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Caffeic Acid Methyl and Ethyl Esters Exhibit Beneficial Effect on Glucose and Lipid Metabolism in Cultured Murine Insulin-Sensitive Cells

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Abstract : Caffeic acid methyl ester (CAME) and caffeic ethyl esters (CAEE) were previously reported to potently stimulate glucose uptake in cultured C2C12 skeletal muscle cells via insulin-independent mechanisms involving the activation of adenosine monophosphate-activated protein kinase (AMPK). In the present study, we investigated the effect of the two compounds on the translocation of glucose transporter GLUT4 in L6 skeletal muscle cells. The cells were treated with the optimum non-toxic concentration (50 µM) of either CAME or CAEE for 18 h. Levels of GLUT4myc at the cell surface were measured by O-phenylenediamine dihydrochloride (OPD) assay. The effects of CAME and CAEE on GLUT1 and GLUT4 protein content were also measured by western immunoblot. Our results show that CAME and CAEE significantly increased glucose uptake, GLUT4 translocation and GLUT4 protein content. Furthermore, the effect of the two CA esters on two insulin-sensitive cell lines: H4IIE rat hepatoma and 3T3-L1 adipocytes were investigated. CAME and CAEE reduced the enzymatic activity of the key hepatic gluconeogenic enzyme glucose-6-phosphatase in a concentration-dependent manner. In addition, they exerted a concentration-dependent antiadipogenic effect on 3T3-L1 cells. Mitotic clonal expansion (MCE), a prerequisite for adipocytes differentiation was also concentration-dependently inhibited. The two compounds abrogated lipid droplet accumulation, blocked MCE and maintained cells in fibroblast-like state when applied at the maximum non-toxic concentration (100 µM). In addition, the expression of the early key adipogenic transcription factors CCAAT enhancer-binding protein beta (C/EBP-β) and the master regulator of adipogenesis peroxisome-proliferator-activated receptor gamma (PPAR-γ) were inhibited. We, therefore, conclude that CAME and CAEE exert pleiotropic benefits in several insulin-sensitive cell lines through insulin-independent mechanisms involving AMPK, hence they may treat obesity, diabetes and other metabolic diseases.

Keywords : type 2 diabetes mellitus, insulin resistance, GLUT4, Akt, AMPK.
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