Planet Akt. Are there alternate life forms in the insulin action galaxy?

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(Introduced by Mark Febbraio)

The Ser/Thr kinase Akt has been shown to play an important role in the insulin dependent trafficking of GLUT4 in both muscle and fat cells. This is based upon the use of inhibitors of components in the pathway that are upstream of Akt, the expression of either dominant inhibitory or constitutively active versions of Akt in cells or suppression of Akt in physiologically relevant tissues using either siRNA or knock out mice. Despite considerable evidence for the role of Akt in GLUT4 trafficking it remains unclear if activation of Akt alone is sufficient to active glucose transport for a number of reasons. First, suppression of Akt expression is not accompanied by complete suppression of insulin action. Second, a role for other insulin responsive pathways such as Rac, aPKC and c-Cbl/TC10 have been proposed. Third, the steps required to elicit increased glucose transport in response to insulin are complex and numerous and it has been suggested that insulin may both increase GLUT4 exocytosis, reduce GLUT4 endocytosis as well as activate the intrinsic activity of the transporter itself and so one can envisage a role for multiple signalling pathways in this complex process. One of the most important observations to suggest that Akt acts alone in the insulin action pathway is the observation that overexpression of a constitutively active version of Akt in adipocytes results in increased GLUT4 at the plasma membrane. However, this experiment is confounded by both the amplitude and duration of Akt signalling that was evoked prior to assessment of GLUT4 trafficking. In the present study we have used a dimerisation strategy to transiently activate Akt in adipocytes. We have found that Akt becomes active within 5 min after addition of the dimerisation agent to the cells as indicated by measurement of phosphorylation of downstream targets such as AS160. Moreover, cell surface levels of GLUT4 and cellular glucose transport were significantly increased following addition of the dimeriser following similar kinetics to that observed with insulin addition alone. We have been unable to find any evidence for alternate pathways in response to the dimeriser in these cells. These data suggest that Akt is the major signalling intermediate activated by insulin in order to stimulate glucose transport in adipocytes. These data do not support a major role for other signalling pathways in insulin mediated glucose transport in the adipocyte.