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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 25296
Title: Urotensin II-induced insulin resistance are mediated by NADPH oxidase-derived reactive oxygen species in HepG2 cells
Reviewer's code: 00289402
Reviewer's country: United States
Science editor: Jing Yu
Date sent for review: 2016-03-04 11:06
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[Y] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

In this study, Li et al reported that a vasoactive peptide, Urotensin II, had a regulatory effect on insulin signaling pathway, including suppression of insulin-induced IRS-1 phosphorylation, Akt activation and insulin-stimulated glucose consumption and glycogen synthesis. Furthermore, Urotensin II treatment led to accumulation of Reactive oxygen species, which leads to the activation of JNK signaling pathway, and possibly inhibition of insulin signaling pathway at cellular level. While the overall studies are very interesting, there are certain drawbacks compromising the overall quality of the study. First, HepG2 cell line itself is not a very good model for physiological studies, including the glucose consumption and glycogen synthesis. The overall conclusion of this study would be significantly strengthened by examining the regulatory effect of Urtensin II at transcriptional level. Second, several chemical compounds were used to examine the signaling pathway. The authors need to use more than one inhibitor to eliminate any effects associated with the chemical compound per se. Finally, urotensin II was suggested to induce ROS production, which further activates JNK activation to suppress insulin signaling pathway in this article. This

hypothesis could be further tested by investigating the effect of JNK inhibitor, in addition to the NADPH-synthase inhibitor in insulin signaling pathway.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Urotensin II (UII), a vasoactive peptide, has been reported to be upregulated in insulin resistance, and to contribute to the exacerbation of the insulin resistant phenotype. Studies in rodent models have shown that UII impairs i) glucose-stumulated insulin release from beta cells and 2) insulin-stimulated glucose uptake in skeletal muscle. However, the possible effects of UII as an inducer of insulin-resistance in the liver have not been studied to date. Here, Li and collaborators, attempt to address this gap by studying the impact of a 24-h UII pre-treatment of hepatic cells HepG2 on subsequent insulin action. Using mainly a western blotting approach (but also through quantification of endogenous glucose and glycogen synthesis) the authors show, quite convincingly, that UII is an inducer of insulin resistance. Pre-treatment of HepG2 with UII decreased hepatic glucose uptake, glycogen synthesis and diminished the activation of the key insulin-signalling molecules IRS1, PKB and GSK3 as assessed by the use of phospho-specific antibodies. Putative mechanisms are presented, including the upregulation of JNK activation and the NADPH oxydase complex and consequent oxidative stress. This is a very well performed study, and the results are

quite convincing to me. However, I would like to raise two major comments to the authors, to be addressed either experimentally or in the discussion section. 1) HepG2 cells are a tumor-derived cell line, and the use of this cell line might in part diminish the physiological meaning of the finding. Would the authors be able to reproduce at least some of the key data (PKB phosphorylation, glycogen synthesis) in primary hepatocytes, or an independent hepatocyte-derived cell line (e.g. HuH7) to show that the effects of UII are reproducible to multiple hepatic cell lines ? 2) I think an interesting question to address is reklated to the persistency of the insulin-resistant phenotype. It would be interestin to investigate whether upon UII removal the hepatocytes retain their insulin-resistant state, and in the affirmative case the duration of the insulin-resistant state. Minor : the paragraph ? comments ? (page 14), is unclear to me. I believe that it should be merged within the discussion.