EDITORIAL COMMENT

Peroxisome Proliferator-Activated Receptors as Therapeutic Targets in Inflammation*

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For decades, advances in endocrinology were characterized by a process in which hormones were first identified based upon their physiologic roles and then purified, often from vast quantities of biologic material. This purified material was then used to identify the receptors through which the hormone signaled. In this classic progression, science moved from physiology to cellular signaling. More recently, technological advances have turned this process literally inside out. With the advent of rapid complementary deoxyribonucleic acid screening, multiple genes were identified whose predicted structure revealed a steroid hormone receptor. This produced a group of so-called orphan receptors, whose cognate ligands and physiologic role remained completely obscure (1).

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Peroxisome proliferator-activated receptors (PPARs) were one such group of orphan receptors, with three different isoforms: PPAR-alpha (-α), PPAR-gamma (-γ), and PPAR-delta (-δ) (2). Chemical screening led to the serendipitous discovery of compounds that uniquely bound to and activated PPAR isoforms (2). For PPAR-α, the first PPAR identified, these compounds, when fed to rodents, increased the size and number of the subcellular peroxisome organelle (3). This induction of "peroxisome proliferation" also gave rise to the term PPAR, a name as imprecise as it is unwieldy, given the apparent absence of peroxisome proliferation in humans (4). More clinically relevant was the unexpected discovery that thiazolidinediones (TZDs), a class of synthetic compounds under study for their glucose-lowering effects, did so by binding to PPAR-γ (2). This fit with burgeoning data establishing PPAR-γ as a ligand-activated nuclear receptor highly expressed in fat and critical to adipogenesis, glucose homeostasis, and lipid metabolism (5). The TZD-targeted responses included increased expression of the glucose transporter GLUT4, possibly underlying its clinical effects (6). Three TZDs have come to clinical use as antidiabetic insulin sensitizers (2,7). The first

TZD released, troglitazone (ReZulin, Warner-Lambert Co., Morris Plains, New Jersey), was ultimately withdrawn because of cases of irreversible liver toxicity. Subsequent TZDs, pioglitazone (Actos, Takeda Chemical Industries Ltd., Osaka, Japan) and rosiglitazone (Avandia, Glaxo-SmithKline, New York, New York), have lacked such toxicity despite significant patient exposure and study. The TZDs have been a welcome addition to the armamentarium against the increasing onslaught of type 2 diabetes mellitus, a disease characterized by insulin resistance. Agents that sensitize patients to insulin, as opposed to those compensating for insulin resistance by increasing insulin levels, would seem a more directed approach to the problem.

Insulin sensitizers as antidiabetic agents are also appealing for their possible cardiovascular benefits, offering hope for definitive evidence that improved glucose control decreases cardiovascular complications (8). Arguably the best evidence to date for decreased cardiovascular outcomes through a diabetes intervention comes from trials with metformin, an insulin sensitizer albeit with a PPAR-independent mechanism of action (9). Cardiovascular outcomes with TZDs are under intense study. Cardiovascular benefits with TZD use could come from two distinct effects. Certainly, the improved insulin sensitivity, lower circulating glucose levels, and better lipids seen with TZDs might indirectly limit atherosclerosis or its complications. Alternatively, if PPARs were expressed in vascular and inflammatory cells, then PPAR activation could have direct effects on atherosclerosis by inducing or repressing specific relevant target genes (10). In fact, extensive data from many groups now establish PPAR-α, -γ, and -δ expression throughout the vasculature and in many inflammatory cells, as well as an ever-expanding list of PPAR target genes involved in vascular biology (11,12). Most, but not all, of these data suggests activation of PPAR-γ and -α, the isoforms targeted by synthetic agonists in current clinical use, would decrease atherosclerosis and/or inflammation. In vivo studies support this possibility. Several PPAR-γ agonists have been shown to limit atherosclerosis in various mouse models of atherosclerosis (12). Moreover, clinical data in humans on surrogate end points of atherosclerosis also are suggestive of potential TZD benefits. Thus far, PPAR-γ agonists reportedly decrease circulating levels of C-reactive protein (CRP) (13), CD40 ligand (14,15), and MMP-9 (13,16). In small studies, PPAR-γ agonists also decreased carotid intimal:medial thickening (17,18) and in-stent restenosis.

In this issue of the *Journal*, Sidhu et al. (19) extend similar surrogate approaches to ask whether PPAR-γ agonists might improve markers of endothelial responses as well as more general measures of inflammation and atherosclerosis. Peroxisome proliferator-activated receptors are expressed in the endothelium (20), a cellular element in the vascular wall now recognized as a dynamic organ integrally involved in vascular responses (21). In these studies, the authors gave an escalating amount of rosiglitazone (4 mg then 8 mg) or

placebo to a small group of patients (46 in each arm) with angiographically established coronary artery disease for just 12 weeks (19). Rosiglitazone treatment significantly decreased CRP levels as well as a group of endothelial markers, including von Willibrand factor and E-selectin. Fibrinogen was also decreased, as were indicators of insulin sensitivity. Theoretically, such TZD benefits in the general population might derive from improved glucose parameters as well as direct transcriptional effects. One intriguing aspect of this study is the possible circumvention of these confounding possibilities: these individuals did not have diabetes. Interestingly, these various parameters were improved even while low-density lipoprotein (LDL) and triglyceride levels were modestly increased in the active therapy arm (113 vs. 102 mg/dl and 130 vs. 108 mg/dl, respectively).

This article, even with the limitations of studies like it, touches upon a host of intriguing issues moving increasingly to the center of the cardiologist's field of vision. The extensive laboratory work suggesting PPAR-γ activation as a potential target for ameliorating diabetes/insulin resistance and atherosclerosis continues to be translated to clinical settings, facilitated by the clinical use of TZDs. Although much of the attention on gene therapy has focused on introducing exogenous genes, the possibility exists, fueled by expanding insight into cellular transcriptional machinery, for transcriptionally active drugs to have clinical effects through altered gene expression. Indeed, such effects on gene expression may contribute to responses with other agents like statins (22) or estrogens. Did the changes seen by Sidhu et al. (19) result from PPAR-γ activation and altered gene expression? The answer is not known, especially because less insulin resistance was seen even among this presumably nondiabetic cohort. If improved insulin sensitivity were at work, this result would be consonant with the move in preventive cardiology toward earlier intervention in the course of this disease. Both atherosclerosis and diabetes have proven themselves as chronic processes arising over decades (23,24). Waiting for patients to cross a defined and often-arbitrary threshold before initiating therapy is a practice derived from necessity but defined by our current insight or lack thereof. It is also potentially dangerous. Many first myocardial infarcts are fatal (25). Most such individuals would have as much evidence of atherosclerosis the day before their event as they did at its onset, absent perhaps an intact fibrous cap (24). Such issues are perhaps even more obvious in diabetes given clinical markers—high triglycerides/low high-density lipoprotein (HDL), central obesity, hypertension—that suggest underlying insulin resistance, future conversion to diabetes, and their concomitant cardiovascular risk. C-reactive protein itself may predict the development of diabetes (26). The TZDs may offer a unique opportunity for earlier intervention or their use in nondiabetics, given their lack of induced hypoglycemia (7). Larger studies will hopefully resolve whether earlier intervention translates into benefits in atherosclerosis, diabetes, or both.

As studies expand the list of potential TZD benefits, it will remain important to consider if any potential untoward effects became apparent. Although Sidhu et al. (19) did find the TZD to be generally well-tolerated even among these "nondiabetic" individuals, rosiglitazone did modestly increase LDL and triglyceride levels. Although these changes were perhaps easily modifiable by titrating other drugs, that is, statins, they remain potentially proatherogenic responses. The modest LDL increases observed previously with TZDs may be offset by a more buoyant, less-dense, less-atherogenic LDL particle (27). Different TZDs may also have different lipid effects (28), perhaps as a result of unique ligand/receptor interactions. Both rosiglitazone and pioglitazone have been reported to increase HDL levels (27,28), at times to an extent rivaling HDL intervention trials; no changes in HDL were evident here. The increase in weight seen with TZDs represents another potentially undesirable side effect. Interestingly, some suggest this may predict clinical response and/or involve a shift in fat from visceral to subcutaneous depots (29). Of note, one TZD-induced fat-derived cytokine, adiponectin, may limit inflammation (30), whereas a TZD-repressed protein, resistin, may promote insulin resistance (31). Some weight gain may also derive from fluid retention and edema (32), fostering concerns over TZD-precipitated heart failure. This has led to avoiding TZDs when the ejection fraction is low or clinical heart failure is present. The extent to which this edema is due to the known vasodilatory effects of these drugs versus more worrisome left-sided failure with elevated pulmonary capillary wedge pressures remains unclear. Some retrospective data suggest a significant element of the former (33). This issue is under study and requires resolution, especially given recent data that many heart failure patients take insulin sensitizers (34) and because this problem, if unfounded or minor, may preclude some patients from access to the other benefits of TZDs.

No doubt TZDs will continue to be the subject of ongoing interest in terms of their clinical and especially cardiovascular effects. Several factors will drive this. One issue is simple numbers. The incidence of diabetes among Americans is increasing in seemingly direct proportion to the expanding waistline of the population (35). Especially troubling is the trend towards adolescents who are presenting with classic insulin-resistant, obesity-related type 2 diabetes mellitus (36). A second issue is science. Biologic insight into PPARs and other orphan nuclear receptors is rapidly increasing in parallel with the pursuit of many novel PPAR agonists now in various stages of development (37). These later-generation PPAR agonists include single compounds capable of activating both PPAR-α and -γ, dangling the prospect of a drug that treats dyslipidemia like PPAR-α–activating fibrates while sensitizing to insulin-like PPAR-γ–activating TZDs (38,39). A third force is the unmet clinical need for cardiovascular risk interventions that add something to the impressive but not curative effects of statins among people with diabetes. Agents that either delay

or prevent the onset of diabetes would also fall into this category; a possibility already raised for TZDs (40). One final potent stimulus to this arena may be synergism. Two of the most dominant recent trends in cardiovascular science—atherosclerosis as an inflammatory disease and diabetes as a vascular disorder—seem to unite in the study of PPAR-γ and the basic and clinical consequences of its activation. Early studies of the effects of TZD on surrogate markers like CRP and adhesion molecules support PPAR-γ as a therapeutic target for inflammation. It remains to be seen in TZD studies in larger numbers of patients if a clinical cardiovascular benefit results from hitting this target.

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