Another Mechanism behind Cadmium Toxicity

Impaired NAT-Dependent Pathway Alters Chemical Biotransformation

Cadmium is a complex carcinogen that may contribute to carcinogenesis through multiple mechanisms, including inhibition of enzymes that help repair damaged DNA. A new study provides information on another possible mechanistic pathway by revealing that cadmium impairs NAT-dependent carcinogen metabolism as demonstrated by altered biotransformation of environmental aromatic amines (AAs) [***EHP* 118(12):1685–1691; Ragunathan et al.**].

Cadmium accumulates in body tissues and causes disease of the lungs, kidneys, liver, testes, prostate, and bladder. It also is thought to potentiate the carcinogenicity of many common workplace chemicals. NATs, or arylamine *N*-acetyltransferases, are metabolic enzymes known to play a major role in the biotransformation of exogenous chemicals including AAs, many of which are known or suspected human carcinogens.

In the current study the authors exposed purified NAT enzymes to cadmium and found the exposure led to rapid and irreversible functional impairment—removing the cadmium could not restore enzyme activities. They also exposed lung epithelial cells and laboratory mice to cadmium, then assessed NAT acetylation activity in the cells and mouse tissue samples. Biologically relevant concentrations of cadmium similar to those found in the lung tissue of heavy smokers impaired the NAT-dependent acetylation of carcinogenic AAs in lung epithelial cells, and NAT activity was strongly impaired in multiple tissues of mice exposed to cadmium.

These findings indicate acute cadmium exposure can alter the metabolism of carcinogenic AAs through impairment of the NAT-dependent pathway, with potentially important toxicologic effects—especially considering AAs are commonly found in cigarette smoke along with cadmium. The authors recommend further studies to address whether chronic cadmium exposure leads to similar effects.

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A Break in the Continuum

Analyzing the Gap in Particle Exposure Research

Researchers have examined the effects of fine particulate matter ($PM_{2.5}$) doses spanning nearly three orders of magnitude. Cardiovascular disease risks have been documented for active smoking exposures at the higher end of that continuum and for environmental tobacco smoke (ETS; sometimes called secondhand smoke) and ambient air pollution exposures at the lower end. However, there is a distinct lack of information on the cardiovascular risks of exposures in the middle range, which are experienced by hundreds of millions of people who burn biomass and coal indoors. A new commentary analyzes the implications of this crucial knowledge gap [***EHP* 118(12):1643–1645; Smith and Peel**].

The authors note that plots of average inhaled doses of $PM_{2.5}$ and associated cardiovascular health risks in the literature reveal a highly nonlinear exposure response. That is, exposure to ETS and ambient air pollution yield higher risks of heart disease than might be expected on the basis of exposure risks of active smokers.

Analysis of three intermediate estimated $PM_{2.5}$ doses (inhaling 100 mg/day for a light smoker, 10 mg/day for a resident exposed to smoke from biomass burning, and 1 mg/day for someone exposed to ETS) similarly indicated that small $PM_{2.5}$ dose reductions in populations with relatively low levels of exposure may achieve greater health gains than more drastic reductions in populations with high levels of exposure. Comparing a theoretical population of smokers with the same number of nonsmokers living in a heavily polluted city, this suggests similar numbers of cardiovascular deaths—or possibly more—may be prevented in the nonsmokers by adopting strict ambient $PM_{2.5}$ reduction measures than by convincing the smokers to quit smoking. This counterintuitive idea could have major policy ramifications, so the authors urge further examination of these relationships.

The gap in studies of exposures greater than those from ETS but less than those from active smoking reflects a dose range of 1–20 mg/day. Filling in the missing information for this gap should receive research priority, the authors write, because of the potentially large cardiovascular disease health burden it represents, particularly for the people worldwide who burn biomass for household cooking and heating.

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The health effects of particulate exposure through active and passive smoking have been studied extensively. Less is known about similar exposures that result from indoor biomass and coal burning, a part of daily life for hundreds of millions of people worldwide.