Adipose extracellular signal-regulated kinase 2 protected from endothelial dysfunction and the oxidative stress of perivascular adipose tissue in obese mice

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Topic(s):
Lipid Metabolism, Metabolic Syndrome, Diabetes

Introduction:
Extracellular signal-regulated kinase (ERK) modulates differentiation and maturation of adipocyte and the hypertrophy and differentiation of adipocytes affected the vascular diseases in obese. Changes in characters of adipocytes could develop the oxidative stress and inflammations. Moreover, changes in perivascular adipose tissue (PVAT) could modulate vascular tonus in obesity. However, the role of adipose ERK2 in endothelial function and characters of PVAT in obese in vivo had not been clarified, yet.

Purpose:
This study aims to elucidate the role of the adipose ERK2 in endothelial-dependent relaxation (EDR) in mice model of obesity. The role of PVAT in EDR was also assessed.

Methods and Results:
We created adipose-specific ERK2 knock out mice (AE2KO) by crossing fatty acid binding protein 4 Cre and ERK2 flox mice and fed them with normal diet (ND) or high fat/high sucrose diet (HFHSD) for 24 weeks. AE2KO fed with HFHSD gained more weight and revealed the heterogeneity in sizes of adipocyte in subcutaneous fat (SF). Furthermore, the mRNA levels of lipoprotein lipase, hormone-sensitive lipase, and peroxisome proliferator-activated receptor γ, which was the master genes of adipocyte differentiation, were markedly down-regulated in SF. PVAT in AE2KO with HFHSD was markedly enlarged and the mRNA expression of inflammatory adipocytokines, such as IL-1β and leptin were up-regulated. Next, we assessed EDR by acetylcholine (ACh) -induced relaxation in aortic rings with or without PVAT. EDR without PVAT was modestly decreased in AE2KO with HFHSD compared with wild type mice (WT) with HFHSD. Aortic rings with PVAT increased EDR in WT with ND. PVAT modestly decreased EDR in WT with HFHSD and mostly eliminated EDR in AE2KO with HFHSD. To assess the contraction factors released from PVAT, the solutions incubated with PVAT (SIP) were transferred to the normal aortic rings. SIP from WT with HFHSD mildly increased vascular tone and SIP from AE2KO with HFHSD further increased it. Tempol, which was superoxide scavenger, restored endothelial dysfunction with PVAT and suppressed the contraction with SIP from AE2KO with HFHSD. Fluorescence intensity of dihydroethidium stain of aorta and PVAT, which indicated that aortic and adipose superoxide production were elevated in AE2KO with HFHSD, which were mostly eliminated with tempol.

Conclusions:
Adipose ERK2 selectively modulated differentiation in SF, suppressed the aortic oxidative stress and protected from endothelial dysfunction in obese. Moreover, adipose ERK2 suppressed the hypertrophy, inflammation, and oxidative stress of PVAT in obese. The oxidative stress with the inflammation in PVAT released vasoconstriction factors, which contributed to endothelial dysfunction in obese mice.
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