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**Bisphenol A at Environmentally Relevant Doses Inhibits Adiponectin
Release from Human Adipose Tissue Explants and Adipocytes**

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Running Title: Inhibition of Adiponectin Release by Bisphenol A

Key Words: adipocytes, adiponectin, bisphenol A, estradiol, estrogen receptors, estrogen-related receptors, human adipose explants, obesity

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Abbreviations:

BPA-	bisphenol A
CM -	conditioned media.
E2-	estradiol.
ELISA -	enzyme-linked immunosorbant assay.
ER α/β -	estrogen receptor α or β .
ERR -	estrogen-related receptor.
GPR30 -	G protein-coupled receptor 30.
sc -	subcutaneous.
vis -	visceral.

Outline

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Abstract

Background: The incidence of obesity has risen dramatically over the last few decades. This epidemic may be affected by exposure to xenobiotic chemicals. Bisphenol A (BPA), an endocrine disruptor, is detectable at nM levels in human serum worldwide. Adiponectin is an adipocyte-specific hormone which increases insulin sensitivity and reduces tissue inflammation. Thus, any factor which suppresses adiponectin release could lead to insulin resistance and increased susceptibility to obesity-associated diseases.

Objectives: To compare: a) the effects of low doses of BPA and estradiol (E2) on adiponectin secretion from human breast, subcutaneous (sc) and visceral (vis) adipose explants and mature adipocytes, and b) expression of putative estrogen and estrogen-related receptors in these tissues.

Methods: Adiponectin levels in conditioned media (CM) from adipose explants or adipocytes were determined by enzyme-linked immunosorbant assay (ELISA). Expression of estrogen receptors (ER) α and β , G-protein-coupled receptor 30 (GPR30), and estrogen-related receptors (ERR) α , β and γ was determined by quantitative real-time PCR.

Results: BPA at 0.1 and 1 nM doses suppressed adiponectin release from all adipose depots examined. In spite of a substantial variability among patients, BPA was as effective, and often more effective, than equimolar concentrations of E2. Adipose tissue expresses similar mRNA levels of *ER α* , *ER β* and *ERR γ* , and 20-30 fold lower levels of *GPR30*, *ERR α* and *ERR β* .

Conclusions: BPA at environmentally-relevant doses inhibits the release of a key adipokine that protects humans from the metabolic syndrome. The mechanism by which BPA suppresses adiponectin and the receptors involved remain to be determined.