



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 59445

Title: Effect of acetyl-L-carnitine on hypersensitivity in acute recurrent caerulein-induced pancreatitis and microglial activation along the brain's pain circuitry

Reviewer's code: 00947129

Position: Editorial Board

Academic degree: DSc, MD, PhD

Professional title: Professor

Reviewer's Country/Territory: Hungary

Author's Country/Territory: United States

Manuscript submission date: 2020-09-11

Reviewer chosen by: Ya-Juan Ma

Reviewer accepted review: 2020-11-06 06:38

Reviewer performed review: 2020-11-19 00:59

Review time: 12 Days and 18 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

This interesting study set out to investigate the effects of acetyl-L-carnitine (ALC) on secondary hypersensitivity and anxiety-like behavioral changes in caerulein (CAE)-induced recurrent acute pancreatitis. Morphological changes indicative of microglial activation in pain and anxiety-related brain regions were quantified after 6 weeks of CAE induced recurrent acute pancreatitis. Efficacy of ALC treatment to alleviate these symptoms in the last 3 weeks of CAE pancreatitis was determined. Mice with pancreatitis had significantly reduced mechanical withdrawal thresholds and heat response latencies, indicating ongoing pain. Treatment with ALC attenuated hypersensitivity. Major points 1. It would be much better to start the results section with characterization of pancreatitis severity in the various groups (Figure 4 is not enough). Please show histological pictures (with quantification). Do you have characteristic features of chronic pancreatitis? Would it be possible to demonstrate the extent of fibrosis as well? 2. The title needs to be more specific and should reflect the main findings of the study. 3. The aim in the abstract is too general (pathological changes) and does not refer to the brain. 4. The introduction is a bit redundant (e.g. the antioxidant and free radical scavenger activity of ALC is mentioned in two sentences). 5. Methods. On page 7 it would be better to indicate that daily doses of 2x100 mg/kg ALC was administered to mice. It is unclear to me why this dose was chosen. On page 9, the method of euthanasia should be stated. 6. On page 10, the first part of the results is really a repetition of the methods, it should be deleted. 7. I think that it is pointless to provide results to the decimals when the values are in the hundreds or thousands (see main text and suppl. table 1). 8. Figure 1 is not essential and could be moved to the supplementary part. 9. Figs. 5-6 and 7-8 could perhaps be combined in two figures. 10. On page 19, conclusions, there is nothing stated on the effect of ALC which is odd. 11. There are far



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too many references (more than double) in this paper. 12. In general, the size of figures is too small. In figure 4, the n=3/timepoint could be moved to the legends. 13. n numbers and the definition of asterisks and # should be provided in all figure legends. The title of Figure 3 should convey the main message rather than the test used. Minor points 1. All abbreviations should be defined at first used and should be used in the abbreviated form thereafter (e.g. CAE, ALC). There is no point in abbreviating words that are only used once (e.g. BDNF). 2. CAE induced acute recurrent pancreatitis should be written with a hyphen (CAE-induced...).



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Position: Editorial Board

Academic degree: DSc, MD, PhD

Professional title: Professor

Reviewer's Country/Territory: Hungary

Author's Country/Territory: United States

Manuscript submission date: 2020-09-11

Reviewer chosen by: Chen-Chen Gao

Reviewer accepted review: 2020-12-10 13:27

Reviewer performed review: 2020-12-12 23:07

Review time: 2 Days and 9 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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The manuscript has been improved, but unfortunately some of my points have not been adequately addressed or were completely neglected. 1. Most importantly, it would be essential to quantify the severity of pancreatitis in the various groups in more detail. Determining the translucence of pancreatic tissue is not enough; other histological and/or laboratory parameters need to be measured to confirm the effect of ALC. Without this, I do not recommend the acceptance of this paper. 2. The revised title stated in the rebuttal letter does not match that of the auto-edited manuscript file (circuitry vs neuraxis). Also, it is inappropriate to use non-standard abbreviations like ALC in the title. 3. On page 7, the daily dosing of ALC should be written as 2x100 mg/kg instead of 200 mg/kg. 4. On page 22, conclusions, there is still nothing stated on the effect of ALC. 5. Even though the manuscript includes many different research areas, I think that the number of references is way too many and could be reduced. 6. n numbers and the definition of asterisks and # have not been provided in all figure legends.