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EDITORIAL

Stable Gastric Pentadecapeptide BPC 157: Prompt Particular Activation of Collateral Pathways

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We propose that severe (or even deadly) vascular disturbances and syndromes might be treated with the stable gastric pentadecapeptide BPC 157 [1, 2]. To re-establish blood flow, the effective upgrading of the bypassing loops of minor vessels to withstand the function of failed major vessels [3-17] should be an essential common principle. This might be considered as an advantageous extension of the principle of vascular cytoprotection.

As prototype conditions, the following were all counteracted/attenuated by BPC 157 therapy: inferior caval vein occlusion [3], Pringle maneuver ischemia, reperfusion [4], ischemic/reperfusion ulcerative colitis [5], occlusion of both carotid arteries [6] (BPC 157 is equally effective in ischemic as well as in full reperfusion conditions [4-6], *i.e.*, it counteracted both early and delayed neural hippocampal damage and completely recovered debilitated functions in rats after stroke [6]), Budd-Chiari syndrome [7], superior sagittal sinus occlusion [8], occluded superior mesenteric artery [9], occluded superior mesenteric vein [10], occluded superior mesenteric artery and vein [11], and episcleral veins cauterization-glaucoma syndrome [12]. Likewise, severe worsening (*i.e.*, occlusion-like) circumstances of alcohol intoxication [13], lithium intoxication [14], sustained intra-abdominal hypertension grade III and IV [15], bile duct occlusion and acute pancreatitis [16], and isoprenaline-induced myocardial infarction [17] were also counteracted/attenuated by BPC 157 therapy. All these disturbances, initiated either peripherally or centrally, might converge to severe vascular failure (resistant to any spontaneous compensation, peripherally and centrally, and therefore, a special target for application of a suitable agent) [3-17]. Commonly, there is a shared syndrome, termed occlusion or occlusion-like syndrome, with multiorgan failure generally seen peripherally, *i.e.*, lesions in the heart (*i.e.*, sub-endocardial infarction), congestion and hemorrhage in the lung, liver, kidney, and gastrointestinal tract (including frank ulcerations), and in particular, muscle weakness, as well as centrally, with large brain lesions and hemorrhage (including intraventricular hemorrhage) [3-17]. Upon BPC 157 therapy, intracranial (superior sagittal sinus) hypertension was counteracted, *i.e.*, a recovered ability to drain venous blood adequately for a given cerebral blood inflow without raising venous pressures, rapidly attenuated brain swelling, and providing evidence of rapidly counteracted venous and intracranial hypertension; portal and caval hypertension and aortal hypotension were also found to be resolved

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[3-17]. Progressive venous and arterial thrombosis, both peripherally and centrally (in the Virchow cause-consequence triad, evidencing counteracted stasis and recovered endothelial function), were also nearly completely abrogated [3-17]. Electrocardiogram (ECG) disturbances were also attenuated [3-17]. Moreover, congested (*i.e.*, inferior caval vein and superior mesenteric vein) and failed (azygos vein) blood vessels were markedly counteracted. Illustratively, recruited activation of the azygos vein means direct blood delivery rescuing the inferior-superior caval vein pathway along with the reversal of inferior caval vein and superior mesenteric vein congestion and a return to normal vein appearance, along with attenuated portal and caval hypertension [7, 8, 13-17]. All mentioned organ lesions were markedly lessened, and muscle weakness was reversed [3-17]. Eye lesions (episcleral veins, increased intraocular pressure, retinal ischemia) [12] and oxidative stress in tissues [3-5, 9-11, 14, 17] were counteracted. Evidently, this therapy supports the venous system, and thereby provides resistance to closely interrelated increased pressures in three body cavities. It should be noted that, without major injury, rats undergone BPC 157 therapy sustained severe intra-abdominal hypertension, grade III and IV, at a pressure of 25-50 mmHg [15].

To verify the suggested peripheral and central interplay, some studies have also employed several routes of BPC 157 administration, with equipotent beneficial therapeutic effects [3-17]. Local application to the swollen brain implies a direct counteracting effect: intraperitoneal or intragastric administrations mean a systemic effect, and μg- and ng-regimens mean a common beneficial effect. Conceptually, the intragastric application shows the importance of BPC 157 as an original cytoprotective anti-ulcer peptide (native and stable in human gastric juice for more than 24 h), with effects on epithelial/endothelial maintenance and protection [1, 2].

Evidently, BPC 157 therapy is in line with the considerable interest in developing new strategies for currently insurmountable problems in cardiovascular disease and in rediscovering old concepts, as BPC 157 has emerged as a late extension of Robert's cytoprotection concept [1, 2]. This might be essential for preventing and treating vascular occlusion with thrombosis or any other form of blockade, *i.e.*, ligation, vascular failure due to the application of agents, major noxious events, mechanical compression (intra-abdominal hypertension), or unresolved Virchow's triad.

As recently reviewed [1], for a long time, the resolution was to focus on the stomach, and it was approached *via* intragastric alcohol studies [18, 19]. The classic cytoprotection concept, put forward years ago by Robert (epithelial protection/maintenance) [18] and supplemented by Szabo (endothelial protection/maintenance) [19], and their synergistically working axiom (endothelial maintenance → epithelial maintenance), indicated endothelial/epithelial lesions, thrombus and stasis occur within less than one minute of each other [19]. *Vice versa*, this concept suggests a rapid damage-rapid response principle, since these events could all be circumvented with the application of a cytoprotective agent. On the other hand, as the practice is limited by the (inadequate) activity of standard cytoprotective agents, *i.e.*, prostaglandins (effective only before, but not after injury) [18], the practical theory [18, 19] postulates endothelial maintenance to epithelial maintenance as the main inherent activity of the rapid damage-rapid defensive response of cytoprotective agents, but this is mostly observable as stomach lesion recovery [19]. Now, with BPC 157 therapy, it might appear that the original endothelium/epithelium cytoprotection prediction of rapid damage-rapid defensive response might be fully realized both in theory and in practice. Moreover, there has been increased use of BPC 157 therapy, with considerable efficacy also after injury [1, 2]. The effect of the rapid damage-rapid defensive response as a whole might support this concept [3-17], and implies greater potential cytoprotection with pleiotropic BPC 157 therapy [1] as a novel cytoprotection mediator largely involved in wound healing [1,2]. This treatment may also be applicable as a novel method to recover vessels as a specific emergency therapy for damaged vessels and consequent multiorgan failure [1]. It should be noted that, upon BPC 157 therapy, corneal ulcers are resolved as well, along with recovered corneal transparency and a distinctive effect on angiogenesis, depending on tissue healing [20]. However, even more importantly, as demonstrated in all of the mentioned prototypic disturbances [3-17], this endothelial maintenance to epithelial maintenance, as an upgraded maxim, is applicable peripherally and centrally with the specific activation of a (minor) vessel to take over the function of a failed (major) vessel [3-17]. There are particular collateral shunts that are activated upon injury to recover and reorganize blood flow to compensate for vascular failure [3-17]. Of note, there is a correspondingly high range of collateral blood vessels that may be involved, in which minor vessels are upgraded to take over the function of a disabled major vessel, *i.e.*, the azygos vein (a superior-inferior caval vein shunt to provide more direct blood flow delivery) [7, 8, 13-17], the left ovarian vein [3], and the inferior mesenteric vein in the portocaval shunt [4]. More specifically, the inferior and superior anterior pancreaticoduodenal and pyloric veins in the superior mesenteric vein-portal vein shunt [10, 11]

and the inferior mesenteric artery and inferior anterior pancreaticoduodenal artery [9, 11] play important roles, as does the (para)sagittal venous collateral circulation centrally [8]. In a glaucoma model (three of four episcleral veins cauterized), one episcleral vein following BPC 157 therapy might perform the entire function, normalize intraocular pressure, and rescue retinal ischemia [12]. Thus, this 'bypassing key' appears to be an essential rapid effect and general defensive response [3-17]. On the other hand, also as a part of its cytoprotection effect (in general, cytoprotection agents that provide direct cell protection are thought to have considerable beneficial effects [18, 19]), BPC 157 therapy might beneficially affect all of the mentioned organ lesions (*i.e.*, brain, heart, lung, liver, and gastrointestinal lesions) [1, 2].

As a successful result, these particular effects of BPC 157 therapy might be due to the particular combination of maintained endothelial function, induced nitric oxide (NO) release, NO synthase (NOS) blockade, N(gamma)-nitro-L-arginine methyl ester (L-NAME)-mediated hypertension, and suppressed NOS-substrate L-arginine-mediated hypotension [21]. These might occur along with maintained thrombocyte function, a suppressed L-NAME-prothrombotic effect, a suppressed L-arginine-anti-thrombotic effect, as well as unaffected coagulation pathways [22]. Furthermore, BPC 157 might specifically maintain the function of thrombocytes (as noted in the aggregometry and thromboelastometry studies) [23]. When given with aspirin, clopidogrel, or cilostazol in rats, BPC 157 counteracted their inhibitory effects on aggregation activated by arachidonic acid, adenosine diphosphate (ADP), collagen, and arachidonic acid/prostaglandin E1 (PGE1) [23]. Besides, given the strong interrelations between arrhythmias (evidently, this includes attenuated ECG disturbances [3-17]), heart failure, and thrombosis [3], and assuming that venous and arterial thrombosis are two aspects of the same disease [3], the counteracting effect of BPC 157 might be reciprocally related. This implies modulatory effects on the NO system (*i.e.*, NO release, NOS inhibition, and NO overstimulation are all affected) [21]. Moreover, without the need for other known ligands or shear stress, BPC 157 might activate the VEGFR2-Akt-eNOS signaling pathway [24] and maintain vasomotor tone through activation of the Src-caveolin-1-eNOS pathway [25]. These might be taken as an effective upgrade of the cytoprotection maxim of endothelial maintenance to epithelial maintenance [1] acting as a powerful cytoprotective agent that rapidly acts to recruit collateral pathways. Illustratively, in myocardial infarction therapy, NO system function might be recovered due to the interaction with eNOS and COX2 gene expression, as well as counteraction of the aggravating effect of the NOS-blocker, L-NAME [17]. In eye injury, BPC 157 therapy fully counteracted retinal ischemia induced by retrobulbar L-NAME application [26]. Also, there might be a modulatory effect on the prostaglandin system [27, 28]. BPC 157 also counteracts non-steroidal anti-inflammatory drug (NSAID) toxicity [27], indomethacin-induced leaky gut syndrome [28], prolonged bleeding and thrombocytopenia [27]. Of particular note, BPC 157 counteracts thrombocyte consumption, and thereby the prolonged bleeding and thrombocytopenia in deep vein thrombosis [3].

Furthermore, in addition to being isolated from human gastric juice, BPC 157 was found, using *in situ* hybridization and immunostaining studies in humans, to be largely distributed in many tissues [29]. Thus, BPC 157, although still clinically unknown (it has been used in ulcerative colitis trials) [1, 2], may have additional physiological regulatory roles that may be fully implemented due to its profound cytoprotective activity (it does not have a lethal dose (LD1)) [1, 2] and it may be safely used in purposeful therapy. Finally, due to the described effects (especially given that NO is an important therapeutic target in diseases caused by coronaviruses, including COVID-19 [30]), the stable gastric pentadecapeptide BPC 157 has been suggested as a potential treatment for COVID-19 [30].

In conclusion, BPC 157 therapy exerts a particular action to organize bypassing of the defect, re-establish blood flow and reorganize the circulation to compensate for vascular defects and/or reverse induced failure [3-17]. A BPC 157 regimen may be useful for the resolution of the shared syndrome of Virchow's triad (endothelial lesion, hypercoagulability, stasis) in vascular and multiorgan failure peripherally and centrally. This likely occurs due to its modulatory effects *via* a particular interaction with several molecular pathways, *i.e.*, BPC 157 therapy counteracts tumor-induced cachexia [31], leaky gut as it is a stabilizer of cellular junctions [28], and acts as a free radical scavenger, in particular in vascular occlusion studies [3-5, 9-11, 14, 17]. Moreover, it is useful in controlling vasomotor tone and the activation of the Src-caveolin-1-eNOS pathway [25]. Thereby, the consistently evidenced specific recruitment of bridging blood vessels and collateral shunt activation may largely improve the original cytoprotection (endothelium/epithelium) axiom introduced by Robert and Szabo [1]. The key rescue potential of this therapy against one or more targets (occlusion of one or more major vessels, widespread vascular injury by noxious agents, or mechanical compression) can be seen in the resolution of multiorgan failure by BPC 157 *via* mechanisms that are commonly shared in severe or even deadly occlusion and occlusion-like syndromes [3-17]. A final advantage is the

very safe profile of BPC 157, *i.e.*, no adverse effects in clinical trials (ulcerative colitis, phase II); additionally, in toxicological studies, the LD1 could not be achieved [1, 2, 21, 27, 29]. This latter point was recently confirmed in a large study conducted by Xu and collaborators [32]. Together, these findings [1, 2, 21, 27, 29] might be suggestive for the further application of BPC 157 therapy in cases of vascular injury.

LIST OF ABBREVIATIONS

ECG = Electrocardiogram

NO = Nitric Oxide

NSAID = Non-steroidal Anti-inflammatory Drug

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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

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