

Hydroxyoctadecadienoic acids (HODEs) regulate fatty acid binding protein-4 (FABP4) secretion in human monocytes and macrophages

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9-HODE is an oxidation product of linoleic acid (LA, C18:2), is pro-inflammatory, and is a ligand for GPR132 which is involved in atherogenesis. By contrast, 13-HODE is protective and acts through PPARgamma. Plasma FABP4 is increased in diabetes and coronary artery disease. 9-HODE increases FABP4 expression in macrophages. We investigated whether GPR132 is a monocyte activation marker in diabetes, and if it mediates the effect of 9-HODE on FABP4. Monocyte populations from 31 type 2 diabetic patients and controls were studied using FACS. Plasma cytokines were measured using bead arrays and ELISA. THP-1 cells were used to investigate regulation of FABP4 secretion. Diabetic subjects had increased circulating CD14⁺, CD14⁺CD36⁺, CD14⁺CD11b⁺, CD14⁺CD54⁺ cells (p<0.01), and also increased GPR132 mRNA expression in CD14⁺ monocytes (p < 0.01). Levels of GPR132 expression did not correlate with any of the above cell populations, or with increased plasma levels of FABP4, sTNF-R, osteoprotegerin, MCP-1, resistin or leptin. FABP4 mRNA expression was markedly increased in both THP-1 monocytes and macrophages (differentiated with 100nM PMA) by 9-HODE and 13-HODE (all p < 0.001). 9-HODE (p < 0.01) and 13-HODE (p < 0.05) also increased GPR132 expression. The stimulatory effect of HODEs was replicated by the PPARgamma agonist rosiglitazone (p<0.001). The PPARgamma antagonist T0070907 decreased the effect of all three ligands (p<0.001). Similar effects on FABP4 protein secretion were documented (ELISA). LA and alpha-linolenic acid (C18:3) were without effect on FABP4 mRNA or protein. GPR132 gene silencing using siRNA had no effect on increased FABP4 expression in response to 9-HODE, 13-HODE, or rosiglitazone. In conclusion, GPR132 is an independent activation marker for monocytes, but does not mediate the increase in FABP4 expression induced by 9-HODE. FABP4 secretion is regulated through PPARgamma. Study of the signaling functions of fatty acids may lead to new treatments for diabetes and atherosclerosis.