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REVIEW

The brain mineralocorticoid receptor and stress resilience

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Summary Stress exposure activates the HPA-axis and results in the release of corticosteroids which bind to two receptor types in the brain: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). While the role of the GR in stress reactivity has been extensively studied, the MR has received less attention. Nevertheless, pioneering in-depth studies over the past two decades have shown the importance of the brain MR in the processing of stressful information. Moreover, a membrane-bound MR mediating the rapid effects of cortisol was recently discovered. This review summarizes how the MR may play a role in stress resilience. Both preclinical and clinical studies suggest that the MR is an important stress modulator and influences basal as well as stress-induced HPA-axis activity, stress appraisal, and fear-related memories. These MR effects are mediated by both genomic and non-genomic MRs and appear to be at least partially sex-dependent. Moreover, the majority of studies indicate that high MR functionality or expression may confer resilience to traumatic stress. This has direct clinical implications. First, increasing activity or expression of brain MRs may prevent or reverse symptoms of stress-related depression. Second, individuals with a relatively low MR functionality may possess an increased stress susceptibility for depression. Nevertheless, the number of clinical MR studies is currently limited. In conclusion, the recent emergence of the MR as a putative stress resilience factor is important and may open up new avenues for the prevention and treatment of psychiatric disorders.

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Contents

1. Introduction

Exposure to stress results in the release of (nor)adrenaline via the sympatho-adrenomedullary system and the release of corticosteroids via the hypothalamic-pituitary-adrenal (HPA)-axis. Both systems act in concert to enable an individual to successfully adapt to a changing environment (de Kloet et al., 2005). Corticosteroid hormones (cortisol in humans and corticosterone in rodents) ensure that sufficient energy is available and dampen the immune function. At the same time, cortisol exerts negative feedback on the HPA-axis and prevents a damaging overshoot. An efficient and adaptive stress response requires a rapid activation of the HPA-axis after stress exposure but also an effective termination once the stressor has subsided (McEwen, 2004). Prolonged or excessive HPA-axis activity following chronic stress can exceed an individual's allostatic load and may subsequently result in the development of psychiatric and somatic disorders (Juster et al., 2010). Indeed, exposure to traumatic stress is a major risk factor for many psychiatric disorders, including schizophrenia, bipolar disorder, major depressive disorder, and anxiety disorders (Heim et al., 2008).

Corticosteroids bind to two receptors in the brain: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). These receptors operate in a complementary fashion to regulate HPA-axis activity (de Kloet, 2013; Harris et al., 2013). Activation of the GR and MR triggers a signalling pathway involving a cascade of cellular, immunological and physical changes via genomic transcriptional regulation (Joëls et al., 2009). Whereas the GR is expressed throughout the brain, the MR is predominately expressed in limbic areas such as the hippocampus and amygdala (Patel et al., 2001; Reul and de Kloet, 1985; Seckl et al., 1991). In the hippocampus, MRs are co-localized with GRs (Patel et al., 2001). Compared to the GR, corticosteroids have a 10-fold higher MR affinity (Grossmann et al., 2004; Rupprecht et al., 1993). These high-affinity characteristics result in a high MR occupancy rate even under basal (non-stressful) conditions in order to maintain low basal corticosteroid levels through negative feedback (de Kloet and Reul, 1987; Reul and de Kloet, 1985). In contrast, full GR occupancy is only reached when cortisol concentrations peak, for example after awakening or as a result of stress. It is therefore not surprising that the GR has dominated endocrine stress research. With regard to the relation between the MR and GR, both receptors have complementary roles in the regulation of HPA-axis functionality (de Kloet et al., 2007). In contrast to the MR, the genomic GR facilitates recovery and adaptation and normalizes brain functioning some hours after stress exposure when corticosteroid levels have returned to baseline due to negative feedback (Joëls et al., 2012). The high affinity of MR for cortisol has been reason to believe that the MR mainly facilitated GR functionality by binding cortisol rather than having an independent role in stress reactivity. Pioneering in-depth studies over the past

two decades have revealed significant insight how the brain MR operates in the processing of stressful information.

MR-related research was accelerated by the finding that the MR exerts rapid effects on neurotransmission and synaptic plasticity in the hippocampus and the amygdala under stressful circumstances (Karst et al., 2005, 2010). These rapid and non-genomic effects of cortisol appear to be mediated by MRs located at the plasma membrane rather than genomic receptors (Groeneweg et al., 2012; Karst et al., 2010). The discovery of these stress-responsive membrane MRs in the brain has put the MR forward as an important stress moderator. Several reviews have come out over the last decade focusing on the role of the MR in HPA-axis activity and behaviour (Berardelli et al., 2013; Joëls et al., 2008; Reul et al., 2000). Therefore, we review the current evidence for a role of the MR in stress resilience and vulnerability for psychiatric disorders and focus on the existing clinical literature. First, we will briefly discuss the structure and function of the MR. Then, we will summarize preclinical and clinical studies examining the role of the MR in (i) basal and stress-induced HPA-axis activity and (ii) stress appraisal and memory formation. Subsequently, we will outline how the MR may play a role in stress resilience in the context of psychiatric disorders. In addition, we will discuss how sex-dependency may influence the effects of the MR. Finally, we outline how future research targeting the MR may be integrated to more directly benefit psychiatry.

Box 1 The membrane-bound MR

Initial evidence for the existence of a membrane-bound MR was found in an electrophysiological study of hippocampal neurons in which corticosterone rapidly and reversibly altered signalling in pyramidal CA1 neurons (Karst et al., 2005). High levels of corticosterone increased the frequency of miniature excitatory postsynaptic potentials (mEPSC). The MR agonist aldosterone but not the GR agonist RU28362 increased mEPSC frequency, and these effects could be blocked with the MR antagonist spironolactone. Moreover, BSA-corticosterone, unable to pass the cell membrane, increased hippocampal signalling, whereas the translational inhibitor cyclohexidine did not block these corticosterone effects. Qiu et al. (2010) demonstrated that the MR was present in synaptosomal fractions and in purified membranes of the hippocampus. Subsequently, Prager et al. (2010) found MR to be expressed in the lateral amygdala at both nuclear and extranuclear sites including presynaptic terminals, neuronal dendrites, and dendritic spines. Furthermore, MR expression was present on post-synaptic membrane densities of excitatory neurons. This anatomical location of the membrane-bound MR enables this receptor to regulate synaptic plasticity. Also, a membrane-bound MR in the basolateral amygdala rapidly enhances glutamatergic transmission yet, unlike in the hippocampus, this enhancement is long-lasting (Karst et al., 2010). Taken together these studies provide evidence for a membrane-bound MR responsible for facilitating fast synaptic transmission.

2. MR structure and function

2.1. MR function

The MR has received the most attention in its role as a genomic cytoplasmic nuclear transcription factor. Upon corticosteroid binding, the receptor—ligand MR complex translocates to the nucleus, affecting transcription of various genes including growth factors, cell-adhesion molecules and neuropeptides (Gekle et al., 2013; Meinel et al., 2014; Pascual-Le Tallec and Lombès, 2005). Due to the high corticosteroid affinity, most genomic MRs remain occupied during trough levels of the diurnal HPA cycle, compared to 10% of the total GR population (de Kloet and Reul, 1987). As a result, the genomic MR is capable of setting the threshold for HPA-axis activation.

However, cortisol has rapid effects incompatible with genomic pathways (for a review see Tasker et al., 2006). Already from functional behavioural studies, cortisol was found to acutely influence risk assessment (Mikics et al., 2005). Recent breakthroughs have shown that, in addition to the slower genomic effects, the MR is capable of rapidly responding to elevated cortisol levels which has been ascribed to a membrane-bound MR (see Box 1) (Groeneweg et al., 2012; Karst et al., 2005, 2010). In support, the MR agonist aldosterone exerts rapid effects on the HPA axis which can be blocked with an MR antagonist but not with a GR antagonist (Atkinson et al., 2008). Furthermore, cortisol has a reduced affinity for the membrane-bound MR compared to the genomic MR, with 10- to 20-fold higher corticosterone concentrations required to increase hippocampal signalling via the membrane-bound MR (Karst et al., 2005). In this context, the membrane-bound MR may process the rapid effects of stress-induced increased corticosteroid levels and pulses and influence the appraisal of an acute stressful situation in the initial phase (Joëls et al., 2008). In contrast, the genomic MR is thought to have a more regulatory function and determines HPA-axis sensitivity and the threshold for stress reactivity. This discovery of a non-genomic membrane-associated receptor in addition to the 'classic' genomic receptor has increased the importance of the MR as a determinant of stress susceptibility.

2.2. The MR gene (*NR3C2*)

The MR is encoded by *NR3C2* located on chromosome 4 where it spans approximately 450 kB and consists of 10 exons and was first cloned by Arriza et al. (1988). The first two exons 1α and 1β are untranslated and result in two different mRNA isoforms. Exons 3 and 4 code for the DNA binding domain, exons 5—8 and the first part of exon 9 code for the ligand binding domain (Pascual-Le Tallec and Lombès, 2005). Several mRNA splice variants have been described. In humans, the complete MR protein is composed of 983 amino acids and MR diversity results from two translation start sites which lead to the 107 kDa MR-A and the 15 amino acid smaller 105.4 kDa MR-B (Pascual-Le Tallec et al., 2004).

Exonic sequencing of *NR3C2* in fifty individuals from the Dutch population resulted in the identification of several single nucleotide polymorphisms (SNPs) (van Leeuwen, 2010).

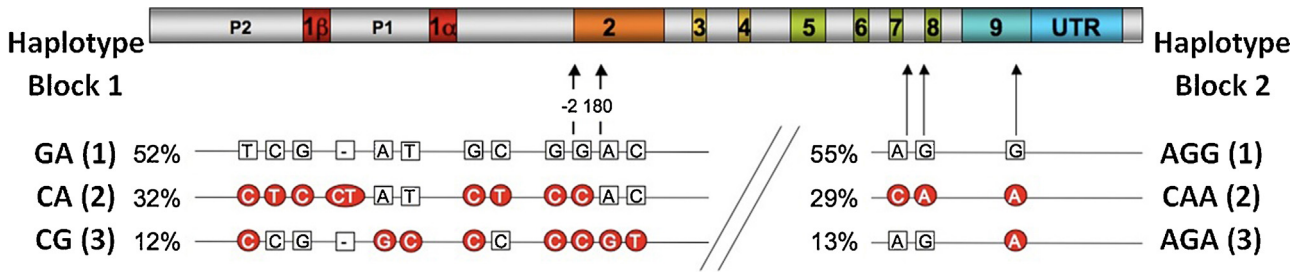

Figure 1 The human MR-gene and two major haplotype blocks. Introns are indicated in grey and the exons (1b, 1a and 2—9) in colour. P2 and P1 are promoter regions. UTR = untranslated region. In the 5′ region three common functional haplotypes have been described, based on two SNP, MR-2C/G (rs2070951) and MRI180V (rs5522). In the 3′ region (exon 9), a second haplotype block is present based on rs5534 and rs2871 from which three (other) common haplotypes can be constructed. Frequencies of the haplotypes are indicated.

Haplotype analyses showed that two common haplotype blocks exist: one in the 5′ region (based on rs2070951 and rs5522) and one in the 3′ region (based on rs5534 and rs2871) (Fig. 1).

In haplotype block 1, MR-2C/G (rs2070951) is located 2 nucleotides before the translation site of exon 2, and MRI180V (rs5522) is located within exon 2 (Table 1). Both SNPs affect in vitro transactivation by altering either MR expression or functionality. MRI180V substitutes isoleucine (A) for valine (G) in the N-terminal of the MR protein and in vitro testing shows that the Val-allele results in a mild loss of function compared to the Iso-allele (DeRijk et al., 2006; van Leeuwen et al., 2011). The MR-2C/G SNP is located outside the MR coding region but inside a Kozac translation regulatory sequence which regulates MR transcription. In vitro, the C-allele results in increased MR expression (van Leeuwen et al., 2010a). MRI180V and MR-2C/G are in low linkage disequilibrium ($r^2 = 0.11$), and the combination of these 2 SNPs results theoretically in 4 MR haplotypes of which three are common in the general population while haplotype 4 has hardly been observed (Table 1) (DeRijk et al., 2008). These haplotypes also influence MR functionality and are frequently used to investigate the effects of common and functional genetic MR variation in clinical studies (Klok et al., 2011b; van Leeuwen et al., 2011). Of these haplotypes, in vitro the GA haplotype (haplotype '1') shows a significant lower maximal transactivation and a lower protein expression compared to the CA and CG haplotype (haplotypes '2' and '3', see Table 1). Additional testing of the promoter region of the three haplotypes in vitro revealed different activities under basal non-stimulated conditions with the GA haplotype (haplotype '2') having the highest activity and the CG haplotype (haplotype '3') the lowest (Klok et al., 2011b). In addition to these three haplotypes, MR diplotypes (specific combinations of haplotypes) could display even additional unexpected regulations and activities (Fig. 2). Taken together, loss of function, changes in translational activity and different promoter activities all contribute to high variability of in vivo MR-expression and activity with regard to these two exon 2 SNPs.

2.3. MR expression

The MR is expressed in different tissues including the kidney, adipose tissue, endothelium, epithelial lining cells and macrophages. Classically, the MR is expressed in epithelial tissue of the kidney (Martinerie et al., 2013). In the kidney, aldosterone (part of the renin—angiotensin—aldosterone

Table 1 Characteristics of MR-2C/G (rs2070951) and MRI180V (rs5522) (A) and the three derived functional haplotypes (B) on which the majority of clinical studies investigating genetic MR variation are based.

A: SNPs

	SNP	Minor allele frequency (%)	Homozygous minor allele carriers (%)	MR functionality in vitro
MR-2C/G	rs2070951	±50 (C)	±25%	↓ for G-allele carriers
MR-II80V	rs5522	±12 (G)	±1—2%	↓ for G-allele carriers

B: MR haplotypes

	Frequency (%)	MR-2C/G	MRI80V	MR functionality
GA Haplotype	50	G	A	Reference
CA haplotype	35	C	A	↑ expression, transactivation and activity (Klok et al., 2011b; van Leeuwen et al., 2011)
CG haplotype	12	C	G	↑ expression and transactivation (van Leeuwen et al., 2011), no changes in activity (Klok et al., 2011b)

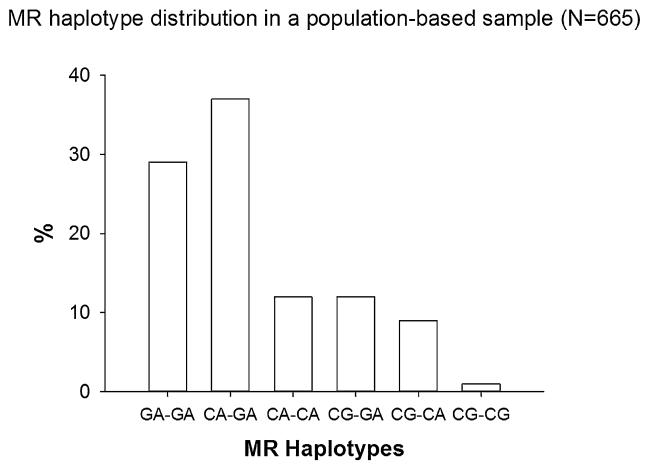

Figure 2 Distribution of MR diplotypes (combination of MR haplotypes) based on rs5522 (and rs2070951) in a population-based cohort (665 healthy individuals) (Unpublished data).

system) is the main endogenous MR ligand with a high MR affinity due to the activity of the kidney enzyme 11-beta hydroxysteroid dehydrogenase type 2 (11β-HSD2) which catabolizes cortisol into the inactive metabolite cortisone. Type 1 11β-HSD is expressed throughout the brain where it is responsible for the regeneration of active cortisol from its inactive 11-keto derivate (for a review on the opposing functions of the 11β-HSD isoforms see Wyrwoll et al., 2011) Aldosterone increases retaining of sodium and water in the renal collecting duct of the kidney (Carey and Padia, 2008). Conversely, aldosterone levels in the brain are very low (over 100-fold) due to the absence of the cortisol converting enzyme aldosterone synthase (Ferrari, 2010). Therefore, cortisol is the main ligand for the brain MR, especially in limbic brain regions. Moreover, extensive MR expression has been described in adipose tissue with a role in adipose tissue development, metabolism as well as the production of pro-inflammatory mediators (Marzolla et al., 2012). In the heart, MR-expression in macrophages was found to be an important factor contributing to ongoing inflammation after a myocardial infarct (Rickard et al., 2009).

MR expression in the brain is largely restricted to neurons in limbic areas such as the hippocampus and amygdala. This contrasts with the GR which is expressed throughout the brain (Reul and de Kloet, 1985).

MR expression has direct protective effects at a neuronal level. MR overexpression reduced neuronal cell death after transient cerebral global ischaemia (Lai et al., 2007), and this effect was reversed with MR antagonists (Macleod et al., 2003). Similarly, cell-lines overexpressing the MR result in higher neuronal survival which could be reversed by knocking down the MR (Munier et al., 2012). Conversely, transgenic mice lacking MR show decreased density of granule cells in the hippocampus and a significant reduction of granule cell neurogenesis (Berger et al., 2006). Moreover, MR blockade by spironolactone dose-dependently increased cell death (Crochemore et al., 2005). Therefore, both in vitro and in vivo studies indicate that the MR is essential to maintain neuronal integrity and promotes neurogenesis. Moreover, MR blockade accentuated GR-mediated apoptosis after co-administration with dexamethasone (Crochemore et al., 2005). Thus, the MR may also have an anti-apoptotic and regulatory role in preventing GR-mediated apoptosis. An interesting phenomenon is the fact that in Brown Norway rats which display long healthy ageing, there is an increased constitutive activation of the MR (Marissal-Arvy et al., 2000). In these rats, a relation was found between a gain-of-function mutation in the MR and the effects of adrenalectomy (Marissal-Arvy et al., 2004).

Together, these neuroprotective properties may provide a neurobiological basis for the putative pro-resilience effects of the MR. Downregulation of the MR in the hippocampus and amygdala could affect neuronal integrity, thereby disrupting limbic system outputs to the hypothalamus and increasing the risk for stress-related psychiatric disorders.

One important factor affecting MR expression is age. Increased age is associated with decreased MR expression, resulting in a loss of HPA-axis inhibition and, consequently, a chronic elevation of cortisol levels (Giordano et al., 2005; Heuser et al., 2000; Van Eekelen et al., 1991). These chronically elevated cortisol levels may play a role in the reduced cognitive functioning seen in the elderly (Yau and Seckl, 2012). Animal studies support the inverse relation between age and MR expression. Aged dogs showed a decrease in septal and hippocampal MR levels accompanied by elevated basal ACTH and cortisol levels (Reul et al., 1991; Rothuizen et al., 1993), and ageing in rats decreased MR mRNA expression in the hippocampus and hypothalamus paired with a progressively attenuated but prolonged corticosterone stress response (Van Eekelen et al., 1991; Workel et al., 2001). It is currently unclear whether age-related changes in MR expression influence the risk for stress-related psychiatric disorders. Moreover, GR expression — and therefore also the GR/MR balance — may also play a role in age-related effects of the HPA-axis. Indeed, age-related changes in GR mRNA levels have been found in the human brain (Perlman et al., 2007). Nevertheless, age-induced decreases in MR expression were positively correlated to age-dependent impairments in spatial memory (Yau et al., 2002a). Interestingly, amitriptyline treatment in young rats increased hippocampal MR, but not GR, expression and simultaneously increased spatial memory whilst the same treatment had no significant effect in aged rats (Yau et al., 1995). This supports the hypothesis of an age-induced decrease in MR functionality which has implications for the use of MR agonists in the treatment of elderly patients. Furthermore, long-term treatment with amitriptyline in relatively young rats (16 months old) until they were aged (24 months) prevented cognitive impairments and reduced anxiety-related behaviours in aged rats (Yau et al., 2002b). Together, these data suggest that MR expression is vital for neuronal survival and an adequate HPA-axis functionality. Reduced MR expression may therefore affect an individual resilience potential and increase the risk for detrimental outcomes after stress exposure.

3. The MR and HPA-axis activity

3.1. Preclinical studies

Several preclinical studies have investigated the involvement of the MR in HPA-axis functionality. First,

pharmacological studies using MR antagonists have demonstrated a role for the MR in basal HPA axis activity (Bradbury et al., 1991; Ratka et al., 1989). Moreover, mice lacking forebrain MR display enhanced and prolonged corticosterone levels in response to restraint stress, indicating that forebrain MR may specifically inhibit stress-induced HPA-axis activity (Ter Horst et al., 2012b). In these mice, basal corticosterone levels were only slightly elevated (Ter Horst et al., 2012b) or did not significantly differ (Berger et al., 2006). Apparently, loss of the forebrain MR leads to increased stress-induced corticosterone levels but does not affect basal levels. In contrast, overexpression of MR in the forebrain was associated with similar basal and stress-induced HPA axis activity in male mice (Lai et al., 2007; Rozeboom et al., 2007), but in female transgenic mice, restraint stress resulted in a moderate suppression of corticosterone levels (Rozeboom et al., 2007). Moreover, overexpression of the MR in the basolateral amygdala resulted in lower stress-induced plasma corticosterone levels in MR-overexpressing animals with no effect on basal corticosterone levels (Mitra et al., 2009). Interestingly, overexpression of forebrain MR rescued the overshoot in HPA-axis activity seen in mice with a reduced GR expression. The combination of high forebrain MR and an overall reduced GR expression restored HPA-axis activity under stressful conditions, implying that in the case of reduced GR activity, an increase in MR activity functions to normalize stress-induced HPA-axis activity providing evidence that the two receptors work in a complementary fashion to promote an adequate coping style (Harris et al., 2013). Also, the selective MR antagonist spironolactone (but not a GR antagonist) could reverse blunting of the endocrine stress response after repeated restraint stress in rats (Cole et al., 2000). However, not all studies are consistent. For example, male and female mice lacking the MR in the entire limbic system showed normal corticosterone levels at circadian trough and peak as well as after 40 min of restraint stress (Berger et al., 2006).

In rodents, studies show that the relation between MR expression and stress reactivity is bidirectional in that stress exposure can also affect MR expression. These effects appear to be dependent on the duration of the stressor. Acute stress increased hippocampal MR expression which peaked after 24 h and subsequently decreased over a period of 48 h (Gesing et al., 2001). This increase was found to be functional in restraining the HPA axis. Even after a single bout of physical exercise, a decrease in hippocampal MR expression was observed within 30 min (Chang et al., 2008). These results show that MR expression is highly dynamic which has important consequences at least for neuroendocrine control. In contrast, chronic unpredictable stress caused a 20% decrease in hippocampal MR mRNA compared to a control group (Lopez et al., 1998), and chronic corticosterone administration reduced hippocampal MR but not GR expression (Wu et al., 2013).

Together, even though results of rodent studies are not completely consistent, the majority of rodent studies shows that MR effects particularly emerge under stressful circumstances. In response to stress, increased MR expression is associated with a blunted endocrine stress response. Since genomic MRs are substantially occupied under non-stress conditions, non-genomic MRs may be involved in regulation of the cortisol stress response.

3.2. Clinical studies

3.2.1. Basal HPA-axis activity

Clinical studies investigating the relation between MR functionality and HPA-axis activity have recently emerged and complement the existing preclinical literature (DeRijk et al., 2011). The majority of these studies have focused on common and functional genetic variation in the MR based on rs5522 and rs2070951 (Table 1 and Fig. 1).

With regard to basal HPA-axis activity, G-carriers of the MR-2C/G allele (rs2070951) display higher basal cortisol levels accompanied by an increased cortisol awakening response (CAR) (Muhtz et al., 2011). Conversely, C-carriers have lower basal cortisol levels (Kuningas et al., 2007) and an attenuated CAR (Klok et al., 2011c). Consistent with these studies, MR haplotypes containing the C-allele of rs2070951 (the CA and CG haplotype, see Table 1) are associated with increased MR expression (Klok et al., 2011c; van Leeuwen et al., 2011). Thus, in C-allele carriers, a higher MR expression may enhance tonic inhibition and result in lower basal cortisol levels. However, not all studies have shown consistent results. In a cohort of 218 healthy volunteers, no significant effect of rs5522 and rs2070951 were found on the CAR (van Leeuwen et al., 2010b). Nevertheless, following 0.25 mg dexamethasone administration, a sex-specific modulation suppression was found in this study for rs5522 (blunted suppression in homozygous male A-carriers) and rs2070951 (enhanced female suppression and impaired male suppression in G-carriers), suggesting that MR effects may be sex-dependent and become visible under challenging (dexamethasone) conditions (see Section 6).

3.2.2. Stress-induced HPA-axis activity

Several clinical studies have investigated whether MR effects are also present following stress exposure. In a study of 166 school teachers, the CA MR haplotype was associated with an increased endocrine stress response as measured by ACTH and both blood and saliva cortisol levels (van Leeuwen et al., 2011) (Table 1). Increased stress reactivity was accompanied by lower perceived stress levels. In contrast, GA haplotype-carriers displayed a blunted endocrine stress response. However, not all studies have found significant effects for these two SNPs on stress reactivity. First, no significant effects of rs5522 and rs2070951 were found on the cortisol stress response in adolescents (Bouma et al., 2011). The effects of haplotypes were not investigated in this study. Second, the I180V SNP (rs5522) did not significantly influence stress-induced cortisol levels in 64 healthy individuals (Ising et al., 2008), and the rare CG haplotype (largely driven by I180V) did also not alter the endocrine stress response in the above mentioned high school teacher cohort (van Leeuwen et al., 2011). In contrast, in 110 male twins, Val-carriers of I180V consistently displayed an increased cortisol stress response after repeated exposure to the Trier Social Stress Test (DeRijk et al., 2006). Discrepancies across these I180V studies should be interpreted in light of the relatively small minor allele frequency of rs5522 (12% frequency) (Table 1),

and larger sample sizes may be required to detect consistent and meaningful differences.

Interestingly, stress-related effects of genetic MR variation are not limited to the endocrine system. Both the GA haplotype (van Leeuwen et al., 2011) and rs5522 (DeRijk et al., 2006) influenced stress-induced heart rate levels, indicating that MR SNPs can influence the autonomic stress response. Another illustration of the far-reaching effects of MR functionality is an fMRI study in which Val-carriers of the MRI180V SNP showed a greater threat-related amygdala reactivity (Bogdan et al., 2012). In this study, childhood neglect selectively increased amygdala reactivity in Iso-carriers, suggesting that the impact of traumatic stress on the brain is moderated by genetic variation in the MR.

3.2.3. Drug-induced HPA-axis activity

Pharmacological studies have also pointed to a pivotal role of the MR in regulating HPA-axis activity. First, MR antagonists such as caneroate (Arvat et al., 2001; Wellhoener et al., 2004) and spironolactone (Cornelisse et al., 2011; Deuschle et al., 1998; Otte et al., 2007; Young et al., 1998) increase basal cortisol levels. Because ACTH levels are generally not affected, this effect is probably the result of an altered HPA-axis threshold. Chronic MR antagonism with caneroate for 28 days yielded similar results with increased basal cortisol levels but no changes in ACTH levels (Berardelli et al., 2010). Vice versa, fludrocortisone, which activates both the GR and MR but has a much higher MR affinity (Grossmann et al., 2004), inhibits the HPA-axis and subsequently decreases basal cortisol levels (Otte et al., 2003a). In this study, metyrapone (which inhibits the production of endogenous cortisol) was co-administered to minimize the impact of basal endogenous cortisol secretion and to ensure sufficient reactivity of the otherwise substantially occupied MR. Effects of fludrocortisone on the HPA-axis activity via GR activation were considered unlikely as fludrocortisone does not suppress morning cortisol levels, a process which is mainly GR-related (Otte et al., 2003a). Furthermore, fludrocortisone inhibits HPA-axis activity, in both healthy controls and depressed patients, regardless of whether basal endogenous cortisol secretion is inhibited with metyrapone (Buckley et al., 2007; Wingenfeld et al., 2014). This suggests that, even though the MR is largely occupied during circadian nadir trough levels, further MR activation is still possible after administration of an exogenous MR agonist. Extrapolating these findings to the field of stress would suggest that MR-mediated modulation of HPA-axis activity is still possible during stress exposure. In support, stress-induced increases in cortisol after the Trier Social Stress Test are enhanced after administration of the MR antagonist spironolactone (Cornelisse et al., 2011).

It is important to notice that pharmacological manipulation of the MR appears to be age-dependent. First, MR activation with fludrocortisone induces a stronger cortisol decrease in younger individuals compared to older subjects, suggesting an impaired MR-related negative feedback (Otte et al., 2003b). Similarly, administration of the MR antagonist canrenoate results in stronger HPA-axis activation in young individuals compared to older ones (Giordano et al., 2005). These studies are consistent with age-related effects on MR expression levels (see Section 2.3). Therefore, age-induced reductions of MR expression may lead to a more active but less dynamic HPA-axis which could subsequently disproportionally increase the risk for stress-related disorders. However, studies linking age and MR functionality in the context of psychiatric disorders are lacking.

3.3. Summary

In summary, preclinical and clinical studies point to a role for the MR in basal and stress-induced HPA-axis activity. Thus, MR functionality is probably important for an adaptive and dynamic HPA-axis. The dampening MR effect on HPA-axis activity under stressful conditions may be the result of an excitatory threshold of hippocampal MRs acting on inhibitory hypothalamic interneurons. Subsequently, stress-induced increases in corticosteroids may strengthen inhibition and result in a blunted endocrine stress response. However, clinical studies suggest that the MR can also affect basal cortisol levels. Moreover, clinical studies also indicate that an altered MR expression and/or functionality is associated with changes in drug-induced cortisol levels. However, the evidence is inconsistent across studies and not all studies have found significant MR effects. Several factors may explain discrepancies across studies, including (i) differences in sex and age (ii) unaccounted variation by traumatic stress exposure and a history of psychiatric disorders, (iii) methodological differences, e.g. in the applied stress test and the use of single SNPs or haplotypes, (iv) relatively small sample sizes.

4. The MR and stress-related appraisal and memory

Different stages of memory processing in the brain are generally distinguished: encoding, consolidation, retrieval of the memory, and finally, reconsolidation. Stress can (positively or negatively) influence all of these memory stages but these effects depend on several factors, for example whether stress exposure occurs before or after a memory-related process and the interval between stress and testing (for reviews see Joëls et al., 2006; Schwabe et al., 2012). For memory formation, stress exposure prior to learning can either enhance or weaken this process depending on the time interval between the stressor and learning as well as the emotional load of the stressor. Consolidation is typically enhanced by stress, whereas stress prior to retention tests generally impairs memory retrieval. In light of the stress effects on memory, suboptimal HPA-axis functionality may be involved in memory impairments which exist in several psychiatric disorders (Wingenfeld and Wolf, 2011).

In light of its close involvement in HPA-axis activity (see Section 3), a role for the MR in regulating stress-related learning and (fear) memories is biologically plausible. Several lines of converging evidence have implicated the MR in stress-related memory processes. First, the MR antagonist spironolactone impaired long-term potentiation (LTP) formation and even induced long-term depression in stressed animals (Avital et al., 2006). In contrast, administration of the GR antagonist RU38486 prior to stress produced a striking LTP facilitation and indicated that the MR and GR exert an opposing influence on hippocampal plasticity.

Moreover, using intracellular recording techniques, MR activation induced opposite effects to the GR on after-hyperpolarization of rat CA1 pyramidal neurons (Joëls and de Kloet, 1990), including a suppression of 5-HT-induced hyperpolarization (Joëls et al., 1991), indicating different and even opposing effects on neuronal activation.

Second, several behavioural rodent studies show that the MR is involved in memory. MR-overexpressing mice display improved spatial memory (Lai et al., 2007) and enhanced consolidation of non-spatial memory (Ferguson and Sapolsky, 2007). In contrast, the MR antagonist spironolactone reduced context fear, indicating that the MR is pivotal for contextual memory retrieval and formation (Zhou et al., 2011). Conversely, mice lacking limbic MR expression show impaired learning (Ter Horst et al., 2012a) and working memory deficits as a result of behavioural perseverance (Berger et al., 2006). Moreover, MR antagonists directly influence the spatial learning strategy in response to novelty (Oitzl and de Kloet, 1992; Oitzl et al., 1994).

Third, studies on the MR antagonist spironolactone have shown that the MR mediates many different aspects of stress-related memory formation. In a cohort of 64 young men, administration of the MR antagonist spironolactone prior to stress exposure (but not prior to the control condition) resulted in short-term working memory impairments but enhancement of long-term memory (Cornelisse et al., 2011). Thus, MR blockade combined with increased cortisol levels impairs working memory, and this may be the result of a relative increase in GR binding. In addition, spironolactone administration prevented stress-induced increases in response inhibition, suggesting a role for the MR in this process (Schwabe et al., 2013a). Similarly, spironolactone also prevented stress-induced and MR-mediated switch from hippocampus-based learning (explicit knowledge) to striatum-based learning approach (procedural) which is needed to preserve memory performance during and shortly after stress (Schwabe et al., 2013b). In support, Val-allele carriers of the I180V SNP — associated with reduced MR functionality — showed a deficiency in stress-induced reward learning (Bogdan et al., 2010). Thus, a decreased MR functionality may have detrimental effects on stress-related learning. Consequently, this could increase the risk of fear generalization as is commonly found in anxiety disorders.

The MR is also important for the adequate appraisal of stressful situations. This effect is closely related to the effects on memory because both processes are the result of MR-related learning plasticity (de Kloet et al., 1999; Oitzl et al., 1994). After appraisal of a novel situation, an appropriate learning strategy is selected which determines memory formation. Subsequently, formed memories will influence appraisal in future stressful situations. As such, appraisal and memory formation function in a complementary fashion to ensure an adaptive behavioural response when faced with a stressor.

The MR facilitates stress appraisal by an appropriate evaluation of contextual influences. For example, MR antagonism was found to alter search patterns in the Morris water maze without affecting retention times per se (de Kloet et al., 1999; Oitzl et al., 1994). Similarly, mice lacking the forebrain MR showed alterations in exploratory behaviour indicative of impaired acquisition of novel information (Arp et al., 2014). Moreover, these mice could not distinguish between cue-related and context-related freezing in a fear conditioning test (Brinks et al., 2009). When mice are exposed to stress and a switch to stimulus-response learning is required, pre-treatment with the MR antagonist RU28318 prevents this switch (Schwabe et al., 2010; Ter Horst et al., 2012b), suggesting a role for the MR in spatial memory formation and the appraisal of novel situations. Moreover, aggressive behaviour during a conflict in rats for violent aggression appeared to be mediated through the brain MR (Kruk et al., 2004, 2013). In this experimental design, the initial corticosterone response facilitated the learning of aggressive behaviour in a MR-dependent fashion. This is a lasting effect which could only be blocked by spironolactone during the first aggressive encounter but not during a follow up aggressive encounter. Together, these data suggest that the MR is involved in appraisal and learning of long lasting behaviour.

A recent study in 483 healthy participants showed that *NR3C2* variance was associated with negative memory bias, especially in individuals with a history of life adversity (Vogel et al., 2014). Specifically, this interaction was significant for the functional exon 9 haplotype block (based on rs5534/rs2871), but not for the exon 2 haplotype block (rs5522/rs2070951). Particularly, homozygotic A-carriers of rs5534, associated with increased microRNA-induced repression of MR expression, showed a significant increase in negative memory bias. The relation between impaired regulation of MR expression and enhanced memory formation for sad and pessimistic information indicates that an altered MR functionality can negatively influence memory formation during stressful situations. Together, these studies underscore that MR functionality is important for contextual recognition and the subsequent correct appraisal of a stressful situation. In this context, reduced MR activity or expression may result in a suboptimal assessment of a stressful situation and increase the risk for dysfunctional cortisol regulation and persisting fear and anxiety symptoms after stress exposure.

With regard to the MR effects of stress on memory, both genomic MRs and non-genomic MRs are involved (Chauveau et al., 2010). For example, the protein synthesis inhibitor anisomycin was unable to reverse corticosterone-induced memory deficits in young rats during the water maze task, indicating that cortisol-induced impairment of long-term memory retrieval is regulated via non-genomic pathways (Khaksari et al., 2007). In this study, the MR antagonist spironolactone but not the GR antagonist RU38486 was able to reverse this effect. Similarly, a study using BSA-bound corticosterone, which cannot pass the cell membrane, induced memory retrieval deficits which can be reversed by an MR antagonist but not a GR antagonist (Dorey et al., 2011). Therefore, it appears that the membrane-bound MR also mediates stress-induced effects on memory processes.

Even though this paragraph focused on stress-induced learning processes, it is important to notice that the MR also affects learning strategies under non-stressful circumstances. For example, the MR is required for an optimal spatial learning strategy in the circular hole-board test under basal conditions (Arp et al., 2014), while in humans

MR blockade by spironolactone impaired selective attention under non-stressful conditions (Otte et al., 2007). Furthermore, MR stimulation with fludrocortisone improved verbal memory in both healthy controls and depressed patients (Wingenfeld et al., 2014).

Although stress-induced memory formation is a complex process, several studies indicate that the MR plays an important role in mediating appraisal as well as memory formation and retrieval. Memory formation seems to be enhanced via genomic MRs, whereas retrieval of long-term memory during acute stress seems to be hampered by non-genomic MRs. It may be hypothesized that these MR receptor types act in concert, allowing the formation of new memories relevant to the stressful situation. In this context, an optimal MR functionality may be pivotal for an adequate memory formation and appraisal during stress. Therefore, a decreased MR functionality could have detrimental effects on stress-related learning and impair the appraisal of stressful situations. These MR effects on stress appraisal are plausible in light of the selective MR expression in the limbic system which forms the interface between incoming sensory information and the selection of a learning strategy.

5. The MR and susceptibility for psychiatric disorders

5.1. General

So far, we have summarized the evidence for a role of the MR in basal and stress-induced HPA axis activity, stress-related appraisal, and memory formation. This begs the question what the implications are for the development and course of stress-related psychiatric disorders. This topic is also relevant in light of the overwhelming number of studies reporting either blunted or excessive HPA-axis activity in psychiatric disorders such as anxiety disorders, mood disorders, and schizophrenia (Spijker and Van Rossum, 2012). We therefore expect that the MR plays a role in stress resilience and vulnerability. Consequently, variation in MR expression or functionality may, at least partially, determine the likelihood that an individual will develop a psychiatric disorder after exposure to (traumatic) stress. Here, we will discuss the evidence linking the MR to susceptibility for psychiatric disorders.

5.2. MR expression in psychiatric disorders

Several postmortem studies have investigated MR expression in psychiatric disorders which have yielded quite consistent results (see Table 2A). Compared to non-depressed subjects, postmortem analysis of brains of MDD patients showed a decrease in MR mRNA expression in the hippocampus (Klok et al., 2011a; Medina et al., 2013), inferior frontal gyrus, and cingulate gyrus (Klok et al., 2011a). The same result was found in a study examining hippocampal MR expression of suicide victims (Young et al., 1998). Similarly, patients with schizophrenia and bipolar disorder showed a decrease in expression of MR mRNA in the dorsolateral prefrontal cortex (Qi et al., 2013; Xing et al., 2004). In the same study, MR mRNA levels were negatively correlated with the duration of the psychiatric illness, indicating that a longer duration of disease was associated with a further decrease of MR expression. In contrast, one study found an increase of MR expression in the paraventricular nucleus (PVN) of the hypothalamus in MDD which may compensatory to reduced hippocampal and cortical MR expression (Wang et al., 2008). Overall, psychiatric disorders seem to be consistently accompanied by a loss of MR expression in limbic areas independent of psychiatric diagnosis. Such a decrease in MR expression would result in a reduced MR-mediated tonic inhibition which in turn could chronically elevate cortisol levels, increasing the risk for MDD after stress exposure. This may also be related to secondary changes in other neurotransmitter systems such as the 5-HT system (Karten et al., 1999). In support, data from preclinical studies show that various classes of antidepressants (among which MAO inhibitors, selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants (TCAs)) consistently increase hippocampal MR expression in rodents (Bjartmar et al., 2000; Lopez et al., 1998; Reul et al., 1994; Seckl and Fink, 1992; Yau et al., 1995) (Table 2B). This effect is, in part, dependent on the duration of antidepressant treatment as it has been shown that, in contrast to long-term treatment, shorter treatment (9 days) with either fluoxetine or venlafaxine decreased MR mRNA expression in all hippocampal subregions (Yau et al., 2001). In the context of the relation between the MR and antidepressants, it is interesting that the effects of rs2070951 on the CAR in 1026 individuals from a Dutch longitudinal cohort occurred only in individuals taking SSRIs (Klok et al., 2011c). Moreover, MR expression in the hippocampus affects 5-HT_{1A} receptor expression (Rozeboom et al., 2007). Therefore, clinically used antidepressants, by increasing MR expression, could restore an adequate HPA-axis functionality, behavioral response, and enhance recovery from depression (Zobel et al., 1999).

5.3. MR-related HPA-axis functionality in psychiatric disorders

Mood disorder patients commonly display blunted HPA-axis suppression after administration of the GR agonist dexamethasone (for a review see Spijker and Van Rossum, 2012). In contrast, prednisolone — which has comparable GR and MR affinity — appears to suppress HPA-axis activity to a similar extent in both MDD patients and healthy controls (Juruena et al., 2010). Moreover, the MR antagonist spironolactone significantly enhanced HPA-activity in MDD patients compared to healthy controls, despite the chronically elevated cortisol levels in these MDD patients (Young et al., 2003). Conversely, there was diminished feedback inhibition of the HPA-axis in response to the MR agonist fludrocortisone in MDD patients compared to healthy controls (Lembke et al., 2013). Therefore, the current evidence suggest that, even though MR expression may be decreased in MDD, brain MRs can still alter HPA-axis activity after a pharmacological challenge, and this may be even enhanced in MDD. Nevertheless, in post-traumatic stress disorder patients, no changes in MR functionality were found using a combined metyrapone-fludrocortisone test, indicating that

Table 2 MR expression in the brain of individuals with a psychiatric disorder (A) and effects of antidepressant treatment on MR expression in the rodent brain (B).

A: Psychiatric disorders and MR expression in the human brain

Psychiatric disorder (*N*)	Brain region	MR expression	Reference
MDD (12)	Hippocampus, inferior frontal gyrus, and cingulate gyrus	Decreased (30%)	Klok et al. (2011a)
MDD (18)	Anterior hippocampus	Decreased (28%)	Medina et al. (2013)
Suicide victims (12)	Hippocampus	Decreased (37%)	Lopez et al. (1998)
Schizophrenia, bipolar disorder (49)	Dorsolateral prefrontal cortex	Decreased (20%)	Xing et al. (2004)
Bipolar disorder and MDD (14)	Anterior cingulate cortex and dorsolateral prefrontal cortex	Decreased (38%)	Qi et al. (2013)
MDD (14)	Hypothalamus	Increased (54%)	Wang et al. (2008)

B: Antidepressant use and MR expression in the rodent brain

Antidepressant	Brain region	MR expression	Reference
Buspirone, fluoxetine, and moclobeminde	Hippocampus	Increased for all 3 antidepressants (27—37%)	Bjartmar et al. (2000)
Amitriptyline, desipramine, and citalopram	Hippocampus	Increased for all 3 antidepressants (23%)	Seckl and Fink (1992)
Desipramine	Hippocampus	Reversal of stress-induced decreases in MR	Lopez et al. (1998)
Moclobemide	Hippocampus, hypothalamus and neocortex	Increased (hypothalamus 19—76%, neocortex 24—44%), unchanged (hypothalamus)	Reul et al. (1994)
Amitriptyline	Hippocampus	Increased (17—28%)	Yau et al. (1995)

differences and variability may exist across psychiatric disorders (Otte et al., 2006).

5.4. Genetic MR variation and susceptibility for psychiatric disorders

Surprisingly, the number of studies linking genetic MR variation to susceptibility for psychiatric disorders is scarce. A recent study showed that the CA haplotype, resulting in an increased MR activity (see Table 1), was associated with enhanced resilience to depression in females from a the Dutch NESDA cohort study ($N = 3523$) (Klok et al., 2011b). In two other independent cohorts, this haplotype was associated with a higher dispositional optimism ($N = 450$) and fewer thoughts of hopelessness ($N = 150$) (Klok et al., 2011b). Consistently, Val-allele carriers of rs5522, decreasing MR activity, displayed an increased vulnerability for depressive symptoms in elderly individuals (Kuningas et al., 2007). Therefore, functional MR haplotypes in exon 2 of *NR3C2* not only affect HPA-axis functionality but also have behavioural consequences and subsequently influence the risk for psychiatric disorders. In these studies, the effects of traumatic stress have not been investigated which may be relevant since MR-related depression susceptibility may particularly emerge after exposure to (traumatic) stress.

5.5. The MR as a drug target in psychiatric disorders

From the previous paragraphs, it is apparent that several lines of evidence generally support a decreased MR expression or functionality in mood disorders. Therefore, increasing MR could constitute a possible treatment for MDD as well as other psychiatric disorders. In support, fludrocortisone administration in both healthy woman and in woman suffering from borderline personality disorder improved the emotional empathy (Otte et al., 2014). This suggests that the MR may play a more general role in emotion processing and mood across psychiatric disorders.

For MDD, there is convincing evidence that the MR plays an important role. A recent double-blind placebo-controlled randomized clinical trial indeed showed that MR activation with fludrocortisone as an add-on treatment in 64 MDD patients receiving treatment with the SSRI escitalopram showed an accelerated antidepressant response of approximately 6 days in the responder group. Escitalopram responders receiving fludrocortisone showed decreasing cortisol levels which could possibly explain the accelerated antidepressant effects (Otte et al., 2010). This corresponds with findings from Holsboer showing that the MR antagonist spironolactone decreased the antidepressant effects of the TCA amitriptyline (Holsboer, 1999). Furthermore,

add-on treatment with metyrapone, a cortisol synthesis inhibitor, enhances effectiveness of antidepressant medication which was hypothesized, to be at least partially due to metyrapone-induced upregulation of hippocampal MRs (Jahn et al., 2004). In summary, there are indications that directly or indirectly enhancing MR functionality exerts antidepressant effects. Nevertheless, this effect was only apparent in escitalopram responders but not in escitalopram-resistant patients (Otte et al., 2010). As a result, impaired MR function may predict non-response to antidepressant treatment. In support, SSRI responders in two studies showed an intact MR functionality in response to the prednisolone suppression test, whereas non-responders displayed impaired MR functionality (Juruena et al., 2006, 2009). Also, the absence of restoration of HPA-axis response to the MR antagonist spironolactone in treatment-resistant MDD patients supports the notion that treatment resistance may be associated with impaired MR functionality (Juruena et al., 2013). In this case, further stimulation of the MR may not be possible and fludrocortisone may not be effective in treatment-resistant depression. Interestingly, MDD patients with early life stress showed suppression of salivary cortisol levels in response to the MR agonist fludrocortisone and the GR agonist dexamethasone, indicating comparable MR and GR sensitivity (Baes et al., 2014). In contrast, MDD patients without early life stress, dexamethasone but no fludrocortisone suppression was found.

Nevertheless, chronic aldosterone treatment in rats increased anxiety and induced depressive-like phenotypes (Hlavacova and Jezova, 2008; Hlavacova et al., 2012). This would suggest that excessive MR stimulation leads to an increased vulnerability for anxiety and depression (Murck et al., 2012), even though chronic aldosterone treatment did not induce basal or stress-induced HPA-axis activity. An additional complicating factor is the fact that MR activation under pro-inflammatory conditions in cardiac tissue increases cardiac fibrosis. The MR antagonist eplenorone exerts protective, anti-inflammatory effects and reduced apoptosis in myocytes not only at the level of the heart but also via the brain MR (Rafatian et al., 2014). This indicates different mechanisms of brain MR with regard to psychopathology as opposed to pro-inflammatory effects of MR stimulation. Clearly, these seemingly opposing effects should be taken into account during clinical application of MR agonists or antagonists.

5.6. Summary

In summary, evidence for a role of the MR in vulnerability and resilience for psychiatric disorders stems from several lines of evidence: postmortem studies, pharmacological manipulations, genetic studies and treatment studies. These consistent findings are not surprising as a maladaptive stress response and impaired HPA-axis functionality commonly occur in psychiatric disorders. Therefore, it seems plausible that, in addition to a role in orchestrating an optimal stress response, increased MR functionality is also associated with resilience to MDD. However, studies directly investigating the moderating role of the MR in the relation between traumatic stress and the development of psychiatric disorders are lacking.

6. Sex-dependent effects of the MR: an overlooked but important topic

From the previous paragraphs, it may have appeared that the role of the brain MR is rather straightforward. However, sex differences in MR effects are frequently reported in preclinical and clinical studies. These sex-dependent effects are plausible from a biological perspective in light of the affinity of the female steroid hormone progesterone for the MR (Carey et al., 1995; Quinkler et al., 2002). Furthermore, oestrogen (Turner, 1990) and progesterone (Castrén et al., 1995) can both influence MR expression levels. Recently the oestrogen receptor was found to inhibit transactivational effects of the MR in several cell types (Barrett Mueller et al., 2014). This could account for the decreased occurrence of cardiovascular diseases in premenopausal woman. Even though often overlooked, consistent sex differences exist in the cortisol stress response which is dependent on female hormones (Kudielka and Kirschbaum, 2005). These sex differences are important in light of consistent gender differences in the prevalence of stress-related psychiatric disorders (Cyranowski et al., 2000; Piccinelli and Wilkinson, 2000). Here, we will summarize the current evidence for sex-dependent MR effects in preclinical and clinical studies.

6.1. Preclinical studies

Preclinical studies support a sex-dependent regulation of MR expression with subsequent behavioural consequences. First, basal circular hole board performance was influenced by the estrous cycle in female mice lacking forebrain MR compared to wildtype mice (Ter Horst et al., 2013). Moreover, in contrast to males, female mice lacking the forebrain MR were unable to extinguish fear memory (Ter Horst et al., 2012a). Furthermore, hippocampal MR but not GR expression was increased in female mice after 14 days of restraint stress, whereas male rats showed a limited MR downregulation but a strong GR downregulation (Karandrea et al., 2000). In both cases, the result is an increased MR:GR ratio in both sexes. Comparably, after 21 days of chronic stress, male rats showed decreased GR expression but no changes in MR expression in the hippocampal CA1 region (Kitraki et al., 2004). In contrast, female rats showed an increased MR expression in the CA3 region but also an increase in GR expression in the CA1 region. The increase in MR expression was accompanied by an improved memory performance. In another study, maternal deprivation and chronic unpredictable stress resulted in distinct sex-dependent effects on MR and GR hippocampal expression in adulthood, with maternal deprivation inducing long-term GR downregulation in males (Llorente et al., 2011). In adult rats, chronic or excessive stress seems to increase hippocampal MR expression in females but decrease GR expression in males. In contrast, chronic unpredictable stress in young rats sex-dependently affected MR expression but in an opposite manner, with female rats showing MR downregulation but MR upregulation in male rats. An explanation of the discrepancy is the fact that rats were stressed at young age (4 weeks) and sacrificed 47 days later at reached adulthood. The previous studies used adult rats which were sacrificed directly after stress exposure (Karandrea et al., 2000; Kitraki et al., 2004).

This delay in sacrifice offers a time frame in which further alteration of expression is possible. In summary, even though not completely consistent, these studies support the view that a high degree of sex-dependent MR (and GR) plasticity exists in the hippocampus in response to stress.

6.2. Clinical studies

In addition to the preclinical evidence, a number of clinical studies have pointed to sex-dependent MR effects in humans. First, as previously discussed, resilience to depression associated with the MR CA haplotype only emerged in females (Klok et al., 2011b). Moreover, dexamethasone suppression of the CAR was highest in female carriers of the GA haplotype whereas male GA haplotype carriers showed an attenuated suppression (van Leeuwen et al., 2010b). Also, female but not male homozygotic C-carriers of rs2070951 possessed an attenuated CAR increase (Klok et al., 2011c). Sex differences also exist for MR mRNA levels in the human hippocampus, with higher concentrations in women compared to men (Watzka et al., 2000). However, not all studies show similar sex-dependent effects (Kuningas et al., 2007; Muhtz et al., 2011; van Leeuwen et al., 2011). Therefore, sex effects relating to MR functionality and expression in humans appear to be subtle, diverse and are not yet fully understood.

6.3. Summary

Based on preclinical and clinical studies, the dynamics of MR functionality seems to be of particular importance in females. In female rats, loss of MR induces memory deficiencies whilst an increase in expression of the MR is associated with resilience to depression in humans. The binding of female sex hormones directly to the MR, a direct interaction with oestrogen or modulation of MR-expression by oestrogen and progesterone could explain these sex-dependent effects (Barrett Mueller et al., 2014). Even though an interaction between female steroid hormones and the MR is evident, it is currently unknown how female hormones modulate MR-related HPA-axis activity and to what extent these effects modulate the risk for stress-related psychiatric disorders (for a review see Fernandez-Guasti et al., 2012).

Nevertheless, future research on the role of the MR in stress vulnerability and resilience should take sex-specific effects into account. Considering that women have an increased risk for mood disorders compared to men, sex-dependent MR effects could, in part, play a role in these sex differences.

7. Discussion

An adaptive stress response is essential to remain healthy and overcome the detrimental consequences of stress. Both the MR and GR are important in determining HPA-axis activity, stress coping and, ultimately, an individual's vulnerability for psychiatric disorders. However, whereas GR has been extensively studied, it only paints half of the picture. Although the genomic brain MR has a high affinity for cortisol and is largely occupied under basal non-stress conditions, it is clear that the MR also plays a significant role during stressful conditions via non-genomic MRs and the effects of genomic MRs in setting the threshold of the HPA axis. Therefore, even though the MR and the GR work in a complementary fashion to promote an adequate coping style, the MR is equally important as the GR.

In summary, there is convincing evidence that the MR directly affects basal and stress-induced HPA-axis activity and stress-related appraisal and learning in both animals and humans. From the literature, an increased MR expression or functionality seems to result in enhanced stress resilience which reduces the risk for psychiatric disorders. In accordance, patients with MDD generally show a reduced MR expression. Therefore, it may be argued that an increase in MR functionality contributes to a more adaptive stress response and will be associated with an increased ability to cope with stressors. In contrast, a decrease in MR functionality may lead to a maladaptive stress response and consequently increase an individual's vulnerability for the effects of chronic stress. The discovery of a membrane-bound MR has further expanded the importance of the MR in the stress response as this receptor type has a distinct function from the genomic MR (see Box 1). The role of the membrane-bound MR for memory retrieval and memory formation during stressful situations is relevant since malfunctioning of memory formation alters appraisal of stressful situations and can increase the likelihood of developing psychiatric disorders.

Moreover, sex differences play an important role in the endocrine and behavioural effects of the MR and are of direct relevance in light of the consistent sex differences in the prevalence of stress-related psychiatric disorders. Age also affects MR expression, and this is directly relevant for sex-dependent MR effects considering the menopause. Additionally, the finding that both (traumatic) stress and age affect MR functionality is of interest in light of the long-lasting but heterogeneous MR effects of traumatic stress across different developmental stages of life (Pryce, 2008). MR expression is not constant across the life span, and stress during certain sensitive periods may particularly affect MR expression and increase the risk for psychopathology. To integrate the different aspects of the MR in the relation between stress, the HPA-axis, and psychopathology, Fig. 3 summarizes the proposed interactions between factors in shaping the risk for psychiatric disorders.

If an increase in brain MR expression promotes resilience to depression, it is reasonable to assume that enhancing MR functionality may be used as a potential new drug target in the treatment of psychiatric disorders (Kellner and Wiedemann, 2008). Currently, only a few studies have been published in which an MR agonist was used as add-on treatment for depression (see Section 5.5), but no large RCTs have to our knowledge been carried out. Even though the MR may constitute a promising drug target, the applicability of MR agonists is not without problems in light of the effects of MR activation in the kidney and its role in inflammation. This effect poses a challenge for the direct applicability of synthesized (selective) MR agonists in the treatment of psychiatric disorders.

In addition to the MR as a possible drug target, genetic variation in the MR may play a role in the prediction who are at risk for psychiatric disorders following stress

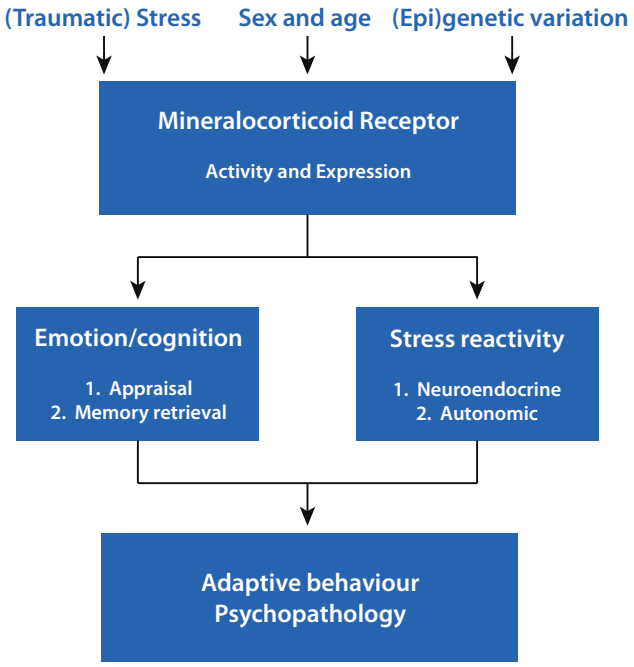

Figure 3 Overview conceptualizing how the MR influences resilience or vulnerability. MR activity and/or expression appear to be at least dependent on sex and age, (epi)genetic variation and exposure to (traumatic) stress. The MR is an important stress modulator and influences stress appraisal and fear-related memories. Moreover, the MR is involved basal and stress-induced HPA-axis activity, determining both the threshold and the magnitude of the stress response. In light of these MR effects, MR functionality or expression can influence adaptive behaviour and susceptibility for psychiatric disorders. Cortisol is the main ligand for the brain MR since aldosterone levels in the brain are very low (over 100-fold) due to the absence of the cortisol converting enzyme aldosterone synthase.

exposure. For example, common and functional MR haplotypes have not only been found to influence HPA-axis activity and stress appraisal, but also the risk for depression. As such, the MR genotype, in part, could determine the risk for stress-related disorders. However, our knowledge on the interplay between different relevant factors is currently limited, and sex and age probably play a role as well. There is also some preliminary evidence that genetic MR variation could also influence treatment efficacy for MDD. For example, SSRI use affected cortisol levels related to genetic variation of rs2070951, suggesting that genetic MR variation and SSRI use are interrelated (Klok et al., 2011c). On the other hand, antidepressants induce MR expression (see Section 5.2) which may be one of the mechanisms underlying the effects of antidepressants.

In conclusion, there is increasing and convincing evidence from fundamental, preclinical, and clinical studies that genomic and non-genomic brain MRs are important in health and disease. These results have put the MR forward as a principal mediator of the impact of stress in the brain. An adequate functionality of brain MRs allows individuals to successfully adapt to a stressful environment. MR functionality may therefore, in turn, determine the resilience potential of an individual. In contrast, maladaptive changes in MR expression and functionality in the context of stress can increase the risk for psychiatric disorders. Even though there is some evidence that targeting the MR in humans may have potential benefits, either as a genetic risk factor or as a possible pharmacological treatment target, our current knowledge is still limited. Further elucidation of neurobiological pathways underlying MR-related resilience is necessary to identify who is at risk and to enhance early intervention strategies.

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