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Prevention of Acetaminophen Hepatotoxicity by the Hypolipidemic Drug Clofibrate: Mechanistic Studies

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Overdosing with the analgesic and antipyretic acetaminophen (APAP) can produce severe liver damage. Drug-induced liver injury accounts for over 50% of all cases of acute liver failure in the United States. Approximately 40% of these cases are attributed to APAP. Hepatotoxicity by APAP results from the formation of the reactive intermediate, N-acetyl-*p*-benzoquinone imine (NAPQI). This electrophile covalently binds to targets proteins and produces oxidative stress, resulting in cell necrosis. The hypolipidemic drug clofibrate (CFB) belongs to a group of compounds known as peroxisome proliferators (PPs). These compounds produce enlargement and proliferation of peroxisomes, hepatomegaly and liver tumors in rodents. PPs produce their effects via activation of a group of nuclear hormone receptors known as peroxisome proliferators activated receptors. PPAR isoform α is highly expressed in the liver and its activation is required for most of the responses produced by CFB. Treatment of male CD-1 mice with CFB protects against APAP hepatotoxicity. This protection is associated with a significant reduction in selective binding of NAPQI to cytosolic and microsomal liver proteins and lower depletion of glutathione. *In vitro* and *in vivo* studies showed that protection by CFB is not due to alterations in bioactivation and detoxication pathways for APAP in the liver. Additional studies indicate that this protection is not limited to APAP only. CFB also prevents the hepatotoxicity produced by carbon tetrachloride, bromobenzene and chloroform. Since these chemicals differ in their mode of toxicant action, our findings suggest that more than one protective mechanism is involved. Studies with PPARα knockout mice indicate that the presence of this receptor is required for the hepatoprotective effect of CFB. Pretreatment of wild-type mice with CFB provided marked protection against APAP hepatotoxicity, while this response was abolished in PPARα mice. This indicates that the cellular constituent(s) responsible for the hepatoprotective effect of CFB is under transcriptional regulation by PPARα. At the present time, we are investigating the contribution of antioxidant,

transport and other detoxifying pathways in this protection. Subtractive gene expression profiling studies are also currently underway to identify PPAR α-dependent pathways contributing to this protection by CFB.