Editorial

New Mechanisms of GI Ulceration & Healing: Physiology, Pharmacology & Pathology

As it is pointed out in this special issue of Current Pharmaceutical Design, despite the extensive and multidisciplinary research during the last years, a lot of basic and clinical research is still needed to better understand the manifestations, central and peripheral molecular regulators of new mechanisms of GI ulceration and healing, physiology, pharmacology and pathology, especially in relation to the classic modes of prevention/management of gastrointestinal ulceration and healing or their transformation into new concepts and the treatment of gastrointestinal ulceration and healing. This is particularly important for acquiring new vistas in the therapy of gastrointestinal tract disturbances.

Therefore, “New mechanisms of GI ulceration & healing: Physiology, pharmacology & pathology” attempts to cover a huge area of the pertinent scientific research. Between various concepts, the Robert’s cytoprotection concept is still one of the most fascinating concepts in science development, particular with respect to conceptual disagreements, or on the other hand, novel agents, and attempts to improve concept, as well as to finally realize some or all of the concept postulates in gastrointestinal tract therapy. Therefore, it seems interesting to review again this issue, covering a huge area, by eminent experts, providing their most recent findings, including the development of new medicines and new approaches.

Bilski et al. [1] in their review Exploiting significance of physical exercise in prevention of gastrointestinal disorders revealed the particular relationship between physical exercise with different intensity and alterations the morphology and function of the gut including its protective influence on the lipid metabolism and chronic systemic inflammation as well as the diversity, distribution and metabolite of the gut microbiota. Based on the evidence provided in this overview, the regular, moderate exercise can reduce the risk of colorectal cancer and exert a beneficial effect on upper and lower GI-tract disorders such as reflux esophagitis, peptic ulcers, choledolithiasis, constipation and IBD leading to the attenuation of the symptoms. On the other hand, the high-intensity training or prolonged endurance training can exert a negative influence on these same entities [1].

Olsen et al. [2] in the review New approaches for weight loss: experiments in animal models emphasized the interesting points such as animal models (i.e., VBLOC (implanted hunger-blocking device) and knockout of muscarinic acetylcholine M3 receptor) known to reduce food intake and body weight versus the expression of energy-balance regulating peptides in the hypothalamus as a drive for increased food intake. Finally, emphasizing that the brain-gut axis plays an important role in the regulation of body weight, they proposed that the brainstem may be more important in the regulation of food intake than hypothalamus in the context of the brain-vagus nerve-gut axis [2].

Review Similar and distinct mechanisms in the protective processes of upper and lower GI tract by Gyires et al. [3] is an excellent overview of the protective mechanisms of upper and lower gastrointestinal tract providing their own findings purposefully elaborated. This review analyzed many factors involved in various forms and levels of protection of mucosal tissues, mucosal protection in the periphery (barriers and mediators), intestinal defense mechanisms (mucosal barriers, bile acids), stimulation of gastrointestinal mucosal protection (pre-epithelial, epithelial, sub-epithelial possibilities) and central nervous system involvement [3].

The authors, Kang E.A. and collaborators [4] in review BPC 157 as potential agent rescuing from cancer cachexia summarized signaling pathways and promising drug candidates to treat cancer-associated cachexia and focused their review on the possible application of BPC 157 for cancer cachexia with the mode of action. They showed the significant relieving effects of BPC 157 on C-26 colon adenocarcinoma-induced muscle degeneration and inflammation. The presented review is very informative and may provide support for the potential use of stable gastric pentadecapeptide BPC 157 as a cachexia-rescuing therapeutic agent [4].

The author, Gaetano Iaquinto [5] in his review, The several activities of 4-methypyrrozole in animals and humans, reviews 4-methypyrrozole (4-MP), a pyrazole derivative in animal and humans. 4-MP is a potent competitive inhibitor of ADH activity with an affinity about a 1000 times more than toxic alcohols. 4-MP was shown to reduce the formation of toxic metabolites in lethal methanol and ethylene glycol poisoning in animal models and in methanol poisoning in humans, and in particular, 4-MP provides significant protection of the human stomach against alcohol-induced acute mucosal injury [5].

Kodama et al. [6] in their review MALT lymphoma, stress ulcer and cholinergic nerves from the viewpoint of bilateral and unilateral truncal vagotomy and substance P follow the evidence that the vagal nerves play an important role in gastric function providing rich innervation to this area and that the vagal nerve activity was shown to be related to both gastric cancer development and progression, but its relation to the mesenchymal tumors such as MALT lymphoma is not known. Thereby, the authors were focused on the effect of vagotomy on gastric MALT lymphoma development by in the Helicobacter heilmannii-mouse infection model [6].

The review Role of formyl peptide receptors in gastrointestinal healing by Prevete and collaborators [7] assessed the role of a particular class of PRRs, the Formyl Peptide Receptors (FRP), in gut mucosa homeostasis. They report studies that strongly suggest the possibility that
FRP activation is crucial for the maintenance of gut homeostasis. Furthermore, they provide indications for the potential clinical relevance of novel directions related to FPR modulation in various gastrointestinal disorders [7].

The authors, Seiwerth and collaborators [8], in review BPC 157 and standard angiogenic growth factors. Gastrointestinal tract healing, lessons from tendon, ligament, muscle and bone healing focused on gastric pentadecapeptide BPC 157, a peptide always given alone vs. standard peptidergic angiogenic growth factors such as EGF, FGF and VEGF, and numerous carriers. They also reviewed how the healing could happen involving angiogenic factors in the gastrointestinal tract and in extra-gastrointestinal tissues, such tendon, ligament, muscle and bone, providing a carrier, use (i.e., EGF, FGF and VEGF) or no use (BPC 157). The effects of EGF, FGF, VEGF, and BPC 157 were compared in various injuries, such as gastrointestinal ulcer, tendon, ligament, muscle and bone healing. They found that BPC 157 was the only factor being consistently effective in all of the models, given per-orally or locally, unlike FGF, EGF, and VEGF. The authors found that on the healing mechanism of BPC 157 is related to its own angiogenic effect in the healing [8].

The authors, Sikiric and collaborators [9], in review Novel cytoprotective mediator, stable gastric pentadecapeptide BPC 157. Vascular recruitment and gastrointestinal tract healing cover an intriguing story about the stable gastric pentadecapeptide BPC 157 and the whole story about the concept of the cytoprotection and possibly new insights. The basic concept providing the stomach cytoprotection as the most fundamental concept, stomach cell protection and endothelium protection was largely elaborated. Having managed these two points, stomach cell protection and endothelium protection, either one or together, even much more than standard cytoprotective agents do, BPC 157 employed large scale of its beneficial effects seen in various organs. This provides an additional realization of blood vessels controlling, described as “vessel recruitment depending on injury”, “bypassing vessel occlusion” or “running toward the defect”, leading to reestablishing blood flow. This was taken as a final implementation of the concept of cytoprotection. Obviously, the reestablished blood flow, and largely reversed injurious course may practically implement the cytoprotection concept [9].

The authors K. Takeuchi and K. Amagase [10] in their review Roles of cyclooxygenase, prostaglandin E2 and EP receptors in mucosal protection and ulcer healing in the gastrointestinal tract reviewed how the PGE2 prevents acid-reflux esophagitis and affords protection of the stomach against NSAIDs through the activation of EP1 receptors. Although CRS-induced gastric lesions were aggravated in IP but not EP1 KO mice, endogenous PGE2 may also be partly responsible for mucosal protection during CRS via the activation of EP4 receptors, in addition to that afforded by PGI1 IP receptors. Similar observations were done in the other parts of GI tract (duodenum, small intestine, stomach, large bowel) [10].

Racz et al. [11] in their review Defense mechanisms against acid exposure by dental enamel formation, saliva and pancreatic juice production review defense mechanisms of different tissues. The similarities of enamel, salivary glands and pancreas are well emphasized and described. The authors highlight the importance of bicarbonate buffer system and highlight the possible failures as well. The intracellular transport and secretion mechanism are also reviewed [11].

Yanaka in his review Contribution of NRF2 in gastrointestinal protection from oxidative injury [12] reviews the evidence that dietary intake of sulforaphane, derived from broccoli sprouts, ameliorates H. pylori-induced gastritis, NSAIDs-induced small intestinal injury, and functional constipation. The additional focus was on many other compounds, which enhance the nuclear factor erythroid 2-related factor 2-mediated antioxidant system, and in particular on some reports, which have shown that excessive stimulation of nuclear factor erythroid 2-related factor 2 enhances chemoresistance and facilitates the growth of cancer cells [12].

The review Lifestyle and peptic ulcer disease from Yegen [13] extends a general point such as the risk of developing peptic ulcer disease shown to be associated with genetic inheritance, lifestyle and social status of the patients, to an extensive and very informative review providing particular chapters (Stress, NSAIDs, Diet and body weight, Alcohol, Smoking, Physical activity, Sleep) with a list of the references that seems to be quite extensive and well chosen [13].

We hope multidisciplinary topics discussed with the theme issue will promote further discussion among pharmaceutical industry and researchers. As the guest editor, I would like to thank all the authors and co-authors for their excellent contributions. Also, I would sincerely thank and acknowledge the diverse group of experts and colleagues who offered their substantial reviewing efforts and suggestions. Last but not least, I would like to express my gratitude to the Bentham Science Publishers for the wonderful experience while working with the journal on this thematic issue. It was a great pleasure working with the Director Kazim Baig and for the opportunity to publish in Current Pharmaceutical Design. It was a wonderful experience working with Editorial Assistant Aamer M. Khan at the time of submission and processing of the manuscripts. I would like to acknowledge the contributions of others who took care of editing and processing the manuscripts to obtain the best final quality at the time of publication.

REFERENCES
