

Open peer review report 1

Reviewer: *Shuichi Hara, Tokyo Medical University, Japan.*

Comments to the authors:

The authors showed that dexmedetomidine, an alfa2 adrenergic receptor agonist, attenuated TBI in an in vivo mouse model and reduced alterations of immune markers in the brain. They concluded that the protective effect of dexmedetomidine might come from disturbance of activation of the immune system, in which NLRP3 plays a major role. Comments are as follows:

General

1. I would suggest English language editing. See P1 L22 (abstract), P2 (L3 (disease?), 24, 30, 36), P3 (L7, 17-21, 30-31, 49-50, 53-54), P4 (19, 36 44), P5 (L4, 13 (incubator?), 19, 23, 38) etc., etc.
2. "NOD" and "MPO" should be spelled out at first appearance.
3. "Ipsilateral" and "contralateral" should be replaced with other words or expressions.
4. The last sentences of the subsections in the results should be move to the discussion or deleted.

Major

1. It is well established that brain temperature is a critical factor which influences brain damage due to various brain insults, namely, its decrease and increase attenuates and aggravates brain damage, respectively. Dexmedetomidine decreases body temperatures in mice (30 µg/kg, ip) (doi:10.1016/S0028-3908(03)00080-7) and brain temperature in hypothermic neonatal rats (25 µg/kg, sc) (doi:10.1038/pr.2015.45), although dexmedetomidine at 3 µg/kg (ip) has no effect on body temperature of mouse pups (doi: 10.1097/ALN.0b013e318286cf36). Therefore, the dose of dexmedetomidine is extremely important in this study. Which dose was used, 25 µg/kg (P1 (abstract) and P4 L31) or 10 µg/kg (Fig1)?
2. Although physiological parameters, including blood pressure, were measured in this study (P7 L57-59), their data were not shown in the manuscript because of no effects of dexmedetomidine on those parameters. Dexmedetomidine even at 10 µg/kg (ip) is still likely to lower body temperature and also affect blood pressure. Therefore, all data on physiological parameters measured in this study MUST be shown. At least, body temperature data are mandatory.
3. If "dexmedetomidine does not affect physiological parameters" (P7 L57-59), its protective effect against TBI is unlikely to be mediated through alfa2 adrenergic receptors. This must be discussed.
4. The methods to measure physiological parameters are lacking.
5. What are "brain samples" and "peri-contusional cortex"? How much (mg) was used?
6. The source of anti-beta-actin antibody is lacking (P6 L42)
7. Is "8 mg/lane" (P6 L19) correct?
8. Give the numbers of mice used in each Fig or figure legend.
9. It is unclear why the effects of dexmedetomidine were examined in each brain hemisphere (Fig1).
10. It is unclear why the immune markers, including brain edema, were measured and why they were measured on Day1, Day3, or both days. Data on both Day1 and Day3, namely time course data, would be necessary. I would suggest that the authors keep in mind that all readers are not immune specialists.
11. What is the difference between IL1beta (Fig2) and "mature" IL1beta (Fig4)? Why no data on them on Day1?
12. Expression of NLRP3 mRNA is much more strongly stimulated than that of NLRP3 protein, on Day3, indicating that NLRP3 protein might be starting to increase. It seems that the response of NLRP3 is duller than those of other factors, including IL1beta, caspase1 and so on. This may not support the story made by the authors ("Discussion"). How about NLRP3 on Day1?
13. Further data (comments 8 to 11) would facilitate clearer discussion on the complex immune system (the linkage or interaction among the immune factors) associated with the protective effect of dexmedetomidine.