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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, but also functional gastrointestinal disorders, provide great therapeutic potential.

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The intestinal microbiota colonization 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 carcinogens and the CNS, and immune related aspects to be considered. Although the gut microbiome-gut-brain 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 early colonization of 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 Bacteroidetes 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 proposed in this context as studies with 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 functions. 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.

MICROBIOTA, INFLAMMATION AND EPIGENETICS

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 anxiety states. There exists a complex network of inflammatory mediators and signalling pathways including bacterial cell wall components (e.g. LPS), inflammatory molecules (e.g. IL-6, TNF-α), Toll like receptors (TLR), NFKB and MAP kinases. For example, an increased proinflammatory cytokine expression is activated through TLRs and NFκB pathways. Cytokine production and other inflammatory processes can modulate the peripheral and central nervous system and are associated with mood and behaviour.

However, the link between gut microbiota, inflammation and epigenetic phenomena is still far from being understood. Although the immune system clearly plays a crucial role in the communication between gut bacteria and the CNS, there are also many non-immune related aspects to be considered.

MICROBIOTA & HPA AXIS

Gut microbiota can interfere with the hypothalamic-pituitary-adrenal (HPA) axis. According to the hypothalamic-pituitary-adrenal (HPA) 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 early colonization of gut bacteria are able to change the HPA axis as well as other molecules in the CNS that are associated with depression.
on adult mice. 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 corticos- terone 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 behav-ioural consequences are sex-dependent.

**INVOLVED SIGNALLING PATHWAYS**

The exact mechanisms by which GI micro-biota induce changes in nervous system activity and altered mood and behaviour re-main unclear. However, two possible and promising pathways are discussed below.

**NEUROTRANSMITTERS**

The first one is signalling through neu-rotransmitters, which are serotonin, melatonin, γ-aminobutyric acid (GABA), catecholamines, histamines and acetyl-choline. 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 in-volved in immune and nervous systems regulation. In addition, hydrogen sulphide (H2S), which is produced by specific in-testinal bacteria, is associated with gut motility modulations. Lactobacilli have also been shown to interfere with the enzymatic system involved in tryptophan metabolism. As many of the enzymes in-volved in neurotransmitter synthesis and metabolism have prokaryotic origin, it was proposed that late horizontal gene trans-fer from bacteria may be involved. It is hypothesized that bacteria are producing small molecules thought for bacteria-bac-teria 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 ep-i-thelia. 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 de-pendent on commensal bacteria and there are almost no SCFA found in GF mice. Recent research implicates that epigenetic modifications are involved in the eti-ology of mood disorders. Butyrate, which is produced by obligate anaerobic bac-teria, is a potential candidate to histone deacetylase inhibitors, an emerging class of epigenetic drugs. Systemic injection of butyrate lead to histone hyperacytlation in some brain regions and showed anti-depressant effects in mice. Furthermore, butyrate has significant effects on the en-teric 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 con-traversial and the consequences of altera-tions in fermentation metabolites, such as SCFAs, on neural development and be-haviour need to be further investigated. Nevertheless, it was shown that omega-3 fatty acids were able to alter gut micro-biota 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.

**REFERENCES**


**Disease** | **Reference**
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