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Mini Review

Different Toxicity of Aristolochic Acids in Kidney and Liver

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Introduction

Aristolochic acid (AAs) is a group of nitrophenanthrene compounds comprised of AAI, AAII, AAIII and AAIV, which are widely found in Aristolochia plants and used in herbal therapy and traditional Chinese medicine [1]. Consistent use of aristolochic acids- containing drugs could lead to aristolochic acid nephropathy and subsequent urinary tract tumors [2-4]. Active metabolites of AAs form adducts with DNA, inducing characteristic A-T transversion (A:T to T:A mutation) known as AA mutational signature [5]. In 2017, a study has analyzed AA mutational signature of several datasets and concluded that AAs and their derivatives were widely implicated in liver cancers in Taiwan and throughout Asia [6]. Ever since the paper published, there has been an intensive debate on whether the prevalence of AA signature mutation is high in HCC patients and if this mutation spectra is really correlate with traditional Chinese medicine consumption in Asia. Since no case report has linked AAI to liver cancer by far, many researchers held doubts regarding AA-induced liver cancer. Herein, we summarized previous reports of animal experiments indicating the organ specified toxicity in kidney other than liver and shared our opinion about the possible reasons.

For long, several reports have linked AAs to the development of urothelial cancer, kidney and forestomach tumors in rodents [7-11]. Although AA could be bioactivated in both kidney and liver, in most studies, it only induces tumors in kidney [12]. Therefore, kidney was usually considered as the prior target organ of AAs. AA-DNA adduct is a well-known biomarker for AA exposure. Studies conducted on rat kidney and liver found that kidney had at least two-fold higher levels of DNA adducts and mutant frequency than livers inducted by AAI [13, 14]. The same dose didn't cause liver tumor in rat, but DNA adducts were detectable at lower levels than kidney [13]. The experiment on Muta mice showed the same tendency [15]. A most recent study also indicated that although forestomach carcinoma was the main cause of death in long-term small dose (0.3-3.0 mg/kg) AAI-treated mice, kidney was still the organ with most AA-DNA adducts accumulation compared with forestomach and liver [16].

There are several possible reasons for the tissue specificity of AA, one of which could be the ability of proximal tubules to transport and concentrate AA and their metabolites, resulting in renal toxicity. OAT family, mainly expressed on renal proximal tubules, is considered to be one of the pivotal determinants mediating the accumulation of AAI into the proximal tubules [17]. In addition, the level of enzymes catalyzing the reductive activation of AAI are varied in different cells. The activation pathway for AAI is nitroreduction catalyzed by both cytosolic and microsomal enzymes. One of the main human and rat enzymes activating AA-I toxicity was NAD(P) H:quinone oxidoreductase (NQO1), present in hepatic and renal cytosolic subcellular fractions. Other involving enzymes include NADPH: CYP reductase (POR) in kidney microsomes and protaglandin H synthase (cyclooxygenase, COX) in urothelial tissues [18]. In addition to gene expression level of the AAI activation related enzymes in liver and kidney, in vivo oxygen concentration in specific tissues might also affect the balance between AAI nitroreduction and demethylation, which in turn would influence tissue-specific toxicity or carcinogenicity [19]. A recent study also indicated that hepatocyte-specific metabolism of AA-I substantially increases its cytotoxicity toward kidney proximal tubular epithelial cells, including formation of aristolactam adducts and release of kidney injury biomarkers [20].Moreover, AA exposure could cause significantly altered gene expression profiles between kidney and liver, involving defense response, apoptosis and immune response, cell cycle etc, which might also be possible reasons for the tissue-specific toxicity and carcinogenicity of AA [12, 21].

Although the toxicity and carcinogenesis of AAs in kidney is well-defined, their role in liver damage and tumor development may be different. Besides, AA exposure as the main cause of liver cancer was not consistent with the actual scenario in Asia since hepatitis B virus infection remains as the highest risk. Therefore, we believe the toxicity of AAs in liver and kidney should be considered separately.

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