Myotendinous Junction Recovery

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The reported myotendinous junction recovery as novel outbreak may have a general significance in the issue of healing. For general significance, the recovery means that the innate problem was essentially resolved by BPC 157 therapy alone. This means the interrelated muscle and tendon healing— including recovery of the muscle–tendon junction injury and the recovery of the muscle and tendon—occurred simultaneously.

stable gastric pentadecapeptide BPC 157 | muscle healing | therapy

1. Introduction

As shown in some literature (for review, see [1][2][3][4][5][6]), all of the studies to date that have tested the stable gastric pentadecapeptide BPC 157 peptide—native to and stable in human gastric juice, even for periods of time longer than 24 h—as a treatment have demonstrated extremely positive healing effects for various injury types in numerous organ systems, particularly for the muscular system. These might be injuries directly to the muscle or various muscle disabilities deriving from a multitude of causes, peripheral and/or central (for review, see [1][7][8][9]). As an additional effect, there is also the maintenance and recovery of smooth muscle function, and BPC 157 therapy might promote recovery of sphincter functions (for review, see [1][2][3][4][5][6]). As an illustration, it has been shown to counteract tumor-induced muscle cachexia and the signaling process implicated in cancer cachexia [10] and leaky gut [11], as well as its membrane stabilizing and free radical scavenging activities (for review see, [10][11]). Furthermore, its effects on damaged skin, muscle, tendon, and bone are comparable to those in the gastrointestinal tract (and liver, pancreas lesions) [1], kidney and cardiovascular system (particularly affecting blood vessels and vessel recruitment as part of therapy for heart failure and lung lesions, counteracting arrhythmias and thrombosis) [5][6]. Conceptually, its practical significance has been ascribed to its particular role in the Selye's stress response [3][7][8], as well as to its resolving of activities of the brain–gut and gut–brain axes [7][12]. Of note is the way that BPC 157 might counteract various encephalopathies [13][14][15][16][17][18][19][20][21], behavioral disturbances [22][23][24][25][26][27] (particularly those representing psychiatric illness models [25][26][27]) and CNS disturbance-induced muscle disabilities [19][20][21][22][25][28][29][30][31], in particular. However, the findings that the stable gastric pentadecapeptide BPC 157 might beneficially affect striated and smooth muscle and heart might suggest that it most perfectly matched [32][33][34] with the original Robert's and Szabo's cytoprotective theory and concept [35][36][37][38][39][40][41][42]. Originally, the concept holds the epithelium/endothelium protection achieved against direct injury made by noxious agents by contact in the stomach, as direct cell protection, to be translated unlimitedly to the

entire body [35][36][37][38][39][40][41][42]. For BPC 157, its essential gastric juice origin and stability in human gastric juice for periods of time longer than 24 h [3][4][32][33][34], due in particular to its special structure (GEPPPGKPADDAGLV), might ascertain the function of the new mediator of cytoprotection. Thus, in the stomach there is the permanent maintenance of mucosal integrity, and thereby in the entire gastrointestinal tract [3][4][32][33][34]. Epithelium/endothelium protection might be easily achieved and further extended to the general level (protection of other organs) (cytoprotection to organoprotection) [3][4][32][33][34]. This implies simultaneous healing of the different tissues (i.e., fistula healing [2], but also myotendinous junction recovery [43]), and thereby particular wound healing potential [1][9], providing a particular potential for the recovery of damaged muscle function [2][19][20][21][22][25][28][29][30][31][43][44][45][46][47][48]. Therefore, BPC 157 has a particular therapeutic effectiveness, including via a therapeutic per-oral regimen, and pleiotropic beneficial effects in terms of cytoprotection [3][4][32][33][34]. Furthermore, BPC 157 might particularly interact with many essential systems, i.e., the nitric oxide (NO)- [49], prostaglandins- [50], dopamine- [26][51][52][53][54][55][56][57], and serotonin- [24][25] systems, known to be essential for both cytoprotection and muscle function integrity, and might interact with many molecular pathways [58][59][60][61][62][63][64][65][66]. Illustratively, this might be the for the control of the vasomotor tone and the activation of the Src-Caveolin-1-eNOS pathway [60][61]. This likely occurred as the particular modulatory effects of the NO-system as whole [49][60][61][67][68]. Indicatively, BPC 157 induced a NO-release of its own [49][67][68] and therefore counteracted both NO-synthase (NOS) inhibition (i.e., N(G) nitro-L-arginine methylester (L-NAME) hypertension and pro-thrombotic effects) and NO overstimulation (L-arginine hypotension and anti-thrombotic, pro-bleeding effects) [49][67][69].

Together, this might be a suitable background for a review within the wider frame of the cytoprotection concept [1][3][4][9][32][33][34]. As mentioned, the entirety of BPC 157's beneficial effect on damaged or disabled muscle function recovery includes the striated and smooth muscle and heart, allowing a new cytoprotective approach to therapy for these muscle disorders. However, standard growth factors are typically rapidly destroyed in human gastric juice, within 15 minutes [1][3][4][32][33][34]. Commonly, these are practical obstacles that cannot be avoided; unable to be applied alone, these growth factors require the addition of various carriers or biological scaffolds [1][70].

Furthermore, with BPC 157 therapy, the epithelium/endothelium protection is an innate cytoprotective capability of the agent, and represents, thereby, the essential principle of the cytoprotection principle. Endothelium protection→epithelium protection has been promoted as the particular upgrade of a minor vessel in taking over the function of a disabled major vessel (for review, see [5][6][33]). With severe syndromes, such as vascular and multiorgan failure following major vessel occlusion or similar noxious procedures [66][71][72][73][74][75][76][77][78][79][80][81][82], the particular activation of the collateral pathways (i.e., azygos vein direct blood delivery) might be essential to counteract severe central and peripheral lesions, intracranial (superior sagittal sinus), portal and caval hypertension and aortal hypotension. Likewise, overwhelming thrombosis can be counteracted, and widespread Virchow triad circumstances fully removed [66][71][72][73][74][75][76][77][78][79][80][81][82]. Therefore, the severe muscle weakness that appeared as a decisive outcome was accordingly counteracted as well [80].

Thus, particularly following demonstration of the recovery of the myotendinous junction (dissection of quadriceps tendon from quadriceps muscle) [43], this study might provide a particular (cytoprotective) view and evidence of the

muscle healing and function recovery with the cytoprotective stable gastric pentadecapeptide BPC 157 therapy [1][3][4][9][32][33][34]. As mentioned, in practice the cytoprotection approach should combine therapy for striated, smooth and heart muscle. Practically, this might be considered a native peptide therapy with high wound healing capacity [1][9] (used without any carrier addition), easily used as a therapy (parenteral, intragastric, per-oral (in drinking water), topical (i.e., cream, solution, eye drops)) [1][3][4][9][32][33][34] and that might also be highly effective in muscle disorders.

As an indicative point, the significance of the BPC 157/cytoprotection review for muscle healing functioning is in its resolution of the perception of the cytoprotection complex as a point of interest at the current time, providing more than 2100 studies for “muscle cytoprotection” in Pubmed. This might be perceived as a considerable problem, given that muscle disorders therapy has remained unresolved in general, and that there is neither a conceptual implementation of the original cytoprotection theory nor cytoprotective agents for therapy. On the other hand, the purposeful cytoprotective conceptualization of muscle disturbances with cytoprotective agents might be worthy, given Robert’s and Szabo’s original prostaglandin cytoprotection (stomach) background [35][36][37][38][39][40][41][42], cytoprotection as a commonly acknowledged ongoing physiologic process [83] and prostaglandin E2 as a crucial inflammatory mediator of muscle stem cells and as the building blocks of muscle regeneration [84]. Noteworthily, the concomitant use and mutual counteraction of cytoprotective agents and non-steroidal anti-inflammatory drugs (NSAIDs) has been a common proof of the cytoprotective concept [32][33][34][35][36][37][38][39][40][41][42]. Thus, cytoprotective agents and the cytoprotection concept in general might be suitable for exceedingly common acute muscle injuries. Therefore, the cytoprotective agents and cytoprotection concept in general mandate common acute muscle injuries, NSAIDs to reduce the associated inflammation, swelling and pain, given that NSAIDs prophylactic use, early or delayed administration might delay muscle regeneration and contribute to loss of muscle strength after healing [85]. At the cellular and structural level, evidence exists for a negative influence of NSAIDs on the muscle stem cell population (satellite cells) and on muscle connective tissue’s significant remodeling during muscle regeneration [85]. Furthermore, cardiovascular risk of NSAIDs has appeared to be an under-recognized public health issue [86]. It is important to note that BPC 157, given as therapy, might reestablish prostaglandin system functions, and may promote a counteraction of the adverse effects of NSAIDs [50]. This counteraction might involve the central (i.e., encephalopathies) [15][16][17][18][50], and/or peripheral (i.e., gastrointestinal and liver lesions, bleeding disorders, and muscle disabilities) [15][16][17][18][50][87][88] adverse effects, acting as a membrane stabilizer (counteracted leaky gut) [11] and free radical scavenger, particularly in the vascular studies [10][11][55][66][75][76][79][80][89][90][91].

2. Myotendinous Junction Recovery

In practical principle, myotendinous junction failure occurs when the quadriceps tendon completely tears and the muscle is no longer anchored to the kneecap, so that the quadriceps muscles contract but without function [43]. Thereby, in general, the more complex the injury, the more complex the healing effect that the BPC 157 therapy realized, the more complex are the requirements to confirm the obtained findings. Furthermore, the therapy was fully effective from the very beginning and congruent functional, biomechanical, microscopic and macroscopic

assessments consistently support each other. Illustrating the full function as the definitive hallmark of the recovery, regardless of the mechanism, the BPC 157-treated rats had no leg contracture, and no failure to walk (which is otherwise characteristic, wherein, along with the initiation of the swing phase, the foot slides backward as a sudden jerk of the limb towards the back) [43]. The therapy link might also be indicative (note the wide range of the regimen (ng–µg)). It was consistent at each of the investigated post-injury periods and was easily applicable as either an intraperitoneal or per-oral (in drinking water) therapy regimen [43]. More precisely, with the same BPC 157 dose regimen, the myotendinous junction healing [43] occurred alongside the demonstrated restoration of the osteotendinous junction (whereby the Achilles tendon is detached from the calcaneus) and the elimination of the systemic corticosteroid damaging effect [92][93][94][95]. This occurred also as the restored neuromuscular junction function antagonized the effect of the neuromuscular blocker succinylcholine, thereby opposing the inability of the muscle cell to repolarize, and opposing the desensitization at the nerve terminal [96]. Thus, BPC 157 therapy might have a wide but selective healing capacity to restore the disabled junctions and their functions. This might be a healing effect that is particular to the tissue and injury involved. The worst circumstances resolved might be the specific confirmation of the required therapies relating to either transection or detachment of either the tendon or the muscle [44][92][93][94][95][97]. Tendon–tendon continuities were reported to have re-established well, with no ossicles forming in other tissues [92][93][94][95][98] (note, with bone morphogenetic proteins (BMPs) [99][100][101], the initial tendon healing process is misleading, due to its similarity to the process of fracture healing [99] and the formation of ossicles in other tissues [99][100][101]). Likewise, with BPC 157 therapy, there was a re-established muscle–muscle continuity, and thereby a re-established tendon–muscle continuity as well [43][44][45][46][47][48][92][93][94][95][97]. Similarly, this might also occur with a ligament transection, with a reestablished ligament–ligament continuity, and fully recovered function upon medial collateral ligament transection [98].

Additionally, given reestablished muscle–tendon, muscle–muscle, tendon–tendon, and tendon–bone continuity [43][44][45][46][47][48][92][93][94][95][98], BPC 157 therapy has considerable bone healing capacity. It heals pseudoarthrosis in rabbits, and femoral head osteonecrosis in rats, and counteracts inflammation and alveolar bone loss in experimental periodontitis [32][33][34].

This might be practical evidence that BPC 157 accordingly manages tendon healing and muscle healing [43][44][45][46][47][48][92][93][94][95][97][98], so that myotendinous junction healing may be achieved [43]. Together, the BPC 157 course description (through six weeks) brings a myotendinous junction restoration by BPC 157 as the particular healing course, which is also obviously specific and valuable [43] for the healing other injured tissues, such as muscle, tendon, ligament and bone [32][33][34][43][44][45][46][47][48][92][93][94][95][98], and is probably indicative of other effects as well. Thus, as at no specific point was there a recorded muscle fiber atrophy within the myotendinous area, this is likely a result of the continuously maintained function [43]. Initially, there was significant vascularity, as well as penetrating capillaries, mild edema, infiltration of inflammatory cells, and prominent proliferation of fibroblasts, with the synthesis of the reticulin and collagen fibers of the myotendinous junction. These were later transmitted toward the only well-oriented dense connective tissue, with no edema and inflammatory cells, completely vanished revascularization of the myotendinous junction, and a well oriented dense connective tissue and muscular fibers within the myotendinous junction area [43].

Finally, as an indicative hallmark of recovery solely in the disabled myotendinous junction, the BPC 157 therapy showed a suggestive effect. An additional increase of the increased eNOS mRNA level occurred but so did a decrease of the increased COX-2 mRNA levels, as well as a consistently normal level of NO, and a decrease of the increased MDA values almost to the normal level [43]. Thus, a particular interaction with the NO system and prostaglandins system, leading to a counteraction of oxidative stress, occurred [43]. It is likely that BPC 157 specifically acts in conditions of disease as, in the healthy rats, it had no effect. Likewise, myotendinous junction healing as an effect of oxidative stress and stress on the NO and prostaglandin systems [43] might be approached with BPC 157 as a particular modulation of the activities of the NO and prostaglandins systems, and as a counteraction to the oxidative stress [49][50][60][61][67][68][69]. These were observable as the spontaneous release of NO [67][68], as a counteraction of the adverse effect of a NOS blockade (i.e., L-NAME hypertension and pro-thrombotic effect), a counteraction of the adverse effect of NOS overstimulation (i.e., L-arginine hypotension and anti-thrombotic effect) [67][69], as control of vasomotor tone and as the activation of the Src-Caveolin-1-eNOS pathway [60][61]. There was also evidence of the maintenance of the thrombocytes function (i.e., without interfering with coagulation pathways) [69][87][88], the counteraction of all adverse effects of NSAIDs [50], and the role of membrane stabilizer (counteracting leaky gut) [11] and free radical scavenger, particularly in the vascular studies [10][11][55][66][75][76][79][80][89][90][91].

In summary, the myotendinous junction healing and its further applicability might be seen as realization of the particular wound healing effect of BPC 157 as particular cytoprotective agent (for review, see [1][3][4][5][6][9][32][33][34][102]). The advantage of the native peptide therapy is its combination of both local and systemic effectiveness, avoiding all problem associated with the need for carriers. Most importantly, there is clear evidence of the effect, which is contrary to the peptide–carrier complex (for review, [1][3][4][5][6][9][32][33][34][102]). Thus, it can be claimed that the myotendinous junction recovery [43] occurred alongside the described beneficial effect in the healing of the muscle [43][44][45][46][47][48] and the tendon [92][93][94][95][98]. There were consistent functional, biomechanical, macroscopic, and microscopic effects for the exemplified mechanism(s) that allowed the definition of myotendinous junction healing in practice [43]. Therefore, the functional recovery, muscle size recovery, and oxidative stress may be particularly illustrative [43]. This might also be seen in further prolonged studies.

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