Pearson Edexcel International Advanced Level

Monday 5 June 2023

Morning (Time: 1 hour 45 minutes)

Paper reference **WBI15/01**

Biology

International Advanced Level
UNIT 5: Respiration, Internal Environment, Coordination and Gene Technology

Scientific article for use with Question 8

Do not return this Insert with the question paper.

Turn over

P71938A

©2023 Pearson Education Ltd.

N:1/1/1/1/1/

P 7 1 9 3 8 A

Pearson

Scientific article for use with Question 8

Microbiota-gut-brain axis and the central nervous system

Gut microorganisms

1. The human gut contains various microorganisms, such as bacteria, fungi, parasites, and viruses, and more than 100 million bacteria reside in human gastrointestinal tract, which is 10-100 times the number of eukaryotic cells in our body. After years of common development with the human body, the gut bacteria have reached a mutually beneficial symbiotic state with the human body.

2. Gut microorganisms play an important role in promoting adult development and homeostasis; for example, they can affect human metabolic functions by decomposing the complex polysaccharides in food. In addition, gut microorganisms can regulate gut movement, the gut barrier system and fat distribution. Gut microorganisms can affect immune function through the development of gut-associated lymphoid tissue and by preventing the colonization of pathogens, and they can affect the energy metabolism and mitochondrial function of the host. The intricate relationship governing host and microorganism interactions suggest that when this relationship is abnormal, the microorganisms may cause the pathogenesis of disease or promote the progression of disease. Therefore, recent research has focused on determining the diversity of these microorganisms to clarify the physiological roles they play and eventually to prevent and treat diseases by controlling the microorganism species.

3. There are three main methods for detecting gut microorganisms: the bacteria culture technique, the traditional molecular biology technique that is independent of culture, and high-throughput sequencing technology. The former is mainly used for stool culture, this method is time-consuming, and the bacterial species obtained are limited. The latter two mainly isolate the bacterial DNA from the stool for the detection, the detection is fast, and the bacterial species are complete.

Microbiota gut-brain axis

4. The central nervous system (CNS) is closely related to the gastrointestinal tract, and the CNS plays an important role in regulating gut function and homeostasis. In turn, the gut flora may affect the CNS and nerve cells, participate in the regulation of nervous system function, affect the pathogenesis and progression of nervous system-related diseases. Due to the complex relationship between the gut microorganism population and the host, the authors proposed a new concept: the microbiota gut-brain axis. The microbiota gut-brain axis is the focus of recent research on the gut microecology. In addition to studies of the relationship between the gut microecology and neurological function, recent studies have emphasized how this relationship affects human health.

5. The brain and gut can be connected through a variety of pathways, including the enteric nervous system (ENS), vagus nerve, the immune system, or the metabolic processes of gut microorganisms.

6. The vagus nerve of the body can control the function of multiple organs, such as heart rate and gut motility; the vagus nerve can also transmit peripheral immune signals to the CNS. The vagus signal from the gut can trigger an anti-inflammatory response against the sepsis induced by microorganisms. Gut microorganisms can affect brain functions through the vagus nerve; after a vagotomy, the microorganisms will not be able to regulate behaviors.

7. Because gut microorganisms can directly affect the immune system, immune activation may be the pathway for transmitting microbial actions to the CNS. Microorganisms can also enhance the anti-tumor immune effect of drugs by promoting T cell accumulation and transformation, and microorganisms are very important for the immune function of organisms. The immune system plays an important role in maintaining health by maintaining gut homeostasis.

8. Microorganisms can also cause neurophysiological changes in the host by producing chemical substances that bind to the receptors inside and outside of the gut.

9. In addition, studies have shown that the microbiota may affect the CNS by altering adult hippocampal neurogenesis (AHN). The adult hippocampus and lateral ventricle have the function of generating new neurons. AHN has a role in learning and memory and can have affect on the pathogenesis of many neurological disorder-related diseases and symptoms, such as epilepsy, depression, Alzheimer’s disease (AD), and Parkinson’s disease (PD).

Microorganisms and brain function

10. The impact of microorganisms on behavior and cognition has been increasingly recognized. Microbial signals can regulate important functions of healthy human bodies, and growing evidence has demonstrated that many diseases are due to disturbances of gut microorganisms. Early studies in animals showed that the introduction of single, unique flora could lead to the development of anxiety-like behavior, and this change was accompanied by the activation of neurons in the brain that relied on the gut information transmitted to the brain via the vagus nerve.

11. The change in gut microorganisms found in sterile animals or with the use of probiotics, antibiotics, and colonization with fecal microorganisms can influence the cognitive function of the host. For example, supplementation with probiotics for a week prior to infection can not only prevent the microorganism disturbance caused by the infection but also prevent the changes in cognitive behavior caused by stress. Liang et al. found that probiotics could significantly improve the cognitive dysfunction induced by chronic restraint stress. In a human experiment, fMRI tests found that the activities in the brain regions that control brain memory and the processing of sensation were altered after female volunteers consumed fermented milk that contained probiotics. The above various studies found that the stability of the equilibrium state of normal microorganisms in the gut was closely related to brain development and function.

Microbiota-gut-brain axis and neuropsychological disorders

12. Schizophrenia is a neuropsychological disorder, and whole-genome analysis suggests that immunity-related genes may be changed in schizophrenia patients. Microorganisms and intestinal mucosal cells can regulate the changes in chemical factors, such as the proinflammatory interleukin-8 (IL-8) and IL-1 or the anti-inflammatory IL-10 and transforming growth factor β (TGFβ). The serum levels of proinflammatory cytokines in schizophrenia patients are higher than those of normal controls, and the levels of serum inflammatory markers are positively correlated with the clinical symptoms of schizophrenia patients.

13. Gut bacteria can also produce harmful substances that damage the intestinal epithelial barrier, causing neurotoxic bacterial products and proteins to enter the circulatory system. Severance et al. found that the concentration of antibodies against Saccharomyces cerevisiae was higher in the body of schizophrenia patients, and this genus was a marker of gut inflammation. An increase in the levels of circulating pathogen antigen can cause the host to respond to its own tissues and cells through a form of molecular induction, and this response is the central process of autoimmune diseases. Compared with the normal population, schizophrenia patients have a higher probability of developing autoimmune disorders, and specific brain regions of schizophrenia patients, such as the hippocampus, amygdala, and frontal cortex, have higher levels of autoimmune antibodies.

Microbiota-gut-brain axis and neurodegenerative diseases

14. Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the nervous system, and its etiology is still unclear. MS is associated with a significant increase in the number of cells that have immune response to the patients' own nervous system because gut microorganisms play an important role in the development of the autoimmune system and are associated with a variety of autoimmune and metabolic diseases. Therefore, it is speculated that gut symbiotic microorganisms play an important role in the susceptibility to MS.

15. Proinflammatory factors associated with chronic bowel diseases can induce intracranial inflammation, lead to the death of dopaminergic neurons, and eventually cause the development of PD. The inflammatory changes observed in PD patients and PD animal models are associated with increased gut permeability. LPS is a gut-derived proinflammatory bacterial endotoxin that can cause changes in the substantia nigra, and it can act as a PD-promoting substance. Similarly, Keshavarzian A et al. used high-throughput sequencing technology to examine the stool samples from 38 PD patients and 34 healthy individuals, and they found that the LPS synthesis gene was significantly higher in PD patients than in normal controls.

16. AD is a degenerative disease of the CNS, its onset is recessive, and its disease course is chronically progressive. The pathological markers of AD include extracellular β-amyloid (Aβ) senile plaques and intracellular neurofibrillary tangles. The number and maturation of microglial cells in sterile mice are abnormal, resulting in damage to the immune system and ultimately leading to the development of neurological diseases, such as AD. Cognitive behavior impairment is a characteristic of AD patients, and the influence of gut microorganisms on cognitive behavioral capability has demonstrated the role of gut microorganisms in the pathogenesis of AD.

17. The integrity of the BBB is important for brain function and development. The inflammation caused by the changes in gut microorganisms will lead to changes in BBB integrity, which in turn affects brain function. Under normal conditions, LPS cannot enter the bloodstream due to the tight junction between intestinal epithelial cells. However, when the tight junction of cells is disrupted and the permeability is increased, LPS can enter the bloodstream and induce inflammatory response. Studies found that the plasma LPS concentration in AD patients is three times that of normal patients. Furthermore, intraperitoneal injection of LPS into mice can cause an Aβ-protein increase in hippocampus, cognitive defects, and memory impairment. The increase of the inflow and the decrease in the outflow of the Aβ protein in AD patients cause the aggregation of the Aβ protein in AD patients, and this finding suggests a decrease in the capacity to clear the Aβ protein and an increase in BBB permeability in AD patients. The increased concentration of plasma LPS in AD patients implies an impairment of the gut barrier function and increased gut inflammation and permeability, which further suggests that gut microbiota may participate in the pathophysiological process of AD.

18. Gut microorganisms can also affect brain functions through the synthesis of various substances. Serotonin is very important for cognitive function, 95% of serotonin is synthesized in the gut, and gut microorganisms play an important role in serotonin synthesis. The gut serotonin level in sterile mice was 60% lower than the normal value. The use of serotonin reuptake inhibitors can reduce Aβ-protein levels in the brain, indicating that serotonin can reduce the formation of Aβ plaques, thereby reducing the risk of AD. In sterile mice, BDNF was significantly reduced, and this change was accompanied by cognitive function changes. Similarly, in AD patients, the BDNF levels in the brain and in the serum were significantly reduced. The Aβ production and clearance in the CNS is a dynamic change, and some bacteria and fungi can secrete amyloid, resulting in an increase of amyloid levels in the CNS that disrupts the dynamic balance of the Aβ protein, which leads to Aβ-protein aggregation in the brain and a high AD risk. Therefore, an imbalance in gut microbiota may promote the development of AD by affecting intestinal function and the synthesis and secretion of substances.

Summary

19. The interactive relationship between the brain and the gut includes neurology, metabolism, hormones, immunity, and other aspects, and changes in any component may lead to a functional change in the two interactive systems. The normal ecological balance of gut microorganisms plays an important role in the maintenance of this relationship. Microorganisms affect the development and function of the CNS through the microbiota-gut-brain axis. The mechanisms of many CNS diseases are still unclear, and the discovery of this complex relationship, the microbiota gut-brain axis, has provided a new research direction for the study of CNS diseases that do not have a clear pathogenic mechanism.

Adapted from: 'Microbiota-gut-brain axis and the central nervous system' by Xiqun Zhu, Yong Han, Jing Du, Renzhong Liu, Ketao Jin and Wei Yi in *Oncotarget* (2017).