Dysmetabolism of Bile Acids in feces: implications in human colon pathologies

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Dysmetabolism of Bile Acids in feces: implications in human colon pathologies

1) Bile acids: metabolism, original functions

2) Bile acids and the gut: «The News»

3) Bile acids «Dysmetabolism»
   - Irritable Bowel Syndrome
   - Inflammatory Bowel Diseases
1) Bile acids: metabolism, original functions
Bile acids metabolism in human

- Synthesized by liver from cholesterol
- Secreted in gut lumen during digestion
- Allow lipid absorption by fat micellization
- 95% reabsorption by terminal ileum and return to the liver

Permanent recirculation: effective pool >>> quantitative pool

5% faecal excretion

- Bile Acids are endogenous laxatives
- Expansion of Bile Acids pool size causes diarrhoea (Bile Acids Malabsorption)

Laxative effect varies with the species of bile acids
Bile Acids Metabolism

Gut Microbiota

Fecal bile acids pool

4 main bile acids subtypes in human

Cholic acid ➔ Deoxycholic acid
Chenodeoxycholic acid ➔ Lithocholic acid
2) Bile acids and the gut: «The News»

FGF 19 and Bile Acids Malabsorption: the GHOST Slide
With the discovery of bile acids receptors FXR and TGR5, Bile Acids became *HORMONES*

2 receptors - NUCLEAR: FXR
- MEMBRANAR: TGR5

Linked to - basal metabolism regulation
- Fats storage (liver and peripheral fat
- Inflammation
Bile acids are endogenous laxatives?

**Bile Acids in the Colon**

- **Water and electrolytes**
  - Modulation of mucosal permeability (Keating vs Munch)
  - Modulation of water and electrolyte secretion (Karlström)

- **Motility**
  - Ex/In vivo in animal
  - In vivo and Per os
  - In human
  - Motor response

**Enteric nervous system??**
Bile Acids in the colon

Endogenous laxatives: a role for the TGR5 receptor

Water and electrolytes

Motility

The Receptor TGR5 Mediates the Prokinetic Actions of Intestinal Bile Acids and Is Required for Normal Defecation in Mice

Farzad Alemi,1 Daniel P. Poole,2 Jonathan Chiu,1 Kristina Schoonjans,9 Fiore Cattaruzza,1 John R. Grider,4 Nigel W. Bunnett,5 and Carlos U. Corvera18

Gastroenterology 2013;144:145-154

Contraction

Relaxation
Firt Study in IBS : AIMS

• To compare the composition of faecal bile acid pool between IBS-D patients and healthy subjects.
• Microbiota analysis in the same stool samples
• Look for correlation between fecal bile acids species and symptoms
PATIENTS AND METHODS

PATIENTS
- 14 Diarrhoea predominant IBS vs 18 HS
- 18 - 75 years old, no previous treatment 3 months before
  (Antibiotics, transit modulator, corticotherapy, probiotics)

CLINICAL DATAS the week before sampling
• Bristol stool scale
• Stool frequency / day
• Abdominal pain score / day
• Bloating score / day
Bile acids and microbiota analysis

• Measure of faecal Bile Acids (HPLC MS / MS)

Normal fecal BA profil by HPLC MS/MS

• Microbiota by qPCR

- Bacteria
- Bifidobacterium
- Lactobacillus
- F.prausnitzii
- Leptum
- Bacteroides
- E.coli
- Coccoides

Bacterial species implicated in Bile acid Transformation
Bile acids in feces:

A. % primary bile acids in faeces

- **HS**: 5%
- **IBS-D**: 20%

P = 0.02

B. % CA and CDCA in faeces

- **CA**: 5%
- **CDCA**: 10%

P = 0.03

P = 0.04

C. % secondary bile acids in faeces

- **HS**: 90%
- **IBS-D**: 70%

P = 0.03

D. % DCA and LCA in faeces

- **DCA**: 60%
- **LCA**: 20%

P = 0.007

P = ns
Correlation between % of primary BA and symptoms

A
Correlation between % of fecal primary BA and bristol stool score

\[ r = +0.409^* \]

B
Correlation between % of fecal primary BA and daily stool frequency

\[ r = +0.366^* \]
Dysbiosis in IBS-D patients
Perspectives: Mechanism?

**Primitive** gut microbiota
dysbiosis in IBS-D

- Incoming publication in IBS-C patients
- Role of TGR5?

**Less secondary BA**
More primary BA (CDCA)

SHORTER TRANSIT TIME

Lower bacterial Bile Acids transformation
(due to decrease in Leptum group ?)
## Second Study in IBD

Colonic IBD: **23 flares, 19 remission, 29 HS / 12 CD, 32 UC**

<table>
<thead>
<tr>
<th>IBD</th>
<th>Active CD</th>
<th>Active UC</th>
<th>Total</th>
<th>Remission CD</th>
<th>Remission UC</th>
<th>Total</th>
<th>Healthy subjects</th>
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<tbody>
<tr>
<td>n (%)</td>
<td>7 (17)</td>
<td>16 (38)</td>
<td>23 (55)</td>
<td>5 (12)</td>
<td>14 (33)</td>
<td>19 (45)</td>
<td>29</td>
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<tr>
<td>Mean age (±SEM)</td>
<td>37.6±19</td>
<td>36.0±14</td>
<td>37.0±15</td>
<td>42.1±19</td>
<td>37.5±12</td>
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<td>Male %</td>
<td>43</td>
<td>44</td>
<td>43</td>
<td>40</td>
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<td>Montreal classification</td>
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<td>0</td>
<td>–</td>
<td>0</td>
<td>–</td>
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<tr>
<td></td>
<td>L2 (%)</td>
<td>–</td>
<td>7 (17)</td>
<td>5 (12)</td>
<td>–</td>
<td>5 (12)</td>
<td>–</td>
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<tr>
<td></td>
<td>L3</td>
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<td>0</td>
<td>0</td>
<td>–</td>
<td>0</td>
<td>–</td>
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<tr>
<td></td>
<td>E1 (%)</td>
<td>–</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td>–</td>
<td>0</td>
<td>–</td>
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<tr>
<td></td>
<td>E2 (%)</td>
<td>–</td>
<td>6 (14)</td>
<td>4 (10)</td>
<td>4 (10)</td>
<td>8 (17)</td>
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<tr>
<td></td>
<td>E3 (%)</td>
<td>–</td>
<td>7 (17)</td>
<td>8 (17)</td>
<td>–</td>
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<td>Treatment</td>
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<tr>
<td>Corticosteroids (%)</td>
<td>3 (7)</td>
<td>8 (19)</td>
<td>11 (26)</td>
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<td>1 (2)</td>
<td>1 (2)</td>
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<td>Mesalazine (%)</td>
<td>1 (2)</td>
<td>5 (12)</td>
<td>6 (14)</td>
<td>1 (2)</td>
<td>6 (14)</td>
<td>7 (17)</td>
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<tr>
<td>Methotrexate (%)</td>
<td>1 (2)</td>
<td>3 (7)</td>
<td>4 (10)</td>
<td>0</td>
<td>0</td>
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<td>Purine analogues (%)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>2 (5)</td>
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<td>5 (12)</td>
<td>7 (17)</td>
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<td>Infliximab (%)</td>
<td>3 (7)</td>
<td>7 (17)</td>
<td>10 (24)</td>
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<td>Adalimumab (%)</td>
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<td>Ciclosporin (%)</td>
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<td>Antibiotics</td>
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Connecting dysbiosis, bile-acid dysmetabolism and gut inflammation in inflammatory bowel diseases
Dysbiosis and dysmetabolism in IBD:

- F. prausnitzii - E. coli ratio
- Secondary BA in feces
- Conjugated BA in feces
- Sulphated BA in feces
Does the dysbiosis lead to dysmetabolism?
Does the dysbiosis lead to dysmetabolism?

Experiments with dried feces of HS, IBD in remission and Active IBD

- Transformation deficiency
- Deconjugation deficiency
- Desulfation deficiency

The dysmetabolism depends on the disease activity
Does the changes in BA can be involved in the inflammatory loop?
A TGR5 pathway?

→ The anti-inflammatory effect of BAs, (decreased secretion of TNFα, Interleukin-1β, interleukin-6) in macrophages and monocytes have been described 20 years ago

TGR5 decrease the release of proinflammatory cytokines by Kupffer cells (liver macrophages)

The chicken and the egg?

→ Parallèle entre profondeur de la dysbiose, du dysmétabolisme des acides biliaires, et de l’activité de la maladie

→ Mesure d’activité enzymatiques fécales = permet de s’affranchir du temps de transit.

→ Dépistage de BAM: moins d’intérêt dans cette population

Effet anti inflammatoire: Perspective TGR5 ?

*LCA et DCA sont les plus puissants ligands de TGR5*

Kawamata et Al, 2003
A Model

Healthy subjects

Bile acids liver secretion

Normal microbiota enzymatic activity

Desulfation (bacterial sulfatases)

Primary BA

Secondary BA

Fecal BA pool

Sulfation (epithelium sulfotransferase)

Gut epithelium

IBD

Bile acids liver secretion

Lower microbiota enzymatic activity

Dysbiosis

Lower desulfation (bacterial sulfatases)

Primary BA

Secondary BA

Sulfated BA

Inflammation loop

Gut epithelium
Conclusion

Dysbiosis and Dysmetabolisms of bile acids:

Strong arguments, > IBD than IBS, and maybe and a possible role in inflammation

But... a story to be continued
Thank you very much for your attention