PHARMACIA

Pharmacia 67(4): 311–315
DOI 10.3897/pharmacia.67.e47298

Review Article

Aryl hydrocarbon receptors as potential therapeutic targets

Pavlina Andreeva-Gateva[1], Dimitar Bakalov[2], Zafer Sabit[2], Radka Tafradjiiska-Hadjiolova[2]

1 *Department of Pharmacology and Toxicology, Medical University of Sofia, Sofia, Bulgaria*
2 *Department of Pathophysiology, Medical University of Sofia, Sofia, Bulgaria*

Corresponding author: Pavlina Andreeva-Gateva (pandreeva_gateva@outlook.com)

Received 14 October 2019 ♦ **Accepted** 5 May 2020 ♦ **Published** 6 November 2020

Citation: Andreeva-Gateva P, Bakalov D, Sabit Z, Tafradjiiska-Hadjiolova R (2020) Aryl hydrocarbon receptors as potential therapeutic targets. Pharmacia 67(4): 311–315. https://doi.org/10.3897/pharmacia.67.e47298

Abstract

Aryl hydrocarbon receptors (AhR) are regulators of the expression of cytochrome P-450 isoforms, mediating a wide variety of the effects of substances from the endogenous or exogenous origin, including those produced from the microbiome. An exciting new aspect of their activity is their localization in the brain and their potential to modulate the action of the immune system. AhR is emerging as an essential toxicological and therapeutic target for neuromodulation. Further studies are needed for elucidating their utility as drug-targets.

Keywords

dioxin, indoles, toxicology, neuroprotection

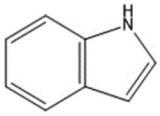
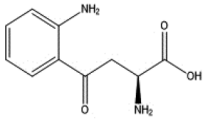
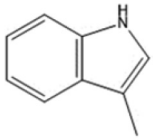
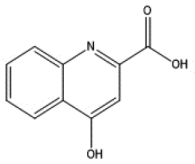
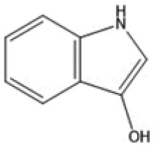
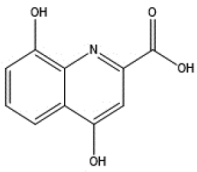
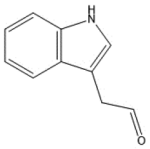
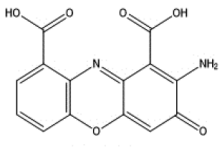
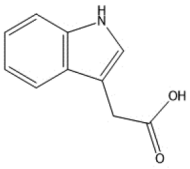
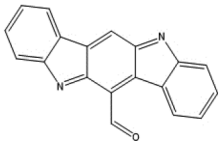
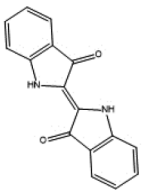
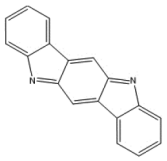
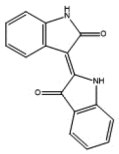
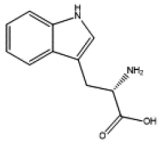
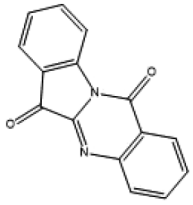
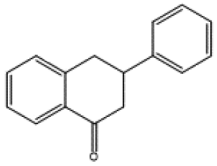
Introduction

Aryl hydrocarbon receptors (AhR) are ligand-activated receptors. They form nuclear heterodimer complexes with AhR-dependent nuclear translocator protein, and this complex binds to cis-xenobiotic responsive elements in the promoter region of AhR-responsive genes (Denison et al. 2011). These receptors were initially identified as having a high binding affinity for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, dioxin), which is a highly toxic industrial toxin (Poland et al. 1976). Subsequent studies in the 1980s identified various substances used in the industry (Denison et al. 1998) and pharmacology as ligands of these receptors, such as: carbidopa (Safe 2017), omeprazole (Jin 2015), endogenous substances indole derivatives (Hubbard 2015), constituents of certain fruits and vegetables (Hooper et al. 2011) and microbiome metabolism products (Korecka et al. 2016) that have a protective effect on the gastrointestinal tract.

Many of those ligands have a much lower binding affinity for AhR than TCDD and structure-like toxic halogenated aromatic substances (Murray and Perdew 2017). Among the many xenobiotic ligands for AhR, polycyclic aromatic hydrocarbons have been the most widely studied (Mulero-Navaro and Fernandez-Salguero 2016). Many of the AhR ligands are also estrogen receptor ligands (Abdelrahim et al. 2006). AhR regulates the expression of CYP. Conjugating enzymes not only in the liver but also in the brain. Studies have demonstrated the induction of CYP1A1 by TCDD in rat brain astrocytes (Sakakibara et al. 2016), suggesting the involvement of AhR in the metabolism of xenobiotics.

After being identified as mediators of the cellular response to xenobiotics, epidemiological studies in humans were conducted. The attention was focused on the pathological conditions of the immune system, lipid metabolism, epithelial integrity, porphyria manifestations, thymus involution, and neoplasms. The involvement of AhR

Table 1. Examples of Ah ligands.

Chemical structure and name	Source	References	Chemical structure and name	Source	References
 Indole	microbial	Hubbard (2015)	 Kynurenine	endogenous	Novikov et al. (2016)
 Skatole	microbial	Hubbard (2015)	 Kynurenic acid	endogenous	Novikov et al. (2016)
 3-hydroxy indole	microbial	Hubbard (2015)	 Xanthurenic acid	endogenous	Novikov et al. (2016)
 Indole-3-acetaldehyde	microbial endogenous	Zelante et al. (2013)	 Cinnabarinic acid	endogenous	Lowe et al. (2014)
 Indole-3-acetic acid	microbial endogenous	Jin et al. (2014)	 FICZ	endogenous	Wincent et al. (2009)
 Indigo	microbial	Sugihara et al. (2004)	 Indolo(3,2-b) carbazole	endogenous	Shertzer and Senft (2000)
 indirubin	microbial	Flaveny et al. (2009)	 Tryptophan	dietary	Jin et al. (2014)
 Truptanthrin	microbial	Murray and Perdew (2017)	 Flavonoids	dietary	Jin et al. (2014)

inspired scientific researches (Flesch-Janys et al. 1995). The creation of transgenic mouse models subsequently helps to establish the role of AhR in critical physiological and homeostatic processes. AhR-deficient mice show abnormalities in the liver, hematopoietic, cardiovascular, and immune system development (Lahvis et al. 2000). The physiological significance of AhR is further supported by the fact that they are evolutionarily conserved and exist in all multicellular animals. In some lower-order invertebrates, e.g., *D. melanogaster*, AhR does not have a detoxifying function but is required for the development of eyes, feet, and wings (Cespedes et al. 2010). In *C. elegans*, AhR is essential for neuronal differentiation and migration (Quin and Powell-Coffman 2004). According to modern understanding, the xenobiotic-dependent functions of AhR represent an adaptive mechanism that overlaps its physiologically determined features (Mulero-Navarro and Fernandez-Salguero 2016). Epigenetic mechanisms are involved both in the expression of AhR (Mulero-Navarro et al. 2006) and in regard of genes that are regulated by AhR. Exposure of the maternal organism to the action of AhR agonists is considered to be one of the possible mechanisms for the development of breast cancer in the offspring through epigenetic mechanisms (Romagnolo et al. 2016).

AhR as a therapeutic target

The identification of AhR ligands and their well-described positive health effect and beneficial pharmaceutical properties has stimulated studies aimed at developing drugs for various tumors, immune and inflammatory diseases, and enhancers of hematopoietic stem cell production. In the development of drugs that target AhR, the aim is mainly directed to selective AhR modulators, in which the ligand exhibits tissue-specific agonist or antagonist activity (Jin et al. 2012). Different classes of AhR ligands and different molecular types in the same class can differentially modulate AhR activity, inducing the expression of various genes. For this reason, AhRs can be considered as potentially interesting drug targets with cell-specific regulation.

Since AhRs are widely expressed in a number of tumors, molecules with antagonistic activity against AhRs could be considered as potential candidates for the treatment of such diseases. The most well-known AhR antagonist is alpha-naphtoflavone (Gasievicz and Rucci 1991). The potent AhR antagonist StemRegenin 1 has recently been developed as an inducer of human hematopoietic stem cell proliferation in vitro (Boitano et al. 2010). Interesting effects of bilirubin, as a potential AhR ligand on the immune system, have been reported (Bock and Kohle 2010) – in bilirubin-treated mice, it suppresses the development of the autoimmune disease. After endogenous bilirubin depletion, there is an increased incidence of exacerbation of autoimmune disease (Liu et al. 2008).

Throughout the many plant nutrients and chemicals of plant origin in the human diet, flavonoids are the most abundant and ubiquitous in fruits, vegetables, and wine. Quercetin, apigenin, and campherol, which are included in some foods, such as rose hips, linden flowers, honey, grapes, have been shown to exert agonist / antagonistic effects on AhR in various tissues (Hooper 2011). In addition, many flavonoids have anti-allergic and anti-inflammatory effects. Resveratrol (Papoutsis et al. 2010) has been found to inhibit CYP1A1 transcription in vitro, preventing AhR activation. Indole-glucosindolates in cruciferous vegetables is metabolized to compounds with high affinity for AhR. One of these metabolites, indole-3-carbinol, has been successfully tested in clinical trials as a dietary supplement (Reed et al. 2005). Probiotic bacteria and yeasts related to the human gut and skin microbiome also produce AhR ligands (e.g., indole-3 aldehyde, indirubin), thus enhancing the body's barrier functions (Zelante et al. 2013).

Neuroprotective properties of AhR modulators

AhR expression in vertebrate brain has recently been demonstrated by immunohistochemistry, with the brain stem, pineal gland, and some hypothalamic nuclei (including the suprachiasmatic nucleus controlling the circadian rhythm) having significantly elevated AhR levels compared to other areas of the brain (Juricek and Coumoul 2018). AhR regulates neurogenesis, cell proliferation, differentiation, and migration (Imran et al. 2015). The neuroprotective potential of 3,3'-diindolylmethane, a selective AhR modulator, has recently been demonstrated in cellular and animal models of Parkinson's disease, in lipopolysaccharide-induced inflammation and neuronal hypoxia (Rzemieniec et al. 2016). Activation of apoptotic signals by AhR ligands, on the other hand, can lead to NMDA (N-Methyl-d-Aspartate) receptor-mediated excitotoxicity, increased levels of calcium in the cytoplasm and oxidative stress (Wan et al. 2015). Interestingly, NMDA receptors also modulate the AhR function (Lin et al. 2008). In mouse stroke models, the kynurenine-aryl hydrocarbon receptor pathway is an essential mediator of brain neuronal damage (Cuartero et al. 2014) and represents a potential therapeutic modulation opportunity.

Conclusion

All these data put the importance of AhR as a toxicological and pharmacological target. Further evaluation of the neuropharmacological potential of substances that bind and modulate AhR is needed.

Acknowledgements

With the support of the Council of Medical Sciences of the Medical University of Sofia, grant D-62/2019.

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