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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Biological Chemistry
ESPS manuscript NO: 16771
Title: Novel and unexpected roles of butyrate and butyrate derivatives in the control of metabolism
Reviewer's code: 02681548
Reviewer's country: Portugal
Science editor: Xue-Mei Gong
Date sent for review: 2015-02-01 13:33
Date reviewed: 2015-02-04 19:29

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[Y] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] 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

The manuscript submitted by Sabrina Chriett and Luciano Pirola is highly interesting, very well organized and written in a quite attractive way. Congratulations! The review is accepted for publication in its present form. Just few little minor things: 1. Introduction: 2nd phrase "Obesity predisposes (…) certain cancers". Please add a reference in this statement. 2. Page 9: 3rd paragraph G-protein coupled receptors is the first mention. Add GPCRs abbreviation here. Remove the mention without abbreviation from the next paragraph. 3. Page 10: 3rd paragraph "Moreover, (…) by skeletal muscle." Please add a reference in this statement.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Biological Chemistry
ESPS manuscript NO: 16771
Title: Novel and unexpected roles of butyrate and butyrate derivatives in the control of metabolism
Reviewer's code: 02615858
Reviewer's country: Spain
Science editor: Xue-Mei Gong
Date sent for review: 2015-02-01 13:33
Date reviewed: 2015-02-25 18:54

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[Y] 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	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This paper briefly reviews the emerging biological role of short fatty acids (SCFAs), mainly butyric acid as well as the related compounds 4-phenylbutyric acid, D-β-hydroxybutyrate, α-hydroxybutyrate and β-aminoisobutyric acid, and summarizes the current knowledge and the mechanisms involved in the regulation of body weight and metabolism exerted by these molecules. The manuscript is well conceived and is of interest, providing useful and current information on this topic. Specific comments: 1. The title should be modified to avoid uncertainties, and should reflect clearly the content of the review. In this sense, 4-phenylbutyric acid is not a four-carbon molecule. 2. It is not clear in which sense 4-phenylbutyric acid is a derivative of butyric acid, as mentioned in the abstract. Please explain. 3. Besides α-hydroybutyrate, which other four-carbon molecules have been found to be early predictors of insulin resistance and glucose intolerance? Although this point is stated in the abstract, no other compounds have been quoted within the manuscript. 4. p.5. The connection between inflammatory response and the development of obesity and associated pathologies should be stressed. 5. The mechanism by which butyrate increases muscle ATP

consumption should be explained in detail. 6. The proposed mechanisms for the increased levels of α-hydroxybutyrate and for its role in insulin resistance and glucose intolerance should be discussed. α-cetobutyrate might not be defined as the final product of methionine and threonine catabolism, and its formation in the cysteine biosynthetic pathway should be mentioned. 7. The description of the effects of β-aminoisobutyric acid on adipose tissue is somehow puzzling. Please, explain them accurately. 8. The writing needs polishing and some text editing; there are frequent awkward sentences and unnecessary repetitions [e.g., p.5, within 2nd paragraph; p.6, 3rd, 4th and 5th paragraphs; p.9, 2nd (last lines), 3rd, 4th, and 5th paragraphs]. Thus, manuscript assembly should be extensively improved; a detailed account of such errors does not seem warranted. 9. p.7, 4-phenylbutyric acid section, first three lines. It is not clear what it is meant. 10. p.8, Hydroxybutyrate section, 2nd paragraph, line 4: the sentence "Once in the target tissues, ketone bodies are converted back to Acetyl-coA, through the sequential action of D-β-hydroxybutyrate dehydrogenase …", is not correct. The described sequential reactions are specific for β-hydroxybutyrate, and not for other ketone bodies. Please, indicate the pathway and metabolites accurately. 11. p.10, β-aminoisobutyric acid section, 1st paragraph, line 2. It should be stressed that β-aminoisobutyric acid can be generated only from the split of thymine, and not from other pyrimidines, and as a byproduct from the catabolism mainly of the branched-chain amino acid valine. 12. p.3, last line. Some of the molecules described in the manuscript do have a pharmacological rather than a physiological action; this point should be addressed. Minor points: 1. p.8, Hydroxybutyrate section, 2nd paragraph. There is no need to write Acetyl-coA starting with a capital letter, and the abbreviation previously defined for "ketone bodies" should be used within this paragraph. 2. Why is it an abbreviation used for 4-phenylbutyric acid (4-PBA), for α-hydroybutyrate (αHB), for β-aminoisobutyric acid (BAIBA), and not for β-hydroxybutyrate? "Type 2 diabetes" and "histone deacetylase" should be referred within the text as defined in p. 3 (T2D) and p.6 (HDAC), respectively. It seems not to be needed an abbreviation for "high fat and high sugar diets" (HFHS), as it is only used once (p.5). The abbreviation for "G-protein coupled receptor" (GPCR) should be given the first time it is mentioned (p.9, 3rd paragraph), and used thereafter. The abbreviations for white adipose tissue (WAT) and brown adipose tissue (BAT) are not needed. 3. Definitions should be given for AMPK (adenosine monophosphate-

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Biological Chemistry
ESPS manuscript NO: 16771
Title: Novel and unexpected roles of butyrate and butyrate derivatives in the control of metabolism
Reviewer's code: 02618027
Reviewer's country: United States
Science editor: Xue-Mei Gong
Date sent for review: 2015-02-01 13:33
Date reviewed: 2015-03-08 04:56

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
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		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

In this invited mini-review, the authors provide a critical review of current literature regarding butyric acid and short chain fatty acids, 4-phenylbutyric acid, hydroxybutyrate, and β-aminoisobutyric acid. The authors propose that dietary supplementation with butyric acid and its analogues molecules can attenuate obesity-related oxidative stress by increasing energy expenditure through glycolysis and fatty acid oxidation and increase insulin sensitivity in patients with type 2 diabetes. While the analysis of current literature and conclusions were interesting, the following major concerns need to be addressed before this mini-review may be suitable for publication: 1. This manuscript needs to be edited by a native English speaker. There are many errors in grammar and syntax throughout. 2. Can the authors comment on 4-PBA's ability to "shift" energy expenditure towards glycolysis and what effects that might play on compensatory mechanisms of energy expenditure by fatty acid oxidation? 3. Are the authors proposing that short chain fatty acid supplementation occur in conjunction with use of insulin sensitizers, such as peroxisome proliferator-activated receptor gamma (PPARg) ligands, as a therapeutic approach in treating type 2

diabetics? How would these two therapeutic strategies interact with each other? 4. What concentration of fermentable dietary fibers would one have to consume for enough butyric acid to be produced biologically to shift cellular metabolic energy generation towards fatty acid oxidation? 5. Is there anything known about the long terms effects of continued short chain fatty acid supplementation in animal models? 6. Cellular oxidative stress from mitochondria and ER are as important in cellular signaling as cellular damage. Can the authors reflect on any existing literature and comment on how butyric acid and its analogues molecules affect tissue immunity?