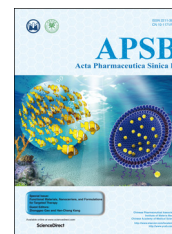




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Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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## REVIEW

# Isoniazid metabolism and hepatotoxicity

Pengcheng Wang<sup>a</sup>, Komal Pradhan<sup>a</sup>, Xiao-bo Zhong<sup>b</sup>, Xiaochao Ma<sup>a,\*</sup>

<sup>a</sup>Center for Pharmacogenetics, Department of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA 15261, USA

<sup>b</sup>Department of Pharmaceutical Sciences, School of Pharmacy, University of Connecticut, Storrs, CT 06269, USA

Received 15 April 2016; received in revised form 9 June 2016; accepted 27 June 2016

### KEY WORDS

Isoniazid;  
Metabolism;  
Hepatotoxicity;  
Anti-tuberculosis;  
N-Acetyltransferase 2;  
Amidase

**Abstract** Isoniazid (INH) is highly effective for the management of tuberculosis. However, it can cause liver injury and even liver failure. INH metabolism has been thought to be associated with INH-induced liver injury. This review summarized the metabolic pathways of INH and discussed their associations with INH-induced liver injury.

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**Abbreviations:** AcHz, acetylhydrazine; AcINH, acetylisoniazid; ALP, alkaline phosphatase; ALT, alanine aminotransferase; DiAcHz, diacetylhydrazine; GSH, glutathione; GST, glutathione *S*-transferase; Hz, hydrazine; INA, isonicotinic acid; INH, isoniazid; MPO, myeloperoxidase; NAD<sup>+</sup>, nicotinamide adenine dinucleotide; NAT, *N*-acetyltransferase; P450, cytochrome P450; R.M., reactive metabolite; TB, tuberculosis

\*Corresponding author. Tel.: +1 412 648 9448.

E-mail address: [mxiaocha@pitt.edu](mailto:mxiaocha@pitt.edu) (Xiaochao Ma).

Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

<http://dx.doi.org/10.1016/j.apsb.2016.07.014>

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Please cite this article as: Wang Pengcheng, et al. Isoniazid metabolism and hepatotoxicity. *Acta Pharmaceutica Sinica B* (2016), <http://dx.doi.org/10.1016/j.apsb.2016.07.014>

## 1. Introduction

Tuberculosis (TB) is a global health issue<sup>1</sup>. The standard therapies for TB include a combination treatment of isoniazid (INH), rifampicin, pyrazinamide, and ethambutol<sup>2</sup>. INH can also be used alone for TB prevention<sup>3</sup>. Despite the beneficial effects of INH, severe adverse effects especially peripheral neuropathy and hepatotoxicity are associated with INH therapies<sup>4–7</sup>. About 10%–20% of patients consuming INH have a transient elevation of serum alanine aminotransferase (ALT) level. Most of the patients can adapt to it and their serum ALT levels return to normal without discontinuation, while some patients (less than 1%–3%) develop severe liver injury and even liver failure<sup>4,8–10</sup>. The most current report from the Drug-Induced Liver Injury Network (DILI) indicates that the true incidence of INH-induced liver injury is largely under-reported in the United States, and it is the second-ranking drug that causes liver injury in spite of under-reporting<sup>11</sup>.

Clinically, INH-associated treatments usually cause a hepatocellular-type of liver injury, as characterized by a marked elevation of ALT levels (>10 times upper limit of normal [ULN]) but minimal increases in alkaline phosphatase (ALP) levels (usually <2 times the ULN)<sup>6</sup>. Even though INH-induced liver injury has been known and extensively studied, its underlying mechanisms are still poorly understood<sup>4,6,8,9,10,12–15</sup>. Different experimental animal models have been used to study the hepatotoxicity of INH, including rats<sup>13,16–18</sup>, mice<sup>15,19–21</sup>, and rabbits<sup>15,22–24</sup>. Unfortunately, there is no validated animal model to recapitulate the human patterns of INH-induced liver injury<sup>6</sup>. Even though 6 doses of 100 mg/kg of INH given to rats hourly can cause necrosis in rats that were pretreated with phenobarbital, the injury and administration patterns in this study were different from those in clinic where chronic administration was used and a late onset of liver injury was observed<sup>13</sup>. In addition, recent studies suggest that rat is not a good model to replicate the delayed type of INH hepatotoxicity based on comparison of the formation of INH-bound proteins in mice, rat, and human liver microsomes<sup>15,25</sup>. Furthermore, INH was found to induce microvesicular steatosis in different animal models, including mice<sup>20</sup>, rabbits<sup>22,26</sup>, and rats<sup>15,23</sup>, but these phenotypes are usually not observed in patients with INH-induced liver injury.

INH metabolism is thought to be associated with INH-induced liver injury<sup>13–15,16–19,26–33</sup>. Acetylhydrazine (AcHz), hydrazine (Hz), and acetylisoniazid (AcINH) are the major metabolites of INH. Studies of INH hepatotoxicity in rats showed that AcINH and AcHz can cause hepatic necrosis; however, treatment with INH directly even at high dose and long term did not cause toxicity<sup>9,15</sup>. These results suggested INH metabolites are responsible for INH hepatotoxicity. Covalent binding of acetyl group to liver proteins were observed after treating rats with <sup>14</sup>C-acetyl-labeled AcINH but not with aromatic ring <sup>14</sup>C labeled AcINH, indicating that AcHz is responsible for INH hepatotoxicity in rats<sup>13,16</sup>. Studies carried out in mice showed different results. When Hz or AcHz was administered at a dose of 300 mg/kg to mice, Hz produced hepatic necrosis, macrovesicular degeneration, and steatosis, whereas AcHz did not<sup>34</sup>, suggesting that Hz is responsible for INH-induced liver injury in mice. In a rabbit model of INH-induced liver injury, the plasma level of Hz is correlated with the extent of INH-induced necrosis and steatosis, but plasma levels of INH and AcHz are not<sup>26</sup>. In addition, Hz inhibits mitochondrial complex II and affects the function of electron transport chain and ATP production in mouse primary hepatocytes. Co-treatment with Hz and a complex I inhibitor can cause

hepatocyte death<sup>35</sup>. Recent studies also found INH itself can bind to liver proteins and cause immune-mediated hepatotoxicity<sup>15,36</sup>.

In summary, despite extensive studies in INH metabolism and its role in INH-induced liver injury, the observations and conclusions are inconsistent and even controversial. This review summarized and updated the pathways of INH metabolism. We also discussed and provided novel insight into the association of INH metabolism with INH-induced liver injury.

## 2. The metabolic map of INH

INH is a low-molecular weight and water-soluble compound that can be rapidly absorbed from the gastrointestinal tract<sup>37</sup>. Pharmacokinetic properties of INH are affected by various patient-specific factors, like genetic status, age, comorbidities, and the co-administered food or drugs<sup>38–44</sup>. The peak plasma concentration is achieved around 1–3 h after administration of the drug<sup>45,46</sup>. Meals containing high fats can decrease absorption of INH as revealed by the reduction of  $C_{max}$  by 51% and the increasing of  $T_{max}$  to 2 times<sup>47,48</sup>. Hence it is recommended to consume INH on an empty stomach. After absorption, INH diffuses into all tissues and body fluids rapidly, including cerebrospinal fluid, saliva, pleural and peritoneal exudates, bronchi and pulmonary alveoli<sup>49–52</sup>. INH also can be excreted into breast milk<sup>53,54</sup>.

The major pathways of INH metabolism (Fig. 1) include: (1) Acetylation to form AcINH through *N*-acetyltransferase (NAT) 2; and (2) Hydrolysis to produce isonicotinic acid (INA) and Hz through amidase. AcINH can also be hydrolyzed to form INA and AcHz. In addition, Hz can be acetylated to AcHz and diacetylhydrazine (DiAcHz)<sup>55</sup>. Hz and AcHz are thought to be further oxidized to reactive metabolites and involved in INH hepatotoxicity<sup>13,16,28,56,57</sup>, which was proposed to be mediated by microsomal P450s, especially CYP2E<sup>56,58</sup>.

Besides these major metabolic pathways, INH can also conjugate with several endogenous metabolites<sup>59,60</sup>, including ketone acids, vitamin B6 (pyridoxal and pyridoxal 5-phosphate), and NAD<sup>+</sup>. In addition, INH was found to disturb the homeostasis of endogenous metabolites, such as vitamin B6, bile acids, cholesterol, and triglycerides<sup>21,61,62</sup>. The major metabolic pathways of INH are enzymatic-dependent reactions, including acetylation and hydrolysis of INH by NAT and acyl amidase, respectively<sup>6</sup>. Catalase-peroxidase (KatG) of *Mycobacterium tuberculosis* (Mtb) and human neutrophil myeloperoxidase can catalyze the formation of INH-NAD<sup>+</sup> adducts<sup>60,63</sup>. Nevertheless, conjugation of INH with ketone acids and vitamin B6 are non-enzymatic reactions. We illustrated these metabolic pathways of INH in details in the following sections and discussed their associations with INH hepatotoxicity.

## 3. Role of NATs in INH metabolism and hepatotoxicity

NATs (EC 2.3.1.5, *N*-acetyltransferase, arylamine *N*-acetyltransferases) are a class of enzymes that catalyze the acetylation of arylamines from acetyl-CoA. It is widely found in different species, both in eukaryotes and prokaryotes<sup>64–66</sup>. NATs are responsible for acetylation of hydrazine drugs and carcinogenic aromatic amines, as well as endogenous molecules, such as serotonin<sup>67,68</sup>. NAT1 and NAT2 are the major NATs that are involved in the biotransformation of xenobiotics. The NAT genes are located in close vicinity in the genome and share high

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