Another animal model for nonalcoholic steatohepatitis: how close to the human condition?1,2

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Nonalcoholic fatty liver disease (NAFLD) is emerging as one of the most common liver diseases in North America. The histologic spectrum of NAFLD ranges from fatty liver alone to nonalcoholic steatohepatitis (NASH) (1). Increasing evidence suggests that NASH is associated with progressive fibrosis, cirrhosis, and eventually hepatocellular cancer.

The medical conditions that are most frequently associated with NAFLD and NASH are obesity, diabetes mellitus, and dyslipidemia. All these conditions can be induced by feeding mice and rats diets that are high in fat or sucrose (2). Importantly, strain-related factors are significant in influencing vulnerability to the dietary effects. The study by Lieber et al (3) in this issue of the Journal shows that rats fed a high-fat diet (71% of energy from fat) develop steatosis, patchy inflammation, enhanced oxidative stress, abnormal mitochondria, increased plasma insulin concentrations, and increased hepatic concentrations of tumor necrosis factor α and collagen.

Several of the abnormalities seen in patients with NAFLD and NASH have also been found in various animal models of steatohepatitis. Some of these have been reproduced in the rat model used by Lieber et al. For example, the increased insulin concentrations suggest the presence of insulin resistance. Numerous studies have documented the presence of hyperinsulinemia and abnormal glucose tolerance in patients with NAFLD (4). As pointed out by Sanyal (4), the term “insulin resistance” is somewhat ambiguous because it does not specify to which actions of insulin there is resistance. With regard to the buildup of fat in the liver, note that the sensitivity to insulin concentrations of lipolytic and lipid oxygenation pathways is different from that of glucose disposal pathways (5). Also of interest is that in patients with fatty liver and those with precirrhotic NASH, suppression of lipolysis in response to hyperinsulinemia does not occur (4). Thus, large amounts of free fatty acids are available for hepatic uptake. Furthermore, studies in these patients also show that mitochondrial fatty acid β oxidation is relatively resistant to insulin-mediated suppression. These metabolic abnormalities are accompanied by structural mitochondrial abnormalities and increased lipid peroxidation, which are similar to observations described by Lieber et al. Importantly, the mitochondrial abnormalities, albeit of unknown significance, could be the consequence rather than the cause of the pathologic lesions seen in the rat model. Also relevant to the study by Lieber et al is a major question yet to be satisfactorily answered by experimental animal models: whether the process of hepatocyte damage and its subsequent complications are dependent on direct fatty acid–induced cytotoxic damage resulting from oxidized products of fatty acids and triacylglycerols, inflammatory cytokines, or some combination of these pathways acting in concert.

Although the amount of dietary fat and its accumulation in the liver play an important role in the pathogenesis of NASH, the type of dietary fat may also be an important factor. Studies in experimental alcoholic liver disease have highlighted the role of polyunsaturated fatty acids in promoting ethanol-induced liver injury (6). In initial studies, intragastric ethanol administration for 6 mo resulted in severe liver injury (fatty infiltration, necrosis, inflammation, and fibrosis) in animals fed unsaturated fat (corn oil) that contained mainly linoleic acid (6). In contrast, no evidence of liver injury was seen in rats fed a diet containing mainly saturated fat. When a more unsaturated fat (fish oil) was fed with ethanol, the degree of liver injury was greater than that seen with corn oil and ethanol (6). Furthermore, the degree of lipid peroxidation and the expression of cytokines and chemokines were greater in the animals fed fish oil than in those fed corn oil. Of interest is that female rats fed fish oil and dextrose develop fatty liver, necrosis, and inflammation (7). Note that in that study the percentage of total calories derived from fatty acids was 35%. Associated with the pathologic changes was an increase in nuclear factor κB binding activity, elevated concentrations of tumor necrosis factor α and cyclooxygenase 2, and enhanced oxidant stress. Thus, this model in female rats feeding fish oil with dextrose shows that it may not be necessary to feed the extraordinarily large amounts of fat used in the study by Lieber et al. In consideration of the observed link between oxidative stress, induction of cyclooxygenase 2, and activation of collagen gene expression in hepatic stellate cells (8), it is tempting to speculate that a longer period of feeding fish oil and dextrose could lead to fibrogenesis.

The relation between oxidative stress and the induction of cytochrome P450, particularly the 2E1 isoform, provides a plausible explanation for hepatic damage in NASH (9). Furthermore, oxidative stress can also induce the expression of proinflamma-

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tory cytokines, such as tumor necrosis factor, chemokines, and adhesion molecules (10). Inflammatory activity, as well as oxidative stress, can activate stellate cells and promote fibrogenesis. Additionally, mitochondrial dysfunction generates reactive oxygen species, which invoke a wide variety of biological consequences that lead to hepatocyte dysfunction, cell death, inflammation, and fibrosis.

The existing literature, taken as a whole, supports the “multiple-hit” hypothesis in which insulin resistance allows for enhanced lipolysis and the generation of free fatty acids for hepatic reesterification and oxidation. The accumulation of fat in the liver increases its vulnerability to various secondary insults, which cause necroinflammatory changes, fibrosis, and eventually cirrhosis. Many animal models have been used to investigate the pathogenesis of NAFLD and NASH, and studies in these animals will hopefully help to elucidate the cellular mechanisms of hepatic insulin resistance and steatohepatitis. The study by Lieber et al is one such example of the use of an animal model that may help to answer many of the questions regarding the mechanisms that are important in the pathogenesis of NAFLD and NASH.

REFERENCES