GW23-e2120

VASCULAR EXTRACELLULAR MATRIX (ECM) REMODELLING INDUCED BY LEPTIN COULD BE ANTAGONISED BY ADIPONECTIN THROUGH THE ACTIVATION OF AMPK VIA ADIPOR1 OF VECS IN 3D VESSEL MODEL

doi:10.1136/heartjnl-2012-302920a.114

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Objectives Observe in 3D vessel model whether Leptin could increase the expression level of collagen II / IV and TIMP-1 or reduce that of MMP-2/-9 in HUASMCs (human umbilical artery vascular smooth muscle cells); whether Adiponectin could antagonise the above changes; whether AMPK pathway was activated via Adiponectin receptor 1 (AdipoR1) in the endothelial cells and then SOCS-3 (suppressor of cytokine signalling 3) was promoted to inhibit phosphorylation of STAT3.

Methods 3D vascular models built by HUVECs (human umbilical vein endothelial cells) and HUASMCs were divided into three groups: control, Leptin group, Leptin+Adiponectin group. Elisa was used to detect expression levels of collagen II / IV, TIMP-1 and MMP-2/-9 in HUASMCs; Real-time PCR was used to detect the gene transcription level among three groups. RNAi technology was used to inhibit the AdipoR1 and AdipoR2 expression in HUVECs then the antagonistic effects of adiponectin were re-examined. Western Blot was used to test the changes of p-AMPK/AMPK, p-STAT3 / STAT3 and SOCS-3 among three groups. Blocks such as Compound C, PD98059, Okadaic acid and SB202190 were used to confirm the signalling pathway involved in this process.

Results Leptin increased the expression level of collagen II / IV, TIMP-1 and reduced that of MMP-2/-9 (referred as Leptin-induced vascular ECM remodelling effect);when Adiponectin was added, the above effect disappeared ($p>0.05$); Results of Real-time PCR were the same. Receptors of HUVECs could be effectively inhibited by AdipoR1-siRNA and AdipoR2-siRNA with inhibition rates of 71.83±1.45% and 74.89±1.12% ($p<0.01$). The antagonistic effect of Adiponectin was diminished by the depression of AdipoR1 ($p<0.01$). Western blot showed that Leptin increase p-STAT3 level in HUASMCs; Adiponectin alone had no effect on the p-STAT3 level in HUASMCs but Adiponectin could inhibit Leptin-induced STAT3 phosphorylation. Adiponectin increased the level of p-AMPK in HUVECs and that of SOCS-3 in HUASMCs. Compound C could inhibit the antagonistic effect of Adiponectin against Leptin and also reduce the expression level of SOCS-3 promoted by Adiponectin.

Conclusions Leptin could cause vascular ECM remodelling, characterised by increasing the collagen's synthesis and inhibit its degradation. And STAT3 signal transduction pathway might be involved in it. As SOCS-3 was one of the inhibitors of phosphorylation of STAT3, Adiponectin might promote the expression of SOCS-3 through AMPK pathway via AdipoR1 receptor on HUVECs, and then exert the antagonistic effect on Leptin-induced vascular ECM remodelling. Adiponectin alone had no effect on vascular ECM remodelling, indicating that the antagonistic effect depending on the activation of STAT3 pathway by Leptin.