PPARs and Myocardial Ischemia

Subjects: Endocrinology & Metabolism

Contributor: Kay-Dietrich Wagner

Peroxisome proliferator-activated receptors (PPARs) are nuclear proteins. They exist in three isoforms - PPARalpha, PPARbeta/delta, and PPARgamma. They exhibit tissue and cell type-specific expression patterns and functions. Besides the established notion of the therapeutic potential of PPAR agonists for the treatment of glucose and lipid disorders, more recent data propose specific PPAR ligands as potential therapies for cardiovascular diseases.

Keywords: peroxisome proliferator-activated receptor,cardiovascular disease ; diabetes ; angiogenesis ; lipid lowering

1. PPARα

In the late 1980s, the Helsinki heart study suggested the PPARα agonist gemfibrozil for the prevention of coronary artery disease [1]. At this time, it was not known that gemfibrozil actually was a PPARα agonist, as PPARα had been identified as the first PPAR in 1990 [2]. In the Helsinki heart study, the effect of modifying plasma low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol on the primary prevention of coronary heart disease in middle-aged men with hypercholesterinemia was investigated over a five year trial period. A 34% reduction in the incidence of coronary artery disease had been observed [1]. In 1998, the bezafibrate infarction prevention (BIP) study was initiated. Bezafibrate is a lipid-lowering fibric acid derivate and a pan (α, β/δ, γ)-PPAR agonist. The aim of this trial was to investigate if bezafibrate would reduce the risk of myocardial infarction in coronary artery disease patients. An eight-year follow-up demonstrated a 17% reduction of major cardiac events [3]. 1999 was the start of the ACCORD (action to control cardiovascular risk in diabetes) trial, which aimed at elucidating whether combination therapy with a statin (simvastatin) plus fenofibrate, as compared with statin monotherapy, would reduce the risk of cardiovascular disease in patients with type 2 diabetes mellitus. Combination of the PPARα agonist fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone [4]. Later, first experimental studies investigating the effects of PPARα modulation on the outcome of myocardial infarction emerged. In 2002, the group of C. Thiemermann was the first to examine the effects of PPARα agonists (clofibrate and WY14643) after experimentally induced myocardial infarction. They also investigated the effects of PPARγ agonists (thiazolidinediones and cyclopentanone prostaglandins) on myocardial infarct size [5]. The detailed information about the substances or experimental interventions used as well as the outcome on myocardial infarction for all PPARs.

The initial enthusiasm regarding the potential therapeutic benefits of PPARα agonists as activators of cardiac FAO and inhibitors of glucose utilization in the prevention and cure of myocardial infarction has not only been dampened by negative or not clearly beneficial outcomes in large clinical trials but also extremely contrasting results of experimental studies. The role of PPARα in myocardial infarction remains unclear as both beneficial and detrimental effects of PPARα activation have been reported. This might be due to ligand-dependent variations, differences in experimental settings, the timing of administration, and species used.

2. PPARβ/δ

PPARβ/δ is the predominant PPAR subtype expressed in cardiac tissue [6]. Conditional cardiomyocyte-specific deletion of PPARβ/δ has been shown to induce myocardial lipid accumulation and cardiomyopathy, resulting in congestive heart failure with reduced survival. As the main mechanism for the cardioprotective action of PPARβ/δ, its leading role in maintaining normal fatty acid oxidation (FAO) was identified [7]. Animals with cardiomyocyte-specific deletion of PPARβ/δ were also examined in a study that aimed to establish an open-chest method for acquiring in vivo ^{31}P nuclear magnetic resonance (NMR) cardiac spectra from mice at 4.7 Tesla. Interestingly, mice lacking PPARβ/δ in cardiomyocytes had even lower mean phosphocreatine (PCr)/adenosine triphosphate (ATP) ratios than control animals with myocardial infarction [8]. Given these important findings, it is astonishing that relatively few investigations focused on the implication of PPARβ/δ in myocardial infarction. Accordingly, nearly no clinical trials exist investigating the consequences of PPARβ/δ modulation in cardiovascular disease. The PPARβ/δ agonist GW501516 entered clinical trials to treat metabolic syndrome and diabetes

at the beginning of 2000. These trials were stopped in 2007 due to multiple appearances of cancers in mice and rats [9], a finding which our group could confirm using either the PPARβ/δ agonist GW0742 or animals with conditional inducible vessel-specific overexpression of PPARβ/δ [10][11]. Currently, the angiotensin II receptor blocker telmisartan is one drug on the market that targets PPARβ/δ [12], as well as PPARγ [13][14]. Two clinical trials for telmisartan were completed: TRANSCEND (Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease) and ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipiril Global Endpoint Trial). No significant differences were observed between the groups in terms of primary and secondary outcomes, except for female patients who showed a 20% overall risk reduction for myocardial infarction [15]. It is, however, difficult to say if this beneficial effect of telmisartan can be attributed to angiotensin II receptor blockade or PPARβ/δ activation.

Concerning expression levels of PPARβ/δ after myocardial infarction, no changes could be observed after the infarction of rats [16]. The group around R. N. Willette examined the effects of the specific PPARβ/δ agonist GW610742X on the outcome after myocardial infarction in rats. The PPARβ/δ agonist did not ameliorate reduced left ventricular ejection fractions, and decreased phosphocreatine/adenosine triphosphate ratios, nor changed left ventricular weights or infarct sizes. In contrast, GW610742X normalized cardiac substrate metabolism after infarction and reduced right ventricular hypertrophy and pulmonary congestion [17]. Indirectly, cardioprotective functions of PPARβ/δ have been postulated in work from Li and coworkers. The authors investigated the beneficial effects of remote ischemic preconditioning (rIPC) for cardiac protection after myocardial infarction and the underlying molecular pathway. rIPC reduced infarct size and apoptosis and improved functional recovery. The authors demonstrated that protective effects of rIPC were mediated via the phosphoinositide 3-kinase (PI3K)/Akt/glycogen synthase kinase 3β (GSK3β) signaling pathway, which associates the nuclear accumulation of β-catenin and the up-regulation of its downstream targets E-cadherin and PPARβ/δ involved in cell survival [18]. Our group specifically aimed at elucidating a hypothetical benefit from vessel-specific overexpression of PPARβ/δ on recovery after myocardial infarction. This was prompted by our earlier finding that PPARβ/δ agonist treatment induced a rapid increase in cardiac muscle mass and vascularization [19]. We also wanted to know if vascular specific PPARβ/δ overexpression would be sufficient to induce cardiac growth. In mice with inducible vascular specific overexpression of PPARβ/δ, we observed not only a rapid increase of cardiac vascularization but also a fast induction of cardiac growth, indicating that myocardial hypertrophy was due to enhanced angiogenesis. Vascular-specific PPARβ/δ overexpression impaired cardiac function, as evidenced by increased systolic and diastolic volumes, a reduced fractional shortening, and decreased ejection fractions. PPARβ/δ vessel-specific overexpression also increased capillary densities in the setting of myocardial infarction but failed to improve the outcome. We observed bigger infarct sizes, enhanced fibrosis, and significantly impaired echocardiographic parameters in the animals with the induction of vessel-specific overexpression of PPARβ/δ compared to controls. This indicates that the specific, unbalanced activation of PPARβ/δ only in the vasculature is not sufficient to protect against chronic ischemic heart disease [20][21]. Treatment with the PPARβ/δ agonist GW610742 after myocardial infarction in rats similarly has been reported to increase vessel densities and fibrosis, however, echocardiographic examinations revealed no differences between PPARβ/δ agonist treated animals and controls. GW610742 increased bone marrow-derived mesenchymal stem cell (MSC) recruitment in the heart and augmented the differentiation of fibroblasts into myofibroblasts. This was accompanied by increased serum platelet-derived growth factor B, stromal-derived factor-1 alpha, and MMP 9 levels. However, despite the enhanced angiogenesis, fibrosis, and myofibroblast differentiation in the early phase after infarction, the authors could not conclude the beneficial effects of PPARβ/δ activation on cardiac function after myocardial infarction [22]. In contrast to these studies, Magadum and coworkers observed a beneficial effect of PPARβ/δ activation on the outcome after myocardial infarction. It remains to be determined if different PPARβ/δ agonists used or different experimental settings might contribute to these discrepancies. Using an inducible mouse model with cardiomyocyte-specific overexpression of PPARβ/δ, Magadum and colleagues demonstrated smaller infarct sizes, enhanced cardiomyocyte proliferation, and improved functional parameters upon overexpression of PPARβ/δ in cardiomyocytes. They constated similar favorable effects by treating mice after ligation of the left anterior descending artery (LAD) with the PPARβ/δ agonist GW0742 [23]. These results partially confirm our hypothesis that a proper balance of PPARβ/δ activation in the different cardiac cell types may be important for potential cardioprotective effects of PPARβ/δ [20], and highlights the significance of cardiomyocyte PPARβ/δ expression for cardiac repair.

3. PPARγ

Thiazolinediones are the major class of PPARγ agonists, including rosiglitazone, pioglitazone, and troglitazone indicated for the treatment of type 2 diabetes. However, their usefulness has become controversial due to severe cardiovascular side effects [24][25]. In the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study, enrolling patients with type 2 diabetes and pre-existing cardiovascular disease, pioglitazone increased the incidence of heart failure [26]. Especially, rosiglitazone has been associated with a higher risk for myocardial infarction and stroke [27]. However, the

RECORD (rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes) trial could not confirm an increased risk for cardiovascular morbidity or mortality, but admitted inconclusive data about the incidence of myocardial infarction upon rosiglitazone therapy [28]. A science advisory from the American Heart Association and American College of Cardiology Foundation finally concluded that “thiazolidinediones should not be used with an expectation of benefit with respect to ischemic heart disease (IHD) events” [29]. Doney and colleagues investigated PPARγ variants in diabetic patients. They found an association between the *PPARG* Pro12Ala variant and decreased risk of myocardial infarction, while the C1431T genotype had the opposite effect. These polymorphisms might contribute to the conflicting results mentioned above; mechanistic consequences of the polymorphisms are currently unknown [30]. Later meta-analyses did not support a role of P12A polymorphism in the PPARγ gene in myocardial infarction or coronary heart disease risk [31]. Expression levels of PPARγ were found to be up-regulated after myocardial infarction in rats, however, increased PPARγ could not counteract the decrease in metabolic genes [16]. Experimental studies investigating a possible therapeutical potential for PPARγ agonists in ischemic heart disease started in 2001 with a report from Eliot H. Ohlstein’s group. Using ischemia/reperfusion manipulations in rosiglitazone treated rats, they observed reduced infarct sizes, an improvement of myocardial contractile dysfunction, less macrophage/neutrophil invasion, which correlated with decreased ICAM-1 and MCP-1 expression upon PPARγ activation with rosiglitazone. They ascribed the cardioprotective effect of rosiglitazone to the inhibition of inflammatory responses [32]. Similar results were obtained, as already mentioned in the PPARα section, by Wayman and colleagues, who in addition to rosiglitazone investigated the effects of ciglitazone, pioglitazone, 15D-PGJ_2, and PGA_1 [5], also by Ito and colleagues who focused only on pioglitazone [33]. The group of J. L. Mehta concentrated on the interplay of PPARγ and the renin-angiotensin system in myocardial ischemia. Rats treated with rosiglitazone or vehicle were subjected to ischemia (1hr)/reperfusion (1hr). Infarct sizes were smaller in the rosiglitazone group, and the authors found decreased ATR1 and increased ATR2 expression of angiotensin II (ANGII) receptors in the hearts from PPARγ agonist treated animals. This was accompanied by a down-regulation of mitogen-activated protein kinases (MAPKs) 42/44, indicating that the inhibition of MAPKs 42/44 by ATR2 ANGII represents one mechanism of rosiglitazone cardioprotective effects [34]. Similar beneficial results of rosiglitazone on left ventricular remodeling and cardiac function after myocardial infarction in rats were reported, however, in this study, no expression differences for ANGII, ATR1, and ATR2 were found [35]. In addition, in mice as well as in rabbits, cardioprotection by rosiglitazone after ischemia/reperfusion has been reported [36][37]. Comparable, administration of the PPARγ agonist pioglitazone after ischemia/reperfusion decreased myocardial necrosis, apoptosis, MMP2 levels, and improved systolic cardiac function in rats [38]. In rabbits treated with pioglitazone for seven days before ischemia/reperfusion, reduced infarct sizes, improved left ventricular function, and activation of (PI3K)/Akt and eNOS pathways were reported [39]. Zhang and colleagues also proposed activation of the (PI3K)/Akt pathway as a mechanism of rosiglitazone mediated cardioprotection in mice subjected to ischemia/reperfusion [40]. Curcumin [41], vitamin D [42], apigenin [43], the traditional Chinese medication qiliqiangxin [44], melatonin [45], the flavonoids chrysin [46][47] and fisetin [48], hesperitin derived from citrus fruits [49], and the purin alkaloide theacrine [50] have all been suggested to be cardioprotective in the setting of myocardial ischemia through the activation of PPARγ. Shinmura and colleagues used the PPARγ agonist pioglitazone to enhance the cardiomyogenic transdifferentiation potential of human marrow-derived mesenchymal stem cells (MSCs), which they injected two weeks after myocardial infarction in nude rats. Pioglitazone treated MSCs improved left ventricular function significantly more than non-treated MSCs [51]. Similarly, simultaneous pioglitazone treatment after MSC injection following myocardial infarction in rats ameliorated cardiac function more efficiently than MSC transplantation alone [52]. The group of Ferreira employed lysophosphatidic acid (LPA) to enhance the survival of human umbilical cord blood-derived hematopoietic stem/progenitor cells to boost the regenerative potential in the setting of myocardial infarction. LPA enhanced survival through activation of PPARγ and pro-survival extracellular signal related kinases (ERK) and Akt signaling pathways and inhibition of mitochondrial apoptotic pathway. Injection of LPA treated cells improved cardiac fractional shortening and ejection fraction parameters after myocardial infarction [53]. The importance of PPARγ expression in myeloid cells for cardiac repair after infarction has been supported by the group of Duan, which analyzed the outcomes of myocardial infarctions in mice with myeloid specific knockout for PPARγ. Pioglitazone increased the repair potential of adipose tissue-derived regenerative cells (ADRCs) upon grafting on the anterior left ventricular wall two weeks after myocardial infarction in rats as reflected by improved functional cardiac parameters [54]. Myeloid PPARγ knockout animals had bigger infarct sizes, worse cardiac functional parameters, and enhanced oxidative stress and immune responses compared to their control counterparts [55]. The angiotensin II receptor blocker telmisartan, which also targets PPARγ [14], has been evaluated in an experimental model of isoproterenol (a synthetic non-selective β-adrenoceptor agonist) induced myocardial injury. Telmisartan lowered left ventricular end-diastolic pressure and improved biochemical, histopathological, and ultrastructural parameters [56]. The same group reported similar beneficial effects of telmisartan in diabetic rats with isoproterenol induced myocardial injury, which could be counteracted using the PPARγ antagonist GW9662 [57]. In a profound study using LAD ligation in rats, Maejima and colleagues demonstrated that Telmisartan attenuated unfavorable left ventricular remodeling after myocardial infarction, but did not influence infarct sizes or blood pressure, indicating that the favorable effects were blood pressure independent. Furthermore, co-administration of GW9662 abolished the

beneficial effects of telmisartan on left ventricular remodeling, further suggesting PPARγ agonistic activity of this drug [58]. In 2010, Tao and colleagues aimed at solving the discrepancies of experimental and clinical studies regarding the effects of PPARγ agonists of the thiazolidinedione class in cardioprotection. They used adiponectin (an adipocytokine secreted from adipose tissue) knockout and wildtype mice to show that anti-oxidative, anti-ischemic, anti-apoptotic, and cardioprotective actions of the PPARγ agonist rosiglitazone depend on normal adiponectin (APN) levels. Rosiglitazone improved post-MI survival rate and cardiac function in wildtype mice after ligation of the LAD, but not in APN knockout animals. The PPARγ agonist further reduced infarct sizes, apoptosis, and oxidative stress in normal mice, however, failed to produce these beneficial effects in the APN knockout group and provoked an enhanced superoxide production only in the APN deficient hearts. Treatment with a superoxide dismutase mimic reversed the detrimental effects of rosiglitazone in APN knockout animals, indicating that the anti-oxidant effect of rosiglitazone relies on APN. Adiponectin is down-regulated in obesity related diseases such as Diabetes type 2 or coronary artery disease, which might partially explain the unfavorable outcomes in clinical studies using rosiglitazone in such pathologies [59]. An original approach demonstrated that nanoparticle (NP) mediated targeting of pioglitazone to monocytes/macrophages, but not systemic intravenous treatment with pioglitazone solution, ameliorated ischemia/reperfusion injury, and cardiac remodeling. Pioglitazone-NPs antagonized monocyte/macrophage-mediated acute inflammation and promoted cardiac healing after myocardial infarction as also evidenced by improved cardiac functional parameters [60]. In addition, microRNA studies focused on PPARγ: Zhao and colleagues demonstrated that PPARγ promotes microRNA (miR) 711 expression after myocardial infarction in rats, which in turn induced downregulation of the chaperone calnexin leading to enhanced cardiac apoptosis due to endoplasmatic reticulum stress [61]. Downregulation of miR-130 expression has been shown to promote PPARγ-mediated cardioprotective effects by suppressing inflammation and myocardial fibrosis [62].

Although, as already mentioned in the PPARα chapter, several clinical trials testing dual PPARα/γ agonists had either to be stopped due to increased rates of heart failure as the AleCardio trial for Aleglitazar [63] or due to elevation of serum creatinine, bodyweight increase, and edema formation with tesaglitazar [64], or major adverse cardiovascular events as for muraglitazar [65], experimental research continued on the concept of dual PPARα/γ agonism. In rats with myocardial infarction, the dual PPARα/γ agonist TZD18 improved left ventricular function and increased the expression of enzymes related to myocardial energy metabolism and the content of high energy phosphate in mitochondria [66].

In conclusion, although PPARγ agonists offer benefits in the treatment of diabetes and atherosclerosis, known risk factors associated with cardiovascular disease, they also have deleterious effects such as increased risk incidence of myocardial infarction and heart failure. Their clinical use remains, therefore, limited.

References

1. Huttunen, J.K.; Heinsalmi, P.; Manninen, V.; Mänttäri, M.; Frick, M.H.; Heinonen, O.P.; Romo, M. Helsinki Heart Study. New perspectives in the prevention of coronary heart disease. Drugs 1988, 36, 32–36.
2. Issemann, I.; Green, S. Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. Nat. Cell Biol. 1990, 347, 645–650.
3. Goldenberg, I.; Benderly, M.; Goldbourt, U. Secondary prevention with bezafibrate therapy for the treatment of dyslipidemia: An extended follow-up of the BIP trial. J. Am. Coll. Cardiol. 2008, 51, 459–465.
4. Ginsberg, H.N.; Elam, M.B.; Lovato, L.C.; Crouse, J.R.; Leiter, L.A.; Linz, P.; Friede-Wald, W.T.; Buse, J.B.; Gerstein, H.C.; Probstfield, J.; et al. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. New Engl. J. Med. 2010, 362, 1563–1574.
5. Wayman, N.S.; Hattori, Y.; McDonald, M.C.; Mota-Filipe, H.; Cuzzocrea, S.; Pisano, B.; Chatterjee, P.; Thiemermann, C. Ligands of the peroxisome proliferator-activated receptors (PPAR-γ and PPAR-α) reduce myocardial infarct size. FASEB J. 2002, 16, 1027–1040.
6. Gilde, A.J.; Van Der Lee, K.A.; Willemsen, P.H.; Chinetti, G.; Van Der Leij, F.R.; Van Der Vusse, G.J.; Staels, B.; Van Bilsen, M. Peroxisome Proliferator-Activated Receptor (PPAR) α and PPARβ/δ, but not PPARγ, Modulate the Expression of Genes Involved in Cardiac Lipid Metabolism. Circ. Res. 2003, 92, 518–524.
7. Cheng, L.; Ding, G.; Qin, Q.; Huang, Y.; Lewis, W.; He, N.; Evans, R.M.; Schneider, M.D.; A Brako, F.; Xiao, Y.; et al. Cardiomyocyte-restricted peroxisome proliferator-activated receptor-δ deletion perturbs myocardial fatty acid oxidation and leads to cardiomyopathy. Nat. Med. 2004, 10, 1245–1250.
8. Lee, J.; Hu, Q.; Nakamura, Y.; Wang, X.; Zhang, X.; Zhu, X.; Chen, W.; Yang, Q.; Zhang, J. Open-chest31P magnetic resonance spectroscopy of mouse heart at 4.7 Tesla. J. Magn. Reson. Imaging 2006, 24, 1269–1276.

9. Mitchell, J.A.; Bishop-Bailey, D. PPARβ/δ a potential target in pulmonary hypertension blighted by cancer risk. Pulm. Circ. 2018, 9, 2045894018812053.
10. Wagner, K.D.; Du, S.; Martin, L.; Leccia, N.; Michiels, J.-F.; Wagner, N. Vascular PPARβ/δ Promotes Tumor Angiogenesis and Progression. Cells 2019, 8, 1623.
11. Wagner, N.; Wagner, K.D. PPAR Beta/Delta and the Hallmarks of Cancer. Cells 2020, 9, 1133.
12. Mikami, D.; Kimura, H.; Kamiyama, K.; Torii, K.; Kasuno, K.; Takahashi, N.; Yoshida, H.; Iwano, M. Telmisartan activates endogenous peroxisome proliferator-activated receptor-δ and may have anti-fibrotic effects in human mesangial cells. Hypertens. Res. 2013, 37, 422–431.
13. Amano, Y.; Yamaguchi, T.; Ohno, K.; Niimi, T.; Orita, M.; Sakashita, H.; Takeuchi, M. Structural basis for telmisartan-mediated partial activation of PPAR gamma. Hypertens. Res. 2012, 35, 715–719.
14. Benson, S.C.; Pershadsingh, H.A.; Ho, C.I.; Chittiboyina, A.; Desai, P.; Pravenec, M.; Qi, N.; Wang, J.; Avery, M.A.; Kurtz, T.W. Identification of Telmisartan as a Unique Angiotensin II Receptor Antagonist With Selective PPARγ–Modulating Activity. Hypertension 2004, 43, 993–1002.
15. Kappert, K.; Boehm, M.; Schmieder, R.; Schumacher, H.; Teo, K.; Yusuf, S.; Sleight, P.; Unger, T. Impact of sex on cardiovascular outcome in patients at high cardiovascular risk: Analysis of the Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease (TRANSCEND) and the Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial (ONTARGET). Circulation 2012, 126, 934–941.
16. Fliegner, D.; Westermann, D.; Riad, A.; Schubert, C.; Becher, E.; Fielitz, J.; Tschöpe, C.; Regitz-Zagrosek, V. Up-regulation of PPARγ in myocardial infarction. Eur. J. Hear. Fail. 2008, 10, 30–38.
17. Jucker, B.M.; Doe, C.P.; Schnackenberg, C.G.; Olzinski, A.R.; Maniscalco, K.; Williams, C.; Hu, T.C.-C.; Lenhard, S.C.; Costell, M.; Bernard, R.; et al. PPARdelta activation normalizes cardiac substrate metabolism and reduces right ventricular hypertrophy in congestive heart failure. J. Cardiovasc. Pharmacol. 2007, 50, 25–34.
18. Li, J.; Xuan, W.; Yan, R.; Tropak, M.B.; Jean-St-Michel, E.; Liang, W.; Gladstone, R.; Backx, P.H.; Kharbanda, R.K.; Redington, A.N. Remote preconditioning provides potent cardioprotection via PI3K/Akt activation and is associated with nuclear accumulation of β-catenin. Clin. Sci. 2011, 120, 451–462.
19. Wagner, N.; Jehl-Piétri, C.; Lopez, P.; Murdaca, J.; Giordano, C.; Schwartz, C.; Gounon, P.; Hatem, S.N.; Grimaldi, P.; Wagner, K.-D. Peroxisome proliferator-activated receptor β stimulation induces rapid cardiac growth and angiogenesis via direct activation of calcineurin. Cardiovasc. Res. 2009, 83, 61–71.
20. Wagner, K.-D.; Vukolic, A.; Baudouy, D.; Michiels, J.-F.; Wagner, N. Inducible Conditional Vascular-Specific Overexpression of Peroxisome Proliferator-Activated Receptor Beta/Delta Leads to Rapid Cardiac Hypertrophy. PPAR Res. 2016, 2016, 7631085.
21. Wagner, N.; Wagner, K.-D. PPARs and Angiogenesis—Implications in Pathology. Int. J. Mol. Sci. 2020, 21, 5723.
22. Park, J.R.; Ahn, J.H.; Jung, M.H.; Koh, J.-S.; Park, Y.; Hwang, S.-J.; Jeong, Y.-H.; Kwak, C.H.; Lee, Y.S.; Seo, H.G.; et al. Effects of Peroxisome Proliferator-Activated Receptor-δ Agonist on Cardiac Healing after Myocardial Infarction. PLoS ONE 2016, 11, e0148510.
23. Magadum, A.; Ding, Y.; He, L.; Kim, T.; Vasudevarao, M.D.; Long, Q.; Yang, K.; Wickramasinghe, N.; Renikunta, H.V.; Dubois, N.; et al. Live cell screening platform identifies PPARδ as a regulator of cardiomyocyte proliferation and cardiac repair. Cell Res. 2017, 27, 1002–1019.
24. Delea, T.E.; Edelsberg, J.S.; Hagiwara, M.; Oster, G.; Phillips, L.S. Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: A retrospective cohort study. Diabetes Care 2003, 26, 2983–2989.
25. Nissen, S.E.; Wolski, K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. New Engl. J. Med. 2007, 356, 2457–2471.
26. Erdmann, E.; Charbonnel, B.; Wilcox, R.G.; Skene, A.M.; Massi-Benedetti, M.; Yates, J.; Tan, M.; Spanheimer, R.; Standl, E.; Dormandy, J.A.; et al. Pioglitazone Use and Heart Failure in Patients With Type 2 Diabetes and Preexisting Cardiovascular Disease: Data from the PROactive Study (PROactive 08). Diabetes Care 2007, 30, 2773–2778.
27. Graham, D.J.; Ouellet-Hellstrom, R.; MaCurdy, T.E.; Ali, F.; Sholley, C.; Worrall, C.; Kelman, J.A. Risk of Acute Myocardial Infarction, Stroke, Heart Failure, and Death in Elderly Medicare Patients Treated with Rosiglitazone or Pioglitazone. JAMA 2010, 304, 411–418.
28. Home, P.D.; Pocock, S.J.; Beck-Nielsen, H.; Curtis, P.S.; Gomis, R.; Hanefeld, M.; Jones, N.P.; Komajda, M.; McMurray, J.J.V.; Team, R.S. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): A multicentre, randomised, open-label trial. Lancet 2009, 373, 2125–2135.

29. Kaul, S.; Bolger, A.F.; Herrington, D.; Giugliano, R.; Eckel, R.H. Thiazolidinedione drugs and cardiovascular risks: A science advisory from the American Heart Association and American College of Cardiology Foundation. Circulation 2010, 121, 1868–1877.

30. Doney, A.S.F.; Fischer, B.; Leese, G.; Morris, A.D.; Palmer, C.N.A. Cardiovascular risk in type 2 diabetes is associated with variation at the PPARG locus: A Go-DARTS study. Arter. Thromb. Vasc. Biol. 2004, 24, 2403–2407.

31. Zafarmand, M.H.; Van Der Schouw, Y.T.; Grobbee, D.E.; De Leeuw, P.W.; Bots, M.L. Peroxisome proliferator-activated receptor gamma-2 P12A polymorphism and risk of acute myocardial infarction, coronary heart disease and ischemic stroke: A case-cohort study and meta-analyses. Vasc. Heal. Risk Manag. 2008, 4, 427–436.

32. Yue, T.-L.; Chen, J.; Bao, W.; Narayanan, P.K.; Bril, A.; Jiang, W.; Lysko, P.G.; Gu, J.-L.; Boyce, R.; Zimmerman, D.M.; et al. In Vivo Myocardial Protection From Ischemia/Reperfusion Injury by the Peroxisome Proliferator–Activated Receptor-γ Agonist Rosiglitazone. Circ. 2001, 104, 2588–2594.

33. Ito, H.; Nakano, A.; Kinoshita, M.; Matsumori, A. Pioglitazone, a Peroxisome Proliferator-Activated Receptor-Agonist, Attenuates Myocardial Ischemia/Reperfusion Injury in a Rat Model. Lab. Investig. 2003, 83, 1715–1721.

34. Molavi, B.; Chen, J.; Mehta, J.L. Cardioprotective effects of rosiglitazone are associated with selective overexpression of type 2 angiotensin receptors and inhibition of p42/44 MAPK. Am. J. Physiol. Heart Circ. Physiol. 2006, 291, H687–H693.

35. Geng, D.-F.; Wu, W.; Jin, D.-M.; Wang, J.-F.; Wu, Y.-M. Effect of peroxisome proliferator-activated receptor γ ligand. Rosiglitazone on left ventricular remodeling in rats with myocardial infarction. Int. J. Cardiol. 2006, 113, 86–91.

36. Mersmann, J.; Tran, N.; Zacharowski, P.A.; Grotemeyer, D.; Zacharowski, K. Rosiglitazone is cardioprotective in a murine model of myocardial I/R. Shock 2008, 30, 64–68.

37. Liu, H.-R.; Tao, L.; Gao, E.; Qu, Y.; Lau, W.B.; Lopez, B.L.; Christopher, T.A.; Koch, W.; Yue, T.-L.; Ma, X.-L. Rosiglitazone inhibits hypercholesterolaemia-induced myeloperoxidase upregulation—A novel mechanism for the cardioprotective effects of PPAR agonists. Cardiovasc. Res. 2008, 81, 344–352.

38. Cao, Z.; Ye, P.; Long, C.; Chen, K.; Li, X.; Wang, H. Effect of Pioglitazone, a Peroxisome Proliferator-Activated Receptor Gamma Agonist, on Ischemia-Reperfusion Injury in Rats. Pharmacology 2007, 79, 184–192.

39. Yasuda, S.; Kobayashi, H.; Iwasa, M.; Kawamura, I.; Sumi, S.; Narentuoya, B.; Yamaki, T.; Ushikoshi, H.; Nishigaki, K.; Nagashima, K.; et al. Antidiabetic drug pioglitazone protects the heart via activation of PPAR-γ receptors, PI3-kinase, Akt, and eNOS pathway in a rabbit model of myocardial infarction. Am. J. Physiol. Heart Circ. Physiol. 2009, 296, H1558–H1565.

40. Zhang, X.-J.; Xiong, Z.-B.; Tang, A.-L.; Ma, H.; Ma, Y.-D.; Wu, J.-G.; Dong, Y.-G. Rosiglitazone-induced myocardial protection against ischaemia-reperfusion injury is mediated via a phosphatidylinositol 3-kinase/Akt-dependent pathway. Clin. Exp. Pharmacol. Physiol. 2010, 37, 156–161.

41. Lv, F.-H.; Yin, H.-L.; He, Y.-Q.; Wu, H.-M.; Kong, J.; Chai, X.-Y.; Zhang, S.-R. Effects of curcumin on the apoptosis of cardiomyocytes and the expression of NF-κB, PPAR-γ and Bcl-2 in rats with myocardial infarction injury. Exp. Ther. Med. 2016, 12, 3877–3884.

42. El-Gohary, O.A.; Allam, M.M. Effect of vitamin D on isoprenaline-induced myocardial infarction in rats: Possible role of peroxisome proliferator-activated receptor-γ. Can. J. Physiol. Pharmacol. 2017, 95, 641–646.

43. Mahajan, U.B.; Chandrayan, G.; Patil, C.R.; Arya, D.S.; Suchal, K.; Agrawal, Y.O.; Ojha, S.; Goyal, S.N. The Protective Effect of Apigenin on Myocardial Injury in Diabetic Rats mediating Activation of the PPAR-γ Pathway. Int. J. Mol. Sci. 2017, 18, 756.

44. Shen, Z.; Jiang, H.; Bei, Y.; Zhang, J.; Zhang, H.; Zhu, H.; Zhang, C.; Yao, W.; Wei, C.; Shang, H.; et al. Qiliqiangxin Attenuates Adverse Cardiac Remodeling after Myocardial Infarction in Ovariectomized Mice via Activation of PPARγ. Cell. Physiol. Biochem. 2017, 42, 876–888.

45. Zhou, H.; Li, D.; Zhu, P.; Hu, S.; Hu, N.; Ma, S.; Zhang, Y.; Han, T.; Ren, J.; Cao, F.; et al. Melatonin suppresses platelet activation and function against cardiac ischemia/reperfusion injury via PPARγ/FUNDC1/mitophagy pathways. J. Pineal Res. 2017, 63, e12438.

46. Yang, M.; Xiong, J.; Zou, Q.; Wang, D.-D.; Huang, C. Chrysin attenuates interstitial fibrosis and improves cardiac function in a rat model of acute myocardial infarction. J. Mol. Histol. 2018, 49, 555–565.

47. Rani, N.; Arya, D.S. Chrysin rescues rat myocardium from ischemia-reperfusion injury via PPAR-γ/Nrf2 activation. Eur. J. Pharmacol. 2020, 883, 173389.

48. Garg, S.; Khan, S.I.; Malhotra, R.K.; Sharma, M.K.; Kumar, M.; Kaur, P.; Nag, T.C.; Ray, R.; Bhatia, J.; Arya, D.S. The molecular mechanism involved in cardioprotection by the dietary flavonoid fisetin as an agonist of PPAR-γ in a murine model of myocardial infarction. Arch. Biochem. Biophys. 2020, 694, 108572.

49. Meng, C.; Guo, Z.; Li, D.; Li, H.; He, J.; Wen, D.; Luo, B. Preventive effect of hesperidin modulates inflammatory responses and antioxidant status following acute myocardial infarction through the expression of PPAR-γ and Bcl-2 in model mice. Mol. Med. Rep. 2017, 17, 1261–1268.
50. Song, L.L.; Zhang, Y.; Zhang, X.R.; Song, Y.N.; Dai, H.Z. Theacrine attenuates myocardial fibrosis after myocardial infarction via the SIRT3/β-catenin/PPARγ pathway in estrogen-deficient mice. Eur Rev Med Pharmacol. Sci. 2019, 23, 5477–5486.
51. Shinmura, D.; Togashi, I.; Miyoshi, S.; Nishiyama, N.; Hida, N.; Tsuji, H.; Tsuruta, H.; Segawa, K.; Tsukada, Y.; Ogawa, S.; et al. Pretreatment of Human Mesenchymal Stem Cells with Pioglitazone Improved Efficiency of Cardiomyogenic Transdifferentiation and Cardiac Function. Stem Cells 2011, 29, 357–366.
52. Hou, J.; Wang, L.; Guo, T.; Xing, Y.; Zheng, S.; Zhou, C.; Huang, H.; Long, H.; Zhong, T.; Wu, Q.; et al. Peroxisome Proliferator-Activated Receptor Gamma Promotes Mesenchymal Stem Cells to Express Connexin43 via the Inhibition of TGF-β1/Smads Signaling in a Rat Model of Myocardial Infarction. Stem Cell Rev. Rep. 2015, 11, 885–899.
53. Kostic, I.; Fidalgo-Carvalho, I.; Aday, S.; Vazão, H.; Carvalheiro, T.; Grãos, M.; Duarte, A.; Cardoso, C.; Gonçalves, L.; Carvalho, L.; et al. Lysophosphatidic acid enhances survival of human CD34+ cells in ischemic conditions. Sci. Rep. 2015, 5, 16406.
54. Mori, D.; Miyagawa, S.; Matsuura, R.; Sougawa, N.; Fukushima, S.; Ueno, T.; Toda, K.; Kuratani, T.; Tomita, K.; Maeda, N.; et al. Pioglitazone strengthen therapeutic effect of adipose-derived regenerative cells against ischemic cardiomyopathy through enhanced expression of adiponectin and modulation of macrophage phenotype. Cardiovasc. Diabetol. 2019, 18, 39.
55. Shen, Z.-X.; Yang, Q.-Z.; Li, C.; Du, L.-J.; Sun, X.-N.; Liu, Y.; Sun, J.-Y.; Gu, H.-H.; Sun, Y.-M.; Wang, J.; et al. Myeloid peroxisome proliferator-activated receptor gamma deficiency aggravates myocardial infarction in mice. Atherosclerosis 2018, 274, 199–205.
56. Goyal, S.; Arora, S.; Mittal, R.; Joshi, S.; Nag, T.C.; Ray, R.; Kumari, S.; Arya, D.S. Myocardial salvaging effect of telmisartan in experimental model of myocardial infarction. Eur. J. Pharmacol. 2009, 619, 75–84.
57. Goyal, S.; Arora, S.; Bhatt, T.K.; Das, P.; Sharma, A.; Kumari, S.; Arya, D.S. Modulation of PPAR-γ by telmisartan protects the heart against myocardial infarction in experimental diabetes. Chem. Biol. Interact. 2010, 185, 271–280.
58. Maejima, Y.; Okada, H.; Haraguchi, G.; Onai, Y.; Kosuge, H.; Suzuki, J.-I.; Isobe, M. Telmisartan, a unique ARB, improves left ventricular remodeling of infarcted heart by activating PPAR gamma. Lab. Investig. 2011, 91, 932–944.
59. Tao, L.; Wang, Y.; Gao, E.; Zhang, H.; Yuan, Y.; Lau, W.B.; Chan, L.; Koch, W.J.; Ma, X.-L. Adiponectin: An indispensable molecule in rosiglitazone cardioprotection following myocardial infarction. Circ. Res. 2009, 106, 409–417.
60. Tokutome, M.; Matoba, T.; Nakano, Y.; Okahara, A.; Fujiwara, M.; Koga, J.-I.; Nakano, K.; Tsutsui, H.; Egashira, K. Peroxisome proliferator-activated receptor-gamma targeting nanomedicine promotes cardiac healing after acute myocardial infarction by skewing monocyte/macrophage polarization in preclinical animal models. Cardiovasc. Res. 2019, 115, 419–431.
61. Zhao, N.; Mi, L.; Zhang, X.; Xu, M.; Yu, H.; Liu, Z.; Liu, X.; Guan, G.; Gao, W.; Wang, J.; et al. Enhanced MiR-711 transcription by PPARγ induces endoplasmic reticulum stress-mediated apoptosis targeting calnexin in rat cardiomyocytes after myocardial infarction. J. Mol. Cell. Cardiol. 2018, 118, 36–45.
62. Chu, X.; Wang, Y.; Pang, L.; Huang, J.; Sun, X.; Chen, X. miR-130 aggravates acute myocardial infarction-induced myocardial injury by targeting PPAR-γ. J. Cell. Biochem. 2018, 119, 7235–7244.
63. Lincoff, A.M.; Tardif, J.-C.; Schwartz, G.G.; Nicholls, S.J.; Rydén, L.; Neal, B.; Malmberg, K.; Wedel, H.; Buse, J.B.; Henry, R.R.; et al. Effect of aleglitazar on cardiovascular outcomes after acute coronary syndrome in patients with type 2 diabetes mellitus: The AleCardio randomized clinical trial. JAMA 2014, 311, 1515–1525.
64. Ratner, R.E.; Parikh, S.; Tou, C. Efficacy, safety and tolerability of tesaglitazar when added to the therapeutic regimen of poorly controlled insulin-treated patients with type 2 diabetes. Diabetes Vasc. Dis. Res. 2007, 4, 214–221.
65. Nissen, S.E.; Wolski, K.; Topol, E.J. Effect of Muraglitazar on Death and Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes Mellitus. JAMA 2005, 294, 2581–2586.
66. Chen, X.-L.; Liu, Z.-R.; Xue, Y.-J.; Chen, X. Dual PPARα/γ ligand TZD18 improves myocardial metabolic remodeling after myocardial infarction in rats. Eur. Rev. Med Pharmacol. Sci. 2017, 21, 5765–5773.