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Minireview

Protein kinase B (PKB/Akt) – a key regulator of glucose transport?

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Abstract The serine/threonine kinase protein kinase B (PKB/Akt) has been shown to play a crucial role in the control of diverse and important cellular functions such as cell survival and glycogen metabolism. There is also convincing evidence that PKB plays a role in the insulin-mediated regulation of glucose transport. Furthermore, states of cellular insulin resistance have been shown to involve impaired PKB activation, and this usually coincides with a loss of glucose transport activation. However, evidence to the contrary is also available, and the role of PKB in the control of glucose transport remains controversial. Here we provide an overview of recent findings, discuss the potential importance of PKB in the regulation of glucose transport and metabolism, and comment on future directions.

Key words: Insulin; Muscle; Adipose; Glycogen synthase kinase-3; GLUT4; Phosphoinositide 3-kinase; Diabetes

1. Introduction

The cloning of the serine/threonine kinase protein kinase B (PKB) also known as c-Akt (the cellular homologue of the viral oncogene v-Akt) nearly 10 years ago heralded a new era in our understanding of the propagation of hormonal and survival signals in mammalian cells (for reviews see [1,2]). PKB, a 57 kDa protein, was so named because of its high homology with protein kinase A and protein kinase C (PKC), and it is known to exist as three isoforms, α, β and γ (Akt1, Akt2 and Akt3, respectively) [2]. Each isoform possesses an amino-terminal pleckstrin homology (PH) domain, a kinase domain and a carboxy-terminal regulatory domain [1]. PKB is activated rapidly in response to insulin and growth factors in a phosphoinositide 3-kinase (PI3K)-dependent fashion, in what is believed to be a two step process. The first step involves the stimulus-dependent production of 3-phosphoinositides (PtdIns(3,4)P_2 and PtdIns(3,4,5)P_3) by PI3K, which bind to the PH domain of PKB and are thought to induce a conformational change in the kinase. The second step involves the translocation of PKB from a mainly cytosolic localisation to the plasma membrane, where the kinase is activated by phosphorylation [3]. The nature of the mechanism by which PKB is recruited to the cell surface is far from clear, but recent work from our laboratory indicates that an intact actin cytoskeleton, which permits the insulin-dependent production of 3-phosphoinositides, appears to be necessary [4]. The phosphorylation of PKB occurs at two specific regulatory sites, one localised in the kinase domain (Thr^{308} for PKBα) and the other in the C-terminal regulatory domain (Ser^{473} for PKBα) [1,2]. The kinase responsible for the phosphorylation of the Thr^{308} site has been identified as a 3-phosphoinositide-dependent kinase (PDK1) [5,6]. The identity of the kinase responsible for phosphorylating the Ser^{473} site (putatively termed PDK2) remains elusive, although integrin-linked kinase [7], PDK1 [8], and PKB autophosphorylation [9] have all been proposed as potential mediators of the phosphorylation of this second regulatory site.

The importance of PI3K in the propagation of multiple signals including insulin and cell survival signals, led naturally to an investigation of the role of PKB in these processes. Numerous studies have demonstrated recently that PKB has a key function in relaying the PI3K survival signal, and that it acts as an anti-apoptotic signalling kinase in a variety of cell types (for review see [10]). PKB has been shown to modulate the activity of proteins mediating apoptosis, including the pro-apoptotic factor, BAD, members of the forkhead family of transcription factors, the nuclear factor CREB, the pro-apoptotic protease caspase 9 and the transcription factor NF-κB [10]. In addition to its involvement in regulating cell survival, there is accumulating evidence to indicate that PKB is important in mediating the effects of insulin on glucose utilisation in skeletal muscle and adipocytes, and this review will focus on recent progress made in this area.

2. PKB – a regulator of glycogen synthesis and glucose transport

Insulin promotes a variety of important biological responses, but among the best documented is its ability to stimulate the disposal of blood glucose, primarily in target tissues such as skeletal muscle and adipocytes, where the sugar is either oxidised or stored as glycogen or fatty acids. In both tissues insulin promotes a rapid activation of specific PKB isoforms. PKBα is the major isoform expressed in skeletal muscle, whereas PKBβ is the predominant subtype in adipocytes [11]. Although PKBγ is not activated to any significant extent in skeletal muscle or adipocytes, its stimulation has been observed in several cell lines [11]. One of the first physiological targets of PKB to be identified was glycogen synthase kinase-3 (GSK3) [12], which has been implicated in the control of many cellular processes, including glycogen and protein synthesis, and the modulation of transcription factor activity [1]. In unstimulated cells, GSK3 is active and contributes significantly towards the phosphorylation and inhibition of glycogen synthase [12]. Insulin stimulates glycogen synthesis both

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by inactivating GSK3 and also by promoting the dephosphorylation of glycogen synthase. The inactivation of GSK3α and GSK3β is achieved through phosphorylation of Ser^{21} and Ser^{9}, respectively [12], and this is mediated by PKB in a PI3K-dependent fashion. Thus PI3K, PDK, PKB and GSK3 constitute one important arm of the insulin signalling cascade regulating glycogen synthesis.

Another important metabolic response to insulin is the stimulation of glucose transport in skeletal muscle and adipocytes, which is largely due to the translocation of the insulin-regulated glucose transporter, GLUT4, from its intracellular storage pool to the plasma membrane (for review see [13]). PI3K is a crucial intermediate in the insulin signalling process that leads to the translocation of GLUT4 and the associated stimulation of glucose transport [14]. As it became clear that PKB activation was dependent on the production of 3-phosphoinositides by PI3K [15], workers were quick to test the hypothesis that PKB might play a role in the stimulation of glucose transport by insulin. The potential involvement of PKB isoforms in the hormonal regulation of glucose transport has been based largely on studies involving over-expression of constitutively active mutants of PKB in isolated rat adipocytes [16], 3T3-L1 adipocytes [17,18] and L6 muscle cells [19,20]. In L6 cells expression of such mutants led to an increase in the basal activity of PKB that was accompanied by a significant stimulation in glucose uptake, to a level comparable to that elicited normally by insulin in untransfected control cells. The observed increase in glucose transport was primarily attributable to an increase in the plasma membrane recruitment of GLUT4, but not that of the GLUT1 transporter [18,19]. In addition to inducing an increase in glucose transport, over-expression of PKB in L6 muscle cells elicited an inhibition of GSK3 and a concomitant increase in glycogen and protein synthesis [19,20]. Another recent study showed that microinjection of either a PKB substrate peptide or an antibody directed against PKB into 3T3-L1 adipocytes could prevent, in part, the translocation of GLUT4 by insulin [21]. However, whilst these findings are consistent with the idea that PKB plays a role in the hormonal activation of glucose transport, work from Kasuga's group suggested otherwise. Kitamura et al. [22] suppressed the hormonal activation of the endogenous PKB in 3T3-L1 adipocytes by expressing a dominant negative form of the kinase, in which both regulatory phosphorylation sites (Thr^{308} and Ser^{473}) had been mutated to an alanine. In cells transfected with this double 'AA' mutant, the hormonal activation of PKB was suppressed by ~80% [22]. The authors reported that under such circumstances insulin failed to activate protein synthesis, but was nevertheless able to stimulate GLUT4 translocation and glucose transport [22]. The reason why this study is at odds with the majority, which have implicated PKB in the regulation of glucose transport, is unclear. However, our studies in L6 muscle cells over-expressing wild-type PKB have indicated that the stimulation of glucose transport requires only a very small activation of PKB (~3-fold), whereas other cellular responses such as the inactivation of GSK3 may require a greater stimulation in PKB activity [19]. Thus, given that the activity of the endogenous PKB was not suppressed completely by the over-expressed dominant negative mutant in the study by Kitamura et al. [22], it is plausible that the residual endogenous activity was sufficient to elicit an increase in glucose transport. More evidence supporting this view comes from the work of Wang et al. [23], who assessed PKB involvement in the insulin-stimulated translocation of GLUT4 in L6 myoblasts. These workers co-transfected constructs expressing c-myc-tagged GLUT4 and an 'AAA' PKB mutant, which contained a replacement of both the regulatory phosphorylation sites and of the Lys^{179} residue that participates in ATP binding [3]. Muscle cells transfected with this mutant failed to display any stimulation of the endogenous PKB and, furthermore, failed to induce GLUT4 translocation in response to insulin [23].

An important issue that remains unresolved concerns the mechanism by which PKB promotes GLUT4 translocation to the plasma membrane in response to insulin. Studies in 3T3-L1 adipocytes suggest that insulin induces the re-localisation of PI3K from the cytosol to GLUT4-containing vesicles [24–26]. This observation implies that targeting of PI3K to such vesicles may result in the localised production of 3-phosphoinositides that may support the recruitment of PKB to vesicles harbouring GLUT4. Indeed, studies in 3T3-L1 adipocytes and rat cardiac ventricular muscle have shown that PKBβ associates with GLUT4 vesicles following insulin treatment [27,28]. It is thus plausible that activated PKB phosphorylates specific GLUT4 vesicle-associated proteins involved in the translocation of the transporter to the plasma membrane. For such a scenario to operate there may also be a requirement to localise PDK1/2 to such membranes. However, whilst this scheme appears attractive, there is no evidence at present to indicate that PDK1 co-localises with GLUT4 in its intracellular storage compartment. Alternatively, PKB may be activated at the plasma membrane by PDK1/2 in response to insulin and then relocalise to GLUT4 vesicles, where it may promote their translocation to the cell surface (Fig. 1).

3. Modulators of PKB signalling – consequences for glucose metabolism and insulin sensitivity

An important caveat to interpretation of the above studies involving either stable or transient expression of active or dominant negative forms of PKB is the possibility that such approaches may have unforeseen consequences for the expression and/or activity of proteins regulating glucose utilisation. Thus the issue of whether PKB is truly an upstream component in the signalling cascade initiating GLUT4 translocation may only be resolved when selective cell permeable inhibitors of PKB become available. Nevertheless, one would assume that if PKB is a crucial insulin signalling intermediate regulating glucose metabolism, then its impaired activation should have important implications for the hormonal stimulation of glucose transport. Indeed, there is mounting evidence to support this assumption, some of which is reviewed below.

3.1. Possible modulators of PKB activity during insulin signalling

Recent work has provided evidence that atypical PKC has a role to play in insulin signalling and glucose transport activation. PKCζ/λ is activated by insulin in a PI3K-dependent manner in rat adipocytes [29], 3T3-L1 adipocytes [30] and L6 muscle cells [31]. The use of PKCζ inhibitors and inactive mutants has demonstrated a requirement for this kinase for full insulin stimulation of glucose transport. Moreover, insulin induces the phosphorylation of PKCζ by PDK1, and the relocalisation of PKCζ to GLUT4 vesicles in rat adipocytes [32]. These studies indicate that there may be a requirement for activation of both PKB and PKCζ for GLUT4 translocation and subsequent glucose transport stimulation, but there is also evidence that atypical PKC may regulate PKB activity negatively in certain cells [33,34]. In any case, the precise role of atypical PKC in regulating or potentiating PKB-directed GLUT4 translocation is yet to be determined.

Since PKB activation is dependent upon the generation of 3-phosphoinositides including PtdIns(3,4,5)P_3, a potential mechanism for regulation of the kinase is via lipid phosphatases, and recent work from Olefsky's group suggests that this may in fact be the case. Vollenweider et al. investigated the effect of SH2-containing inositol phosphatase (SHIP) on insulin signalling in 3T3-L1 adipocytes [35]. This study indicated that SHIP, a 5-phosphatase, inhibited hormone-stimulated GLUT4 translocation, and was also effective in preventing GLUT4 translocation induced by expression of a membrane-targeted catalytic subunit of PI3K. SHIP expression also inhibited hormone-stimulated membrane ruffling (a consequence of actin rearrangement), p42/44 mitogen-activated protein kinase (MAPK) phosphorylation and DNA synthesis [35]. The same group then examined the effect of tumour suppressor PTEN (phosphatase and tensin homologue deleted on chromosome 10), a lipid 3-phosphatase [36]. Nakashima et al. over-expressed PTEN in 3T3-L1 adipocytes and observed a

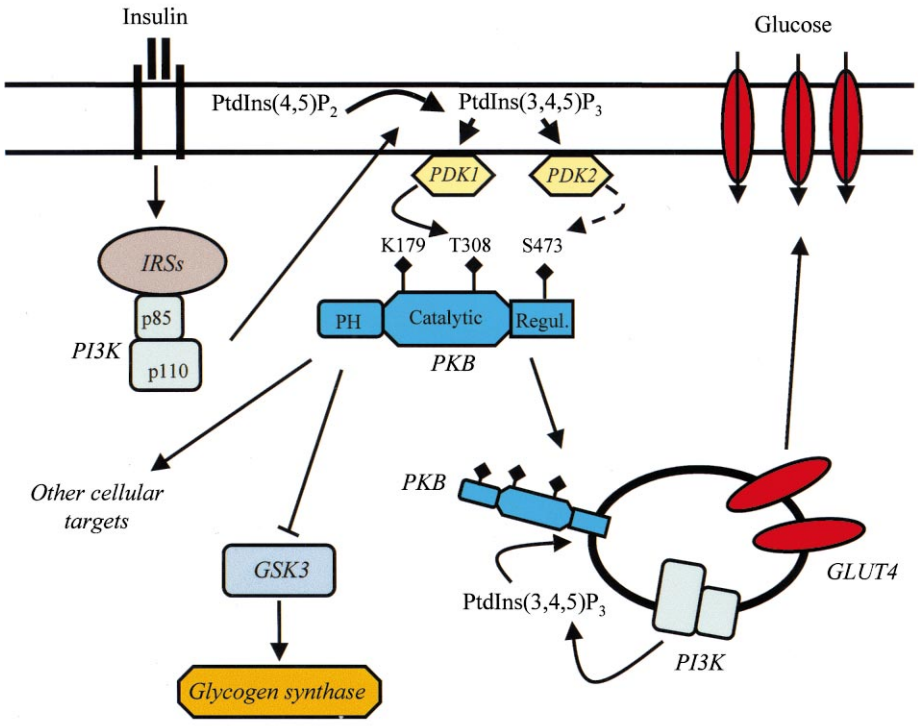

Fig. 1. Proposed model outlining the role played by PKB in the hormonal regulation of glucose metabolism. Insulin promotes the activation of PKB in a PI3K-dependent fashion, resulting in the phosphorylation and inactivation of GSK3 and concomitant activation of glycogen synthase. Activated PKB may also associate with GLUT4-containing vesicles, promoting their translocation to the plasma membrane leading to a stimulation of glucose transport.

decrease in insulin-stimulated GLUT4 translocation, glucose transport and membrane ruffling, which coincided with reduced phosphorylation of PKB and p70S6K but normal phosphorylation of p42/44 MAPK [36]. Furthermore, inhibition of endogenous PTEN by microinjection of anti-PTEN antibodies resulted in increased basal and insulin-stimulated glucose transport [36].

3.2. *Effects of ceramide on PKB activation and glucose transport*

Tumour necrosis factor (TNF)-α, a potent cytokine produced by macrophages, causes a profound reduction in insulin-stimulated glucose transport in skeletal muscle and adipocytes of rats [37]. The molecular mechanism by which TNF-α induces insulin resistance in these tissues remains unclear, but a key event in signal transduction pathways initiated by TNF-α involves the increased turnover of membrane sphingomyelin, and the concomitant production of ceramide [38]. Levels of ceramide are elevated in skeletal muscle of insulin resistant rats [39]. Ceramide has been shown to impair the hormonal activation of IRS-1 and PI3K [40–43], although in other studies it has been reported to act downstream of PI3K and to target PKB [44–46]. These latter studies have shown that in adipocytes and muscle cells, ceramide induces a profound inhibition in the insulin-induced stimulation of PKB. This finding raises the possibility that the loss in insulin-stimulated glucose transport in adipocytes and muscle cells may, at least in part, be the consequence of reduced PKB activation. Studies in cultured muscle cells indicate that this diminished activation of PKB cannot be attributed to a loss in the insulin-dependent synthesis of 3-phosphoinositides or to defects in PDK1, but instead is primarily due to the impaired translocation of PKB to the plasma membrane [47]. Expressing a membrane-targeted form of PKB in both 3T3-L1 adipocytes [45] and L6 muscle cells [47] circumvents the inhibition exerted by ceramide on insulin-stimulated glucose transport. These studies provide strong evidence that PKB activation is likely to be a key step in the signalling sequelae that promote an increase in glucose transport. It is unclear whether the 3-phosphoinositide-dependent translocation of PKB, which can be disrupted by ceramide, involves other accessory factors, or simply reflects a greater proportion of PKB binding at the membrane in the presence of increased 3-phosphoinositide concentrations.

3.3. *Regulation of PKB activation and glucose transport by oxidant and osmotic stresses*

Increased oxidant levels are a characteristic feature of insulin resistant states, and may be important in the progression of diseases such as diabetes mellitus. Evidence exists in the literature showing that acute treatment of cells with hydrogen peroxide (H_2O_2) activates PKB in a PI3K-dependent manner [48,49]. However, under these circumstances glucose transport is not activated by H_2O_2 [49]. The reason for this may be the parallel activation of the stress-activated p38 MAPK pathway by H_2O_2, which is thought to arrest insulin signalling at a point downstream of PKB [49]. Preventing the activation of this stress signalling pathway, using SB 203580, enables H_2O_2 to exert full insulin-like effects on glucose transport, probably through its ability to activate PKB [49]. However, it is noteworthy that prolonged exposure of cells to high levels of oxidants impairs early insulin signalling events, resulting in a substantial loss in PKB activation that correlates with reduced insulin-mediated translocation of GLUT4 [50,51]. In either

case, the effects of acute or chronic H_2O_2 treatment on PKB yield results consistent with the idea that this kinase participates in the regulation of glucose transport.

Chen and colleagues have examined the influence of hyperosmotic shock on insulin signalling in 3T3-L1 adipocytes [52]. In this study, Pessin's group observed that osmotic shock was effective in inhibiting insulin-stimulated responses including glucose transport and GLUT4 translocation. They found that the addition of sorbitol had no effect on early insulin signalling events including PI3K activation, but observed an inhibition of PKB phosphorylation and downstream p70S6K activation, which was attributable to a PP2A-type phosphatase activity [52]. The inhibition of insulin responses by hyperosmotic shock at the level of PKB is entirely consistent with the perceived role of the kinase as a key regulator of glucose transport, and may reflect the chronic in vivo effects of hyperglycaemia.

3.4. The actin cytoskeleton, PKB activation and glucose transport – possible inter-relationships

There is growing recognition of the idea that the actin cytoskeleton may act as a scaffold for the binding of molecules involved in insulin signalling, and that this may be important both for remodelling of the actin network and for signal propagation to key end-point responses [25,53]. Indeed, disassembly of the actin network, using cytochalasin D, has been shown to prevent activation of glucose transport by insulin [53]. Recent work from our laboratory indicates that this loss in glucose transport stimulation may be the consequence of a substantial reduction in insulin's ability to stimulate PKB [4]. Translocation analyses of tagged PH domains, which act as sensitive and selective probes to detect the membrane generation of 3-phosphoinositides [54], indicate that the reduced activation of PKB stems from a loss in the stimulus-mediated synthesis of these phospholipids. The impaired production of 3-phosphoinositides occurs despite normal catalytic activation of PI3K in vitro, indicating that an intact cytoskeleton may be necessary for placing PI3K in close proximity to its lipid substrates. Reformation of the actin network reinstates the capacity of the cells to (i) generate 3-phosphoinositides, (ii) phosphorylate PKB and GSK3, and (iii) stimulate glucose transport, in response to insulin [4,55].

3.5. Does impaired PKB activation have a role to play in the pathogenesis of insulin resistance?

If PKB signalling is an important determinant of glucose metabolism in vivo then one might expect that its activation would be dysfunctional under circumstances when utilisation of glucose in tissues such as skeletal muscle and fat is significantly impaired. If this is so, defects in PKB activation may play an important role in the pathogenesis and progression of insulin resistance. However, a number of recent studies performed in rats, mice and humans have been unable to provide any clarity on this issue. For example, PKB activation by insulin has been shown to be impaired significantly in adipocytes isolated from diabetic rats [56], mice [57] and from type II diabetic humans, as well as in skeletal muscle from hyperglycaemic rats [58–61]. In contrast, data also exist showing that the insulin-mediated phosphorylation of PKB is not altered significantly in fat cells of diabetic rats [62] or in skeletal muscle from humans with type II diabetes [63,64]. Moreover, analysis of genomic DNA or skeletal muscle-derived cDNAs from NIDDM patients did not result in the identification of any mutations in PKBα or PKBβ [65]. The reasons for the above discrepancies are unclear, but may, in part, be attributable to the involvement of certain PI3K-independent signalling mechanisms that are known to regulate PKB [66,67]. Thus, it is not possible at present to assess what contribution, if any, defects in PKB activation may make toward the pathogenesis of insulin resistance in vivo.

4. Conclusions and future directions

Our understanding of the molecular mechanisms by which insulin modulates glucose transport into muscle and fat cells has progressed rapidly in recent years. Since the discovery of PKB it has become increasingly clear that this kinase performs a key intermediary role in the hormonal regulation of glucose metabolism. However, there are many questions that remain unanswered. One priority is to establish the identity of the putative PDK2 kinase, and another to elucidate in greater detail the mechanism by which PKB is recruited to the membrane for activation. In addition, more knowledge is required about the identity of downstream substrates and effectors of PKB. In this regard, we still know very little about the manner in which activated PKB effects the translocation of GLUT4 vesicles to the plasma membrane, and how other signalling molecules, such as PKCζ/λ, may be involved in regulating this process. Although it seems likely that impairment in PKB function is a feature of insulin resistance, it remains to be established whether this represents a causal factor or is merely a consequence of some other molecular defect. In addition, it is an intriguing possibility that artificial restoration of the downstream effects of PKB activation may provide beneficial effects during insulin resistant states. By addressing some of the above issues, we should gain further important insights into the fundamental physiological process of glucose homeostasis, and develop better strategies to combat its pathological dysfunction.

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