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A review of analytical methods for eicosanoids in brain tissue☆

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ABSTRACT

Eicosanoids are potent lipid mediators of inflammation and are known to play an important role in numerous pathophysiological processes. Furthermore, inflammation has been proven to be a mediator of diseases such as hypertension, atherosclerosis, Alzheimer's disease, cancer and rheumatoid arthritis. Hence, these lipid mediators have gained significant attention in recent years. This review focuses on chromatographic and mass spectrometric methods that have been used to analyze arachidonic acid and its metabolites in brain tissue. Recently published analytical methods such as LC–MS/MS and GC–MS/MS are discussed and compared in terms of limit of quantitation and sample preparation procedures, including solid phase extraction and derivatization. Analytical challenges are also highlighted.

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1. Introduction

Eicosanoids are specific biomarkers of inflammation. Their biosynthesis from polyunsaturated fatty acids can be catalyzed by cyclooxygenase (COX-2), lipoxygenases (LOX), and cytochrome P450 enzymes. Depending on the mechanism/pathway of biosynthesis and parent molecule, different classes of eicosanoids are defined. Brain lipids such as neuroprostanes are produced by peroxidation of docosahexaenoic acid. These lipids are different from eicosanoids and will not be the subject of this review. This article focuses on eicosanoids from Arachidonic Acid (AA).

Arachidonic acid (ϖ-6 polyunsaturated fatty acid) can be metabolized to hydroxyeicosatetraenoic acids (HETEs), dihydroxyeicosatetraenoic acids (DiHETEs), epoxyeicosatreinoic acids (EETs), prostaglandins (PGs) and thromboxane (TX) (Fig. 1). These endogenous eicosanoids are present in small levels in biological fluids and tissues including the brain. In the brain, these markers are important to maintain homeostasis and normal functions such as synaptic plasticity related to long-term depression [1] and protecting cortical neurons against glutamate toxicity [2]. On the other hand, alterations in the levels of these lipids in the brain have been associated with numerous diseases such as Alzheimer's, Parkinson's, Multiple sclerosis, schizophrenia, and epilepsy [3]. The past decade has produced numerous excellent reviews describing the metabolism of these lipid molecules and their role in diseases [4–7].

1.1. Cycloxygenase enzymes, prostaglandins and brain

Cyclooxygenase enzyme is present in the human body in the form of three isozymes: COX-1, COX-2 and COX-3. COX-1 is thought to be only responsible for maintaining homeostasis in numerous physiological functions in the body [8]. COX-3, which was discovered only in 2003, is considered to be an intron-splice variant of COX-1 [9]. On the other hand, COX-2 is involved in numerous inflammatory processes [9]. Both COX-1 and COX-2 are expressed in brain tissue [10]. Additionally COX-1 and COX-2 enzymes can catalyze the reaction that converts arachidonic acid to a stable hydroxyendoperoxide (PGH_2) [11,12]. PGH_2 is then converted into primary prostanoids by various enzymes [11,12]. Prostanoids can be classified into prostaglandins (PGE_2, PGF_2 and PGD_2), prostacyclins (PGI_2) and thromboxanes (TXA_2). PGD_2 is the most abundant prostaglandin synthesized in the central nervous system. It not only regulates functions like temperature and sleep [13] but it also protects the brain from excitotoxic injury [14]. PGE_2 is involved in brain maturation and in regulation of synaptic activity and plasticity [15]. Furthermore being one of the most abundant prostaglandins, PGE_2 is involved in processes leading to classic signs of inflammation

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Nomenclature

AA Arachidonic acid
BHT Butylated hydroxyl toluene
CID Collision-induced dissociation
CLASS Comprehensive lipidomic analysis by separation simplification
COX Cyclooxygenase
CSF Cerebral spinal fluid
CV Coefficient of variance
CYP-450 Cytochrome P450
CyPGs Cyclopentenone prostaglandins
DiHETEs Dihydroxyeicosatetraenoic acids
DiHETrEs Dihydroxyeicosatreinoic acids
DTPA Diethylenetriaminepenta-acetic acid
ECNCI Electron capture negative chemical ionization
EDTA Ethylenediaminetetra-acetic acid
EETs Epoxyeicosatrienoic acids
ESI Electrospray ionization
ESI-LC-MS/MS Electrospray ionization coupled to high pressure liquid chromatography with tandem mass spectrometry
fmol Femtomol
GC Gas chromatography
GC-FID Gas chromatography-flame ionization detection
GC–MS Gas chromatography–mass spectrometry
GC–MS/MS Gas chromatography–tandem mass spectrometry
GC–MS/NICI Negative ion chemical ionization coupled to gas chromatography–mass spectrometry
HESI Heated electrospray ionization
HETEs Hydroxyeicosatetraenoic acids
HETP Height equivalent theoretical plates
HILIC Hydrophilic interaction chromatography
HPETEs Hydroxyperoxyeicosatetraenoic acid
HPLC High pressure liquid chromatography
HPLC-UV High pressure liquid chromatography-ultraviolet detector
LC Liquid chromatography
LC–MS Liquid chromatography–mass spectrometry
LC–MS/MS Liquid chromatography–tandem mass spectrometry
LOD Limit of detection
LOQ Limit of quantitation
LOX Lipoxygenases
LTs Leukotrienes
MRM Multiple reaction monitoring
MS Mass spectrometry
MS/MS Tandem mass spectrometry
NE-OTf 2-(2,3-naphthalimino)ethyl-trifluoromethanesulphonate
NICI Negative ion chemical ionization
NP-HPLC Normal-phase high pressure liquid chromatography
ODS-silica Octadecylsilyl-silica
PCA Principle component analysis
PFB Pentafluorobenzyl
pg Picogram
PGH_2 Hydroxyendoperoxide
PGs Prostaglandins
Q1 Quadrupole 1
Q3 Quadrupole 3
Q-TOF Quadrupole time-of-tlight mass spectrometer
QTRAP Quadrupole-linear ion trap
RP-HPLC Reverse-phase high pressure liquid chromatography
SAH Subarachnoid hemorrhage
sEH Soluble epoxide hydrolase
SIM Selective ion monitoring
sMRM Scheduled multiple reaction monitoring
SPE Solid phase extraction
SRM Selected reaction monitoring
SV Symptomatic cerebral vasospasm
TBI Traumatic brain injury
TLC Thin layer chromatography
TOF Time-of-flight
TX Thromboxane
UPLC Ultra high pressure liquid chromatography
UPLC–MS/MS Ultra high pressure liquid chromatography–tandem mass spectrometry
UV Ultraviolet

and pain [16]. PGF_2 plays an important role in brain injury and pain [16]. PGI_2 and TXA_2 are potent vasodilators and vasoconstrictors respectively.

1.2. Lipoxygenase enzymes, leukotrienes and the brain

Lipoxygenease are a group of enzymes that catalyzes the reaction, which involves the addition of oxygen to AA producing hydroxyperoxyeicosatetraenoic acid (HPETEs) [17,18]. HPETE then reduces to give leukotrienes (LTs) and hydroxyeicosatetraenoic acid (HETEs) [19]. Cysteinyl leukotrienes, which include LTC4, LTD4 and LTE4, are found to alter cerebral vessel functions [20] and disrupt the blood brain barrier [20]. Moreover, they have been related to brain edema formation [20]. They are also produced in response to numerous acute brain injuries [21]. LTB4 may also be involved in the pathogenesis of ischemic brain edema [22]. Another role LTB_4 plays in inflammation is attracting leukocytes [97]. Inflammation as a result of alterations in blood flow and vascular permeability can be described by the actions of LTC_4 and LTD_4 [97]. Leukotrienes can be involved in inflammatory diseases such as asthma. HETEs are potent vasoactive agents and are altered in cerebrovascular pathologies [22].

1.3. Cytochrome P450 enzymes (CYP-450), DiHETEs, HETEs and the brain

AA undergoes metabolism by CYP-450 to give epoxyeicosatrienoic acid (EETs). CYP enzyme produces four regioisomers of EET from AA: 5,6-, 8,9-, 11,12-, and 14,15-EET [23]. EETs are quickly metabolized in the presence of soluble epoxide hydrolase (sEH) to the corresponding inactive diols, the DiHETEs [24,25]. In the brain, EETs are involved in controlling the cerebral blood flow (CBF) [26]. They are neuroprotective agents because of their anti-inflammatory and anti-thrombotic effects [26]. Zhang et al. found that deletion of sEH, the enzyme that metabolizes EETs to DiHETEs, is protective against ischemic brain injury [27].

2. Quantification of eicosanoids

Currently, immunoassays [28], GC–MS [29], LC–MS [30] and LC–MS/MS [31,32] have been used to analyze eicosanoids. For a long time, immunoassays, (enzyme-linked immunoassays and radio-labeled immunoassays) were considered to be the standard method for lipid analysis. Though these assays were sensitive, they suffered from reproducibility and reduced specificity. A regular

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