Human Stomach Cell Gastrin Inhibits Renal NHE3 and NaKATPase in Concert with the Renal D1R

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Gastro-renal axis: Stomach tells kidney to alter sodium excretion through gastrin.

Slide courtesy of PA Jose MD PhD
Introduction

• Sodium balance:
  Sodium intake = Sodium excretion in urine

• Sodium intake > Sodium excretion
  Increase blood pressure

• Oral NaCl load produces a greater natriuresis than an intravenous infusion of the same amount of NaCl*.

• Several gut hormones have been proposed to mediate the natriuresis following an oral sodium load, including uroguanylin, cholecystokinin, and gastrin.

Gastrin

- Secreted by G cells in the antrum of the stomach, duodenum, and the pancreas.
- Stimulates secretion of gastric acid (HCl) by the parietal cells of the stomach and aids in gastric motility.
- Food which contains sodium increases serum gastrin levels.
Expression of gastrin in mouse stomachs exposed ex vivo (30 min) to distilled water, 0.56% NaCl, or 0.84% NaCl

*P<0.05 vs. Distilled H₂O, #P<0.05 vs. others, n=3/group, one-way ANOVA, Holm-Sidak test

Dr. Pedro Jose (GW University)
Mice lacking of Gastrin are hypertensive and salt sensitive

Dr. Pedro Jose (GW University)
Gastrin interacts with dopamine receptors in kidney

G = glomerulus  
PCT = proximal convoluted tubule  
CCKBR = Cholecystokinin B receptor  
NHE3 = sodium–hydrogen exchanger 3

Chen et al., 2013  
Banday and Lokhandwala 2013

Dr. Pedro Jose (GW University)
Hypothesis: G-cells are sodium sensing cells in stomach, and similar to the kidney are regulated by the dopaminergic system.
Gastrin Expression Increased with Sodium Treatments in Two Gastrin-secreting Cell lines

**Gastrin RNA Expression (2^ΔCT)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SW</th>
<th>SW150</th>
<th>SW200</th>
<th>AGS</th>
<th>AGS150</th>
<th>AGS200</th>
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<td>VEH</td>
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<td>MON</td>
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**SW:** SW626  
**AGS:** AGS gastric carcinoma  
**150:** 150 mM NaCl  
**200:** 200 mM NaCl  
**VEH:** Vehicle  
**MON:** Monensin  
**LE:** LE300, D_1R/D_5R antagonist
G-Cells Identification

Gastrin Pha-l

Gastrin + Pha-l Merge

Gastrin Pha-l Merge

G-cell G-cell G-cell

G-cell SW626

Gastrin No Primary

Pha-l: Phytohaemagglutinin-leucoagglutinin

RT-PCR

G-Cell SW626

Gastrin

Actin

Lab of Salt Sensitivity, Hypertension and Automation
Human G-Cells Express the Dopamine-1 Receptor (D₁R)
Fenofibrate Treatment - a PPARα Agonist

A

Control (CT)  Fenofibrate (FENO)

Gastrin  Gastrin

B

C

* P=0.0789

FENOH: Fenofibrate, PPARα agonist
LE300: D₁R/D₅R antagonist

Lab of Salt Sensitivity, Hypertension and Automation
Gastrin Inhibits NHE3 and Na/KATPase through PLC Pathway

SKF83822 (822, cAMP specific D1-like agonist), Gastrin1 (GAS, CCKB agonist), U73122 (PLC inhibitor). PLC (Phospholipase C). AngII (Angiotensin II agonist)

* P<0.05 VS VEH; # P<0.05 VS GAS or 822; ** P<0.05 VS 822+GAS
The Molecular View of the Gastro-Renal Axis

Fenofibrate = PPARα agonist; PLC, Phospholipase C
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