Brain Research Bulletin 87 (2012) 154–171

Contents lists available at SciVerse ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Review

Imaging brain signal transduction and metabolism via arachidonic and docosahexaenoic acid in animals and humans

Mireille Basselin, Epolia Ramadan*, Stanley I. Rapoport

Brain Physiology and Metabolism Section, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA

ARTICLE INFO

Article history:
Received 1 November 2011
Received in revised form 1 December 2011
Accepted 2 December 2011
Available online 9 December 2011

Keywords:
Arachidonic acid
Bipolar disorder
Brain imaging
Docosahexaenoic acid
Mood stabilizers
Neuroinflammation

ABSTRACT

The polyunsaturated fatty acids (PUFAs), arachidonic acid (AA, 20:4*n*−6) and docosahexaenoic acid (DHA, 22:6*n*−3), important second messengers in brain, are released from membrane phospholipid following receptor-mediated activation of specific phospholipase A_2 (PLA_2) enzymes. We developed an *in vivo* method in rodents using quantitative autoradiography to image PUFA incorporation into brain from plasma, and showed that their incorporation rates equal their rates of metabolic consumption by brain. Thus, quantitative imaging of unesterified plasma AA or DHA incorporation into brain can be used as a biomarker of brain PUFA metabolism and neurotransmission. We have employed our method to image and quantify effects of mood stabilizers on brain AA/DHA incorporation during neurotransmission by muscarinic $M_{1,3,5}$, serotonergic 5-$HT_{2A/2C}$, dopaminergic D_2-like (D_2, D_3, D_4) or glutamatergic *N*-methyl-D-aspartic acid (NMDA) receptors, and effects of inhibition of acetylcholinesterase, of selective serotonin and dopamine reuptake transporter inhibitors, of neuroinflammation (HIV-1 and lipopolysaccharide) and excitotoxicity, and in genetically modified rodents. The method has been extended for the use with positron emission tomography (PET), and can be employed to determine how human brain AA/DHA signaling and consumption are influenced by diet, aging, disease and genetics.

Published by Elsevier Inc.

Contents

Abbreviations: AA, arachidonic acid; AChE, acetylcholinesterase; BD, bipolar disorder; CBZ, carbamazepine; COX, cyclooxygenase; DAT, dopamine transporter; DHA, docosahexaenoic acid; HIV, human immunodeficiency virus; 5-HT, serotonin (5-hydroxytryptamine); 5-HTT, serotonin transporter; IL, interleukin; LOX, lipoxygenase; LTG, lamotrigine; PLA_2, phospholipase A_2; cPLA_2, Ca^{2+}-dependent cytosolic PLA_2; sPLA_2, secretory PLA_2; iPLA_2, Ca^{2+}-independent PLA_2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B; NMDA, N-methyl-D-aspartic acid; NMDAR, NMDA receptor; PGE_2, prostaglandin E_2; PET, positron emission tomography; rCBF, regional cerebral blood flow; rCMRglc, regional cerebral metabolic rate of glucose; TXB_2, thromboxane B_2; VPA, valproic acid; GFAP, glial fibrillary acidic protein; LPS, lipopolysaccharide.

* Corresponding author at: Brain Physiology and Metabolism Section, National Institute on Aging, National Institutes of Health, Building 9, Room 1S126, Bethesda, MD 20892, USA. Tel.: +1 301 496 8994; fax: +1 301 402 0074.
E-mail address: ramadanir@mail.nih.gov (E. Ramadan).

0361-9230/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.brainresbull.2011.12.001

1. Introduction

Phospholipids and their component fatty acids play critical and dynamic roles in brain development, aging and disease [112,217]. They participate in signal transduction, synaptic membrane remodeling, gene transcription and brain blood flow, and they modulate the brain's responses to drugs, neuroinflammation and ischemia. Brain phospholipid and fatty acid metabolism are abnormal in a number of human brain diseases, including stroke and vascular dementia, Parkinson's and Alzheimer's diseases, multiple sclerosis, HIV-1 associated dementia, bipolar disorder (BD), and depression. Thus, having a method to quantify and image different aspects of their metabolism in animal or human brain could elucidate and localize the active roles of lipids in health and disease.

Despite growing *in vitro* evidence that phospholipids and their components participate in multiple dynamic brain processes, important kinetic and energy-demanding aspects of this participation involving *in vivo* postsynaptic signaling frequently were misunderstood or ignored [198]. Current *in vivo* neuroimaging methods can quantify regional neuroreceptor densities, neurotransmitter synthesis, and parameters of energy metabolism such as regional cerebral blood flow (rCBF) and regional cerebral metabolic rates for glucose (rCMRglc), but largely ignore neuroreceptor-initiated signal transduction. This has limited our understanding of how and where acutely or chronically administered drugs act in the brain, how these drugs modulate behavior and cognition, and how age, disease, genetic or dietary factors influence their signaling effects. Furthermore, it has only been since about 1988 [8] that pharmacologists began to realize that, like phospholipase C and adenylate cyclase, phospholipase A$_2$ (PLA$_2$, EC 3.1.1.4) is a major effector enzyme coupled to neuroreceptors by G proteins to initiate arachidonic acid (AA, 20:4*n*−6) or docosahexaenoic acid (DHA, 22:6*n*−3) release as a second messenger. Nevertheless, a major neuropharmacology text [65] has largely ignored drug or functionally induced PLA$_2$ signaling.

To overcome these limitations, we have elaborated a new "neuroimaging pharmacology of *in vivo* signal transduction" by: (1) identifying in unanesthetized rodents which neuroreceptors, reported from *in vitro* studies to be coupled to PLA$_2$ and AA or DHA release by a G protein or by allowing Ca^{2+} into the cell, can be activated or modified in response to an acute dose of an appropriate agonist, antagonist or response modifier; (2) relating patterns of activation to neural networks, behavioral changes and reported patterns of altered rCBF and rCMRglc; (3) imaging neuroplastic (long-term) effects on AA signaling by chronically administered centrally active drugs, as many drugs are clinically effective after chronic but not acute administration; (4) seeing how such neuroreceptor signaling is altered in disease or genetic rodent models; (5) translating our animal observations to generate clinical imaging protocols with positron emission tomography (PET).

2. Receptors coupled to phospholipase A$_2$ enzymes

2.1. Receptors coupled to PLA$_2$ by G proteins

Agonist binding to specific neuroreceptors can activate a PLA$_2$ to release the second messenger AA or DHA from the stereospecifically numbered *sn*-2 position of brain membrane phospholipid. Receptors that are coupled to a PLA$_2$ to release AA via G proteins include cholinergic muscarinic $M_{1,3,5}$ receptors, dopaminergic D_2-like receptors and serotonergic 5-$HT_{2A/2C}$ receptors [29,82,263] (Fig. 1), bradykinin β_2 and adrenergic β_2 receptors [189,197]. Additionally, AA can be released via coupling to cytokine tumor necrosis factor alpha (TNFα) and interleukin-1β (IL-1β) receptors on astrocytes [74]. DHA can be released following agonist activation of serotonergic 5-$HT_{2A/2C}$, bradykinin B_2, or purigenic P2Y receptors glial cells *in vitro* [90,247].

There are four major classes of PLA$_2$ enzymes in the rodent brain: AA-selective cytosolic Ca^{2+}-dependent cPLA$_2$ (85 kDa, Type IVA, cPLA$_2$α), AA or DHA releasing secretory sPLA$_2$, DHA-selective Ca^{2+}-independent PLA$_2$ (iPLA$_2$, 85–88 kDa, Type VIA and VIB, or β and γ, respectively) and the Ca^{2+}-independent plasmalogen-selective PLA$_2$ (39 kDa, PlsEtn-PLA$_2$) [46,248]. All have been identified in astrocytes and neurons [135,270,271]. cPLA$_2$ has been localized at postsynaptic neuronal membranes in brain [182,188], requires a low concentration of Ca^{2+} (0.3—1 μM), in the physiological range of intracellular Ca^{2+} during neuronal activation [122], for its translocation to the membrane followed by phosphorylation and activation, and is selective for AA during acute stimulation of cells by diverse agents *in vitro* [59]. sPLA$_2$, which requires millimolar Ca^{2+} concentrations for activation, releases AA and DHA *in vitro* [73], and is localized in presynaptic vesicles that are released by exocytosis during membrane depolarization [267]. iPLA$_2$ does not require Ca^{2+} for activation *in vitro* [270], and is selective for DHA in isolated glial cells and in the test tube [247].

The released AA and its bioactive eicosanoid metabolites play important roles in neural functions including membrane excitability, gene transcription, apoptosis, cerebral blood flow, spatial learning and synaptic plasticity, resolution of inflammation, sleep