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Review

Cyclooxygenase- and cytochrome P450-derived eicosanoids in stroke

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ABSTRACT

Arachidonic acid (AA) is metabolized by cyclooxygenase (COX) and cytochrome P450 (CYP) enzymes into eicosanoids, which are involved in cardiovascular diseases and stroke. Evidence has demonstrated the important functions of these eicosanoids in regulating cerebral vascular tone, cerebral blood flow, and autoregulation of cerebral circulation. Although COX-2 inhibitors have been suggested as potential treatments for stroke, adverse events, including an increased risk of stroke, occur following long-term use of coxibs. It is important to note that prolonged treatment with rofecoxib increased circulating levels of 20-hydroxyeicosatetraenoic acid (20-HETE), and 20-HETE blockade is a possible strategy to prevent coxib-induced stroke events. It appears that 20-HETE has detrimental effects in the brain, and that its blockade exerts cerebroprotection against ischemic stroke and subarachnoid hemorrhage (SAH). There is clear evidence that activation of EP2 and EP4 receptors exerts cerebroprotection against ischemic stroke. Several elegant studies have contributed to defining the importance of stabilizing the levels of epoxyeicosatrienoic acids (EETs), by inhibiting or deleting soluble epoxide hydrolase (sEH), in stroke research. These reports support the notion that sEH blockade is cerebroprotective against ischemic stroke and SAH. Here, we summarize recent findings implicating these eicosanoid pathways in cerebral vascular function and stroke. We also discuss the development of animal models with targeted gene deletion and specific enzymatic inhibitors in each pathway to identify potential targets for the treatment of ischemic stroke and SAH.

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1. Introduction

Stroke, the fifth leading cause of death, is one of the most life-threatening cerebrovascular disorders in the U.S [1,2]. According to a 2015 report from the CDC, every year more than 795,000 people in the U.S. have a stroke. Also, strokes kill almost 130,000 Americans each year, accounting for about 1 out of every 20 deaths. There are two main types of stroke: ischemic and hemorrhagic. It has been estimated that ischemic stroke accounts for about 80–85% of all stroke incidents, while hemorrhagic stroke accounts for the remaining 15–20% of stroke incidents [1,2]. Ischemic stroke occurs when a thrombus or embolus blocks cerebrovascular circulation, resulting in irreversible damage to the ischemic core and its surrounding region. Hemorrhagic stroke is mainly due to the rupture of cerebral aneurysms, resulting in subarachnoid hemorrhage (SAH) and intracranial hemorrhage [3].

The use of recombinant tissue plasminogen activator (rtPA) has been the standard of care for treatment of acute ischemic stroke. However, patients with ischemic stroke need to receive this drug within therapeutic window of four-and-a-half hours. Also, there is increasing concern that treatment of rtPA may cause side effects, including the disruption of the blood brain barrier, as well as seizures and progressive neuronal damage. Although rtPA treatment provides significant benefits for stroke patients, this therapy did not show significant benefits for patients with large artery occlusions [4]. To resolve this issue, five clinical trials, including MR CLEAN, ESCAPE, EXTEND IA, SWIFT PRIME, and REVASCAT, were conducted to evaluate the use of endovascular thrombectomy in stroke patients [4,5]. The results from these clinical trials show that this therapy provides consistent benefits for stroke patients even when it was performed beyond 4.5 h in patients who had already received rtPA [5,6]. Thus, although more clinical studies are needed to validate the outcomes of these studies, endovascular thrombectomy could be a promising therapy for the treatment of ischemic stroke in the near future. Although there have been significant advances in understanding the pathophysiology following stroke, current treatments for stroke are limited in both their utility (e.g., rtPA) and effectiveness (e.g., aspirin). Therefore, there is a critical need for basic and clinical research to investigate potential therapeutic targets for the treatment of stroke.

Since cerebral vascular function and dysfunction are the key factors in the onset and progression of stroke, this review aims to provide important information about how cyclooxygenase (COX) and cytochrome P450 (CYP)- derived eicosanoids affect cerebral vascular function, as well as the role of these lipid effector molecules in ischemic stroke and SAH.

2. Regulation of cerebral vascular function by COX- and CYP-eicosanoids

2.1. Role of COX-eicosanoids in cerebral vascular function

Arachidonic acid (AA) is a 20-carbon polyunsaturated fatty acid that is usually esterified to the second carbon in membrane phospholipids. The release of AA from phospholipids is achieved through the activity of phospholipase A_2 (PLA_2), which specifically recognizes the *sn*-2 acyl bond of phospholipids and catalytically hydrolyzes the bond releasing AA and lysophospholipids. AA is metabolized to prostaglandin H_2 (PGH_2) by COX-1 or COX-2. COX-1 is constitutively expressed in most cells and is involved in normal physiologic functions [7]. COX-2 is expressed in many organs, such as the brain, and it is highly inducible by pro-inflammatory cytokines [7]. PGH_2 is the substrate for the activities of tissue-specific isomerases and synthases that synthesize PG_2 and TX (Fig. 1) [8]. The major PGs are PGD_2, PGE_2, PGI_2, and $PGF_{2\alpha}$; the major TX is TXA_2. The action of these PGs and TXA_2 is mediated through the binding of these products into their membrane-bound receptors, including DP, EPs (EP_1 to EP_4), IP, FP, and TP receptors (Fig. 1) [9,10]. For an overview and function of COXs, there are several excellent reviews regarding to COX-1 and inducible COX-2 in the brain [11–13].

In the cerebral vascular system, COX-1 and COX-2 are important in the modulation of cerebral blood flow [14]. For example, indomethacin, a nonselective inhibitor of COX-1 and COX-2, reduced resting cerebral blood flow and attenuated elevations in cerebral blood flow produced by endothelium-dependent vasodilators [15,16]. However, previous studies [17,18]. demonstrated that indomethacin has off-target effects that are unrelated to COX inhibition, including inhibition of IP receptor and cAMP-dependent protein kinase activity. Interestingly, Niwa et al. [19]. have found that COX-1 knockout (KO) and SC-560 (a selective COX-1 inhibitor) significantly attenuated resting cerebral blood flow by 13–20%, respectively. Further investigation showed that SC-560 attenuated the cerebral blood flow induced by hypercapnia, bradykinin, calcium ionophore A23187, and AA in wild-type mice but not COX-1 KO mice [19]. These findings demonstrate that COX-1 has a critical role in maintaining resting vascular tone and in selective vasodilator responses in cerebral circulation. To determine the importance of COX-2 in cerebral circulation, Niwa et al. [20]. showed that NS-398, a selective inhibitor of COX-2, attenuated the increase of somatosensory cortex blood flow induced by vibrissal stimulation. However, neither NS-398 nor COX-2 KO affected increases in cerebral blood flow induced by hypercapnia, acetylcholine, or bradykinin. These results provide solid evidence that COX-2 is important to increase cortex blood flow that accompanies neural activity.

2.2. Role of 20-hydroxyeicosatetraenoic acid (20-HETE) in cerebral vascular function

20-HETE, the ω-hydroxylation product of AA, is the principal AA metabolite of CYP enzymes in vascular smooth muscle [21] and kidney [22]. Synthesis of 20-HETE is catalyzed by the CYP4A gene family [21] (Fig. 2). This subfamily encodes several CYP enzymes in different species. In the rat, four CYP4A enzymes have been identified: CYP4A1, CYP4A2, CYP4A3, and CYP4A8 [23]. These isoforms, although sharing 66–98% homology and common catalytic activity, are expressed in the liver, kidney, and brain [24]. The recombinant CYP4A1, CYP4A2, and CYP4A3, but not CYP4A8, catalyzed AA ω-hydroxylation to 20-HETE with the highest catalytic efficiency (V_{max}/K_m) for CYP4A1, followed by CYP4A2 and CYP4A3 [25]. In the mouse, four Cyp4a enzymes have been identified: Cyp4a10, Cyp4a12a, Cyp4a12b, and Cyp4a14. Muller et al. [26]. have demonstrated that AA ω-hydroxylation is catalyzed by Cyp4a10, Cyp4a12a, and Cyp4a12b. Cyp4a12a and Cyp4a12b have similar catalytic activity for 20-HETE production, with a V_{max} value of about 10 min and a K_m value of about 20–40 μM [26]. The ω-hydroxylase activity of AA for Cyp4a10 is about 25–75-fold lower than that of Cyp4a12 isoforms. These results suggest that Cyp4a12 isoforms constitute the major source of 20-HETE synthesis. Notably, besides CYP4A enzymes, CYP4F isoforms are also important for 20-HETE production [27].

In the cerebral vascular system, 20-HETE production was first identified in 1994 [28] and a study by Gebremedhin et al. [29]. has demonstrated that CYP4A1, CYP4A2, CYP4A3, and CYP4A8 are expressed in rat cerebral microvessels. 20-HETE is a potent vasoconstrictor that depolarizes vascular smooth muscle cells by inhibiting K^+ channel activity and is important in regulating renal hemodynamics and renal function [30]. In cerebral microcirculation, Gebremedhin et al. [29]. showed that an elevation in transmural pressure, from 20 to 140 mm Hg, increased 20-HETE