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Proteomics reveals mechanisms of metabolic disruptive effects of emerging di-(2-ethylhexyl) phthalate substitutes

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The obesity pandemic and associated cardiovascular complications are presumed to be accelerated by endocrine disruptors such as the phthalate plasticizer di-(2-ethylhexyl)-phthalate (DEHP). However, the mode of action underlying their metabolic disruptive effects is insufficiently understood, and poorly studied emerging plasticizer alternatives require further investigation.

Given that adipose tissue functionality was reported to be impaired by phthalate plasticizers, we focused on the master regulator of adipogenesis, the peroxisome proliferator-activated receptor gamma (PPARγ) and examined 20 alternative plasticizers as well as their metabolites for binding to and activation of PPARγ and lipid accumulation in human preadipocytes. Among several compounds that showed molecular interaction with PPARγ, the metabolites MINCH, MHINP, and OH-MPHP of the plasticizers DINCH, DINP, and DPHP exerted the most potent induction of lipid accumulation [1].

These compounds were further analyzed in human preadipocytes and mature adipocytes using *in vitro* assays and global proteomics. In preadipocytes, the plasticizer metabolites significantly increased lipid accumulation, induced adipogenesis, enhanced leptin and adipsin secretion, and upregulated markers and pathways associated with PPARγ activation in a similar pattern to the PPARγ agonist rosiglitazone. Proteomics of mature adipocytes revealed that both, the plasticizers and their metabolites, induced a hypertrophic remodeling caused by oxidative stress and excessive deposition of extracellular matrix. This cellular stress led to impaired metabolic homeostasis, disturbed lipid storage, and induction of proinflammatory pathways as well as insulin resistance promoting adipokine secretion.

In conclusion, the plasticizer metabolites enhanced preadipocyte differentiation, at least in part through PPARγ activation and, together with their parent plasticizers, impaired the functionality of mature adipocytes similar to reported effects of a high-fat diet. This mechanistic knowledge may support adverse outcome pathway (AOP) development for the effects of xenobiotics on cardiovascular disease as investigated by the EU Horizon 2020 research project ALTERNATIVE. Moreover, this highlights (A) the need to further investigate the currently used plasticizer alternatives for potential associations with obesity and cardiovascular diseases and (B) the convenience of omics for regulatory risk assessment.

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Reference

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