Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Toxicology

Ligand activation of the Ah receptor contributes to gastrointestinal homeostasis

Iain A. Murray and Gary H. Perdew

Abstract

The Ah receptor (AHR) is capable of binding a structurally diverse group of compounds that can be found in the diet, produced by bacteria in the gut and through endogenous metabolism. The gastrointestinal tract is a rich source of AHR ligands, which have been shown to protect the gut upon challenge with either pathogenic bacteria or toxic chemicals. The human AHR can be activated by a broader range of ligands compared to the mouse AHR, suggesting that studies in mice may underestimate the impact of AHR ligands in the human gut. The protective effect of AHR activation appears to be due to modulating the immune system within the gut. While several mechanisms have been established, due to the increasingly pleiotropic nature of the AHR, other mechanisms of action likely exist that remain to be identified. The major contributors to AHR function in the gut and the most appropriate level of receptor activation that maintains intestinal homeostasis warrants further investigation.

Address

Department of Veterinary and Biomedical Sciences, and Center for Molecular Toxicology and Carcinogenesis, Penn State University, University Park, PA 16802, USA

Corresponding author: Perdew, Gary H (ghp2@psu.edu)

Current Opinion in Toxicology 2017, **2**:15–23

This review comes from a themed issue on **Metabolic Toxicology**

Available online 19 January 2017

For a complete overview see the Issue and the Editorial

http://dx.doi.org/10.1016/j.cotox.2017.01.003

Keywords

Ah receptor, AHR, Indole, IL22, Intestine, Gastrointestinal.

1. Introduction

Evidence suggests the predominant biological activities of the AHR are evoked through ligand binding. Thus, one key aspect of AHR research has centered upon the identification of the endogenous ligand for this receptor. However, the characterization of multiple, structurally diverse physiological AHR ligands have led to a complex story likely to be context specific. It is now apparent that a biological 'cocktail' of endogenous, pseudo-endogenous[1] and dietary AHR ligands exist and that spatiotemporal availability, generation (or metabolic elimination) and competition between disparate ligands represent the major factors dictating the physiological activities and functions of the AHR. Importantly, emerging evidence highlights the physiological relevance of intrinsic AHR ligand activation beyond xenobiotic metabolism.

2. Dietary AHR ligands

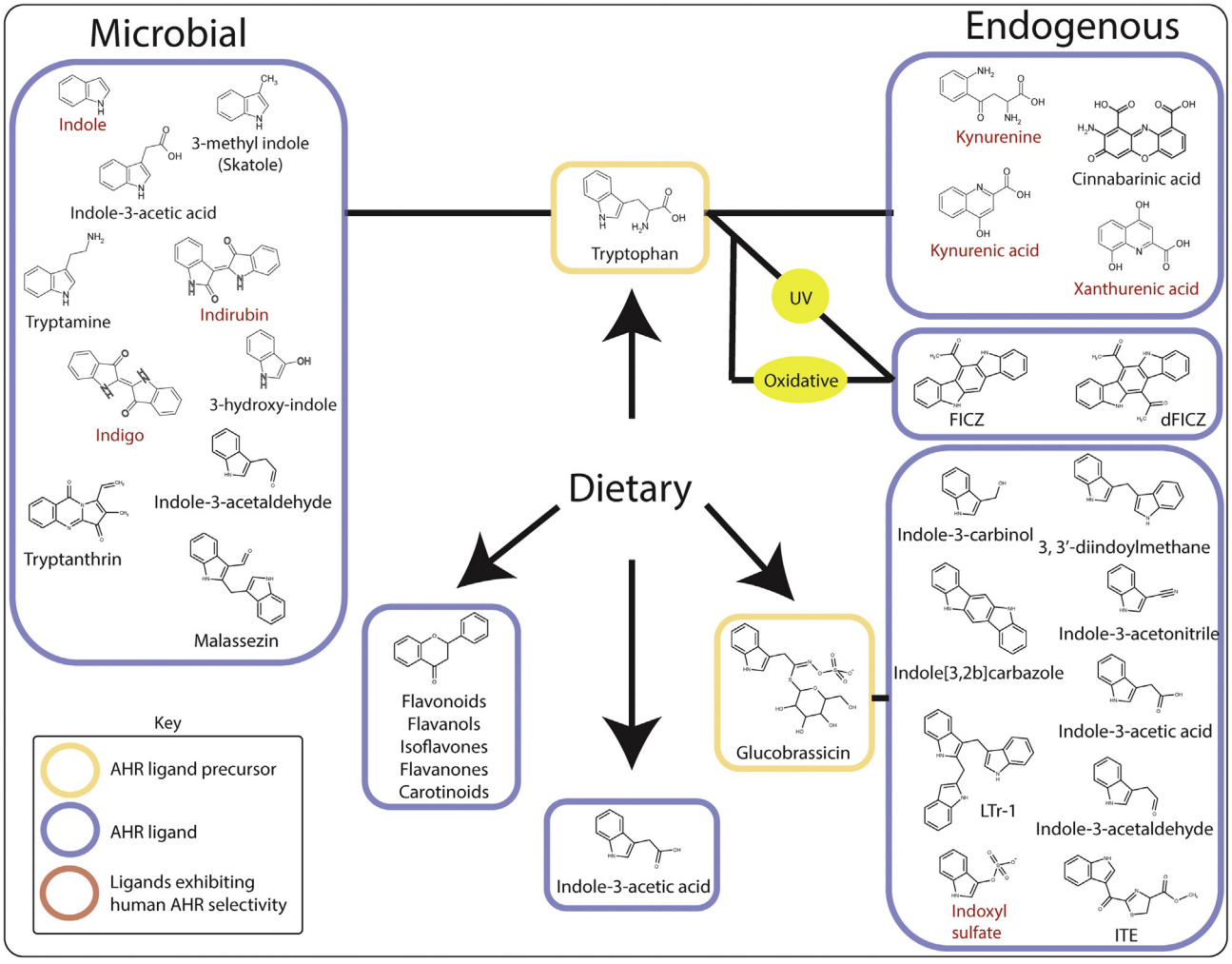
In essence, an organisms' diet comprises a complex mixture of xenobiotics, some of which provide nutritional and/or other physiological value while others may be toxins. Barring environmental, occupational or lifestyle (smoking) exposure to dioxins *etc*., the diet is now recognized as a major source of AHR ligands. The AHR has a promiscuous capacity to bind and respond to raw and cooked dietary components; including those derived from plants e.g. fruits and cruciferous vegetables (Figure 1) [1–7]. AHR ligation by dietary components likely serves to prime phase I cytochrome P450 metabolism within the gastrointestinal tract and through hepatic first-pass metabolism at the onset of ingestion to detoxify/eliminate potentially harmful dietary constituents [8]. In addition, the emergence of AHR as a pleiotropic factor with activities beyond metabolism suggests that dietary AHR ligands likely influence a wide range of physiological processes such as immune surveillance and microbiota/host interactions [9–11].

The most widely investigated dietary AHR ligands are those generated from the plant glucosinolates such as glucobrassicin, a component of cruciferous vegetables. Mechanical breakdown facilitates myrosinase-dependent hydrolysis of glucobrassicin to a number of products, including indole-3-carbinol (I3C) and indole-3-acetonitrile (I3ACN), both of which exhibit AHR agonist activity [7,12–15]. Within the acidic environment of the stomach, I3C is susceptible to acid condensation, yielding indolo[3, 2*b*]carbazole (ICZ), and 3,3′-diindolylmethane (DIM), both of which exhibit AHR binding potential [13,14,16,17]. These acid condensation products may represent the dominant AHR ligand binding activity *in vivo* when compared to I3C [18]. Pharmacokinetic data points to rapid absorption but low systemic retention of I3C, whereas ICZ, and DIM are present at steady-state levels due to a combination of higher chemical stability and longer plasma half-life relative to I3C [19,20].

In addition, numerous other dietary constituents including flavones, isoflavones, flavanones, and

[1] Pseudo-endogenous AHR ligands are defined as any metabolite that is produced by the microbiota and are capable of binding to the AHR.

Figure 1



Sources and examples of known dietary, endogenous and microbiota-derived AHR ligands.

carotenoids have been shown to elicit AHR activity and are either known or inferred AHR ligands [21–24]. It is clear that the diet represents a rich source of AHR ligands, however this generates a degree of complexity, which makes it difficult to determine the relative contribution of individual AHR ligands with regard to overall physiology. Although ICZ exhibits high-affinity (low nM) AHR binding similar to that exhibited by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the majority of the dietary AHR ligands identified to date are weak ligands by comparison. Additional complexity due to the fact that, despite being AHR ligands, many are characterized as AHR antagonists with regard to canonical AHR signaling. In addition, those that exhibit weak agonist activity may, if present at sufficient concentrations, act as competitive antagonists of more potent ligands e.g. flavonoids [25]. Although manifesting as AHR ligands, it is likely that many dietary components influence signaling through AHR-independent means, thus their contribution to physiology through AHR binding is difficult to interpret, particularly *in vivo*.

3. Tryptophan, a precursor to AHR ligands

A theme has emerged, which highlights a central role for the essential amino acid tryptophan as a major physiological reservoir for the synthesis of AHR ligands. A large body of evidence has demonstrated that tryptophan can undergo a range of spontaneous and enzyme-catalyzed conversions provided by the host and its associated microbiota to yield numerous physiologically relevant AHR ligands. Early observations indicating enhanced *in vitro* and *in vivo* AHR activity following exposure to ultra-violet radiation implicated light as a factor associated with endogenous AHR ligand production [26–28]. A series of studies identified a number of UV-dependent tryptophan photo-oxidation products, including 6-