Agonists of the Dioxin Receptor: Environmental Contaminants, Food Constituents, Microbial Metabolites, and Tumor Promoters

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The dioxin- or aryl hydrocarbon receptor (AhR) is a member of the Per-Arnt-Sim family of nuclear transcription factors exhibiting a basic helix-loop-helix structure. In its non-ligated state the AhR is associated with hsp 90 and the immunophilin-type XAP2. Upon ligand binding the associated proteins are released, the receptor dimerizes with the AhR nuclear translocator protein Arnt, and binds to XREs (xenobiotic-responsive elements) in the 5'-flanking region of responsive genes thus modulating their transcription.

Induction of cytochrome P450 (CYP) 1A1 and its catalytic activity measured as 7-ethoxyresorufin O-deethylase (EROD) in mammalian cells are well-established functional parameters for AhR activation. We used the analysis of CYP1A1 induction, e.g., as a tool to analyze the relative potencies of polychlorinated dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), and biphenyls (PCBs) as dioxin-receptor agonists. In rat hepatocytes in primary culture and in the rat hepatoma cell line H4IIE, a rank order of relative inducing potencies, usually measured as EC_{50} values, was established for these compounds. In human HepG2 hepatoma cells, a lower potency and a different rank order of relative potencies was found.

Furthermore, CYP1A1 induction allows the screening for yet unknown AhR agonists, e.g., among natural compounds. This approach led to the identification of tryptanthrins, secondary metabolites formed by *Candida lipolytica* from tailor-made precursors as AhR agonists. AhR activation by tryptanthrins was confirmed by gel-retardation and supershift analysis using a labeled XRE-oligo. Another novel group of AhR agonists comprises microbial metabolites formed *in situ* such as malassezin produced by the dermal fungus *Malassezia furfur*.

Furocoumarins, a family of almost planar molecules found in a variety of plants of the *Compositae* (celery, parsnip) or *Citrus* (lemon, lime) families also act as inducers of CYP1A1 in rat liver cells without detectable activation of DNA binding of the AhR or activation of an XRE-containing reporter gene. Thus, an alternative mechanism of CYP1A1 induction seems to be operative with furocoumarins possibly related to their pronounced capacity to inhibit the catalytic activity of the enzyme.

Finally, CYP1A1 induction can serve as a parameter of AhR activation in comparison to other effects of AhR agonists. Likewise, the potent tumor-promoter of rodent liver 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is thought to suppress the rate of apoptosis usually found in preneoplastic hepatocytes. This effect thought to represent a crucial mechanism of liver tumor promotion, can also be found *in vitro* in rat hepatocytes in primary culture. Our experiments suggest that suppression of apoptosis is mediated by enhanced phosphorylation of key regulators of apoptosis such as p53. In fact, hyperphosphorylation of p53 and EROD induction upon TCDD treatment of rat hepatocytes exhibited identical concentration-response relationships suggesting involvement of the AhR in hyperphosphorylation of p53.

In conclusion, AhR agonists with various potencies can be found among environmental contaminants, food constituents, and microbial metabolites. Persistent agonists such as TCDD act as tumor promoters in rodent liver. Their tumor-promoting activity seems to be related to an AhR-mediated suppression of apoptosis of preneoplastic hepatocytes.