GUT MICROBIOTA

Gut microbes: a role in melamine-induced renal toxicity?

Gut microbes mediate melamine-induced renal toxicity by converting melamine to cyanuric acid, resulting in the development of melamine–cyanurate crystals in kidneys, say researchers. “We found that melamine-induced kidney stones contained melamine and uric acid—in relatively high concentrations, and a small amount of cyanuric acid,” says investigator Wei Jia. “Melamine and uric acid don’t tend to form crystals, but in the presence of cyanuric acid they will quickly crystallize; it only takes a small amount of cyanuric acid to trigger stone formation and kidney toxicity. Gut microbes play a key role in this process because they produce cyanuric acid from melamine.”

Previous research by Jia and colleagues demonstrating that gut microbial-related metabolites were markedly altered in rats exposed to melamine led the researchers to hypothesize that gut microbiota are involved in the mechanism of melamine-induced renal toxicity.

To assess the effect of microbiota activity on melamine nephrotoxicity *in vivo*, the researchers first suppressed gut microbial activity in rats by administering an antibiotic, followed by

administration of melamine for 15 days. Histologic analysis of kidneys from rats given melamine without antibiotics revealed severe damage, with crystal formation, dilatation of renal tubules and interstitial haemorrhage. By contrast, rats given antibiotics showed reduced melamine-induced renal toxicity. In addition, metabolic profiling of urinary metabolites demonstrated that suppression of gut microbiota normalized levels of gut microbiota-related metabolites and increased urinary excretion of melamine.

To assess the existence of gut microbes that are able to metabolize melamine, the researchers cultured rat faecal specimens in medium containing melamine. The concentration of melamine in the culture decreased over 36 h, whereas cyanuric acid concentration concomitantly increased. In control cultures without faecal specimens, no cyanuric acid was detected. 16S ribosomal DNA sequencing subsequently identified *Klebsiella terrigena* in rat faeces. Cultivation of *K. terrigena* in medium containing melamine resulted in the rapid production of cyanuric acid. To assess the effect of *K. terrigena* on melamine-induced renal toxicity, the researchers colonized the guts of rats

Ingram Publishing/Thinkstock

with *K. terrigena* before exposing them to melamine. Colonization with *K. terrigena* increased the concentration of cyanuric acid in the kidneys of rats given melamine and exacerbated kidney toxicity.

“The mechanisms involved in melamine-induced renal toxicity have been a matter of debate, since melamine is not a toxic material and is not readily absorbed *in vivo*,” says Jia. “In our study, we found that *K. terrigena* was responsible for the conversion of melamine to cyanuric acid and the subsequent formation of melamine–uric acid–cyanuric acid stones.”

Susan J. Allison

Original article Zheng, X. *et al.* Melamine-induced renal toxicity is mediated by the gut microbiota. *Sci. Transl. Med.* 5, 172ra22 (2013)