Abstract

Thesis: Characterization of the Effects of NRG-1 on HepG2 Cell Metabolism

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Neuregulin-1 (NRG-1) is an epidermal growth factor-like ligand that binds to the human epidermal growth factor receptor 3 (HER3) resulting in increased glucose uptake, mitochondrial activity, and insulin sensitivity in skeletal muscle. HER3 dimerizes with HER2 to stimulate activation of the AKT and mitogen activated protein kinase (MAPK) pathways that are associated with increased glucose metabolism, lipogenesis, protein synthesis, and altered apolipoprotein secretion. The liver is the primary organ responsible for coordinating apolipoprotein secretion, lipogenesis, and glucose metabolism in response to metabolic need. This thesis sought to identify if NRG-1 stimulated common hepatic processes such as protein synthesis, apolipoprotein secretion, apolipoprotein uptake, *de novo* lipogenesis, and glucose metabolism in hepatocytes. Experimentation on HepG2 cells, a transformed cell line derived from hepatic carcinoma tissue, demonstrated that NRG-1 stimulates hepatic processes through activation of AKT and MAPK pathways. This thesis found that NRG-1 increases intracellular glycogen concentrations, protein synthesis, and glucose metabolism through AKT pathway stimulation. These studies also found that NRG-1 decreased the secretion of ApoB100 and increased LDL uptake independent of AKT suggesting the MAPK pathway might be involved in mediating this response. These findings provide evidence that NRG-1 may play a role in hepatic regulation of LDL uptake, protein synthesis, glucose metabolism, and apolipoprotein secretion in the presence of HER3 and HER2.