CHAPTER I

INTRODUCTION

Nonalcoholic steatohepatitis (NASH) is a chronic liver disease that occurs in patients who do not consume significant amounts of alcohol and its histology resembles that of alcoholic liver disease including macrovesicular steatosis, hepatocyte necrosis, inflammation, Mallory bodies, and fibrosis (Chalasani et al., 2004). NASH associates with obesity, diabetes mellitus, and hyperlipidemia. As the prevalence of obesity and diabetes mellitus continues to increase, many patients will be diagnosed with NASH (Sligte et al., 2004). In initial phases, during which fat accumulates in the liver, no clinical symptoms are evident. In advanced stages, fibrosis is detectable (eventually progressing to cirrhosis in some patients) (Medina et al., 2004). NASH is one of the predominant types of chronic liver disease in the United States with an estimated prevalence of 5% in the general population (McCullough, 2002). Several studies have now demonstrated that this is not a benign condition, some patients with NASH progress to cirrhosis over time (Lee, 1989; Powell et al., 1990 and Bacon et al., 1994).

Based on present concepts of pathogenesis, oxidative stress is likely involved in the progression of disease from steatosis to NASH and potentially cirrhosis. It has been shown that chronic oxidative stress, generated through the oxidation of cytotoxic free fatty acids, can lead to upregulation of cytokines (Garcia-Ruiz et al., 1995), induction of the liver cytochrome P450 enzyme 2E1 (CYP2E1), and depletion of hepatic antioxidant concentration (Weltman et al., 1996). In addition, enhanced lipid peroxidation leads to the generation of byproducts, such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), which have been shown to further enhance cytokine stimulation. They are involved in hepatic stellate cell activation (Robino et al., 2000), fibrogenesis, and enhanced extracellular matrix protein deposition. Seki et al. have

recently shown that lipid peroxidation products are elevated in NASH patients, occur more prominently in zone 3 of the liver parenchyma, and correlate directly with increasing necroinflammatory activity and fibrosis (Seki et al., 2002).

No effective medical treatment is currently available for patients with NASH. Reduction of weight is frequently advocated but it is a difficult goal to maintain and some patients have been reported to have worsening of their liver damage with extreme weight loss (Lee, 1989 and Capron et al., 1982). According to concepts of pathogenesis of NASH, these might make a wise basis for the use of antioxidants or drugs that could protect hepatocytes from oxidative stress. N-acetylcysteine (NAC) is a glutathione precursor which increases glutathione levels in hepatocytes (Gulbahar et al., 2000). Increased glutathione levels, in turn, limit the production of reactive oxygen species (ROS) which cause hepatocellular injury (Pastor et al., 1997). There are two studies using NAC for treating NASH. Gulbahar et al. administered NAC (1g/day) orally in 11 NASH patients for 3 months. The result showed that liver function test was improved significantly at the end of treatment period (Gulbahar et al., 2000). In 2003, the controlled study, NAC (600mg/day) was administered to NASH patients for 4 weeks. They found a significant improvement in aminotransferase levels (Gulbahar et al., 2003). Therefore, in this study, I work with NASH with or without treatment using NAC, measuring the many parameters such as total glutathione, liver function, lipid profile, lipid peroxidation, and liver histopathology in rats with NASH.

The study was conducted to prove the hypothesis that 100% fat diet can induce NASH in rats and treatment with NAC can reduce oxidative stress and improve histology in rats with NASH.