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ORIGINAL ARTICLE

Research Advances Regarding the Role of the AHR Signaling Pathway in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder predominantly affecting the elderly population, imposing significant burdens on both society and the families of affected individuals. As investigations into AD advance, the involvement of the aromatic hydrocarbon receptor (AHR) signaling pathway in the AD progression has garnered increasing attention. AHR functions as a receptor that detects and responds to a various of environmental stimuli, playing a crucial role in numerous biological processes, including cellular differentiation, metabolic regulation, and immune responses. During the progression of AD, the AHR signaling pathway may be intricately linked to several pathological factors, including β-amyloid (Aβ) accumulation, neuroinflammation, oxidative stress, mitochondrial dysfunction, changes in the blood–brain barrier (BBB) permeability, and alterations in neuronal metabolic processes. Inhibitors of AHR such as indoleamine 2,3-dioxygenase 1 (IDO1) present potential therapeutic approaches for AD treatment. A comprehensive understanding of the AHR signaling pathway's mechanisms in the context of AD is essential for elucidating the disease's pathogenesis and for the development of novel therapeutic strategies. This review aims to provide a detailed overview of recent research advancements related to the AHR signaling pathway in AD, thereby offering valuable references and insights for future studies.

Keywords: Aryl Hydrocarbon Receptor, AHR; Alzheimer's disease

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by an insidious onset and slow progression of symptoms. It represents the most prevalent type of dementia, comprising 60–80% of all dementia cases. The disease initially manifests as memory impairment and cognitive decline, but it ultimately leads to changes in behavior, language, visuospatial orientation, and the motor function (Scheltens et al. 2016).

The pathophysiological mechanisms underlying AD involves many factors. Notably, the hallmark pathological alterations associated with AD include the development of diffuse plaques, which are primarily composed of extracellular β-amyloid (Aβ) in the prefrontal cortex and hippocampus, as well as the presence of neurofibrillary tangles and neurofilaments formed by hyperphosphorylated tau proteins within neuronal cells. Both types of protein aggregates exhibit neurotoxic properties, contributing to a cascade of detrimental effects including oxidative stress, mitochondrial dysfunction, neuroinflammation, endoplasmic reticulum stress, disruption of the blood–brain barrier (BBB), and disturbances in lipid metabolism. These processes ultimately culminate in synaptic impairment and neuronal degeneration (Tiwari et al. 2019).

Moreover, the etiology of AD is influenced by a combination of biological, environmental, and genetic factors, rendering its pathogenesis highly intricate and multifactorial. Consequently, there is currently no universally effective therapeutic intervention available. The initial stages of AD are often characterized by mild and nonspecific symptoms, and the absence of sensitive and specific diagnostic tools further complicates early detection and intervention efforts. Presently, the pharmacological options primarily consist of cholinesterase inhibitors and N-methyl-D-aspartic acid receptor (NMDA) receptor antagonists, which may alleviate certain symptoms of AD but do not halt or reverse the disease process. These medications can also be associated with adverse effects, including nausea, vomiting, and diarrhea, and prolonged use may lead to increased drug resistance.

Nonpharmacological approaches, such as cognitive training, physical therapy, and social support, have shown potential in enhancing the quality of life for patients, yet they do not provide a cure for AD. Despite extensive research efforts spanning several decades, the intricate molecular mechanisms of AD remain incompletely understood, and yet, there is still no effective cure. Therefore, further investigation into the pathophysiological mechanisms of AD may yield novel insights that could inform future therapeutic strategies.

The aryl hydrocarbon receptor (AHR) is an evolutionarily conserved, ligand-dependent transcription factor, exhibiting widespread distribution across various regions of the brain, including the hippocampus, cortex, and hypothalamus. AHR plays a crucial role in protecting organisms against environmental toxins and is implicated in several physiological processes, including circadian rhythms, glucose metabolism, retinoid homeostasis, cell differentiation, cell division, memory, neurogenesis, and protein degradation via the ubiquitin–proteasome system (Ramos-García et al. 2020). The modulation of AHR activity can significantly influence numerous physiological functions within the body. In recent years, researches have begun to investigate the potential involvement of AHR in neurodegenerative diseases (NDDs), particularly AD. Although there is a limited number of studies directly investigating the relationship between AD and AHR, it is plausible to hypothesize that AHR may contribute to the pathogenesis of AD through multiple mechanisms. This article aims to review the current research advances regarding the role of the AHR signaling pathway in the context of AD.

1. AHR signaling pathway

As a transcription factor with diverse biological functions, AHR is involved in the pathogenesis of numerous diseases and conditions, including autoimmune disorders, inflammatory diseases, endocrine disruptions, presenility, and cancer. Beyond the traditional AHR/aryl hydrocarbon receptor nuclear translocator (ARNT) signaling pathway, AHR engaged in various signaling pathways in vivo. It is capable of interacting with other transcription factors and signaling molecules, thereby modulating gene expression patterns and their corresponding physiological or pathophysiological functions in a manner that is dependent on ligands, cell types, and the surrounding microenvironment.

2.1 AHR and ARNT

AHR was initially identified as a cell signaling molecule that mediates the toxic effects of dioxin and similar compounds (Rothhammer and Quintana 2019). In its inactivate state, AHR associates with several chaperone proteins, including chaperones heat shock protein 90 (HSP90), P23, AHR-interacting protein (AIP), and the nonreceptor tyrosine kinase SRC. This complex primarily functions to keep AHR in a nonactivated form and sequestered within the cytoplasm (Kerr et al. 2017). Additionally, it plays a role in preventing ubiquitin-mediated degradation of AHR, thereby preserving its cytoplasmic levels(Kerr et al. 2017). Upon ligand activation, AHR undergoes a conformational change, leading to the dissociation of AIP from the complex. This process reveals the amino-terminal nuclear localization signal and the adjacent nuclear export signal of AHR. The AHR-ligand complex then translocates into the nucleus in a manner that is dependent on transporter proteins but independent of importin β, subsequently binds to its nuclear transporter, ARNT, to form an AHR/ARNT complex. This complex interacts with the xenobiotic response element (XRE) in the enhancer region of target genes to initiate the transcription of associated downstream genes (Rothhammer and Quintana 2019), including members of the cytochrome P450 family 1 (CYP1) , such as CYP1A1, CYP1A2, and CYP1B1 (Solvay et al. 2023). The aryl hydrocarbon receptor repressor (AHRR) can inhibit the transcriptional activation of these downstream genes by competing with the AHR-ligand complex for interaction with ARNT (Larigot et al. 2018) (Figure1). Furthermore, hypoxia inducible factor 1α (HIF1α) has been demonstrated to competitively inhibit the interaction between AHR and ARNT (Mascanfroni et al. 2015).

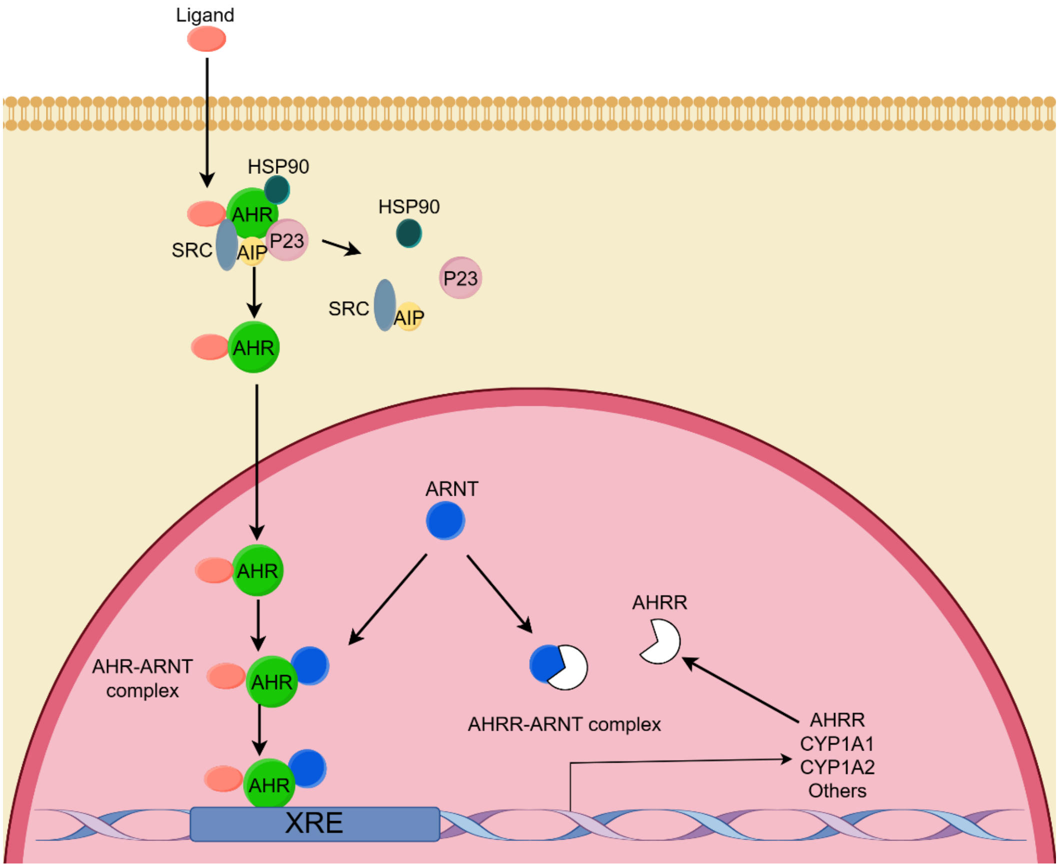


Figure1 AHR-ARNT signaling pathway

In the classical AHR-ARNT signaling pathway, the inactive AHR exists in a complex with HSP90, P23, AIP and the nonreceptor tyrosine kinase SRC. Upon ligands binding, AIP dissociates from the complex, revealing the amino-terminal nuclear localization signal and the adjacent nuclear export signal of AHR. The AHR-ligand complex translocates to the nucleus and binds to ARNT to form an AHR/ARNT heterodimer. This complex subsequently binds to XRE, leading to the transcriptional activation of target genes associated with AHR. AHRR competes with the AHR-ligand complex for interaction with ARNT, resulting in the formation of inactive AHRR-ARNT heterodimer. AHR: aryl hydrocarbon receptor; AHRR: aryl hydrocarbon receptor repressor; ARNT: aryl hydrocarbon receptor nuclear translocator; AIP: AHR-interacting protein; CYP1: cytochrome p450 family 1; SRC: nonreceptor tyrosine kinase gene; XRE: xenobiotic response element.

2.2 Other signaling pathways

In addition to the classical AHR/ARNT pathway described above, AHR also exerts regulatory functions within the organism through its interaction with estrogen receptors (ERs) (Ohtake et al. 2003) and nuclear factor kappa-B (NF–κB) (Li et al. 2021) signaling pathway. Moreover, AHR also regulates cell cycle by influencing growth factor signaling, mediating cell cycle arrest, and promoting apoptosis. AHR exerts its regulatory effects on transcriptional modules by altering the half-life of other transcription factors.

Furthermore, AHR is capable of regulating the degradation of other transcription factors, such as the tumor suppressor gene p53, the oncogene MYC, the proto-oncogene FOS, the embryonic stem cell marker OCT4, and hypoxia inducible factor-1α (HIF1α), through analogous mechanisms (Bunaciu and Yen 2011; Mejía-García et al. 2015).

2.3 Ligands of AHR

AHR can be activated by a variety of both exogenous and endogenous molecules, which include dietary compounds, flavonoids, toxins, and pharmaceuticals. Notably, environmental pollutants such as TCDD, polychlorinated biphenyls (PCBs) and polycyclic aromatic hydrocarbons (PAHs) are recognized as common activators of AHR. Exposure to these toxic substances has been identified as a potential risk factor for NDDs (Zhang et al. 2024). In the absence of external stimuli, many intracellular pathways and signaling mechanisms associated with AHR can also facilitate its activation. Recent research has revealed that various endogenous ligands play significant roles in vivo. Furthermore, the interaction of AHR with different intracellular pathways and receptors in various cell types can elicit diverse intracellular responses. Studies have indicated that AHR may have a critical function in NDDs such as AD.

2. AHR signaling pathway in NDDs

NDDs represent a category of intricate disorders stemming from dysfunctional nervous system activity, characterized by the progressive deterioration of neuronal structure and function across various regions of the nervous system(Wang et al. 2021). This degeneration leads to impairments in motor skills, language, and cognitive abilities. The pathogenesis of NDDs is notably complex, with recent studies have shown that the AHR signaling pathway plays a significant role in many age-related degenerative processes.

AHR is extensively distributed throughout several brain regions, including the hippocampus, cerebral cortex, and hypothalamus (Keshavarzi et al. 2020). The expression level of AHR diminishes during brain development (Ojo and Tischkau 2021), suggesting its critical involvement in the maintenance of normal embryonic development. Conversely, aberrant activation of AHR accelerates the process of age-related senescence in the later stages of life (Salminen 2022). The level of AHR is low to moderate in neurons in the cortex and hippocampus of normal mice but increases significantly after traumatic brain injury (Rajendran et al. 2022). Autopsy studies have revealed that the AHR protein levels are significantly elevated in the hippocampal tissue of elderly individuals compare to younger counterparts (Ramos-García et al. 2020). Numerous studies have indicated that AHR signaling contributes to various age-related degenerative processes, including the inhibition of cellular autophagy, promotion of cellular senescence, disturbances in the extracellular matrix, and vascular dystrophy (Andreasen et al. 2007; Kim et al. 2020; Kondrikov et al. 2020). These findings suggest that AHR signaling is essential for normal nervous system development while also facilitating the aging process and contributing to degenerative processes when abnormally activated.

Interestingly, additional research has revealed that both AHR knockout mice and those exposed to TCDD exhibit impairment in hippocampus-dependent memory. The dentate gyrus of adult mice shows reduced cell proliferation, survival and differentiation. Behavioral analyses have shown that AHR influences hippocampal neurogenesis and scene-related fear memory in mice (Latchney et al. 2013). In AHR-deficient mice, there is a reduction in white matter volume, an increase in age-related gliosis within the hippocampus, and deficits in early memory functions (Bravo-Ferrer et al. 2019).

Furthermore, AHR signaling has been implicated in various pathological changes, including hypoperfusion, vascular disturbances, compromised BBB integrity, neuroinflammation, neurotoxicity, immunosuppression, disruptions in circadian rhythms, and impaired lymphatic flow (Rothhammer and Quintana 2019). These alterations are also observed in the pathogenesis of NDDs such as AD, Parkinson’s disease (PD), multiple sclerosis (MS) and ALS. Thus, AHR may play a pivotal role in the etiology of NDDs through these mechanisms.

In conclusion, AHR exhibits a dual role in the aging process, facilitating healthy aging while also promoting aging-related phenotypes across different species. Thus, AHR presents as a promising therapeutic target for age-related diseases.

3. The role of the AHR signaling pathway in AD

Research has shown that serum AHR levels are significantly increased in AD patients (Ramos-García et al. 2020). Nonetheless, the precise physiological and pathological functions of AHR in the context of AD remain inadequately understood. AHR may influence the pathological process of AD through the following mechanisms.

4.1 Effects of AHR on central nervous system inflammation

Neuroinflammation is a defining pathological characteristic of NDDs, including AD, PD and ALS. Astrocytes and microglia exhibit dual roles in these conditions, both exacerbating inflammation and mediating cellular damage, while also providing protective functions for the nervous system. The dysregulation of astrocyte and microglial activation within the central nervous system (CNS) fosters chronic inflammatory processes, which can lead to neuronal death, thereby exacerbating the pathological progression of AD. The influence of AHR on CNS inflammation in AD primarily encompasses the inhibition of inflammatory pathways, modulation of the immune response and the regulation of glial metabolism.

4.1.1 Inhibition of inflammatory pathways

NDD pathology is often associated with metabolic dysfunction, heightened autophagy and aberrant immune system activity. Irritable bowel syndrome (IBS), characterized by a homeostatic imbalance of the gut microbiota, has been identified as a potential risk factor for the onset of AD(Chen et al. 2016). On one hand, dietary and microbial metabolites, particularly tryptophan metabolites such as kynurenine (Kyn), may exacerbate the pathological process associated with IBS through AHR activation (Berstad et al. 2014). On the other hand, metabolites produced by the gut microbiota can also activate AHR signaling via various pathways, thereby exerting significant anti-inflammatory effects within the CNS.

The gastrointestinal tract (GI) and CNS function as sensory organs that detect, transmit, integrate, and respond to signals from both internal and external environments. These systems are interconnected through complex networks of immune and neuronal cells that monitor nociceptive stimuli and coordinate local and systemic inflammatory responses. inflammatory signals traverse the gut–brain axis in both afferent ("gut–brain") and efferent ("brain–axis") directions, with crosstalk along this axis regulating inflammatory nociception, the inflammatory response, and immune homeostasis (Agirman et al. 2021). The interplay of metabolic products derived from dietary tryptophan in the intestines and IFN-I produced in the CNS can activate the AHR signaling pathway in astrocytes, thereby inhibiting CNS inflammation (Rothhammer et al. 2016).

Furthermore, studies have demonstrated that indole metabolites derived from microbe can induce AHR activation, inhibit the NF–κB signaling pathway and prevent the formation of NOD-like receptor thermal protein domain associated protein 3 (NLRP3), leading to a reduction in the release of inflammatory cytokines and a mitigation of the inflammatory response in APP/PS1 mice (Sun et al. 2022). Under inflammatory conditions, IFN-γ promotes the expression of IDO1, which enhances the production of the AHR agonist L-Kyn, subsequently triggering triggers the upregulation of interleukin (IL)-10 receptor 1 via AHR, thereby amplifying the anti-inflammatory effects of IL-10 (Lanis et al. 2017). These findings elucidate the molecular mechanisms by which the gut microbiota may regulate the progression of AD.

4.1.2 Modulation of the immune response

AHR servers as a significant regulator of cellular morphology, phagocytosis, and cellular migration (Josyula et al. 2020). Recent research has increasingly highlighted the critical role of AHR within the immune system, particularly in mediating both pro-inflammatory and anti-inflammatory response in lipopolysaccharide (LPS)-activated microglia. Photooxidative derivatives of tryptophan, such as 6-formyl-5,11-dihydroindolo [3,2-B] carbazole (6-formylindolo [3,2-B] carbazole, FICZ) and 3-methylcholanthrene (3-methylcholanthrene, 3MC), have been shown to mitigate LPS-induced immune responses in microglia and modulate inflammation within the central nervous system (Lee et al. 2015). Furthermore, AHR knockdown has been observed to counteract the anti-inflammatory effects of indole 3-carbinol (I3C) on microglial cells (Khan and Langmann 2020). Interferon (IFN)-I signaling in astrocytes have been shown to inhibit inflammation through ligand-activated AHR and SOCS2 (Rothhammer et al. 2016). These findings suggest that AHR deficiency may exacerbate inflammatory process within the CNS, potentially contributing to NDDs. In BV2 mouse microglia, the novel AHR antagonist HBU651 has been found to inhibit the LPS-mediated nuclear translocation of NF–κB and the subsequent NF–κB-dependent production of pro-inflammatory cytokines, including tumor necrosis factor α (TNF-α), IL-1β and IL-6, while also ameliorating LPS-induced mitochondrial dysfunction (Kang et al. 2022).

The AHR signaling pathway is also integral to the regulation of the immune responses. By modulating the activation and functionality of immune cells, AHR may play a role in addressing immune dysregulation in AD. This immunomodulatory capability may contribute to the attenuation of inflammatory responses in AD, thereby enhancing clinical outcomes associated with the disease.

The AHR signaling pathway is involved in the pathological process of AD by influencing glial metabolism, particularly the glucose metabolism of astrocytes. Activation of AHR signaling have been shown to inhibit the glycolysis in astrocytes, which subsequently impacts the energy supply and metabolic equilibrium within the brain, potentially worsening neuroinflammation and neurodegeneration associated with AD (Sałat et al. 2016). In the context of AD, Aβ oligomers and tau proteins can activate IDO1 in astrocytes. IDO1 catalyzes the conversion of tryptophan to Kyn, which serves as a ligand for AHR, promoting its translocation to the nucleus. Within the nucleus, AHR dimerizes with ARNT and regulates transcription. Kyn-dependent AHR signaling has been implicated in the inhibition of glycolysis in astrocytes. Notably, the inhibition of IDO1 have been shown to restore glucose metabolism in astrocytes to preserve hippocampal memory function in preclinical mouse models of AD (Minhas et al. 2024).

4.2 Interaction of AHR and Aβ

Aβ, or amyloid-beta, is a peptide derived from the proteolytic cleavage of the β-amyloid precursor protein (APP) by β-secretase (BACE1) and γ-secretase. This peptide is synthesized by a variety of cell types and is found in circulating blood, cerebrospinal fluid, and interstitial fluid of the brain, predominantly in association with chaperone proteins. A minor fraction of Aβ exists in an unbound form, which exhibits neurotoxic properties when it accumulates within the cellular matrix. The early amyloid cascade hypothesis suggests that the accumulation of Aβ in the brain lead to the formation of plaques, initiating a cascade of pathological events, including Tau protein phosphorylation, neurofibrillary tangle formation, and subsequent neuronal death. These pathological processes further exacerbate Aβ deposition, thereby perpetuating the cascade and ultimately results in cognitive decline (Barage and Sonawane 2015). However, the neurotoxic effects of Aβ alone do not sufficiently account for the observed increases reactive oxygen species (ROS) levels and the abnormalities in energy metabolism associated with the progression of AD. Other factors, such as impaired mitochondrial function, may contribute to Aβ deposition, Tau protein hyperphosphorylation, energy metabolism disruption, and oxidative stress augmentation, culminating in neuronal loss and the advancement of AD (Swerdlow 2018).

While there is a paucity of research directly examining the direct interaction between AHR and Aβ, some studies have suggested that such interactions may be pertinent to the pathological mechanism underlying AD. AHR serves as a critical transcription factor, and the AHR signaling pathway is integral to the regulation of cellular metabolism, immune responses, and the inflammatory processes. Therefore, it is plausible that interactions between AHR and Aβ may influence the pathological trajectory of AD.

The AHR signaling pathway may influence the processes involved in the clearance of Aβ. Studies have shown that Aβ clearance involves multiple mechanisms, including BBB transportation, extracellular degradation, cellular uptake, and intracellular degradation (Greenberg et al. 2020). The modulation of AHR signaling pathways could potentially disrupt the normal functions of these mechanisms, thereby impacting the efficiency of Aβ clearance. The activation of the AHR signaling pathway may impair the ability of microglia to clear Aβ due to its immunosuppressive effects, resulting in neurotoxicity and contributing to the pathogenesis of AD. However, other studies have demonstrated that indole derivatives such as I3C can activate AHR, leading to the upregulation of the endogenous Aβ-degrading enzyme neprilysin. This activation has been shown to decrease Aβ42 in N2a cells and in the brain tissue of APP/PS1 mouse models, thus alleviating cognitive deficits in these AD models (Qian et al. 2021).

As previously noted, the AHR signaling pathway is integral to the regulation of the inflammatory response. In the context of AD, the accumulation of Aβ triggers an inflammatory response that activates glial cells and promotes the release of inflammatory factors. Thereby, the regulation of the AHR signaling pathway may indirectly influence Aβ deposition and clearance by modulating the intensity and duration of the inflammatory response.

The deposition and aggregation of Aβ may also impact the AHR signaling pathway. The Wnt/β-catenin signaling pathway is essential for hippocampal development and is crucial for the maintenance and differentiation of adult neural stem cells (NSCs). The interplay of AHR and Wnt/β-catenin/Notch signaling pathways influences cognitive functions such as learning and memory in murine models by modulating the expression of APP at both messenger RNA and protein levels. The interaction between AHR and Wnt/β-catenin has been shown to promote neuronal apoptosis, contributing to cognitive decline in AD patients (Keshavarzi et al. 2022). In neurons, Aβ triggers the overexpression of Dickkopf-related protein 1 (Dickkopf-1, DKK1) via the indoleamine-2,3-dioxygenase-1 (IDO1)-Kyn-AHR pathway, which inhibits the Wnt/β-catenin signaling pathway, leading to neurotoxic effects (Duan et al. 2020).

The interaction between Aβ and AHR signaling pathway may influence various cellular processes, including metabolism, immune responses, and inflammatory reactions. Nonetheless, studies on the specific effects of Aβ on the AHR signaling pathway remain limited, necessitating further experimental validation

4.3 Effects of AHR on oxidative stress

Oxidative stress is characterized by the excessive production of free radicals and other reactive oxygen species (ROS) within the organism, surpassing the capacity of the body's antioxidant defenses, which ultimately leads to cellular damage. Elevated levels of oxidative stress are notably prevalent in NDDs, including AD. AHR has been identified as a crucial factor associated with oxidative stress.

AHR is capable of the expression of several key antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) (Huang et al. 2011). These antioxidant enzymes are crucial for the detoxification of ROS and the maintenance of the redox homeostasis. Variation in the AHR activity may influence the expression levels of these antioxidant enzymes, thereby affecting cellular susceptibility to oxidative stress. In the brain, ROS levels are exacerbated by the production of superoxide anions, the regulation of the cytochrome P450 system, mitochondrial dysfunction, and the heightened activation of arachidonic acid mediated by the AHR pathway (Ojo and Tischkau 2021). The activation of AHR can stimulate the expression of CYP1A1 and CYP1B1 across various brain regions, resulting in the release of superoxide and hydrogen peroxide (H2O2) through uncoupling process, triggering inflammatory responses and cellular senescence (Albertolle and Peter Guengerich 2018).

Furthermore, mitochondria serve as the primary energy source within cells and are also the principal site of ROS generation. In the context of AD, mitochondrial dysfunction contributes to increased ROS production and an insufficient energy supply. AHR has the capacity to regulate the expression of multiple genes associated with mitochondrial biosynthesis and functionality, thereby influencing mitochondrial performance and ROS generation.

AHR signaling pathway has been demonstrated to modulate oxidative stress through direct regulation of gene expression, impacting mRNA stability, translation efficiency, and protein functionality. These regulatory mechanisms may involve intricate signal transduction networks and protein interaction networks. For instance, TCDD has been shown to induce ROS and oxidative DNA damage in neuronal cells via AHR activation, potentially leading to premature senescence (Wan et al. 2014). Additionally, the activation of nicotinamide adenine dinucleotide (NADH) and the reduction in nitric oxide (NO) levels in the aorta of rats, as induced by the AHR signaling pathway, can result in ROS overproduction (Nakagawa et al. 2021). Indolephenol sulfate has also been observed to activate the AHR signaling pathway, thereby increases ROS levels (Salminen 2023).

4.4 Effects of AHR on mitochondrial function

Mitochondria are integral to maintaining cellular and organismal homeostasis, exhibiting the ability to alter their shape and localization in response to intracellular energy and metabolic requirements (Friedman and Nunnari 2014). The primary cellular function of mitochondria is the synthesis of adenosine triphosphate (ATP) via the electron transport chain (ETC) (Billingham et al. 2022). Furthermore, mitochondria are responsible for regulating intracellular calcium ion concentrations, which are essential for various local neuronal activities, including synaptic transmission, axonal and dendritic transport, and the circulation of synaptic vesicles (Jadiya et al. 2019; Tang et al. 2019). They also generate ROS and are implicated in steroid and hormone synthesis as well as apoptosis signaling (Szychowski et al. 2020). Studies have shown that these precisely regulated processes are disrupted in the context of NDDs, implying a close relationship between altered mitochondrial functions and the pathological process of NDDs (Tang et al. 2019). Mitochondrial disfunction is recognized as a hallmark of degenerative changes. In AD, mitochondria exhibit a variety of impairments, including reduced expression of respiratory chain complex proteins and enzyme activities, diminished ATP generation, decreased membrane potential, mitochondrial DNA (mt-DNA) damage, and increased ROS production (Lou et al. 2020). The ROS produced during mitochondrial respiration can lead to cumulative and irreversible molecular and cellular damage, resulting in a progressive decline in mitochondria function and associated degenerative changes. Various environmental and nutritional factors can affect mitochondrial function and exacerbate the process of degenerative changes, while also directly or indirectly impact the biological activity of AHR signaling pathway.

AHR is known to regulate the expression of numerous genes related to mitochondrial biosynthesis and functionality (Sahebnasagh et al. 2021). AHR is crucial for the maintenance of mitochondrial homeostasis, and the disruptions of the AHR signaling pathway can lead to mitochondrial dysfunction. Exposure to Atrazine (ATR) has been shown to induce oxidative stress and mitochondrial dysfunction by activating AHR and disrupting the equilibrium of CYP450s in the brains of quail (Lin et al. 2018). Furthermore, urokinase A has been found to inhibit the AHR-mediated expression of transglutaminase type 2 (TGM2) and to impede mitochondrial calcium influx by disrupting the interactions between mitochondria and the endoplasmic reticulum. (Lee et al. 2021). In addition, some researchers have identified the presence of AHR on the mitochondrial membrane, where it regulates voltage-dependent anion channels (VDACs) to modulate calcium influx (Sarioglu et al. 2008). AHR also interacts with the mitochondrial transporter (TSPO) (Steidemann et al. 2023), thereby influencing mitochondrial function.

4.5 Effects of AHR on BBB permeability

The BBB is composed of endothelial cells, astrocytes, pericytes, and basement membranes surrounding the capillary lumen (Kadry et al. 2020). It functions as a selectively permeable barrier, preventing the entry of harmful substances from the bloodstream into brain tissue, thereby maintaining homeostasis of the central nervous system. Dysfunction of the BBB is associated with the onset of NDDs such as AD and cognitive impairment (Barisano et al. 2022). AHR has been identified in human microvascular endothelial cell lines and astrocytes derived from the mouse BBB. AHR is involved in BBB dysfunction by activating the thrombospondin-1/transforming growth factor (TGF-β)/vascular endothelial growth factor (VEGF) signaling pathway (Ren et al. 2021). Kyn, which is a metabolite of tryptophan, is capable of traversing the BBB, suggesting that it may influence BBB function via AHR. Furthermore, the AHR signaling pathway may exacerbate the progression of AD through stimulation of the renin–angiotensin system or inhibition of NO production, which results in reduced local perfusion of brain tissues and subsequent secondary damage.

Studies have shown that activated AHR can alter the permeability of the BBB by compromising its structural integrity, thereby inducing toxicity to the CNS and contribute to the development of AD. Activation of AHR has been shown to downregulate the expression of connexin 43 (Cx43), a prominent gap junction protein within the BBB. Additionally, activated AHR can also disrupt the integrity of BBB gap junctions. Studies have revealed that overexpression of indolephenol sulfate can activate the AHR signaling pathway, resulting in an abnormal increase in BBB permeability and leading to cognitive dysfunction. However, AHR-knockout mice exposed to indoxyl sulfate did not exhibit increased BBB permeability or cognitive deficits (Bobot et al. 2020). These findings suggest that aberrant activation of the AHR signaling pathway compromises BBB integrity and affects the cognitive function of mice. In vivo AHR knockdown has been shown to alleviate BBB damage and improve neurobehavioral function in murine models (Ren et al. 2021).

The cytotoxic effects of AHR on the CNS may also arise from indirect mechanisms, such as BBB disruption. In cultured mouse brain endothelial cells, activation of the AHR/RhoA signaling pathway has been found to enhance the proteasomal degradation of β-catenin through PKCδ/GSK3β-mediated phosphorylation, resulting in reduced β-catenin protein level and compromised BBB integrity. Treatment with simvastatin and pravastatin has been shown to prevent AHR-mediated disruption of cerebrovascular integrity by inactivating RhoA and reducing β-catenin degradation (Chang et al. 2012). Additionally, AHR signaling regulates cerebrovascular blood flow through the renin–angiotensin system, which is also implicated in the pathogenesis of AD (Salminen 2023).

These findings indicate that activated AHR can undermine the integrity of the BBB through multiple mechanisms, thereby facilitating the pathological procession of AD. Although further investigation is required to elucidate the precise mechanisms by which the AHR signaling pathway influences cerebral microvascular integrity, modulating BBB permeability through the regulation of AHR signaling pathway may represent a potential therapeutic strategy for AD treatment.

4.6 Effects of AHR on sphingolipid metabolism

The brain exhibits a high concentration of sphingolipids (SL), and disturbances of lipid metabolic homeostasis are closely associated with the pathogenesis of AD. AHR is essential for the normal expression of mRNA for several pivotal genes related to SL biosynthesis. Activation of the AHR signaling pathway can regulate SL levels in cells and tissues by enhancing the expression of serine palmitoyltransferase small subunit A (SPTSSA) (Majumder et al. 2020).

Sphingomyelin (SM) is a principal component of cellular membranes, and its metabolites, such as ceramide, sphingosine, and sphingosine-1-phosphate (S1P), function as crucial bioactive signaling molecules of the organism. SM serves as both first and second messenger in regulation of various of cellular activities, including cell growth, differentiation, aging, apoptosis, and other critical signal transduction processes (Crivelli et al. 2021). Notably, SM levels are elevated in the inferior parietal lobe of individuals with AD (Pettegrew et al. 2001). In AHR-knockout HeLa cells and tissues, the expression of key genes in the SL biosynthesis pathway and ceramide levels were significantly diminished. Furthermore, AHR-knockout mice exhibited reduced levels of sciatic ceramide and decreased myelin thickness (Majumder et al. 2020). AHR activation was found to upregulate serine palmitoyltransferase long chain base subunit 2 (SPTLC2) in murine models, resulting in ceramide accumulation (Liu et al. 2021). Additionally, modulating the AHR signaling pathway may lead to the downregulation of sphingosine 1 phosphate lyase (S1PL), the principal enzyme responsible for the degradation of S1P, resulting in the disturbance of S1P metabolism (Wang et al. 2019).

Numerous studies have demonstrated that the delicate regulated metabolic balance between SM and its metabolites is implicated in the pathology of AD; however, the precise mechanisms by which the AHR signaling pathway may contribute to AD pathology through sphingolipid metabolism modulation still require further investigation.

4.7 Effects of AHR on neurogenesis and neuronal plasticity

Beyond its involvement in the CNS through the mechanisms described above, AHR also plays a critical role in the regulation of neurogenesis and neuronal plasticity. Neurogenesis refers to the process of generating new neurons or restoring the structure of neurons, which is essential for brain plasticity and the functions of learning and memory. In AD, neurogenesis is significantly impaired, leading to a reduction in neuronal populations and a loss of synaptic connections. Neuronal plasticity compasses the capacity of neurons to undergo structural and functional changes, which is essential for adaptation to environmental changes and for learning and memory processes. In the context of AD, neuronal plasticity is markedly compromised, resulting in diminished synaptic connections and abnormal neural network function(Stampanoni Bassi et al. 2019). Variations in AHR activity may influence both neurogenesis and neuroplasticity. Kynurenic acid (KYNA)/AHR signaling has been shown to inhibit the plasticity of the neural stem cells and neurogenesis in an adult zebrafish model of AD (Siddiqui et al. 2021). Conversely, several nontoxic AHR ligands have demonstrated neuroprotective properties. The activation of AHR signaling by these nontoxic ligands promotes neurogenesis. Tryptophan metabolites derived from the gut microbiota have been found to stimulate neurogenesis in adult mouse hippocampal tissue in an AHR-dependent manner (Wei et al. 2021).

4.8 Others

In addition to the previously discussed mechanisms, AHR may also be involved in NDDs such as AD through the following pathway. The activation of AHR has been shown to elevate the levels of cytochrome P450 enzymes CYP1A1 and CYP1B1. This elevation can lead to the demethylation of melatonin, thereby exacerbating degenerative changes by disrupting circadian rhythms (Mokkawes and de Visser 2023).Furthermore, AHR activates BDNF receptor tyrosine kinase B (TrkB) by facilitating the conversion of melatonin O-acetylserotonin (OAS) to N-acylserotonin (NAS) (Jang et al. 2010). Owing to its nutritional and metabolic benefits, full-length TrkB (TrkB-FL) represents a promising therapeutic target for AD (Povarnina et al. 2022). However, the presents of Aβ can significantly elevate levels of truncated TrkB-T1, which is associated with considerable neuronal loss and the progression of AD (Wong et al. 2012). By increasing the NAS/melatonin ratio and activating TrkB-T1, AHR and its ligands may contribute to the pathophysiology of AD through multiple mechanisms. These findings suggest a significant relationship between AHR and circadian rhythm in the regulation of AD pathology.

Additionally, AHR signaling also interferes with cellular energy metabolism. Activated AHR enhances the expression of poly ADP–ribose polymerase (PARP), leading to the depletion of NADH and the initiation of protein–adenosine diphosphate ribosylation (Ma 2002). NADH deficiency may result in mitochondrial dysfunction, oxidative damage, autophagy disruption, and dysregulation of chromatin and epitopes. Moreover, exposure to NADH precursors has the potential to exacerbate the pathological processes of dementia and AD (Wang et al. 2021).

4. Summary

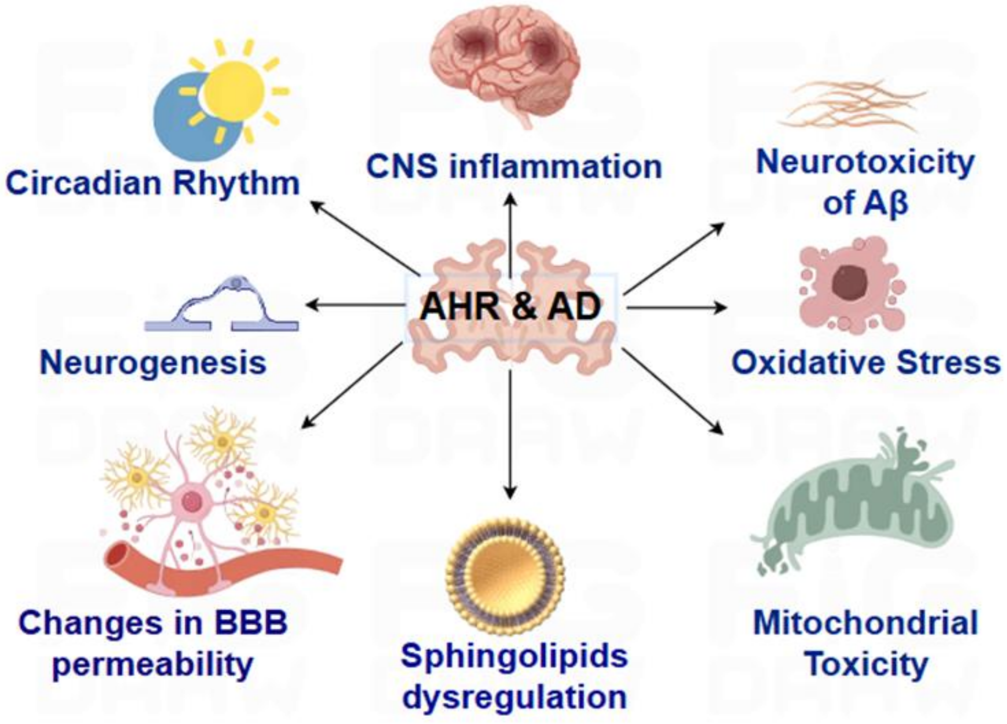
In recent years, the AHR signaling pathway has gained significant attention in scientific research. Numerous studies have demonstrated that AHR is extensively expressed across various regions of the brain. It is posited that AHR may play a critical role in the pathological process of AD by modulating neuronal inflammation, inducing oxidative stress, interacting with Aβ, contributing in mitochondrial toxicity, altering BBB permeability, and influencing sphingolipid metabolism, as well as neurogenesis and neuroplasticity (Figure2).

In light of the potential implications of AHR in AD, future therapeutic strategies may encompass the following approaches:

1. The development of inhibitors or antagonists specifically targeting AHR could be pursued to mitigate its activity, thereby alleviating its detrimental effects on neurogenesis and neuronal plasticity.

2. The neurotoxic effects may be diminished by modulating the upstream and downstream molecules of the AHR signaling pathway. pharmacological agents that inhibit AHR ligands could be formulated to prevent their interaction with AHR, thereby obstructing the activation of the AHR signaling cascade. Currently, inhibitors of IDO1, originally designed for oncological applications, may be repurposed for the treatment of AD. By inhibiting IDO1, the production of Kyn

can be reduced, which in turn may decrease the activation of AHR signaling and restore glucose metabolism in astrocytes, potentially ameliorating AD symptoms. These pharmacological agents may also enhance the proliferation and differentiation of neural stem cells and precursor cells, facilitating their maturation into new neurons, thereby replenishing damaged neurons, and restoring the functionality of neural networks.



AHR is implicated in various processes, including the modulation of inflammatory responses, the induction of oxidative stress, interactions with β-amyloid (Aβ), the elicitation of mitochondrial toxicity, alterations in blood-brain barrier (BBB) permeability, the regulation of sphingolipid metabolism, the modulation of circadian rhythms, and contributions to neurogenesis and neuroplasticity. Aβ: β-amyloid; AHR: aryl hydrocarbon receptor; AD: Alzheimer's disease; BBB: blood–brain barrier; CNS: central nervous system.

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