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Pharma Europe 2020: Mitophagy and oxidative stress in early stage acetaminophen-induced liver injury - Yan Gao - Xuanwu Hospital of Capital Medical University

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ABSTRACT

Background: Mitochondria go through frequent cycles of fusion and fission, a process required for mitochondrial quality control by eliminating ROS damaged mitochondria through mitophagy. Acetaminophen (APAP) overdose causes liver injury in animals and humans usually by mitochondria damage, which needed further study. Toxicity is mediated by the metabolism of APAP to the reactive metabolite N acetyl-p-benzoquinone imine, which forms adducts on cellular proteins in mitochondria. The aim of the current study is to assess the changes between oxidative stress and companied mitophagy in a rodent model which mimics APAP-induced liver injury (AILI) in humans.

Methods: Different approaches were used including different detective methods. Liver damage was monitored by measuring levels of biochemical indexes. Proteins associated with oxidative stress were inspected by western blot analyses.

Results: After given both Nrf2-/- and wild-type mice APAP, Nrf2-/- mice were highly susceptible to APAP treatment. Rapamycin can promote the process of autophagy, reducing the formation of giant mitochondria and lipid droplets. Both tBHQ and NAC can protect liver cells, promoting Nrf2 translocated into nucleus and increasing the expression of downstream enzymes and proteins. C57BL/6 mice with stabilization of Nrf2 had increased hepatic up-regulation of Nrf2 and other antioxidant enzymes and reduced mitochondria dysfunction. Interestingly, APAP-induced mitochondrial translocation of Drp1; however, the initiation of mitochondria fission was inhibited by MDIVI-1, resulting much more serious hepatic injury.

Conclusion: In the early stage of AILI, Nrf2 played a protective role in antioxidant activity while mitophagy protected against oxidative stress damage by scavenging function. Promoting Drp1 translocation and Nrf2 expression could be a promising new approach to AILI

Introduction:

Acetaminophen (APAP) overdose is that the leading explanation for drug-induced acute liver failure in many developed countries. Mitochondrial oxidative stress is taken into account to be the predominant cellular event in APAP-induced liver injury. Accordingly, N-acetyl cysteine, a known scavenger of reactive oxygen species (ROS), is suggested as an efficient clinical antidote against APAP-induced acute liver injury (AILI) when it's given at an early phase; however, the narrow therapeutic window limits its use. Hence, the event of novel therapeutic approaches which will offer broadly protective effects against AILI is clearly needed.

To this end, it is necessary to better understand the mechanisms of APAP hepatotoxicity. Up to now, additionally to mitochondrial oxidative stress, many other cellular processes, including phase I/phase II metabolism, endoplasmic reticulum stress, autophagy, sterile inflammation, microcirculatory dysfunction, and liver regeneration, have been identified to be involved within the pathogenesis of AILI, providing new targets for developing simpler therapeutic interventions against APAP-induced liver injury. In this review, we summarize intracellular and extracellular events involved in APAP hepatotoxicity, along side emphatic discussions on the possible therapeutic approaches targeting these different cellular events.

Acetaminophen (APAP) hepatotoxicity is characterized by an in depth oxidative stress. However, its source, pathophysiological role and possible therapeutic potential if targeted, are controversially described. Earlier studies argued for cytochrome P450-generated reactive oxygen species (ROS) during APAP metabolism, which resulted in massive lipid peroxidation and subsequent liver injury. However, subsequent studies convincingly challenged this assumption and the current paradigm suggests that mitochondria are the main source of ROS, which impair mitochondrial function and are responsible for cell signaling resulting in cell death. Although immune cells can be a source of ROS in other models, no reliable evidence exists to support a role for immune cell-derived ROS in APAP hepatotoxicity. Recent studies suggest that mitochondrial targeted antioxidants are often viable therapeutic agents against hepatotoxicity induced by APAP overdose, and re-purposing existing drugs to focus on oxidative stress and other concurrent signaling events can be a promising strategy to increase its potential application in patients with APAP overdose..

Acetaminophen (APAP) hepatotoxicity is that the leading explanation for acute liver failure in many Western countries . A key mechanism of the toxicity is that the cytochrome P450-catalyzed metabolic activation of APAP, which generates the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI) and initiates toxicity in both rodents and humans . Excessive

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NAPQI formation after APAP overdose depletes cellular glutathione (GSH), adducts proteins including mitochondrial proteins, and induces mitochondrial oxidant stress and dysfunction. This leads to nuclear DNA fragmentation and necrotic necrobiosis and a subsequent inflammatory response, including the discharge of pro-inflammatory cytokines and activation of immune cells . Currently, APAP-induced liver injury has served because the hottest , mechanistically well studied and clinically relevant model for testing of phyto therapeutics and other hepato-protective interventions. In spite of serious evidence pointing towards the existence of a general oxidative stress during APAP hepatotoxicity, the cellular or intracellular sources and therefore the nature of the ROS during this context remain debatable. This has led to controversial conclusions and ultimately jeopardized the interpretation of latest therapeutic approaches to the human pathophysiology,.especially , the pathophysiological role of ROS within the mechanism of toxicity has not been clearly discussed and still requires further investigation. This review will provide an updated overview of the potential sources of ROS in APAP hepatotoxicity. The corresponding pathophysiological role of every source within the toxicity are going to be also summarized and discussed. We propose that mitochondrial targeted antioxidants or re-purposing of existing drugs which target mitochondrial ROS may have therapeutic potential for APAP poisoning in animals and potentially in humans.

Reactive oxygen species have long been implicated in the pathophysiology of acute liver injury. However, the interpretation of those findings to the clinic and therefore the development of therapeutic agents are slow mainly thanks to the poor mechanistic understanding of the pathophysiology and the many indirect approaches used to characterize the role of oxidant stress in liver injury. The current review discusses in depth the sources of reactive oxygen, the oxidants involved and the impact of this oxidant stress in the mechanism of cell death in 3 different clinically relevant acute liver injury models.

Generation of oxygen free radicals is a necessary by-product of an aerobic existence and the liver has substantial anti-oxidant defences, such as the tri-peptide glutathione to prevent damaging effects of these radicals during normal physiology. This was clear in early experiments, where evaluation of glutathione disulfide efflux into bile demonstrated an extremely high resistance of the liver against intracellular reactive oxygen formation (even with impaired detoxification systems) . However, in pathophysiological conditions, either due to metabolism of drugs such as acetaminophen, obstruction of the bile duct or conditions of ischemia, the balance between generation of free radicals and their capacity to detoxify them can be shifted such that oxidative stress can negatively influence cellular homeostasis and organelle function. The current information on the role of free radicals in various clinically relevant acute liver injury models will be examined here.

Biography

Yan GAO obtained her Ph.D. in Pharmacology in July, 2017, from Institute of Material Medica, Tsinghua University School of Medicine, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China. During the course of her research work, she became very interested in the work. Doing pharmacology is just like running, since science is sexy. Much like her insistence on running, her striving for academic excellence in graduate study is endless. During these years in IMM, CAMS & PUMC, she was mainly exploring the mechanisms of ginsenosides Rg1 and its metabolite Ppt, which modulate hepatic diseases and Huntington's disease.

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