Glucagon-like peptide 1 (GLP-1) as treatment for chemotherapy induced mucositis (CIM)

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Introduction: Chemotherapy induced mucositis (CIM) is a frequent complication to anticancer treatments. Glucagon-like peptide-2 (GLP-2) has been suggested for treatment of CIM, unfortunately the peptide is also shown to accentuate colonic dysplasia in carcinogen treated mice. Glucagon-like peptide 1(GLP-1) is secreted simultaneously with GLP-2 from the L-cell. GLP-1 is responsible for maintaining glucose homeostasis. Recently, an intestinal growth effect was discovered for GLP-1.

Aim: The aim of this experiment was to elucidate if GLP-1 had a potential role in treating CIM.

Methods: Mice were injected with 5-Fluorouracil (5-FU) or saline to induce mucositis and treated with a GLP-2 analogue, a GLP-1 analogue or vehicle. Mice were sacrificed 48 h after 5-FU injections. Endpoints were intestinal weight, villus height and histological scoring of mucositis severity. Rats were injected with 5-FU or saline and after 48 h blood was analysed for concentrations of GLP-1 and GLP-2.

Results: Both peptides could significantly prevent the loss of mucosal mass and villus height and significantly decrease mucositis severity score in duodenum and jejunum. The effect was equivalent. GLP-1 and GLP-2 levels in blood were more than ten fold and seven fold increased respectively.

Discussion: Both endogenous GLP-1 and GLP-2 were increased after intestinal injury, indicating an importance for the peptides for protection of the intestine. We found an equal effect of GLP-1 and GLP-2 in the treatment of CIM which opens up the possibility that mucositis as well as other acute intestinal disorders can benefit from treatment with GLP-1 analogues.

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BNP infusion during reperfusion increases cardiac triglyceride accumulation and decreases cardiac contractility after myocardial ischemia in pigs

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Introduction: Natriuretic peptides as therapy are promising in acute myocardial infarction (AMI). They are also involved in adipose tissue lipolysis and β-oxidation in skeletal muscle. A curiosum is that cardiac lipid accumulation is associated with cardiomyocyte apoptosis, endoplasmic reticulum stress and contractile dysfunction.

Aims: To study the effect of RF on peripheral clock gene expression and several functions associated with increased ghrelin signaling.

Methods: Wild-type (WT) and ghrelin receptor knockout (GHSR-KO) mice were fed either ad libitum or put on RF (access to chow: 12–4 AM) for 2 weeks.

Results: RF resulted in a significant increase in plasma octanoyl ghrelin levels in both WT and GHSR-KO mice. Body weight, but not food intake, was significantly diminished in GHSR-KO compared to WT mice on RF. In both genotypes, gastric emptying was significantly accelerated. RF increased the affinity of the contractile response toward ACh and SuP and caused neural hyperexcitability in fundic smooth muscle strips. Histology revealed inflammation in WT mice on RF, which was accompanied by significant increases in MPO activity and IL-1β expression. In GHSR-KO mice, inflammation was subsided and post-inflammatory changes were evident. The anti-phasic expression of the clock genes BMAL1 and PER2 in the stomach was significantly decreased and increased, respectively, by RF. BMAL1-KO mice did not survive RF.

Discussion: Ghrelin plays a role in the recovery of body weight after RF, but not in the acceleration of gastric emptying. Gastric contractility changes are triggered by RF-induced inflammation, which is dampened by ghrelin. Further research is warranted to investigate the role of the clock genes in the observed changes.

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Restricted feeding induces inflammation: Role of ghrelin and clock genes?

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Introduction: Circadian feeding functions may depend on a peripheral clock system which is possibly located within the ghrelin-secreting cells of the stomach. Restricted feeding (RF) has been shown to increase plasma ghrelin secretion.

Aims: To study the effect of RF on peripheral clock gene expression and several functions associated with increased ghrelin signaling.

Methods: Wild-type (WT) and ghrelin receptor knockout (GHSR-KO) mice were fed either ad libitum or put on RF (access to chow: 12–4 PM) for 2 weeks.

Results: Muscle biopsies from the non-ischemic right heart ventricle revealed a >4-fold increase \((P=0.03)\) in triglyceride in the BNP infused group compared with the untreated group. Plasma free fatty acids increased by 3.1-fold \((P<0.0001)\) and glycerol by 2.2-fold \((P=0.0005)\) in the BNP infused group compared with the untreated group. The correlation between triglycerides and plasma free fatty acids (AUC) in the BNP infused animals was \(r=0.88\) \((P=0.0007, 95\%\) confidence interval \([0.59:0.97]\)). Furthermore, a decrease in left ventricular contractility \((dP/dT)\), \(P=0.03\) was noted.

Discussion: Infusion of BNP, in the early reperfusion phase of AMI affects lipolysis, presumably in the adipose tissue, which leads to increased cardiac lipid accumulation. Furthermore, the BNP infusion leads to a decrease in ventricular performance measured as \(dP/dT\) max.

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