Reviewer's report

Title: Pretreatment with Intrathecal Amitriptyline Potentiates the Analgesic Effects of the Compound on Axotomy-Induced Neuropathic Pain upon Post-Injury Intra-Abdominal Treatment

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Reviewer: jana sawynok

Reviewer's report:

Summary

This manuscript reports on behavioural (hyperalgesia), molecular (Nav channels) and cellular (microglia, astrocytes) effects of postsurgical i.p. administration of amitriptyline 50 mg/kg (2X per day, for 3 days) following spinal nerve ligation (SNL) surgery in rats, and the additional influence of an i.t. pretreatment with amitriptyline (90ml of 7.5 mM) 10 min prior to surgery. It reports: (a) changes in sensory thresholds on POD4-7 extended in one case to POD14 with the i.t. ami; (b) sustained upregulation of Nav1.3 and downregulation of Nav1.8 channels and restoration of changes with ami i.p.+i.t. (but not i.p.); (c) upregulation of microglia and astrocytes with SNL and restoration with ami.

There are interesting features to this study and the results are original and of interest, but the presentation of the paper requires quite a bit of revision.

Major and required revisions

1. What was the rationale for the doses chosen? 50 mg/kg i.p. twice daily is a very high dose – acute effects occur with doses of 10 mg/kg, and daily doses of <20 mg/kg produce long lasting effects on sensory changes. Also what was the i.t dose in mg? This needs to be stated directly rather than left to the reader to perform calculations.

2. Amitriptyline given i.t. is known to produce neurotoxic effects. The authors must consider and reference this literature.

3. The paper considers only Na+ channels blocking properties of amitritpyline – it is a complex drug with many actions, and recognition of this complexity of action needs to be made. Can refer to a review on mechanisms of action.

4. The figures require some attention to detail. In the text, the sequence of considering groups is consistently S, L, A then P. The legends in Fig 2 should read in that order from the bottom (it is LSAP – needs to be SLAP). Ditto for Fig. 3 (it is SLPA, needs to be SLAP) - AND the data should be presented in that order, i.e. dark green A group beside the L group. SLAP for Figs 4 and 5 as well.

5. Discussion. This was generally not very well written. The first sentence is meaningless and just dangles. Begin with a summary of key and original
observations. The authors need to consider differential effects of ami on thermal thresholds (reversal POD4, POD7 and POD14) but only modest effects on pressure thresholds POD4 and POD7. There is a literature on differential effects on ami on thermal vs mechanical thresholds (particularly allodynia determined by von Frey thresholds) and this needs to be meaningfully considered. Ref 12 shows differential long lasting effects on sensory thresholds with a 7 day post surgical regimen of ami – some sort of direct comparison with that other study that used a post-surgical ami regimen needs to be made.

Minor edits

Change Title: Pretreatment with intrathecal amitriptyline potentiates antihyperalgesic, Na+ channel and microglial effects of postsurgical systemic amitriptyline following spinal nerve ligation (the study does NOT use an axotomy model; need to be more specific in terms of what was examined)

POD day numbers can be regular numbers (as in figures) rather than subscripts.

Fig 2: Fonts need to be consistent, and larger – these will be far too small when the figure is reduced. Fig 3 is very nice, but may lose information with shrinkage.

The text needs many minor edits. Here are a few examples, but it is not a complete list. The authors should read the final manuscript version carefully for details.

Abstract: Do not need to include p values in the abstract. page 4, line 1: intrathecal pretreatment with amitriptyline potentiates the intra-abdominal amitriptyline effect on thermal hypersensitivity, reverses (present tense) Nav1.8 changes, and attenuates…

Conclusions: Concomitant …line 7: hypersensitivity; it also decreased activated microglia and astrocytes, and restored dysregulated … (DO NOT subscript the 1.3 and 1.8 – in several places it is fine but it is inconsistently presented)

Page 5
Line 11: axotomy, neurons require less depolarization… line 12: and easily fire due to actions… Nav1.7 channels… line 14: injured nerve [11] (wrong ref is cited)

Page 6
Line 1: the mechanism… line 2: is ref 16 correct here? Line 8: In view of the above reports, we hypothesized…

Page 15
Line 2: Surgery and …line 4: In the S group, ipsi… In the P group, intrathecal …(put the group identity up front as much as possible) Line 11: hypersensitivity responses as indicated by a …

Page 16
Line 2: Regardless of the treatment with ami,
Line 9: 3A and 3B, group S vs group L) any vs indicates a comparison and so no need to state “compare” (here and elsewhere); line 12: expression for 3 weeks (not 2 weeks, check the figure)

Page 17
Line 3: Ami inhibited glial cell activation ...line 5: and increased activation was most (the start of the sentence uses the past tense, be consistent)

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare I have no competing interests