Mechanism of Biosynthesis of Methylsulfones from PCBs and Related Compounds

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Mercapto-, methylthio-, methylsulfinyl- and methylsulfonyl metabolites of PCBs, 2,5,2',5'-tetrachlorobiphenyl, 1,3,5-trichlorobenzene and some other chlorobenzenes were identified in adipose tissues of mice, rats and guinea pigs by using GC/MS/COM systems. By means of administration of CD₃-methionine, it was confirmed that the methyl group in methylthio metabolites was derived from the methionine. Moreover, after pretreatment with either esterification of urinary metabolites in guinea pigs with 1,3,5-trichlorobenzene and 1,3-dichlorobenzene or N-acetylation after esterification, it was confirmed that cysteine, cysteine, N-acetylcysteine, cysteamine, mercaptopyruvate, mercaptolactate, mercaptacetate, thiol and disulfide conjugates were detected as a serial modified derivatives of glutathione moiety.

These results are summarized as a metabolic proposed pathway of halogenated aromatic compounds. Three routes in pathway correspond to oxygenation (initial route), glutathione thioether disposition (intermediate route) and sulfoxidation (final route) in connection with both reactive intermediates of epoxide and thiol. Methylation of the thiol by S-adenosylmethionine may be important in inhibiting covalent binding of reactive intermediates with biocomponents, similar to the glutathione conjugation for the detoxification of epoxide.

Introduction

Methylsulfonfylation, the process leading to the formation of mercapto-(SH), methylthio-(SCH₃), methylsulfinyl-(SOCH₃) and methylsulfonyl-(SO₂CH₃) metabolites of xenobiotics, is one of the many novel biological pathways of metabolism discovered during the past several years. The serial methylsulfonfyl pathway for xenobiotic metabolism has been studied in numerous laboratories for numerous compounds such as the drugs caffeine (1), bromazepam (2), bromovalerylurea (3), acetaminophen (4), alfoqualone (5), and 3-hydroxyxanthine (6); pesticides and fungicides, including propaclor (7), naphthalene (8), AF-2 (9) and PCNB (10); and pollutants such as DDE (11), PCBs (11-13), HCB (14) and monochlorodibenzo-p-dioxin (15). During the time that xenobiotic thioether derivatives were discovered, precursors including glutathione, cysteinylglycine, cysteine and N-acetylcysteine (mercapturic acid) conjugates (2,4,5,7,14) have been reported. Furthermore, it is believed that serial methylsulfonfyl metabolites might be discovered by more detailed analysis.

Mechanism of Biosynthesis of Serial Methylsulfonfyl Metabolites

Miller and Miller et al. first reported that methylthio derivatives of carcinogens such as aminobiphenyl (16), acetylatedaminofluorene (17) and dimethylaminoazobenzene (18) were isolated as alkaline degradation products from liver protein in rats treated with these compounds. They proposed that to obtain methylthio derivatives, the process would involve the direct attachment of these compounds to the sulfur atom of the methionyl residue of liver protein and the splitting of the methylthio group from the electrophilic intermediate interacting between the aromatic amine and the methionyl residue in liver protein (16-18).

The formation of xenobiotic thioether derivatives, including glutathione, cysteinylglycine, cysteine and N-acetylcysteine (mercapturic acid) conjugates, is generally considered a pathway for the detoxification of reactive intermediates. For example, the epoxide (arene oxide) of carcinogenic polycyclic aromatic hydrocarbons can be metabolized to a glutathione conjugate and appears as N-acetylcysteine and cysteine derivatives in urine. Thus, in vivo studies for thioether excretion may indicate that formation of a chemically reactive interme-
diate has occurred (19,20). The epoxide of naphthalene would change any hydroxymetabolite nonenzymatically or would convert the dihydroxy metabolite through the dihydrodihydroxy metabolite by epoxide hydrolase, or the glutathione conjugate by glutathione-S-epoxide transferase. It was proposed by Stillwell et al. (8) that methanethiol derived from the 2-keto-4-methylthiobutyrate form by deamination of methionine was the nucleophilic agent responsible for the formation of the methylthio metabolite from the epoxide of naphthalene.

In another mechanism, it has been confirmed that the bromazepam thiol conjugate was produced through scission of the β-C-S bond of the bromazepam cystein conjugate by β-lyase, which is found in the liver cytosol (21) or in the intestinal flora of rats (22). Subsequently, a bromazepam methylthio conjugate was produced by transmethylation from S-adenosylmethionine to bromazepam thiol conjugate by the thiol-S-methyltransferase. Those facts indicate that detection of the serial methylsulfonyl metabolites of xenobiotics alone could not explain their carcinogenicity. However, the findings of serial methylsulfonyl metabolites may indicate that xenobiotics interact with sulfhydryl groups.

In our laboratory, serial methylsulfonyl metabolites were detected by using GC/MS/COM from the adipose tissues of mice treated with commercial PCBs (Kenechlor-300, -400, -500) or 2,5,2',5'-tetrachlorobiphenyl (TCB) (23). The PCBs containing 3 to 5 chlorine atoms clearly produced methylsulfonyl metabolites, but Jensen et al. (11) reported that methylsulfonyl metabolites were found in trichlorinated to heptachlorinated biphenyls. Jansson et al. (12) also reported that the methylthio metabolite of hexachlorobenzene was to be a dechlorinated type of HCB. This finding may possibly indicate that decachlorinated biphenyl produces serial methylsulfonyl metabolite. HCB detected in adipose tissues (24) is known to be one of the contaminants in various herbicides polluting the environment.

Ten metabolites (Fig. 1) were detected in the feces of mice treated with 2,5,2',5'-TCB, a major component of Kenechlor-400. By groups of sulfur-containing metabolites and nonsulfur-containing hydroxy metabolites, the excretion rates for one week were 1.7% and 43%, respectively. The amounts of sulfur-containing metabolites were very small, 1.25 compared with metabolites not containing sulfur (25). Methylsulfonyl metabolites accumulated in the liver and adipose tissues of mice. Another paper reported that methylsulfonyl metabolites containing trichlorinated to hexachlorinated biphenyls also accumulated in lungs of mice (26).
In the case of simultaneous administration of 2,5,2',5'-TCB and CD₃-methionine to mice, the SCH₃ group of methylthio metabolite was initially converted to SCD₃ group. Later, the SOCH₃ moiety of the methylsulfonyl group was converted to the SCD₃ group (24). It was confirmed that the methyl moiety in the serial methylsulfonyl metabolite was derived from methionine. Similar results in caffeine were reported by Kamei et al. (1). After the conversion of hydrogen of the serial methylsulfonyl metabolite to deuterium with D₂SO₄, a part of the molecular ion at m/z 252 shifted one mass unit to the high-mass side. This showed that the 3-SOCH₃-2,5,2',5'-TCB mass peak contained 3-OH-4-SCH₃-2,5,2',5'-TCB and 3-SCH₃-4-OH-2,5,2',5'-TCB as the same molecular ions of the isomer, suggesting that the precursor of these metabolites was 2,5,2',5'-TCB epoxide. The epoxide may have been opened by nucleophilic attack of the sulfhydryl group in cysteine (as will be described later) and the intermediate subsequently converted to the hydroxy metabolite by dehydration.

This metabolic process is similar to the metabolic activation of polycyclic aromatic hydrocarbons in each epoxide, but the product was different from the ultimate carcinogenic form of benzopyrene, which was the 7,8-dihydroxy-9,10-epoxide produced through two epoxidations in one benzene ring (27). The route of metabolism of 2,5,2',5'-TCB shown in Figure 2 indicates that PCB was metabolized preferentially in whichever benzene ring had fewer chlorine atoms. Therefore, in order to analyze in detail the mechanism for the PCB metabolism, an experiment using chlorobenzene was performed. It was confirmed that a methylsulfonyl metabolite was found in the urine of mice treated with mono- to tetrachlorinated benzene, but the methylthio metabolite from HCB was found in smaller amounts (28). Dichlorobenzenes showed a high excretion rate of the serial methylsulfonyl metabolite. 1,3,5-Trichlorobenzene produced dichloromethylsulfonyl metabolites of dechlorinated type resulting from the replacement of the chlorine atom by a sulfur atom. In the case of simultaneous administration of 1,3,5-trichlorobenzene and CD₃-methionine to mice, the SCH₃ group of the methylthio metabolite was initially converted to a SCD₃ group. Later, the SOCH₃ and SO₂CH₃ groups were converted to SCD₃ and SO₂CD₃ groups just as in 2,5,2',5'-TCB. Furthermore, each methylsulfonyl metabolite contained a hydroxy group in the position adjacent to the methylsulfonyl group. 2-OH-3-SCH₃-1,5- and 2-OH-3-SH-1,5-dichlorobenzences were converted to 2-OD-3-SCH₃- and 2-OD-3-SD-1,5-dichlorobenzences respectively, on treatment with deuterium sulfide. Bis(2-OH-3-S-1,5-dichlorobenzene) disulfide was also found by using GC/MS/COM.

On administering 1,3,5-trichlorobenzene with glutathione to mice, a hydroxy metabolite not containing sulfur was detected in quantities as high as in the control without GSH (3 days urine collection) but the methylsulfonyl compound was present at levels 1.5 times higher than the control. The excretion ratio of nonsulfur-containing metabolite to sulfur-containing metabolite was 1:7.8. After methylation of freeze-dried urine with hydro-chloric methanol, water-soluble metabolites other than the serial methylsulfonyl metabolite found were 2-OH-3-mercaptopoacetate, -mercaptopolactate, -mercaptopryruvate and -N-acetylcysteine-1,5-dichlorobenzene. Furthermore after N-acetylation of the water-soluble residue with acetic anhydride, 2-OH-3-mercaptopo-
ethylamine (cysteamine), -cysteine and -cysteinylglycine-1,5-dichlorobenzene were found in addition to the previous metabolites (29). In 1,3-dichlorobenzene, metabolites of mercaptoacetate, mercaptolactate, mercaptoypyrate, cysteamine, cysteine, N-acetylcysteine, cysteinylglycine and thiol dimer were also detected. Figure 3 shows the gas chromatogram and mass spectra of peak components on the gas chromatogram of 1,3,5-trichlorobenzene metabolites in mouse urine. Those conjugates have been considered to be the customary metabolic products of halobenzenes. The results are summarized for one metabolic model for halogenated aromatic compounds in Figure 4. Three routes, as shown in Figure 4, correspond to oxygenation (upper route), glutathione thioether disposition (middle cycle) and sulfoxydation (under route) in connection with both reactive intermediates of epoxide and thiol. Methylation of the thiol from S-adenosylmethionine may be important in inhibiting covalent binding of reactive intermediates with biocomponents, similar to the glutathione conjugation for the detoxification of epoxide. Subsequently, sulfoxydation of the methylthiol metabolite to the methylsulfonfyl derivative will result in a decrease in the molecular polarity of this metabolite and induce slow excretion of the methylsulfonfyl metabolite.

For example, mice receiving 1-SCH$_3$-3,5-dichlorobenzene completed excretion of this compound in an unchanged form after 6 hr, but mice treated with 1-SO$_2$CH$_3$-3,5-dichlorobenzene took 240 hr for excretion. Comparing 1-SO$_2$CH$_3$-3,5-dichlorobenzene with phenobarbital administration in mice, the amount of cytochrome P-450 in liver microsome treated with

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**Figure 3.** Gas chromatograms and mass spectra of urine after intraperitoneal administration of 1,3,5-trichlorobenzene. Broken lines (D$_1$, D$_2$) represent mass spectra after conversion of hydrogen into deuterium; D$_3$ represents CD$_3$. 
methylsulfone was 18 times higher than that treated with phenobarbital. Therefore, Kimura et al. (30) suggested that the substance inducing mixed-function oxidase was the methylsulfone metabolite produced from treated compounds. 4-Chlorothiophenyl glucuronide was found in urine from rats treated with O-ethyl-S-4-chlorophenyl ethane phosphonodithioate with 4-chlorophenylmethylsulfonyl metabolite produced. The amount of glucuronic metabolite excreted was 1/8 of the methylsulfonyl metabolite (31). Generally, glucuronidation of a hydroxy (phenolic) metabolite provides protection from phenolic compounds affecting the mitochondria as the uncoupler in the energy transfer system. Glucuronidation of the thiophenolic compound might also have the same function.

**Excretion Routes of Xenobiotic Compounds**

Excretion pathways of xenobiotic metabolites consist of two main routes: in the feces and in the urine. Low molecular weight compounds will be excreted into the urine, but higher molecular ones will be excreted into the bile and mixed with digested foods and intestinal microorganisms in the intestinal tract. PCB, DDE, PCT, polychlorinated dibenzo-p-dioxin (PCDD) and related metabolites are considered to belong to the latter. Bakke et al. (7) pointed out that the process of cleavage of the C-S bond of metabolites was thought to be catalyzed by C-S lyase of intestinal microorganism and intestinal tissues. In the case of alfoqualone, serial methylsulfonyl metabolite in urine decreased significantly on antibiotic treatment or bile duct ligation. At the same time, the N-acetylcysteine of alfoqualone was detected as a metabolite in bile duct, and residual half components were assumed to be glutathione and cysteine conjugates of alfoqualone (32).

The chemical forms of methylmercury in the bile duct are thought to be the glutathione and cysteine conjugates (33). This glutathione conjugate may be converted to cysteine conjugate through cysteinylglycine conjugate by γ-glutamyltranspeptidase and cysteinylglycinase in the bile duct. An analogous phenomenon may occur in primary urine due to the high activity of these enzymes in the brush border of the kidney tubules (34).

Figure 5 shows the biotransformation and circulation of xenobiotics. The circulation process is separated into two routes and two compounds according to molecular weight: high molecular weight compounds in the enterohepatic circulation and low molecular weight compounds in the nephrohepatic circulation. The glutathione conjugate is finally converted to a cysteine or thiol conjugate, and then two conjugates are translocated into the liver. The thiol conjugate derived from
cysteine moiety derivatives is transmethylated by thiol-S-methyltransferase and is oxygenated by cytochromes P-450 and P-448 oxidase or is glucuronidated by UDP-glucuronoyltransferase in the liver. The end form of the thiol conjugate may be represented as a methylsulfone or glucuronidated conjugate. If the chemical form inducing cytochrome P-450 were in the methylsulfonyl form of xenobiotic compounds, both enterohepatic and nephronephrotic circulations might be important for the rapid detoxification by mixed-function oxidase during period of introduction of xenobiotics.

**Origin of Sulfur Atom in Serial Methylsulfonyl Group**

In order to determine whether the source of the sulfur atom in serial methylsulfonyl metabolite of PCBs and related compound is cysteine or methionine, Bergman et al. (35) administered 2,4,5-trichlorobiphenyl and either radiolabeled $^{35}$S-cysteine or $^{35}$S-methionine to mice. The results showed that the labeled sulfur atom from both cysteine and methionine was incorporated into the methylsulfonyl group of the biphenyl metabolites, which was detected by using thin-layer radiochromatography from the lung extract of mice. Methionine could possibly be metabolized into cysteine through cystathionine, but it could not be formed from cysteine since it is essential in mammals. It is quite certain that the sulfur atom donated to the sulfur-containing metabolites comes from the sulphydryl group of cysteine. In another study by Tulp et al. (15), monochlorodibenzo-p-dioxin was metabolized to the methylthio derivative, but the fate of PCDF was not described.

In our laboratory, it was confirmed that the C-S splitting of S-methylmercucic cysteine and S-methylmercucic cysteamine conjugate caused the formation of bis(methylmercuric)sulfide, and that the methylmercury covalently bound to the sulphydryl residue in albumin was released with the anion exchange reaction by hydrosulfide such as thiocysteamine and thiouracine. Methylmercucic thiocysteamine and thiouracine also converted nonenzymatically to bis(methylmercuric) sulfide (36).

**Conclusion**

The formation of serial methylsulfonyl metabolites for xenobiotics will be summarized as follows. The incorporation of sulfur atom into the xenobiotics starts from glutathione conjugation in liver, and thiol derivatives are successively produced by the cleavage of glutathione moiety. The thiol derivative is converted to the methylthio derivative by the transmethylation from S-adenosylmethionine by the action of thiol-S-methyltransferase. This methylthio derivative changes to a methylsulfonyl derivative through methylsulfonyl form by S-oxidation by the action of mixed function oxidase. The other route to the methylthio derivative may start from the methionine through reactive intermediates.

Many xenobiotics might have as a metabolic process these methylsulfone routes. However, it is necessary to determine the biological effects in each of the methylsulfonyl metabolites for xenobiotics.

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