MR-Based Metabonomic Approaches in Toxicology, Disease Diagnosis and Global Systems Biology

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Synopsis
Metabonomics involves the use of MRS and other spectroscopic tools to enable multivariate profiling of the integrated metabolic responses of complex systems to patho-physiological stress and disease. High frequency MRS can be applied to characterize a wide range of metabolites in biological fluids as spectra are changed characteristically in different toxicity or disease conditions. Pattern recognition analysis can give direct diagnostic information and aid the detection of novel biomarkers of disease. Novel methods of metabolic screening using probabilistic modelling approaches can now enable rapid toxicological and clinical assessments based on MRS of biofluids.

A number of post-genomic technologies are now being widely applied to improve the understanding of adverse drug reactions and the molecular basis of human disease (1). Metabonomics is an approach that enables multivariate profiling of the integrated metabolic responses of complex systems to patho-physiological stress and so involves understanding the way the whole metabolic regulatory system responds to disease processes thus providing complementary information to genomics and proteomics (2). Mammalian system biochemistry is also strongly influenced by the gut microfloral symbionts which also alter drug metabolism and toxicity; the study of these interactions is termed "global systems biology' (3). High frequency MRS is a well-established tool for characterizing and quantifying a wide range of metabolites in biological fluids and tissues and exploring the biochemical consequences of drug-induced toxicity and human disease (4-6). In disease or toxicity states metabolic profiles and MR spectra are changed characteristically in different toxicity or disease conditions according to the exact site and mechanism of the lesion (5,6). ^{1}H MRS is particularly useful as it allows rapid non-destructive analysis of small quantities of biofluids using robotic flow-injection systems. This can be coupled to cryo-flow probe technology to give unparalleled MRS sensitivity (capable of sub-nanomolar detection) or the ability to analyse less receptive nuclei without isotopic enrichment (7). The use of pattern recognition (PR) allows interrogation of MR data and can give direct diagnostic information and aid the detection of novel biomarkers of disease (8). Expert system approaches (9) can also be implemented to give direct diagnostic outputs on toxicity type based on spectroscopic input data. Such diagnostics can be extremely sensitive for the detection of low level damage in a variety of organ systems and is potentially a powerful new adjunct to conventional procedures for toxicity and disease assessment and can help explain environment-gene interactions that give rise to idiosyncratic toxicity of drugs in man (3). In particular novel methods of metabolic screening using probabilistic modelling approaches (10) have been developed that will enable rapid toxicological and clinical assessments based on MRS of biofluids that are now suitable for wider diagnostic implementation.

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