



Review

Prostacyclin among prostanoids

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Abstract:

Prostanoids are cyclic lipid mediators which arise from enzymic cyclooxygenation of linear polyunsaturated fatty acids, e.g. arachidonic acid (20:4 n 6, AA). Biologically active prostanoids deriving from AA include stable prostaglandins (PGs), e.g. PGE₂, PGF_{2α}, PGD₂, PGJ₂ as well as labile prostanoids, i.e. PG endoperoxides (PGG₂, PGH₂), thromboxane A₂ (TXA₂) and prostacyclin (PGI₂). A “Rabbit aorta Contracting Substance” (RCS) played important role in discovering of labile PGs. RCS was discovered in the Vane’s Cascade as a labile product released along with PGs from the activated lung or spleen. RCS was identified as a mixture of PG endoperoxides and thromboxane A₂. Stable PGs regulate the cell cycle, smooth muscle tone and various secretory functions; they also modulate inflammatory and immune reactions. PG endoperoxides are intermediates in biosynthesis of all prostanoids. Thromboxane A₂ (TXA₂) is the most labile prostanoid (with a half life of 30 s at 37°C). It is generated mainly by blood platelets. TXA₂ is endowed with powerful vasoconstrictor, cytotoxic and thrombogenic properties. Again the Vane’s Cascade was behind the discovery of prostacyclin (PGI₂) with a half life of 4 min at 37°C. It is produced by the vascular wall (predominantly by the endothelium) and it acts as a physiological antagonist of TXA₂. Moreover, prostacyclin *per se* is a powerful cytoprotective agent that exerts its action through activation of adenylate cyclase, followed by an intracellular accumulation of cyclic-AMP in various types of cells. In that respect PGI₂ collaborates with the system consisting of NO synthase (eNOS)/nitric oxide free radical (NO)/guanylate cyclase/cyclic-GMP. Both cyclic nucleotides (c-AMP and c-GMP) act in synergy as two energetic fists which defend the cellular machinery from being destroyed by endogenous or exogenous aggressors. Recently, a new partner has been recognized in this endogenous defensive squadron, i.e. a system consisting of heme oxygenase (HO-1)/carbon monoxide (CO)/biliverdin/biliverdin reductase/bilirubin.

The expanding knowledge on the pharmacological steering of this enzymic triad (PGI₂-S/eNOS/HO-1) is likely to contribute to the rational therapy of many systemic diseases such as atherosclerosis, diabetes mellitus, arterial hypertension or Alzheimer disease. The discovery of prostacyclin broadened our pathophysiological horizon, and by itself opened new therapeutic possibilities. Prostacyclin sodium salt and its synthetic stable analogues (iloprost, beraprost, treprostinil, epoprostenol, cicaprost) are useful drugs for the treatment of the advanced critical limb ischemia, e.g. in the course of Buerger’s disease, and also for the treatment of pulmonary artery hypertension (PAH). In this last case a synergism between prostacyclin analogues and sildenafil (a selective phosphodiesterase 5 inhibitor) or bosentan (an endothelin ET-1 receptor antagonist) points out to complex mechanisms controlling pulmonary circulation. At the Jagiellonian University we have demonstrated that several well recognised cardiovascular drugs, e.g. ACE inhibitors (ACE-I), statins, some of β-adrenergic receptor antagonists, e.g. carvedilol or nebivolol, anti-platelet thienopyridines (ticlopidine, clopidogrel) and a metabolite of vitamin PP – N¹-methyl-nicotinamide – all of them are endowed with the *in vivo* PGI₂-releasing properties. In this way, the foundations for the Endothelial Pharmacology were laid.

Key words:

Vane Bioassay Cascade, RCS (Rabbit aorta Contacting Substance), prostacyclin, thromboxane, prostaglandins, prostaglandin endoperoxides, arachidonic acid, eicosanoids, critical limb ischemia, pulmonary artery hypertension, atherosclerosis, diabetes mellitus, angiopathies, the endothelial pharmacology