Oral treatment with trehalose is neuroprotective in a non-human primate model of Parkinson's disease alpha-synucleinopathy.

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Objective

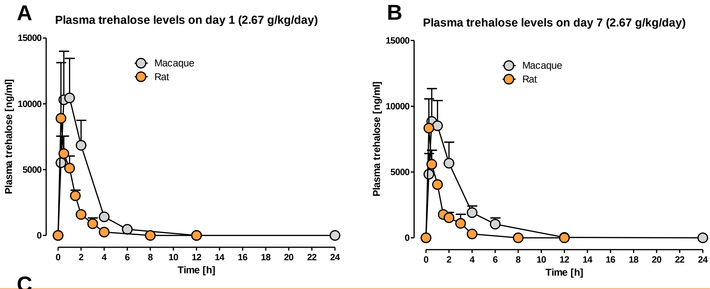
- Trehalose (JNX3001), a disaccharide and autophagy enhancer, is efficacious in providing neuroprotective benefit in several rodent models of Parkinson's disease (PD) when administered in the drinking water *ad libitum* (Sarkar et al., 2014, Wu et al., 2015, Ferguson et al., 2015, Tanji et al., 2015, He et al., 2016).
- We have previously demonstrated that, in rats, single, daily, oral doses of trehalose (2.67 g/kg/day) provided a more robust efficacy compared to the same daily doses administered in the drinking water *ad libitum.*
- We also previously defined the pharmacokinetics of single daily administrations of trehalose in rats and thus defined plasma and brain exposure levels associated with efficacy
  - Plasma C_{max} and $AUC_{0\text{-}inf}$ were approximately 9,000 ng/ml and 11,000 h.ng/ml respectively.
  - Brain C_{max} and $AUC_{0\text{-}inf}$ were approximately 90 ng/g and 100 h.ng/g respectively.
- Here, we present evidence that administration of single, daily, oral doses of trehalose (2.67 g/kg/day) to macaques produces trehalose exposures similar to those associated with efficacy in rats.
- We also demonstrate that 17 weeks treatment with trehalose can significantly reduce dopaminergic dysfunction in an AAV1/2 A53T-aSyn macaque model of PD.

Methods

- For the pharmacokinetic study, 3 female macaques were administered trehalose (2.67 g/kg/day, p.o.) for 7 days and plasma collected on days 1 and 7.
- The same macaques were subsequently administered trehalose (2.67 g/kg/day, p.o.) for 2 days and brain and CSF samples collected 1 h post-administration on day 2.
- Trehalose was analysed by a liquid chromatography tandem mass spectrometry (LC-MS/MS) method.
- For the efficacy study, 22 female macaques were split into 3 groups (N=7-8 macaques/group).
- Using magnetic resonance imaging (MRI)-guided stereotaxy, AAV1/2 A53T-aSyn or AAV1/2 empty vector was delivered into the substantia nigra (4 injections per hemisphere).
- On the day following surgery, trehalose (2.67 g/kg/day) or vehicle (distilled water) was administered once daily by oral gavage for 17 weeks.
- After 17 weeks of treatment, the macaques were killed and brain samples collected for post-mortem analysis.
- Striatal dopamine was measured by high performance liquid chromatography, striatal dopamine transporter was measured by autoradiography and tyrosine hydroxylase positive cells in the substantia nigra were counted by stereology.

Results

Pharmacokinetic study



C

	Day 1			Day 7		
Parameter	**Rat**	**Macaque**	**% of rat**	**Rat**	**Macaque**	**% of rat**
Plasma C_{max} (ng/ml)	8900	10918	123	8336	9578	115
Plasma $AUC_{0\text{-}inf}$ (h.ng/ml)	11136	27445	246	9876	27363	277
Brain level (ng/g)	87.0	81.3	-	73.0	-	-
CSF level (ng/ml)	-	562	-	-	-	-

Figure 2. Plasma trehalose timecourse following 1 (**A**) and 7 (**B**) days oral administration of trehalose (2.67 g/kg/day) to rats and macaques. Mean ± s.e.m, N=5 rats/timepoint and N=3 macaques/timepoint. In both rats and macaques, no accumulation of trehalose was observed over 7 days of dosing.

Pharmacokinetic parameters of trehalose in rats and macaques (**C**) demonstrate that, for an equivalent dose of trehalose, exposure in the macaques is similar to, but slightly greater than, exposure in rats. Therefore, a daily dose of trehalose of 2.67 g/kg/day p.o. was considered sufficient to evaluate efficacy in AAV1/2 A53T-aSyn macaques.

Efficacy study

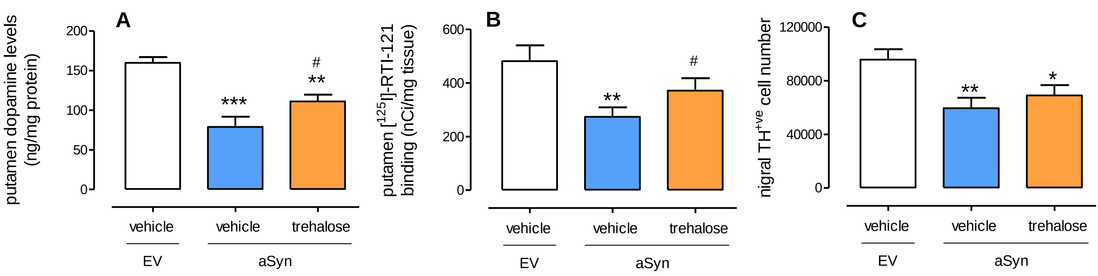


Figure 1. Effect of trehalose in the AAV1/2 A53T-aSyn macaque model of PD. Trehalose (2.67 g/kg/day) was administered as a single administration (2.67 g/kg/day, p.o) for 17 weeks. Trehalose significantly reduced AAV1/2 A53T-aSyn induced loss of striatal dopamine (**A**) and striatal dopamine transporter (**B**) but did not significantly AAV1/2 A53T-aSyn induced TH^{+ve} cell loss in the substantia nigra **(C)**. Data is mean ± s.e.mean, N=7-8 macaques/group. */ **/ ***=P<0.05, 0.01 and 0.001 vs. EV control, #=P<0.05 vs. AAV1/2 A53T-aSYN vehicle group. One-way ANOVA followed by Fisher's LSD post-hoc test.

Summary

- We have demonstrated that single, daily, oral administration of trehalose (2.67 g/kg/day) to macaques produces exposures similar to those obtained in rats that was associated with efficacy.
- Oral administration of trehalose (2.67 g/kg/day) for 17 weeks reduced aSyn-induced loss of striatal dopamine and dopamine transporter. However, treatment with trehalose did not significantly alter aSyn-induced loss of TH^{+ve} cells in the substantia nigra.
- Oral administration of trehalose (2.67 g/kg/day) for 17 weeks was well tolerated and did not alter the blood chemistry of the macaques.
- These data demonstrate, for the first time, the beneficial effects of trehalose in a macaque model of PD and support the continued development of trehalose as a disease-modifying for PD.

References

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