Mitochondrial Complex 1 Inhibition Increases 4-Repeat Isoform Tau by SRSF2 Upregulation

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Research question and background

Progressive Supranuclear Palsy (PSP) is a neurodegenerative disorder characterised by intracellular aggregation of the microtubule-associated protein tau. The tau protein exists in 6 predominant isoforms. Depending on alternative splicing of exon 10, three of these isoforms have four microtubule-binding repeat domains (4R), whilst the others only have three (3R). In PSP there is an excess of the 4R tau isoforms, which are thought to contribute significantly to the pathological process. The cause of this 4R increase is so far unknown. Several lines of evidence link mitochondrial complex I inhibition to the pathogenesis of PSP.

Methods and tissues used

Human fresh frozen brain sections of the locus coeruleus area were obtained from The Netherlands Brain Bank, Netherlands Institute for Neuroscience, Amsterdam (www.brainbank.nl). Further *in vitro* tests were performed on LUHMES human neuronal cells. Analysis was by quantitative PCR, Western blotting, siRNA silencing, as well as biochemical assays of cell viability (ATP, MTT).

Results and conclusion

We have demonstrated for the first time that annonacin and MPP+, two prototypical mitochondrial complex I inhibitors, increase the 4R isoforms of tau in human neurons. We show that the splicing factor SRSF2 is necessary to increase 4R tau with complex I inhibition. We also found SRSF2, as well as another tau splicing factor, TRA2B, to be increased in brains of PSP patients. Thereby, we provide new evidence that mitochondrial complex I inhibition may contribute as an upstream event to the pathogenesis of PSP and suggest that splicing factors may represent an attractive therapeutic target to intervene in the disease process.

Scientific publications that have resulted from the material obtained from NBB:

Bruch J, Xu H, De Andrade A, Hoglinger G. Mitochondrial Complex 1 Inhibition Increases 4-Repeat Isoform Tau by SRSF2 Upregulation. PloS one 2014:9;e113070.