Can COX-2 Inhibitor-induced Increase in Cardiovascular Disease Risk Be Modified by Essential Fatty Acids?

UN Das

Abstract
Selective COX-2 inhibitors increase the risk of myocardial infarction and stroke. This has been attributed to their ability to inhibit endothelial COX-2 derived prostacyclin (PGI2) but not platelet COX-1 derived thromboxane A2 (TXA2). On the other hand, aspirin blocks both COX-1 and COX-2 enzymes without decreasing PGI2 but blocks TXA2 synthesis that explains its beneficial action in the prevention of coronary heart disease (CHD). The inhibitory action of aspirin on COX-1 and COX-2 enzymes enhances the tissue concentrations of dihomo-gamma-linolenic acid (DGLA), arachidonic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). These fatty acids form precursors to PGE1, PGI2, PGI3, lipoxins (LXs), and resolvins that have anti-inflammatory actions. In contrast, increase in the concentrations of DGLA, AA, EPA, and DHA is much less with specific COX-2 inhibitors since they do not block the formation of eicosanoids through COX-1 pathway. COX-2 inhibitors interfere with the formation of LXs and resolvins that have neuroprotective and cardioprotective actions. EPA and PGI2 have anti-arrhythmic action. EPA, DHA, and AA augment eNO formation that prevents atherosclerosis. This suggests that COX-2 inhibitors increase cardiovascular and stroke risk by interfering with the formation of eNO, PGI2, LXs, and resolvins and implies that combining EFAs with COX-2 inhibitors could prevent these complications.

INTRODUCTION
Cyclo-oxygenase-2 (COX-2) inhibitors increase the risk of coronary heart disease (CHD) and stroke compared to non-selective non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin. COX-2 inhibitors specifically block the formation of endothelial prostacyclin (PGI2) without affecting COX-1-mediated formation of thromboxane A2 (TXA2) by platelets. This has been offered as the explanation for the increased incidence of thrombotic cardiovascular events due to COX-2 inhibitors. But it is possible that COX-2 inhibitors may have actions, which are not well appreciated, that are not shown by NSAIDs that could be responsible for their side effects. For instance, aspirin enhances the formation of very useful and anti-inflammatory compounds such as lipoxins (LXs) and resolvins, which are derived from arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid. Both LXs and resolvins have potent anti-inflammatory and cardioprotective and neuroprotective actions. Thus, COX-2 inhibitors may actually induce an imbalance between various eicosanoids that ultimately enhances the progression of atherosclerosis and thrombotic events resulting in increased incidence of cardiovascular events due to their use.

Metabolism of essential fatty acids
Dietary cis-linoleic acid (LA, 18:2 w-6) and a-linolenic acid (ALA, 18:3 w-3) are essential nutrients and hence are called as “essential fatty acids” (EFAs). LA is converted to gamma-linolenic acid (GLA, 18:3, w-6) by the action of the enzyme D6 desaturase, and GLA is elongated to form di-homo-GLA (DGLA, 20:3, w-6), the precursor of the 1 series of prostaglandins. D6 desaturase is the rate-limiting step in the metabolism of EFAs. DGLA can be converted to arachidonic acid (AA, 20:4, w-6)) by the enzyme D5 desaturase. AA forms the precursor of 2 series of prostaglandins (PGs), thromboxanes (TXs) and the 4 series leukotrienes (LTs). ALA is converted to eicosapentaenoic acid (EPA, 20:5, w-3) by D6 and D5 desaturases. EPA forms the precursor of the 3 series of PGs and the 5 series of LTs. EPA can be elongated to form docosahexaenoic acid (DHA, 22:6, w-3). AA, EPA and DHA form precursors to a group of novel compounds called as lipoxins (LXs) and resolvins that have been shown to have anti-inflammatory action.
Actions of aspirin and COX-2 inhibitors on EFAs and eicosanoids

Aspirin has a weak inhibitory action on the activity of the enzymes \( \Delta^6 \) and \( \Delta^5 \) desaturases\(^8,9\) (\(\Delta^6 > \Delta^5\) desaturase) and potent suppressive action on COX-1 and COX-2 enzymes. Hence, aspirin enhances the cellular content of DGLA, AA, EPA, and DHA (Fig. 1). On the other hand, increase in the intracellular concentrations of DGLA, AA, EPA, and DHA will be much less with specific COX-2 inhibitors since they do not block the formation of eicosanoids through COX-1 pathway.

DGLA, AA, and EPA form precursors to PGE\(_1\), prostacyclin (PGI\(_2\)), and PGI\(_3\), respectively, which are potent vasodilators and platelet anti-aggregators. Hence, increase in the concentrations of DGLA, AA, and EPA due to aspirin use is expected to lower the risk of cardiovascular disease.\(^10\) Further, EPA, DHA, AA, and PGI\(_2\) have anti-arrhythmic action and thus, prevent ischemia-induced ventricular fibrillation and sudden cardiac death.\(^10-14\) Low-grade systemic inflammation is known to occur in CHD as evidenced by increased circulating levels of interleukin-6 (IL-6), tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), and C-reactive protein (CRP).\(^15-18\) DGLA, EPA, DHA, and PGE\(_1\), inhibit TNF-\(\alpha\) and IL-6 production\(^19,20\), suggesting that when adequate concentrations of DGLA, EPA, and DHA are present the production of IL-6 and TNF-\(\alpha\) will be low.

Endothelial cells produce IL-6 and TNF-\(\alpha\) and are the source of these cytokines in subjects with insulin resistance.\(^21\) Insulin resistance and endothelial dysfunction is common in patients with CHD. IL-6 and TNF-\(\alpha\) stimulate free radical generation, especially superoxide anion (O\(_2^-\)) that inactivates endothelial NO (eNO). AA, EPA, and DHA augment eNO generation.\(^9,10,22\) Thus, presence of adequate concentrations of DGLA, AA, EPA, and DHA in endothelial cells will prevent endothelial dysfunction by suppressing IL-6 and TNF-\(\alpha\), and consequent superoxide anion generation and helps maintain NO production. In addition, adequate amounts of DGLA, AA, and EPA in endothelial cells will lead to the formation of significant amounts of PGE\(_1\), PGI\(_2\), and PGI\(_3\), that prevents atherosclerosis and thrombosis.

Aspirin decreases the formation of platelet TXA\(_2\) and TXA\(_3\) from AA and EPA. This tilts the balance between endothelial PGI\(_2\)/PGI\(_3\) and platelet TXA\(_2\)/TXA\(_3\), more in favour of the former that prevents atherosclerosis and thrombosis. This explains the beneficial actions of aspirin in CHD. In contrast, selective COX-2 inhibitors block the formation of PGI\(_2\) without affecting the COX-1 mediated generation of TXA\(_2\) by platelets.\(^4\) This leads to increased tendency for thrombosis and atherosclerosis. This is one of the reasons for the increased incidence of thrombotic cardiovascular diseases seen with COX-2 inhibitors. This is supported by the observation that COX-2 derived PGI\(_2\) confers protection against the development of atherosclerosis.\(^23\) But, it is also possible that there could be other reasons as to why aspirin is beneficial and COX-2 inhibitors enhance the incidence of CHD as discussed below.

Aspirin-triggered 15 epimer LXs (ATLs) and resolvins

AA not only forms precursor to pro-inflammatory compounds such as TXs and LTs and beneficial PGI\(_2\) but also gives rise to LXs. In the presence of aspirin, AA, EPA and DHA are converted to form aspirin-triggered 15 epimer LXs (ATLs) that are potent counter regulators of polymorphonuclear neutrophils (PMNs)-mediated injury and acute inflammation.\(^24,25\) Aspirin acetylates COX-2 enzyme and prevents the formation of prostanoids. Despite this, the acetylated enzyme remains active \textit{in situ} to generate 15R-hydroxyeicosatetraenoic acid (15R-HETE) from AA that is released and converted by activated inflammatory cells such as PMNs to the 15-epimeric LXs. These LXs have potent anti-inflammatory properties.\(^26,27\) This cross-talk between endothelial cells and PMNs leading to the formation of 15R-HETE and its subsequent conversion to 15-epimeric LXs by aspirin-acetylated COX-2 is a protective mechanism to prevent local inflammation on the vessel wall by regulating the motility of PMNs, eosinophils, and monocytes.\(^28,29\) Furthermore, endothelial cells oxidize AA (and possibly EPA and DHA) via P450 enzyme system to form 11,12-epoxy-eicosatetraenoic acid(s) that blocks endothelial cell activation, while non-enzymatic oxidation products of EPA (and possibly AA and DHA) inhibit phagocyte-endothelium interaction and suppress the expression of...
adhesion molecules.29 These evidences suggest that COX-2 inhibitors inhibit the formation of these novel and highly beneficial LXs (Fig. 1). In the absence of these useful LXs, interaction between PMN-endothelial cells occurs leading to endothelial damage. As a result, endothelial damage, atherosclerosis, thrombus formation and CHD will occur.

Now it is known that beneficial 15R-HETE and 15-epimeric LXs are formed not only from AA but that EPA and DHA also form precursor to similar compounds. Human endothelial cells when treated with IL-1b (that stimulates COX-2 enzyme) and EPA, in the presence of aspirin, converted EPA to 18R-HEPE, 18-HEPE, and 15R-HEPE. Similar to the ability of PMNs to convert aspirin triggered, COX-2 derived 15R-HETE to 15-epi-LXA$_3$, and EPA to 5-series LXs, activated human PMNs converted 18R-HEPE to 5,12,18R-triHEPE and 15R-HEPE to 15-epi-LXA$_3$, by their 5-lipoxygenase. 18R-HEPE and 5,12,18R-triHEPE inhibited LTB$_4$-stimulated PMN transendothelial migration similar to 15-epiLXA$_3$. 18R-HEPE and 5,12,18R-triHEPE effectively competed with LTB$_4$ for its receptors and inhibited PMN infiltration.29

Murine brain cells expressing COX-2, when treated with aspirin, transformed enzymatically DHA to 17R series of hydroxy DHAs (HDHAs) that, in turn, are converted enzymatically by PMNs to di- and tri-hydroxy containing docosanoids.7 It is noteworthy that similar small molecular weight compounds (similar to HDHAs) are generated from AA and EPA. Thus, 15R-hydroxy containing compounds are formed from AA, 18R series from EPA, and 17R-hydroxy series from DHA (Fig. 1). These compounds have potent anti-inflammatory actions, resolve the inflammatory process and hence are called as “resolvins”(Rvs).

Resolvins inhibited cytokine generation, leukocyte recruitment, leukocyte diapedesis, and exudate formation. AA, EPA, and DHA-derived resolvins from acetylated COX-2 are formed via transcellular biosynthesis (eg, due to cell-cell communication between endothelial cells and PMNs) and are potent suppressors of inflammation. Resolvins inhibited brain ischemia-perfusion injury.30 Hence, it is suggested that lipoxins (LXs) and resolvins formed from EPA and DHA are responsible for the cardioprotective actions seen with EPA and DHA.

**Why COX-2 inhibitors enhance the risk of CHD?**

It is evident from the preceding discussion that COX-2 enzyme is not only essential for the initiation and perpetuation of inflammation, but also for the generation of anti-inflammatory compounds LXs and resolvins. This implies that inappropriate suppression of COX-2 activity for prolonged periods may lead to unanticipated side effects including an increase in the risk of CHD and stroke.

LXs and resolvins inhibit the generation of pro-inflammatory cytokines TNF-a and IL-6 and inhibit leukocyte recruitment. Hence, when the concentrations of LXs and resolvins are low in a given tissue, it will lead to an increase in the adherence of macrophages and PMNs to endothelial cells. Adherent macrophages and PMNs release free radicals that cause injury to the endothelium. This, in turn, initiates and perpetuates atherosclerosis and endothelial dysfunction. Since endothelial dysfunction is common in hypertension, type 2 diabetes mellitus, hyperlipidemias, and coronary heart disease,31,32 it is likely that in these conditions the plasma and/or tissue concentrations of LXs and resolvins will be low. This is indirectly supported by the observation that the plasma levels of various EFAs and their metabolites (AA, EPA, and DHA) are decreased in hypertension, type 2 diabetes mellitus, and coronary heart disease34 that are necessary for the formation of LXs and resolvins. Supplementation of 1gm EPA and 0.7 gm DHA and 160mg aspirin to healthy human volunteers leads to the formation of about 0.1 to 0.4 ng/ml of resolvin E1 in their plasma.35 The formation of resolvin E1 observed is consistent with the scheme that endothelial cells expressing COX-2 treated with aspirin transform EPA to produce and release 18R-HEPE as discussed above. When human leukocytes and endothelial cells interact within the vasculature, 18R-HEPE is converted to resolvin E1 via transcellular biosynthesis.35,36 It is possible that in patients with hypertension, type 2 diabetes mellitus, CHD, and stroke the plasma concentrations of resolvin E1 will be < 0.1 ng/ml.

**Conclusions**

In the light what is known about EFAs, eicosanoids, LXs, and resolvins as discussed above, it is likely that plasma, red blood cell (RBC) membrane and tissue concentrations of these lipids (namely DGLA, AA, EPA, and DHA, and LXs and resolvins) will be low in those who are on COX-2 inhibitors compared to those on aspirin. It is possible that the concentrations of EFAs, LXs, and resolvins are more likely to be low in the affected tissues such as heart and endothelial cells. Hence, it is necessary that the concentrations of EFAs, LXs and resolvins should be measured in the biopsy specimens of these tissues. It is also likely that co-administration of EFAs along with COX-2 inhibitors will not only potentiate the anti-inflammatory actions of COX-2 inhibitors but may also prevent thrombotic cardiovascular events. Combined use of EFAs and aspirin/NSAIDs/COX-2 inhibitors will also protect gastric mucosal damage that is associated with aspirin and COX-2 inhibitors since AA, EPA, and DHA are known to protect gastric mucosa.8,9 LXs and resolvins also enhance eNO generation that could yet another mechanism by which they prevent atherosclerosis, CHD, and stroke. EPA and DHA are of benefit in Alzheimer’s disease27 and colon cancer36,39 that could also be attributed to their
neuroprotective and anti-inflammatory actions as a result of increased formation of LXs and resolvins from these fatty acids.

REFERENCES


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**Announcement**

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The Secretariat
Diabetes in Pregnancy Study Group India (DIPSI)
Dr V Seshiah Diabetes Care and Research Institute
31A, Ormes Road, Kilpauk, Chennai – 600 010.
Tel: + 91 44 26612296, 26615757 Fax: + 91 44 26610110
e-mail: dipsi@drvSeshiah.org

For further information visit our official website: wwwdrvSeshiah.org/dipsi