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Bericht & Report: Microbiota and diseases of the nervous system


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Microbiota and diseases of the nervous system

Bacterial colonization of the intestine is critical for normal physiology, especially the immune and endocrine system. There is increasing evidence that the influence of the gut bacteria extends to modulation of the host’s nervous system. Gut-brain axis alterations and their role in the psychiatric treatment of anxiety and depression, as well as functional gastrointestinal disorders, provide great therapeutic potential.

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The intestinal microbiota colonizes the body plays a crucial role in nutrient digestion and synthesis, energy metabolism, vitamin synthesis, epithelial development as well as modulation of the host’s immune and endocrine system. Furthermore, it has been associated with the extraction of calories from diet, metabolism of carcinogenic and drugs, pain perception in the skin or fat deposition in the liver. There is growing evidence that their influence even extends to the CNS. Their overall composition and the signalling of certain species are involved in neural development and functioning as well as modulation of brain physiology, mood and behaviour. New insights in this microbiome-gut-brain communication might help to define new therapeutic strategies combating mood disorders. Regarding human behaviour and psychology it is essential to determine the relative contributions of genes and environment. The human microbiome might be involved in shaping neurodevelopmental and behavioural phenotypes as it affects a variety of complex processes such as cognition, personality, mood, sleep, and eating behaviour and has also been associated with a variety of psychiatric disorders.

MICROBIOTA & CNS

Gastrointestinal and psychiatric illnesses are closely interrelated. For example, IBS is often accompanied by emotional state disorders. The gut microbiota is thought to contribute to the pathogenesis of many of these diseases. Comparison of germ-free mice with conventionally raised mice revealed gut microbiota involvement in behavioural changes and anxiety and stress responses. It was shown that oral administration of the antibiotics neomycin and bacitracin along with the antifungal agent primarin, can induce transient changes in gut microbiota composition as well as behavioural changes. Instead, antibiotic treatment did not influence the behaviour of GF animals.

The gut-brain axis (GBA) contributes to the homeostasis of several systems, including GI function, appetite, and weight control. Perturbations of behaviour, such as stress, can change gut microbiota composition. These changes are associated with increased vulnerability to inflammatory stimuli in the gut tract and induction of CNS modulations. There is growing acceptance that the gut-brain axis operates in two directions using neural, immunological and hormonal routes. While it is well known that the brain regulates gut activity recent studies show that gut microbes can also modulate brain function. In hepatic encephalopathy intestinal bacteria are able to change the HPA axis as well as other molecules in the CNS that are associated with depression.

MICROBIOTA & HPA AXIS

Activation of immune and inflammatory pathways in the gut may contribute to IBD, allergy, obesity and metabolic diseases as well as aging. Depression is associated with the presence of inflammatory biomarkers and similar patterns were seen in depression and other psychiatric disorders. Studies have shown that the human appendix is associated with mental disorders. Studies have shown that intestinal commensals may be involved peripherally in the enteric nervous system, and centrally in the brain. More knowledge is needed to determine the role of microorganisms in the development and function of the CNS. The development of new therapeutic methods concerning gastrointestinal and psychiatric illnesses might be a promising aim. Research should focus on selectively improving the bidirectional interactions between human-associated microbiota and GI physiology. The microbiota-GBA relationship could increase our understanding of chronic inflammatory diseases of the GI tract as well as behavioural illnesses such as depression.

MICROBIOTA & HPA AXIS

Gut microbiota can interfere with the hypothalamic-pituitary-adrenal (HPA) axis. According to the hypothalamic-pituitary-adrenal axis hypothesis depressed patients show elevated plasma cortisol levels as well as elevated corticotrophin releasing hormone (CRH) levels in the cerebrospinal fluid. Severely depressed patients are unable to exhibit normal cortisol-suppression. Antidepressant therapy was able to partly reverse these abnormalities. Stress, which is also linked to disruptions of the HPA axis, is considered a causal factor in mood disorders and has been shown to alter gut microbiota composition. Indeed, stress can promote the growth of pathogenic bacteria through endocrine host signalling. In order to clarify the microbiota interaction with the HPA axis studies with GF mice were conducted. A hyper response of the HPA axis to stress was observed in GF mice, whereas colonization with a single organism, the probiotic Bifidobacterium infantis, reversed this reaction. A shift in HPA set point was even persistent into adulthood, but only when colonization occurred before 6 weeks of age. The findings indicate that the host’s gut bacteria are able to change the HPA axis as well as other molecules in the CNS that are associated with depression.

Furthermore, the early colonization of germ-free mice can normalize several germ-free behavioural patterns, but fails between carbohydrate malabsorption and depressive-like behaviour.

In IBD, pathogenesis involves a reduction of Lactobacillus spp and Bacteroides as well as an increase in the Firmicutes/Bacteroidetes ratio. An altered microbiota composition causes activation of cytokines in the CNS and hence gut related inflammation. There is also evidence that an abnormal gut microbiota composition is involved in autism spectrum disorders (ASD) as short chain fatty acids in these patients were found to be neuroactive. It is believed that there are specific mediators contributing to the communication between gut microbiota, gut immune system and the CNS.

Some of the observed effects have also been induced by heat or radiation killed bacteria, which implicates that specific components of the bacteria may be responsible for some of the effects observed. Bacterial cell wall structures have been pro-

posed in this context as stressors that altered cell wall constituents showed deviating effects than those obtained with the original bacteria. Also administration of isolated cell wall complex carbohydrates from commensal bacteria was able to reproduce specific effects. It can be concluded that cell wall structure signalling, for example via Toll like receptors, is one important determinant of the immune and neuronal effects.

CONCLUSION

The role of the human-associated microbiota goes far beyond the GI tract. Interactions can lead to changes in behavioural and psychiatric disorders. Studies have shown that intestinal commensals may be involved in the development and function of the CNS. The development of new therapeutic methods concerning gastrointestinal and psychiatric illnesses might be a promising aim. Research should focus on selectively improving the bidirectional interactions between human-associated microbiota and GI physiology. The microbiota-GBA relationship could increase our understanding of chronic inflammatory diseases of the GI tract as well as behavioural illnesses such as depression.
on adult mice\textsuperscript{5}. The observed behavioural changes have been associated with altered brain-derived neurotropic factor (BDNF) levels in the brain. BDNF is involved in regulation of multiple aspects of cognitive and emotional behaviours as well as neural development. It was found to be decreased in plasma of depressed patients and in the post-mortem hippocampal tissue of depressed suicide patients. In a study conducted by Neufeld et al. the GF mice demonstrated decreased anxiety-like behaviour but baseline plasma corticosterone has been found to be elevated. In addition there has been an upregulation BDNF expression in these mice. The link between anxiety and BDNF is still not clear with conflicting results existing but it seems that neurochemical and behavioural consequences are sex-dependent\textsuperscript{14}.

**INVOLVED SIGNALLING PATHWAYS**

The exact mechanisms by which GI microbiota induce changes in nervous system activity and alter mood and behaviour remain unclear. However, two possible and promising pathways are discussed below.

**NEUROTRANSMITTERS**

The first one is signalling through neurotransmitters, which are serotonin, melatonin, γ-aminobutyric acid (GABA), catecholamines, histamines and acetylcholine. For example, many bacteria are able to synthesize GABA. It might serve as a protection against the acid environment encountered in the stomach as its production requires proton exchange. In GF mice reintroduction of bacterial strains results in a rapid increase in serotonin and other neuroactive metabolites. Furthermore, certain organisms, including Lactobacilli, can convert nitrate to NO, which is involved in immune and nervous systems regulation. In addition, hydrogen sulphide (H2S), which is produced by specific intestinal bacteria, is associated with gut motility modulations. Lactobacilli have also been shown to intervene with the enzymatic system involved in tryptophan metabolism. As many of the enzymes involved in neurotransmitter synthesis and metabolism have prokaryotic origin, it was proposed that late horizontal gene transfer from bacteria may be involved. It is hypothesized that bacteria are producing small molecules thought for bacteria-bacteria communication but are now involved in bacteria-host interactions. In the case of GABA, bacteria are able to sense and take up GABA and this substance and its receptor are also found on host gut epithelia. The gut epithelial cells as well as the enteric nervous system are thought to mediate signals to the nervous system and hence modulate central and peripheral neural functioning.

**SHORT CHAIN FATTY ACIDS**

The second pathway involves short chain fatty acids (SCFAs), which are the end-product of anaerobic bacterial fermentation in the GI tract. Their production is dependent on commensal bacteria and there are almost no SCFAs found in GF mice. Recent research implicates that epigenetic modifications are involved in the etiology of mood disorders. Butyrate, which is produced by obligate anaerobic bacteria, is a potential candidate to histone deacetylase inhibitors, an emerging class of epigenetic drugs. Systemic injection of butyrate lead to histone hyperacetylation in some brain regions and showed antidepressant effects in mice. Furthermore, butyrate has significant effects on the enteric nervous system and could modulate brain physiology through indirect control of BDNF transcripts. Other SCFA have similar important implications. Propionic acid infusions have been associated with irreversible behaviour changes associated with autism. However, results are still controversial and the consequences of alterations in fermentation metabolites, such as SCFAs, on neural development and behaviour need to be further investigated. Nevertheless, it was shown that omega-3 fatty acids were able to alter gut microbiota composition. Some clinical studies indicate a beneficial effect of omega-3 fatty acids in various psychiatric disorders. Positive effects have been found for major depressive and bipolar disorders, but the results for treatment of depression are not clear or even controversial\textsuperscript{6}.

**REFERENCES**


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