

Mineralocorticoid receptor and glucocorticoid receptor work alone and together in cell-type-specific manner: Implications for resilience prediction and targeted therapy

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ABSTRACT

'You can't roll the clock back and reverse the effects of experiences' Bruce McEwen used to say when explaining how allostasis labels the adaptive process. Here we will for once roll the clock back to the times that the science of the glucocorticoid hormone was honored with a Nobel prize and highlight the discovery of their receptors in the hippocampus as inroad to its current status as master regulator in control of stress coping and adaptation. Glucocorticoids operate in concert with numerous neurotransmitters, neuropeptides, and other hormones with the aim to facilitate processing of information in the neurocircuitry of stress, from anticipation and perception of a novel experience to behavioral adaptation and memory storage. This action, exerted by the glucocorticoids, is guided by two complementary receptor systems, mineralocorticoid receptors (MR) and glucocorticoid receptors (GR), that need to be balanced for a healthy stress response pattern. Here we discuss the cellular, neuroendocrine, and behavioral studies underlying the MR:GR balance concept, highlight the relevance of hypothalamic-pituitary-adrenal (HPA) -axis patterns and note the limited understanding yet of sexual dimorphism in glucocorticoid actions. We conclude with the prospect that (i) genetically and epigenetically regulated receptor variants dictate cell-type-specific transcriptome signatures of stress-related neuropsychiatric symptoms and (ii) selective receptor modulators are becoming available for more targeted treatment. These two new developments may help to 'restart the clock' with the prospect to support resilience.

1. Introduction

It was at the wonderful Frontiers in Stress and Cognition conference, September 23–26, 2012 in Ascona organized by Carmen Sandi, that Bruce McEwen gave a presentation entitled the "Brain on Stress: how the social environment gets under the skin." The story evolved along the allostasis/allostatic load concept until Bruce stated rhetorically that the magic bullet to treat the health risk due to maladaptive stress-coping has not been discovered yet. A voice with a Dutch accent arose from the audience stating: "but Bruce the magic bullet is staring right in your face: that bullet is related to cortisol, your life's work!"

2. Stress and glucocorticoids

And why not? If cortisol is a master regulator of the myriad of neural, endocrine, immune and metabolic stress mediators for better or worse, it also should harbor somehow a key towards prevention and treatment of stress-related health problems. This notion, however, has been entertained before when the science of the adrenal evolved. Remember, the 1950 Nobel Prize in Physiology or Medicine was awarded jointly to Edward Calvin Kendall, Tadeus Reichstein and Philip Showalter Hench "for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects." (see www.nobelprize.org/prizes/medicine/1950/hench/lecture/).

To explain the miraculous action of cortisone in relief from

Abbreviations: MR, Mineralocorticoid receptor; GR, Glucocorticoid receptor; HPA-axis, Hypothalamic-pituitary-adrenal-axis; ACTH, Adrenocorticotropic hormone; CRH, Corticotrophin-releasing hormone; GREs, Glucocorticoid response elements.

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rheumatoid arthritis and other inflammatory diseases one of the Nobel laureates stated, by using a figure of speech: “*these hormones appear not to extinguish the fire, not to act like a carpenter to repair the damage of fire. Instead, they appear to dampen the fire or to provide, as it were, an asbestos suit behind which the patient, like some biblical Shadrach, Meshach, or Abednego, protects his tissues from the fire*” (Philip Hench, Nobel Lecture, December 11, 1950). In retrospect, that view was entirely wrong. The correct view is that the endogenous glucocorticoid action prevents the initial stress (e.g., inflammatory, and immune) reactions to overshoot and become damaging (Munck et al., 1984). Or as Marius Tausk (1952), Director of NV Organon in The Netherlands, metaphorically stated in the language of the Nobel laureates: “*glucocorticoids are required to limit the water damage caused by the fire brigade*”.

This all happened at the time Selye had formulated the ‘stress concept’ more than 10 years before (Selye, 1936). To that effect Selye distinguished specific actions (e.g., tissue damage) from the apparent ‘non-specific stereotypical reaction of stress’, that activates the HPA-axis and increases the level of its end-product the ‘adaptive hormone’ cortisol. The regulation of the inflammatory or tissue reactivity (in Selye’s terms) by cortisol determines whether “*the body succumbs or resists by means of adaptation*”, distinguished as distress vs eustress, respectively. All effects of cortisol depend on external and internal (hereditary, constitution, previous exposure) “*conditioning factors*”. Of note, the ‘non-specific stereotypical action of stress’ can -in retrospect- be disputed; there are numerous highly specific pathways and neuronal circuits that mediate the activation of the HPA-axis and that show plasticity over time. Moreover, cortisol has in every cell- and tissue-type distinct and conditional actions. Such pleiotropic action allows the hormone to coordinate and integrate cell and tissue function over time at the organismal level.

According to Selye “*the adaptation syndrome in itself is not pathogenic, but an indispensable physiological defense reaction to damage as such*”. The imperfection (e.g., an absolute or relative excess or deficiency of one or more adaptive hormones) plays an important role in the pathogenesis of many diseases. “It is not stress that kills us, it is our reaction to it”. Such maladies, in which inadequacies of cortisol actions, are even more important than the specific actions of the pathogen itself, are considered “*diseases of adaptation*”. This line of reasoning led to the ‘*pendulum hypothesis*’ by which the action of antagonistic adaptive hormones (pro-inflammatory mineralocorticoids and anti-inflammatory glucocorticoids) can set disease susceptibility at different levels (Selye, 1950).

The process of restoring balance towards a new homeostatic setpoint, is at the root of the allostasis concept (McEwen and Wingfield, 2010). Thus, information, perceived and/or anticipated as a psychological stressor, is processed in the brain, and triggers the release of multiple stress mediators that operate in complex self-regulating feedforward and feedback regulations with the goal to establish homeostasis via physiological and behavioral adaptations (Levine, 2005). This adaptive process in anticipation of, or in response to, is called allostasis and can be described in terms of metastable energetic states of the fitness landscape, according to Brian Fertig in a two volume book on Metabolism and Medicine, advised by Bruce (Fertig, 2022). The energy expenditure is ‘the cost’ or allostatic load and subsequent ‘wear and tear’ is a sign of allostatic overload. Attempts are under way to provide a quantification of the allostatic load index based on levels of circulating stress mediators of the autonomic, immune and HPA-axis systems, blood lipids and glucose (Guidi et al., 2021; Juster et al., 2010; Wiley et al., 2016).

Bruce was capable to explain the ‘good and bad’ glucocorticoid action in succinct and comprehensible language. For instance, in a commentary in Chronic Stress (McEwen, 2017) he addressed in just 1000 words the question: “*What is the confusion of Cortisol?*”. The narrative highlighted the composite of ultradian, circadian and stress response patterns of cortisol secretion as critical for balanced neuroendocrine, immune and metabolic adaptations. During chronic stress, cortisol promotes adaptive changes in structure and function of the brain: the

shrinkage of hippocampus and medial prefrontal cortex vs. growth of amygdala and orbital frontal cortex, are manifestations of adaptation and need to be interpreted as sign of plasticity rather than damage. Cortisol’s and corticosterone’s actions vary over the life time, from programming of stress-induced ‘early’ amygdala awakening (see Box 2) and potentiation of stress-related functions in sex-dependent fashion during puberty (Brydges et al., 2014; Papilloud et al., 2019) to facilitation of age-related adaptations (Landfield, 1987; Lupien et al., 2009; Sapolsky et al., 1986).

The key question posed by Bruce was: “*when conditions change, and the stressor is gone, can the brain adapt to the new situation?*” If not, information processing gets “*stuck*” and resilience becomes compromised, leading to the equally important query “*how can this be treated?*” The commentary is clarified with a cartoon illustrating the inverted U-shape effects of increasing glucocorticoid and excitatory amino acid exposure on synaptic function and plasticity culminating into risk for excitotoxicity. In the next sections the avenue towards understanding this overarching action of the glucocorticoid hormone is discussed in terms of cooperation between its two complementary receptor systems (McEwen, 2017).

3. Discovery of MR and GR function

It was in the pioneering phase of the neurosciences in the late 1960’s, heralding the emergence of Psychoneuroendocrinology, that Bruce identified the receptors for the rat’s glucocorticoid corticosterone in the purified cell nuclear fraction of the rat hippocampus, thus, surprisingly, not in the hypothalamic PVN, which releases corticotrophin releasing hormone (CRH). As Bruce pleasantly recalled, he initially thought having catastrophically changed the labels of the samples to be counted in the liquid scintillation counter. But the replication inexorably confirmed that corticosterone targets the hippocampus, a finding that was further supported by high resolution autoradiography visualizing the hour-long retention of radioactive labelled corticosterone in all pyramidal and dentate gyrus neurons and abundantly also in other limbic areas (lateral septum and amygdala), but not in the PVN (Gerlach and McEwen, 1972; McEwen et al., 1968).

Attempts to reproduce the *in vivo* identification of the hippocampal corticosterone receptors with the potent synthetic glucocorticoid dexamethasone initially turned out to be a total failure. It was found that dexamethasone targets the pituitary corticotrophs, and not the hippocampus [(de Kloet et al., 1974; De Kloet et al., 1975); for a detailed account see the Box ‘The dexamethasone story’ in (de Kloet et al., 2018)]. By acting at the pituitary, dexamethasone potently suppressed stress-induced HPA-axis activity leading to a condition of minimal amounts of circulating corticosterone, which was called ‘chemical adrenalectomy’. Twenty years later it was discovered that the synthetic glucocorticoid poorly penetrates the blood brain barrier, because it is a substrate for multidrug resistance P-glycoprotein (Meijer et al., 1998; Schinkel et al., 1995).

In the early 1980’s it was already current wisdom that *in vitro* in hippocampus cytosol two receptor populations were present that could be distinguished by inclusion of the pure glucocorticoid RU28362 (Krozowski and Funder, 1983; Moguilewsky and Raynaud, 1980; Veldhuis et al., 1982) in the medium: one soluble receptor did bind with high affinity not only the naturally occurring glucocorticoids corticosterone and cortisol, but also aldosterone, deoxycorticosterone and progesterone. It was also known that *in vivo* aldosterone and corticosterone did compete for this apparent promiscuous mineralocorticoid receptor (MR) retained in hippocampal cell nuclei, while progesterone and deoxycorticosterone although having appreciable affinity to MR, did not interfere with *in vivo* cell nuclear retention of corticosterone (De Kloet et al., 1983; McEwen et al., 1976). The other soluble receptor population, the classical glucocorticoid receptor (GR), did bind with a ten-fold lower affinity corticosterone, but with high affinity dexamethasone and the ‘pure’ glucocorticoid RU28362 (Veldhuis et al., 1982).

Box 1

An overactive renin-angiotensin-aldosterone system (RAAS) aggravates the course of COVID-19; the RAAS system may become overactive because SARS-CoV-2 targets ACE2 (Rysz et al., 2021; Young et al., 2020). Such RAAS imbalance can be restored with angiotensin II inhibitors, and *in vitro* more recently mineralocorticoid antagonists appeared active in reducing pro-inflammatory mediators including galectin-3 (Jover et al., 2021). While this preliminary observation supports a pro-inflammatory mineralocorticoid action in the course of COVID-19, in the later stage when the cytokine storm arises, the potent anti-inflammatory synthetic glucocorticoid dexamethasone appeared a life-saver, which is in line with the role of glucocorticoids in limiting overshoot of immune defense (Horby et al., 2020). Collectively, these findings illustrate the pendulum hypothesis, if further validated for mineralocorticoids (Akin et al., 2022).

Box 2

In rodents, there is a stress hypo-responsive period (SHRP) in which responses to mild and moderate stressors do not increase glucocorticoid secretion (Levine et al., 1991), and pups learn to remain with the dam irrespective the aversiveness of the environment (Moriceau and Sullivan, 2006). The SHRP provides the context for the brain to develop, while being protected from excessive glucocorticoid-mediated actions. However, the SHRP can be interrupted by challenges. For instance, in response to maternal absence the offspring's HPA-axis is activated. Interestingly, baseline ACTH and corticosterone secretion can be reinstated in the deprived animals by mimicking different aspects of maternal care: increased CRH and ACTH is normalized by tactile stimulation and corticosterone release by feeding (van Oers et al., 1998). Another interesting phenomenon is the premature expression of amygdala-based aversion learning upon corticosterone exposure during early life (Moriceau et al., 2006, 2009; Moriceau and Sullivan, 2006). The programming of an amygdala-based fearful phenotype was supported in a model of early stressful experience during repeated daily separations. The premature amygdala awakening resulted during later life in reduced social interaction, increased emotional reactivity and memory, increased stereotypy, and impaired sensorimotor gating (Daskalakis et al., 2011, 2012, 2014b). In clinical realm, a role of maternal depression in programming of childhood anxiety disorder involving placenta 11HSD-2, DNA methylation of NR3C2 and infant cortisol reactivity anxiety was suggested recently in a series of publications arising from the Mercy Pregnancy and Emotional Wellbeing Study (Galbally et al., 2019, 2020, 2021). See also section 6.

We realized that *in vivo* the low affinity GR escaped detection by the tracer amount of corticosterone (see Box 3). Indeed, *in vivo* dose-response studies with corticosterone revealed a differential occupancy of the high and low affinity corticosterone receptors; the neuro-anatomical distribution of the dual corticosterone receptor system was mapped with micropunches of brain nuclei and by using *in vitro* autoradiography (Reul and de Kloet, 1985, 1986; Reul et al., 1987). It was an interesting time, full of confusion. For instance, the glucocorticoid cascade theory (Sapolsky et al., 1986), and the developmental programming actions of corticosterone were initially still based on high-affinity ³H-corticosterone binding in hippocampus called GR, while these high affinity sites are in fact the MR.

In the spring of 1987 Jeff Arriza and Ron Evans cloned the NR3C2 (MR gene), after having revealed the genetic structure of NR3C1 (GR gene) two years earlier (Arriza et al., 1987; Hollenberg et al., 1985). By referring to the receptor pharmacology they suggested the two receptor types may operate as a "binary signaling system" (Arriza et al., 1988; Evans and Arriza, 1989). Then, in 1988 in Edinburgh, Chris Edwards

discovered the critical role of 11 β -hydroxysteroid dehydrogenase type 2 (11HSD-2) in conferring aldosterone specificity to MR in kidney epithelial cells. Accordingly, we showed in a collaborative study with *in vivo* autoradiography that after a licorice block of 11HSD-2 activity the aldosterone-selective receptor in kidney was labelled with the ³H-corticosterone tracer (Edwards et al., 1988). A similar conclusion on the role of 11HSD-2 in conferring aldosterone specificity was around the same time reached by John Funder (Funder et al., 1988). Meanwhile, the concentration of immunoreactive (ir) aldosterone present in purified rat hippocampal nuclei was *in vivo* only 1–5% of the amount of ir-corticosterone suggesting that the MR is exposed to predominantly the naturally occurring glucocorticoid (Yongue and Roy, 1987). Actually, in hippocampus, the abundance of glucocorticoids over aldosterone is probably even much larger in many brain cells given their co-localization with 11-HSD1 reductase that regenerates locally bio-active glucocorticoids (Chapman et al., 2013).

During fetal rat life, 11HSD-2 is abundantly expressed in brain, but soon after birth the oxidase is found mainly restricted to the

Box 3

In 1984 at a French Riviera conference organized by Roussel Uclaf, Jan-Åke Gustafsson presented the very first brain immunocytochemistry (ICC) with antibodies raised against the liver glucocorticoid receptor (GR). However, the rat hippocampal CA2 and CA3 areas, surprisingly, appeared poorly labelled with immunoreactive GR, while these pyramidal neurons were shown by high resolution to abundantly retain the ³H-corticosterone tracer (De Kloet et al., 1983; Fuxe et al., 1985). A voice with a Dutch accent arose from the audience stating rather bluntly the error of the mismatch between GR ICC and ³H-corticosterone autoradiography. The chairman then interfered and expressed his dismay by proposing this remark ought to be withdrawn from the proceedings since it discredited the craftsmanship of the Swede, which was of course not the intention of the discussant. However, in a flash, the mystery was resolved: the ³H-corticosterone tracer apparently did not provide enough ligand to visualize *in vivo* the lower affinity GR, while ³H-dexamethasone did not reach the brain in sufficient quantity!

Box 4

Writing this MR:GR overview is a reminder to a friendship of more than half a century ago that started even before the time of ERdK's post-doctoral fellowship in the McEwen lab [see Box 1 in (de Kloet et al., 2018)]. That postdoc project was inspired by the failure of ERdK to demonstrate -as a PhD student in The Netherlands-dexamethasone binding to hippocampal corticosterone receptors. And indeed, in the Bruce lab we established that dexamethasone and corticosterone could not be lumped together in binding to, what later appeared to be, the mineralocorticoid receptor (De Kloet et al., 1975). At that time the McEwen lab, located at the Gasser Hall, was already densely populated and night shifts were needed to accommodate all students of stress in the brain. Bruce's office was so small that the lab had to be evacuated to provide sufficient space if he decided to roll back his chair for consultation of a literature archive. In the subsequent 50 years ERdK has visited numerous times the 13th floor of the Weiss building, sometimes unexpectedly, by pretending he called from Holland, but, in reality, was just sitting next door to Bruce's office in New York. Bruce returned briefly to his Dutch roots, the Lenters family in Hardenberg in the east of The Netherlands, when he was awarded in 2006 in Leiden the Marius Tausk Guest Professorship. Such events reinforced our ever-ongoing friendship and resulted in several more recent common publications of the Leiden-New York labs along Bruce's Leitmotiv that 'you can't do things on your own' (Datson et al., 2013; Hunter et al., 2012, 2016; Polman et al., 2012).

subcommissural organs, locus coeruleus, ventromedial hypothalamus and amygdala and nucleus tractus solitarius (NTS) in non-aminergic cells near the periventricular area postrema (Geerling et al., 2006; Robson et al., 1998). These aldosterone-selective MR are involved in salt appetite and contribute to central cardiovascular regulation (Geerling and Loewy, 2009; van den Berg et al., 1990). The aldosterone-selective MR expressing neurons project from the NTS to discrete midbrain and forebrain regions, notably the parabrachial nucleus near the locus coeruleus and the ventrolateral bed nucleus of the stria terminalis (vBNST) (Gasparini et al., 2019). From these nodes extensive crosstalk is possible with limbic forebrain and hypothalamic agouti related peptide (AgRP) networks in regulation of emotional, motivational and cognitive functions associated with salt appetite and energy metabolism (Gasparini et al., 2019). This crosstalk likely underlies the anxiety, dysphoric and anhedonic symptoms experienced by patients suffering from hyperaldosteronism (Hlavacova and Jezova, 2008; Murck et al., 2020).

These initial findings on MR and GR diversity were shared with Bruce in his influential 1986 Physiological Review (McEwen et al., 1986). The various versions + corrections of the manuscript were communicated by snail mail, for all of us the trigger to start writing with word processors. In a subsequent 1987 position statement with Hans Reul the GR-mediated feedback action was distinguished from tonic influences exerted via the corticosterone-preferring limbic MR in regulation of the stress response (De Kloet and Reul, 1987). This reasoning was based on the extensive occupancy of the brain MR even under basal conditions, while GR activation only occurred with rising corticosterone concentrations during the circadian peak and after stress (but see (Mifsud et al., 2021; Polman et al., 2013)). Moreover, rat brain MR expression was highest in the morning when corticosterone levels are low. MRs decreased during the aging process, while neurotrophic peptides and surprisingly, ginsenoside RG1, could restore this age-dependent decrease, a finding that was recently confirmed in the zebrafish (De Kloet and Reul, 1987; He et al., 2020; Reul et al., 1988). Accordingly, we concluded that for brain MR the receptor activity rather than the ligand concentration is rate-limiting. The notion that the brain MR was predicted to be involved in regulation of the *setpoint* of the stress response system rather than it mediated the feedback action exerted via GR (De Kloet and Reul, 1987) is until today a source of inspiration.

4. MR and GR: neuroendocrine, cellular and behavioral aspects

4.1. Neuroendocrine regulation

The notion that brain MR could be linked to the *setpoint* of the HPA-axis was readily demonstrated by Mary Dallman's group. They showed that the increased level of adrenocorticotrophic hormone (ACTH) after

adrenalectomy (ADX) was normalized with amounts of corticosterone that were sufficient for MR occupancy, and only little GR activation (Dallman et al., 1989). At the same time, it was demonstrated that, in adrenalectomized animals, the MR antagonist RU28318 administered systemically, icv or in hippocampus, increased basal am and pm circulating ACTH and corticosterone levels and enhanced stress-induced HPA-axis activity (Oitz, 1997; Oitzl et al., 1995; Ratka et al., 1989; van Haarst et al., 1997). That blockade of the brain MR increased HPA-axis activity was confirmed in humans (Deuschle et al., 1998; Young et al., 1998). Accordingly, the MR is important for the *threshold or sensitivity* of the stress response system. This role of the MR in the *onset* of the stress response is also demonstrated in genetically modified as well as genetically selected mice: high hippocampal MR expression corresponds with low basal and attenuated stress-induced HPA-axis activity (Harris et al., 2013; Veenema et al., 2003).

The GR antagonist mifepristone only caused increased glucocorticoid secretion during the circadian peak when there is sufficient GR occupancy in pituitary corticotrophs and brain. If the GR antagonist was given under the stressful conditions of a systemic injection a large and prolonged HPA-axis activation occurred that lasted almost 24 h; the same is observed with a 100 000 fold lower dose locally in the PVN (Dalm et al., 2019; De Kloet et al., 1988; Ratka et al., 1989). Surprisingly, the stress-induced HPA-axis activation was strongly suppressed, upon subsequent daily administrations of the GR antagonist (Dalm et al., 2019). How that is possible is not precisely known. One explanation may be the MR, which gets a more prominent role if colocalized GR is blocked. Indeed, when the antagonist was infused locally in the dorsal hippocampus in amounts of 10 ng per rat, a blunting of stress-induced levels of ACTH and corticosterone was observed (van Haarst et al., 1997). Such opposing MR- and GR-mediated effects on the HPA-axis were supported in a transgenic animal model where MR and GR were expressed in different expression ratios (Harris et al., 2013).

4.2. Cellular studies

Meanwhile, pioneering *in vitro* cellular studies by Marian Joëls et al. with the dorsal hippocampal CA1 neurons had clearly demonstrated an U-shaped dependency of opposing MR- and GR-mediated actions (Joëls, 2006; Joëls and de Kloet, 1989, 1990). The depolarization-induced influx of Ca²⁺ via L-type voltage-dependent Ca²⁺ channels is high after ADX, suppressed via predominant MR activation, but increased again with high concentrations of corticosterone in a process requiring GR homodimerization (Chameau et al., 2007; Karst et al., 1994, 2000). A similar U-shape dose response was observed for other processes that depend on Ca²⁺ influx such as cell firing accommodation and slow afterhyperpolarization (Joëls and de Kloet, 1989, 1990). Neurotransmitter responses in the dorsal hippocampal CA1 neurons obey the

U-shaped dose-response relationship such as the inwardly rectifying K^+ -hyperpolarization linked to serotonin 1A (5HT1A) receptor activation (Joels and De Kloet, 1992; Joels et al., 1991) which is suppressed by MR and increased after ADX as well as high dose GR activation.

An U-shaped action of glucocorticoids on neuronal excitability by a complementary MR- and GR-mediated action is also observed in e.g., the ventral hippocampus (Maggio and Segal, 2009) and the basolateral amygdala (BLA) (Karst et al., 2010). Neurons that express predominantly GR as in hypothalamus and the ascending aminergic neurons, lack this U-shaped curve upon corticosterone stimulation. However, in the hippocampal granular dentate neurons that express both MR and GR, the ADX-induced increase in Ca^{2+} current and the 5HT1A linked K^+ hyperpolarization (and 5HT1A expression) is suppressed by MR occupancy, while GR activation does not reverse this effect (Joels, 2006; Meijer et al., 1997). There is no straightforward explanation for this lack of GR-mediated effect in dentate gyrus neurons. It could be, however, related to the observation that GR activation following stress occurs in hippocampus only in sparsely distributed neurons, that are linked to the memory engram (Bonapersona et al., 2022; Lesuis et al., 2021; Reul et al., 2015), but this obvious needs further investigation. In the dentate gyrus, cellular differentiation depends on MR, while proliferation and migration is GR-dependent. When both MR and GR are deleted the granular dentate gyrus neurons do not survive and apoptosis is observed (Fitzsimons et al., 2013; Oakley et al., 2021; Sloviter et al., 1989; Woolley et al., 1991).

Altogether, the role of MR in maintaining a stable and high excitatory tone is important for viability, while GR activation suppresses transiently raised excitability [for overview see (Joels et al., 2008, 2012, 2018)]. Neuronal function under basal conditions with predominant MR occupation (the trough in the U-shape) is characterized by a high and stable excitatory tone. The high excitatory hippocampal outflow activates the inhibitory hypothalamic GABA-ergic network suppressing CRH neuronal activity as can be measured with Ca fiber photometry (Kim et al., 2019; Ulrich-Lai and Herman, 2009). Accordingly, this mechanism would explain why hippocampal inhibition of HPA-axis activity is an MR-rather than GR-dependent phenomenon.

While the above cellular mechanisms are genomic, a fast non-genomic GR-mediated suppression of PVN neuronal excitability was discovered that depends on the trans-synaptic action of endocannabinoid (Di et al., 2003, 2016). Next to this GR-mediated endocannabinoid-driven mechanism, a non-genomic MR-mediated action was identified in hippocampal CA1 neurons that rapidly increases miniature excitatory postsynaptic potential (mEPSP) as measure of pre-synaptic glutamate release (Karst et al., 2005; Olijslagers et al., 2008). The actual visualization of the putative membrane localization of MR and GR has met so far only limited success (Groeneweg et al., 2011), but see imaging of the nuclear receptor localization (Groeneweg et al., 2014).

Subsequent studies focused on 'metaplasticity' of the amygdala neurons, i.e., the phenomenon that various signals cooperate to ensure responsiveness. Metaplasticity was studied by exposure of the amygdala neurons to different concentrations of the β -adrenergic agonist isoproterenol and corticosterone. By combined exposure to concentrations of isoproterenol mimicking moderate stress initially excitability increased, before it was suppressed by the steroid. However, by combining high concentrations of noradrenaline agonist and corticosterone, mimicking severe stress, the later excitability suppression 'flips' to excitation (Karst et al., 2010; Karst and Joels, 2016). Such a mechanism would make sense in behavioral realm when an extended period of increased excitability would reflect the excessive strong encoding of a severely stressful experience (Henckens et al., 2012, 2015). The findings on the cellular level are therefore important for translation to behavioral studies that showed a similar synergy of glucocorticoid and noradrenergic signaling in consolidation of fear-motivated behavior (see next section) (Roozendaal et al., 2009a).

4.3. Behavior

On the behavioral level, the pioneering studies by Melly Oitzl et al. revealed the outcome of MR and GR complementarity over the different domains of information processing. Using the Morris water maze as example, it was shown that GR activation in hippocampus promoted memory consolidation of the escape platform location, which could be blocked by the GR antagonist mifepristone icv (Oitzl and de Kloet, 1992; Oitzl et al., 2001). In contrast, 24 h after memory storage, MR appeared involved in memory retrieval to locate this escape platform. Interestingly, the MR antagonist icv not only impaired retrieval, but also facilitated a switch in search strategy when the original escape platform was removed. Intact animals continued to swim to the original platform location, but with MR blockade the animal seemed to have forgotten the location and started to search elsewhere for an escape (Oitzl and de Kloet, 1992). Also, in fear-motivated behavior, MR blockade was found to interfere with memory retrieval, to affect risk assessment and response selection. The latter selection of a behavioral response was very nicely demonstrated in the radial maze where animals either used a stimulus response or a spatial learning strategy to locate an exit. Without stress, all animals (males) used spatial and contextual (hippocampal) information, but upon stress exposure the animals readily relied on a habitual stimulus-response (striatal) strategy (Arp et al., 2014; Dias-Ferreira et al., 2009; Schwabe et al., 2010b, 2013; Souza et al., 2014, Ter Horst et al., 2013a).

GR activation promotes memory storage in fear conditioning paradigms which is further enhanced by a noradrenergic – cAMP mechanism, possibly involving endocannabinoid interaction (Roozendaal et al., 2009b). Accordingly, GR activation promotes consolidation and memory storage of a great variety of paradigms based on active or passive fear-motivated behaviors, social competence, problem solving behavior, drug and alcohol dependence (De Kloet et al., 1988; Roozendaal and McGaugh, 2011; Sandi and Haller, 2015; Vendruscolo et al., 2015).

To test the effect of MR:GR imbalance on behavior, male mice were generated (with littermates as controls to avoid different maternal influences) with limbic brain overexpression of MR (MRhi) and global GR underexpression (GRlo) (Harris et al., 2013). The mutants were not affected in basal secretion of corticosterone but showed an HPA-axis response pattern that is consistent with knowledge on MR and GR function gained from pharmacological manipulations and genetically selected lines (Veenema et al., 2005). Thus, MRlo/GRlo animals show an enhanced and prolonged HPA-axis response but this overshoot in peak secretion was strongly suppressed in MRhi mutants. Behaviorally, the MRhi animals maintained readily their acquired coping strategy suggesting superior retrieval or a more readily switch to habitual behavior, which is typically facilitated in case of excess limbic MR functionality (Harris et al., 2013). The switch from spatial/declarative (thinking) to habitual (doing) behavior is a characteristic feature of human behavior under stress, particularly in individuals carrying a gain of function MR polymorphism that are protected against depression and display dispositional optimism (Klok et al., 2011b; Wirz et al., 2017). Gain of function MR supports healthy aging, as observed in Brown Norway rats (Marissal-Arvy et al., 2004; Oitzl et al., 2000).

Coordination of MR- and GR-mediated actions in learning and memory processes was also demonstrated during the circadian cycle. Using live imaging with transcranial 2-photon microscopy, Conor Liston reported that a non-transcriptional GR-mediated action promotes during the circadian corticosterone peak the formation of dendritic spines in layer 5 of the motor cortex, while the animals are learning the rotarod task (Liston and Gan, 2011). This GR-mediated non-genomic mechanism readily triggered the LIM1-kinase cofilin pathway, which underlies modulation of the actin cytoskeleton. The response to high glucocorticoid concentrations is superimposed on a transcriptional MR-mediated action, which operates during the circadian trough as a prerequisite for retention of the motor skill. This MR-mediated action is involved in

pruning the apparent superfluous dendritic spines (Heshmati and Russo, 2013; Liston et al., 2013). Accordingly, over the sleep-wake cycle stabilization of dendritic spine formation is under control of the genomic MR (Hall et al., 2015; Ikeda et al., 2015).

Interestingly, also dexamethasone interferes with learning and spine fate in the mouse cerebral cortex, but formation, stabilization and pruning can be reinstated however with a corticosterone regime mimicking the circadian rhythm (Liston et al., 2013). Previous research had demonstrated that dexamethasone cannot replace corticosterone in the brain because the potent synthetic GR ligand shows only little affinity for the MR and poorly penetrates the blood brain barrier (Karssen et al., 2005). In humans, dexamethasone can have severe side effects (Judd et al., 2014). Dexamethasone reduces slow wave sleep and causes dysphoric effects, which can be turned into euphoria by co-administration of cortisol activating MR (Born et al., 1991; Groch et al., 2013; Plihal et al., 1996). The utility of cortisol add-on was shown with dexamethasone treatment of children with acute lymphoblastic leukemia. In about 30% of the children’s severe adverse neuropsychological effects and sleep disturbances occurred, which were ameliorated by cortisol add-on (Warris et al., 2016).

4.4. MR:GR balance concept

The cellular studies demonstrate coordinate MR- and GR-mediated actions of corticosterone in metaplasticity: MR activation increases excitability, and the transient increase in excitability is suppressed via GR. The neuroendocrine data show that central MR activation regulates the onset and peak HPA-axis activity, and GR its duration. The behavioral data show MR-mediated actions are engaged in risk assessment,

response selection and behavioral flexibility. MR activation enhances learning, encoding and retrieval of the experience. The subsequent GR-mediated actions promote contextualization and rationalization of the experience, while supporting memory consolidation, behavioral adaptation and recovery. These actions mediated by MR and GR were disturbed with selective antagonists and genetic deletion of either receptor and reinstated by restoring the balance in MR- and GR-mediated actions. Accordingly, the neuroendocrine, cellular, and behavioral data illustrate the concept 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 behavioral adaptation, which potentially can aggravate stress-related deterioration and promote vulnerability” (de Kloet et al., 2005, 2018; De Kloet et al., 1998; Holsboer, 2000).

5. HPA-axis patterns matter

Imaging of the human brain has provided insight in the circuits that are activated sequentially during behavioral adaptation (Fig. 1). Initially, a salience circuit is recruited that processes perception of sensory information towards increased attention, vigilance, and emotional reactivity, along the fight-flight-fright scenario (Berretz et al., 2021; Hermans et al., 2014). This alarm reaction is coordinated by CRH, vasopressin and other stress neuropeptides, central aminergic and sympathetic nervous system and the HPA-axis.

Meanwhile resources are gradually made available to the executive circuitry to mobilize higher cognitive functions directed by neuronal ensembles in the medial prefrontal cortex (PFC). The goal is then to suppress emotional reactivity and to support coping and adaptation, and

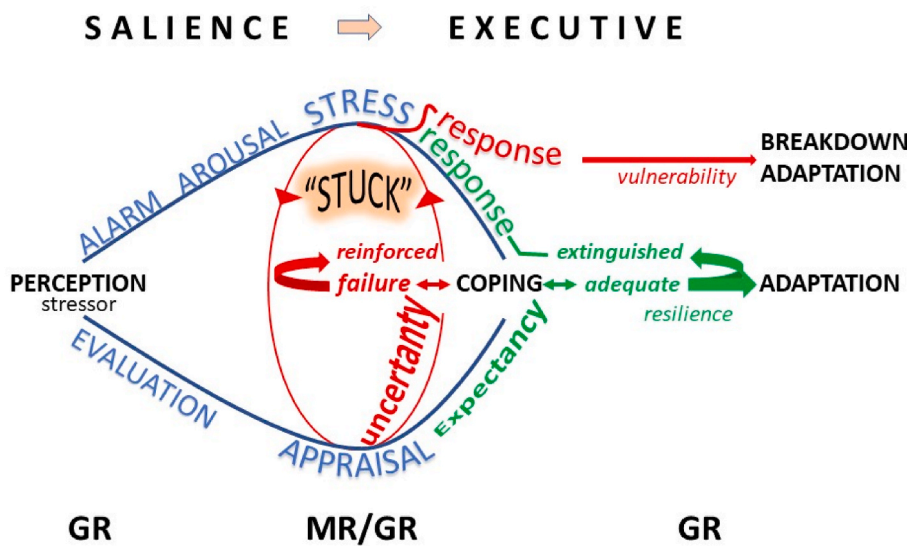


Fig. 1. The Brain Gets “Stuck”. The anticipation and/or perception of a stressor may trigger an alarm reaction causing arousal while a behavioral (vigilance, attention), autonomic (sympathetic nervous system) and neuroendocrine stress response develops. At the same time the stressor is appraised for its controllability. While appraisal and stress response networks interact (Cabib et al., 2020; Douma and de Kloet, 2020), resources are shifted from the salience to the executive network underlying rationalization, selection of an appropriate coping style and contextualization to label the experience for memory storage (Cabib et al., 2020; Henckens et al., 2012, 2015; Hermans et al., 2014). If coping fails because of uncertainty about outcome, the stress response is reinforced and prolonged (in red). Upon repeated failure to cope with the stressor, the neurons that underlie emotional reactivity grow (amygdala, orbital frontal cortex), while hippocampus and medial PFC shrink and compromises their role in cognitive control (Wellman et al., 2020), a condition described by Bruce as ‘the brain gets stuck’ (McEwen, 2017; McEwen and Akil, 2020; McEwen et al., 2016). Under these ‘chronic stress’ conditions a novel stimulus cannot be processed appropriately, which may lead to breakdown of adaptation, a condition that can be

read from altered patterns of glucocorticoid secretion upon challenge by an acute stressor (McEwen, 1998, 2007; Papilloud et al., 2019; Tzanoulinou et al., 2020). If coping is adequate, because expectancy is rewarded and control is regained, the activated stress response system is extinguished, and adaptation promoted (Douma and de Kloet, 2020). Using fMRI, optogenetics and DREADD technology much progress has been made in recent years to understand how medial PFC neuronal ensembles gain control over stress- and emotional reactions, and how this control is translated top down into an altered pattern of neuroendocrine and behavioral responses; glucocorticoids integrate and coordinate in bottom up fashion the brain-body dialogue in stress-coping and adaptation (de Kloet et al., 2019; Herman et al., 2020; Lingg et al., 2020; Ulrich-Lai and Herman, 2009). GR seems involved in regulation of detection thresholds that are relevant for perception of sensory signals (Henkin and Daly, 1968; Obleser et al., 2021) and MR for the threshold or sensitivity of the stress response system; the balance in MR:GR-mediated actions is crucial for proper processing of information in the salience and executive networks (de Kloet et al., 1999, 2018; Joels et al., 2018; Wirz et al., 2017). MR activation facilitates retrieval processes, risk assessment and response selection; GR activation promotes rationalization and contextualization facilitating memory storage and behavioral adaptation (Oitzl and de Kloet, 1992; Roozendaal and McGaugh, 2011). Cartoon inspiration from discussions with Pieter Smelik, Nuno Sousa and Bruce McEwen. Green denotes that adequate coping extinguishes the stress response and promotes resilience, while red color denotes that failure to cope reinforces the stress response and leads to a crash of information processing. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

thus recovery from the stressor. Underlying the shift towards executive control are appraisal processes such as risk assessment as prelude to decision-making in selection of behavioral solutions to cope and to adapt, which coincides with hippocampus-based contextualization and memory storage. The executive function is more than just a homeostatic reset to prevent the initial stress reaction from overshoot, which is the essential of glucocorticoid physiology; it is allostasis-at work underlying adaptation to change and its cost weighted as allostatic load (Henckens et al., 2012).

Studies have demonstrated that the salient phase tapers off over 30–60 min, until shortly after the cortisol peak, while meanwhile executive control is gradually reinforced when genomic actions of the hormone take shape (Henckens et al., 2015). In animal studies, using pharmacological, optogenetic, DREADD and CRISPR-cas technology, the prefrontal-limbic-periaqueductal circuitry that underlies executive cognitive control over salient emotional reactivity is being identified (Cabib et al., 2020; Herman et al., 2020; Lingg et al., 2020; McKlveen et al., 2019; Nawreen et al., 2020; Radley and Johnson, 2018).

It is not unreasonable to postulate that the balance in activity of salient and executive networks can be read from patterns of HPA-axis activity and glucocorticoid secretion that drives the complementary MR- and GR-mediated actions. This is demonstrated in animal studies on the effects of chronic stress showing profound adaptations in structure and function of the salient and executive networks. Thus, the amygdala and orbital cortex hypertrophy, while the dendritic organization in medial PFC and hippocampus atrophies, including suppression of neurogenesis (McEwen et al., 2016). While under these conditions the individual may still manage with a shift towards habitual behavior, adaptation breaks down upon exposure to a heterotypic stressor, since the executive network is not equipped anymore at that time to deal with the novel challenge. This can be read in hippocampus from gene expression patterns. Expression patterns do not differ very much under steady-state conditions in chronically stressed individuals from controls. However, an acute challenge with corticosterone or with a heterotypic stressor shows a profoundly different response between the two conditions. In chronically stressed animals the challenge reveals prominent expression of e.g., inflammatory, epigenetic, chromatin reorganization pathways, while pathways supporting neurogenesis and synaptic plasticity are suppressed (Datson et al., 2013; Gray et al., 2014; Polman et al., 2012).

In the influential 1998 NEJM article (McEwen, 1998), Bruce proposed that under these conditions of chronic stress three potential maladaptive cortisol secretion patterns can be distinguished. Firstly, upon exposure to a repeated homologous stressor a vulnerable condition would develop if the corresponding glucocorticoid response *does not adapt or habituate* and continues to show a response of the same or perhaps even larger amplitude. Secondly, if a ‘chronic stress’ condition is challenged with an acute heterologous stressor *a too low or too high cortisol peak* would signal a problem with containment of stress- and emotional reactions, functions ascribed to the MR. Thirdly, *a prolonged cortisol response* would indicate lack of control, inadequate coping and thus poor adaptation, which is typical GR business. An aberrant initiation or termination of the stress reaction thus can be read from HPA-axis activity and cortisol and implies risk for compromised resilience and increased vulnerability.

For understanding the significance of HPA-axis activity and cortisol secretion, elaborate tests are needed that record patterns rather than a single cortisol value, preferably based on certified challenges such as the Trier Social Stress Test (TSST) (Rothe et al., 2020) or dexamethasone suppression test (Carroll et al., 1976; Heuser et al., 1994; Shorter and Fink, 2010). Alternatively, such patterns have been exploited in animal experiments for the identification of susceptible phenotypes. In a series of studies in the laboratory of Carmen Sandi animals were selected by a protocol of repeated peripubertal stress exposure. While in part of the animals the corticosterone secretion pattern adapts, there are also animals that show resistance to adaptation of the peak corticosterone

secretion, while others maintain a prolonged secretion. Then, during adulthood the peak-resistant animals showed deficits in cognitive functions, as shown in learning a maze task, while those displaying resistance to shut-off are characterized by impaired social competence (Papilloud et al., 2019, 2020; Tzanoulinou et al., 2020). Interestingly, these altered corticosterone patterns and impaired behaviors can be reset with mifepristone (Papilloud et al., 2019). Thus, the glucocorticoid hormone is a master regulator and its function in stress coping and adaptation can be read from its secretory pattern. MR-mediated actions are prominent during the onset and peak of the stress reaction, while GR is involved in its duration.

6. Sex differences

In a systematic review and meta-analysis (Zorn et al., 2017) revealed sex differences in saliva free cortisol secretion patterns of psychiatric patients in response to the TSST or a similar psychosocial stressor characterized by socio-evaluative threat and lack of control. Data collected from 14 studies showed a blunted cortisol response in women diagnosed with major depressive disorder, whereas cortisol secretion of depressed men was exaggerated, both in comparison with controls. In remitted male patients, the enhanced cortisol reactivity disappeared, while in females the difference with controls became less. The TSST-induced cortisol profiles from 9 studies with patients suffering from anxiety disorders (including posttraumatic stress disorder (PTSD) and social anxiety disorder) showed also decreased cortisol reactivity in females vs., increased reactivity in males. In healthy individuals the HPA-axis response shows a similar sex difference in the TSST: adult males show higher ACTH, saliva free and blood total cortisol responses than females in the luteal phase; generally HPA-axis is increased during the follicular phase and contraceptive use (Kudielka and Kirschbaum, 2005; Stephens et al., 2016).

In contrast, the rodents’ HPA-axis activity in response to a variety of stressors is, however, generally more enhanced in females over males. Highest ACTH and corticosterone levels are in the pro-estrus phase when estrogen and progesterone levels peak (Bangasser and Valentino, 2014; Heck and Handa, 2019). Interestingly, estrogens decrease hippocampal MR mRNA and protein expression rather than GR, while progesterone is a competitive inhibitor of the hippocampal MR (Carey et al., 1995). Accordingly, when the levels of both sex steroids are high, as is the case in the pro-estrus, the consequent reduced MR functionality predicts elevated HPA-axis activity. Indeed, in ovariectomized animals the stress-induced ACTH and corticosterone levels are highest when substituted with both sex steroids (Carey et al., 1995). However, under conditions of chronic mild stress or chronic variable stress, male rather than female animals have the highest HPA-axis response, if challenged with an acute novel stressor (Dalla et al., 2005; Kokras et al., 2021). For understanding the implication of the sex difference in circulating glucocorticoids various other factors play a role beyond the balance of MR and GR, such as e.g., the sex difference in bio-available amount of free vs. total corticosterone because of increased corticosteroid binding globulin in females, liver metabolism and clearance rate and last possibly sexual dimorphism in glucocorticoid action (see below).

That there are sex differences in the stress induced HPA-axis response is perhaps not so surprising since males and females may have different coping strategies (Bale and Epperson, 2017; Bangasser and Valentino, 2014; Moisan, 2021). While the preferred initial response to a threat in males is ‘fight or flight’, that of females seems rather pro-social ‘tend-and-befriend’ strategy (Taylor et al., 2000). In rodent studies, sex differences can be demonstrated in coping with an inescapable forced swim stressor, in fear conditioning paradigms, during spatial learning and in social discrimination tests (Kokras et al., 2021; ter Horst et al., 2012). For instance, acute and chronic stress impairs performance of males in a variety of spatial memory tasks, but not of females, who showed actually an improved spatial performance (Luine et al., 2017). Such impaired performance of males in spatial learning tasks during stress seems to be

compensated by a switch towards stimulus-response (habitual) behavior. For this purpose a circular 'hole board' is used where the mice had to locate an exit hole using extra- (spatial) and intra-maze (stimulus) cues (Schwabe et al., 2010a) (see section 4.3.). In this test, the switch of behavior in females is opposite to that of males: the females show under stress rather improved spatial skills -a sign of cognitive resilience-particularly in the estrous phase, rather than the habitual behavior displayed by the males (ter Horst et al., 2013b). However, the switch in coping strategy of both sexes under stress is lost following MR deletion from the forebrain (Ter Horst et al., 2013a). In an intriguing series of experiments, yet another sexual dimorphic aspect was uncovered using BDNFVal66Met mutants in a spatial learning: the object placement (or recognition) test. It was found that, in this mutant, estrogens impair spatial learning, while males are not deficient. This deficiency in females could be predicted by a particular transcriptional signature in the hippocampal CA3 region, where MR dominates GR expression (Marrocco et al., 2017).

The studies reported in the previous paragraphs suggested that hippocampal MR is involved in sex-specific risk assessment and response selection. This is further demonstrated in a test that measures social approach and discrimination between familiar and non-familiar conspecifics. After forebrain MR deletion, it appeared that the male rather than the female mutants had lost their ability to discriminate between a familiar and un-familiar mouse. Administration of a MR antagonist, and not a GR antagonist, to male mice also impaired their ability of social discrimination (Ter Horst et al., 2014). Recently, a MR hotspot, with relatively little GR expression, was identified in the hippocampal CA2 network that displayed a molecular identity distinct from the other pyramidal cell groups (McCann et al., 2021; Oakley et al., 2021). Deletion of the MR from the CA2 hub impaired social behavior. Interestingly, the CA2 neurons are also densely innervated by vasopressin acting via V1B receptors which are known to regulate social behavior (Pagani et al., 2015; Young et al., 2006).

The different learning strategies could be due to 'activational' effects of sex steroids on structure and function of limbic forebrain circuitry, a field of science that was explored by the McEwen lab for half a century (Marrocco and McEwen, 2016; McEwen, 2020a). In addition, the MR seems involved because it binds progesterone and responds to estrogen. Besides these direct effects, the sex steroids have long-term 'organizational' actions that can enable the sexual differentiation because of "interaction between genetic influences of the X and Y chromosome and mitochondrial DNA inherited primarily via the mother" (McEwen, 2020a). In the 'classic' view this regards the function of the Y chromosome Sry causing testis formation and subsequent masculinization of the fetal brain by testosterone (McEwen, 2020a). In the 'revisionist' view, transcriptomics of the sex chromosome complement revealed that the developing male brain does express much more immune and inflammatory genes. A mechanism was proposed involving the increased immune function of microglia's that seem to bias sexual differentiation in the brain towards a male signature (McCarthy et al., 2017). Glucocorticoids also have sexual dimorphic effects firstly because of mutual interaction with sex steroids via their respective receptors (Kroon et al., 2020). Secondly, because of the much larger number of glucocorticoid responsive immune genes in males than females (Duma et al., 2010). These two aspects raise the question why glucocorticoids, either via MR and/or GR, would not be an additional signal in sexual differentiation of the brain (Bale, 2016; Marrocco et al., 2017; McCarthy, 2020; Quinn et al., 2014), a notion that received recently further support by the sex-dependent role of GR-responsive miRNA's in neuronal architecture (Tejos-Bravo et al., 2021). The interaction between glucocorticoid, sex steroids and potentially immune factors is important for understanding the perinatal basis of sex differences in the brain mechanism underlying stress resilience (Maccari et al., 2017).

In the human, several studies have shown associations between increased maternal cortisol, or maternal depression characterized by a history of early life trauma, with increased volume c.q. connectivity of

the 'right' amygdala, in female offspring only (Buss et al., 2012; Graham et al., 2019; Soe et al., 2018). Remarkable is that the female prevalence of the maternal programming effect is associated with the 12 months infant cortisol reactivity and with internalization and emotional problems at an age of 4 years (Galbally et al., 2022b). In a subsequent study, the association of maternal depression appeared to be female-specific for infant cortisol reactivity and later emotional disorder of the 4 year old. These associations were found mediated by reduced expression of placental 11HSD-2 mRNA. A diminished 11HSD-2 activity would result in excess cortisol that passes through the placenta, and which then could become engaged in female-specific programming of an emotional 'amygdala' (Galbally et al., 2021, 2022a, 2022b; Jahnke et al., 2021). In animal studies the GR-mediated glucocorticoid amygdala programming of an emotional phenotype was uncovered before (Daskalakis et al., 2014b; Moriceau et al., 2006), but if this is also sex-specific and involves lateralization of the amygdala awaits further research.

7. What next?

A signature of chronic stress can be revealed as aberrant glucocorticoid secretion pattern and signaling in response to an acute stressor, taking also into account the sex difference (Bale, 2016; Kokras et al., 2021; Kroon et al., 2020; Quinn et al., 2014). Furthermore, it has been demonstrated that changes in cortisol secretion pattern may signal not only an upcoming precipitation of depression and other affective disorders, but also its remission (Holsboer, 2000). This link between the pattern of cortisol secretion and disease vulnerability or resilience raises the question how it can be exploited as biomarker for a successful treatment strategy. In other words, would it be possible with pharmacological and/or psychological approaches to restore a healthy glucocorticoid pattern as point of departure 'to restart the clock'. Such an approach would better match Bruce's positivity rather than figuring out 'why one cannot roll the clock back' question to cure stress-related disorders.

A fruitful approach 'to restart the clock' could be to *teach* glucocorticoid patterns with interventions such as e.g., psychotherapy, mindfulness, exercise, and other non-pharmacological approaches that have been advocated by Bruce repeatedly himself (McEwen, 2020b). Another approach to restart would be pharmacological, but unfortunately, the application of a GR antagonist, CRH antagonists or V1B antagonists has made little progress in this respect (Kokras et al., 2019). One problem with using glucocorticoid-based pharmacotherapy, however, is that the stress hormone is pleiotropic with different actions in every cell and tissue, also over time. This is because -as noted before-glucocorticoids coordinate and integrate the function of cells and tissues over the ultradian pulses and circadian cycle, and during stress coping and adaptation. That's why cortisol substitution therapy is so cumbersome; one needs to mimic the ultradian/circadian and stress-induced patterns to meet the need (Kalafatakis et al., 2016; Violaris et al., 2021).

For real progress, therefore, it is absolutely required to precisely identify the defect in glucocorticoid signaling down to the level of individual cells. This would allow a precise repair of the defect with a targeted treatment, i.e., personalized medicine '*avant la lettre*'. In the next sections progress in two novel developments is highlighted. Firstly, the identification of cell type-specific MR and GR genomics allowing to detect molecular changes responsible for defects in glucocorticoid action. Secondly, the development of an entirely novel generation of highly specific modulators of MR and/or GR function based on bringing selectivity to the interactions of the multimeric receptor complex with DNA/chromatin.

7.1. Genomics to predict stress resilience or vulnerability

Predisposition for altered glucocorticoid signaling has been studied in a variety of genomic studies as biomarker of trait and state, and predictor of longitudinal outcomes such disease progression and

treatment response. Genetic studies focused on common *NR3C1* single nucleotide polymorphisms (SNPs) linked to enhanced transactivation [primarily Bell (rs41423247) and N363S (rs6195/; alias rs56149945)] and revealed association with altered HPA-axis response to stress and to the dexamethasone suppression test (DST) (Huizenga et al., 1998; Jewell et al., 2016; van West et al., 2010; Wust et al., 2004). Genetic variation in *NR3C2* in interaction with childhood maltreatment is associated with DST cortisol outcome, hippocampal and amygdala volume and depression status (top SNP, rs17581262) (Gerritsen et al., 2017; Vinkers et al., 2015). A *NR3C2* haplotype consisting of the 2G/C (rs2070951) and I180V (rs5522) SNPs in the promoter region that affects gene transcription, translation, and transactivation was associated with increased subjective stress- and cortisol stress response (van Leeuwen et al., 2011), changes in amygdala activation (Bogdan et al., 2012), dispositional optimism and protection against depression (Gerritsen et al., 2017; Klok et al., 2011a; Vinkers et al., 2015).

The latest GWAS of basal plasma cortisol did not identify any genome wide significant associations for SNPs in *NR3C1* and *NR3C2* genes but rather in the *SERPINA6* gene, which encodes corticosteroid binding globulin (Crawford et al., 2021). The GWAS Catalog however includes multiple SNP-trait associations (STAs) primarily with non-brain phenotypes (*NR3C1*: atrial fibrillation, height, lung function; *NR3C2*: blood pressure, electrocardiogram morphology, lymphocyte counts; Supplementary Tables 1–2), but also brain phenotypes (*NR3C1*: migraine, response to ketamine, sleep; *NR3C2*: Alzheimer’s disease, hippocampal volume, neurofibrillary tangles; Supplementary Tables 1–2). Finally, rare variants in *NR3C2* are associated with autism spectrum disorder (De Rubeis et al., 2014; Ruzzo et al., 2019) and schizophrenia (Singh et al., 2022). The two genes did not share many trait-associations (~6%,

Fig. 2A) with the shared traits being generic/not disease-specific: lymphocyte percentage, neutrophil percentage, and liver protein quantitative trait loci.

Approximately a third of the disease-associated *NR3C1* variants are involved in the cis-regulation of *NR3C1* gene expression (Fig. 2B, Table S1) either as expression or splicing quantitative trait loci (eQTLs or sQTLs) or as members of polygenic prediction of gene expression [e.g., PrediXcan models (Gamazon et al., 2015)]. Interestingly, the disease-associated *NR3C2* variants had none of those properties (Fig. 2C Table S2). Using expression predictive models to conduct transcriptome-wide association studies (TWAS) of tissue- and cell-type-specific genetically regulated mRNA expressions and pathways with traits (Chatzinakos et al., 2020, 2021a). Using the webTWAS resource (Cao et al., 2022), the identified gene-trait associations (GTAs) for *NR3C1* and *NR3C2* were more overlapping (~30%, Fig. 2D) compared to the STAs. The shared traits were centered around heart and thyroid diseases. For stress-related mental disorders, TWAS-based GTAs have been identified for glucocorticoid regulated genes and pathways (Dalvie et al., 2021; Gelernter et al., 2019; Huckins et al., 2020; Stein et al., 2021).

NR3C1 and *NR3C1* exon expression patterns are tissue-specific (Fig. 3). Seminal studies by the Meaney group focused on epigenetic regulation (increased methylation) of the hippocampus *Nr3c1* primary exon 1F promoter by early life stress (i.e., low maternal care) that was found linked to reduced GR mRNA and protein expression, hyper-responsivity to stress and impaired cognitive performance (Liu et al., 1997; Weaver et al., 2004). Further investigation revealed that these methylation changes were not unique to *Nr3c1* (Suderman et al., 2012) and that also MR levels were reduced (Champagne et al., 2008). A study

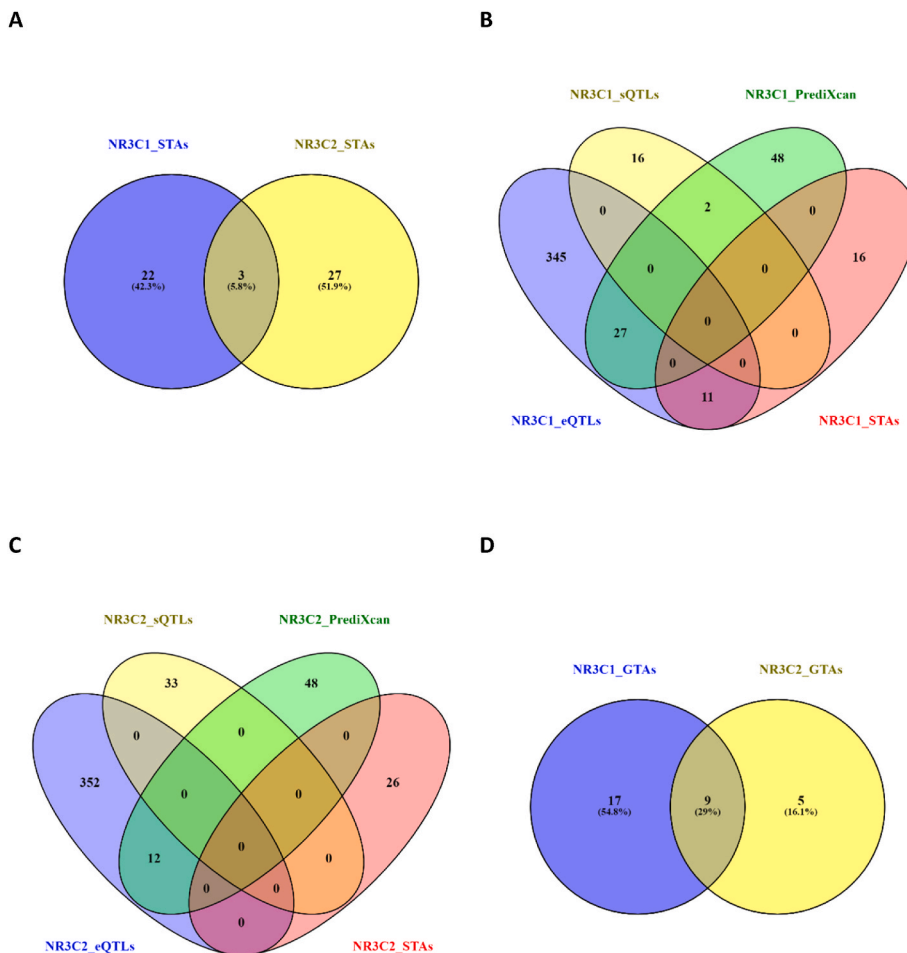


Fig. 2. *NR3C1* and *NR3C2* trait associations. (A) Overlap of *NR3C1* and *NR3C2* SNP trait associations (STAs) based on GWAS (NHGRI-EBI GWAS catalog database: <https://www.ebi.ac.uk/gwas/>). Overlap of *NR3C1* (B) and *NR3C2* (C) STAs with their expression and splicing quantitative trait loci (GTEx project: <https://gtexportal.org/home/>) and predictive models of expression based on cis-regulation (Barbeira et al., 2021). Overlap of *NR3C1* and *NR3C2* gene-trait-associations (GTAs; D) based on TWAS included in webTWAS database (<http://www.webtwas.net/#/>).

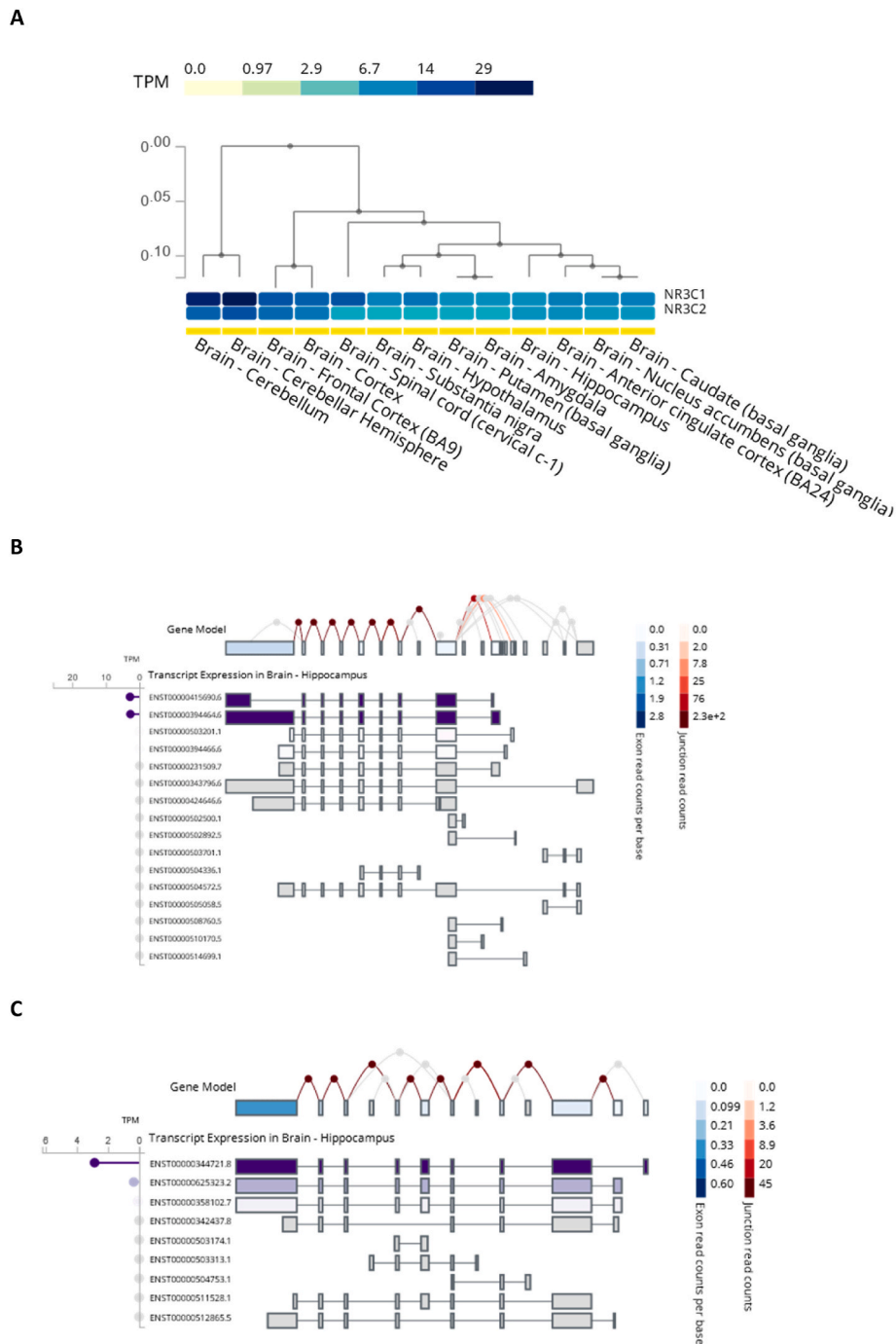


Fig. 3. *NR3C1* and *NR3C2* expression in the brain. **A:** Clustering of *NR3C1* and *NR3C2* expression in the brain loci. **B/C:** Exon-specific transcription of *NR3C1* (**B**) and *NR3C2* (**C**) genes in hippocampus. Plots generated at GTEx project portal: <https://gtexportal.org/home/>.

of analogous genomic loci in the human GR gene (i.e., *NR3C1*) was conducted in brain (McGowan et al., 2009) and peripheral tissue as a function of stress exposure during different phases of life (intergenerational, fetal, child and adult) and/or in relation to stress-related psychopathology (Daskalakis and Yehuda, 2014). Trauma exposure during military deployment was associated with an increase in all methylation measures, but development of mental health problems after deployment was only significantly associated with an increased functional methylation (i.e., methylation sites affecting gene expression) (Schur et al., 2017). DNA methylation patterns in *NR3C2* are less studied, with the first study showing an association with aggressive behavior in males (Qing et al., 2021). Finally, a pilot study revealed that genetic variation

and DNA methylation in *NR3C1* were predictors of treatment response to psychotherapy in PTSD subjects (Yehuda et al., 2013). This was an intriguing study that was followed up by genome wide investigations of DNA methylation changes associated with psychotherapy (Vinkers et al., 2021; Yang et al., 2021).

Gene expression studies have investigated components of the GR signaling complex as biomarkers and predictors of stress-related psychopathology. The largest studies and meta-analyses revealed the involvement of GR as a master regulator of the expression signatures, but not as an explicitly altered GR gene expression which of course would not be necessary when glucocorticoid concentration patterns are altered (Breen et al., 2015, 2018; Daskalakis et al., 2016; Glatt et al.,

2013; Guardado et al., 2016; Kuan et al., 2017; Logue et al., 2015; Mehta et al., 2013; Neylan et al., 2011; Segman et al., 2005; Su et al., 2008; Tylee et al., 2015; Yehuda et al., 2009, 2013; Zhang et al., 2015; Zieker et al., 2007). Animal models confirmed this notion by revealing, in the brain, glucocorticoids and the glucocorticoid-activated GR as a primary regulator of transcription in association with individual differences in behavioral responses to stress (Caradonna et al., 2022; Daskalakis et al., 2014a). In the first five studies evaluating gene expression in postmortem brain tissue of PTSD patients, changes were found in immune, neuronal, and stress regulatory pathways (Holmes et al., 2017; Licznarski et al., 2015; Morrison et al., 2019; Su et al., 2008; Young et al., 2015). Next, the first three adequately sized postmortem RNA-seq PTSD studies of cortical and subcortical tissue indicated changes in cell type specific functions like GABA-ergic interneuron pathways and immune/cytokine pathways (Girgenti et al., 2021; Jaffe et al., 2021; Logue et al., 2021).

Nowadays, tissue-specific gene expression has advanced to the single cell level. Thus, using single cell transcriptomics of dorsolateral PFC, we have recently identified in post-mortem brains of PTSD and major depressive disorder (MDD) patients differentially expressed genes within excitatory and inhibitory neurons (not the other cell types), suggesting that cell-type-specific dysregulations are associated with both disorders (Chatzinakos et al., 2021b; Chatzinakos et al., Under Review). Expression signatures of PTSD and MDD in excitatory- and inhibitory-neurons were differentially enriched for GR-dependent cortisol-induced gene expression alterations, especially in Ex-neurons (GR activation in PTSD, GR deactivation in MDD). These findings need to be expanded to other brain regions and need to incorporate MR as well, but they already confirm the hypothesis proposing that PTSD and MDD differ in excitatory- and inhibitory-neuronal GC signaling (Daskalakis et al., 2013b; Yehuda, 2002).

Taken together, stress-related psychopathology arises from differences at various levels of gene regulation in diverse brain cell types that converge on specific pathways (e.g., GC signaling) potentially harboring clinical significance (Dalvie et al., 2021). Adopting the three-hit concept of stress susceptibility (Daskalakis et al., 2013a), the interaction of genetic factors (hit-1) with early-life environmental factors (hit-2) precipitates in altered cell-type-specific glucocorticoid signaling that is mediated by epigenetic modifications, which in turn program brain plasticity with consequences for susceptibility (resilience or vulnerability) to later-life environment (hit-3). This hypothesis is being tested in animal stress studies [e.g., (Bouet et al., 2021)], with the goal to model human findings on stress susceptibility [e.g., (Daskalakis et al., 2021; Vinkers et al., 2014)].

7.2. From pleiotropic action of glucocorticoids to design of novel specific modulators of resilience

Although MR- and GR-mediated processes are complementary and sometimes opposite, at first sight molecular signaling is very similar. The long-term effects of MR and GR activation depend on their activity as transcription factors. Without ligand, both receptor types are predominantly complexed to chaperone proteins in the cytoplasm, and they translocate to the cell nucleus upon binding of agonists and most antagonists. Once nuclear, they can bind to the chromatin/DNA to affect gene expression. The best understood transcriptional mechanism involves binding of receptor dimers to two palindromic hexanucleotide sequences: the glucocorticoid response elements (GREs). Also, the progesterone and the androgen receptors can bind the GRE. Accordingly, PR, AR, MR and GR share a number of target genes that are induced in many different cell types. However, interactions with transcription factors that bind in the vicinity of GREs can result in exclusive DNA binding of a specific receptor, such as NeuroD factors that confer specific binding for MR in the hippocampus (van Weert et al., 2017).

A strongly induced shared target gene codes for *FKBP5*. The FK506 binding protein 5 (*FKBP5*) protein is a co-chaperone in the cytoplasmic

steroid receptor complex, and negatively affects ligand binding of the GR (and presumably the other receptors). Thus, the transcriptional regulation of *FKBP5* constitutes an intracellular negative feedback system, and the fact that MR is also able to induce its expression is one of the ways by which MR activation can limit GR functionality in cells that express both receptor types (Hartmann et al., 2021). Interestingly, the GRE sequence in the *FKBP5* gene can be methylated in a haplotype dependent manner, and this has been suggested to be a mechanism for long term regulation of GR sensitivity, e.g., by early life stress in association with PTSD (Klengel et al., 2013), and *FKBP5* inhibitors are being considered for clinical development. Of note, the consequences of *FKBP5* regulation have been almost exclusively interpreted in relation to GR function, and effects on the MR functionality are understudied. Genes like *FKBP5* that are regulated via both MR and GR should respond to corticosterone over a broader concentration range given the affinity differences. However, GR and MR may also differ in their strength of transactivation of the *FKBP5* gene. Understanding the details and relevance of ‘joint targetness’ await further experimentation.

Classically, GR-mediated actions have been distinguished as to depend on GRE binding, binding in a ‘tethering’ mode to other transcription factors, and binding to negative GREs (nGREs) to exclusively repress (transiently induced) transcription. *CRH* (encoding CRH) and *POMC* (encoding *proopiomelanocortin*, the precursor of *ACTH*) are two examples of genes that likely are transrepressed through nGREs, as part of slow negative feedback. The nGRE mechanism is unique for GR, based on its biophysical properties (Hudson et al., 2013). Also, transrepressive interactions with other transcription factors (classically called ‘transrepression’) seem to be stronger for GR than for MR. However, a number of recent papers in cell models suggest that some form of direct (monomeric or dimeric) GR binding to GREs always involved in its transcriptional activity in a chromatin setting (Escoter-Torres et al., 2020; Johnson et al., 2021). The obligatory involvement of some form of GR-DNA interaction is somewhat of a paradigm shift away from what became a classical ‘transactivation-transrepression’ dogma (Reichardt et al., 1998; Saatcioglu et al., 1994). Indeed, genome wide occupancy studies in the hippocampus suggest that the vast majority of GR binding occurs at the GRE (Buurstede et al., 2021; Mifsud and Reul, 2016; Polman et al., 2013; Pooley et al., 2017). We also found this for MR binding (van Weert et al., 2017), but a recent study by Hans Reul and coworkers suggests that MR also may bind other elements (Mifsud et al., 2021). Of note, any call on the presence of GREs depends on statistical algorithms and is complicated by binding of receptors to half sites (Johnson et al., 2021). Thus, the GRE for now seems to be the most important way by which the hippocampal genome responds to changes in glucocorticoids.

MR and GR bind as dimers to the GRE, either as homodimers or MR:GR heterodimers, or in fact as tetrameric complexes, stabilized by one DNA-docking dimer (Presman and Hager, 2017). The existence of MR:GR heterodimers was elegantly shown by two complementary mutations in the DNA binding domain, that forced MR:GR heterodimers (Liu et al., 1995). Later co-occupancy of MR and GR at the same chromatin fragments (re-ChIP) strongly suggested the existence of heterodimers in the rat hippocampus (Mifsud and Reul, 2016). The presence of MR and GR in the same molecular complexes was also elegantly shown by proximity ligation assay (Oakley et al., 2021). With the emergence of higher order complexes, MR and GR may occur in different stoichiometries in tetramers (Rivers et al., 2019). Almost 30 years after their discovery, the jury is still out with respect to the consequences that MR and GR can form heterodimers for transcription.

Heterodimers would not necessarily be needed to explain differential effects like those on CA1 pyramidal cell excitability. For such phenomena, one would expect that the distinct DNA binding of each receptor type would lead to receptor-specific target genes. From whole hippocampus analysis, the transcription factor Jdp2 may be such a MR specific target gene (van Weert et al., 2019). The work by Mifsud suggests that the formation or maintenance of the cellular cilia may be a function process uniquely regulated via MR (Mifsud et al., 2021). However, the

exact molecular underpinning of the differential MR and GR-mediated effects on cellular excitability remains to be determined – although the relevant target genes are known. In fact, the genomic effects on cellular responsiveness may well involve sets of cooperating target genes. Likely, revealing these will rely on single cell sequencing approaches, as RNA sequencing on bulk hippocampus, or even laser-dissected micropunches (Datson et al., 2013), reflects effects in many different cell types, often diluting each other (Buurstede et al., 2021).

The statement that steroid receptors are transcription factors is seemingly straightforward, but in fact involves an extensive ‘signal transduction’ from the GRE-bound receptor in the form of steroid receptor coregulators. First identified by Bert O’Malley, coactivator proteins link the DNA-bound receptors (often many thousands of base pairs away from the gene) to the RNA polymerase at the promoter of target genes. Some of these proteins can also remodel the local chromatin structure to allow other transcription factors to also access the DNA (Lonard and O’Malley, 2012). Conversely, corepressor proteins bind to steroid receptors mediate inhibition of transcriptional responses, e.g., at nGREs (Hudson et al., 2013). Of note, the coregulator recruitment differs between genomic loci, and therefore genes (Zwart et al., 2011). GR (and MR) mechanisms that involve chromatin remodeling may enable the GR to reprogram neurons and circuits during (early life) traumatic stressors.

Coregulators should be of considerable interest to stress researchers. First, they are shared to varying degrees between members of the nuclear receptor superfamily. This implies that they may become limiting for receptor function and provide a mechanism for cross talk between these types of receptors (Lonard and O’Malley, 2012). Second, coregulators show substantial differences in neuroanatomical distribution (Mahfouz et al., 2016; Viho et al., 2022). This may explain why in the PVN glucocorticoids can suppress the expression of the *Crh* gene, while in other brain regions such as the amygdala GR potentially stimulates its expression (Zalachoras et al., 2016). Thirdly, coregulator recruitment is strongly ligand dependent, and this may allow targeting a subset of MR and/or GR dependent transcriptional targets (Zalachoras et al., 2013b).

MR and GR both have two large protein domains that can bind coregulators. The AF-1 function is localized in the intrinsically unstructured N-terminal part of the receptor, and shows little apparent overlap between MR and GR. The AF-2 function is localized in the LBD, and -at least *in vitro*-there are only modest differences in the coregulator

recruitment between MR and GR via this domain (Broekema et al., 2018; Meijer et al., 2005). For some coregulators MR specificity has been shown, but this knowledge has not yet been integrated with MR function in the brain (Fuller et al., 2017). Thus, which coregulators are recruited by a particular receptor at a particular locus, the subsequent consequences for gene expression remain unknown for now. Given cell type specific (co-)expression of MR, GR and the many coregulators, also here progress in knowledge awaits single cell level -omics approaches in specific brain structures and behavioral contexts (Viho et al., 2022); similarly to the analysis of changes in gene expression in the brains of different patient population (see section 7.1).

The coregulator recruitment is of specific interest because it may be targetable by GR and MR ligands. By definition, a full MR or GR agonist like corticosterone should allow recruitment of a broad range of coregulators, and an antagonist should not. However, new receptor ligands have shown coregulator recruitment profiles that are intermediates of these extremes [(Atucha et al., 2015; Zalachoras et al., 2013a), Fig. 4]. It is likely that GR-negative feedback regulation uses different coregulators compared to other brain cells (Meijer, 2002). Also, the coregulator repertoire of brain microglia is distinct from that other brain cells with respect to the important p160 Steroid Receptor Coactivator family (Viho et al., 2022). These are just two examples that could allow specific targeting of e.g., negative feedback mechanisms distinct from brain inflammatory processes with ‘selective receptor modulators’ (Viho et al., 2019).

In fact, the new GR antagonist, Relacorilant, differs substantially from the classical mifepristone in its interference with GR negative feedback (Hunt et al., 2018). One of the explanations for this phenomenon may be differential recruitment of coregulators by the antagonist-bound GR. Such selective modulators may be used in research to link coregulators to specific biological processes, and they may turn out to be of clinical interest, as exemplified by the activity of CORT118335 in treating fatty liver in mice (Koorneef et al., 2018). Also for MR, selective receptor modulation has been explored (Young and Clyne, 2021), and this new pharmacology may offer readily applicable ways to study the mechanisms of MR and GR effects in the brain. An important caveat is that at present it is impossible to predict coregulator interactions of newly designed ligands. Yet, with the available ligands it should be possible to link specific GR-dependent processes to particular (sets of) coregulators.

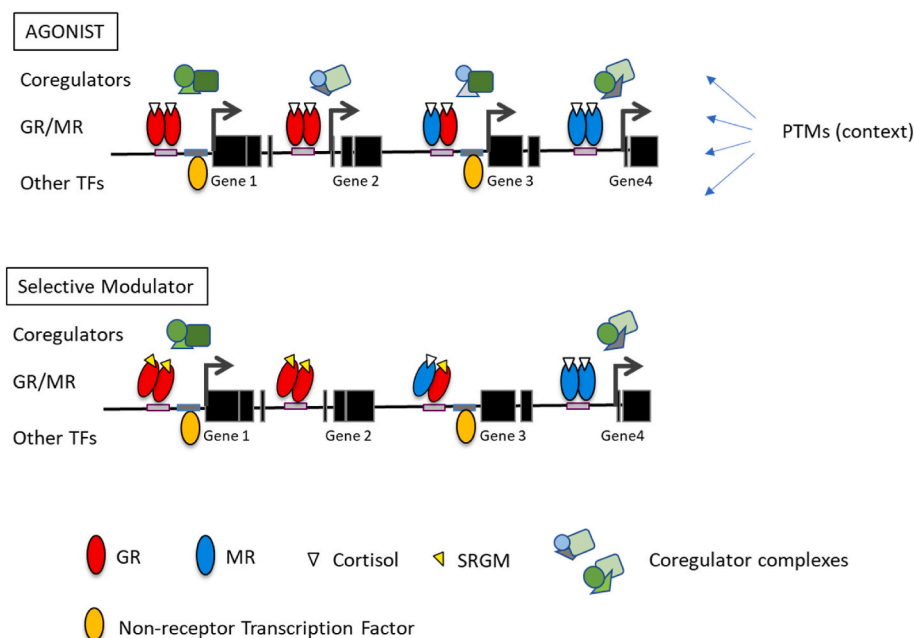


Fig. 4. DNA context and ligand dependent mineralocorticoid receptor (MR)/glucocorticoid receptors (GR) signaling. A. At high concentrations of agonist, MR and GR may bind as homo/or heterodimers to GREs, in conjunction with other, non-receptor, transcription factors (TFs). Depending on the DNA locus, coregulator complexes are recruited to mediate effects on transcription (arrows) and chromatin remodeling. Different ensembles of geometric shapes reflect different coregulator complexes. Other extracellular signals such as synaptic input can impinge at all levels via post-translational modifications (PTMs). B. When selective receptor modulators bind (here: for GR: a selective GR modulator or SGRM), the conformation of the receptor changes in such a way that only part of the interactions with coregulators may be formed. This allows for agonistic activity at some genes, but no or partial activity (antagonism) at others. Selective receptor modulation may allow to separate wanted from unwanted effects of MR/GR activation, although it is yet hard to predict which effects will separate.

In sum, the transcriptional effects of glucocorticoids depend not only on cell type specific receptor expression, but also on chromatin accessibility, the presence of transcription factors that confer DNA binding specificity to specific loci, and on the cell type and locus specific recruitment of steroid receptor coregulators to the transcription complex. These ensembles mediate acute transcriptional effects, but also are responsible for the layer of epigenetic modification in adaptive processes. An exciting prospect is that 'straightforward' pharmacological tools are becoming available to target these processes with a certain degree of specificity.

8. Epilogue

In the past half a century Bruce McEwen has been an indisputable leader in the neuroendocrinology of stress and adaptation. His serendipitous discovery of corticosterone receptors in the hippocampus opened an entirely new field of research on the question how glucocorticoids can coordinate body and mind in dealing with environmental challenges. This action exerted by the glucocorticoid was further dissected in fast non-genomic and slower genomic components that allow integration over time from seconds and minutes to hours and even years when the programming effects on the developing brain are taken into account. The distinction between MR- and GR-mediated actions reflected the feedforward and feedback cascades in distinct neuronal networks. Such cascades can be translated in secretory patterns of stress mediators that critically regulate the MR/GR-mediated balance in emotional reactivity and cognitive control, pro- and anti-inflammatory/immune regulations and metabolic performance.

The secretory patterns themselves may serve as indicator of resilience i.e., the ability to bounce back. The depth of this analysis is embodied by the understanding that altered glucocorticoid exposure due to the repeated failure to cope with a stressor, can alter structure and function of the networks underlying emotional reactivity and cognitive control. An altered balance in these networks can progress until a point of 'no return', so the brain gets 'stuck', according to Bruce. Such emotion/cognition imbalance can be probed by an acute heterotypic stressor to reveal the altered secretory patterns of glucocorticoids. In collaborative studies between the New York and Leiden labs such a heterotypic challenge was also found instrumental in demonstrating the entirely different genomic responsiveness in the brains of chronically stressed rodents (Datson et al., 2013; Gray et al., 2014). It also revealed striking sex differences in the brain, perhaps illustrating the potential mechanism underlying the different strategies males and females may use to cope with stress (McEwen, 2020a).

This recognition of a dynamic brain was the impetus for advancing the homeostasis 2.0, or allostasis concept. While homeostasis describes the negative feedback processes necessary to guard the constancy of the 'milieu intérieure', allostasis is a feedforward process towards a new equilibrium; you 'can't roll the clock' back, Bruce used to say, 'and truly reverse the effects of experiences' while he explained allostasis as the process of adaptation to (anticipated) change with its price tag of allostatic load. Entirely in line with Bruce's take on life, he used the allostasis concept as basis to launch ideas how to revitalize mechanisms of resilience by 'restarting the clock again'. The future of the concepts of allostasis and allostatic load will depend, however, on how these can be translated into clinically accessible measures. The current measure based on blood levels of glucose, lipids and stress mediators is only the beginning of the ambition to calibrate fitness (Fertig, 2022; Guidi et al., 2021; Picard et al., 2017).

Based on the pioneering research of Bruce the contours of three new developments are becoming visible. Firstly, the combined genetic/bioinformatics approach where genetic variants are translated into cell-type specific transcriptome signatures of resilience to stress-related neuropsychiatric symptoms (see 7.1.). The idea is to use this computation strategy in combination with imaging and digital biomarkers as a novel means to identify individuals at risk with the option to follow the

effect of preventive or treatment interventions. Secondly, the pharmacological approach to activate cell-type- and tissue-type-specific functions within the pleiotropic spectrum of glucocorticoid actions. Although CNS cell type-specific drug delivery is challenging, recent advances in bispecific antibody drug design have made feasible this important/promising treatment paradigm (Sedykh et al., 2018). Indeed, glucocorticoid analogs are currently being developed that can activate a specific cocktail of receptor coregulators to allow curative modulation of, for instance, only inflammatory processes without devastating neuroendocrine and metabolic side effects (see 7.2.).

The third approach refers to the new discipline of molecular sociology that precipitated in a hallmark paper by Bruce and brother Craig (McEwen and McEwen, 2017). Central in this approach is the open question whether lifestyle patterns, exercise, social support, socio-economic conditions and interventions of all kind actually maybe helpful in 'taking back control' and "teach" secretory and action patterns of stress mediators to create conditions that may facilitate recovery (Chen et al., 2017; Collins et al., 2009; Guidi and Fava, 2021; Lee et al., 2021). Or, as stated in the McEwen and McEwen (2017) paper, to exploit a model that "captures ways in which social structures interact with biological characteristics and systems to shape life trajectories". While uncovering the biology underlying social patterns Bruce would say: "What I have always liked about science is discovering the unexpected", a notion that is underscored by his seminal discovery of hippocampal corticosterone receptors as inroad to a potential magic bullet for boosting resilience.

Declaration of competing interest

In the past 3 years, NP Daskalakis has been a consultant for Sunovion Pharmaceuticals and is on the scientific advisory board for Sentio Solutions and Circular Genomics for unrelated work. OC Meijer collaborates with and receives research funding from Concept Therapeutics. ER de Kloet owns stock of Concept Therapeutics.

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Appendix A. Supplementary data

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