

Increased Expression Levels of Soluble Epoxide Hydrolase in Obese and Its Modulation by Physical Exercise

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Abstract : Soluble epoxide hydrolase (sEH) is an emerging therapeutic target in several chronic states that have inflammation as a common underlying cause such as immunometabolic diseases. Indeed, sEH is known to play a pro-inflammatory role by metabolizing anti-inflammatory, epoxyeicosatrienoic acids (EETs) to pro-inflammatory diols. Recently, it was shown sEH to be linked to diet and microbiota interaction in rat models of obesity. Nevertheless, the functional contribution of sEH and its anti-inflammatory substrates EETs in obesity remain poorly understood. In the current study, we compared the expression pattern of sEH between lean and obese nondiabetic human subjects using subcutaneous adipose tissue (SAT) and peripheral blood mononuclear cells (PBMCs). Using RT-PCR, western blot and immunofluorescence confocal microscopy, we show here that the level of sEH mRNA and protein to be significantly increased in obese subjects with concomitant increase in endoplasmic reticulum (ER) stress components (GRP78 and ATF6 α) and inflammatory markers (TNF- α , IL-6) when compared to lean controls. The observation that sEH was overexpressed in obese subjects' prompt us to investigate whether physical exercise could reduce its expression. In this study, we report here 3-months supervised physical exercise significantly attenuated the expression of sEH in both the SAT and PBMCs, with a parallel decrease in the expression of ER stress markers along with attenuated inflammatory response. On the other hand, homocysteine, a sulfur containing amino acid deriving from the essential amino acid methionine was shown to be directly associated with insulin resistance. When 3T3-L1 preadipocytes cells were treated with homocysteine our results show increased sEH levels along with ER stress markers. Collectively, our data suggest that sEH upregulation is strongly linked to ER stress in adiposity and that physical exercise modulates its expression. This gives further evidence that exercise might be useful as a strategy for managing obesity and preventing its associated complications.

Keywords : obesity, adipose tissue, epoxide hydrolase, ER stress

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