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REVIEW ARTICLE

Novel Cytoprotective Mediator, Stable Gastric Pentadecapeptide BPC 157. Vascular Recruitment and Gastrointestinal Tract Healing

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Abstract: Years ago, we revealed a novel cytoprotective mediator, stable gastric pentadecapeptide BPC 157, particular anti-ulcer peptide that heals different organs lesions when given as a therapy, native in human gastric juice while maintaining GI-tract mucosal integrity, already tested in trials (ulcerative colitis and now multiple sclerosis). The stomach cytoprotection is the most fundamental concept, stomach cell protection and endothelium protection are largely elaborated, but so far cell, protection and endothelium protection outside of the stomach were not implemented in the therapy. However, having managed these two points, stomach cell protection and endothelium protection, either one or together, even much more than standard cytoprotective agents do, BPC 157 employed large scale of its beneficial effects seen in various organs. Providing endothelium protection, BPC 157 was shown to prevent formation and reverse established thrombosis in anastomosed abdominal aorta as well as venous thrombosis after inferior caval vein occlusion, and attenuate bleeding prolongation and thrombocytopenia after amputation, without or with anticoagulants, or venous occlusion, and finally counteract effect of L-NAME and/or L- arginine. Now, with BPC 157 application, we reveal the third most important part of the cytoprotection concept: with the stomach cell and endothelium protection to recover mucosal integrity, BPC 157 as prototype cytoprotective agent should also control blood vessel function, depending upon injury, perforated defect or vessel obstruction. After a perforated injury (*i.e.*, stomach), BPC 157 therapy activates blood vessels "running" towards defect. After obstruction (*i.e.*, inferior caval vein), BPC 157 activates vessels "running" towards bypassing defect, collaterals functioning. Reestablished blood flow, and largely reversed injurious course may practically implement the cytoprotection concept.

Keywords: Stable gastric pentadecapeptide BPC 157, cytoprotection, stomach cells protection, organoprotection, endothelium protection, control of blood vessels function.

1. INTRODUCTION

Years ago, we revealed a novel cytoprotective mediator, stable gastric pentadecapeptide BPC 157, particular anti-ulcer peptide that heals different organs lesions when given as a therapy, native in human gastric juice preserving the mucosal integrity, already tried in ulcerative colitis and now multiple sclerosis trials [1-10]. So far, these findings were quite extensively already reviewed [1-10]. Now, the materials we had gathered, taking the more extensive view of cytoprotection concept [1-10], amounted not to an admiration but to a wider implementation.

Nevertheless, since Robert [11-13] the stomach cytoprotection is the most fundamental concept, stomach cell [11-13] and endothelium protection [14-17], largely elaborated since very beginning [18-24]. Having managed these two points, either one or together, even much more than other cytoprotective agents do, BPC 157 employed large scale of its beneficial effects [1-10]. To emphasize again all possible potential of having these two points managed, stomach cell protection [11-13] and endothelium stomach protection [14-17], each of them would be separately reviewed (see chapter 2: *The stomach cell protection concept elaborated with standard cytoprotective agents as well as elaborated with the stable gastric pentadecapeptide BPC 157*; and chapter 3: *The endothelium cell protection concept elaborated with standard cytoprotective agents as well as elaborated with the stable gastric pentadecapeptide BPC 157*), particularly with respect to the original studies [11-17] that had motivated our subsequent cytoprotective agents research with the stable gastric pentadecapeptide BPC 157 as a novel cytoprotection mediator [1-10], when it came to the definitive limitations of the activity of prostaglandins and other standard cytoprotective agents, and thereby concept applicability [11-17]. Now, the special focus with the application of BPC 157, we reveal the third most important part of the cytoprotection concept: with the stomach cell and endothelium protection to recover mucosal integrity [1-10], the cytoprotective agent such as BPC 157 would also control blood vessel function, depending upon injury, perforated defect or vessel obstruction [25-27] (see chapter 4: *The third most important part of the cytoprotection concept: with the stomach cell and endothelium protection to recover mucosal integrity, BPC 157 as a prototype cytoprotective agent should also control blood vessel function, depending upon injury, perforated defect or vessel obstruction)*. This particular rapid effect would explain its prompt beneficial effect initiation and ascertain also its long-term effectiveness.

As mentioned, the stomach cytoprotection is the most fundamental concept using alcohol and non-steroidal anti-inflammatory drugs (NSAIDs) gastric injuries [11-13], stomach cell and endothelium protection, largely elaborated [11-17]. As indicated in a very prophetic way in reviewing at that time achieved concept realization [28], the concept of cytoprotection was as

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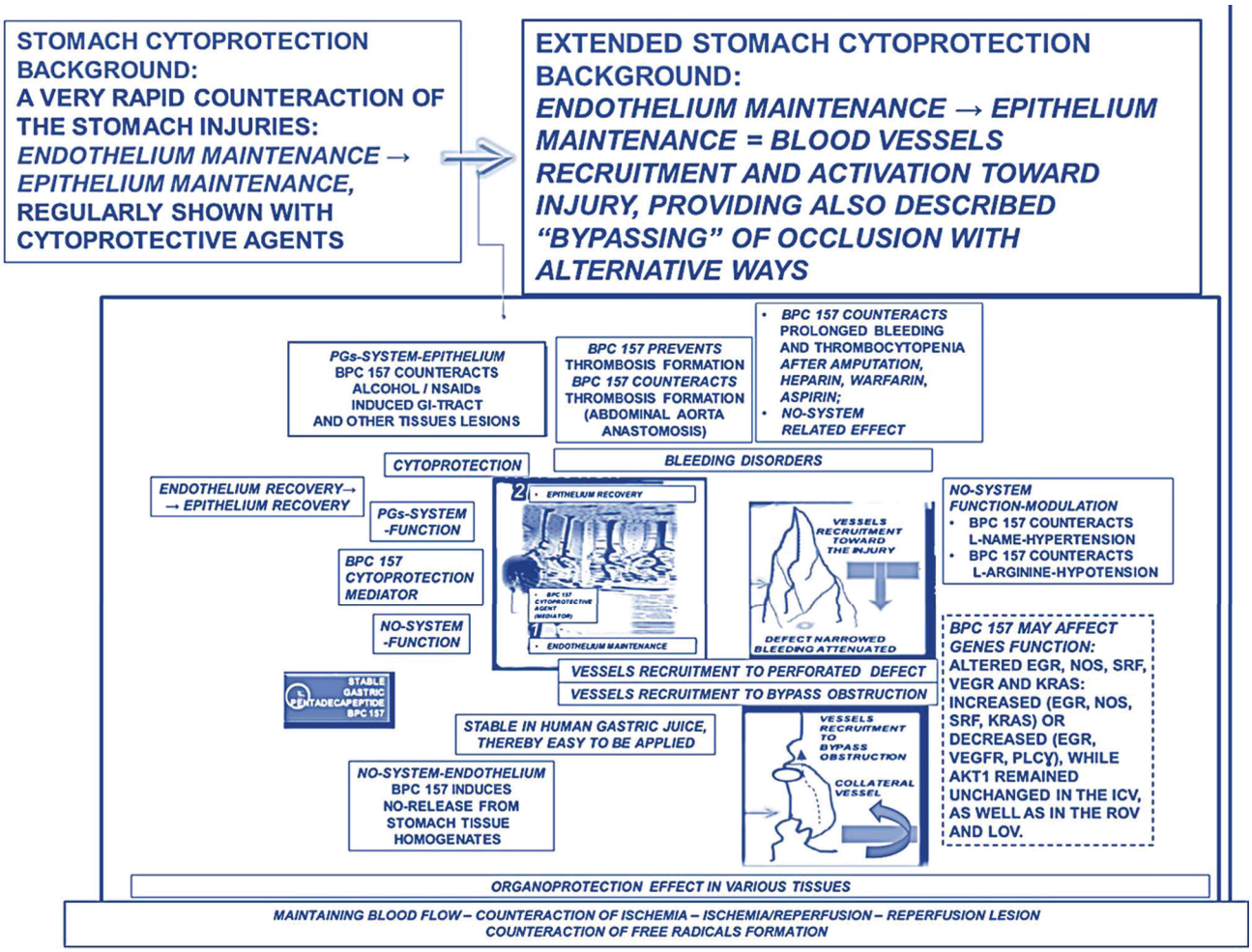

Fig. (1). Blood vessels recruitment in cytoprotection concept terms. Hypothesis elaboration. The stomach cytoprotection is the most fundamental concept because providing stomach cell and endothelium protection for stomach mucosal protection [11-17] that could be further extended (a point already reviewed [1]), largely elaborated. In this review we emphasized that of the upmost importance is thereby having managed these two points, either one separately, and then, both together in order to obtain a reasonable therapy benefit. This had to be however done to even much more extent than standard cytoprotective agents were shown to be able to do. By contrast, these were completely achieved by BPC 157, and thereby, BPC 157 employed large scale of its beneficial (orgoprotective) effects [1-10] and a particular therapy effect in rats underwent abdominal aorta anastomosis (and thereby arterial thrombosis), inferior caval vein ligation (and thereby Virchow triad), or amputation and anticoagulants application (and thereby, prolonged bleeding, thrombocytopenias) [1-10, 25, 93, 112, 113]. Very likely, these may be also due to the modulating of the two essential defensive systems, prostaglandins-system and NO-system [1-10]. Conclusively, these points should be all essential for revealing by BPC 157 a particular blood vessel recruitment that appears alongside with BPC 157 administration as the third most important part of the cytoprotection concept and its implementation [1-10, 25-27]. This would be recruitment of blood vessels toward (perforated) injury (Fig. **3**) as well as recruitment of vessels with collaterals activation to bypass vessels occlusion (Fig. **2**) [25-27]. The end result would be maintained and/or reestablished blood flow, and thereby a prominent therapy effect on ischemia and reperfusion injury. Consequently, BPC 157 provided a constant effectiveness in either of them, and thereby, effectively counteracted ischemia/reperfusion injuries, and free radical formation largely counteracted (and BPC 157 does not require preconditioning as follows from application of the standard agent during ischemia to prevent injuries of the subsequent reperfusion) [26].

original and revolutionary as any true biomedical innovation can be, yet it was not free of flaws [28].

2. THE STOMACH CELL PROTECTION CONCEPT ELABORATED WITH STANDARD CYTOPROTECTIVE AGENTS AS WELL AS ELABORATED WITH THE STABLE GASTRIC PENTADECAPEPTIDE BPC 157

In principle, the prime advantage with the stomach cell protection in cytoprotection concept is the revealing of the concept that is directly originated in the stomach against mucosal lesions [11-13, 21-24]. In this, the particular advantage is that it is particularly related to quickly resolving damaged epithelial integrity [11-13, 21-24]. Although originally prostaglandins related, mucosal stomach protection of many agents (as well as standard anti-ulcer drugs) defines Robert's stomach cell protection and vice versa, and thereby, all of them as cytoprotective agents [29-36]. Likewise, the original concept of Robert (concept of cytoprotection and adaptive cytoprotection (protection (gastric acid nondependent) against one irritant challenge in stomach (exogenous irritant studies for cytoprotection) [11]; strong irritants and strong lesions in the stomach prevented by pretreatment with small irritants and small lesions (exogenous irritant + exogenous irritant studies for adaptive cytoprotection) [12, 13]) may be taken as a common class effect.

On the other hand, the first practical drawback with standard cytoprotective agents is the proposed generalization of the concept (the original cytoprotective beneficial effect from the stomach cells

to the innate cells protection in other organs [11-13, 37-39]; stomach cytoprotection→organoprotection; providing stomach cytoprotection=organoprotection), which is not easy to be achieved.

As we had already pointed out [1, 6], if additional generalization of the concept of the stomach cell protection is attempted, this essential cytoprotective beneficial effect in stomach appears with particular theoretical/practical inconsistencies. Namely, the achieved generalization would be, at the best, only the partial generalization - but not the wide generalization of the original cytoprotective beneficial effect from the stomach cells to the cells in other organs [11-13, 37-39] (and thereby, stomach cytoprotection≠organoprotection and no clear clue for stomach cytoprotection=organoprotection). Illustratively, Robert's concept acknowledged prostaglandins protection mostly in the stomach, and intestine [11-13]. Thereby, such restricted protective effect is in apparent contrast with the suggested wider involvement of the other epithelia (i.e., skin, liver) [11-13, 37-39] in prostaglandins cytoprotective effects. Thus, the proposed generalization (stomach cytoprotection/adaptive cytoprotection→organoprotection) could not be achieved by prostaglandins effects. Likewise, somatostatin or sulphydrils [31, 32] were not further recognized as organoprotective agents.

Vice versa, NSAIDs, as in the case of alcohol, although with known toxicity in gastrointestinal tract, liver, kidney and brain [1, 4], remain in original Robert's study limited to their damaging effect in stomach mucosa where counteraction was used as a full hallmark of cytoprotective agent's effect [11-13, 37-39]. The second major pitfall providing only restricted generalization is within stomach cell protection concept itself. Namely, if *Robert's killing cells by contact*-phenomenon occurs, the innate cell protection in gastric mucosa occurs, the cytoprotective agent constantly holds mucosal integrity against all non-specific offending agents [11-13, 37-39]. Thereby, the cytoprotective agent's ability to exert beneficial effect should act prophylactically. Likewise, it should also act in the already advanced injurious course, given either before or after noxious agent [11-13, 37-39]. Unfortunately, unlike the original intention, only prophylactic (pretreatment) effectiveness would appear with the standard cytoprotective agents [11-13, 37-39]. Prophylactic potential - without any further therapeutic potential - represents a shared class limitation for activity and concept application [11, 40-44].

Thus, instead a full overlap, providing that either alcohol or NSAIDs always have their own activity and that this inherent activity would result in all lesions depending about the target organ, where all would consequently need action of cytoprotective agent(s), there is still an apparent gape in research and understanding between local damaging effect on the stomach mucosa and general toxicity, seen in other organs, with the parent noxious agents alcohol and NSAIDs. Furthermore, the activity limitation (only prophylactic activity) [11-13, 37-39] seems to be most commonly accepted as a real cytoprotective essential, the only possible to be realized in practice. Over time, abandonment of the original intention realization (cytoprotective agent is continuously exerting innate cell protection being effective given either before or after noxious agent [11-13, 37-39]) provides an imperfect concept that erroneously allows that an agent even without therapeutic potential given after noxious agent, and exhibiting only prophylactic activity, would be still considered to be standard cytoprotective agent [1, 4]. More logically, confronted with the parent noxious agents, alcohol or NSAIDs, an agent with a relevant cytoprotective effect should compete with both stomach and other organs damages that may be induced by those agents application [1, 4]. Likewise, proving constant innate cell protection [11-13, 37-39], the real cytoprotective agent (unlike standard cytoprotective agents) should be effective given before as well as after injury induction as a proof of beneficial activity [1]. Of note, these methodological and theoretical disadvantages should not be further ignored but fully evaluated in further cytoprotective research [1].

With realized ↑*stomach cytoprotection*→↑*organoprotection; thereby stomach cytoprotection=organoprotection* BPC 157, considering all of its beneficial effects in therapy, resolves all of these drawbacks [1-10]. First, BPC 157, authentic in human gastric juice (stability longer than 24 hours), continuously maintains gastrointestinal mucosa integrity [1-10]. The next argument is that it was always given alone [1-10]. Thereby, the beneficial effects are unmistakably attributed to its own activity [1-10], and then, taking into account various systems involved, its beneficial effects clearly attributed to an organoprotective agent activity [1-10]. Furthermore, a wound healing concept (common healing failure considering gastrointestinal ulcers as essential internal unhealed wound vs. healing commonality, gastrointestinal/extra-gastrointestinal healing to be improved) [45, 46] in cytoprotection/organoprotection concept would reveal a particular aspect of BPC 157 application [1-10] in theory and practice. Within the same dose range and routes of application as with gastrointestinal ulcers healing, BPC 157 in wound healing exhibited healing of deep skin burn [47-49], transected/injured muscle [50-53], tendon, ligament [53-58] and bone (pseudoarthrosis) [59-61], and nerve peripheral and central [62, 63], as well as in particular tissues such as cornea [64, 65], thought to be related to the endothelium protection [64, 65]. Likewise, along with the commonality emphasized in cytoprotection concept appears with BPC 157 application healing of fistulas, otherwise resistant to healing, external [66-69] and internal [70, 71] and healing of the failed anastomoses [72-76], thus, simultaneous healing of dissimilar tissues.

On the other hand, with respect to alcohol [1], its local effect as well as its systemic effect [1], BPC 157 acts as a full antagonist. Its strong antagonization of intragastric ethanol-gastric lesions is particularly indicative [44, 78-82] for cytoprotection, adaptive cytoprotection (as specially pointed out in relation with standard anti-ulcer agents [1, 77, 78]) and organoprotection abilities (as emphasized before [1-10]). Furthermore, strongly antagonized intragastric ethanol-gastric lesions [44, 78-82] combined with mentioned long lasting no degradation in human gastric juice (as well as isolation from human gastric juice) [1] may provide convincing evidence for constantly maintained mucosa [1]. Likewise, the same alcohol essential background, ethanol lesions in stomach and the other damaging effects, the more likely is the demonstration of the full counteraction of alcohol intoxication, acute (i.e., increased alcohol blood values, sustained anesthesia and hypothermia, no righting reflex and reaction to external stimuli result in 25% mortality) as well as chronic (i.e., withdrawal prominent seizures) [1, 83, 84]. Thus, had it been assailed by the alcohol, BPC 157 local to systemic effect was about to determine an active gut-brain axis or brain-gut axis functioning (a point especially reviewed elsewhere [8]). And accordingly, in alcohol chronically drinking rats BPC 157 antagonizes chronic gastric lesions [81], prevents as well as reverses liver lesions and portal hypertension [86], and lung lesions aggravated by alcohol [82, 85].

As mentioned, the original cytoprotection prostaglandins contention is based on the congruent lesions induced by either intragastric instillation of alcohol or NSAIDs application [11-13]. Consequently, the BPC 157 arguments (*i.e.*, the effects above described; thereby, a suitable candidate for more relevant mediator in Robert's stomach cytoprotection [1-10]) would indicate also its additional antidote activity against NSAIDs injuries (gastrointestinal tract, liver and brain lesions and finally bleeding disturbances) (as already reviewed [4]) corresponding to its antagonistic activity against the entire alcohol damaging process [1]. It was demonstrated that BPC 157 confronted with various NSAIDs indeed may counteract gastric, duodenal (including lower esophageal and pyloric sphincter failure), small intestine, colon, liver, brain lesions and blood disturbances that may be induced by

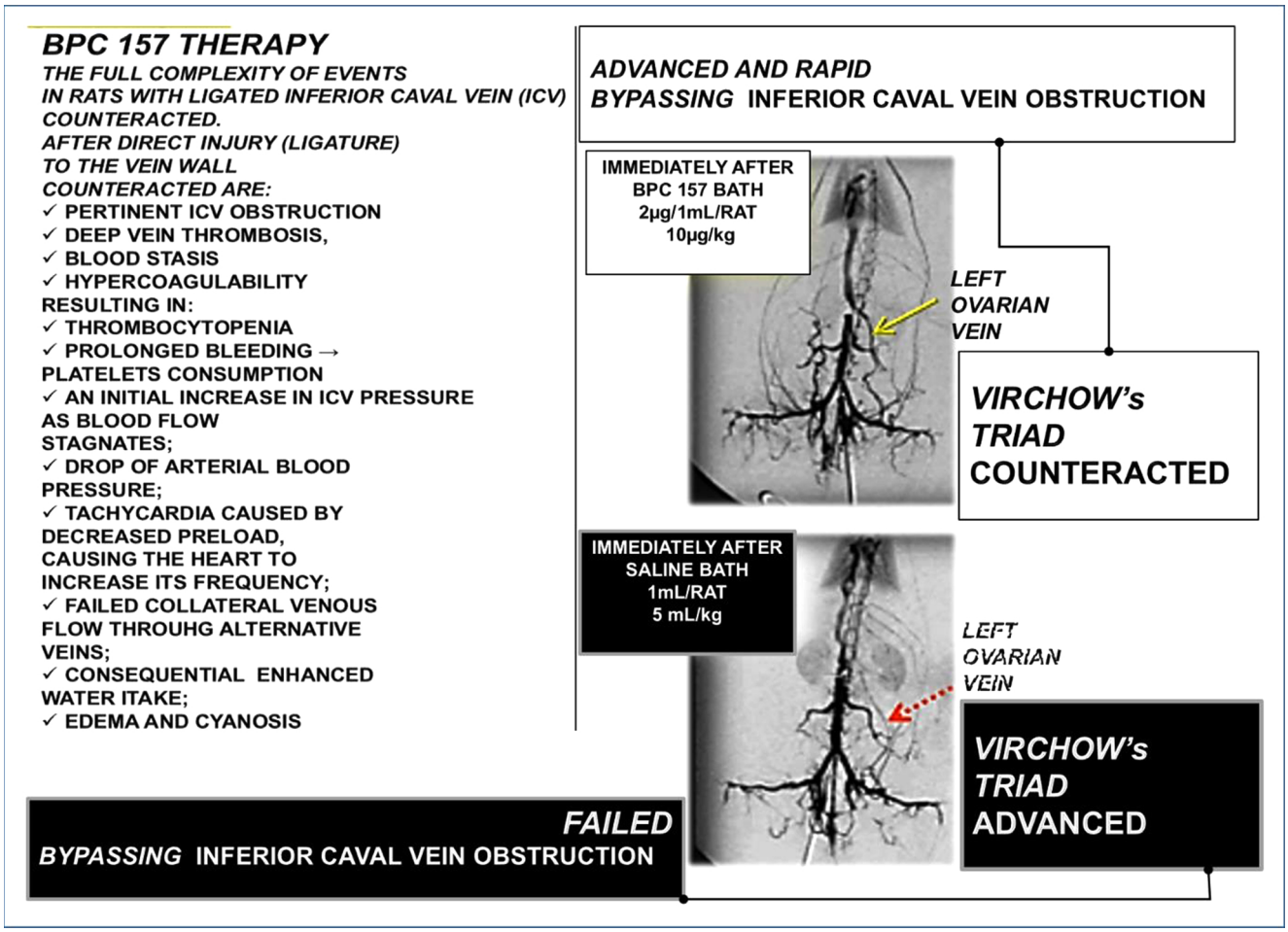

Fig. (2). Inferior caval vein occlusion (up to the right ovarian vein) [26] in rats, circumventing blockades, blood flow restored. Fast rescue occurs along with BPC 157 application, fast activation of collaterals and trapped blood volume through the refilled left ovarian vein and other veins and quickly results in mitigation or full antagonization of all the disorders of the inferior caval vein syndrome [26] (in particular, thrombus formation and stasis, venous hypertension, arterial hypotension and tachycardia [26]). Also, the effect on NO/MDA presentation [26] corresponds to the antagonization of the changes noted in the ischemia/reperfusion colitis [25] (counteracted were low NO-values and increased MDA-values in inferior caval tissue [26]).

either non-selective (COX-1 and COX-2-blockers) [73, 78, 80, 87-93] or selective (COX-2 blocker) [91, 92]. Besides counteraction of the inherent ulcerogenic potential of NSAIDs, NSAIDs induced-gastrointestinal lesions counteraction by BPC 157 also occurred in additionally disturbed conditions, presented with ethanol stomach lesions [78], somatosensory neurons depletion [80], short bowel [73], NOS-blockade by L-NAME application [73, 92]. Likewise, the NSAIDs induced-liver lesions were counteracted irrespective whether they appear even without gastrointestinal lesions (*i.e.*, paracetamol-lesions) [87] or with gastrointestinal lesions [73, 88, 89, 93], presented as more severe (diclofenac) [88] or less severe (ibuprofen, celecoxib) [89, 93]; or consequent to free radical formation (*i.e*., paracetamol, diclofenac) [87, 88] or cholestasis (*i.e*., ibuprofen) [89]. Similarly, BPC 157 consistently counteracted all brain lesions induced by NSAIDs in rats, including those that would appear along with gastrointestinal and liver lesions (diclofenac, ibuprofen, celecoxib) [73, 88-90, 92] as well as those occurring along with liver lesions presented without gastrointestinal lesions (paracetamol) [87]. Likewise, regardless that brain lesions after various NSAIDs application occurred in different brain areas, they were all counteracted by BPC 157 therapy [73, 87-89, 92]. Thus, as in the case with alcohol application, it is evident with the described effects that confronted with NSAIDs induced derangement, BPC 157 may form a particular gut-liver as well as gut-brain axis [4, 8]. Furthermore, antagonization of bleeding time and thrombocytopenia also occurred in aspirin-treated rats [93], as well as adjuvant arthritis prevention, and once established, reversal with BPC 157 therapy [90]. Obviously, in general conceptual terms, BPC 157 effect on the full extent of both of the alcohol and NSAIDs induced lesions - by going into active cytoprotective defensive axes - envisaged the cytoprotection-alcohol-NSAIDs relations [11-13]. Thus, local to systemic effects, gut-liver axis and gut-brain axis may have a practical corresponding significance [1-10]. As a beneficial example, a successful response from periphery that may attenuate the damage arising from either primary or secondary brain injury [1-10], we should mention the mice underwent head trauma and BPC 157 application [62]. After trauma, pentadecapeptide BPC 157-mice had less dysfunction and they preserved consciousness and had less mortality immediately and thereafter [62]. Brain damage subarachnoidal and intraventricular hemorrhage, brain laceration, hemorrhagic laceration and, brain edema were reduced, thus the threats that were due to primary (due to biomechanical effects) and secondary damage (due to activation of pathophysiologic cascades) [62].

Illustratively for the effect on Robert's stomach injuries that could be likely extended to other injuries, BPC 157 counteracts various gastric (as well gastrointestinal lesions), even those quite beyond original Robert's injuries [1-10] thought to be produced by the direct insult to stomach [11-13]. An illustrative hallmark is the lesions induced by cyclophosphamide application, its toxic

metabolite, excessive free radicals formation, which were fully counteracted [94].

Likewise, in accordance with BPC 157's cytoprotection/ organoprotection terms, liver therapy acts in a non-specific way antagonizing various liver lesions after insulin [95], paracetamol (fatty liver and necrosis) [87], diclofenac (pronounced parenchymal necrosis [88]), ibuprofen (hepatomegaly) [89], celecoxib [92] or massive intestine resection and short bowel syndrome [73]. The effectiveness preserving liver function would ascertain also the mentioned counteraction of concomitant different brain lesions otherwise induced by NSAIDs application [73, 87-89, 92]. In addition, with insulin (using 250 IU/kg i.p. over-dose insulin), illustrative is pleotropic pathology and thereby the pleotropic beneficial effect of BPC 157 (equally obtained using intraperitoneal or intragastric application immediately after insulin) [95]. Downhill course characterizes gastric ulcers, seizures (eventually fatal), severely damaged neurons in cerebral cortex and hippocampus, hepatomegaly, fatty liver, increased AST, ALT and amylase serum values, breakdown of liver glycogen with profound hypoglycemia and calcification development, calcium deposits in the blood vessel walls, hepatocytes surrounding blood vessels and sometimes even in parenchyma of the liver [95] all counteracted by BPC 157 therapy [95]. Previously, liver necrosis or fatty changes in rats subjected to 24 h bile duct + hepatic artery ligation, 48 h-restraint stress, CCl_4 treatment [96] were significantly prevented. Likewise, BPC 157 antagonized acute pancreatitis [97, 98]. In retrospect of original studies [32, 92], *the stomach cytoprotection→ organoprotection* used antagonization of liver lesions (*i.e.*, somatostatin [32]) and acute pancreatitis (*i.e.*, prostaglandins [92]). This particular point makes BPC 157's liver and acute pancreatitis lesions findings to be particularly illustrative.

Together, alcohol or NSAIDs toxicity counteraction in stomach, and thereby also in other organs lesions represent the original cytoprotection hallmarks [11-13]. With the general antidotal effect against these agents, these BPC 157 findings are suggesting an even more general antidotal beneficial effect based on the extended follow up of the original stomach cell protection [1-10]. Summarizing, a progress in comparison with Robert's prostaglandins seems to be quite evident. Namely, unlike Robert's restricted preventive effect of prostaglandins (only prophylactic effect), prophylactic and therapeutic capability of BPC 157 is effective against the lesions induced by Robert's intragastric administration of various necrotizing agents, systemic NSAIDs and corticosteroids applications [1-10].

3. THE ENDOTHELIUM CELL PROTECTION CONCEPT ELABORATED WITH STANDARD CYTOPROTECTIVE AGENTS AS WELL AS ELABORATED WITH THE STABLE GASTRIC PENTADECAPEPTIDE BPC 157

Although at that time many reviews within Robert's stomach cell protection concept as cytoprotection [18-20, 22], as well as Robert himself explaining his original stomach protection concept [21, 23, 24], witnessed the imagination and the efforts of investigators like few other phenomena in gastroenterology [100], *i.e.*, rapid restitution [101], it was also claimed that its nonspecific designation and the lack of understanding of involved mechanisms (the surface epithelial cells are not protected [101]) have detracted from its usefulness, particularly since specific cellular changes related to protection have seldom been identified [102, 103]. Besides, as pointed out [28], the original rat stomach was examined only grossly after administration of concentrated solution of ethanol, HCl or NaOH with or without pretreatment with prostaglandins [11, 12] while in other experiments, neither macroscopic nor microscopic, but only electrophysiologic parameters of membrane injury (*e.g.*, potential difference) were used as indicators to assess the extent of tissue injury [104]. One of the additional possibilities, was establishing a stomach-heart connection, based on the beneficial effect of lidocaine in stomach and heart as revealed at organelle to organ functional levels [102].

However, as a new real breakthrough, a subsequent solution revealed a rapid inherent damaging effect of instilled noxious agents (100% ethanol, strong acid or strong base, boiling water, within minute time) on stomach endothelium, and thereby very consistent demonstration that the epithelial lesion originally thought to be related to direct assault to the stomach, are preceded by a near endothelial damage [14-17]. Thus, the particular contention (increased vascular permeability and morphologically detectable vascular lesions → the development of grossly visible hemorrhagic erosions in the glandular mucosa) emphasizes the early vascular injury resulting in the development of ethanol-induced gastric hemorrhagic erosions.

To prevent stomach epithelial lesions, intragastric prostaglandin or a small dose of cysteamine, as a prototype of sulfhydryl agents, would protect the endothelial lesions [14-17]. Of note, an interesting somewhat controversial point was that cysteamine [14], instead of having beneficial potential, although in much higher doses, at that time, had an established prominent opposite effect, ulcer induction [105-110], and that it is in general use as a prototype for induction of duodenal lesions closely resembling those in humans [105-110]. On the other hand, with standard cytoprotective agents, the rapid protective effect on endothelium that maintains endothelium integrity and thereby prevents stomach lesion, thought to be crucial for cytoprotective agents activity, was not used outside of the stomach [14-17]. In our view, the problem that should be resolved is that in the concept of cytoprotection, the endothelium protection was added to original stomach cell protection [14-17], and that thereby, the stomach cell protection and the endothelium protection should go alongside. However, with the standard cytoprotective agents, even the original stomach cell protection potential to be generalized and widely applied (organoprotection, as a cell protection in the designated organ), was used to a very limited extent providing their protective effect in other organs, liver lesions (*i.e.*, somatostatin [32]) as well as on acute pancreatitis lesions (*i.e.*, prostaglandins [99]). It is also interesting with respect to angiogenesis (as a concept that appears later [111]), that this early beneficial effect on endothelium maintenance (minutes), although thought to be essential for stomach lesion healing in cytoprotection terms [14-17], was not combined with [111], and not further elaborated in the context of the angiogenesis (days) and chronic ulcer healing [111].

By contrast, taking a likely parallelism between the stomach cell protection and the endothelium protection [11-17], BPC 157 was shown to fully collaborate against both of the essential noxious chains of events that appear in cytoprotection with alcohol or NSAIDs administration, and thereby, shown to be able to exert full beneficial effects in other organs, supposed to be an extension and practical implementation of the known original stomach cell protection concept [1-10]. Thereby, since the first demonstration, the BPC 157 efficacy against ethanol gastric lesions, shown with prophylactic, co-treatment, and therapy regimen (*i.e.*, the superficial epithelium obvious regeneration, and a demarcation of the necrotic debris by newly sprouting glandular elements in areas of deep necrosis) is fully combined with the endothelium maintenance that would appear in minute time [44]. Thus, with BPC 157 use in cytoprotection concept, its local to its systemic terms, this combined effect could envisage its controlling of endothelium maintenance (as before the stomach cell protection) to be suited for an alike therapy generalization. This point was illustrated by the evidence obtained in rats underwent abdominal aorta anastomosis (and thereby arterial thrombosis) [112], or inferior caval vein occlusion (and thereby venous thrombosis) [25], or amputation and anticoagulants application (and thereby prolonged bleeding and thrombocytopenias) [93, 113, 114].

Specifically, in rats, with the anastomosed abdominal aorta, thrombosis was either prevented, or once established, reversed [112]. In rats, with the inferior caval vein, ligation direct vein injury and thrombosis were counteracted [25] (occlusion up to the right ovarian vein leading to vessel injury, stasis, thrombosis and hemodynamic changes a recapitulation of Virchow [25]). In rats with tail or foot amputation, and heparin, warfarin and aspirin application, without or with NO-agents, NOS-blocker L- NAME or NOS-substrate L-arginine, prolonged bleeding and thrombocytopenia were counteracted [93, 113]. Likewise, in rats with inferior caval vein-ligation thrombocytopenia and prolonged bleeding were all counteracted [25].

First, rats with aortic termino-terminal anastomosis (below renal arteries) represent an instructive model of aortic lumen obstructed by a formed cloth, and thereby, painful sensation, weak muscle strength, severely compromised walking. BPC 157 action has an immediate appearance: if applied soon after surgery, formation of cloth is decreased and muscle strength and walking ability maintained; if BPC 157 therapy is postponed till the late period (*i.e.*, 24 hours), at 3 minutes after application, taking the moment of the recovery of lower limbs function and muscle strength as a sign, no cloth is seen at the site of anastomosis [112].

Second, ligation of the inferior caval vein in rat [25] shows that the prompt, as well as the late regimen, are both curative treatment of deep vein thrombosis [1-10].

Conceptually, this was regarded as an extension of the innate endothelium protection inherent to BPC 157 permitting that it counteracts diverse gastrointestinal lesions due to its potent cytoprotective activity as a prototypic anti-ulcer agent [1-10]. Further novelty with beneficial effect in both arterial and venous thrombosis models [25, 112] considers arterial *vs*. vein disturbances, diversity or similarity [25]. Of note, diversity of arterial and venous disturbances (*i.e.*, venous thrombosis depends on the combination of stasis and hypercoagulability much more than endothelial damage [114]) should nevertheless acknowledge BPC 157 against thrombosis in the anastomosed abdominal aorta as a particular effect (*i.e.*, it rapidly rescues leg function [112]). Besides, BPC 157 also results in normalization of blood pressure [25, 80, 115, 116] and antagonizes various arrhythmias [117-120] (a point supporting contribution of the mentioned stomach-heart axis in original stomach cytoprotection concept [103] that could be also formed by BPC 157 administration). But, considering with the respect of BPC 157 efficacy [25, 112], the more relevant point of arterial and venous disturbances similarity, and venous and arterial thrombosis as two features of the same illness [121, 122], the consistent BPC 157 beneficial effects in rats with anastomosed aorta [112] as well as in rats with occluded inferior caval vein [25] could be an indicative common link and real novel insight.

Third, the indicative common point could be seen also with the evidence that bleeding time and amount of bleeding after amputation and/or heparin, warfarin, aspirin as well as after venous occlusion [25, 93, 113] was reduced after BPC 157 application. Its route of administration (intravenous, intraperitoneal, intragastric) correspondingly follows the route of bleeding-agents application. After BPC 157, lesser fall in platelets count was noted in all heparin-, warfarin-, and aspirin-rats and normal-rats. A special point may appear in heparin-rats (over-increased APTT-, TT-values were attenuated, but heparin activity (anti-Xa test) not influenced; thrombocytopenia (fall to <20% of initial values close to detrimental type II HIT) counteracted; after right foot amputation survival time prolonged in heparin 25 mg/kg-rats) [93].

In principle, this evidence [25, 93, 113] follows cytoprotection concept as a wound healing concept, mentioned before [1-10, 93], the clot as conductive matrix or "scaffold" to both speed up wound healing process, and decrease bleeding [93]. Conceptually, the loss of vascular integrity follows the wound healing process [93], vascular constriction, loose platelet plug, fibrin mesh and dissolution of the clot. And therefore, BPC 157, effective in wound healing, accomplishes these four major events. Then, for BPC 157 concept, it is likely that as an agent implemented in wound healing is correspondingly efficacious agent also in bleeding disorders and *vice versa* [1-10, 25, 93, 112, 113]. Along with this may be NO-hemostatic mechanisms [113] (L-NAME (prothrombotic) and the NOS-substrate L-arginine (antithrombotic)), counteraction of L-NAME (thrombocytopenia), L-arginine (increased haemorrhage) [113], BPC 157 own effect (decreased haemorrhage, counteracted thrombocytopenia) interpreted as a modulatory and balancing role with rescued NO-homeostatatic system [5, 113]. In support, favoring such an effect on endothelium, advancing its local to systemic effect, BPC 157 largely interacts with NO-system, as already reviewed [5, 6]. Of note, the evidence consistently obtained in many different models and species highlights these special BPC 157-NO-system relationships [5, 6, 26, 68, 69, 74, 75, 80, 84, 93, 95, 113, 117-119, 123-129]. In particular, BPC 157 induces a release of NO (just in the rat stomach tissue using original Whittle's procedure an effect that could be alike in other tissue as well) resistant to L-NAME, and competing with NO-release induced by L-arginine [80]. In that study, BPC 157 antagonizes the ulcerogenic effect of NO-synthase blockade (induced by L-NAME) and L-arginine (NO-precursor), along with their effect on blood pressure (BPC 157 counteracted L-NAME-hypertension and L-arginine-hypotension) [80]. In addition, it seems that BPC 157 may also rescue thrombocytes function providing that impedance aggregometry demonstrated that when BPC 157 was given with aspirin, clopidogrel and cilostazol in rats, BPC 157 counteracted their effects on aggregation activated by arachidonic acid, ADP, collagen and arachidonic acid/PGE1 used as aggregation agonists while coagulation pathways seem to be not affected (Konosic, unpublished data).

4. THE THIRD MOST IMPORTANT PART OF THE CYTOPROTECTION CONCEPT: WITH THE STOMACH CELL AND ENDOTHELIUM PROTECTION TO RECOVER MUCOSAL INTEGRITY, BPC 157 AS A PROTOTYPE CYTOPROTECTIVE AGENT SHOULD ALSO CONTROL BLOOD VESSEL FUNCTION, DEPENDING UPON INJURY, PERFORATED DEFECT OR VESSEL OBSTRUCTION

As mentioned, the stomach cytoprotection is the most fundamental concept because providing stomach cell and endothelium protection for stomach mucosal protection [11-17] that could be further extended (a point already reviewed [1]), largely elaborated. In this review, we emphasized that of the utmost importance is thereby having managed these two points, either one separately, and then, both together in order to obtain a reasonable therapy benefit. This had to be however done to even much more extent than standard cytoprotective agents were shown to be able to do [11-17, 31, 32, 99]. By contrast, these were completely achieved by BPC 157, and thereby, BPC 157 employed large scale of its beneficial effects [1-10]. Conclusively, these combined points (*i.e.*, extended stomach cell and endothelium protection) should be all essential for revealing by BPC 157 a particular blood vessel recruitment that appears alongside with BPC 157 administration as the third most important part of the cytoprotection concept and its implementation [1-10, 25-27] (see Fig. **1**). BPC 157 - with the stomach cell and endothelium protection to recover mucosal integrity, and to provide an interesting approach to counteract bleeding disorders, both thrombosis (arterial and venous) and prolonged bleeding [1-10, 25, 93, 112, 113] - as a prototype cytoprotective agent should further also control blood vessel function, depending upon injury, perforated defect or vessel occlusion [1-10, 25-27].

After perforated injury (stomach, cecum), BPC 157 therapy activates blood vessels "running" toward defect [27].

After vessel occlusion, BPC 157 activates vessels "running" toward bypassing defect, collaterals functioning [25, 26].

Reestablished blood flow, and largely reversed injurious course may practically implement the cytoprotection concept [1-10]. As a particular tool and hallmark of the maintained tissue integrity, this also implies beneficial effect that effectively counteracted ischemia/reperfusion injuries, and largely counteracted free radical formation [25-27]. BPC 157 was given in rats having vessels occlusion, or alternatively, once reperfusion was initiated in rats used to have vessels occlusion [25-27]. Thus, BPC 157 effect could be initiated in the ischemia conditions as well as the equal effect could be successfully initiated later, in the subsequent reperfusion condition [25-27]. Consequently, BPC 157 provided a constant effectiveness in either of them, and thereby, effectively counteracted ischemia/reperfusion injuries, and free radicals formation largely counteracted (and does not require preconditioning as follows from application of the standard agent during ischemia to prevent injuries of the subsequent reperfusion) [26].

Thus, using stable gastric pentadecapeptide BPC 157 [25, 26], specific and rapid activation of the collateral circulation from existing blood vessels can circumvent occlusions and rebuild the blood flow continuousness, making the occlusive events harmless (ischemic colitis; inferior caval vein obstruction), could be a key in vascular studies which will be now elaborated.

For ischemic colitis and reperfusion in rats [26], the occlusive events were complex (colon segment excluded, left colic artery and vein excluded by proximal and distal ligature, and their removal, and combined two blockades, vessels and additional colon obstruction) to follow immediate injury (vessels emptied - disappear upon injury) toward immediate recovery (vessels refilled - reappear upon treatment) [26]. Rescue was along with BPC 157 application, interconnections between arcades reappear at both proximal and distal site as rapidly rescued collaterals [26]. Consequently, circumventing blockades, blood flow restored, pale areas without mucosal folds did not occur [26]. This corresponds to the general evidence that BPC 157 was used in ulcerative colitis trial [1-10]. As a proof of the integrative healing evidence (rapid cytoprotective endothelium rescue that BPC 157 exerted may be useful against damaging chain of events during ischemia (two ligations) and during reperfusion (ligations removed) [26]) appear normalized NO- and MDA-values in colon tissues, oxidative stress markers [26].

In principle, the counteraction of the events occurring in rats with occluded inferior caval vein (up to the right ovarian vein) [26] corresponds to the circumventing blockades, blood flow restored described in rats with ischemic colitis [25]. When confronted with inferior caval syndrome that could be not spontaneously resolved [26], fast rescue occurs along with BPC 157 application, fast activation of collaterals and trapped blood volume through the refilled left ovarian vein and other veins and quickly result in lessened or fully antagonized all the disorders (in particular, thrombus formation and stasis, venous hypertension, arterial hypotension and tachycardia [26]) of the inferior caval vein syndrome [26]. Also, the effect on NO/MDA presentation [25] corresponds to the antagonization of the changes noted in the ischemia/reperfusion colitis [26] (counteracted were low NO-values and increased MDA-values in inferior caval tissue [25]).

A similar rapid bypassing through particular collaterals was noted after occlusion of various blood vessels: superior mesenteric vein and artery, superior anterior pancreaticoduodenal vein; portal triad obstruction; inferior caval vein with suprahepatic occlusion presenting Budd-Chiari syndrome (data in preparation). These beneficial effect is very important providing that already 5 minutes of venous occlusion may damage intestine [130].

Finally, the evidence that BPC 157 therapy activates blood vessels „running" toward defect was demonstrated with BPC 157 therapy that rescues perforated stomach lesion in rats [27]. Post-injury, a treat full syndrome appears (*i.e.*, during/after saline bath, vessels continue rapid disappearance; defect enlarged; bleeding; MDA-levels increased; NO-levels decreased) [27]. By contrast, post-injury, rapid cytoprotective-rescue occurs alongside with the BPC 157's application at the perforate injury, vessels gross reappearance at the stomach surface, quickly propagating toward the defect. These clearly affect defect contraction and bleeding attenuation; at 15-minute MDA-levels that increased and NO-levels that decreased were normal MDA- and NO-levels in stomach tissue; at 1 and 7-day stomach lesion were markedly less or completely closed and adhesion severity was markedly attenuated. These effects were shown to be NO-dependent, and quite resistant to standard H2-blocker or proton pump inhibitor administration [27]. A similar beneficial effect was noted in rats underwent cecum perforation (*i.e.*, rapid vessels recruitment toward the defect, defect contraction and bleeding attenuation, MDA-levels that increased and NO-levels that decreased brought to the normal values, at the corresponding very early interval, and defect completely closed and adhesion severity markedly attenuated at the final 7th day) [131]. Along with BPC 157 application, illustrative is also abundant vessels presentation around injured area produced by the acetic acid subserosal application (unpublished data) (Fig. **3**). A supporting demonstration was the effect of BPC 157 in rats with the esophagogastric anastomosis [75]. It may be that the elimination of perilous course and mortality is related to the notation that after the creation of anastomosis when BPC 157 is applied at stomach serosa blood vessels reappeared and remained present [75].

Thus, an immediate effect was always a rapid "running" of blood vessels toward the injury (*i.e.*, perforated defect, subserosally applied acetic acid, anastomosis) [27, 75, 131]. With vessel occlusion, a similar effect is rapid bypassing through particular collaterals [25, 26]. Thus, the above data indicate that the stable pentadecapeptide BPC 157 termed as organoprotective and integrative [1-10] with particular effect on blood vessel function may have an additional advantage potential for treatment of life-threatening disturbance. A conceptually supporting point is a complete lack of toxicity, a very safe profile, LD1 is not obtained [1-10]. This may be an indicative departure from the attempts devoid of the final realization [1].

CONCLUSION

There have been criticisms of the cytoprotection process [28, 101] since the first year because of the disappearance of the role of the fully definable mechanism(s), thought to be an independent scrutinizer whose task it was to take serious account of criticisms of the candidate agent's effect significance. On the other hand, the writing of the position dating from 1979 [11-17], is meant to compensate for the adversarial loss by the incorporation of studies affirmative of the candidate agents, prostaglandins [11-13, 99], sulfhydryls [14-17], somatostatin [31, 32]. Having come to the end of their own efficacy through the presented studies of further elaboration of the stomach cell protection to the cell protection in other organs as well (cytoprotection → organoprotection, only partly achieved [11-17, 31, 32, 99]; prostaglandins, sulfhydryls, somatostatin unsuited for further generalization, having a limited effect on the lesions that would appear in other organs [11-17, 31, 32, 99]), while endothelium protection remains quite strictly confined to stomach endothelium protection [37-43], we are convinced that cumulative beneficial evidence of the new candidates, and in particular, BPC 157 story (extended both stomach cell and endothelium protection; ↑cytoprotection → ↑organoprotection) would show BPC 157 to be a prototype exemplar for future generation [1-10]. Nevertheless, a deeply reasoned conceptual model [11-17] from whom therapy, and conceptual stomach relations with other systems, can best profit by expressing particular control of blood vessels functioning, blood vessels recruitment toward the injury, or bypassing occlusion, and

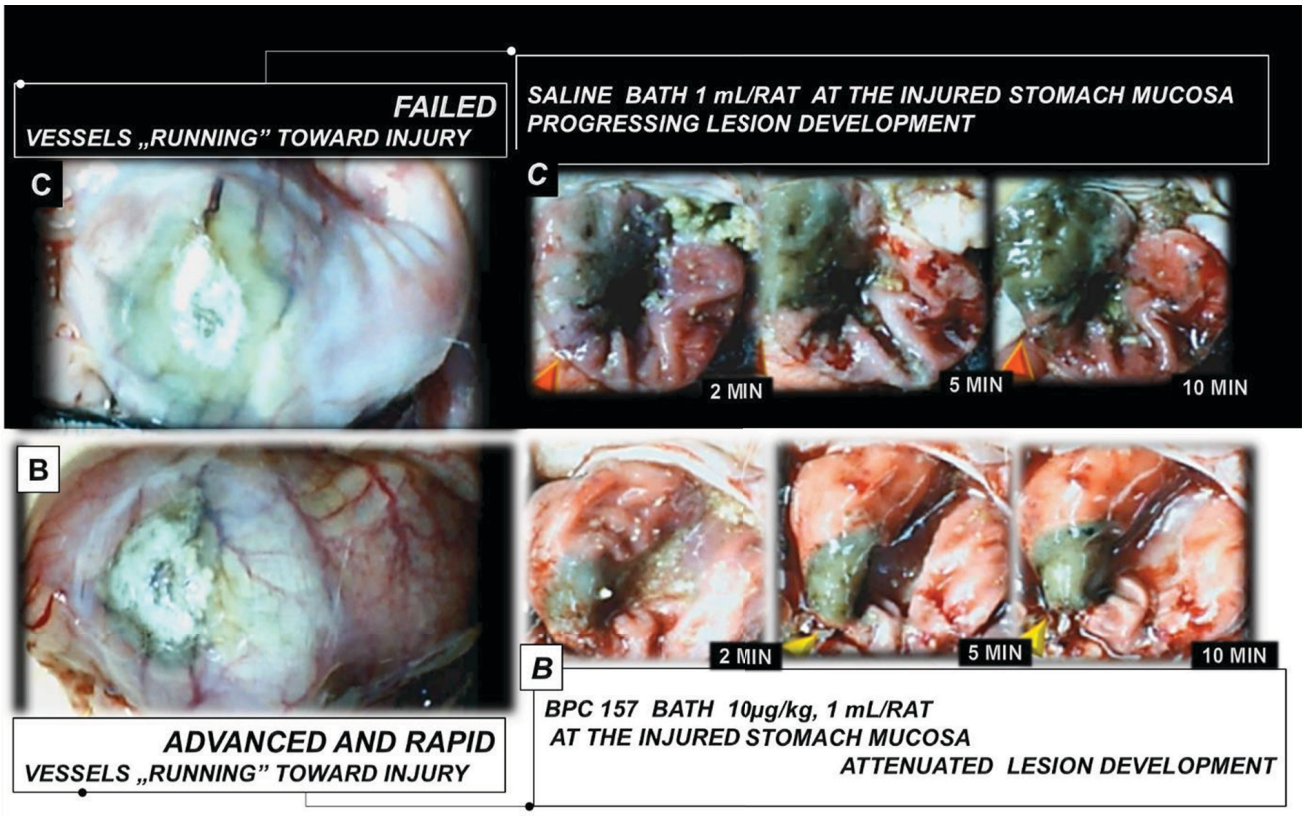

Fig. (3). Vessels running toward the injury or perforated injury, the illustrative is the rapid presentation of the vessels around the lesions with acetic acid subserosal application (8 min after acetic acid subserosal application 0.1 mL/stomach; saline bath (**C**) or BPC 157 bath, 1 mL/stomach serosa, 10 µg/kg (**B**), at 1 min after acetic acid) along with attenuation of the lesions development (saline bath (**C**) or BPC 157 bath, 1 mL/injured stomach mucosa, 10 µg/kg (**B**), at 1 min after acetic acid.

reestablishing blood flow continuity as the innate final benefit of the practical realization of the new third most important point in cytoprotection concept [1-10, 25-27]. If better relations are to be built between the concept and concept realization (*i.e*., "proof of beneficial activity" should be that crucial point [1]), it will result not from blind faith in the single mechanism or even mechanisms that could be hardly fully defined, thereby persistent background of negative apologetics, but from clear experimental demonstration of the facts heeding unflinchingly "the pluralist narratives" of the concept and candidate agent such as the stable gastric pentadecapeptide BPC 157.

Thereby, we would skip out to fully discuss the issue of angiogenesis (that was, however, previously reviewed in particular [4-7]). Namely, it is likely that the prominent angiogenic effect in following days [4-7, 9, 53, 132-137] is consequent to the described particular control of blood vessels functioning, blood vessels recruitment towards the injury, or bypassing occlusion, and reestablishing blood flow continuity as an extended both stomach cell and endothelium protection; ↑cytoprotection → ↑organo-protection. Its angiogenic response [4-7, 9, 53, 132-137] combined with its healing assets (note, BPC 157 would heal corneal ulcer and lesions and maintain corneal transparency [64, 65]) and a number of molecular pathways [25, 133-137]. Consequently, it significantly exceeds regular anti-ulcer agents and their effect on angiogenesis [132].

Some points, however, remain to be specially mentioned: eNOS expression in rats is continuously increasing with inferior caval vein ligation that received BPC 157 [25]. This may be that BPC 157 generally interacts with NO-system as seen in diverse models and species [1-10, 26, 68, 69, 74, 75, 80, 84, 93, 95, 113, 117-119, 123-129] and thereby, its specific activity as rapidly recovered endothelium function, then continuously preserved. Also indicatively, with BPC 157, early growth response protein 1 (EGR-1) stimulation means a stimulation of its co-repressor nerve growth factor 1-A binding protein-2 (Nab2), and thereby, guaranteed adequate and controlled EGR-1 activity [132]. Finally, in inferior caval vein, right ovarian vein and left ovarian vein of rats with short-lasting or prolonged occlusion of an inferior caval vein, beneficial effects appear with the altered EGR, NOS, SRF, VEGR, PLCγ and KRAS, but not AKT1 pathways [25]. They may reflect crucial pathways likely additional to those already included in the BPC 157-angiogenesis, recently related in particular with the increased expression, internalization of VEGFR2, and the activation of the VEGFR2-Akt-eNOS signaling pathway [25, 133-137].

Finally, these findings may have special significance with the respect to a special overlap between Robert's cytoprotection concept [11-13] and Selye's stress response [138, 139], as it has been already emphasized in our recent review [5] (Selye's general adaptation (mild stress protects against severe stress) [138, 139] ≈ Robert's statement (small irritant protects against strong irritant), stomach cytoprotection [11-13] to adaptive cytoprotection [11-13]); Selye's reestablished homeostasis, Selye's "response to damage as such", (undiscovered) integrative mediator that integrates the adaptive bodily response to stress [138, 139] ≈ Robert's stomach cell protection that should be generalized, prostaglandins cyto-protective for many epithelia (i.e., stomach, intestine, skin, liver) [11-13]). To transform theory into practice, the crucial point is the beneficial effect readily reproduced in therapy by administration of such agents supposed to be released endogenously. Obviously, combining Selye's and Robert's concept could provide additional both theoretical and practical advantages [5]. And thereby, it may

be as we claimed [5], that a particular importance may have the endogenous compounds (*i.e.*, prostaglandins [11-13], sulfhydryls [14-17], somatostatin [32]) suggested before as cytoprotection mediators. But, even much more credit deserves BPC 157, which we argue [1-10] that it continuously maintains innate cell protection against all non-specific offending agents that may damage gastric mucosa (*Robert's killing cells by contact*) [11-13] and has an organoprotective and integrative activity [1-10] with particular effect on blood vessel function. Conceptually, BPC 157 could have an essential practical significance for the whole cytoprotection concept and now, an adequate extension to an extended both stomach cell and endothelium protection: ↑cytoprotection → ↑organoprotection, and final practical implementation.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

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

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