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Cornelius Goerdeler (MOLTOX): 13C Metabolic Tracing in Human Adipocytes for Assessing Metabolism-Disrupting Properties

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Abstract: Exposure to certain environmental chemicals, including phthalates, may promote the development of metabolic diseases, including obesity. Since specific regulatory methods to identify metabolism-disrupting chemicals are currently lacking, the assessment of safer alternatives is hampered. The plasticizer DINCH was introduced as a replacement for banned phthalate plasticizers. However, previous studies have shown that its primary metabolite MINCH promotes adipogenesis of human adipocytes. To assess the effects of MINCH on adipocyte metabolism, human SGBS preadipocytes were exposed for 12 days to MINCH and subsequently incubated with different 13C tracing sources. The 13C labeling pattern of central carbon metabolites was analyzed using a targeted MRM approach and the effects were compared to cells differentiated with the PPARG agonist rosiglitazone and untreated control cells. After 24 h incubation with [U-13C]glucose, analysis of the 13C enrichment indicated a higher glycolytic and pentose phosphate pathway (PPP) flux for energy production and increased acetyl-CoA generation for lipid formation in MINCH-treated and rosiglitazone-differentiated cells. Analysis of the labeling pattern after [1,2-13C]glucose incubation confirmed the upregulation of glycolysis and the PPP cycle in MINCH- and rosiglitazone-treated cells, but showed an increase in the PPP/glucose metabolism ratio only in rosiglitazone-differentiated cells. The [U-13C]glutamine labeling pattern revealed reduced cycling through the TCA cycle and transient upregulation of reductive glutaminolysis for lipid production in MINCH and rosiglitazone-treated cells. In conclusion, our 13C tracer data indicate that MINCH leads to a rewiring of metabolism towards lipid accumulation and adipogenesis similar to the PPARG agonist rosiglitazone, but they also reveal subtle differences in metabolic pathway activity. This emphasizes the applicability as a potential New Approach Method for the assessment of adipogenic effects.

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