Stress Biology Research Exemplified by Alcohol Mediated Tissue/Cell Damage

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Recent epidemiological studies strongly indicate that many people suffer from various forms of mental and physical stress. If this stress is not properly managed or prevented, this may cause serious problems in living organisms. In humans, excess stress can cause the following partial list of disease states. These include: alcohol- and drug-mediated tissue damage, Alzheimer's Disease, cancer, cardiovascular diseases including heart attack, diabetes, drug abuse, emphysema due to chronic smoking, endocrine and gastric disorders, immune dysfunction, infectious diseases, insomnia, obesity, neurodegenerative diseases including Huntington's Disease and Parkinson's Disease, skin diseases due to UV exposure or x-ray irradiation, stroke, toxic shock syndrome, viral infections, etc. Alternatively, individuals under stressful environments are more susceptible to the above disease states than those with less stresses. Although the etiological factors of the above disease states are different, they share common underlying pathways toward full-blown disease states. All these disease states are directly and indirectly linked to oxidative stress through imbalance between harmful oxidants and protective anti oxidants. Because of a time limit, I will briefly mention about some of the common features of the oxidative stress and general mechanism leading to full-blown disease states. I will specifically talk about a model of alcohol mediated tissue or cell damage as an example for stress mediated disease states.

It is well established that long-term heavy alcohol (ethanol) consumption causes damage in most tissues including the liver, brain, kidneys, heart, muscles, pancreas and fetus, while disrupting the immune and endocrine functions. In the liver, it causes alcoholic fatty lver, hepatitis, fibrosis, and cirrhosis. In the brain, it causes alcoholic dementia, cerebellar degeneracy, or Wernicke-Korsakoff Syndrome and aggravates the conditions of many other neuro-psychotic disorders. The alcohol-mediated tissue damage is believed to result from elevated levels of alcohol-mediated oxidative stress and lipid peroxides, partly due to metabolic activation of potentially toxic substrates by a heme containing protein, ethanol-inducible cytochrome P450 2E1 (CYP2E1), changes in redox states, and reduction in anti-oxidant levels in target tissues. However, the details of the molecular mechanism leading to tissue damage are still unknown and need to be further studied.

The overall goal of my laboratory is to investigate the regulatory mechanism of gene expression and the biomedical consequences of the metabolism of both endogenous and exogenous substrates by the alcohol-metabolizing enzymes including CYP2E1, alcohol dehydrogenase (ADH), and aldehyde dehydrogenase (ALDH). In the past, we have cloned the CYP2E1 gene and demonstrated at least seven distinct regulations of the CYP2E1 gene and protein. Currently, we are studying the mechanism of alcohol-mediated hepatic damage and their regeneration in animal models (rats or mice). We also use cultured cells of human hepatoma (HepG2) or neuronal origin, which contain a high level of the human CYP2E1 protein by stable transfection of the cDNA, to study the molecular mechanism leading to cell death via either apoptosis or necrosis mechanism. We are particularly interested in time-dependent changes in the enzyme activities involved in early signal transduction pathways (mitogen activated protein (MAP) or stress activated protein (SAP) kinase systems) after alcohol, acetaminophen (Tylenol®), or CCl_4 treatment. Our recent data suggest that cell damage caused by some of the CYP2E1 substrates or lipid peroxides appears to be mediated through an apoptosis mechanism via selective activation of the c-jun kinase pathway followed by Ca^{2+} movement and activation of caspases.