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PLASTICIZERS AS POSSIBLE METABOLIC DISRUPTORS: MIXTURE EFFECTS ON ADIPOCYTE DIFFERENTIATION AND LIPID ACCUMULATION IN 3T3-L1 CELLS

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A subset of Endocrine Disrupting Chemicals (EDCs), named Metabolic Disruptors, have been demonstrated to be able of promoting adiposity and alteration of energy homeostasis. We investigated the adipogenic activity and nuclear receptor interactions of four plasticizers approved for the manufacturing of food-contact materials (FCMs). Differentiating 3T3-L1 mouse preadipocytes were exposed to scalar concentrations of DiNP (Di-iso-nonyl-phthalate), DiDP (Di-iso-decyl-phthalate), DEGDB (Diethylene glycol dibenzoate), or TMCP (Tri-m-cresyl phosphate). Rosiglitazone, a well-known pro-adipogenic peroxisome proliferator activated receptor gamma (PPAR γ) agonist, and the plasticizer BPA were included as reference compounds. All concentrations of plasticizers were able to enhance lipid accumulation. Accordingly, *in silico* and gene-reporter experiments showed binding affinities and receptor activities to the nuclear receptor PPAR γ comparable to those of Rosiglitazone. Differently from BPA, the four plasticizers were most effective in enhancing lipid accumulation when added in the mid-late phase of differentiation. qRT-PCR studies showed that all plasticizers were able to increase the expression of CCAAT/enhancer binding protein β (*Cebp β*), in the early steps of adipogenesis, and *Ppar γ 2*, the adipogenesis master gene, in the middle phase. In addition, TMCP and DEGDB were both able to modulate the expression of Fatty Acid Binding Protein 4/Adipocyte Protein 2 (*Fabp4/Ap2*) transcripts in the late phase of adipogenesis. It is well known that exposure in daily life is not restricted to individual compounds and humans are exposed to complex mixtures of EDCs. We therefore began to investigate the effects of different combinations of these plasticizers in 3T3-L1 cells. Our preliminary results suggest an enhancement of lipid accumulation, without an apparent additive effect. Taken together, our results suggest that exposure to single plasticizers or mixtures at low, environmentally relevant doses can affect adipogenesis and lipid accumulation in fat cells *in vitro*. Future experiments will better characterize the combined molecular and cellular effects of these chemicals in differentiating adipocytes.