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Redox signal-mediated TRPM2 promotes Ang II-induced adipocyte insulin resistance via Ca^{2+}-dependent CaMKII/JNK cascade

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ABSTRACT

Background and Objective: Redox-sensitive transient receptor potential melastatin 2 (TRPM2) is a Ca^{2+}-permeable, nonselective cation channel which plays a crucial role in various physiological processes. However, little is known whether TRPM2 is involved in adipocyte dysfunction during hypertension. In the present study, we determined the role of TRPM2 in angiotensin II (Ang II)-induced insulin resistance in adipocytes and the underlying mechanisms.

Methods: Ang II-induced adipocyte insulin resistant model was conducted. Data from Ang II-induced hypertensive mice were used to measure the effects of TRPM2 inhibitor on insulin resistance in vivo. Whole-cell patch clamp technique, intracellular Ca^{2+} concentration measurement, glucose uptake assay, western blot, cDNA and siRNA transfection were employed to investigate the TRPM2/Ca^{2+}/CaMKII/JNK signaling.

Results: Ang II rose a cation current similar to that activated by hydrogen peroxide (H_2O_2) or ADP-ribose (ADPR), which was blocked by TRPM2 inhibitor or TRPM2 siRNA in adipocytes. Knockdown of TRPM2 significantly improved the lowered insulin sensitivity induced by Ang II, including insulin stimulated glucose uptake, phosphorylation of IRS1 and Akt, interaction between IR and IRS1 and the membrane translocation of GLUT4, whereas overexpression of TRPM2 resulted in the opposite effects. These results were related to the potentiated effects of TRPM2 on Ca^{2+} influx and CaMKII/JNK cascade activation upon Ang II-induced challenge. Notably, the pharmacological TRPM2 inhibitor, N-(p-amylcinnamoyl)anthranilic acid (ACA), was proved to improve insulin sensitivity in adipose tissue during Ang II-induced hypertension progress.

Conclusions: These data suggested that TRPM2 is a positive regulator of Ang II-induced adipocyte insulin resistance via Ca^{2+}/CaMKII/JNK-dependent signaling pathway. Targeting TRPM2 may be a novel therapeutic strategy to treat hypertension-associated insulin resistance.

1. Introduction

Insulin resistance, a smaller than expected response to a given dose of insulin, is commonly associated with systolic/diastolic hypertension [1]. Abnormal glucose metabolism and hypertension often appear together in individuals with insulin resistance and hyperinsulinemia clinically. Among skeletal muscle, liver, adipose tissue and pancreas, which represent important sites of insulin resistance, adipose tissue is now recognized by many as the primary site of insulin resistance [2]. Angiotensin II (Ang II), a critical component of the renin-angiotensin system (RAS) in the pathogenesis of hypertension, has been concerned as participant in development of insulin resistance [3,4]. Boschmann et al. [5] have demonstrated that perfusion with Ang II in young healthy men resulted in a dose-dependent decrease in glucose uptake in adipose tissue. Recent researches indicate that Ang II type 1 receptor

Abbreviations: TRPM2, transient receptor potential melastatin 2; Ang II, angiotensin II; H_2O_2, hydrogen peroxide; ADPR, ADP-ribose; ACA, N-(p-amylcinnamoyl)anthranilic acid; NAC, N-acetylcysteine; RAS, renin-angiotensin system; AT1R, Ang II type 1 receptor blocker; ACEI, angiotensin-converting enzyme inhibitors; ROS, reactive oxygen species; $[Ca^{2+}]_i$, intracellular calcium concentration; CaMK II, Ca^{2+}/calmodulin-dependent protein kinase II; IRS1, insulin receptor substrate 1; IR, insulin receptor; JNK, c-Jun N-terminal kinase; GLUT 4, Glucose transporter type 4; OGTT, oral glucose tolerance test; ITT, insulin tolerance test; ELISA, enzyme linked immunosorbent assay; KRPH buffer, Krebs-Ringer phosphate Hepes buffer; 2-NBDG, 2-Deoxy-2-[(7-nitro-2,1,3-benzoxadiazol-4-yl) amino]-D-glucose.

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blockers (AT1R) as well as angiotensin-converting enzyme inhibitors (ACEI) improve glucose metabolism [6,7] and ameliorate adipose tissue dysfunction [8], and the response elicited by AT1R and ACEI appears to be independent of the antihypertensive effects.

Ang II activates NAD(P)H oxidases to produce reactive oxygen species (ROS), which contributes to hypertension, atherosclerosis, insulin resistance and diabetes [9–11]. ROS derived from NADPH oxidase have shown to be involved in regulating Ca^{2+} influx, which causes various cellular dysfunction and diseases [12–14]. Interestingly, in obese hypertensive patients with hyperinsulinemia, $[Ca^{2+}]_i$ were elevated in adipocytes [15,16] and therapy with calcium channel blocker improved insulin resistance [15] and reduced the mortality of diabetes [17]. These findings suggest that disturbing Ca^{2+} homeostasis in hypertension may have the power to inhibit insulin action, but the underlying mechanisms remain largely unknown.