How can we treat visceral pain in GI diseases?

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Challenges in 2009

Can we fill the gap between rodent experiments and human clinical studies?
Human tissue

Translate input

+ve mediators?

mechanisms?

Nociceptor – pain sensing nerve

Translate output
IBS-D (Diarrhoea)

- 42 IBS-D patients (ROME III)
- Mean of daily scores from 14 day symptom diary
- Sensory symptoms
  - Pain severity (0-10)
  - Urgency to defecate (0-10)
- Motility symptoms
  - Stool frequency
  - Stool consistency
- Psychological
  - Anxiety
  - Depression

Probing 3x3s 0.6mg

100μL IBS-D supernatant
12 min incubation

Mean of peak 2s
Total change in action potential firing over 12 min application period
% change in probing
Correlation with pain score

Change in nociceptor activity (total spikes)

P = 0.008
r = 0.40

Pain severity score (0-10)

Change in nociceptor activity (total spikes)

Cibert-Goton Clin Trans Gastro 2021
Paediatric IBD & FAP

- 50% responder rate (vehicle - Krebs buffer) used to determine responder cut off
Macrophage Metalloelastase (MMP-12)

Human nociceceptor

Change in afferent firing (spikes/min)

MMP12 mRNA

P=0.025

MMP-12 (100nM)

Human nociceptor activation

Wavemark unit

Neurogram (mV)

Δ Nerve Activity (spikes 10s⁻¹)

Stuart Brierley

TNBS supernatant (n=8)

TNBS + MMP-12 inhibitor (n=6)

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Where next?

RNA Seq

CD vs
UC vs
IBS vs
Control

### FOLD CHANGE | P VALUE
--- | ---
MMP8 | 122.6 | 0.000085
MMP1 | 73.9 | 0.000209
**PROK2** | 48.8 | 0.000295
IL11 | 44.2 | 0.000364
CXCR1 | 36.3 | 0.000114
CXCL6 | 33.1 | 0.000040
CXCR2 | 23.9 | 0.000026

Ewan St
John Smith

James
Hockley

Diseased Tissue

Sensory Neuron

Mediator
PK2

TRPA1
PKR1
PKR2
ASIC3
Visceral nociception in IBD

Translate input

+ve mediators?

MMP-12

Translate output

Nociceceptor – pain sensing nerve
Visceral nociception in IBD/IBS

Challenges

- Tractability
- Efficacy - disease
- Side effects – disease

![Diagram of nociception in IBD/IBS](image)
Opportunity

Challenges

- Expertise

IBD

IBS

Microbiome

Metabolites
Kyureninic acid

Protease inhibitors

MMP-12

TRPV4

PAR-2

Em

+EVE