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Aegeline from *Aegle marmelos* stimulates glucose transport via Akt and Rac1 signaling, and contributes to a cytoskeletal rearrangement through PI3K/Rac1

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ABSTRACT

Aegeline is an alkaloidal-amide, isolated from the leaves of *Aegle marmelos* and have shown anti-hyperglycemic as well as antidyslipidemic activities in the validated animal models of type 2 diabetes mellitus. Here we delineate, aegeline enhanced GLUT4 translocation mediated 2-deoxy-glucose uptake in both time and concentration-dependent manner. 2-deoxy-glucose uptake was completely stymied by the transport inhibitors (wortmannin and genistein) in C2C12 myotubes. Pharmacological inhibition of Akt (also known as protein kinase B) and Ras-related C3 botulinum toxin substrate 1 (Rac1) suggest that both Akt and Rac1 operate aegeline-stimulated glucose transport via distinct parallel pathways. Moreover, aegeline activates p21 protein-activated kinase 1 (PAK1) and cofilin (an actin polymerization regulator). Rac1 inhibitor (Rac1 inhib II) and PAK1 inhibitor (IPA-3) completely blocked aegeline-induced phosphorylation of cofilin and p21 protein-activated kinase 1 (PAK1). In summary, these findings suggest that aegeline stimulates the glucose transport through Akt and Rac1 dependent distinct parallel pathways and have cytoskeletal roles via stimulation of the PI3-kinase-Rac1-PAK1-cofilin pathway in the skeletal muscle cells. Therefore, multiple targets of aegeline in the improvement of insulin sensitivity of the skeletal muscle cells may be suggested.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a common metabolic disorder characterized by defects in the insulin signaling, during which both insulin stimulated receptor tyrosine kinase activity and phosphorylation of insulin receptor are reduced and caused insulin resistance (Goodyear et al., 1995). Insulin activates the downstream target of the phosphatidylinositol 3 kinase (PI3-kinase), i.e. Akt and Rac1. Activation of Akt increases phosphorylation of Akt substrate of 160 kDa (AS160) and activates the Rab proteins. It is known that Rac1 or/and Akt caused actin remodeling, which is necessary for the GLUT4 mediated glucose uptake in the L6 myotubes (Kramer et al., 2006; Sun et al., 2010; Tapon and Hall, 1997; Je Bailey et al., 2004; Khayat et al., 2000).

Skeletal muscle is the primary peripheral tissue, which has a paramount role in energy balance and defects in the skeletal muscle glucose uptake that lead to the insulin resistance (Taniguchi et al., 2006; Zierath et al., 1996). The process of glucose transport into the skeletal muscle cells occurs by the translocation of GLUT4 protein from the cytoplasm to the plasma membrane (Bryant et al., 2002). Thus, it is necessary to stimulate glucose transport in the skeletal muscle cells to reduce insulin resistance and improvement in metabolic disorders (Koistinen et al., 2003a, 2003b; Petersen and Shulman, 2006; Zaid et al., 2008).

Therapeutics approaches which are based on the natural products may create a fruitful source for searching safe, efficient and relatively inexpensive new remedies for the treatment of diabetes and related metabolic disorders (Moller, 2001; Tan et al., 2008). A wide array of flora-derived active principles have been identified which either increase glucose uptake or reverse insulin resistance in the skeletal muscle cells (Huang et al., 2010; Lakshmi et al.,

Abbreviations: IRS-1, Insulin receptor substrate-1; PI-3-K, Phosphatidylinositol-4,5-bisphosphate 3-kinase; AS160, Akt substrate of 160 kDa; SE, Standard error; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; HG-DMEM, High glucose-Dulbecco's Modified Eagle's medium; ATCC, American type culture collection; PAK1, p21 protein-activated kinase 1; Rac1, Ras-related C3 botulinum toxin substrate 1; GTP, Guanosine-5'-triphosphate; EGF, Epidermal growth factor; EGFR, Epidermal growth factor receptor; 2-DG, 2-Deoxy-D-glucose; RIPA, Radio-Immunoprecipitation Assay

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