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What are differences among Dioxins, Benzopyrenes and Indoles in terms of Toxicity through the Aryl hydrocarbon Receptor (AhR) system

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Abstract

There are remarkable progresses on understanding toxicity of TCDD, Benzo(a)pyrene in terms of gene and protein molecular science. We can understand up- and down regulation of genes involved after those chemicals coming into cell. In spite of understanding that those chemicals mobilize many genes through mediation of AhR, we still do not know yet fates of those chemicals inside the cell and how they are metabolized or not. This paper describes firstly finding of authentic AhR ligands such as Indirubin and Indigo in human urine. Their binding capacity with human AhR is higher than that of TCDD. However, they are easily oxidized with CYPs, and conjugated in to sulfate conjugates. They are easily discharged into human urine, while TCDD is not oxidized nor conjugated so that it stays longer inside cell, continuing AhR mediated gene up- and down regulation. It could be explained that one of multiple toxicity of TCDD may be attributed to over and unnecessary gene mobilization inside cell until it is discharged out of cell. Compared to TCDD and Indirubin, Benzo(a)pyrene, a typical mutagen and carcinogen found in diesel exhaust gas, etc is also a substance that is AhR mediated. It also mobilizes the same genes as those of TCDD and Indirubin involved. After CYPs are mobilized, it can be changed into many different variations through oxidation and reduction until a conjugate form for discharging out of cell. During the oxidation and reduction processes, attention has been given to the use of DNA adducts as the exposure index of Benzo(a)pyrene, DNA adducts derived from Benzo(a)pyrene, were searched by using LC/MS/MS, and several adducts such as BPDE-dG adducts, the metabolites of B[a]P, were detected. On the other hand, the DNA adducts resulted from oxidative damages were clearly observed by treating

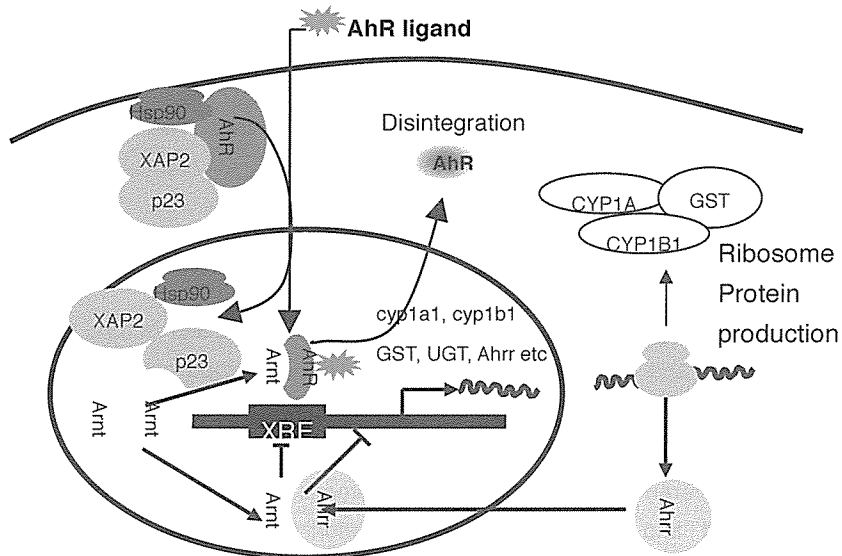
human cells with benzo(a)pyrene. LC/MS/MS method used in this study has a good performance in easily and high- selective detection of objective peaks in a small amount of mixture. It can be postulated that at least there are three types of different toxicity groups of chemicals that are AhR mediated, one TCDD type, the second Benzo(a)pyren type and the third Indirubin type. There many indoles in natural food as well as physiological substances including Indrubin, Indigo and Indole-3-carbinol. There are many natural poly-aromatic hydrocarbons (PAHs) in fossil fuel. They are potential air pollutants that many of them are mutagenic and carcinogenic.

We found there are three different types in de-toxicity mechanism.

- (1) Indirubin type: Indoles found in human urine, blood and natural food are easily oxidized and conjugated. They are rapidly discharged out of cell. They do not interfere with other biochemical reactions, nor form DNA adducts, thus no toxicity.
- (2) Benzopyrene type: Many poly-aromatic hydrocarbons are oxidized and reduced, and conjugated. During oxidation some are epoxidized forming DNA adducts that are origin of mutation, while oxidation process produces hydroxyl radicals that react with DNA forming OH adducts leading to mutation and carcinogenesis.
- (3) Dioxin type: Dioxins and dibenzofurans are not oxidized nor reduced nor conjugated thus remained prolonged period inside cell over inducing the AhR receptor system upsetting other biochemical reactions leading to many types of toxicity, that are not yet understood in their mechanisms.

Keywords: TCDD, Indirubin, Benzo(a)pyrene, PAHs, DNA adducts, LC/MS/MS

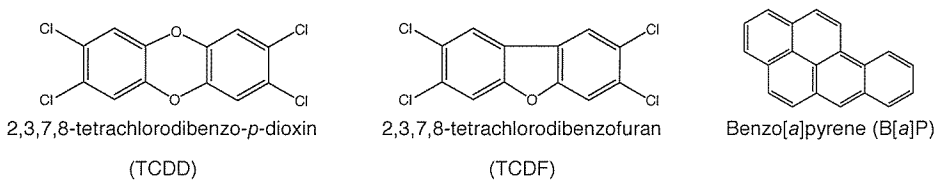
Fig 1. Gene mobilization through AhR



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Control of protein formation for metabolism, cytokine, and regulation of cell division

Fig 2. Toxicity through AhR system



Dioxin;TCDD, Dibenzofuran;TCDF

Typical carcinogen of PAHs

Fig 3. DNA damages by B(a)P

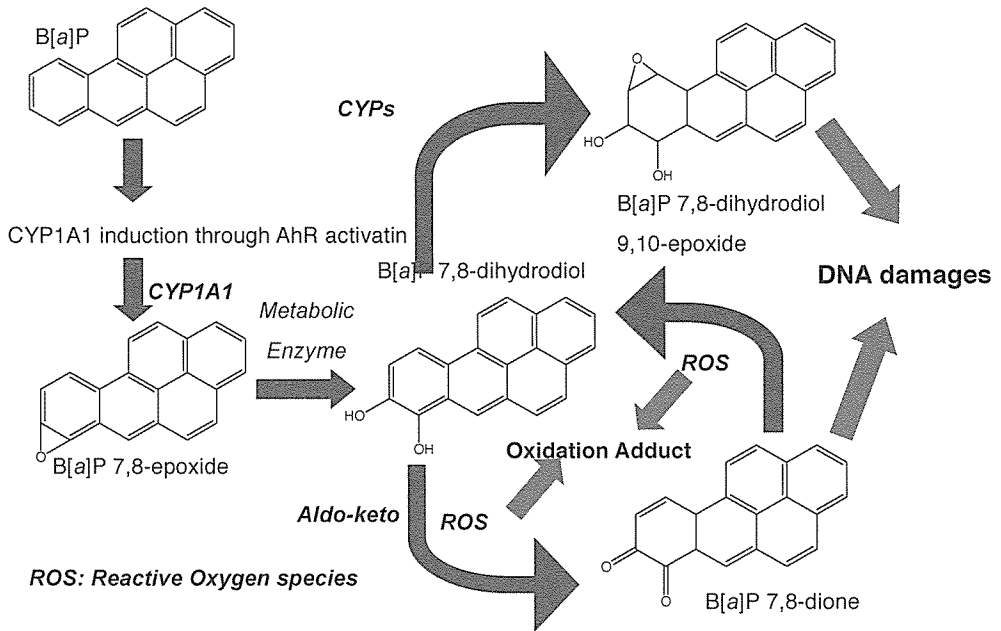
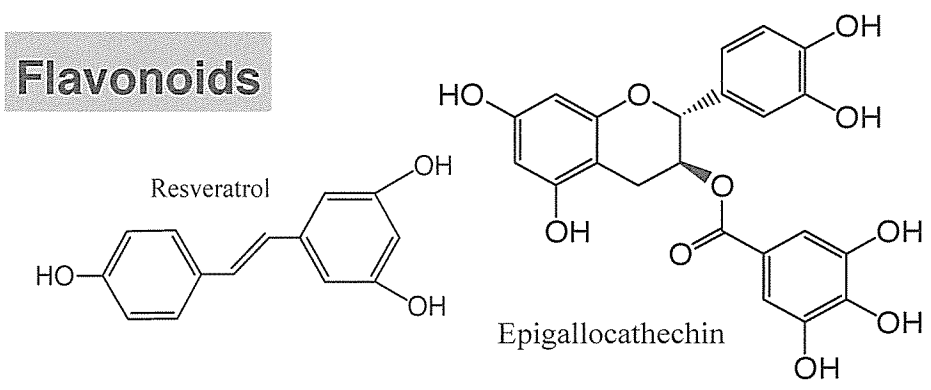


Fig 4 . AhR ligands found in nature and food



Indoles

