Gastrointestinal tract 6: the effects of gut microbiota on human health

Previous articles in this series on the gastrointestinal (GI) tract sequentially examined the components of the GI tract from mouth to anus and described the processes of mechanical and chemical digestion and absorption. This final article examines the gut microbiota (the community of micro-organisms living in the GI tract) and the role it plays in the GI tract and in general health.

Overview of the microbiota

The human GI tract has a massive total surface of 250-400m² (Thursby and Judge, 2017). This enhances the processes of digestion and absorption, and functions as a surface substrate for microbial attachment and colonisation. Larger numbers of microbes are also found suspended and replicating within the nutrient-dense medium of the gastrointestinal secretions and partially digested food. An estimated 100 trillion micro-organisms, including bacteria, viruses, fungi and protozoa, colonise the GI tract, with microbes outnumbering human cells between three and 10 to one (European Commission, 2018). The combined microbial genome is thought to comprise over 3 million genes, which dwarfs the 23,000 genes present in the human genome. This huge microbial genome is collectively known as the gut microbiome and codes for a multitude of microbial metabolites, which are released into the gut and subsequently absorbed and distributed throughout the body. The combined gut microbiota is often referred to as a ‘super-organism’, which, as it releases biologically active molecules, can be thought of as a ‘virtual endocrine organ’ that exerts powerful and diverse effects on human physiology (Valdes et al, 2018). With an estimated collective weight of 2kg, the gut microbiota has a larger mass than the liver, which is the largest internal organ.

For many years it has been understood that bacteria living in the gut, such as Escherichia coli (E.coli), perform vital functions, such as the biosynthesis of vitamin K (a key co-factor in the blood clotting cascade), but it is only in the last decade that the complex interplay between the micro-organisms of the gut microbiota and human tissues is gradually being understood. Today it is

Keywords
Micro-organisms/Gut microbiota/Dysbiosis/Probiotics

This article has been double-blind peer reviewed

In this article...

● Gut microbiota and its role in the gastrointestinal tract
● The diverse effects of the gut microbiota on human physiology
● How imbalances could increase risk of certain diseases and conditions

Key points

The community of micro-organisms living in the gastrointestinal tract exerts powerful and diverse effects on human physiology.

Gut bacteria have a direct influence on the immune system and the body’s ability to deal with disease and infection.

Factors such as antibiotic therapies, poor diet, psychosocial stress and direct exposure to pathogenic organisms can all affect gut microbiota.

Imbalances in gut microbiota could increase the risk of certain diseases and conditions.

Evidence for the effectiveness of probiotics is contradictory, but stool pills and faecal transplants appear to be effective in reducing Clostridium difficile infection and colitis.

Authors
John Knight is associate professor in biomedical science; Zubeyde Bayram-Weston is lecturer in biomedical science; Yamni Nigam is professor in biomedical science; all at the College of Human Health and Sciences, Swansea University.

Abstract
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Citation
Microbial species forming the gut microbiota

A major challenge in trying to identify the microbes that live within the human GI tract is that many cannot be grown using the standard microbiological culturing techniques. However, the advent of modern genome sequencing has allowed rapid identification of micro-organisms without the need for culturing. The bacterial species of the gut have been the most heavily researched, while knowledge of the viral and fungal micro-organisms of the gut microbiota is currently sparse. The low oxygen levels present within the internal environment of the GI tract favours the growth of strict anaerobic species of bacteria, which greatly outnumber facultative anaerobes (bacteria that can switch between aerobic and anaerobic metabolism depending on oxygen concentration) and the aerobic species (bacteria that require the presence of oxygen) (Sekirov et al, 2010).

Two major groups of bacteria dominate the GI tract (Fig 1) with the Firmicutes (for example, Lactobacillus and Streptococcus species) comprising around 65% of the total and the Bacteroidetes (for example, Bacteroides intestinalis) around 30%. The remaining 5% are composed of primitive bacterial groups, including the proteobacteria (for example, E coli) and the actinobacteria such as Bifidobacteria species (Yang et al, 2009).

It is estimated that all individuals have between 500 and 1,000 species of bacteria colonising their gut. Population studies indicate much variation between individuals, with each person having a unique profile of microbial species. It is suggested up to 35,000 species form the collective human gut bacterial microbiota, with new species continually being discovered, including many previously unknown to science (Barras, 2019).

Initial colonisation after birth

Babies emerge from the usually sterile environment of the uterus with minimal bacterial colonisation. Unsurprisingly, those born via natural vaginal delivery have an early gut microbiota that is similar to the vagina, with groups such as Lactobacillus dominating. This contrasts with babies born via caesarean section, who have early gut microbiota similar to that found on the mother’s skin, with groups such as Corynebacterium and Staphylococcus species present in high numbers (Dominguez-Bello et al, 2011). The diversity of bacterial species generally increases with age, as different species are acquired from environmental contact, particularly from eating different foods and through contact with other people and animals. It is thought the acquisition of a mature microbiota resembling that of an adult is attained in the first three years of life, with country of residence also affecting the microbiotic profile (Yatsunenko et al, 2012).

Differences along the gut

Due to vastly different conditions, particularly in terms of pH, the populations of bacteria and other micro-organisms vary markedly in the different gut regions (Fig 2, p48). Unsurprisingly, the strongly acidic conditions of the stomach limit microbial colonisation and so relatively few species of bacteria are able to survive there. Notable exceptions are Lactobacillus species and Helicobacter pylori, which is a key bacterium linked to the formation of gastric ulcers (see part 2). Similarly, active proteases enzymes, such as trypsin, chymotrypsin and intestinal peptidases, limit the growth of bacteria in the small intestine, which is dominated by Lactobacillus and Streptococcacal species.

As can be seen in Fig 2, the colon plays host to the most diverse communities of bacteria, with the vast bulk of the estimated 2kg of gut microbial biomass found in this location. Increased microbial diversity in the colon reflects significantly reduced enzyme activity in this region, which is primarily dedicated to water and salt re-absorption (see part 5). The pH of the colon is also more favourable, being slightly acidic to neutral (typical pH5.5-7.0).

Effects on human physiology

Research into how the microbiota affects physiological processes is still in its infancy. One of the major problems in this field of study is the inability to culture many of the key bacterial species found within the gut. Culturing is essential to allow investigation of the biochemistry of gut microbes and identify the microbial metabolites that can modulate human physiology. Despite this problem, useful information on the role played by the gut microbiota in modulating human physiological processes has recently been established.

Role in digestion

The microbial communities of the large intestine are predominantly reliant on partially digested food arriving from the small intestine for nutrition and survival. The gut microbiota itself plays an active role in digestion of the carbohydrate, fat and protein components of food. Bacteria residing in the large intestine play a particularly important role in digestion of dietary fibre to yield short-chain fatty acids (SCFA) such as acetate, propionate, and butyrate. Propionate is thought to play an important role as a satiety molecule, with the ability to contribute to the switching off of hunger, while butyrate promotes programmed cell death (apoptosis) in malignant epithelial cells lining the large intestine, thereby reducing the risk of bowel cancer. The digestion and fermentation of dietary fibre by the gut microbiota yields large quantities of gasses such as odourless methane, carbon dioxide and hydrogen, together with smaller amounts of pungent odoriferous gasses such as hydrogen sulhide (Rowland et al, 2018).

Vitamin biosynthesis

Human cells and tissues are unable to synthesise directly many of the essential vitamins required for health and survival, and so these must be acquired through a combination of dietary intake and biosynthesis by the GI tract microbiota. A healthy, well-balanced microbial community rich in Bifidobacteria, Lactobacilli and E. coli is able to synthesise many of the water-soluble vitamins, including key B vitamins – such
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as folic acid (B9), riboflavin (B2), biotin (B7), cobalamin (B12), nicotinic acid (B3), pantothenic acid (B5), and thiamine (B1) – together with essential fat-soluble vitamins, such as the vitamin K group (Yoshii et al 2019; Leblanc et al, 2013).

**Xenobiotic metabolism and interactions**

Xenobiotics are chemicals found within the human body, but not actually produced by it. These chemicals include environmental pollutants, such as pesticides and food additives – including preservatives, artificial flavourings, sweeteners, and pharmaceutical agents in most of the major drug groups. Most xenobiotics are usually metabolised by the liver into predictable breakdown products, which are then excreted into the bile for elimination in the faeces, or into the blood for elimination by the kidneys.

Metabolism of xenobiotics by the gut microbiota is currently poorly understood, but as knowledge of the microbial communities of the gut tract develops, pharmacologists have to factor in differences in drug metabolism by the hugely variable communities of microbes present in different individuals. This new field of pharmacological research is known as pharmacomicrobiomics (Das et al, 2016).

A recent extensive study examining how 76 common bacterial species from the human gut microbiota metabolised 271 orally administered drugs, found 176 of these were metabolised by at least one of the bacteria investigated. It is hypothesised that metabolism of a drug by resident bacteria in the gut may result in metabolites that can produce adverse side-effects, while individuals who lack bacteria capable of metabolising the drug may experience no side-effects (Zimmermann, 2019).

**Gut-brain axis and brain-gut-microbiome axis**

In part 1 of this series, we briefly examined the role of the enteric nervous system in controlling movement of food through the gut by co-ordinating the process of peristalsis. This is achieved by a dense network of nerve fibres known as the myenteric plexus, which extends into the muscular layers of the gut wall. The gut-brain axis refers to the direct and indirect links and signalling between the enteric and central nervous systems. This cross talk is bi-directional, allowing gut physiology to be influenced by the brain, and brain activity, including cognition and mood, to be affected by the gut tissues (Carabotti et al, 2015).

With increasing knowledge of the gut microbiota, it soon became apparent that the resident microbial communities and their cocktails of secreted metabolites could influence the activity of both the enteric and central nervous systems. This complex interplay between the gut microbiota and the nervous system is referred to as the brain-gut-microbiome axis (Martin et al, 2018). Although this is currently poorly understood, mainly due to the diversity of chemical signals produced by the gut microbiota and complexity of the neural pathways involved, some important discoveries have recently been made.

Metabolites from the gut microbiota, particularly short-chain fatty acids, are able to stimulate the release of hormones from the neuroendocrine cells of the gut; these include peptide YY (PYY), which is a satiety hormone that reduces the urge to eat, and glucagon-like peptide-1 (GLP-1), which is a hormone that reduces the urge to eat, and glucagon-like peptide-1 (GLP-1), which in addition to promoting satiety enhances the secretion of insulin in response to increased blood glucose (Farzi et al, 2018). This suggests that imbalances (dysbiosis) in the gut microbiota could contribute to overeating and obesity and may be linked to poor glucose homeostasis and potentially diabetes.

**Immune modulation**

The bacteria that colonise the gut have a direct influence on the body’s ability to deal with disease and infection. It is well understood that breast-fed babies have an immunological advantage over their bottle-fed counterparts, due to the passing of secretory antibodies from mother to baby, which confer protection against pathogens in early infancy.

Until fairly recently breast milk was thought to be sterile and free from microorganisms, however, recent research has indicated that breast milk contains a variety of ‘friendly’ probiotic bacteria (bacteria that promote health) including Lactobacillus and Bifidobacterium species, which are known to enhance both gut and systemic health (Ojo-Okunola et al, 2018). The bacteria present within breast milk appear to supplement the friendly bacteria (mainly Lactobacillus species) that are initially acquired through natural vaginal delivery, resulting in a healthy initial gut microbiota. Breast milk also appears to prevent colonisation of the gut with pathogenic micro-organisms and breast-fed babies appear to have a gut microbiome that promotes an environment that is...
generally anti-inflammatory throughout the body, reducing the risk of inflammatory diseases such as asthma and atopic dermatitis (Toscano et al, 2017).

The oligosaccharides (short-chain) sugars present within breast milk are rich in fructans (short chains of fructose), which encourage the growth of probiotic bacteria, including both Lactobacillus and Bifidobacterium species. This ensures the initial probiotic populations of breast-fed babies are maintained in high numbers; conversely the powdered formula milk given to bottle-fed babies seems to encourage the growth of potentially pathogenic entroccocal and enterobacterial species (Lazar et al, 2018).

As babies are gradually weaned onto solid foods they are exposed to more diverse populations of bacteria and attain a mature gut microbiota. Gradually the immune system becomes tolerant to the resident gut bacteria, which are effectively regarded as extension of ‘self’ (Lazar et al, 2018).

Understanding of the “cross talk” between the gut microbiota and the immune system is currently minimal. However, a healthy population of probiotic bacterial species is generally associated with a fine-tuned immune system and a general anti-inflammatory environment. Conversely, reduced numbers of probiotic bacteria increase the risk of colonisation by potentially pathogenic species, which disturbs the fine tuning of immune responses and increases the risk of inflammatory disorders and other forms of immune dysfunction (Cianci et al, 2018).

Dysbiosis

The diversity of micro-organisms living as a community within individual’s GI tracts is referred to as their enterotype and this may vary significantly between different people. Dysbiosis can be defined as an imbalance in the numbers or diversity of the microbiota. With knowledge of the gut microbiota still in its infancy, diagnosing what constitutes a ‘self’ (Lazar et al, 2018). Unfortunately, a course of antibiotics disrupts the natural balance of the gut microbiota, potentially depleting populations of friendly bacteria and allowing potentially pathogenic bacteria such as C difficile to grow unchecked (Mullish, 2018).

Dysbiosis and infection

It is well established that certain groups of friendly bacteria can frequently out-compete other pathogenic micro-organisms, helping maintain gut and tissue health throughout the body. Bacteria, such as Lactobacillus species, produce acids (lactic acid) and other antimicrobial and anti-fungal molecules (such as hydrogen peroxide and chitinase), which make environmental conditions in the gut, mouth and reproductive tract inhospitable to other bacteria and yeasts, such as Candida albicans (Allonsius et al, 2019). A course of antibiotics disrupts the natural balance of the gut microbiota, potentially depleting populations of friendly bacteria and allowing potentially pathogenic bacteria such as C difficile to grow unchecked (Mullish, 2018).

Dysbiosis and Parkinson’s disease

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Parkinson’s disease is a progressive neurodegenerative disorder that affects movement, with the person developing resting tremor, rigidity, bradykinesia (slowness of movement) and postural instability, together with other non-motor symptoms. A pathological hallmark is the presence of Lewy bodies, which form when a protein called alpha synuclein is deposited in neurons (nerve cells). As Lewy bodies accumulate, they interfere with neural function and the ability to produce neurotransmitters, such as dopamine, which is depleted in people with Parkinson’s disease. Lewy bodies accumulate in their brains, but have also been discovered in other regions, including enteric nervous system (Kalra and Lang, 2015).

While it is generally believed Parkinson’s disease begins in the neural tissues of the brain, some researchers have suggested it originates in the gut, with changes to gut microbiota able to influence the structure and integrity of the gut tissues (Lionnet, 2018). The disease appears to be associated with changes in the composition of the gut microbiota: a study examining colonisation of the gut in patients with Parkinson’s disease found depletion of 15 species of bacteria, including: Bacteroides massilienisis, Bacteroides coprocola, Blautia glComea, Dorea longicatena, Bacteroides plebeius, Prevotella copri, Coprococcus eutactus and Rumino- coccus altilis. This same research also indicated enhanced colonisation by the bacteria Christensenella, Catabacter, Lacto- bacillus, Oscillospira, Bifidobacterium, Chris- tensenella minuta, Catabacter hongkongensis, Lactobacillus mucosaee, Ruminococcus bromii and Papillibacter cinnamomivorans. The researchers speculated that this demographic of gut bacterial species may predispose people to a pro-inflammatory environment, where Lewy body deposition can occur (Petrov et al, 2017).

Dysbiosis and autism spectrum disorder

Autism spectrum disorder is typically characterised by impaired social interactions and communication, and repetitive and restrictive behaviour patterns. Although its aetiology is poorly understood, genetic and environmental factors have been associated with an increased risk of developing the disorder, including nutritional imbalance, errors during pre-natal development and immune system dysfunction (Risch, 2014).

Large numbers of individuals with autism spectrum disorder have significant GI dysfunction, such as changes to bowel habit, frequency, diarrhoea or constipation, and chronic abdominal pain. Nutritional status and GI symptoms experienced appear to strongly correlate with the severity of the disorder (Adams et al, 2011; Horvath and Perman, 2002). A diet high in fat and sugar during pregnancy and the presence of gestational diabetes all seem to be associated with an increased risk of autism spectrum disorder, potentially by altering the composition of the gut microbiota (Fattorusso et al, 2019; Connolly, 2016). Breast feeding babies for four
months is associated with a lower risk compared with bottle feeding; this may reflect increased risk of dysbiosis, with babies fed with formula milk having a gut that favours the growth of pathogenic groups of bacteria (Azad, 2013). The gut microbiota of children with autism spectrum disorder frequently differs from their neurotypical siblings and healthy controls (De Angelis et al, 2015).

A recent study of 18 participants with autism spectrum disorder and chronic gastrointestinal problems reported that microbiota transfer (via faecal transplant from healthy donors) significantly increased bacterial diversity and relative abundance of key probiotic species, including Bifidobacteria and Prevotella, and improved symptoms associated with autism spectrum disorder (Kang, 2019). The author recommended that the study was followed up with a double-blind, placebo-controlled trial.

Use of probiotics

Since dysbiosis, involving loss of probiotic bacteria and microbial diversity within the gut microbiota, is now well known to be detrimental to health, a whole industry has emerged dedicated to producing probiotic bacteria in the hope of enhancing numbers of friendly bacteria within the gut. In their simplest form, probiotics can be given in the form of commercially available live yoghurts and drinks containing viable populations of probiotic bacteria such as Lactobacillus and Bifidobacterium species. Studies examining the effectiveness of such probiotics have been contradictory and many researchers have pointed to the fact that many of the ingested microorganisms will not survive the cocktail of acid, alkalis and enzymes in sufficient numbers to significantly affect the balance of micro-organisms in the gut microbiota.

Other approaches have been adopted including the use of ‘stool pills’, which involve ingesting small pellets of faecal material enclosed in an enteric coating from a donor with a predetermined healthy microbiota. In theory, these should allow micro-organisms to survive the damaging environments of stomach and small intestine before the enteric coating dissolves releasing the stool pellets into the large intestine, in the hope that the healthy donor bacteria will begin to colonise the more hospitable environment of the colon.

Direct faecal transplants have also been used where donor faecal material is implanted in the recipient, usually via endoscopic procedures. Although the effectiveness of these techniques still needs to be fully evaluated ‘stool pills’ and faecal transplants appear to be effective in reducing C difficile infection and colitis (Wischmeyer et al, 2016; Mayor 2017).

Conclusion

Despite the explosion of research into the gut microbiota over the last decade, knowledge of the role played by this diverse community of micro-organisms is still limited and further research is needed to more comprehensively understand its role in health and disease.

References