

FENRETINIDE TREATMENT ACCELERATES ATHEROSCLEROSIS DEVELOPMENT IN APOLIPOPROTEIN E-DEFICIENT MICE IN SPITE OF BENEFICIAL METABOLIC EFFECTS

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Aim. Fenretinide, a synthetic retinoid derivative first investigated for cancer prevention and treatment, has been shown to ameliorate glucose tolerance and the plasma lipid profile, and to reduce body fat mass. These effects, together with its ability to inhibit ceramide synthesis, have suggested that fenretinide may display anti-atherosclerotic effects.

Methods. To this aim, 9-weeks-old apoE-knockout (EKO) female mice were fed for 12 weeks a Western diet, without (EKO-Ctrl) or with (0.1% w/w) fenretinide (EKO-Fen). As a reference, wild-type (WT) mice were likewise treated. Growth and metabolic parameters were monitored throughout the study. Atherosclerosis development was evaluated in the aorta and at the aortic sinus. Blood and lymphoid organs were further characterized with thorough cytological/histological and immunocytofluorimetric analyses.

Results. Fenretinide treatment significantly lowered body weight, glucose levels and plasma levels of total cholesterol, triglycerides and phospholipids. In the liver, fenretinide remarkably reduced hepatic glycogenosis and steatosis driven by the Western diet. Treated spleens were abnormally enlarged, with severe follicular atrophy and massive extramedullary hematopoiesis. Severe renal hemosiderin deposition was observed in EKO-Fen. Treatment resulted in a threefold increase of total leukocytes (WT and EKO) and raised the activated/resting monocyte ratio in EKO-Fen. Finally, atherosclerosis development was markedly increased at the aortic arch (34.4Å}7.3% vs 26.1Å}5.8%, +32%), thoracic (14.3Å}4.9% vs 4.9Å}2.1%, +191%) and abdominal aorta (7.6Å}3.3% vs 3.3Å}1.8%,+130%) of fenretinide-treated mice. Plaque extent was further quantified at the aortic sinus and provided similar results (810.000 µm² vs. 540.000 µm², +50% in EKO-Fen). Plaques of treated mice were characterized by an increased collagen content and a larger necrotic core, whereas the area occupied by macrophages, foam cells and neutral lipids was comparable between EKO-Fen and EKO-Ctrl.

Conclusion. We provide the first evidence that, despite beneficial metabolic effects, fenretinide treatment may prove detrimental for atherosclerosis development.