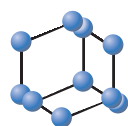


## REVIEW ARTICLE

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SCIENCE

## Brain-gut Axis and Pentadecapeptide BPC 157: Theoretical and Practical Implications



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**Abstract: Background:** Brain-gut interaction involves, among others, peptidergic growth factors which are native in GI tract and have strong antiulcer potency and thus could from periphery beneficially affect CNS-disorders. We focused on the stable gastric pentadecapeptide BPC 157, an antiulcer peptidergic agent, safe in inflammatory bowel disease trials and now in multiple sclerosis trial, native and stable in human gastric juice.

**Methods:** Review of our research on BPC 157 in terms of brain-gut axis.

**Results:** BPC 157 may serve as a novel mediator of Robert's cytoprotection, involved in maintaining of GI mucosa integrity, with no toxic effect. BPC 157 was successful in the therapy of GI tract, periodontitis, liver and pancreas lesions, and in the healing of various tissues and wounds. Stimulated Egr-1 gene, NAB2, FAK-paxillin and JAK-2 pathways are hitherto implicated. Initially corresponding beneficial central influence was seen when BPC 157 was given peripherally and a serotonin release in particular brain areas, mostly nigrostriatal, was changed. BPC 157 modulates serotonergic and dopaminergic systems, beneficially affects various behavioral disturbances that otherwise appeared due to specifically (over)stimulated/damaged neurotransmitters systems. Besides, BPC 157 has neuroprotective effects: protects somatosensory neurons; peripheral nerve regeneration appparent after transection; after traumatic brain injury counteracts the otherwise progressing course, in rat spinal cord compression with tail paralysis, axonal and neuronal necrosis, demyelination, cyst formation and rescues tail function in both short-terms and long-terms; after NSAIDs or insulin overdose or cuprizone encephalopathies were attenuated along with GI, liver and vascular injuries.

**Conclusion:** BPC 157, a gastric peptide, may serve as remedy in various CNS-disorders.

**Keywords:** Brain-gut axis, CNS-disorders, stable gastric pentadecapeptide BPC 157, therapy.



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## INTRODUCTION

The discovery of the brain-gut axis belongs to the seminal Pavlov's work, his sham-feeding of dogs with gastric fistula, and the role of vagus nerve in the control of gastric acid secretion [1]. This has been further proven with the Selye's discovery that agents, although very diverse, always elicit the same neuroendocrine response and that gastroduodenal ulcers are the last segment of morphologic triad: hypophyseal-adrenocortical stimulation, thymo-lymphatic involution and gastroduodenal ulceration [2]. However, the current view of the brain-gut axis relies on the extensive evidence carried out by many groups in the late 1980s (most

of them were Selye's students) showing that the most potent effect of many peptides (*i.e.*, bombesin, thyrotropin-releasing hormone, corticotropin-releasing factor, neurotensin) is the modification of gastrointestinal (GI) functions. The most prominent action of these peptides on gastric lesions [3-10] appears when applied within the specific hypothalamic and brain stem sites or into the cerebrospinal fluid [11]. Since the brain-gut axis purports an interaction between the brain and the gut, and vice versa [12], this concept also implies neurotransmitters and/or peptidergic growth factors, native in GI tract which have strong anti-ulcer potency and thus would from periphery beneficially affect CNS disorders as well. For the therapy purpose this means a harmony that has to be established between the brain and the gut. Supporting is the research providing evidence that the gut-brain axis, as a bidirectional neurohumoral communication system in the

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human body, also function as a pathway for the gut microbiota to modulate brain function of its host [13].

### **POSSIBILITY FOR PRACTICAL REALIZATION OF THE BRAIN-GUT AXIS IN THERAPY**

A practical realization of the brain-gut axis in therapy is still mainly lacking. As a peripheral counterpart of the brain-gut axis we assumed Robert's stomach cytoprotection concept implying maintenance of GI mucosa as convincing background for other beneficial effects [14-22]. Thereby, we focused our research on the stable gastric pentadecapeptide BPC 157 (GEPPGKPADAGLV, M.W. 1419), an anti-ulcer peptidergic agent with a possible therapeutic effects (toxicity has not been reported) in diverse neurological disturbances. Since BPC 157 is native and stable in human gastric juice, it is thought to be a potent mediator of Robert's cytoprotection, maintaining GI mucosa integrity [14-22].

### **BPC 157 IN PERIPHERY-BIOLOGICAL ACTIONS AND SIGNIFICANCE FOR CENTRAL EFFECTS**

Likely, due to cytoprotection and endothelium maintenance capability, BPC 157 was successfully used in the therapy of periodontitis, and for esophagus, stomach, duodenum, intestine, liver and pancreas lesions [14-21]. In addition, BPC 157 counteracts alcohol-induced (acute and chronic) and NSAIDs-mediated lesions [23-27]. BPC 157 may prevent, but also reverse adjuvant arthritis [23], counteracts aspirin-induced prolonged bleeding and thrombocytopenias [24], recovers lower esophageal sphincter and pyloric sphincters function, heals the intestinal anastomosis and fistulas, and improves adaptation of the intestinal wall layers after massive resection [14-21]. BPC 157 counteracts many lesions that may appear, for instance, within insulin- or NSAIDs-overdose, as well as GI, liver and brain lesions [25-28] implicating its strong influence on the central disturbances following peripheral administration.

The wound healing effect of BPC 157 related to the endothelium protection was noted in deep skin burns [29-31], transected/injured muscle [32-34], tendon, ligament [35-40] and bone (pseudoarthrosis, periodontitis) [23, 41, 42] and nerve [43] healing, as well as in particular tissues such as cornea [44]. BPC 157 interacts with nitric oxide (NO) system, both NOS-substrate (L-arginine) and NOS-blocker (L-NAME) in different models and species [15], including the regulation of a blood pressure [14]. The observed effects are related to the stimulatory effect of BPC on Egr-1 gene and its corresponding co-repressor gene NAB2, stimulation of FAK-paxillin and JAK-2 signalling pathways [45-47]. Endothelium protection [14-21] leads to its particular effect on arterial thrombosis, counteraction of prolonged bleeding after amputation and anticoagulants administration [24, 48], as well as NO-substrate and NOS-blocker administration, and opposite conditions arising from NO-system overstimulation or blockade [48], and finally, rescue of animals with a major vein obstruction (inferior caval vein) [49]. Likely, this effect could be responsible for the counteracted dextran-induced anaphylactoid reaction and increased vascular permeability [50]. Also, BPC 157 exerts a particular beneficial effect on chronic heart failure induced by doxorubicin and

arrhythmias induced by digitalis as well as hyperkalemia and potassium-induced membrane disturbances [51-53].

Conceptually, the beneficial background on the periphery implies a corresponding beneficial central influence [22, 54-66]. Namely, given peripherally, BPC 157 induces the release of serotonin in particular brain nigrostriatal regions and has influence on serotonergic [58] and dopaminergic systems [57]. The observed beneficial effects were obtained within the specifically (over)stimulated or damaged dopaminergic, serotonergic, GABAergic and opioid systems. The ample evidence on BPC 157 potential beneficial effects includes the positive influence on many central disturbances: akinesia [55, 56], catalepsy [55, 56, 65], somatosensory disorientation [65], tremor [55, 56], seizures, stereotypies (both acute and chronic) [66], hypothermia [55, 56], hyperthermia, serotonin syndrome [58], acute and chronic alcohol intoxication [55,56], climbing and helpless behaviour [60], morphine-induced analgesia [63], diazepam tolerance and dependence [62], muscle weakness and function failure [54], dopamine vesicle depletion [54], amphetamine given acutely [66] and chronically [57], amphetamine tolerance [57], amphetamine supersensitivity [66], morphine and naloxone [63], picrotoxin and isoniazid convulsions [61, 62], cuprizone effects, a neurotoxin mimicking multiple sclerosis brain lesions and presentation [22].

Besides, with a direct neuroprotective effect, BPC 157 protects somatosensory neurons [67], strongly improves nerve regeneration after peripheral nerve transection and counteracts autotomy [43]. BPC 157 attenuated the course of traumatic brain injury, postponed deleterious outcome and counteracted the primary injury with respect to the secondary injury process [68]. Recently we also reported its beneficial effects on neuronal necrosis, demyelination, cyst formation after spinal cord injury and rescue of tail function [69]. Thus, we suggest that this pentadecapeptide is a promising candidate to realize all beneficial effects of suitably activated brain-gut axis.

### **COUNTERACTION OF CATALEPSY AND AKINESIA**

Conceptually, in therapy terms of brain-gut axis we discuss together muscle healing [32-34] and neuroprotective capabilities [43, 67, 68] of BPC 157 with the counteracting effect on catalepsy (muscular rigidity and fixed posture regardless of external stimuli) and akinesia (inability to initiate movement) and thereby, on severely diminished dopaminergic cell activity which is involved in the direct pathway of movement [54, 65]. Besides, the gastric lesions that appeared along with the catalepsy/akinesia development were accordingly counteracted and these phenomena may be particularly interesting [54, 64, 65].

### **INTERACTION WITH NEUROLEPTICS**

The intriguing point was the evidence about anti-cataleptogenic effect [65] followed demonstration that BPC 157 blocks the stereotypy produced acutely by amphetamine, and the development of haloperidol-induced supersensitivity to amphetamine [66]. Nevertheless, pentadecapeptide BPC 157, that by itself has no effect on behavior (in particular not

cataleptogenic effect) that would explain the counteracted amphetamine-effects [66], attenuated the immediate effects of neuroleptics, especially catalepsy, likely in a non-competitive way [65]. The evidence encompasses that BPC 157 blocks catalepsy induced by haloperidol and fluphenazine as well as somatosensory disorientation after sulpiride and clozapine [65]. This suggests a generalization and that BPC 157 may counteract side effects of different groups of neuroleptics, typical and atypical. Besides, this beneficial effect on catalepsy was combined with antagonization of gastric lesions after haloperidol [64, 65]. These findings indicate that pentadecapeptide BPC 157 fully interacts with the dopaminergic system, both centrally and peripherally, or at least, that BPC 157 interferes with some steps involved in both catalepsy and/or ulcer formation [64, 65].

#### **INTERACTION WITH PARKINSONGENIC AGENTS: MPTP AND RESERPINE**

BPC 157 to a great extent prevented the development of catalepsy when administered along with reserpine. Likewise, even when applied 24h after reserpine, BPC 157 reversed the established catalepsy. In addition, the mitigation of reserpine-induced hypothermia (pre-treatment) and abolishment of further prominent temperature fall (post-treatment) have been observed. BPC 157 also improved the MPTP-induced impairment of somatosensory orientation and decreased hyperactivity [54]. MPTP-related motor abnormalities (tremor, akinesia, catalepsy) were also counteracted and BPC 157 almost completely rescinded lethal course of MPTP treatment. In addition, it has been noted that stomach lesions which occur following MPTP administration were strongly attenuated [54] in a non-competitive manner [65, 70].

#### **INTERACTIONS WITH DOPAMINERGIC, SEROTONERGIC, GABAergic AND OPIOID SYSTEMS**

It has been proven that BPC 157 may particularly interact with dopaminergic [54, 65] and serotonergic systems [58-60], but also may interact with other neuronal systems, such as GABAergic [61, 62] and opioid [63]. As emphasized, it may exhibit beneficial effect even after complete dopamine blockade (reserpine and haloperidol dual treatment) [70]. Thus, BPC 157 may counteract the consequences of dopamine-related nigrostriatal neuronal damage, dopamine vesicle depletion, dopamine receptors blockade, and the consequences of reduced dopaminergic activity [54, 66]. All these notions suggest a special interaction of gastric peptide with dopaminergic system and an ability of BPC 157 to counteract the effect of a noxious agent within the central dopaminergic system and through dopamine, the interaction with other systems as well.

BPC 157 may have a particular interaction with serotonergic system in a similar way like it does with dopaminergic system [58, 59]. In particular, a specific effect on serotonergic system and the release of serotonin in different brain areas was assessed using autoradiography [59]. Even a single dose of BPC 157 significantly reduces the regional rate of serotonin synthesis in the dorsal thalamus, hypothalamus, hippocampus, and lateral geniculate body, while in the substantia nigra reticulata and medial anterior

olfactory nucleus the synthesis was enhanced (although expected, no change in the synthesis rate was observed in the raphe nuclei) [59]. Following 7-day treatment a significant decrease of serotonin synthesis was demonstrated in the dorsal raphe nucleus, and an enhancement in the superior olive, substantia nigra, lateral caudate, and accumbens nucleus. The mechanism of this action is certainly involved in a particular anti-depressant activity of BPC 157 [60] and its counteraction of serotonin-syndrome, symptoms and/or initiation [58]. BPC 157 diminished or even abolished mild disturbances in rats underwent pargyline (MAO-A-inhibitor) (mild hypothermia, feeble hind limbs abduction) and even severe serotonin syndrome in rats that received both pargyline and L-tryptophan (serotonin precursor) [58]. Possibly, beneficial activity of BPC 157 within serotonergic system may be at least partly related to a rather specific counteraction of 5-HT<sub>2A</sub> receptors phenomena [58].

Considering the GABAergic system, combining diazepam and BPC 157 evidenced lack of tolerance development, prolonged residual anticonvulsive activity, and postponed physical dependence/withdrawal hallmark in diazepam and BPC 157 chronically treated mice [62]. These findings showed that BPC 157 may improve the effectiveness of diazepam [62]. Likewise, a direct comparison between the anxiolytic effects of BPC 157 and diazepam, shock probe/burying test and light/dark test, fully emphasized that background [62]. However, several distinctions indicated that the activity of pentadecapeptide BPC 157 was particular, and different from diazepam [61]. Thus, these results offer evidence that BPC 157 acts by favouring the homeostasis of the GABAergic system, as well as by upregulating the GABAergic neurotransmission, and having a mechanism(s) of action, at least in part, different from that implicated in the development of diazepam tolerance and withdrawal [71, 72].

Using an interaction between dopaminergic and opioid system, the effect of naloxone and BPC 157 on morphine-induced antinociceptive action was demonstrated. Both naloxone and BPC 157 counteracted the morphine-analgesia [63]. Naloxone immediately antagonized the analgesic action and the reaction time returned to the basic values, while the development of BPC 157-induced action required 30 minutes. Although, BPC 157 counteraction was slower than that of naloxone, it may be seen with very small dose as well. When haloperidol, a central dopamine-antagonist, enhanced morphine-analgesia, BPC 157 counteracted this enhancement and naloxone reestablished the basic values of pain reaction. Thus, with respect to interaction between dopaminergic and opioid systems demonstrated in analgesia, BPC 157 counteracted morphine-analgesia and haloperidol-induced enhancement of the antinociceptive action of morphine, indicating that BPC 157 acts mainly through the central dopaminergic system [63]. Of note, BPC 157, naloxone, and haloperidol per se failed to exert analgesic action.

#### **BPC 157 IN CORRELATION WITH AMPHETAMINE AND HALOPERIDOL**

First, BPC 157 given prophylactically or therapeutically attenuated amphetamine-stereotypic behaviour and acoustic startle response with the reversal of excitability when given at the time of maximum amphetamine-induced excitability.

This is interesting since BPC 157 alone does not affect behaviour or induce stereotypy, and in particular, since BPC 157 almost completely reverses behavioural supersensitivity to the amphetamine stimulating effect induced by pretreatment with haloperidol [66]. Further study extends the BPC 157 evidence from a counteraction of an acute effect [66] to the counteraction of a chronic amphetamine effect [57]. Demonstrated counteracting effect of pentadecapeptide BPC 157 on chronic exposure to amphetamine in rats encompass particularly the changes commonly referred in chronic amphetamine studies as tolerance (lesser grade of stereotyped behavior, without increased excitability) and reverse tolerance (*i.e.*, prominent stereotyped behavior and heightened startle response upon late amphetamine challenges). Therefore, it seems that this gastric pentadecapeptide BPC 157 has a modulatory effect on dopamine system, and it could be used in both acute and chronic amphetamine disturbances [57].

### **BPC 157 IN DEPRESSION**

Various antidepressants have antiulcer activity and we shown that depression disorders could be effectively influenced by a primary antiulcer agent with a cyto/organoprotective activity, such as the stomach pentadecapeptide BPC 157 [60]. In the forced swimming test a lowering of the immobility time in BPC 157 treated rats corresponded to the activity seen with classical antidepressant drugs such as imipramine or nialamide, while in chronic unpredictable stress aggravation of experimental conditions affected the effects of conventional antidepressant drugs, whereas BPC 157 effectiveness was continuously present. Moreover, a reduction of the immobility of chronically stressed rats was observed [60].

### **BPC 157 INHIBITS BOTH ACUTE ALCOHOL INTOXICATION AND ALCOHOL WITHDRAWAL SYMPTOMS**

We also demonstrated that BPC 157 could be a particular antagonist of alcohol-effects [56]. Namely, it may be equally effective in counteracting both acute and chronic alcohol intoxication (withdrawal), a particular effect possibly related to its action on NO-system since when combined with NO-system related substances (L-NAME and/or L-arginine) its effect was mostly counteracted [55, 56]. Besides, in favour of the brain-gut interrelations, alcohol receiving rats treated with BPC 157 had portal pressure at control levels and liver and GI disturbances were counteracted [73, 74]. These results offer promising strategy to treat alcohol intoxication with BPC 157 as potential alcohol antagonist [55].

### **BPC 157 INHIBITS THIOPENTAL GENERAL ANAESTHESIA**

BPC 157 causes significant antagonism of general anaesthesia produced by thiopental with a parallel shift of the dose-response curve to the right while in combination with L-NAME thiopental-induced anaesthesia duration was tripled. We have also shown that thiopental-induced anaesthesia is simultaneously manipulated in different ways within NO-system regulation: L-NAME caused prolongation and BPC 157 shortening/counteraction. BPC 157 and L-

arginine might possibly influence two alternative NO-system pathways, which are alternatively activated [75, 76].

### **THE EFFECTS OF BPC 157 ON NSAIDS DETERIORATING ACTION**

Encephalopathy induced by NSAIDs and the GI and liver lesions generated are diminished or totally disappeared following BPC 157 treatment [25-28]. In the study on paracetamol overdose [27] we revealed a particular aspect of the sudden onset of encephalopathy not reported until then: rapidly induced progressive hepatic encephalopathy with generalized convulsions and the corresponding significant damage within several brain areas. BPC 157 therapy was effective against paracetamol toxicity. BPC 157 lessened liver and brain lesions. Specifically, when given immediately following paracetamol BPC 157 abolished convulsions (histological search showed less neuronal damage and reduced interstitial oedema without inflammatory reaction). These results offer evidence that BPC 157 may serve as highly effective paracetamol antidote even against advanced damaging processes induced by an extreme overdose [27].

This effect [27] might be likely generalized [25, 26]. Namely, animals treated with ibuprofen chronically evidenced a series of pathologies and BPC 157 reduces them: hepatomegaly is abolished, liver enzymes increased, hepatic encephalopathy is counteracted (ischemic neurons are not present in any brain area), as well as the gastric lesions [25]. In addition, BPC 157 treated rats maintained normal weight gain and showed no behavioural disturbances [25].

Extensive counteraction of diclofenac toxicity (stomach, intestine, liver, brain lesions) achieved with BPC 157 may be promising for its further research and a possible use in therapy [26]. Specifically, brain oedema and cyanosis, with ischemic and otherwise damaged neurons were diminished with BPC 157 treatment [26].

### **ANTAGONIZATION OF INSULIN TOXICITY**

We used a consistently higher insulin regimen to avoid known problems in patients with insulin application (variations from patient to patient and from time to time in a given patient) and experimental inconsistency (for instance, different doses were used to induce stomach ulcer or hypoglycemic seizures). Thus, the applied insulin-regimen combines insulin action with gastric ulcer, seizures, severely damaged neurons in cerebral cortex and hippocampus, hepatomegaly, fatty liver, breakdown of liver glycogen with profound hypoglycemia and calcification development, and BPC 157 counteracted all disturbances. BPC 157-treated animals survived, they were mostly without hypoglycemic seizures, had higher blood glucose levels with hepatocyte glycogen unchanged. Liver pathology in such animals was less apparent or even not present, with markedly less number of damaged neurons and only occasionally small gastric lesions were seen. In addition, BPC 157 treated rats had only dot-like calcium deposits, if any. Thus, we suggest a useful enrolment of BPC 157 as possible antidote in the control of insulin levels [28].

### BPC 157 IN CUPRIZONE-INDUCED BRAIN DAMAGE

Cuprizone-induced demyelination in animals is accepted for studying multiple sclerosis-related lesions and is characterized by degeneration of oligodendrocytes more than by a direct attack on the myelin sheet (for review see, *i.e.*, [22]). BPC 157 successfully counteracts development of severe encephalopathy and muscle disability induced by neurotoxin cuprizone even when it was used in an extremely high regimen that highly exceeds those commonly applied. We used a simple test to determine animal responsiveness. Briefly, experimenter lowers the forceps in cylinder in front of a rat, stimulates its whiskers and slightly touches its chest while recording and scoring rat's reaction to stimuli. Control animals rear, raise their both forelimbs and grasp the forceps nose defensively. Animals affected with cuprizone spare right forelimb, and thereby react only with one or no forelimb and have difficulties with maintenance of body balance while rearing. BPC 157 treated rats do not spare right forelimb, react simultaneously with both forelimbs, grasp the forceps, and maintain the body balance while rearing. As described in details elsewhere [68], we particularly focused on the nerve damage in cingular gyrus, parietal neocortex, temporal neocortex, laterodorsal thalamus, nucleus reuniens, CA1 hippocampal region and found the most prominent damage in laterodorsal thalamus and nucleus reuniens. With consistently less damage, the most evident beneficial effect of BPC 157 was seen in laterodorsal thalamus and nucleus reuniens. Considering the evidence that multiple sclerosis is characterized by the progressive damage or the loss of oligodendrocytes and that this may be closely related to Egr-1 gene [74], a particular emphasize on the BPC 157 effect should be made. Namely, in respect with the recent introduction of the agents used in ulcerative colitis in the therapy of multiple sclerosis (*i.e.*, natalizumab), it will be interesting to explore further BPC 157 with respect on its effect on Egr-1 gene and its co-repressor gene NAB-2 [46].

### BPC 157 IN TRAUMATIC NERVE INJURY

Previously it has been shown that BPC 157 has a beneficial effect on muscle healing [32-35], with the suggested role in regeneration of the damaged intramuscular nerve branches [43]. In accordance, we demonstrated that BPC 157 could also influence the healing of transected nerve [43]. This particular effect was obtained with both anastomosed and non-anastomosed nerve. With anastomosed nerve, the neuroprotection has been studied as indirect (BPC 157 given intragastrically or intraperitoneally) and direct (BPC 157 applied at the site) effect. In addition, with non-anastomosed nerve when a 7 mm gap between nerve ends was made, inserted into the tube alongside with nerve endings, BPC 157 treatment also stimulated nerve healing, thereby exhibiting its beneficial activity *via* direct and indirect effect [43]. The substantial improvement has been consistently demonstrated behaviourally but also microscopically/morphometrically and functionally. The fascicles in each nerve had enhanced diameter of myelinated fibres, thickness of myelin sheet, number of myelinated fibres per area and myelinated fibres and the augmented number of blood vessels. Using electrophysiological

methods we found enhanced motor action potentials. Thus, BPC 157 markedly improved rat sciatic nerve healing [43].

### BPC 157 IN TRAUMATIC BRAIN INJURY

It is commonly recognized that brain trauma results in brain damage and dysfunction from both primary injury (due to biomechanical effects) and subsequent secondary damage due to activation of pathophysiologic cascades [68]. Brain-trauma study demonstrated that BPC 157 may preserve neuroconsciousness and lower brain edema, decrease the number and size of the hemorrhagic traumatic lacerations, and mitigate the intensity of subarachnoidal bleeding with significantly decreased intraventricular hemorrhage, and diminish mortality [68]. Also in supportive analogy, after contusion, BPC 157 (given locally or intraperitoneally) improved crushed muscle healing, with less post-injury haematoma and edema and a complete restitution of function [32, 33].

### BPC 157 IN SPINAL CORD INJURY

Briefly, to verify the influence of BPC 157 on rat spinal cord injury animals were subjected to surgery: laminectomy on level L2-L3 followed by 60 second compressions with neurosurgical piston (60-66 g) on exposed dural sac [69]. A single BPC 157 application significantly improved tail motor score and rats had decreased spasticity starting from 4 weeks to the end of experiment. Histology of spinal cord showed reduction in grey matter oedema and less cyst and axonal necrosis in white matter with increased number of all and specifically small axons. Thus, BPC 157 recovered rat tail function probably through the abolishment of secondary injury of the spinal cord, and consequently, improved neurological function recovery [69].

### BPC 157 IN SOMATOSENSORY NEURONAL INJURY

We investigated the possible involvement of sensory neurons in the salutary actions of BPC 157 using capsaicin [67]. After neonatal capsaicin treatment complete abolition of BPC 157 gastroprotection was observed, but the mucosal protection was fully reversed when BPC 157 was applied for several days. When the excitatory dose of capsaicin was administered, the beneficial activity of BPC 157 appears to increase as well. These results provide evidence for possible complex synergistic interaction between the effects of BPC 157 and peptidergic sensory afferent neuronal activity [67]. It has to be added that similar BPC 157 beneficial effect was noted in capsaicin-induced rhinitis in rats [77].

### CONCLUDING REMARKS

In theory, as a follow up of the seminal Pavlov, Selye and his students implications, that various peptides may exert potent effect on peripheral functions (most notably anti-ulcer potency) [2-10], the brain-gut axis controls how quickly the body uses its defensive capabilities, makes responses and controls how sensitive the body is to other axes activation. In practice, the therapy realization, as a feedback defensive response from the periphery (*i.e.*, GI-tract) (*i.e.*, a peptidergic agent capable to transmit its huge beneficial potency on periphery (most notably with strong anti-ulcer effect) on the central upsetting) is hitherto highly elusive.

As a peripheral counterpart of brain-gut axis we assumed Robert's stomach cytoprotection concept implying maintenance of GI mucosa as convincing active background for other beneficial effects. There, as a breakthrough, we revealed stable gastric pentadecapeptide BPC 157 an endogenous anti-ulcer peptide, native and stable in human gastric juice, thought to be novel mediator of Robert's cytoprotection, maintaining gastrointestinal mucosa integrity, with no toxicity being reported that however still did not reach full clinical application [22, 54-66].

Thereby, it is conceivable for realization of the brain-but axis and for stable gastric pentadecapeptide BPC 157 that its strong beneficial background on the periphery implies a corresponding beneficial central influence [22, 54-66]. Thus, it seems to us, that the evidence provided in this review highlights a possibility that this pentadecapeptide given peripherally likely achieves a corresponding beneficial central influence that could be effectively used in further therapy.

We should emphasize that BPC 157 avoids all the practical pitfalls for healing using peptidergic growth factors (*i.e.*, standard growth factors rapidly dissolved in human gastric juice would hardly combine peripheral and central healing due to the drawback that they are given with carriers and require special delivery systems, for instance, for skin). Of note, BPC 157 is always given alone, and thereby may act directly, always using the same dosage range, and thereby a suitable therapy and physiology link between the periphery and central nervous system in terms of practical resolution of the brain-gut axis concept.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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