［Review］

# Biological Effects of Polycyclic Aromatic Hydrocarbon Derivatives

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***Abstract*** **:** Polycyclic aromatic hydrocarbons (PAHs) are included in various environmental pollutants such as airborne particles and have been reported to induce a variety of toxic effects. On the other hand, PAH derivatives are generated from PAHs both through chemical reaction in the atmosphere and metabolism in the body. PAH derivatives have become known for their specific toxicities such as estrogenic/antiestrogenic activities and oxidative stress, and correlations between the toxicities and structures of PAH derivatives have been shown in recent studies. These studies are indispensable for demonstrating the health effects of PAH derivatives, since they would contribute to the comprehensive toxicity prediction of many kinds of PAH derivatives.

***Key words*** **:** PAH derivative, structure activity relationship, estrogenic/antiestrogenic activity, reactive oxygen species.

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## Introduction

An important group of pollutants associated with airborne particulate matter (PM) are polycyclic aromatic hydrocarbons (PAHs), which are constructed of two or more aromatic rings and are produced by incomplete combustion of fossil fuels. PAHs have carcinogenicity and mutagenicity [1], and have been classified according to International Agency for Research for Cancer (IARC) as carcinogenic or probably carcinogenic compounds [2, 3]. PAHs are believed to be the main causal compounds in the health effects of ambient air pollutants. PAHs generate various derivatives both in the atmosphere and in the body. PAH derivatives are becoming known to have particular effects, such as oxidative stress and endocrine disruption. Many studies give information on the possible roles of PAH derivatives in several diseases which have been increasing for several decades worldwide. However, a comprehensive assessment of the toxicities of these compounds is not easy, since numerous PAH derivatives exist in the atmosphere and they have different toxicities.

In recent years, studies of the structure and activity relationship have developed in the study of environmental science. This study can predict the possibility of the toxicities of compounds according to the relationship between chemical three-dimensional (3D) structures, even though the toxicities of their compounds have not been measured. Therefore, an analysis of the structure and activity relationship is a key to know the health risk of numerous compounds in the

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atmosphere, including PAH derivatives.

This review provides information mainly about our recent observation assessing the relationship between structural and biological activities of PAH derivatives.

## Generation of PAH derivatives

It is well known that PAH derivatives such as hydroxylated PAHs (OHPAHs) and PAH quinones (PAHQs) are generated in the atmosphere through chemical reactions with nitrogen radicals ($\bullet NO^3$), hydroxide radicals (•OH) and ultraviolet light [4–6]. These PAH derivatives are also generated in the body. After entering the body, PAHs bind to one of the nuclear receptors, the aryl hydrocarbon receptor (AhR), and then induce the cytochrome P450 drug-metabolizing enzymes such as *Cyp1a1*, *Cyp1a2* and *Cyp1b1*, which metabolize PAHs into various PAH derivatives.

## Toxicities of PAH derivatives

Concerning the toxicities of PAH derivatives, the mutagenicity induced by nitrated PAHs (NPAHs) has been well known for many years [7]. In recent years, it has been shown that other PAH derivatives also show various toxicities. For instance, PAHQs produce reactive oxygen species (ROS) through redox cycle, leading to ROS-related toxicities, such as physical DNA damage, oxidative stress and cell death [8–10]. The most important information is that PAH derivatives-induced oxidative stress might be involved in various diseases, such as allergic reaction, circulatory organ system disease, infection and aging [11–17]. Cho *et al*. have recently reported that phenanthrenequinone (PQ) induced the recruitment of inflammatory cells, such as eosinophils and neutrophils, into the lung with the lung expression of pro-inflammatory molecules such as interleukin (IL)-5 and eotaxin *in vivo* [19]. PQ also aggravates antigen-related airway inflammation in mice, and PQ has adjuvant activity for antigen-specific immunoglobulin G (IgG), leading to aggravation of antigen-related airway inflammation in mice [20]. Because PQ is a major quinone in diesel exhaust particles (DEP) [18], which have been reported to cause lung inflammatory-related impacts, these reports suggest a key role of PQ in lung diseases by air pollutants.

Interestingly, there are several reports suggesting that PAH derivatives have endocrine disruptor-like activities. DEP extracts including numerous PAH derivatives exhibit estrogenic and/or antiestrogenic activities in human MCF-7 breast cancer cells and recombinant yeast cells [21–23]. These samples also exhibited a significant antiandrogenic effect in PC3/AR human prostate carcinoma cells [24]. Actually, one of the OHPAHs, hydroxyphenanthrene (OHPhe) and hydroxyfluoranthene (OHFrt), constructed with three or four rings, were determined in the DEP extracts as antiandrogenic compounds. Furthermore, strong estrogenic activities of several OHPAH isomers, hydroxybenz[*a*]anthracene (OHBaA) and hydroxychrysene (OHCh), were also detected by screening evaluation using yeast two-hybrid assay [25].

## Structure activity relationship of estrogenic/antiestrogenic activity of PAH derivatives

It has gradually become known that the endocrine disruptor-like activities of PAH derivatives are related to their structure. It has been reported theoretically that the common structure of estrogenic compounds is a phenol with a hydrophobic moiety at the *para*-position without a bulky group at the *ortho*-position [26]. This theory could be applied to the activities of PAH derivatives. In our recent study, we investigated whether OHPAHs, PAHQs and PAH ketones (PAHKs) having two to six rings show estrogenic or antiestrogenic activities [25, 27] by using the yeast two-hybrid assay system [28], in order to elucidate the characteristics of PAH derivatives in more detail.

Among the OHPAHs we tested, strong estrogenic activity was observed mainly in OHPAHs having 4 rings. We also observed strong antiestrogenic activity in several OHPAHs having 4 and 5 rings [25]. Because PAHs can't bind to the active site of human estrogen receptor (hER), it is strongly suggested that the hydroxyl modification and its location are key factors for the large difference in estrogenic activities between PAHs and OHPAHs. At this time, relative binding affinity (RBA) is also correlated with estrogenic or antiestrogenic activity [29]. On the other hand, we have found that several PAHQs also showed strong antiestrogenic activities, suggesting that exhibition of

antiestrogenic activity mainly depends on the location of substituted groups rather than on the kinds of functional groups [30].

It has been reported that the phenol group (OH-3) of 17β-estradiol ($E_2$) makes hydrogen bonds with Glu353 and Arg394 of hER and $H_2O$ and that the alcohol group (OH-17) of $E_2$ has an affinity for the nitrogen atom of His524 of hER. On the other hand, van der Walls interaction takes place between the benzene ring of $E_2$ and the benzene ring of Phe404 of the binding site of hER [31, 32]. These reports suggest that 4-ring OHPAHs interact with the binding site of hER, and this binding mechanism depends on the phenol group. Furthermore, several physical parameters, such as the length-to-breadth (L/B) ratios of the rectangular van der Walls plane surrounding each PAH molecule and O-H distance, the distance between the oxygen atom of the phenol group and the hydrogen atom located farthest from the phenol group and partial charge, might be correlated with these binding mechanisms between $E_2$ and estrogen receptor (ER), showing a correlation with estrogenic/antiestrogenic activities of OHPAHs and PAHQs. Especially, L/B and O-H distance showed an effect on the activity (Fig. 1).

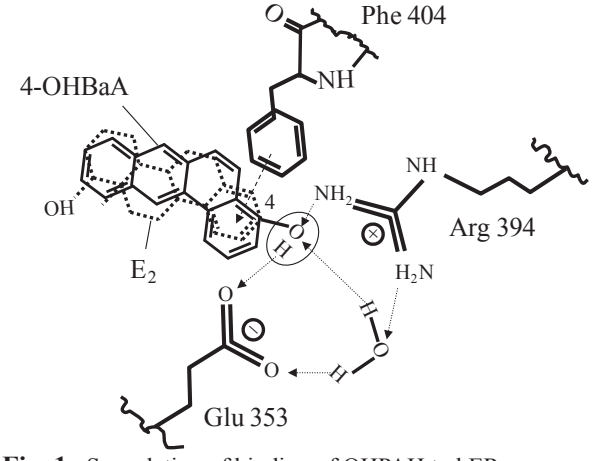


**Fig. 1.** Speculation of binding of OHPAH to hER.

Furthermore, compounds having a strong affinity to hER, such as E and diethylstilbestrol (DES), have two hydroxyl groups with the appropriate O-O distance [31]. The L/B ratios of $E_2$ and DES were 1.545 and 1.515, respectively. These L/B ratios and O-O distances were close to the value of L/B ratios and O-H distances of the above strongly estrogenic OHPAHs in the small circle area (Fig. 2). The area of the L/B ratio and O-H distance of the strongly antiestrogenic OHPAHs was much larger than that of the strongly estrogenic OHPAHs described above. Although it is unclear why 9-OHBaA was an exception, this result suggests that antagonistic OHPAHs can exhibit activity even when they bind to sites other than the active site of hER.

These facts suggest that the activities of OHPAHs and PAHQs can be roughly predicted from their physical parameters, although differentiation between agonistic and antagonistic effects is not easy.

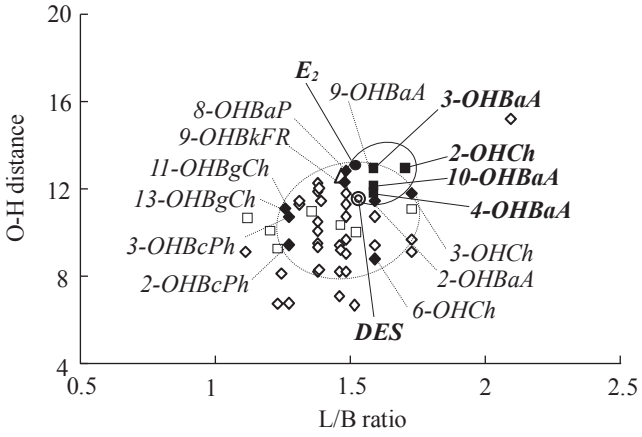


**Fig. 2.** Correlations between L/B ratio and O-H distance of estrogenic/antiestrogenic OHPAHs. hERα was used in the assay. ■: Relative effective potency of estrogenic activity ($REP_E$) > 0.001, □: $REP_E$ < 0.001, ◆: Relative effective potency of antiestrogenic activity ($REP_{AE}$) > 0.1, ◇: $REP_{AE}$ < 0.1, ◎: diethylstilbestrol (DES), ●: 17β-estradiol ($E_2$). In the case of $E_2$ and DES, O-O distance was used instead of O-H distance (Reproduced from ref. [25] with permission of Journal of Health Science).

## Structural characteristic of oxidative stress induced by *ortho*-PAH quinones

The oxidative stress induced by PAHQs has been extensively studied and several reviews are available [33–37]. Among PAHQs, *ortho*-PAHQs could form either *ortho*-semiquinone anion radicals or catechols by electron nonenzymatic reduction. These compounds are unstable, and easily return to quinones. At that

time, superoxide anion radical and hydrogen peroxide are generated (Fig. 3). In addition, it was demonstrated that *ortho*-PAHQs, such as 9,10-phenanthrenequinone (9,10-PQ), can catalyze the transfer of electrons from dithiol to oxygen, generating superoxide anion radical. Regarding the *para*-quinone group, the generation of superoxide by semiquinone of Coenzyme Q (ubiquinone) has been also reported [38]. In fact, a large part of the electron leak to molecular oxygen results from the semiquinone form of CoQ generated during the Q-cycle in complex III or by a similar, less defined mechanism in complex I [39–41]. Therefore, most quinone compounds induce oxidative stress through an electronic mechanism induced by semiquinone.

We recently gathered more information about ROS generation from various PAHQs that exist in the atmosphere. In a study using thiol consumption as an index for ROS generation of PAHQs, we showed that *ortho*-PAHQs (9,10-PQ, 5,6-chrysenequinone (5,6-CQ) and benzo[*a*]pyrene-5,6-quinone (B[*a*]P-5,6-Q) consumed much more of the thiol groups, while *para*-PAHQs (1,4-naphthoquinone (1,4-NQ), 9,10-anthraquinone (9,10-AQ), 1,4-anthraquinone (1,4-AQ), 1,4-phenanthrenequinone (1,4-PQ), 1,2-benzoanthraquinone (1,2-BAQ), 1,4-chrysenequinone (1,4-CQ) and benzo[*c*]phenanthren-1,4-quinone (B[*c*]P-1,4-Q) didn't. We got the same results of viability for each PAHQ. Three of the *ortho*-PAHQs (9, 10-PQ, 5, 6-CQ and B[*c*]P-5,6-Q) significantly reduced the viability of A549 cells to about 20% of the control, but *para*-PAHQs had little effect on viability (Fig. 4). These results provided the initial evidence that there was a structure activity relationship by which *ortho*-PAHQs have a stronger potential for ROS generation than *para*-PAHQs.

Actually, several *ortho*-PAHQs such as 9,10-PQ and 9,10-AQ have been reported to exist in the atmosphere at the concentration range of 20 to 730 pg $m^{-3}$ [18, 42, 43]. Other *ortho*-PAHQs with strong biological activities might also exist in the atmosphere. In addition, *ortho*-PAHQs can be generated in the human body through the metabolism of PAHs by cytochrome P4501A1 [44, 13]. Therefore, our data suggest that PAHQs, especially *ortho*-PAHQs, need to be paid more attention from the aspect of many kinds of diseases, such as pulmonary dysfunctional diseases, carcinogenesis, chronic inflammatory process, and acute symptomatic responses in the respiratory tract *et al*. [18, 45–47].

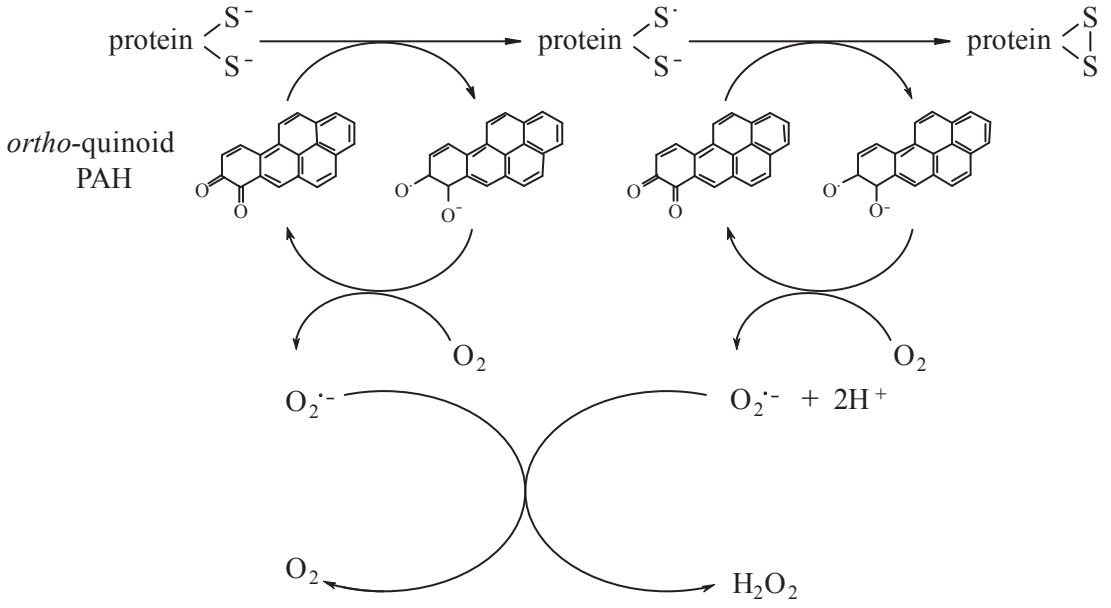


**Fig. 3.** Redox cycle for overproducing $H_2O_2$ by *ortho*-PAHQs.

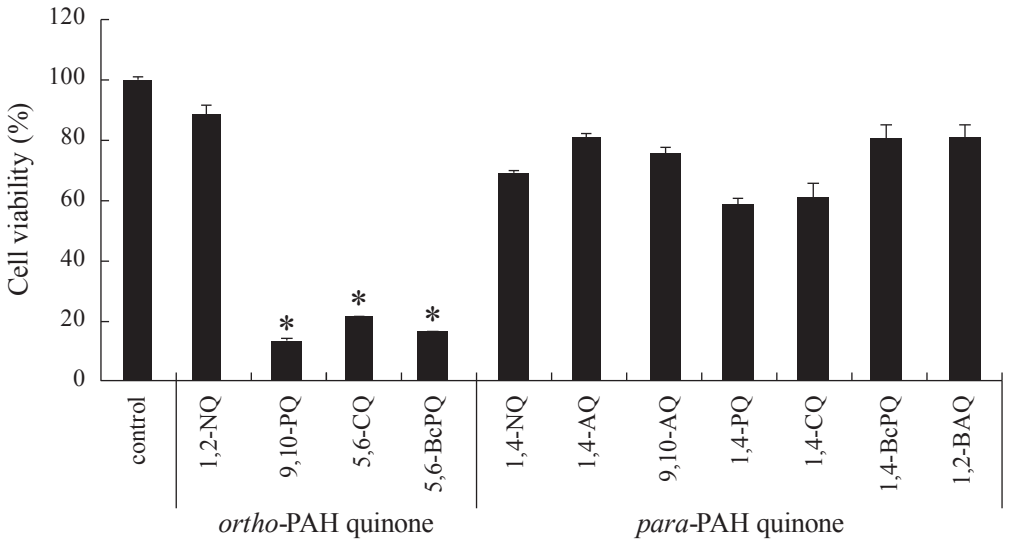


**Fig. 4.** Effects of PAHQs on the cell viability. A549 cells were incubated with 10 μM quinoid PAH for 12 h. The viability of the cells was determined by MTT assay. Each value is the mean ± SD of three determinations. Statistical significance, ✻ : $P < 0.001$ vs. control (Reproduced from ref. [48] with permission of Journal of Health Science).

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# 多環芳香族炭化水素誘導体が示す毒性作用

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**要　　旨**：多環芳香族炭化水素類（PAHs）は大気粉塵などの多種類の環境汚染物質に含まれ，長年の研究によって多様な生体影響を引き起こすことが知られている．一方で，PAHsは生体内での代謝反応や，大気中での化学反応によって多種多様な誘導体を生成することが知られている．近年では，PAHだけでなくPAH誘導体の毒性影響が着目されており，エストロゲン様/抗エストロゲン作用，酸化ストレス反応など，PAHとは異なる誘導体独自の毒性影響の存在が報告されている．また，生成するPAH誘導体には多くの構造異性体が存在するが，PAH誘導体が示す毒性作用と構造との間に相関性，いわゆる構造活性相関があることが示されている．以上の研究は，環境中に存在するPAH誘導体の生体影響を解明する上で重要な研究であるとともに，多種多様なPAH誘導体の総合的な毒性影響予測に貢献できると考えられる．

**キーワード**：PAH誘導体，構造活性相関，エストロゲン様/抗エストロゲン作用，活性酸素種．

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