Title: Role of CYP2E1 in regulation of glucose transporter GLUT4 expression and function in diabetes

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Background: Impaired GLUT4 function/expression in insulin target tissues is well-documented in diabetes and obesity. Cytochrome P450 isoform 2E1 (CYP2E1) induces oxidative stress, leading to impaired insulin action. We have found that CYP2E1 knockout mice are protected against high fat diet-induced insulin resistance and obesity; however the molecular mechanisms are still unclear.

Working hypothesis and aims: Presently, we examined whether CYP2E1 impairs GLUT4 gene expression and function in adipose and muscle cells, well-established cellular models of insulin responsiveness.

Methods and Results: CYP2E1 overexpression in skeletal muscle-derived L6 cells inhibited insulin-stimulated Glut4 translocation and 2-deoxyglucose uptake, with the latter inhibition being blocked by vitamin E. CYP2E1 overexpression in L6 and primary rat adipose (PRA) cells suppressed GLUT4 gene expression at promoter and mRNA levels, whereas CYP2E1 silencing had opposite effects. In PRA, CYP2E1-induced suppression of GLUT4 expression was blocked by chlormethiazole (CYP2E1-specific inhibitor) and the antioxidants vitamin E and N-acetyl-l-cysteine. CYP2E1 effect was mediated by the transcription factor NF-E2-related factor 2 (NRF2), as evident from its complete reversal by a coexpressed dominant-negative, but not wild-type, NRF2. GLUT4 transcription was suppressed by NRF2 overexpression, and enhanced by NRF2 silencing. Promoter and ChIP analysis showed a direct and specific binding of NRF2 to a 58-326 GLUT4 promoter region that was required to maintain CYP2E1 suppression; this binding was enhanced by CYP2E1 overexpression.

Conclusions: We suggest a mechanism for CYP2E1 action that involves: a) suppression of GLUT4 gene expression that is mediated by NRF2; b) impairment of insulin-stimulated Glut4 translocation and function. CYP2E1 and NRF2 are introduced as negative regulators of GLUT4 expression and function in insulin-sensitive cells.

Key words: NRF2, CYP2E1, GLUT4, insulin resistance, CYP2E1-knockout mice.
Publications associated with the project:
