Abstract

Type 2 diabetes is a major public health problem that is associated with aging, obesity, and insulin resistance. The role of AKT, an important insulin signaling molecule, in the development of age-related insulin resistance remains unclear. In the present study four experimental groups: young wildtype (YG-WT), aged wildtype (AG-WT), AKT 1 knockout (AKT 1 -/-), and AKT 2 knockout (AKT 2 -/-) mice were examined to determine the effect of age and isoform specific AKT knockout on whole body and skeletal muscle insulin action. For all experimental animals insulin sensitivity was assessed by a glucose assisted insulin tolerance test (GAITT). AKT 2 -/- mice were significantly more insulin resistant than all other groups, while AKT 1 -/- mice had no decline in insulin sensitivity with age. Epididymal white adipose tissue (EWAT) weight was shown to be significantly lower in AKT 1 -/- mice compared to AG-WT. This is one possible explanation for the insulin sensitivity seen in this experimental group. However, AKT 2 -/- mice showed a severe deficit in EWAT that is representative of lipodystrophy. This pathological lipodystrophy could be responsible for the insulin resistance in the AKT 2 -/- mice. Another possible explanation for increased insulin sensitivity in the AKT 1 -/- mice in EDL and SOL muscle was significantly higher Thr^{308} phosphorylation in AKT 1 -/- mice. In EDL and SOL muscles AKT 2 expression was dramatically reduced in AKT 2 -/- mice ($p = 0.055$ and $p = 0.018$ respectively). In EDL muscle AKT 1 expression was significantly lower in AKT 1 -/- and AKT 2 -/- mice. In SOL muscle AKT 1 expression was significantly reduced in only AKT 1 -/- mice. There were no significant differences in -1 expression in EDL muscles, suggesting aging and AKT isoform knockout do not change rates of protein degradation. These findings indicate that AKT specific isoform deletions have significant impacts on glucose metabolism with advancing age.