Insulin receptor substrates-1 and -2 are both depleted but via different mechanisms after down-regulation of glucose transport in rat adipocytes

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Alterations in muscle and adipose tissue insulin receptor substrate (IRS)-1 and IRS-2 are associated with, and commonly believed to contribute to, development of insulin resistance. In this study, we investigated the mechanisms behind previously observed reductions in IRS levels due to high concentrations of glucose and insulin and their significance in the impairment of glucose uptake capacity in primary rat adipocytes. Semiquantitative RT-PCR analysis showed that insulin (10(4) microU/ml) alone or in combination with glucose (15 mm) markedly suppressed IRS-2 gene expression, whereas IRS-1 mRNA was unaffected by the culture conditions. The negative effect of a high glucose/high insulin setting on IRS-1 protein level was still exerted when protein synthesis was inhibited with cycloheximide. Impairment of glucose uptake capacity after treatment with high glucose and insulin was most pronounced after 3 h, whereas IRS-1 and IRS-2 protein levels were unaffected up to 6 h but were reduced after 16 h. Moreover, impaired glucose uptake capacity could only partially be reversed by subsequent incubation at physiological conditions. These novel results suggest that: 1) in a high glucose/high insulin setting depletion of IRS-1 and IRS-2 protein, respectively, occurs via different mechanisms, and IRS-2 gene expression is suppressed, whereas IRS-1 depletion is due to posttranslational mechanisms; 2) IRS-1 and IRS-2 protein depletion is a secondary event in the development of insulin resistance in this model of hyperglycemia/hyperinsulinemia; and 3) depletion of cellular IRS in adipose tissue may be a consequence rather than a cause of insulin resistance and hyperinsulinemia in type 2 diabetes.