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The integration of lipid-sensing and anti-inflammatory effects: how the PPARs play a role in metabolic balance

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Abstract

The peroxisomal proliferating-activated receptors (PPARs) are lipid-sensing transcription factors that have a role in embryonic development, but are primarily known for modulating energy metabolism, lipid storage, and transport, as well as inflammation and wound healing. Currently, there is no consensus as to the overall combined function of PPARs and why they evolved. We hypothesize that the PPARs had to evolve to integrate lipid storage and burning with the ability to reduce oxidative stress, as energy storage is essential for survival and resistance to injury/infection, but the latter increases oxidative stress and may reduce median survival (functional longevity). In a sense, PPARs may be an evolutionary solution to something we call the 'hypoxia-lipid' conundrum, where the ability to store and burn fat is essential for survival, but is a 'double-edged sword', as fats are potentially highly toxic. Ways in which PPARs may reduce oxidative stress involve modulation of mitochondrial uncoupling protein (UCP) expression (thus reducing reactive oxygen species, ROS), optimising forkhead box class O factor (FOXO) activity (by improving whole body insulin sensitivity) and suppressing NFkB (at the transcriptional level). In light of this, we therefore postulate that inflammation-induced PPAR downregulation engenders many of the signs and symptoms of the metabolic syndrome, which shares many features with the acute phase response (APR) and is the opposite of the phenotype associated with calorie restriction and high FOXO activity. In genetically susceptible individuals (displaying the naturally mildly insulin resistant 'thrifty genotype'), suboptimal PPAR activity may follow an exaggerated but natural adipose tissue-related inflammatory signal induced by excessive calories and reduced physical activity, which normally couples energy storage with the ability to mount an immune response. This is further worsened when pancreatic decompensation occurs, resulting in gluco-oxidative stress and lipotoxicity, increased inflammatory insulin resistance and oxidative stress. Reactivating PPARs may restore a metabolic balance and help to adapt the phenotype to a modern lifestyle.

Background

Peroxisomal proliferating-activated receptors (PPARs) were discovered in 1990 with the cloning of a murine orphan receptor that was activated by peroxisomal proliferating compounds (such as the fibrates), hence their name [1]. They probably arose during metazoan evolution and at least three isoforms have been identified, α, γ and δ (also referred to as PPAR β), each encoded by a different gene [2]. They are ligand-activated transcription factors that act as lipid sensors and work as dimers with the