HUMAN MICROBIOTA UNDER STRESS

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Physical and psychological stress affects not only the immune system, but also hormonal and digestive homeostasis. Immune and neuroendocrine systems provide integrated responses to environmental signals, and the relationship between stress and immune function in many contexts, including a proliferative response to mitogens and cellular activity, has been demonstrated. Stress can lead to an imbalance between pro-and anti-inflammatory cytokines or uncontrolled production of cytokines. Dysregulation of congenital and adaptive intestinal immune responses directed against bacterial flora, including the destruction of oral tolerance to environmental antigens and commensals, are involved in several pathogenetic mechanisms. The integrity of intestinal microbiota can be influenced by some external factors, including the use of antibiotics, radiation, changes in the GIT, changes in the diet, psychological and physical stress. Psychological stress can directly affect the composition of the microflora, in particular with a noticeable decrease in lactic acid bacteria. GIT changes caused by stress factors make the conditions of the intestinal medium less favorable for survival, adhesion and replication of lactic acid bacteria [2].

Classical transmission of CNS-intestine-microbial signals works through central regulation of satiety. Changes in the nature of the diet as a result of CNS control of food intake can affect the availability of nutrients for the intestinal microbiota and its composition. Signal saturation proteins are key molecular mediators that provide this control. CNS can affect intestinal microbiome through the nerve and endocrine pathways both in direct and indirect ways. The autonomic nervous system and the hypothalamus-pituitary-adrenal axis that maintain the connection between CNS and internal organs can modulate intestinal physiology, for example, motility, secretion and permeability of the epithelium, as well as systemic hormones, which in turn affect the environment in the biotopes of microbiota residence and the host-microbial interaction on the mucosa. Stress causes defects in the epithelial barrier and subsequent activation of cells on the mucosa has been experimentally shown.

Long psychological stress also leads to a significant reduction in the production of mucin and the reduction of the presence of acid mucopolysaccharides on the surface of the gut mucosa, which facilitates the colonization of the intestine by pathogenic microorganisms. The balanced intestinal microflora is important not only for the maintenance of intestinal homeostasis, but also for regulating the functionality of the immune system with a direct effect on the intestinal system - the brain.

The contribution of beneficial gut bacteria to human health is now scientifically well established. The predominant well-studied probiotic bacteria are Firmicutes such as *Lactobacillus* species, Actinobacteria such as *Bifidobacterium* species and Bacteroidetes such as *Bacteroides* species. Several others, including Proteobacteria such as certain *Escherichia coli* strains, have also been shown to exhibit probiotic qualities. In fact, all of these microbes have beneficial consequences to the host organism. In only a few cases have the probiotic bacterial mechanisms of action been elucidated.

Since these bacteria influence so many aspects of human physiology, it should not be considered surprising that recent studies have revealed that they also have pronounced effects on brain function. Indeed, these bacteria produce tryptophan, a precursor of serotonin (5-hydroxytryptamine), tyrosine, a precursor of L-3,4-dihydroxyphenylalanine (DOPA) and dopamine, and other amino acids such as γ-amino butyric acid (GABA) and glycine, both of which serve as neurotransmitters in animals. In fact, the microbiota strongly influences brain activity and consequently behavior. It exerts effects on our moods, cognition and sensitivities to pain.

During fetal and early childhood development, probiotic organisms such as bifidobacteria and lactobacilli maintain a healthy balance between pro- and anti-inflammatory responses during their primary colonization stages. They play essential roles in the neuroimmune and neuroendocrine development of the host. Microbially derived peptides and neuroactive mediators of neurotransmission (e.g. GABA, catecholamines and acetylcholine) induce synthesis and release of molecules by gut epithelial cells that modulate neural signaling. Different classes of nerve and immune cells express quantitatively different receptors for neurotransmitters, and consequently they respond differently to these compounds.

Neurotrophic factors produced by the gut microbiota trigger an immunogenic reaction in the infant, producing a mixture of local and systemic responses. Norepinephrine, for example, produces sympathetic proinflammatory effects at low-to-moderate systemic levels, which in the presence of bacterial lipopolysaccharide, stimulate leukocytes to produce adrenocorticotropic hormone (corticotropin), a local peptide stress hormone. On the other hand, acetylcholine, produced by many probiotic bacteria, decreases proinflammatory cytokine release. Bifidobacteria and lactobacilli lack bacterial lipopolysaccharide and adrenergic factors, thus decreasing the proinflammatory response during colonization. Changes in neuroplasticity can also occur depending on glial cell responses to GABA and serotonergic neurotransmitters.

The gut microbiota has been shown to raise the levels of serotonin and serotonergic precursors in newborn mice during gut colonization. Aside from their psychological effects, these compounds depress indoleamine-pyrrole 2,3-dioxygenase, a proinflammatory enzyme, moderating hypothalamic-pituitaryadrenal production of cortisone and cortisone-related factors. The balance of pro-/anti-inflammatory pathways and the serotonergic regulatory mechanism operate synergistically, affecting appetite, sleep and mood, and modulating cortisol and cortisolderivative release. Thus, the gut microbiota is likely to play a fundamental role in the interplay of neural, immune and hypothalamic-pituitaryadrenal development in young people [3].

It is not surprising that disruption of the human infant microbiota may lead to severe consequences. For example, extensive use of antibiotics has been shown to disrupt the microbial community in healthy infants, leading to microbial imbalance or dysbiosis. Alterations of the gut microbiota, especially in the formative years, have been implicated in altered brain development and plasticity. This can lead to changes in motor function and social behavior. Moreover, breast-fed infants have a completely different microbial population than formula-fed babies with consequent health benefits that can last a lifetime.

The concept of parallel evolution, with complex microbial-neural interactions and interdependencies, opens up new therapeutic preventative approaches in early life to combat childhood and adult mental illnesses. Naturalistic medicine seeks to develop nutritional strategies to foster strong probiotic environments in patients, while the biotechnology industry investigates potential prebiotic drugs for practical applications. A detailed understanding of the evolutionary and physiological importance of the host-microbial system as a coevolved ecosystem with interdependencies typical of complex, long-standing, multiorganismal systems must be emphasized. In this regard, it should be recalled that the adult human body contains roughly 10 times the number of bacterial cells as human cells. The ecological, metabolic, physiological and psychological interrelationships are only now becoming fully recognized. This fertile field of study is ripe for further investigation.

Thus using of probiotics can be useful for improving bowel homeostasis and preventing the development of dysbiosis associated with physical and psychological stress states.

Conclusions. Microbiome controls the canonical aspects of CNS, immunity and behavior in norm and in pathology. Nevertheless, the details of the role of microbiome in CNS disorders are unknown. The microbiome study has a perspective for prognosis and therapy associated with CNS disorder. Probiotics and functional foods can affect the action of the intestinal microbe on the central nervous system and the brain function. Along with the diet, they can restore intestinal homeostasis to improve cognitive or emotional function, and can be used to prevent, treat neurological disorders and to maintain the function of the immune system in stressful subjects.

Literature

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