Reviewer’s report

Title: Resolvin D1 reverses chronic pancreatitis-induced mechanical allodynia, phosphorylation of NMDA receptors, and cytokines expression in the thoracic spinal dorsal horn

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Reviewer: Ihsan Ekin Demir

Reviewer’s report:

In their current study, Feng et al. investigated the potential analgesic effect of resolvin, an omega-3-polyunsaturated fatty acid-derived molecule, in experimental chronic pancreatitis (CP) in rats. Intrathecal administration of resolvin (termed RvD) reduced mechanical allodynia of rats with TNBS-induced CP, reduced the amount of IL6, TNFalpha and IL-1beta mRNA in the thoracic spinal cord, and reversed the phosphorylation of NMDA receptor subtypes NR1 and NR2B. Based on these results, the authors concluded that resolvin may be a novel anti-inflammatory therapeutic for the treatment of CP-associated pain.

Overall, the study conveys a straightforward message and investigated a molecule class of high interest to treat inflammatory pain. However, despite these clear messages within the manuscript, the provided data remain very superficial, and the applied methodology is insufficient to support the proposed analgesic effect of resolvin. In particular, I have the following major and minor comments:

1) Assessment of pain in murine experimental models should contain true parameters of pain-related “behavior” and not be limited to evaluation of mechanical allodynia, which represents a single facet of the complex “pain phenomenon”. In line with the majority of experimental pain studies, the authors should make use of additional tests to assess CP-related pain behavior (e.g. open field test, elevated maze or resistance-to-capture, etc.). Without these, the authors should refrain from referring to the effects of resolvin upon “pain behavior” in the manuscript.

2) Although the manuscript stems from a group with experience in histological assessment of intrinsic cells of the spinal cord in murine CP-induced pain, the study in no way touches the affected cell type by resolvin treatment. Which cells in the spinal cord lose their NMDA receptor phosphorylation upon resolvin treatment? This can be easily demonstrated by phosphor-NR1/2B-specific antibodies via immunohisto-/cytochemistry.

3) The demonstrated alterations in the level of pro-inflammatory cytokines in the spinal cord vary between 1-2-fold, which, although statistically significant, are very unlikely to represent biologically relevant alterations. Furthermore, the assessment of these cytokines at RNA level does not contribute significantly towards understanding the actual modulation of inflammation in the spinal cord through resolvin, which seems to be the leading mechanism in resolvin-mediated
analgesia. Therefore, the investigators should measure the levels of these cytokines at protein level.

4) In the whole manuscript, the administered drug is termed “resolvin/Rvd”, which, however, normally designates a “class” of resolvins and contains several resolvin subtypes. Did the authors administer one or more resolvin subtypes in their experiments? This remains totally unclear.

Minor comments:

1) How were the dosages for Rvd chosen in the study? This is particularly interesting seeing the large leap between the two applied dosages (10 vs. 500 ng).

2) In the methods, the authors specify that pancreatic inflammation was histologically assessed. Were there also any differences in the severity of intrapancreatic inflammation between treated vs. non-treated groups? Furthermore, can resolvin also be detected in the serum and reach distant targets other than spinal cord (e.g. pancreas)?

3) The location of NR1 and NR2B expression should be mentioned in the abstract.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.