COMMENTARY

Ligands of the peroxisome proliferator-activated receptor-γ and heart failure

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Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of ligand-activated transcription factors that are related to retinoid, steroid and thyroid hormone receptors. The PPAR subfamily comprises of three members, PPAR-α, PPAR-β and PPAR-γ. There is good evidence that ligands of PPAR-γ, including certain thiazolidinediones, reduce myocardial tissue injury and infarct size. The use of PPAR-γ agonists in the treatment of heart failure is, however, controversial.

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Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of ligand-activated transcription factors that are related to retinoid, steroid and thyroid hormone receptors. The PPAR subfamily comprises three members: PPAR-α, PPAR-β and PPAR-γ. Two isoforms of PPAR-γ are known: PPAR-γ1 and PPAR-γ2. PPAR-γ1 is the major isoform and accounts for approximately 85% of PPARs in adipose tissue. These isoforms are generated from the same gene by mRNA splicing and differ in their amino-terminal end, with PPAR-γ2 having an additional 30 amino acids. The name PPAR is derived from the fact that activation by xenobiotics of PPAR-β results in peroxisome proliferation in rodent hepatocytes. Activation of PPAR-β or PPAR-γ, however, does not elicit this response. Most tissues in humans (and rodents) express all three receptor subtypes, although there is considerable variability in the relative expression. PPARs regulate gene expression by binding, as heterodimers with retinoid X receptors (RXRs), to specific PPAR response elements (PPRE) in the promotor regions of specific target genes, resulting in either the activation or suppression of a specific gene (see Bishop-Bailey, 2000 for review).

The recent development of a novel class of insulin-sensitising drugs, the thiazolidinediones (TZDs), represents a significant advance in antidiabetic therapy. Type II diabetes, also known as noninsulin-dependent diabetes mellitus (NIDDM), is a chronic disease that affects 5–10% of adults over the age of 30 in most populations. Type II diabetes is characterised by resistance of peripheral tissues to the effects of insulin, which is manifested as a reduction in insulin-stimulated glucose uptake in skeletal muscle and adipose tissue, defective insulin-dependent suppression of hepatic glucose output and reduced insulin secretion of pancreatic beta cells. There is now good

evidence that the beneficial effects of TZDs are due to the activation of PPAR-γ. For instance, the synthetic TZDs were the first class of compounds to be identified as PPAR-γ ligands. The insulin-sensitiser rosiglitazone is the most potent and selective PPAR-γ agonist and there is a good correlation between the potency of the TZDs as PPAR-γ agonist *in vitro* and their efficacy at lowering glucose levels *in vivo*. There is less information regarding endogenous ligand(s) for PPAR-γ. However, the cyclopentanone prostaglandin 15-deoxy$\Delta^{12,14}$ PGJ_2 (15d-PGJ_2), which is the metabolite of prostaglandin D_2, has been suggested to function as an endogenous ligand for PPAR-γ (see Bishop-Bailey, 2000 for review).

Several recent, independent investigations provide evidence that TZDs and other ligands of PPAR-γ reduce the tissue injury caused by regional myocardial ischaemia and reperfusion in rodents. PPAR-γ1 is expressed in the rat heart (Wayman *et al.*, 2002), and various chemically distinct ligands of PPAR-γ (including the TZDs rosiglitazone, ciglitazone and pioglitazone, as well as the cyclopentanone prostaglandins 15d-PGJ_2 and PGA_1) cause a substantial (30–50%) reduction of myocardial infarct size in the rat when given prior to the onset of myocardial ischaemia (Thiemermann & Wayman, 2001; Yue *et al.*, 2001; Wayman *et al.*, 2002). Rosiglitazone also improves the functional recovery of rat hearts obtained from diabetic animals subjected to global ischaemia and reperfusion (Khandoudi *et al.*, 2002). The mechanisms underlying the cardioprotective effects of TZDs are not entirely clear, but may include (i) inhibition of the activation of NF-κB, (ii) reduced expression of inducible nitric oxide synthase (iNOS), monocyte chemo-attractant protein-1 (MCP-1) and the adhesion molecule ICAM-1, and (iii) inhibition of Jun NH(2)-terminal kinase (Yue *et al.*, 2003; Khandoudi *et al.*, 2002; Wayman *et al.*, 2002). Thus, there is growing evidence that ligands of PPAR-γ may be useful in the therapy of conditions associated with inflammation and ischaemia–reperfusion of the heart (e.g. myocardial infarction, heart transplantation, bypass surgery) and inflammation and ischaemia–reperfusion of other

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organs (Takano *et al.*, 2000; Nakajima *et al.*, 2001; Cuzzocrea *et al.*, 2002; 2003; Kon *et al.*, 2002; Naito *et al.*, 2002; Shiojiri *et al.*, 2002; Collin & Thiemermann, 2003; Enomoto *et al.*, 2003; Sivarajah *et al.*, 2003).

The role of PPAR-γ in heart failure is controversial. On the one hand, PPAR-γ ligands reduce the hypertrophy caused by mechanical strain in neonatal cardiac myocytes (Yamamoto *et al.*, 2001) and pioglitazone improves left ventricular remodelling in mice hearts subjected to myocardial infarction (Shiomi *et al.*, 2002; discussed below). On the other hand, there is clinical evidence of an increase in the incidence of heart failure in patients with type II diabetes who are treated with TZDs (Delea *et al.*, 2002).

In this issue of the *British Journal of Pharmacology*, Frantz *et al.* (2003) have investigated the effects of pioglitazone in a mouse model of heart failure. They report that pioglitazone (single dose of $20 \, \mathrm{mg \, kg^{-1}}$ at day 7 after infarction) had no effect on mortality, left ventricular remodelling, cytokine expression, collagen content or endothelial dysfunction in mice that had been subjected to myocardial infarction prior to onset of treatment with the TZD. In contrast, have recently reported that administration of pioglitazone in mice subjected to infarction ($3 \, \mathrm{mg \, kg^{-1} \, day^{-1}}$ starting 6 h after surgery for 4 weeks) significantly reduced left ventricular dysfunction, and this effect was associated with a decrease in myocyte hypertrophy and interstitial fibrosis and a reduced expression of tumour necrosis factor-α, transforming growth factor-β and MCP-1.

The reasons for the observed differences in the results of the above studies are likely to be due to differences in study design. It is possible that the dose regimen of pioglitazone chosen by was not appropriate, as the authors did administer only a single dose of $20 \, \mathrm{mg \, kg^{-1}}$ pioglitazone on day 7 after occlusion of the coronary artery. In contrast, administered pioglitazone ($3 \, \mathrm{mg \, kg^{-1} day^{-1}}$) for a period of 4 weeks starting immediately after the onset of surgery. The latter strategy has the advantage that the treatment covers any events occurring during the early reperfusion period as well as during the period of cardiac remodelling. Indeed, it is likely that proinflammatory cytokines and other proinflammatory mediators produced in the hours and days after the ischaemic event importantly contribute to the development of left ventricular remodelling. Interestingly, injections of single doses of the PPAR-γ ligand 15d-PGJ$_2$ are sufficient to reduce the tissue injury associated with acute inflammation (pleurisy), while repetitive injections of this PPAR-γ ligand (every 48 h over weeks) are needed to reduce the tissue injury associated with chronic inflammation (collagen-induced arthritis) (Cuzzocrea *et al.*, 2002). Thus, a continuous administration of TZDs over a prolonged period of time appears to be more suitable to combat more prolonged disease processes, such as the development of left ventricular remodelling and heart failure, than a single bolus administration of the same drug.

The conclusion of that pioglitazone does not reduce left ventricular remodelling and heart failure could have been strengthened if the authors had included data documenting the effects (or lack of effects) of different dose regimen of pioglitazone or if they had been able to document that appropriate dose regimens of other TZDs also do not reduce the degree of heart failure in mice subjected to coronary artery ligation. One could also argue that the degree of heart failure caused in the study by was too severe to allow any treatment to be effective. This argument could be overcome by the inclusion of a 'positive control group' to document that a reduction in the degree of remodelling can indeed be achieved by administration of a single bolus injection of a 'reference drug' at 7 days after coronary artery ligation.

Given the evidence that pretreatment of rodents with ligands of PPAR-γ reduces myocardial infarct size, it is likely that any reduction in infarct size would result in an attenuation of the degree of cardiac dysfunction caused by the ischaemic event. Thus, further studies are warranted that compare the effects of TZDs given prior to the onset of ischaemia with those of TZDs given at various times after the onset of reperfusion of the previously ischaemic myocardium. Whether PPAR-γ agonists are ultimately able to reduce the degree of left ventricular remodelling following acute myocardial infarction (or not) remains to be seen. Nevertheless, it is interesting to realise that the beneficial effects of TZDs are not limited to insulin-sensitising effects in type II diabetes, but can be observed in a multitude of (animal models of) diseases associated with ischaemia–reperfusion and inflammation (Takano *et al.*, 2000; Nakajima *et al.*, 2001; Cuzzocrea *et al.*, 2002; 2003; Kon *et al.*, 2002; Naito *et al.*, 2002; Shiojiri *et al.*, 2002; Collin & Thiemermann, 2003; Enomoto *et al.*, 2003; Sivarajah *et al.*, 2003). These anti-inflammatory effects of TZDs in animal models are corroborated by clinical data demonstrating that rosiglitazone reduces the serum levels of the proinflammatory marker c-reactive protein as well as the serum levels of matrix-metalloproteinase-9 in patients with type II diabetes (Haffner *et al.*, 2002).

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