

Synergistic effects of quercetin and metformin on insulin resistant C3A hepatocytes and L6 myotubes

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Metformin is the most widely used drug for treatment of Type 2 diabetes mellitus (T2DM). The natural flavonoid quercetin, which is abundant in many fruits and vegetables, has also shown significant potential to reduce insulin resistance. Metformin and quercetin both exert their effects through multiple targets and could potentially have synergistic effects. This study compared the effects of metformin, quercetin, and a combination of the two on insulin resistant C3A hepatocytes and L6 myotubes. Insulin resistance was induced using a combination of palmitic acid, fructose, and dexamethasone for 48h. Cells were concurrently treated with 10 μ M quercetin (Q), 0.1 mM metformin (M), or their combination (QM). Insulin sensitivity was assessed by measuring glucose uptake and quantitative fluorescence microscopy was used to monitor phosphorylation levels (activation) of protein kinase B (PKB/Akt). Phosphoenolpyruvate carboxykinase (PCK) levels were used as a measure of gluconeogenesis. Potential insulin sensitizing synergism with QM was observed in both cell lines. In C3A cells, insulin increased glucose uptake in insulin resistant control cells by $3.65 \pm 1.9\%$ and by $13.94 \pm 2.15\%$ in QM treated cells. This increase was significantly higher than with Q or M alone. Similar trends were seen in L6 myotubes. PCK levels in C3A cells decreased by 15% compared to insulin resistant cells, potentially lowering gluconeogenesis. Insulin-stimulated Akt phosphorylation at Thr308 and Ser473 was increased by 31% and 29%, respectively in QM treated C3A cells compared to insulin resistant cells and by 17% and 29%, respectively in L6. The observed increased efficacy of the combination of quercetin and metformin warrants further investigation. Combination treatment may lead to dosage reductions; thereby improving the overall adverse effect profile compared to metformin monotherapy.