides prolactin and placental lactogen have been extensively investigated with regard to effects on β-cell proliferation. GH has been reported to stimulate the *in vitro* replication of fetal, neonatal and adult rat β-cells (Hellerstrom et al., 1991). In most of these studies there was also a stimulatory effect of GH on the insulin content and/or secretion and the majority of effects were mimicked by prolactin and placental lactogen (Hellerstrom et al., 1991; Zhang et al., 2006). Mutation of GHR was found to abolish GH-stimulated insulin production (Moldrup et al., 1991).

Because GH in many other tissues appears to elicit its biological activities by inducing local production of insulin-like growth factors (IGFs) in target cells, the issue of whether a similar paracrine pathway operates also in islets has been addressed. Previous reports have shown that this probably is not the case in the β-cell (Billestrup and Nielsen, 1991). Recent studies in GHR-deficient mice revealed that the reduced β-cell mass in the transgenic model was restored, associated with an improved insulin secretion by pancreatic islet-specific overexpression of IGF-1 on the $GHR^{-/-}$ background (Guo et al., 2005). Since GHR gene deficiency causes a concurrent decrease in the production of IGF-1, which also plays a role in islet cell growth, insulin secretion, and maintaining insulin sensitivity (Fernandez et al., 2001; Yakar et al., 2001; Lu et al., 2004), the result observed in $GHR^{-/-}$ mice suggests that IGF-1 deficiency may be involved in the mechanisms underling the reduced β-cell mass and function in this animal model.

2. GH receptor signaling pathways

The effects of GH are mediated through its receptors, which are expressed in most tissues, including β-cells (Moldrup et al., 1990; Nielsen et al., 1990). The GH receptor was the first identified member in the cytokine receptor superfamily, which includes the prolactin (PRL) receptor and receptors for other cytokines. The common nature of the family of the receptors is that they do not contain intrinsic kinase activity. Activation of the receptors, such as GH receptors, results in association and activation of the cytoplasmic tyrosine kinases (Dominici et al., 2005). The Janus family of tyrosine kinases (JAK) is believed to be the major non-receptor tyrosine kinases required for the initiation of GH signal transduction upon ligand binding to the receptor (Foster et al., 1988; Lis and Wu, 1993; Silva et al., 1993). Among the JAK members (JAK1-3 and Tyk2), the predominant JAK kinase utilized in GH signaling is JAK2 (Lis and Wu, 1993; Waters et al., 2006), although GH has also been shown to induce tyrosine phosphorylation of JAK1 (Smit et al., 1996) and JAK3 (Johnston et al., 1994). JAK proteins have a molecular mass of approximately 130 kDa. Knockout of JAK2 in mice is embryonic lethal (Neubauer et al., 1998; Parganas et al., 1998), suggesting an important role of the kinase in early development. The interaction site of JAK2 with the GH receptor is at Box1 region, which consists of eight residues (Argetsinger