AhR in the Hallmarks of Brain Aging

Subjects: Neurosciences
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AhR, a member of the basic helix-loop-helix (bHLH)-PAS superfamily, performs various functions within the brain. It is an ancient protein that possesses shared functions and structures across various species in the evolutionary tree. It is widely distributed in various regions of the brain, such as the hippocampus, the cortex, and the hypothalamus, and its expression changes during the course of brain development.

Keywords: aryl hydrocarbon receptor ; AhR endogenous/exogenous ligands ; brain aging hallmarks

1. AhR Expression, Functions, and Signaling in the Brain

In neuronal progenitor cells, AhR interacts with its partners to direct differentiation into several neuronal subtypes, as well as to influence dendrite morphogenesis [1][2][3]. Although AhR expression decreases from the embryonic period into adult life [4][5], several physiological functions remain in the adult brain, which include the regulation of neurotransmitter levels, blood-brain barrier functions, and immune responses [6][7][8]. Furthermore, AhR contributes to glial cell and neuroendocrine system function [9][10]. AhR activation interacts at various levels in the neuroendocrine system, from the hypothalamus down to the target organ [9]. For example, the AhR agonist, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) disrupts the secretion of several releasing hormones in the hypothalamus, such as corticotropin-releasing factor and vasopressin [11]. Furthermore, AhR activation in the brain leads to decreased estrogen receptors and estrogen levels [12][13]. Depending upon the ligand, AhR may act through different mechanisms to mediate its cellular and physiological functions [13]. AhR signaling is complex and broadly divided into canonical and non-canonical pathways. In the absence of ligands, AhR is predominantly found in a cytoplasmic complex with heat shock protein 90 (HSP90) dimers, HBV X-associated protein 2 (XAP-2), and p23 chaperone protein. However, in the canonical pathway, ligand activation of AhR leads to the dissociation of HBV X-associated protein 2 (XAP-2) from heat shock protein 90 (HSP90) in the cytoplasm; the activated AhR translocates into the nucleus, where it dimerizes with aryl hydrocarbon receptor nuclear translocator (ARNT) and binds to xenobiotic response elements (XREs) on the DNA, leading to the transcription of various cytochrome P450s (CYPs), and glutathione transferase (GST), which, among other events, feedback to metabolize the initial ligand. Some toxicological AhR ligands, such as TCDD and related compounds, are slowly metabolized following receptor induction, leading to persistent AhR activation [14]. Aryl hydrocarbon receptor repressor (AhRR), which is also an AhR target gene, helps mediate negative feedback through the sequestration of ARNT; ligand-activated AhR is subsequently degraded by the ubiquitin-proteasome system (**Figure 1**a). Apart from regulating phase 1 and phase 2 metabolic target genes for chemical defense, AhR also regulates several protein kinases, such as $p21^{Cip1}$, and $p27^{kip1,}$ that are necessary for organ development [15]. Inflammatory genes, such as Interleukin (IL)-6 and IL-1beta, and energy homeostasis genes, such as TCDD-inducible poly-ADP-ribose polymerase (TiPARP/PARP7), are also direct targets of AhR [15]. Thus, the target genes for AhR are broad, and many are unrelated to the toxicological functions of AhR. Physiologically, AhR may form alternative partnerships with other transcription factors, such as nuclear factor kappa-light-chain-enhancers of activated B cells (NF-κB), proto-oncogene c-Maf, Krueppel-like factor 6 (KLF6), and others, in the cytoplasm. For example, AhR interacts with NF-κB, which is involved in inflammation, immune and stress responses [16]; the induction of antioxidant genes requires the presence of both AhR and NF-E2 p45-related factor (Nrf2) at the promoter [17][18]. AhR also interacts with circadian clock components and intracellular signaling, such as the mitogen-activated protein kinase (MAPK) cascade involved in apoptosis, inflammation and cell senescence [19][20] (**Figure 1**b). ARNT shares similar sequences with brain and muscle Arnt-like protein-1 (BMAL1), a clock component, which may contribute to AhR/circadian clock interactions [21]. In HT22 hippocampal neuronal cells, the activation of AhR by α-naphthoflavone (α-NF) induces the phosphorylation of MAPK, leading to cell death in an AhR-dependent manner [22]. ARNT-2, a neuronal transcription factor that also belongs to the bHLH-PAS superfamily, is mainly expressed in the central nervous system and has been shown to be involved in neuronal survival [23]. Although ARNT-2s have been shown to form dimers with AhR in vitro [24], the question of whether ARNT-2 can interact with AhR in vivo remains, and is of importance to the understanding of whether ARNT-2 dimerization with AhR also participates in the activation of gene transcription in a similar way to AhR/ARNT in the brain and other organs.

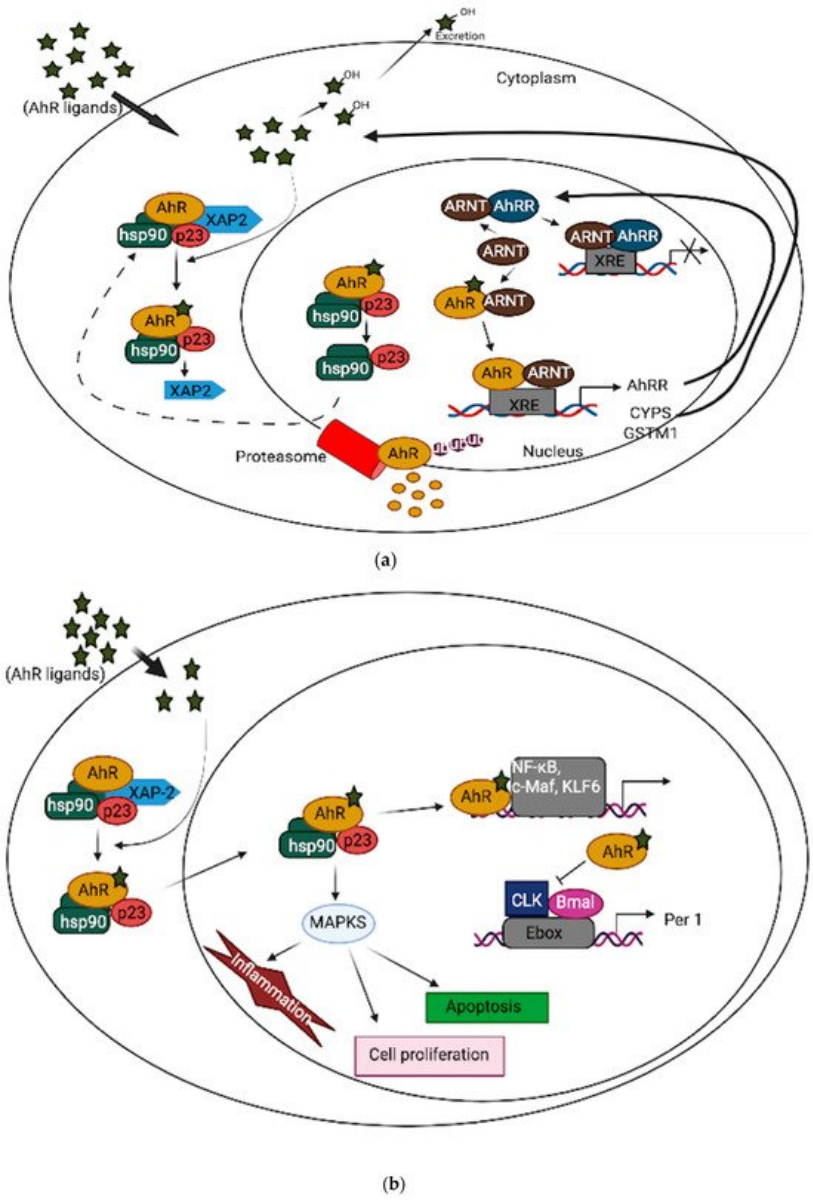

Figure 1. (**a**): AhR canonical pathway activation. (**b**): AhR non-canonical pathway activation.

Apart from xenobiotics, such as TCDD, and other polycyclic aromatic hydrocarbons (PAHs) that cross the blood-brain barrier (BBB) to mediate some of AhR's effects in the brain, several endogenous tryptophan metabolites, such as kynurenine, serotonin, and 6-formylindolo [3,2-b] carbazole (FICZ), are implicated in AhR-related brain function and pathology [25][26]. Recently, attention has been drawn to the kynurenic pathway and microbial metabolites in the gut-brain axis, as well as central nervous system (CNS) development and diseases [26][27]. In the brain, L-tryptophan is primarily metabolized through kynurenic pathways, producing several ligands that bind to AhR [28]. AhR activation in glial cells by the microbial metabolism of dietary tryptophan interferes with the NF-κB inflammatory transcription program, thereby reducing neuroinflammation, which raises the possibility that this pathway could be targeted in neurodegenerative and autoimmune diseases in the CNS [29][30]. In addition to several gut microbiota metabolites, FICZ, an endogenous ligand of AhR, promotes neurogenesis in adult neurons, which is needed for hippocampal memory maintenance in mice. Several brain-related pathological conditions may also involve the non-canonical activation of AhR. For instance, in Alzheimer's disease pathology, tryptophan derivatives (kynurenic acid and 5-hydroxyindole-acetic acid) can increase neprilysin expression, which is necessary for regulating amyloid beta clearance by proteolysis [31].

2. AhR and Aging Hallmarks in the Brain

2.1. Oxidative Stress

For years, the phenomenon of oxidative stress has been implicated in aging. Although several theories exist, the free radical theory of aging originally proposed by Denham Harman in the 1950s remains the most widely accepted, with modifications [32][33]. Aged tissues and senescent cells produce oxidative stress products, which lead to an imbalance between the oxidative and antioxidant defense network [34][35]. Besides, the exposure of cells to environmental oxidant generators, such as pesticides, heavy metals, and others, also contributes to this imbalance [36]. Just like other organs, a

strong correlation exists between aging in the brain and increased reactive oxygen species (ROS) formation [37]; increased ROS can be attributed to mitochondrial dysfunction associated with aging [38][39]. Moreover, protein aggregation/modifications found in most aging-related brain diseases, including Alzheimer's, have been attributed to increased ROS formation, which tends to impair proteasome and lysosome functions [40][41].

Aryl-hydrocarbon-receptor has been mechanistically shown to be involved in the generation of oxidative stress in the brain, as its activation by several ligands shifts the cellular redox balance towards favoring oxidative stress production [42][43][44]. The AhR agonist, TCDD, induces ROS production and oxidative DNA damage in astrocytes, leading to premature senescence, which is a hallmark of brain aging [45]. The generation of superoxide anions, the modulation of the CYP P450 system, mitochondrial dysfunction, and increased activation of arachidonic acid signaling are among the AhR-dependent pathways (**Figure 2**) that lead to increased ROS production in the brain [46][47]. Just like other organs in the body, the activation of AhR induces the expression of CYP1A1 and CYP1B1 in most brain regions, as well as the associated pituitary gland [48]; an increased expression of these xenobiotic metabolism enzymes can result in mitochondrial ROS production through an uncoupling process that leads to the release of superoxide and hydrogen peroxide (H_2O_2), which are believed to accelerate the aging process in the brain [49][50]. Increased production of ROS in mitochondria also regulates inflammasomes (NLRP3) by increasing the activation of inflammatory caspases in macrophages, which are necessary for cytokine synthesis, further contributing to brain inflammation [51]. In addition to the uncoupling process, arachidonic acid pathway activation by AhR leads to the increased generation of ROS through the metabolism of arachidonic acid by CYPs and other intracellular signaling processes [52][53].

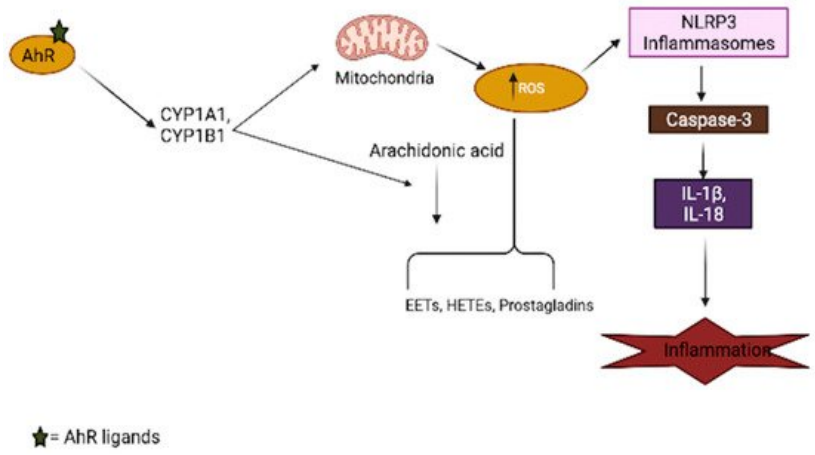

Figure 2. Involvement of AhR in oxidative stress generation. AhR activation by its ligands increases xenobiotic metabolism enzymes (CYPs), which results in mitochondrial toxicity, leading to the generation of reactive oxygen species (ROS). These enzymes also interact with the arachidonic acid pathway and increase the production of several arachidonic acid metabolites, such as EETs (epoxyeicosatrienoic acid), HETEs (hydroxyeicosatrienonic acid) and prostaglandins, which are sources of ROS in several tissues, including the brain. The generation of ROS in turn activates the inflammasome, which aids the secretion of inflammatory cytokines.

Although AhR has also been implicated in antioxidant responses through its cross-regulation with Nrf2 in various tissues [17][18], the evidence for this pathway in the brain is yet to be fully established. The activation of AhR with the agonist, β-Naphthoflavone (BNF), has no significant effect on Nrf2 mRNA levels or antioxidant enzymes, such as glutathione transferase, in the brain regions of pigs [54]. In mice, the absence of AhR helps reduce oxidative stress in the brain [55]. Therefore, it is reasonable to suggest that the antioxidant role of AhR is either cell-specific and absent in the brain, or that the oxidant response overwhelms the antioxidant response in the brain.

2.2. Stress Response

During stress, the body produces an adaptive response to reestablish the homeostasis that has been disrupted by the stressor [56]. Stress responses can either be cellular or generalized. The generalized stress response involves the release of glucocorticoids (stress hormone) via the neuroendocrine hypothalamic-pituitary axis. The cellular stress response involves various molecular changes, which may include the induction of heat shock proteins that are necessary for cell survival [57][58]. Brain aging can impose detrimental effects on both generalized and cellular stress responses, thus shifting away from an adaptive response towards a harmful effect. For instance, the age-related elevation of glucocorticoid levels contributes to hippocampal neuronal loss and cognitive impairment [58]. Postmortem cerebrospinal fluid in aged and Alzheimer's patients contained elevated levels of cortisol [59], which suggests that the brain could be rejuvenated by inhibiting stress responses in the brain. Furthermore, organelle-specific stress response pathways and the ubiquitin

proteasome system are also affected during aging [60]. Proteasome activities decline during aging, leading to increased protein modifications (a hallmark in various neurodegenerative diseases), which subsequently may reduce the effectiveness of the endoplasmic reticulum (ER) stress response [61]. Therefore, understanding stress response pathways during brain aging might provide relevant targets for therapeutic strategies in neurodegenerative diseases [62].

Aryl-hydrocarbon-receptor activation can modulate the neuroendocrine stress response system [9]. In the brain of rainbow trout, BNF acts through AhR signaling to downregulate steroidogenic acute regulatory protein, which is important for the biosynthesis of neurosteroids during stress. Furthermore, BNF suppressed pro-opiomelanocortin A (POMC-A), a precursor for adrenocorticotropic hormone (ACTH) that is necessary for the cortisol-induced stress response [63]. AhR also helps modulate the elevation in monoamine neurotransmitters that occurs during prolonged stress. For instance, AhR activation by PAHs and PAH-like compounds helps reduce cortisol and brain monoaminergic activities in rainbow trout after prolonged stress [64]. Cellular stress responses are also influenced by AhR activation [65][66], although these effects are yet to be explored specifically in the brain. Exploring AhR receptor involvement in glial cell cellular stress response mechanisms would be interesting, since these cells have been shown to be involved in brain stress responses [67][68].

2.3. Neurogenesis and Neuronal Plasticity

In the adult brain, neurogenesis appears to be important for the maintenance of the brain's neuronal circuitry [69]. In the subgranular zone (SGZ) of the hippocampal dentate gyrus in young adult rats, newly generated neuronal cells tend to integrate with the pre-existing hippocampal circuit, which is necessary for learning and memory [70]. Neuronal stem/progenitor cells (NSC) are also found in the subependymal zones and olfactory bulbs of adult primates/humans [71][72]. Several neurodegenerative diseases, including Alzheimer's disease, have been linked with aging-associated decline in neurogenesis and plasticity that occurs secondary to a loss in the proliferating potential of NSC [73][74]. Moreover, aged animals produce significantly fewer new neurons in the subventricular zone (SVZ) and SGZ of the hippocampus, which may contribute to a decline in cognitive functions that accompanies brain aging [75][76]. Aging also leads to the activation of glial cells and the subsequent secretion of pro-inflammatory cytokines, such as IL-1, which negatively impact NSC state and differentiation [76][77].

Aryl-hydrocarbon-receptor enhances neuronal proliferation during development; however, its role in adult neurogenesis is less well-investigated. AhR activation can regulate several genes involved in multiple aspects of synaptic plasticity and neurogenesis after brain development. A study using the Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis revealed that the administration of TCDD in the adult brain upregulates the genes required for synaptic plasticity and neuronal activities, including genes encoding for postsynaptic density 95 (PSD-95) protein and early growth response 1 (EGR1) [78]. The conditional deletion of AhR in adult mice also showed that AhR activation is necessary for SGZ neurogenesis by increasing the number of newborn granule cells in the DG of the hippocampus, which in turn improves hippocampus-dependent memory [79]. Similarly, AhR signaling helps restore neurogenesis after brain injury by enhancing ependymal glial cells to generate the new neurons necessary for repair in zebrafish [80]. Although several exogenous toxic AhR ligands have been studied for their neurotoxic effects targeting NSC in the adult brain, FICZ, an endogenous ligand of AhR, showed positive effects on the fate of NSCs by upregulating the ASCL1 and Ngn2 genes necessary for neuronal differentiation in the SGZ area of the adult mouse hippocampus [81]. Additionally, AhR activation by FICZ improves hippocampal-dependent memory and learning tasks, which was reversed following treatment with the AhR antagonist, CH22319 [81].

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