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Mini review

AhR signalling and dioxin toxicity

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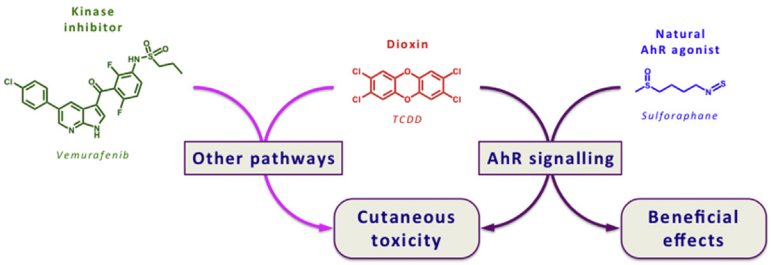
HIGHLIGHTS

- Besides its canonical pathway, AhR may activate other receptor-mediated pathways.
- AhR activity may be assessed by chemical or biological assays.
- Dioxin toxicity cannot be explained only by AhR activation.
- AhR activation leads to either upregulation or downregulation of genes.
- TCDD as a human carcinogen is still a matter of debate.
- Natural AhR agonists found in vegetables might have a beneficial effect.

GRAPHICAL ABSTRACT



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ABSTRACT

Dioxins are a family of molecules associated to several industrial accidents such as Ludwigshafen in 1953 or Seveso in 1976, to the Agent Orange used during the war of Vietnam, and more recently to the poisoning of the former president of Ukraine, Victor Yushchenko. These persistent organic pollutants are by-products of industrial activity and bind to an intracellular receptor, AhR, with a high potency. In humans, exposure to dioxins, in particular 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) induces a cutaneous syndrome known as chloracne, consisting in the development of many small skin lesions (hamartoma), lasting for 2–5 years. Although TCDD has been classified by the WHO as a human carcinogen, its carcinogenic potential to humans is not clearly demonstrated. It was first believed that AhR activation accounted for most, if not all, biological properties of dioxins. However, certain AhR agonists found in vegetables do not induce chloracne, and other chemicals, in particular certain therapeutic agents, may induce a chloracne-like syndrome without activating AhR. It is time to rethink the mechanism of dioxin toxicity and analyse in more details the biological events following exposure to these compounds and other AhR agonists, some of which have a very different chemical structure than TCDD. In particular various food-containing AhR agonists are non-toxic and may on the contrary have beneficial properties to human health.

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Contents

Abbreviations: AhR, aromatic hydrocarbon receptor; MADISH, metabolising acquired dioxin-induced skin hamartoma; NAHRA, natural AhR agonist; PCB, polychlorinated biphenyls; PCDD, polychlorinated dibenzodioxins; PCDF, polychlorinated dibenzofurans; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEF, TCDD-equivalent factor; TEQ, TCDD-equivalent.

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1. Introduction

The dioxin-like family includes polyhalogenated aromatic hydrocarbons such as polychlorinated dibenzodioxins (PCDD), polychlorinated dibenzofurans (PCDF) and polychlorinated biphenyls (PCB) (Fig. 1). PCDD and PCDF are by-products of organic synthesis and incineration procedures, whereas PCB were used as dielectric and coolant fluids in transformers, capacitors, and electric motors (Van den Berg et al., 1994; WHO, 2002). These persistent organic pollutants were associated to industrial accidents such as the BASF plant in Ludwigshafen in 1953 (Thiess et al., 1982) and the Icmesa factory in Seveso in 1976 (Assennato et al., 1989), to the toxic contaminant of the Agent Orange used by the U.S. army during the war of Vietnam in the 1960s (Steele et al., 1990), and more recently to the poisoning of the former Ukrainian President Victor Yushchenko in 2004 during his presidential campaign (Ryan, 2005; Saurat et al., 2012; Sorg et al., 2009).

The aryl hydrocarbon receptor (AhR) is a member of the bHLH (basic Helix–Loop–Helix)—PAS (Per-ARNT-Sim) family of transcription factors that regulate various physiological and developmental processes (McIntosh et al., 2010; Moglich et al., 2009; Tian, 2009; Zudaire et al., 2008). Many human tissues including the lung, the liver, the kidney, the skin, the spleen and the placenta express AhR (Abel and Haarmann-Stemmann, 2010). The receptor is localised in the cytoplasm and is activated by a variety of xenobiotic (exogenous) compounds diffusing through plasma membranes owing to their lipophilic properties. Following AhR activation, the signalling pathway leads to the modulation of genes involved in the metabolism of these lipophilic compounds (Abel and Haarmann-Stemmann, 2010; Guyot et al., 2013; Hahn, 2002). The notoriety of AhR is mostly due to the clinical manifestations following activation by a very potent agonist, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (Poland and Knutson, 1982; Van den Berg et al., 1994). For this reason AhR is sometimes called "the dioxin receptor", which is a quite restrictive point of view when considering the great variety of the physiological processes modulated by AhR. Indeed, besides the well known and misnomer chloracne syndrome (Saurat and Sorg, 2010), AhR activation induces a broad spectrum of biochemical and toxic effects, such as teratogenesis, modulation of the immune system and tumour promotion (Mimura and Fujii-Kuriyama, 2003; Quintana, 2013). Regarding the toxicity of dioxins, the relationships between AhR activation and toxicity has to be re-evaluated, as various compounds induce a similar toxic syndrome without activating AhR, and some natural AhR agonists (NAHRA) found in vegetables for instance do not induce chloracne (Connor et al., 2008; de Waard et al., 2008).

2. AhR signalling

2.1. Canonical pathway

In the absence of agonists, AhR is localised in the cytoplasm and maintained in an inactive form by chaperone proteins: (i) the prostaglandin E synthase 3 (cytosolic), also called p23; (ii) the heat shock protein 90 (HSP90); (iii) the AhR-interacting protein (AIP), also called ARA9, or HBV X-associated protein 2 (XAP-2). When a lipophilic agonist such as TCDD diffuses through the plasma membrane and binds to AhR, the chaperone proteins are released and the [AhR-agonist] complex binds to the transcription factor AhR nuclear translocator protein (Arnt). The new [AhR-agonist-Arnt] complex migrates to the nucleus where it binds to specific DNA sequences called xenobiotic-response elements (XRE), found on the promoter region of various genes, and this binding modulates the expression of downstream genes, among them phase I (e.g. CYP1A1) and phase II (e.g. UGT1A1) enzymes, and the AhR repressor (AHRR), which down-regulates AhR signalling (Abel and Haarmann-Stemmann, 2010; Beischlag et al., 2008; Bock and Kohle, 2009; Schmidt and Bradfield, 1996) (Fig. 2).

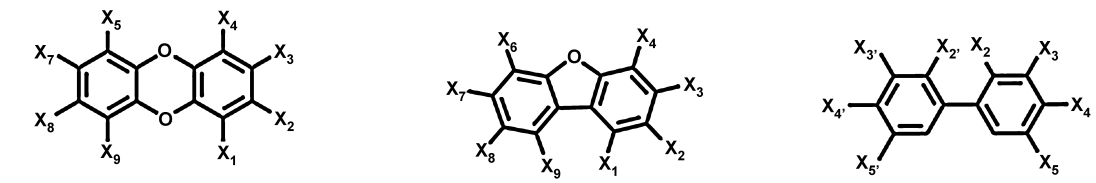

Fig. 1. Dioxin-like compounds. Chemical structures of PCDD, PCDF and PCB, commonly referred to as dioxin-like compounds.

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