Prostacyclin in the cardiovascular system: new aspects and open questions

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Abstract:
Several indications exist that prostacyclin (PGI₂) release in the cardiovascular system might be affected by cyclooxygenase (COX)-2-specific inhibitors. This could reflect an inhibition of PGI₂ synthesis in the endothelium although in these cells mainly COX-1 is expressed. Inflammation and stress induce COX-2 in smooth muscle cells which could have happened in patients with cardiac diseases. Herein, we show that also cardiomyocytes contain PGI₂ synthase in intercalated discs as a third source of PGI₂ in the cardiovascular system. Another aim of this study was to explain the finding that PGI₂ synthase in lipopolysaccharide (LPS)-treated smooth muscle cells, in contrast to endothelial cells, is resistant to nitration and inhibition by peroxynitrite. By using redox cyclers, the nitration occurred and confirmed our previous hypothesis that a high peroxidative activity of such cells keeps peroxynitrite below the effective levels of 50 nM. Considering enhanced oxidative stress in aged vessels, we postulated and verified that endothelial dysfunction in aged vessels is due to nitration and inhibition of PGI₂ synthase. Such data underline the role of PGI₂ as a potent mediator for regaining and maintaining the normal resting state of cells in a COX-2 dependent fashion.

Key words: prostacyclin synthase, nitration, nitric oxide, peroxynitrite, cyclooxygenase, endothelium, smooth muscle, cardiomyocyte

Introduction

It has been a paradigm in vascular physiology that prostacyclin (PGI₂) is released from the endothelium by the consecutive action of phospholipase A₂, the constitutive cyclooxygenase-1 (COX-1) and PGI₂ synthase [11]. On the other hand, the inducible COX-2 was considered to provide prostaglandin endoperoxide (PGH₂) for PGI₂ biosynthesis only under stress conditions [4]. Therefore, the findings that the newly developed COX-2 inhibitors can affect PGI₂ formation under normal conditions asked for a reinvestigation of the sources and the regulation of PGI₂ release.

A first result in that direction was the old observation of a localization of PGI₂ synthase not only in the vascular endothelium but also in smooth muscle [6]. However, the levels of COX-1 or COX-2 in resting smooth muscle cells (SMC) are low, but considering the large mass of PGI₂ synthase, it might be anticipated that PGI₂ could also be derived from SMC. This would be favored under inflammatory or stress conditions that would upregulate COX-2. Since adverse reactions of COX-2 inhibitors have been noticed in patients with cardiac problems [9], an endogenous coun-