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Title: Brain infusion of α-synuclein oligomers induces motor and non-motor Parkinson's disease-like symptoms in mice

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ACCEPTED MANUSCRIPT

<AT>Brain infusion of α-synuclein oligomers induces motor and non-motor Parkinson's disease-like symptoms in mice

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<ABS-HEAD>ABSTRACT

<ABS-P>Parkinson's disease (PD) is characterized by motor dysfunction, which is preceded by a number of non-motor symptoms including olfactory deficits. Aggregation of α-synuclein (α-syn) gives rise to Lewy bodies in dopaminergic neurons and is thought to play a central role in PD pathology. However, whether amyloid fibrils or soluble oligomers of α–syn are the main neurotoxic species in PD remains controversial. Here, we performed a single intracerebroventricular (i.c.v.) infusion of α-syn oligomers (α-SYOs) in mice and evaluated motor and non-motor symptoms. Familiar bedding and vanillin essence discrimination tasks showed that α-SYOs impaired olfactory performance of mice, and decreased TH and dopamine levels in the olfactory bulb early after infusion. The olfactory deficit persisted until 45 days post-infusion (dpi). α- SYO-infused mice behaved normally in the object recognition and forced swim tests, but showed increased anxiety-like behavior in the open field and elevated plus maze tests 20 dpi. Finally, administration of α-SYOs induced late motor impairment in the pole test and rotarod paradigms, along with reduced TH and dopamine content in the caudate putamen, 45 dpi. Reduced number of TH-positive cells was also seen in the substantia nigra of α-SYO-injected mice compared to control. In conclusion, i.c.v. infusion of α-SYOs recapitulated some of PD-associated non-motor symptoms, such as increased anxiety and olfactory dysfunction, but failed to recapitulate memory impairment and depressive-like behavior typical of the disease. Moreover, α-SYOs i.c.v. administration induced motor deficits and loss of TH and dopamine levels, key features of PD. <ABS-P><ST>Results</ST> point to α-syn oligomers as the proximal neurotoxins responsible for early non-motor and motor deficits in PD and suggest that the i.c.v. infusion model characterized here may comprise a useful tool for identification of PD novel therapeutic targets and drug screening.

<KWD>Keywords: intracerebroventricular (i.c.v.) infusion; olfactory dysfunction; anxiety-like behavior; olfactory bulb; dopamine; tyrosine hydroxylase; Parkinson's disease.

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