Article

Novelties regarding pentadecapeptide BPC-157

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ABSTRACT

Stable gastric pentadecapeptide BPC-157 is a novel anti-ulcer peptide, used in trials for the treatment of ulcerative colitis and now multiple sclerosis. That fifteen amino acid molecule is likely mediator of Robert's stomach cytoprotection/adaptive cytoprotection and organoprotection, as well as novel mediator of the Selye's stress coping response, to reestablish the homeostasis. First, BPC-157 exhibits stomach cell protection to maintain stomach integrity against various noxious agents (Robert's killing cell by contact) and continuous presence in gastric mucosa and gastric juice. Additionally, it protects against the adverse effects of alcohol and NSAIDs on the stomach epithelia and other epithelia, i.e. skin, liver, pancreas, heart, (organoprotection), and brain, and thereby suggests its use for the concept of wound healing. BPC-157 also influences blood vessels, resulting in new vessel recruitment that circumvents the vessel occlusion, presenting additional shunting and rapid bypassing loops to rapidly reestablish blood flow integrity (ischemic/reperfusion colitis; duodenal lesions; cecum perforation; inferior vena cava occlusion). Lastly, BPC-157 counteracted tumor cachexia, muscle wasting, increase of proinflammatory/ pro-cachectic cytokines such as IL-6 and TNF-alpha, significantly corrected deranged muscle proliferation as well as myogenesis through the changes in the expression of FoxO3a, p-AKT, p-mTOR, and P-GSK-3beta (mitigating cancer cachexia).

KEYWORDS:

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INTRODUCTION

The original concept of Robert's cytoprotection developed with BPC-157 as a prototype of cytoprotective agents / mediators (pleiotropic beneficial activity)

Unlike the inactivity of standard agents (prostaglandins, somatostatin, sulfhydryl) (1), the stable gastric pentadecapeptide BPC-157 fully satisfies these complete criteria of activity (1). Stable and native in nature in human gastric juice, BPC-157 is highly effective when given prophylactically and therapeutically in the suppression of various lesions throughout the gastrointestinal tract (1, 2).

This efficacy accordingly includes characteristic modes of administration, acute and chronic (i.e. bolus application intraperitoneally, intravenously, intragastric, enema, topical application to the lesion site, continuous application in drinking water, topical gel or cream) (1, 2).

Of interest is the local application of the cream in wound research in mice where local application of the cream leads to the simultaneous healing of deep skin burns and stress-induced gastric lesions) (1, 2).

As a true mediator of Robert's cytoprotection, in addition to lesions in the stomach and gastrointestinal tract, it has pleiotropic beneficial activity and acts against lesions of other organs: liver, pancreas, lungs, heart and brain (1, 2). In particular,

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in BPC-157 studies, although each lesion of different organs involves different deleterious procedures, regularly the same dosing regimen of BPC-157 allows for a combination of beneficial effects consistently obtained (1, 2). Illustratively, beneficial activity in cardiac studies includes suppression of doxorubicin cardiomyopathy (3), severe digitalis-induced arrhythmias (4), and lesions caused by hyperkalemia (5), succinylcholine (6), and bupivacaine (7).

Pleiotropic beneficial activity based on the opposing relationship with the harmful effects of alcohol and NSAIDs

In general, cytoprotective/adaptive cytoprotective / organoprotective conditions, and the pleiotropic range of beneficial activities of BPC-157, and its opposite relationship to the harmful effects of alcohol and NSAIDs, have already been reviewed (8), and make this extension quite logical. The main argument is that Robert's standard harmful agents, alcohol and NSAIDs, which are used as a prototype of harmful agents in the initial demonstration of cytoprotective lesions in the stomach, have pleiotropic harmful activity (1). Alcohol and NSAIDs would also regularly induce various lesions in other organs (1). Also, it is likely that if cytoprotective agents induce innate resistance to initial Robert lesions (alcohol, NSAIDs) in the stomach, the same agent shows similar resistance to other lesions that are regularly induced by alcohol and NSAIDs (i.e. liver, brain) (1).

As shown, this combination, which should characterize the effects of any suitable cytoprotective agent, in practice meets the appropriate range of beneficial effects of BPC-157. Antagonism of the corresponding alcohol-induced (9) and NSAID-induced (10) gastric lesions, like the suppression of alcohol- and brain-induced liver and brain damage (10, 11) or NSAIDs (10).

It should be noted, similar to the prototype acute alcohol-stomach lesion (10), the useful range of BPC-157 is to act against alcohol in acute intoxication (prolonged drowsiness, elevated blood alcohol levels, hypothermia) and chronic intoxication (convulsions) (12). It also acts against the consequences of chronic alcoholism (alcohol consumption for 3 months) (11), such as chronic gastric lesions (13) or liver damage with portal hypertension (11). Regarding the adverse effects of chronic NSAID therapy (i.e. gastrointestinal, liver, and brain injuries), BPC-157 suppresses them by acting on COX-1 and COX-2 blockers (10). BPC-157 reduces post-amputation bleeding and may also act against aspirin-induced bleeding prolongation and thrombocytopenia (14-16). Interestingly, BPC-157 may also prevent and reverse adjuvant arthritis in rats (16). Therefore, unlike the mentioned standard agents, BPC-157 achieves gastric cytoprotection (1). The important thing is that this innate stability (resistance to degradation in human gastric juice for more than 24 h) gives preference to the application due to the different possible routes of application (1, 17).

BPC-157 with the concept of gastric cytoprotection - the concept of wound healing

Furthermore, the second point considers the concept of gastric cytoprotection (the concept of wound healing) (2). It should be borne in mind that the original cytoprotective program (with generalized cell protection, within the same "cytoprotective" background) involves improved healing in different tissues (18). Indicatively, BPC-157 improves the healing of skin wounds (19), muscles (20), tendons (20), ligaments (21), and bone injuries (22). Furthermore, significant recovery of the wound on the skin and muscles, tendons, ligaments and bones was observed, after a severe injury that could not heal spontaneously (22). These healing processes may suggest that BPC-157 may have a significant effect on tissue healing (i.e. with BPC-157, the tendon heals with the tendon rather than the bone; in rats, a separate Achilles tendon from the calcaneus would be properly attached to the calcaneus without surgery) (20).

Therefore, it is suggested that BPC-157 simultaneously acts on the healing of different tissues and adapts the healing processes in different tissues (2). As an auxiliary analogy, there is a clear demonstration of healing and closure of fistulas in rats (23) thus achieving healing in different tissues at the same time. In studies in rats (23), surgical creation of anastomotic fistulas between different tissues ensures a precisely defined defect in each tissue. Due to the comparatively small size of the rats and the large size of the defects, these defects mimic large fistulas quite well in patients who find it difficult to heal spontaneously (23). A similar demonstration should be in models with the creation of different gastrointestinal anastomoses (24) that would, accordingly, heal better versus the usual poor healing in appropriate control rats. Furthermore, healing of esophago-cutaneous (23), gastro-cutaneous (25), duodenal-cutaneous (26), vesicovaginal (27) and rectovaginal fistulas (28) with macroscopic, biomechanical and microscopic confirmation means demonstration of healing of external and internal

fistulas (28), and thus the realization of simultaneous healing of different tissues. Also, improved healing of gastrointestinal anastomoses (24), (i.e. esophagogastric, gastrointestinal, esophago-jejunal, ileo-ileal, jejunoileal, colon anastomoses) (24), but also nerves (femoral nerve) has been shown (29) and vascular anastomoses (abdominal aorta) (30).

Therefore, evidence that it can close and heal various fistulas (23) and improve anastomotic healing (24) may also be evidence of a fulfilled concept of wound healing.

BPC-157 concept of gastric cytoprotection - the concept of wound healing with respect to angiogenesis and differentiation from standard angiogenic growth factors

Another generalization of the concept of gastric cytoprotection (the concept of wound healing) is the application of standard peptidergic growth factors (provided they are mediators of treatment) in the healing of gastrointestinal tract (i.e. ulceration healing) and skin wounds and soft tissue injuries (i.e. muscle, tendon, ligament) , bone healing) (2). In particular, this is due to the effect on angiogenesis as a common healing point (31). A careful comparison between BPC-157 and standard angiogenic growth factors provides convincing evidence in favor of BPC -157 over standard angiogenic growth factors (2).

First, BPC-157 significantly exceeds the effect of common antiulcer agents on angiogenesis (32).

Second, its angiogenic response (1, 2) is quite specific, integrating its beneficial effect (20) and a number of molecular pathways (33). Illustratively, BPC-157 treats corneal ulcers and lesions and maintains corneal transparency (34).

Third, BPC-157 shows a beneficial effect within the same dose range in the treatment of lesions throughout the gastrointestinal tract, as well as wound healing, healing of severely damaged muscles (including transection), tendons, ligaments, and finally bone healing (including pseudoarthrosis treatment) (2).

In contrast, standard angiogenic growth factors have a limited effect in the gastrointestinal tract, and their effect may be different depending on which part of the gastrointestinal tract is involved (2). Especially for a wound on the skin, muscles, tendons, ligaments, and bone healing, various carriers are obviously needed as well, and are thus largely limited to local effect (2). In addition, standard angiogenic growth factors require a different carrier supplement, and together may have an uncertain contribution to activity (peptide; carrier; peptide + carrier complex) (2). In contrast to this common situation for the administration of standard agents, BPC-157 is always given on its own, acting alone, and therefore all effects can be clearly attributed to its own activity (2). Furthermore, it is important that BPC-157 can induce nerve healing, both peripherally (29) and centrally (35). Such a clear difference in angiogenesis is essential (and thus "control of angiogenesis") (2) and is common with BPC-157 (2). Of particular note is the fact that a similar distinction is uncommon for standard growth factors (2), raising the issue of tumor proliferation as is known for standard growth factors (angiogenesis / healing / tumor promotion). In contrast, "control of angiogenesis" means increased angiogenesis to promote healing (20), increased expression of VEGF and similar pathways (33), and as Kang et al. documented in 2018 (36), BPC-157 completely neutralized tumor cachexia, and prolonged survival and counteracted the increase in pro-cachectic and proinflammatory cytokines and related effects of molecular pathways (36). This point has already been elaborated especially in the model of short bowel syndrome (37) in which in rats subjected to large resection of the small intestine, BPC-157 leads to a balanced adaptation of all three layers of the intestinal wall, resulting in normal mass and less damage to distant organs: liver, brain), in contrast to the control group (37).

The next important point of the cytoprotection concept is the injury of the gastric endothelium that would precede and cause damage to the gastric epithelium, and thus the protection of the gastric endothelium to protect the gastric epithelium as a natural effect of cytoprotective agents (38). While the originally recorded endothelial protection remains rather strictly limited to gastric endothelial protection (38), as described, "gastric endothelial protection" could be generalized and extended to endothelial and other vascular protection (2).

Thus, with BPC-157, used in addressing the concept of cytoprotection, its local in the stomach, in terms of its systemic concept, this combined effect could predict its control of endothelial maintenance (as well as prior to gastric cell protection) to be suitable for similar therapy (2). This point was illustrated by evidence obtained in rats in which the abdominal aorta (and thus arterial thrombosis) was anastomosed (30), or the inferior vena cava occluded (venous thrombosis) (39), or amputation performed and anticoagulant applied (prolonged bleeding and thrombocytopenia) (16). Namely, in rats, with an anastomosed abdominal aorta, thrombosis was either prevented, or once established, removed (30). In rats with inferior vena cava ligation, direct

vein injury and thrombosis were neutralized (occlusion to the right ovarian vein, leading to vascular damage, congestion, thrombosis, and hemodynamic changes) (39).

In rats with amputation of the tail or foot, and the use of heparin, warfarin, and aspirin, without (14) or with NO-agents, NOS-blocker L-NAME or NOS-substrate L-arginine (15), prolonged bleeding and thrombocytopenia were neutralized (15). Finally, the general argumentation within the generally accepted concepts, considers that the wound healing process performed all 4 main events (vascular constriction, loose platelet plug, fibrin network- to ensure platelet plug stability, clot dissolution) occurring in a certain order after the loss of integrity of blood vessels (14).

Thus, a wound-promoting agent (19), such as the stable gastric pentadecapeptide BPC-157, has been shown to be effective in wound healing, but is also effective in bleeding disorders (14).

CONCLUSION

When introducing the new BP- 157 concept, it first follows the guidelines of the classical concepts of gastric endothelial cytoprotection (40) and Selye's concept of stress response against stress injuries to re-establish disturbed homeostasis (41), and then significantly expands, with recently proven recruitment of blood vessels to bypass vascular occlusion (39). Therefore, in practice, these results may be relevant for addressing Robert's cytoprotective / adaptive cytoprotective / organoprotective (40) and thus Selye stress responses (41), and most importantly BPC-157 has enormous potential for practical clinical application due to the wide range of action, efficacy, and ease of use.

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