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Perspective

Role of Leptin in Hepatic Triglyceride Export and Lipogenesis

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DESCRIPTION

The development of hepatic steatosis occurs when the liver faces an excess of lipid input and production, surpassing its capacity to effectively utilize and export triglycerides. Obesity increases steatosis and is associated with leptin resistance. The discovery of recombinant leptin restores steatosis in hypoleptinemic patients with lipodystrophy through an unknown mechanism suggests a function for leptin in hepatic lipid management. Because leptin primarily acts through Central Nervous System (CNS) transmission, they investigated whether leptin modulates hepatic lipid flux *via* the brain in rats using a series of stereotaxic infusion procedures. They show that brain leptin protects against steatosis by increasing hepatic triglyceride export and lowering *de novo* lipogenesis regardless of calorie intake.

Leptin's anti-steatotic effects are created in the dorsal vagal complex, require hepatic vagal innervation, and are sustained when the blood brain barrier is breached in rats fed a high-fat diet. Thus, CNS leptin protects against ectopic lipid accumulation *via* a brain-vagus-liver axis and could be used as a therapeutic method to treat obesity-related steatosis. Fatty liver disease, which is linked to diabetes and obesity, is the hepatic manifestation of the metabolic syndrome. While the full pathogenesis of Non-Alcoholic Fatty Liver Disease (NAFLD) is yet unknown, steatosis is widely thought to be a major beginning event.

Hepatic lipids accumulate when the total amount of lipid production and input outpaces the rate at which the liver uses up or excretes Triglycerides (TGs). Because TGs are exported after being packed into Very-Low-Density Lipoproteins (VLDL), the primary carriers of TGs in plasma, adequate hepatic VLDL particle synthesis and secretion are significant prerequisites for the prevention of steatosis and NAFLD. Both genetic ablation and pharmacological inhibition of Microsomal Triglyceride Transfer Protein (MTP), the rate-limiting enzyme for VLDL assembly, cause hepatic steatosis, demonstrating the physiological relevance of this process.

Apolipoprotein B (ApoB) is a fundamental structural component of VLDL particles, and its absence results in hepatic lipid buildup, whether due to genetic defects or pharmacological intervention using antisense oligonucleotides. As a result, VLDL export to shuttle TGs into adipose tissue represents a critical lipid disposal strategy by the liver, avoiding excessive ectopic lipid accumulation and lipotoxicity.

Severe hepatic steatosis is also a feature of widespread lipodystrophy, a condition marked by a lack of adipose tissue. Leptin, an adipokine released mostly by adipocytes, is significantly diminished in lipodystrophy patients. Aside from hypoleptinemia, leptin resistance, which is widespread in obese people, appears to be a primary driver of hepatic triglyceride buildup and steatosis.

The primary mechanism underlying leptin's anti-steatosis action is unknown, but some suggest that leptin replacement improves hepatic steatosis simply by reducing hyperphagia. This belief has lately been challenged by findings that leptin treatment improves hepatic lipid content in lipodystrophic patients primarily independently of calorie restriction.

The liver can compensate for excessive energy supply to some extent in mild steatosis by accelerating hepatic TG export, but VLDL secretion plateaus with the progression to NAFLD, implying that endogenous signals promoting hepatic lipid storage gradually outweigh those driving hepatic lipid export. The brain and the autonomic nervous system can control VLDL secretion. They recently discovered that insulin activity in the brain can cause such a signal. Direct insulin distribution to the central nervous system increases hepatic lipid export and protects against NAFLD, despite the fact that direct insulin effects *via* receptors on hepatocytes result in suppression of hepatic VLDL secretion.

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As a result, hepatic steatosis is caused by systemic hyperinsulinemia and long-acting insulin analogs with hepatic specificity. These findings imply that an imbalance in the brain-liver interorgan interaction may play a significant role in hepatic TG retention and steatosis, ultimately contributing to the development of NAFLD. They hypothesized that leptin, like insulin, could boost liver lipid export and protect from NAFLD *via* receptors expressed in the CNS because it predominantly acts as signaling through specific receptors expressed in the brain and because leptin replacement in lipodystrophy counteracts hepatic steatosis.

However, direct leptin infusion into a cerebral ventricle, which bypasses the limited leptin transport across the Blood-Brain Barrier (BBB), can recover at least partially the anorexic effects of leptin in obese rodents. A putative brain-dependent rather than direct route of leptin action on hepatic steatosis could also explain the normal hepatic lipid content seen in mice with a leptin receptor liver-specific knock-out. Thus, direct leptin administration into the CNS likely avoids any leptin transporter deficiencies that occur progressively in obesity.