Prostanoids in Cardiovascular Health and Disease

Miao Wang*

Pfizer Worldwide Research and Development, Cardiovascular and Metabolic Diseases Research Unit, Pfizer Inc, USA

Prostanoids, including Prostaglandins (PG) and thromboxane, are small lipid molecules produced from Cyclooxygenase (COX)–mediated metabolism of Arachidonic Acid (AA), a polyunsaturated omega-6 fatty acid 20:4 (ω-6) released from membrane phospholipids [1]. Aspirin and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) suppress formation of prostanoids and are widely used anti-inflammatory agents. Produced by virtually all cells of the body, prostanoids exhibit their biological function in manner of both autocrine and paracrine. Prostanoids play an important role in maintaining cardiovascular homeostasis, including blood fluidity, vascular tone, blood pressure, and inflammation. Recent research reveals new roles of prostanoids, novel mechanisms of action, and therapeutic opportunities of targeting prostanoids, yet many issues remain to be clarified.

Pharmacology study of aspirin and NSAIDs calls for a systemic evaluation of the cardiovascular function of individual prostanoids. Aspirin reduces the risk of myocardial infarction and thrombotic stroke [2,3], and this is attributed to inhibition of platelet COX1 derived thromboxane, a potent platelet activator. On the other hand, clinical trial studies consistently show an increased risk of myocardial infarction and stroke in patients taking COX-2 selective inhibitors [4-6]. Diverse lines of evidence indicate that this is attributable to suppression of COX-2-derived prostacyclin (PGI1) [7,8], which is a platelet activation inhibitor and protects endothelium. Indeed, meta-analysis suggests an increased cardiovascular hazard may exist for other NSAIDs [9]. The actual mechanism underlying the cardiovascular risk appears to be not fully explainable with changes only in thromboxane and prostacyclin. The net cardiovascular outcome of NSAIDs may depend on (1) what prostanoids are affected, (2) cardiovascular function of individual prostanoids, (3) specificity and duration of drug action, (4) drug-drug interaction, and (5) cardiovascular health status/disease stage in subjects. Many questions surrounding these aspects are yet to be answered. An ongoing clinical trial (PRECISION) is designed to compare cardiovascular risk of Celecoxib, a COX-2 selective inhibitor, with traditional NSAIDs (COX1&2 non-selective) [10].

Prostanoid function is mainly mediated by its receptor(s) [11] and the receptor expression profile often dictates the responses of a particular cell population. Vascular cells differ in their profile in prostanoid production and may respond differentially to inflammatory stimulation [12]. Delineation of tissue/cell-specific function of prostanoids is particularly important, since dominant cells involved in cardiovascular disease development/regression may differ over time [12,13].

Interest in therapeutic discovery has shifted to downstream prostanoid biosynthetic/responding components. In contrast to the suppressed production of PGI by COX-2 inhibition, blocking microsomal PGE synthase-1 augments PGI formation, minimizes thrombotic risk [7], and may represent a potential drug target for treating vascular restenosis [14] and other inflammatory condition [15]. Beyond its inhibitory effect on platelet, PGI analogue has been utilized in treating pulmonary hypertension, and may have utility in cardiomyocyte regeneration [16].

Elucidation of the function of prostanoids in cardiovascular system is fundamental to understanding disease pathogenesis, drug efficacy and toxicity, and may lead to optimized or personalized drug application, as well as discovery of new therapeutics.

References

10. Prospective Randomized Evaluation Of Celecoxib Integrated Safety Vs Ibuprofen Or Naproxen (PRECISION).

*Corresponding author: Miao Wang, Pfizer Worldwide Research and Development, Cardiovascular and Metabolic Diseases Research Unit, Pfizer Inc. 620 Memorial Drive, Cambridge, MA 02139 E-mail: wangmiao9@gmail.com
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