EDITORIAL

Brain Gut Axis-New View

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We strongly hope that the title of this special issue of Current Neuropharmacology, *Brain Gut Axis – New view*, is an indicative general title, which manifests a concern between the brain and gut beneficial activities which is also an interesting topic.

Brain-gut axis implies an interaction between the brain and gut, and vice versa, neurotransmitters and/or peptidergic growth factors, and for the therapy purpose, a harmony between the brain and gut beneficial activities. A practical realization of the brain-gut axis in therapy is still lacking.

Likewise, the brain-gut axis plays a role in regulation of digestion and the involuntary movement of food along the gastrointestinal system and cognitive and emotional processes altered through brain-gut axis. Unfortunately, when the signal coming from the brain is wrongly interpreted, the dysregulation of nervous systems (both central and enteric) may alter intestinal motility, increase visceral sensitivity and consequently contribute to the development of various gastrointestinal disorders (*e.g*., mucosal damage and inflammation and in severe cases inflammatory bowel disease and other gastrointestinal pathologies). Therefore, the most recent findings (providing a new insight in the future development) may be a pertinent scientific focus.

Based on several lines of evidence, Bartosz Brzozowski, Agnieszka Mazur-Bialy, Robert Pajdo, Slawomir Kwiecien, Jan Bilski, Malgorzata Zwolinska-Wcislo, Tomasz Mach, and Tomasz Brzozowski [1] provide an overview of experimental and clinical evidences that stress activates the brain-gut axis which results in a mucosal mast cells activation and an increase in the production of proinflammatory cytokines and other mediators. In addition, they discuss the concept of acute and chronic stress-induced increased intestinal permeability leading to weakening of the tight junctions and an increased bacterial translocation into the intestinal wall. An increased microbial load in the colonic tissue, excessive cytokine production and a partially blunted immune response in response to stress may result in inflammation and all these changes have been hypothesized to be involved in developing inflammatory bowel disease [1].

Providing that nucleobindin2 (NUCB2)/nesfatin-1 plays a well-established role in homeostatic functions associated with food intake and stress integration, Miriam Goebel-Stengel and Andreas Stengel [2] review NUCB2/nesfatin-1's central effects on gastrointestinal functions and summarize the effects on food intake, motility and secretion with focus on the upper gastrointestinal tract. They highlight the stressors that influence brain NUCB2/nesfatin-1 expression and discuss functional implications. In addition to traditional acute psychological and physical stressors such as restraint stress and abdominal surgery this review focuses on immunological, visceral and metabolic stressors as well as a chronic combination stress model shown to affect NUCB2/nesfatin-1 signaling and associated functional consequences [2].

Dolores Sgambato, Annalisa Capuano, Maria Giuseppa Sullo, Agnese Miranda, Alessandro Federico, and Marco Romano [3] review the role of gut-brain axis in gastric damage and protection and, in particular, they examine the role of steroids, TRH, PGs, melatonin, hydrogen sulfide (H_2S) and peptides influencing food intake (leptin, cholecystokinin (CCK), peptide YY, central glucagon–like peptide-1 [GLP-1], ghrelin), GABAergic and glutamatergic pathways in gastric mucosal protection [3].

Klara Gyires and Zoltan S. Zadori [4] in their review summarize the effects of cannabinoids on gastric functions (*i.e*., on gastric acid secretion, gastric motor activity and emptying, as well as on gastric mucosal integrity), and provide an overview of current knowledge on the cannabinoid receptor-mediated beneficial effects in inflammatory bowel diseases (IBDs). In particular, they review the intensive research focusing the development of new structures that modulate the endocannabinoid system without inducing the central undesired side effects, thus, likely safe, effective compound(s) suited for clinical praxis [4].

Filaretova and collaborators [5] outlined the main components of the brain-gut axis, then focused on the HPA system as a key hormonal branch of the brain-gut axis in stress. They emphasized endocrinological approach to gastroenterological understanding of the hypothalamus-pituitary-adrenal axis role in regulation of gastric mucosal integrity, and thereby, new findings. This provides the hypothalamus-pituitary-adrenal axis system as the gastroprotective component of the brain-gut axis in stress but not ulcerogenic one as it was generally accepted [5].

Naoko Abe, Aiko Kumano, and Koji Takeuchi [6] examined the influence of adrenalectomy on NSAID-induced small intestinal damage in rats and investigated the possible involvement of adrenal glucocorticoids in the protective effects of urocortin I (a corticotropin-releasing factor agonist). Their results suggest that adrenalectomy aggravated the intestinal ulcerogenic response to indomethacin, and endogenous glucocorticoids played a role in intestinal mucosal defense against indomethacin-induced enteropathy, but did not account for the protective effects of urocortin I, which were mediated by the activation of peripheral corticotropin-releasing factor 2 receptors [6].

Imre L. Szabo, Jozsef Czimmer and Gyula Mozsik [7] reviewed vagotomy as an interesting issue of brain-gut functioning under the title *Cellular energetical action of "chemical" and "surgical" vagotomy in gastrointestinal mucosal damage and protection: similarities, differences and significance for brain-gut function.* They made interesting conclusions, *i.e.*, capsaicin-induced gastric mucosal damage independent from the chemical vagotomy [7].

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Hanne-Line Rabben, Chun-Mei Zhao, Yoku Hayakawa, Timothy C. Wang and Duan Chen [8] review the issue of vagotomy and gastric tumorigenesis and the potential treatment strategies to target the nerve, neurotransmitters, corresponding receptors and their down-stream signaling pathways for the malignancy. This has been done since early studies on the effects of vagotomy in chemically-induced rodent models of gastric cancer and reported an increased risk of developing gastric cancer. Further emphasis is on a recent study using three different mouse models of gastric cancer (including genetically engineered, chemically-induced and *Helicobacter pylori*-infected mice), and evidence that unilateral vagotomy or bilateral truncal vagotomy with pyloroplasty significantly attenuate tumorigenesis in the denervated side of the stomach at early preneoplastic stages as well as at later stages of tumorigenesis. The final emphasis goes to the pharmacological denervation using botulinum toxin A or muscarinic acetylcholine receptor 3 (M3R) blockade and inhibited tumorigenesis [8].

Tsang, Auyeung, Bian, and Ko [9] in *Pathogenesis, experimental models and contemporary pharmacotherapy of irritable bowel syndrome: story about the brain-gut axis* describe advances in understanding the pathophysiology and experimental models of irritable bowel syndrome. This review provides an update of present and future therapies directed to the brain-gut axis in the treatment of the disease [9].

Sikiric and collaborators [10] review the evidence that brain-gut axis is brain-gut interaction, and vice versa, the evidence that peptidergic growth factors, native in GI-tract with strong anti-ulcer potency would from periphery beneficially affect CNS-disorders, while the therapy purpose remains elusive. To realize brain-gut axis therapy they assumed Robert's stomach cytoprotection, as a peripheral counterpart, agents involved there in maintained GI mucosa and endothelium integrity backing the other peripheral beneficial effects, and thereby, their beneficial effect in CNS-disorders. They focused on the stable gastric pentadecapeptide BPC 157 as an anti-ulcer peptidergic agent, safe in inflammatory bowel disease clinical trials and now in multiple sclerosis trial, native and stable in human gastric juice, as a novel mediator of Robert's cytoprotection, maintaining gastrointestinal mucosa integrity, with no toxicity being reported. Thereby, this study reviewed particular mechanisms behind BPC 157 as a prototype therapy in various CNS-disorders [10].

Foldes, Kadar, Keremi, Gyires, Zadori and Varga [11] compared the immunopathomechanisms of the above mentioned neurodegenerative, neurotraumatic and neuroinflammatory diseases with inflammatory bowel disease. Additionally, they seeked for the potential use of mesenchymal stem cells, especially those from dental origin to treat such disorders, and thereby, considerable advance in the foreseeable future in treatment options for central and peripheral disorders related to inflammatory degeneration [11].

Vlainic and collaborators in *Brain-gut axis: Probiotics as an adjuvant therapy in major depressive disorder* emphasized relatively new research strategies of psychiatric illness and their connections with disturbances in gastrointestinal tract, and thereby, they discussed the possibilities of classical antidepressant drug treatment being supported with the psychobiotics/ probiotic bacteria in patients suffering from major depressive disorder [12].

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