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REVIEW ARTICLE

BPC 157 and Standard Angiogenic Growth Factors. Gastrointestinal Tract Healing, Lessons from Tendon, Ligament, Muscle and Bone Healing

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Abstract: Commonly, the angiogenic growth factors signify healing. However, gastrointestinal ulceration is still poorly understood particularly with respect to a general pharmacological/pathophysiological role of various angiogenic growth factors implemented in growth factors wound healing concept. Thereby, we focused on the stable gastric pentadecapeptide BPC 157, a peptide given always alone *vs.* standard peptidergic angiogenic growth factors (EGF, FGF, VEGF), and numerous carriers. Further, we reviewed how the gastrointestinal tract healing could be generally perceived (i) in terms of angiogenic growth factors, and/or (ii) through the healing of extra-gastrointestinal tissues healing, such as tendon, ligament, muscle and bone, and *vice versa*. Respected were the beneficial effects obtained with free peptides or peptides with different carriers; EGF, FGF, VEGF, and BPC 157, their presentation along with injuries, and a healing commonality, providing their implementation in both gastrointestinal ulcer healing and tendon, ligament, muscle and bone healing. Only BPC 157 was consistently effective in all of the models of acute/chronic injury of esophagus, stomach, duodenum and lower gastrointestinal tract, intraperitoneally, per-orally or locally. Unlike bFGF-, EGF-, VEGF-gastrointestinal tract studies demonstrating improved healing, most of the studies on tendon, muscle and bone injuries provide evidence of their (increased) presentation along with the various procedures used to produce beneficial effects, compared to fewer studies *in vitro*, while *in vivo* healing has a limited number of studies, commonly limited to local application, diverse healing evidence with diverse carriers and delivery systems. Contrary to this, BPC 157 - using same regimens like in gastrointestinal healing studies - improves tendon, ligament and bone healing, accurately implementing its own angiogenic effect in the healing. Thus, we claim that just BPC 157 represents in practice a pharmacological and pathophysiological role of various peptidergic growth factors.

Keywords: Angiogenic growth factors, pentadecapeptide BPC 157, gastrointestinal healing, tendon, ligament and bone healing, VEGF.

1. INTRODUCTION

Our pertinent focus is the anti-ulcer peptides, the stable gastric pentadecapeptide BPC 157 and its healing potential (for review see, *i.e.*, [1-6]). Gastrointestinal ulceration is still poorly understood particularly with respect to a pharmacological and pathophysiological role of various peptidergic growth factors [7, 8]. To solve the issue of the stable gastric pentadecapeptide BPC 157 [1-6] and peptidergic angiogenic growth factors [7, 8], this review focused on whether the gastrointestinal tract healing could be generally perceived in terms of angiogenic growth factors, through the healing of extra-gastrointestinal tissues healing, such as tendon, ligament, muscle and bone, and *vice versa*, and whether this relation could be perceived through the general significance of peptidergic angiogenic growth factors. The standard angiogenic growth factors healing significance as commonly acknowledged [7, 8] is in the principle defined in line of the consequent order, *i.e.*, *presence → responsibility → the healing effect* that has to be accomplished when peptide was given. Alternatively, we suggest that their healing significance is defined in a reverse order, first, the healing effects themselves of the given peptide, and then the responsibility and the presence of growth factors (thus, *the healing effect → responsibility → presence*) [1-6]. Thereby, this review focused on this healing issue poorly investigated together with the gastrointestinal tract healing and lessons from tendon, ligament, muscle and bone healing. This will be done with the respect to the various angiogenic growth factors, Epidermal Growth Factor (EGF), Fibroblast Growth Factor (FGF), Vascular Endothelial Growth Factor (VEGF) [7, 8], and stable gastric pentadecapeptide BPC 157, and a healing commonality, providing that they are implemented in both gastrointestinal ulcer healing and tendon, ligament, muscle and bone healing [1-6]. Special focus will be on the stable gastric pentadecapeptide BPC 157 [1-6].

While still far less investigated [1-6] than generally established angiogenic growth factors EGF, basic fibroblast growth factor (bFGF), VEGF [7, 8], the stable gastric pentadecapeptide BPC 157 (for review see, *i.e.,*[1-6]) could be still interesting. Stable in human gastric juice, originally an entire anti-ulcer peptide in whole gastrointestinal tract, thought to be a novel mediator of Robert's cytoprotection (GEPPPGKPADDAGLV, M.W. 1419, a partial sequence of human gastric juice protein BPC, in all studies, a peptide used with 99% (HPLC) purity, freely soluble in water at pH 7.0 and in saline), was always given alone, without any carrier in µg-ng dose ranges with different ways of application, intraperitoneal, intragastrical, in drinking water or topically, at the site of injury [1-6]. Besides being tested in therapy of inflammatory bowel disease (PL 14736) in clinical phase II, it has a very safe profile and LD1 could be not achieved [1-6], with particular wound healing effect (that specifically involves skin [9-11], and gastrointestinal tract [12-15], but also the healing of severe lesions of tendon [16-19], ligament [20],

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muscle [21-24], bone [25-27] and blood vessels [2, 28, 29] and even simultaneous healing of different tissues (*i.e*., fistulas [12, 15, 30]) and thereby, a particular angiogenic effect [2, 9-16, 20-24, 28-32] and interaction with NO-system in different models and species [33-40]). Thereby, these special healing characteristics may have a particular impact on the healing of gastrointestinal tract and other tissues healing (for review see, *i.e.* [1-6]), however, so far less commonly acknowledged. Namely, although, for instance, BPC 157 stimulates both egr-1 and naB2 genes [41-43], and egr-1 is a key mediator gene in the multifactorial mechanisms of duodenal ulcer development and healing because its protein, transcription factor product egr-1, regulates the expression of angiogenic growth factors [44], it still remains outside the scope of the generally established growth factors (*e.g*., EGF, bFGF, HGF, VEGF) [7, 8] particularly providing their molecular mechanisms carefully postulated [45].

Of note, BPC 157 with "wound healing effect" [1-6] (*i.e.*, that should be particularly considered as different tissues involved, skin [9-11], tendon [16-19], ligament [20], muscle [21-24], bone [25-27], nerve [46, 47], cornea [48], gastrointestinal tract [12-15] and blood vessels [2, 28, 29], simultaneous healing of different tissues (*i.e.*, fistulas [12, 15, 30])) markedly crosses the standard angiogenic growth peptides, *i.e*., a peptide given always alone, a peptide carrier free [1-6] *vs.* numerous carriers with standard angiogenic growth peptides (for review, see, *i.e*., [49, 50]), a distinction that should be particularly considered. Interestingly, based on its healing capabilities, particular wound healing ability, Wood suggested that this anti-ulcer pentadecapeptide may be a solution for Pavlov's physiology concept [51].

2. GASTROINTESTINAL HEALING WITH STANDARD ANGIOGENIC GROWTH FACTORS AND BPC 157

As an illustration, EGF prototypic importance in gastric ulcer healing was established [7, 8] based on persistence of increased EGF-R expression in the mucosal scar that replaced the gastric ulcer composed of dilated glands lined with poorly or aberrantly differentiated cells [52] and thereby, an important role of EGF in gastric ulcer healing and scar formation, and with exogenous EGF that significantly accelerates experimental gastric ulcer healing and increases the expression of cyclooxygense 2 (Cox2) [53, 54].

These claims of EGF greatest significance [7] were, however, commonly not combined with the route of application of EGF therapeutic regimen in gastric ulcer healing, nor they were particularly considered [7]. But, important notation (particularities in application way may underline particularities in tissues healing) is that the application in gastrointestinal research was intraperitoneal [55], submucosal, close to the ulcerated area [54], subcutaneous, bolus [56] or infusion [57, 58] while intragastrical application requires special microemulsion formulation [59]. Likewise, although not tested for gastric ulcer healing, unlike intraperitoneal or intravenous application, EGF, when given intraduodenally, did not affect gastric or pancreatic secretion and failed to raise significantly plasma EGF level [60].

This is at least party complicated by the introduction of the recombinant peptides [61]. Namely, besides subcutaneous infusion [61], human recombinant EGF was given in drinking water after induction of esophagitis [62]. Of note, patients identified with severe short bowel syndrome received human recombinant EGF 1-53 given mixed with enteral feeds and patients were treated for 6 weeks [63].

Along with upregulation of angiogenic growth factors, *e.g*., VEGF, bFGF, PDGF [64], EGF, HGF, IGF-1, VEGF, bFGF [7], EGF and TGF alpha [65, 66], the commonly acknowledged significance of standard growth factors considers all processes in gastroduodenal ulcers to be controlled by growth factors, cytokines, hormones and transcription factors [7]. Emphasis on particular angiogenic growth factors mentioned before suggests that they should be the major players responsible for this healing concept, and capable of concept realization in practice [7, 8].

All gastroduodenal ulcers [7, 8] were considered as caused by vascular and microvascular injury such as thrombi, constriction or other occlusions [7, 8], as a result of the tissue necrosis triggered by mucosal ischemia, free radical formation and cessation of oxygen and nutrient delivery, the initial pool of growth factors should be derived from the platelets, macrophages and injured tissue [7, 8]. Accordingly, ulceration triggers in cells lining mucosa of the ulcer margin, genes encoding for the growth factors and Cox2 in a well synchronized spatial and temporal manner [7, 8], and these growth factors produced locally, activate epithelial cell migration and proliferation *via* autocrine and/or paracrine actions [7, 8]. Thereby, without decreasing gastric acid secretion or concentration [67, 68] - but not viewed [7, 8] in terms of Robert's cytoprotection (gastric acid non-dependend protection) as we did indicate [3] - these growth factors contention fully reveals the long-standing wound theory in ulcer healing [69] toward these growth factors' use in gastroduodenal ulcer (long-ago, a hypothetical model was proposed in which prevention of ulcer formation or accelerated healing of ulcers by conventional therapies may be FGF dependent [70] or EGF dependent (*i.e*., rebamipide significantly accelerated ulcer healing, produced a significant increase in EGF and EGF-R expression in normal gastric mucosa, and increased expression of EGF and EGF-R in regenerating glands of the ulcer scar) [71]).

Additionally, this concept certainly holds their similar application also in the whole gastrointestinal tract (since gastroduodenal ulcers histologically and pathologically look similar to ulcers in the lower GI tract [69]). But also, this growth factors-wound healing concept accordingly reveals, at least in theory providing that gastrointestinal ulcers are essentially internal wounds that resist normal healing processes [69], the growth factors concurrent healing ability for extra-gastrointestinal tissues healing, *i.e*., tendon, ligament, muscle and bone healing. So far, these remained beyond consideration in gastrointestinal review of angiogenic growth factors [7, 8].

Obviously, for all of the mentioned growth factors, the healing potential and significance should be very high [7, 8]. In gastrointestinal ulcers, this healing generalization still provides that particular growth factors are responsible for particular activities. Specifically, it was claimed [7] that hypoxia triggers the activation of some of these genes (*e.g*., VEGF) *via* Hypoxia Inducible Factor (HIF), growth factors: EGF, HGF, IGF-1, their receptors and Cox2 for epithelial cell proliferation, migration, re-epithelialization and regeneration of gastric glands during gastric ulcer healing, Serum Response Factor (SRF), critical limiting factor for VEGF-induced angiogenesis, for re-epithelialization and muscle restoration, VEGF, bFGF (along with angiopoietins, nitric oxide, endothelin, prostaglandins and metalloproteinases) for angiogenesis, vascular remodeling and mucosal regeneration within gastric ulcer scar [7].

But, the healing generalization in gastrointestinal lesions regardless many detailed evidence [7, 8], seen from our point of view, should resolve a complex interplay with growth factors by defining the final beneficial healing effect and rescue from injury when growth factors are given. First, this should be proved by the extent to which realization of the healing has an effect on all gastrointestinal ulcers upon administration of these growth factors. And second, we argue fully considering the suggested healing commonality [1-6] and the growth factors common healing significance [7, 8] – that in gastrointestinal lesions healing - these should be proved by the realization of the extra-gastrointestinal tissues healing, the tendon, ligament, muscle and bone healing in practice upon an alike administration of these growth factors. And the final proof of concept should be the delivery of the effects by alike routes and dose ranges for their effective applications. Thus, when summarized (*alike healing effects ≈ alike routes and doses of application*), these should together reveal their real practical healing significance and potential in gastrointestinal and extra-gastrointestinal tissues healing [1-6].

The discrepancy gap between the theoretical consideration and practical realization (*dissimilar healing effects, dissimilar routes and doses of application*) in experimental models of corresponding injuries may challenge the healing commonality assessed in terms of those standard growth factors, particularly gastrointestinal lesions healing.

As an illustration of healing (non)commonality in terms of the mentioned standard angiogenic growth factors, in addition to the mentioned EGF-significance estimation [7, 8, 54-60], the initial demonstration revealed that intragastric administration of bFGF-w, acid-resistant bFGF-CS23 and PDGF-BB healed chronic cysteamine (mercaptamine)-induced duodenal ulcer in rats, and then, the healing of chronic gastric ulcers, chronic erosive gastritis and ulcerative colitis although they have no or modest acute gastric protective activity [67]. Likewise, rectal enemas containing bFGF or PDGF indeed accelerated the healing of chemically induced ulcerative colitis in rats [67]. On the other hand, VEGF, in addition to stimulating angiogenesis and granulation tissue production in duodenal ulcer healing, also had an acute gastroprotective effect, but no effect on or slightly aggravated the colonic lesions, while the injection of anti-VEGF neutralizing antibodies significantly improved healing in the lower GI tract lesions [69]. Increased expression of VEGF was positively correlated with duodenal ulcers [72] and negatively with ulcerative colitis inducing pathologic angiogenesis [69]. However, at least from our point of view [73], these generally contrast with the common healing role of VEGF-angiogenesis, *i.e.*, in skin wound healing [74, 75], as well as with general VEGF application, where the role of delivery systems should be particularly considered [50]. Also, with intestinal lesions, the others combined VEGF presentation with mucosal maintenance, and decrease with breakdown [76, 77]. Finally, providing that intragastric administration of peptide growth factors is limited by acid-proteolytic degradation in the stomach, and an expensive process for large-scale production of human recombinant proteins, the gene transfer of the cDNA of angiogenic growth factors into the lesion directly was proposed as a possible solution [72].

Contrary, in BPC 157 search (see for review, *i.e.*, [1-6]), we focused on its wide anti-ulcer potential in the whole gastrointestinal tract. In this, after initial presentation in stomach mucosa and lumen but also in other tissues (*i.e.*, central nervous system) [1] (note, presentation of mRNA of stable gastric pentadecapeptide BPC 157 was shown in human fetuses (Fig. **1**)), its particular stability in gastric juice (h-EGF, h-TGF alpha destroyed within 15 minutes while BPC 157 is stable more than 24 hours in human gastric juice [78]) claims *per se* its pharmacological and pathophysiological role along with the consistent beneficial effect of BPC 157 in different gastrointestinal models largely pointed out [1-6]. However, the studies showing more precisely the increased expression along with ulcers development are still absent. Anyway, pentadecapeptide BPC 157 along with prominent acute gastric, duodenal, small intestinal and colonic protective activity exhibited also the healing of chronic gastric and duodenal ulcers, and ulcerative colitis, given intragastrically, intraperitoneally, intrarectally or per-orally in drinking water, regularly within the same dosage (10 μg - 10 ng/kg) range (interestingly, in burned animals, given as a thin cream layer at the burned skin, BPC 157 strongly counteracted development of gastric stress lesions in burned animals) [1-6]. Also, providing a particular effect on both acute and chronic alcohol stomach lesions, and lesions induced by various NSAIDs, this pentadecapeptide was largely implemented in Robert's cytoprotection concept [1-6], exhibiting both cytoprotection and adaptive cytoprotection [1-6], and accordingly claimed to be a novel mediator of Robert's cytoprotection [1-6]. As such, BPC 157 exhibits a particular endothelium protection, and particular angiogenic response, maintains stomach blood vessels integrity, and strongly interacts with NO-system [1-6].

While demonstration of BPC 157 angiogenic effect includes different models (*i.e.*, sponge [32], and then gastrointestinal tract lesions [12-15, 30], skin [9-11], tendon [18, 31], ligament [20], muscle [21-23, 31], bone [26] healing) as well as interaction with NO-system [33-40] (see section BPC 157 and NO-system), BPC 157-stomach blood vessels integrity is well substantiated as well [2, 79] by a simple but accurate direct assessment [2, 79]. The presentation of serosal blood vessels with absolute alcohol instillation in fully distended rat stomach (the more distension, the more jeopeardized integrity, more stretched mucosa, sphincters more prone to reflux, more tiny and less filled blood vessels) accurately substantiates maintained stomach blood vessels integrity and supply along with original demonstration alcohol-necrotic injuries in stomach [2, 79, 80], and endothelium lesions and increased vascular permeability preceding alcohol-mucosal injuries [81], and thereby, endothelium protection and no vascular permeability as a prerequest for cytoprotective agent's activity [79, 81]. And thereby, as a consequence of a direct demonstration, BPC 157 exhibits an important counteraction after alcohol instillation, counteracting rapid blood vessels disappearance from serosa (in minutes) and lesions progression, after pentadecapeptide BPC 157 instillation (more than after standards (atropine, ranitidine, omeprazole)) the vessels presentation remains constant, and lesions of stomach, esophagus, and duodenum inhibited [2].

Also importantly, while compared with other gastrointestinal tract injuries, more direct studies of esophageal injuries with standard angiogenic growth factors are still lacking *i.e.*, [62, 82-85], in esophagitis, BPC 157 was shown to rescue esophagitis, given intraperitoneally or per-orally in drinking water along with recovered functions of different sphincters, *i.e.*, lower esophageal and pyloric sphincter [15, 40, 86-89], (and also urethral sphincter [90]), and consequently, BPC 157 rescues esophagitis that was induced by different noxious procedures [15, 40, 86-89].

On the other hand, as mentioned [62, 82-85], the evidence for standard angiogenic growth factors demonstrated that the increasing severity of esophagitis in rats with sialoadenectomy was prevented by exogenous administration of EGF (15 μg/kg/day of human recombinant EGF in drinking water after induction of esophagitis) [62]. Topical application of bFGF reduces esophageal stricture and esophageal neural damage after sodium hydroxide-induced esophagitis in rats [82]. Contrary, in esophagitis, FGF is suggested to be irreversibly bound to the extracellular matrix after its release, further amplifying its fibrotic capabilities [83]. FGF may be further upregulated in the repair response after injury to the esophageal endothelium, leading to proliferation of fibroblasts and resulting fibrosis [84]. The mechanism(s) responsible for the induction of VEGF expression during esophageal and/or gastrointestinal ulcer healing are illustrated with 100 μg of plasmid DNA encoding the full-length cDNA of rhVEGF165 injected into the esophageal muscle layers around the area of ulcer induction and the smaller ulcers in the VEGF group after seven days [85].

Also, important for the BPC 157's anti-ulcer effect, the counteraction of gastrointestinal, *i.e.*, stomach ulcer, was along with counteraction of other presented disturbances, thus, stomach ulcer may be a part of a larger syndrome, and counteraction of stomach ulcer a part of its larger therapeutic effect [1-6]. Ilustrative may be the beneficial effect on alcohol (*i.e.*, BPC 157 counteracts alcohol acute [33, 91] and chronic gastric lesions [92], liver lesion and portal hypertension [93], and aspiration [94, 95] and behavioral disturbances after acute alcohol intoxication and seizures withdrawal after chronic alcohol intoxication) [35, 96]), NSAIDs (*i.e.*, BPC 157 counteracts NSAIDs-gastric, intestinal, liver and brain lesions and bleeding disturbances) [97-100]. Also, we demonstrated that BPC 157 counteracts the development of alloxan-induced gastric ulcer [101], increases the healing of the skin wound in diabetic animals given topically [102], counteracts hypertension induced by fructose intake and resistance to insulin [1]. Likewise, besides stomach ulcer, BPC 157 (intraperitoneally or intragastrically immediately after insulin) consistently counteracts all insulin (over-dose of 250 IU/kg

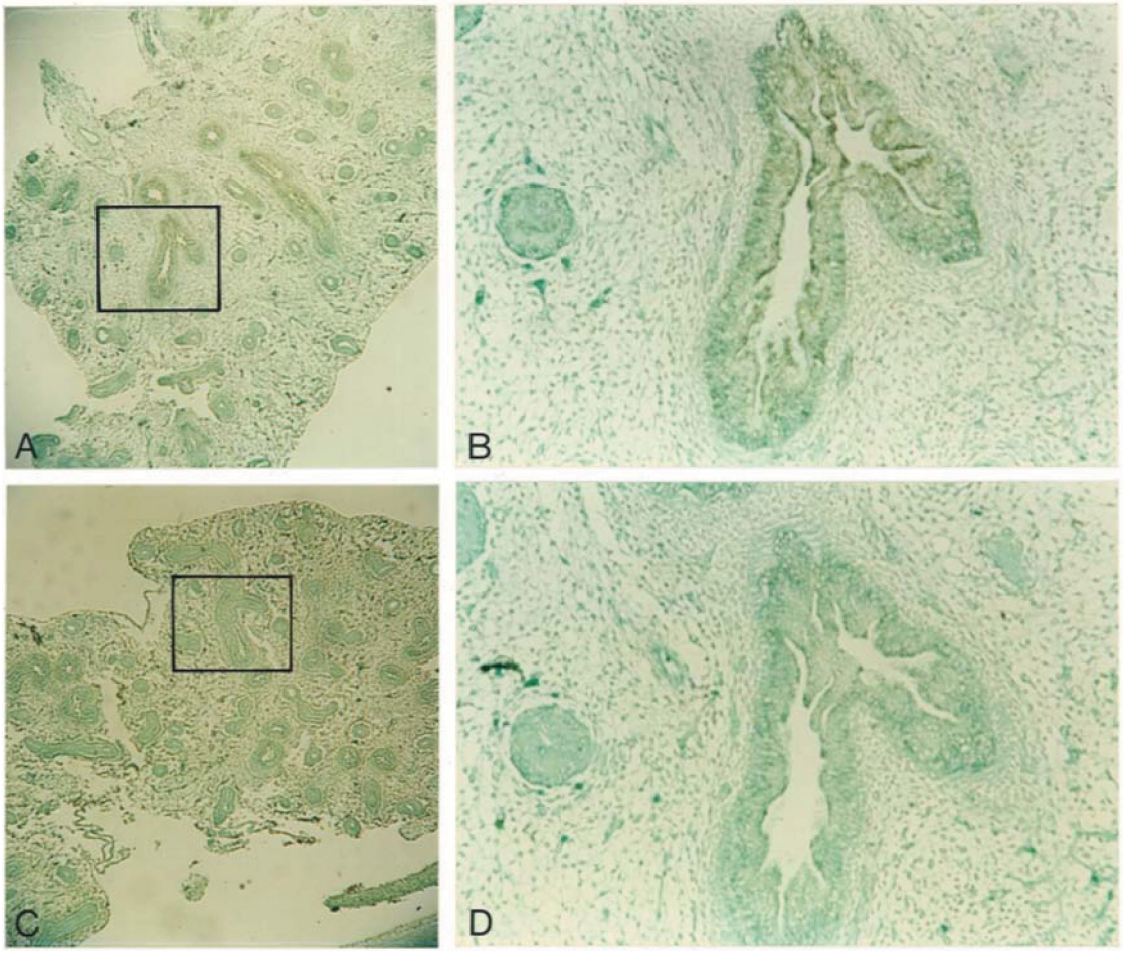

Fig. (1). Study used human BPC oligonucleotide probes and a specific BPC 157 polyclonal antibody to analyze BPC 157 expression and synthesis in human fetal and adult tissues. Northern blot hybridization revealed two mRNA species of 3 and 1.8 kb. Higher mRNA size was more pronounced in adult, while equal quantities of both mRNA species were detected in fetal tissues. High levels of BPC mRNA were found in adult gastrointestinal epithelium. By *in situ* hybridization and immunostaining BPC 157 was found in gastrointestinal mucosa, lung bronchial epithelium, epidermal layer of the skin and kidney glomeruli. These data suggest that in addition that BPC has been isolated from gastric juice and probably primarily acts in the gastrointestinal system, it may have additional regulatory roles in the function of human lung, kidney and skin. Presented is immunostaining of lung with a BPC 157 polyclonal antibody of a 12-week human embryo. (**A**) Positive staining is observed in bronchi and buds of bronchial branches. (**B**) Enlarged area from insert in A. (**C**) An adjacent section to A stained with a control-pre-immune serum. (**D**) Higher magnification of C (insert) does not yield a positive signal. Vector peroxidase staining, counter-stained with light green.

i.p.) disturbances and fatal outcome (*i.e.*, seizures (eventually fatal), severely damaged neurons in cerebral cortex and hippocampus, hepatomegaly, fatty liver, breakdown of liver glycogen with profound hypoglycemia and calcification development (*i.e.*, in the blood vessel walls, hepatocytes sourrounding blood vessels and sometimes even in parenchyma of the liver)) [103].

Thus, summarizing evidence based on the demonstrated beneficial effects of the given peptidergic factors in gastrointestinal lesions models, it seems that the healing commonality in gastrointestinal tract best fits with the evidenced beneficial effects of stable gastric pentadecapeptide BPC 157 [1-6]. This conclusion specifically accounts the effects seen in models of acute/chronic injury of esophagus, stomach, duodenum and lower GI tract used in the presented studies, beneficial activity, no activity or even worsening activity, and the general evidence that the gastroduodenal ulcers and ulcers in the lower gastrointestinal tract shear similar histological and pathological presentation, and all (patho)physiology processes supposed to be controlled by emphasized growth factors, *i.e.*, EGF, bFGF, HGF, VEGF as suggested [7, 8] while only BPC 157 [1-6] was most consistently found to be effective in all of the models of acute/chronic injury of esophagus, stomach, duodenum and lower GI tract.

Further, the significance of their obtained healing of gastrointestinal lesions [7, 8] and the alike delivery of the healing effect to the injured tissue (*i.e.*, the acceleration of gastric ulcer healing and hyperemia at the ulcer margin exhibited by locally applied EGF, HGF and bFGF were similar to those obtained with systemic administration of these growth factors [54]) will be challenged with their beneficial effect for extra-gastrointestinal tissues healing, *i.e.*, tendon, ligament, muscle and bone healing.

2.1. Tendon and Ligament vs. Ulcer Healing

One essential combining point should be the angiogenesis providing the growth of new capillaries from existing blood vessels surrounding the ulcer crater as the rate-limiting step in ulcer healing [7, 8] and the tendon as a hypovascular, hyponeural, hypocellular tissue that could thereby hardly heal [16, 18, 19, 31]. Of note, tendons are during development rich in cells, metabolically active and containing high number of blood vessels [104] eventually maturing to hypocellular, hypovascular and hyponeural structures [105, 106] a point generally not appreciated in angiogenesis search [107].

Thus, from theoretical point of view of growth factors angiogenesis/effectiveness, the tendon tissue would be more suited for angiogenic factors activity assessment (and thereby, for practical demonstration of the effectiveness as we did with BPC 157 [16, 18, 19, 31]) providing that the cornea and subcutaneous locales (*i.e.*, FGF and VEGF) are not representative of the sites where angiogenesis occurs during pathologic development [107].

Although the methods for assessing angiogenesis, however, vary dramatically in what they measure, frequently lack quantification, and are limited in their clinical relevance [107], in experimental gastric and duodenal ulcers, situation is well defined: stimulation of angiogenesis leads to development of granulation tissue that is essential for the healing process, and thereby, stimulation of angiogenesis in granulation tissue by treatment with exogenous bFGF, PDGF or VEGF dramatically accelerates healing of experimental gastric and duodenal ulcers in rats [70, 108, 109] while blockade of these angiogenic factors resulted in impaired healing of duodenal ulcer [70, 108, 109].

On the other hand, in tendon healing, most of angiogenic growth factors evidence combined their increased values with the various procedures used to produce beneficial effects (*i.e.*, tendon repair and regeneration, tensile strength at the time of mobilization). Used beneficial procedures combined with increased presentation of growth factors were: *i.e.*, platelet-rich plasma injection (increased were human growth hormone (hGH), insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), bFGF or FGF-2, VEGF, and platelet-derived growth factor-BB (PDGF-BB)) [110], adipose-derived stem cells (FGF and VEGF increased) [111], intra-articular tendon transfer in rabbits to stimulate ACL reconstruction (fibroblast growth factor-2 (FGF-2), VEGF, bone morphogenetic protein-2 (BMP-2), and BMP-7 increased) [112], and finally, spontaneous tendon repair (increased were bFGF, BMP-12, BMP-13, BMP-14, cartilage oligomeric matrix protein (COMP), connective tissue growth factor (CTGF), platelet-derived growth factor-B (PDGF-B), and transforming growth factor-beta1 (TGF-beta1) [113]. The other studies were *in vitro* [114, 115].

In vivo studies, FGF-2 (100 microg/kg) was applied, for instance, in a fibrin sealant [116-118]. Thomopoulos and collaborateurs [119] showed that a bFGF and PDGF-BB linked to a heparin-fibrin sustained release delivery system can improve tendon range of motion and excursion in a dog tendon repair model. However, the tensile properties were not improved. Besides, it was pointed out [120] that these results [119, 121] could have been due to the growth factor itself or to the heparin portion of the delivery system. Likewise, native to tendon, IGF-1 [122], with binding proteins keeping it more stable and locked with matrix, can drive collagen systhesis, still needs variant form (the recombinant LR3-IGF-1), carrier and injection into the wound [123]. Likewise, GDFs 5, 6, 7, need collagen sponges in the tendon defects [124].

Thus, these angiogenic growth factors provide diverse healing evidence [116-124]. It seems that with diverse carriers and delivery systems their possible own angiogenic effect like their own healing effect could be not adequately represented, and therefore, common clue with the beneficial effect in ulcer healing, at least from the tendon healing and common viewpoint of the angiogenic effect, not established. Likewise, for EGF delivery, for example, wound dressing composed of hylorunic acid and collagen sponge containing EGF [125] or wound pH-responsive sustained release of therapeutics from a poly(NIPAAm-co-AAc) hydrogel [126] contrast with subcutaneous infusion or bolus used in EGF-gastric ulcer studies [7, 8, 53-60] (and the evidence that the effects of locally applied EGF, HGF and bFGF were similar to those obtained with systemic administration of these growth factors [54]).

And thereby, for mentioned standard angiogenic growth factors, with respect to their more limited effect on tendon healing that always needs carrier [116-124], and with respect to the indicated angiogenic commonality [7, 8], the significance of their particular angiogenic effect postulated in gastrointestinal ulcers healing and their particular healing of gastrointestinal lesions [7, 8], seem to be less certain.

Contrary, in addition to *in vitro* studies [16, 17], *in vivo* studies using the same protocol like in gastrointestinal studies, BPC 157 was shown to ameliorate healing of tendon [16, 18, 19] as it previously did ameliorate bone pseudoarthrosis healing [25], respectively, as well as other tissues (for review see, *i.e.*, [1-6]). Thereby, the subsequent focus was on Achilles tendon-to-bone healing: tendon to bone could not be healed spontaneously, but it was recovered by this peptide [18, 19]. In this, the angiogenic potential of BPC 157 was carefully reevaluated [31]. In an attempt to show the particular significance of BPC 157's angiogenesis in the *in vivo* healing (no direct angiogenic effect of BPC 157 on cell cultures), we demonstrated [31] that in early post-injury periods, BPC 157 therapy induced a prominent increase of angiogenesis in rats with transected Achilles tendon or quadriceps muscle and in rats with crushed muscle. This was consistently visualized with different endothelial cell antigens, FVIII (involved in platelet adhesion and aggregation, present on endothelial cells of mature blood vessels) and CD34 (involved in leukocyte adhesion and endothelial cell migration during angiogenesis, present on capillary endothelial cells), as well as with VEGF presentation (main factor in angiogenesis, expressed on endothelial cells, mitogen for vascular endothelial cells) [31]. Generally, BPC 157 increased the number of VEGF, CD34 and FVIII positive vascular elements, and angiogenic response was regularly augmented and shifted toward the left. And, most importantly, this angiogenic effect was along with functional, biomechanical, microscopical and clinical recovery in tendon-injured rats, peptide stability (along with suggested unusual stability (no degradation in human gastric juice), high resistance to otherwise highly degradating media) [1-6]) presented with pentadecapeptide BPC 157 systemic administration, ascertaining suitable delivery even to otherwise highly hypocelullar, hypovascular, hyponeural tissues (*i.e.*, tendon) characteristics that generally impair medication accessibility and therapeutic efficacy. Note, the same angiogenic effect was with functional, biomechanical, microscopical and clinical recovery in transected ligament-injured rats [20]. Illustratively for tendon/ligament healing commonality and BPC 157 healing potential, all BPC 157 regimens (μg-ng-regimens given alone intraperitoneally, per-orally and topically, dose-regimens and application methods that had been successfully used before) [1-6] demonstrated a consistent and extensive improvement [20]. Improved were function (walking, absent postinjury contracture of the knee and no valgus instability, motor function), biomechanic (the 14th postoperative day achieved normal healthy values (*i.e.*, in breaking force, elongation, absorbed energy, stiffness) subsequently maintained (as seen at the 21st postsurgery day), macroscopic presentation (silvery striated structure in the whole ligament as a final outcome fully approached to the presentation of normal noninjured ligament) and microscopically, during the first seven postoperative days, the formation of granulation tissue synchronous with faster and better organization of connective tissue, more collagen fibers that were longitudinally oriented improvement [20]. Contrary, formation of ossicles/cartilage in tendon/ligament [127] or tendon/ligament formation in general [128] produced by some standard peptides growth factors' application commonly used to prove the healing [127, 128] may rather indicate an essentially anomalous (healing) overlap after use of these growth factors that could not substitute regular ligament healing course [20].

Thus, unlike standard angiogenic growth factors, providing the diversity of the obtained evidence [116-124], we could argue that BPC 157 should be regarded as one of angiogenic peptidergic factors, since peptide has peptidergic activity and stability of its own and not need for carrier or carrier's activities, evidenced ameliora-

tion unmistakably attributed to its own healing effect [1-6]. Thus, it seems that the value of its angiogenic effect is adequately represented, and therefore, with particular tendon healing and angiogenesis, common clue with the better beneficial effect in ulcer healing, at least from the common viewpoint of the angiogenic effect clearly established. In support, in tendon healing, the in vivo evidence (a particular effect on tendocytes) [16, 18, 19] was along with evidence obtained *in vitro* studies [16, 17]. Note, BPC 157's tendon healing was shown to be mediated by the activation of the FAK-paxillin pathway [17]. This may have a general significance, endothelial cell migration during vascular remodeling occurs by means of a Rac1 and FAK activation pathway *in vivo* [129].

Finally, these are also supported with the results in human endothelial cells, showing that there is no direct angiogenic effect of BPC 157 on cell cultures. Thus, these *in vivo* and *in vitro* findings together substantiate that the angiogenic potential of BPC 157 seems to be closely related to the healing process *in vivo* with BPC 157 stimulating angiogenesis by up-regulating VEGF expression. And finally, these effects are along with the evidence that BPC 157 stimulates both egr-1 and naB2 genes [41-43].

2.2. Muscle Healing vs. Ulcer Healing

Based on the evidence (over-expression of FGF2 increased fibroblast proliferation and collagen deposition, accelerated endothelial proliferation, and enhanced cardiomyocyte hypertrophy after infarction, curbed infarct expansion and preserved left ventricular function) obtained with FGF2-knockout (FGF2-KO) animals, FGF2 may be more important in healing of infarcts compared with skin wounds (*i.e.*, skin wound healing in FGF2-knockout (FGF2-KO) animals is only slightly delayed) [130].

Likewise, in muscle healing most evidence relates the increased values of growth factors during post-injury muscle regeneration (*i.e.*, increased were IGF-I, IGF-II, bFGF-2, and TGF-beta1 [131], bFGF-2 [132], bFGF-2, and TGF-beta1 [133], or exercise (*i.e.*, exercise-induced VEGF-A expression was shown to be greater in capillaries than in muscle fibers [134]). Interestingly, the immune neutralization of bFGF reduced the number of capillaries, macrophages and mast cells, and delayed necrotic myofiber phagocytosis, but, the immune neutralization of IGF1 or TFG beta 1 promoted muscle revascularization, macrophage infiltration and necrotic myofiber phagocytosis [135].

In vivo evidence goes with continuous release polygalactone polymer rod containing basic fibroblast growth factor (bFGF) that prevents incisional hernia formation [136], or decreases increased vimentin expression of strain injured skeletal muscle [137]. Using different delivery systems of bFGF (injection or sustained release from polymers) in various animal models (crush injured, denervated dystrophic muscle) did not result in an improvement of muscle healing [138]. Mostly limited to direct local administration, bFGF, IGF-1, and NGF elicit no full muscle recovery, but rather scar tissue accumulation [139, 140]. Illustratively, systemic delivery of recombinant IGF-I protein *via* mini-osmotic pump (~1.5 mg/kg/day) was compared with a single electrotransfer-assisted plasmid-based gene transfer, to hasten functional repair of mouse tibialis anterior muscles after myotoxic injury [141]. Thus, commonly, the relative efficacy of different modes of delivery was considered to be an important consideration when assessing the therapeutic potential of various proteins for treating muscle injuries and skeletal muscle diseases [141]. Thereby, to promote efficient muscle healing, the others [139, 140] emphasized the ability of adenovirus to mediate direct and *ex vivo* gene transfer of beta-galactosidase into the injured site delivering an efficient and persistent expression of these growth factors in the injured muscle (of note, unlike those angiogenic growth factors, EGF inhibits the proliferation and fusion of myoblasts *in vitro* [139, 140]. Contrary, the use of antifibrotic agents was also suggested [142].

Thus, while FGF potential to induce skeletal muscle angiogenesis was extensively investigated (for review see, *i.e.*, [143]), the significance of such FGF, and even VEGF [144] for muscle healing means a mostly limited effect to direct local administration combined with different modes of delivery [141]. Taking all these caveats in consideration, the possible angiogenic effect is not adequately represented for efficient healing demonstration. Namely, in extensive muscle injury, the proliferation of fibroblasts can quickly lead to an excessive formation of dense scar tissue, which impedes regeneration of the muscle and results in an incomplete recovery [139], and thereby use of antifibrotic agents, *i.e.*, suramin, that inhibits angiogenesis [145], was also suggested [142]. Thus, concluding, it seems to us that for muscle healing with standard angiogenic factors (*i.e.*, the controversy arises since during muscle regeneration, it is presumed that trophic substances released by the injured muscle activate the satellite cells [139] while the relative efficacy is considered to be depended on different modes of delivery [146]) the role of standard angigoenic factors in angiogenesis as the common healing clue, with their beneficial effect in ulcer healing, at least from the viewpoint of the common angiogenic effect, seems to be not established.

Consequently, we could argue from the muscle healing point of view, respecting indicated angiogenic commonality that the significance of their suggested particular angiogenic effect in gastrointestinal ulcers healing and their particular healing of gastrointestinal lesions [7, 8], may be also less certain.

Contrary, using the same protocol like in gastrointestinal studies [1-6], thus, always a peptide, given alone, carrier free, BPC 157 was shown to ameliorate healing of severely injured muscle in various animal models (Fig. **2**) (complete transection [21], crush [22, 23], denervation [23], systemic corticosteroid application after crush injury [24] that would spontaneously hardly heal. BPC 157 therapy as the systemic peptide treatment induces healing of transected quadriceps muscle promptly and then maintains the healing with functional restoration [21]. Prompt recovery is extensive involving biomechanic (load of failure increased), (ii) function (walking recovery and extensor postural thrust/motor function index returned toward normal healthy values), microscopy/immunochemistry (*i.e.*, always mostly muscle fibers connect muscle segments, absent gap, significant desmin positivity for ongoing regeneration of muscle, larger myofibrils diameters on both sides, distal and proximal (*i.e.*, normal healthy rat-values reached)), macroscopic presentation (stumps connected, subsequently, atrophy markedly attenuated, finally, presentation close to normal non-injured muscle, no post-surgery leg contracture) [21]. Subsequently, the muscle healing after severe crush was markedly improved, also given as a peptide cream locally [22], even in the conditions of the severe healing impairment induced by systemic corticosteroids [23]. Taking these findings in muscle healing accordingly with the noted effect on tendon and ligament healing) [16-20], it means that muscle-tendon unit function is commonly improved. In these terms, it seems that its angiogenic effect is effectively functioning (*i.e.*, BPC 157- muscle/tendon angiogenesis shered increased the VEGF, CD34 and FVIII presentation, angiogenic response augmented and shifted toward the left) the beneficial value of its angiogenic effect is adequately substantiated [31], and therefore, common clue with the better beneficial effect in ulcer healing effect [1-6], at least from the common viewpoint of the muscle healing and angiogenic effect clearly established.

Thus, muscle post-transection healing and injured muscle generally - consistently improved - may suggest this peptide effective therapeutic application (particularly providing muscle/tendon/ligament healing), and in gastrointestinal lesions better healing effect [1-6]. This reveals the value of regenerating myofibers, not impeded by connective tissue with constantly reestablished damaged cytoarchitecture, permiting a more suitable environment in which the myotubes grow as the improved values (both functional

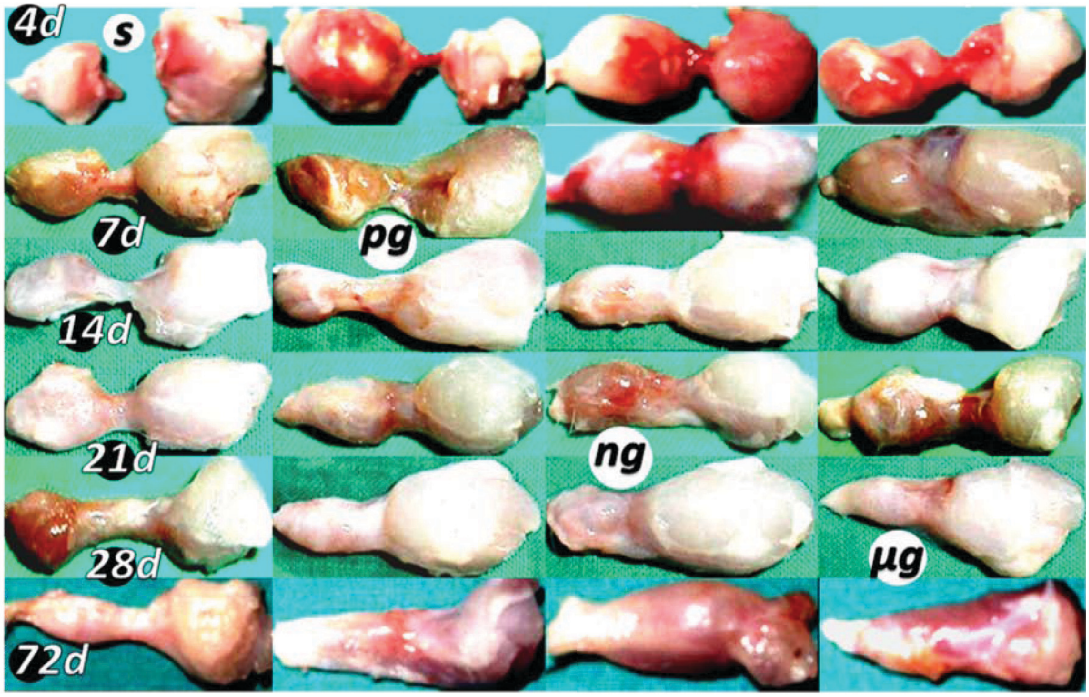

Fig. (2). Healing of rat quadriceps muscle after complete transection (day 4-72) without (*s*) or with BPC 157 medication (pg, ng, μg). Muscle transected transversely, 1 cm proximal to patella. BPC 157 medication given intraperitoneally, once time a day, 10 μg/kg, 10 ng/kg, 10 pg/kg (see ref. [21]). Essentially same results were obtained using per-orall regimen (*i.e*, 0.16 μg/ml, 0.16 ng/ml, 12ml/rat/day) or local topical application (*i.e*., thin layer, 1 μg/g neutral cream).

and tensiometry assessment) consistently prove [21-24]. The positive improvement cycle in this case also included decreased serum enzyme levels in the postinjury period, in other words, a decrease of the otherwise increased muscle proteolysis after local trauma [147, 148] was clearly emphasized [22].

In support, pentadecapeptide BPC 157 interacted with the somatosensory neurons and their function in ulcer healing (as well as in nasal mucosa healing and pain sensation) [149-151], and this led to nerve healing and regeneration [46, 47], which is very important for muscle healing (providing nerve healing (regeneration of damaged intramuscular nerve branches) as prerequisite for muscle healing [152], and thereby, BPC 157 may successfully combine muscle healing and neuroprotective capabilities (*i.e*., we briefly reported the lack of atrophy even in long term after gracilis muscle had been denervated [24]). More specifically, BPC 157 markedly improved sciatic nerve regeneration after transection given intraperitoneally/intragastrically/locally, at the site of anastomosis, or after non-anastomozed nerve tubing (7 mm nerve segment resected), applied directly into the tube [46]. Likewise, pentadecapeptide BPC 157, also given intraperitoneally and in the same dose range was shown to directly reduce both immediate and delayed damage induced by brain trauma [47].

Also, an important point in the applicability of muscle healing capability of the pentadecapeptide BPC 157 therapy is the recovery of the failed sphincters function, that was shown to appear rapidly, even after long term presented failure. Besides lower esophageal and pyloric sphincter [40, 87-89] the BPC 157's effectiveness demonstration involves the urinary sphincter as well [90], and counteracted consequences of obviously various disturbing procedures (*i.e.*, mechanical distension, fistula, esophagitis, pancreatitis, hyperkalemia for lower esophageal and pyloric sphincter [15, 40, 87-89], in rat stress urinary incontinence, transabdominal urethrolysis and prolonged vaginal dilatation [90]).

An additional point may be a certain parallelism noted between the recoveries of the injured striated muscle [21-24] and accelerated healing of the smooth muscle seen after intestinal anastomosis [13] and even more as the markedly improved adaptation after massive small intestine resection in rats with short bowel [14]. Of note, strands of newly formed muscle in all BPC 157- rats during ileo-ileal anastomosis healing accord well with the particular effect of BPC 157 on inner smooth muscle during remaining intestine adaptation and repair [13, 14]. This may be a special feature in BPC 157 healing that may be accounted for the weight gain in rats with short bowel that finally achieved the level noted in normal, non-operated rats [14].

A further supporting point for the applicability of muscle healing capability of the pentadecapeptide BPC 157 therapy may be an additional parallelism between the striated muscle injury [13, 14, 21-24] that were successfully healed, muscle regeneration achieved even after severe traumas such as quadriceps muscle transection (that otherwise healed only with scar tissue and severely disable function) and heart muscle healing and its function maintenance, and thereby, the reduction of heart muscle injuries, and function maintenance with BPC 157 therapy [36-40].

An additional indicating point may be that BPC 157 may strongly interact with dopamine system (known to be essential for muscle functioning [153], in a particular way, providing that it counteracts the consequences of dopamine receptors blockade, catalepsy and somatosensory disturbances induced by different neuroleptics, haloperidol, flufenazin, sulpiride, clozapine [154], dopamine vesicles depletion, induced by reserpine, akinesia and hypothermia [155], nigrostriatal dopamine destruction, induced by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydrophyridine (MTPT) neurotoxin application, BPC 157 strongly improved the MPTP-impaired somatosensory orientation and reduced the MPTP-induced hyperactivity, and most importantly, MPTP-motor abnormalities (tremor, akinesia, catalepsy - otherwise very prominent in saline control), leading to almost complete abolition of otherwise regularly lethal course of MPTP treatment in controls [155]). Likewise, BPC 157 counteracts also the effect of dopamine over-release from dopamine

nerve terminals and subsequent activation of dopamine receptors in striatum that may be induced by acute amphetamine administration (*i.e.*, stereotypies, heightened startle response [156], and dopamine striatal receptors up-reguation following chronic amphetamine administration [157], or dopamine striatal receptor up-regulation as a delayed result of dopamine receptor antagonist application and dopamine receptors blockade (haloperidol/amphetamine-climbing behavior) [156], that both otherwise cause an over-effect upon amphetamine challenge [156, 157]). Besides, BPC 157 completely counteracts also the gastric lesions that appear along with haloperidol, reserpine or MPTP application [155, 156, 158-160].

These interactions may be interesting particularly in respect of the growth factors, and the evidence that EGF is one of the ErbB receptor ligands implicated in schizophrenia neuropathology as well as in dopaminergic development [161]. Likewise, BPC 157 exhibits a particular antidepressant effect since counteracts helpless behavior better than imipramine [162], all manifestations of serotonin-syndrome [163], and induced release of serotonin in particular brain areas, especially in substantia nigra [164]. Finally, these findings should be regarded with respect to presentation of more than 90% of total serotonin in gastrointestinal tract [165], BPC 157 initial presentation in stomach mucosa and lumen but also in central nervous system) [1] and thereby, it may be suggested that this pentadecapeptide that acts both at periphery and in central nervous system (for review see, *i.e.*, [1-6]) may significantly participate in so called peptides "brain-gut" axis.

2.3. Bone Healing vs. Ulcer Healing

As suggested [166], the integrated growth and development of bone and muscle is likely, regardless the cellular and molecular mechanisms linking muscle and bone not well understood. These two tissues anabolism and catabolism are tightly coupled during growth, development, and aging, and the muscle is an important, local source of growth factors for bone tissue. FGF-2 and IGF-1, two growth factors known to play a major role in regulating bone formation, are localized to muscle fibers along the muscle-bone interface of the mouse forelimb, and secreted upon wounding likely regulated in part by paracrine mechanisms at the muscle-bone interface involving growth factor signaling [166]. In this, however, the mentioned evidence in FGF2-knockout animals (over-expression of FGF2 curbed infarct expansion and preserved left ventricular function) and thereby, FGF-2 more important in healing of infarcts compared with skin wounds [130] should be combined with the FGF2-knockout animals-evidence showing that over-expression of FGF-2 caused a variety of skeletal malformations including shortening and flattening of long bones and moderate macrocephaly [167].

Likewise, in bone healing the evidence relates both the increased and decreased values of growth factors during bone healing, *i.e.*, in peridontitis (decreased bFGF presentation) [168] mandibular distraction osteogenesis (increased bFGF-2) [169], surgical treatment for a long bone fracture (serum concentrations of VEGF, bFGF and PDGF increased in patients with nonunion and union) [170], occlusal stimuli and the periodontal healing after tooth replantation (increased bFGF) [171], irradiated bone (decreased expression of PDGF, bFGF, and TGF-beta in cortical and cancellous bone samples compared to nonirradiated rabbit tibiae) [172], periodontal regeneration (bFGF and VEGF mRNA showed a significant increase in periodontal ligament) [173].

As already emphasized [146], different delivery systems were used, *i.e.*, colloidal gels solely made of oppositely charged gelatin nanospheres to obtain controlled release of angiogenic and osteogenic growth factors [174], poly(lactide-co-glycolide) (PLGA) microspheres [175], combined porous poly-lactic acid-co-glycolic acid-co-ε-caprolactone (PLGC) as a barrier membrane and collagen sponge containing basic bFGF [176], porous calcium phosphate cement (CPC) [177], gelatin sponge [178], coated hydroxylapatite implants [179], a carrier (200 muL of fibrin gel) [180], bFGF and hyaluronic acid gel (HAG) combined with freeze-dried bone allograft in repairing segmental bone defect [181], Kirschner-wire coated with ethylene vinyl acetate co-polymer embedded with growth factors, inserted as an intramedullary nail (administration of bFGF or IGF-1 increased the ratio of cartilaginous to mesenchymal tissues in the fracture callus) [182].

Thereby, the effect highly depends on the used delivery system. For instance, an obvious stimulatory effect on bone regeneration was observed for the colloidal gels loaded with BMP-2, whereas bFGF-loaded colloidal gelatin gels did not influence the rate of bone regeneration [183]. In contrast, with the colloidal gelatin gels combined, the delivery of BMP-2 and bFGF resulted in an inhibitory effect on osteogenesis [183] or with loaded porous calcium phosphate cement, BMP-2 and bFGF together are more effective than either one alone in promoting the formation of a new bone and may exert a synergistic activity at bone defects around dental implants [184]. bFGF-coated hydroxylapatite implants [179] showed an unexpected ineffectiveness compared to the control groups with no significant difference of bone growth after 35 days. The local delivery of bFGF from poly(lactide-co-glycolide) (PLGA) microspheres into areas around titanium implants may improve osseointegration in diabetic rats [175]. Combining porous poly-lactic acid-co-glycolic acid-co-ε-caprolactone (PLGC) as a barrier membrane and collagen sponge containing basic fibroblast growth factor (bFGF) promoted bone regeneration in the canine mandible [176].

Thus, mostly limited to direct local administration [49], the studies focused on delivery systems to increase bFGF activity. Consequently, it seems to us that its own activity could be hardly ascertained with a huge variety of different carriers used, and thereby, the possible angiogenic effect is not adequately represented for efficient healing demonstration. And therefore, the angiogenic effect for bone healing with standard angiogenic factors, that should represent the common clue with their beneficial effect in ulcer healing, at least from the common healing viewpoint, seems to be not established. Consequently, we argue from the bone healing point of view, respecting indicated angiogenic commonality [7, 8], that the significance of their particular angiogenic effect in gastrointestinal ulcers healing and their particular healing of gastrointestinal lesions [7, 8] seems to be also less certain.

Furthermore, it is commonly considered that reconstruction of bone defects requires coordinated coupling between osteogenesis and angiogenesis [49] and thereby, it should be solved with bFGF or FGF-2 as a protein which acts actively in osteogenesis and angiogenesis during skeletal healing and development. However, an illustration may be the study designed to examine the impact of bFGF-BMSCs, seeded on nano-hydroxyapatite/polyamide66 (n-HA/PA66) composite scaffold, to enhance angiogenesis and osteogenesis in a calvarial critical-sized defect model in rats [185]. Likewise as a further illustration, in the avascular necrosis of femoral head when coordinated coupling between osteogenesis and angiogenesis is needed, the therapy was the recombinant plasmid pCD-rbFGF mixed with collagen and implanted in the necrotic femoral head [186].

Thus, summarizing, numerous carriers and delivery systems commonly used to improve the growth factors activity in bone healing contrast with the general evidence that multiple growth factors and cytokines themselves equally play a major role in tissue repair [49]. Furthermore, they are not specific to bone, and are an integral part of the platform that supports tissue repair in both hard and soft tissues [49]. Thereby, an obvious contrast between a need for a better and better carrier or delivery system in bone healing (as well as in tendon, ligament, muscle healing) *vs.* a very simple way of application in gastrointestinal ulcer healing, suggest that numerous growth factors *i.e.*, acidic fibroblast growth factor (aFGF), bFGF, PDGF, and TGF- β [49], are not clearly implicated in the repair of fracture healing nor in gastrointestinal ulcer healing.

Contrary, using the same protocol like in gastrointestinal healing studies (for review see, *i.e.* [1-6]), BPC 157 was shown to ameliorate healing of bone, pseudoarthrosis healing [25], and periodontitis [26], and femoral head osteonecrosis [27]. Initially, as original anti-ulcer peptide stable in human gastric juice, the BPC 157 application in bone healing follows the particular evidence of gastrectomy/bone healing evidence [25]. Namely, gastrectomy produces increased osteoporosis, metabolic aberration and risk of fractures [187, 188] and gastrectomy-induced bone loss not corrected by calcium addition [188], not considered being related to vitamin D deficiency [187], together favor the possible involvement of a hypothetical gastric hormone [188]. Consequently, the possibility that a peptide originated from stomach mucosa would promote fracture healing was not entirely unexpected [25] since gastric epithelial cells are known to have a property of inducing osteogenesis if appropriately transplantated [189]. This study, using a segmental osteoperiosteal bone defect (0.8 cm, in the middle of the rabbits left radius that regularly remained incompletely healed) confirmed that pentadecapeptide BPC 157 significantly improved the healing of segmental bone defects (either percutaneously given locally (10 μg/kg body weight) into the bone defect, or applied intramuscularly (intermittently, at postoperative days 7, 9, 14, and 16 at 10 μg/kg body weight) or continuously (once per day, postoperative days 7–21 at 10 μg or 10 ng/kg body weight)) [25]. Important for angiogenesis implementation, in rat periodontitis with a considerable increase in vascular permeability in the gingival tissue, extravasation of the Evans blue dye (a clear sign of tissue inflammation), and alveolar bone resorption, BPC 157 treatment significantly reduced both plasma extravasation, histological alterations and alveolar bone resorption [26]. Likewise, in the avascular necrosis of femoral head (after violent femoral luxation, cut ligament, incised periosteum, interrupted blood supply, and drainage of epiphysis, with consequential healing instability and soft tissue damage) when the maintenance of femoral head evidenced that coordinated coupling between osteogenesis and angiogenesis was accomplished, the most recent Raman study shows a consistent therapy effect (*i.e.*, the spectra from the samples sacrificed 6 weeks after injury showed substantial structural similarity between the BPC157-treated and the healthy groups) [27]. Finally, bone is fractured, skin is torn, blood vessels are ruptured, or ligaments or tendon or muscles are damaged, the tissue acquires a "wounded phenotype" [49]. Therefore, it is quite important that BPC 157 wound healing effect demonstrated skin [9-11], muscle [21-24], tendon [16-19], ligament [20], nerve [46, 47], healing as well.

Thus, we could argue for BPC 157 (*i.e.*, as one of angiogenic peptidergic factors, this peptide exhibited again peptidergic activity and stability of its own and not need for carrier or carrier's activities) (for review see, *i.e.* [1-6]), evidenced amelioration unmistakably attributed to its own healing effect. Thus, it seems that the value of its angiogenic effect is adequately represented, and therefore, common clue with its better beneficial effect in ulcer healing (for review see, *i.e.* [1-6]), at least from the bone healing and the common viewpoint of the angiogenic effect, clearly established. And finally, these effects are along with the evidence that BPC 157 stimulates both egr-1 and naB2 genes [41-43], providing that egr-1 gene is also responsible for bone formation as well [49]. Of note, when bone is injured, one of the earliest events to occur is the activation of intracellular signaling cascades. These cascades serve to stimulate the rapid transcription of growth factors and cytokines, and they are initiated, at least in part, by the stimulation of immediate early genes (IEGs). Responsive to mechanical stimuli such as shear stress [49], the induction of Egr-1 protein stimulates the production of many genes whose products play a role in cellular growth, development, and differentiation. These include genes encoding cytokines (TNF-α), adhesion molecules (intercellular adhesion molecule-1), members of the coagulation cascade (tissue factor, urokinase-type plasminogen activator), and growth factors such as aFGF, bFGF, TGF-β, PDGF-A and -B, hepatocyte growth factor, vascular endothelial growth factor, and IGF-II [49].

In analogy to bone healing [49], ulcer healing is a complex process of tissue regeneration, which involves cell migration, proliferation, reepithelialization, gland reconstruction, angiogenesis – new blood vessel formation from pre-existing vessels, vasculogenesis - new blood vessel formation from bone marrow-derived angiogenic precursor cells, and matrix deposition [7, 8], thus, after tendon transection, or tendon-bone detachment [16-19], or after ligament transection [20], BPC 157 healing realizes a general repair of connective tissues presenting evidence of full tendon healing, or full ligament healing [16-20]. Thus, specific cellular events in tendon or ligament healing were well characterized, and well controlled (along with full biomechanical and functional improvement) [16-20], as BPC 157 has a strong osteogenic effect, and heals various bone defects (*i.e.*, non-union, alveolar bone loss, avascular femoral head osteonecrosis [25-27]), but avoided were ossicles formation within tendon or ligament as a side effect (common for BMPs, and ossicles formation since tendon/ligament repair is similar to repair of other connective tissue [127, 128]).

2.4. Gastrointestinal Tract Healing, Lessons from Tendon, Ligament, Muscle and Bone Healing

Similarly, well-organized healing is present in gastrointestinal tract. It could be illustrated after a massive surgery [14], by an improved adaptation with BPC 157 application, all intestinal layers exhibit additional increase, well balanced effect on intestinal adaptation, the effect in increasingly exhausted rats with short bowel after massive small bowel resection (*i.e.*, BPC 157 (10 μg/kg or 10 ng/kg) was given perorally, in drinking water (12 ml/rat/day) or intraperitoneally (once daily, first application 30 min following surgery, last 24 h before sacrifice)). First, BPC 157 successfully healed intestinal anastomosis [13], as internal intestinal wounds, and fistula [12, 15, 30] in rat. This may be important, as standards peptide growth factors sometimes have not even been tested for healing of small intestine bowel anastomosis, as it is the case for EGF [190, 191]. Additional adaptive intestine increase produced by standards peptide growth factors was exhibited in one layer, but not others [191-199], and did not induce weight gain, and might only decrease (but not eliminate) weight loss [191-199]. Contrary, constant weight gain above preoperative values was observed immediately with BPC 157 therapy, both perorally and parenterally, thereby improved adaptation, all intestinal layers exhibit additional increase, and villus height, crypt depth, and muscle thickness (inner (circular) muscular layer) also increased, at 7, 14, 21, and 28 days [14]. Moreover, rats treated with pentadecapeptide BPC 157 showed not different jejunal and ileal diameters, constant jejunum-to-ileum ratio, and increased anastomosis breaking strength. Notably, till this study [14], only vilus height and crypt depth had been commonly investigated and muscle thickness occasionally, whereas inner (circular) and outer (longitudinal) muscular layers have been ignored [191-199]. Also, this supportive evidence along with other BPC 157 evidence no toxic effect, limit test negative, lethal dose not achieved, no side effect in trials (for review see, *i.e.*, [1-6]) may counteract the caution commonly exercised with the use of some of the peptidergic agents, particularly those used on a long-term basis [190]. For instance, the epidermal growth factor has been shown to promote growth of several tumor cell lines [200], and the development of hyperplastic lesions in the colons of subjects treated with GLP-2 for prolonged periods of time needs a careful surveillance [194], while BPC 157 inhibits growth of several tumor cell lines and counteracts the effect of VEGF [201].

On the other hand, this generally indicates this pentadecapeptide BPC 157 for therapy complication of IBD, *i.e.*, surgery, fistula healing [12-15, 30].

2.5. Concept of Simultaneous Healing of Gastrointestinal and Extra-gastrointestinal Tissue

Of note, the gastrointestinal fistulas healing may have key for determination of concept of angiogenic growth factors, gastrointestinal and extra-gastrointestinal tissue healing with respect to a pharmacological and pathophysiological role of various peptidergic growth factors.

As recently reviewed, BPC 157's strong anti-ulcer activity in the whole gastrointestinal tract (for review see, *i.e.*, [1-6]) led to its application in inflammatory bowel disease therapy, with no toxic effect, negative limit test, lethal dose (LD1) not achieved, and no side effects in trials (for review see, *i.e.*, [1-6]), thus a very safe peptide profile may be advantageous for colocutaneous fistula therapy. Colocutaneous fistula as regular healing failure is present in diseases, such as diverticular disease, Crohn's disease, and colon malignancies, or recovery from surgery [202]. Of note, in relation of the success of the standard therapy (in particular infliximab), the rehabilitation *i.e.*, fistulas closing tolerates even remarkable side effects [203-205].

For our concept approval, the key is that colocutaneous fistula is an anomalous connection between the skin and colon that provides the direct contact of these different, normally separated tissues, and thereby it presents special new unusual circumstances and particular healing difficulties [12]. Basically, fistula closing should correlate with the agents' potency to (simultaneously) induce the healing of the skin and colonic wounds [12]. Surprisingly for our BPC 157-studies [12-15, 30], until recently, these were not investigated in experimental studies or with angiogenic growth factors. Thereby, the colocutaneous fistula closure, skin and colon defect healing with the stable gastric pentadecapeptide BPC 157 (for review see, *i.e.* [1-6]) therapy (10 μg/kg, 10 ng/kg applied in drinking water or once daily intraperitoneally for 28 days) could have a particular relevance in colocutaneous fistula healing. Given in the same dose range, it ameliorated the skin [9-11, 41, 206, 207] and visceral (*i.e.*, anastomosis) [13, 14, 208] and both skin and visceral (*i.e.*, fistula [12]) wound healing. Finally, with respect to the indicated general healing significance of the angiogenic growth factors [7, 8], this advantage claims toward a generalization of the healing of fistulas, *i.e.*, providing that angiogenic growth factors hold a wound-healing of gastroduodenal ulcers, and consequently all gastrointestinal lesions, along with the skin wounds healing [7, 8]. Thereby, accordingly with general theory [7, 8], it is logically [1-6] that we assume that angiogenic growth factors as a class would induce healing of different gastrointestinal fistulas, in upper and lower part of gastrointestinal tract. As they are acknowledged the key healing factors in the whole gastrointestinal and skin healing [7, 8], we argue that they should simultaneously influence both skin and gastrointestinal tract healing, and thereby, simultaneously induce closure of both skin and gastrointestinal defects. Accordingly, while a similar evidence is still lacking for standard angiogenic growth factors, we demonstrated in addition to colocutaneous fistulas healing [12], that BPC 157 may rapidly induce the healing of esophagocutaneous fistulas and gastrocutaneous [15, 30].

In fact, previously, the discordant effects of standard anti-ulcer agents on skin wound healing suggested that only famotidine can promote skin wound healing, whereas omeprazole and sucralfate do not [209]. With unhealed gastrocutaneous fistulas and then, healing, we resolved theory of the analogous nonhealing of wounds and persistent gastric ulcers that standard drugs that promote healing of gastric ulcers may at the same time exhibit an at least equal effect on cutaneous wounds [30] (in order atropine>ranitidine/omeprazole cutaneous defect first starts to decrease). But, we also demonstrated that stable gastric pentadecapeptide BPC 157 is the only one that starts healing of both gastric and skin defect rapidly and simultaneously (macro/microscopically, and biomechanically (lack of leaking due to fistula closure)) and thereby, can have a greater healing effect even under corticosteroid aggravation [30].

Furthermore, we believe that such a general healing effect required to be demonstrated in the most unfavorable conditions, in the simultaneous healing of the different tissues, normally not connected, in relation with major systems generally involved in the healing processes. This was a particular relation with the NO-system demonstrated in many models [32-40]. In particular, this was demonstrated with two different fistulas healing, colocutaneous [12] and esophagocutaneous fistulas (a much more affected nutritional status, otherwise overall debilitation and inevitably lethal outcome were resolved with the therapeutic effect of BPC 157) [15]. Thus, defects closed macro/microscopical, and fistula closed with no leaking clearly means that complex injuries that would spontaneously not heal (and may mean even inevitable lethal outcome within short time (*i.e.*, esophagocutaneous fistulas [15]) were healed since requiring of simultaneous healing of different tissues now interrelated was efficiently resolved by orchestrations of likely different healing processes ongoing in different tissues.

Contrary, reviewing this issue in terms of standard growth factors [7, 8], these angiogenic growth factors are variously expressed close to the fistulas [210-212]. Plasma EGF and TGF-beta levels increased in patients with improvement but were unchanged in patients without improvement [212]. But, at present, as mentioned, similar studies showing possible healing of different gastrointestinal tract fistulas with angiogenic growth factors, are still lacking.

As mentioned before, considering the involvement of one of the major systems in defense, in the healing effect, BPC 157 may have the particular background to interact with NO-system. It is also known that angiogenic growth factors may largely interact with NO-system [212-216].

However, our hypothesis seems to be a particular one [33]. We suggested that BPC 157 (since formed constitutively in the gastric mucosa, stable in human gastric juice, along with significance of NO-synthase and the basal formation of NO in stomach mucosa, greater than that seen in other tissues) exhibits a general, effective competing both with L-arginine analogues (*i.e.*, L-NAME) and L-arginine, and that this has some physiologic importance (NO-generation). Later, this practically supports its beneficial effects illustrating BPC 157 and NO-system mutual (with L-NAME/L-arginine, alone and together) relations in (i) gastric mucosa and mucosal protection, following alcohol lesions, in cytoprotection course, NO-generation, and blood pressure regulation [33, 34], (ii) alcohol acute/chronic intoxication, and withdrawal [35], (iii) cardiovascular disturbances, chronic heart failure, pulmonary hypertension, and arrhythmias [36-40], (iv) disturbances after hypokalemia and hyperkalemia, and potassium-cell membrane dysfunction [39, 40], and finally, in (v) complex healing failure, proved by the fistulas healing, colocutaneous and esophagocutaneous [12, 15]. However, how this advantage of modulating NO-system (*i.e.*, particular effect on eNOS gene [15]), may be practically translated into an enhanced clinical performance remains to be determined.

In this, the effect on both hyperkalemia and hypokalemia-disturbances [39, 40], without affecting concentration of potassium ions itself, merits particular attention. To solve this, in vitro membrane voltages (Vm) of HEK293 cells were measured using the slow-whole cell patch clamp technique. In hypokalemic conditions (0.4 mM) cells hyperpolarized while with repeating hypokaliemic step in the presence of BPC 157, cells did not hyperpolarize. After washing BPC 157 from bath solution, under hypokalemic conditions cells hyperpolarized again [39]. In HEK293 cells, hyperkalemic conditions, BPC 157 directly affect potassium conductance, counteracting the effect on membrane potential and depolarizations caused by hyperkalemic conditions [40]. Thus, these clearly emphasize a particular and direct effect of its own on cell membrane integrity, an effect that could be in generally along with long-ago defined BPC 157 cytoprotective effect [1-6].

Furthermore, unlike standard angiogenic growth factors-NO-system studies (which used only L-NAME-application [218-222]), we used both L-NAME and L-arginine, alone and together in BPC 157-NO-system studies [12, 15, 33-40] to resolve NO-system dualities, and well define L-NAME/L-arginine, BPC 157/L-NAME, BPC 157/L-arginine, BPC 157/L-NAME+L-arginine, and thereby, fully defined BPC 157/NO-system relations [12, 15, 33-40]. Specific analysis of this counteracting capability itself (NO-specific blockade by NOS-blocker (*i.e*., L-NMMA [217], L-NAME [12, 15, 33-40], requires specific blockade (L-arginine) [217]) was always in focus in all our studies [12, 15, 33-40]. Thus, the well defined combining of L-NAME/L-arginine, L-NAME-L-arginine mutual counteraction [12, 15, 33-40] *vs.* BPC 157/L-NAME (*i.e*., L-NAME effect regularly nullified) together mean that BPC 157/NO-system findings are in all circumstances quite accurate [12, 15, 33-40]. And consequently, this signifies real BPC 157 effectiveness higher than that of L-arginine (*i.e*., in all models, L-NAME effects (NOS-blockade) was better antagonized with BPC 157), and BPC 157 significance for NO-system, in order BPC 157>L-arginine well revealed [12, 15, 33-40]. Thus, seen from this point of view, BPC 157 could thereby be responsible for NO-system functions ([12, 15, 33-40], as indicated by Moncada [217], maintained vascular integrity, platelets control, homeostatic healing response of NO-system to injury).

2.6. Influence on All Events After Vascular Integrity Loss

Thus, generation of NO (*i.e*., *in vitro*, in gastric mucosa from rat stomach tissue homogenates, BPC 157, given in the same dose 100 microM as L-arginine, induced a comparable generation of NO [30, 31]) and other convincing evidence for particular BPC 157/NO-ratio (an effect on endothelin serum level [36], BPC 157 protects endothelium (*i.e*., [2, 28, 29, 31, 32]), counteracts both L-NAME-hypertension and L-arginine-hypotension [30], exhibits prominent healing angiogenesis (and accelerates VEGF-expression) [9-16, 20-32]) should be combined with healing effect so far demonstrated with consistent strong healing after severe injuries that would otherwise not heal in different tissues, skin [9-11], tendon [16-19], ligament [20], muscle [21-24], bone [25-27], nerve [46, 47], cornea [48], gastrointestinal tract [12-15] and blood vessels[2, 28, 29], providing also evidence for simultaneous healing of different tissues as well (*i.e*., fistulas [12, 15, 30]).

In these terms, in general, the BPC 157-wound healing appears to be well defined. For instance, when a bone is fractured, skin is torn, blood vessels are ruptured, or ligaments or muscles are damaged, the tissue acquires a "wounded phenotype", tissue repair results from a number of temporally coordinated processes driven by locally released mediators [49]. The first event is immediate and consists of the activation of the coagulation cascade and the formation of a blood clot (shortly afterward there follows an acute inflammatory response resulting in tissue edema and cytokine and growth factor release) [49]. Thus, since BPC 157 may improve bone healing [25-27] along the healing of all mentioned damaged tissues [9-11, 16-24] its beneficial effects on these earliest events have to likely assume.

Likewise, all gastroduodenal ulcers [7, 8] were considered as caused by vascular and microvascular injury such as thrombi, constriction or other occlusions, as a result of the tissue necrosis triggered by mucosal ischemia [7, 8]. And as demonstrated with absolute alcohol injuries [218, 219], the early maintenance of the damaged vascular endothelium is thought to be essential for the beneficial effects of cytoprotective anti-ulcer agents [218, 219]. Of note, as mentioned, BPC 157 was recently claimed to be the novel Robert's cytoprotective mediator [1-6]. And thereby, BPC 157's influence on all events after vascular integrity loss follows from the long-ago demonstration of endothelium integrity maintenance following absolute alcohol intragastric instillation [28], and rapid wound healing demonstration in both gastrointestinal and extra-gastrointestinal tissues [9-32]. Thus, with BPC 157's influence on the all events after vascular integrity loss based on its endothelium protection, cytoprotective and wound healing effects [1-6, 9-32] it was logically to demonstrate that after abdominal aorta anastomosis [29], BPC 157 application may prevent obstructive thrombus formation and rapidly destroy already formed obstructing thrombus along with the rescuing of lower leg function [29], as well as after amputation, consistently counteracts aspirin, warfarin and heparin prolonged bleeding [100] as well as thrombocytopenias [100]. Specifically, BPC 157 attenuated over-increased APTT-, TT-values in 10 mg/kg heparin-rats, but did not influence heparin activity (anti-Xa test). Indicatively, unless counteracted in BPC 157 rats, excessive bleeding-acute thrombocytopenia (<20% of initial values in heparin-rats) approaches substantial fall in platelets count known in type II HIT. Also, BPC 157 markedly prolongs the survival time (heparin-rats, 25 mg/kg, right foot amputation) [100].

On the other hand, from the healing point of view, the effects of BPC 157 may not be surprising. Namely, as pointed out [100], the wound healing process accomplished all of 4 major events (vascular constriction, loose platelet plug, fibrin mesh to ensure stability of platelet plug, dissolution of the clot) that occur in a set order following the loss of vascular integrity. And thereby, not only in theory, as a mutual proof of concept [100], an agent really implemented in wound healing, and shown to be largely effective in wound healing, skin [9-11], tendon [16-19], ligament [20], muscle [21-24], bone [25-27], nerve [46, 47], cornea [48], gastrointestinal tract [12-15] and blood vessels [2, 28, 29], even in the simultaneous healing of different tissues (as shown in fistulas healing) [12, 15, 30] as it was the case with BPC 157 [1-6], should be particularly effective in all events after loss of vascular integrity, and thereby, in both developing thrombosis [29] and bleeding disorders [100]. These findings may be a practical demonstration that the wound healing concept as implemented by BPC 157 application [1-6], could be an additional successful background in allowing that aspirin-prolonged bleeding and thrombocytopenia [100] like various other side effects of NSAIDs (gastrointestinal tract, liver and brain-lesions) could be accordingly counteracted [97-99]. Finally, although these studies were highly focused on the direct demonstration of particular counteraction of NSAID-lesions by BPC 157, the evidence that it acts as a very safe peptide (LD1 could be not achieved) and as a novel mediator of Robert's cytoprotection [1-6], also revealed its capability to cope with NSAIDs side effects as a class, while maintaining some of their beneficial effects on arthritis, pain and increased temperature [1-6].

For instance, we evidenced that BPC 157 reduces the release of inflammatory mediators (*i.e*., myeloperoxidase, leukotriene B_4, tromboxane B_2) *in vitro* and *in vivo* [19, 220, 221]. BPC 157 successfully antagonized several models of acute, non-specific inflammation (*i.e*., carrageean, turpentine, cotton pellet) as well as DNFB-injuries [1]. Also, BPC 157 decreased vascular permeability and extravasation of the Evans blue dye [26]. Likewise, it was briefly reported that BPC 157 enhances the function of immunological effector cells in mice [222]. Likewise, BPC 157 antagonized temperature both decreased (*i.e*., water immersion-test) and increased (yeast-induced) [1], and both decreased/increased (serotonin syndrome) [163] temperature. Consistently, BPC 157 antagonized both inflammatory pain (acetic acid-writing), prostaglandin-dependent, and non-inflammatory pain (MgSO4-writing), prostaglandin-non-dependent [150]. Likewise, Gyires evidenced that BPC 157 increased pain threshold in carrageenan challenged rats and exhibited an anti-hyperalgesic effect in Randall-Selitto test. Equally, after sciatic nerve transection, without and with anastomosis, with improving nerve regeneration, BPC 157 strongly reduced neuropathic pain, and consequent autotomy in rats [46]. Finally, BPC 157 counteracts morphine-induced analgesia [223]. In arthritis studies, BPC 157 given as a single application (at 1 h either before or following the application of Freund's adjuvant) or in a once-daily

regimen (0-14th day, 14-30th day, 14th day-1 year), strongly both prevents arthritis development and rescues already established arthritis [224]. To encompass all these healing effects, BPC 157 was suggested to link inflammatory bowel disease and multiple sclerosis and shown to equally counteract the models of both of those diseases [225].

And finally, in relation to its response to injury, BPC 157 promoted healing, this goes in parallel with the BPC 157 relation with early growth response 1 gene (egr-1)/nerve growth factor 1-A binding protein-2 (naB2), stimulated expression of egr-1 (responsible for cytokine and growth factor generation and early extracellular matrix (collagen) formation) but also its repressor naB2 [41-43]. In addition to BPC 157 specific relation with most important defense systems (*i.e.*, dopamine [152-158], serotonin [160-162], NO-system [12, 15, 33-40], this implies a strong advantage (*i.e.*, BPC 157 and nab2 [226] could be part of a feedback mechanism that serves to regulate egr-1-mediated gene transcription) [99]), most complete healing effect accordingly demonstrated (for review see, *i.e.*, [1-6]). And most importantly, although still far less investigated than the standard angiogenic growth factors [7, 8], since always applied alone, with the same dose range, and same equipotent routes of application, regardless the injury tested, this could be clearly generalized, and thus, its own effect ascribed only to the given peptide (for review see, *i.e.*, [1-6]). Thus, providing that concept of growth factors essentially means a common concept of healing [7, 8], BPC 157 seems to be more than a suitable candidate to realize it when given as a therapy. In support are safe profile (LD1 could be not achieved), no side effect in clinical trials so far carried out (for review see, *i.e.*, [1-6]).

Unlike this, far more investigated angiogenic standard growth factors and commonly implied in the growth factors healing concept [7, 8] have several caveats in practical realization of growth factors healing concept. They are generally hampered by the diverse effectiveness and non-effectiveness in different lesions, highly restricted way of application (systemic application *vs.* application that prefers to be local, at the site of injury, given into injury defect (for review see, *i.e.*, [227]) and thereby, the use of different carriers, hiding the own peptide activity, making highly diverse peptide+carrier complexes to establish their therapeutic effect).

These pitfalls (*i.e.*, as more carriers, as less own peptides activity) are not fully considered for angiogenic growth factors [7, 8], and the suggested mechanisms fully elaborated even at the high molecular level [7, 8]. Thereby, these conclusions, regardless given highly sophisticated evidence, could be argued, considering that these attribution problems interfere with the current growth factors healing concept [7, 8], and thereby, the evidence still may be erroneously ascribed to the given peptide. Likewise, seen from our point of view, the continuous search for new and new carriers and delivery systems with all standard angiogenic growth factors, logically, potentiates the activity – methodology dilemma unable to identify the real active part in peptide+carrier complex (peptide, carrier, peptide+carrier complex or neither of them) or specify their particular contribution (for review see, *i.e.*, [227]).

CONCLUSION

Thus, concluding, considering the growth factors healing concept in theory and practice, BPC 157 may be clearly further investigated directly with respect to a pharmacological and pathophysiological role of various peptidergic growth factors [7, 8] providing the evidence how the gastrointestinal tract healing could be perceived through the healing of extra-gastrointestinal tissue healing, such tendon, ligament, muscle and bone, and *vice versa*. And thereby, BPC 157 relation could be at the best perceived through the defined beneficial significance of growth factors where the healing effects of the given peptide itself could be consistently demonstrated (or no effect, when one or more of the carriers), and then the responsibility and the presence of growth factors [1-6]). In this, to solve this healing issue, this review combined together the gastrointestinal tract healing and lessons from tendon, ligament, muscle and bone healing.

Thus, concluding, considering the growth factors healing concept in theory and practice, BPC 157 may be clearly further investigated directly with respect to a pharmacological and pathophysiological role of various peptidergic growth factors [7, 8] providing the evidence how the gastrointestinal tract healing could be perceived through the healing of extra-gastrointestinal tissue healing, such tendon, ligament, muscle and bone, and vice versa. And thereby, BPC 157 relation could be at the best perceived through the defined beneficial significance of growth factors where the healing effects of the given peptide itself could be consistently and clearly demonstrated (or contrarily, no effect, when one or more of the carriers, and then come the responsibility and the presence of growth factors [1-6]). In this, to solve this healing issue, this review combined together with the gastrointestinal tract healing and lessons from tendon, ligament, muscle and bone healing.

Finally, very recently, as a new point revealed was the particular effect of BPC 157 on blood vessels recruitment to reestablish blood flow [228, 229], also reviewed in this issue [230], the recent demonstration that BPC 157 rapidly activates from the existing vessels, the collateral circulation in rats with ischemic colitis (bypassing loop through arcade vessels [228] or inferior caval vein occlusion (bypassing loop through left ovarian vein and other veins) [229], bypassing occlusion (*i.e.*, segment of left colic artery and vein excluded by two ligations; infrarenal occlusion of inferior caval vein) and reestablishing blood flow, along with its free radical scavenger effect, in both ischemia and reperfusion [228, 229]. Finally, BPC 157 has a general healing argument, since always applied alone (unlike other growth factors which need carrier(s) addition), with the same dose range, and same equipotent routes of application, regardless the injury tested, this could be clearly generalized, and thus, its own effect ascribed only to the given peptide (for review see, *i.e.*, [1-6]) (on the other hand, considering particular contribution of any of the used carriers with standard growth factors (*i.e.*, peptide+carrier(s) complex) this again raised the discriminative question [227] whether the effects of one growth factor could be unified when obtained with addition (and help) of different carriers). Thereby, based on the implementation of the wide range of its beneficial effects in various organs [1-6], the evidence was recently reviewed [231] that this stable gastric pentadecapeptide BPC 157 may provide a particular defensive system, interacting with other important systems (in particular with NO-system [232]), and thereby, may have a particular beneficial effect in the organization and realization of the stress bodily response [231].

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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