

Enhanced release of endothelin-1 may directly participate to impaired synthesis of adiponectin in childhood obesity

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Childhood obesity predicts the development of type 2 diabetes mellitus and cardiovascular disease (Juonala M et al, 2011). Pediatric obesity is associated with endothelial dysfunction and hypoadiponectinemia, but the relationship between these two conditions remains to be fully clarified. Since adipose tissue is known to play a key role in vascular and metabolic asset (Eringa EC et al, 2007), it is likely that dysregulation of vascular-adipocyte axis may importantly contribute to both endothelial dysfunction and metabolic disturbances. Previous studies suggest that endothelin-1 (ET-1) may regulate adiponectin (Ad) production and secretion from adipocytes (Bedi D et al, 2006), and circulating levels of ET-1 are increased in obese and diabetic subjects (Barath A et al, 2006). Whether enhanced release of ET-1 may directly impair Ad production in obese children is not known. The aim of this study was to explore whether and how high circulating levels of ET-1 may contribute to impair Ad production, release and vascular activity.

Sixty children were included into obese (Ob, 30), overweight (OW, 11) and lean (19) groups. Total and high molecular weight (HMW) Ad, ET-1, VCAM-1 and vWf levels were measured in serum samples by ELISA assay. Correlation between ET-1 and HMW or total Ad was assessed through Pearson correlation coefficient. Least squares regression analysis was performed to test the relation between variables. An ANCOVA model was used to compare slope among groups. Mature adipocytes were serum-starved for 6 h and then left untreated or stimulated with ET-1 (10 nM), or with sera from lean, OW or Ob children (20% of total incubation medium) in the absence or in the presence of ET_A (BQ-123) and ET_B (BQ-788) receptor blockers (10 μM). In a parallel set of experiments, adipocytes were pre-incubated with or without p42/44 MAPK inhibitor PD-98059 (20 μM), or JNK inhibitor SP-600125 (20 μM) for 1 h. Ad mRNA and protein levels as well as total and phosphorylated isoforms of c-Jun and p42/44 MAPK were measured by RT-PCR and WB, respectively, in cell homogenates. Vasodilation to Ad was evaluated in rat isolated arteries in the absence or in the presence of BQ-123/788.

Total and HMW Ad were significantly decreased and ET-1 levels significantly increased in OW ($p < 0.01$) and Ob ($p < 0.001$) children. A statistically significant linear regression ($p < 0.01$) was found between Ad and ET-1, thus suggesting that the decreased Ad depends, at least in part, on increased ET-1 values. Exposure of adipocytes to exogenous ET-1 or serum from OW and Ob children significantly decreased Ad mRNA and protein levels ($p < 0.001$). The inhibitory effect of ET-1 on Ad was reverted by BQ-123/788 or PD-98059, but not by SP-600125. In isolated and perfused rat mesenteric arteries pre-constricted with noradrenaline (NA, 10 μM) acute stimulation with Ad (10-30 μg) dose-dependently increased vasodilation. Ad-mediated vasodilation was further increased in vessels pretreated with ET-1 receptor blockers BQ-123/BQ-788. This study provides evidence that increased circulating levels of ET-1 in overweight and obese children may contribute, at least in part, to reduce levels of Ad, and suggests that ET-mediated activation of p42/44 MAPK signaling pathways may be one possible mechanism for ET-1-dependent inhibition of Ad synthesis. Imbalance in the relationship between Ad and ET-1 may provide a possible explanation for hypoadiponectinemia in pediatric obesity, and contribute to the development of both metabolic disturbances and cardiovascular complications in future adults.

References:

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