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Review article

Importance of the brain corticosteroid receptor balance in metaplasticity, cognitive performance and neuro-inflammation

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ABSTRACT

Bruce McEwen's discovery of receptors for corticosterone in the rat hippocampus introduced higher brain circuits in the neuroendocrinology of stress. Subsequently, these receptors were identified as mineralocorticoid receptors (MRs) that are involved in appraisal processes, choice of coping style, encoding and retrieval. The MR-mediated actions on cognition are complemented by slower actions via glucocorticoid receptors (GRs) on contextualization, rationalization and memory storage of the experience. These sequential phases in cognitive performance depend on synaptic metaplasticity that is regulated by coordinate MR- and GR activation. The receptor activation includes recruitment of coregulators and transcription factors as determinants of context-dependent specificity in steroid action; they can be modulated by genetic variation and (early) experience. Interestingly, inflammatory responses to damage seem to be governed by a similarly balanced MR:GR-mediated action as the initiating, terminating and priming mechanisms involved in stress-adaptation. We conclude with five questions challenging the MR:GR balance hypothesis.

1. Introduction

Fifty years ago, Bruce McEwen discovered that receptors in hippocampal neurons retain with high affinity circulating ^{3}H-corticosterone injected as an 0.5 μg tracer dose into adrenalectomized male rats (McEwen et al., 1968). That discovery expanded the Science of Neuroendocrinology into higher brain circuits. Also about half a century ago the first volumes of Frontiers in Neuroendocrinology appeared that were edited by Luciano Martini and William F. Ganong. It is therefore important that this Frontiers issue is dedicated to Bruce as one of the founders of Neuroendocrinology.

The identification of corticosterone receptors in the hippocampus sparked a dynamic research field: the neuroendocrinology of higher brain regions involved in coordination of emotional expressions and cognitive performance (McEwen, 2017; McEwen et al., 2016, 2015). It appeared that for this purpose the naturally occurring glucocorticoid hormones corticosterone and cortisol activate during stress a dual receptor system. First, the high affinity mineralocorticoid receptors (MRs) previously discovered by Bruce, and next, the glucocorticoid receptors (GRs) that become gradually occupied by stress-induced rising hormone concentrations (Reul and de Kloet, 1985; Joëls and De Kloet, 1992a,b; Oitzl and de Kloet, 1992). These MR:GR-mediated actions need to be in balance for maintenance of homeostasis and health (see Box 1 The dexamethasone story).

Previously, Selye (1950) had formulated the 'pendulum' hypothesis to describe the opposing actions of 'pro-phlogistic' mineralocorticoids and 'anti-phlogistic' glucocorticoids. The MR:GR balance hypothesis states that these opposing actions by two hormones can be achieved by actually one single class of hormones: the naturally occurring glucocorticoids cortisol and corticosterone. The recognition of such MR:GR interplay supports the view that glucocorticoids on the one hand seem to mediate the initial stress response (Selye, 1946), while on the other hand – as Munck et al. (1984) argued- glucocorticoids can prevent the initial stress reactions from an overshoot that may become damaging. Or, as the Dutch endocrinologist Marius Tausk defined already in 1952 metaphorically the potent synthetic glucocorticoids as '*agents limiting the water damage that has been caused by the fire brigade*' (Tausk, 1952). In a well-cited review the actions of glucocorticoids were further

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categorized as permissive, stimulatory, suppressive and preparative to deal with upcoming stressors, depending on physiological endpoint (Sapolsky et al., 2000).

In this contribution we will start with some of the early neuroendocrine and behavioural studies that led to the recognition of the complementary MR:GR-mediated actions (de Kloet, 1991, 2014; de Kloet et al., 1998, 2005; Joëls and de Kloet, 2017). Then, we will argue that at the neuronal level 'corticosterone metaplasticity' of the basolateral amygdala may explain how, as a function of time and context, resources can shift from limbic MR-driven neuronal networks underlying emotions and rapid coping decisions towards slower GR-dependent cognitive processes aimed to rationalize, contextualize and store the experience in the memory (Karst et al., 2010; Karst and Joëls, 2016; Vogel et al., 2017; Joëls et al., 2012). The ratio in MR:GR-mediated phases of stress-adaptation is biased by MR gene variants and (early) stressful experiences (Sutanto et al., 1996; Klok et al., 2011a; Wirz et al., 2017).

On the molecular level, a major breakthrough has been the identification of rapid non-genomic MR- and GR-mediated actions (Karst et al., 2005). These non-genomic actions were discovered with electrophysiology, and, in spite of encouraging results (Olijslagers et al., 2008), so far no clear molecular basis of these rapid responses has been defined. The genomic MR- and GR-mediated actions are much better understood because of the identification of DNA sequences that bind the receptors. Transcription factors and co-regulators have been identified that confer specificity to MR- and GR-mediated actions depending on other stimuli characteristic for the environmental context. Novel data will be presented on the role of the NeuroD transcription factor and coregulators assigning such a context-dependent genomic specificity of MR and GR (Lachize et al., 2009; van Weert et al., 2017).

Perhaps, at first glance somewhat beyond the scope of stress, neural circuits and behavior, we report recent data showing that the hippocampus of the deoxycorticosterone acetate (DOCA)-salt treated rat is damaged in a similar way as that of the spontaneous hypertensive rat (SHR). This is to illustrate that there are also aldosterone-selective MRs in discrete brain regions and vascular endothelial cells that drive both the rise in blood pressure and the damage-induced microglial inflammatory response (Brocca et al., 2017). These data support pioneering work by (Frank et al., 2015) on pro- and anti-inflammatory actions of glucocorticoids and the subsequent generation of inflammasomes. It seems therefore that glucocorticoid actions via MR and GR on inflammation proceed along similar initiating, terminating and priming phases as the mechanism underlying the influence of stress on cognitive performance.

2. Mineralocorticoid and glucocorticoid receptors

It is well established that the naturally occurring glucocorticoids cortisol and corticosterone can activate both MRs and GRs in e.g. the rodent, dog and human brain (Reul and de Kloet, 1985; Sutanto and De Kloet, 1987; Reul et al., 1990; Seckl et al., 1991). The mapping of these receptors became feasible with immunocytochemistry and in situ hybridization upon their cloning in the mid 1980s (Arriza et al., 1987). It turned out that both receptors are expressed in neurons, glia's and vascular endothelial cells, but to a variable extent (Tanaka et al., 1997; Davel et al., 2017). MRs are abundantly expressed in limbic neurons, notably the hippocampus, lateral septum and amygdala (Arriza et al., 1988; van Eekelen et al., 1991; Ahima et al., 1991). GRs are more widely expressed with highest level in the typical stress-regulating centers such as the PVN, the PFC-hippocampal – amygdala circuitry and the ascending aminergic neuronal networks. Yet, within these regions, there is differential expression over time; for instance, GR immunoreactivity is highly expressed the first week of life in hippocampal CA3 and suprachiasmatic neurons, but then fades from these regions in later life (Van Eekelen et al., 1987, 1991; Cintra et al., 1994).

Box 1

The dexamethasone story: a personal note of ERdK.

When ERdK forwarded an air mail to Bruce McEwen in the fall of 1971 that in his experiments the uptake of dexamethasone did not match that of tritium labeled corticosterone in brain but rather preferred to accumulate in the pituitary, the return mail two weeks later said: "*Please forgive me a personal inquiry: are you by any chance a relative of Dr. Siwo de Kloet, a biochemist now at Florida State University? I ask because he is also from Maarssen and was here at Rockefeller approximately 10 years ago*." Indeed Bruce was in 1961 a student working with my brother at Rockefeller; also it appeared that I already had met Bruce as early as 1964 when "the American with backpack" was visiting us in The Netherlands. This event is, therefore, ingrained in my memory as a corner stone of my career. It was a prelude to my postdoc period from 1973 to 1975 at the Rockefeller University. During that time we found that low doses of dexamethasone indeed target the pituitary rather than the brain (de Kloet et al., 1974, 1975). Twenty years later it appeared that the hampered penetration of dexamethasone in brain was due to a multidrug resistance P glycoprotein in the blood brain barrier (de Kloet, 1997; Meijer et al., 1998). Also, in 1975 we had the idea that in brain, corticosterone receptors are distinct from those for dexamethasone. Ten years later this idea materialized in the description of the brain MR and GR (Reul and de Kloet, 1985). Thus, dexamethasone treatment inhibits the HPA axis and leaves the MR devoid of endogenous glucocorticoids. Currently, we test the hypothesis that refill of MR will minimize dexamethasone adversity in brain (Meijer and de Kloet, 2017). The dexamethasone story has been the root of a productive research field and a lifelong friendship. "*Bruce is Bruce, a sincere and important person to know*" according to Efrain Azmitia (personal communication), his very first PhD student. He could not have said it better.

Receptor activation depends on the corticosterone concentration in rat brain, which reflects the amount of free circulating hormone, i.e. not bound to corticosteroid binding globulin (CBG; Droste et al., 2008). MRs are promiscuous and bind with high affinity to a range of steroids, including the mineralocorticoids aldosterone and deoxycorticosterone, and also progesterone (McEwen et al., 1976; De Nicola et al., 1981; Krozowski and Funder, 1983). Aldosterone circulates in a 10–100 fold lower concentration than cortisol or corticosterone. An assessment of immunoreactive steroid in purified cell nuclei of the rat hippocampus revealed a tenfold higher amount of corticosterone than aldosterone under basal conditions. This nuclear ratio of corticosterone over aldosterone further increases towards the circadian peak, when corticosterone starts to occupy GRs. During stress the exposure of hippocampal MRs to corticosterone relative to aldosterone is even further increased towards 100 over 1 (Yongue and Roy, 1987). Accordingly, the brain MR mainly is exposed to corticosterone, which binds with a 10-fold higher affinity to MR than GR (Reul and de Kloet, 1985; Reul et al., 1987). In pharmacological doses aldosterone and corticosterone can mutually block each other's cell nuclear retention in the hippocampus, further underscoring their competition for the same MRs (de Kloet et al., 1983). As mentioned, corticosterone and cortisol are the main ligands for (non-epithelial) brain MR and GR.

On top of this difference in circulating hormone levels, the 11β-hydroxysteroid dehydrogenase (HSD) type 1 reductase regenerates bioactive glucocorticoid hormone making hippocampal cells truly corticosterone and cortisol responsive. When 11-HSD-type 2 is co-expressed, the glucocorticoids are inactivated and the MR becomes responsive to

aldosterone. Such 11-HSD-2 expressing cells exist in brain and are discreetly distributed, but abundant in the n. tractus solitarii (NTS), in circumventricular neurons and also in the vascular endothelial cells (Geerling and Loewy, 2009; DuPont and Jaffe, 2017). The aldosterone-responsive network is the substrate of the autonomous outflow in the central regulation of cardiovascular function (de Kloet et al., 2000; Gomez-Sanchez and Gomez-Sanchez, 2014; Evans et al., 2016). The aldosterone-MR governed projections arising from the NTS and the circumventricular organs innervate forebrain networks including the PVN, hippocampus, amygdala, n. accumbens and the bed nucleus of stria terminalis, which are also a target of corticosterone (Geerling and Loewy, 2009). The crosstalk between the aldosterone-selective network and the limbic corticosterone-preferring network may explain the arousal, motivation and spatial clues used in the search for salt, the sense of satiation and the switch from appetite to disgust when excess salt is being ingested (see Section 5; Krause and Sakai, 2007; Geerling and Loewy, 2009; de Kloet and Joëls, 2017).

Then, two additional points can be made. First, the action of corticosteroids shows a wide diversity in different cells; this is perhaps not surprising because the hormone's physiological function is to promote stress-adaptation by coordinating and integrating various processes. Second, the hormone acts conditional, i.e. occurs when the membrane potential is shifted from its resting level (Joëls and de Kloet, 1992a) or when tissue damage has triggered an inflammatory reaction (Brocca et al., 2017). As will be shown in Section 6 the co-regulators and interacting transcription factors are extremely important for understanding the context-dependent conditional steroid effects.

2.1. Neuroendocrinology

The HPA axis – and its corticosteroid end products - has two modes of operation: to coordinate circadian events and to promote stress-adaptation (Oster et al., 2016). Within the circadian cycle corticosterone displays an hourly (ultradian) rhythm, which helps to maintain responsiveness of its targets (Sarabdjitsingh et al., 2010). Studies agree that MR antagonists given in mg amounts to rats increase basal ultradian- and stress-induced corticosterone levels by increasing the amplitude of the secretory bouts. In contrast, GR antagonists prolong the duration of corticosterone response to stress (Ratka et al., 1989; Dallman et al., 1989; Young et al., 1998). This disinhibition of the HPA axis occurs with a 100,000 fold lower doses when the antagonists are given intracerebroventricularly (icv; Ratka et al., 1989; van Haarst et al., 1997). Mutants with forebrain overexpression of MRs showed a reduced stress-induced HPA axis activity peak, and also a prolonged duration if the mice are heterozygous for a null allele of GR (GR +/−), which expresses half of the GRs normally present in brain (Harris et al., 2013). These findings have led us to postulate that the MR exerts a tonic inhibitory influence on HPA axis activity, which determines the threshold of reactivity of the axis during stress.

Site-specific conditional knockout of GR in the pituitary corticotrophs disinhibits HPA axis activity early postnatally, but is not effective in adulthood (Schmidt et al., 2009). This observation reinforces the notion that pituitary GRs are protected from corticosterone by intracellular CBG molecules. This barrier is bypassed by dexamethasone, which explains why the synthetic glucocorticoid targets the pituitary in blockade of stress-induced HPA axis activity (de Kloet et al., 1977). However, also rapid non-genomic glucocorticoid feedback has been reported at the level of the pituitary and even in the adrenals (Dallman et al., 1972; Russell et al., 2010; Walker et al., 2015; Deng et al., 2015).

Conditional deletion of GR from the CRH-producing cells in the PVN of the mouse caused increased and prolonged stress-induced corticosterone levels and disrupted metabolism (Laryea et al., 2013). If GRs were deleted from extrahypothalamic limbic regions, corticosterone secretion was generally higher and more prolonged. This disinhibition of HPA axis activity occurred while memory storage of the stressful experiences was prevented (Oitzl et al., 2001; Laryea et al., 2015). The GR antagonist mifepristone (RU486) did not affect basal HPA axis activity because of only little GR occupation during the circadian trough. During stress, mifepristone increased and prolonged stress-induced HPA axis activation systemically and icv, but when given intrahippocampal the antagonist inhibited the axis. This effect might be caused because blockade of the GRs leaves MRs occupied which inhibits HPA axis activity (van Haarst et al., 1997). MRs and GRs also interact in the control of the circadian rise in HPA axis activity (Spencer et al., 1998).

Thus, MRs are involved in basal activity and onset of stress-induced HPA axis activity and GRs in its termination. Regarding termination, several levels of feedback regulation can be distinguished (Dallman, 2011) and the circuitry involved has been documented with great precision (Herman et al., 2016), more recently by using e.g. optogenetic approaches (Johnson et al., 2016; de Kloet et al., 2017). In our version: first, the rapid or rate sensitive feedback involving GR-regulated, non-genomic actions at the pituitary and brain level (Russell et al., 2010; Dallman, 2005; Hill and Tasker, 2012). Second, an intermediate feedback action that occurs with a delay of 30 min to several hours in the PVN and its afferent pathways, probably as part of the behavioural adaptation repertoire (de Kloet, 2014). Third, a slow- and long-lasting feedback that seems more concerned with regulation of the HPA axis setpoint and involves both MR and GR-mediated epigenetic processes in the PVN (Elliott et al., 2010) and its afferents (Hunter et al., 2012). Finally, the genomic pituitary GR which seems to function rather as an emergency brake in response to extremely high corticosterone/cortisol levels. This pituitary GR is the principal site of action of synthetic glucocorticoids such as dexamethasone (de Kloet et al., 1974).

2.2. Behavior

Glucocorticoids administered to rodents post-learning promote consolidation of tasks that are motivated by reward or fear (see Section 3.4, for time- and context dependency). This includes retention of the acquired immobility response in the forced swim test, the memory storage of an escape route in the Morris water maze, or of the spatial map required for collecting a reward in a hole board configuration, and fear-motivated behaviors (de Kloet et al., 1999; Joëls et al., 2012). These effects exerted by the steroids are mediated by GRs. They involve corticosterone action on (i) the hippocampus to preserve the spatial and temporal coordinates of context and (ii) noradrenergic and dopaminergic pathways to boost the emotional experience and to assign a certain valence to (and in humans to rationalize) the experience. Memory storage is impaired when GRs are deleted in the amygdala or hippocampus. Memory impairment also occurs when GR antagonists are administered icv or locally in the hippocampus in doses that are 100,000 fold lower than when given systemically. For this purpose the antagonists need to be given immediately after learning, prior to consolidation (Micco et al., 1979; de Kloet et al., 1999; Rodrigues et al., 2009; Roozendaal and McGaugh, 2011; Luksys and Sandi, 2011; Schwabe et al., 2012).

GR activation after the 24 h retest of a contextual fear paradigm facilitates extinction, a finding that was first reported by Bela Bohus (Bohus and Lissák, 1968) in the late sixties. Such extinction occurs because of the subsequent re-appraisal of the context at retest 24 h later. The re-appraisal implies that fear-motivated behavior is no more relevant in absence of the cue. Glucocorticoids facilitate reconsolidation of this new experience, and thus facilitate extinction (Cai, 2006). There is some debate in the literature regarding 'memory impairment' if glucocorticoids were given briefly prior to the retrieval session (de Quervain et al., 1998; de Kloet et al., 1999). In this debate is context a critical determinant; stress or glucocorticoids signal threats, which makes the retrieval of previously learned behavioural responses less relevant (Sandi et al., 1997; de Kloet et al., 1999). Other experiments revealed that memory retrieval rather depends on rapid MR-mediated actions, and is blocked by MR antagonists (Oitzl and de Kloet, 1992; Khaksari et al., 2007; Dorey et al., 2011). It cannot be excluded that

excess GR activation causes a similar impairment of MR function by depletion of endogenous ligand (Rimmele et al., 2013).

Obviously unaware of today's expert behavioural studies, we wondered around 1980 how we could exploit the – at that time – peculiar binding specificity of the hippocampal corticosterone receptors. In these early experiments we used a *forced extinction* paradigm. This implies that the animal was exposed to a mild electric shock in an inhibitory (passive) avoidance apparatus. Common practice was then to measure the latency to re-enter the compartment 24 h later when the animal was placed on the attached brightly lit tray. This generates a conflict in the animal between the choice to deal with either one of the two threats: light vs electric shock. This conflict is affected by MR manipulation (Souza et al., 2014). However, if the animal is returned in the shock compartment at 3 h after cue exposure, allowing exploration of the shock-compartment (context) for 5 min without experiencing the electric shock, the inhibitory response was entirely extinguished the next day (hence forced extinction when exposed to context only). Adrenalectomy 1 h prior to context exposure at 3 h post-shock eliminated the effect of forced extinction, which was re-instated again with a low dose of corticosterone (systemically or icv) replacement at the time of adrenalectomy; dexamethasone, progesterone, deoxycorticosterone and aldosterone were not effective and even could block the normalizing effect of corticosterone (Fig. 1). Accordingly, we concluded at the time that the corticosterone-dependent re-appraisal of the context during the forced extinction procedure likely was mediated by the 'corticosterone' receptors (Bohus and de Kloet, 1981) which we now know are the MRs.

In 1992, Melly Oitzl, (Oitzl and de Kloet, 1992) was the first to demonstrate in male rats that MRs- and GRs mediate in a coordinated manner the storage of spatial information. To arrive at this conclusion, she used the Morris water maze and showed that adrenalectomy (but not removal of the adrenal medulla only) impaired memory storage of spatial information. Memory storage was also impaired when tested 24 h after icv administration of the GR antagonist mifepristone given immediately after the learning trial; the GR antagonist was not effective when given 15 min prior to the retrieval session. The MR antagonist icv did not affect consolidation of the spatial information, but interfered with retrieval if given 15 min before the retest. The animals not only took more time to locate the escape platform, but when the platform was removed – the so-called *probe trial* – they also used an alternative strategy. While the control animals remained in the quadrant where originally the platform was located, the group treated with the MR antagonist icv switched to another strategy and explored the space to find an alternative escape route. A similar switch in behavioural strategy was observed in ADX animals where obviously MR is not activated.

In subsequent experiments, Melly Oitzl and Lars Schwabe (Schwabe et al., 2010) used another spatial test for hippocampus function: the so-called circular hole board paradigm in which the rat could spatially access a hole to locate a reward. The animals could use either a hippocampal based spatial strategy by using distal cues to locate the reward or a specific stimulus in the form of a sign (i.e. a bottle) placed nearby the reward. Once the animals had learned the task, the stimulus was switched to another location. After an acute restraint stress or a corticosterone injection, part of the animals exhibited a switch from the hippocampal spatial- to a striatal stimulus–response strategy; if these animals were pretreated with the MR antagonist the switch from spatial *thinking* to striatal *doing* did not occur (see Section 3.4; Schwabe and Wolf, 2013). However, these results were obtained with male animals; female rats actually performed better in spatial learning and memory processes after stress (ter Horst et al., 2013a; ter Horst et al., 2013b) reinforcing the notion of profound sex differences in brain function. See for review (Hamson et al., 2016).

Thus, it was proposed that the action on behavior is mediated in a complementary manner by MRs and GRs. Indeed GR deletion from the dentate gyrus or central amygdala impaired the conditioned fear response and direct application of a GR antagonist in the dentate gyrus interfered with the memory storage of acquired immobility in the forced swim test (Arnett et al., 2011; de Kloet et al., 1988; de Kloet and Molendijk, 2016). Also, in a series of studies from the Sapolsky lab using viral delivery of genes in the dentate gyrus of rats the potential benefit of increasing MR signaling or decreasing GR signaling was demonstrated for specific aspects of cognitive function (Mitra et al., 2009; Ferguson and Sapolsky, 2008; Dumas et al., 2010). Fig. 2 depicts a temporal sequence of events under control of MR and GR from the onset towards termination of the stress response followed by priming of the brain in preparation of the future (see also Sections 3.4,5 and 7).

2.3. The MR:GR balance hypothesis

Based on receptor properties and the outcome of cellular and behavioural studies (see also Section 3), the MR:GR balance hypothesis was formulated. This hypothesis states that "*upon imbalance of the MR- and GR-mediated actions, the initiation and/or management of the stress response becomes compromised. At a certain threshold this may lead to a condition of neuroendocrine dysregulation and impaired behavioural*

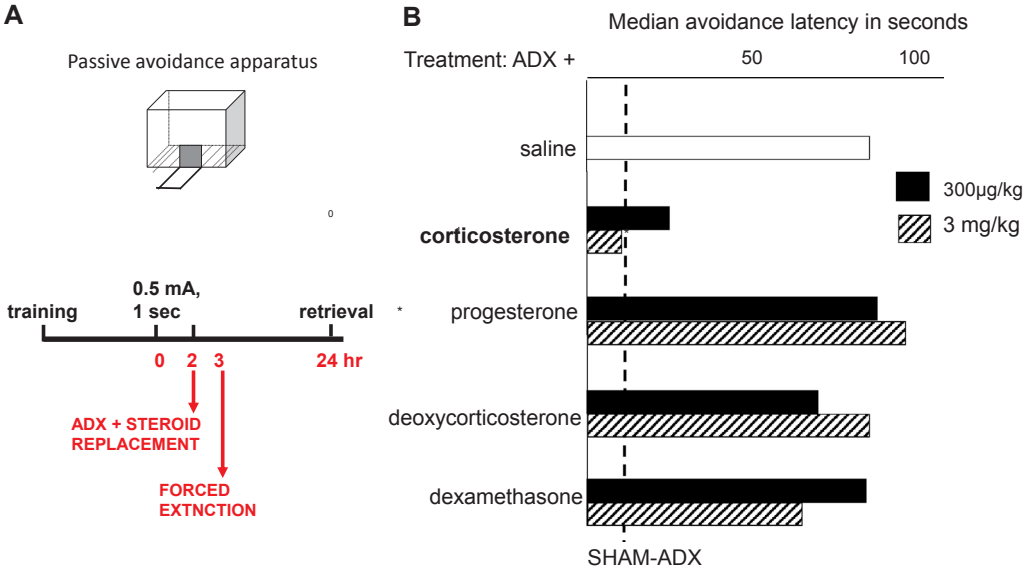

Fig. 1. Forced extinction reveals corticosterone specificity. Agonistic effect of corticosterone and no effect of progesterone, deoxycorticosterone and dexamethasone on extinction behavior of adrenalectomised rats. Treatment was given sc 60 min before forced extinction, that is immediately after adrenalectomy, in doses of 300 µg (open bars) or 3 mg/kg body weight (hatched columns), The broken vertical line represents the median avoidance latebncy of sham-adrenalectomised rats (n = 12 per group). .
Adapted from Bohus and de Kloet, 1981

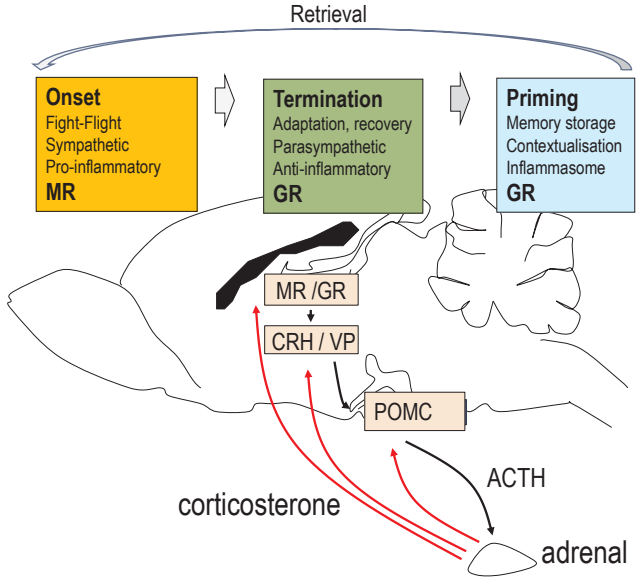

Fig. 2. MR, GR and the neuroendocrine stress response. Stressful stimuli activate CRH and vasopressin release from the median eminence terminals of the parvocellular neurons of the paraventricular nucleus that stimulate the synthesis of pro-opiomelanocortin (POMC) and its cleavage product ACTH, which in turn promotes the adrenocortical secretion of cortisol (human) and corticosterone (human, rodents). The binding of the naturally occurring glucocorticoids to its mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) procedes in the brain in three stages. 1. Onset: MR and sympathetic outflow. 2. Termination: GR behavioral adaptation and recovery. 3. Priming: GR, memory storage and inflammasome in preparation of future challenges.

adaptation, which potentially can aggravate stress-related deterioration and promote vulnerability" (de Kloet, 1991; de Kloet et al., 1998; Holsboer, 2000). The balance hypothesis extends Selye's pendulum hypothesis on opposing mineralocorticoid and glucocorticoid actions during inflammation to the receptors for these steroids. In Section 7 the MR:GR balance hypothesis is revisited in light of questions raised over the past years.

Meanwhile, support for the hypothesis came from studies using dexamethasone. The synthetic glucocorticoid decreases HPA-axis activity and thus depletes the brain of endogenous corticosteroids, so that corticosterone/cortisol is less available for binding to MR and loss of MR function may result (Karssen et al., 2001, 2005). For instance, in dexamethasone-treated animals changes in properties of cortical neuronal spines occur during the sleep-wake cycle, which could be restored with corticosterone replacement (Liston and Gan, 2011; Liston et al., 2013; Ikeda et al., 2015). In humans dexamethasone reduced slow wave sleep and caused dysphoric effects. Co-administration of cortisol restored slow wave sleep and led to an euphoric mood likely via activation of MRs (Born et al., 1991; Plihal et al., 1996; Groch et al., 2013). The potent MR agonist fludrocortisone was found to promote the efficacy of anti-depressants (Otte et al., 2010).

Dexamethasone can have severe side effects in a subgroup of patients (Judd et al., 2014) and a recent clinical trial demonstrated the utility of cortisol add-on in ameliorating adversity. Dexamethasone therapy of young patients suffering from acute lymphoblastic leukemia caused in about 30% of these patients severe adverse neuropsychological effects and sleep disturbances, which were ameliorated by cortisol add-on in doses used for replacement of adrenally deficient patients (Warris et al., 2016). The benefit of this refill for the brain MR supports the validity of the MR:GR balance concept (Meijer and de Kloet, 2017).

3. From cellular function to cognitive processing

3.1. Slow gene-mediated effects on cell signaling

As will be described in Section 6, the rodent hippocampus appears to contain selective MREs and GREs that mediate different effects of one and the same hormone: corticosterone. This provides a molecular basis for an observation made more than 25 years ago, i.e. that doses of corticosterone preferentially activating MRs generally exert very different effects on hippocampal cells than high doses which (in addition to MRs) activate GRs. In subsequent years it has become evident that the two receptors often mediate opposite actions, although there are clear regional differences.

In CA1 hippocampal pyramidal neurons, preferential MR activation was found to be associated with small Ca^{2+} currents through L-type channels (Karst et al., 1994). Conversely, high doses of corticosterone increased the amplitude of L-type Ca^{2+} currents via a mechanism involving binding of GR homodimers to the DNA (Kerr et al., 1992; Karst et al., 2000); this hinges on –at least- regulation of Ca^{2+} channel β4 subunit transcription (Chameau et al., 2007). Interestingly, in hippocampal CA1 neurons from adrenalectomized rats –where due to the absence of corticosterone both MR and GR are unoccupied- the amplitude of L-type Ca^{2+} currents were also high, overall resulting in a U-shaped dose-dependency. Such a dose-dependency was also observed for cell firing frequency accommodation –a phenomenon causing cells to gradually decrease their firing rate during a period of depolarization-, and for the so-called slow afterhyperpolarization (Joëls and de Kloet, 1989, 1990). Firing accommodation depends (among other things) on the activation of a Ca^{2+} dependent K^+ current, and thus indirectly on Ca^{2+} influx; deactivation of the Ca^{2+} dependent K^+ current after a period of depolarization causes the slow afterhyperpolarization. Other Ca^{2+} currents or currents mediated by Na^+, K^+ or Cl^- ions appeared to be less sensitive to corticosteroids, although some effects have been described (Joëls et al., 2012).

Such opposite MR- and GR-mediated effects were also described for hippocampal cell responses to neurotransmitters. Serotonin (5-HT) binds to 5-HT_{1A} receptors on CA1 hippocampal cells, which opens inwardly rectifying K^+ channels resulting in hyperpolarization of the cell membrane. Low corticosterone concentrations, via MR, resulted in a small 5-HT induced hyperpolarization, whereas high levels of corticosterone increased the 5-HT dependent hyperpolarization, again via GR homodimers binding to the DNA (Karst et al., 2000). Similarly, noradrenaline-dependent changes in cell firing were found to increase after selective activation of GRs (Joëls and de Kloet, 1989). With respect to glutamate it was found that selective activation of GRs promotes lateral diffusion and enhanced surface expression of AMPA receptors, particularly of subunit 2 (Groc et al., 2008; Martin et al., 2009). This is compatible with an earlier described slow GR-induced increase in glutamatergic responses of CA1 neurons, beit synaptically evoked or spontaneous (Karst and Joëls, 2005).

Interestingly, the lateral diffusion of AMPA receptor 2 subunits was found to be very similar to the effects of chemical long-term potentiation (Groc et al., 2008). Convergence of corticosterone-induced effects on the one hand and cellular changes underlying long-term potentiation on the other hand may lead to occlusion of the latter by the former. This may be one of the explanations for a frequently described fact, i.e. that exposure of hippocampal CA1 cells to a high dose of corticosterone (either by stress-induced or exogenous delivery of the hormone) hampers the subsequent induction of long-term synaptic potentiation (Pavlides et al., 1996; Kim et al., 2002; Krugers et al., 2010) – the presumed neurobiological substrate of memory formation. If so, this would protect the storage of stress-related information from being overwritten by information impinging on the same circuit shortly after the stressor (Diamond et al., 2007). In all of these phenomena, the MR determines the trough of the U-shape (Joëls, 2006), in other words the lower limit of the range over which the cell property under study can

vary. This is generally considered to be a healthy state of the cell, promoting viability (Joëls et al., 2012). The importance of the MR for cellular stability and viability only becomes apparent when the receptor is either inactivated, down-regulated or unoccupied due to the absence of corticosterone.

The interplay between MR and GR on cell signaling is region-dependent. For instance, activation of MR in dentate gyrus cells resulted –similar to the CA1 region- in relatively small Ca^{2+} current amplitudes. Yet, activation of GRs was ineffective in increasing the amplitude (Van Gemert et al., 2009). The dissociation between the two areas was not found at the level of transcripts: in both areas corticosterone increased mRNA levels of the calcium channel-β4. However, the conversion to the protein level was apparently impaired in the dentate since β4 protein levels were unaffected by corticosterone in the dentate, yet up-regulated in the CA1 region. The delayed effects of corticosterone on glutamate transmission seen in CA1 pyramidal cells is also seen in the prefrontal cortex (Liu et al., 2010; Yuen et al., 2011). We further argued that in areas where MR is expressed at a much lower level than GR, effects of corticosterone linearly depend on the hormone concentration rather than in a U-shaped manner (Joëls, 2006). This subject, however, is still heavily understudied.

3.2. Rapid non-genomic effects of MR

Over the past decade it has become clear that the MR can also play a different role. When corticosterone was applied to hippocampal CA1 pyramidal cells, this did not only induce delayed changes e.g. in glutamate signaling, but also rapid effects. The rapid effects were extensively studied regarding miniature excitatory postsynaptic currents (mEPSCs), which each reflect the postsynaptic response to the spontaneous release of a single glutamate-containing synaptic vesicle. In 2005, Karst et al. (2005) reported that selective activation of MRs but not GRs rapidly increases the frequency (but not amplitude) of the mEPSCs in CA1 pyramidal cells; mEPSC frequency was quickly restored when corticosterone concentrations dropped back to baseline. This is clearly a non-genomic effect for which corticosterone does not have to enter the cell and hence is most likely mediated by MRs located close to the cell membrane. Of note, the membrane location of such MRs is still a matter of debate (Groeneweg et al., 2011; Groeneweg et al., 2012). In addition to the rapid changes in mEPSC frequency, MR was also reported to increase the mobility of AMPA receptor 2 subunits in cultured hippocampal cells (Groc et al., 2008). Moreover, rapid corticosteroid effects facilitate the induction of long-term potentiation (Wiegert et al., 2006). Interestingly, to achieve rapid effects via MR, hippocampal cells required relatively high concentrations (~10 nM) of corticosterone (Karst et al., 2005), a dose-range where nuclear MR are already fully occupied. This suggests that the rapid MR-dependent actions could very well play a role in the early phase of the stress response (Joëls et al., 2008)

Rapid MR-dependent effects on mEPSC frequency were also described for dentate granule cells (Pasricha et al., 2011). Likewise, in principal cells of the basolateral amygdala, corticosterone raises the mEPSC frequency (Karst et al., 2010). Yet, in these cells the mEPSC frequency remained high, even after wash-out of the hormone. The prolonged nature of the response turned out to be GR- and transcription-dependent. A similarly prolonged elevation in mEPSC frequency was observed after animals had been stressed. Notably, exposure to a (first) pulse of corticosterone changes the cell's response to a subsequent pulse of corticosterone. Thus, a second pulse of corticosterone delivered > 1 h after the first pulse quickly and lastingly *reduced* the mEPSC frequency, through a non-genomic GR-dependent pathway (Karst et al., 2010; Karst and Joëls, 2016). This phenomenon was dubbed 'corticosterone metaplasticity'. It shows that also with respect to the rapid corticosteroid actions, MR and GR exert opposite actions.

3.3. Membrane MR as a sensor for shifts in circulating corticosterone level

In view of the concentration range and time window in which rapid MR-dependent effects develop, these effects may be of relevance for two situations during which rapid changes in corticosteroid level occur.

The first situation is related to the ultradian release pattern of corticosterone. The hormone is released in pulses with an inter-pulse interval of approximately 1 h (Lightman and Conway-Campbell, 2010). The pulse amplitude is high just before the onset of the active period during the day and drops at the end of the active period, overall causing a circadian release pattern. We showed that hippocampal cell activity can reasonably well follow this pattern of hourly pulses. During the pulses, mEPSC frequency, surface expression of AMPA receptor subunits and LTP were found to be enhanced, although some attenuation developed during the 3rd and 4th pulse (Sarabdjitsingh et al., 2016). This study design with a sequence of 4 pulses also showed an interesting interaction between delayed genomic actions of corticosterone and rapid non-genomic effects (Sarabdjitsingh et al., 2014). As stated before, a (first) pulse of corticosterone results in hippocampal neurons in synaptic enrichment of AMPA receptor 2 subunits and increased mEPSC frequency, hampering the ability to subsequently induce long-term synaptic potentiation. Unexpectedly, a second pulse of CORT > 1 h after the first completely normalized all aspects of glutamate transmission investigated, thus restoring the plastic range of the synapse. This restoring capacity of the second pulse may ensure that hippocampal glutamatergic synapses remain fully responsive and able to encode new stress-related information when daily activities start.

A second situation where corticosterone levels quickly change occurs during the stress response. Microdialysis studies (McIntyre et al., 2002; Bouchez et al., 2012) showed that neurons are exposed first to a wave of noradrenaline and with a delay of approximately 20 min (Droste et al., 2008) to a wave of corticosterone. We mimicked these waves with various concentrations of isoproterenol (a β-adrenoceptor agonist) and corticosterone (Karst and Joëls, 2016; Fig. 3). We measured mEPSC frequency in basolateral amygdala cells over the course of 2 h, an interval that is relevant for memory consolidation. At low to moderate concentrations of the hormones, mEPSC frequency first increased and –with a delay of approximately 1 h – decreased. However, with high concentrations of the two compounds, the initially raised mEPSC frequency remained high for at least 2 h. This suggests that basolateral amygdala excitability is high for a very long time under conditions that both β-adrenoceptor and corticosteroid receptor activation is substantial, such as may occur during severely emotional stress situations.

Overall, these data show that neuronal activity is markedly affected by stress and specifically corticosteroid hormones, in a (i) time-dependent, (ii) receptor-dependent and (iii) region-dependent manner, with evidence for interactions between the time-domains, receptor-mediated actions and effects in the various brain areas. This results in a complex picture. In general, amygdala (and to a lesser extent hippocampal) activity is increased shortly after stress. With a delay of approximately 1 h, activity in the prefrontal area and hippocampus is increased, while amygdala activity is decreased (Joëls et al., 2012) unless the stressor is very severe (Karst and Joëls, 2016).

3.4. Relevance of rapid MR effects for cognition

In view of the time-, receptor- and region-dependency of cellular actions by corticosteroids, one can wonder how this affects cognitive processing after stress. This was studied in a series of experiments, in rodents and humans, in which specific cognitive domains were probed directly after a rise in corticosteroid level or > 1 h later, at a time that genomic actions have developed. In some cases, this was combined with the use of selective receptor antagonists.

The current view (Fig. 4) is that directly after stress corticosteroid hormones, via MR and in interaction with monoamines, promote

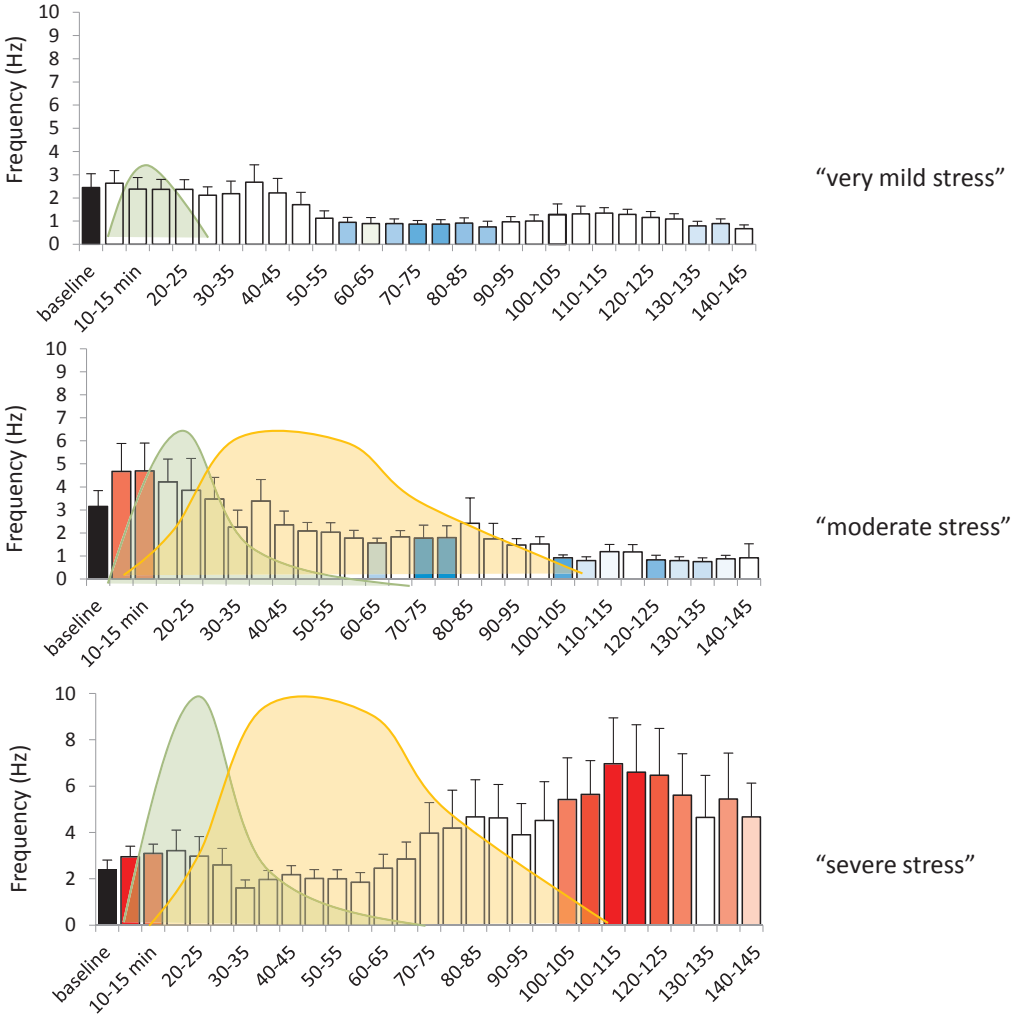

Fig. 3. Basolerateral amygdala cells were exposed to waves of first isoproterenol (green) and next corticosterone (yellow), at various concentrations. The top panel shows a brief wave of 0.3 μM isoproterenol (very mild stress), the middle panel waves of 1 μM isoproterenol followed by 30 nM corticosterone (moderate stress); and the lower panel the application of 3 μM isoproterenol followed by 100 nM corticosterone (severe stress). Depicted is the averaged (+SEM) frequency of mEPSCs over time. The intensity of the bar's color (red is highest) corresponds with the significance of the effect. The difference between very mild and moderate stress is characterized by the appearance of a brief excitatory response, whereas the transgression from moderate to severe stress is associated with the appearance of a delayed excitatory effect. Based on (Karst and Joëls, 2016).

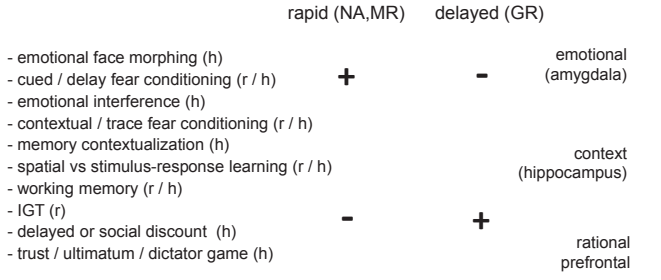

Fig. 4. Summary of behavioral observations in rodents (r) and human subjects (h) directly after stress/corticosteroid administration and > 1 h after stress/corticosteroid administration. The tests are arranged from those involving primarily amygdalar/striatal circuits (top), through hippocampal circuits (middle) to prefrontal circuits (bottom). Directly after stress monoamines and corticosteroids acting primarily via MR promote emotional processing, at the cost of higher cognitive functions such as contextual memory formation or reward-based decision making. At a longer interval (> 1 h after stress or corticosteroid administration), the reverse is seen. Most of the studies are discussed in (Vogel et al., 2016). IGT = Iowa Gambling Task.

vigilance, attention and the choice of a simple yet effective strategy to face environmental challenges, with a focus on the 'self' or close ones (Joëls et al., 2011; Schwabe and Wolf, 2013; Hermans et al., 2014; Vogel et al., 2016). Conversely, at this point in time higher cognitive functions, such as linking the context to the event or selecting altruistic solutions that may be beneficial in future, are suppressed. This behavioural pattern is enabled by an MR-dependent redistribution of resources from the hippocampus to the amygdala and striatum (Schwabe et al., 2013; Vogel et al., 2015, 2017).

Interestingly, starting approximately 1 h after the rise in corticosteroid level (due to stress or induced by exogenous administration of corticosteroids), cognitive function is steered in a different direction. This is not simply the normalization of the earlier phase, but an active process, involving a new set of actions depending -as far as investigated- on GR function. This phase is characterized by suppression of amygdala activity and increased activity in 'higher' brain areas e.g. in the dorsolateral prefrontal cortex. Behaviourally, individuals have (compared to controls) a higher ability to contextualize information, are less distracted by emotional information and rationalize stressful events, can store stress-related information for the future and make more altruistic choices.

Evidently, both phases of the cognitive repertoire after stress are important. Individuals need an appropriate first reaction to imminent danger to survive. Being attentive, going for the quickest solution of the situation and being self-centered all help to get through this period of potential threat. Yet, at some time the available brain resources should be redistributed to help processes that promote survival in the long run: putting things in the right perspective –thus preventing generalization of fear-related information-, building up a reference map for future use and 'befriending' those that may be of help in the future. An imbalance between these two phases, e.g. caused by lower or higher functionality of one of the corticosteroid receptors, may compromise the rapid or delayed response and thus increase the susceptibility of genetically vulnerable individuals to develop diseases, including those related to the brain. Corticosteroid receptor variants may contribute to such lower

or higher functionality, especially under conditions of cumulating (early) life adversity. This will be further highlighted in the context of genetic receptor variants and psychopathology in the next section.

4. Genetic variants

A recent twin study estimated heritability of major depressive disorder at about 35% (Geschwind and Flint, 2015) taking gene × environment interactions into account. Yet, large scale GWAS studies have not revealed which genes are involved leading these multi-author studies to conclude that this type of hypothesis-searching approaches probably point to numerous genes that each contribute very little to the overall risk of this stress-related disorder (Akil et al., 2017). Yet, using the Google 23andme database and self-reports about depressive mood as well as the response to antidepressants some gene associations were identified e.g. neurodevelopmental, circadian rhythmicity and growth factor-related genes (Hyde et al., 2016; Li et al., 2016). The Task Force of the Hope for Depression Research Foundation (Akil et al., 2017) concluded that 'convergence of these genetic risk factors with transcriptional abnormalities observed in rodent depression models' might give some perspective in the search for a molecular mechanism in depression. Indeed, a recent report assigned a key role for glucocorticoid responsive genes in resistance to anti-depressant therapy (Carrillo-Roa et al., 2017). In addition, lasting GR epigenetic marks are known as signatures of (early) life experiences (Turecki and Meaney, 2016).

We have studied in-depth MR genetic variation. First, in exon 2, at codon 180, rs5522, an ATT to GTT single nucleotide polymorphism (SNP, minor allele frequency 12%) resulted in an isoleucine to valine change (I180V) in the N terminal receptor domain. *In vitro* the G allele resulted in a loss of function MR variant at EC50 in response to cortisol, but not aldosterone. Young male carriers of two G alleles showed a much larger plasma ACTH, plasma and saliva cortisol, and heart rate response in the Trier Social Stress Test, while no changes were found in aldosterone-dependent measures (DeRijk et al., 2006). The G-allele was associated with a reduced ability to modulate behavior as a function of reward in the face of stress and increased amygdala reactivity in individuals with a history of early trauma (Bogdan et al., 2010, 2012), and in combination with other functional genetic variants of HPA axis genes (Di Iorio et al., 2017). This suggested a role in psychopathology and indeed G allele associations were found with depressive symptoms in an elderly cohort (Kuningas et al., 2007).

Second, at position -2, that is two nucleotides before the first ATG start codon, a C/G SNP (rs2070951, minor allele frequency 49%) is found. The G allele caused reduced translation and thus reduced MR expression. The phenotype associated with this G allele is characterized by higher systolic blood pressure, higher renin activity and higher circulating levels of aldosterone (van Leeuwen et al., 2010a).

Based on the two SNPs (rs2070951 & rs5522) four haplotypes can be expected (Fig. 5). Accordingly, allele frequencies were *in vivo* of Haplotype 1 (GA) 50%, Haplotype 2 (CA) 35% and Haplotype 3 (CG) 12%. Haplotype 2 and 3 displayed highest activity and highest MR protein expression in an *in vitro* transactivation assay. Lower activity was observed with haplotype 1. However, the putative "haplotype 4", that would be G for rs2070951 and G for rs5522 with an expected frequency of approximate 6%, has not been detected in the thousands of samples we have genotyped. In addition, haplotype 4, which has been constructed and tested, showed *in vitro* much lower transactivational activity as compared to the other three haplotypes. This suggest that perhaps a too low MR-activity is not compatible with life (van Leeuwen et al., 2011).

We found sex dependent effects on basal levels of saliva cortisol, the cortisol awaking rise (CAR) and in the low dose (0.25 mg) dexamethasone suppression test (Klok et al., 2011c; van Leeuwen et al., 2010b). Male haplotype 1 displayed a much higher CAR and more resistance to dexamethasone suppression than the male haplotype 2 carriers. In haplotype 1 carriers, the males had higher CAR and a more

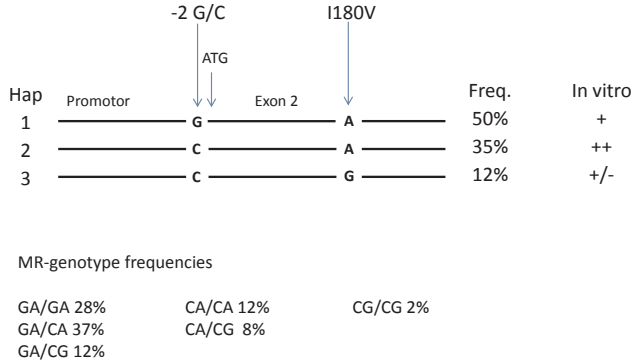

Fig. 5. Common functional MR-gene haplotypes. In the 5′ region of the MR-gen 3 haplotypes were constructed based on linkage disequilibrium of two SNPs, the rs2070951 (G/C: 50/50) and the rs5522 (A/G: 80/20). The G/C is located in the promotor region two nucleotides before the translation start site (ATG) while the rs5522 is located in codon 180 of exon 2 changing an amino acid from Isoleucine (ATT) to Valine (GTT). The frequencies of the haplotypes as well as the frequencies of the genotypes are indicated (latter based on a Dutch cohort (Vinkers et al., 2015). *In vitro* testing of the activities of the haplotypes in a transactivation assay in CV-1 cells revealed haplotype 2 as having highest activity, slightly less activity by haplotype 1 and lower activity by haplotype 3. Haplotype 4 was not detected yet *in vivo*; haplotype 4 showed much lower expression and transactivational activity *in vitro* as compared to the other three haplotypes (van Leeuwen et al., 2011).

readily escape from dexamethasone suppression than females. In a cohort of school teachers, the stress-induced autonomic and HPA axis response were associated with MR-haplotypes. Carriers of MR-haplotype 2 showed the highest heart rate, ACTH (in blood) and cortisol responses (blood and saliva) in the Trier Social Stress test. Together, the data support the notion from pharmacological studies that the human MR is involved in the regulation of stress reactivity as shown by measures for HPA axis and autonomous activity.

In addition, part of these effects were sex specific. For instance, in the Dutch Arnhem Elderly Study we tested 450 subjects (aged 65–85); MR haplotype 2 was associated with higher mean levels of dispositional optimism in women but not in men and the effect was estimated to explain 6% of the variance in optimism (Klok et al., 2011b). Interestingly, GR haplotypes were not related to the optimism scores. In a follow-up study in a group of young students we found that MR haplotype 2 predicts fewer thoughts of hopelessness and lower levels of rumination (Klok et al., 2011b). In another study with young female students a significantly higher implicit happiness score of MR-haplotype 2 homozygotes was observed. Haploptype-2 carriers are less sensitive to the effects of variations in estrogens and progesterone during the menstrual cycle on emotional information processing. Haplotype 2 carriers are also protected against the negative mood effects of oral contraceptives containing synthetic progestins (Hamstra et al., 2015, 2016, 2017).

Neuroticism is a vulnerability factor for psychopathology. In a group of young students less neuroticism was found in carriers of MR haplotype 2 (although this group in general showed low levels of neuroticism) and lower levels of depression and anxiety. To validate our hypothesis that higher dispositional optimism and less neuroticism would be protective to negative mood, we performed an association study with depression using data from the NESDA cohort and found that MR haplotype 2 was associated with a lower risk of depression, particular in females of reproductive age. Vinkers et al. (2015) tested the association between MR haplotypes and depression in two independent cohorts: a population based cohort (N = 665) and the clinical NESDA sample (N = 1639). Sex and early life trauma are important determinants with an apparent protective effect of MR haplotype 2 in females, but haplotype 1 and 3 were an advantage for males in this respect (Vinkers et al., 2015).

Thus, in several different cohorts MR haplotype 2 was associated

with a lower risk for symptoms of depression, in line with their positive psychological effects and increased cortisol reactivity. These associations were strongly influenced by gender and early trauma (ter Heegde et al., 2015; de Kloet et al., 2016). In line with the increased expression and transactivation of MR haplotype 2, heterozygous and homozygous carriers showed during stress a shift towards striatal habit learning at the expense of amygdala-hippocampus processing of stressful information measured with fMRI and EEG (Wirz et al., 2017). This finding underscores the relevance of the MR in selecting a coping style during stress, which is fundamental for understanding the pathogenesis of stress-related disorders. Interestingly, in hippocampal tissue obtained post-mortem from depressed patients MR mRNA levels are decreased (Klok et al., 2011a, 2011b, 2011c).

Current transgenic animal models have been generated with conditional site-specific under- or overexpression of MR and GR, but animal models carrying the MR gene variants have not been generated yet. The Brown Norway rat expresses, however, a naturally occuring mutation identified as tyrosine to cysteine substitution (Y73C) in the N-terminal part of the MR, providing *in vitro* a greater transactivational activation in response to aldosterone, but also to progesterone (Marissay-Arvy et al., 2004).

The MR- genetic association studies add valuable information to a growing database of candidate genes predicting stress-related disorders and/or efficacy of treatment strategy. Thus, genetic polymorphisms of α_2-adrenergic receptors, catecholamine-O-methyltransferase (COMT), neuropeptide Y, the 5HT-transporter, dopamine D4 receptor and BDNF can modify emotional and cognitive aspects of the stress response and therefore are obvious candidates for further research (Wu et al., 2013; Southwick and Charney, 2012). Genetic variants of FKBP5, GR and CRH binding protein predict risk of depression and the efficacy of antidepressant therapy (Quax et al., 2013; Binder, 2009; Claes et al., 2003; O'Connell et al., 2017).

Bogdan's group (Di Iorio et al., 2017) reported recently that a biologically-informed multilocusprofile score (BIMPS) of genetic variation CRH- and cortisol receptors was found associated with the function of these genes. This implies that a higher BIMPS score correlates with higher HPA axis- and stress reactivity. Such a polygenic risk score, if combined with neuroendocrine challenge tests and psychological analysis of the stress system, thus may have an important added value in the prediction of individual stress vulnerability and resilience. As advocated by Dirk Hellhammer, this assessment of a 'conceptual endophenotype' is promising not only as a translational tool to detect stress pathology, but also as an assist in selection of treatment strategy of depression and other stress-related disorders (Hellhammer et al., 2012, 2018).

5. MR and neuro-inflammation

Several genetically selected lines have been tested for expression of MR and GR in brain. One interesting line is the spontaneous hypertensive rat (SHR) which depends on MR stimulation for its development of hypertension at 2 – 3 months of age (Okamoto and Aoki, 1963). Despite the importance of MR in this model, no MR genetic variants were identified as risk factors in SHR, but surprisingly these animals expressed variants of the dopamine transporter ***Slc6a3*** gene associated with hypertension ((Zhang-James et al., 2013). The young SHR animals show indeed hyperactive behavior and memory impairment which explains why these animals are used as model for attention deficit hyperactivity disorder (ADHD; Meneses et al., 2011; Killeen et al., 2012).

The SHR is a genetic rat model that reproduces several aspects of human essential hypertension. SHR's also demonstrate a similar neuropathology of brain damage and inflammation as observed in animals exposed to excess deoxycorticosterone acetate (DOCA) and 2% saline drinking solution (Pietranera et al., 2006). DOCA-salt exposure increases vasopressin synthesis in the brain of SHR, but not of WKY control animals (Pietranera et al., 2004). Hypertension does not develop in adrenalectomized SHR rats unless aldosterone is given, which acts on the kidney to elevate pressure (Kenyon et al., 1981). The brain is also involved, however, since 100 ng MR antagonist administered icv lowered blood pressure, provided the animals were sensitised by sodium loading (Rahmouni et al., 2001). This effect that was abolished after denervation of the kidney (de Kloet et al., 2000; Rahmouni et al., 2002). Furthermore, in the adult hypertensive SHR's, the MR is increased in binding capacity and expression in the hippocampus and hypothalamus (Sutanto et al., 1992; Pietranera et al., 2012). This increased expression of MRs seems generalised in SHR because it is also observed in heart, kidney and peripheral vasculature (Mirshahi et al., 1998; Delano and Schmid-Schönbein, 2004; DuPont and Jaffe, 2017).

A recent study (Brocca et al., 2017) confirmed that SHR has 2.5-fold more MR mRNA and increased immunoreactive MR in GR positive cells of hippocampus as compared to WKY control rats. The adult SHR hippocampus also displays a higher density of Iba1 + ramified as well as hypertrophic microglia, which are markers of inflammation. In the Brocca et al. study the steroid responsive Serum and Glucocorticoid regulated Kinase 1 (SGK1; Artunc and Lang, 2014) as well as Cox2, an enzyme associated with vascular inflammation (Renna et al., 2013), and the inflammasome component Nlrp3 (Liu et al., 2015) all showed increased expression. In contrast, the anti-inflammatory Tgfβ level (Qian et al., 2008) and NADPH-diaphorase activity (Hojná et al., 2010) were significantly lower in the hippocampal CA1 area of SHR. These data demonstrate that increased hippocampal MR expression in SHR rats is associated with a shift towards increased expression of pro-inflammatory genes at the expense of anti-inflammatory factors. This shift in pro- vs anti-inflammatory factors corroborates the microglia phenotype of Iba1 + overexpression in hypertrophied microglia which is typical for chronic inflammation (Brocca et al., 2017).

The findings with the SHR animal model raise a number of issues. First, although, hippocampal neuropathology of SHR is remarkably similar to that of DOCA-salt animals, causality by mineralocorticoids still needs to be proven. In this respect, oxidative stress caused by tissue damage may play a significant role in the switch towards a pathophysiological MR function (Davel et al., 2017; Dinh et al., 2016). While under healthy conditions MR is protective, it seems that during adversity MR may foster inflammation (Funder, 2004).

Second, since the MR antagonist icv appeared active in SHR animals in lowering blood pressure, it would be of interest to examine if the same treatment attenuates damage in the hippocampus. This experiment would allow to test whether the antagonist interferes with a physio-pathological feedforward cascade starting with hypertension-induced damage to the vasculature, development of microgliosis and astrogliosis, production of pro-inflammatory mediators and oxidative stress leading to inappropriate MR activation. The neuronal damage resulting from vasculopathy-induced hypoxia would further stimulate release of pro-inflammatory factors, which would then exacerbate oxidative stress and further dysregulation of MR (Brocca et al., in press). A similar chain of events was envisioned following ischemic damage, where MR antagonists and genetic deletion of MR are protective (Frieler et al., 2011)

Third, the SHR model may provide insight in the role of the aldosterone-selective MR present in a in the NTS and circumventricular organs, which regulate salt appetite and indirectly emotion and cognition (see section This may explain how pharmacological amounts of aldosterone administered to rats exert anxiogenic effects and cause behavioural changes in coping style (Hlavacova and Jezova, 2008). After all, a substantial number of patients with essential hypertension actually appear to secrete relatively large amounts of aldosterone during stress (Markou et al., 2015).

Fourth, studies with the SHR animal may shed light on the interplay between the corticosterone responsive MR in neurons, and possibly astrocytes and microglial cells (Hwang et al., 2006), with the discrete aldosterone-selective MR. Regarding neuronal MR, SHR rats show

alterations in corticosteroid negative feedback (Gómez et al., 1998). Furthermore, in experiments mimicking the presumed excessive release of cytokines during neuro-inflammation, we found in Wistars that hippocampal MR binding of corticosterone is increased with about 60% after a systemic or icv challenge with IL-1. At the same time, the affinity for corticosterone decreases as is evidenced by a poor nuclear retention of ^{3}H-corticosterone in hippocampal neurons *in vivo*. This decrease in hippocampal nuclear binding is associated with less inhibitory input to the HPA axis, and increased circulating levels of corticosterone. Learning of the Morris water maze was not affected, but the IL-1 treated animals showed altered spatial navigation in the Morris maze re-test 24 h after learning (Oitzl et al., 1993; Schöbitz et al., 1994). This finding suggests that microglia's cytokine release may affect neuronal function.

In conclusion, the pendulum hypothesis states that pro-phlogistic mineralocorticoids increase the risk for inflammation, while the anti-phlogistic glucocorticoids increase vulnerability to infection. In the above experiments, excessive activation of aldosterone-selective MRs produces undesirable effects including the induction of salt appetite, hypertension and damage to the vasculature. Alternatively, excessive corticosterone-preferring MR-mediated actions enhance sympathetic drive, and affect neurogenesis and neuronal plasticity. It is still unknown to what extent the aldosterone-selective and corticosterone preferring actions via the brain MR cooperate in the feedforward cascade of oxidative stress and inflammation involving glial cells and neurons (Vallee et al., 1995; Sabbatini et al., 2002; Pietranera et al., 2006; Lopez-Campistrous et al., 2008; Gomez-Sanchez and Gomez-Sanchez, 2014; Tayebati et al., 2016; DuPont and Jaffe, 2017).

6. About receptors, coregulators and GRE's

To further understand the mechanistic underpinning of the steroid effects on brain function and behavior, MRs and GRs, as members of the superfamily of nuclear receptors, mediate powerful effects on gene transcription and subsequently on expression of enzymes, receptors, pumps, ion channels, structural proteins and other transcription factors that may affect excitability, proliferation, differentiation and cell death. Early studies on the molecular factors underlying the effects of glucocorticoids on the brain focused on regulation of neurotransmitter synthesis, and – upon the availability of radioligands – their receptors. In 1969, Efrain Azmitia, demonstrated that corticosterone stimulates the activity of tryptophan hydroxylase activity, the rate limiting enzyme for 5HT synthesis (Azmitia and McEwen, 1969). Subsequently, glucocorticoids were shown to have effects on 5HT turnover (de Kloet et al., 1982) and receptor binding (de Kloet et al., 1986; Mendelson and McEwen, 1992), and after cloning, on receptor mRNAs. Meanwhile, it had become clear that the hippocampal response to 5HT1A receptor activation was under bimodal control of corticosterone. As discussed in detail in Section 3, MR activation suppresses, while GR activation stimulates the response to the 5HT1A receptor activation in hippocampal CA1 pyramidal cells (Joëls et al., 1991; Section 3). Accordingly, one prominent gene that emerged as a likely transcriptional target, based on mRNA suppression, was the 5HT1A receptor gene (Chalmers et al., 1993; Meijer and De Kloet, 1994). Although its regulation by corticosterone has not fully explained the effects that were observed for cellular excitability to 5HT, the 5HT1A mRNA suppression was among the very first transcriptional effects that are regulated via the MR (Meijer and De Kloet, 1995; Meijer et al., 1997, 2000a, 2000b).

6.1. Interactions with the DNA

To this date, the MR-mediated intrinsic genomic effects of corticosterone on neuronal excitability remain unexplained. As these effects can be opposite to those of GR, comparing activities of MR and GR has been a strategy to understand MR function. During the early 1990s, it was discovered that GRs affect transcription in two fundamentally different ways. The first mechanism is via direct binding to glucocorticoid response elements (GREs) in the DNA. As MR and GR have a DNA binding domain that is almost (96%) identical, and the isolated DNA binding domain is able to bind identical DNA sequences (Nelson et al., 1999), until recently the existence of specific 'MRE' sequences on the DNA was not a favoured hypothesis. Indeed, transcriptional regulation via binding of MR and GR to the same GREs occurs for genes such as *Sgk1* (Webster et al., 1993; Chen et al., 1999) and *Gilz* (Soundararajan et al., 2005; D'Adamio et al., 1997). In fact, steroid receptors bind as dimers or even tetramers to GREs (Presman and Hager, 2017). MR and GR have been shown to heterodimerize *in vitro* (Liu et al., 1995; Trapp and Holsboer, 1996), and were indeed found to occupy the same GREs in the hippocampus (Mifsud and Reul, 2016). The second mechanism of GR-mediated action is via protein-protein interactions with other, non-receptor transcription factors such as AP-1 and NF-kB. This form of protein–protein interaction attracted much attention, because of its role in transrepression of pro-inflammatory genes in the immune system (Yang-Yen et al., 1990; Schüle et al., 1990; Jonat et al., 1990). Soon after the discovery of the protein-protein interaction mechanism, Pearce & Yamamoto demonstrated that MR was much less potent at repressing AP-1 activity than GR (Pearce and Yamamoto, 1993). Thus for a decade or so, most researchers assumed that differential MR/GR effects were caused by such 'classical transrepression' mechanisms that would be mediated by GR but not MR.

With more recent genome wide analysis of receptor binding in a diversity of cell lines, both GR and MR were demonstrated to bind to DNA motifs that point to protein-protein interactions, independent of direct DNA binding (Le Billan et al., 2015; John et al., 2011). For some target genes, MR binding to SP-1 sites was shown in cell lines, presumably by tethering to SP-1 protein (Meijer et al., 2000a, 2000b, 2013). However, with a few exceptions (Kovács et al., 2000), not much evidence for transrepression by cortisol on neuronal transcription was found, be it via GR, or MR. Both GR and MR binding in the hippocampus of rats was found to be almost exclusively associated with GREs after ChIPseq analysis (Polman et al., 2013; Pooley et al., 2017; van Weert et al., 2017). Therefore, at least in neurons in healthy animals direct binding to GREs seems to be the dominant mode of action for both hippocampal MR and GR. For GR, these data corroborate earlier findings that GR binding to DNA is indispensible for GR-dependent effects on neuronal excitability and learning and memory (Karst et al., 2000; Oitzl et al., 2001). Thus, cellular context (cell type, cell cycle state, or inputs e.g. inflammation) seems to be important to determine whether MR and GR use their ability to engage in 'transrepression' mechanisms.

Although the large majority of hippocampal MR/GR binding sites depends on GREs, there does seem to be crucial cross talk on the genome, notably with transcription factors that bind in the vicinity of the steroid receptors. For hippocampal GR this was first shown by comparing potential GRE-like sequences in proven corticosterone regulated genes (Datson et al., 2013). The potential binding sites could be divided in either functional GREs or non-functional GRE-like sequences. Actually, GR binding GREs exclusively harboured binding sites for a number of other transcription factors in their vicinity, such as MAZ-1. Non-functional identical sequences lacked these fingerprints. Thus, proteins that bind these accessory sites (be it MAZ-1 or related transcription factors) may interact with GR, and determine whether or not GR can stably bind to the chromatin to affect gene transcription (Datson et al., 2011).

The approach that led to the identification of MAZ-1 sites was based on GR binding in the vicinity of genes that were actually regulated by corticosterone. This represents only a modest subset of all GREs where GR binds. The ChIPseq approach identifies GR/MR binding sites at a genome wide scale, but these sites cannot necessarily be directly linked to actual transcriptional target genes. Analysis of two hippocampal genome wide DNA binding profiles for GR revealed the presence of binding sites for transcription factor NF-1 in about 50% of the cases. It

remains to be established if and how transcription factors that bind these sites affect GR binding and signaling, but at present these data give cues to potential cross talk between cortisol and other signaling pathways. Apparently, it is not direct DNA binding '*or*' but rather '*and*' interaction with other transcription factors that determines the outcome of MR/GR activation for transcriptional regulation. It is also unclear whether GRs in these cases enhance NF-1 binding and function, or rather vice versa.

A notable finding from hippocampal genome wide MR binding is that *all* MR binding was predicted to have an additional binding site for NeuroD factors within 250 nucleotides up- or downstream of the GRE (van Weert et al., 2017). The proteins NeuroD1, 2 and 6 are expressed in principal neurons of the adult hippocampus; each of these proteins can bind to this sequence. NeuroD factors are basic Helix-Loop-Helix (bHLH) type transcription factors. Similar to MyoD factors they are critically involved in cellular differentiation (Fong et al., 2015), and may in a combinatorial way determine the exact phenotype of the principal hippocampal neurons that express them (Mo et al., 2015). Hippocampal GR binding was also associated with the NeuroD element in < 20% of the sites, which may reflect heterodimerization with MR (Mifsud and Reul, 2016). Thus, somehow, corticosterone via MR links to factors that are important for the exact neuronal identity of the different principal neurons in the hippocampus. In reporter assays, NeuroD factors potentiate transcriptional activity of both MRs and GRs, when a GRE and a NeuroD site are present in a promoter. This confirms a functional interaction, but does not explain the observed prevalence of MR-NeuroD pairing *in vivo*.

And so, 25 year or so after the discovery of differential intrinsic effects of MR and GR on hippocampal excitability, we know that there are indeed MR-specific loci on the hippocampal chromatin. Somewhat surprisingly, MR and GR specificity does not seem to hinge on transrepression via DNA-binding independent interaction with other transcription factors, but rather on selective MREs and GREs that represent two of the subsets of functional MR and GR binding DNA sequences. The cross talk partners, and the target genes that are associated with the specific binding sites may help us to understand the nature of bimodal MR/GR action in the hippocampus.

6.2. Coregulators

DNA binding is only the first step to transcriptional regulation via MR and GR. The actual signal transduction upon binding to the DNA consists of the recruitment of transcriptionally active protein complexes that either remodel local chromatin structure, or lead to formation of transcription initiation complexes (for positively regulated genes). These downstream proteins form a large group, known as transcriptional coregulators, that may be either coactivators, corepressors, or both (O'Malley, 2007). GR and MR may directly interact with scores of coregulators (Zalachoras et al., 2013). In turn, these coregulators may interact with any number of nuclear receptors, and other transcription factors, and have been considered 'hubs' that integrate signals from many different steroid and non-steroid pathways (O'Malley, 2007). A case in point for the stress system is the joint regulation of the *Crh* gene in hypothalamus by both glucocorticoids and BDNF, which is mechanistically linked at the level of the coregulator CRTC2 (Jeanneteau et al., 2012).

Similar to interacting transcription factors, the role of MR and GR coregulators is of great interest to understand the cellular context in which corticosteroids act. For example, the *Crh* gene that is pivotal to both the HPA axis and emotional regulation, is regulated in opposite directions by glucocorticoids in the hypothalamus (repression via GR) and amygdala/bed nucleus stria terminalis (BNST) (induction via GR; Makino et al., 1994). MR and GR coregulators are differentially distributed in different brain areas and cell types (Mahfouz et al., 2016). The brain region specific machinery that is available to MR and GR to regulate particular target genes may explain cell type specific effects of corticosteroids on the *Crh* gene and other genes (Meijer et al., 2000a).

While many coregulators are shared between MR and GR, such as the Steroid Receptor Coactivators 1, 2 and 3 (Meijer et al., 2005), others may differentially interact with MRs and GRs. This suggests a mechanism for MR and GR specific effects, even after binding to similar response elements. For example, the coregulator ELL was shown to enhance MR-, but inhibit GR-dependent transcription (Pascual-Le Tallec et al., 2005). Moreover, coregulators may even distinguish between aldosterone-bound MR and cortisol-bound MR (Fuller et al., 2017). However, examples of specific coregulators are sparse, as they likely interact with the N terminal domain of the receptors, which is difficult to study (McEwan et al., 2007).

Lastly, coregulators act in a gene specific manner at MR and GR. At individual promoter and enhancer regions, specific transcriptional complexes are formed to affect gene expression, which leads to gene-dependent requirement of coregulators for MR and GR target genes (Grenier et al., 2004; Meijer et al., 2005). In mice lacking Steroid Receptor Coactivator-1 (SRC-1), *Crh* and *Pomc* mRNA regulation via GR was abolished, but regulation of other genes was intact, and functional consequences were very modest, due to redundancy in coregulators needed for GR-mediated gene expression and developmental compensation in the knockout mice (Lachize et al., 2009). Selective GR-resistance of the *Crh* gene was later demonstrated after selective knockdown of a SRC-1 splice variant in the central nucleus of the amygdala – suggesting that targeting coregulator pathways is a strategy to interfere in mood- and anxiety-related disorders (Zalachoras et al., 2016; Fig. 6).

The diversity in interacting transcription factors and coregulators not only defines an intricate context that allows coordinated responses to corticosteroids, but also forms an opportunity for directed interventions. The basis for protein-protein interactions is the specific conformation of the receptor after binding of full agonists of the receptor, such as cortisol, corticosterone and dexamethasone. While such agonists allow all possible interactions between receptors and downstream partners, there are also synthetic (and perhaps natural – (Morgan et al., 2017)) ligands that allow only part of the interactions, and in that way combine agonism and antagonism. In immune disease, this concept has been pursued extensively, inspired by the hope to separate anti-inflammatory actions from other effects by separating classical 'transrepression' from 'transactivation' (De Bosscher et al., 2003). More recently, compounds that separate GR-mediated effects based on differential coregulator recruitment were developed, and these may be of benefit in treating stress-related and neurodegenerative disorders in which glucocorticoids play a role (Zalachoras et al., 2013; Pineau et al., 2016).

6.3. Variations on the theme: context & history

The generic mode of transcriptional regulation via MR and GR is by binding to the DNA and subsequent recruitment of coregulators. This then leads to regulation of the MR- or GR- 'transcriptome' in a

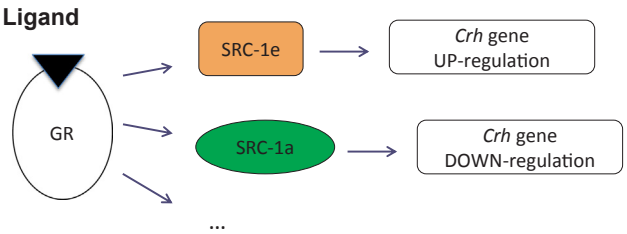

Fig. 6. Coregulators mediate the effects of MR and GR on transcription in a cell type, gene, and ligand dependent manner. As an example, *Crh* expression upregulation in the central nucleus of the amygdala was shown to depend on the 1E splice variant of the steroid receptor coactivator-1 (Zalachoras et al., 2016). SRC-1a seems necessary for *Crh* and *Pomc* downregulation in the core of the HPA axis (Winnay et al., 2006; Lachize et al., 2009).

particular brain area or cell type. However, there are many variations on this theme. For example, the MRs or GRs themselves may be subject to posttranslational modification, e.g. as a consequence of BDNF signaling, and this in turn affects the transcriptome of the receptor (Lambert et al., 2013).

An important issue is that there is not a simple dose-response relationship in terms of target genes: there is a substantial range of EC_{50} values for gene induction by corticosteroids (Reddy et al., 2012), perhaps because the GR – GRE interactions are also defined by affinities of receptor for the DNA binding sites. In fact, ChIPseq analysis of GRs in the hippocampus showed a discrete population of GREs that only gets occupied at very high circulating levels of hormone (Polman et al., 2013). This differential target gene sensitivity makes sense, in that severe stressors should induce changes that are not only quantitatively, but also qualitatively different from for example modest circadian variations (Meijer, 2006; Chatzopoulou et al., 2015).

The GR-occupied loci that are sensitive to only high elevations of hormone most likely have particular roles in adaptation to stress, which may require short *or* long term changes in behavioural, neuronal and – underlying – transcriptional reactivity to stimuli. In other words: exposure to high levels of glucocorticoids may act as a switch to neuronal reactivity. Such (re-)programming effects are likely strongest during early life, but can also occur during adulthood. These programming effects have been observed as a consequence of stress, at different ages and time scales (Turecki and Meaney, 2016; Nasca et al., 2015a, 2015b). The contribution of GR (and MR) to such stress-related reprogramming is often unclear, but may well be there. If so, the programming 'switches' may be targets for GR antagonists to reinstate previous regulations, and one of these molecular switches in the hippocampal dentate gyrus may be CREB-BP (Oomen et al., 2007; Datson et al., 2012).

While in cell systems, GR mostly requires 'open', or active, chromatin in order to bind, GRs can also open up chromatin, and act as local 'pioneers' to activate genomic loci (John et al., 2011). Such a mechanism would constitute a mechanism for permissive actions of cortisol. In the hippocampus, work from the McEwen laboratory showed that there are large scale epigenomic changes even after short term GR activation (Hunter et al., 2012). Vice versa, changed responsiveness as a consequence of earlier stress, even during adulthood, has profound consequences for the transcriptional response to corticosteroids. In a collaboration with Bruce McEwen, Nicole Datson found that in the laser-dissected dentate gyrus of the rat hippocampus, *half* the transcriptional changes to corticosterone treatment were unique to either naïve or earlier stressed animals (Polman et al., 2012; Datson et al., 2013). Thus, both early and late life stressors impact on neuronal reactivity *and* on subsequent adaptations to stressors. In fact, in our experimental designs over the past decades many response characteristics of acute stressors were investigated in rodents that previously had been exposed to chronic repeated stressors or chronic variable stressors (Karst and Joëls, 2003; Datson et al., 2013; Gray et al., 2014), see for review (Joëls et al., 2007).

Long term adaptations and switches are – logically – considered to be the consequence of either exposure to stressors or inflammatory conditions that conditionally activate MR and/or GR (Joëls et al., 2012; Vogel et al., 2015; Brocca et al., 2017; Funder, 2017) in combination with high levels of corticosteroids that saturate of even supersaturate GR (Kaouane et al., 2012). Changes in membrane potential, oxidative stress and altered redox potential activate the MR, which is otherwise not considered to play a role in such programming effects. Whether or not this is the case during particular phases of life remains to be addressed, however. In recent studies on chromatin occupancy by MR, there was a surprisingly broad dose range that extended beyond the assumptions from direct ligand-receptor binding studies (Mifsud and Reul, 2016) suggesting that also receptor turnover should be taken into account (Conway-Campbell et al., 2007). In any case, it is clear that corticosteroids affect via transcriptional mechanisms the organization and activity of chromatin in the brain, which forms, in cross talk with other signals, the genomic basis for the response to stressors (Fig. 7).

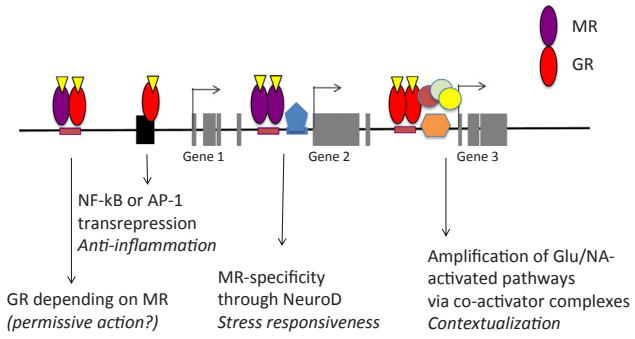

Fig. 7. Genomic action of MR and GR through multiple mechanisms. These mechanisms are (perhaps non-exclusively) linked to particular types of glucocorticoid actions (mentioned in italics). Transrepression of proinflammatory factors is clearly a reactive, dampening mode. MR-dependent activity includes pro-active signaling, setting the stage for stress responsiveness. Heterodimerization is conceptually ill understood, and may involve increasing the dynamic range of responses, and permissive action of basal steroid levels for stress responses. Lastly, co-activator-mediated interactions with other signaling pathways may form a basis for contextualization of the – by itself generic' glucocorticoid signal to affect those cells and circuits that are relevant for a particular stress situation.

7. Questions raised about the MR:GR balance hypothesis

7.1. Is MR always occupied?

Or in other words, are the much lower levels of free rather than total CBG-bound CORT perhaps within the nuclear MR signaling range? This question refers to early statements that MR is already occupied for 80–90% with basal a.m. trough corticosterone levels of 1 μg% (~30 nM; Reul and de Kloet, 1985; Reul et al., 1987; Spencer et al., 1990), which corresponds to a hippocampal free steroid concentration ~0.3 nM as measured with microdialysis (Qian et al., 2012). Although, these free corticosterone levels are indeed around the Kd of MR at 0 °C, occupancy of the receptor depends, however, on the hourly pulses of corticosterone. Such a pulse can be mimicked by a bolus injection. Thus, saturation of nuclear bound MR occurred at one hour after injection of a tracer dose of 0.7 μg ^{3}H-corticosterone/100 gr body weight to ADX rats (McEwen et al., 1968; de Kloet et al., 1975), which results 1 h later in circulating corticosterone levels in the range of the ultradian trough (Reul and de Kloet, 1985). The binding affinity of the MR is so high that immunoreactive (ir)MR stays in the hippocampal nucleus *in vivo* during the 1 h interpulse interval. In contrast, irGR nuclear translocation reflects the ultradian rhythm (Sarabdjitsingh et al., 2009; Sarabdjitsingh et al., 2010) and imposes cyclic gene expression patterns (Conway-Campbell et al., 2010). The distinct differences in occupancy and translocation between the two receptor types led us to propose that the nuclear MR is important for tonic control maintaining the threshold or sensitivity of the stress system, while GR is subsequently essential for recovery and stress adaptation (De Kloet and Reul, 1987). For MR, receptor turnover and activity seem the rate-limiting factors rather than the concentration of the ligand as is the case for GR.

There are however, two new facts to consider in the receptor occupancy story. One fact refers to the ChIPseq studies which suggest that the capacity of some genome binding sites for MR exceeds the ligand binding capacity of the receptor (Polman et al., 2013; Mifsud and Reul, 2016). Although part of this phenomenon can be explained by the formation of MR:GR heterodimers (Mifsud and Reul, 2016), it also highlights that under *in vivo* conditions the rate of synthesis and degradation rather than the absolute levels of the receptors are important. Accordingly, the receptor turnover (Conway-Campbell et al., 2007) rather than the receptor levels assessed by radioligand binding,

immunoreactivity or hybridization assays probably will determine how much of the steroid receptor complex eventually will accumulate at the MR (and GR) binding sites in the genome. This of course does not take into account yet the on-off DNA-receptor binding kinetics observed with molecular imaging (Voss et al., 2011; Groeneweg et al., 2014).

The other novel fact is that MR and GR can mediate rapid non-genomic actions of corticosterone. The action of corticosterone on mEPSC frequency of limbic neurons has an approximately ten fold higher EC50 for corticosterone than can be predicted from the Kd of steroid binding to the nuclear form of these receptors (Karst et al., 2005). Since the membrane receptor is not yet available for binding studies, we are left with the notion that the membrane rather than the nuclear variant of the MR is capable to sense changing corticosterone concentrations during stress and the circadian / pulsatile rhythm. This membrane MR likely mediates the rapid corticosterone effects on coping styles and cognitive processing.

7.2. Is the MR:GR balance not too simple a concept?

In other words, this question would imply that a stochiometric relationship of MR and GR would be too simple to predict the outcome of corticosterone-regulated molecular, cellular and behavioural responses. We entirely agree that this could be inferred at face value from the simple 'MR:GR balance' stochiometry. However, the actual hypothesis refers to a 'balance in MR- and GR-mediated actions' (Section 2.3). At the molecular level this accounts for the context-dependent recruitment of transcription regulators, factors and specificity conferring mechanisms as outlined in the previous section. At the cellular level MR- and GR mediated actions are complementary, often in a U-shape as in the hippocampal CA1 neurons, but also sigmoidal as in dentate gyrus neurons or linear as in PVN or aminergic neurons where mainly GR is present. As pointed out (Joëls, 2006), these widely divergent effects may depend on local bio-availability of the ligand, receptor diversity and the above-mentioned complexity of the genomic machinery. The importance of the MR:GR balance on the organismic level is addressed below.

7.3. Does the MR:GR balance account for the enormous diversity in hormone action?

We argue that the function of the glucocorticoid hormone is primarily aimed to *coordinate* widely divergent cellular and tissue reactions and to *integrate* their outcome over time with one specific goal: to promote coping and adaptation. It is therefore of interest that MR-mediated actions –in interaction with effects by other quickly acting stress mediators- are prominent in the onset of the stress response and are linked to coordination of vigilance, attention, fear, appraisal processes and selection of an appropriate coping strategy to deal with a stressor. These actions are all directed to defend the 'self'. Subsequently, after MR-dependent encoding of the experience, the GR-mediated actions coordinate contextualization, rationalization and memory storage of the experience with the goal to promote adaptation and recovery from the stressor (Sections 2 and 3).

Thus, acute stress involving MR first activates a salience network and over time GR redistributes resources to an executive network enhancing cognitive processes (Henckens et al., 2012; Hermans et al., 2014). Finally, memory storage can be considered a GR-mediated action that primes brain circuits for coping with future encounters. There is still very little understanding how these complementary MR- and GR-mediated actions can coordinate the emotional and cognitive aspects of the stress response within the spectrum of other signals involved (e.g. neurotransmitters, neuropeptides and growth factors). A glimpse of the underlying mechanism towards integration over time has become apparent from the recently discovered phenomenon of metaplasticity (Section 3) (Joëls et al., 2012; Karst and Joëls, 2016). Thus, we have begun to dissect the hormone-dependent mechanism of resource allocation that coordinates and integrates distinct phases of defense, adaptation and priming of the brain under stress.

MR and GR also interact over time. While GR activation promotes memory storage, the retrieval of this memory trace in the right context at a later time depends on rapid MR-mediated actions. MR antagonists administered prior to re-testing individuals can block the retrieval of previously learned behavior (Oitzl and de Kloet, 1992; Khaksari et al., 2007; Dorey et al., 2011; Vogel et al., 2016; Wirz et al., 2017). Also in the immune defense domain, the pendulum hypothesis illustrates how mineralocorticoids and glucocorticoids have sequentially opposing pro- and anti-inflammatory responses over time. The priming phase was uncovered by the pioneering research of the Maier lab: the formation of the inflammasome involved among others GR-mediated activation of NLRP3 (Frank et al., 2015).

7.4. What is the role of MR and GR in long-term priming effects?

The late Seymour Levine (Levine, 2005) discovered in the mid 1950s that early life experience is one of the most profound primers of life-long changes in brain circuits. As was first reported by Michael Meaney, Moshe Szyf and coworkers (Weaver et al., 2004) these priming events at least involve epigenetic modification of DNA encoding GR expression. Since this epigenetic programming is a topic deserving a whole review by itself (McEwen, 2017), we will just allude to a few fundamental principles.

The *first* issue is that early life experience is an important determinant of individual differences in cognition and emotion in later life and hence also depends on the testing conditions in adulthood. Generally, whole litters are exposed in numerous studies to a variety of paradigms based on variations in maternal care or neglect. That has led to the notion that increased maternal care reduces stress reactivity in later life. However, when these well-groomed animals were exposed to severe stressful challenges in later life, they were unable to cope. This contrasted with their neglected littermates who outperformed them in e.g. fear-motivated behavior, a phenomenon known as the 'mismatch' hypothesis (Champagne et al., 2008; Daskalakis et al., 2013).

The *second* issue concerns amplification of individual differences at later life. For instance, Brown Norway rats exposed to maternal deprivation at postnatal day 3 for 24 h show a remarkable trajectory of cognitive aging. While at senescence most of the control animals are partially impaired, albeit with some poor and some excellent performers, this is not the case with the deprived rats. Deprivation of maternal care drives at senescence cognitive performance to the extremes (either impaired or non-impaired) at the expense of the average partially impaired performance (Oitzl et al., 2000; de Kloet and Oitzl, 2003; Sandi and Touyarot, 2006).

While these two examples demonstrate that DNA methylation is very important for long-term priming of the brain, this at the same time raises the *third* issue, i.e. whether there are windows during life to modify such enduring effects. In recent experiments it appeared that the priming effect induced by an unstable maternal environment (Rice et al., 2008) – a procedure that evokes an inappropriate corticosterone release - appears reversible by treatment with the GR antagonist mifepristone several weeks after early life adversity during early puberty (Arp et al., 2016).

These examples demonstrate the importance of epigenetics for priming brain circuits in an enduring manner. Evidence is accumulating for DNA methylation of GR as well as other stress signaling molecules including the GR-dependent programming switches discussed in Section 6.3, but results for the MR are still lacking.

7.5. Which ratio of MR:GR signaling is favorable for coping and adaptation?

In a healthy individual MR:GR signaling adapts to demand. This implies that a given ratio of MR and GR activities may become

maladaptive when the individual is faced with challenges that exceed coping resources or when either one of the receptors becomes defunct. For instance, MR signaling in hippocampus modulates the initiation and magnitude of the stress reaction (Ratka et al., 1989; Harris et al., 2013) and its dysregulation may affect coping. If, GR signaling is inadequate the stress response becomes prolonged and recovery is hampered which is unfavorable for stress adaptation (Sapolsky et al., 2000).

There are different strategies in learning to cope with a stressor (see section 2 and 3). Under mild stressful conditions most individuals use a hippocampal-based cognitive strategy, but with more severe stressors the striatal stimulus-response performance (habit learning) is preferred. Such stressor exposure increases hippocampal and prefrontal MR expression (Gesing et al., 2001; Workel et al., 2001; Brydges et al., 2014; Zhang et al., 2012). Also, individuals with genetically determined higher MR expression prefer a stimulus-response strategy as is observed with human carriers of MR haplotype 2 (Wirz et al., 2017). These functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) studies showed that the selection of habit learning coincided with a bias towards amygdala-striatal connectivity at the expense of hippocampal function (Wirz et al., 2017, Schwabe et al., 2013).

Stress-sensitive DBA mice with high hippocampal MR expression display an active coping style in the forced swim test. These DBA mice show increased amygdala-striatal connectivity as opposed to C57Bl6 mice, which use a passive hippocampus-linked strategy (Colelli et al., 2014). The genetic trait for high MR expression is also found in dominant 'short attack latency' mice that learn an active coping style (Veenema et al., 2003). In humans and rodents habit learning can be reversed to a hippocampal spatial strategy by MR antagonist treatment (Schwabe and Wolf, 2013; Vogel et al., 2016). The MR antagonist also attenuates sympathetic outflow, aggressive behavior and anxiety (de Kloet et al., 2000; Korte et al., 1995; Kruk et al., 2013). It seems that high limbic MR activity favors an active coping style and habit learning.

Activation of nuclear and membrane MRs enhances excitatory transmission (Joëls et al., 2012). High MR signaling was found to correspond with low mGlu2 receptor expression in mice selected for anxiety and a passive coping style in the forced swim test following exposure to chronic stress (Nasca et al., 2015a, 2015b). The finding was recapitulated with the Flinders stress-sensitive mouse model for depression which shows besides a passive coping style and anxiety, also insulin resistance. Administration of acetyl-L-carnitine -an acetyl donor and rapidly acting candidate antidepressant- increased mGlu2 receptor expression, decreased MR expression, and reversed the behavioural and metabolic phenotype (Nasca et al., 2013, 2015a, 2015b). Interestingly, the Flinders mice that were resistant to acetyl-L-carnitine, were not affected in glutamate homeostasis and the high MR expression was not reduced (Bigio et al., 2016). It thus seems, that in these mice in spite of the high MR signaling, the switch to the active coping strategy during stressor exposure does not occur.

In post-mortem brain tissue of depressed patients MR expression is decreased (Klok et al., 2011a), while antidepressants increase MR (and GR) expression (Seckl and Fink, 1992). Furthermore, mice with forebrain overexpression of MR generally show improved cognitive function and less anxiety (Rozeboom et al., 2007; Mitra et al., 2009; Harris et al., 2013). In these mutants, MR overexpression partly protected against the adverse outcome of chronic (early life) stress on spatial memory, neurogenesis and synaptic function (Kanatsou et al., 2015; Kanatsou et al., 2017). Likewise, rats exposed as pups to enhanced maternal care have increased hippocampal MR (and GR) expression and showed improved hippocampal cognitive performance (Champagne et al., 2008). However, if these animals are faced with severe stressors they show increased anxiety and impaired hippocampal learning.

A testable hypothesis is, therefore, that limbic MR signaling protects under healthy conditions, but may switch during adversity to a proverbial 'disease' receptor (Jaisser and Farman, 2016) if the ability to select an efficient coping style fails. By testing this hypothesis, MR signaling should be aligned with the function of the ventral tegmental dopamine circuitry in stress coping, which depends on limbic afferents (Belujon and Grace, 2017).

8. Concluding remarks

And so, half a century after the discovery of the hippocampal corticosterone receptors, the neuroendocrinology of stress has witnessed a number of interesting twists. Thus, there are actually two receptor systems, MR and GR, for glucocorticoids, which comprise not only the classical nuclear receptors but also membrane-associated variants that mediate rapid non-genomic actions. MR- and GR occur in genetic variants which associate with physiological and behavioural traits. Epigenetic processes induced by chronic and/or acute (early) life stressors can result in enduring changes in expression of MR and GR with consequences for the stress response. During a stressful experience, brain circuits are primed for storage of memory traces, which can be retrieved again via MR for coping with a challenge. Evidence is obtained that a similar principle of storage and retrieval may apply to the inflammasome in brain. Rapid progress was made with the identification of coregulators and transcription factors, notably the NeuroD and NF1 family, to assign context-dependent specificity to glucocorticoid action.

Of great help to accommodate the new knowledge of MR and GR is the concept of *allostasis*, which is defined as the *process to re-establish homeostasis*, i.e. by acquiring stability through physiological and behavioural change (Sterling and Eyer, 1988; Karatsoreos and McEwen, 2011; McEwen and Gianaros, 2011). Allostasis relies on metastability describing "the capacity of the brain to switch or to even lock into several available patterns which can be either adaptive or maladaptive" (Sousa, 2016; Kelso, 2012). Energy expenditure to maintain such a labile equilibrium is calibrated with the metric of allostatic load (McEwen, 2003; Juster et al., 2010; McEwen and Wingfield, 2010). The brain corticosteroid receptors are important mediators of allostasis, not only because of their specific effects on synaptic plasticity, but also because of their ability to supply through mitochondrial mechanisms the energy resources on demand to cells and circuits activated in a time-, receptor- and circuit-dependent manner (Picard et al., 2014; Hollis et al., 2015), (see Section 3.3 and Figs. 2–4).

The coming decades much more knowledge will be gained about the signaling mechanism underlying coping, resilience and adaptation to stress. A major task will be to translate these molecular details to cell function and particularly to behavior. The unraveling of molecular signaling pathways will learn how an environmental experience can shape brain and behavior. This knowledge is fundamental for understanding the actions of glucocorticoids in stress-related mood- and anxiety disorders. These findings no doubt will be helpful to alleviate and perhaps even *prevent* stress-related brain disorders. One can envision a world where individuals may be able to predict their resilience ability using a combination of neuropsychology with polygenic and other biomarkers of neuro-endocrine, cognitive and emotional aspects of stress reactivity. Once a certain tipping point has passed, prevention probably is no option anymore and treatment is needed. The above-mentioned bio-psychology defined in conceptual endophenotypes can then be helpful to predict the outcome of therapy (Hellhammer et al., 2018).

Current *pharmacotherapy* with glucocorticoids is still symptomatic and there are adverse side effects. Initial success is booked with balancing MR- and GR-mediated effects in this respect: i.e. to provide cortisol to refill the depleted brain MR during dexamethasone (Meijer and de Kloet, 2017). The advent of selective glucocorticoid receptor modifiers (SGRM) presents another very interesting option: new medicines are being designed that target coregulators with the goal to modulate -in a cell-, tissue or context-dependent manner- receptor function (Zalachoras et al., 2013; Van Den Heuvel et al., 2016; Kroon et al., 2018). Alternatively, *replacement therapy* of the adrenally-

deficient individuals is still far from optimal. Although such patients are in a stable medical condition, quality of life (QoL) is diminished by e.g. cognitive deficits and fatigue (Tiemensma et al., 2016). This important medical need likely will be met by mimicking the ultradian cortisol cycle (Spiga et al., 2015). In future, one can envision biosensors monitoring the need for cortisol during stress and exercise that are combined with a bio-device releasing the hormone on demand with the goal to improve Qol.

But even in the short-term, our current insight may help clinical practice. Rather than hoping that a hypothesis-free research endeavor will bring the magic bullet which can boost resilience and will deliver successful treatment of stress-related psychopathology, one target may be staring us already right in the face: cortisol. This endproduct of the endocrine stress system drives two complementary receptor systems -MR and GR- which coordinate and integrate the enormous diversity in cell and tissue responses to stress over time. What began with hippocampal corticosterone receptors half a century ago has grown today into a dual MR:GR signaling system overarching rapid non-genomic and delayed genomic actions, serving cognitive functions that promote coping, adaptation, memory and resilience in a changing world.

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Conflict of interest

RHdeR and ERdK are on the Scientific Advisory Board of DynaCorts Therapeutics. ERdK also serves on the SAB of Pharmaseed Ltd and owns stock of Corcept Therapeutics. OCM receives research funding from Corcept Therapeutics.

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