Editorial

Peroxisome Proliferator Activated Receptor-δ
The Middle Child Vies for Attention

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Adaptation to changes in energy balance is critical for survival of all organisms. Successful adaptation during mammalian evolution was driven by starvation, but energy excess leading to insulin resistance and atherosclerosis presents challenges for adaptation in the current era. The highly orchestrated response to nutritional status is mediated, in part, by peroxisome proliferator activated receptors (PPARs), which control lipid and glucose utilization as well as inflammatory responses in many tissues. The 3 members of the PPAR family, PPARα, PPARδ, and PPARγ, form heterodimers with the retinoid X receptor and bind to peroxisome proliferator response elements. PPAR expression patterns overlap, but PPARα is present in liver and muscle, PPARγ is mostly in adipocytes, PPARδ is present in many tissues, and all 3 are in macrophages.

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PPARδ, the least characterized family member, is induced in skeletal muscle after exercise. In mice, PPARα activation increased muscle fatty acid oxidation and improved exercise tolerance. In healthy humans, a synthetic PPARδ agonist, GW501516, reduced postprandial plasma triglycerides, increased high-density lipoprotein, and increased muscle expression of enzymes involved in fatty acid oxidation. Similar effects were observed when PPARδ was activated in obese individuals, people with low high-density lipoprotein, and those with elevated low-density lipoprotein on statin therapy. PPARδ is also known to affect macrophage biology because its deletion in this cell type disrupts phagocytosis and promotes insulin resistance in addition to impairing the M1 (more inflammatory) to M2 (more inflammation resolution) transition.

Some, but not all, studies of PPARδ agonists report beneficial effects on experimental atherosclerosis. Notably, treatment with GW501516 decreases atherosclerotic lesions in apolipoprotein E–null mice fed a high-fat diet. It is unknown whether PPARδ activation provides benefit in the setting of pre-existing insulin resistance and atherosclerosis, a condition relevant to common presentations in the clinic.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Bojic and colleagues report that PPARδ activation is atheroprotective in low-density lipoprotein receptor–deficient mice with established insulin resistance and atherosclerosis induced by diet. Compared with controls, GW501516-treated mice had decreased lesions concomitant with reduced very low-density lipoprotein and elevated high-density lipoprotein. Besides these beneficial effects on circulating lipids, other mechanisms may have contributed to the diminished plaque burden. First, drug treatment was associated with fewer macrophages in plaques, and these cells had predominantly M2 as opposed to M1 characteristics. Second, drug treatment was associated with decreased activation of ERK, p38, and NFκB in the vascular wall. Third, drug treatment was associated with fewer markers of endoplasmic reticulum stress, such as Grp78 and CHOP, and restoration of Akt phosphorylation. Collectively, these results suggest that PPARδ activation decreases high-fat diet–induced proinflammatory aortic signals and improves vascular insulin sensitivity.

Are the effects of GW501516 specific to PPARδ and not because of activation of other PPARs? PPARα and PPARδ have overlapping expression patterns and target gene profiles. PPARα agonism by fibrates may have a protective effect on atherosclerosis, and binding data suggest that PPARδ may also be a fibrate target. Drug concentration is an important determinant of target specificity. In the Bojic study, the dose of GW501516 was carefully titrated to achieve serum levels severalfold lower than the EC50 values for PPARγ and PPARδ. Moreover, drug treatment activated target genes relatively specific to PPARδ such as Acox, Angptl4, and Cpt1a but did not affect Acox, a PPARα target, or Lpl1 and Fabp4, PPARγ targets.

Clearly, the authors have performed a rigorous preclinical study demonstrating beneficial effects of PPARδ activation on lipids, systemic insulin sensitivity, macrophage polarization and infiltration, and arterial insulin sensitivity and inflammation (see Figure). As with any intervention that impacts multiple end points, it is difficult to determine the relative contributions of these processes to the diminution of lesion progression. Further, diverse effects in response to drug treatment raise the question of whether these findings are the direct consequence of PPARδ target gene expression in individual tissues or because of endocrine effects induced by a circulating mediator. There is precedent for the latter. A serum phosphatidylcholine species was recently identified as a link between hepatic PPARδ activity and skeletal muscle PPARα activity. These findings contribute to the emerging body of data indicating that phospholipids can regulate nuclear receptor activity and raise the possibility that a circulating lipid generated by PPARδ activation could be antiatherogenic.

Could the findings from Bojic and colleagues have broader implications for vascular disease? Insulin resistance in vascular endothelial cells probably contributes to disease. In
the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate was associated with ≈50% reduction in minor amputations compared with placebo. This reduction was not associated with serum lipids, raising the possibility of a direct effect of PPAR activation at the endothelium or perhaps fenofibrate induction of a beneficial circulating lipid not detected in conventional serum assays. Patients randomized to fenofibrate in both the FIELD and Action to Control Cardiovascular Risk in Diabetes (ACCORD) studies were less likely to show progression of diabetic retinopathy, another devastating vascular disease. Such data prompt the speculation that specific PPARδ agonists could ameliorate peripheral vascular and microvascular disease in the setting of insulin resistance. Although previously neglected as the middle child in the PPAR family, PPARδ seems to mediate metabolic responses in multiple tissues. Continued understanding of its signaling and regulation might lead to novel approaches to human metabolic and cardiovascular disease.

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**Disclosures**

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**References**


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In the article by Rajagopal and Semenkovich, which appeared in the January 2014 issue of the journal *Arterioscler Thromb Vasc Biol.* 2014;34:5–7. DOI: 10.1161/ATVBAHA.113.302777), the authors’ institutional affiliation was incorrect in the Correspondence line. The institution should have appeared as Washington University, and instead was Washington State University.

The online version of the article has been corrected and is available at http://atvb.ahajournals.org/content/34/1/5.