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Antidiabetic properties of rosemary polyphenols: Carnosol increases skeletal muscle cell glucose uptake via AMPK-dependent GLUT 4 glucose transporter translocation**Evangelia Litsa Tsiani**
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Statement of the Problem: Skeletal muscle is highly important in glucose homeostasis since it is quantitatively a major insulin-target tissue. Insulin action in muscle cells activates the phosphatidylinositol-3 kinase (PI3K)/Akt signaling pathway causing the translocation of intracellularly stored GLUT4 glucose transporters to the plasma membrane leading to increased glucose uptake. Impaired insulin action in muscle leads to insulin resistance and type 2 diabetes mellitus (T2DM). AMP-activated kinase (AMPK) is a cellular energy sensor and its activation increases glucose uptake by skeletal muscle cells. Finding AMPK activators is viewed as an effective approach to combat insulin resistance and T2DM. Rosemary extract (RE) has been shown to increase muscle glucose uptake and AMPK activity but the components responsible for these effects have not been identified yet. In the current study, we investigated the effect of carnosol, a polyphenol found in high concentrations in RE.

Methodology: L6 rat muscle cells were used to measure uptake of [3H]-2-deoxy-D-glucose and the signaling molecules involved were investigated by immunoblotting.

Findings: Carnosol stimulated glucose uptake in L6 myotubes in a dose- and time-dependent manner. A response comparable to maximum insulin stimulation (196±9.2 % of control) was seen with 50µM of carnosol (2h) (182±7.8 % of control). Carnosol did not affect Akt phosphorylation while it significantly increased AMPK phosphorylation. Furthermore, the increase in glucose uptake in the presence of carnosol was significantly reduced by the AMPK inhibitor compound C (CC) while it was not affected by the PI3K inhibitor wortmannin. Carnosol increased plasma membrane GLUT4 glucose transporter levels in GLUT4myc overexpressing L6 cells and this response was abolished by the AMPK inhibitor CC.

Conclusion & Significance: Our study is the first to show a significant increase in muscle glucose uptake by carnosol via a mechanism that involves AMPK. Carnosol has potential as a glucose homeostasis regulating agent and deserves further study.

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