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SUMMARY

It is well established that gut bacteria help to maintain a healthy intestine by providing nutrients and guarding against pathogens. Recent evidence however suggests that their actions reach beyond the gut, as they appear to influence various aspects of host physiology, ranging from the regulation of food intake to behaviour and mood. Bacteria and their metabolites can interact with the host via routes involving the immune, nervous and endocrine system.

How our gut microbes influence our behaviour

The forgotten organ

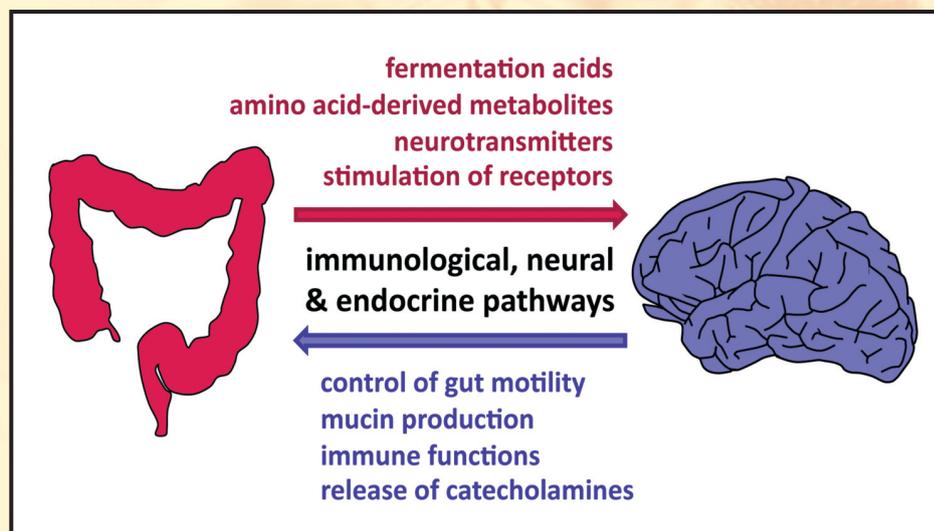
A brief reflection on your last bout of food poisoning will tell you that gut microbes (and their toxins) can have profound effects on neurological function, both conscious and autonomic. In the healthy state we can try to ignore events in the gut, of course, but does this mean that they have no influence upon our behaviour, mood, physiology, and brain function? Increasingly the answer is "no". Our intestines harbour very large numbers of resident bacteria, reaching densities of 10^{11} cells/g contents in the colon; indeed these bacterial cells typically outnumber human cells in the body by a factor of ten.

At the level of gene diversity the disparity is even greater, reflecting the phylogenetic diversity within the community, with the gut microbial 'metagenome' estimated to contain at least 100 times more distinct genes than the human genome. This corresponds to a vastly greater repertoire of metabolic capabilities, protein sequences and cell surface structures than is encoded by the host genome.

Changes in gut microbes can change behaviour

Gut bacteria help digest dietary fibre, and they form an effective barrier against pathogenic microbes. Their interactions with the immune system of the host are under intense research, and more recently their potential role in affecting wider human physiology and behaviour is being recognised. Psychiatric conditions are often associated with gut disorders and concomitant changes have been observed in the composition of the gut microbiota. Are these changes a cause or consequence of the disease? Some lines of evidence point towards a direct involvement of the microbes in disease development. For example, alterations in the microbiota triggered by antibiotics have been shown to lead to changes in behaviour allied to altered levels of brain-derived neurotropic factor in different brain regions in mice. Furthermore, behavioural traits could be transferred between different strains of mice by reciprocal

The gut-brain axis is a bidirectional communication system composed of neurological, hormonal and immunological pathways between the two organs. Examples of bacterial and host activities believed to be involved in the cross-talk are given.



transplantation of their respective microbial communities. There has also been much interest in the possible role of the gut microbiota in obesity, initially based on the hypothesis that the composition of the microbial community affects the recovery of energy from the diet via microbial fermentation. Recently, attention has turned rather more to the possible impact of microbial community composition upon other factors that can influence obesity,

“behavioural traits can apparently be transferred between strains of mice by transplanting their gut microbiota”

including host lipid metabolism, energy expenditure and satiety. Some intriguing experiments with small animals suggest that the microbiota of obese animals can transmit the tendency to adiposity to previously lean animals.

Rules of engagement

In the healthy state the microbial community is strictly separated from the rest of the body by the gut barrier; however, potential influences upon the host abound through a variety of mechanisms (Figure 1). Importantly, direct metabolic products of microbial activity have a major influence on the gut environment and many are known to be recognised by host receptors on the gut lining. These include the short chain fatty acids that are the principal products of anaerobic fermentation of dietary and host-derived substrates (including dietary fibre and mucin) in the large intestine. These short chain fatty acids are transported across the gut wall and provide additional energy to the host. Short chain fatty acids are known to interact with free fatty acid receptors and could potentially

influence the levels of satiety-related gut hormones. Microbial activity is also responsible for the formation of an exceedingly wide range of metabolites that result from fermentation of dietary components and host secretions, or from de-conjugation, transformation or degradation. Many of these compounds appear in the systemic circulation and many have potential or known bioactivity that can include neurophysiological effects. Accumulated D-lactate of bacterial origin for example can act as a neurotoxin at high concentration, as can occur in short bowel syndrome.

Fermentation products of amino acids derived from dietary or endogenous proteins are highly diverse, including amines and phenolic compounds (from aromatic amino acids), some of which (especially tryptophan metabolites) directly affect brain function. Meanwhile, diets rich in plant-derived foodstuffs deliver a wide variety of potentially bioactive aromatic compounds to the gut, many of which are released and modified upon entering the large intestine through the enzymatic activities of the resident colonic bacteria. The picture is further complicated by the fact that phenolic compounds directly absorbed by the gut are often handled as ‘xenobiotics’ and are conjugated by the liver e.g. to form glucuronides. When these conjugates are released into the gut (in the bile) this process is reversed by microbial de-conjugation, setting up an enterohepatic circulation. Importantly, this applies equally to many important neuroactive drugs, and should therefore be a very important consideration in estimating effective doses, and in individual responses to drug administration. Bacteria also produce neurotransmitters and may influence systemic cytokine levels through their interactions with the immune system. Conversely the host influences the gut microbiota via the immune system, and also via the nervous system by changing the physical conditions in the gut (for example by modulating gut motility). Thus many routes of communication

exist between gut microbes and their host; hopefully, future research aimed at unravelling these complex interactions will help to develop novel treatment strategies for a range of conditions.



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