Deficiency of aryl hydrocarbon receptor in adipocytes augments the development of diet-induced obesity

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Abstract

Objectives: Ligands of the aryl hydrocarbon receptor (AhR) have been shown to regulate adipocyte differentiation and promote expression of proinflammatory adipokines. We investigated the effect of adipocyte-specific deletion of AhR on the development of diet-induced obesity.

Methods/Results: AhR floxed mice (AhRfl/fl) and the stromal vascular fraction (SVF) were isolated from AhRfl/fl mice treated with doxycycline. The SVF was then cultured to generate mature adipocytes. Increased adipocyte-specific AhR deficiency was associated with significant elevations in mRNA abundance of F4/80, a macrophage marker, in epididymal adipose tissue (AhRAdQ, 3.52 ± 0.68; AhRfl/fl, 1.62 ± 0.67; ΔΔ Ct; P<0.05). Compared to AhR-deficient mice, increased adiposity in AhR-deficient mice exhibited increased fat mass and decreased lean mass compared to HF-fed controls. Increased adipocyte size in HF-fed adipocyte-specific AhR-deficient mice was associated with increased VLAD (Valproic Acid, 2-Mercaptopropionylglycine, and 2-Aminoacetophenone) to generate adipocyte-specific AhR deletion

Development of a mouse model with adipocyte-specific AhR deletion

Adipocyte size is increased in HF-fed adipocyte AhR-deficient mice

Conclusions

Mice with adipocyte AhR deficiency exhibit increased body weight during the development of obesity compared to wild-type controls. HF-fed adipocyte AhR-deficient mice have increased adiposity associated with increased fat mass and decreased lean mass. Excess adiposity in HF-fed AhR-deficient mice is associated with increased adipose size. Increased adiposity in HF-fed adipocyte-specific AhR-deficient mice is associated with elevated mRNA abundance of F4/80 in epididymal adipose tissue.

Obese adipocyte AhR-deficient mice exhibit more pronounced impairments in glucose homeostasis.

Taken together, these data suggest a role for endogenous AhR ligand(s) acting at adipocyte AhRs in the regulation of body weight, adiposity, and adipose inflammation.

Clinical and Nutritional Implications

The endogenous ligand(s) of AhR is unknown.

Putative endogenous ligands include nutritional metabolites such as tryptophan degradation products and fatty acid metabolites.

Future studies will focus on the role of putative ligands to regulate adipocyte differentiation and proliferation.

Nutritionally mediated endogenous ligands of the AhR found to regulate adipocyte function and body weight may be effective therapeutic targets for the treatment of obesity and metabolic disorders.

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References