Long Term Metabolic Changes Induced in Idiosyncrasy-like Liver Toxicity

Raphaël Conotte, MS and J.M. Colet, PhD
University of Mons, Department of Human Biology and Toxicology, 7000 Mons, Belgium

Question : Idiosyncrasy-like liver toxicity was created in rats* by co-treating them with the inflammagen LPS and Ranitidine (RAN), a drug known to cause idiosyncratic liver injury in humans. Early (<48h) metabolic changes were identified using a metabonomics approach. Here, we evaluated later (up to 34 days) metabolic changes induced in the LPS/RAN rat model.

Methods : Wistar rats (3/group) were given $2.5x10^6$ EU/Kg LPS, followed by a sub-toxic dose of RAN. Another group received daily doses of RAN alone for 34 days. Urine samples were collected once a week and analysed by ^{1}H-NMR spectroscopy at 9.4T. NMR spectra were reduced to integrated regions and principal component analysis (PCA) was applied to the data set.

Results : NMR spectra of urine samples from rats treated with LPS/RAN showed significant changes as compared to controls. Major changes included decreases in citrate, hippurate, and α-ketoglutarate together with large increases in creatine, taurine, TMAO, and acetate.

Similar changes were observed in animals receiving RAN alone, although the PCA clearly separated those animals from the co-treated rats, suggesting additional metabolic alterations.

Conclusions: Our observations are consistent with the induction of liver injury. PCA allowed a clear temporal resolution of rats treated with LPS alone, RAN alone, and co-treated. This should allow us to better understand the metabolic contribution to IDR's. However, full identification of unknown metabolites is needed.

*Maddox J.F. et al. Metabonomic evaluation of idiosyncrasy-like liver injury in rats cotreated with ranitidine and lipopolysaccharide. Toxicology and Applied Pharmacology 212 (2006) 35 – 44.