OPEN PEER REVIEW REPORT 2

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-21-00033
Title: ATP–P2X4R signaling mediates Nod-like receptor family protein 3 inflammasome activation in a male rat model of Parkinson's disease
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Reviewer's country: USA

COMMENTS TO AUTHORS

The main criticism I have of this study and others like it is in regards to the use of young rats for the studies. Parkinson's disease is a disease characterized by the loss of neuromelanin from the substantia nigra, and young rats have not had time to accumulate neuromelanin. As such, none of the conclusions is directly translatable to the human condition and nowhere is this ever addressed. Injection of 6-OH dopamine will result in some neuromelanin accumulation in an unusually rapid fashion and there is evidence that accumulation of neuromelanin leads to the down-regulation of tyrosine hydroxylase, but not cell death. As such, the exclusive use of TH-positivity in making any conclusions is again highly suspect.

Figures 6-9 are very repetitive. Although clearly a great amount of work has gone into this study and if it were my experiments, I'd want them published. However, in the interest of the reader and space considerations, I would suggest that this data would be much easier to digest in a single table format. I've suggested a major revision for this reason, but in all, I don't think the rest of the manuscript needs much work.

In all, this is a complicated subject and the authors have done an excellent job of making it comprehensible. The results definitely point to a role for P2X4R signaling in the progression of inflammation in an accepted PD model.