Antagonist of the glucagon-like peptide 2 (GLP-2) receptor

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Title: Antagonist of the glucagon-like peptide 2 (GLP-2) receptor

Approved ethical committee ID: H-24000668

Project Group:
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Background:
Previous studies have shown that GLP-2 increase abdominal blood flow to the intestines. The studies that reveal this effect are built on results of exogenous distributed GLP-2 and have not investigated the endogenous effects of GLP-2. We have previously performed a single study in healthy males with the use of flow sensitive magnetic resonance imaging (MRI) where supraphysiological doses of GLP-2 injections greatly increased the blood flow in the superior mesenteric artery and portal vein but there were surprisingly no changes after intake of oral glucose. In this study we investigate if physiological doses of GLP-2 will increase the blood flow to the intestines and if different doses of the GLP-2 receptor antagonist (GLP-2(3-33)) can alter these flow changes in humans of both genders.

Aim*:* We aim to determine the right dose of the GLP-2-receptor antagonist to use in physiological research in healthy humans. We hope to be able to achieve the maximal blocking of the GLP-2 receptor possible and at the same time reduce expenses and infusion volume for the participants in future studies. We thereby hope to characterize the use of the GLP-2 receptor antagonist GLP-2(3-33) as an essential tool in research of the role of the human GLP-2 receptor in bone metabolism and nutrient uptake in the future.

Hypothesis*:* The hypothesis of this study is that the GLP-2(3-33) can block the effects of GLP-2 on the blood flow to the superior mesenteric artery and the portal vein.

Design:
Randomized, placebo controlled, crossover, single blind design in 10 healthy participants.

Baseline information:
A description of the baseline measured will be presented in a table, including the following measures: Age, Weight, Height, BMI, Hemoglobin, Leucocytes, Vitamin D, Fasting glucose, HbA1c, Sex, and Blood pressure. The data will be presented in Median and range.

Statistical analysis and graphs:

The flow data is analyzed in Rs studio by a linear mixed model, that pairs the data, and compared the interventions after steady state of the infusion of GLP-2(3-33) antagonist. The primary statistical analysis will be done between the interventions: Physiological dose of GLP-2 injection and highest dose of GLP-2-antagonist infusion + GLP-2 injection and placebo infusion. Furthermore, the data will be presented in GraphPad Prism 10. A data table will present the flow measurements of each intervention, including mean and 95% confidence intervals

Criteria:

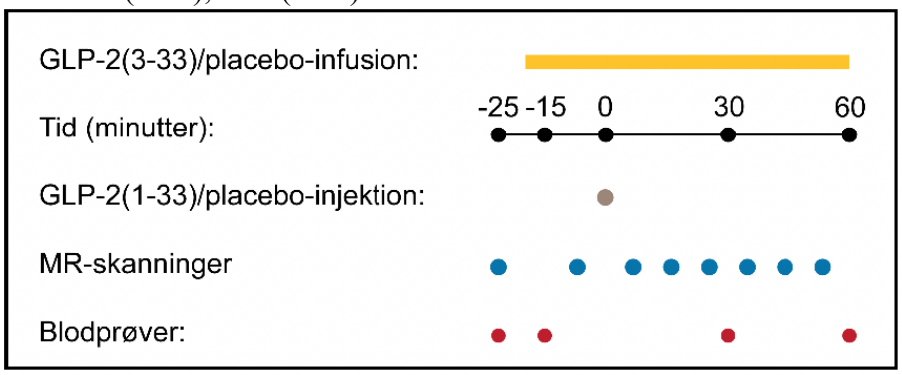
Inclusion

1) Age 18-70 years
2) BMI 19-28 kg/m2

Exclusion

3) Chronic illness that affects the cardiovascular system or gastrointestinal tract
4) Treatment with medicine or supplements that cannot be paused for 12 hours
5) Intake of above 14 alcoholic drinks per week or substance abuse
6) Liver enzymes (ALAT) above 2 times normal values
7) Decreased kidney function (eGFR below 90 or creatinine levels over reference value)
8) Low blood percentage (hemoglobin below reference value)
9) Any condition or disease that the persons responsible for the study find would interfere with the participation of the study.

Methods and outcomes*:* Phase-contrast magnetic resonance imaging (PC-MRI) is used to calculate blood flow in the blood vessels: superior mesenteric artery, portal vein, celiac trunk and hepatic artery during the infusion of either saline or GLP-2(3-33) receptor antagonist and injection of GLP-2.
The main outcome of the study is blood flow in superior mesenteric artery. On each study day, 8 MRI scans are performed (-32 min to 60 min after start of infusion) and four blood samples are taken. Blood glucose is measured bedside on whole blood. The blood samples collected are kept for analysis of GLP-2(1-33), GLP(3-33) and markers of bone metabolism.



Adverse event:

All adverse events (AEs) or serious adverse event (SAE) are reported throughout the whole study period, any adverse event reported will be informed to the ethical committee responsible for the study. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form. Information to be collected includes event description, time of onset, qualified medical professional's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.