What matters to metabolic health: microbes, metabolites or both?”

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Gut microbiome in diet induced obesity; causal in pathophysiology?

CONSENSUS: Low butyrate producers & levels in obesity/metsyn

Hartstra/Nieuwdorp, Diabetes Care. 2015 Jan;38(1):159-65
HOW FECAL TRANSPLANTATION WORKS

1. In a fecal transplant, stool from a healthy donor is used to replace a patient’s gut microbial flora.

2. Exact preparations vary, but usually the stool is blended with saline and put through a strainer. It can be frozen before use.

3. The stool can be applied into the small intestine via a tube through the nose or mouth (a) or deep into the colon, using a colonoscopy (b). Enemas are popular for at-home treatments, but they only reach the lower end of the colon (c).

4. In the future, scientists hope to replace fecal transplants with an odorless mix of bacterial strains derived from human stool, grown in the lab. It could be applied using existing methods or in capsules.

EU USA

Vrieze, Science 2013
www.mynewgut.eu
Effect lean donor microbiota (FMT) on insulin sensitivity in metsyn

Vrieze, Gastroenterology 2012; Kootte, Cell Metabolism 2017

Lean donor FMT increased SCFA butyrate producers
Relation gut microbiota composition and plasma metabolites

Microbiome Influence on Energy Balance and Brain Development and/or Function Put into Action to Tackle Diet-Related Diseases has received funding from the European Union’s Seventh Framework Programme for research, technological development and demonstration. Grant Agreement no: 613979

Holmes E, Cell Metabolism 2012 16, 559-564
Short chain fatty acids (ScFA) are best studied microbial metabolites in relation to metabolism

- SCFA-acetate (50%)
- butyrate (30%)
- propionate (20%): 1

CONSENSUS: Low butyrate producers & levels in obesity/metS

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Serotonin/dopamine production (involved in central regulation of metabolism and colonic transit time) is mediated by gut microbiota composition (butyrate producers) in animals.

Cervenka, Science 2017; Battaray, Am J Physiol 2017
Lean donor FMT affects fasting plasma metabolites profile

Cervenka, Science 2017

LEAN FMT increases plasma metabolites involved in proteolysis (serotonin/dopamine)
OWN FMT increases oxidative stress related metabolites

Kootte/Nieuwdorp, Cell Metabolism 2017

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Striatal dopamine D$_{2/3}$ receptor availability increases after long-term bariatric surgery-induced weight loss.

Striatum Dopamin receptors involved in impulse control and food intake

How about using donor FMT from postbariatric surgery subjects?

Roux-en-Y Gastric Bypass

40kg weight loss in 3 years

Enrichment in butyrate producing bacteria upon bariatric surgery in mice

Liou, Sci Transl Med. 2013 Mar 27;5(178):17
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Does gutbrain axis exists in human subjects and are gutmicrobiota drivers of Dopamine and serotonin brain metabolism in humans?
RCT Appetite study (WP 3 MyNewGut)

Does FMT from postbariatric surgery donors affect serotonin and dopamine brain receptor expression in human metabolic syndrome?

And

is oral butyrate a beneficial treatment in diet induced obesity?
Does donor FMT affect brain serotonin-dopamin metabolism in humans?
Relation with butyrate or butyrate-producing bacteria?

N=12 male-female metabolic syndrome
Placebo tablets 4 wks
Post-bariatric surgery donor FMT (butyrate-producing bacteria)

N=12 male/female metabolic syndrome
Butyrate tablets 4 wks
Placebo (autologous) FMT
• **Study design**
  – randomised double blinded placebo controlled

• **Subjects**
  – 24 male or postmenopausal females 50-70 yr with:
    • obesity (BMI≥30)
    • metabolic syndrome (fasting glucose ≥ 5.6 mmol/l)
    • no medication

• **Treatment**
  – Randomised:
    1. **Allogenic** post-RYBG donor (who lost 30% of weight in 1 year) feces transplantation + placebo tablets for 4 weeks
    2. **Autologous** feces transplantation + sodiumbutyrate tablets 4g/day for 4 weeks
Primary endpoints

• Insulin sensitivity and lipolysis:
  – Hyperinsulinemic euglycemic clamp (glucose and glycerol stable isotopes)
  – Plasma, urine and fecal metabolomics

• Intestinal microbiota:
  – Gut microbiota changes

• Serotonin function:
  – Brain: MRI + SPECT-scan (serotonin and dopamin receptor expression)
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Visit 1: Screening
Visit 2:
- 2x24h feces + morning stool
- MRI/SPECT-scan brain
- diet intake/ VAS list
- 24h-urine/blood sample

Visit 3:
- Clamping + calorimetry

Randomisation

Visit 4:
- Duodenal biopsy
- Fecal transfusion

Visit 5:
- 2x24h feces + morning stool
- MRI/SPECT-scan brain
- diet intake/ VAS list
- Duodenal biopsy

Visit 6:
- Clamping + calorimetry
- 24h-urine/blood sample

Baseline
4 weeks

End of study

APPETITE Study design
My New GUT

Post-RYBG donor feces + placebo tablets (n=12)

Autologous feces + butyrate tablets (n=12)
Hard endpoints: hyperinsulinemic euglycemic clamp
Endogenous (hepatic) glucose production and (peripheral) glucose utilization

Overnight fast
[6,6-\textsuperscript{2}H\textsubscript{2}]glucose bolus
0 min
Steady state the last 20 min

Basal
Step 1 Clamp Step 2
Constant \([6,6-\textsuperscript{2}H\textsubscript{2}]\text{glucose infusion (0.11 \(\mu\text{mol \cdot kg}^{-1} \cdot \text{min}^{-1}\) )}

2h Constant insulin infusion (20 mU \cdot m^{-2} \cdot \text{min}^{-1})
2h Constant insulin infusion (60 mU \cdot m^{-2} \cdot \text{min}^{-1})

Variable 10\% glucose infusion for plasma glucose 5 mmol/l

EGP = hepatic
Insulin sensitivity

Rd = peripheral
Insulin sensitivity
Intravenous Radiotracer labeled 100 MBq $^{123}$I-FP-CIT binds to:
- Serotonin receptor expression in **thalamus** and **hypothalamus** (2h after infusion)
- Dopamin receptor expression in **striatum** (visualized 3h after infusion radiotracer)
Brain SPECT coregistered to individual MRI (ROI analysis)

ROI striatum for Dopamine receptor binding (DAT)
ROI thalamus and hypothalamus for Serotonin receptor binding (SERT)

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Thank you

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Stratification of patients based on gut microbiome related metabolites and microbiota strains may help to tackle diet induced obesity problem?