Pentadecapeptide BPC 157 and the central nervous system

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Review

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Abstract

We reviewed the pleiotropic beneficial effects of the stable gastric pentadecapeptide BPC 157, three very recent demonstrations that may be essential in the gut-brain and brain-gut axis operation, and therapy application in the central nervous system disorders, in particular. Firstly, given in the reperfusion, BPC 157 counteracted bilateral clamping of the common carotid arteries-induced stroke, sustained brain neuronal damages were resolved in rats as well as disturbed memory, locomotion, and coordination. This therapy effect supports particular gene expression in hippocampal tissues that appeared in BPC 157-treated rats. Secondly, there are L-NG-nitro arginine methyl ester (L-NAME)- and haloperidol-induced catalepsy as well as the rat acute and chronic models of 'positive-like' schizophrenia symptoms, that BPC 157 counteracted, and resolved the complex relationship of the nitric oxide-system with amphetamine and apomorphine (dopamine agents application), MK-801 (non-competitive antagonist of the N-methyl-D-aspartate receptor) and chronic methamphetamine administration (to induce sensitivity). Thirdly, after rat spinal cord compression, there were advanced healing and functional recovery (counteracted tail paralysis). Likewise, in BPC 157 therapy, there is specific support for each of these topics: counteracted encephalopathies; alleviated vascular occlusion disturbances (stroke); counteracted dopamine disturbances (dopamine receptors blockade, receptors super sensitivity development, or receptor activation, over-release, nigrostriatal damage, vesicles depletion), and nitric oxide-system disturbances ("L-NAME non-responsive, L-arginine responsive," and "L-NAME responsive, L-arginine responsive") (schizophrenia therapy); inflammation reduction, nerve recovery in addition to alleviated hemostasis and vessels function after compression (spinal cord injury therapy). Thus, these disturbances may be all resolved within the same agent's beneficial activity, i.e., the stable gastric pentadecapeptide BPC 157.

Key Words: BPC 157; central nervous system; cytoprotection; injury; nitric oxide system; peptide; regeneration

Introduction

The pleiotropic beneficial effects of the stable gastric pentadecapeptide BPC 157 have been reported in several organ systems (Sikiric et al., 2013, 2018, 2020a, b; Seiwerth et al., 2014, 2018; Kang et al., 2018; Gwyer et al., 2019; Park et al., 2020) (for an illustration; **Additional Table 1**). In this review, we focus on the effects of BPC 157 in central nervous system (CNS) pathology, with a specific focus on three very recent studies that highlight the essential role of the gut-brain axis in therapy application for CNS disorders (Perovic et al., 2019; Vukojevic et al., 2020; Zemba Cilic et al., 2021). Vukojevic et al. (2020) examined the therapeutic effects of BPC 157 in rats subjected to stroke and hippocampal ischemia/reperfusion injuries. Zemba Cilic et al. (2021) explored how BPC 157 can prevent catalepsy induced by L-NG-nitro arginine methyl ester (L-NAME) and haloperidol and counteracts deficits in acute and chronic rat models resembling 'positive-like' schizophrenia symptoms. Finally, Perovic et al. (2019) investigated the beneficial effects exerted by BPC 157 after rat spinal cord compression, namely advanced healing and functional recovery (counteracted tail paralysis).

BPC 157 is a native gastric pentadecapeptide that is non-toxic and has profound cytoprotective activity; it has been used in ulcerative colitis and multiple sclerosis trials (Sikiric et al., 2013, 2018, 2020a, b; Seiwerth et al., 2014, 2018; Kang et al., 2018; Gwyer et al., 2019; Park et al., 2020). In human gastric juice, BPC 157 is stable for more than 24 hours (Veljaca et al., 1995), and thus it has good oral bioavailability (always given alone) and beneficial effects in the entire gastrointestinal tract (Seiwerth et al., 2014, 2018; Kang et al., 2018; Sikiric et al., 2018, 2020a, b; Gwyer et al., 2019; Park et al., 2020). Furthermore, there is no need for carrier(s); this is an important distinction from the other standard peptides, which are functionally dependent on the addition of carrier(s) (Seiwerth et al., 2018) or are otherwise rapidly destroyed in human gastric juice (Veljaca et al., 1995). Consequently, stable BPC 157 is suggested to be a mediator of Robert's cytoprotection, which maintains the integrity of

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gastrointestinal mucosa (Seiwerth et al., 2014, 2018; Kang et al., 2018; Sikiric et al., 2018, 2020a, b; Gwyer et al., 2019; Park et al., 2020). We suggest that the contribution of BPC 157 to Robert's cytoprotection – that is, the ability to counteract fundamental alcohol-induced gastric lesions, which Robert called cytoprotection – and the ability to counteract lesions arising from the direct injurious contact of the noxious agent with the cell represent the peripheral connection between the gut and the brain axis.

Search Strategy and Selection Criteria

Studies cited in this review, which were published in the period from 1995 to 2020, were searched on the PubMed and the Google scholar database using the following keywords: BPC, BPC 157, pentadecapeptide BPC.

BPC 157 and Brain Lesions

In our recent study, we found that BPC 157 has a direct therapeutic effect in rats after a stroke (i.e., counteracts the injuries due to hippocampal ischemia/reperfusion). Specifically, BPC 157 was given after bilateral clamping of the common carotid arteries for 20 minutes, followed by reperfusion (Vukojevic et al., 2020). In the rats subjected to ischemia, BPC 157 was administered during reperfusion; it counteracted both early and delayed neural damage (i.e., 24 and 72 hours after reperfusion). In addition, BPC 157 promoted full functional recovery; this compound ameliorated the declines in several behavioral tasks: the Morris water maze, inclined beam-walking, and lateral push tests (Vukojevic et al., 2020). We also examined changes in messenger RNA (mRNA) expression in the brain 1 and 24 hours after the injury to determine the potential BPC 157 mechanism of action. BPC 157 treatment led to the upregulation of *Egr1*, *Akt1*, *Kras*, *Src*, *Foxo*, *Srf*, *Vegfr2*, *Nos3*, and *Nos1* and the downregulation of *Nos2* and *Nfkb* compared with untreated rats (*Mapk1* was not activated) (Vukojevic et al., 2020). The marked *Egr1* and *Vegfr2* upregulation suggests that BPC 157 has vascularisation properties, and this mechanism likely underlies its ability to modulate ischemia/reprofusion injury. The most interesting finding is the strong upregulation of *Nos3*, slight upregulation of *Nos1*, and suppression of *Nos2* compared with control animals. These effects may potentially provide a novel therapeutic solution for stroke, imparting specific beneficial effects on the CNS (i.e., for reperfusion, the amelioration of neuronal damage and, thereby, recovery without memory, locomotor, and coordination disturbances, and the expression of the particular genes in the hippocampus) (Vukojevic et al., 2020).

Reinforcing our findings, BPC 157 also counteracts various encephalopathies that appear after exposure to different agents or noxious procedures irrespective of the affected brain area: traumatic brain injury (Tudor et al., 2010), selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs; i.e., brain cyclooxygenases are a preferential inhibitory target of paracetamol; Sikiric et al., 2013; Lojo et al., 2016; Drmic et al., 2017), massive intestinal resection, cuprizone-induced multiple sclerosis-like pathology, insulin overdose, or magnesium overdose (Sikiric et al., 2013; Medvidovic-Grubisic et al., 2017). BPC 157 can also be applied to ameliorate concomitant convulsions due to NSAID-induced encephalopathy (Sikiric et al. 2013) (**Additional Table 1**). BPC 157 treatment regimens markedly attenuate brain damage induced by traumatic brain injury (a falling weight); there is an improved early outcome and minimal postponed mortality throughout the 24-hour post-injury period in mice (Tudor et al., 2010). Ultimately, BPC 157 therapy induces an apparent improvement: the subarachnoid and intraventricular hemorrhage, brain lacerations, hemorrhagic laceration, and consecutive brain edema becomes less intense (Tudor et al., 2010). Furthermore, BPC 157 treatment promoted recovery from severe muscle weakness that appears alongside brain lesions (Sikiric et al., 2013; Medvidovic-Grubisic et al., 2017).

When applied directly to the brain (Belosic Halle et al., 2017), BPC 157 may act as a possible antioxidant (Duzel et al., 2017; Drmic et al., 2018; Kolovrat et al., 2020). Notably, BPC 157 may scavenge reactive oxygen species due to its structure: it contains four carboxylic groups, and when they are reactivated (by glutathione or enzymes), the antioxidant activity is very high (Seiwerth et al., 2014, 2018; Kang et al., 2018; Sikiric et al., 2018, 2020a, b; Gwyer et al., 2019; Park et al., 2020). In addition, because most tissues contain BPC 157 (Seiwerth et al., 2018), it can bind and inactivate reactive free radicals at crucial positions not reachable by other antioxidants (Seiwerth et al., 2014, 2018; Kang et al., 2018; Sikiric et al., 2018, 2020a, b; Gwyer et al., 2019; Park et al., 2020).

The beneficial effects of BPC 157 on hippocampal ischemia/reperfusion injury (caused by bilateral clamping of the common carotid arteries) (Vukojevic et al., 2020) are supported by the course of Robert's cytoprotection, originally described for intragastric absolute alcohol-induced epithelial/endothelial injuries (Sikiric et al., 2020b), regarded as the Virchow triad. The ability to counteract Robert's gastric hemorrhagic lesion – the epithelial, endothelial, and thrombotic lesions arising from the direct, injurious contact of a noxious agent with a cell – underscores the cytoprotection (Szabo et al., 1986; Sikiric et al. 2020b). The cause–consequence relationship attributes the beneficial effects of BPC 157 with cytoprotection and implicates a rapid injury defense response (Sikiric et al., 2020b). BPC 157 directly protects the endothelium (Sikiric et al., 2006). Furthermore, after abdominal aorta anastomosis and major vein occlusion, BPC 157 both stops thrombosis formation and resolves already formed thrombi (Vukojevic et al., 2018; Gojkovic et al., 2020; Kolovrat et al., 2020). BPC 157 can also alleviate peripheral vascular occlusion disturbances and consequent syndromes by rapidly activating alternative bypass pathways (Duzel et al., 2017; Drmic et al., 2018; Vukojevic et al., 2018, 2020; Berkopic et al., 2020; Gojkovic et al., 2020; Kolovrat et al., 2020). The therapeutic effect is stable, despite continuous ligation (occlusion), and the ligation-induced disturbances do not reappear (Duzel et al., 2017; Vukojevic et al., 2018, 2020; Gojkovic et al., 2020; Kolovrat et al., 2020). Thereby, the evidence has demonstrated that the advanced injurious circle may be stopped and reversed with BPC 157 therapy. Namely, BPC 157-treated animals exhibit more extensive and faster reperfusion. Such recovery of vascular capacity may be an essential mechanism by which BPC 157 administration facilitates reperfusion because it counteracts all pre-existing disturbances and markedly attenuates organ lesions (Vukojevic et al., 2018; Kolovrat et al., 2020). Thus, it is likely that such rapid rescue of vascular capacity may contribute to the beneficial effects of BPC 157 on rats subjected to stroke and hippocampal ischemia/reperfusion damage recovery (Vukojevic et al., 2020).

There is additional evidence that BPC 157 leads to a rapid rescue of vascular capacity. In an acute ethanol intoxication in mice, there is sustained anesthesia, hypothermia, increased ethanol blood values, and 25% fatality over a 90-minute assessment period (Blagaic et al., 2004). BPC 157, regardless of whether it is administered before or after ethanol intoxication, rapidly counteracts the above-mentioned negative effects (Blagaic et al., 2004). Furthermore, BPC 157, when given after abrupt cessation of ethanol – continuous drinking of 20% alcohol drinking for 13 days, with a provocation on day 14 – attenuates withdrawal (assessed over 24 hours) (Blagaic et al., 2004). BPC 157 maintains vascular integrity to counteract alcohol leakage to tissues (Sikiric et al., 2020b), an effect that substantiates the previously emphasized evidence that BPC 157 directly protects the endothelium (Sikiric et al., 2006; 2018), which is a hallmark in cytoprotection studies (Szabo et

al., 1986). Consequently, researchers have consistently shown that BPC 157 strongly counteracts the effects of alcohol administered into the rat stomach, namely the rapid damage to the endothelium (Sikiric et al., 2006; 2018; Becejac et al., 2018). In addition, BPC 157 is a strong membrane stabilizer (Park et al., 2020). Therefore, BPC 157 also counteracts portal hypertension induced by chronic alcohol consumption. Based on the role that BPC 157 may play a role in antagonizing the effects of alcohol, Zemba et al. (2015) showed that BPC 157 can mitigate the general anesthetic potency of thiopental as well as the more prolonged anesthesia induced by the L-NAME/thiopental combination.

BPC 157 and Behavioral Disorders

Researchers have increasingly reported the importance of the nitric oxide (NO) system in the therapy of schizophrenia (MacKay et al., 2010) and extrapyramidal deficits linked with the more severe psychiatric symptoms (Weng et al., 2019), such as haloperidol-induced catalepsy (Jelovac et al., 1999a). Recently, Zemba Cilic et al. (2021) demonstrated that BPC 157 counteracts catalepsy induced by L-NAME and haloperidol as well as the deficits of acute and chronic rat models resembling "positive-like" schizophrenia symptoms in rat models (Moore and Grace, 2002; Rung et al., 2005). That combined counteraction may be the key to resolve the complex relationship between the NO system, amphetamine and apomorphine (the application of dopaminergic agents), MK-801 (a non-competitive antagonist of the N-methyl-D-aspartate receptor), and chronic methamphetamine administration (to induce sensitivity) (Zemba Cilic et al., 2021). This finding implicates interactions between BPC 157, dopamine, glutamate, and NO, which seem to be well-controlled by BPC 157 administration (Zemba Cilic et al., 2021). BPC 157 application resolves the unusual parallel matching action in counteracting the amphetamine-induced disturbances that L-NAME and L-arginine may cause, as well as the deficits in rat models resembling "positive-like" symptoms of schizophrenia (Przewlocka et al., 1996). We identified two distinctive NO system responses. Effects induced by acute apomorphine, chronic methamphetamine, acute MK-801, or acute haloperidol administration (catalepsy) are "L-NAME non-responsive, L-arginine responsive" (Zemba Cilic et al., 2021). Acute amphetamine-induced effects are "L-NAME responsive, L-arginine responsive" (Zemba Cilic et al., 2021). The fact that the NO-mediated effects are responsive to BPC 157 (Zemba Cilic et al., 2021) may be a consequence of the aforementioned counteracting potential of BPC 157 on disturbances induced by dopamine (Jelovac et al., 1999a; Sikiric et al., 2020b) and NO (Zemba et al., 2015; Kokot et al., 2016; Duzel et al., 2017). Besides, BPC 157 counteracts the symptoms in Parkinson's disease rodent models (induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or reserpine (Zemba Cilic et al., 2021)). Likewise, BPC 157 mitigates gastric lesions induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or reserpine (Zemba Cilic et al., 2021). Thus, the BPC 157/dopamine relationship exerts many effects. It includes the interference with dopamine receptor blockade (Jelovac et al., 1999a), the development of receptor supersensitivity (Jelovac et al., 1999a), dopamine receptor activation (Zemba Cilic et al., 2021), dopamine over-release (Zemba Cilic et al., 2021), damage to nigrostriatal dopaminergic neurons (Sikiric et al., 2020b), and depletion of dopamine vesicles (Sikiric et al., 2020b). BPC 157 also counteracts the adverse effects of neuroleptic application that appear outside of the CNS, such as prolonged QT intervals observed with electrocardiography (Strinic et al., 2017) or adverse effects in the gastrointestinal tract, such as gastric lesions or sphincter dysfunction (Belosic Halle et al., 2017). Consequently, BPC 157 might be essential for adequate dopamine function, and vice versa. Serotonin and BPC 157 show a similar relationship (Tohyama et al., 2004; Boban Blagaic et al., 2005). In rats, BPC 157 counteracts the symptoms of Porsolt's depression model and the chronic unpredictable stress depression model; it also fully counteracts all manifestations of serotonin syndrome and induces acute and chronic serotonin release in specific brain nigrostriatal regions (Tohyama et al., 2004; Boban Blagaic et al., 2005). Thus, unlike imipramine, BPC 157 exhibits a particular antidepressant effect, even when given systemically (Tohyama et al., 2004; Boban Blagaic et al., 2005).

Considering the BPC 157/NO relationship (Zemba et al., 2015; Kokot et al., 2016; Duzel et al., 2017), studies in stomach tissue have revealed that BPC 157 alone induces NO release, even in a condition that precludes the effect of L-arginine (Turkovic et al., 2004). In the most recent study, the authors reported that BPC 157 induces NO generation in the isolated aorta, likely through the activation of the Src/caveolin-1/endothelial nitric oxide synthase pathway (Hsieh et al., 2020). Thus, there is an advantage when using a substance (i.e, BPC 157) to modulate the NO system. This phenomenon may counteract the adverse effects of L-NAME, a nitric oxide synthase inhibitor, and L-arginine, a nitric oxide synthase substrate – that is, both L-NAME-induced hypertension and L-arginine-induced hypotension. Researchers have investigated how this effect may be practically translated into enhanced clinical efficacy regarding its interactions with the NO system, based on its particular effects seen in various models and species. There is also a supporting analogy with its counteracting effect on dopamine-induced adverse effects. A particular example is an amphetamine-induced stereotypy and haloperidol-induced catalepsy, both of which are counteracted by BPC 157 administration (Jelovac et al., 1999a; Zemba Cilic et al., 2021).

Although animal models have possible limitations (Jones et al., 2011), the BPC 157 mechanism of action, the BPC 157/dopamine/glutamate/NO interaction and effects, and the safe clinical profile of BPC 157 cannot be neglected (Seiwerth et al., 2014, 2018; Kang et al., 2018; Sikiric et al., 2018, 2020a, b; Gwyer et al., 2019; Park et al., 2020). These findings suggest that BPC 157 may influence essential functions and counteract the dysfunction underlying schizophrenia-like symptoms (Zemba Cilic et al., 2021). A contributing factor may be that BPC 157 increases serotonin release in nigrostriatal brain areas (during either acute or chronic administration, determined with highly specific alpha methyl-L-tryptophan autoradiography measurements). This release has a consequent antidepressant effect (including counteraction of serotonin syndrome) and relationships with the serotonin system (Tohyama et al., 2004; Boban Blagaic et al., 2005). Together with the counteracting effects of BPC 157 against ethanol exposure (Blagaic et al., 2004) and diazepam withdrawal (Jelovac et al., 1999b), we may speculate that BPC 157 has a particular modulatory effect, which may be necessary for maintaining the proper functioning of several systems.

BPC 157 is a novel and efficacious ethanol antagonist; it always counteracts negative effects due to ethanol exposure. Given that few pharmacological agents consistently act as ethanol antagonists, the negative effects elicited by acute or chronic alcohol disturbances (Blagaic et al., 2004) cannot be modulated by traditional pharmacotherapy (for a review, see Fadda and Rossetti, 1998). The GABAergic transmission was long ago implicated in the regulation of dopamine-mediated events (associated with extrapyramidal systems) and behavior that is dependent on striatal functions (catalepsy, stereotypies). Hence, it is interesting that BPC 157 counteracts GABA system disturbances, such as diazepam-induced tolerance/withdrawal (Jelovac et al., 1999b). Perrault et al. (1992) examined physical dependence, which is commonly studied in similar models as increased sensitivity to convulsant challenge, in mice that were chronically treated with diazepam for different times. After discontinuation of diazepam conditioning, the authors examined the latency to convulse

induced by the convulsant challenge (Perrault et al., 1992). The development of tolerance and physical dependence are among the most serious side effects of benzodiazepine therapy. Importantly, BPC 157 has anticonvulsant activity against several challenges (Sikiric et al., 2013; Lozic et al., 2020).

Boban Blagaic et al. (2009) addressed how BPC 157 application affects morphine-induced analgesia compared with the opioid antagonist naloxone. The authors used the hot plate test to determine how naloxone and BPC 157 counteract morphine-induced analgesia. Naloxone had an immediate counteracting effect on morphine-induced analgesia, but BPC 157 required more time (30 minutes) to produce an effect (Boban Blagaic et al., 2009). Haloperidol, a central dopamine antagonist, enhances morphine-induced analgesia, and BPC 157 counteracts this enhancement; this represents an additional dopamine-related effect. On the contrary, naloxone completely abrogates the analgesic effect; specifically, the pain reaction returns to basic levels. BPC 157, naloxone, and haloperidol per se fail to exert analgesic action (Boban Blagaic et al., 2009). It had been noted that in mice, BPC 157 counteracts inflammatory and non-inflammatory, prostaglandin-dependent and prostaglandin-independent pain (i.e., tail pinching, acetic acid, and magnesium sulfate-induced writhing in mice). Thus, BPC 157 may specifically interact with the opioid system and the pain reaction. In rats, BPC 157, in relation to the NO system, counteracts lidocaine-induced adverse effects and also prolongs local anesthesia (Lozic et al., 2020). Likewise, BPC 157 counteracts lidocaine-induced depolarisation *in vitro* (Lozic et al., 2020).

It is evident that BPC 157 has a particularly safe profile, which is quite distinctive from standard pharmacological agents. Indeed, unlike neuroleptics and antidepressants, BPC 157 has a particular cardioprotective and antiarrhythmic activity (Strinic et al., 2017; Lozic et al., 2020).

BPC 157 and Spinal Cord Injury

Perovic et al. (2019) reported that BPC 157 has a marked therapeutic effect pertaining to the recovery of rats with a spinal cord injury with tail paralysis (1-minute compression injury of the sacrocaudal spinal cord [S2–Co1]). Specifically, a single intraperitoneal BPC 157 administration at 10 minutes post-injury counteracts the negative effects. By contrast, the spinal cord injury and tail paralysis persist in untreated rats, assessed days, weeks, months, and a year after the injury (Perovic et al., 2019). Of note, BPC 157 attenuates the commonly caused damage (i.e., the substantial hemorrhagic zone in lateral and posterior white columns with sparing of the grey matter) (Perovic et al., 2019). Thereby, BPC 157 therapy results in evident functional (recovered tail paralysis), microscopic, and electrophysiologic recovery (Perovic et al., 2019). Of note, in rats with spinal cord injury, there is permanent reperfusion. Once BPC 157 is administered 10 minutes post-compression injury (which represents the advanced reperfusion stage), there is continuous protection and no spontaneous spinal cord injury-induced disturbances reappear (Perovic et al., 2019).

All spinal cord injuries immediately provoke hemorrhage, with subsequent death of neurons and oligodendrocytes (Fan et al., 2016). Hence, it is conceivable that early hemostasis may be beneficial and enable functional recovery after spinal cord contusion in rats (Fan et al., 2016). However, the effect exerted by BPC 157 is likely different from the simple hemostatic effect that would attenuate spinal cord injury (Fan et al., 2016), because BPC 157 also markedly improves thrombocyte function in rats without affecting coagulation factors (Stupnisek et al., 2015; Vukojevic et al., 2018; Konosic et al., 2019). During recovery from spinal cord injury, BPC 157 also directly protects the endothelium (Sikiric et al., 2006), alleviates peripheral vascular occlusion disturbances, rapidly activates alternative bypass pathways, and counteracts venous occlusion–induced syndromes (Duzel et al., 2017; Drmic et al., 2018; Vukojevic et al., 2018, 2020; Berkopic et al., 2020; Gojkovic et al., 2020; Kolovrat et al., 2020). Thus, assuming that there is a substantial venous contribution to the spinal cord compression (Bakker et al., 2015), it is conceivable that the reestablished blood flow mediated by BPC 157 may undoubtedly contribute to the rapid recovery effect (Perovic et al., 2019). Furthermore, considering that BPC 157 promotes permanent reperfusion after spinal cord compression, it should be noted that when BPC 157 is given during reperfusion, it counteracts stroke induced by bilateral clamping of the common carotid arteries. BPC 157 resolves neuronal damage and prevents memory, locomotor, and coordination deficits (Vukojevic et al., 2020). BPC 157 apparently exerts these effects by altering gene expression in the hippocampus (Vukojevic et al., 2020).

BPC 157 exerts multifactorial therapeutic activity in rats subjected to spinal cord injury (Perovic et al., 2019). There is the anti-inflammatory activity, amelioration of capsaicin-induced somatosensory neuronal damage (Sikiric et al., 1996), recovery of the sciatic nerve after transection (Gjurasin et al., 2008), and protection of cultured enteric neurons and glial cells (Wang et al., 2019). BPC 157 also ameliorates concussive trauma-induced brain injury (Tudor et al., 2010) and severe encephalopathies that affect various brain areas (Sikiric et al. 2013; Lojo et al., 2016; Drmic et al., 2017; Medvidovic-Grubisic et al., 2017). Furthermore, BPC 157 mitigates other consequences such as gastrointestinal and/or liver lesions (Sikiric et al. 2013; Lojo et al., 2016; Drmic et al., 2017) as well as severe muscle weakness (Medvidovic-Grubisic et al., 2017) (**Additional Table 1**). In addition, BPC 157 induces healing of mechanically severed muscles due to complete transection, crush, and denervation injuries (Mihovil et al., 2009) and intramuscular succinylcholine application (Stambolija et al., 2016). These benefits include muscle function recovery and counteraction of muscle lesions due to neuromuscular junction failure, fasciculation, paralysis, and hyperalgesia (Mihovil et al., 2009; Stambolija et al., 2016). BPC 157 interacts with various molecular pathways (Tkalcević et al., 2007; Chang et al., 2011, 2014; Cesarec et al. 2013; Huang et al., 2015; Hsieh et al., 2017, 2020; Kang et al., 2018; Vukojevic et al., 2018, 2020; Wang et al., 2019; Park et al., 2020) and, thereby, counteracts the increased levels of pro-inflammatory and pro-cachectic cytokines and annihilates tumor induced-muscle cachexia (Kang et al., 2018). Finally, BPC 157 shows intrinsic antidotal activity against the adverse effect of lidocaine and local anesthetics (in particular, limb function failure due to L4–L5 spinal cord intrathecal block, bradycardia and tonic-clonic convulsions, and depolarisation of HEK293 cells) (Lozic et al., 2020).

Based on the myriad of beneficial effects mediated by BPC 157, the functional rescue of the paralyzed tail, as well as the mitigation of axonal and neuronal necrosis, demyelination, and cyst formation (Perovic et al., 2019), may be the cause or consequence of the beneficial effects of BPC 157 on related disturbances (Seiwerth et al., 2014, 2018; Kang et al., 2018; Sikiric et al., 2018, 2020a, b; Gwyer et al., 2019; Park et al., 2020). Thereby, BPC 157 may impact all stages of the secondary injury phase (Perovic et al., 2019).

In conclusion, BPC 157 exerts beneficial effects on stroke, schizophrenia, and spinal cord injury (Perovic et al., 2019; Vukojevic et al., 2020; Zemba Cilic et al., 2021). Researchers have consistently demonstrated that BPC 157 exerts a myriad of beneficial effects throughout the body. There is no reason to indicate that the benefits of BPC 157 are limited by the validity of the utilized models and/or methodology limitations. Indeed, we can argue that the effectiveness, easy applicability,

safe clinical profile and mechanism of BPC 157 (i.e., BPC 157/dopamine/glutamate/NO system) represent an alternative, likely successful, future therapeutic direction for neurological conditions. Therefore, additional studies are needed to clarify how potential BPC 157 therapy would specifically deal with a mechanism of action that involves multiple subcellular sites in the CNS. The influence on the function of most, if not all, neuronal systems at the molecular, cellular, and systemic levels should be explored. Some visceral repetitive relay of the CNS or circumventricular organs, one of the few regions in the brain without the blood-brain barrier, is a known pathway by which a systemically administered peptide can exert a central effect. Thus, it must act within the gut-brain axis, regardless of whether this action is direct or indirect.

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Addi ional Table 1: *Sever encephalophaties and BPC 157.*
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Table 1 Sever encephalophaties and BPC 157

Study	Noxious procedure	BPC 157 regimens	Assessed injured targets, which BPC 157 therapy beneficially affected
Ilic et al., 2011a	Diclofenac (12.5 mg/kg intraperitoneally, once daily for 3 days) in rats.	BPC 157 (10 µg/kg, 10 ng/kg) was strongly effective throughout the entire experiment when given (i) intraperitoneally immediately after diclofenac or (ii) per-orally in drinking water (0.16 µg/mL, 0.16 ng/mL).	*Gastrointestinal lesions* Severe gastric and intestinal lesions *Liver lesions* Pronounced parenchymal necrosis, extensive microvesicular steatosis, and sinusoidal dilation; increased bilirubin, aspartate transaminase (AST), alanine transaminase (ALT) serum values, increased liver weight. *Brain lesions* Prolonged sedation/unconsciousness, brain edema particularly located in the cerebral cortex and cerebellum, more in white than in gray matter, damaged red neurons, particularly in the cerebral cortex and cerebellar nuclei, Purkinje cells and less commonly in the hippocampal neurons.
Ilic et al., 2010	Paracetamol overdose (5 g/kg intraperitoneally) in rats	BPC 157 therapy (10 µg, 10 ng, 10 pg/kg, intraperitoneally or intragastrically) was effective (microg-ng range) against paracetamol toxicity, given in early (BPC 157 immediately after paracetamol, prophylactically) or advanced stage (BPC 157 at 3 hours after paracetamol, therapeutically).	*Liver lesions* Increased ALT, AST, and ammonium serum values precede liver lesion, hepatomegaly. *Brain lesions* Neurons presented severe damage in several brain areas, Significant damage became apparent, accompanied by generalized convulsions. Edema was already present at 25 min following paracetamol application at the time of initiation of the generalized convulsions.
Ilic et al., 2009	Insulin overdose (250 IU/kg i.p.) in rats	BPC 157 (10µg/kg) given (i) intraperitoneally or (ii) intragastrically immediately after insulin.	*Gastrointestinal lesions* Severe gastric ulcers *Liver lesions* Hepatomegaly, fatty liver, increased AST, ALT, amylase serum values, and liver glycogen breakdown with profound hypoglycemia and calcification development. Calcium deposits were present in the blood vessel walls, hepatocytes surrounding blood vessels, and sometimes even in the parenchyma of the liver, mainly as linear and only occasionally as granular accumulation. *Brain lesions* Seizures (eventually fatal), severely damaged neurons in the cerebral cortex and hippocampus.
Drmic et al., 2017	Celecoxib (1 g/kg b.w. ip) in rats	Stable gastric pentadecapeptide BPC 157 (known to inhibit these lesions, 10 µg/kg, 10 ng/kg, or 1 ng/kg ip) and L-arginine (100 mg/kg ip), as well as NOS blockade (L-NAME) (5 mg/kg ip) given alone and/or combined immediately after celecoxib.	*Gastrointestinal lesions* Severe gastric lesions *Liver lesions* Marked steatosis, congestion, and necrosis at 24 h and at 48 h, along with increased enzyme serum values. *Brain lesions* Brain edema was commonly absent, though damaged (balloonized) red neurons were markedly expressed, particularly in the cerebral cortex and in the Purkinje cells.
Ilic et al., 2011b	Chronic ibuprofen (0.4 g/kg intraperitoneally, once daily for 4 weeks)	Stable gastric pentadecapeptide BPC 157 (10 µg, 10 ng/kg) inhibited the pathology seen with ibuprofen (i) when given intraperitoneally, immediately after ibuprofen daily or (ii) when given in drinking water (0.16 µg, 0.16 ng/mL).	*Gastrointestinal lesions* Severe gastric lesions *Liver lesions* Hepatomegaly, increased AST and ALT serum values with, and weight loss. *Brain lesions* Prolonged sedation/unconsciousness In particular, ibuprofen toxicity was brain edema,

			particularly in the cerebellum, with the white matter being more affected than in gray matter. In addition, damaged and red neurons, in the absence of anti-inflammatory reaction was observed, particularly in the cerebral cortex and cerebellar nuclei, but were also present, although to a lesser extent in the hippocampus, dentate nucleus, and Purkinje cells.
Lojo et al., 2016	Immediately after anastomosis creation, short-bowel rats were untreated or administered intraperitoneal diclofenac (12 mg/kg)	BPC 157 (10 μg/kg or 10 ng/kg), L-NAME, 5 mg/kg, L-arginine (100 mg/kg) alone or combined, intraperitoneally, and assessed 24 h later.	*Gastrointestinal lesions* Rats with surgery (short-bowel) alone exhibited mild stomach/duodenum lesions, while those also administered diclofenac showed widespread severe lesions in the gastrointestinal tract. *Liver lesions* Rats with surgery (short-bowel) alone exhibited considerable liver lesions, while those also administered diclofenac showed widespread severe liver lesions. *Brain lesions* Rats with surgery (short-bowel) alone exhibited severe cerebral/hippocampal lesions, while those also administered diclofenac showed widespread severe lesions in cerebellar nuclear/Purkinje cells and cerebrum/hippocampus.
Medvidovic-Grubisic et al., 2017	Magnesium sulfate (560 mg/kg intraperitoneally)	Medication (given intraperitoneally/kg at 15 min before magnesium) [BPC 157 (10 μg, 10 ng), L-NAME (5 mg), L-arginine (100 mg), alone and/or together] in rats.	*Muscle weakness, muscle lesions* Severe muscle weakness and prostration decreased muscle fibers in both quadriceps muscle and diaphragm. Rats that received either L-NAME or L-arginine as individual agents and then magnesium became feeble immediately after magnesium treatment and exhibited more muscle weakness and prostration. *Hypermagnesemia, hyperkalemia, increased serum enzyme values* Additionally increased hypermagnesemia, and newly emerged hyperkalemia (L-NAME or L-arginine). *Brain lesions* Prominent damage was observed in the cerebral cortex (also extended to cerebellar nuclei with both L-NAME and L-arginine). In HEK293 cells, the increasing magnesium concentration from 1 to 5 mM could depolarize the cells at 1.75 ± 0.44 mV.
Klicek et al., 2013	Multiple sclerosis suited toxic rat model, cuprizone (compared with standard, a several times higher regimen, 2.5% of diet regimen + 1 g/kg intragastrically/day)	BPC 157 (in drinking water 0.16 μg or 0.16 ng/mL 12 mL/d/rat + 10 μg or 10 ng/kg intragastrically/day) till the sacrifice at day 4.	*Muscle weakness* Cerebellar ataxia and impaired forelimb function. Control animals affected with cuprizone toxicity spare right forelimb, and thereby react only with one or no forelimb and have difficulty with maintaining body balance while rearing *Brain lesions* Cuprizone-controls clearly exhibited an exaggerated and accelerated damaging process; nerve damage appeared in various brain areas, with most prominent damage in the corpus callosum, laterodorsal thalamus, nucleus reunions, anterior horn motor neurons.

To illustrate the pleiotropic beneficial effect of the BPC 157 therapy, we summarized the BPC 157 studies of the severe encephalopathies that affect various brain areas.