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Cytotoxicity of mitochondrial Complex I inhibitor rotenone: a complex interplay of cell death pathways

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Reviewer 3

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*Only major points from review and responses included.

Reviewer 3

You showed that 48-h rotenone treatment inhibits Complex I-III activity by 50 %. Is there any information available in the literature how much the Complex I-III is inhibited in Parkinson's disease (or in animal models of Parkinson's disease)?

Authors

In the original paper first describing Complex I deficiency in post-mortem PD brain, 31% inhibition of Complex I and 39% of Complex I-III were reported. In rotenone-induced PD animal models, reported values are variable; some did not find any inhibition, others reported 30 to 40% inhibition and still others even more (around 80%). These variations are because of different strains of rats used, different doses, duration and administration procedures of rotenone (oral, intravenous or intraperitoneal or intracerebroventricular) and different assay procedures. Since cell culture based results cannot be extrapolated directly at the quantitative level with either post-mortem or animal model studies, we did not mention all these in the manuscript.

Reviewer 3

How ferrostatin-1 and liproxstatin-1 exert their ferroptosis-specific antioxidant effect? What is the mechanism of action? Why it is considered that these antioxidants are specific to ferroptosis? Please add it to the introduction.

Authors

Ferroptosis apparently depends on the accumulation lipid hydroperoxides, lipid derived oxyradicals and other lipid peroxidation intermediates. Thus, lipophilic antioxidants like ferrostatin-1 and liprotaxin-1 are very good inhibitors of ferroptosis. However, other lipophilic antioxidants like alpha-tocopherol and butylated hydroxytoluene are also potent inhibitors of ferroptosis. Thus, ferrostatin-1 and liproxstatin-1 are not specific inhibitors of ferroptosis; these are novel inhibitors of ferroptosis identified by high throughput screening procedures. We have, therefore, rephrased some sentences and added these statements in the Introduction as suggested by the reviewer.

Reviewer 3

Do you know any publication describing the positive effect of the antioxidants ferrostatin-1 and liproxstatin-1 in animal models of Parkinson's disease (or any other disease models accompanied with ferroptosis) given as food supplement?

Authors

Ferrostatin-1 and liproxstatin-1 are being explored as neuroprotective compounds in animal models of traumatic brain injury and ischemic stroke. However, we have not discussed this in our manuscript.