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REVIEW ARTICLE

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A viewpoint on aldosterone and BMI related brain morphology in relation to treatment outcome in patients with major depression

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Abstract

An abundance of knowledge has been collected describing the involvement of neuroendocrine parameters in major depression. The hypothalamic–pituitary–adrenocortical (HPA) axis regulating cortisol release has been extensively studied; however, attempts to target the HPA axis pharmacologically to treat major depression have failed. This review focuses on the importance of the adrenocortical stress hormone aldosterone, which is released by adrenocorticotropic hormone and angiotensin, and the mineralocorticoid receptor (MR) in depression. Depressed patients, in particular those with atypical depression, have signs of central hyperactivation of the aldosterone sensitive MR, potentially as a consequence of a reactive aldosterone release induced by low blood pressure and as a result of low sensitivity of peripheral MR. This is reflected in reduced heart rate variability, increased salt appetite and sleep changes in this group of patients. In addition, enlarged brain ventricles, compressed corpus callosum and changes of the choroid plexus are associated with increased aldosterone (in relation to cortisol). Furthermore, subjects with these features often show obesity. These characteristics are related to a worse antidepressant treatment outcome. Alterations in choroid plexus function as a consequence of increased aldosterone levels, autonomic dysregulation, metabolic changes and/or inflammation may be involved. The characterization of this regulatory system is in its early days but may identify new targets for therapeutic interventions.

KEYWORDS
aldosterone, autonomic nervous system, choroid plexus, lateral ventricle volume, major depression

1 | COMPLEXITY OF MAJOR DEPRESSION

Depressive syndromes are common, severely debilitating and economically very expensive. Depressive syndromes occur in various psychiatric disorders, especially in affective disorders such as unipolar depression, bipolar depression or dysthymia. Unipolar depression is the most common affective disorder with a lifetime prevalence of approximately 16% worldwide.[1] Chronic depression is referred to when the symptoms persist for a period of at least 2 years.[2,3] For the treatment of depressive syndromes, partially effective

pharmacological, psychotherapeutic and other somatic treatments are available. However, often, the first chosen therapeutic approach does not work. For example, a large American study (STAR-D) showed, that when treated with a selective serotonin reuptake inhibitor, full remission is only achieved in approximately 30% of all patients.[4] Good predictors for the selection of therapy are not established, and it is therefore often necessary to test various therapeutic approaches one after the other or to introduce combination therapies. A major reason for this is the biological heterogeneity of depressive disorders. Parameters for differentiation have been collected in individual studies, but, because of the technical complexity, often only low numbers of cases and a limited number of parameters for a given study are available. These include neuroendocrine factors, such as cortisol,[5] inflammatory mediators[6] and sleep electroencephalogram parameters,[7,8] as well as parameters of the autonomic nervous system function,[9,10] such as heart rate variability.

2 | NEUROENDOCRINE CHANGES IN DEPRESSION: QUESTIONING THE PROMINENT ROLE OF CORTISOL

Neuroendocrine research in major depression has focused mainly on the HPA axis and one of its final end-products, cortisol.[11] The complexity of the underlying hypothesis, comprising dysfunction of the glucocorticoid receptor (GR) has been outlined, which indicated that different types of GR in different tissues may explain the apparent discrepancy between the assumed GR dysfunction and the potentially detrimental role of hypercortisolism.[12] One paradigm that was discussed as a target for glucocorticoid involvement is hippocampal neurogenesis,[13] based on the observation of a smaller hippocampal volume in subjects with depression.[14,15] Whether this phenomenon is a cause or a consequence of depression and which potential moderators, including inflammatory changes, are involved[16] is an important research question. From a clinical perspective, a somewhat confined focus on the role of the HPA axis and GR function has left many questions open and has not yet led to an approved treatment option.[17] However, the importance of the mineralocorticoid receptor (MR), has been brought forward[18] and a role of brain MR activation has been recognized by the leaders in the field.[19] Nevertheless, the main focus remained the role of cortisol as an MR ligand. As a complement to this view, the role of aldosterone is discussed in detail in the current viewpoint.

3 | INVOLVEMENT OF THE RENIN–ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS) IN MAJOR DEPRESSION

Stress-induced increases in aldosterone release have been described in humans[20,21] and animal models.[22–25] In patients with major depression, increased plasma or salivary aldosterone concentrations have been observed in a number of independent studies.[26–30] This can be interpreted in the context of aldosterone as a stress hormone, which is both activated via the HPA axis by adrenocorticotropic hormone (ACTH) and the sympathetic nervous system via the release of renin and angiotensin.[31] It appears that the aldosterone concentrations reflect the severity and chronicity of a depressive episode.[30] This relationship may, however, depend on gender, reproductive stage and subtype of depression. It was more pronounced in female postmenopausal subjects compared to male patients in the study by Segeda et al,[30] whereas Emanuel et al.[27] found no effect of gender. A potential gender difference is indeed not unexpected because the female sex hormone progesterone also has MR activity. Aldosterone levels fall with clinical improvement, which indicates that high aldosterone may be a state marker of depression.[29] In addition, a high aldosterone/cortisol ratio is a predictor of worse treatment outcome,[32] as well as low, rather than high, blood pressure. The connection between low blood pressure and poorer therapy response was confirmed in a recent large study, in particular in female subjects.[33] The pattern of these markers indicates lower activity of peripheral MR in patients who respond less well to antidepressant therapy. This is accompanied by decreased heart rate variability, increased slow wave sleep, an increased threshold for salty taste and an increased preference for salt, all of which indicate increased central MR activation.

As mentioned before, aldosterone levels appear to decline with clinical improvement,[29] whereas blood pressure levels stay the same or tend to increase.[34,35] This may indicate an increase in peripheral MR activity with clinical improvement. In accordance, an increase in MR expression has been demonstrated with antidepressant treatment in the brain of animals,[36–38] although data on peripheral MR activity with antidepressant treatment have not yet been reported. The assumed increase in peripheral MR expression or function would lead to the observed reduction in the RAAS in the absence of a blood pressure reduction.

4 | THE NEED FOR DIFFERENTIATION OF MAJOR DEPRESSIVE SUBTYPES

Is the association between depression and signs of hyperaldosteronism true for all forms of depression? A possibility that the association between RAAS and depressive symptoms characterizes a specific subset of depressed patients emerges. For example, in patients with Conn's syndrome (primary hyperaldosteronism), not only associations between aldosterone levels and depression severity, but also high levels of anxiety, somatic symptoms and irritability have been observed.[39–42] These symptoms share some features with atypical depression rather than with the classic melancholic form of depression: somatic symptoms are related to one of four of the specific symptoms of atypical depression, namely “leaden paralysis” and can be linked to alterations in bodily perception, that is, interoception. Irritability, which occurs in hyperaldosteronism, is related to the observed “rejection sensitivity” that defines atypical depression.

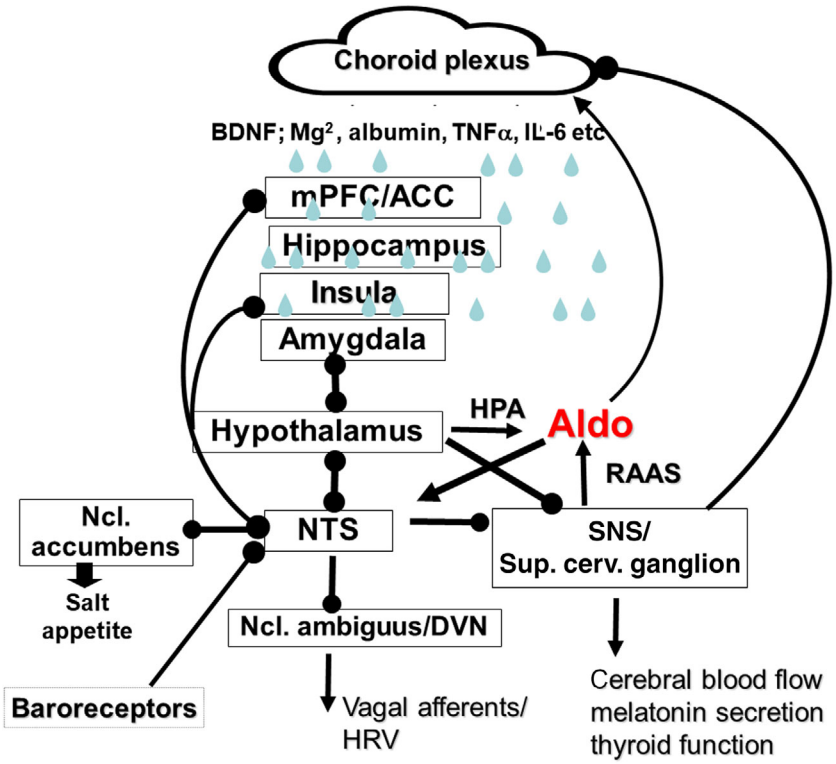

FIGURE 1 A schematic overview of the regulation and action of aldosterone. Aldosterone (Aldo) is released by stress through the hypothalamic–pituitary–adrenocortical (HPA) axis and through the renin–angiotensin aldosterone system (RAAS), which is activated by sympathetic influences. Via an effect on the activity of the nucleus of the solitary tract (NTS) aldosterone affects higher cortical and subcortical structures. Via projections to the sympathetic nervous system, the RAAS is activated, potentially leading to a feed forward cycle. The SNS is also involved in the regulation of cerebral blood flow and the regulation of choroid plexus mediated cerebrospinal fluid (CSF) release. Increased CSF release may increase ventricular volume and compress anatomical areas adjacent to the ventricles, in particular the corpus callosum. In addition, both beneficial compounds, including trophic factors such as brain derived neurotrophic factor (BDNF), and deleterious substances, including inflammatory mediators, are released by the choroid plexus and affect brain activity broadly via volume transmission. ACC, anterior cingulate; DVN, dorsal vagal motor nucleus; HRV, heart rate variability; IL, interleukin; mPFC, medial prefrontal cortex; Ncl., nucleus; Sup. cerv. ganglion, superior cervical ganglion; TNF, tumor necrosis factor

Finally, atypical depression is associated with a high body mass index (BMI) and changes in lipid metabolism,[5,43,44] which is also observed in primary aldosteronism. Consistently, obesity, alterations in lipid metabolism[45,46] and clinical features of atypical depression[47] are linked to lesser responsiveness to standard antidepressant treatment. However, contradictory findings regarding the influence of BMI have also been reported.[48] Interestingly, the association of obesity and plasma lipid alterations with depression appears not to be overlapping, but synergistic in a way such that more expressed plasma lipid abnormalities are associated with a higher level of depression, but the presence of adiposity adds to that.[49]

Furthermore, recent studies have found additional evidence for an overlap between signs of hyperaldosteronism and atypical depression. An increase in proteomic markers of RAAS activity (concentration of angiotensin-converting enzyme) for atypical vs. melancholic depression[43] was described. An additional feature of atypical versus melancholic depression is an increase in inflammatory markers. We discuss the link between aldosterone and inflammation further below. Overall, these findings are consistent with the observation that inflammatory changes are linked to lesser response to antidepressant treatment,[50] as well as the finding that obesity is related to inflammatory changes and may play a role in this context.[51–54] Patients with atypical depression also show a lower level of plasma cortisol compared to melancholic depressed subjects,[5] in line with our finding of a higher aldosterone/cortisol ratio as a sign of therapy refractoriness. Unfortunately, aldosterone has not been determined in the mentioned studies. Overall, the preponderance of atypical depressive symptoms with signs of hyperaldosteronism is consistent with a similar underlying pathology.

5 | NETWORK MODEL OF ALDOSTERONE EFFECT

The role of aldosterone as a behaviorally active compound has long been dismissed based on the fact that most brain MR are fully occupied by cortisol at relevant concentrations.[55] However, as mentioned above, specific brain areas have been identified in which aldosterone can act at the MR. These are mainly areas that co-express both the MR and the enzyme 11beta-hydroxysteroid-dehydrogenase type 2 (11betaHSD2). This enzyme metabolizes cortisol intracellularly and

allows aldosterone, which is present in much lower concentrations, to bind to the classic intracellular receptors. This is the basis for the specificity of aldosterone action not only in the periphery, but also in certain brain areas. The clearest indication for such action was described for the pontine nucleus of the solitary tract (NTS).[56,57] This nucleus not only has a role in the autonomic regulation, but also projects indirectly (via the locus coeruleus) to behaviorally relevant areas in the prefrontal cortex, the nucleus accumbens, the insula and other brain regions (Figure 1).[58,59] It is tightly linked to the autonomic regulation because of its connections with the nuclei of the parasympathetic and sympathetic nervous system.[60,61] Autonomic parameters, including heart rate, heart rate variability and blood pressure, reflect the activity of this system. It is the entry point of the vagus nerves and therefore mediates the clinical effects of vagus nerve stimulation, as well as the baroreceptor reflex. This has been described extensively before and will not be covered in detail here.[58,59]

As we have described, the role of 11betaHSD2 is to provide aldosterone uncompromised access to the MR. This leads to the specificity of aldosterone to activate MR in the NTS. Of importance, the action of this enzyme in the periphery, in particular at the level of the kidney, also inhibits the access of cortisol to the MR, although this blockade is not complete: genetic and biological influences can affect the activity of the 11betaHSD2.[62–64] A lower activity allows cortisol to bind to MR, which leads to an increase in MR activation and, as a consequence, high blood pressure accompanied by low renin and aldosterone release. Increased activity of the 11betaHSD2 is therefore linked to lower blood pressure and higher aldosterone levels (i.e. resembling MR dysfunction). Whether the 11betaHSD2 activity is causally involved in the earlier reported similar changes in patients with therapy refractory depression[32] or whether other reasons for a reduced peripheral MR function play a similar role needs further investigation. Nevertheless, a role of peripheral MR dysfunction in increased aldosterone levels and, as a consequence, lesser treatment response to antidepressants may exist in some forms of depression. This is in accordance with the observation that the activation of peripheral MR by the administration of the MR agonist fludrocortisone leads to a reduction in RAAS activity and is associated with a faster clinical improvement in patients with depression.[65] The observed reduction of aldosterone is suggested to reduce the MR activity at specific brain areas, including the NTS. The alternative explanation of a MR activating effect of fludrocortisone within the central nervous system (CNS) appears to be conceivable but not very likely: in areas without 11betaHSD2, the MR is occupied by cortisol (see above). Unless fludrocortisone has a higher intrinsic activity than cortisol, this compound should not have an effect in most brain areas. Also, it is unclear whether fludrocortisone is able to cross the blood–brain barrier. The only available study, carried out in rats, found low penetrance into the brain.[66]

Not to confuse but to complete the picture, it may be conceivable that aldosterone has actions on the brain independent of the presence of 11betaHSD2. Overall, the action of aldosterone is rather complex and may involve non-genomic activation, which has also been demonstrated at the NTS,[67] as well as the hippocampus or amygdala,[68] and is involved in the initiation of rapid stress mechanisms[69] and anxiety induction.[70] It has also been demonstrated that aldosterone administration in humans has rapid effects on heart rate variability.[71] The conclusion from these observations is that the reduction in aldosterone has relevant CNS effects, primarily in regions, co-expressing MR and 11betaHSD2, but possibly also outside of them.

Interestingly, neuroendocrine studies have provided evidence for peripheral MR dysfunction in depressed subjects who experienced childhood trauma[72] and in antidepressant resistant subjects.[73] In the latter study, the aldosterone concentration itself was not determined, but the sensitivity of the peripheral MR was examined. In addition, genetic data support a role of peripheral MR activity. Polymorphisms of the MR, rs2070951 and rs5522 have been characterized. The G-allele of rs2070951 accounts for approximately 50% of subjects (accounting primarily for the G-A haplotype, the G-G haplotype is very rare) and the remainder is constituted of the C-A and C-G haplotype.[74] The G-allele leads to a lower intrinsic activity and is associated with higher plasma aldosterone levels,[75] a lower cortisol awakening response and, somewhat inconsistently, a higher blood pressure, which is confined to males. The C-A haplotype, which is the second most frequent (approximately 40%) is a gain of function haplotype and is associated with higher optimism and a lower risk of depression in females, but no effect in males.[74] Interestingly, the G-allele containing haplotypes that are associated with higher aldosterone levels has been associated with features of atypical depression.[76] This is in line with our observation of the overlap between hyperaldosteronism and this subtype of depression. However, whether these differences are causally related to aldosterone levels or whether aldosterone levels are an epiphenomenon needs to be further explored. A role of cortisol needs to be considered because MR activation regulates ACTH release at the hippocampus and possibly the pituitary, both of which are not protected by 11betaHSD2.[77,78] With that in mind, the lower activity G-allele should be associated with higher cortisol levels. Again, the complex interaction of several regulatory influences[78] is not yet fully resolved.

A clear difference between subjects with hyperaldosteronism and subjects with treatment-resistant depression is the difference in blood pressure: it is high in Conn's syndrome and low in patients with the characterized type of depression. This indicates that it is the high aldosterone level that is the primary trigger for the psychiatric symptoms. Nevertheless, low blood pressure in patients with depression appears to contribute to the pathology. A higher blood pressure via activation of the baroreceptor reflex may actually have some protective effect.[58,79,80] The complexity of the threefold interaction between aldosterone levels, blood pressure and electrolyte concentrations need to be considered in this context.[58]

6 | RAAS AND INFLAMMATION

In depressed patients, changes in inflammatory markers are frequently found. A meta-analysis revealed a positive association between depression and C-reactive protein, interleukin-1 and interleukin-6.[81] Enhanced inflammatory responsiveness to psychosocial stress was observed in major depression patients with increased early-life stress.

Depression is closely related to coronary heart disease, in which an inflammatory component is strongly assumed,[82,83] which may be mediated by aldosterone.

The role of mineralocorticoids as inflammatory factors was stated a long time ago by Selye.[84] This has been rediscovered and clarified in recent years.[51,85–87] Regarding CNS disorders, it is of particular importance that subchronic administration of aldosterone in animal models leads not only to depression- and anxiety-like behavior, but also to an increase in inflammation related gene expression in the hippocampus.[88,89] A potential molecular mechanism that links aldosterone to inflammation, is its synergism with lipopolysaccharide (i.e. endotoxin) to activate the Toll-like receptor 4 (TLR4).[90] This molecular mechanism may contribute to the increase in vulnerability with respect to developing anxiety and depression-like behavior. In accordance with this, a recent pilot study[91] has suggested that administration of the aldosterone release reducing[92,93] and TLR4 inhibiting compound glycyrrhizin (from an extract of glycyrrhiza glabra) improves outcome in hospitalized patients with major depression.

7 | CONNECTION OF MORPHOLOGICAL BRAIN ALTERATIONS TO NEUROENDOCRINE SYSTEMS

Morphological changes have been described in major depression; one example comprises the recently reported changes in cortical thickness and subcortical structures.[94,95] Changes in more easily accessible structures, the ventricles, are often not considered. This is despite the fact that an increased ventricular volume in patients with depression compared to that in healthy controls[96–98] was reported previously; more importantly, ventricular volume appears to be related to treatment outcome.[99] We have recently demonstrated an association between the increased ventricular volume and worse treatment outcome in hospitalized patients with depression and identified mediators and moderators of this relationship,[100] comprising BMI, aldosterone/cortisol ratio and, potentially as a consequence of increased ventricular pressure, a reduced volume of corpus callosum segments. Because an increase in the BMI is predominantly a sign of atypical depression,[101] this observation is in line with the assumption of a predominance of the ventricle volume increase in this population, and is in line with the recently reported association between BMI and ventricular volume in bipolar patients.[102]

The previously described constellation of high aldosterone levels and low blood pressure could be an expression of traumatization in childhood.[103] Childhood trauma also appears to be associated with atypical depression according to most,[104–106] but not all studies.[107] The connection between traumatization in childhood and patients with a poorer treatment response is suggested by an overlap of structural changes: both conditions have increased volumes of the brain ventricles and reduced volumes of the corpus callosum.[100,108] As might be expected, several,[109,110] but not all[111] studies support the notion that patients with major depression and childhood trauma have a greater risk of not responding well to antidepressant therapy,[109,110] in accordance with the notion that these subjects may have larger ventricle volumes.

In the broader context, it is worth noting that an increased BMI and metabolic disturbances can be a consequence of childhood trauma,[112,113] although this does not appear to be a universal association. It appears to dependent on the genetic background[114] and autonomic vulnerability, as expressed as high frequency heart rate variability.[113] It is nevertheless possible that these metabolic pathways mediate the increase in ventricular volume.

The link to endocrine data comes from both animal and human data. Animal data show an increase in ventricular volume with chronic unpredictable stress, comprising an animal model of depression.[115] As we described above, stress leads to a release of aldosterone, which may provide a link. Support for the connection to neuroendocrine mechanisms comes from the observation that cerebrospinal fluid (CSF) secretion is associated with circadian rhythm[116] and/or sleep,[117] phenomena that are associated with neuroendocrine control: aldosterone secretion increases during sleep[118,119] on the one hand, but may also be dependent on the circadian rhythm of ACTH. Indeed, an influence of aldosterone on the secretion of the CSF has been reported.[120,121]

In humans with depression, the role of aldosterone on brain morphology is suggested by the positive correlation (trend) between the volume of the lateral ventricles and the significant inverse correlation to corpus callosum volume vs. the salivary aldosterone/cortisol concentration ratio in patients with depression.[100] Enlarged lateral ventricles and a possible compression-related reduction in the adjacent anterior portion of the corpus callosum were associated with non-response. The association between increased ventricles and reduced corpus callosum volume on the one hand and worse treatment outcome on the other hand has recently been confirmed in a larger study.[122] From a therapeutic aspect, it may be considered that a reduction in the release of aldosterone could thus also be associated with a reduction in ventricle size, which recently was reported with the use of selective serotonin reuptake inhibitors, and an improved treatment outcome.[123] Further precedence is provided by rapid acting antidepressant manipulations: Sleep deprivation has a fast, but only temporary antidepressant effect.[124,125] During the recovery night after sleep deprivation, an increase in nocturnal renin but not aldosterone release occurs.[124] This may highlight a reactive increase in RAAS activity in the recovery night, which wipes out the antidepressant effect. A change in ventricular volume would be expected based on the findings of Bernardi et al.[117] Other fast acting antidepressant interventions, including ketamine administration[126] and electroconvulsive therapy,[127] also reduce ventricular volume. Interestingly, in the latter study, the volumes of the lateral ventricles correlated with the clinical severity of depression. Potential mechanisms of the reduction in ventricular volume are further discussed below.

Because of the resemblance of these findings to those of normal pressure hydrocephalus (NPH), it is interesting to note that the cardinal signs of NPH, namely gait disorders, cognitive deficits[128–130] and bladder disorders, have also been described in a proportion of patients with depression.[131,132] Whether these patients had predominantly

atypical features or increased ventricles has, however, not been reported. Mechanistically interesting in this context are data from our pilot study. Glycyrrhizin, an active component of the extract of glycyrrhiza glabra, which has previously been shown to reduce aldosterone secretion, as an adjunct therapy to standard antidepressants, improved clinical signs of the NPH and depressive symptoms, whereas there was no improvement in NPH signs in a group treated only with standard antidepressants (L. Lehr, unpublished data).

8 | CONSEQUENCES OF VENTRICLE VOLUME CHANGES

The widening of the ventricles has consequences for the structure of the surrounding brain regions, including the hippocampus,[15,133,134] habenula[135] and the caudate nucleus.[136] These are, however, not universal, but may differentiate subtypes of depression. A reduced volume of the corpus callosum has, for example, been described as a risk factor for developing late-life depression in female, but not male subjects.[137]

Enlarged ventricles may also have consequences for brain metabolism and consequently for neurochemical regulation. In an animal model, hydrocephalus appears to induce changes similar to those described in depression. This includes a change in metabolic markers in the spectroscopic examination of the brain, such as *N*-acetylasparate and glutamine,[138,139] the precursor of both glutamate and GABA, as well as the activity of the glutamine-generating enzyme glutamine synthetase.[140] With regard to *N*-acetylasparate and glutamate, similar findings were observed in humans. The association between the activity of glutamine synthetase, GABA and glutamate concentrations has been repeatedly described in patients with depression.[141–144] Whether these observations correlate with ventricular volume has not yet been reported.

9 | CHOROID PLEXUS AS A MEDIATOR OF DEPRESSIVE SYMPTOMS?

Until now, we have primarily described commonly reported characteristics in imaging studies (i.e. ventricular volume and corpus callosum volume). The mediator of these changes may be the choroid plexus and its function to release CSF and therefore regulate ventricle volume. The increase in ventricular volume may be responsible for the compression of the corpus callosum. In addition, molecular moderators, released from the choroid plexus, may spread into brain tissue via volume transmission[145,146] (Figure 1). Those moderators may be produced in the choroid plexus itself. These may include proinflammatory molecules, which, for example, are also involved in sickness behavior.[147] These inflammation mediators,[145,148] in addition to compression, may lead to a change in white matter volume and/or integrity. It has recently been demonstrated that the volume of the choroid plexus in association with a reduction of cortical volume is a marker of disease activity and is associated with higher cognitive impairment in patients with multiple sclerosis.[148] Accordingly, low grade inflammation affects the corpus callosum volume in elderly humans.[149] Changes in oligodendrocyte function may lead to changes in myelination or changes in the volume regulation of axons within the corpus callosum. Disturbance of white matter integrity may then secondarily affect gray matter activity. Altered structures of the corpus callosum have indeed been described in patients with depressive disorders, mainly using diffusion tensor imaging methods.[150–155]

In support of the hypothesis of the involvement of the choroid plexus in these mechanisms, the activity of the choroid plexus is affected by neuroendocrine influences, which have been linked to major depression, in particular vasopressin and aldosterone,[100,120] as well as markers related to metabolic syndrome and increased BMI.[100,156] Whether aldosterone has a direct effect on the function of the choroid plexus is not clear. For that to occur, either a co-expression of the classical MR with 11betaHSD2 should exist or, alternatively, a high affinity membrane MR need to be present. The latter has not been reported for the choroid plexus. A co-expression of MR and 11beta HSD2 has been reported in the literature, but the only study in animals (rabbits) did not find 11betaHSD2 expression.[157]

An alternative explanation could be the action of aldosterone on the autonomic nervous system via NTS activity changes and projections to the sympathetic nervous system. Indeed, the choroid plexus is innervated by noradrenergic, serotoninergic and cholinergic fibers, and expresses a number of peptidergic receptors, which may influence CSF secretion.[156] The sympathetic influence is mediated via the superior cervical ganglion, which also regulates melatonin secretion from the pineal gland,[158] which is involved in sleep regulation. The exact regulatory mechanisms are, however, complex. For example, beta-adrenergic blockade led to a reduction in CSF secretion[159] despite the fact that noradrenaline itself is also known to reduce CSF secretion.[156] Alternatively, this inconsistency may point to an indirect regulatory mechanism via a reduction in renin release, which is stimulated by beta-adrenergic activation. It may be suggested that a complex network involving the superior cervical ganglion regulates brain perfusion and function (Figure 1), although this needs to be further explored.

The role of the choroid plexus in neuropsychiatric disorders in the context of increased inflammation has been highlighted previously.[160] As discussed, the choroid plexus expresses MR[161] and TLR4 receptors,[162] which may act synergistically to increase inflammation.[90] Furthermore, a number of depression relevant genes, several of them related to inflammatory activity, are expressed at this structure and are sensitive to stressors, including $5HT_{2c}$ receptor, $5HT_{2a}$ receptor, GRs, tumor necrosis factor alpha, interleukin-6, interleukin-1beta and brain derived neurotrophic factor (BDNF).[163]

Further evidence for an involvement of the choroid plexus in the therapy of refractory depression comes from the observation that compounds produced by the choroid plexus such as transthyretin, or released by it such as total protein, are increased in the CSF of treatment-resistant patients, whereas other markers are reduced, including the BDNF.[164] As already mentioned, the choroid plexus expresses genes for growth factors, including neuroprotective

BDNF.[165,166] In this context, it is interesting to note that an increase in neuronal BDNF does not translate into an increase in CSF or plasma BDNF.[167] If confirmed, this implies that the reported BDNF level in the CSF, which is regarded as a marker for depression, appears to have a different source than neurons, potentially the choroid plexus. Indeed, the expression of BDNF in the choroid plexus is increased with electroconvulsive therapy and may contribute to the antidepressant effect of this treatment method.[168]

Finally, lipopolysaccharide treatment induced depression-like behavior, which was accompanied by a reduction in BDNF in the hippocampus.[169] This was prevented by ketamine[170] and is in accordance with the observation that ketamine blocks TLR4 receptor function.[171] This blockade also appears to mediate the antidepressant-like effect of ketamine in a chronic restraint animal model of depression,[172] which is associated with increased CNS inflammation. In relation to the effect of mineralocorticoid function, aldosterone unexpectedly appears to increase BDNF in neuronal cells,[173] which would indicate a potential beneficial effect, whereas, in contrast, the MR antagonist eplerenone prevents the stress-induced BDNF reduction in the hippocampus.[174] A difference of short-term and more chronic effects may play a role here. Notably, ketamine does not appear to have a direct effect on the activity of the RAAS. Its effect with respect to inhibiting the RAAS is rather indirect through the ketamine-induced increase in blood pressure,[175] as determined in patients undergoing anesthesia. Together, this may point to a benefit of reducing aldosterone in combination with inhibiting TLR4 activity.

10 | CONCLUSIONS

Hyperaldosteronism, more specifically an increase in the aldosterone/cortisol ratio, appears to define a specific subtype of depression, which is less responsive to standard monoamine-based antidepressant therapy. Additional characteristics of this subtype are low systolic blood pressure as a sign of peripheral MR dysfunction and, possibly, in a gender specific way, reduced heart rate variability, increased salt preference, increased slow wave sleep or sleep duration and an increase in inflammatory markers. Clinically and biologically, this type shows an overlap with atypical depression and depression in the context of obesity. Mechanistically, these changes could be mediated via two interdependent pathways. The first possible pathway is an activation of the nucleus of the solitary tract, which influences higher cortical and subcortical structures, including prefrontal cortical areas, the insula and the nucleus accumbens. The second possibility is an alteration in the choroid plexus function, mediated either directly or indirectly via a change in the autonomic activity, which goes along with increased volumes of the choroid plexus, the lateral ventricles and a compression of adjacent brain regions, in particular the corpus callosum. Alterations of choroid plexus function could also involve the release of mediators, which affect neuronal or white matter integrity, including trophic substances, such as BDNF or inflammatory mediators. To address these targets specifically, the development of new therapeutic approaches is required. One of these is the strengthening of peripheral MR function via inhibition of 11betaHSD2 with glycyrrhizin, which also acts to reduce inflammation via inhibition of TLR4 related inflammatory pathways. Further work needs to be carried out to explore the connection between the neuroendocrine and autonomic pathways, as well as how these may mediate changes in brain morphology and treatment outcome.

AUTHOR CONTRIBUTIONS

Harald Murck: Conceptualization; data curation; writing – original draft. **Lisa Lehr:** Conceptualization; visualization; writing – review and editing. **Daniela Jezova:** Conceptualization; writing – review and editing.

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CONFLICT OF INTEREST

Harald Murck is the owner of Murck-Neuroscience LLC and has developed a patent in the area of treatment refractory depression.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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