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Clarification of blood-retinal barrier on AQP4-peptide immunized mice

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Introduction:

Neuromyelitis optica spectrum disorder (NMOSD) is a severe inflammatory demyelinating disease of spinal cord, optic nerve or retina. Despite the importance of utilizing animal model, there had been no autoimmune mice model which developed high incidence rate and myelitis. Our group has created and reported novel aquaporin-4 (AQP4) peptide-immunized mouse model. This model develops motor dysfunction and inflammation with loss of AQP4 on spinal cord. In addition, it also shows blood-brain barrier (BBB) disruption which is supressed by Interleukin-6 (IL-6) receptor antibody. However, we have not conducted optical dysregulation or blood-retinal barrier (BRB) disruption of this model.

Objectives/Aims:

Here, we confirmed retinal tight junctional (TJ) molecule of the AQP4-immunized mice and the barrier function of the murine primary retinal microvascular endothelial cells (RMECs) stimulated with the AQP4-immunized mice sera.

Methods:

AQP4 peptide emulsified in complete Freund's adjuvant (CFA) have intradermally been immunized to C57BL/6J mice followed by administration of pertussis toxin on the day and 2 days after. Control mice were treated with CFA and saline alone. Two to three weeks after the immunization, retinal tissue from these mice were collected to clarify the expression of TJ molecule. Trans-endothelial electrical resistance (TEER) of RMECs have measured under the collected serum from immunized mice or recombinant IL-6 with IL-6 receptor antibody MR16-1.

Results:

In the AQP4-immunized mice, ZO-1 mRNA showed significant decrease and Claudin-5 tended to decrease compared to Control mice. Interestingly, the exposure of AQP4-immunized mice sera to RMECs resulted in decreasing their TEER after 24 hours of stimulation. Furthermore, IL-6 stimulation to RMECs significantly decreased the TEER, while MR16-1 treatment showed the inhibiting effect of the IL-6 stimulation induced TEER decreasing.

Conclusion:

Our results suggest that AQP4 peptide immunization disrupts not only BBB but also BRB mediated by some factors such as IL-6.

Disclosures:

All authors are employees of CHUGAI PHARMACEUTICAL CO., LTD.