HHS Public Access

Author manuscript

Neurochem Res. Author manuscript; available in PMC 2012 November 01.

Published in final edited form as:

Neurochem Res. 2012 May ; 37(5): 903–910. doi:10.1007/s11064-012-0708-2.

Neuroinflammation and synaptic loss

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Abstract

Neuroinflammation plays a critical role in the progression of many neurodegenerative diseases and neuropsychiatric illnesses. It is evident that microglia in particular are central to mediating the effects of neuroinflammation. Activated microglia release a number of cytokines and chemokines, which in turn activate many signal transduction pathways. For instance, interleukin-1 beta and tumor necrosis factor alpha regulate transcription of a number of genes within the brain including proinflammatory products of the arachidonic acid (AA) cascade. Co-activation of pro-inflammatory markers and associated cytotoxic products during neuroinflammation process are detrimental to neurons by altering the synaptic proteins. In this review, we discuss both neuroinflammation as well as excitotoxicity insults reduce synaptic markers such as synaptophysin and drebrin in rat brain. Further we discuss here, neurodegenerative and neuropsychiatric illness are associated with increased neuroinflammatory and excitotoxicity markers as well as upregulated brain arachidonic acid markers and the loss of synaptic markers. The decrease in synaptic markers might contribute to reported cognitive defects in neurodegenerative and neuropsychiatric illnesses.

Introduction

It is becoming increasingly clear that neuroinflammation plays a crucial role in the development and progression of many neurodegenerative and psychiatric illnesses including Alzheimer's, Parkinson's, Huntington's disease, bipolar disorder, schizophrenia and depression (Bales *et al*, 2000; Dobos *et al*, 2010; Doorduin *et al*, 2009; Hunot and Hirsch, 2003; Rao *et al*, 2010; Silvestroni *et al*, 2009). Neuroinflammation is a complex combination of the responses of all cell types present within the central nervous system (CNS), including neurons, macroglia, microglia and infiltrating leukocytes. Infection, trauma, and toxins are capable of producing an immediate short lived induction of innate immune response within the CNS (Crutcher *et al*, 2006; Popovich and Longbrake, 2008). Acute neuroinflammation triggers activation of resident microglia and the release of inflammatory mediators such as cytokines and chemokines (Tansey *et al*, 2007). Acute insult is typically short-lived and unlikely to be harmful to long term neuronal survival. It is believed that an acute neuroinflammatory response is generally beneficial to the CNS, since it tends to minimize further injury and contributes to repair of damaged tissue. On the other hand chronic

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Conflict of interest: No

inflammation produces long lasting and self perpetuating neuroinflammatory mediators that remain after the initial neuroinflammatory insult.

Neuroinflammation: induction of proinflammatory cytokines and arachidonic acid cascade enzymes

During neuroinflammation, proinflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNFα), IL-6 and chemokines including interferon gamma, macrophage inflammatory protein and inducible protein (IP)-10 are released by activated microglia that promote neuroinflammatory state. IL-1β and TNFα regulate expression of many genes, including gene transcription for arachidonic acid (AA) cascade enzymes in various cell types via nuclear kappa B (NF-κB) or AP-2 (Acarin *et al*, 2002; Bauer *et al*, 1997; Hoeck *et al*, 1993; Jupp *et al*, 2003; Spriggs *et al*, 1990). In the brain, AA and its metabolites influence signal transduction, gene transcription, neuronal activity, apoptosis, and other processes (Kam and See, 2000; Leslie and Watkins, 1985; O'Banion, 1999). AA released from membrane phospholipids by Ca^{2+}-dependent cytosolic phospholipase A_2 (cPLA$_2$-IVA), secretory (sPLA$_2$ IIA), or Ca^{2+}- independent (iPLA$_2$ VIA), which differ in their calcium requirement, phosphorylation, and substrate specificities (Akiba *et al*, 1999; Murakami *et al*, 1999; Murakami and Kudo, 2002; Murakami *et al*, 1998; Yang *et al*, 1999). The released AA can be metabolized to prostaglandin (PG)H$_2$ by cyclooxygenase (COX)-1 or COX-2, converted to cytoprotective epoxyeicosatrienoic acids by cytochrome p450 epoxygenase or to cytotoxic leukotrienes by 5, −12 or −15 lipoxygenase (LOX) (Funk, 2001). PGH$_2$ is converted to PGE$_2$ by membrane prostaglandin E synthase (mPGES) or cytosolic PGES (cPGES), or by thromboxane synthase (TXS) to TXA$_2$. COX-1 and cPGES are expressed constitutively in the brain, whereas COX-2 and mPGES are inducible (Pepicelli *et al*, 2002; Seibert *et al*, 1995) (Figure-1).

Cross-talk between neuroinflammation and excitotoxicity

Neuroinflammatory markers and AA cascade markers are elevated by excitotoxicity. For instance, activated microglia release nitric oxide which blocks reuptake of glutamate at the presynaptic site, which results in excessive glutamate at the synaptic cleft and activation of NMDA receptors. It is well known that excessive glutamate levels causes excitotoxicity. Activation of NMDA receptors activates AA turnover via upregulation of cPLA$_2$ activity, protein and mRNA levels in an AP-2 dependent manner (Rao *et al*, 2007b). In addition, chronic NMDA administration to rats upregulates levels of proinflammatory IL-1β, TNFα, glial fibrillary acidic protein (GFAP) and inducible nitric oxide synthase (iNOS) in rat brains (Chang *et al*, 2008b). Altogether finding suggests that there is cross-talk between neuroinflammation and excitotoxicity that involves release of AA products in the brain. Upregulation of neuroinflammatory and AA cascade markers in chronic NMDA administrated rat has been shown to cause neuronal loss (Kim *et al*, 2009a). This suggests that both neuroinflammation and associated elevated AA cascade are detrimental to neuronal survival. In those conditions synaptic markers (synaptophysin and drebrin) are also prone to damage.

Synaptic proteins

Drebrin is an actin-binding protein neuron-specific isoform (Kojima *et al*, 1988), abundantly found within dendritic spines that are located at postsynaptic excitatory synapses (Aoki *et al*, 2005). Drebrin expression was found to be maximal during embryogenesis and decreases thereafter (Shirao, 1995). The over expression of drebrin provokes the elongation of spines in mature neurons (Hayashi and Shirao, 1999) and the change of dendritic filopodia into aberrantly enlarged megapodia in immature neurons (Mizui *et al*, 2005). Conversely, the suppression of drebrin expression reduces spine density and results in the formation of thin immature spines (Takahashi *et al*, 2006). These findings support the idea that the drebrin–actin complex plays a crucial role in the regulation of dendritic spine morphology.

Synaptophysin is a 38-kd glycoprotein localized in synaptic vesicle membranes. The main functions of synaptophysin include docking, fusion, and endocytosis, otherwise known as membrane trafficking (Evans and Cousin, 2005).

Neuroinflammation: synaptic protein loss

Neurodegenerative disease

Hatanpaa and others reported decreased cortical drebrin in Alzheimer's as well as normal aging (Hatanpaa *et al*, 1999). Studies also report that drebrin is decreased in postmortem hippocampal (Harigaya *et al*, 1996) and temporal (Counts *et al*, 2006) regions obtained from severe and mildly cognitively impaired patients. In Alzheimer disease (AD), neuroinflammation plays a role in altering the neuronal synaptic proteins. In recent year's decreased drebrin have been shown to correlate with cognitive impairment in patients with Alzheimer disease (AD) (Counts *et al*, 2006; Kobayashi *et al*, 2004; Kojima and Shirao, 2007; Zhao *et al*, 2006). The decreased drebrin in AD might be due to upregulated neuroinflammatory and AA cascade markers, since an excess of neuroinflammatory markers such as TNFα, IL-1β and AA have been shown to damage neurons by increasing pro-apoptotic marker and caspase 3 activities (Fang *et al*, 2008; Gibson *et al*, 2004; Zhu *et al*). It is possible that elevated AA alone or in combination with neuroinflammation might be involved in reducing the synaptic proteins. Upregulated neuroinflammation, AA cascades and reduced drebrin can occur in bipolar disorder (Kim *et al*, 2009b; Rao *et al*), HIV-1 transgenic rat (Basselin *et al*), schizophrenia (Rao et al upublished data) and in n-3 polyunsaturated fatty acid deprived animals (Rao *et al*, 2007a).

Synaptophysin has been shown to be reduce during aging (Haley *et al*) as well as in neurodegenerative disease including AD (Hamos *et al*, 1989).

Neuropsychiatric illness

Postmortem brains from bipolar disorder (BD) and schizophrenic patients showed upregulated neuroinflammatory markers and AA cascade markers as well as decreased synaptic markers (drebrin and synaptophysin) (Glantz and Lewis, 1997a, b; Kim *et al*, 2009b; Rao *et al*). Cognitive impairment has been reported in BD and SZ patients (Wingo *et al*, 2009; Wobrock *et al*, 2009).

Animal models of neuroinflammation

Similar to clinical studies, in animal models of neuroinflammation such as a non-infectious rat model of HIV-1 and rats treated with a high dose of lipopolysaccharide (LPS) (200 ng/hr) infusion for six days both exhibited upregulated neuroinflammatory markers TNFα, and cd11b (figure-1 and 2). In both models there are upregulated AA cascade markers (Rao et al 2009; Kellom *et al* unpublished data). However, low dose infusion of LPS (0.5ng/hr) for six days increased TNF alpha protein level without a significant change in $cPLA_2$ transcription or drebrin protein in rat brain. This suggests that TNFα alone cannot decrease drebrin levels in rat brain. In combination, these findings suggest neuroinflammation associated with AA signaling could downregulate drebrin levels in rat brain.

Excitotoxicity

In a model of excitotoxicity, an intense stimulation of NMDA results in drebrin loss in cultured hippocampal neurons (Halpain *et al*, 1998). Chronic NMDA administration to rats upregulates brain AA turnover with increased $cPLA_2$ activity and $cPLA_2$ transcription in rat brain. Chronic NMDA exposure in rats result in upregulated protein and mRNA levels of neuroinflammatory markers such as IL-1β, TNF α, GFAP and iNOS in rat frontal cortex (Chang *et al*, 2008a). These studies imply that excitotoxicity and neuroinflammation signaling pathways cross-talk with each other and involve AA signaling. Further, chronic NMDA administration to rats, results in upregulation of pro-apoptotic factors Bad and Bax which causes neuronal loss (Kim *et al*, 2009a). The combination of neuroinflammation and AA signaling could influence the synaptic loss.

N-3 polyunsaturated dietary deprivation model

Clinical and pre-clinical studies support the idea that neuroinflammation associated AA cascade signaling results in synaptic loss. A recent study of triple transgenic AD mice has shows that n-3 polyunsaturated fatty acid(PUFA) dietary deprivation in mice reduces brain drebrin levels (Julien *et al*, 2008). Dietary n-3 deprivation in rats shows upregulated brain AA signaling with increased activity and transcription of both $cPLA_2$ and $sPLA_2$ (Rao *et al*, 2007a). This finding suggests either neuroinflammation or AA cascade increase could influence the reduction of the synaptic proteins in brain. The role of neuroinflammation or AA influence on synaptic proteins loss is not clear. It is apparent that drebrin is regulated by the transcriptional factor NXF and is modulated by DHA via phosphotidyl inositol kinase (Calon *et al*, 2004; Ooe *et al*, 2004). It perhaps AA may be act on this kinase and transcription factor of drebrin which could result in the reduction of drebrin transcription. A recent study demonstrate that $cPLA_2$ inhibitor protects against prion and amyloid beta 1-42 induced synaptic loss in cultured rat cortical and hippocampal neurons (Bate *et al*). Further detailed molecular studies are needed to understand the role of proinflammatory AA and its metabolites effects on the drebrin and synaptophysin transcription factors.

Drugs

The classical antidepressant fluoxetine, upon chronic administration to rats, upregulates hippocampal drebrin level compared with the chronically stressed group (Yang *et al*, 2003). Unlike antidepressants, antipsychotic drugs, olanzapine and haloperidol did not significantly

change the hippocampal drebrin level in monkeys (Hill *et al*, 2006). Thus suggests drebrin is modulated by various factors including neuroinflammatory markers. The influence of AA on drebrin transcription is not clear. Further studies are warranted to understand the role of neuroinflammation and AA on drebrin regulation.

Conclusions

Neuroinflammatory and arachidonic acid markers are associated with synaptic protein loss of drebrin and synaptophysin. These changes could contribute to cognitive impairments in neurodegenerative and neuropsychiatric illnesses.

Acknowledgments

This research was entirely supported by the Intramural Research Programs of the National Institute on Aging, National Institutes of Health, Bethesda, MD 20892. We thank the National Cancer Institute (NCI), Center for Cancer Research (CCR) Fellows Editorial Board and Dr. Ed Reese, for proofreading the manuscript.

Abbreviations

AA	arachidonic acid
AD	Alzheimer disease
BD	bipolar disorder
cPGES	cytosolic prostaglandin E synthase
cPLA$_2$	calcium-dependent phospholipase A$_2$
COX	cyclooxygenase
GFAP	glial fibrillary acidic protein
gp120	glycoprotein 120
HIV	human immunodeficiency virus
HAD	HIV-associated dementia
IL-1β	interleukin-1β
iPLA$_2$	calcium-independent phospholipase A$_2$
mPGES	membrane prostaglandin E synthase
LOX	lipoxygenase
NF-κB	nuclear factor-kappa B
PG	prostaglandin
sPLA$_2$	secretory phospholipase A$_2$
TNFα	tumor necrosis factor α

Tg	transgenic
TX	thromboxane
TXS	thromboxane synthase

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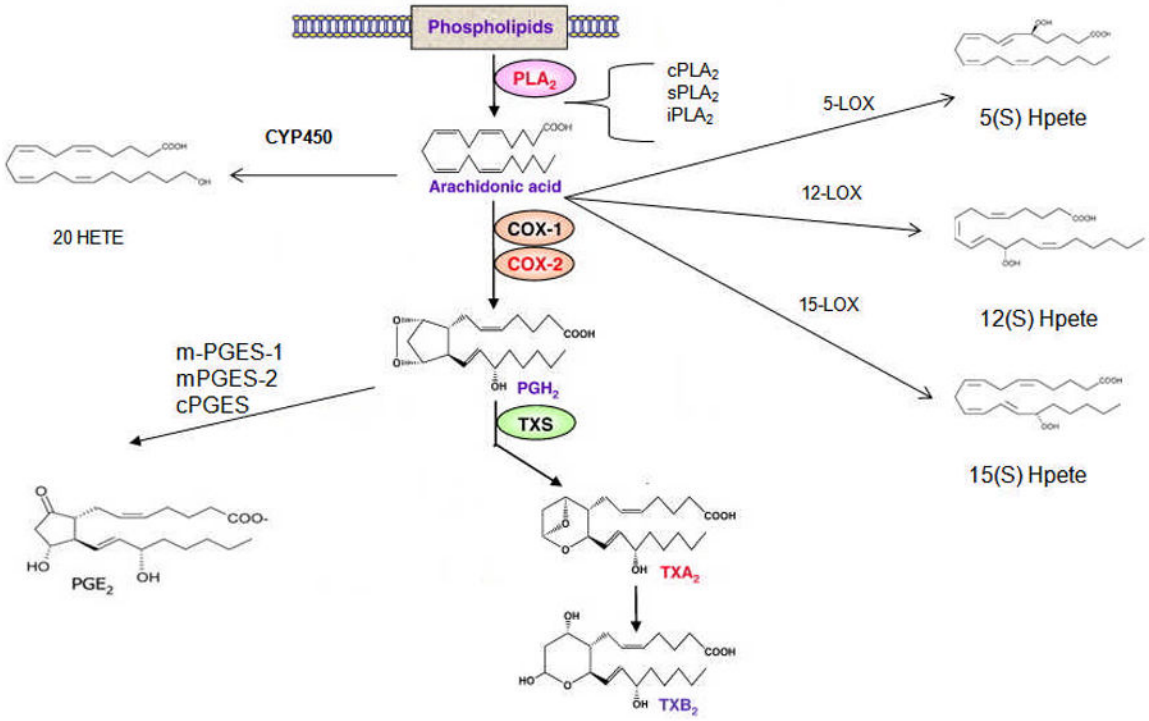

Figure 1.
Schematic representation of arachidonic acid cascade

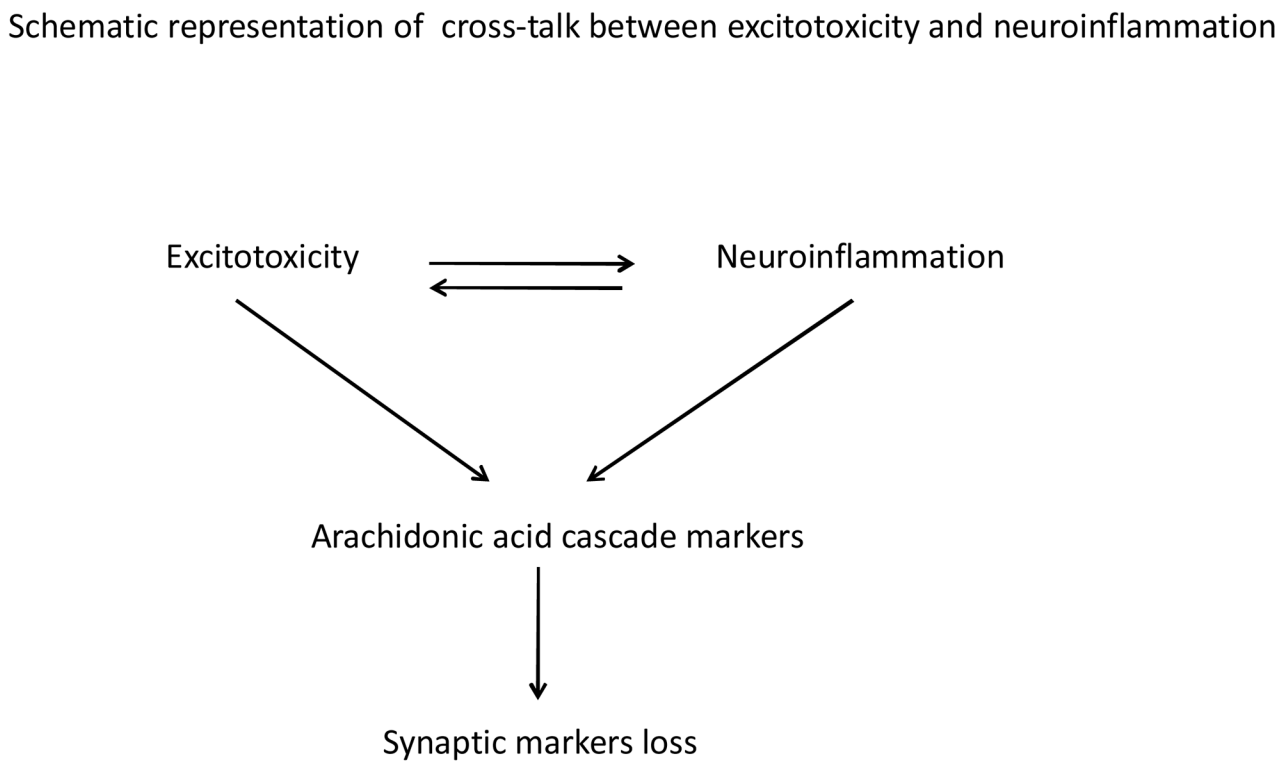

Figure 2.
Representation of cross-talk between neuroinflammation and excitotoxicity involving arachidonic acid cascade.