

Re: Manuscript 51985 revision

Dear Editor,

Thank you very much for your kind letter, and as you suggested, we are sending the revised manuscript accordingly.

The following comments were raised by the reviewers:

Number ID	Review Info	Specific Comments To Authors	Specific Comments To Authors (File)
00053659	Conclusion: Accept (General priority) Scientific Quality: Grade A (Excellent) Language Quality: Grade C (A great deal of language polishing)	Kolovrat et al. investigated rat models that Pentadecapeptide BPC 157 attenuated organ injuries after Pringle maneuver. Although clinical impact of the Pringle maneuver is no longer important as a decade ago, the results seem to be promising with meticulous experiment. However, the manuscript seems to be informal, and it needs native editing with formal certification. In fact, the English editing certificate is invalid due to lack of date. Figure legend is too premature and complex to understand them. They need more detail descriptions. Otherwise, it is interesting. Fig. 3 needs some explanations for the labels. What do S, Bug, and Bng stand for? Fig.4 needs some explanations too. What does each column stand for?	
02540650	Conclusion: Minor revision Scientific Quality: Grade C (Good) Language Quality: Grade B (Minor language polishing)	This topic although is frequently studied, however is well designed, informative and properly designated, some points are needed to be clarified: 1. Why you specifically use BPC 157 however many better drugs are available? 2. All figures are images and some of them with very bad resolution and small font 3. Discussion is very long and introduction is long, both need to be more concise. 4. Many spelling and grammar mistakes are needed to be corrected	

To their comments see our arguments.

Ad reviewer 00053659

We appreciate the comments given by the reviewer. Figures legends for previous Fig. 3 and Fig. 4 were additionally explained.

We are attaching formal certification of the language editing.

Ad reviewer 02540650

We appreciate the comments given by the reviewer. The rationale for the use of BPC 157 was explained in the Introduction.

To this point see previous text (paragraphs 1 and 2)

We focused on the therapy of the Pringle maneuver [1]. First, we focused on so far not described severe preportal hypertension and treatment in rats [1], the temporary portal triad obstruction (PTO), ischemia. Thereafter, we focused on the therapy of the short and prolonged reperfusion. Commonly, the lack of adequate portocaval shunting appears as the most detrimental feature that should be counteracted. With stable gastric pentadecapeptide BPC 157 [2-6], we suggest the resolution of the damages, either those following occlusion or those following re-opening of the hepatic artery, portal vein and bile duct.

Therapy is the recovering effect it has on occluded vessels, bypassing the occlusion [7-11] as the specific effect of BPC 157 in ischemia/reperfusion [7-11]. There is benefit arising from BPC 157 therapy of the deep vein thrombosis, inferior caval vein occlusion,

colitis ischemia/reperfusion, duodenal venous congestion and cecum perforation [7–10]. Recently, after induction of liver cirrhosis due to both bile duct ligation [11] and portal hypertension, prevention and reversal of the already pre-existing portal hypertension to normal values [11] have become possible.

To this point is now more focused and it seems to us, clearly emphasized

We focused on the therapy of the Pringle maneuver in rats [1], so far not described severe preportal hypertension [1], the temporary portal triad obstruction (PTO), ischemia, the short and prolonged reperfusion, the lack of adequate portocaval shunting as the most detrimental feature that should be counteracted. With stable gastric pentadecapeptide BPC 157 [2–6], we suggest the resolution of the damages, either those following occlusion or those following re-opening of the hepatic artery, portal vein and bile duct.

Therapy is the recovering effect it has on occluded vessels, bypassing the occlusion [7–11] as the specific effect of BPC 157 in ischemia/reperfusion [7–11]. There is benefit arising from BPC 157 therapy of the deep vein thrombosis, inferior caval vein occlusion, colitis ischemia/reperfusion, duodenal venous congestion and cecum perforation [7–10]. Recently, after induction of liver cirrhosis due to both bile duct ligation [11] and portal hypertension, prevention and reversal of the already pre-existing portal hypertension to normal values [11] have become possible.

Considering the comment of the reviewer about „many better drugs“ which are available, it seems to us that none of the agents had been given during the reperfusion, and therefore, there is no evidence for such better drugs which can directly affect the reperfusion events. This point is emphasized since all of them were given already at the previous ischemia, therefore they require a considerable preconditioning period. To this point, see the following papers, cited in manuscript **Khodosovskii MN**, Zinchuk VV. [The role of NO-dependent mechanisms in melatonin antioxidant activity during hepatic ischemia-reperfusion in rats]. *Eksp Klin Farmakol* 2014; **77**:33–8 [PMID: 25102734]; **Liao X**, Chen L, Fu W, Zhou J. Heparin-binding epidermal growth factor-like growth factor protects rat intestine after portal triad clamping. *Growth Factors* 2013; **31**: 74–80 [PMID: 23534509 DOI: 10.3109/08977194.2013.784757]; **Oguz A**, Kapan M, Kaplan I, Alabalik U, Ulger BV, Uslukaya O, Turkoglu A, Polat Y. The effects of sulforaphane on the liver and remote organ damage in hepatic ischemia-reperfusion model formed with pringle maneuver in rats. *Int J Surg* 2015; **18**: 163–8 [PMID:

25924817 DOI: 10.1016/j.ijsu.2015.04.049]; **Xu F**, Dai C-L, Peng S-L, Zhao Y, Jia C-J, Xu Y-Q. Preconditioning with Glutamine Protects against Ischemia/Reperfusion-Induced Hepatic Injury in Rats with Obstructive Jaundice. *Pharmacology* 2014; **93**: 155–65 [PMID: 24801881 DOI: 10.1159/000360181]**Tüfek A**, Tokgöz O, Aliosmanoglu I, Alabalik U, Evliyaoglu O, Çiftçi T, Güzel A, Yıldırım ZB. The protective effects of dexmedetomidine on the liver and remote organs against hepatic ischemia reperfusion injury in rats. *Int J Surg* 2013; **11**: 96–100 [PMID: 23261946 DOI: 10.1016/j.ijsu.2012.12.003]

On the other hand, BPC 157 evidence for the specific effect is substantiated in the cited papers (note, some of them were presented in World Journal of Gastroenterology) (**Amic F**, Drmic D, Bilic Z, Krezic I, Zizek H, Peklic M, Klicek R, Pajtak A, Amic E, Vidovic T, Rakic M, Perisa MM, Pavlov KH, Kokot A, Tvrdeic A, Blagaic AB, Zovak M, Seiwerth S, Sikiric P. Bypassing major venous occlusion and duodenal lesions in rats, and therapy with the stable gastric pentadecapeptide BPC 157, L-NAME and L-arginine. *World J Gastroenterol* 2018; **24**: 5366–78 [PMID: 30598581 DOI: 10.3748/wjg.v24.i47.5366]; **Drmic D**, Samara M, Vidovic T, Malekinusic D, Antunovic M, Vrdoljak B, Ruzman J, Perisa MM, Pavlov KH, Jeyakumar J, Seiwerth S, Sikiric P. Counteraction of perforated cecum lesions in rats: effects of pentadecapeptide BPC 157, L-NAME and L-arginine. *World J Gastroenterol* 2018; **24**: 5462–76 [PMID: 30622376 DOI: 10.3748/wjg.v24.i48.5462]; **Vukojević J**, Siroglavić M, Kašnik K, Kralj T, Stančić D, Kokot A, Kolarić D, Drmić D, Sever AZ, Barišić I, Šuran J, Bojić D, Patrlj MH, Sjekavica I, Pavlov KH, Vidović T, Vlainić J, Stupnišek M, Seiwerth S, Sikirić P. Rat inferior caval vein (ICV) ligation and particular new insights with the stable gastric pentadecapeptide BPC 157. *Vascul Pharmacol* 2018; **106**: 54–66 [PMID: 29510201 DOI: 10.1016/j.vph.2018.02.010]; **Duzel A**, Vlainic J, Antunovic M, Malekinusic D, Vrdoljak B, Samara M, Gojkovic S, Krezic I, Vidovic T, Bilic Z, Knezevic M, Sever M, Lojo N, Kokot A, Kolovrat M, Drmic D, Vukojevic J, Kralj T, Kasnik K, Siroglavic M, Seiwerth S, Sikiric P. Stable gastric pentadecapeptide BPC 157 in the treatment of colitis and ischemia and reperfusion in rats: New insights. *World J Gastroenterol* [Internet] 2017; **23**: 8465–88 [PMID: 29358856 DOI: 10.3748/wjg.v23.i48.8465]; **Sever AZ**, Sever M, Vidovic T, Lojo N, Kolenc D, Vuletic LB, Drmic D, Kokot A, Zoricic I, Coric M, Vlainic J, Poljak

L, Seiwert S, Sikiric P. Stable gastric pentadecapeptide BPC 157 in the therapy of the rats with bile duct ligation. *Eur J Pharmacol* 2019; **847**: 130-142 [PMID: 30690000 DOI: 10.1016/j.ejphar.2019.01.030]). Therefore, BPC 157 certainly deserves to be further investigated in this issue.

Introduction and Discussion, considered to be too long by the reviewer, are both considerably focused and shortened.

We also appreciate the comments of the reviewers about the Figures. To this point, previous Figure 2, Figure 3, Figure 4 are accordingly modified.

In conclusion, we hope that we adequately replied to the comments given by the reviewers, and we hope that this manuscript is now suited for final presentation in your distinguished journal.

Sincerely

Predrag Sikiric, MD, PhD

Professor