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Review

Epoxyeicosanoid signaling in CNS function and disease

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ABSTRACT

Epoxyeicosatrienoic acids (EETs) are arachidonic acid metabolites of cytochrome P450 epoxygenase enzymes recognized as key players in vascular function and disease, primarily attributed to their potent vasodilator, anti-inflammatory and pro-angiogenic effects. Although EETs' actions in the central nervous system (CNS) appear to parallel those in peripheral tissue, accumulating evidence suggests that epoxyeicosanoid signaling plays different roles in neural tissue compared to peripheral tissue; roles that reflect distinct CNS functions, cellular makeup and intercellular relationships. This is exhibited at many levels including the expression of EETs-synthetic and -metabolic enzymes in central neurons and glial cells, EETs' role in neuro-glio-vascular coupling during cortical functional activation, the capacity for interaction between epoxyeicosanoid and neuroactive endocannabinoid signaling pathways, and the regulation of neurohormone and neuropeptide release by endogenous EETs. The ability of several CNS cell types to produce and respond to EETs suggests that epoxyeicosanoid signaling is a key integrator of cell–cell communication in the CNS, coordinating cellular responses across different cell types. Under pathophysiological conditions, such as cerebral ischemia, EETs protect neurons, astroglia and vascular endothelium, thus preserving the integrity of cellular networks unique to and essential for proper CNS function. Recognition of EETs' intimate involvement in CNS function in addition to their multi-cellular protective profile has inspired the development of therapeutic strategies against CNS diseases such as cerebral ischemia, tumors, and neural pain and inflammation that are based on targeting the cellular actions of EETs or their biosynthetic and metabolizing enzymes. Based upon the emerging importance of epoxyeicosanoids in cellular function and disease unique to neural systems, we propose that the actions of "neuroactive EETs" are best considered separately, and not in aggregate with all other peripheral EETs functions.

Contents

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1. Introduction

Arachidonic acid (AA) is liberated from membrane phospholipid pools by phospholipase A2 (PLA2) and subsequently metabolized by cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP) epoxygenase and hydroxylase enzymes to form a group of metabolites collectively termed 'eicosanoids' (Fig. 1) [1,2]. Epoxyeicosatrienoic acids (EETs), epoxide metabolites of CYP epoxygenases, have garnered increasing attention since their initial identification in the liver in the early 1980s. Interest in EETs signaling has centered predominantly upon their role in the regulation of renal and cardiovascular function, particularly in their potent vasodilator actions. EETs signaling has been the subject of numerous research articles, and their effects on cellular function have been investigated in different tissues, including heart, lung, kidney, gastro-intestinal tract and brain. The vasomotor actions of EETs have been studied in the renal, coronary, pulmonary, skeletal muscle, sub-cutaneous, carotid, mesenteric, and cerebral vascular beds. These studies have yielded much valuable insight into the biochemical mechanisms of EETs synthesis, action, and metabolism [3,4].

At first glance, the role of EETs in the brain and broader central nervous system (CNS) appears to closely parallel functions described in other peripheral tissues, including a key role in the regulation of the cerebral vasculature [1,3]. A more detailed review of the defined functions of EETs in the CNS, however, suggests that EETs signaling may play an important and distinct role in CNS function compared to that of peripheral tissues. Indeed, based upon expression data, EETs production and metabolism in the brain spans many regions and extends to peripheral and central neurons, astroglia and oligodendrocytes, vascular endothelium and vascular smooth muscle (VSM) (for references, see Table 1). In terms of cellular actions, EETs signaling in the CNS is importantly involved in processes that are specific to CNS function. Furthermore, EETs often appear to specifically mediate processes in which communication is integrated across multiple cell types. EETs' role in the regulation of cerebral blood flow (CBF) extends beyond that of an endothelium-derived hyperpolarizing factor (EDHF) as described in peripheral circulatory beds, and includes the astrocyte-mediated coupling of cortical neuronal activity to cerebral blood supply as well as the regulation of the cerebral surface vasculature by perivascular nerve fibers [5–8]. EETs modulate neuronal pain processing in the brainstem [9] and the CYP epoxygenase metabolic pathway interacts with the neuroactive endocannabinoid pathway at a number of mechanistic levels [10–14]. Indeed, the long-established and often overlooked role for EETs in regulating neurohormone release from neuroendocrine regions of the brain [15,16] in addition to very recent data implicating EETs in the neurogenic regulation of cerebral blood flow suggest that EETs may be key regulators of synaptic transmission, a function distinct to CNS function. Lastly, during conditions of stress or injury such as cerebral ischemia, the EETs signaling pathway is actively up-regulated and exerts a concerted protective action upon the many interacting cellular components of the brain, including neurons, glia, vascular and inflammatory cells [17].

The emerging involvement of EETs signaling in CNS-specific processes suggests that epoxyeicosanoid signaling in the CNS is in many ways distinct from EETs' actions in other peripheral tissues. The common biochemical mechanisms governing the EETs pathway ensure that many mechanistic insights into EETs signaling in the CNS will be gained from studies in the periphery. However, the distinct actions of EETs in the CNS argue that epoxyeicosanoid signaling in this system is best considered independently within the specific framework of CNS function and disease. Towards this end, the present review will outline the well-established role for the epoxyeicosanoid pathway in cerebrovascular regulation and the targeting of this pathway in the treatment of cerebral ischemia. We will then critically evaluate the evidence for the broader involvement of epoxyeicosanoid signaling in CNS function and disease.

2. Brain epoxyeicosatrienoic acids (EETs) synthesis and metabolism

Identification of EETs production in the brain followed very closely on the heels of the initial discovery of these novel CYP-derived epoxyeicosanoids [18]. In the 1990s, studies reporting the specific synthesis of EETs first by astrocytes and then by the vascular endothelium helped to secure EETs' place as key astrocyte- and endothelium-derived regulators cerebrovascular function [19–21]. At the time, these findings appeared to fit well with results from peripheral circulatory beds indicating that EETs functioned as an EDHF and were key regulators of vascular function [3]. More recent studies, however have characterized both the expression of CYP epoxygenases and the function of CYP-derived EETs in cell types throughout many brain regions (Table 1). The result of these studies has been the demonstration that enzymes capable of EETs synthesis and metabolism, CYP epoxygenases and soluble epoxide hydrolase (sEH), are dominantly expressed in non-vascular cells throughout the CNS including both neuronal and glial cells. These findings suggest that the role of EETs signaling in the CNS may extend beyond simply that of vascular regulation and may subserve functions that are specific to the activity of the CNS, including those processes involving the concerted action of multiple CNS cell types.

2.1. EETs production in the brain

Cytochrome P450 enzymes are members of the hemoprotein superfamily, important players in the cellular adaptation to stress.