Abstract 2968

A NOVEL GENE THERAPY APPROACH FOR THE TREATMENT OF MULTIPLE SYSTEM ATROPHY

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Aims

To evaluate the potential therapeutic efficacy of an adeno associated virus expressing monoclonal anti alpha synuclein intrabody (AAV-CGX208) with capabilities of recognizing and engaging the pathogenic forms of this intracellular protein in a 6-OHDA/QA intracerebral injection MSA-P/SND rat model.

Methods

We developed an engineered adeno associated virus for the potentially treatment of multiple system atrophy (MSA) by incorporating a monoclonal anti alpha synuclein intrabody (CGX208) into an AAV9 backbone. Protein levels of intrabody CGX208 and alpha synuclein in rats intrastriatal injected with AAV9-CGX208 were detected and analyzed using western blot immunoassay. A mild stage of MSA with striatonigral degeneration (MSA-P/SND) phenotype was incorporated in rats by stereotaxic injections of 6-hydroxidopamine followed by quinolinic acid into the brain. These rats were treated with AAV-CGX208 or control AAV by IC injection into the striatum 4 weeks post 6-OHDA injection. Cylinder test for motor assessment were conducted at various predetermined time points before animals were sacrificed and brains were removed for immunohistochemistry studies.

Results

CGX208 expression detection is only seen in rats injected with AAV9-CGX208 and not in AAV9-CMV-GFP (control virus) injection group. 6-OHDA/QA IC injections in the MSA rat model, develop extensive and significantly greater loss of dopaminergic neurons in striatum 9 weeks post injections as seen in tyrosine hydroxylase immunostaining of brain coronal slices from control treated animals. IC injection of AAV-CGX208 decreases loss of TH+ nigral neurons induced by 6-OHDA/QA in rats.

Conclusions

In conclusion, we describe a novel gene therapy approach of IC treatment with engineered AAV expressing anti alpha synuclein intrabody for targeting intracellular alpha synuclein protein for the treatment of MSA. Thus, promising therapeutic potential in patients with MSA.

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