Novel regulation of kidney function by gastrointestinal hormones

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Abstract

The control of whole-body energy metabolism involves intricate crosstalk between multiple organ systems including the gut and the brain that play well-recognized roles in this process. However, the important contributions and mechanisms by other organs are poorly understood. Errors in metabolic regulation can lead to human metabolic diseases including diabetes and obesity that affect 75% of the population and can lead to significant comorbidities. Improving our mechanistic understanding of multi-organ metabolic crosstalk in health and disease is essential for developing highly efficient and new therapeutic approaches. We hypothesized that the kidney is a major regulator of body metabolism via a new mechanism of gut-to-kidney crosstalk that involves the gut hormones gastrin and cholecystokinin (CCK) activating intrarenal mechanisms to increase blood flow and filtration, progenitor cells and the secretion of tissue growth factors.

This study tested the hypothesis that gut hormones gastrin and cholecystokinin (CCK) activate MD cells in the kidney via gut-kidney crosstalk to increase blood flow and filtration, progenitor cells and the secretion of tissue growth factors.

Methods

Cell culture studies

• Immunolabeled MD cell line
• Western Blot analysis of the expression of traditional (Cox2) and novel (Ccn1) MD cell specific factors

Mouse studies

• MD single cell RNA seq and transcriptome analysis
• Sox2-GCaMP6 reporter mouse

• Ren1d-Confetti mice with Darunavir (DVR) treatment for 1 week
• CCK8 treatment

• Ren1d-Confetti mice + DVR treatment for 1 week to study tissue remodeling/growth

Results

CCKBR is specifically expressed in MD cells in the kidney

• MD cell bulk and single cell RNA Seq and transcriptome analysis showed that CCKBR is highly enriched in MD cells compared to control kidney cells.

• Sox2-GCaMP6/fdTomato mouse model is a great tool for comparative analysis of cell physiology.

• Robust [Ca2+]i increases in MD cells in response to intracortical gut hormone injection.

• Gastrin and CCK specifically activates MD cell function in the kidney in vivo.

Introduction

• Errors in metabolic regulation can lead to human metabolic diseases including diabetes and obesity that affect 75% of the population and can lead to significant comorbidities.

• Macula densa (MD) cells are specialized sensory epithelial cells in the kidney and are known as the chief regulators of renal blood flow and tissue remodeling.

• Gastrin is a hormone produced by the G cells in the lining of the stomach, primarily known to enhance gastric mucosal growth, gastric motility, and secretion of hydrochloric acid (HCl) into the stomach in response to the presence of amino acid-rich food. In addition, it is also secreted into the bloodstream to act on distant organs.

• Cholecystokinin (CCK) is another gastrointestinal hormone which is secreted by the cells in the duodenum in response to fat rich food intake and stimulates the release of bile into the intestine and the secretion of enzymes by the pancreas. CCK is also released into the circulation and has distant organ effects.

• CCKBR is one of the two gastrin/CCK receptors that is coupled to calcium signaling and via nuclear transcription regulates tissue growth in the pancreas and stomach.

• It is well known that glomerular filtration rate (GFR) increases after food intake well before an increase in nutrient/waste levels in the plasma.

• Cellular/molecular understanding of gut-kidney axis is lacking.

• Darunavir (DVR) is a HIV protease inhibitor and works by decreasing HIV protease activity, allowing the drug to prevent the proteolytic processing of viral proteins and the production of virus. DVR has been in clinical use for over a decade and is approved by the FDA for the treatment of HIV.

• DVR has shown to be effective and new therapeutic approaches. We hypothesized that the kidney may play a role in DVR's efficacy.

• Repurposing the commonly used HIV drug Darunavir for kidney and metabolic diseases may provide therapeutic benefit for millions of patients worldwide.

Aim

Gastrointestinal hormones (gastrin and CCK) increase MD cell function in vitro

• The addition of gut hormones gastrin and CCK in cultured MD cells significantly increased:
  - the expression of Cox2, traditional MD cell marker/function to increase blood flow and GFR
  - the expression of Ccn1, non-traditional MD cell factor of tissue growth

Results

Darunavir increases endogenous tissue remodeling

• Treatment with HIV protease inhibitor DVR for 1 week increased:
  - the number of Ki67+ cells / field.
  - the number of WT1+ cells in the glomerulus.
  - the number of WT1+ cells at the vascular pole – at the base of the macula densa.

Summary and Conclusion

• This study uncovered new regulatory mechanisms of systemic metabolism especially the role of MD cells in the kidney.

• Repurposing the commonly used HIV drug Darunavir for kidney and metabolic diseases may provide therapeutic benefit for millions of patients worldwide.