Antioxidant Therapy Restores Hepatic Metabolic Enzymes Altered by Exposure to Microcystin-LR in a Murine Model of Non-Alcoholic Fatty Liver Disease

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Introduction: We have shown that exposure to the environmental liver toxin Microcystin-LR (MC-LR) in the setting of pre-existing Non-alcoholic Fatty Liver Disease (NAFLD) induces significant hepatotoxicity and oxidative stress. Therefore, we hypothesized if targeted antioxidant therapy would improve MC-LR metabolism and reduce hepatic injury.

Methods: Six-week-old C57Bl/6J mice fed with choline-deficient high fat diet with 0.1% methionine to induce NAFLD were gavaged with 100 µg/kg MC-LR/24 hrs for 15 days. Antioxidants included augmentation of the glutathione detoxification pathway with N-acetylcysteine (NAC) given at 40 mM in drinking water; and interruption of specific Src kinase-mediated oxidant signaling pathways with a novel peptide (pNaKtide) at 25 mg/kg injected intraperitonially once a week.

Results: Histologic analysis revealed significant increase in hepatic inflammation with MC-LR exposure which was attenuated in both antioxidant treatment groups. 8-OHDG levels in urine and protein carbonylation in liver, both markers of oxidative stress, were significantly downregulated upon antioxidant treatment after MC-LR exposure. Analysis of key drug transporters as well as Phase I & II enzymes using quantitative PCR revealed that exposure to MC-LR significantly upregulated expression of the drug transporter Abcb1a; Cyp3a11, Phase I enzyme belonging to the Cytochrome P450 family whereas Phase II enzymes, Pkm (Pyruvate kinase, muscle), Pklr (Pyruvate kinase, liver, and RBC) and Gad1 (Glutamic acid decarboxylase) were significantly downregulated. Antioxidant therapy with both pNaKtide and NAC significantly attenuated these changes and restored microcystin detoxification.

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Conclusion: These results suggest that NAFLD significantly alters the metabolism of MC-LR, and this can be reversed with targeted antioxidant treatment.

