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Inflammatory, Apoptotic, and Survival Gene Signaling in Alzheimer's Disease

A Review on the Bioactivity of Neuroprotectin D1 and Apoptosis

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Abstract Aging is associated with an enhanced susceptibility to brain dysfunction, loss of memory, and cognitive decline and significantly influences the quality of life for the affected individual. Recent molecular–genetic approaches have provided powerful insights into common age-related diseases that are both progressive and multifactorial, such as Alzheimer's disease (AD), and in vitro in AD models. These investigations have uncovered consistent deficits in brain gene signaling mechanisms and neurotrophic substances known to contribute to normal brain function. Inflammatory signaling pathways involving upregulation of cytosolic phospholipase A_2 and the arachidonic acid cycle, the depletion of the brain-essential fatty acid docosahexaenoic acid (DHA) and DHA-derived neuroprotectin D1, and changes in the expression of key proapoptotic and antiapoptotic members of the Bcl-2 gene family are thought to be major contributors to pathogenic processes in degenerating brain tissue. This review will focus on the roles of stress genes, apoptosis-related genes, and inflammation in the molecular genetics of AD with emphasis on the interactive nature of inflammatory, neurotrophic, and apoptotic signaling and will highlight areas of rapid progress in the characterization of action of DHA and neuroprotectin D1 and address important research challenges. We also attempt to integrate these molecular, genetic, and neurochemical changes with cellular pathways involved in brain aging to formulate an integrated understanding of multifactorial age-related neurologic disease and pharmacotherapeutic strategies that may be useful in the restoration of homeostatic brain function.

Keyword Alzheimer's disease (AD) · Apolipoprotein E4 (ApoE4) · Apoptosis · Bcl-2, docosahexaenoic acid (DHA) · Multifactorial · Neuroprotectin D1 (NPD1) · Phospholipase A2 · Reactive oxygen species (ROS)

List of Abbreviations

Aβ42	amyloid beta 42-amino-acid peptide
AA	arachidonic acid
AD	Alzheimer's disease
ApoE4	apolipoprotein E4 allele
βAPP	beta-amyloid precursor protein
COX-2	inducible cyclooxygenase-2
$cPLA_2$	cytosolic phosphoilpase A_2
DHA	docosahexaenoic acid
HNE	hydroxynonenal
LOX	lipoxygenase
LPX	lipoxins
LTR	leukotrienes
NFT	neurofibrillary tangles
NPD1	neuroprotectin D1
PG	prostaglandin
PLA_2	phosphoilpase A_2
PUFA	polyunsaturated fatty acid
ROS	reactive oxygen species
SP	senile plaque
sAPPα	soluble amyloid precursor protein alpha fragment
$sPLA_2$	secreted phosphoilpase A_2
TNFAIP2	tumor necrosis factor alpha inducible protein-2 (B94)

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Introduction

Neuropathological and cognitive changes that accompany dementia syndromes in aged humans are progressive, interrelated, and highly complex. Alzheimer's disease (AD) represents the most prevalent neurologic dysfunction in aging Western and Asian populations, currently affecting about 6 million Americans, or about 2% to 3% of the populations of modern industrialized societies. Although the first case of AD was described over 103 years ago, the pathogenic evolution of AD is still not completely understood. Contributory and highly interrelated factors for AD include familial and inherited gene polymorphisms, environmental toxins, prior viral infection, cerebral hypoxia, ischemia and hypoperfusion, cerebrovascular and neurovascular disease, dysregulated proinflammatory signaling, and the appearance of molecular lesions that include deposition and aggregation of amyloid beta (Aβ) peptides as senile plaques (SPs) and tau-protein containing neurofibrillary tangles (NFTs; *1-5*). Importantly, SP and NFT lesions show nonrandom patterns of deposition in the association neocortex and hippocampus, relatively recently evolved brain compartments in humans. These limbic regions are involved in higher cognitive function and memory and where AD-type neuropathological changes make their earliest as well as most severe appearance [1, 2]. Similarly, large pyramidal neurons in layers 3 and 5 of the association neocortex seem to be preferentially atrophied by the AD process and display significant loss of arborization [1–3]. Why these large pyramidal neurons are preferentially targeted by the AD process is not well understood, but may be related to their large relative surface area and high rates of metabolism and DNA transcription [4–8]. Aged and AD-affected brains both exhibit somewhat similar physiological and pathological changes; however, the extent and severity of these changes are greatly amplified in transition from normal, healthy aging to AD. Full genome-wide gene expression profiling studies using high-density DNA array technologies have indicated a generalized depression in the expression of brain-specific genetic information in AD when compared with cognitively normal, age-matched brain [5–12]. These changes include deficits in the abundance of RNAs encoding neurotrophic factors, synaptosomal and signaling elements, caspases and other apoptosis-related factors, metal ion regulatory proteins, and signaling pathways involved in energy metabolism [4–9]. Importantly, in AD, there appear to be specific defects in the mechanisms that regulate gene transcription, translation, and protein processing for structural molecules that define the cytoarchitecture, and thereby the synaptic circuitry, connectivity, and signaling capabilities of the neural network. Cumulatively, these genetic deficiencies correlate well with the characteristic atrophy of vulnerable neurons and synaptic structures within AD-affected brain areas at postmortem examination and the degree of cognitive decline observed in premortem clinical testing [5, 6, 10]. In contrast to the approximate two thirds of the total expressed brain genome found to be repressed in AD, there exists an additional family of NF-kappaB up-regulated genes that encode interactive elements involved in stress response, proinflammatory, and proapoptotic signaling [4–6, 11–13].

Recent research evidence suggests that at least three major molecular–genetic pathways contribute to the progressively dysfunctional, gene-mediated pathogenesis observed in AD-affected brain: [14] inflammatory signaling pathways that involve an up-regulation of cytosolic phospholipase A_2 ($cPLA_2$) and the arachidonic acid (AA) cycle, [15] the depletion in critical brain regions of the essential fatty acid docosahexaenoic acid (DHA) and the 15-lipoxygenase (15-LOX) DHA-derived neuroprotectin D1 (NPD1), and [16] changes in the expression of key proapoptotic and antiapoptotic members of the ~25 member Bcl-2 gene family that regulate brain cell fate decisions and caspase-3-mediated events that trigger cytochrome *c* release and apoptosis (Fig. 1). Interestingly, caspases may have a proximal role in the progression of neurodegenerative disease and not just in the terminal stages of neurodegeneration. For example, increased expression and activation of caspases is observed in subjects with mild AD [17–20]. Aβ peptide-triggered oxidative stress induces caspase activation through the intrinsic mitochondrial pathway, and activation of executioner caspases, particularly caspase-3, may preferentially promote amyloidogenic βAPP cleavage, potentially resulting in a feed-forward cycle of Aβ peptide production and caspase-3 activation [18, 19]. Tau is also a substrate for caspase-3, and cleavage of tau may promote Aβ peptide aggregation, paired helical filament formation, and nerve terminal degeneration [18–20]. The benefit of inhibiting the intrinsic apoptotic biochemical cascade has been further demonstrated in a triple transgenic AD mouse model wherein overexpression of the antiapoptotic Bcl-2 gene blocked activation of caspase-9 and caspase-3; tau and βAPP processing were suppressed, numbers of NFTs and Aβ42 peptide deposition were reduced, and memory performance was enhanced [19, 20]. As will be emphasized in the following review, these apoptotic signals and gene-mediated pathways are highly interwoven in the fabric of the AD process and represent several attractive pharmacotherapeutic targets for the clinical management of this devastating neurologic disorder.

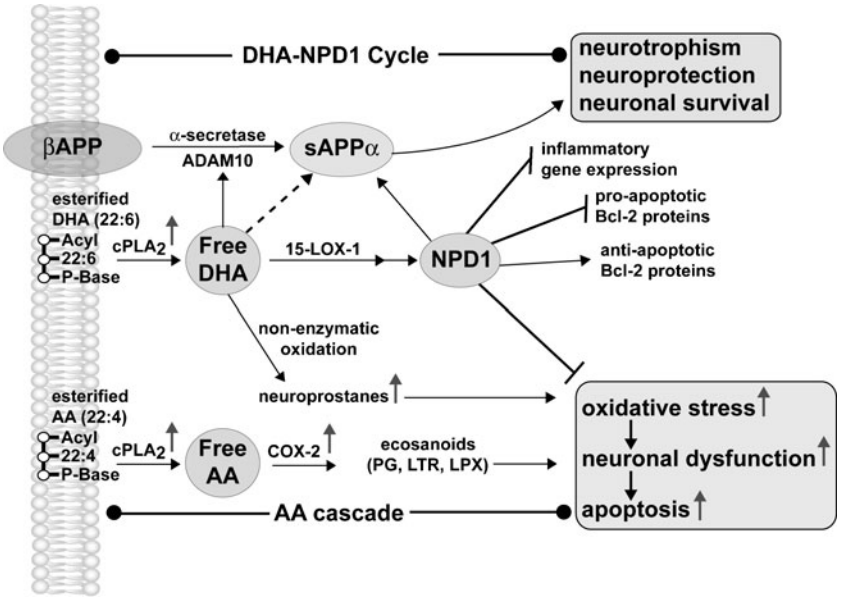

Fig. 1 Essentials of membrane-esterified DHA–free DHA and 15-LOX-mediated NPD1 generation and the AA cascade, including enzymatic and nonenymatic processing pathways for free DHA. Liberation of free DHA and AA from phospholipid membrane stores is rate-limited by a tightly regulated brain-enriched, $cPLA_2$. DHA from the omega-3 essential fatty acid family preferentially accumulates within neuronal and retinal phospholipids of central nervous system membranes, concentrating specifically within neuronal plasma membranes, synapses, and retinal photoreceptors. Free DHA derived from membrane DHA stores (*upper*) liberated via $cPLA_2$ cleavage may subsequently be converted into the 10,17S docosatriene NPD1 through an enzyme-mediated lipoxygenation via a 15-LOX, or 15-LOX-like enzymes. Deficits in 15-LOX abundance correlate with low NPD1 levels in stressed primary brain cells and in AD brain tissue. The neurobiological activity of DHA-derived NPD1 in cultured human retinal pigment epithelial and human neural cells has been characterized as a potent cytoprotective and neuroprotective oxygenated lipid mediator. Some of these neurotrophic and neuroprotective properties may be mediated through an integral membrane protein βAPP-derived sAPPα via a nonamyloidogenic, α-secretase (ADAM10)-mediated pathway that supports neurotropism, neuroprotection, and neuronal survival. NPD1 may also directly stimulate the expression and activity of sAPPα. Neurotrophic support mediated by DHA and NPD1 enables homeostatic brain functions, and a DHA-NPD1 cycle between exogenous DHA supplies and membrane stores is maintained. Membrane-esterified and free DHA is also rapidly oxidized nonenzymatically by molecular oxygen (O_2) and free nitrogen radicals to form F4 neuroprostanes, a class of peroxidized lipids that further support oxidative stress and cellular apoptosis leading to brain cell dysfunction. These nonenzymatic reactions may be quenched by specific antioxidants or free radical scavengers. Increases in $cPLA_2$ expression are highly characteristic of AD neuropathology. Free AA derived from membrane phospholipid stores (*lower*) liberated via $cPLA_2$ may be subsequently acted upon by a constitutive COX-1 or an inducible COX-2 enzyme to yield eiconasoids, including prostaglandins (PG), leukotrienes (LTR), lipoxins (LPX), and other highly active lipid mediators. When overproduced, these trigger oxidative stress, inflammatory signaling, and brain cell apoptosis leading to cellular dysfunction and apoptotic brain cell death. The specific paracrine interactions between neurons, astroglia, and endothelial cells of the neurovascular unit are just beginning to become understood [53]. Pharmacologic strategies that increase DHA and NPD1 signaling and quench AA-mediated pathogenic signaling might be expected to be beneficial to brain cells in reducing oxidative stress, brain cell dysfunction and apoptosis, and extend homeostatic neural network functions of the brain that include memory and cognition [54]. Some outstanding research questions are summarized in Table 1

Cytosolic Phospholipase A_2 and the Arachidonic Acid Cycle

A consistent observation in the neocortex and hippocampal region of AD affected brains is increases in the expression and activity of cytosolic phospholipase A_2 ($cPLA_2$), a ~ 100 kDa, intracellular, calcium-dependent membrane-associated esterase. As a brain-enriched member of a larger phospholipase A_2 gene family, $cPLA_2$ hydrolyzes the *sn*-2 position of membrane glycerophospholipids, liberating free arachidonic acid (AA), docosahexaenoic acid (DHA), and an array of bioactive lipids that regulate vital aspects of neural membrane biology, including protein–lipid interactions, transmembrane, and transsynaptic signaling. An omega-6 fatty acid (20:4,n-6), AA is one of the most abundant lipids in the brain and is present in similar quantities to DHA (22:6,n-3), and these two polyunsaturated fatty acids account for approximately 20% of the brain's total lipid content [21]. Like DHA, which is discussed further below, neurologic health is highly reliant on sufficient levels of AA, which maintain hippocampal cell membrane fluidity and other brain essential signaling functions [21, 22].

Table 1 Interactions between the AA cascade, DHA, and NPD1 and other aspects of DHA-NPD1 metabolism in AD are not well understood, and several key questions remain to be answered (see also Fig. 1)

Outstanding Research Questions
Does an impairment in NPD1 biosynthesis take place during the early development of AD?
Does NPD1 act at the convertase level to regulate ADAM10 maturation?
Does NPD1 modulate chaperone transcription related to βAPP processing?
Is NPD1-mediated alpha secretase activation the driving mechanism of neurotrophism?
Are astrocytes, glial, or endothelial cells engaged in NPD1-mediated actions?
What mechanisms regulate $cPLA_2$ activity to specifically liberate DHA and AA?
Is the redox status of the cell an important regulating $cPLA_2$ activity or the presence of free, nondegraded DHA pools?
What signaling elements of the DHA-NPD1 cycle and the AA cascade are biologically interconnected?

Metabolites of $cPLA_2$ may act as second messengers themselves, or are further metabolized to yield bioactive lipid mediators such as free fatty acids, lysophospolipids, platelet-activating factor, eicosanoids such as the prostaglandins, and reactive oxygen species (ROS) from AA, the end-product of $cPLA_2$ action on membrane phospholipids, and the rate-limiting enzyme in the AA cycle. Overactivation of $cPLA_2$ is believed to be an important instigator of inflammatory brain diseases—interestingly, secretory PLA_2 ($sPLA_2$) are primary constituents of insect and snake venom that releases large amounts of AA from the phospholipid membrane stores at the site of injury resulting in a highly localized inflammatory response [23, 24]. Cyclooxygenase-2 (COX-2) and $cPLA_2$ are inducible brain enzymes that act in tandem on the breakdown of membrane glycerophospholipid stores interrelated bioactive lipids that promote neural inflammation and apoptotic signaling up-regulation in AD brain [25–31].

Docosahexaenoic Acid and Neuroprotectin D1 in Aging and in Alzheimer's Disease

The essential marine-derived omega-3 polyunsaturated fatty acid docosahexaenoic acid (DHA; 22:6n-3) is selectively concentrated in neuronal, synaptic, and retinal membranes. In fact up to 60% of fatty acids esterified in neuronal cell membrane phospholipid stores consist of DHA, so brain cells have a convenient and readily accessible supply of DHA, that through phospholipase activites, liberate DHA from membranes to serve in neural signaling, cell survival, and cell fate pathways. Stereospecific oxygenated derivatives of DHA created through 15-lipoxygenase (15-LOX) action on free DHA, further generate neuroprotectin D1 (NPD1) that elicits potent cytoplasmic, neural, and retinal protective effects. The neurophysiological actions of esterified DHA occur in part through the highly flexible nature of this 22:6n-3 fatty acid, the maintenance of plasma membrane integrity, and lipid bilayer biophysical effects, improving neurotransmission via increased receptor binding and enhancement in the function of ion channels and affinity of receptors [32–34].

The beneficial actions of free DHA and NPD1 appear to mainly occur (a) through the repression of the induction of inflammatory signaling mediators such as the inducible COX 2 enzyme, (b) through the recruitment of antiapoptotic members of the Bcl-2 gene family, and (c) through the repression of proinflammatory and proapoptotic signaling genes and their translation products [34, 35]. AD exhibits a progressive deposition of ragged amyloid beta (Aβ) peptides derived from the beta-gamma (β-γ) secretase pathway that processes beta-amyloid precursor protein (βAPP) into the more toxic forms of βAPP-derived fragments. Aβ peptides themselves and downstream consequences of Aβ peptide signaling are pro-oxidative, neurotoxic, proinflammatory, and proapoptotic. The enzymatic generation, speciation, and trafficking of βAPP and Aβ peptides in AD and in experimental AD models are impacted by DHA concentration, by the bioavailability of unesterified DHA, and by derivatives of DHA such as NPD1.

DHA is essential for prenatal brain and retinal development and normal, homeostatic cognitive, and visual functions. Dietary deficiencies in DHA are associated with neurologic and retinal dysfunction and cognitive and visual decline. Deficits in DHA and NPD1 abundance are associated with the neurodegenerative mechanisms that characterize AD [35–38]. DHA levels are lower in the blood plasma and brains of AD patients, which may be the result from low dietary intake and/or enhanced oxidation of these highly labile polyunsaturated fatty acids [35, 38]. Moreover, diets enriched in DHA reduces amyloid burden in an aged AD transgenic mouse models [32–34]. Interestingly, apolipoprotein E4 (apoE) genotype influences responsiveness to dietary DHA treatment and DHA supplementation to patients containing ApoE4 genotypes are not as effective as patients with "lower risk" genotypes, such as those homozygous for ApoE3 [39–42]. In a more

recent study of 2,233 at-risk patients in four different US communities, the consumption of fatty fish was associated with a reduced risk of dementia and AD for those without the ApoE4 allele; carriage of an ApoE4 allele greatly reduced or eliminated DHA benefit in these patients [40]. A recent review that includes the results of several additional DHA clinical trials has recently appeared in the literature [41].

NPD1 and Activation of Antiapoptotic Members of the Bcl-2 Gene Family

Neurons cease to function and die via necrotic or apoptotic mechanisms, depending on the nature and severity of the physiological insult. In contrast to necrosis, a form of traumatic cell death that results from acute ischemic or traumatic brain injury, apoptosis is a process of programmed cell death that involves a series of biochemical events that lead to a variety of morphologic changes, including cellular blebbing, loss of membrane asymmetry and attachment, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation. However, the boundaries between these cell death mechanisms are not always distinct, and crosstalk between necrosis and apoptosis is apparent [42–44].

In aging and the more chronic and progressive AD, neuronal cell death by apoptosis is thought to be the prominent mechanism of brain cell functional decline and death. The morphologic and biochemical features and mechanisms of the different phases of apoptotic neuron death are overlapping and progressive until neuronal death occurs [44, 45]. Key proapoptotic and antiapoptotic members of the ~25-member Bcl-2 gene family regulate brain cell fate decisions, and various caspase-3-mediated events trigger cytochrome *c* release and apoptotic events. The Bcl-2 gene family can be roughly separated into two groups—those that are proapoptotic, including the members Bax, BAD, Bak and Bok, and those that are antiapoptotic, including the members Bcl-2, Bcl-xL, Bcl-w, Bfl-1(A1), and others. Bcl-2 family members appear to govern mitochondrial membrane permeabilization, achieved in part by activation or inactivation of inner mitochondrial permeability transition channels involved in the regulation of mitochondrial matrix pH and calcium levels. Bcl-2 family proteins induce (proapoptotic members) or inhibit (antiapoptotic members) the release of mitochondrial bound cytochrome *c* into the cytosol where it activates caspase-3 and caspase-9 that leads to apoptosis and cellular demise [46–48]. Interestingly, NPD1 has been shown to both up-regulate the antiapoptotic genes encoding Bcl-2, Bcl-xl, and Bfl-1(A1) in human brain cells in culture and to down-regulate the proapoptotic genes Bax and Bik [48–52]. In parallel with these beneficial effects on Bcl-2 family gene expression, NPD1 also down-regulated the expression of interleukin-1beta (IL-1β), tumor necrosis factor alpha (TNFα), cyclooxygenase-2 (COX-2), and the tumor necrosis factor alpha inducible protein-2 B94 (TNFAIP2), all members of a proinflammatory gene family known to be up-regulated in AD brain [4–9].

Summary

Due to the high metabolic index of nervous tissues, brain cells and systems require sustained antioxidative and neurotrophic support to maintain their homeostatic signaling functions. Neurodegenerative disorders such as Alzheimer's disease (AD) are associated with dysfunction and decline of key, highly interconnected pyramidal cell groups in the association neocortex and hippocampus, in part through the appearance of insoluble SP and NFT deposits, and the proinflammatory and proapoptotic pathology that these insoluble pathogenic lesions induce. Administration of DHA in clinical trials and NPD1 in cellular studies has shown multifaceted benefit in the preservation of cognition, memory, and healthy brain cell function. Lifelong impairment in the supply of DHA and NPD1 to the brain might be expected to result in a chronic loss of neurotrophic support for nervous tissues and contribute to progressive disturbances in cognition, memory, and associated higher brain functions.

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