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Primary Research Interest:	Internal Medicine
Description of Research:	Non-alcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease in Veterans and its prevalence continues to increase with the growing obesity epidemic. Hepatic steatosis is a component of NAFLD, wherein there is accumulation of triglycerides in the liver. Currently more than 25% of our Veterans are obese and a larger number are overweight. In 2008, complications arising from obesity and its related metabolic syndrome cost the US health care system $147 billion (CDC MMMR report, August 2010). Strategies to prevent and treat obesity can reduce obesity related complications like NAFLD and health care costs. The long term goal of our laboratory is to understand the role of the enteric nervous system in the pathophysiology of diabetes and obesity as well as gastrointestinal motility disorders. We are currently examining the pleiotrophic effects of GDNF on hepatocytes. Recently we discovered that GDNF transgenic (GDNF-tg) mice when fed a high fat diet resist diet-induced weight gain and development of hepatic steatosis despite similar food intake and physical activity as their WT littermates (GDNF transgenic mice overexpress GDNF in glia under the control of the GFAP promoter). The mechanisms for these potentially beneficial effects of GDNF have yet to be explored. We will examine the mechanism underlying these processes utilizing in vitro and in vivo approaches and dissect the signaling pathways involved.
Relevance to VA:	Nonalcoholic fatty liver disease (NAFLD) is increasingly recognized as the leading cause of chronic liver disease, affecting 20-30% of the population in Western countries. NAFLD is a major complication of obesity. Of the Veterans receiving care at VA medical facilities in the US during 2000, 68.4-73% were at least overweight (body mass index [BMI] = 25 kg/m) with 32.9-37.4% classified as obese (BMI = 30 kg/m). In a report by the US Department of Veterans Affairs, updated on October 22, 2009, while the incidence of NAFLD was about one out of five Americans, the incidence of NAFLD significantly increased to four out of five diabetic Americans. Hepatic steatosis is often associated with altered liver function, hyperlipidemia, and progression to liver cirrhosis. Increased hepatic fat causes dysfunction of various organs and abnormal production of adipokines. Currently there are very limited FDA approved drugs for the treatment of NAFLD. We have identified a novel role for the neurotrophic factor, glial cell line derived neurotrophic factor (GDNF), which causes a reduction in hepatic steatosis. Understanding the mechanistic underpinnings of GDNF's regulation of hepatic steatosis will allow for more effective targeting and prevention of NAFLD.