ODOMENE JUSTICE

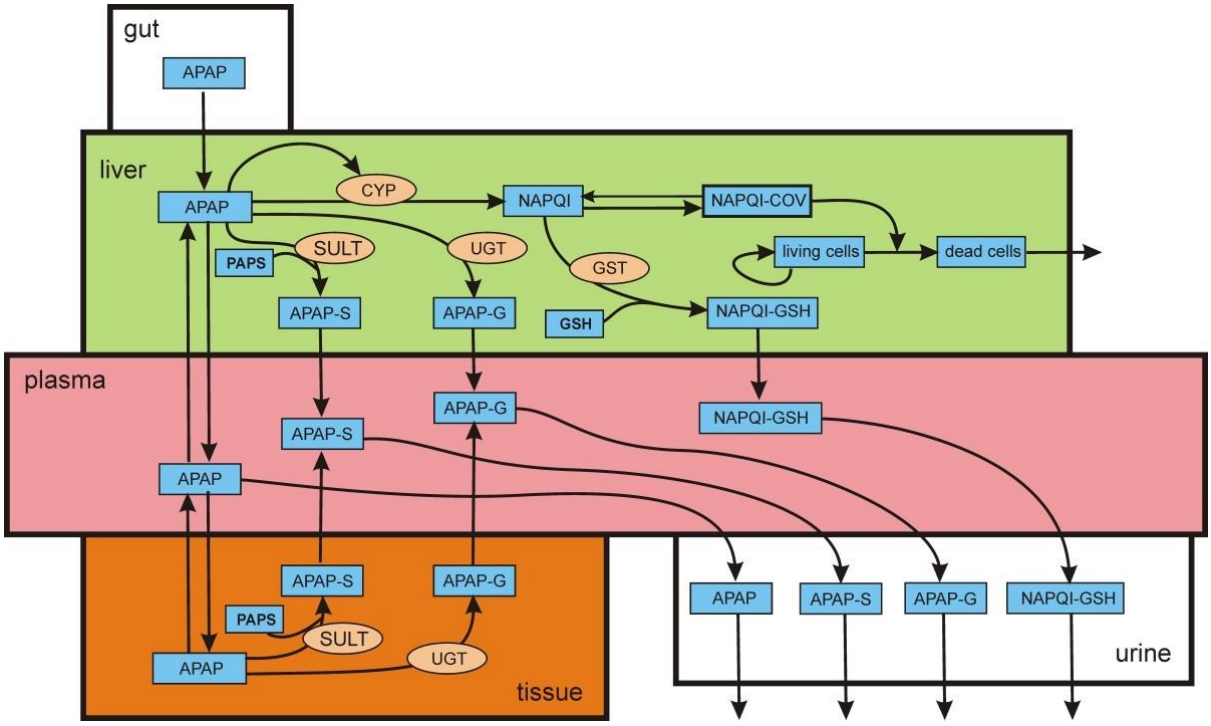
17/SCI03/006

BCH 306

Write explicitely on the process of metabolism of acetaminophen and how it exits the body.

METABOLISM

Acetaminophen is metabolized by conjugation with sulfate and glucoronidate, which are inert and are excreted in the urine. Depending on dose, a fraction of acetaminophen is converted into a highly reactive toxic intermediate, N-acetyl-p-benzoquinone imine (NAPQI) by several P450 cytochromes. Substantial amounts of NAPQI are effectively eliminated by conjugation with glutathione (GSH). However, after a large dose of acetaminophen, the sulfonation reaction becomes saturated and the build up of NAPQI depletes GSH in the liver, causing further accumulation of NAPQI. Unconjugated NAPQI binds to proteins and subcellular structures and induces rapid cell death and necrosis that can lead to liver failure. The main biochemical pathways of acetaminophen metabolism and the transports between various compartments are pictured below:



Blue boxes indicate substrates: APAP, acetaminophen; APAP-S, APAP-sulfonate; APAP-G, APAP-glucoronidate; NAPQI, N-acetyl-p-benzoquinone imine; NAPQI-COV, covalent binding of NAPQI; NAPQI-GSH, NAPQI conjugated with glutathione; PAPS, 3'-Phosphoadenosine-5'-phosphosulfate; GSH, glutathione. The light orange ovals indicate the enzymes that catalyze reactions: SULT, sulfotransferase; UGT, glucuronosyltransferase; CYP, cytochrome P-450 oxidase; GST, glutathione S-transferase.

The metabolism of APAP has been well-studied and the distributions of its metabolites in the plasma and urine of humans are well-documented, as are the hepatic values in mice and rats[8]. What

has been lacking is an integrated and quantitative understanding of the kinetics of APAP metabolism, of how APAP dosage affects NAPQI synthesis and GSH concentrations in the liver, of how NAC stimulates the synthesis of GSH, and of how the dosage and timing of NAC affect detoxification of NAPQI.

Most of acetaminophen is eliminated by glucuronidation and sulfation. These reactions are catalyzed by UDP-glucuronosyltransferases (UGT1A1 and 1A6) and sulfotransferases (SULT1A1, 1A3/4, and 1E1), respectively. However, some is converted by CYP2E1 and other cytochrome P450 enzymes to a reactive intermediate that can bind to sulfhydryl groups. The metabolite can deplete liver glutathione (GSH) and modify cellular proteins. GSH binding occurs spontaneously, but may also involve GSH-S-transferases. Protein binding leads to oxidative stress and mitochondrial damage.