

ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6636

Title: Hypoxia and Fatty Liver

Reviewer code: 00011378

Science editor: Ma, Ya-Juan

Date sent for review: 2013-10-26 12:42

Date reviewed: 2013-12-29 05:53

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

The review by Suzuki et al about hypoxia and fatty liver is timely and on an important issue providing mechanistic explanation and relating clinical condition such as OSA and FLD. However, this reviewer found some minor concerns, in particular that the revision of the contributions of other authors on this issue is not comprehensive. In general the review can be shortened (in example last paragraph of page 8 and first of page 9 referring to cardiomyocytes may not be relevant to the main topic of the review) and in particular several points deserve considerations: In page 4, line 7, authors affirm that lipogenesis-related genes such as SCD1 are up-regulated in FLD, and this topic is, at least, controversial. (as an example please see 1 below). In the same page, authors affirm that PPAR γ is upregulated in FLD. However, several lines of evidence indicate that PPAR γ agonists (i.e. telmisartan a mixed AT1R antagonist/PPAR γ agonist) may have beneficial effects on FLD. This issue, which is opposed to the anterior conclusion should be briefly discussed. In several places (page 5, 6, 7 and so on) of the manuscript the reported increase of HIF1 α in a HFD-fed rodent model of FLD and the relation with mitochondrial function and expression of mitochondrial biogenesis-related genes such as PPAR γ is ignored (i.e. see 2 below). In the important subsection OSA and FLD, a recent systematic review and meta-analysis on OSA being associated with FLD, ALT, AST and liver fibrosis in more than 1000 subjects should be described and properly cited (see 3 below. References (1) Fernandez GT, Burgueno A, Gonzales MN, Pirola CJ, Sookoian S. Fatty liver is associated with transcriptional downregulation of stearoyl-CoA desaturase and impaired protein dimerization. PLoS One. 2013;8:e76912. (2) Carabelli J, Burgueno AL, Rosselli MS, Gianotti TF, Lago NR, Pirola CJ, Sookoian S. High fat diet-induced liver steatosis promotes an increase in liver mitochondrial



Baishideng Publishing Group Co., Limited

Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China

biogenesis in response to hypoxia. J Cell Mol Med. 2011;15:1329-1338. (3) Sookoian S, Pirola CJ. Obstructive Sleep Apnea Is Associated with Fatty Liver and Abnormal Liver Enzymes: a Meta-analysis. Obes Surg. 2013;23:1815-1825.

ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6636

Title: Hypoxia and Fatty Liver

Reviewer code: 00006459

Science editor: Ma, Ya-Juan

Date sent for review: 2013-10-26 12:42

Date reviewed: 2014-01-03 18:19

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	language polishing	BPG Search:	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Minor revision
		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

An interesting review. I have some suggestions for improving clarity. 1. page 8 start of para; why say "despite"? I feel this sentence is not helpful for clarity of the overall message. It should be modified. 2. . page 13 sentence "The combination of obesity and OSA causes"? I feel this sentence is too strong; you present evidence for an association rather than prove cause. This sentence should be modified. 3. The figure legends need some detail and each legend needs to define the abbreviations used in the figure. By detail, I mean the legend needs to tell the story of the figure. 4. for example: In fig 1, I do not see why at the left there is a multi-colour triangle; what is it intended to communicate about the image at the right side? Explain HO, OH, U etc. 5. Fig 1 Target not target.

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6636

Title: Hypoxia and Fatty Liver

Reviewer code: 00053727

Science editor: Ma, Ya-Juan

Date sent for review: 2013-10-26 12:42

Date reviewed: 2014-01-06 19:06

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Major revision

COMMENTS TO AUTHORS

The review manuscript discusses about the role of HIF in NAFLD and Sleep Apnea .The review is interesting and following points needs to be discussed for better output of the review . The genes involved in HIF and their expression should be made in tabular form. Plasminogen activator Inihibitor-1 (PAI-1) Prolyl-4 hydroxylase alpha-2, Heme Oxygenase 1 (HO1) Vascular endothelial growth factor and hematopoietic growth factor can be discussed. In Recent study, hypoxia, through up-regulation of angiogenesis, contribute to fibrogenic progression of CLDs can be discussed. What is the role of HIF during NASH and fibrosis of Liver /Cirrhosis of liver?

ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6636

Title: Hypoxia and Fatty Liver

Reviewer code: 00068657

Science editor: Ma, Ya-Juan

Date sent for review: 2013-10-26 12:42

Date reviewed: 2014-01-07 10:58

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of	<input type="checkbox"/> No records	
<input checked="" type="checkbox"/> Grade D (Fair)	language polishing	BPG Search:	<input checked="" type="checkbox"/> Rejection
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

The authors discuss the molecular mechanisms by which hypoxia and HIFs regulate lipid metabolism in the development of FLD. However, the structure of the article is out of line, which does not point out the relationship of SREBP and HIF. Secondly, authors cite their unpublished research results, whose authenticity and accuracy we can not confirm.

ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6636

Title: Hypoxia and Fatty Liver

Reviewer code: 00058441

Science editor: Ma, Ya-Juan

Date sent for review: 2013-10-26 12:42

Date reviewed: 2014-01-07 17:56

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	language polishing	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

This is a well written review with an interesting et important issue: hypoxia. I only have few suggestions: 1) authors are suggested to provide a paragraph explaining the role of "hypermetabolism caused oxygen consumption" in both alcohol and high fat diet induced liver hypoxia because I believe this manuscript requires this initiative mechanisms to complete the whole picture. 2) Fig 1 has color code for oxygen level. I suggested that "black colored arrows" in cells should be correlated to this color code. ie. blue arrows for hypoxia and red arrows for normal oxygen level.

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6636

Title: Hypoxia and Fatty Liver

Reviewer code: 00069618

Science editor: Ma, Ya-Juan

Date sent for review: 2013-10-26 12:42

Date reviewed: 2014-01-09 06:12

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	language polishing	BPG Search:	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Minor revision
		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

This review is comprehensive and well written. I would suggest the authors to say a few words more about the role of Hypoxia-Inducible Factors when the pathological sequelae of fatty liver are established and if, at this level, a possible modulation of HIFs could prevent further evolution of liver disease.