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EDITORIAL

□-Lipoic Acid and Combination PPAR □/□-Agonism

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The peroxisome proliferators activated receptor (PPAR) family of nuclear receptors is a complex signaling circuit designed to coordinate precise metabolic changes in glucose, lipid, and inflammatory mediator metabolism, among other functions. A number of PPAR isoforms have been identified, including PPAR□, PPAR□/∂, and PPAR□. The PPARs have many naturally occurring ligands including fatty acids. After binding their ligands, PPAR□ and PPAR□can heterodimerize with the retinoid X receptor. These heterodimers can then bind to the peroxisomal proliferator response elements within the promoters of a large number of genes, thereby activating transcription. PPAR□ agonism promotes increased high-density lipoprotein (HDL) biosynthesis and reverse cholesterol transport, triglyceride catabolism via the activation of lipoprotein lipase, and favorable changes in low-density lipoprotein (LDL) particle size characteristics. PPAR□agonism improves insulin sensitivity and systemic tissue glucose uptake and utilization, can reverse hepatic steatosis, downregulates the expression of a variety of inflammatory mediators, and promotes the expression of adiponectin.

The fibrates and thiazolidinediones are synthetic ligands for PPAR□ and PPAR□, respectively. The fibrates have been shown to reduce cardiovascular events[1] and rates of atheromatous plaque progression[2] in patients with coronary artery disease. The thiazolidinediones (TZDs) beneficially impact glycemic control and a variety of surrogate markers of endothelial function. In one recent clinical trial, pioglitazone was shown to reduce risk for mortality, stroke, and nonfatal myocardial infarction.[3] The fibrates and TZDs are widely used to treat the dyslipidemia and impaired glycemic control of diabetics.

Given the therapeutic success of PPAR modulation, it comes as no surprise that in recent years much research has been focused on the development of agents that can induce the simultaneous agonism of both PPARa and PPAR□. One such agent is muraglitazar. However, because of concerns over its cardiovascular safety profile, the future of this drug is uncertain.[4] Another combination agent, tesaglitazar, remains in

development and has been shown to beneficially impact indices of both lipid and glycemic control.

In this issue of *The Journal of Applied Research*, Pershadsingh and coworkers elegantly demonstrate that □-lipoic acid (LA) is also a combination PPAR□/□agonist. Earlier experiments with this agent in animal models demonstrated its ability to reduce serum glucose and insulin levels and decrease heart mitochondrial oxygen free radical production. In human studies, LA has been shown to relieve oxidative stress and improve insulin sensitivity and systemic tissue glucose uptake. Both LA and a synthetic ester of LA activate PPAR□ and PPAR□in a dose-dependent manner. PPAR∂-dependent genes are not activated by LA or its ester. LA and its ester induce the differentiation of preadipocyte fibroblasts to adipocytes. Interestingly, LA and LA ester also dramatically reduce the elaboration of intracellular reactive oxygen species.

It is estimated that 24% of the US population has metabolic syndrome. The incidence of diabetes mellitus is escalating rapidly throughout the world. It is crucial that antiglycemic medications that can impact multiple pathogenic pathways (inflammation, oxidation, lipoprotein metabolism) undergo continued exploration and development.

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