Brain Mineralocorticoid receptor in health and disease: from molecular signaling to cognitive and emotional function

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Abstract

Brain mineralocorticoid receptors (MR) mediate effects of aldosterone in relation to salt homeostasis, and of glucocorticoid stress hormones corticosteroids in the context of stress adaptation. Brain stem MRs respond to aldosterone, while forebrain MRs mediate rapid and delayed MR-mediated glucocorticoids effects in conjunction with the glucocorticoid receptor. MR-mediated effects depend on gender, genetic variations and environmental influences. Disturbed MR activity by chronic stress or in certain (endocrine) diseases can cause deleterious effects on affective state, cognitive and behavioural function in susceptible individuals. High MR activation may have protective effects in healthy individuals, whereas dysregulated high MR activity during a stress response would require treatment with mineralocorticoid receptor antagonists (MRAs). Here, we discuss recent pharmacological and genetic developments, from the molecular underpinnings of MR signaling and function, to pharmacological interventions in the clinic. Improved understanding of MR dependent pathways will help to improve glucocorticoid therapy, unwanted side effects and psychiatric symptoms.

Introduction

Corticosteroid hormones affect the brain via the Mineralocorticoid Receptor (MR) and Glucocorticoid Receptor (GR), controlling development, metabolism, homeostasis, cognition, and mood. Both receptor types can exert rapid non-genomic effects on neuronal activity, but they are best known as ligand activated transcription factors that regulate gene transcription. Both receptors, with differing affinities to corticosteroids and specific expression patterns throughout the brain, can bind at the same regulatory target sequences of genes. However, they also control distinct transcriptional networks to differentially regulate broadly defined neuronal processes from cell differentiation and survival to cognitive and emotional functions (de Kloet, Joëls and Holsboer, 2005).

Corticosteroids include both glucocorticoids like cortisol and corticosterone, and mineralocorticoids such as aldosterone and the less potent deoxycorticosterone (DOC). Glucocorticoids are the main ligands for both MR and GR in the brain. They are synthesized and released in a circadian and ultradian rhythm from the zona fasciculata of the adrenal cortex, regulated by the hypothalamic-pituitary-adrenal (HPA) axis, which in conjunction with the sympathetic nervous system coordinates the response to stress (figure 1). The HPA axis is critical for life and operates by feed-back loops to regulate glucocorticoid concentrations to maintain a dynamic and allostatic system homeostasis (Lightman, Birnie and Conway-Campbell, 2020). In addition, brain aldosterone-preferring MRs regulate salt and water balance, including their associated behaviours (de Kloet and Joëls, 2017).

Corticosteroid signaling becomes dysregulated in certain disease states or by chronic exposure to synthetic glucocorticoids used in treatment and replacement strategies, and this can enhance vulnerability to disease

(Lightman, Birnie and Conway-Campbell, 2020). Furthermore, MR and GR may contribute to (brain) disease in conditions that are not typically associated with high hormone levels. Here, we focus on the specific role of MR (inevitably in concert with GR) in mediating the effects of corticosteroids in the brain on gene transcription, cellular processes, and control of cognitive and emotional function.

MR pharmacology

Brain corticosteroid concentrations are influenced by several factors including brain penetration and local enzymatic conversion in specific areas. Access of synthetic glucocorticoids and cortisol to the brain is limited by P-glycoprotein (Pgp) expression (Karssen *et al.* , 2001), a multidrug transporter expressed in luminal blood facing membranes of endothelial cells of the Blood Brain Barrier (BBB) (Chapman, Holmes and Seckl, 2013). Pgp is encoded by the Mdr1a gene in rodents and MDR1 in humans (Jetté *et al.* , 1995). A hypo-glucocorticoid brain state may be induced using low doses of dexamethasone, based on the combination of the Pgp barrier and HPA-axis feedback at the pituitary level (Karssen *et al.* , 2005).

The potential effects of corticosteroid hormones on neuronal activity are determined by the distribution of receptors to which they bind. In limbic-frontocortical neurons high in MR expression (figure 1), preferential binding by GCs occurs with aldosterone being outcompeted, due to a 100-1000 higher circulating concentration of the hormone, even when cortisol is partially bound to corticosteroid-binding globulin (CBG) in the blood. Whether aldosterone is locally synthesized remains to be confirmed (Gomez-Sanchez *et al.* , 2005), but aldosterone selective MR binding mostly occurs by inactivation of 11-OH steroids (cortisol) to their inactive keto-variants (cortisone) by 11β-hydroxysteroid dehydrogenase type 2 (11HSD-2) (Baker and Katsu, 2017). In the brain this occurs predominantly in the brain stem nuclei of the solitary tracts (NTS), and discrete subpopulations of hypothalamic neurons (Geerling and Loewy, 2009) (figure 1+2). Its counterpart, 11HSD-1 reductase is more widely present in neurons and glial cells (Wyrwoll, Holmes and Seckl, 2011), returning local GCs to their active state, further encouraging MRs binding endogenous GCs (Edwards *et al.* , 1996). The well described interactions of MR with GR should be limited to glucocorticoid preferring MRs, for lack of endogenous GR ligand in 11HSD-2 expressing cells. Ligand-dependent interactions with transcriptional coregulator proteins may further add to cortisol/aldosterone specific effects in a cell and gene-dependent manner (Fuller, Yang and Young, 2017).

MR affinity to endogenous glucocorticoids is about 10-fold higher than that of GR, which has led to the notion that MR is substantially occupied under basal conditions (de Kloet, Joels and Holsboer, 2005). Given that brain access of cortisol is lower than that of corticosterone, the situation in the human brain may differ slightly from laboratory rodents (Karssen *et al.* , 2001). MR's high affinity for corticosterone and cortisol predicts that receptor expression levels can be limiting for its effects. MR's higher binding affinity to glucocorticoids is demonstrated in the ultradian rhythm of the HPA axis, where MR has extended activation and DNA binding duration during the inter-pulse interval (Lightman *et al.* , 2008). In contrast, GRs activated at the oscillating pulse peak transiently bind and dissociate DNA, termed 'rapid cycling', tracking the rise and fall of ligand concentration (Stavreva *et al.* , 2009). Functionally, MR activation under basal conditions is in line with a 'preparative' role in the stress response, where it determines stressor appraisal and initial reactivity (Oitzl and de Kloet, 1992; Schwabe, Wolf and Oitzl, 2010), whereas GR becomes activated with gradual increases in stress hormones and is (for example) involved in the consolidation of stress-related memories (ter Horst *et al.* , 2012; de Kloet*et al.* , 2018).

The high MR affinity for GCs has been mainly interpreted in relation to its genomic effects. Rapid non-genomic effects have been demonstrated for membrane associated MR and GR, which require 10-fold higher corticosteroid levels, in comparison to their genomic nuclear counterparts (Karst, 2005; Nahar *et al.* , 2015). In rats, non-genomic effects have for example been related to regulation of territorial aggression (Haller *et al.* , 2000). Recent genomics data suggest some genomic MR mediated responses require high levels of corticosterone (Mifsud and Reul, 2016; van Weert *et al.* , 2017), which is as of yet an unexplained contrast to the original ligand binding data (Reul and de Kloet, 1985).

In terms of transactivation strength, endogenous GCs seem less potent than aldosterone, by the comparative

slow dissociation of aldosterone from the receptor and different ligand induced receptor conformational changes (Grossmann *et al.* , 2004). In fact, synthetic glucocorticoids display a very rapid off-rate, potentially explaining why *in vivo* potency is much less than would be anticipated purely from steady state ligand binding affinity measures (Reul *et al.* , 2000). Progesterone binds MR with high affinity but with minor transactivation and is a physiological antagonist of the MR. Spironolactone, a very powerful mineralocorticoid receptor antagonist (MRA) (IC_{50} 66 nM), is less selective than eplerenone (IC_{50} 990 nM) (Kolkhof and Bärfacker, 2017), and both are structurally based on the progesterone molecule. Esaxerenone potently and selectively interferes with MR mediated transcription (IC_{50} 3.7 nM) (Arai *et al.* , 2015). The non-steroidal MRA finerenone exerts strong and selective MR inhibitory action (IC_{50} 18 nM) (Bärfacker *et al.* , 2012), with no active metabolites and short half-life ˜2h (Heinig *et al.* , 2018). In comparison to steroidal MRA mechanisms, finerenone reduces aldosterone induced nuclear translocation of GFP-MR more than that of spironolactone (Amazit *et al.* , 2015) and is further characterized by a bulky substituent that alters the MR LBD conformation observed with MR agonists causing rapid dissociation from the receptor (Amazit *et al.* , 2015). Fludrocortisone (Fludro) is a potent synthetic and selective MR agonist (Grossmann *et al.* , 2004; Gesmundo *et al.* , 2016).

While the GR is abundantly expressed throughout the brain, MRs expression profile is typically reported as more restricted (Reul and de Kloet, 1985). The highest proportion of aldosterone selective MRs in NTS, (figure 1) controls physiology and behaviour related to sodium balance and transport in epithelial cells (Geerling and Loewy, 2009). A proportion of these NTS neurons project to the parabrachial/locus coeruleus nuclei, some innervate the ventrolateral bed nucleus of the stria terminalis (BNST), and less project to the ventral tegmental area (VTA), central amygdala and hypothalamus regulating motivation and arousal, reward pathways and cognitive functions related to salt balance (de Kloet and Joëls, 2017). These receptors may be important in human psychopathology in relation to Conn's disease or other forms of hyperaldosteronism (discussed in detail later) (Gendreitzig *et al.* , 2021).

Glucocorticoid preferring MR is reported in the pre-frontal cortex, hippocampus, lateral septum thalamic nuclei, and hypothalamic nuclei and, the medial and central amygdala (Reul and de Kloet, 1985; Chao, Choo and McEwen, 1989) (figure 1). Hippocampal MR contributes to indirect negative feedback regulation of the HPA axis, and affects processes in the control of emotion, cognition, and behaviour (Vogel*et al* ., 2016). Hippocampal MR expression is high throughout all principle glutamatergic cell layers (Reul and de Kloet, 1985) with its highest levels in the Cornu Ammonis 2 (CA2), from embryonic through to adulthood and this may be directly linked to differentiation (McCann*et al.* , 2021). MR-directed cell type–specific molecular signatures, involved in cellular processes and disease states in the brain, requires further interrogation using techniques such as single cell RNA sequencing (scRNA-seq). In fact, scRNA-seq under basal conditions has identified higher expression of MR than GR also in GABAergic neurons in the hippocampus (Viho et al, JNE in revision). Models assessing fear extinction and behavioral responses to stress identified cortisol preferring MR projections from infralimbic origin to innervate the locus coeruleus (LC) and NTS, and also intercalate amygdala neurones that exert GABA-ergic control over the central amygdala (Milad and Quirk, 2012; McKlveen, Myers and Herman, 2015). What is more, the prelimbic- and infralimbic PFC were identified as important for fear expression and extinction (Milad and Quirk, 2012).

MR signaling

MR signaling involves four generally defined interactions (ligand binding, direct and indirect DNA binding, inter domain interactions and coregulatory interactions) (Poulsen *et al.* , 2018; Rivers *et al.* , 2019) (Poulsen et al 2018; Rivers 2019), but our mechanistic understanding is incomplete (Fuller *et al.* , 2021). The MR harbors three main functional domains: a N-terminal domain (NTD) with a intrinsically disordered N terminus, a DNA-binding domain (DBD), and a C-terminal ligand-binding domain (LBD) (linked to the DBD via a 'hinge region' (Huang, Chandra and Rastinejad, 2010)). Unliganded MR is mostly cytosolic within a HSP90-FKBP51 containing multiprotein complex. Ligand (agonist) binding induces changes to the complex and subsequent nuclear translocation (Davies, Ning and Sanchez, 2002; Gallo *et al.* , 2007; Wang *et al.* , 2007). Now nuclear, MR dissociates from its chaperone HSP90 to form homo- (Liu *et al.* , 1996) or MR-GR hetero-

dimers (Mifsud and Reul, 2016; Rivers *et al.* , 2019; van Weert *et al.* , 2019) that bind GREs of target genes (Koning*et al.* , 2019). In the brain, interactions with GREs seem to predominate over other potential types of interactions with the RNA (Le Billan *et al.* , 2015; van Weert *et al.* , 2017). MR, GR, and progesterone receptor (PR) can all bind GRE sequences, and nearby binding of other transcription factors can induce specificity as has been observed for NeuroD proteins and MR (Hudson, Youn and Ortlund, 2014; Le Billan *et al.* , 2015; van Weert *et al.* , 2017). Nevertheless, steroid receptors share GRE-driven targets genes, and MR regulation of FKBP5 abundance is in fact a mechanism by which GR sensitivity can be affected (Hartmann *et al.* , 2021).

At the DNA the specific ligand induced conformational changes facilitate recruitment of coregulatory proteins and interactions explicit to the cell type and regulate gene expression (Fuller, Yang and Young, 2017). Interestingly, aldosterone selectively induces an interaction between the NTD and the C-terminus (N/C) of the LBD, defining the ligand response (Pippal *et al.* , 2009). Lastly, MR (and GR) activity differs by varying N-terminus lengths that result from alternative mRNA translation (Faresse, 2014). Our current understanding of modulation of all mechanisms above, via post-translational modifications of MR and its interacting partners (Jiménez-Canino *et al.* , 2017), and of their upstream regulatory pathways is limited for the brain, despite its likely relevance.

MR mediated effects in the brain

The MR became a central focus as a moderator of early stress responses since the receptor was found to mediate non-genomic rapid and transient effects of corticosteroids on neurotransmission and synaptic plasticity in the hippocampus and amygdala after stress (Karst and Joëls, 2005; Karst *et al.* , 2010; Nahar *et al.* , 2015; Treviño and Gorelick, 2021). This was specifically shown with the rapid and transient increase of miniature excitatory postsynaptic currents (mEPSC) following treatment with corticosterone, whereby signaling was transduced by MRs located pre-synaptically at the plasma membrane regulating the eventual release of glutamate, in contrast to genomic receptors (Karst *et al.* , 2010; Groeneweg *et al.* , 2012). A distinct mechanism of non-genomic MR signaling could involve receptor dissociation from chaperone complexes within the cytoplasm (Gutierrez-Mecinas *et al.* , 2011) in concert with mediators like noradrenalin and CRH. Of note, non-genomic MR effects can determine subsequent genomic mechanisms, which has been termed metaplasticity (Karst *et al.* , 2010; Chatterjee and Sikdar, 2014; Sarabdjitsingh*et al.* , 2014).

MR effects on the peripheral stress response

In response to stressors, circuits converge on the brainstem to stimulate sympathetic nervous system activation (Herman *et al.* , 2016), and on the hypothalamic paraventricular nucleus to stimulate the HPA axis (Lightman, Birnie and Conway-Campbell, 2020). MRs can stimulate sympathetic outflow, as demonstrated by denervation studies in rat models for hypertension (Rahmouni *et al.* , 2001). MRs also crucially maintain the HPA axis set point, demonstrated by Mary Dallman's study that reinstated the hypothalamic and pituitary set point in adrenalectomised rats with low dose corticosteroids (Dallman *et al.* , 1989). In a more physiological setting, the MR antagonist RU28318 increased basal HPA axis activity and potentiated the initial rise in ACTH and corticosterone secretion in response to stress (Ratka *et al.* , 1989; van Haarst, Oitzl and de Kloet, 1997). In humans, systemic treatment using MR antagonist spironolactone increased basal and stress induced cortisol secretion (Cornelisse, Joels and Smeets, 2011). In contrast, GR antagonism did not affect basal HPA axis activity but instead attenuated the initial HPA stress response and prolonged cortisol secretion by inhibiting GR negative feedback (Ratka *et al.* , 1989; van Haarst, Oitzl and de Kloet, 1997).

MR effects on neuronal activity in rodent models

Nuclear MR-mediated effects set the reactivity of neurons to (stress-related) stimuli. Non-genomic MR detects changes in glucocorticoid levels (by ultradian pulsing or from a stress stimulus) and translates them into functional adaptations (Karst, 2005). As such, mEPSC frequency in dorsal hippocampal CA1 neurons follows the CORT pulse amplitude (Sarabdjitsingh *et al.* , 2016) necessary for neuronal electrical activity (Sarabdjitsingh *et al.* , 2014). Early studies in the dorsal hippocampal CA1 demonstrated subsequent genomic GR-mediated effects on excitability are opposite to those by genomic MR. In L-type calcium currents, absence

of CORT produced high amplitude that gradually reduced with low CORT doses and increased following high CORT application (Joels, 2006; Diamond *et al.* , 2007). Such findings form the basis of considerations on the importance of an MR/GR balance (de Kloet *et al.* , 2018). However, in the amygdala a rapid MR-dependent increase in excitability occurs by cooperation with nuclear GR and is prolonged with noradrenalin exposure (as seen in stress; (Karst and Joëls, 2016).

MR effects on cognitive and emotional function

MR mediates emotional and cognitive reactivity by affecting the appraisal of novel situations, learning strategies, and response selection (Vogel *et al.* , 2016). Pharmacological water maze studies demonstrated that MR affected search-escape strategies and behavioural reactivity to spatial novelty (Oitzl and de Kloet, 1992; Oitzl, Fluttert and Ron de Kloet, 1994; Zhou *et al.* , 2011). The stress induced switch from hippocampal to dorsal striatal based habit learning was further demonstrated to depend on MR (Vogel *et al.*,2016; Arp *et al.* , 2014; Ter Horst *et al.* , 2014) and enhanced MR expression facilitated this learning shift to guide behaviour under stress (Wirz et al 2017). Genetically modified MR-deficient models showed reduced learning and memory performance, and behavioural adaptation in strategic contexts (Berger *et al.* , 2006; Brinks *et al.* , 2009; Schwabe *et al.* , 2010; ter Horst*et al.* , 2013). These were improved by overexpressing MR (Lai*et al.* , 2007; Rozeboom, Akil and Seasholtz, 2007; Mitra, Ferguson and Sapolsky, 2009). Combined increased MR and decreased GR expression improved spatial memory and behavioural flexibility (Harris *et al.* , 2013). Prolonged stress in adulthood or early life stress (ELS) shifted hippocampal dependent contextual learning to fear learning (Kanatsou *et al.* , 2015, 2017), which was somewhat prevented by overexpressing forebrain MR, likely by neuronal and synapse regeneration in granular cells of the DG. Thus, MR is involved in behavioral reactivity in rodents as dependent on the substantial occupancy pre-stress, and the rapid non-genomic signalling in the early phases of a stress response. All this work was performed under the implicit assumption that antagonist effects acted on the GC-preferring MRs. Interpretation of interactions between MR expression and the effects of ELS is challenging in relation to the time at which MR is required. Interesting, these effects show sex differences, similarly to the consequence of human genetic variants of the MR gene ((Bonapersona*et al.* , 2019), see below)

Role of MR on cognitive and emotional function in humans: healthy individuals

Much of our understanding of MR function on HPA axis, cortisol, and cognition (Joels *et al.* , 2008) from animal studies has proven to be transferable to humans. Here, we focus on studies that have examined MR effects on cognitive and emotional function in healthy individuals and patients with stress-associated disorders.

The effects of cortisol *per se* on cognition, such as memory and executive function of healthy individuals have been investigated intensively (Shields *et al.* , 2017). Increased cortisol concentrations have been consistently shown to enhance memory consolidation but impair memory retrieval (Wolf, 2017). Most of these experimental studies administered cortisol or used psychosocial stress exposure, which leads to a stimulation of both GR and MR. More specific pharmacological MR targeting have been used to block or stimulate receptor function by single administration of spironolactone or fludrocortisone, respectively (Wingenfeld and Otte, 2019).

MR blockade

Blocking the MR impairs certain forms of memory retrieval, including verbal, autobiographic, and visuo-spatial memory (Otte *et al.* , 2007; Rimmele *et al.* , 2013; Young *et al.* , 2016). This highlights the role of MR specifically in hippocampal-based memory. In contrast, MR blockade did not affect learning and immediate memory retrieval or working memory (Otte *et al.* , 2007; Cornelisse, Joels and Smeets, 2011; Young *et al.* , 2016). Non-hippocampal cognitive processes, such as selective attention and psychomotor speed, were also unaffected by spironolactone (Otte *et al.* , 2007; Cornelisse, Joels and Smeets, 2011). Thus, intact hippocampal MR activation appears important for optimal human memory regulation. However, MR blockade increases cortisol concentrations, potentially shifting MR/GR balance towards more GR activation, and so GR involvement must still be considered in these effects.

Another line of research investigated the role of MR after psychosocial stress. Interestingly, spironolactone treatment prevented stress-induced cortisol effects on response inhibition, stimulus-response learning and delay conditioning Vogel *et al.* , 2016, 2017), including cognitive function beyond hippocampus-dependent processes. On a neuronal level, stress is associated with a reduced activation of the hippocampus, enhanced amygdala activation and amygdala-striatal connectivity, which were found to depend on MR availability (Vogel *et al.* , 2016, 2017). These studies emphazise the importance of amygdalae MR, in line with the observation that MR blockade was most effective for emotional stimuli (Rimmele *et al.* , 2013).

In sum, MR blockade has mostly impairing effects on human cognition, which fits closely to the animal data. Of note, the observed effects reflect a one-time administration of a MR antagonist, while the effects of chronic or repeated MR blockade are less well investigated. Importantly, one study treated obese individuals with low-dose spironolactone over 6 weeks and found improved rather than impaired learning performance (Rotenstein *et al.* , 2015). This may be relevant to situations like obesity, which is associated with increased MR activity in peripheral tissues and possibly in central tissues as well (Infante *et al.* , 2017).

MR stimulation

Given that MR antagonism rather impairs cognitive performance, MR activation may improve it. Indeed, several studies suggest that a single administration of fludrocortisone acutely enhances verbal learning performance and visuo-spatial memory retrieval (Groch *et al.* , 2013; Hinkelmann *et al.* , 2015; Piber *et al.* , 2016) but not autobiographic memory retrieval (Fleischer *et al.* , 2015). Notably, visuo-spatial memory is strongly hippocampus-dependent, and the effects of fludrocortisone are likely to be explained by high MR density in this brain region.

The data are less clear regarding other cognitive domains. No effects of MR activation were found with respect to executive function (Groch*et al.* , 2013; Otte, Wingenfeld, Kuehl, Kaczmarczyk, *et al.* , 2015), but healthy humans made riskier decisions (Deuter *et al.* , 2017). Furthermore, an enhanced attentional bias towards negative faces was observed (Schultebraucks K, Wingenfeld K, Otte C, 2016), although unreplicable in a more heterogeneous sample (Nowacki *et al.* , 2021). These findings are compatible with the hypothesis that MR activation stimulates the brain salience network and suggests involvement in appraisal of novel situations, attentional vigilance to salient information, and behavioural flexibility (Vogel *et al.* , 2016).

The salience network is also important for social cognition. Humans often must perform complex social tasks whilst stressed, challenged or in emotionally aroused. Accordingly, several studies demonstrated that psychosocial stress enhanced several aspects of social cognition and prosocial behaviours (von Dawans *et al.* , 2012; Deckers *et al.* , 2015; Wolf 2017). Additionally, MR stimulation was shown to increase empathy scores (Wingenfeld *et al.* , 2014; Nowacki, Wingenfeld, Kaczmarczyk, Chae, Abu-Tir, *et al.* , 2020), adding to a role for MR in adequate and successful social functioning.

Considerations

Pharmacological MR manipulation comes with some considerations. Fludrocortisone binds to some extent to the GR (Agarwal, Coupry and Philippe, 1977; Grossmann *et al.* , 2004). Furthermore, fludrocortisone administration reduces cortisol release (Nowacki, Wingenfeld, Kaczmarczyk, Chae, Abu-Tir, *et al.* , 2020), highlighting MR function in HPA axis feedback regulation, but complicating interpretation, given potential consequences for GR. Fludrocortisone also activates aldosterone-selective MR in the NTS, although, no effects were found on blood pressure (Otte, Wingenfeld, Kuehl, Richter, *et al.* , 2015; Wingenfeld *et al.* , 2015) or aldosterone release (Nowacki, Wingenfeld, Kaczmarczyk, Chae, Salchow,*et al.* , 2020). Spironolactone is known to have effects on PR and progesterone acts as an MR antagonist (Quinkler and Diederich, 2002; Struthers, Krum and Williams, 2008). Therefore, sex specific effects on MR function and cognition must be considered in future studies. Although some studies report none (Piber *et al.* , 2016; Deuter *et al.* , 2017), the consequence of genetic MR haplotypes did depend on sex (M D Klok *et al.* , 2011; Wirz *et al.* , 2017). Notably, age related differences were reported in fludrocortisone effects in major depressive disorder (MDD) patients (see below (Otte, Wingenfeld, Kuehl, Kaczmarczyk, *et al.* , 2015; Otte, Wingenfeld, Kuehl, Richter,*et al.* , 2015)) compared to controls (Hinkelmann *et al.* , 2015).

Overall, increasing evidence strongly suggest MR function as essential for cognitive and emotional function. These MR mediated effects seem to be moderated by age, sex, and potentially other variables. Thus, further research into MR effects is not only warranted in healthy humans but also in patients with stress-related mental disorders who often show alterations in cognitive and emotional function.

Mineralocorticoid receptors in major depressive disorder (MDD) and borderline personality disorder (BPD).

Several mental disorders are characterized by HPA axis dysfunction. In this review, we specifically focus on MDD and BPD as two examples of stress-associated disorders. Historically, research on corticoid receptor function in mental disorders is predominantly focused on GR alterations (Binder *et al.* , 2004; Martín-Blanco *et al.* , 2014). However, variations in the MR gene are commonly associated with negative memory bias, amygdala reactivity, and life adversity in mental disorders (Bogdan, Williamson and Hariri, 2012; Vogel *et al.* , 2016; Vinkers *et al.* , 2015) and altered aldosterone concentrations have been repeatedly found in MDD (Murck H, Büttner M, Kircher T, 2014; Nowacki, Wingenfeld, Kaczmarczyk, Chae, Salchow,*et al.* , 2020). Therefore, an association of the MR function with cognitive and emotional dysfunction is plausible.

Major depressive disorder

MDD is one of the most prevalent mental disorders (Otte *et al.* , 2016). A major depressive episode has depressed mood and/or loss of interest or pleasure as its core symptoms. Cognitive deficits, such as memory complaints and lack of concentration are also frequent in MDD (Bora *et al.* , 2013; Rock *et al.* , 2014) and some studies suggest an association between elevated cortisol and cognitive impairments (Gomez *et al.* , 2006; Hinkelmann *et al.* , 2009). Endocrine features often include increased basal cortisol release, reduced feedback sensitivity and changes in GR function (Holsboer and Ising, 2009; Otte *et al.* , 2016). In addition to high cortisol levels in MDD patients, enhanced aldosterone secretion was reported (Nowacki, Wingenfeld, Kaczmarczyk, Chae, Salchow, *et al.* , 2020), as was decreased MR expression in the hippocampus and prefrontal cortex (Melanie D Klok *et al.* , 2011; Medina *et al.* , 2013; Qi*et al.* , 2013).

Haplotypes of single nucleotide polymorphisms (SNPs) of the MR gene (NR3C2) have been associated with depression (M D Klok *et al.* , 2011) and cognitive function (Keller *et al.* , 2017). An association between MR polymorphisms and emotional memory has been reported in remitted MDD patients (Vrijsen *et al.* , 2015). Interestingly, this association was more prevalent with a history of childhood trauma, which fits nicely to an earlier study in adolescents (Bogdan, Williamson and Hariri, 2012). In general, the gain of function haplotype (CA), by MR-2G/C and MRI180V, has a protective effect in all these aspects.

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Interestingly, cognitive empathy scores were higher in patients with MDD compared with controls in the placebo condition but not after single administration of spironolactone (Wingenfeld *et al.* , 2016). Thus, MR blockade appeared to 'normalise' cognitive empathy in MDD patients. Together, these findings fit to the model presented in figure 3, hypothesizing that enhanced MR signalling due to increased cortisol secretion might be responsible for some aspects of impaired cognition in MDD patients. Future studies should therefore investigate whether treatment with MR antagonists might exert beneficial effects on cognitive symptoms in MDD.

Given that several studies have demonstrated acute beneficial effects on cognition in healthy humans, it is plausible that MR stimulation with fludrocortisone could improve cognitive performance in MDD. A dedicated study found promising initial results: relatively young medication-free patients with MDD as well as healthy control individuals showed improved verbal memory and executive function after one-time administration of fludrocortisone compared with placebo (Otte, Wingenfeld, Kuehl, Richter,*et al.* , 2015). However, a recent study tested if such effects could be extended to depression-related emotionally salient stimuli, but there was no effect of fludrocortisone on selective attention to emotional stimuli or on facial emotion recognition in MDD and healthy controls (Nowacki *et al.* , 2021).

In sum, the available few studies suggest that (acute) MR effects in MDD differ depending on the cognitive

domain that is examined. Further age and sex seem to be important moderators in this respect (Hinkelmann*et al.* , 2015; Otte, Wingenfeld, Kuehl, Kaczmarczyk, *et al.* , 2015). Finally, the MDD population is heterogenous with melancholic, psychotic, or anxious subtypes. Some evidence suggests MR alterations are most pronounced in patients with psychotic symptoms or treatment resistance (Juruena *et al.* , 2013; Lembke *et al.* , 2013).

Borderline personality disorder

Borderline personality disorder (BPD) is characterized by intense and rapidly changing mood states and impulsivity, self-injurious behaviours, fear of abandonment, unstable relationships, and unstable self-image. Early life adversities are highly prevalent and childhood trauma is a major antecedent for BPD. Several studies suggest alterations in the HPA axis in patients with BPD (Wingenfeld and Wolf, 2015) but MR function is mostly neglected in these studies. However, MR and GR sensitivity did not differ in a study between BPD patients and controls (Fischer*et al.* , 2014), albeit with a small sample size. Fludrocortisone treatment led to improved working memory performance in BPD patients (Wingenfeld *et al.* , 2015). In contrast, verbal and visuospatial memory were impaired in BPD women compared to controls (Wingenfeld*et al.* , 2015). Interestingly, an earlier study found the GR and MR activating hydrocortisone to enhance memory retrieval in BPD patients (Wingenfeld *et al.* , 2013). In sum, differences between patients and healthy individuals were only seen in hippocampus-associated cognitive domains.

BPD symptoms are exacerbated by stressful interpersonal events and in patient social cognition and emotional empathy scores deteriorated after stress. Similar to healthy controls, patients had higher emotional empathy scores after MR stimulation (Wingenfeld *et al.* , 2014). However, stress per se impaired social empathy scores. These findings are interpreted as a stress-induced "fight-and-flight" response pattern in BPD patients leading to symptoms such as increased impulsivity as compared to a prosocial behavioural pattern observed in healthy individuals. Thus, the role of the MR in the context of stress effects on social cognition might be of high clinical relevance in BPD.

Endocrine disease and glucocorticoid treatment: Cognitive and emotional *function*

Given the central role that MR and GR play in cognitive and emotional processes as outlined above, it is not surprising that endocrine diseases and long-term steroid treatment are associated with alterations in these processes. While it is often difficult to exactly disentangle MR vs. GR-mediated effects, it is increasingly becoming clear that the MR has an important role in these effects. The support for MR directly effecting mood states stems from the use of potent synthetic glucocorticoids in the clinic, which are accompanied by adverse psychological, behavioural, and cognitive effects (Fardet, Petersen and Nazareth, 2012; Judd *et al.* , 2014). Dexamethasone (DEX) is an example of such potent synthetic GCs and is *in vivo* highly selective for GR (Reul *et al.* , 2000). This strong activation of GR by DEX causes suppression of HPA axis activity leading to a reduction in cortisol levels and consequently depletes MR of its ligand. As such, it is thought that this aberrant increase and decrease in GR and MR activity, respectively, causes disturbances in system homeostasis regulated by the two receptors (Meijer and de Kloet, 2017).

Primary Aldosteronism

Primary Aldosteronism (PA), or Conn's Disease, is characterized by autonomous hypersecretion of aldosterone either due to an aldosterone-producing adenoma or due to bilateral adrenal hyperplasia. A systematic review that included 15 studies (Velema *et al.* , 2017) demonstrated that untreated patients with PA showed lower physical and mental quality of life compared to the general population independent of the cause of PA. Furthermore, PA patients exhibited more psychopathologies including depressive symptoms, anxiety, agitation, and sleep problems. It is likely that overstimulation of central MR by aldosterone contributes to psychopathology in PA (Künzel, 2012). In fact, a recent study demonstrated that adrenalectomy in patients with PA normalized aldosterone secretion, which was associated with improved depressive symptoms (Murck *et al.* , 2021). To our knowledge, no study has specifically examined cognitive function in patients with PA versus a matched healthy control group.

Adrenal insufficiency

Adrenal insufficiency (AI) is characterized by insufficient glucocorticoid and mineralocorticoid secretion and requires replacement therapy with hydrocortisone and fludrocortisone. Several reviews concluded that AI patients exhibited impaired physical and mental health as well as increased psychopathology independent of the aetiology of AI (Hahner *et al.* , 2021). Importantly, several studies have shown that psychopathology, cognition, and quality of life depend on hydrocortisone treatment regimens that closely mimic physiological cortisol secretion and on sufficient MR activation through fludrocortisone (Øksnes *et al.* , 2014; Schultebraucks K, Wingenfeld K, Otte C, 2016). The (interdependent) contributions of MR and GR to these psychopathological symptoms remain however undefined.

Cushing's Syndrome

Separating MR from GR mediated effects is also very challenging in Cushing's syndrome (CS), that is characterized by chronic glucocorticoid overproduction by the adrenal glands. Apart from a plethora of well-known metabolic and cardiovascular complications, there are several neuropsychiatric sequelae of increased endogenous glucocorticoid secretion (Piasecka *et al.* , 2020), as already noted by Harvey Cushing himself (Cushing, 1994). Additionally, brain atrophy due to excessive cortisol secretion has been repeatedly described in CS. Again, considering the important role of MR in emotional and cognitive functions, some of these alterations may be in part mediated by MR. Mifepristone, a GR antagonist, is used clinically in Cushing's. Because of its GR antagonism, it may shift the MR/GR balance towards MR function which may have beneficial effects on depressive symptoms, cognitive function, and metabolic/cardiovascular risk factors (Howland, 2013).

Glucocorticoid treatment

An interaction between GR and MR in humans is likely based on the widespread treatment with synthetic glucocorticoids, that are associated with pronounced psychopathology in a subset of users (Fardet, Petersen and Nazareth, 2012; Judd *et al.* , 2014; Laugesen *et al.* , 2021). In their review Judd *et al* (2012) put forward the hypothesis that an extreme imbalance between GRs and MRs is caused by exogenous glucocorticoids, based on preferential GR binding and suppression of the HPA axis, and that this may underlie cognitive impairment and disturbed emotions by many individuals during glucocorticoid therapy. Based on this hypothesis, it would be plausible to stimulate MR in parallel of very strong GR stimulation during treatment with steroids such as dexamethasone. Indeed, (Warris *et al.* , 2016) examined whether add-on hydrocortisone would ameliorate cognitive and emotional side effects of dexamethasone therapy as part of leukaemia treatment in children. As hypothesized, hydrocortisone attenuated the dexamethasone mental side effects in those individuals that suffered most strongly from mental side effects. This is compatible with the MR/GR balance concept of mental vulnerability to glucocorticoids (Meijer and de Kloet, 2017).

Future perspectives

The role of MR in the initial physiological and behavioural reactions to novel circumstances or stressors, are crucial for an adaptive stress response (Vogel *et al.* , 2016; de Kloet and Joëls, 2017) and, for dynamic and allostatic system homeostasis of the HPA axis (Lightman, Birnie and Conway-Campbell, 2020). There is increasing evidence for an important role of MR function in an effective neuroendocrine response, in signaling cascades for resilience, in the development of psychiatric disease (McEwen, Gray and Nasca, 2015) and even for brain function in hypertensives (Brocca *et al.* , 2017). We did not discuss all roles of MR – e.g., it also plays an important role in pain related pathways. Acute antagonism of membrane bound MR on nociceptive and peripheral neurons produces (non-genomic) antinociceptive effects (Johansson, Hao and Sjölund, 1990; Liu *et al.* , 2007; Shaqura *et al.* , 2016). Perhaps best studied non-genomic MR mediated effects are in the vasculature via aldosterone activated MR pathways and, the interplay with striatin and MR interactomes. MR-STRN3 (striatin 3) interactions (Coutinho *et al.* , 2014) are possibly relevant for key cellular processes in the brain, but regulation of brain vasculature per se may also be relevant (Gomez-Sanchez, 2014; Ruhs *et al.* , 2017).

As described, complementary actions of MR and GR are predominantly regulated by GCs, but the promis-

cuity of MR alludes to sex specific responses, possibly explaining an increased incidence of depression and anxiety in women. The antagonism of MR by its high affinity binding with progesterone as seen from increases during the menstrual cycle or with contraceptives, blunts MR function and causes inappropriate HPA axis activation (Carey *et al.* , 1995), although most MR studies are performed in males. With regards to circuits involved in salt seeking behaviours, cognition and emotion, cell (and region) selective and non-selective brain MRs, that is aldosterone and glucocorticoid preferring cells, innervate to other physiological processes with which the receptor is involved. Such as the aldosterone selective MR neurons of the NTS innervating to GC preferring MRs in the forebrain and mesolimbic cortical dopaminergic pathways of the VTA (de Kloet and Joëls, 2017). Overall, cortisol and aldosterone mediate their effects by targeting cell and region-specific brain MRs, and yet our understanding of aldosterone effects in the brain remains undoubtedly hindered by experimental challenges with the NTS and other brain regions.

Developing the molecular mechanistic underpinnings of brain MR will further define MR biology, and its cell and context specificity requires further teasing out of genomic interactions with its GR companion and other TFs, coregulatory proteins, as well as rapid membrane-mediated actions (van Weert *et al.* , 2017). Extensive prediction of cell-specific MR transcriptional partners should be identified using mass spectrometry-based approaches such as RIME (Papachristou *et al.* , 2018). Likely, these interactions also depend on the specific DNA locus (Meijer *et al.* , 2005; Meijer, Buurstede and Schaaf, 2019), and this may be better understood by combining genome wide MR occupancy with that of different coregulators. Finally, MR variants, as reported with the haplotype 2' (CA) mediated protective action (M D Klok *et al.* , 2011; Vinkers *et al.* , 2015; Hamstra *et al.* , 2017) and epigenetic modifications (Martín-Blanco, A. *et al.,* 2014) require further attention and expansion by researchers, to delineate the mechanisms involved in adaptation and resilience.

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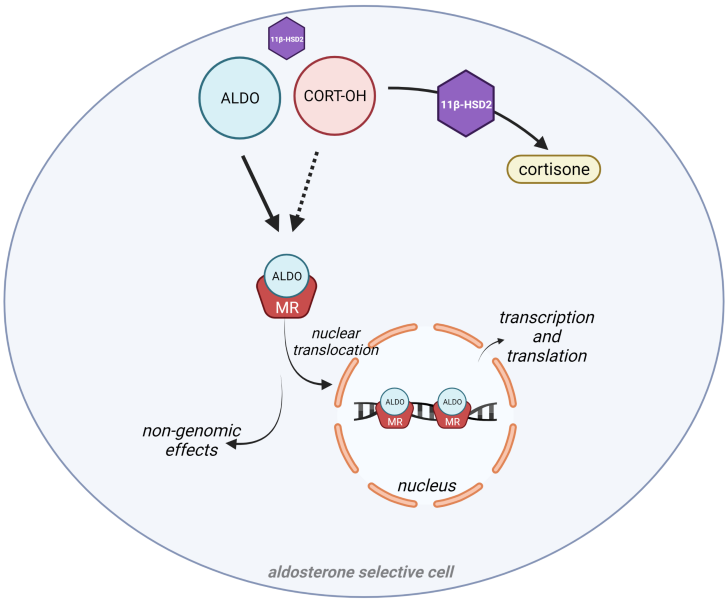
Figure legends

Figure 1. The HPA axis: CRH (and AVP) are secreted from the PVN. These hormones in turn, stimulate the secretion of ACTH from the anterior pituitary, which in turn, drives the secretion of glucocorticoids (cortisol or corticosterone) from the adrenal cortex. Aldosterone selective MRs that mediate behaviours involved in salt appetite are mostly located in neurons of the nucleus tractus solitarii (NTS) and the circumventricular organs. The MR-NTS neurons innervate to limbic forebrain regions, notably the hippocampus and locus coeruleus areas involved in arousal where they reciprocally modulate pathways involved in emotions, memory performance, and reward processing. Created with BioRender.com

Figure 2. In the blood Cortisol (CORT) circulates at 1000-fold higher concentrations than aldosterone (ALDO), but bind with equally high affinity to the MR. This CORT:ALDO ratio is more profound in the brain, which in MR-expressing cells results in CORT occupied MRs, restricting binding by ALDO. However, ALDO selective cells express 11-hydroxysteroid dehydrogenase type 2 (11HSD-2) which converts CORT into its inactive keto variant cortisone. Upon ligand binding, nuclear translocation of MR occurs, enabling rapid non-genomic effects or DNA binding at targeted sequences to exert genomic effects. Created with BioRender.com

Figure 3. Hypothetical model of MR activity in patients with major depressive disorder and healthy individuals and the potential effects of MR blockade.



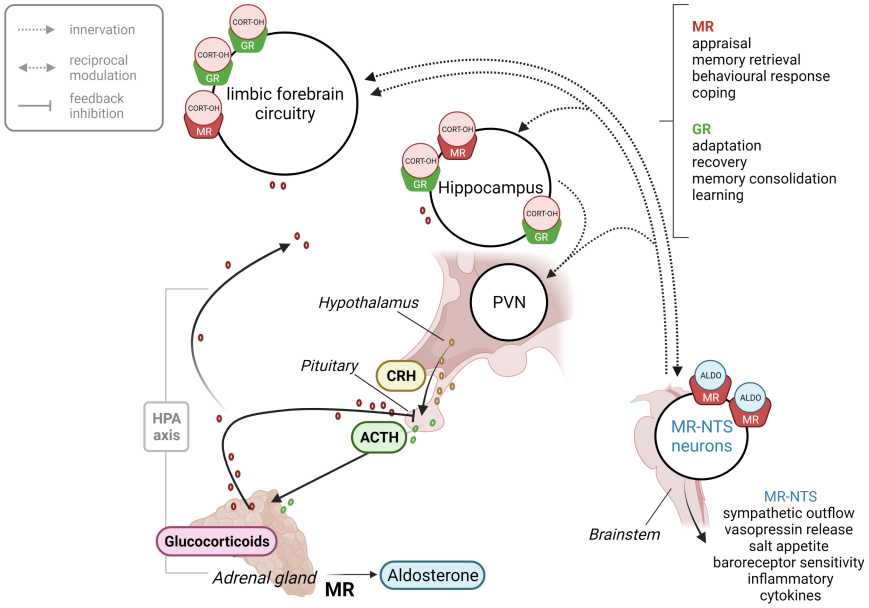


Figure 3