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## **Obesity-induced insulin resistance and hepatic steatosis are alleviated by omega-3 fatty acids: a role for resolvins and protectins.**

[González-Pérez A](#), [Horrillo R](#), [Ferré N](#), [Gronert K](#), [Dong B](#), [Morán-Salvador E](#), [Titos E](#), [Martínez-Clemente M](#), [López-Parra M](#), [Arroyo V](#), [Clària J](#).

Department of Biochemistry and Molecular Genetics, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi I Sunyer, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, University of Barcelona, Barcelona, Spain.

### **Abstract**

Omega-3-polyunsaturated fatty acids (omega-3-PUFAs) have well-documented protective effects that are attributed not only to eicosanoid inhibition but also to the formation of novel biologically active lipid mediators (i.e., resolvins and protectins). In this study, we examined their effects on ob/ob mice, an obesity model of insulin resistance and fatty liver disease. Dietary intake of omega-3-PUFAs had insulin-sensitizing actions in adipose tissue and liver and improved insulin tolerance in obese mice. Genes involved in insulin sensitivity (PPARgamma), glucose transport (GLUT-2/GLUT-4), and insulin receptor signaling (IRS-1/IRS-2) were up-regulated by omega-3-PUFAs. Moreover, omega-3-PUFAs increased adiponectin, an anti-inflammatory and insulin-sensitizing adipokine, and induced AMPK phosphorylation, a fuel-sensing enzyme and a gatekeeper of the energy balance. Concomitantly, hepatic steatosis was alleviated by omega-3-PUFAs. A lipidomic analysis with liquid chromatography/mass spectrometry/mass spectrometry revealed that omega-3-PUFAs inhibited the formation of omega-6-PUFA-derived eicosanoids, while triggering the formation of omega-3-PUFA-derived resolvins and protectins. Moreover, representative members of these lipid mediators, namely resolvin E1 and protectin D1, mimicked the insulin-sensitizing and antisteatotic effects of omega-3-PUFAs and induced adiponectin expression to a similar extent that of rosiglitazone, a member of the thiazolidinedione family of antidiabetic drugs. Taken together, these findings uncover beneficial actions of omega-3-PUFAs and their bioactive lipid autacoids in preventing obesity-induced insulin resistance and hepatic steatosis.

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