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Characterisation of a novel rat model of Parkinson's disease involving a small-molecule inducer of α-synuclein oligomerisation and a viral mimetic

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Introduction: Current animal models of Parkinson's disease (PD) are limited and not ideal for drug screening. Studies suggest that viral infections may increase the incidence of developing PD.[1] We report a novel dual-hit model combining viral-mediated neuroinflammation and α-synuclein aggregation.

Methods: Male Sprague Dawley (SD) rats (n=7-8 per group) received unilateral intra-nigral injections of poly I:C (30μg), a synthetic mimetic of viral dsRNA or saline followed two weeks later by unilateral intra-nigral injection of synthetic FN075 (1.93μg)[2] used to produce α-synuclein aggregates or vehicle. Stepping and Whisker behavioural tests[3] were conducted for seven weeks post-surgery (n=7-8). Post-mortem immunohistochemical analysis quantified neuronal (tyrosine hydroxylase), astrocytic (GFAP) and microglial (OX42) markers in the substantia nigra (SN) (n=3-4). *In vitro* E14 ventral mesencephalic SD rat cell cultures[4] treated with poly I:C (20 μg/ml for 24 hours) and/or FN075 (25 μM for 48 hour) (n=6-9) were assessed for synaptic (PSD95 & synaptophysin) and autophagy (p62) protein changes using immunocytochemistry. Data were analysed using Two-way ANOVA or Three-way Repeated Measures ANOVA, followed by appropriate post-hoc tests.

Results: The poly I:C+FN075 combination rat group had significantly fewer steps in the Stepping (S) and Whisker (W) tests at five and seven weeks post-surgery compared to all other groups (S: $p<0.01$, W: $p<0.001$). At eight weeks post-surgery, aggregate-specific α-synuclein protein was increased at least 3-fold in the SN for the FN075 ($p<0.05$) and combination groups ($p<0.01$) compared to the vehicle. Also, the number of astrocytes was increased by 50% ($p<0.01$), while the number of TH+ neurons was decreased by 50% ($p<0.05$) in the SN of the combination group (vs. vehicle). Qualitative staining for OX42 revealed activated SN microglia in the combination group. In vitro, aggregate-specific α-synuclein protein was increased after FN075 treatment ($p<0.05$ vs. control). FN075 alone increased p62 punctate in E14 rat cells ($p<0.001$ vs. all other groups), but priming with poly I:C before FN075 treatment suppressed this effect ($p>0.05$).

Conclusion: This novel model of PD successfully recapitulates the motor deficits, α-synuclein aggregation, neuroinflammation, and TH+ neuronal loss in the SN making it more suitable for future drugs testing.

References:

1. Bu XL *et al.* (2015). Parkinsonism Relat. Disord. **21**: 877-881.
2. Horvath I *et al.* (2012) *J. Am. Chem. Soc.* **134**: 3439-3444.
3. Concannon *et al* (2016) *Exp. Neurol*. **283**: 204-12.
4. Clayton KB and Sullivan AM (2007). Neurosci Lett. **427**: 132-137.