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The role of AQP4 in the pathogenesis of depression, and possible related mechanisms

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Abstract

Modulation of the aquaporin 4 (AQP4) water-regulatory channel or production of autoantibodies against this protein have been implicated in a variety of neuropsychiatric conditions, and possible mechanisms have been proposed. However, the nature of the interaction between AQP4 expression and its implications in depression remain elusive. To our knowledge, this is the first review summarising data for the involvement of AQP4 in the context of depression and related mechanisms across a wide range of experimental studies: *pre-clinical* (KO and wild-type), *post-mortem*, *ex vivo*, and *clinical* studies in depression. Overall, preclinical AQP4 wild-type studies showed that exposure to stress or inflammation, used as models of depression, decreased AQP4 protein and gene expression in various brain regions, including prefrontal cortex (PFC), choroid plexus and, especially, hippocampus. In preclinical AQP4 KO studies, AQP4 expression is necessary to prevent the effect of stress and inflammation on reduced neurogenesis and gliogenesis, and increased apoptosis and depressive-like behaviours. While in *post-mortem* and *ex vivo* studies of depression AQP4 expression was usually decreased in the hippocampus, prefrontal cortex and locus coeruleus, in clinical studies, where mRNA AQP4 expression or serum AQP4 autoantibodies were measured, there were no differences in depressed patients when compared with controls. In the future, studies should further investigate the mechanisms underlying the action of AQP4, and continue exploring if AQP4 autoantibodies are either contributing or underlying mechanisms of depression, or whether they are simply a mechanism underlying other autoimmune conditions where depression is present.

1. Introduction

Depression is one of the leading causes of disability worldwide (Reddy, 2010). Until now, several mechanisms have been proposed in an attempt to define the aetiological causes of depression. Notably, the occurrence of stressful life events and stress in general have been established as causal factors of depression (Kessler, 1997; Hammen, 2005). In the same way, inflammation has been linked to depression (Brigitta, 2002; Zunszain et al., 2012), and increased peripheral and central levels of various cytokines have been reported in patients suffering from this condition (Maes et al., 1997). While stress and inflammation are independently linked with depression, they can influence each other (Tian et al., 2014) and both negatively affect neurogenesis, a well-known process through which new neurons are generated in the human brain (Gould and Tanapat, 1999; Ekdahl et al., 2003; Mirescu and Gould, 2006; Das and Basu, 2008). Interestingly, it has been proposed that a multifactorial decrease in neurogenesis could be an important aspect of depression and antidepressant action (Jacobs et al., 2000), a hypothesis further supported by the discovery of increased hippocampal neural progenitor cell numbers in depressed patients following antidepressant treatment (Boldrini et al., 2009; Boldrini et al., 2014). However, despite the extensive evidence produced so far in this field, the way stress, inflammation and neurogenesis are regulated in depression still remains relatively poorly understood.

One of the most interesting molecules putatively involved in the forementioned mechanisms, and therefore potentially relevant for depression, is aquaporin-4 (AQP4). AQP4 is a trans-membrane bidirectional water channel belonging to the water-regulatory family of aquaporins. It is the most abundant aquaporin in neural progenitor cells and perivascular astrocyte processes in the brain (Jung et al., 1994; Nielsen et al., 1997; Oklinski et al., 2016), and crucial in the development and maintenance of blood-brain barrier (BBB) integrity (Nicchia et al., 2004). AQP4 in involved in the regulation of both the stress and immune response (Meli

et al., 2018a; Xu et al., 2019). Moreover, AQP4 can exert both pro- and anti-inflammatory properties, depending on the type of experimental models used, being pro-inflammatory in mice models of cerebral ischemia (Shi et al., 2012), and Parkinson Disease (Prydz et al., 2020), while showing anti-inflammatory properties in autoimmune models of neuromyelitis optica spectrum disorder (Wang et al., 2019). Similarly, the AQP4 water channel is also a key modulator of several brain neurogenic processes, including cell proliferation, differentiation and apoptosis (Kong et al., 2008; Kinoshita et al., 2009). In particular, evidence show that AQP4 knock out (KO) impairs cell proliferation and neuronal differentiation in mice hippocampi (Kong et al., 2008), and decrease glial proliferation in striatal astrocytes cultures (Küppers et al., 2008). AQP4 is also able to regulate cell migration, axonal sprouting and synaptogenesis (Zheng et al., 2010), overall, suggesting a major role of AQP4 in the modulation of key molecular and cellular pathways relevant for depression.

More recently, evidence has started to investigate the involvement of AQP4 also as a putative target of autoimmune responses in the context of depression, ultimately proposing autoimmunity as an additional mechanistic component of the depressive psychopathology (Maes et al., 1993). Interestingly, around fifty percent of patients with autoimmune diseases, such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), commonly show depressive symptoms (Pryce and Fontana, 2017). Similarly, patients suffering from the autoimmune disorder neuromyelitis optica (NMO) also report severe depressive symptoms (Chavarro et al., 2016). This is of particularly relevance as NMO is an AQP4-related autoimmune disease affecting the optic nerve and spinal cord, in which the presence of autoantibodies against AQP4 leads to central nervous system (CNS) neurodegeneration, including increased neuroinflammation and disruption of distinct neurogenic processes, such as loss of hippocampal neurons and astrocytes (Lennon et al., 2004), similar to what is often observed in animal models of depression (Price and Duman, 2020). Therefore, detection and

measurement of AQP4 autoantibodies in patients with depression might be a useful strategy to understand if autoimmune-related mechanisms are indeed contributing to the development of this psychopathology.

Although an increasing number of studies have suggested several levels of involvement of AQP4 in depression, at the moment there is still lack of a comprehensive understanding of the mechanistic significance of these findings. The aim of our review is to elucidate data generated so far in this field and to provide a more extensive understanding of the role exerted by AQP4 in depression. Therefore, in this review we will summarise evidence coming from: (1) *pre-clinical studies* of depression, which have measured AQP4 (protein or gene) expression and depressive-like behaviours as outcomes, or which have used AQP4 knock-out (KO) models to investigate AQP4 mechanisms of action; (2) *post-mortem*, *ex-vivo* and *clinical* studies in patients with depression which have again measured AQP4 (protein or gene) expression; and finally (3) *clinical studies* in patients with depression, which have instead measured AQP4 autoantibodies.

2. Involvement of AQP4 in depression

Amongst the 30 studies collected in this review, 20 are *pre-clinical* studies of depression measuring AQP4 (protein or gene) expression and relevant mechanisms (neurogenesis, gliogenesis, apoptosis and inflammation) (Tables 1 and 2); 4 are *post-mortem*, 2 *ex vivo*, and 2 *clinical* studies in patients with depression measuring AQP4 expression (protein or gene) (Table 3); finally, 2 are *clinical studies* in patients with depression measuring AQP4 autoantibodies (Table 4).

2.1 AQP4 in pre-clinical studies of depression

Out of the 20 included *pre-clinical* studies of depression, 14 studies investigated AQP4 (protein or gene) expression as outcome (Table 1), whereas 6 studies used AQP4 KO models

to investigate AQP4 mechanisms of action (neuroinflammation and neurogenesis) as well as depressive-like behaviours (Table 2). All studies used either immune or stress models of depression.

2.1.1 AQP4 protein or gene expression in wild-type studies of depression

Stress models of depression

Nine studies, of which 7 *in vivo* (Suda et al., 2008; Sakaida et al., 2013; Xia et al., 2017; Azis et al., 2019; Wei et al., 2019; Liu et al., 2020; Taler et al., 2021), 1 *in vivo* and *ex vivo* (Di Benedetto et al., 2016) and 1 *in vitro* (Salaria et al., 2006) measured AQP4 (protein or gene) expression and behavioural outcomes (whenever possible) in stress models of depression, and found that stress can decrease AQP4 protein and gene expression in the brain, especially in animals experiencing increased anhedonic and anxiety-like behaviours.

In the first *in vivo* study, exposure to chronic unpredictable mild stress (CUMS) decreased AQP4 protein expression in the prefrontal cortex (PFC) and choroid plexus in mice, and increased despair, anhedonia and anxiety-like behaviours. Interestingly, treatment with omega-3 polyunsaturated fatty acids (PUFA) supplementation, known to have anti-depressant properties, prevented the effect of CUMS on both AQP4 expression as well as behaviour (Liu et al., 2020). Similarly, in the second *in vivo* study, exposure to CUMS decreased AQP4 protein expression in the dentate gyrus (DG) of the hippocampus in mice, and increased anhedonia and anxiety-like behaviours, which were prevented by administration of lithium, a mood stabiliser (Taler et al., 2021). In line with the aforementioned studies, two other *in vivo* studies showed that exposure to CUMS decreased cortical and hippocampal AQP4 protein (Xia et al., 2017) and antero-cortical AQP4 mRNA expression in mice (Wei et al., 2019), and increased depressive-like behaviours, all of which were reversed by treatment with the antidepressant fluoxetine (Xia et al., 2017) and the glucocorticoid receptor antagonist mifepristone (Wei et al., 2019).

Another study showed similar results, *in vivo* and *ex vivo*. In particular, experiments showed that *in vivo* exposure to high anxiety-like behavior (HAB) decreased AQP4 protein expression in PFC of rats (Di Benedetto et al., 2016). In the same study, *ex vivo* treatment with the antidepressant fluoxetine on PFC cells, isolated from the same rats, restored the decrease in AQP4 protein expression in those cultures (Di Benedetto et al., 2016).

Another *in vivo* study used pregnancy as a murine model of stress. In particular, exposure to ovarian steroids caused a decrease in AQP4 gene expression in the hippocampus of rats (Suda et al., 2008). Finally, one *in vitro* study, using cortisol as a model of "depression in a dish", showed that exposure of human foetal brain aggregates to treatment with cortisol decreased AQP4 gene expression (Salaria et al., 2006).

Findings therefore demonstrate that exposure to stress, used here as a model of depression, decreased AQP4 protein and gene expression levels in both animal and human cells from various brain regions, including PFC, choroid plexus, and hippocampus.

Immune models of depression

Five studies, 2 *in vivo* (Cao et al., 2012; Wen et al., 2016) and 3 *in vitro* (Asai et al., 2013; Borsini et al., 2018; Wu et al., 2019), measured AQP4 expression and behavioural outcomes in immune models of depression, and found that exposure to inflammation, can either decrease or increase AQP4 protein and gene expression levels in animal and human cells from either the cortex or the hippocampus, and that this effect is dependent on the type of immune challenge (cytokines or lipopolysaccharides (LPS)), and on the type of tissue (animal or human). This will be further explained below.

In particular, the first *in vivo* study showed that intracerebroventricular injection of tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) decreased AQP4 protein

expression in the cortex of mice, and increased anhedonic behaviour (Wen et al., 2016). Similarly, another *in vitro* study showed that exposure of human hippocampal neurons to the inflammatory cytokines interferon-alpha (IFN-α) or interleukin 6 (IL-6) decreased AQP4 gene expression (Borsini et al., 2018). However, one *in vivo* study showed that injection of LPS increased AQP4 protein and gene expression in mice homogenised brain tissue (Cao et al., 2012). Similarly, two other *in vitro* studies showed that exposure of mice cortical astrocytes to LPS, or the cytokine IL-1β, TNF-α or IFN-γ increased AQP4 protein and mRNA expression (Asai et al., 2013; Wu et al., 2019).

Findings therefore demonstrate that inflammation, and particularly cytokines treatment, decreased AQP4 protein and gene expression in mice brains and in human neurons *in vitro*, whereas treatment with lipopolysaccharide (LPS) increased AQP4 protein and gene expression in mice brains, as well as in mice cortical astrocytes *in vitro*.

2.1.2 AQP4 protein or gene expression in KO studies of depression

Stress models of depression

Two *in vivo* studies (Kong et al., 2009; Kong et al., 2014) used AQP4-KO strategies and measured neurogenesis, gliogenesis, apoptosis, as well as behavioural outcomes in stress models of depression, and found that AQP4 can prevent the effect of stress on the aforementioned mechanisms as well as behaviour, but only in specific models of stress.

In particular, the first *in vivo* study showed that exposure to treatment with corticosterone decreased the number of bromodeoxyuridine (BrdU)+ and Ki67+ proliferating cells, and of doublecortin (DCX)+ neuroblasts and microtubule-associated protein 2 (MAP2)+ neurons in the subgranular zone (SGZ) and dentate gyrus (DG), respectively, in AQP4-KO mice, but to a lesser extent in wild-type animals. Treatment with corticosterone also decreased the number of glial fibrillary acidic protein-positive (GFAP)+ astrocytes in the hippocampus in

AQP4-KO mice, but not in wild-type, and increased the number of terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL)+ apoptotic cells in AQP4-KO mice, but to a lesser extent in wild-type. The treatment also decreased expression of glial-cell line-derived neurotrophic factor (GDNF) in the hippocampus of AQP4-KO mice and increased depressive-like behaviours (Kong et al., 2014).

In contrast, the second *in vivo* study showed that exposure to CUMS decreased the number of BrdU+ cells, of c-AMP response element binding protein (CREB) and calcium/calmodulin-dependent protein kinase 4 (CaMKIV) phosphorylation in the hippocampus of both AQP4-KO and wild-type mice, and that subsequent administration of antidepressant fluoxetine restored the number of BrdU+ cells and the phosphorylation levels of CREB and CaMKIV in the hippocampus of wild-type mice, but not in AQP4-KO mice. Exposure to CUMS also increased depressive behaviour in both AQP4-KO and wild-type mice, but fluoxetine restored depressive behaviour in wild-type mice, but not in the AQP4-KO mice. In the same study, *in vitro* treatment with fluoxetine restored the decrease in proliferation in wild-type hippocampal adult neural stem cell (ANSC) neurospheres, but not in AQP4-KO mice (Kong et al., 2009).

Findings therefore demonstrate that AQP4 prevents the effect of stress on neurogenesis, gliogenesis, apoptosis and behaviour, only in models where corticosterone, but not CUMS, have been employed as models of stress. However, in CUMS model of stress, AQP4 is necessary for the effect of fluoxetine.

Immune models of depression

Four studies, of which 3 *in vitro* (Li et al., 2011; Ikeshima-Kataoka et al., 2015; Dai et al., 2018) and 1 *in vitro* and *in vivo* (Liang et al., 2016) used AQP4-KO strategies and measured gliogenesis and inflammation in LPS-induced immune models of depression, and found that

AQP4 prevents the effect of LPS on gliogenesis, however AQP4 is necessary for the effect of LPS on the activation of downstream inflammatory mechanisms.

The first *in vivo* study showed that treatment with LPS increased the number of BrdU+ proliferating cells, but decreased the number of GFAP+ astrocytes in the SGZ of the hippocampus of AQP4-KO mice, when compared with wild-type mice. LPS also decreased protein and gene expression of IL-1β, TNF-α, and IL-6 in AQP4-KO mice, when compared with wild-type mice. In the same study, *in vitro* treatment with LPS decreased protein expression of IL-1β, TNF-α, and IL-6 in AQP4-KO murine hippocampal astrocytes, when compared with wild-type cultures (Liang et al., 2016).

In another study, *in vitro* treatment with LPS did not affect cell apoptosis neither in AQP4-KO nor in wild-type cultures, but decreased protein expression of inflammatory markers TNF-α, sphingosine kinase 1 (SPHK1), protein kinase B (AKT1) and mitogen-activated protein kinase (MAPK), but not IL-6, in AQP4-KO mice cortical astrocytes, when compared with wild-type mice astrocytes (Dai et al., 2018). Another *in vitro* study showed that treatment with LPS decreased the number of GFAP+ astrocytes, and TNF-α, IL-1β and IL-6 gene expression in AQP4-KO murine embryonal cortical grey matter astrocytes, when compared with wild-type mice astrocytes (Ikeshima-Kataoka et al., 2015). Accordingly, the last *in vitro* study showed similar results, as treatment with LPS decreased protein expression of TNF-α and IL-6 in AQP4-KO murine cortical astrocytes, when compared with wild-type cultures (Li et al., 2011).

Overall, these studies show that AQP4 prevents the effect of LPS on gliogenesis, but it is necessary for the effect of LPS on the activation of downstream inflammatory pathways.

2.2 AQP4 expression in human post-mortem, ex vivo and clinical studies

Out of the 8 included *post-mortem*, *ex vivo* and *clinical* studies of depression, 4 *post-mortem* studies and 2 *ex vivo* studies investigated AQP4 protein or gene expression levels in brain tissues of depressed patients, and 2 *clinical* studies investigated AQP4 gene expression in blood mRNA of patients with depression (Table 3).

Post-mortem studies

Four *post-mortem* studies measured AQP4 expression levels in the brain of depressed patients (Bernard et al., 2011; Rajkowska et al., 2013; Medina et al., 2016; Waller et al., 2019), and overall they found that AQP4 gene and protein expression is significantly decreased. In particular, the first two studies showed respectively a decrease in AQP4 protein and gene expression in the hippocampus (Medina et al., 2016) and locus coeruleus (Bernard et al., 2011) of depressed patients, when compared with controls. Another study showed a decrease in AQP4 protein expression in the PFC grey matter of depressed patients, but no changes in AQP4 protein expression in the PFC white matter (Rajkowska et al., 2013). In contrast, another study found no changes in AQP4 protein expression in the subcortical white matter in patients with depression, when compared with controls (Waller et al., 2019).

Overall, these studies indicate that AQP4 expression is usually decreased in the brain of patients with depression, particularly in the hippocampus, locus coeruleus and PFC grey matter, but not white matter.

Ex vivo studies

Two *ex vivo* studies investigated AQP4 protein or gene expression levels in brain tissues collected during epilepsy surgery (Kandratavicius et al., 2015; Lu et al., 2019), and showed that AQP4 protein and gene expression levels are decreased in the brain of patients with depression

(and epilepsy), when compared with controls (depressed with no epilepsy and healthy individuals). In particular, the first study showed no difference in AQP4 protein expression in hippocampal tissue specimens from epileptic patients with depression, when compared with specimens from epileptic patients with no prior psychiatric history and with specimens from non-epileptic healthy controls (Kandratavicius et al., 2015). In contrast, the second study showed a decrease in AQP4 gene expression in hippocampal tissue specimens from epileptic patients with depression, when compared with specimens from epileptic patients with no prior psychiatric history and specimens from non-epileptic healthy controls (Lu et al., 2019).

Overall, in line with post-mortem findings, *ex vivo* studies indicate that AQP4 expression is usually decreased in the brain of patients with depression, particularly in the hippocampus.

Clinical studies

Two *clinical* studies investigated AQP4 gene expression levels in blood mRNA of patients with depression (Cattaneo et al., 2020; Wallensten et al., 2021), and found that depressed patients have no differences in AQP4 gene expression in peripheral blood cells, when compared with controls. In particular, the first case-control study found no differences in blood mRNA AQP4 gene expression among responders, drug-free patients and controls, whereas AQP4 gene expression was increased in treatment-resistant depressed patients (Cattaneo et al., 2020). Similarly, the second case-control found no differences in AQP4 protein expression in astrocyte-derived extracellular vesicles (EV), isolated from plasma, when comparing depressed patients with healthy controls (Wallensten et al., 2021).

Overall, this limited evidence seems to suggest that peripheral AQP4 protein or gene expression levels are not decreased in depressed patients, when compared with healthy individuals.

2.3 AQP4 autoimmunity in clinical studies of depression

To our knowledge, only 2 *clinical* studies measured AQP4 autoantibodies in depression (Iorio, 2015; Gur et al., 2020) (Table 4), and overall, the studies found that autoantibodies against AQP4 are not produced in peripheral blood of depressed patients.

The first study is an observational study conducted on one patient with treatment-refractory depression, and found high levels of AQP4 autoantibodies in blood serum. Of note, the patient later developed NMO symptoms (Iorio, 2015). The second study is a case-control study of fifty patients, half of them diagnosed with depression and the other half with bipolar disorder. In this case all patients were seronegative for AQP4 autoantibodies at both baseline and 3-months follow-up, and none of these patients have been tested for symptoms of NMO (Gur et al., 2020).

Overall, this limited evidence seems to suggest that the presence of AQP4 autoantibodies is not involved in the pathogenesis of depression, but rather a mechanism activated by the NMO autoimmune pathology.

3. Discussion

To our knowledge, this is the first review summarising evidence for the involvement of AQP4 in the context of depression, and related mechanisms, across a wide range of experimental studies: *pre-clinical* (KO and wild-type), *post-mortem*, *ex vivo*, and *clinical* studies. Overall, preclinical AQP4 wild-type studies, showed that exposure to stress or inflammation, used as models of depression, decreased AQP4 protein and gene expression in various brain regions, including PFC, choroid plexus and, especially, hippocampus. In preclinical AQP4 KO studies, AQP4 expression is necessary to prevent the effect of stress and inflammation on reduced gliogenesis, and the effect of stress on reduced neurogenesis, and

increased apoptosis and depressive-like behaviours. While in *post-mortem* and *ex vivo* studies of depression AQP4 expression was usually decreased in the hippocampus, prefrontal cortex and locus coeruleus, in clinical studies, where mRNA AQP4 expression or serum AQP4 autoantibodies were measured, there were no differences between depressed and non-depressed patients (see Figure 1 for results summary).

Several pre-clinical studies using either models of stress or inflammation found a decrease in AQP4 protein or gene expression. Interestingly, this effect was mostly prevalent in the hippocampus, a region highly known for its involvement in depression (Sahay and Hen, 2007; Hill et al., 2015). Exposure to stress or inflammatory cytokines can severely disrupt hippocampal neurogenesis (Anacker et al., 2013a; Anacker et al., 2013b; Borsini et al., 2015; Borsini et al., 2017; Borsini et al., 2018; Borsini et al., 2020), and indeed post-mortem studies in depression have revealed a significant reduction in neurogenesis in the hippocampi of untreated depressed patients (Boldrini et al., 2009; Boldrini et al., 2014). Studies from this review showed that independently of the experimental assay used (*in vitro* or *in vivo*) or type of tissue (human or animal), exposure to stress was able to decrease AQP4 expression. In contrast, studies using immune models of depression, found a decrease in AQP4 expression mainly when using cytokines, but not LPS, as experimental immune challenges. A possible explanation for this could be due to the fact that LPS, when compared with cytokines, is a rather stronger challenge which may induce the activation of compensatory mechanisms, including the expression of neuroprotective factors. Several studies have shown that exposure to LPS can also increase the production of anti-inflammatory cytokines, like IL-10, IL-4 and IL-13 (He et al., 2019; Sangaran et al., 2020; Mizobuchi and Soma, 2021), which can ultimately modulate AQP4 expression and reduce cell apoptosis (Shin et al., 2004; Norden et al., 2016; Meli et al., 2018b; Chen et al., 2020). While it is rather speculative to conclude that this was the case for the findings discussed in our review, future studies using LPS as a model of depression should

also include measurements of anti-inflammatory and neurogenic molecules, in order to understand the exact phenotype induced upon stimulation with LPS versus cytokines, and as a consequence, the role of AQP4 in that specific model. In contrast, in knock out studies we found that AQP4 prevents the effect of LPS on gliogenesis, however AQP4 is necessary for the effect of LPS on the activation of downstream pro-inflammatory mechanisms (Li et al., 2011; Ikeshima-Kataoka et al., 2015; Liang et al., 2016; Dai et al., 2018). These studies were all conducted *in vitro* and independently of the concentrations used they observed similar findings. Therefore, overall this evidence suggests that, not only differences between cytokines and LPS challenges, but also the employment of a AQP4 non-knock out or knock model, in presence of LPS, can lead to different cellular and molecular changes.

In knock out studies, evidence showed that AQP4 is necessary to prevent the effect of stress stress on reduced neurogenesis, and increased apoptosis and depressive-like behaviours. However, the role of AQP4 was mostly evident when biological stress, by means of corticosterone administration, but not psychological stress, with CUMS, was induced. This difference may be due to the fact that AQP4 is differentially involved as a regulatory mechanism for the action of corticosterone, when compared with CUMS. Indeed, studies discussed in this review showed that CUMS decreases cell proliferation via phosphorylation of the neurogenic proteins CREB and CaMKIV (Liu et al., 2020), whereas another study found that corticosterone decreases neurogenesis and apoptosis via production of distinct neurotrophic factors, particularly GDNF (Kong et al., 2014). While the effect of CUMS on proliferation is independent of AQP4, the effect of corticosterone on neurogenesis and cell death is present only in AQP4-KO, therefore suggesting that AQP4 is necessary to prevent the neurogenic and apoptotic changes induced by the biological stress challenge, and that this effect is mediated by mechanisms which are activated by AQP4 only in presence of corticosterone, but not CUMS. Clinically, this evidence suggests that exposure to stress, and subsequent increased in cortisol

production, can be negative for hippocampal neurogenesis and cell viability, and ultimately mood, that these effects are more detrimental in presence of a non-functional AQP4 protein.

In post-mortem and *ex vivo* studies of patients with depression, AQP4 expression is decreased in brain tissue, but not in peripheral blood tissue. This inconsistency between central and peripheral measurement of AQP4 suggests that brain tissue is perhaps a more reliable source of information, and in fact studies included in this review and which measured AQP4 in blood did not observe any differences in AQP4 expression between depressed patients and controls. Indeed, physiologically, AQP4 expression is significantly lower in the periphery than in the CNS, with only 12% of myenteric plexus neurons, 8% of submucosal plexus neurons being positive for AQP4 in mice (Ma et al., 2011; Ma et al., 2012), and almost no AQP4 expression in glial cells of peripheral nervous structures in humans (Gao et al., 2006). In contrast, AQP4 is highly expressed centrally in both neural progenitor cells and adult brain astrocytes (Mader and Brimberg, 2019). Indeed, AQP4 participates in the regulation of brain permeability not only through changes in its expression, but also through variation in polarity, which refers to AQP4 expression being mislocalized throughout the astrocytes, and which ultimately leads to impaired function of the BBB (Rajkowska and Stockmeier, 2013). Of note, there is extensive evidence showing an association between BBB permeability and the development of depressive-like behaviours in animals (Menard et al., 2017; Lehmann et al., 2020), which further suggests the relevance of AQP4 as mechanistic target in depression. However, while AQP4 should be primarily measured in the brain (Mader and Brimberg, 2019), it is also worth noticing that its expression may increase in the periphery during certain phases of the pathology. In particular, in patients experiencing a more chronic depressive symptomatology, stress and inflammation might induce water permeability (or vasogenic) changes not only in the brain, but also in the periphery, therefore affecting AQP4 expression and functionality (Papadopoulos and Verkman, 2007). Ultimately, this seems to suggest that

phases and chronicity of the psychopathology should influence methodological strategies (location and tissue type) for the measurement of AQP4.

Autoantibodies to AQP4 were unidentified in any of the studies, suggesting that AQP4 autoimmunity is not involved in the pathogenesis of depression, but rather is a mechanism of the NMO autoimmune pathology (Lennon et al., 2004). Indeed, the depressive phenotype observed between patients with and without NMO is relatively different. In a study of patients diagnosed with NMO, and experiencing depression, prevalence of severe depression was relatively low (10%) but almost 50% of patients had suicidal ideations (Chavarro et al., 2016). In contrast, other studies in depression (without NMO) have shown a prevalence of severe depression in around 30% of patients (Steer et al., 2001), and of suicidal ideation in roughly 25% percent of patients (Han et al., 2014). These findings suggest that there are differences in the depressive phenotype observed in NMO patients, when compared with non-NMO patients, which may explain why AQP4 is uniquely involved, either as an autoimmunity target or as a more regular neuroimmune mechanism, respectively in NMO and non-NMO patients, both experiencing depression. However, it is also worth highlighting that these conclusions are based on only two clinical studies, one of which is a case-study consisting of just one patient. Therefore, additional investigations consisting of larger cohorts of patients are necessary in order to draw more conclusive interpretations of the observed findings.

Our review presents some limitations. Only few pre-clinical and clinical studies measuring AQP4 expression or the presence of AQP4 autoantibodies were identified, which makes it difficult to draw meaningful conclusions. Moreover, the majority of the clinical studies measured AQP4 expression in the periphery (in blood), but not centrally (in CNS or CSF), and showed inconsistencies between these two types of measurements. However, despite the limitations, this is the first review summarising data for the involvement of AQP4 in the context of depression, and discussing its related mechanisms. Overall, preclinical studies, showed that

exposure to stress or inflammation, used as models of depression, decreased AQP4 expression in the brain, and that AQP4 expression is necessary to prevent the effect of stress and inflammation on decreasing gliogenesis, and of stress on decreasing neurogenesis, and increasing apoptosis and depressive-like behaviours. While in post-mortem and ex vivo studies of depression AQP4 expression was usually decreased in the hippocampus, in clinical studies, where mRNA AQP4 expression or serum AQP4 autoantibodies were measured, there were no differences in depressed patients when compared with controls. In the future, studies should continue their investigation into the mechanisms underlying the effect of AQP4, and explore further if AQP4 autoantibodies are either contributing or underlying mechanisms of depression, or whether they are simply a mechanism characterising other autoimmune conditions where depression is present (with different characteristics), and therefore being a consequence of the autoimmune pathology.

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