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Pioglitazone ameliorates motor impairments and spinal cord pathologies in a mouse model of neuromyelitis optica spectrum disorders

Abstract number: 41

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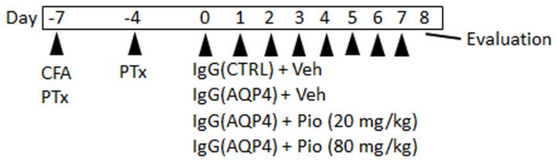
Introduction

- Neuromyelitis optica spectrum disorders (NMOSD) are autoimmune inflammatory demyelinating diseases of the central nervous system (CNS), causing blindness, paralysis and even mortality.
- Binding of pathogenic aquaporin-4 autoantibodies (AQP4-IgG) to AQP4 on astrocytes triggers lesion development that is driven by astrocyte-microglia interaction.
- Pioglitazone, an agonist for peroxisome proliferator activated receptor-γ (PPARγ), has been shown to exert neuroprotective effects through suppressing microglia/macrophage activation and neuroinflammation in various experimental models of CNS insults.
- Here we examined whether pioglitazone ameliorates motor impairments and pathologies in mice which received human AQP4-IgG.

Methodology

- Mice were pretreated with complete Freund's adjuvant (CFA) and pertussis toxin (PTx) to disrupt the BBB.
- From day 0-7, mice received passive transfer of purified IgG from AQP4-IgG-seropositive NMOSD patients (IgG(AQP4)) or from healthy individuals (IgG(CTRL)).
- Pioglitazone or vehicle was administered by oral gavage immediately after passive transfer.
- At day 8, motor impairments were assessed by beam walking test. Spinal cord pathologies were examined by immunofluorescence and ELISA.



Results

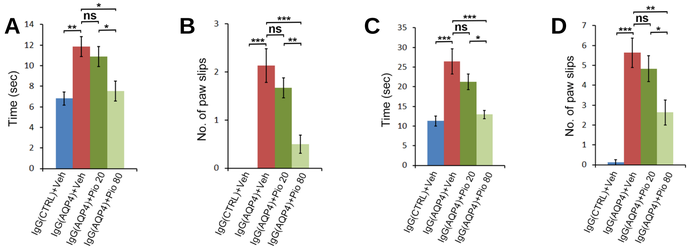


Fig 1. Pioglitazone at 80 mg/kg/day ameliorates motor impairments in IgG(AQP4) mice. **A-B** Time required and number of paw slips during walking across a 1.2 x 80 cm (width x length) beam in beam walking test for IgG(AQP4) mice treated with pioglitazone or vehicle. IgG(CTRL) mice treated with vehicle were used as a sham control. **C-D** Time required and number of paw slips during walking across a 0.6 x 80 cm beam for mice in different groups. n = 8 per group. Data are mean ± SEM. ns, not significant; *p < 0.05; **p < 0.01; ***p < 0.001.

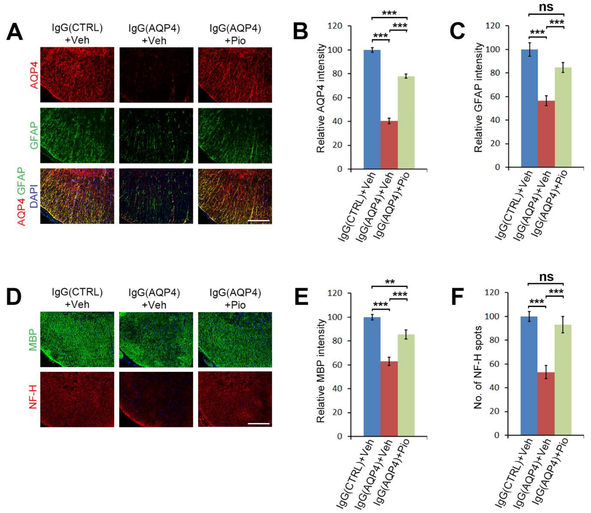


Fig 2. Pioglitazone decreases NMOSD-like pathologies. Pictures are representative photomicrographs showing cross sections of spinal cord white matter . **A** Double immunostaining of AQP4 and GFAP (astrocyte marker) in IgG(AQP4) mice treated with pioglitazone or vehicle. IgG(CTRL) mice treated with vehicle were used as a sham control. Scale bar = 100 µm. **B-C** Relative intensity of AQP4 and GFAP immunofluorescence. **D** Immunostaining of MBP (myelin marker) and NF-H (axon marker) in IgG(AQP4) mice treated with pioglitazone. IgG(CTRL) mice treated with vehicle were used as a sham control. **E-F** Relative intensity of MBP and NF-H immunofluorescence. n = 5 per group. Data are mean ± SEM. ns, not significant; *p < 0.05; ***p < 0.001.

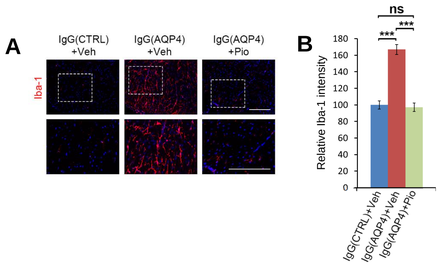


Fig 3. Pioglitazone suppresses microglia/macrophage activation. **A** Immunostaining of Iba-1 (microglia/macrophage marker) in IgG(AQP4) mice treated with pioglitazone or vehicle. IgG(CTRL) mice treated with vehicle were used as a sham control. Scale bar = 100 µm. **B** Relative intensity of Iba-1 immunofluorescence. n = 5 per group. Data are mean ± SEM. ns, not significant; *p < 0.05; ***p < 0.001.

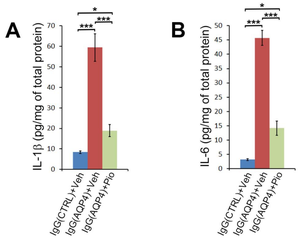


Fig 4. Pioglitazone reduces levels of proinflammatory cytokines. **A-C** ELISA analyses of IL-1β and IL-6 in the spinal cords of IgG(AQP4) mice treated with pioglitazone or vehicle. IgG(CTRL) mice treated with vehicle were used as a sham control. n = 3 per group. Data are mean ± SEM. ns, not significant; *p < 0.05; ***p < 0.001.

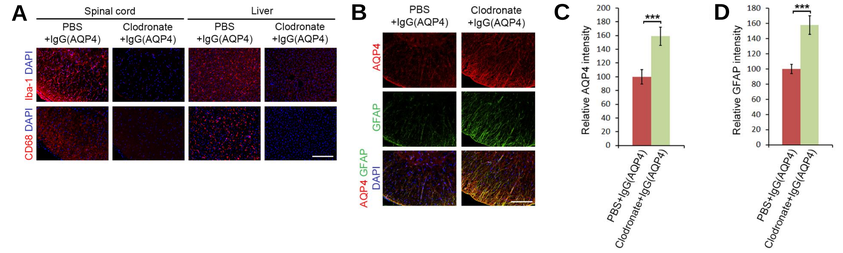


Fig 5. Microglia/macrophage depletion reduces AQP4 and astrocyte loss. **A** Microglia/macrophages were depleted by intraperitoneal injection of clodronate liposomes. **B** AQP4 and GFAP immunofluorescence in IgG(AQP4) mice treated with clodronate or control liposomes. Scale bar = 100 µm. **C-D** Relative intensity of AQP4 and GFAP immunofluorescence. n = 5 per group. Data are mean ± SEM. ***p < 0.001.

Discussion

- Pioglitazone ameliorated motor impairments induced by human AQP4-IgG in mice, associated with:
  - Decrease in astrocytopathy, demyelination and axonal loss
  - Suppression of microglia/macrophage activation
  - Reduction in concentrations of proinflammatory cytokines
- Microglia/macrophage depletion decreased AQP4-IgG-induced pathology.

Conclusion

- Our findings support that microglia/macrophage activation plays an important role in the pathophysiology of NMOSD, and highlight the potential of pioglitazone as a therapeutic agent in NMOSD acute attacks.

Reference

1. Yick LW, Tang CH, Ma OK, Kwan JS, Chan KH. Memantine ameliorates motor impairments and pathologies in a mouse model of neuromyelitis optica spectrum disorders. J Neuroinflammation. 2020 Aug 11;17(1):236.
2. Yick LW, Ma OK, Ng RC, Kwan JS, Chan KH. Aquaporin-4 autoantibodies from neuromyelitis optica spectrum disorder patients induce complement-independent immunopathologies in mice. Front Immunol. 2018 Jun 25;9:1438.

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