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Author
Gomez-Pinilla, Fernando

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Editorial to special issue of BBADIS: Brain-gut interaction and cognitive control

1. Introduction

The interaction between brain and body has captured the curiosity of philosophers and scientists for hundreds of years. The topic has received fresh attention based on new scientific evidence pointing to the possibility that numerous neurological disorders involve the interaction between brain and body. We are starting to understand that the pathogenesis of Alzheimer's disease, Huntington disease, autism, multiple sclerosis, Parkinson's disease, Traumatic brain injury occurs in conjunction with the periphery. The lack of information of the role played by systemic physiology in neurological disorders has limited the understanding of the dimensionality of the pathogenesis and the efficacy of treatments. In the current supplement, we provide an integrative view about the interaction between the mind and gut, and the role of the periphery acting as a gate in the control of important stages of homeostasis and disease.

Most of the efforts to understand the pathology of neurological disorders have been centered on the brain, and a wide range of peripheral symptoms are often overlooked in clinical practice. The brain communicates with the periphery using the autonomic nervous system, and associated endocrine and immune pathways. The enteric nervous system (ENS; also known as the "little brain of the gut") located in the mucosa of the gut organizes the activity of millions of nerve cells, and controls many functions of the GI system including motility of the smooth muscle, release of hormones and other molecules [1]. In turn, the gut is the largest microbial, endocrine, and immune organ in humans and mice. The bacterial composition of the gut has emerged as a crucial regulator of whole-body homeostasis by acting on metabolism and contributing to host immune function [2,3], with subsequent effects on brain function and disease [4–7]. The gastrointestinal (GI) system is an important site of communication among the effects of diet, microbiota, immune system, and CNS function regulation. Given the strong interaction between the gut and brain, behaviors that engage the gut-brain communication such as feeding and exercise are operational to influence a whole range of neurological and metabolic disorders. Therefore, diet and exercise are central topics in this current issue of BBADIS dealing with the interaction between brain and periphery during homeostatic and disease conditions.

2. Exercise and diet as a mean to understand the influence of gut on the CNS

The potential of diet and exercise to influence brain and body physiology is a critical element to illustrate the bidirectional interaction between periphery and the CNS. Exercise can act at several levels along the course of interactions between the body and brain involving several organs and systems such as the neuromuscular system, and the capacity of exercise to promote neural activity is a viable means to stimulate brain centers. Accordingly, we attempt to provide an integrative view about the capacity of exercise and periphery to influence the brain and neurological disorders. In particular, the reviews by Quan et al., and Jimenez-Maldonado provide a thorough analysis about the mechanisms by which the action of exercise on the neuromuscular system can impact the brain. In turn, Bettio el al. discusses the effects of exercise on the brain in conjunction with the hormonal system.

The autonomic nervous system innervates every organ in the body, and provides a tight bidirectional control of brain-gut interaction. In particular, the brain liver communication is of supreme importance for control of brain and body health. The reviews by Palafox, and Royes discuss how TBI can influence brain and body physiology by affecting one of the main functions of the liver, namely synthesis of lipids. It is becoming alarming that disruptions in the function of the liver in detoxification, synthesis of lipids and proteins can have devastating consequences for overall performance of the whole organism. Liver dysfunction can also aggravate metabolic disorders such as type-2 diabetes [8] that reduce the health of TBI patients [9–11]. The

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hypothalamus is the master regulator of body homeostasis and acts as a gate keeper in the interaction between brain and periphery. All foods are metabolized in the periphery involving the gastrointestinal tract (GI tract) and the liver, and commensal bacteria in the gut seem to influence brain body communication; therefore, it is critical to gain an integrative view how microbiota can influence peripheral organs and the brain. Accordingly, the review by Morrison discusses the effects of high caloric diets such as high fat and sugars on peripheral organs and microbiota, and subsequent effects on brain cognitive centers.

3. How the action of exercise in skeletal muscle influence body physiology

Physical activity is one of the modalities in which the interaction between brain and body is fully operational, and has subsequent effects on brain and body health. Studies in animals and humans emphasize the potential of physical exercise to mitigate cognitive decline associated with aging as well as reducing pathological features of various neurological conditions. Exercise seems to influence the brain through a large variety of mechanisms that engage peripheral organs and tissues. Quan et al. discusses the physiological action of exercise on energy expenditure where exercise can elevate the resting metabolic rate of body, and also exercise can influence the metabolic state of the brain. Increased activity of electron transport chain metabolism is associated with increased production of reactive oxygen species (ROS). Given the bioenergetic properties of exercise, exercise bouts induce an intermittent increase in ROS with a subsequent enhancement in housekeeping systems that influence physiological functions. For example, various types of ROS generated by mitochondrial respiration can impinge on specific physiological processes. The strong association between exercise and muscle activity has consequences on brain and body health, such that exercise mechanics including duration and intensity have crucial health implications. Therefore, brain areas such as the hypothalamus and brain stem that are central for brain-gut communication are modulated by the intensity and duration of exercise. Accordingly, Jimenez and Quan in separate articles discuss how changes in exercise protocols can affect cell metabolism and alter the communication between the gut and the brain. In addition, the review by Quan et al. discusses how TBI influences systemic physiology and the influence of exercise to modulate the action of TBI on liver function.

4. Exercise and the brain: hormones, and immune system

The hippocampus plays a central role in the processing of learning and memory and affective behaviors, engaging morphological alterations in neurogenesis, dendrites, and spines, together with functional changes in strengthening (i.e., long-term potentiation) or weakening [12] properties of synapses. The beneficial effects of physical exercise on hippocampal function and plasticity also involves several hormones. Bettio et al. review the potential relationship between physical exercise and hormones associated with sex and metabolism, and how these events may mediate the action of physical activity throughout lifespan. The vast majority of studies support a beneficial role of exercise in maintaining hippocampal hormonal homeostasis that seems operational for regulation of hippocampal plasticity, cognition, and mood. Hormonal levels fluctuate dramatically throughout the lifespan of an individual, with subsequent consequences for hippocampal function and plasticity.

In turn, inflammation is a common biological adaptation to tissue damage that engages the coordinated interplay of pathogenic elements of the immune system, and exercise appears to control immune cells, inflammatory response, and overall homeostasis. A sedentary lifestyle or strenuous exercise is associated with a pro-inflammatory phenotype that can be counteracted by physiological levels of physical activity. Accordingly, the review by Scheffer discusses the action of exercise on inflammation and the antioxidant system, engaging the participation of microglia under various challenges.

5. Diet management as an intermediate for the communication between gut and brain

Management of diet is becoming a realistic strategy to influence brain function during homeostatic and disease conditions. All foods are metabolized in the periphery involving the gastrointestinal tract and other organs and tissues such as the liver, and commensal bacteria, respectively, which byproducts reach the brain through circulation. Leigh and Morrison discuss how the consumption of energy-dense foods and low amounts of physical activity can unbalance energy homeostasis with consequences for development of adiposity and obesity. Together with other environmental and genetic contributors, the increased prevalence of overweight and obesity is becoming an alarming health concern around the world. Indeed, overweight and obesity have increased dramatically in the last three decades and it is predicted that more than one billion adults will be obese in the next decade.

Loss of cognitive and emotional capacities reduces quality of life and places a burden for global health and society, which is already strained due to elevated proportion of the aging populations. An increasing body of preclinical and clinical evidence indicates that obesogenic diets are associated with cognitive impairment and increase risk of dementia. The hippocampus, a region critical for episodic and spatial memory, is largely affected in obesity and may also influence the emotional drive for binge eating and exacerbate weight gain. Understanding the mechanisms underlying obesity-associated cognitive impairment is crucial for restoring quality of life and improving the success of interventions to reduce the likelihood of obesity-related diseases. The review by Morrison provides an overview of the evidence surrounding the impact of obesity and diet on cognition, and discusses current understanding of research on gut microbiome composition, inflammation and blood-brain barrier integrity. The main idea behind is that obesogenic diets act at multiple sites to produce complex physiological weaknesses and our challenge is to identify mechanisms that can be modified to improve cognitive outcomes and quality of life.

Obesity also increases the propensity of immunologic, metabolic and cardiovascular diseases that can influence brain function. It is becoming to be understood how insulin resistance, hyperglycemia, adipose tissue, and liver dysfunction often lead to a cascade of metabolic risk factors collectively referred to as metabolic syndrome (MetS), which can affect the brain and the blood brain barrier (BBB). Hyperglycemia influences several cellular metabolic processes around the production of ROS that foster inflammation, apoptosis, etc. Studies performed in obese rodents show that ROS reduces proteins associated with tight junctions resulting in increases in BBB permeability. Hyperglycemia per se has deleterious effects on brain in patients with T2D, even resulting in brain atrophy and increasing the risk for stroke. Accordingly, glycemic control using lifestyle as a medicine (e.g., physical activity and nutrition) is considered critical to reduce hyperglycemia and the incidence of T2D.

6. Diet and sex

Food preference is tightly linked to culture and society, such that eating disorders have multifactorial psychological and societal etiologies. Obesity and eating disorders are also significantly gendered. Obesity in women is a rapidly growing calamity such that the incidence of eating disorders in women is three times higher than men. Thus, sex factors (typically associated with reproduction) seem to predispose individuals of a certain gender to various food-related environmental pressures. Most research investigating sex differences in feeding has focused on hormonal contributions to food intake, which studies often result in an incomplete understanding of sex difference etiology. Accordingly, the article by Massa et al. discusses the premise that sex is a complex and interacting network of distinct interactive factors, beyond sex hormones, including sex chromosomes and parental imprinting. This

article reviews studies showing how specific components of sex machinery interact with the feeding circuitry in the neuronal control of food intake. In addition, it presents an overview of what is known regarding central and peripheral control of feeding, and explores how sex differences, and the various facets of sex affect feeding physiology.

7. Pathophysiological implications of diet and exercise aberrations

7.1. Traumatic brain injury (TBI)

Given the pivotal action of systemic physiology on brain function, disorders of the gut can influence the pathogenesis of various neurological diseases. The review by Palafox et al. discusses new studies indicating that concussive brain injury in rodents causes disruptions in hepatic energy homeostasis, resulting in higher levels of pro-inflammatory molecules that can, in turn, damage the brain [13]. Lipid metabolism is tightly regulated in the brain in association with the liver via the autonomic nervous system. Given the central role of the liver on the processing of foods and management of toxicity, consumption of unhealthy dietary factors can negatively influence the liver-brain axis. In particular, fructose consumption leads to dramatic accumulation of triglycerides in the liver that may exacerbate brain dysfunction. As discussed, the metabolism of fructose that occurs in the liver provides an excellent example how liver fatty acids can reach the brain and expand the inflammatory reaction started in the periphery [14,15]. Fructose consumption is getting recognition as a powerful contributor to the epidemic of metabolic disorders [16–19], and the fat-promoting effects of high fructose consumption is deleterious for normal brain function [14,15,20–22], and may exacerbate other pathologies.

The fact that patients suffering brain trauma often exhibit sudden abnormalities in glucose control [23–26], inflammation and multiorgan dysfunction syndrome [27,28] that elevates risk for secondary brain injury [29,30], metabolic disorders can worsen the outcome of TBI patients [31–33]. Therefore, the prospect of TBI is becoming even more dreadful considering the rise in consumption of high caloric foods [34] — which account for over 40% of the U.S. population being diabetic or pre-diabetic [35] and vulnerable to neurological and psychiatric disorders [36–38].

7.2. Exercise and epilepsy

Epilepsy is a neurological disorder characterized by spontaneous recurrent seizures which can result in several cognitive and psychosocial alterations. Emphasizing the influence of peripheral inputs on the brain, vagus nerve stimulation and ketogenic diet are considered current options to cope with the burden of epilepsy. Along this line of thought, Arida discusses the management of exercise and gut microbiota is also perceived as being beneficial for epilepsy control. It has been shown that probiotic supplementation reduced seizure severity on an animal model of epilepsy, apparently acting by increasing brain concentration of the GABA neurotransmitter. In turn, acupuncture, botanical/herbals, yoga, chiropractic care, prayers and stress management are the most common complementary therapies for seizures or epilepsy. The influence of physical activity as an adjunctive treatment for epilepsy is relatively new, in which exercise reduces seizure frequency as well as improves quality of life of people with epilepsy. Everything seems to indicate that physical activity is a viable non-pharmacological intervention that can be combined with conventional therapy for epilepsy.

7.3. Diet and Multiple Sclerosis (MS)

The action of diet can also be expressed on the proper composition of cellular membranes which is crucial to maintain neuronal communication. Oligodendrocytes produce myelin that is rich in lipid material and metabolites necessary for nerve impulse conduction. Oligodendrocyte loss and myelin destruction, as occurs in MS, renders axons vulnerable to degeneration and permanent neurological deficits. Although animal studies seem to indicate that dietary factors that reduce inflammation are generally beneficial to fight MS, the mechanisms by which dietary factors modulate oligodendrocyte biology, myelin injury and myelin regeneration remain poorly understood. Accordingly, Langley et al. review current evidence from clinical and animal studies showing the impact of dietary factors on myelin integrity and other pathogenic features of MS. Specific dietary components such as fish/PUFAs, caloric restriction or fasting may reduce the progression of MS, while insufficient vitamin D levels may increase the risk for developing MS. It is recommended to avoid overconsumption of obesogenic diets and meet vitamin D needs in childhood and adolescence to help reduce risk of developing MS.

7.4. Autism as a metabolic disorder

Autism spectrum disorder (ASD) is a complex genetic syndrome characterized by persistent deficits in sociability and communication, as well as restricted and repetitive patterns of behavior. Gevi et al. discusses the influence of intestinal microbiome and metabolomic dysfunction to autistic individuals that has more recently gaining attention besides the contribution of genetic and environmental factors to the etiology of ASD. Intestinal dysbiosis is the main cause of vitamin intestinal malabsorption, and the gut microbiota seems essential for digestion, and synthesis of dietary vitamins and cofactors, such as vitamin B, riboflavin, thiamine, and folate through the so-called “microbiome-gut-brain axis”. The review by Gevi et al. discusses studies using metabolomics to identify the global biochemical signature of autistic individuals.

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Fernando Gomez-Pinilla*
Department of Integrative Biology & Physiology, UCLA, Los Angeles, USA
Department of Neurosurgery, UCLA Brain Injury Research Center, Los Angeles, USA

* Department of Neurosurgery and Integrative Biology and Physiology, University of California Los Angeles (UCLA), 621 Charles E. Young Drive South, Los Angeles, CA 90095, USA.
E-mail address: fgomezpi@ucla.edu.