We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Stable Gastric Pentadecapeptide BPC 157, Somatosensory Neurons and Their Protection and Therapeutic Extensions — A Survey

Predrag Sikiric

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/58681>

1. Introduction

Stable gastric pentadecapeptide BPC 157 (GEPPPGKPADDAGLV, M. W. 1419, a partial sequence of human gastric juice protein BPC, in all studies used peptide with 99% (HPLC) purity, freely soluble in water at pH 7.0 and in saline), was always given alone, without any carrier, μg - ng dose ranges and ways of application, intraperitoneal, intragastrical, in drinking water or topically, at the site of injury. Besides, tested in therapy of inflammatory bowel disease (IBD) (PL 14736) in clinical phase II. (Ruenzi et al., 2005), and now in multiple sclerosis.

As prime importance, BPC 157 was found to be stable at least 24 hours in human gastric juice and consequently, because of its anti-ulcerogenic potential in different, but relevant ulcer models, suggested to be novel mediator of Robert's cytoprotection and adaptive cytoprotection (for review see, i. e., (Sikiric et al., 2010, 2011, 2012)), and thereby, exhibited a particular wound healing effect, and cell protecting ability. At the general level this may likely explain its strong effectiveness and LD1 not achieved.

Thereby, such kind of pathophysiologic importance along with unlimited applications of BPC 157 regimens contrasts with the evidence for standard peptides providing that regardless commonly acknowledged pathophysiologic importance at least in many occasions they need a carrier (one or more) to become effective and furthermore, that their application prefers to be local, at the site of injury, given into the injury defect (for review see, i. e., (Urist, 1996)). Therefore, pentadecapeptide BPC 157 certainly avoids a common scenario with standard peptides where their limited application in pharmacology could hardly acknowledge their suggested prime physiological importance (Sikiric et al., 2010, 2011, 2012, 2013, 2014; Seiwerth et al., 2014)

2. Methods

With BPC 157 given alone, without a carrier, BPC 157 application strategy (for review see, i. e., (Sikiric et al., 2010, 2011, 2012, 2013, 2014; Seiwert et al., 2014)) considerably overrides the standard peptides and their use with different carriers (i. e., peptide+carrier(s) complex) to establish the therapeutic effect (thereby erroneously) ascribed to the given peptide. Therefore, the activity – methodology dilemma whereby it is difficult to identify the real active part in peptide+carrier complex (peptide, carrier, peptide+carrier complex or neither of them) or specify their particular contribution is not applicable to BPC 157 (for review see, i. e., Urist, 1996). Finally, in BPC 157 – standard peptides relation, apart from the evidence that this anti-ulcer peptide may be effective in both upper and lower GI tract injuries (for review see, i. e., (Sikiric et al., 2010, 2011, 2012)), and initial successful use in clinic (Ruenzi et al., 2005), involving also a particular sphincter function control (Sikiric et al., 2010, 2011, 2012), the key difference appears in the healing outside the GI tract. This may be also because since this evidence was based on clear demonstration that it also may interact with the general systems, i. e., the NO-system, providing endothelium protection and angiogenic effect (Seiwert et al. 2014; Sikiric et al., 2014). And even more, important to counteract severe complications of advanced and poorly controlled IBD, this occurs even in severely impaired conditions. Notably, the final background was that it stimulated expression of early growth response 1 gene (*egr-1*) responsible for cytokine and growth factor generation and early extracellular matrix (collagen) formation (but also its repressor nerve growth factor 1-A binding protein-2 (*naB2*)) (Tkalcic et al., 2007).

To this point, it should be noted that BPC 157 markedly improves the healing of both traumatic nerve (Gjurasin et al., 2010) and traumatic brain injury (Tudor et al., 2010), and therefore, exhibits particular neuroprotective ability. Likewise, it ameliorates encephalopathies that occur in severely intoxicated animals (Ilic et al., 2010, 2011, 2011).

In addition, BPC 157 has in general a very safe profile. As an illustration, single dose toxicity studies in mice treated by oral and i. v. routes revealed a LD_{50} of PL 14736 higher than 2000 mg/kg. No mice died during both studies and transient sedation was the only finding in the dose of 2000 mg/kg. In the 4-week repeated i. v. dosing toxicity studies in rats and dogs no morphological findings related to PL 14736 administration were found at any of doses studied. Macroscopical and histological examination of the organs and tissues sampled following 14-day intracolonic administration in rats and dogs did not reveal changes that could be attributed to treatment with PL 14736 (doses up to 25 mg/kg). The only finding, lesions at the area of colon application site in rats, also seen in the control animals, was primarily caused by mechanical trauma of the catheter used. No effect of PL 14736 on female fertility and early embryonal development was noted. No effect of PL 14736 in sensitization study and in acute eye irritation/corrosion study was noted. PL 14736 does not cause chromosomal aberrations in cultures of human lymphocytes, nor it is mutagenic in the AMES test (doses up to 5 mg/plate were tested). Repeated i. v. administration of 10-30 μ g/kg/day to mice did not induce the induction of microsomal liver enzymes *in vitro*. Safety pharmacology of PL 14736 has been

studied in anaesthetised dogs following intraduodenal administration of 10 and 100 µg/kg, with no significant effects on the cardiovascular and respiratory systems.

Based largely upon the use of neurotoxin capsaicin, peptidergic neurons have been postulated to be involved in a physiological protective system (Holzer, 1991, 1991). Protection of the gastric mucosa from various forms of injury occurs with different peptides given centrally (Heiling et al., 1987; Hernandez, 1986; Hernandez et al., 1987) and/or peripherally (Evangelista et al., 1991; Takeuchi et al., 1979).

The integrity of capsaicin somatosensory neurons and their protection were suggested to be related to BPC 157 activity in nociception (Sikiric et al., 1993). Capsaicin-sensitive afferent neurons, regulators of vascular functions in many somatic and visceral tissues (Holzer, 1991, 1991), are involved in local blood flow regulation in gastrointestinal tract (Holzer, 1991, 1991; Szabo et al., 1985). The population of capsaicin-sensitive neurons is heterogenous and comprises most but not all primary afferent neurons with small cells body and unmyelinated (C fiber) axons and some afferent neurons with thinly myelinated (A-δ) axons (Holzer, 1991, 1991). Low doses of capsaicin (micrograms per kilogram range) appear to be protective to the mucosa (Holzer, 1991, 1991) since they induce a transient excitation. In contrast, systemic administration of high doses of capsaicin (miligrams per kilogram range) is deleterious, causing long-lasting damage to these neurons (Holzer, 1991). This effect is age-dependent, being even more pronounced in the adult rat when capsaicin is given to newborn animals (Jancsó et al., 1977).

Therefore, the possibility that BPC 157 causes mucosal protection through capsaicin-sensitive nerves was challenged. The effect of BPC 157 on gastroprotection, in rats treated with capsaicin, was investigated. Because of the mentioned different susceptibility to capsaicin of the adult and newborn animals (Holzer, 1991; Jancsó et al., 1977), and to achieve better insight into a possible mechanism of BPC 157 activity against the background of near maximal neuronal damage, it was necessary to use two different methods to deactivate sensory neurons by capsaicin pretreatment (Holzer, 1991; Jancsó et al., 1977), one in adult rats, the other in newborn rats. Likewise, since the importance of prostaglandins in organoprotection is well known (Robert, 1979; Schmidt et al., 1991), these effects were investigated with and without prostaglandin synthesis inhibition by indomethacin (Sikiric et al., 1988).

Stable gastric pentadecapeptide BPC 157 is an originally anti-ulcer peptide implemented in inflammatory bowel disease trials, and now multiple sclerosis, LD1 could be not achieved recently largely reviewed (Sikiric et al., 2010, 2011, 2012, 2013, 2014; Seiwert et al., 2014).

The integrity of capsaicin somatosensory neurons and their protection were suggested to be related to the activity of BPC 157 (Sikiric et al., 1996).

Therefore, from this viewpoint, the focus was on the gastroprotective effect of the pentadecapeptide BPC 157, on gastric lesions produced in rats by 96% ethanol, restraint stress, and indomethacin (Sikiric et al., 1996). The possible involvement of sensory neurons in the salutary actions of BPC 157 (10 micrograms/kg, 10 ng/kg intraperitoneally) was studied with capsaicin, which has differential effects on sensory neurons: a high dose in adult (125 mg/kg subcutaneously, 3 months old) or administration (50 mg/kg subcutaneously) to neonatal animals (age of

the 7 days) destroys sensory fibers, whereas a low dose (500 micrograms/kg intraperitoneally) activates neurotransmitter release and protective effects on the mucosa (Table 1-4). In the absence of capsaicin, BPC 157 protected gastric mucosa against ethanol, restraint, and indomethacin application. In the presence of neurotoxic doses of capsaicin, the negative influence of capsaicin on restraint, ethanol, or indomethacin lesions consistently affected salutary activity of BPC 157. However, BPC 157 protection was still evident in the capsaicin-treated rats (either treated as adults or as newborns) in all of these assays. Interestingly, after neonatal capsaicin treatment, a complete abolition of BPC 157 gastroprotection was noted if BPC 157 was applied as a single nanogram-regimen, but the mucosal protection was fully reversed when the same dose was used daily. In line with the excitatory dose of capsaicin the beneficial effectiveness of BPC 157 appears to be increased as well (Table 4). Taken together, these data provide evidence for complex synergistic interaction between the beneficial effectiveness of BPC 157 and peptidergic sensory afferent neuron activity (Sikiric et al., 1996). In broader sense, this should be a basis for further suitable generalization that was evidenced with transected peripheral nerve, traumatic brain injury, and brain lesions and subsequent disturbances (somatosensory disorientation, seizures, catalepsy/stereotypies) induced by various agents applications (BobanBlagaic et al., 2005; Gjurasin et al., 2010; Ilic et al., 2010, 2011, 2011; Jelovac et al., 1998, 1999; Klicek et al., 2013; Sikiric et al., 1999; Tohyama et al., 2004; Tudor et al., 2010).

Particularly, the evidence that it both protected somatosensory neurons against capsaicin neurotoxicity and restored their function (Sikiric et al., 1996) suggests BPC 157 as an agent with neuroprotective properties (Sikiric et al., 1996). One extension could be the healing of rat transected sciatic nerve and improvement made by stable gastric pentadecapeptide BPC 157 (10 microg, 10ng/kg) applied shortly after injury intraperitoneally/ intragastrically /locally, at the site of anastomosis, or after non-anastomozed nerve tubing (7 mm nerve segment resected) (It is known that the spontaneous regenerative capabilities of the nerve stumps, as well as Schwann cells abilities to provide a permissive environment for axonal elongation, are insufficient when there is a 7 mm gap between nerve ends in rat, which also presents an obstacle for the standard therapy (Gold, 2000)) directly into the tube) (Gjurasin et al., 2010). Improvement was shown clinically (autotomy), microscopically/morphometrically and functionally (EMG, one or two months post-injury, walking recovery (sciatic functional index (SFI)) at weekly intervals). BPC 157-rats exhibited faster axonal regeneration: histomorphometrically (improved presentation of neural fascicles, homogeneous regeneration pattern, increased density and size of regenerative fibers, existence of epineural and perineural regeneration, uniform target orientation of regenerative fibers, and higher proportion of neural vs. connective tissue, all fascicles in each nerve showed increased diameter of myelinated fibers, thickness of myelin sheet, number of myelinated fibers per area and myelinated fibers as a percentage of the nerve transected area and the increased blood vessels presentation), electrophysiologically (increased motor action potentials), functionally (improved SFI), the autotomy absent. Thus, BPC 157 markedly improved rat sciatic nerve healing with particular point that severe autotomy – regularly present after transected sciatic nerve – was practically completely avoided in BPC 157-treated rats (Gjurasin et al., 2010).

The further extension could be the effect of BPC 157 after an induced traumatic brain injury (TBI) in mice by a falling weight. BPC 157 regimens (10 micrograms/kg, 10 ng/kg intraperitoneally) demonstrated a marked attenuation of damage with an improved early outcome and a minimal postponed mortality throughout a 24h post-injury period. Ultimately, the traumatic lesions (subarachnoidal and intraventricular haemorrhage, brain laceration, haemorrhagic laceration) were less intense and consecutive brain edema had considerably improved. Given prophylactically (30 min before TBI) the improved conscious/unconscious/death ratio in TBI-mice was after force impulses of 0.068 Ns, 0.093 Ns, 0.113 Ns, 0.130 Ns, 0.145 Ns, and 0.159 Ns. Counteraction (with a reduction of unconsciousness, lower mortality) with both micro- and ng-regimens included the force impulses of 0.068-0.145 Ns. A higher regimen presented effectiveness also against the maximal force impulse (0.159 Ns). Furthermore, BPC 157 application immediately prior to injury was beneficial in mice subjected to force impulses of 0.093 Ns-TBI. For a more severe force impulse (0.130 Ns, 0.145 Ns, or 0.159 Ns), the time-relation to improve the conscious/unconscious/death ratio was: 5 min (0.130 Ns-TBI), 20 min (0.145 Ns-TBI) or 30 min (0.159 Ns-TBI) (Tudor et al., 2010)

3. Results

In conclusion, these results should be viewed with numerous compounds and neuroprotective strategies more extensively discussed, evaluated and reviewed elsewhere (Maas et al., 2005; Marklund et al., 2006). However, 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 (Muir, 2006), and this study with BPC 157 (Tudor et al., 2010) evidenced the preserved consciousness and reduced mortality immediately after trauma in pentadecapeptide BPC 157-mice and subsequently, markedly reduced mortality, lowered brain edema, lowered the number and size of haemorrhagic traumatic lacerations, and lowered the intensity of subarachnoidal bleeding with significantly less intraventricular haemorrhage.

The additional extension could be the evidence that pentadecapeptide BPC 157 particularly attenuated neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) damage, including mortality (Sikiric et al., 1999) (of note, neuroprotection by immunophilin ligands lack the effect on MPTP-toxicity (Gold, 2000), significantly affected the dopamine system (Jelovac et al., 1998, 1999; Sikiric et al., 1999) (a system also implicated in the traumatic brain injury course) (Yan et al., 2001) and prevented/reversed catalepsy or stereotypy due to central dopamine system failure induced by various procedures (Jelovac et al., 1998, 1999; Sikiric et al., 1999). Accordingly, regional serotonin synthesis in the rat brain, assessed by α -methyl-L-tryptophan autoradiographic measurements showed that, BPC 157 given peripherally may readily cross the blood-brain barrier, affect region-specific brain 5-HT synthesis in rats leading to significantly increased synthesis in the substantia nigra (compacta and reticulata) structure and counteract serotonin syndrome (Boban-Blažić et al., 2005; Tohyama et al., 2004). Very recently, BPC 157 counteracts cuprizone-brain damage and motoric disability (Klicek et al., 2013). An additional emphasize may be that BPC 157 largely interferes with different NSAIDs-

toxicity, including their brain damages that appear subsequently their gastrointestinal and/or liver toxicity (Ilic et al., 2010, 2011, 2011).

Also, in addition to several other effects of BPC 157 (such as counteraction of acute and chronic gastric lesions, blood pressure modulation and prevention/reversal of chronic heart failure (Balenovic et al. 2009, 2012; Barisic et al., 2013)), BPC 157's antagonization of acute and chronic ethanol intoxication (Blagaic AB et al., 2004) was found to be an effect that is at least partly NO-dependent (Boban-Blagaic et al., 2006; Klicek et al., 2008; Lovric-Bencic et al., 2004; Sikiric et al., 1997).

One possible option of treatment (i. e., injury is often irreversible because inability of nerve tissue to regenerate and no therapeutic solution of this problem to date) is protection of secondary injury – zone of vascular and inflammatory reaction in nerve tissue to primary injury.

Taken together, the data providing the protection and rescue of the capsaicin neurotoxicity, and thereby, the evidence for complex synergistic interaction between the beneficial effectiveness of BPC 157 and peptidergic sensory afferent neuron activity (Sikiric et al., 1996) was useful, in a broader sense, for the further experiments. We argue that the significance of these beneficial effects (Sikiric et al., 1996) was confirmed by the healing effect of pentadecapeptide BPC 157 on transected and anastomosed as well as non-anastomosed rat sciatic nerve (Gjurasin et al., 2010). The final prove was provided from brain trauma studies resulting in brain damage and dysfunction from primary injury and subsequent secondary damage due to activation of pathophysiologic cascades, but the preserved consciousness and reduced mortality in pentadecapeptide BPC 157 treated along with lowered brain edema, lessened number and size of haemorrhagic traumatic lacerations, subarachnoidal bleeding and intraventricularhaemorrhage (Tudor et al., 2010).

Intesity of gastric lesions following 48h restraint stress		
	Adult	Newborn
Healthy	+++	
BPC 157 10ng	+/-	
BPC 157 10µg	+/-	
Capsaicin	+++	+++++
BPC 157 10ng + Capsaicin	++	+++
BPC 157 10µg + Capsaicin	+	+

Table 1. Long-term somatosensory neuron damage. Gastric lesions in 3-month-old adult rats following 48 hours restraint stress, treated with capsaicin two weeks (125 mg/kg subcutaneously) before or as neonates at 7 days old (50 mg/kg subcutaneously). BPC 157 (10 ng or 10 µg per kg intraperitoneally) treatment 1 hour before restraint; 16-20 rats per each experimental group.

Intensity of gastric lesions 24h after indomethacin application

	Adult	Newborn
Healthy	+++	
BPC 157 10ng	+/-	
BPC 157 10µg	+/-	
Capsaicin 50mg		+++++
BPC 157 10ng + Capsaicin 50mg		++
BPC 157 10µg + Capsaicin 50mg		+

Table 2. Long-term somatosensory neuron damage. Gastric lesions in 3-month-old adult rats following subcutaneous application of 30 mg/kg of indomethacin, treated with capsaicin as neonates at 7 days old (50 mg/kg subcutaneously). BPC 157 (10 ng or 10 µg per kg intraperitoneally) treatment 1 hour before indomethacin application; 16-20 rats per each experimental group.

Intensity of gastric lesions following 96% ethanol application

	Adult	Newborn
Healthy	+++	
BPC 157 10ng	+	
BPC 157 10µg	+	
Capsaicin	+++	+++
BPC 157 10ng + Capsaicin	+	+++
BPC 157 10µg + Capsaicin	+	++

Table 3. Long-term somatosensory neuron damage. Gastric lesions in 3-month-old adult rats 1 hour following intragastric application of 96% ethanol, treated with capsaicin two weeks (125 mg/kg subcutaneously) before or as neonates at 7 days old (50 mg/kg subcutaneously). BPC 157 (10 ng or 10 µg per kg intraperitoneally) treatment 1 hour before ethanol; 16-20 rats per each experimental group.

Excitation of somatosensory neurons in adult rats

Healthy	+++++
BPC 157 10ng	++
BPC 157 10µg	++
Capsaicin 500µg	++++
BPC 157 10ng + Capsaicin 500µg	+
BPC 157 10µg + Capsaicin 500µg	+

Table 4. Excitation of somatosensory neurons. Gastric lesions in adult rats 1 hour following intragastric application of 96% ethanol, treated with capsaicin (low dose 500µg/kg, intraperitoneally) and/or BPC 157 (10 ng or 10 µg per kg intraperitoneally) 1 hour before ethanol; 16-20 rats per each experimental group.

Author details

Predrag Sikiric*

Address all correspondence to: Sikiric@mef.hr

Department of Pharmacology, Medical Faculty University of Zagreb, Zagreb, Croatia

References

- [1] Balenovic D, Barisic I, Prkacin I, Horvat I, Udovicic M, Uzun S, Strinic D, Pevec D, Drmic D, Radic B, Bardak D, Zlatar M, Aralica G, LovricBencic M, SeparovicHanzevacki J, Romic Z, Sindic A, Seiwerth S, Sikiric P. Mortal Furosemide-Hypokalemia-Disturbances in Rats NO-System Related Shorten Survival by L-NAME. Therapy Benefit with BPC 157 Peptide More Than With L-Arginine. *J Clin Exp Cardiol.* 2012; 3: 201doi:10. 4172/2155-9880. 1000201
- [2] Balenovic D, Bencic ML, Udovicic M, Simonji K, Hanzevacki JS, Barisic I, Kranjcevic S, Prkacin I, Coric V, Brcic L, Coric M, Brcic I, Borovic S, Radic B, Drmic D, Vrcic H, Seiwerth S, Sikiric P. Inhibition of methyl digoxin-induced arrhythmias by pentadecapeptide BPC 157: a relation with NO-system. *Regul Pept.* 2009; 156(1-3): 83-89.
- [3] Barisic I, Balenovic D, Klicek R, Radic B, Nikitovic B, Drmic D, Udovicic M, Strinic D, Bardak D, Berkopic L, Djuzel V, Sever M, Cvjetko I, Romic Z, Sindic A, Bencic ML, Seiwerth S, Sikiric P. Mortal hyperkalemia disturbances in rats are NO-system related. The life saving effect of pentadecapeptide BPC 157. *Regul Pept.* 2013; 181: 50-66.
- [4] Blagaic AB, Blagaic V, Romic Z, Sikiric P. The influence of gastric pentadecapeptide BPC 157 on acute and chronic ethanol administration in mice. *Eur J Pharmacol.* 2004; 499(3): 285-290.
- [5] Boban Blagaic A, Blagaic V, Mirt M, Jelovac N, Dodig G, Rucman R, Petek M, Turkovic B, Anic T, Dubovecak M, Staresinic M, Seiwerth S, Sikiric P. Gastric pentadecapeptide BPC 157 effective against serotonin syndrome in rats.. *Eur J Pharmacol.* 2005; 512(2-3): 173-179.
- [6] Boban-Blagaic A, Blagaic V, Romic Z, Jelovac N, Dodig G, Rucman R, Petek M, Turkovic B, Seiwerth S, Sikiric P. The influence of gastric pentadecapeptide BPC 157 on acute and chronic ethanol administration in mice. The effect of N(G)-nitro-L-arginine methyl ester and L-arginine. *Med Sci Monit.* 2006; 12(1): BR36-45.
- [7] Evangelista S, Maggi CA. Protection induced cholecystokinin-8 (CKK-8) in ethanol-induced gastric lesions is mediated via vagal capsaicin-sensitive fibres and CCK-A receptors. *Br J Pharmacol.* 1991; 102: 119-122.

- [8] Gjurasin M, Miklic P, Zupancic B, Perovic D, Zarkovic K, Brcic L, Kolenc D, Radic B, Seiwerth S, Sikiric P. Peptide therapy with pentadecapeptide BPC 157 in traumatic nerve injury.. *Regul Pept.* 2010; 160(1-3): 33-41.
- [9] Gold BG. Neuroimmunophilin ligands: evaluation of their therapeutic potential for the treatment of neurological disorders. *Expert Opin Investig Drugs.* 2000; 9: 2331–2342.
- [10] Heiling M, Murison R. Intracerebroventricular neuropeptide Y protects against stress-induced gastric lesions in rat. *Eur J Pharmacol.* 1987; 137:127-129.
- [11] Hernandez DE. Neuroendocrine mechanisms of stress ulceration: Focus on thyrotropin releasing hormone (TRH). *Life Sci.* 1986;39:279-296.
- [12] Hernandez DE, Nemeroff CB, Orlando RO, Prange AJ. Influence of brain peptides on the development of stress gastric ulcers. In: S Szabo, Gy Mózsik, editors. *New Pharmacology of Ulcer Disease. Experimental and New Therapeutic Approaches.* New York: Elsevier; 1987. pp. 375-386.
- [13] Holzer P. Capsaicin: Cellular targets, mechanisms of action and selectivity for thin sensory neurons. *Pharmacol Rev.* 1991; 43:143-201.
- [14] Holzer P. Peptidergic sensory neurons in the control of vascular functions: Mechanisms and significance in the cutaneous and splanchnic vascular beds. *Rev Physiol Biochem Pharmacol.* 1991; 121: 49-146.
- [15] Ilic S, Drmic D, Zarkovic K, Kolenc D, Coric M, Brcic L, Klicek R, Radic B, Sever M, Djuzel V, Ivica M, BobanBlagaic A, Zoricic Z, Anic T, Zoricic I, Djidic S, Romic Z, Seiwerth S, Sikiric P. High hepatotoxic dose of paracetamol produces generalized convulsions and brain damage in rats. A counteraction with the stable gastric pentadecapeptide BPC 157 (PL 14736). *J Physiol Pharmacol.* 2010; 61(2): 241-250.
- [16] Ilic S, Drmic D, Zarkovic K, Kolenc D, Brcic L, Radic B, Djuzel V, Blagaic AB, Romic Z, Dzidic S, Kalogjera L, Seiwerth S, Sikiric P. Ibuprofen hepatic encephalopathy, hepatomegaly, gastric lesion and gastric pentadecapeptide BPC 157 in rats. *Eur J Pharmacol.* 2011; 667(1-3): 322-329.
- [17] Ilic S, Drmic D, Franjic S, Kolenc D, Coric M, Brcic L, Klicek R, Radic B, Sever M, Djuzel V, Filipovic M, Djakovic Z, Stambolija V, Blagaic AB, Zoricic I, Gjurasin M, Stupnisek M, Romic Z, Zarkovic K, Dzidic S, Seiwerth S, Sikiric P. Pentadecapeptide BPC 157 and its effects on a NSAID toxicity model: diclofenac-induced gastrointestinal, liver, and encephalopathy lesions. *Life Sci.* 2011; 88(11-12): 535-542.
- [18] Jancsó G, Király E, Jancsó-Gabor A. Pharmacologically induced selective degeneration of chemosensitive primary sensory neurones. *Nature.* 1977; 270: 741-743.
- [19] Jelovac N, Sikiric P, Rucman R, Petek M, Marovic A, Perovic D, Seiwerth S, Mise S, Turkovic B, Dodig G, Miklic P, Buljat G, Prkacin I. Pentadecapeptide BPC 157 attenu-

- ates disturbances induced by neuroleptics: the effect on catalepsy and gastric ulcers in mice and rats. *Eur J Pharmacol.* 1999; 379(1):19-31.
- [20] Jelovac N, Sikirić P, Rucman R, Petek M, Perović D, Konjevoda P, Marović A, Seiwerth S, Grabarević Z, Sumajstorčić J, Dodig G, Perić J. A novel pentadecapeptide, BPC 157, blocks the stereotypy produced acutely by amphetamine and the development of haloperidol-induced supersensitivity to amphetamine. *Biol Psychiatry.* 1998; 43(7): 511-519.
- [21] Klicek R, Sever M, Radic B, Drmic D, Kocman I, Zoricic I, Vuksic T, Ivica M, Barisic I, Ilic S, Berkopic L, Vrcic H, Brcic L, Blagaic AB, Coric M, Brcic I, Rokotov DS, Anic T, Seiwerth S, Sikiric P. Pentadecapeptide BPC 157, in clinical trials as a therapy for inflammatory bowel disease (PL14736), is effective in the healing of colocutaneous fistulas in rats: role of the nitric oxide-system. *J Pharmacol Sci.* 2008; 108(1): 7-17.
- [22] Klicek R, Kolenc D, Suran J, Drmic D, Brcic L, Aralica G, Sever M, Holjevac J, Radic B, Turudic T, Kokot A, Patrlj L, Rucman R, Seiwerth S, Sikiric P. Stable gastric pentadecapeptide BPC 157 heals cysteamine-colitis and colon-colon-anastomosis and counteracts cuprizone brain injuries and motor disability. *J Physiol Pharmacol.* 2013; 64(5): 597-612.
- [23] Lovric-Bencic M, Sikiric P, Hanzevacki JS, Seiwerth S, Rogic D, Kusec V, Aralica G, Konjevoda P, Batelja L, Blagaic AB. Doxorubicine-congestive heart failure-increased big endothelin-1 plasma concentration: reversal by amlodipine, losartan, and gastric pentadecapeptide BPC157 in rat and mouse. *J Pharmacol Sci.* 2004; 95(1): 19-26.
- [24] Maas AI, Schouten JW, Teasdale GM. Neuroprotection. In: Reilly P, Bullock MR, editors. *Head Injury*. London: Hodder Arnold Publishers; 2005. pp. 406–440.
- [25] Marklund N, Bakshi A, Castelbuono DJ, Conte V, McIntosh TK. Evaluation of pharmacological treatment strategies in traumatic brain injury. *Curr Pharm Des.* 2006; 12: 1645–1680.
- [26] Muir KW. Glutamate-based therapeutic approaches: clinical trials with NMDA antagonists. *Curr Opin Pharmacol.* 2006; 6: 53–60.
- [27] Robert A. Cytoprotection by prostaglandins. *Gastroenterology.* 1979; 77: 761-767.
- [28] Ruenzi M, Stolte M, Veljaca M, Oreskovic K, Peterson J, Ulcerative Colitis Study Group. A multicenter, randomized, double blind, placebo-controlled phase II study of PL 14736 enema in the treatment of mild-to-moderate ulcerative colitis. *Gastroenterology.* 2005; 128: A584.
- [29] Schmidt KL, Miller TA. Cytoprotection: Fact or fancy? The morphologic basis of gastric protection by prostaglandins. *Exp Clin Gastroenterol.* 1991; 1:119-132.
- [30] Seiwerth S, Brcic L, Vuletic LB, Kolenc D, Aralica G, Misic M, Zenko A, Drmic D, Rucman R, Sikiric P. BPC 157 and blood vessels. *Curr Pharm Des.* 2014; 20(7): 1121-1125.

- [31] Sikiric P, Gyires K, Seiwerth S, Grabarevic Z, Rucman R, Petek M, Rotkvic I, Turkovic B, Udovicic I, Jagic V, Mildner B, Duvnjak M, Danilovic Z. The effect of pentadecapeptide BPC 157 on inflammatory, non-inflammatory, direct and indirect pain and capsaicin neurotoxicity. *Inflammopharmacology*. 1993 ; 2:121-127.
- [32] Sikiric P, Seiwerth S, Rucman R, Turkovic B, Rokotov DS, Brcic L, Sever M, Klicsek R, Radic B, Drmic D, Ilic S, Kolenc D, Aralica G, Stupnisek M, Suran J, Barisic I, Dzidic S, Vrcic H, Sebecic B. Stable gastric pentadecapeptide BPC 157-NO-system relation. *Curr Pharm Des*. 2014; 20(7): 1126-1135.
- [33] Sikiric P, Marovic A, Matoz W, Anic T, Buljat G, Mikus D, Stancic-Rokotov D, Separovic J, Seiwerth S, Grabarevic Z, Rucman R, Petek M, Ziger T, Sebecic B, Zoricic I, Turkovic B, Aralica G, Perovic D, Duplancic B, Lovric-Bencic M, Rotkvic I, Mise S, Jagic V, Hahn V. A behavioural study of the effect of pentadecapeptide BPC 157 in Parkinson's disease models in mice and gastric lesions induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *J Physiol Paris*. 1999; 93(6):505-512.
- [34] Sikiric P, Rotkvic I, Mise S, Krizanac S, Gjurić V, Jukić J, Suchanek E, Petek M, Udovicic I, Kalogjera L, Geber J, Tucan-Foretic M, Duvnjak M, Philipp M, Balen I, Anic T. The influence of dopamine agonists and antagonists on indomethacin lesions in stomach and small intestine in rats. *Eur J Pharmacol*. 1988; 158: 61-67.
- [35] Sikirić P, Seiwerth S, Grabarević Z, Rucman R, Petek M, Jagić V, Turković B, Rotkvić I, Mise S, Zorićić I, Gjurasin M, Konjevoda P, Separović J, Ljubanović D, Artuković B, Bratulić M, Tisljar M, Jurina L, Buljat G, Miklić P, Marović A. Beneficial effect of a novel pentadecapeptide BPC 157 on gastric lesions induced by restraint stress, ethanol, indomethacin, and capsaicin neurotoxicity. *Dig Dis Sci*. 1996; 41(8): 1604-1614.
- [36] Sikirić P, Seiwerth S, Grabarević Z, Rucman R, Petek M, Jagić V, Turković B, Rotkvić I, Mise S, Zorićić I, Konjevoda P, Perović D, Jurina L, Separović J, Hanzevacki M, Artuković B, Bratulić M, Tisljar M, Gjurasin M, Miklić P, Stancić-Rokotov D, Slobodnjak Z, Jelovac N, Marović A. The influence of a novel pentadecapeptide, BPC 157, on N(G)-nitro-L-arginine methylester and L-arginine effects on stomach mucosa integrity and blood pressure. *Eur J Pharmacol*. 1997; 332(1): 23-33.
- [37] Sikiric P, Seiwerth S, Brcic L, Sever M, Klicsek R, Radic B, Drmic D, Ilic S, Kolenc D. Revised Robert's cytoprotection and adaptive cytoprotection and stable gastric pentadecapeptide BPC 157. Possible significance and implications for novel mediator. *Curr Pharm Des*. 2010; 16(10): 1224-1234.
- [38] Sikiric P, Seiwerth S, Rucman R, Turkovic B, Rokotov DS, Brcic L, Sever M, Klicsek R, Radic B, Drmic D, Ilic S, Kolenc D, Vrcic H, Sebecic B. Stable gastric pentadecapeptide BPC 157: novel therapy in gastrointestinal tract. *Curr Pharm Des*. 2011; 17(16): 1612-1632.
- [39] Sikiric P, Seiwerth S, Rucman R, Turkovic B, Rokotov DS, Brcic L, Sever M, Klicsek R, Radic B, Drmic D, Ilic S, Kolenc D, Stambolija V, Zoricic Z, Vrcic H, Sebecic B. Focus

- on ulcerative colitis: stable gastric pentadecapeptide BPC 157. *Curr Med Chem.* 2012; 19(1):126-132.
- [40] Sikiric P, Seiwerth S, Rucman R, Turkovic B, Rokotov DS, Brcic L, Sever M, Klicek R, Radic B, Drmic D, Ilic S, Kolenc D, Aralica G, Safic H, Suran J, Rak D, Dzidic S, Vrcic H, Sebecic B. Toxicity by NSAIDs. Counteraction by stable gastric pentadecapeptide BPC 157. *Curr Pharm Des.* 2013; 19(1) : 76-83.
- [41] Szabo S, Trier JS, Brown A, Schnoor J. Early vascular injury and increased vascular permeability in gastric mucosal injury caused by ethanol in the rat. *Gastroenterology* 1985; 88: 228-236.
- [42] Takeuchi K, Johnson LR. Pentagastrin protects against stress ulcerations in rats. *Gastroenterology.* 1979; 76: 788-792.
- [43] Tkalcević VI, Cuzić S, Brajsa K, Mildner B, Bokulić A, Situm K, Perović D, Glojnaric I, Parnham MJ. Enhancement by PL 14736 of granulation and collagen organization in healing wounds and the potential role of egr-1 expression. *Eur J Pharmacol.* 2007; 570(1-3): 212-221.
- [44] Tohyama Y, Sikirić P, Diksic M. Effects of pentadecapeptide BPC157 on regional serotonin synthesis in the rat brain: alpha-methyl-L-tryptophan autoradiographic measurements. *Life Sci.* 2004 ;76(3): 345-357.
- [45] Tudor M, Jandric I, Marovic A, Gjurasin M, Perovic D, Radic B, Blagaic AB, Kolenc D, Brcic L, Zarkovic K, Seiwerth S, Sikiric P. Traumatic brain injury in mice and pentadecapeptide BPC 157 effect. *Regul Pept.* 2010;160(1-3):26-32.
- [46] Urist MR. The first three decades of bone morphogenetic protein. *Osteologie.* 1996; 4: 207-233.
- [47] Yan HQ, Kline AE, Ma X, Hooghe-Peters EL, Marion DW, Dixon CE. Tyrosine hydroxylase, but not dopamine beta-hydroxylase, is increased in rat frontal cortex after traumatic brain injury. *Neuroreport.* 2001; 12(11): 2323-2327.