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Salutary effect of gastric pentadecapeptide BPC 157 in two different stress urinary incontinence models in female rats

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Background: Since an originally anti-ulcer stable gastric pentadecapeptide BPC 157 (PL 14736) was shown to promote healing of injured striated muscle and smooth muscle in the gastrointestinal tract, we explored its therapeutic potentials for leak point pressure (LPP) recovery in rat stress urinary incontinence (SUI) after transabdominal urethrolysis (TU) and prolonged vaginal dilatation (VD).

Material/Methods: During a 7-day period, TU-rats and VD-rats (or healthy rats) received BPC 157, either (i) intraperitoneally, 10 µg/kg or 10 ng/kg, once daily (first administration 30 min after surgery, last 24 h before LPP-testing and sacrifice), or (ii) per-orally, 10 µg/kg in drinking water (0.16 µg/mL, 12 mL/rat/day). Vesicourethral segments were harvested for immunohistochemical evaluation.

Results: All BPC 157 regimens counteracted decrease of LPP values in TU-rats and VD-rats. Additionally, BPC 157-TU rats (µg-intraperitoneally or per-orally) and BPC 157-VD rats (µg intraperitoneally) reached LPP values originally noted in healthy rats. Conversely, in healthy rats, BPC 157 did not alter LPP. Immunohistochemical studies revealed higher desmin (delineates striated organization of skeletal muscle), smooth muscle actin, and CD34 (angiogenic marker) positivity within the urethral wall in BPC 157-treated rats *vs.* controls, as well as overall preserved muscle/connective tissue ratio assessed with Mallory's trichrome staining.

Conclusions: Pentadecapeptide BPC 157, applied parenterally or per-orally, appears to ameliorate the SUI in rat models, improving the otherwise detrimental course of healing after VD and TU, which may be analogous to human injury. These beneficial effects may possibly be selectively used in future strategies for treatment of SUI.

Key words: leak point pressure • pentadecapeptide BPC 157 • rat urethra • stress urinary incontinence

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Background

To date, no standard agents have been shown to improve healing of severely injured or transected muscle to support the effect on stress urinary incontinence (SUI), nor has this possibility been considered from theoretical or practical points of view [1–6].

To alternatively resolve the problem, we focused on SUI and the stable gastric pentadecapeptide BPC 157. Interestingly, it is an antiulcer peptide that cannot be degraded by 24-hour exposure to human gastric juice. Interestingly, it is an antiulcer peptide that cannot be degraded by 24-hour exposure to human gastric juice, with established safe therapy profile (lethal dose not achieved even at 2 g/kg b.w.), efficient in inflammatory bowel disease (PL 14736; for review see, e.g. [7,8]), wound and collagen healing [9–12], with particular effect on muscle healing [13–17], and failed lower esophageal sphincter and pyloric sphincter [18,19]. Therefore, its parenteral and per-oral application in rats after transabdominal urethrolysis (TU) and prolonged vaginal dilatation (VD) may be interesting.

Pharmacological treatment for SUI is mostly focused on the use of nonselective alpha-agonists, which are often ineffective [20], and serotonin and norepinephrine reuptake inhibitors (e.g., duloxetine) [21]. In addition, particular combinations (alpha2-adrenoceptor blockade and duloxetine) [3] and various other possibilities were suggested (eg, angiotensin II) [4]. Most improvements of therapy (e.g., alpha-agonists) aim to selectively (eg, sub-type-selective alpha1-adrenoceptor agonists) affect urethral pressure, peripherally [5], and most recently, centrally [6], and these therapies may affect the bladder or urethral properties of healthy subjects (e.g., selective, partial agonist at the human alpha1(A)-adrenoceptor) [6], explaining the elevation in leak point pressure (LPP). This approach did not offer the necessary degree of separation over cardiovascular events when assessed in *in vivo* models of cardiovascular function [4–6,20]. Moreover, since a synergistically improved continence rate with a combination of physiotherapy [1,2] and pharmacological treatment (e.g., with duloxetine) [22], it is therefore more surprising that none of the standard agents was shown to improve the healing of severely injured or transected muscle to support the effect on SUI. These were the reasons why we suggested the stable gastric pentadecapeptide BPC 157 to recover LPP in rat SUI after TU and VD.

Namely, a particular rescuing effect on failed LPP, avoiding an effect in normal healthy rats, may be even more likely since this originally anti-ulcer stable gastric pentadecapeptide, BPC 157, was shown to particularly heal sphincters in gastrointestinal tract [18,19], as well as both injured striated muscle [13,14,16] and smooth muscle [15,17]. Providing that urethral cross section contains both smooth and striated muscle [23], BPC 157's effect on both smooth muscle and striated muscle was assessed in proximal, middle and distal urethral segments, along with the effect on vessel density. Intriguingly, as mentioned, previous studies have demonstrated this peptide's ability to rescue failed sphincter function in esophagitis rats, rapidly normalizing decreased pressure in lower esophageal and pyloric sphincters [7,18,19]. However, GI and urinary tract dysfunctions (e.g., SUI) may present completely different mechanisms, and therefore it may be interesting to study SUI rats, particularly after VD or TU. Pressure-induced ischemia, pelvic floor injury, and dysfunction of the urethral continence mechanism seen in VD [24], as well as loss of anatomic urethral support, loss of innervations and muscle atrophy presented with TU [25], are commonly regarded as well reproducible SUI features [26]. Taken together, these factors may correspond with SUI complex pathophysiology, leading to a chronic functional syndrome.

Thus, TU-rats and VD-rats (or healthy rats) received BPC 157 in the regimens successfully used before, either intraperitoneally, or per-orally, in drinking water, during a 7-day period,.

Material and Methods

Pentadecapeptide BPC 157

We used pentadecapeptide BPC 157, GEPPPGKPADDAGLV, M.W. 1419 (Diagen, Ljubljana, Slovenia), a partial sequence of human gastric juice protein BPC, freely soluble in water at pH 7.0 and in saline, prepared with 99% high pressure liquid chromatography purity (1-des-Gly peptide as impurity, biologically inactive) (without carrier or peptidase inhibitor) for all treatment protocols, prepared as described before [7].

Animals

Female Wistar albino rats (n=7 in each group), retired breeders, weighing 310–350 g, were used in this study. All experimental protocols were approved by the Ethics Committee at the Medical Faculty, University of Zagreb and conformed to the International Directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes.

Surgery

Surgery was performed in deeply anesthetized rats: ketamine (20 mg/kg b.w. intraperitoneally; Ketanest, Parke-Davis GmbH, Berlin, Germany) and diazepam (6 mg/kg b.w. intraperitoneally; Apaurin, Krka d.d., Novo Mesto, Slovenia).

We utilized 2 well-established rat models [24–26]: TU and VD. In brief, rats assigned to TU group were laparotomized and

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circumferential detachment of proximal and distal urethra from the anterior vaginal wall and pubic bone was carried out by sharp dissection of endopelvic fascia; whereas sham-operated animals underwent laparotomy and bladder manipulation with forceps, but the urethra and bladder neck were untouched. The VD group was subjected to sustained 2-hr inflation (5 ml of saline) of a modified (tip cut off) 12 Fr Foley catheter (Rüsch Inc., Duluth, Georgia, USA) inserted into the vagina and secured into place with one 3/0 silk suture, and the sham group had a catheter inserted and secured, but not inflated.

BPC 157 treatment regimens

BPC 157 was given throughout the 7-day regimen in healthy rats or after TU or VD; intraperitoneally (dissolved in saline [2 µg or 2 ng/mL]) in a single daily dose of the 10 µg/kg or 10 ng/kg b.w., first administration 30 min after surgery, last 24 hr before the LPP testing and sacrifice; or 10 µg/kg/day, dissolved in tap water (0.16 µg/mL, 12 mL/rat/day). Controls received only drinking water or an equal volume of saline (5 mL/kg b.w., intraperitoneally).

LPP testing

On the 7th postoperative day all operated (TU and VD) and sham-operated animals and 7 healthy rats underwent LPP assessment using a methodology based on previously described techniques [24–28]. Under urethane anesthesia (1.2 mg/kg intraperitoneally; SIGMA-Aldrich Chemie GmbH, Steinheim, Germany), used in order to maintain physiologic urethral responses [27], the bladder was exposed via midline abdominal incision and manually emptied. A 24 G transvesical catheter, connected both to an infusion pump (Green Stream VO-P ARGUS 414, Argus Medical AG, Heimberg, Switzerland) and a monitor with an invasive pressure transducer module (model 90309, Spacelabs Medical Inc., Redmond, Washington, USA) via a 3-way stop cock, was inserted and secured into the bladder dome, and the abdominal wall was temporarily closed with sutures. Intravesical pressures [mmHg] were referenced to air pressure at the level of the bladder and were observed continuously as the bladder was subsequently filled with room-temperature saline at the rate of 5 mL/hr. At half bladder capacity (≈0.4 mL), infusion was stopped and gentle pressure was applied increasingly over the bladder until the first drop of fluid was seen on the urethral meatus; the recorded intravesical pressure at that point was regarded as the LPP. By definition, SUI occurs in the absence of bladder contractions [29]. Therefore, if a bladder contraction occurred during LPP measurement (e.g., void is triggered; easily distinguished from leaks [26,28]) those data were omitted, the bladder was drained, refilled and the LPP test restarted. The average of 3 consecutively measured LPPs was taken as a data point for each animal.

Histological studies

The anesthetized animals were killed by exsanguination immediately after completing LPP measurements and the whole bladder and urethra were harvested by removing the symphysis pubis, thus preserving the entire urethral segment. The specimens were fixed in 10% neutral buffered formalin overnight and embedded in paraffin, semi-sequentially cut (5 µm thickness; proximal, middle and distal urethra), and stained with haematoxylin-eosin and with Mallory's trichrome for morphometry assessment of muscle/connective tissue ratio in mid-urethral segment. Additionally, for all 3 urethral segments, immunohistochemistry studies were carried out for desmin (delineates a striated organization of this filamentous protein identical in the external sphincter and the skeletal muscle) [13,14,16,25], smooth muscle actin (SMA; smooth muscle cell marker) and CD34 (angiogenic marker) [30] (1:50; Dako Denmark A/S, Glostrup, Denmark), in order to assess striated and smooth muscular layer thickness and blood vessel count. Each set of slides used for immunohistochemical study was accompanied by control sections known to contain cells positive for the examined antigen. Morphometrical analysis was done using SForm and Issa computer programs (Vams Tec d.o.o., Zagreb, Croatia) were used. Five high power fields were randomly selected for analysis.

Statistical analysis

For analysis we used the software Statistica 7.1. (StatSoft Inc., Tulsa, Oklahoma, USA). Data were tested with Kolmogorov-Smirnoff test for distribution analysis. Subsequently, if normal distribution occurred, one-way ANOVA with post hoc Newman-Keuls was performed. Otherwise, Kruskal-Wallis with Mann-Whitney post hoc test was performed. Significance level was set at $p<0.05$.

Results

LPP testing

All rats survived surgical procedures until they were sacrificed following LPP assessment. LPP values in healthy rats were not changed by BPC 157 medication. Likewise, sham operations did not produce any changes (Figure 1).

On the other hand, TU produced LPP values markedly decreased a week after surgery. BPC 157 therapy, regardless of the given dose-regimen or mode of administration, completely counteracted the decrease of LPP values. On some occasions, BPC 157 values reached those originally noted in healthy rats. Likewise, in the VD group, at the end of the week all control rats exhibited markedly decreased LPP values. Again, all of the used BPC 157 dose regimens or routes of administration completely

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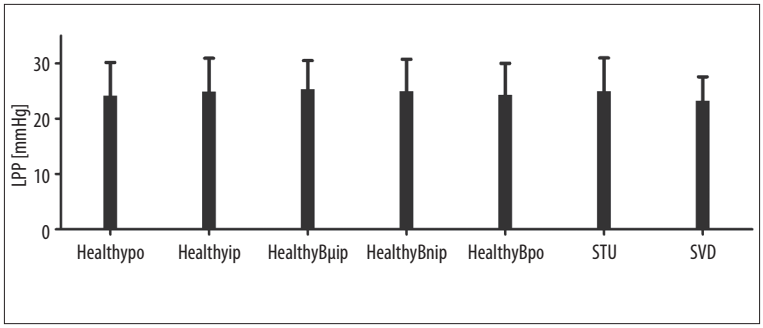

Figure 1. Leak point pressure (LPP) (median – range, mmHg) assessed 7 days after sham-transabdominal urethrolysis (STU) and sham-vaginal dilatation (SVD), or in healthy treated animals (BPC 157 for 7 days intraperitoneally (10 μg/kg (HealthyBμip), 10 ng/kg (HealthyBnip)) or per-orally (10 μg/kg (HealthyBpo)). Controls were receiving only drinking water (Healthypo) or an equal volume of saline (5 mL/kg, intraperitoneally (Healthyip)). No significant LPP difference ($p>0.05$) was found between sham-operated or BPC 157 treated animals when compared to correspondent control groups.

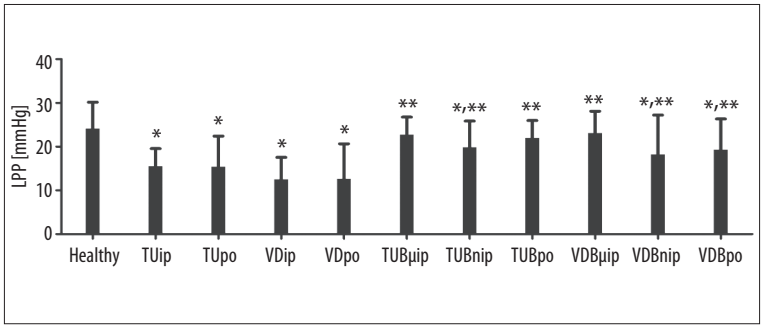

Figure 2. Leak point pressures (LPP) (median – range, mmHg) assessed 7 days after transabdominal urethrolysis (TU) and vaginal dilatation (VD) with BPC 157 intraperitoneal (10 μg/kg (TUBμip, VDμip), 10 ng/kg (TUBnip, VDnip)), and per-oral (10 μg/kg (TUBpo, VDBpo)) therapy. Controls received only drinking water (TUpo, VDpo) or an equal volume of saline (5 mL/kg, intraperitoneally (TUip, VDip)). * $p<0.05$ compared with Healthy. ** $p<0.05$ compared with correspondent control group.

opposed the decrease of LPP values, with some subgroups reaching values originally noted in healthy animals (Figure 2).

Histological studies

The histological findings agree with the LPP studies, finding no particular changes after sham operations. Morphometrical histological studies with Mallory's trichrome staining revealed marked post-operative decrease in muscle tissue content in the mid-urethral segment in all operated animals, but with much more pronounced muscle loss found in control groups. This loss yielded statistically significant differences in muscle/connective tissue ratio between treated and control animals in TU and VD groups (Figures 3 and 4).

Additionally, higher proportion of SMA (Figure 5) and desmin (Figures 6 and 7) positivity was regularly observed in the urethral wall of all BPC 157-treated VD and TU animals, and a noticeable increase in vessel density within all segments of the urethra (immunohistochemical staining for CD34) (Figure 8). Accordingly, while the values in BPC 157 approached the values noted in healthy or sham operated rats, VD and TU controls consistently exhibited markedly lower values.

Discussion

As we hypothesized, based on BPC 157's particular beneficial effect on damaged muscle healing [13–17] and rescue of failed lower esophageal sphincter and pyloric sphincter [7,18,19], failed LPP after TU or VD was successfully recovered, and this was regularly achieved in all BPC 157-treated rats, either with intraperitoneal (both μg and ng dose) or per-oral application, along with microscopic/immunohistochemical improvement involving both striated and smooth muscle, specifically shown in all urethral segments. Unlike the standard therapy that may affect the bladder or urethral pressure of normal rats, and consequently explain the elevation in LPP (e.g., alpha adrenergic agonism) [6], LPP values in healthy rats were not changed by BPC 157 medication, and thereby, failed LPP was specifically recovered. Unlike poor control TU or VD presentation (which corresponds to those regularly noted in other SUI studies) [26], the recovered function in BPC 157-TU or BPC 157-VD rats, as commonly observed in muscle injury studies [13–17], may be consequent to an enhanced healing process, and vice versa; the recovered function by itself promotes healing [31], and such functional recovery could be rather complete, and also dose-dependent, with LPP reaching values originally noted in

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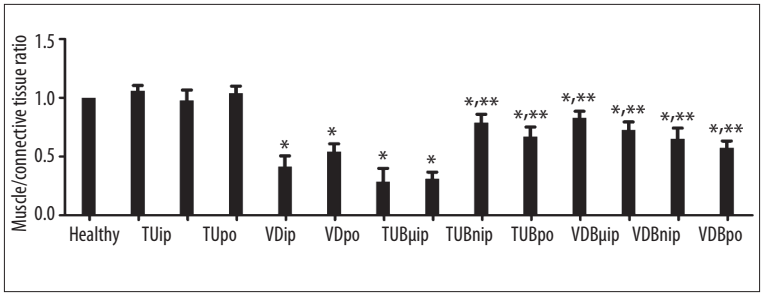

Figure 3. Muscle/connective tissue ratio (mean – SD) assessed in mid-urethral segment 7 days after transabdominal urethrolysis (TU) and vaginal dilatation (VD) with BPC 157 intraperitoneal (10 µg/kg (TUBµip, VDµip), 10 ng/kg (TUBnip, VDnip)), and per-oral (10 µg/kg (TUBpo, VDBpo)) therapy, or sham-TU (STU) or sham-VD (SVD). Operated controls received only drinking water (TUpo, VDpo) or an equal volume of saline (5 mL/kg intraperitoneally (TUip, VDip)). Healthy control animals received only drinking water (Healthy) or BPC 157 (10 µg/kg, intraperitoneally (HealthyB)). * p<0.05 compared with Healthy, ** p<0.05 compared with correspondent control group.

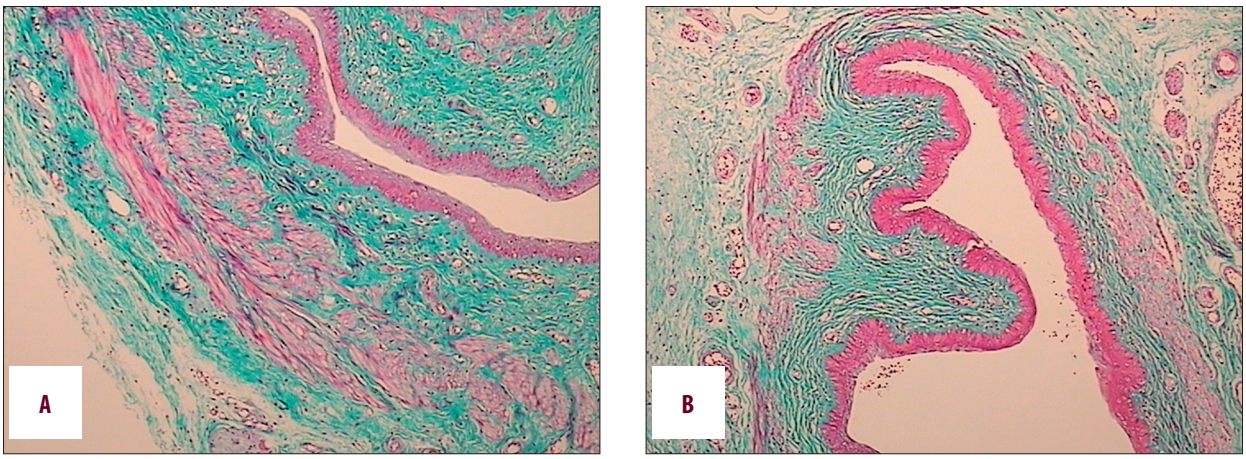

Figure 4. Mallory's trichrome staining of mid-urethral segment 7 day after vaginal dilatation; BPC 157-treated (10 µg/kg, intraperitoneally) rat urethral wall shows thicker and more regular muscle structure (**A**). Control animal presents with thinned muscle layer reduced on account of connective tissue (**B**). Original magnification 100×.

healthy animals. A marked attenuation of both striated and smooth muscle layers in all urethral segments of control animals was alleviated toward nearly normal values with BPC 157 regimens, thus the function of both striated and smooth muscle was improved to rescue failure of LPP.

From the viewpoint of the standard therapy, consistency in severely injured and/or transected muscle healing to support the corresponding effect on SUI [13–17], established by BPC 157, has thus far not been commonly encountered with other agents [1–6], therefore the noted importance of such recovery of failed LPP is better founded in BPC 157-TU-/VD rats. Accordingly, providing the greatest histological evidence of urethral damage is especially obvious in the skeletal muscle layer [24]. Improved microscopy/immunochemistry and restored function (that had to be regularly, definitively debilitated) seen with transected or crushed muscle [13,14,16] is congruous with increased desmin positivity noted in all urethral segments of BPC 157 rats after TU and VD, and LPP values fully recovered.

BPC 157-induced muscle healing implies modulation of the same events; fostering of myocyte regeneration, thus shortening the healing period and avoiding excessive scar formation, again analogous to the preserved muscle/connective tissue ratio in treated rat urethras observed in this study. Additionally, with the same regimens of BPC 157 therapy, along with the previous findings on injured striated muscle [13,14,16], healing effect on peripheral nerve [32], and on smooth muscle of gastrointestinal tract and sphincters [15,17–19], and angiogenesis [30], may be particularly relevant to the noted recovery of the failed LPP in rats after TU and VD. Providing that the procedures used, VD and TU, also directly damaged smooth muscle function, eliminating some of their functions for a while, after GI tract massive resection the remaining part more vigorously adapts in BPC 157 rats, and overwhelms the lack of the removed part [15]. Since both smooth and striated muscle contribute to urethral pressure during filling phase, with accompanying fast twitch fibers contraction reflex that further elevate urethral tone when intraabdominal pressure rises [33],

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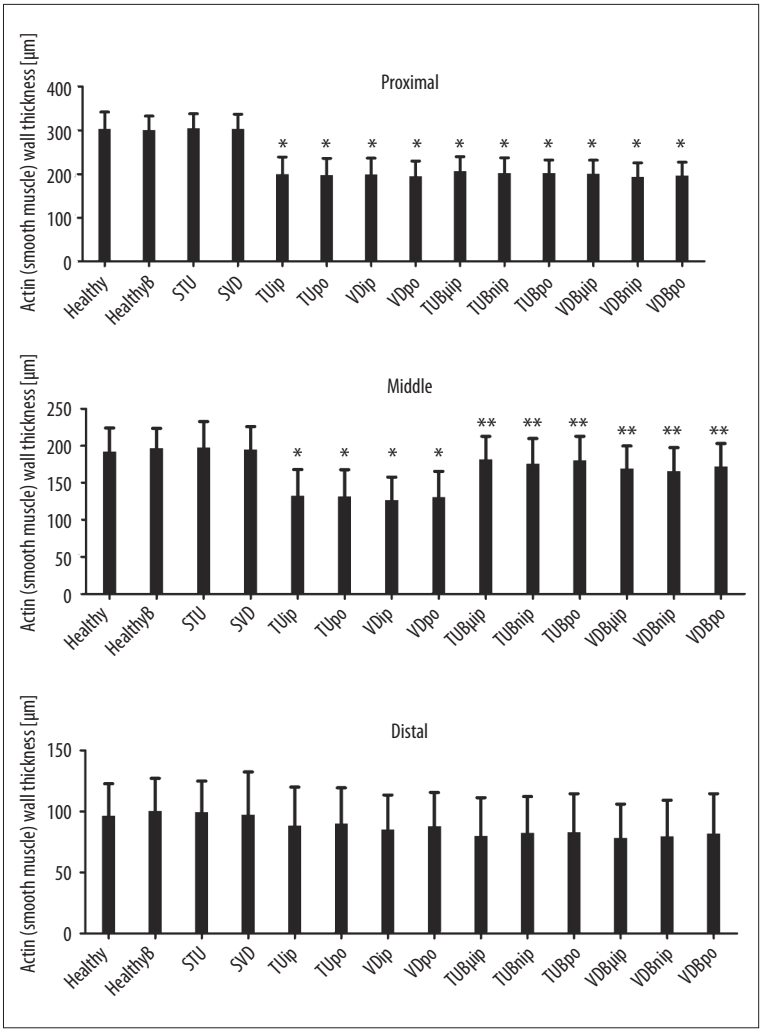

Figure 5. Actin (smooth muscle) wall thickness (mean – SD) assessed in proximal, middle and distal urethral segment 7 days after transabdominal urethrolysis (TU) and vaginal dilatation (VD) with BPC 157 intraperitoneal (10 µg/kg (TUBµip, VDµip), 10 ng/kg (TUBnip, VDnip)), and per-oral (10 µg/kg (TUBpo, VDBpo)) therapy, or sham-TU (STU) or sham-VD (SVD). Operated controls received only drinking water (TUpo, VDpo) or an equal volume of saline (5 mL/kg. intraperitoneally (TUip, VDip)). Healthy control animals received only drinking water (Healthy) or BPC 157 (10 µg/kg, intraperitoneally) (HealthyB). * p<0.05 compared with Healthy, ** p<0.05 compared with correspondent control group.

the restoration of their integrity and functions likely contributed to BPC 157 anti-SUI mechanisms.

Likewise (even if GI and urinary tract dysfunctions (e.g., SUI) may present completely different mechanisms), sphincter failure match esophagitis rats [18,19] and VD rats [3,24,26], with the methods of prolonged dilation, the fairly analogous muscle stretch, and the definitive sphincter failure, did not spontaneously recover until the end of the experiments. In either case, the effect of the BPC 157 is particularly evident in animals with failed sphincter function [18,19] and obtained using both parenteral and per-oral applications.

Considering that pudendal nerve damage is also implicated in SUI pathophysiology, as demonstrated in some other SUI rat model studies (crush, transection) [26], it is important to point out that BPC 157, besides having muscle healing potential [13–19], exhibited significant neuroprotective capabilities [32,34] (e.g., directly improving the transected sciatic nerve healing) [32], thus contributing to regained function after major injury [13,14,16]. Of note, loss of innervations and muscle atrophy [25,35] exists in both VD and TU models as well [25,35]. Since damaged/transected muscle healing [13,14,16] commonly requires regeneration of damaged intramuscular nerve branches [36], it may be that in successful recovery BPC 157 course these parallel healing processes promote each other [37].

Likewise, it was clearly demonstrated that VD results in decreased blood flow to, and hypoxia of, the bladder, urethra and vagina, supportive of hypoxic injury as a possible mechanism of injury leading to SUI [38]. Thus, the observed increase in urethral vessel density, which parallels LPP recovery after TU or VD in BPC 157 treated animals, specifically implies this peptide's previously documented angiogenic effect [30] to be potentially accountable for rapid restoration of urethral function. Noticeably, it is along with a new vascular shift toward the left as shown in different models, particularly in muscle healing [13,14], even in corticosteroid-aggravated conditions [16], and also in hypovascular tissues (e.g.,

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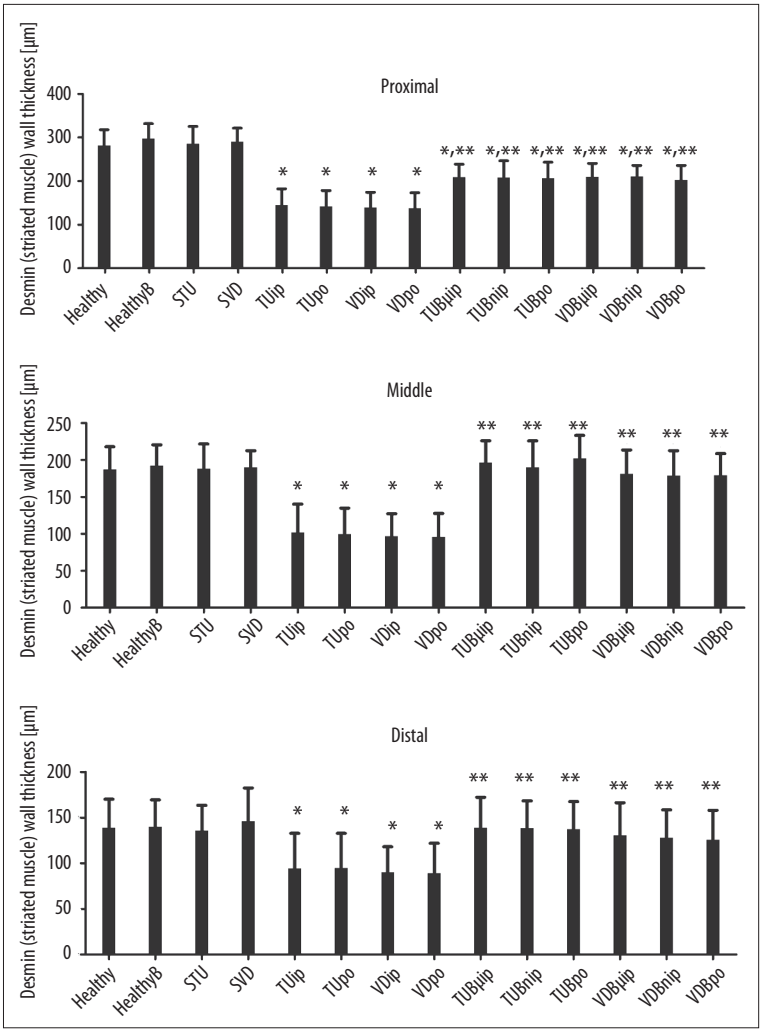

Figure 6. Desmin (striated muscle) wall thickness (mean – SD) assessed in proximal, middle and distal urethral segment 7 days after transabdominal urethrolysis (TU) and vaginal dilatation (VD) with BPC 157 intraperitoneal (10 µg/kg (TUBµip, VDµip), 10 ng/kg (TUBnip, VDnip)), and per-oral (10 µg/kg (TUBpo, VDBpo)) therapy, or sham-TU (STU) or sham-VD (SVD). Operated controls received only drinking water (TUpo, VDpo) or an equal volume of saline (5 mL/kg, intraperitoneally (TUip, VDip)). Healthy control animals received only drinking water (Healthy) or BPC 157 (10 µg/kg, intraperitoneally) (HealthyB). * p<0.05 compared with Healthy, ** p<0.05 compared with correspondent control group.

tendon) [30,39]. This demonstrates the prominent up-regulation of vascular endothelial growth factor (VEGF), likely with particular effect on connective tissue healing, such as the expression of early growth response 1 (EGR-1) gene and its repressor, nerve growth factor 1-A binding protein-2 (NAB2), resulting in early extracellular matrix (collagen) formation [40]. Of note, an enhanced angiogenesis (ie, initial angiogenesis phase followed by accelerated VEGF, CD34 and FVIII [30]) always correlated with increased biomechanical healing rate [9,13,14,16]. Interestingly, BPC 157 has no angiogenic effect on cell cultures [30]). Also, BPC 157 may have a direct effect on myocytes, probably analogous to that on tendon fibroblasts throughout the FAK-paxillin pathway [41].

The evidence was compelling in all of the models used, providing the consistently recovered LPP after VD and TU with all BPC 157 regimens, suggesting that these beneficial effects may be selectively applied to the urethra and treatment of SUI. However, due to the potential limitations of the study, the evidence that BPC 157 ameliorates the SUI is inconclusive. Namely, although the 7-day course obviously is very short compared to clinical situations in which urethral injury usually occurred decades ago, the relevance of the commonly used methods (and also therapies proposed) has been established in a period as short as 4 days [3]. This is not surprising, considering common understanding that the earliest course – its aggravation or attenuation – may be the most relevant for the final (even long-term) positive or negative injury outcome. In other relevant muscle and nerve BPC 157 studies, however, very long injury periods models were also used [13–19,30,32]. In other words, even if this study is about prevention rather than reversal of SUI, this does not diminish the relevant value of the obtained beneficial effects of BPC 157 application in rats that underwent TU and VD, since from the results it is obvious that BPC 157 therapy benefit has a long-term and sustained effect, providing the recovered LPP in TU- and VD-treated rats when the last administration had been at 24 hr before assessment (intraperitoneal regimen). BPC 157 could be easily administered (e.g., also per-orally; in drinking water) [15,17,39]. Furthermore, considering the cardiovascular

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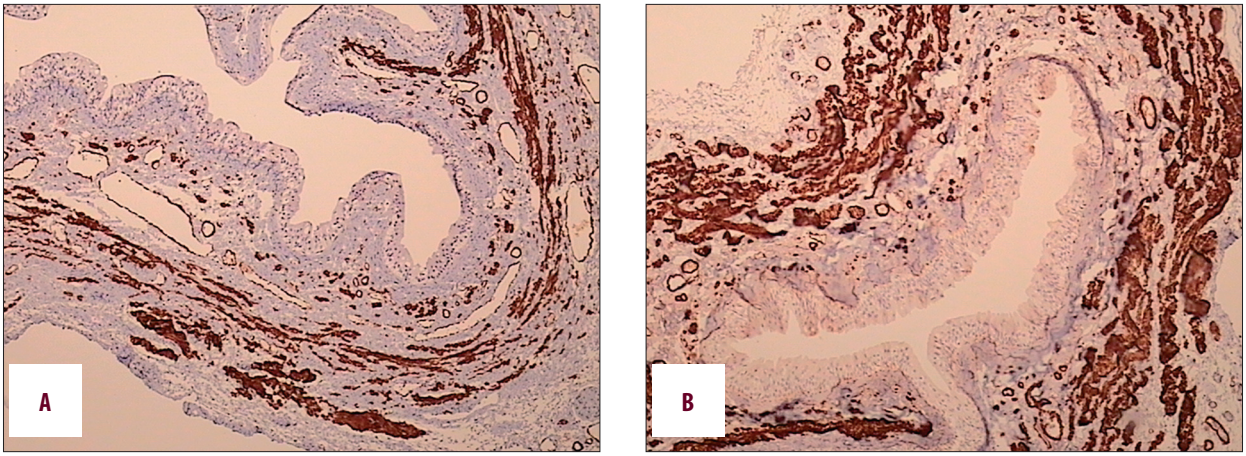

Figure 7. Desmin immunohistochemistry staining of mid-urethral section 7 day after vaginal dilatation; Decreased desmin thickness in the urethral wall of control animal (**A**). BPC 157-treated (10 µg/kg, intraperitoneally) animals show thicker desmin positive muscle wall (**B**). Original magnification 100×.

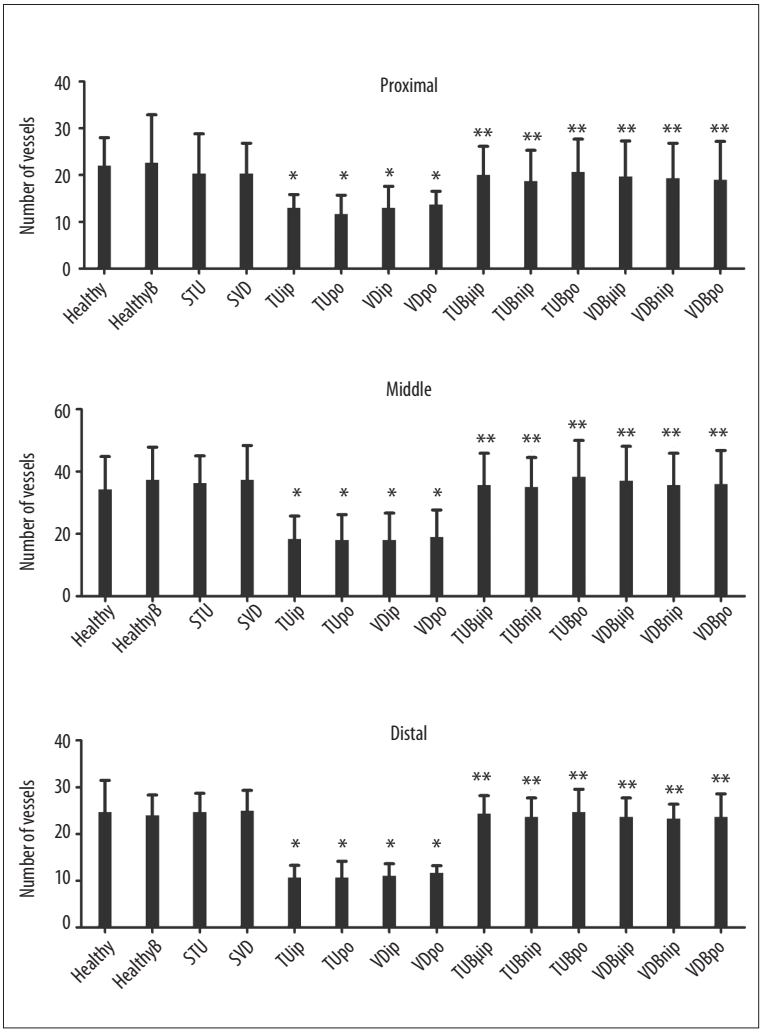

Figure 8. Number of vessels (mean – SD) assessed in proximal, middle and distal urethral segment 7 days after transabdominal urethrolysis (TU) and vaginal dilatation (VD) with BPC 157 intraperitoneal (10 µg/kg (TUBµip, VDµip), 10 ng/kg (TUBnip, VDnip)), and per-oral (10 µg/kg (TUBpo, VDBpo)) therapy, or sham-TU (STU) or sham-VD (SVD). Operated controls received only drinking water (TUpo, VDpo) or an equal volume of saline (5 mL/kg, intraperitoneally (TUip, VDip)). Healthy control animals received only drinking water (Healthy) or BPC 157 (10 µg/kg, intraperitoneally) (HealthyB). * p<0.05 compared with Healthy, ** p<0.05 compared with correspondent control group.

effects that may be a common problem with standard SUI therapy [1,6], *in vivo* models of cardiovascular function showed that BPC 157 does not affect normal blood pressure or heart rhythm [42–44], but it did reduce L-NAME hypertension [44],

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counteract NO system failure by NOS-blockade in different models [43–45] (NO-synthesis is directly related to muscle injury healing [46]), doxorubicine chronic heart failure [42] and digitalis overdose arrhythmias [43], and in toxicology studies a lethal dose could be not achieved and no adverse effects were noted in clinical trials [7,8].

Finally, regardless of the critically assessed standard SUI therapy, duloxetine is still of particular importance [1,3], while imipramine was also suggested [1]. BPC 157 given peripherally may selectively affect regional serotonin synthesis in the rat brain [47] and improve behavioral response in Porsolt's test (*vs.* imipramine) [48], with particular counteraction of pargyline- and L-tryptophan-induced serotonin syndrome, implicated in therapy with specific serotonin (norepinephrine) reuptake inhibitors and triptans [1,50].

Conclusions

Pentadecapeptide BPC 157 applied parenterally or per-orally appears to ameliorate the SUI in rat models, improving the otherwise detrimental course of healing after VD and TU, which may be analogous to human injury. These beneficial effects may be selectively applied to development of future SUI treatment strategies.

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