An alternative approach to protecting the heart under ischaemic stress

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Formyl peptide receptors (FPR) are integral to inflammation regulation and are thus attractive therapeutic targets for myocardial ischaemia-reperfusion (I-R) injury. Dual FPR1/FPR2 agonists potentially offer FPR1-mediated cardiomyocyte preservation together with FPR2 inflammation-limiting actions. We investigated the cardioprotective potential of two small-molecule FPR agonists on myocardial I-R injury *in vivo* and their FPR1/FPR2 signalling fingerprints *in vitro.* Mice subjected to coronary artery occlusion were administered the pyridazin-3-(2H)-one compound-17b (Cmpd17b), Amgen compound-43 (Cmpd43) or vehicle commencing just prior to reperfusion. Significant cardioprotective effects of Cmpd17b (but not Cmpd43) were evident on cardiac necrosis (infarct size and cardiac troponin I after 24h), circulating leukocytes and neutrophil infiltration (after 48h) and adverse cardiac remodelling (after 7-days reperfusion); Cmpd17b similarly exhibited superior cardioprotection in isolated cardiomyocytes and cardiac fibroblasts *in vitro.* Both agonists elicited concentration-dependent activation of multiple intracellular signaling pathways, including Ca^{2+} mobilization and phosphorylation of ERK1/2, Akt1/2/3(Thr308) and Akt1/2/3(Ser474). Statistical evaluation of the signal transduction established that, relative to Cmpd43, Cmpd17b exhibited a significant 30-fold bias away from intracellular Ca^{2+} mobilization. These findings reveal ligand-selective cardioprotection with the dual FPR1/FPR2 agonist Cmpd17b both *in vitro* and *in vivo*, with significant limitation of cardiac necrosis, inflammation and remodelling up to 7-days post-I-R. The biased signalling profile of Cmpd17b is a possible contributing mechanism to its superior cardioprotection, providing a new approach for development of small-molecule FPR pharmacotherapies for myocardial infarction.