Lipotoxicity, Diabetes, Steatosis, Steatohepatitis. Preclinical Animal Models

Rheal A. Towner, Ph.D.

The advancement of proton or hydrogen (1H) magnetic resonance spectroscopy (MRS) in the last two decades has significantly improved our capability of detecting lipid metabolites in animal disease models. Commonly used in vivo MRS methods are single voxel or image-guided or localized spectroscopy (STEAM = stimulated echo acquisition mode or PRESS = point resolved spectroscopy), and chemical shift imaging (CSI) or spectroscopic imaging (SI). Examples on the use of 1H-MRS methods for the detection of alterations in lipids associated with hepatotoxin-induced liver injury (Towner et al., 2002) and hepatocellular carcinoma (HCC) (Foley et al., 2001; Towner et al., 2005; Tesiram et al. 2005 and 2007) from our laboratories will be presented, as well as a summary of research studies conducted by other investigators with applications in lipotoxicity, steatosis, cancer and diabetes in preclinical experimental animal models.

Lipids play major roles in normal physiology as well as the pathogenesis of many disease processes. In diseases where oxidative stress is thought to be involved in a disease process, lipid peroxidation is often associated as causative or secondary factors which results in lipotoxicity. As the liver is the major metabolic organ, alterations in lipid metabolism and lipid transport are often detected as steatosis (fatty liver) or steatohepatitis (fatty liver with associated inflammation). For example it has been previously shown that lipid peroxidation plays a major role during liver injury associated with a number of hepatotoxins, such as carbon tetrachloride and microcystins (microbial toxins such as aflatoxins, microcystins and nodularin). In most hepatotoxin-associated tissue injuries, steatosis is often observed as an initial histologic characteristic feature. MRS has been used in our laboratory to follow these alterations in liver lipid metabolism in vivo.

There have also been a number of reports on alterations in lipid metabolism associated with HCC (primary liver cancer) and other cancers (Foley et al., 2001; Towner et al. 2005; Xu et al., 2006). Alterations in the levels and expressions of enzymes involved in lipid fatty acyl group metabolism (e.g. stearoyl-CoA desaturase and Δ6-desaturase) have been found in liver and other cancers. Rodent models for liver cancer range from chemical (e.g. aflatoxin, diethylnitrosamine, 2-acetylaminofluorene, and/or carbon tetrachloride), diet-induced carcinogenesis (e.g. choline deficiency), to transgenic mouse models with genetic mutations associated with human HCC (e.g. c-myc, TGF-α). Examples using MRS methods to detect in vivo alterations in lipid metabolism associated with nodule and tumor formation will be presented. Apoptosis (programmed cell death) is inhibited in many cancers. Alterations in desaturase enzymes may play a role in decreasing apoptosis via the arachidonic acid cascade which plays a role in apoptosis.

There is also a significant body of evidence that indicates that increased levels of lipids in plasma and many organs (e.g. liver, muscle and pancreas) are causally involved in insulin resistance associated with type 2 diabetes within a Zucker diabetic fatty rat model (Hockings et al., 2003; Kuhlmann et al., 2003; Machann et al., 2004; De Feyter et al., 2008) and obesity mouse models (Strobel et al., 2008).
References:


