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Growth hormone modulation of insulin signaling in the heart

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Insulin regulates various aspects of cardiovascular physiology, including substrate utilization, cardiomyocyte growth and contractility. One of the principal signaling cascades activated by insulin is the phosphatidylinositol-3-kinase (PI3K)/Akt pathway (**Fig. 1A**), which regulates multiple myocardial functions, including cellular growth, proliferation, survival, gene expression, protein translation, glucose uptake and metabolism. Several studies suggest that insulin signaling through PI3K/Akt signaling is involved in the pathogenesis of cardiac hypertrophy. Hyperinsulinemia leads to cardiac hypertrophy ,and mice expressing constitutively active Akt in the heart exhibit increased myocyte size and cardiomegaly. Akt activates the mammalian target of rapamycin (mTOR), an important promoter of protein synthesis, which regulates cardiomyocytes size, mass and proliferation and is believed to participate in insulin-mediated cardiac hypertrophy. The crucial role of this kinase in myocardial hypertrophy is supported by studies showing that pharmacological inhibition of mTOR by rapamycin or rapamycin analogs ameliorates the hypertrophic growth observed in different animal models of cardiovascular disease.[1-4]

Chronic growth hormone (GH) excess in acromegaly induces myocardial hypertrophy, which, in many cases, is associated with cardiac dysfunction and constitutes an important factor for increased mortality rates in these patients.[5] Extensive experimental and clinical evidence indicates that chronic elevation of circulating GH levels exerts anti-insulin effects. Acromegalic patients exhibit hyperinsulinemia, insulin resistance and high risk of developing diabetes. Similarly, sustained exposure to high levels of exogenous GH can induce both hepatic and peripheral insulin resistance.[6] The molecular mechanisms implicated in the acromegalic cardiac pathology are not completely elucidated, but evidence suggests that hyperinsulinemia and altered insulin signaling in the heart may be involved.

Prolonged exposure to GH impairs insulin signaling by multiple mechanisms, including the phosphorylation of insulin receptor substrate (IRS) proteins on serine residues.[6] This covalent modification impairs IRS binding to the insulin receptor, induces IRS degradation and/or inhibits its association with downstream molecules. Ser/Thr kinases downstream of PI3K that are activated by insulin signaling may act as a negative feedback control by inhibiting IRS proteins. Alternatively, other signals that are known to induce insulin resistance, such as tumor necrosis factor α (TNFα), free fatty acids and cellular stress, may also activate Ser/Thr kinases that phosphorylate IRS proteins and inhibit their function.[2,7]

It has recently been shown that chronic exposure to elevated circulating GH levels in mice was associated with impaired insulin signaling in the heart.[8] Transgenic mice overexpressing GH present hyperinsulinemia and insulin resistance and develop a hypertrophic cardiomyopathy similar to that observed in acromegalic patients. As described in **Figure 1B**, these mice displayed elevated basal activation of the insulin receptor and the IRS1/PI3K/Akt/mTOR pathway in the heart, along with mTOR protein content upregulation, which most probably participates in the cardiac hypertrophy. In addition, a role for mTOR in insulin resistance has been described, as it induces Ser phosphorylation of IRS proteins.[7] Accordingly, GH-transgenic mice displayed attenuated activation of the IRS1/PI3K/Akt pathway upon acute insulin stimulation associated with increased Ser phosphorylation of IRS1. Therefore, mTOR seems to have a central role in the impaired sensitivity to insulin and hypertrophy observed in the heart as a consequence of persistent GH overexpression in mice.

In humans, conditions of both GH excess and deficiency are associated with cardiac pathology. While mice exposed to chronically elevated GH levels exhibit cardiac insulin resistance, mice in which the receptor of GH has been disrupted display a marked increase in the activation of insulin signaling in the heart, reflecting higher cardiac sensitivity to insulin.[9] In conclusion, impaired insulin signaling in the heart is believed to play a major role in the cardiac pathology associated to conditions of altered GH levels.

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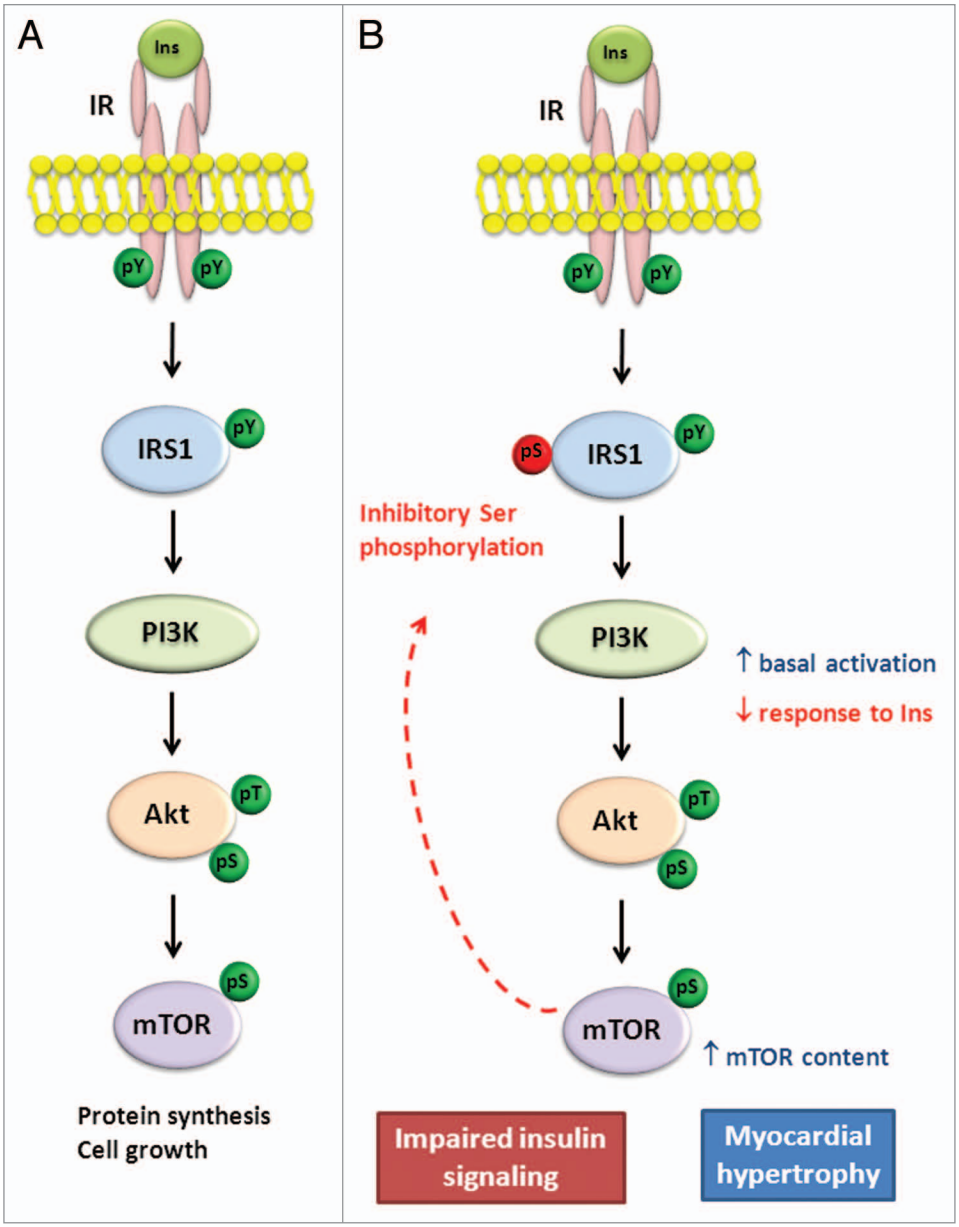

Figure 1. (A) Insulin (Ins) binding to its membrane receptor (IR) leads to the phosphorylation on Tyr residues (pY) of the receptor and the insulin receptor substrate 1 (IRS1), initiating different signaling cascades, including the PI3K/Akt signaling pathway. The Ser/Thr kinase Akt is activated by phosphorylation on Ser473 (pS) and Thr308 (pT) and is a critical mediator of insulin actions on the heart. Akt influences protein synthesis and cell growth through activation of the Ser/Thr kinase mammalian target of rapamycin (mTOR). (B) Chronic growth hormone (GH) excess is associated with hyperinsulinemia and insulin resistance. GH-overexpressing transgenic mice exhibit higher basal activation of IR/IRS1/PI3K/Akt/mTOR pathway and increased mTOR protein levels in the heart, which most probably participate in the cardiac hypertrophy they display. Despite the basal activation of this signaling pathway, a decreased response upon insulin acute stimulation was observed at the post-receptor level, consistent with elevated Ser phosphorylation levels of IRS1 (pS, red circles), an inhibitory modification that interferes with insulin signaling. Although many Ser/Thr kinases are known to phosphorylate IRS1, the upregulation of mTOR observed in this model suggests that it may participate in the negative modulation of insulin signaling in the heart in conditions of chronic GH excess[8].

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