GUT MICROBIOTA FOR HEALTH
World Summit 2014

Summit Report
World Summit "Gut Microbiota for Health" 2014
Miami, FL, USA
8 – 9 March 2014

Programming obesity?

In infants, antibiotics might have long-term consequences

Antibiotics are indispensable for fighting various severe diseases. Nevertheless, they can have unwanted side effects. Is obesity in children among them? And might exposure to antibiotics in infancy lead to this condition? At the Gut Microbiota for Health World Summit 2014 in Miami, FL (USA), Dr Laura Cox (New York University, NY, USA) presented her audience with fresh research results that shed light on the issue.

DR LAURA COX
New York University, USA

For decades, the agricultural industry has been using antibiotics in low doses to promote the growth of their livestock. Dr Cox and her team took this experience as a starting point for investigating the underlying causal mechanisms. Considering the fact that children in Western countries receive on average one course of antibiotics every year, the importance of this issue is plain, to see.

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Antibiotics can disrupt the microbial balance

"As the effects observed in the agricultural industry are induced by very different types of antibiotics and in different kinds of animals, we assumed that the gut microbiota composition and the changes it undergoes through antibiotics might be at the centre of it all," says Dr Cox. Through a number of trials where mice were fed low doses of antibiotics, she could demonstrate which profound and long lasting effects antibiotics have when applied in early lifetime. While the body mass of all mice that had received antibiotics increased as compared to control animals, it turned out that the extent of the antibiotics' effect depended on when the application had started. Mice that had been exposed to antibiotics from birth showed a higher increase in fat mass than those who had not received this treatment before weaning.

RESTORED BALANCE, PERSISTING OBESITY

The causal chain that leads to obesity starts in the gut microbiota. "The antibiotics shift the gut microbiota composition by reducing certain kinds of potentially beneficial bacteria. This disruption of the microbial balance in our lab mice had severe consequences: their food intake was increased; additionally, the architecture of the ileum, as well as the expression of certain genes, changed in a way that weakened the gut's defense mechanisms. This finally resulted in increased weight and adiposity," says Dr Cox. Moreover, the mice remained obese even after the antibiotics had been abandoned and the gut's microbial balance restored. According to Dr Cox, this indicates that infancy is a particularly critical time span, as a disturbed gut microbiota might negatively influence the programming of stem cells and the building of muscle and fat and thus cause persisting health effects. "We discovered that, in mice, exposition to antibiotics over the first four weeks of life is enough to cause long-lasting obesity. With regard to humans, this corresponds to the first six months after birth. Children who receive antibiotics within this time window are at risk of being overweight later in childhood."

CONTENT

Gut Microbiota & Health
section of the ESNM European Society of Neurogastroenterology & Motility Member of UEG
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Experts exchange in Miami

Gut Microbiota for Health World Summit 2014 held in the USA

220 scientists and health-care professionals from 33 nations attended the 3rd edition of the meeting, which was held in the USA for the first time and was hosted by the AGA (American Gastroenterological Association) and the Gut Microbiota & Health Section of the ESNM (European Society of Neurogastroenterology and Motility) — a member of UEG (United European Gastroenterology) — with the support of Danone. A well-balanced mixture of lectures and workshops covered the most recent advances in the rapidly developing field of gut microbiota research. Online interest in the event further increased, with the number of twitter messages quadrupling compared to last year.


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220 scientists and health-care professionals attended the Gut Microbiota for Health Summit

The summit's programme included basic scientific and translational aspects of gut microbiota research. World-leading experts presented a wide variety of topics, ranging from the lifelong impact of microbiota perturbation by antibiotics to the gut microbiota's roles in various gastrointestinal diseases, from pre- and probiotics in paediatrics to a prospective look at non-bacterial microbes in the gut. Six workshops offered continuing education and were very well attended. With over 100 participants, the workshop on diet and the gut microbiota attracted the largest audience. Wrap-up sessions of all workshops can be viewed here. One of the most popular features of the summit was that plenty of time had been set aside for discussion, ensuring that there was an animated exchange of information, opinions and experiences throughout the event. This also applied to the relations the summit's participants maintained with the "world outside": increased use of the digital communication means on offer showed the ever-rising interest in gut microbiota research among the scientific community. More than 1,150 tweets communicated event-related messages via the summit's **Twitter** account (@GMFHx) – almost four times as many as last year. Over 100 new Twitter followers joined during the event. 350 experts from all over the world followed the live stream of the plenary sessions on the Experts Exchange website gutmicrobiotaforhealth.com

The website attracted nearly 700 visits during the summit, with 60 new members joining the platform. In addition, there was an online press conference with journalists from all over the world, and a digital press folder that was downloaded over 300 times.


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This year's summit was held in Miami, USA

The 4th Gut Microbiota for Health World Summit will be held in mid-March 2015 in Barcelona, Spain.

GI diseases in children

Probiotics can be an efficient remedy

Probiotics are helpful not only for adults, but also for infant patients. Although this is widely acknowledged, in clinical practice it can be difficult to decide which probiotic to choose for which condition.

The pediatricians Prof. Michael D. Cabana (University of California, San Francisco, USA) and Prof. Brent Polk (University of Southern California, Los Angeles, USA) gave an overview of what has been found out in terms of efficacy and modes of action of probiotics in children. Looking at a number of studies and meta-studies, they found positive or at least promising results with regard to the treatment of diarrhea and antibiotic associated diarrhea, as well as colic, with *Lactobacillus GG* being the best studied strain in these conditions. By contrast, probiotic treatment for atopic derma- titis does not seem to improve the health status significantly, but it can have preventive effects in certain cases, namely in infants who have not been breastfed, have been exposed to antibiotics and were born via Caesarian section. An overall positive outcome has been observed with respect to necrotising enterocolitis (NEC). Here, probiotics of all kinds seem to have a beneficial effect, while, in the other conditions, the specific bacterial strain matters. In general, the success of applying probiotics is also dependent on the patients' compliance: "The more complicated the regimen, the more likely it is that the childrens' parents will not adhere to the protocoll," said Prof. Cabana. "In addition to such interfering factors in daily health care practice, we have to take into account that the underlying mechanisms are only partly understood, which can make the interpretation of findings challenging," said Prof. Polk.

PROF. BRENT POLK
University of Southern California, Los Angeles, USA

PATTERNS OF GUT COLONISATION

C-section and use of antibiotics in infants are factors that can influence the colonisation of the gut and the microbiota composition in a negative way. However, the precise mechanisms of impact and how they are related to different periods of life are still unclear. The fact that gut microbiota compositions in infants are frequently changing at short intervals makes it difficult to define what a "normal" population might look like. To find out more about colonisation patterns, Prof. Phillip I. Tarr (Washington University inf St Louis, MO, USA) and his team analysed the stools of infants in a neonative intensive care unit. They found that in this strictly controlled ecosphere, where the gut is left to its own devices and a very constrained number of microbes, infants in their very earliest period of life showed mostly the same pattern of gut colonisation: a succession of *Bacilli, Gamaproteobacteria* and *Clostridia*. Environmental factors had only little influence: the mode of delivery had no impact, while the effect of antibiotics was only modest. "How this fits in with other findings remains to be clarified. The research community is just beginning to understand all these processes and we urgently need to improve our data basis, which so far has been rather limited and selective," said Prof. Tarr.

PROF. MICHAEL CABANA
University of California, San Francisco, USA

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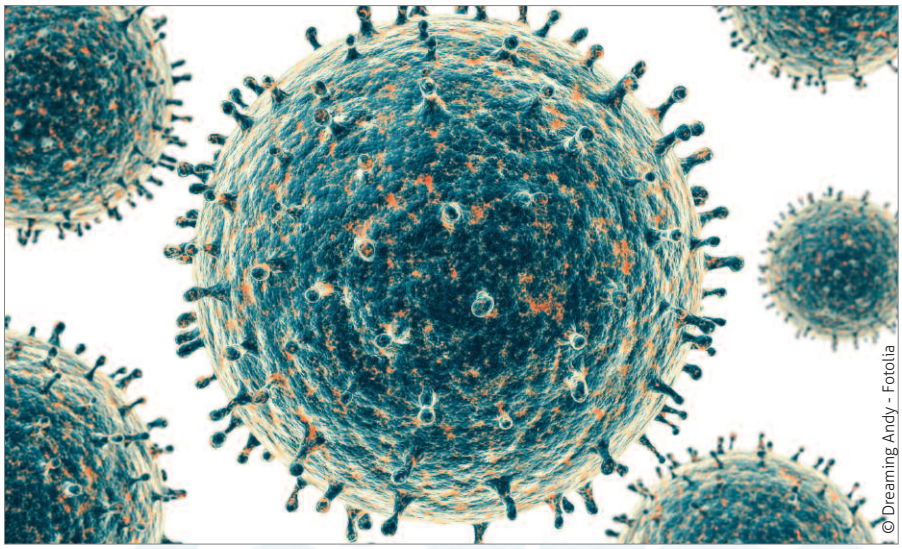
Even infants may profit from probiotics

PROF. PHIL TARR
Washington University in St Louis, MO, USA

Non-bacterial neighbours

Viruses, fungi and archaea form a medically relevant part of the gut microbiota

During the past decade, the gut microbiota has become a prominent research area within gastroenterology. But it is mainly the bacterial section of the intestinal microbial population that the spotlight has fallen on so far. However, the intestine harbours a vast number of other microorganisms, which have similar importance for health maintenance.



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Viruses outnumber bacteria in the gut

The richness of life within the gut is not only based on bacteria, but also on a vast number of non-bacterial microbes which interact in highly complex ways and contribute to the protection of GI health, as well as to the development of diseases. Prof. Gary Wu (University of Pennsylvania, Philadelphia, USA) invited his audience to become more familiar with these not so well-known members of the gut microbiota. "It is through sophisticated bio-informatic tools, namely advanced DNA sequencing technology, that we have been able to begin to characterise the taxonomic abundance of this vast community and to unveil their intricate relationships. This exciting work will hopefully contribute to the development of improved diagnostic and therapeutic methods." The most abundant non-bacterial gut inhabitants are viruses, which can outnumber bacteria by a factor of 10 to one. They divide into eukaryotic viruses that infect humans (which belong to eukaryotes, i.e. organisms with cell nucleus) and prokaryotic ones that can infect bacteria (which belong to prokaryotes, i.e. organisms without cell nucleus). Both sorts can induce intestinal inflammatory diseases.

PROF. GARY WU
University of Pennsylvania, Philadelphia, USA

TIGHT INTERACTION BETWEEN VIRUSES AND BACTERIA

Viruses and bacteria are tightly intertwined through a variety of different interplays: certain viruses can infect bacteria. These "bacteriophages" – which are amongst the most common and diverse entities in the biosphere – transfer genetic material to bacteria and can thus alter the gut microbiota in disease-promoting ways. At the same time, viruses can, for example, be coded by bacterial products in order to suppress the immunosystem of the host so that it can be more deeply infected. Certain bacteria are able to "fight back": by integrating DNA of the viral attacker they can "remember" and destroy the virus in case of another assault. As Prof. Wu pointed out, all this is cutting edge research: "Most of the viruses we are discovering now, have not been described previously." Another non-bacterial life form comprises archaea, which are single cell organisms like bacteria. In the gut, they produce the methane that causes distension. They also interact with bacteria, with both organisms mutually consuming the other's metabolites. This process increases the production of short chain fatty acids, which support intestinal health. A further important part of the gut microbial population is formed by fungi and yeasts. "Fungi are elevated in the guts of IBD patients, so they might play a role in the development of this condition," says Prof. Wu. He pointed out that there seems to be a competition between fungi and yeasts on the one hand and bacteria on the other: decreases in fungal diversity have been shown to correlate with an increase in healthy bacterial colonisation following probiotic therapy, and vice versa following fungal infection after antibiotic treatment.

Probiotics against diabetes

Eubacterium hallii improves obesity symptoms

Finding novel bacterial strains with a beneficial effect on gastrointestinal conditions is a major goal of gut microbiota research. Scientists could show that the butyrate producer *E. hallii* can restore the microbial balance and reduce insulin resistance in obese patients.

Obesity and insulin resistance are connected with type 2 diabetes. These conditions are associated with significant changes of the gut microbiota composition. Prof. Max Nieuwdorp (University of Amsterdam, The Netherlands) and his team are currently working on a precise characterisation of these relationships in order to develop new methods of diagnosis and treatment. They found out that an enrichment of *Lactobacillus gasseri* and *Streptococcus* mutans in the gut – detected by analysing faecal samples – is a good predictor for the development of insulin resistance. The same applies to a reduced production of butyrate, a short chain fatty acid (SCFA) which impacts on glucose metabolism and plays a generally health maintaining role. "Both measurements are valuable criteria to inform you about an increased risk of diabetes," said Prof. Nieuwdorp. The causes that might lead to a disturbed gut microbiota composition with associated diabetes and obesity are manifold. Together with infection, diet and lifestyle, the use of antibiotics is one of them. Prof. Nieuwdorp pointed to studies that showed a marked decrease of insulin sensitivity after intake of vancomycin. This was combined with a considerable drop of bacterial diversity, including a decrease of SCFA producing bacteria.

PROF. MAX NIEUWDORP
University of Amsterdam, The Netherlands

DELAYING THE ONSET OF DIABETES

At the same time, these mutual relationships can be reversed for the benefit of the patient by transplanting healthy individuals' microbiota. "Generally speaking, this is a promising kind of treatment, as well as a way of mining for smart bacteria that can serve as novel therapeutic means, which are so desperately needed," said Prof. Nieuwdorp. With regard to diabetes, he pointed out that the transfer of lean donor faeces to the digestive system of obese patients improves their insulin sensitivity towards the level of the lean donor. This is associated with a regained balance of the formerly disturbed gut microbiota composition. One of the microbial strains that are significantly increased after transplantation is *Eubacterium hallii*, a species, mostly found in the small intestine. As it produces butyrate, it offers an interesting medical potential that Prof. Nieuwdorp and his colleagues intend to exploit. "After feeding mice with *E. hallii* through a daily oral gavage over a period of four weeks, it turned out that, even after this relatively short time span, the insulin sensitivity in these animals was significantly higher than in those that had been fed with placebo," said Prof. Nieuwdorp. "This shows that bacteria such as *E. hallii* are probably suited to restore a healthy gut microbiota composition. Very soon we are going to test *E. hallii* as a potential novel probiotic in humans. This will probably not provide a definite cure, but in an early stage of disease development, it can prevent the onset of real type 2 diabetes at least for a couple of years."

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Obesity is associated with a disturbed gut microbiota composition

A dynamic disease

Many answers to the causes of IBS can be found in the gut microbiota

Irritable bowel syndrome (IBS) affects up to 20 per cent of the population in Western countries. It represents a considerable portion of the workload of family physicians and gastroenterology practitioners, and the development of efficient therapies is still a major challenge.

Among the four factors that contribute to the development of IBS – host genetics, diet, environment and the gut microbiota – it was the latter that Prof. Purna Kashyap (Mayo Clinic, Rochester, MN,USA) put special emphasis on. "In my opinion, the gut microbiota represents a unifying mechanism underlying the patho-physiology of the various symptoms in IBS, from bloating and motility to food intolerance and hypersensitivity," said Prof. Kashyap, who presented a large body of evidence to demonstrate the key role of the gut microbiota. Studies showed that the transplantation of the microbiota of IBS patients into rodents induced IBS symptoms, such as altered intestinal motility, as well as increased sensitivity and contractility. It is through their metabolites that the bacteria mediate these changes. Methane, for instance, slows down the intestinal transit, while lipopolysaccharides (LPS) accelerate it. Another example are short chain fatty acids, that increase the colonic motor function and facilitate water absorption. For the regulation of gut motility, serotonin plays a crucial role, the synthesis of which is being augmented in the gut microbiota. "IBS is a dynamic disease with a waxing and waning of symptoms and this fits to the gut microbiota as a dynamic organ that is sensitive to numerous environmental influences, among which food is certainly one of the most important," said Prof. Kashyap.

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The gut microbiota plays a key role in IBS

PROF. PURNA KASHYAP
Mayo Clinic, Rochester, USA

PROF. GIOVANNI BARBARA
University of Bologna, Italy

PREBIOTICS IMPROVE SYMPTOMS

The key role of nutrition for IBS symptoms was also stressed by Prof. Giovanni Barbara (University of Bologna, Italy). Food that is rich in carbohydrates tends to produce larger amounts of gas than a diet without these ingredients. In some individuals, particularly those who already suffer from a form of IBS, this might lead to repeated bloating and flatulence. Recent studies show that such a "flatulogenic" diet induces profound changes in the microbiota of IBS patients, thus prolonging and increasing the symptoms. However, at the same time, the gut microbiota of healthy subjects remained stable and un-affected by this kind of diet. On the other hand, as Prof. Barbara pointed out, diet containing low fibre content improves these symptoms significantly. Recent research results suggest that a diet low in so-called FODMAPs (fermentable oligosaccharides, dis-accharides, monosaccharides and polyols) reduces symptoms of IBS, including bloating. Prof. Fernando Azpiroz (University of Barcelona, Spain) pointed to the beneficial effects of prebiotics, which are probably due to changes of the gut microbiota with an increase of bacteria that metabolise without relasing gas. "By this mecha-nism, prebiotics might reduce gas production, improve handling and increase tolerance of intraluminal gas. Conceivably, individualised treatments based on microbiota profiling may be an effective tool in the future," said Prof. Azpiroz.

PROF. FERNANDO AZPIROZ
University of Barcelona, Spain

Delicate relations

How gut bacteria can drive liver diseases

It has become common knowledge among the majority of gastroenterologists that many bowel diseases are linked to a perturbed gut microbiota composition. In comparison, the relations between the gut microbial community and liver conditions have attracted less attention so far. In his overview, Prof. David A. Brenner (University of California, San Diego, USA) demonstrated how manifold, complex and medically relevant the connections between the gut microbiota and conditions such as non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic liver disease and cirrhosis are.

A disturbed gut microbial balance can lead to breaches in the gut barrier and thus to an increased permeability of the intestine, together with the leaking of potentially harmful bacterial products. This might have severe consequences since the portal blood transports these components directly to the liver," said Prof. Brenner. He put special emphasis on the role that toll-like receptors (TLR) play in this process. TLR are part of the innate immune system and abundantly present on liver cells. This applies for example, to TLR 4 whose agonist is lipopolysaccharide (LPS), an endotoxine produced by bacteria. When LPS binds to TLR 4, these receptors activate hepatic stellate cells (HSC). These are liver cells that, when "awakened", cause the secreting of collagen scar tissue, which can lead to cirrhosis. TLR 4 is but one of several receptors that are involved, together with their ligands, in the onset of inflammatory and fibrosis-inducing processes.

Liver diseases can be related to the gut microbiota

THE POTENTIAL OF PRE- AND PROBIOTICS

Accordingly, mice with genetically mutant or knocked-out TLR were significantly less sensitive to fibrosis-causing bacterial products than wild-type mice. A similar effect was achieved by feeding mice with antibiotics, thus eradicating potentially harmful microbes and establishing the relationship between liver diseases and the gut microbiota from another angle. One association that physicians have long been aware of is intestinal bacterial overgrowth in patients with cirrhosis. Prof Brenner pointed to numerous studies that show that this quantitative imbalance is connected with a qualitative one, as the total number of bacteria in patients is not only increased, but its composition significantly changed with an unproportionally high amount of potentially pathogenic bacteria and a decreased portion of beneficial strains. The intake of alcohol over an extended period of time brought about similar results. Particularly striking is the decrease in the beneficial *Firmicutes*. On the other hand, these effects can in part be reversed: feeding mice with prebiotics resulted in an improvement of their experimentally induced alcoholic steatohepatitis together with a reduction of intestinal bacterial overgrowth. "Certainly, exploring the potential of pre- and probiotics for treatment of liver diseases is a promising avenue," said Prof. Brenner.

PROF. DAVID BRENNER
University of California, San Diego, USA

Another one of the various interactions between the gut microbiota and hepatic health Prof. Brenner touched upon, is mediated through choline, a substance which is essential for proper liver functions. Lack of it leads to increased storage of fat in the liver. Certain gut bacteria metabolise choline in a manner that it cannot carry out its beneficial role, thus increasing the risk of developing a fatty liver.

Psychobiotics: a promising therapeutic concept

Gastroenterology meets psychiatry – promising outlooks on future treatment options

The gut microbiota is linked to behavioural patterns, emotional states and cognitive functions in numerous ways. A part of these complex interactions has already been elucidated in animal models. Many of these findings are likely to bear fruit on the future treatment of human mental conditions.

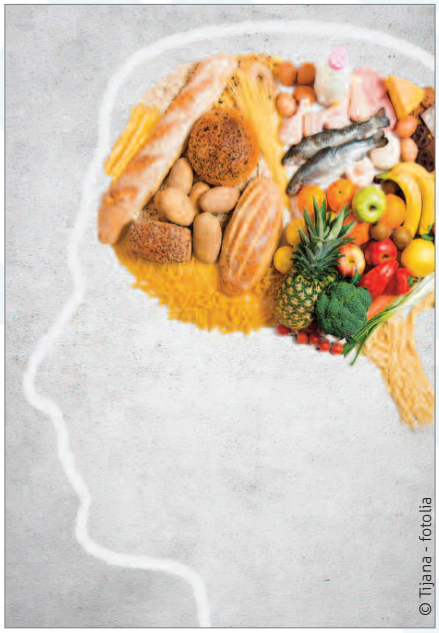
It has long been realised that gastrointestinal and psychological conditions might be associated – IBS being a prominent example – but it is only fairly recently that the role of the gut microbiota as another important counterpart in this intricate interplay between gut and brain has been fully acknowledged. According to Prof. Ted Dinan (University College Cork, Ireland), the community of the intestinal bacteria represents a virtual inner organ that equals the brain not only in weight, but also in complexity. This organ is connected with the gut and the brain through a complex network of bidirectional pathways. "Several routes of communication between the gut microbiota, which itself produces neurotransmitters, and the brain have been explored. These include the vagus nerve, short chain fatty acids, tryptophan, spinal pathways and cytokines,

PROF. TED DINAN
University College Cork, Ireland

and, very importantly, the hypothalamic-pituitary-adrenal axis, which is part of the neuroendocrine system, influencing many physiological as well as psychological processes, including stress reactions, digestion, the immune system, emotional behaviour, sexuality and energy storage," said Prof. Dinan.

MENTAL HEALTH – PARTIALLY ROOTED IN THE GUT

These various and mutually interdependent modes of action have a deep impact on digestive as well as mental health. "Pathogens in the gut and a disrupted gut microbiota can induce not only intestinal health deterioration, but also abnormal changes in behaviour, emotion and cognition, as these factors not only disturb gut functions, but also influence the chemistry of brain circuits," said Prof. Premysl Bercik (McMaster University, Hamilton, Canada).



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Brain-gut relations benefit from a healthy diet

He and Prof. Dinan presented a large number of studies that demonstrated these relationships. In experiments, germ-free mice and those with a disrupted gut microbiota showed anxious-like behaviour, as well as a decrease of their exploratory drive and their memory capacity, which was accompanied by corresponding alterations of brain signalling processes. Similar gut-brain related effects were achieved by exerting environmental stress, such as early maternal separation. Certain trials showed that these psychological conditions could be reversed, within a certain time frame, by restoring the gut microbiota. This corresponds to pre-clinical studies in humans, where probiotics such as *B. longum, L. farciminis* and *L. rhamnosus* exerted anxyiolitic or antidepressant effects. This led Prof. Dinan to introduce the new term 'psychobiotic' by modifying the established definition of probiotics: "A psychobiotic is a live organism that, when ingested in adequate amounts, produces a mental health benefit."

PROF. PREMYSL BERCIK
McMaster University, Hamilton, Canada

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