OPEN PEER REVIEW REPORT 1

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Reviewer's Name: Alfredo Martínez
Reviewer's country: Spain
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COMMENTS TO AUTHORS

The manuscript by Li et al. strives to review our current knowledge on the influence of adrenomedullin (AM) in neurological diseases. In general, the manuscript does a good job but some points need to be polished before it is acceptable for publication:

1) A review is supposed to present all published experiments on a particular field and not just the findings of a single laboratory. The review is full of expressions such as "our laboratory found", "led us to continue", "has attracted much attention for us", etc. This is also reflected in the fact that some issues are only contemplated from the laboratory´s perspective, not taking into consideration studies that propose alternate interpretations (see below). This style should be avoided and all data should be presented and interpreted as a whole.

2) On page 3, the authors review the influence of AM on pain sensitivity. They refer to an article where a knockout for AM is presented but they do not provide the reference for that article. I guess they refer to the manuscript by Fernandez et al (Endocrinology, 151:4908-4915; 2010). I believe the results from that article are interesting and need to be commented further, since they provide an idea of the complexity of the interaction of the AM system with pain sensitivity: apparently AM act as a nociceptive peptide for spinal reflexes but it has analgesic properties when the brain is involved in the processing of pain. Furthermore, a clear difference seems to exist in the distribution of AM-immunoreactivity between rats and mice in the colocalization with IB4. This fact may explain possible differences between species.

3) On pages 4 and 6, the relationship between AM and NO is considered. A recent paper has shown an intimate relationship between these two vasodilators in endothelial cells (Iring et al. Journal of Clinical Investigation, 130:2775-2791; 2019). This will be taking place in the brain capillaries, which are central in many of the neurological diseases studied, and perhaps a similar relationship occurs within the neurons and glia.

4) The chapter on AM and brain injury (page 7) needs to be completely rewritten. Here the authors reference only those papers that agree with their hypothesis but leave out many (the great majority of published studies) that reach the opposite conclusion. It is true that most clinical studies show that higher levels of AM correlate with poor prognosis in stroke. An interesting paper shows that more important than the levels of AM at the time of stroke, may be the temporal evolution of those levels (Serrano-Ponz et al. Molecular Medicine Reports, 13: 3724-3734; 2016). But the main problem is with the experimental injection of AM in stroke animal models. Other than the results from the authors (Wang et al 1995), all other studies found the opposite results (just a few examples: Dogan et al. J Cereb Blood Flow Metab 17:19-25, 1997; Watanabe et al. Acta Neurochir (Wien) 143:1157-1161; 2001; Xia et al. Exp Neurol 2006; 197: 521-30; 2006), showing that injection of AM was neuroprotective. All these articles must be cited and a general explanation may be provided. But this issue is really complex and the studies using genetically modified mice show it well. For instance,

when AM is eliminated from neurons, the infarct volume increases, suggesting a protective role for AM (Hurtado et al. Neuroscience, 171:885-892; 2010); but when AM is eliminated from endothelial cells the opposite occurs and stroke volume is reduced (Ochoa-Callejero et al. Scientific Reports, 6:33495; 2016). These genetic experiments may offer a way to understand the conflicting results obtained by many laboratories around the world.

5) On page 8, the authors say there is a possibility that AM may play a role in other neurodegenerative diseases. At least in the case of Alzheimer´s disease and memory processing, there are several studies already, which should be commented. These include: Buerger et al. J Clin Psychiatry 72:556-563; 2011; Fernandez et al. Curr Alzheimer Res 13:428-438; 2016; Larrayoz et al. Front. Mol. Neurosci. 10:384; 2017; Ferrero et al. Molecular Neurobiology, 55:5177-5183; 2018).

6) Figure 1 should be redrawn taking into consideration the data by Fernandez et al (Endocrinology, 151:4908-4915; 2010), which show that AM plays also a role at higher levels than the spinal cord, actually where the authors drawn the "brain".