ABSTRACT

TCDD-ELICITED STEATOSIS: THE ROLE OF AHR IN LIPID UPTAKE, METABOLISM AND TRANSPORT IN SCD1+/+, SCD1-/-, AND C57BL/6 MICE

By

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Metabolic syndrome (MetS) and its associated disorders such as obesity, type II diabetes, non-alcoholic fatty liver disease (NAFLD), and hypertension are epidemic in Western countries including the United States. Conventional thought holds excess energy consumption accountable for MetS phenotypes, and although Western diet and culture is characterized by too many calories consumed and too few calories burned, environmental endocrine disrupting chemicals (EDCs) have emerged into the spotlight for their role in positive energy balance. Dioxin-like compounds (DLCs) including 2,3,7,8-tetrachlorodibenzo-□-dioxin (TCDD) are environmentally ubiquitous and persistent EDCs that alter energy balance and lipid metabolism in animals and humans. TCDD elicited hepatic steatosis involves aryl hydrocarbon receptor (AhR) activation and is marked by increased triglycerides, free fatty acids, inflammatory cell infiltration, and increased serum alanine aminotransferase levels. Hepatic steatosis in the absence of alcohol consumption is a cryptic, yet significant manifestation of MetS and its associated diseases and may precede cirrhosis as well as other extrahepatic effects. Stearoyl-CoA desaturase 1 (Scd1) catalyzes the rate-limiting step in monounsaturated fatty acid (MUFA) biosynthesis. Its deficiency protects mice from diet-induced steatosis, and the enzyme is a target for the treatment of metabolic related disorders. In this report the role of AhR regulation of lipid uptake, metabolism, and transport in TCDD-elicited steatosis was characterized using Scd1 null mice, diet, and 14C-lipid uptake studies. Collectively, these studies showed that 1) AhR regulation of

Scd1 contributes to the hepatotoxicity of TCDD, 2) dietary fat is the primary source of lipid in TCDD-elicited steatosis, 3) TCDD increases the uptake of dietary lipids, and 4) AhR mediates not only altered hepatic lipid composition, but also systemic lipid composition. This work indicates that AhR activation results in a systemic response that involves coordinated interactions between the digestive tract, circulatory system, and liver, with important health implications for individuals at risk for metabolic disease.