Analyzing Metabolic Effects of Acetaminophen

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Acetaminophen is the most common identifiable cause of acute liver failure, and is an excellent model compound for studying liver toxicity. Acetaminophen toxicity has thus become a very active area of research. Identifying and quantifying metabolites associated with acetaminophen toxicity is an integral part of this research, and Chenomx is uniquely equipped to extract this information from biofluid samples.

Problem

In studying acetaminophen toxicity, commonly available tools like transcriptomic analysis yield results that can be challenging to interpret. Identifying and quantifying metabolites associated with acetaminophen toxicity can guide interpretation of these complex results.

Study Design

The General Clinical Research Center at the University of North Carolina (UNC) School of Medicine, conducted an acetaminophen toxicity study in healthy human subjects. Six healthy adults were given a single four gram dose of acetaminophen while on a controlled, soy-based diet. Daily serum and urine samples were collected for seven days, with the dose administered on day four. The UNC Metabolomics Laboratory performed NMR-based metabolomics analysis on the serum samples using Chenomx software.
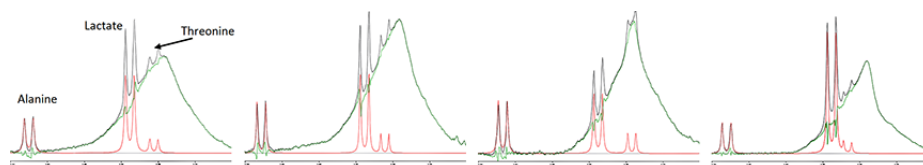

Figure 1. Chenomx NMR Suite is able to deconvolve spectra containing overlapping regions and highly variable resonances between samples.

Metabolomic Analysis

For the metabolomics portion of this study, a total of 85 ^{1}H NMR spectra were acquired on a Varian INOVA 600 MHz spectrometer, using a 400 ms CPMG filter to attenuate signals froms macromolecules in the serum samples. Each sample contained formate, which was used as an internal standard. The spectra were processed and phased, and reference deconvolution was applied to remove shimming artifacts. All 85 samples were analyzed for 23 common metabolites using Chenomx software, and the resulting metabolite concentrations were exported for further statistical analysis.

Despite the use of a CPMG filter, strong signals from the macromolecules like lipids and lipoproteins still appeared in the spectra; however, using Chenomx software, quantitative analysis of the overlapping signals was possible. Figure 1 shows the region from 1.20 to 1.50 ppm, containing alanine, lactate and threonine peaks, in four samples. The positions of the threonine peaks and distortions from macromolecules are highly variable among the samples, but Chenomx software allowed quantitative analysis of these metabolites from all four samples. A time series plot of metabolite concentrations from all 85 samples (Figure 2) provided insight into the metabolic effects of acetaminophen dosage. The concentration of lactate was seen to increase and then decrease after the day 4 dose of acetaminophen.

ABOUT CHENOMX INC.

Chenomx, Inc. is a privately-held Canadian company that specializes in developing complex mixture analysis technology for broad application in life science technologies. With world-class expertise in chemistry, pharmaceutical sciences, and computer software, Chenomx offers a broad range of software products, compound libraries, and services to support researchers worldwide.
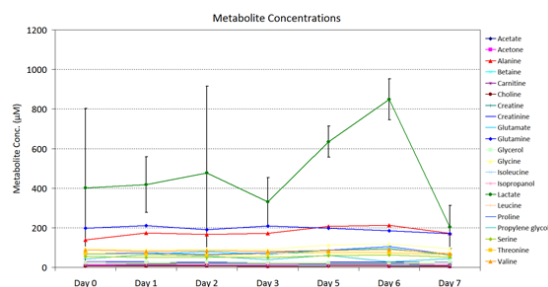
Figure 2. Metabolite concentrations over the seven days surrounding the acetaminophen dose (Day 4).

Results

Quantitative metabolomic analysis provided by Chenomx permitted a comprehensive study of the metabolic response to an acetaminophen dose. This detailed concentration data provided a valuable means of anchoring transcriptomic data from the same samples by helping to sift through the very complex gene array results, allowing detailed exploration of toxicity and drug effects. Complete coverage of this study and its results will appear in an upcoming publication under preparation by the primary researchers.

Acknowledgements

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