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Hypoxia Signaling to Genes

Significance in Alzheimer's Disease

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Abstract

Aberrations in neural signaling, converging to and diverging from oxidative metabolism and blood supply, contribute to the initiation and maintenance of inflammatory responses, neuronal degeneration, and age-related cognitive decline in Alzheimer's disease (AD). Hypoxia/ischemia triggers phospholipase A_2, leading to the accumulation of free arachidonic and docosahexaenoic acids (AA, DHA), as well as that of lysophospholipids. Some of these bioactive lipid messengers in turn give rise to several downstream lipid messengers, such as platelet-activating factor (PAF) and ecosanoids (prostaglandins and leukotrienes). Eicosanoid synthesis is highly regulated in hypoxia and in reperfusion subsequent to ischemia. As one of the consequences, mitochondrial function is disrupted and reactive oxygen species (ROS) both contribute to the expansion of cellular inflammatory responses and reduce the expression of genes required to maintain synaptic structure and function. On the other hand, pro-inflammatory genes are up-regulated. One of these, the inducible cyclooxygenase-2 (COX-2), along with oxygen-starved mitochondria, comprise the major sources of ROS in the brain during hypoxia, ischemia, and reperfusion. One outcome is a sustained metabolic stress that drives progressive dysfunction, apoptosis and/or necrosis, and brain cell death. How hypoxia modulates oxygen-sensitive gene expression is not well understood. Pro-inflammatory gene families that contribute to neurodegeneration are transiently activated in part by the heterodimeric oxygen-sensitive DNA-binding proteins nuclear factor for kappa B (NF-κB) and hypoxia-inducible factor-alpha (HIF-1α). Here the authors summarize current studies supporting the hypothesis that synaptically-derived lipid messengers play significant roles in ischemic stroke and that hypoxia is an important contributor to the onset and progression of AD neurodegeneration.

Index Entries: Alzheimer's disease; beta-amyloid; brain transcription; cyclooxygenase-2 (COX-2); HIF-1α; hypoxia; inflammatory signaling; ischemia; gene expression; presenilin-1 (PS1); presenilin-2 (PS2); reactive oxygen species (ROS).

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Introduction

Neurons are highly vulnerable to impairments in oxygen homeostasis because of their singular dependence on oxygen. The human brain averages just 2% of body mass, yet utilizes 15% of cardiac output and 20% of respiratory oxygen uptake. The brain undergoes damage and neural dysfunction after only a few minutes of oxygen deprivation; if oxygen deprivation lasts longer than 5 min, apoptotic and/or necrotic cell death occurs. In neural cells in primary culture and in the hippocampus in in vivo models, both cyclooxygenase-2 (COX-2) and presenilin-1 (PS1) are induced after only 5 min of hypoxia/ischemia *(1–8)*. Overexpression of these pro-inflammatory genes appears to redirect cellular fate toward intracellular signaling dysfunction and apoptotic cell-death *(9–21)*. For example, hypoxia/ischemia enhances COX-2 expression in neurons of the cerebral cortex and hippocampus, and as a result, prostaglandins (PG) and reactive oxygen species (ROS), principally the peroxides and hydroxides O_2-, OH-, and H_2O_2, are generated. PG overproduction and reactive oxygen species promote transient and concentration-dependent neuronal signaling dysfunction. After brief periods of hypoxia, re-establishment of normoxia is accompanied by a surge of ROS and inflammatory gene induction *(8,10,15,18–22)*. This enhanced physiologic signaling initiates and amplifies brain-specific inflammatory responses to hypoxia, leading to the robust synthesis of cytokines, PGs, eicosanoids, related lipid mediators, and ROS *(18,19,23–25)*. Cell cultures and transgenic models suggest interactive relationships between hypoxia, microglial activation, neuro-inflammation, reduced neuronal function, and apoptosis and/or necrosis *(19–21)*. Indeed, hypoxic injury triggers COX-2-mediated arachidonic acid (AA) metabolite synthesis, which in turn contributes to altered metabolism and AD neuropathology *(8,10,15,26,27)*.

Epidemiology of Alzheimer's Disease

AD is a complex, progressive degeneration of the neurons of the neocortex, characterized by memory loss and deterioration of higher cognitive function. Aging is the most significant risk factor for AD; however, the exact sequence of events that initiates this disorder remains unclear. Both AD prevalence and incidence double every 5 yr after the age of 65 yr. AD currently affects about 8% of the US population aged 65 yr and over and increased cognitive deficits strongly correlate with AD mortality. Demography indicates that the rapidly aging US population will soon incur massive increases in the number of AD cases that will overwhelm our healthcare system and exceed our ability to adequately care for people afflicted with this devastating disorder of the mind *(12–22,26,28–30)*.

Besides aging, an intricate maze of factors contributes to the development and progression of AD. Epidemiologic studies indicate that mutations in gene-coding regions, susceptibility polymorphisms in gene-control regions, traumatic head injury, environmental factors involving zinc and/or aluminum, or other environmental neurotoxins, cerebrovascular disease, and ischemia and/or hypoxia, are factors for AD development *(30–37)*. Classically, the density of neurofibrillary tangles (NFT) and peptides derived from beta-amyloid precursor protein (βAPP) have been correlated with AD progression. However, recent evidence suggests that neuronal atrophy and disintegration of synaptic contacts are more relevant pathologic markers *(9,38,39)*. Molecular genetic evidence indicates considerable heterogeneity in AD. For example, while a small number of familial AD cases exhibit linkage to mutations in the βAPP, PS1, and PS2 genes, which encode integral membrane proteins, or the presence of the apolipoprotein E-epsilon 4 (ApoE4) allele, which encodes a blood-borne lipoprotein carrier, the vast majority of AD cases are of sporadic or unknown origin *(26,29,37,40–43)*. Moreover, while specific βAPP, PS1, PS2, and ApoE genotypes are associated with different relative risks and age-of-onset distributions for AD etiopathology, genetic variation also influences important aspects of clinical AD

phenotype, such as severity, symptomatology, and disease duration *(24–26,40–43)*.

Pathophysiology of Alzheimer's Disease: Amyloid and Reactive Oxygen Species

AD pathophysiology involves proliferation of astrocytes, gliosis and microglial activation, alterations in neuronal shape, cytoskeletal abnormalities, synaptic and neurotransmitter deficits, transcriptional, translational, and protein-processing defects, and progressive atrophy and loss of large neurons. AD was originally characterized by the presence of agyrophilic brain lesions that include abnormally hyper-phosphorylated forms of the microtubule-associated protein tau, which forms the core of intraneuronal NFT, and also by aggregates of insoluble extracellular beta-amyloid (Aβ) protein, derived from tandem β- and γ-secretase cleavage of βAPP. Interestingly, autosomal dominant mutations in familial AD in the βAPP gene-coding region associated with the β- and γ-secretase cleavage sites lead to increases in Aβ peptide generation, and in particular that of the highly toxic Aβ42 variant. Heterogeneous γ-secretase cleavage sites produce an array of ragged Aβ fragments, from 39–43 amino acid residues in length; Aβ peptides and especially the Aβ42 variant appear to be specifically detrimental to neural function. Firstly, Aβ peptides directly induce ROS generation, thereby activating various kinases (such as p38, PKC, ERK2, Src, RTK) via the MAP-kinase and related pathways, leading to aberrant intra-cytoplasmic phosphorylation and clumping and/or crosslinking of neural intermediate filaments *(39–41,44)*. Secondly, ROS potently induce tau glycation and promote lipid peroxidation, leading to disruption in neural membrane physiology *(15,24,27,37,43)*. In addition to deregulating intracellular protein kinase signaling, both NFT and Aβ aggregates contribute to disruption and extracellular disorganization of synaptic circuitry in the association hippocampus, neocortex, and basal forebrain cholinergic system, leading to impairments in inter-neural signaling and cognitive dysfunction *(35–38)*. Moreover, disturbances in βAPP gene expression may have consequences in the expression of other AD modifier genes, such as PS1 and PS2 *(41–43)*. For example, animals doubly transgenic for mutant βAPP and PS1 show altered βAPP processing and accelerated Aβ formation, indicating contributions to AD pathology from at least two chromosomally unlinked genes. However, deficiency of other features of AD in doubly transgenic animals, such as absence of NFT and neuronal loss, suggests that additional factors are involved in modifying AD genotype *(18,24,45)*. Widespread dysregulation in gene transcription supports the idea of alterations in entire families of brain-specific genes in both familial and sporadic AD. Deficits in the expression of neurotrophic factors, transcription factors (TFs), antioxidant enzymes, and cytoskeletal and synaptic components are all implicated in AD *(9,38,39,46–48)*, as are the regulatory mechanisms that control transcription from these genes *(8,48–51)*. Broad-spectrum DNA array analyses further corroborate that selective deregulation of brain RNA-message output is a consistent feature of AD, and that while the majority of gene transcripts are down-regulated, certain RNA messages encoding stress and inflammatory mediators exhibit marked overexpression *(8,52–55)*. In addition, epidemiologic evidence indicates that anti-inflammatory compounds, such as glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs) ameliorate, at least partially, AD progression *(55–58)*. COX-2, the key pro-inflammatory gene encoding an inducible oxidoreductase enriched in brain neurons, is consistently up-regulated both at the RNA-message and protein level in the AD-affected neocortex and hippocampus, again implicating the activation of ROS-mediated signaling and inflammatory pathways in AD etiopathology *(1,2,8,55,58–60)*.

Ischemia and Hypoxia as Risk Factors

Cerebral ischemia (restriction in blood supply) and hypoxia (decreased oxygen availabil-

ity) are potent inducers of Alzheimer-type change *(28,43,61)*. Substantial evidence indicates that increased ROS are associated with aging and age-related degenerative disorders not only in AD, but also in Parkinson's disease, atherosclerosis, arthritis, and stroke *(62)*. Besides selective neocortical neuron-death and progressive Aβ-deposition, AD neuropathology is further characterized by microglial-mediated cytokine signaling. Interestingly, after 24 h of exposure, Aβ can elicit a greater reduction in neuroblastoma cell-viability and a greater increase in ROS than can glutamate *(44)*. Indeed, hippocampal neurons appear to be exceptionally sensitive to gene-expression changes triggered by cytokines such as IL-1β, toxic peptides such as Aβ42, and hypoxia, and there appear to be cumulative and synergistic effects of these factors during aging *(8,55)*. Postmortem examination of asphyxiated infants who have died from hypoxia has shown that the hippocampus was the brain locus where neuronal degenerative changes were most clearly observed, and these changes included astrogliosis and the appearance of stellate glia and AD-type astrocytic changes *(4,7,61–63)*. Under nonlethal clinical conditions, early oxygen deprivation during human brain development may therefore predispose neural tissues to various subsequent events in endothelial cells and neurons during the perinatal period, with progressive metabolic dysfunction as the brain ages *(8,13–15,20,63,64)*. Ischemic episodes later in life, such as repeated transient ischemic events, neurotrauma, or stroke, may also predispose the brain to AD-development, and clinical data support this concept. The authors have tested these ideas in experimental models and portions of these results have been published *(8,15,53)*.

Hypoxia and Nuclear Factor for Kappa B

Originally described as a novel *trans*acting nuclear protein that binds to the promoter of the immunoglobulin kappa light chain gene in human B cells *(65–70)*, the significance of NF-κB has expanded to a more general role as an early and rapid-response, ROS-sensitive regulator of genes involved in apoptosis, inflammation and the immune response, signal transduction, synaptic transmission, and neuronal plasticity *(65–75)*. In the resting cytoplasm, NF-κB exists predominantly as a p50-p65 heterotypic dimer electrostatically complexed with Iκ-B inhibitory protein; however, upon physiologic or pharmacologic induction, Iκ-B is serine-phosphorylated, ubiquitinated, and degraded by the proteasome complex *(72,73)*. This enables NF-κB to undergo translocation to the nucleus, where it binds target-DNA-consensus sequences homologous to 5′-GGGGACTTTCCC-3′ in NF-κB-sensitive gene promoters and modulates transcription *(65,66,68,74)*. The growing family of 20 or more NF-κB and I-kB genetic variants adds a further dimension of complexity to NF-κB and I-kB regulation and brain genetic circuitry under NF-κB control *(55,66,68)*. Because the NF-κB complex exists as a latent cytoplasmic TF with regulated activity, it provides a rapid signaling link between extracellular events, the cytoplasm, and the nucleus, typically on the order of minutes *(55,68,75)*. NF-κB co-localized to postsynaptic densities further suggests a role for this TF in retrograde signal transmission from the synapse to the nucleus *(71,75,76)*. Interestingly, rapid NF-κB-promoter DNA signaling is triggered by a remarkably diverse array of physiologic and pharmacologic ligands, particularly via ROS directly or by events induced by ROS, by ultraviolet irradiation, by viral, bacterial, and membrane or cellular catabolic products resulting from acute or chronic brain injury *(68,72,74)*; by Aβ peptides *(55,77,78)*, by neurotransmitters such as glutamate *(79)*, by chemotactic peptides *(80)*, by growth factors such as nerve-growth factor *(81)*, and by diverse classes of neuroactive pharmacologic agents including salicylates and opioids *(81–83)*. NF-kB knockout mice further illustrate the importance of NF-κB as a ROS-responsive TF in the maintenance of postmitotic neuronal function during aging; neuronal ROS production appears to be specifically involved in signal-transduction pathways that culminate in NF-κB activation and gene signaling *(75,84–86)*. Mobilization of NF-κB occurs in

acute brain-injury models, such as in aluminum-induced neurotoxicity *(33,86,87)*; in hypoxia and ischemia-reperfusion damage; during kainate-induced seizures *(68,85,86)*; in cerebral infarctions *(88)*; in neurodegenerative disorders including amyotrophic lateral sclerosis, Down's syndrome, Parkinson's disease, and AD *(15,55,59,71,89)*; and in the activation of human viral genes associated with neurodegeneration, including human immunodeficiency virus *(68–71)*. Acute brain injury also appears to increase the production of IL-1β and related cytokines, which, through the IL-1 type 1 receptor *(72,90)*, then mediate rapid transcription from pro-inflammatory genes under NF-κB control *(3,75)*. Via ROS production, prominent NF-κB targets include the promoters of genes encoding pathologic cytokines, such as TNFα, IL2, and IL6, vascular and intracellular adhesion molecules (VCAM-1 and ICAM-1), superoxide dismutase, βAPP, PS1, PS2, interferon β, interleukin-1β precursor, cytosolic phospholipase A_2 ($cPLA_2$), and the inducible forms of nitric oxide synthase (NOS) and COX-2 *(55,84–91)*.

Hypoxia-Inducible Factor

Analogous in structure, function, and mechanism of activation to NF-κB is hypoxia-inducible factor-1 (HIF-1). HIF-1 is a heterodimeric DNA-binding protein consisting of a ROS-, cytokine-, growth factor-, and metal ion-induced HIF-1α and a constitutive HIF-1β/aryl hydrocarbon receptor nuclear transporter (ARNT) element, which in hypoxia promotes the expression of adaptive genes involved in angiogenesis, erythropoiesis, glycolysis, and related energy functions *(92–99)*. During normoxia, the HIF-1α subunit is directed to rapid ubiquitination and proteasomal degradation; however, during hypoxia HIF-1α persists, heterodimerizes with HIF-1β, and translocates to the nucleus, where it drives transcription of genes whose *cis*-regulatory domains contain the relatively rare hypoxia response element (HRE) 5′-RCGTG-3′ *(92–94)*. Non-homeostatic or runaway HIF-1α and HIF-1 heterodimer production rapidly triggers aberrant gene expression in angiogenesis, erythropoiesis, glycolysis, and neovascularization, often with progression to a lethal phenotype *(92,93,97–100)*. It is interesting that the inflammatory cytokine IL-1β partially mimics cellular hypoxia, leading to increased HIF-1α-DNA binding and activation of COX-2 and PS2 in human gingival and synovial fibroblasts and in rat and monkey retinal neurons (*53,93–95*; unpublished results from the authors' laboratory). In addition to hypoxia and IL-1β, HIF-1α is also activated by the divalent transition metals Co^{2+}, Fe^{2+}, Ni^{2+}, Mn^{2+}, Zn^{2+}, and the trivalent neurotoxin Al^{3+} *(15,33,95)*, and is blocked by carbon monoxide and nitric oxide, both of which are ligands for flavoheme protein *(93–97)*. Notably, the primary oxygen sensor for the HIF-1 signal-transduction pathway appears to be a plasma membrane-bound flavoheme protein complex that involves a membrane-bound Fe^{2+}-Fe^{3+}/FADH-FAD redox shuttle sensitive to changes in both extracellular oxygen and intracellular ROS *(93,97–100)*. Mitochondrial electron transport chain activity also appears to be required for activation of HIF-1 *(92)*. HIF-1 activation is inhibited by normoxia or factor inhibiting HIF-1 (FIH-1), a transcriptional corepressor that binds to HIF-1α and inhibits its *trans*activation function by recruiting histone deacetylases *(98)*. Features of the HIF-1 signal-transduction cascade and mobilization of HIF-1-sensitive gene families are shown in Figures 1 and 2.

Inflammatory Signaling in Alzheimer's Disease

Activation of ROS, oxidative stress, and pro-inflammatory signaling initiate and accelerate neural cell degeneration in AD association neocortex and hippocampal CA1 *(12,13,56,57,100–103)*. Inducible up-regulation of eicosanoids by COX-2 is observed in AD hippocampus and neocortex. Moreover, in transgenic mice that overexpress functional human COX-2 in hippocampal neurons, cog-

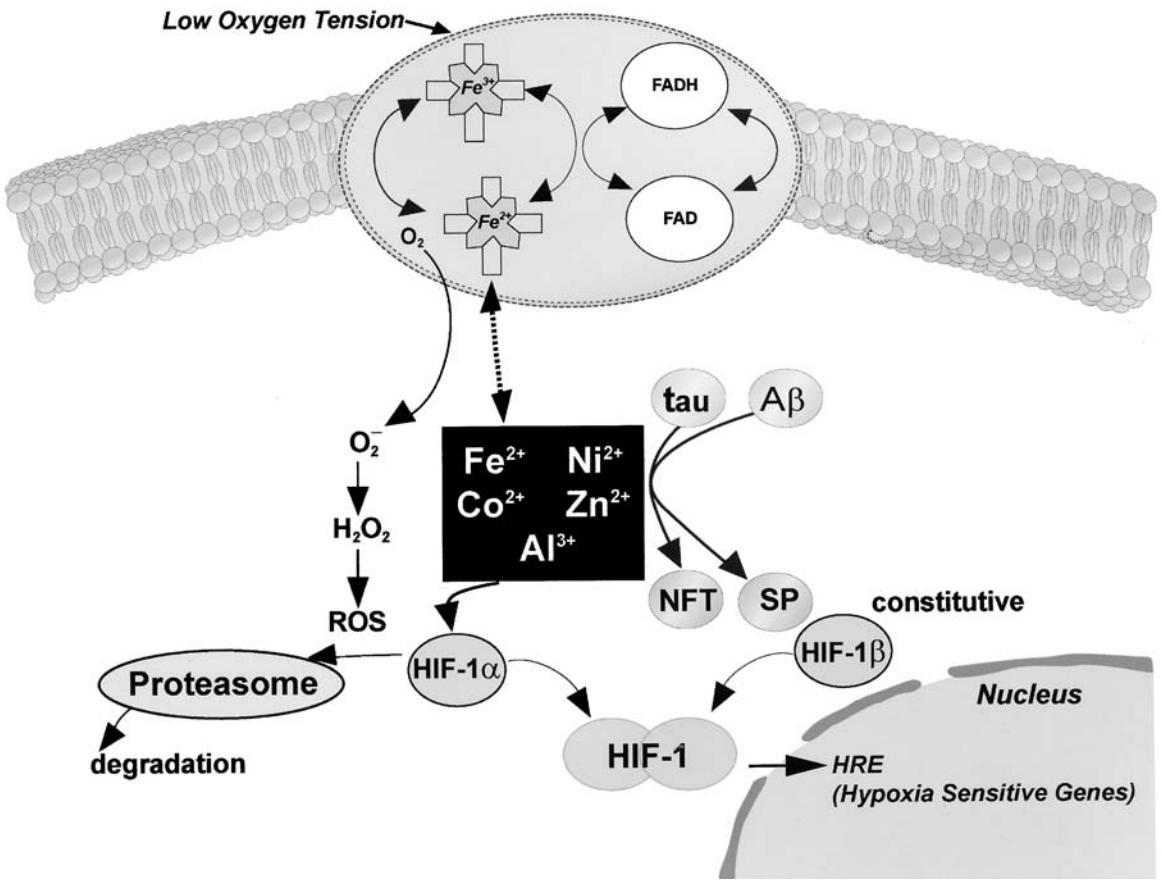

Fig. 1. Hypoxia-inducible factor-1 (HIF-1) in oxygen sensing and signaling (adapted from refs. *92–97*). The primary oxygen sensors are postulated to be heme moieties localized within the plasma membrane *(93,94,96,97)*. During normoxia, the HIF-1α subunit undergoes rapid ubiquitination and proteasomal degradation; however, during hypoxia or pathophysiologic conditions involving prolonged periods of ischemia and/or hypoxia, HIF-1α persists, heterodimerizes with a constitutively generated HIF-1β, and translocates to the nucleus, where it drives transcription of hypoxia-sensitive genes whose *cis*-regulatory domains contain the relatively rare hypoxia response element (HRE) 5′-RCGTG-3′ *(92–94)*. Interestingly, Co^{2+}, Fe^{2+}, Ni^{2+}, Mn^{2+}, Zn^{2+}, and the trivalent neurotoxin Al^{3+} (alone or in combination) do not require hypoxia to activate HIF-1α. These elements also drive tau and Aβ aggregation into neurofibrillary tangles (NFT) and senile plaques (SP), respectively, in AD brain *(93,96,97)*. Neurofibrillary tangles and senile plaque deposits are instrumental in proliferating the brain's inflammatory response, largely via the increased production of ROS (*see* Figure 3).

nitive deficits evolve in an age-dependent manner *(102,103)*. PS1/PS2 holoproteins, localized to lipid raft domains in the nuclear envelope and endoplasmic reticulum, function in a nicastrin-mediated generation from βAPP of neurotoxic, amyloidogenic Aβ peptides *(15,104)*. Importantly, transgenic animals bearing PS1/PS2 mutations or PS1/βAPP doubly transgenic animals exhibit accelerated Aβ generation and brain microglial activation that increase synchronously with Aβ deposition *(105–109)*. The outcome of this pathologi-

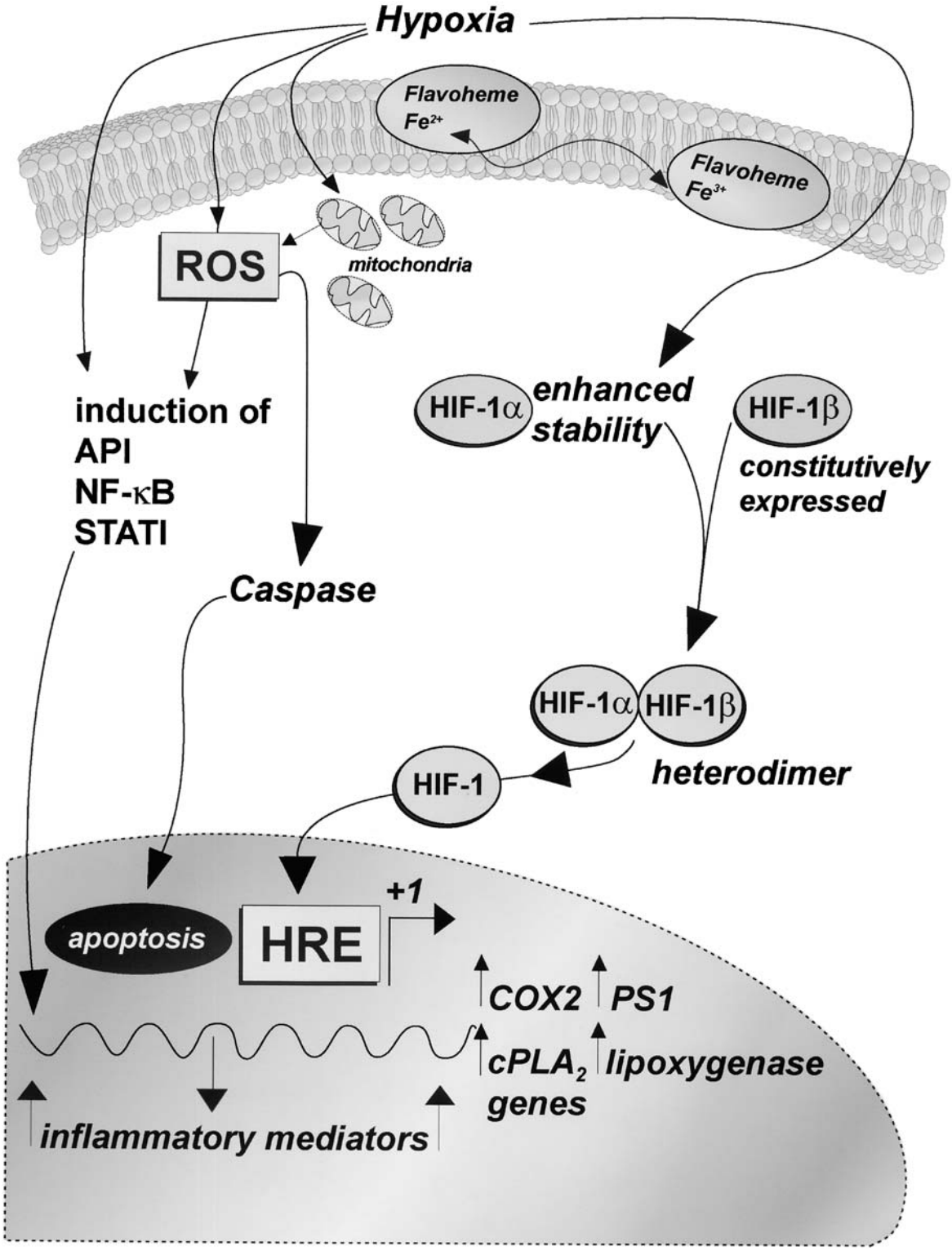

Fig. 2. Hypoxia-sensitive gene transcription. Non-homeostatic or runaway HIF-1α and HIF-1 heterodimer production and binding to the relatively rare hypoxia response elements (HRE) in hypoxia-sensitive gene promoters rapidly trigger aberrant gene expression in angiogenesis, erythropoiesis, glycolysis, neovascularization, and neurodegeneration, often with steady progression to a lethal phenotype *(92,93,97–100)*. ROS also induce a proinflammatory TF triad that includes AP1-, NF-κB-, and STAT-1-DNA signaling and caspases which promote nuclear apoptosis.

cal cascade are hundred-fold increases in microglial-derived IL-1β, related cytokines, and proinflammatory lipids, which directly correlate with increased βAPP processing, generation, and aggregation of Aβ peptides into insoluble brain lesions, and further proliferation of COX-2 and inflammatory AD neuropathology *(15,110,111)*.

During the microglial-mediated inflammatory response to Aβ deposition in AD, overexpression of IL-1β not only contributes to further amyloidogenic events, but also induces a triad of the ROS-sensitive pro-inflammatory TFs: AP-1α, NF-κB, and STAT1α *(11,15,59,112)*. In the human association neocortex IL-1β and AP1α-, NF-κB-, and STAT1α-DNA binding are more abundant in AD than in age-matched control brain *(55,59,111)*. Moreover, IL-1β-triggered AP-1α-, NF-κB-, and/or STAT1α-sensitive genes, such as COX-2 and PS1, appear to have strong potential to further escalate inflammatory neuropathology. While IL-1β up-regulates the expression of COX-2 and post-translational processing of βAPP into Aβ42 neuropeptides, Aβ-triggered proinflammatory and neurodegenerative signaling is also induced by hypoxia, NF-κB, and HIF-1α. Ultimately these events trigger a hypoxia-sensitive pro-inflammatory gene cascade *(8,21,112,113)*. These data collectively suggest that under conditions of NF-κB and HIF-1α activation, IL-1β and Aβ42 are further able to promote an expansion of pro-inflammatory pathology and an escalation of neurodegeneration *(8,15,53)*.

Hypoxia-Triggered Gene Networks in the Brain

Phospholipase A_2-mediated AA release (as well as that of docosahexaenoic acid) and eicosanoid synthesis by COX-2 are a rapid and early response to cerebral hypoxia/ischemia. Hypoxic brain exhibits cell-membrane damage and dysfunction, membrane lipid peroxidation, ROS generation, and activation of COX-2, cytosolic and secretory phospholipase A_2 ($cPLA_2$, $sPLA_2$) activities, and lipoxygenase, which further fuel the AA cascade *(15,61)*. In turn, AA cascades generate inflammatory mediators and trigger cellular degeneration (Figure 3). IL-1β, transforming growth factor-beta (TGFβ) and tumor necrosis factor-alpha (TNFα), secreted by microglia, astrocytes, and neurons, are early-response cytokines that influence the progression of injury by stimulating the synthesis of other cytokines and neuronal injury mediators, such as COX-2. Therefore, via the generation of inflammatory mediators that accompany hypoxia, activation of ROS and oxygen-sensitive AP-1-, HIF-1α-, NF-κB-, and STAT-1α-DNA binding trigger COX-2, PS1, and related gene expression, leading to progressive neural dysfunction. Hypoxia-modulated pathologic gene induction is therefore remarkable in that positive feedback by ROS and oxygen-sensitive TFs further recruits COX-2, PS1, $cPLA_2$, and lipoxygenase gene signaling that propagates and accelerates neurodegeneration *(15,27)*.

COX-2 and PS1 are significant players in the sequence of events leading to the expansion and acceleration of inflammatory neuropathology *(8,15,27)*. Because COX-2 can up-regulate eicosanoid production, and PS1 mediates Aβ generation, these in turn trigger microglial activation, the further release of IL-1β, and COX-2 and PS1 gene expression. Importantly, COX-2 and PS1 up-regulation is observed in IL-1β- and Aβ42-triggered human neural cells in culture, and this up-regulation is further increased after brief periods of exposure to hypoxia *(8,20–22)*. The participation of ROS in inflammatory gene recruitment is a key factor, since both COX-2 and PS1 activation can be blocked by the electron spin-trap agent and free radical scavenger α-phenyl-*N*-tert-butyl nitrone *(8,21,99)*. Interestingly, DNA microarray analysis confirms that COX-2 and PS1, as well as the NF-kBp50/p105, IL-1β precursor, and $cPLA_2$ genes, are induced both in AD and in IL-1β- and Aβ42-induced human neural cells, especially after exposure to hypoxia *(21,52–54)*. Indeed, chromosomally unlinked, inducible TATA-box-containing genes under coregu-

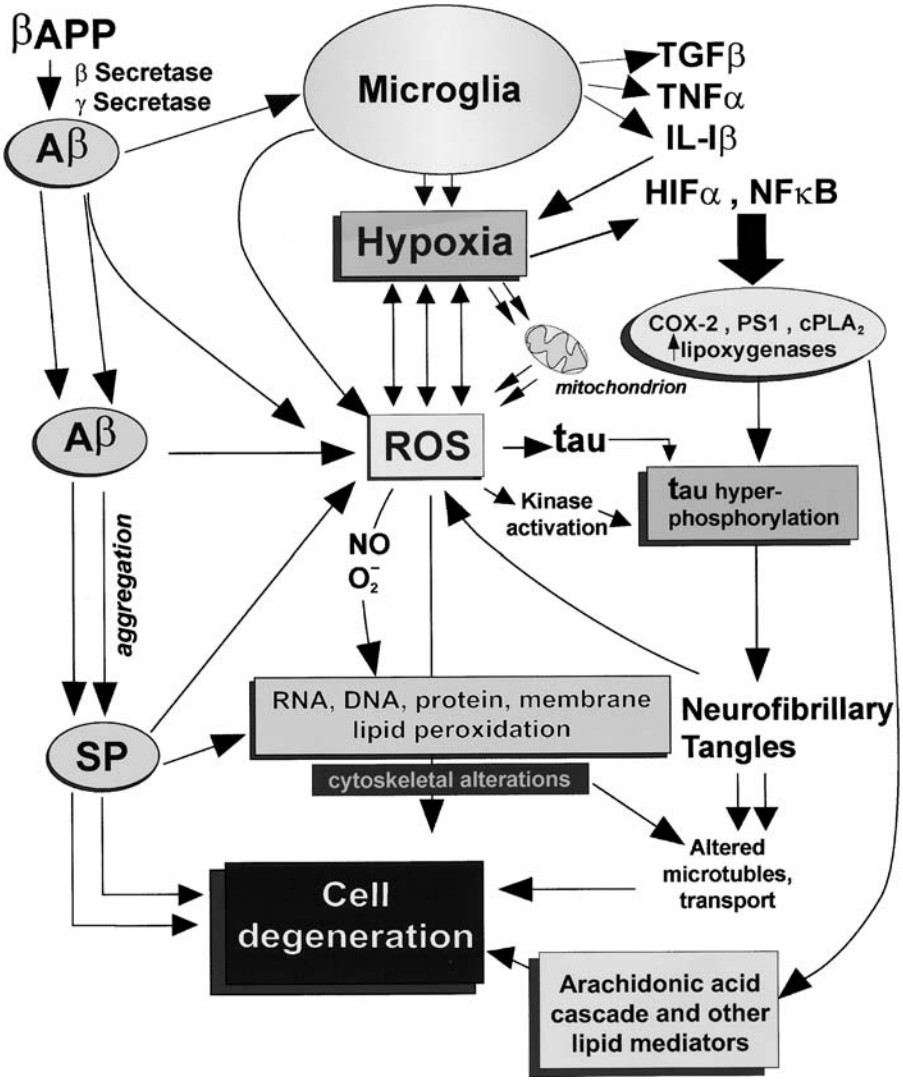

Fig. 3. Hypoxia triggers neuronal-cell degeneration. Pathways involving Aβ production and senile plaque (SP) formation are central to microglial-cytokine release, hypoxia, ROS generation, RNA, DNA, protein, and brain-lipid peroxidation. Microglial-derived cytokines proliferate hypoxia and ROS generation, which in turn, drive inflammatory AA cascades, tau hyper-phosphorylation, NFT generation and altered neural cytoarchitecture, resulting in cellular dysfunction and neurodegeneration.

lated transcriptional control by the ROS-sensitive TFs AP-1, NF-κBp50/p65, STAT1α, and HIF-1α may define, in part, a brain-specific inflammatory gene family that contribute cumulatively to pro-inflammatory neuropathology in AD and related neurodegenerative disorders *(8,15)*.

Hypoxia, Bcl2, p53 and Apoptosis

As in the case of the COX-2, PS1, NF-kBp50/p105, IL-1β precursor and $cPLA_2$ genes, signal-transduction pathways that direct cellular fate toward apoptosis and/or necrosis and neural degeneration appear to be

modulated in part by HIF-1α- and NF-κB-DNA binding in target gene promoters *(8,15,21,46,52–56,59–62)*. Hypoxia also induces NF-κB binding to the Bcl-x promoter, activating transcription and alternate RNA splicing to the Bcl-XS transcript variant that promotes hippocampal neuronal apoptosis *(114,115)*. Similarly, induction of HIF-1α-DNA binding by hypoxia induces PS2, a regulator of intercellular signaling during CNS development and cell-fate determination that is involved in βAPP processing into neurotoxic Aβ peptides *(95,96)*. Intracellular Aβ peptides are cytotoxic to human neurons in part through the p53-Bax cell death-signaling pathways *(28,115,116)*, hence PS2 gene activation during hypoxia may direct cell metabolism towards intercellular PS2-mediated signaling dysfunction. The p53 tumor suppressor that normally limits cellular proliferation by arresting cell-cycle progression also induces apoptosis as a response to hypoxia *(28,99,117,118)*. p53 is thought to mediate apoptosis through Bax transactivation, translocation from the cytosol to membranes, triggering of cytochrome c release from mitochondria, and activation of proteolytic caspases *(115,117)*. Interestingly, both wild-type and mutated PS2 appear to trigger p53-mediated apoptotic cascades, both in HEK293 human cells and in murine neurons *(119)*, suggesting a rapid and immediate link between hypoxia-activated PS2 gene expression and neural apoptosis *(92–99)*.

Summary

The etiopathogenesis of AD is multi-factorial and highly complex. This review suggests key roles for hypoxia in initiating, regulating, and proliferating inflammatory responses and determining cell-fate pathways in the brain. Abundant data from neonatal, developing, aging, and degenerating brain tissue suggest an early involvement of oxidative stress, via ROS, in the pathogenesis of AD. This may provide potential targets for therapeutic intervention, especially in individuals of families at high genetic risk for developing AD. These data also suggest that hypoxia over the course of aging may drive inflammatory gene programs via complementary, interdependent TF signaling pathways, and these may contribute cumulatively to inflammatory signaling and brain-cell degeneration. Because these inflammatory activation mechanisms can be quenched by free radical scavengers, diets enriched in antioxidants may help to repress the potential inception and development of AD and related neurodegenerative conditions.

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