Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal

Journal of Clinical and Basic Cardiology 2010; 13 (1-4), 2-3

Letter to the Editor

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Indexed in
Chemical Abstracts
EMBASE/Excerpta Medica

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz/Austria

Letter to the Editor

Inflammation as a Therapeutic Target of Betablockers in Ischemic Heart Disease

To the editors:

Experimental evidence suggests a crucial role of inflammation in the pathophysiology of atherosclerosis and acute myocardial infarction.

In myocardial ischemia, a pleiotropic proinflammatory imbalance with damaging effects in terms of left ventricular performance and patient outcome is the result of uncontrolled immune response. Cardiac injury activates specific immune mechanisms initiating an inflammatory reaction. Immunological receptor-mediated pathways, the complement cascade, and reactive oxygen generation induce nuclear factor (NF) kappa B activation and up-regulation of chemokine and cytokine syntheses are just some of them. In the infarcted tissue, chemokines stimulate the chemotactic attraction of inflammatory leukocytes into infarcted areas, while cytokines promote adhesion between leukocytes and endothelial cells. The latter elicit invasion of inflammatory cells into the site of injury and thus promote cell damage.

The complexity of the inflammatory cascade involved in the development of atherosclerosis makes it difficult to develop single-target drugs in order to slow down or affect the process. Drug developers have always been in search for new indications and atherosclerosis has been a target since [1]. Just very recently, it has been shown that inflammation *per se* could be an attractive target for pharmacological intervention in primary prevention. The JUPITER trial has directly addressed this problem: in apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, a statin significantly reduced the incidence of major cardiovascular events by unfolding pleiotropic anti-inflammatory actions [2, 3]. Experimental and clinical evidence suggests that hypoxic/ischemic damage induces angiogenesis within a very short time.

The severity of tissue damage is reflected in the extent of angio-neogenesis and inflammation/repair brought about at the ischemic site of the myocardial tissue.

Reduced ischemic damage would lead to reduced angiogenesis and inflammation.

It is generally accepted that not protection of endothelial function alone, but a plethora of anti-inflammatory and antiproliferative actions is brought about by various drugs effective in primary and secondary prevention [4]. More modern techniques such as microarray expression profiling have revealed a very complex molecular action of specific drugs. Even within the same class of drugs, the effect upon gene expression profiles varies markedly. We may illustrate the point by a brief look at the effect of betablockers upon inflammatory mechanisms. Several leukocyte-derived enzyme systems are responsible for the release of oxidizing agents into the myocardium after ischemic injury and provide a means of better preventing ischemic damage. For example, one such key leukocyte-derived marker, myeloperoxidase (MPO), correlates with outcomes [5]. Recent experimental evidence suggests a crucial role of T-lymphocytes in the pathophysiology of atherosclerosis and acute coronary syndromes. It has been indicated that a pro-inflammatory imbalance resulting from T-cell activation could be responsible for activating the inflammatory cascade ultimately responsible for cellular injury, left ventricular dysfunction, remodelling, and outcome [6]. For example, differential effects on T-cell immunity are seen between different betablockers: nebivolol, but not atenolol, inhibits the expression of T-cell immunity-related genes during experimental hypoxia [7]. Certain betablockers also reduced the expression of pro-inflammatory genes in endothelial cells and vascular smooth muscle cells in vitro, whereas others did not. In vivo, betablockers inhibited neointima formation by reducing SMC proliferation and macrophage accumulation [8]. Cellular injury that results from irreversible ischemia leads to left ventricular remodeling. Oxidative stress and inflammation are key elements of this process; elevation of markers of inflammation at the time of myocardial infarction is a predictor of the development of ischemic myopathy and of adverse clinical outcomes.

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Proteins of the matrix metalloproteinase (MMP) family are normally involved in the turnover of extracellular matrix, e. g., during reproduction, embryonic development, and tissue remodeling. MMPs show a wide field of action also in disease processes, in particular during cardiac hypertrophy and ischemia. MMPs are also targeted by statins in cardiovascular primary and secondary prevention. A recent paper supplies direct experimental evidence that metoprolol reduces inflammation in vulnerable plaques [9]. However, a more complex, likely favourable regulation has also been seen in several aspects of early inflammatory response: neuroendocrine/inflammatory and endothelial functions have been indicated as crucial not only in the development of atherosclerosis [5] but also for heart failure (HF) patients.

The effect of carvedilol on cytokines and asymmetric dimethylarginine (ADMA) and left ventricular ejection fraction (LVEF) at baseline and after long-term administration of carvedilol has been studied and carvedilol reduced symptoms as well as parameters of inflammation, regardless of the left ventricular functional response [10]. Carvedilol has also been shown to attenuate inflammation, oxidative response, myocardial fibrosis, and apoptosis, as well as in preserving energy transcription factors and LV function in DCM [11]. It is often cardiac injury itself which propagates immune mechanisms leading to an inflammatory reaction [12]: on the one hand, immunological receptor-mediated pathways and the complement cascade lead to activation of nuclear factor (NF) kappa B and increase chemokine and cytokine syntheses in the ischemic tissue, thus attracting inflammatory leukocytes into the ischemic area. On the other hand, cytokines promote adhesive interactions between leukocytes and the endothelial layer enabling transmigration of inflammatory cells into the site of injury. Inflammatory cytokines stimulate apoptosis through a TNF-α receptor/caspase pathway [13]. Inflammatory mechanisms thus play a role in both the development of atherosclerosis and the effect on coronary artery disease.

In summary, there is a complex relationship between α-adrenergic blockade, sympathetic activity, and inflammation [14]. The next decade will certainly be marked by the investigation of pleiotropic drug effects upon inflammatory processes searching for further and more specific applications of drugs in primary prevention.

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