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EDITORIAL

Targeting inflammation to reduce cardiovascular disease risk

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This joint themed issue of the British Journal of Pharmacology and the British Journal of Clinical Pharmacology stems from a joint British Pharmacological Society - Italian Society of Pharmacology symposium held at the 37th National Congress of the Italian Society of Pharmacology in Naples (Italy) from 27 to 30 October 2015.

LINKED ARTICLES

This article is part of a themed section on Targeting inflammation to reduce cardiovascular disease risk

Abbreviations

apoE<sup>−/−</sup>, apolipoprotein-E deficient mice; AT, adipose tissue; ATL, aspirin-triggered lipoxin A4; CANTOS, Canakinumab Anti-inflammatory Thrombosis Outcomes Study; COX, cyclooxygenase; CVD, cardiovascular diseases; DPP4, dipeptidyl peptidase 4; H<sub>2</sub>S, hydrogen sulphide; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; mPGES-1, microsomal prostaglandin E synthase-1; NO, nitric oxide; NK, natural
killer; PAR2, proteinase-activated receptor 2, PG, prostaglandin; PVAT, perivascular adipose tissue; tNSAIDs, traditional nonsteroidal anti-inflammatory drugs; Tsk mice, tight-skin mice.
Cardiovascular diseases (CVD) are the major cause of morbidity and mortality in Western society and are expected to be the main cause of death globally in the near future (WHO, 2011). Basic research data strongly support a pivotal role played by inflammatory and immune mechanisms in CVD and studies in animal models have shown that specific immune-inflammatory pathways could be targeted for therapeutic utility. However, the translation of this knowledge to humans is still in the early stages (Welsh et al., 2017).

New and selective immune therapies are already in use for the treatment of autoimmune diseases and large clinical trials have just been published or are currently evaluating the effect of several of these treatments on atherosclerosis and related pathologies. The outcome of these studies is likely to lead to new approaches in the management of vascular inflammation.

This joint British Journal of Pharmacology and British Journal of Clinical Pharmacology themed issue assembles scientists that study cardiovascular inflammation over a broad range of topics. The aim is to provide an up-to-date overview of the current understanding of inflammatory and immune mechanisms in CVD, to summarise the current clinical picture regarding the use of anti-inflammatory drugs in cardiovascular medicine and to discuss future directions towards more specific immune therapies.

The themed issue is introduced by Paul Welsh et al. (Welsh et al., 2017). The authors provide an overview of the key therapeutic targets in the treatment of vascular inflammation, placing basic research in a wider clinical perspective. Following the publication of the review article, data from the Phase III Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS: https://clinicaltrials.gov/ct2/show/NCT01327846) have been published, showing that canakinumab - a monoclonal antibody against IL-1β - in combination with standard therapy reduces recurrent cardiovascular events in people with a prior myocardial infarction and high levels of circulating C-reactive protein (Ridker et al., 2017). This is the first demonstration in a large, randomized, double blind, placebo-controlled Phase III study that using anti-cytokine-based therapies may be a viable approach for secondary prevention of atherosclerosis-related CVD. This is particularly relevant given that the use of traditional nonsteroidal anti-inflammatory drugs (tNSAIDs) and coxibs alike is limited by cardiovascular toxicity as comprehensively discussed by Carlo Patrono (Patrono, 2016). He provides an overview of the cardiovascular effects of cyclooxygenase (COX)-2 inhibitors, with a focus on the mechanisms contributing to the clinical readouts of COX-2 inhibition.
Several other key immune-mediated mechanisms in CVD could represent future options for therapeutic targeting and are discussed in detail in the current issue. T cell-mediated immune responses play a key role in ischaemic heart disease and in acute viral myocarditis (Stephenson et al., 2016). The authors propose that the development of novel specific diagnostic biomarkers could help to identify at an early stage patients who may benefit from immunomodulatory therapies. Andy Sage and Ziad Mallat (Sage and Mallat, 2017) discuss therapeutic strategies to target adaptive immunity to reduce atherosclerosis progression, such as regulatory T cell enhancing therapies, B cell depletion and vaccine-based approaches. Their work is complemented by the review from Amanda Foks and Johan Kuiper, where the authors discuss the therapeutic potential to control atherosclerosis through targeting a large variety of costimulatory and inhibitory immune checkpoint proteins (Foks and Kuiper, 2017). In addition, the role of cytotoxic lymphocytes such as natural killer cells, CD8+ T cells, natural killer (NK) T cells, γδ-T cells and human CD4+CD28− T cells in the development of atherosclerosis and unstable atheromas is reviewed (Kyaw et al., 2017).

Inflammation and hypercholesterolemia are linked in a cycle where an excess of cholesterol accumulating in the vessel wall layers induces immune-inflammatory response(s), which in turn increase cholesterol deposition and accelerate pathology formation and development. Catapano et al. provide an overview of the crosstalk between inflammation and lipid metabolism, suggesting that the clinical impact of lipid-lowering drugs on inflammation is proportional to the reduction of low-density lipoprotein cholesterol (LDL-C) levels (Catapano et al., 2017). Concurrently, Iqbal et al. discuss the negative impact of systemic and vascular inflammation on the healthy metabolism and function of high-density lipoprotein cholesterol (HDL-C) (Iqbal et al., 2017).

The contribution of perivascular adipose tissue (PVAT) to vascular inflammation has gained significant attention recently. Adipocytes, immune cells and fibroblasts within adipose tissue secrete a broad range of adipokines exerting endocrine or paracrine effects on the cardiovascular system. Among them, the role of adiponectin in cardiovascular pathogenesis, its capacity to regulate the crosstalk between adipose tissue and the cardiovascular system and its role as a biomarker in CVD are comprehensively discussed (Woodward et al., 2016).

In the final review article, Cirino et al. discuss the role of gasotransmitters in vascular physiology and pathology (Cirino et al., 2017). The authors summarize what is currently known on the interconnection between nitric oxide (NO) and hydrogen sulfide (H2S),
pointing out that addressing the molecular mechanisms underlying the interaction of these two gas mediators may lead to the development of new therapeutic approaches.

The themed issue ends with five original research contributions. The work by Roviezzo et al. analyses the effect of proteinase-activated receptor 2 (PAR2) on aortic contraction in fibrotic tight-skin (Tsk) mice (Roviezzo et al., 2017). Petri et al. investigated the effect of aspirin-triggered lipoxin A4 (ATL) and its receptor Fpr2 on atherosclerosis development and progression, showing anti-atherogenic effects of ATL in apolipoprotein-E (apoE) mice (Petri et al., 2017). The selective Mas receptor agonist AVE0991 was shown to exert anti-atherosclerotic effects by affecting monocyte/macrophage recruitment to the perivascular space in experimental atherosclerosis (Skiba et al., 2016). Esposito et al. demonstrated that the dipeptidyl peptidase 4 (DPP4) inhibitor sitagliptin preserved diastolic function in a rat model of heart failure with preserved ejection (Esposito et al., 2016). Finally, the effect of inhibitors of COX-2 and microsomal prostaglandin E synthase-1 (mPGES-1) enzyme, which catalyses the formation of PGE2 from COX-derived PGH2, was compared in vitro on human vascular tone (Ozen et al., 2017).

In summary, this joint themed issue of British Journal of Pharmacology and British Journal of Clinical Pharmacology will provide readers with a review of the key inflammatory and immune mechanisms in cardiovascular pathologies, the role of lipid and gas mediators in cardiovascular inflammation and the use of conventional anti-inflammatory drugs in cardiovascular medicine. In addition, the interplay between vascular inflammation and lipid metabolism, together with recent clinical trials targeting immune pathways for CVD prevention are comprehensively discussed. Great advances have been made in our understanding of immune mechanisms underlying CVD. Translation of these findings in clinical practice has only just begun; however, promising recent results may pave the way for the design of novel tissue- and or disease-specific immunomodulatory approaches to tackle the challenge posed by CVD on public health.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan et al., 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (Alexander et al., 2015).
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Conflict of Interest

The authors wish to acknowledge that they are co-authors of the articles by Welsh et al. (2017), Cirino et al. (2017) and Roviezzo et al. (2016) in this issue. They have also co-authored papers with Andrew Sage, Ziad Mallat, Liberato Berrino, Francesco Rossi, Antonella De Angelis and Konrad Urbanek.
References


