Effects of Pharmaceutical Exposures

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Questions

• Can pharmaceuticals (drugs) at therapeutic doses affect the gut microbiome?
• If yes, are there consequences for the host?
• Is there evidence that environmental drug exposures act directly on the human gut microbiome?
• What about the impact on human microbiomes of agricultural drug use?
• What about indirect effects?
Background

• The gut microbiomes provide the host with an important external organ with significant metabolic capacity and the microbiota that form it are **not passengers but crew**.

• Environmental factors exert a major influence in the development and evolution of an individual’s microbiome.

• Initially the microbiome is derived from the mother but subsequent exposures to chemicals (including drugs) and environmental microorganisms can modify it.

• The presence of the gut microbiome has direct effects on the host and changes the hosts’ **metabolic profile**.
What else affects the microbiome?

• Age
• Genetics
• Sex
• Diet
• Disease
• Etc. etc, all of which might represent confounding factors
How Does the Microbiome affect the Host Metabolic Phenotype?

Proton NMR Spectrum of Normal Rat Urine
The Absence of a Microbiome

Proton NMR Spectrum of Urine from a Germ-Free Rat

Low aromatics and high formic acid compared to normal rats
So What Effect Does Host Genetics Have?

- Genetic differences reasonably might be expected to have effects on the composition of the microbiome?
- Examination of the fecal microbiome of a number of strains of mouse seems to show that different bacterial composition is associated with the different genetic backgrounds
6 Different strains of mice – 6 different microbiomes

Strain vs Environmental Effects on the Microbiome

• The results for the different strains look fairly unequivocal but....

• What about the fact that they were brought up in different cages and had different mothers?

• Will these factors also affect the resulting microbiome (and the metabolic phenotype)?
Maternal vs Strain Effects on the Micobiome

strains (2 genders) and 1 mother

So, for mice, the maternal “environment” is more important than strain, and so is gender,
Age-Related Effects on Mice of Changing Environments

For mice the environment is more important than the maternal environment.

**Microbiome**

**Host metabolic phenotype**

The Metabolic Phenotype Reflects Microbiotype

The Environment and the Rat Microbiome

3 strains of Zucker rat: 3 animals, 1 of each strain, housed in each of 6 cages

**Key**
- Actinobacteria
- Bacteroidetes
- Firmicutes
- Proteobacteria
- Tenericutes
- Others

**Key**
- Bacteroidaceae
- Coriobacteriaceae
- Peptostreptococcaceae
- Prevotellaceae
- Ruminococcaceae
- Others

O = homozygous obese, L = homozygous lean, H = heterozygous lean
Effects of Antibiotics on the Rat

• 3 groups of rats
• 6 Control Rats
• 6 Antibiotic treated – 8 days
• 6 Antibiotic treated - 4 days then allowed to recover
Can Pharmaceuticals (drugs) at Therapeutic Doses Affect the Human Gut Microbiome?

- Antibiotics are obvious candidates. They can clearly directly affect the microbiomes.
- Proton Pump Inhibitors (PPI’s), their pharmacology changes the gut environment.
- Non-steroidal anti-inflammatory drugs (NSAID’s) can cause gut damage and this results in changes to the gut environment.
Antibiotics: Effects On The Microbiome


• Dethlefsen & Relman ( 2011) Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation PNAS, 108, 4554–4561, suppl. 1
Effects of PPI’s On The Microbiome


Are There Consequences of Drug Induced Microbiome Changes for the Host?

• Antibiotics, Proton Pump Inhibitors (PPI’s) and Non-steroidal anti-inflammatory drugs (NSAID’s) have both short and long term effects on the microbiome.

• Probably ANY drug that acts on the gut microbiota, or directly or indirectly affects the physiology of the gut, has the potential to modify the microbiome.
What about environmental exposure to drugs?

- Environmental contamination of e.g., potable water by antibiotics is typically fairly low well below any likely major direct effects.
- However, local concentrations in waste water or effluent in some areas due to manufacturing waste do have concentration of antibiotics that exceed those expected in therapeutic use.
- Indirect effects are likely to be as a result of stimulating some level of antimicrobial resistance (AMR) giving some species an opportunistic advantage in colonizing the host.
- Agricultural use probably represents a bigger source of affects on the gut microbiome through production of antibiotic-resistant strains.
Agricultural use of Antibiotics

THE UK REVIEW ON ANTIMICROBIAL RESISTANCE

• CHAIRED BY JIM O’NEILL DECEMBER 2015

• ANTIMICROBIALS IN AGRICULTURE AND THE ENVIRONMENT: REDUCING UNNECESSARY USE AND WASTE

• The Review on AMR, commissioned by the British Prime Minister, and hosted by the Wellcome Trust.

• It is tasked with recommending, by the summer of 2016, a comprehensive package of actions to tackle AMR globally.

• In the meantime, they are publishing a series of papers looking at individual aspects of the wider AMR problem.
THE UK REVIEW ON ANTIMICROBIAL RESISTANCE

• Of 139 academic studies the Review found, only seven (5%) argued that there was no link between antibiotic consumption in animals and resistance in humans, while 100 (72 %) found evidence of a link.

• According to the figures in this report 70% (8,893,103kg!) of the antibiotic use in the US is in agriculture compared to 30% for humans

• Of the 41 antimicrobials that were authorised for sale in animals, and sold in the US in 2012, 31 are currently deemed by the FDA to be important for human health.
Consequences

• The gut microbiome is an important organ of DRUG METABOLISM and can modify drug TOXICITY

• Changes in the composition of the microbiome could well modify how drugs are metabolised

• This might affect both efficacy and toxicity

• An example of this is seen for humans for acetaminophen where competition for sulfation between bacterially-derived phenols and the drug alters the overall metabolic fate
Tyrosine to $p$-Cresol sulfate

Microbiome metabolism of tyrosine to $p$-cresol

Host metabolism of $p$-cresol to sulfate

Sulfation is a high specificity, but low capacity, preferred route of metabolism for phenols
Pharmacometabonomics identification of a significant host-microbiome metabolic interaction affecting human drug metabolism


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Changes in 4-cresol production has the potential to impact on host xenobiotic metabolism via competition for sulfation of Paracetamol/acetaminophen.

Pre-dose 4-cresyl sulfate / creatinine

Changes in 4-cresol production has the potential to impact on host xenobiotic metabolism via competition for sulfation of Paracetamol/acetaminophen.
When host sulfation and glucuronidation capacity begins to become limiting then other metabolic routes become more important – with consequences for toxicity.
Drug-Microbiome Interactions

Some Concluding Comments

• The gut microbiota represents both a major forgotten organ of drug metabolism, activating certain prodrugs, and a target for “collateral” damage from therapeutic use.

• Microbes produce waste products to be dealt with by the host – and these might affect the efficacy and toxicity for drugs.

• Effects of environmental exposure to sub-therapeutic doses could be quite difficult to show because of all the confounding factors.

• The effect of the presence in the environment of AMR bacteria, capable of colonizing the GI tracts of humans with unwanted consequences, is clear.