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The protective effect of Angiotensin AT2-receptor stimulation in Neuromyelitis optica spectrum disorder is independent of astrocyte-derived BDNF

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ABSTRACT

Background: Neuromyelitis optica spectrum disorder (NMOSD) is an antibody-mediated autoimmune inflammatory disease of the central nervous system (CNS), resulting in primary astrocytopathy. We have previously shown that Angiotensin AT2-receptor (AT2R) stimulation with the specific agonist Compound 21 (C21) attenuated NMOSD-like pathology. Recent studies have proposed that the mechanism behind protective effects of AT2R includes induction of brain derived neurotrophic factor (BDNF). Astrocytes are a major cellular source of BDNF. In this study we used mice with conditional BDNF deficiency in astrocytes (GfapF) to examine the involvement of astrocyte-derived BDNF in NMOSD-like pathology and in mediating the protective effect of AT2R stimulation.

Methods: Anti-aquaporin-4 IgG (AQP4-IgG) from an NMOSD patient and human complement (C) were co-injected intrastriatally to GfapF and wildtype littermate $BDNF^{fl/fl}$ mice (WT), together with either C21 or vehicle at day 0, followed by intrathecal injection of C21 or vehicle at day 2 and tissue collection at day 4.

Results: Intracerebral/intrathecal injection of C21, alone or in combination with AQP4-IgG + C, induced BDNF expression in WT mice. Injection of AQP4-IgG + C induced NMOSD-like pathology, including loss of AQP4 and GFAP. There was no difference in the severity of pathological changes between GfapF and WT mice. C21 treatment significantly and equally ameliorated NMOSD-like pathology in both WT and GfapF mice.

Conclusion: Our findings indicate that astrocyte-derived BDNF neither reduces the severity of NMOSD-like pathology nor is it necessary for the protective effect of AT2R stimulation in NMOSD-like pathology.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory disease of the central nervous system (CNS), that involves antibodies directed against the water channel aquaporin-4 (AQP4-IgG) on astrocytes, resulting in astrocytopathy with secondary demyelination (Bennett and Owens, 2017; Weinshenker and Wingerchuk, 2017). There is no cure for NMOSD. We have previously demonstrated that Angiotensin AT2-receptor (AT2R) stimulation with the specific AT2R agonist Compound 21 (C21) attenuates NMOSD-like pathology in an interleukin-10 (IL-10) dependent manner (Khorooshi et al., 2019). Recent studies in experimental stroke and spinal cord injury have proposed that the neuroprotective effect of AT2R stimulation might involve brain-derived neurotrophic factor (BDNF) (Alhusban et al., 2015; Namsolleck et al., 2013; Schwengel et al., 2016). BDNF plays a critical role in neuronal survival and development. A common single-nucleotide polymorphism in the human BDNF gene is associated with several CNS disorders including NMOSD (Shen et al., 2019; Shen et al., 2018). However, the involvement of BDNF in the AT2R protective effect in NMOSD has not been studied.

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Astrocytes express AT2R and are one of the major sources of BDNF (Fuchtbauer et al., 2010; Holt et al., 2019). They are also the target for AQP4-IgG in NMOSD. The goal of the present study was to investigate whether AT2R stimulation induces BDNF in NMOSD, and further to examine the role of astrocyte-derived BDNF both in regulation of NMOSD-like lesions as well as in mediating the protective effect of AT2R signaling in the brains of mice. To specifically investigate the role of astrocyte-derived BDNF, we used mice with conditional BDNF deficiency in astrocytes, designated as GfapF mice (Linker et al., 2010).

To induce NMOSD-like pathology, mice received AQP4-IgG purified from an NMOSD patient, and human complement (C). Treatment consisted of intracerebral co-injection of C21, followed by intrathecal injection of C21 alone. NMOSD-like pathology was evaluated by AQP4- and glial fibrillary acidic protein (GFAP) loss. We found that intracerebral/intrathecal injection of C21 alone or in combination with AQP4-IgG + C induced BDNF mRNA in the CNS. Intracerebral injection of AQP4-IgG + C induced characteristic histological features of NMOSD including AQP4 and GFAP loss in the brain of both GfapF and wildtype littermate $BDNF^{fl/fl}$ control mice (WT). The histological features of NMOSD-like pathology were not different between GfapF and WT mice. C21 attenuated NMOSD-like pathology to comparable levels in both GfapF and WT mice. Our findings suggest that astrocyte-derived BDNF contributes neither to modulation of NMOSD-like lesions nor to the protective effect of AT2R signaling.

2. Methods

2.1. Mice and human materials

All mice used in this study were females aged 8-10 weeks (20-22g). C57BL/6J mice were purchased from Taconic Europe A/S. $BDNF^{fl/fl}$ mice were kindly provided by Dr. Fred Lühder, Institute for Multiple Sclerosis Research, University of Göttingen, Göttingen, Germany (Linker et al., 2010), and maintained as a breeding colony in the Biomedical Laboratory, University of Southern Denmark (Odense). They were crossed with GFAP-Cre line 77.6 (The Jackson Laboratory) to generate a conditional knock-out of the BDNF gene in astrocytes. All experiments were approved by the Danish Animal Experiments Inspectorate (approval number 2020-15-0201-00652).

Human AQP4-IgG and human complement were derived from sources described previously (Asgari et al., 2013). The use of human material was approved by the Committee on Biomedical Research Ethics for the Region of Southern Denmark (ref. no. S20080142) and the Danish Data Protection Agency (ref. no. 2008-41-2826).

2.2. Induction of NMOSD-like pathology and treatment

Intracerebral and intrathecal injections as well as C21 treatment were performed as previously described (Khorooshi et al., 2019). In brief, mice were anaesthetized and placed in a stereotactic frame for intrastriatal injections of 180 μg AQP4-IgG plus 2 μl C, in a total volume of 6 μl. Treatment with the AT2R agonist C21 (Vicore Pharma, Gothenburg, Sweden) consisted of intrastriatal co-injection of 0.015 μg C21 / mouse at day 0 followed by an intrathecal injection of 0.125 μg C21 / mouse to cerebrospinal fluid (CSF) via cisterna magna at day 2. Mice were sacrificed on day 4, and brains were dissected out and processed as described previously (Khorooshi et al., 2019). To examine BDNF expression in response to C21 alone, mice received an intrathecal injection of 0.125 μg C21 and were sacrificed 6 hrs later and processed as described below.

2.3. Immunohistochemical staining

Brains were fixed in 4% paraformaldehyde in PBS and cryo-protected in 30% sucrose in PBS, then snap frozen in cryostat embedding medium (Killik, Bio-optica). Brains were cut into 14 μm thick coronal sections on a cryostat (Microm HM 500) and stored at -80℃. Brain sections were incubated with primary antibodies; rabbit anti-AQP4 (Alomone Labs Ltd), rabbit anti-GFAP (Dako), and rabbit anti-Iba1 (Wako). Sections were then incubated with biotinylated- goat anti-rabbit IgG (Abcam), followed by incubation with streptavidin-horse radish peroxidase (GE Healthcare) and developed with 3,3-diaminobenzidine (Sigma-Aldrich), as described in previous study (Khorooshi et al., 2019). Based on 4-5 sections from each mouse, evaluation and grading of histological changes was performed as previously described (Asgari et al., 2013). Grades represented the following histological changes: 1, mild changes of limited extent; 2, moderate changes and loss of staining; 3, marked changes and total loss of staining over an extensive cumulative area. Images were acquired using an Olympus DP71 digital camera mounted on an Olympus BX51 microscope (Olympus, Ballerup, Denmark).

2.4. Sorting procedures

To isolate astrocytes, unmanipulated control and GfapF mice were perfused with ice-cold PBS and the brains were dissected out. The tissue was then dissociated using Adult Brain Dissociation Kits (Miltenyi Biotec), according to the manufacturer's protocol. Astrocytes were sorted from single cell suspensions by positive selection using anti-astrocyte cell surface antigen-2 (ACSA-2) MicroBead Kits (Miltenyi Biotec). After sorting, the astrocytes and the ACSA-2-negative cells were lysed in RLT buffer (Qiagen) to extract total RNA.

2.5. RT-qPCR

RNA from brain regions including striatum, cerebellum, brainstem, or from sorted cells was isolated, reverse-transcribed to complementary DNA, and RT-qPCR was performed using an ABI Prism 7300 Sequence Detection System (Applied Biosystems). Gene expression was calculated relative to 18S rRNA (TaqMan Ribosomal RNA control reagents, Applied Biosystems) by $2^{-\Delta Ct}$, as previously described (Khorooshi et al., 2019). Primer and probe sequences for BDNF detection were: Probe: AGGACGCGGACTTG-MGB, F: GGCCCAACGAAGAAAACCAT, R: AGCATCACCCGGGAAGTGT.

2.6. Statistics

Results were analyzed by two-tailed unpaired t-test using GraphPad Prism software (version 6, GraphPad Software Inc., San Diego, California, USA). A p value < 0.05 was considered to be statistically significant. Data are presented as means ± SEM.

3. Results

3.1. AT2R stimulation induces BDNF

To test whether AT2R stimulation induces BDNF, we analyzed BDNF gene expression 6h after intrathecal treatment with C21. Intrathecal administration of C21 into the CSF resulted in a significant increase in BDNF mRNA in the brain regions including cerebellum and brainstem of healthy mice (Fig. 1A). We next examined BDNF gene expression in mice that had received AQP4-IgG + C together with either C21 or vehicle by intrastriatal administration at day 0, followed by intrathecal injection of either C21 or vehicle at day 2, and sacrificed 2 days later. BDNF mRNA expression was increased in the brains of mice that received AQP4-IgG + C and C21 compared to mice that received AQP4-IgG + C and vehicle, or unmanipulated mice (Fig. 1B). Treatment with AQP4-IgG+C alone did not induce BDNF mRNA. These findings suggested that BDNF might be implicated in the outcome of AT2R signaling.

3.2. Verification of BDNF knockdown in astrocytes from GfapF mice

To examine the functional relevance of C21-induced BDNF in

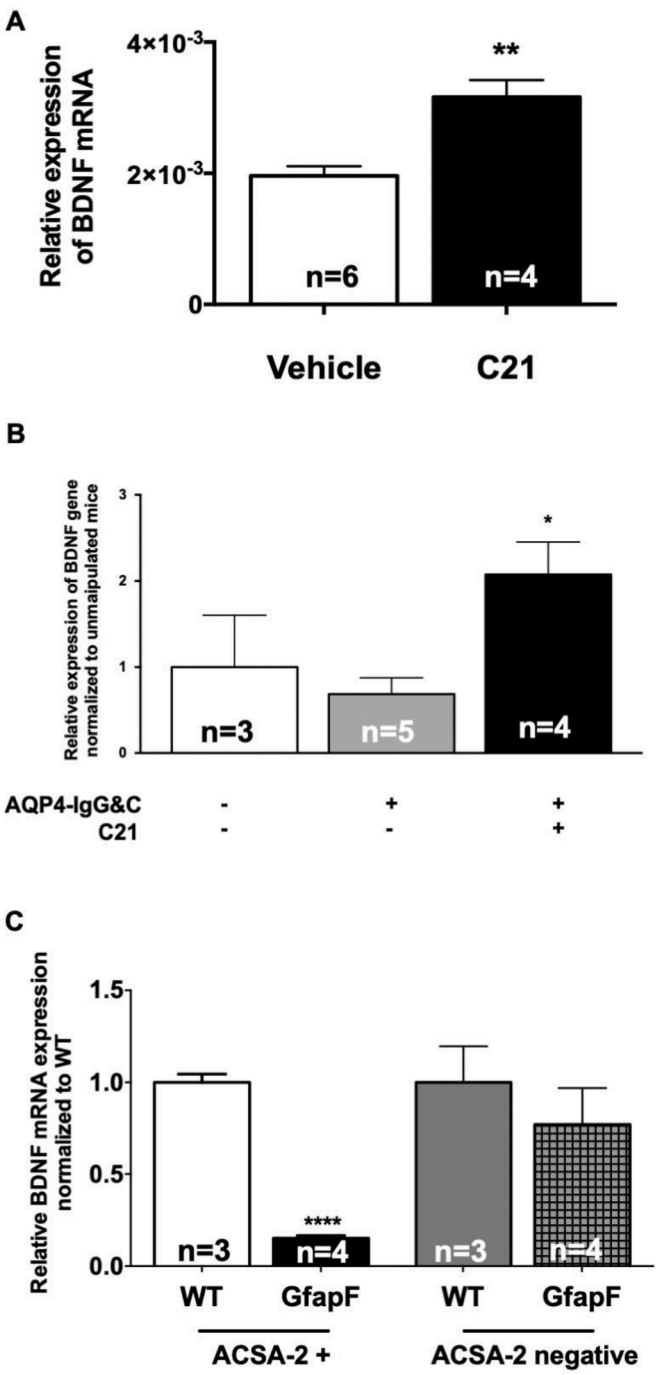

Fig. 1. AT2R stimulation induces BDNF. A) Bar graphs showing BDNF gene expression in brains of WT mice 6 hrs after intrathecal injection with vehicle or C21. Significantly elevated levels of BDNF transcript were detected in mice treated with C21. B) WT mice received AQP4-IgG + C with vehicle or C21 by stereotactic intrastriatal injection, followed by intrathecal administration of vehicle or C21 at day 2, and BDNF gene expression was measured at day 4. Bar graphs show that BDNF mRNA was significantly increased in samples from C21-treated mice. C) BDNF gene expression was examined in sorted ACSA-2-positive and -negative cells from WT mice and mice with conditional deficiency of BDNF in astrocytes (GfapF). Bar graphs show a significant reduction (by nearly 85%) of BDNF gene expression in ACSA-2-positive astrocytes from GfapF mice compared to their littermate WT controls. BDNF expression was not different in ACSA-2-negative cells from GfapF compared to WT mice. Numbers of mice per group are indicated in each bar. Results are shown as means ± SEM. * $p < 0,05$, ** $p < 0,01$, **** $p < 0.0001$

NMOSD-like pathology, we used conditional knockout mice with BDNF deficiency in astrocytes, designated as GfapF

(Linker et al., 2010). We confirmed that BDNF mRNA expression was significantly reduced in ACSA-2 positive astrocytes sorted from GfapF mice compared to those from littermate $BDNF^{fl/fl}$ wildtype control mice (designated as WT) (Fig. 1C). In contrast, there was no difference between BDNF expression in ACSA-2 negative cells isolated from GfapF or WT mice (Fig. 1C).

3.3. AT2R stimulation in NMOSD is independent of astrocyte-derived BDNF

To determine the role of astrocyte-derived BDNF in NMOSD-like pathology, GfapF and WT mice received intrastriatal AQP4-IgG + C with vehicle or C21 at day 0, followed by intrathecal injections of vehicle or C21 at day 2. Semi-quantitative histopathological evaluation of brain sections revealed that AQP4-IgG + C induced loss of AQP4 and GFAP in both GfapF and WT mice (Fig. 2A, B). There was no difference in the severity of pathological changes between GfapF and WT mice (Fig. 2A, B).

As we recently reported (Khorooshi et al., 2019), we could again show that AQP4-IgG + C-induced loss of AQP4 and GFAP was significantly reduced by C21 treatment (Fig. 2A, B). Notably, the protective effect of AT2R stimulation on NMOSD-like pathology was not different between GfapF and WT mice (Fig. 2A, B).

Infiltration (H&E staining) and microglia/macrophage activation (IBA-1 staining) in the areas of AQP4/GFAP loss (Khorooshi et al., 2019; Wlodarczyk et al., 2021) were reduced in C21-treated mice, and BDNF deficiency in astrocytes had no effect on this (Fig. 3A-C).

4. Discussion

This study aimed at answering two main questions: (1) Is an increase in BDNF expression causatively involved in the protective effect of AT2R stimulation in NMOSD-like pathology in mice and (2) is BDNF generally a protective factor that modulates severity of NMOSD pathology?

With regard to the first question, we indeed found a significant increase in BDNF mRNA expression in response to a two-day intracerebral and intrathecal treatment with the AT2-receptor agonist C21 in brains of healthy mice and in mice with NMOSD-like pathology. In mice with NMSOD-like pathology, treatment with C21 further led to protection from astrocyte damage as shown by a significant reduction in GFAP and AQP4 loss.

BDNF regulates neuronal development and function in the CNS. It is expressed throughout the CNS mainly by astrocytes and neurons (Linker et al., 2010). BDNF is produced as pro-BDNF and then enzymatically processed to mature BDNF. In the pathological situation, BDNF is known to mediate neuroprotection and attenuation of demyelination in a broad spectrum of neurological diseases including multiple sclerosis, stroke, brain injury and depression (Kowianski et al., 2018; Lima Giacobbo et al., 2019; Linker et al., 2010).

Similar to the observation in this study, it was shown recently that in spinal cord injury and stroke the neuroprotective effect of AT2R stimulation coincided with an increase in BDNF expression thus suggesting that BDNF is involved in the neuroprotective effect of the AT2R (Alhusban et al., 2015; Namsolleck et al., 2013; Schwengel et al., 2016). Another recent study by Yick et al. made a similar observation as in our study, which was a significant increase in BDNF in a model of NMSDO in mice, which coincided with an improvement of NMSDO markers including AQP4 and astrocyte loss after pharmacological interference with the NMDA receptor antagonist memantine (Yick et al., 2020).

Therefore, we thought it reasonable to hypothesize that the observed increase in BDNF in our model of NMSDO-like pathology is causatively involved in the protective effect of AT2R stimulation.

In order to test this hypothesis of causative involvement of BDNF, we induced NMSDO-like pathology in mice with a conditional knockout of

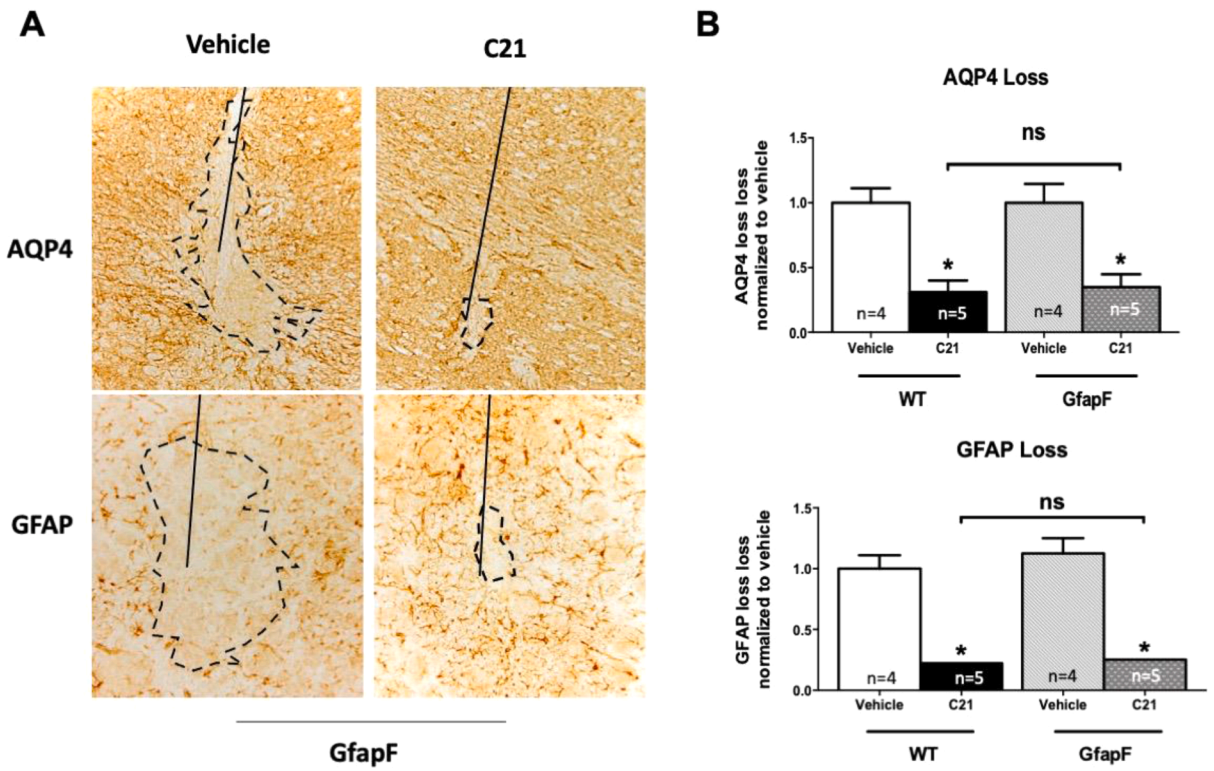

Fig. 2. NMOSD-like pathology induced by intracerebral injection of AQP4-IgG + C is independent of astrocytic-derived BDNF. GfapF and WT mice received AQP4-IgG + C with vehicle or C21 by stereotactic intrastriatal injection, followed by intrathecal administration of vehicle or C21 at day 2, and were sacrificed at day 4. A) Representative sequential sections from GfapF mice treated with vehicle (left panels) or C21 (right panels), stained with AQP4 (top panels) and GFAP (bottom panels) (20x magnification). Areas with pathology (loss of staining) in striatum are outlined. Black lines show needle tracks. B) Bar graphs showing the quantification of AQP4 and GFAP loss, normalized to vehicle treated mice. The degree of pathology was significantly reduced by C21 treatment in both GfapF and WT mice. The extent of pathology was similar between vehicle-treated GfapF and WT mice treated with vehicle. Numbers of mice per group are indicated in each bar. Results are shown as mean ± SEM. Asterisks indicate significant ($p<0,05$) differences between C21 and vehicle treatments. ns; not significant.

BDNF in astrocytes (GfapF mice). We found that the therapeutic effect of AT2R-stimulation by C21 in NMOSD-like pathology induced by intracerebral injection of AQP4-IgG + C as observed in WT mice was not altered by conditional knockout of BDNF in astrocytes in GfapF mice. This indicates that the protective effect of AT2R stimulation with C21 in NMOSD-like pathology is not dependent on astrocyte-derived BDNF. All measured, established markers of NMSDO-like pathology in our study, which were AQP4 loss, GFAP loss and macrophage/microglia infiltration (Wlodarczyk et al., 2021), were equally improved by AT2R stimulation in WT and GfapF mice.

An additional finding of our study was that the severity of NMOSD-like pathology induced by intracerebral injection of AQP4-IgG + C was not worsened by BDNF deficiency in astrocytes, thus indicating that astrocyte-derived BDNF does not serve as an intrinsic protective factor in NMOSD-like pathology.

It is a limitation of our experimental approach that BDNF deficiency was restricted to one cell source (astrocytes) leaving BDNF synthesis by other cells types such as neurons intact.

Dissection of the role of BDNF via global deletion is not possible, since BDNF-KO mice die shortly after birth (Korte et al., 1995). We therefore used mice with conditional deficiency of BDNF in astrocytes for our study, since astrocytes constitute one of the major cellular sources of BDNF (Linker et al., 2010). Consequently, we can only conclude from our results that astrocyte-deived BDNF is not involved in the protective effect of AT2R stimulation in NMOSD-like pathology. However, our results do not exclude a role for BDNF derived from other sources such as neurons or endothelial cells. We could in fact show experimentally in this study that expression of BDNF in other cell types was unaffected by conditional BDNF knockout. Our analysis of ACSA-2 negative cells, i.e. “non-astrocyte cells” including neurons, confirmed that expression of BDNF by cell types other than astrocytes was still intact.

As originally described by Linker and colleagues, the reduction in BDNF mRNA in astrocytes from GfapF mice is about 85% of normal expression levels (Linker et al., 2010). That this level of reduction is sufficient to identify functional significance of astrocyte-derived BDNF is evidenced by the fact that in a model of multiple sclerosis (experimental autoimmune encephalomyelitis; EAE), GfapF mice presented with a more severe course of disease (Linker et al., 2010). This speaks for the general suitability of GfapF mice and sufficiency of the degree of conditional BDNF knockout to study BDNF dependence of pharmacological or pathophysiological effects.

5. Conclusion

Astrocyte-derived BDNF is not involved in the development of NMOSD-like pathology nor in mediating the protective effect of AT2R stimulation

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Author contribution

RK, NA, UMS, TO: Conceptualization, Supervision, Writing - Original Draft, Review and Editing. **RK, TO, JM, MD, RSD, SFS, RMR, HLL, CT:** Methodology, Formal analysis, Review and Editing

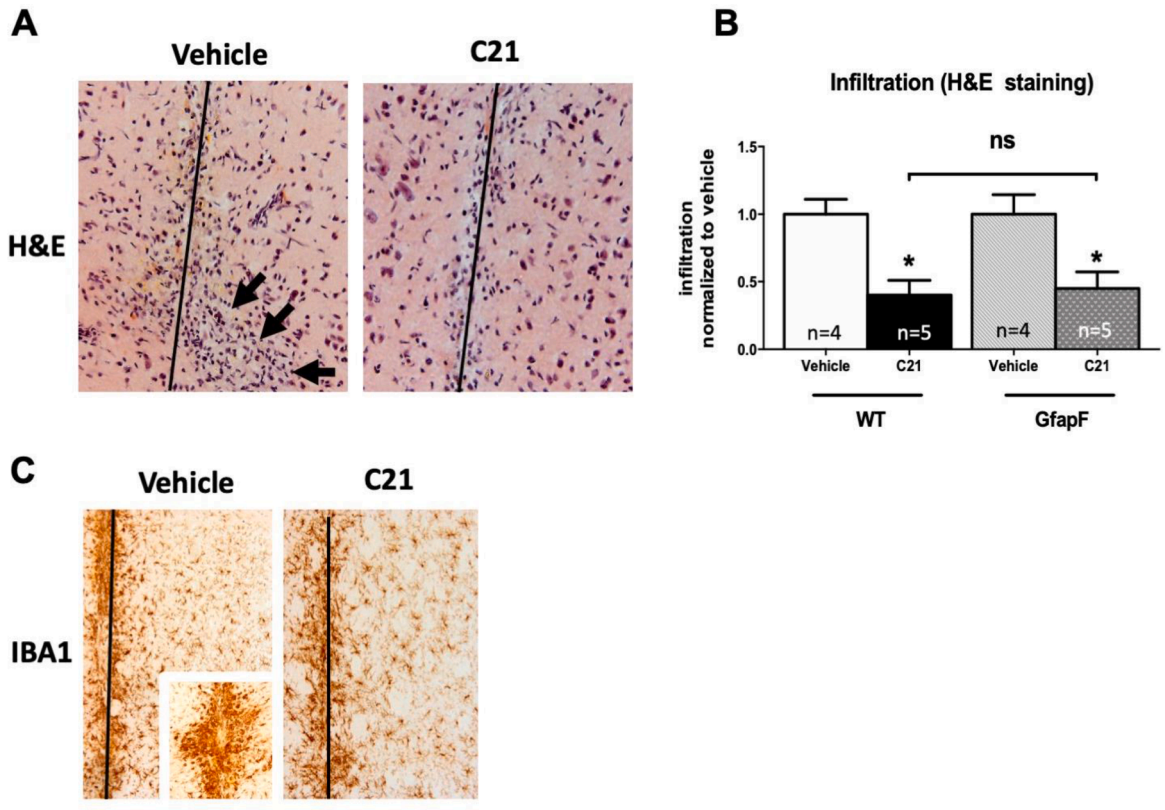

Fig. 3. NMOSD-associated infiltration and macrophage/microglia response induced by intracerebral injection of AQP4-IgG + C is independent of astrocyte-derived BDNF. GfapF and WT mice received AQP4-IgG + C with vehicle or C21 by stereotactic intrastriatal injection, followed by intrathecal administration of vehicle or C21 at day 2, and were sacrificed at day 4. A) Representative brain sections from GfapF mice treated with vehicle (left panel) or C21 (right panel), stained with H&E (20x magnification). Black lines show the needle track. Arrows point to infiltrating cells in vehicle-treated mice. B) Bar graphs showing quantification of infiltration (H&E staining) normalized to vehicle-treated mice. The degree of infiltration was significantly reduced by C21 in both GfapF and WT mice. The extent of pathology was similar between vehicle-treated GfapF and WT mice. Asterisks indicate significant ($p<0,05$) differences between C21 and vehicle treatments. ns; not significant. Results are shown as mean ± SEM. Numbers of mice per group are indicated in each bar. C) Representative brain sections from GfapF mice treated with vehicle (left panel) or C21(right panel), stained with IBA-1 (20x magnification). Insert show strong IBA-1 staining in the area with pathology in a vehicle-treated mouse. Black lines show needle tracks.

Declaration of Competing Interest

The authors declare that they have no competing interests

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