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Dysregulation of PPARa Mediates Lipotoxicity in the Heart During Obesity Through GSK-3-mediated Phosphorylation

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Obesity and metabolic syndrome are growing health problems in developed countries and are accompanied by cardiomyopathy characterized by hypertrophy and diastolic dysfunction. In these hearts, accumulation of toxic lipids are observed and are involved in the development of cardiomyopathy. These conditions are termed lipotoxicity, and dysregulation of PPARα, a nuclear receptor involved in fatty acid metabolism, is linked to this pathology. The molecular mechanism by which obesity leads to activation of PPARα remains unexplored. Here we show that feeding mice with high-fat diet activates glycogen synthase kinase-3α (GSK-3α), which in turn phosphorylates PPARα at a serine residue located in the ligand-binding domain, thereby enhancing DNA binding of PPARα. This modification upregulated a group of genes involved in fatty acid uptake, but not β-oxidation, thereby facilitating lipid accumulation. Gene expression analysis showed that constitutively active GSK-3α is sufficient to drive PPARα signaling even in the absence of obesity, while cardiac-specific knockdown of GSK-3α or suppression of PPARα phosphorylation at the ligand-binding domain attenuated the development of high-fat-induced cardiomyopathy. Fenofibrate, a PPARα ligand, allosterically inhibited PPARα phosphorylation at the ligand-binding domain, thereby reversing lipid-induced PPARα activation and cardiac lipotoxicity. In summary, GSK-3α-mediated dysregulation of PPARα plays an important role in mediating the development of lipotoxicity during obesity. GSK-3α-mediated phosphorylation of PPARα at the ligand-binding domain may be a novel therapeutic target for lipotoxic cardiomyopathy during obesity.