AB043. The glial protein Nogo-A is necessary to maintain retinal structure and function in physiological conditions

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Background: Our previous studies revealed that Nogo-A gene ablation improved visual function recovery after retinal injury. Moreover, Nogo-A expression is highly expressed in the healthy retina. Its physiological role in retinal function is not known. The purpose of this current study was to determine the effects of acute Nogo-A silencing on retinal neuron structure and function in physiological conditions.

Methods: Nogo-A silencing was done by intravitreal injection of adeno-associated virus serotype 2.2 containing a short hairpin RNA sequence (AAV2.2 shRNA-Nogo-A) and a GFP reporter gene in adult C57BL/6J mice. As control, an empty AAV2.2 vector was used. Infection of retinal cells was followed by fluorescent fundoscopy. Changes in Nogo-A expression were analysed by Western blotting in whole retinal lysates. Electroretinography was used to monitor retinal activity. The assessment of optokinetic reflex (OKR) allowed to follow visual acuity in unrestrained mice. Immunofluorescence on histological sections using the following cell markers, i.e., RNA-binding protein with multiple splicing (RBPMS) and sex-determining region Y-box 2 (Sox-2) allowed to visualize retinal ganglion cells (RGCs) and Müller glia respectively.

Results: GFP fluorescence revealed efficient AAV2.2 transfection in the ganglion cell layer and the inner nuclear layer 30 days after viral injection. By Western blotting, Nogo-A expression was decreased by ~75% in AAV2.2-shRNA-Nogo-A-treated retinae (n=3) as compared to the control mice (n=3). Strikingly, AAV2.2-shRNA-Nogo-A-injected animals (n=10) had a visual acuity reduction of 43.7% as compared to control (n=7), 60 days after transfection. Electroretinography (ERG) b-wave and a-wave amplitudes were also decreased by ~35% and 24.4% respectively relative to controls. After two months of transfection, RBPMS-positive RGCs were reduced by ~30% in AAV2.2-shRNA-Nogo-A (n=4) compared to non-injected contralateral eyes (n=4). The number of Sox2-expressing Müller cells was not affected after Nogo-A knockdown.

Conclusions: Nogo-A gene silencing in the retina has deleterious effects on the mouse retinal structure and function, suggesting an important role for Nogo-A in retinal physiology.

Keywords: Nogo-A; gene silencing; visual acuity; electroretinography (ERG)

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