Insulin is the most potent anabolic hormone and is essential for tissue development, growth, and maintenance of whole-body glucose homeostasis. Failure of the target cells to respond to insulin stimulation, ie, insulin resistance, is commonly observed under acute stress conditions and in individuals with obesity, metabolic syndrome, or diabetes. Insulin resistance has been considered a major risk factor for the development and progression of cardiovascular disease.\(^1,2\) Although a well-documented phenomenon, the molecular mechanisms leading to insulin resistance remain elusive, attributable, in part, to the complexity of the insulin signaling pathway.

Circulating insulin binds to and activates its cell surface receptor to elicit its biological actions (Figure). The insulin receptor is a widely expressed transmembrane tyrosine kinase consisting of two α- and two β-subunits.\(^3,4\) The binding of insulin to the extracellular α-subunit results in a rapid configurational change in the receptor leading to the autophosphorylation of specific tyrosine residues of the intracellular region of the β-subunit.\(^5\) This process results in activation of the tyrosine kinase activity of the insulin receptor, which transmits the insulin signal by phosphorylating a number of substrate proteins.\(^6,7\) The insulin-receptor signaling involves two major pathways: the mitogen activated protein kinase (MAPK) pathway, mainly responsible for mitogenesis and cell growth, and the phosphatidylinositol-3-kinase (PI3-K) pathways, mainly accountable for the metabolic responses (Figure; although depicted as linear pathways, these two systems also interact under certain conditions). A critical player in the PI3-K pathway is the Ser/Thr protein kinase Akt (PKB), which serves as a multifaceted intermediary propagating insulin receptor signaling to the diversified downstream biological effectors. Akt has drawn much attention for the versatile roles it plays in these biological processes. A study published in this issue of *Circulation Research* suggests yet another role for this celebrity kinase: communication with the β-adrenergic signaling pathway and inhibition of insulin signaling.\(^11\)

Using 2-deoxyglucose uptake as the readout of insulin response, the authors of this study reported that chronic β-adrenergic stimulation by isoproterenol led to insulin resistance in neonatal rat cardiac myocytes. They provided persuasive evidence showing that β-adrenergic stimulation had a biphasic effect on Akt phosphorylation. The acute effect caused Thr 308 phosphorylation, whereas the prolonged stimulation led to Ser 473 phosphorylation. Although phosphorylation of either site can activate Akt, activated Akt by these two mechanisms apparently perform different tasks. Although Thr 308 phosphorylation of the Akt resulted in increased glucose uptake, Akt activated by Ser 473 phosphorylation acted as a negative regulator that phosphorylated a threonine on the insulin receptor β-subunit causing decreased autophosphorylation of the receptor. In this way, prolonged β-adrenergic stimulation can lead to desensitization of insulin receptor and culminate to insulin resistance. This finding suggests a likely mechanism for insulin resistance often observed during high β-adrenergic states such as acute stress and heart failure.\(^2,7\)

It has been shown that insulin receptor tyrosine kinase activity can be inhibited by increased tyrosine phosphatase activity or enhanced Ser/Thr phosphorylation of the receptor.\(^8\) Previously, treatment of cells with insulin, PKC activators, or cAMP-dependent protein kinase was found to cause Ser/Thr phosphorylation of the receptor resulting in decreased receptor tyrosine kinase activity.\(^5,8\) In these studies, Akt has not been explicitly implicated as the kinase responsible for the Ser/Thr phosphorylation. However, there is emerging evidence showing prolonged activation of Akt leads to negative feedback of insulin signaling using transgenic mice overexpressing constitutively Akt.\(^9,10\) In the present article, Morisco and colleagues\(^11\) showed decreased tyrosine phosphorylation of insulin receptor in mouse hearts expressing constitutively active Akt. Importantly, their study demonstrated that activation of Akt by prolonged β-adrenergic stimulation, a pathophysiologically relevant signal, also yielded a similar outcome. It is interesting to note that this study also found a role of Akt in the feedback inhibition of insulin receptor tyrosine phosphorylation in insulin-induced insulin receptor desensitization (see the online data supplement that accompanies the article). Thus, it is likely that Akt, the propeller of the insulin signaling, also back-pedals from time to time. As it is true for almost any system, the balance of forward and backward motion is the key for normal biological function.

An important issue raised here is the signal specificity that enables Akt to play the right role at the right time/place. The study by Morisco and colleagues\(^11\) suggests that the phosphorylation site dictates the specificity of Akt function. This is consistent with a previous observation that Thr 308 phosphorylation of Akt is necessary for increased glucose uptake, whereas Ser 473 phosphorylation is not.\(^6,12\) The present study shows that phosphorylation of either site is mediated by PI3K but follows a different time course. Furthermore, insulin-induced Ser 473 phosphorylation occurs much sooner than β-adrenergic stimulation-induced phosphorylation of the same site. It is not clear, however, if the signal(s) upstream or downstream of PI3-K...
are responsible for creating task-specific Akt. In either case, it will be extremely interesting to investigate whether the formation of multiple signal complexes containing different subpopulations of Akt accounts for these observations.13

Another important point that has not been addressed in the present study is whether decreased tyrosine phosphorylation of the insulin receptor is sufficient to explain decreased glucose uptake during prolonged β-adrenergic stimulation. The authors showed that transfection of dominant-negative Akt rescued the tyrosine phosphorylation of the insulin receptor during chronic β-adrenergic stimulation. It remains to be seen if normalization of insulin receptor tyrosine phosphorylation can prevent insulin resistance under these conditions. Signaling molecules downstream of insulin receptor, such as IRS proteins and/or PI3K also contribute to the development of insulin resistance.14 Recent studies using transgenic mouse hearts showed that chronic activation of Akt induced feedback inhibition of PI3K through proteasome-dependent degradation of IRS-1 and inhibition of IRS-1/PI3K association.9 It will be worthwhile to determine whether these mechanisms also contribute to insulin resistance attributable to chronic β-adrenergic stimulation.

This study proposes an exciting new role for Akt, adding to the ongoing effort to understand the sophisticated biological role of Akt, which is central for its application in the development of therapeutic strategies. Furthermore, increased sympathetic activity and insulin resistance often coexist in cardiovascular diseases; both are found to be important for the disease progression.1,2 A better knowledge of their relationships at the molecular level will provide new insight for clinical care. Although the present finding warrants further investigation, its relevance to the in vivo conditions needs to be interpreted with caution. The key observations of this study were made using neonatal cardiac myocytes, a preparation with a relatively immature system for insulin-regulated glucose transport. It should also be mentioned that the metabolic states in isolated myocytes are markedly different from that of the contracting hearts, which can profoundly influence glucose transport, the functional readout of insulin response in this study. Furthermore, insulin resistance in this study was observed in myocytes treated with a very high dose of isoproterenol (1 to 10 mmol/L) compared with the circulating catecholamine levels under most (patho)physiological conditions. Whether such an intense β-adrenergic stimulation actually occurs in vivo is in question. This is a difficult question, however, because it is not easy to quantify the amount of β-adrenergic ligands in the vicinity of cardiac myocytes, and it can be much higher than circulating levels. Clearly, future studies in integrated systems are critical for translating the present findings to in vivo settings. Let’s hope the excitement about our celebrity kinase continues.

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**References**


**Key Words:** insulin signaling ■ Akt ■ phosphorylation ■ β-adrenergic stimulation
Another Role for the Celebrity: Akt and Insulin Resistance
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