My journey in Inhalation toxicology of ambient particles: cardiovascular toxicities and beyond

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Ambient particles have been reported in epidemiological studies to be associated with the mortality and morbidity of the respiratory and cardiovascular diseases. However, the causal relationship and underlying mechanisms were unclear for cardiovascular diseases. We have conducted a serial inhalation studies to answer the questions. The state of the art particle concentrator was used to generate particles to expose animals. We first investigated if ambient particles caused acute hemodynamic changes. Blood pressure and electrocardiogram were recorded continuously before, during and after the exposure. We found that acute exposure to ambient particles caused the alterations of blood pressure, heart rate and heart rate variability. This system was also used to investigate the toxicity of particles during Asian dust event. Again, we found an increase of systemic and lung inflammation, heart rate, and blood pressure during the dust event. These studies have demonstrated that acute exposure to ambient particles may affect the autonomic function of the cardiovascular system.

In addition to acute toxicity, we are interested in the health effects from chronic exposure to ambient particles. We constructed a non-concentrated ambient particle exposure system, Taipei Air Pollution Exposure System (TAPES). The system is easy to operate and maintain for chronic exposure as compared to the particle concentrator. Hyperglycemic rats were induced and exposed to ambient particles for three months. The average concentration of ambient particles during the three months of exposure period was around 13 $\mu g/m^3$. We found emphysematous changes of lung, increased wall thickness of aorta, myocardial inflammation, and advanced glomerulosclerosis and proximal tubule changes. There were biochemical changes including increased HbA1c, fibrinogen and systemic inflammation. In the healthy rats, we also observed increased wall thickness, focal myocarditis, systemic inflammation and increased insulin resistance. Thus, PM exposure may induce the macro-and micro-vascular complications in the diabetics through chronic hyperglycemia and systemic inflammation. Furthermore, findings in healthy animals support the hypothesis that diabetes may be caused by PM through insulin resistance.

Recently, associations between ambient particles and central nervous system (NS)

diseases have been reported. We are interested in the toxicity of particles on degenerative CNS diseases. The Alzheimer's diseases (AD) animal model were exposed to low level of ambient particles for 5 months. The spatial learning was not different, however, the memory of animals was delayed in the exposed group. Decreased total brain volume was noted in MRI, and more neuronal death in the cerebral cortex and demyelination of the corpus callosum were noted by the histological staining. There was no difference in the accumulation of amyloid or tau on immunohistochemistry staining. For the protein analysis, amyloid was at higher levels in the cerebral cortex, with lower expression of myelin basic protein in the white matter. A diffuse tensor image study also revealed insults in multiple white matter tracts, including the optic tract. The results showed that even chronic exposure to low level of PM 2.5 still caused brain damage, including gross brain atrophy, cortical neuron damage, and multiple white matter tract damage.

Our study has shown that ambient particles could cause cardiovascular and brain toxicities from respiratory exposure. The results not only provided evidence of causal relationship to support the epidemiological studies, but also provided directions for epidemiological studies. It is also noted that the average concentration of PM2.5 during exposure was lower than the current national standard. Therefore, our results also have policy implications in air pollution control.