

Peroxisome Proliferator-Activated Receptor δ (PPAR δ) Activation Increases Energy Expenditure and Is highly Effective in Treating Metabolic Syndrome

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The cluster of insulin resistance, hypertension, dyslipidemia and obesity has been collectively called metabolic syndrome and accounts for greater than 45 million individuals in the United States. These well known risk factors for cardiovascular disease, diabetes and NASH (nonalcoholic steatohepatitis) are increasing at an alarming rate world-wide. The regulation of energy homeostasis (the balance between energy storage and expenditure) serves as a fundamental point of therapeutic intervention. We have identified and characterized a potent, selective PPAR δ ligand in multiple animal models of metabolic syndrome. In diabetic models, PPAR δ activation results in an increase in energy expenditure leading to a robust improvement in insulin resistance and lipid metabolism. We developed a mouse model of metabolic NASH that resembles many features of the human disease. PPAR δ agonists significantly improve features associated with NASH: including (1) reduced body weight (2) reduced hepatic lipid accumulation (3) normalized levels of serum transaminases and proinflammatory cytokines and (4) attenuated macrophage infiltration in the liver. These changes are accompanied by an improvement in fasting hyperinsulinemia, glucose disposal and hepatic fibrosis. These data suggest that PPAR δ selective ligands hold significant promise in treating risk factors associated with metabolic syndrome. We are currently testing our lead PPAR δ in humans in a variety of metabolic disorders.