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Corticosteroid effects in the brain: U-shape it

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The existence of U-shaped dose dependencies has been known for a long time. With regard to corticosteroid action in brain cells, a dual receptor system that works in opposing directions can explain the occurrence of a U-shaped dose dependency. However, recent evidence indicates that many cell- and tissue-specific factors (e.g. the local availability of corticosterone, the expression of receptor variants and the cellular content of other proteins and molecules) also determine the effectiveness of the hormone. This could result in dose dependencies with a different shape, despite the local presence of two receptor types.

U-shaped dose dependencies

Dose–response relationships of neurotransmitters and hormones are often nonlinear [1,2]. This is not unexpected for ligands that, almost without exception, function through several receptor subtypes, each with specific characteristics such as accessibility, affinity, desensitization or signaling cascade. If a particular cell carries more than one receptor subtype, increased concentrations of the transmitter or hormone are likely to activate a different combination of receptor subtypes, leading to a complex dose–response curve.

One type of curve that was recognized early in many organs is the U-shaped or inverted U (bell)-shaped relationship, a dependence also known by other names such as hormesis [1]. Several explanations of the occurrence of U-shaped dose–response relationships have been suggested, ranging from the aforementioned involvement of multiple receptor systems with different actions to an overshoot reaction that is characteristic of feedback systems attempting to respond to a disturbance in homeostatic control, inherent properties of a single receptor (e.g. desensitization) or a counteracting compensatory response of the effector molecule [3,4].

A well-documented example of a U-shaped dose–response relationship concerns the actions of corticosteroid hormones in the CA1 area of the hippocampus [5,6], a brain region that is important for learning and memory formation. This relationship was observed for the functional properties of individual CA1 cells [6] and network function [5] but it is also reflected in several behavioral tasks involving the CA1 area, including spatial orientation [7] and learned helplessness [8]. In this article, we will: (i) explain how this particular U-shaped dose dependency in the CA1 region is accomplished; (ii) emphasize that, according to recent evidence, this dependency is not generalized in the brain but is region specific; (iii) suggest which factors could contribute to region specificity; and (iv) discuss what the region-specific dose dependency could mean for the overall hormonal effect on a particular function. Because many of the principles that contribute to the dose dependency of corticosteroid actions in the brain reflect common principles in this and other organs, the examples in this article might illustrate a more general phenomenon.

Corticosteroid hormones and their receptors

Corticosteroid hormones are produced in the adrenal cortex and released from there into the circulation. In mammals, the mineralocorticoid hormone aldosterone has a major role in the control of extracellular fluid volume and blood pressure, whereas the glucocorticoid hormone cortisol (corticosterone in most rodents) – the abundance of which is 100 times that of aldosterone – regulates a wide range of body functions that reinstate homeostatic control after temporary disturbances that are collectively called 'stress' (Figure 1). Owing to their lipophilic character, corticosteroid hormones can enter the brain [9], where their actions facilitate behavioral adaptation.

Corticosteroid hormone effects are mediated by two intracellular receptor types that belong to the nuclear receptor family, members of which bind to the DNA of responsive genes and regulate their transcription. The first type is the glucocorticoid receptor, which has a higher affinity for the glucocorticoids cortisol and corticosterone ($K_d \sim 1$–5 nM) and the synthetic compound dexamethasone than for aldosterone [10]. The second receptor type has a high affinity for aldosterone and is called the mineralocorticoid receptor, after the main role of aldosterone [11]. Surprisingly, the mineralocorticoid receptor has a high affinity *in vitro* for not only mineralocorticoids but also the glucocorticoids corticosterone and cortisol ($K_d \sim 0.3$ nM). Pre-receptor conversion of the hormone explains why the excess of glucocorticoids does not saturate mineralocorticoid receptors in organs that are classically associated with mineral balance, such as the kidney; these organs express high levels of the enzyme 11-β-hydroxysteroid dehydrogenase (HSD) type 2, which converts cortisol and corticosterone into their inert 11-keto forms so that the much less abundant hormone aldosterone can access the receptor [12,13]. In the adult

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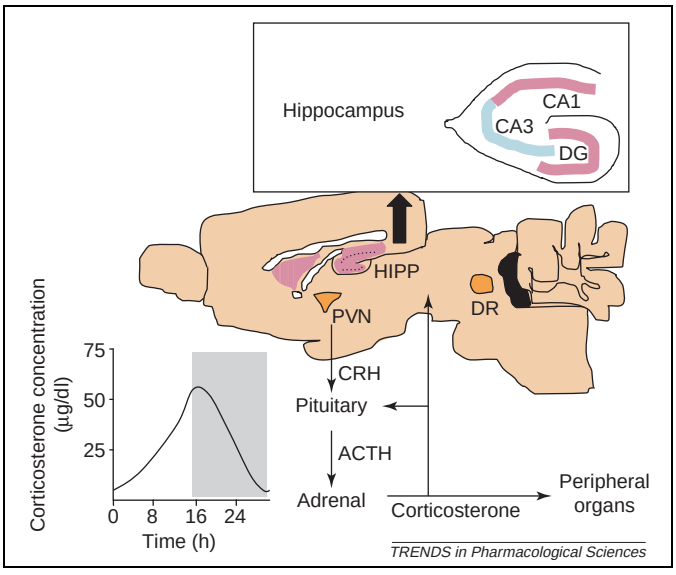

Figure 1. Corticosterone release and the distribution of hormone receptors in the brain. Exposure to stress leads to the release of corticotrophin-releasing hormone (CRH) from the PVN of the hypothalamus. This, in turn, leads to the secretion of adrenocorticotropin hormone (ACTH) from the pituitary, which results in the release of corticosterone from the adrenal cortex. Stress-induced corticosterone release occurs superimposed on a circadian pattern [59] (lower left), exhibiting a peak at the start of the active period (indicated by gray background). In addition to targeting peripheral organs, corticosterone also enters the brain, where it binds to intracellular receptors. Two types of receptor have been described: the glucocorticoid receptor (orange), which is ubiquitous in the brain, and the mineralocorticoid receptor, which is restricted to specific nuclei, including the hippocampus. Within the hippocampus (HIPP, upper right), both receptors are abundantly expressed (denoted by violet shading) in principal cells of the CA1 region and the dentate gyrus (DG), whereas neurons in the CA3 area express mineralocorticoid receptors predominantly (denoted by blue shading). Abbreviation: DR, dorsal raphe nucleus.

brain, however, 11-β-HSD2 expression is low. By contrast, another isoform, 11-β-HSD1, is abundant in several brain regions [14]; this isoform catalyzes the reverse reaction, leading to the local accumulation of glucocorticoids. Consequently, in the brain, glucocorticoids such as corticosterone, which are present in much higher concentrations than aldosterone, can bind to both the mineralocorticoid receptor and the glucocorticoid receptor, which are discretely distributed [15,16]. Because of the difference in affinity between these two receptor types for the endogenous ligand corticosterone, mineralocorticoid receptors are substantially activated by low levels of this glucocorticoid such as those circulating at rest during the circadian trough (Figure 1), whereas the lower-affinity glucocorticoid receptors become fully occupied only when there are high levels of the hormone (i.e. after stress exposure and at the circadian peak). This differential receptor activation is particularly relevant in cells that express both types of receptor, such as the principal pyramidal-shaped neurons of the CA1 hippocampal region.

Dose dependency of corticosteroid actions in the hippocampal CA1 area

Soon after studies of the cellular effects of glucocorticoids in the CA1 area began, it became apparent that, although the hormones had little effect on basal cell properties such as resting membrane potential, temporary changes in activity induced by, for example, a neurotransmitter or current injection were normalized by the hormones with a delay of several hours, in line with a gene-mediated signaling pathway [17]. As expected, it was also found that glucocorticoids are pleiotropic in their activity (i.e. they affect several, but not all, properties of CA1 pyramidal cells). Parameters that seemed to be extremely sensitive to application of the hormone included the excitatory effects evoked by β-adrenoceptor activation [18], the hyperpolarizing responses mediated by the serotonin-1A receptor [19,20] and the activation of voltage-dependent calcium channels [21,22]. Furthermore, a network property called long-term potentiation (LTP), which refers to a prolonged strengthening of synaptic contacts and is thought to contribute to learning and memory formation [23], was affected by corticosteroid hormones [24].

Interestingly, these properties consistently displayed a U-shaped or bell-shaped dose dependency [5,6] (Figure 2). Thus, low levels of corticosterone (sufficient to activate part of the mineralocorticoid receptors) were associated with small responses to serotonin, and little calcium influx but efficient LTP, whereas periods of stress slowly increased the responsiveness to serotonin [25], enhanced the cellular calcium exposure [26], reduced β-adrenoceptor-mediated effects and impaired LTP induction [27]. This dichotomy seen with low versus high levels of corticosterone was associated with the involvement of the mineralocorticoid receptor and the glucocorticoid receptor, respectively, as was evident from studies employing selective antagonists and agonists of these receptors [28]. Because adrenalectomy, a condition in which virtually no corticosteroid hormones circulate, induces properties that resemble those seen after stress, a U-shaped dose dependency evolved. Importantly, it is possible to restore cellular properties after adrenalectomy by giving either aldosterone or a low dose of corticosterone, indicating that the situation after adrenalectomy is caused by the absence of corticosterone rather than by other effects induced by this condition, such as disturbances in catecholamine levels.

The functional consequence of these effects collectively is that, at rest, signal transfer in the CA1 area is promoted. Yet excitation of CA1 cells is not associated with an influx of large amounts of calcium [17]. This is a favorable state for a neuron, so a situation of predominant mineralocorticoid receptor activation predisposes these cells to survival. Conversely, the activity of the CA1 area is reduced with a delay of 1–2 h after glucocorticoid receptor (in addition to mineralocorticoid receptor) activation in response to stress, which is in agreement with the general function of corticosterone (i.e. restoring local activity to its starting-point). Yet, if CA1 neurons are strongly excited during this period (e.g. by additional pathological challenges such as ischemic insults), the glucocorticoid-receptor-dependent enhanced calcium influx puts cells at risk of delayed cell death [29–31].

Corticosteroid effects in other regions: why not always a U-shape?

Recently, the cellular actions of various doses of corticosterone have been examined outside of the CA1 area: for

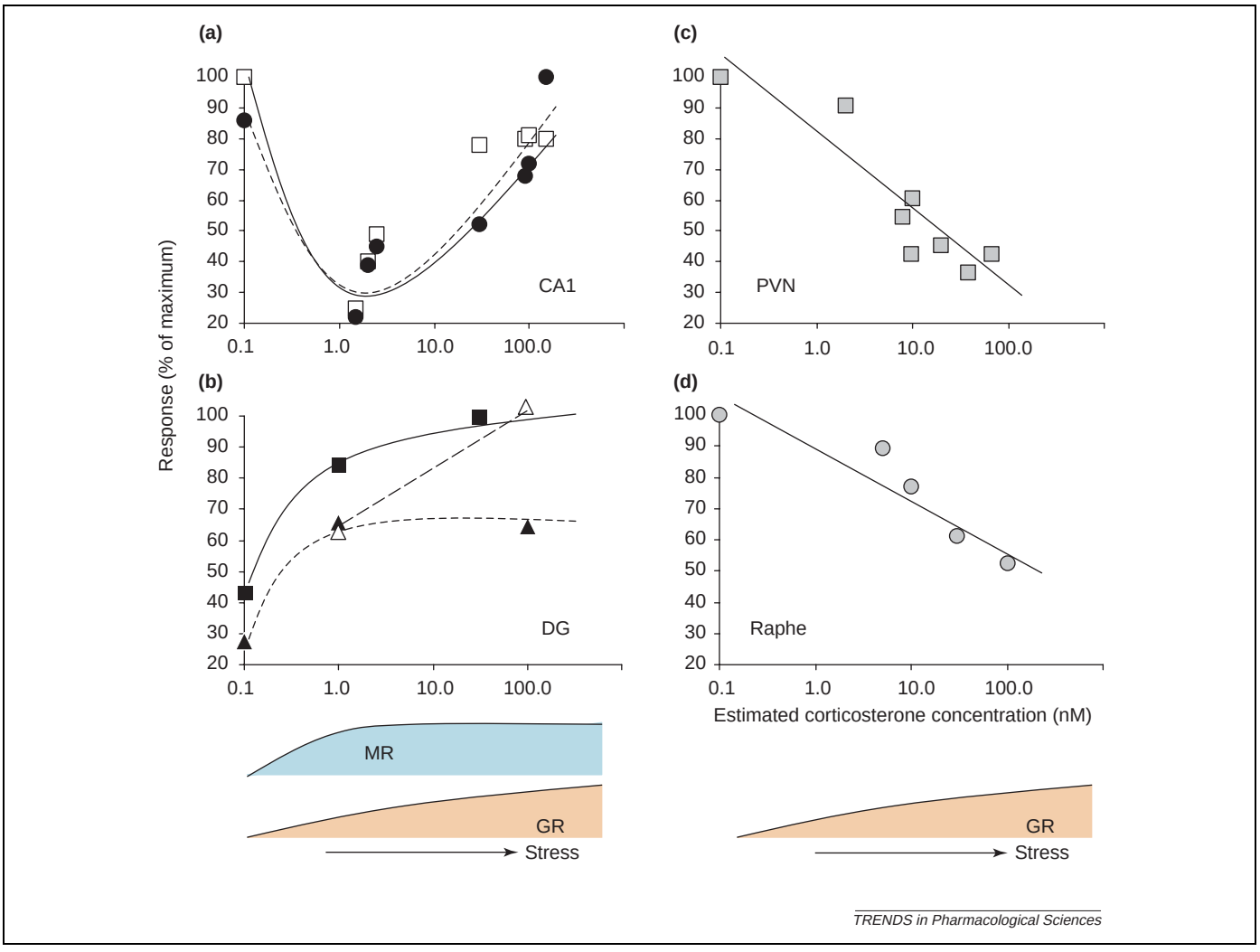

Figure 2. Dose–response relationships of the cellular effects of corticosterone in the brain. Dose–response relationships are shown for **(a)** the CA1 hippocampal area, **(b)** the DG, **(c)** the PVN of the hypothalamus and **(d)** the dorsal raphe nucleus. Graphs show hormone responses expressed as a percentage of the maximal response in these brain regions. The concentration of corticosterone is an approximate estimate of the local concentration based on the solutions perfused on *in vitro* preparations or derived from the plasma concentration when fluctuations in hormone levels were accomplished *in vivo*. (a) In the CA1 area, both the amplitude of depolarization-induced calcium currents (white squares) and the hyperpolarization caused by serotonin-1A receptor activation (black circles) display a U-shaped dose dependency. The descending limb is linked to the activation of mineralocorticoid receptors (MRs), whereas the ascending limb is associated with gradual glucocorticoid receptor (GR) activation in addition to already-activated MRs, as occurs after stress. (b) DG granule neurons show a clear MR-dependent effect on the field potential (black squares) and the single-cell response (black triangles) caused by activation of glutamate AMPA receptors. Although these cells also abundantly express GRs, high doses of corticosterone do not cause additional changes in the signal, except when tested in chronically stressed rats (white triangles). (c) Neurons in the PVN and (d) the raphe nucleus express GRs primarily. In these cells, a linear dose dependency is seen for the frequency of spontaneous γ-aminobutyric acid $(GABA)_A$-receptor-mediated synaptic events (gray squares) and the inhibition caused by serotonin-1A receptor activation (gray circles). Based on Refs [19,22,25,26,32–35,37–39] (corrected for temperature) and [60].

example, in the dentate gyrus [32–34], the raphe nuclei [35,36] and the paraventricular nucleus (PVN) of the hypothalamus [37–39]. The data, although incomplete, indicate that corticosteroid effects do not display a U-shaped dose dependency in any of these areas (Figure 2). An obvious explanation is that some of these areas, such as the PVN and the dorsal raphe nucleus, abundantly express glucocorticoid receptors, whereas mineralocorticoid receptors are virtually absent [16] so that effects depend on one receptor type only – although it should be noted that U-shaped curves can be accomplished even through a single receptor type [4]. Figure 2 shows that a linear relationship for cellular characteristics is observed in two brain areas with almost exclusive glucocorticoid receptor expression. Dentate granule cells, as is the case with CA1 pyramidal neurons, express high levels of both mineralocorticoid receptors and glucocorticoid receptors; however, glucocorticoid receptor activation in these cells seems to have little impact on the cell properties examined. Notably, the cell properties depicted in Figure 2 for the CA1 area are not the same as those shown for the dentate gyrus, leaving open the possibility that the latter do not show a U-shaped dose dependency, whereas others would. How can a binary receptor system lead to opposing actions in one cell type but not in another? We will highlight three mechanisms that can help to explain region-specific responsiveness (Figure 3).

The first explanation relates to hormone bioavailability. As mentioned, enzymes such as 11-β-SDH1 (but potentially also other metabolizing enzymes that catalyze e.g. 3-α or 5-α reduction) determine the local concentration of biologically active hormone. Local enzymatic activity could lead to concentrations that deviate substantially from plasma hormone concentrations [14]. However, the

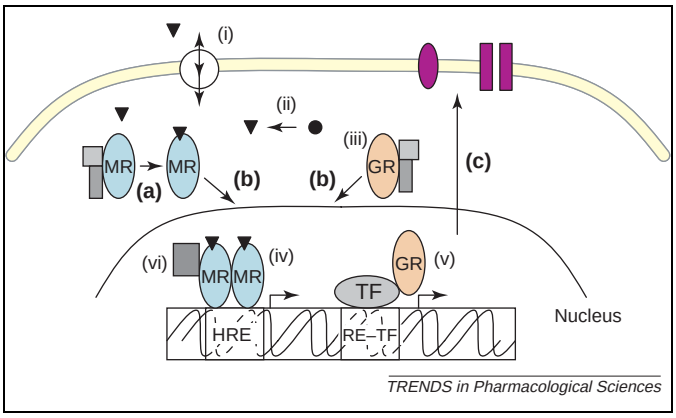

Figure 3. Corticosteroid receptor signaling pathways and putative mechanisms for altering local hormone efficacy. **(a)** Corticosterone enters the cell and binds to intracellular receptors (MRs or GRs) that, upon binding, dissociate from associated molecules such as heat-shock proteins and immunophilins. This exposes nuclear translocation sequences so that the receptor complex is moved to the nucleus **(b)**, where it can either bind as a homodimer to HREs or interact as a monomer with other transcription factors (TFs) that bind to their respective response elements (RE–TF). This results in altered transcriptional activity of responsive genes. The translation products can change the abundance or function of neuronal membrane proteins such as ion channels or neurotransmitter receptors **(c)**. The dose dependency of corticosterone in a cell can vary through: (i) the degree to which corticosterone can enter the cell; (ii) the enzymatic conversion of corticosterone and its metabolites; (iii) the ratio of MR:GR; (iv) the existence of receptor variants with reduced transcriptional activity; (v) the presence of posttranslational receptor modifications that result in altered interactions with other proteins and transcriptional activity; and (vi) the cellular content of proteins that interact with corticosteroid receptors, such as coactivators and transcription factors.

hormone concentration in cells is also determined by hormone transport over the cell membrane. P-glycoproteins are important 'gatekeepers' for synthetic steroids [40] and some of the endogenous hormones such as cortisol [41]. The hippocampus expresses several of these P-glycoproteins (e.g. MDR-1a and MDR-1b) [42]. The regional differences of these proteins in the hippocampus have not been investigated specifically, so their contribution to local dose dependencies remains to be proven. In general terms, however, P-glycoproteins are considered to be important for the efficacy of corticosteroids in the brain; for instance, the upregulation of P-glycoprotein function has been proposed as an explanation of the cortisol resistance in the hypothalamus that is associated with disease states, particularly major depression [43]. In support of this, several antidepressants from different chemical classes inhibit this steroid transporter, thus increasing the intracellular concentrations of cortisol and the synthetic glucocorticoid dexamethasone [43,44]. Overall, regional differences in the existence of steroid-metabolizing enzymes or of transport molecules could restrict the intracellular concentration of hormones and contribute to differences in hormone dose dependency because the high concentrations of hormone that are necessary to activate the low-affinity glucocorticoid receptor are not reached.

The second explanation for local differences in hormone responsiveness refers to the characteristics of the receptor. Many mineralocorticoid receptor and glucocorticoid receptor variants have been described [45–48] (Box 1) that are probably differentially distributed throughout the brain. Several splice variants in the untranslated and translated regions have been recognized for both mineralocorticoid receptors and glucocorticoid receptors [10,49–51], leading to altered transcriptional activity; these variants are species dependent [52]. Moreover, alternative translation initiation takes place, resulting in receptor molecules of variable length [53,54]. Post-translational modifications have been observed at the protein level that involve phosphorylation, ubiquitinylation, sumoylation and acetylation [45,46]. In most cases, modifications of the receptor gene or protein lead to loss of transcriptional activity, although gain of function has been observed occasionally. Local differences in the presence of receptor variants that have a reduced transcriptional activity or even those that exert dominant–negative influence over other receptor variants could result in an apparent attenuation or lack of receptor-dependent actions.

A third determinant of corticosteroid actions is the local cellular context – a factor that is extremely relevant to nuclear receptors. Corticosteroid receptors either bind as homodimers to recognition sites in the DNA (hormone response elements: HREs), at which they alter gene transcription in a protein complex that includes coactivators and corepressors, or interact as monomers with other transcription factors such as activating protein (AP)-1, nuclear factor (NF)κB, cAMP-response-element-binding (CREB) protein or members of the signal transducer and activation of transcription (STAT) family [55] (Figure 3). Protein–protein interactions are essential for both pathways. Regional differences in the expression of these proteins, such as coactivator variants [56], combined with the specific transcriptional activity of these variants through mineralocorticoid receptors and glucocorticoid receptors [57], could have considerable consequences for the efficacy of corticosteroid hormone effects. The cellular ability to evoke posttranslational receptor modifications is also important for their interaction with other proteins or DNA and, thus, transcriptional activity. For instance, sumoylation can lead to a distinction between receptor–DNA interactions that involve single HREs and those that involve multiple elements [46,58]. The ratio between accessible target genes with single versus multiple HREs within a cell can, therefore, also contribute to diversity in responses to the hormone. These examples illustrate that the tissue- or cell-specific expression of proteins with which the receptors interact can introduce a myriad of receptor-mediated actions.

All of these categories (i.e. pre-receptor pathways, receptor variants and the cellular composition of proteins and molecules) can differ in a tissue- and cell-specific manner and, hence, cause local differences in responsivity to corticosterone. This is true not only in the brain but also in the peripheral tissue. For instance, the high expression of 11-β-HSD2 in kidney tubular cells results in an apparent insensitivity to low doses of corticosterone [12–14]. In the same vein, inflammatory processes that occur, for example, during rheumatoid arthritis give rise to a generalized increase in glucocorticoid levels that is meant to reduce inflammation locally [4]; owing to the local presence of these inflammatory factors, however, the effect of high circulating levels of corticosteroids might be attenuated, so additional glucocorticoid treatment would

Box 1. Mineralocorticoid and glucocorticoid receptors: variants and properties

There are many variants of mineralocorticoid receptors and glucocorticoid receptors, each with a different transcriptional activity and ability to interact with other proteins [45,46]. Both the mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) genes are composed of nine exons (top of Figure I). Alternative splicing (indicated in Figure I by red arrows) occurs at several positions, including exon 1, which encodes the 5′-untranslated region, and exon 9 (human glucocorticoid receptor), resulting in shorter forms of the receptor protein that have lower or no transcriptional activity. Alternative translation initiation sites (purple arrows) give rise to at least four glucocorticoid receptor and two mineralocorticoid receptor variants. The resulting protein (bottom of Figure I) comprises an N-terminal domain (NTD) that is important for protein–protein interactions, a DNA-binding domain (DBD) that consists of two zinc fingers, through which receptors bind to HREs of responsive genes, and a ligand-binding domain (LBD) that is coupled to the DBD by a 'hinge region'. Cell-specific posttranslational modifications [e.g. phosphorylation (green arrows), ubiquitinylation (black arrows) and sumoylation (brown arrows)] can further diversify the functionality of the receptors. These modifications can also lead to diverse actions on genes carrying a single versus multiple HREs. For instance, sumoylation is thought to suppress the effectiveness of mineralocorticoid receptor dimers mutually but only in genes carrying multiple HREs [47].

Mineralocorticoid receptor and glucocorticoid receptor proteins differ with respect to their affinity for the endogenous hormones cortisol, corticosterone and aldosterone. Moreover, mineralocorticoid receptor distribution in the brain is restricted, whereas glucocorticoid receptor expression is widespread. Mineralocorticoid receptor and glucocorticoid receptor proteins share a large degree of homology, especially in the DBD (>90%); their transcriptional selectivity is thought to arise from the difference in NTD properties. Owing to the selective actions they mediate, mineralocorticoid receptors and glucocorticoid receptors exert different functions in the brain.

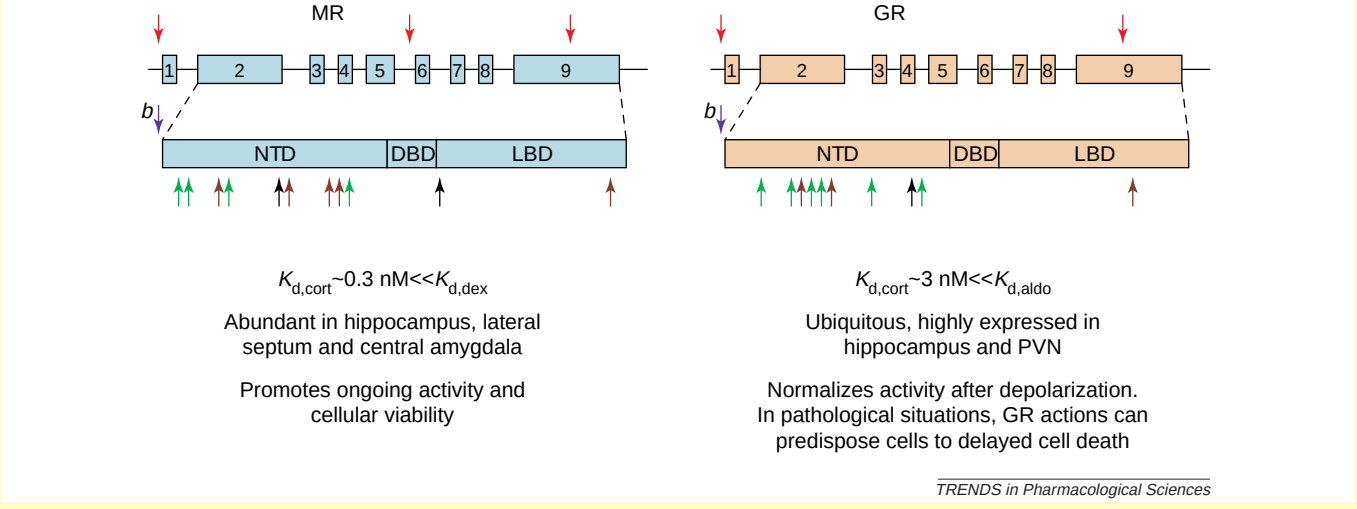

Figure I. Overview of MR and GR genes, proteins, properties and functions.

be necessary. Therefore, circulating corticosteroid levels *per se* are not always informative about the local effectiveness of the hormone.

Clearly, the third category has the greatest potential for variation and, therefore, seems the most important. It probably also explains the observed differences between the CA1 area and the dentate gyrus. Given the importance of the cell-specific content of proteins and molecules to the overall effect of a hormone, it is preferable to test hormone actions in cells that approach the conditions *in situ* as closely as possible, rather than in cell lines that are easier to work with but that might contain a different set of proteins. The cellular context is not static and can vary throughout life (e.g. during development, aging or exposure to chronic stress). This is demonstrated in the dentate gyrus, where the leveled-off curve for AMPA-receptor-mediated responses becomes steep when cells are tested from chronically stressed as opposed to control rats [34] (Figure 2).

Concluding remarks

The functions of an organ are usually the result of effects in multiple groups of interconnected cells. In view of the tissue and cell specificity of hormone actions, the dose dependency of the overall function is likely to be a composite of the dose dependency of the cell groups involved and their weight in the process. In the brain, this means that the hormone dose dependency of behavioral functions – which usually concern a timed information transfer between many regions connected in circuits – is not always easy to predict. Although behavioral processes involving the hippocampus have been found to display bidirectional effects depending on the dose of hormone [7,8], this could be merely a coincidental correlation with the cellular effects. Slight alterations in the task (e.g. shifting the emphasis from the CA1 to the dentate gyrus cells) could lead to entirely different dose–response relationships. At present, understanding hormone action in homogenous cell groups and extending the insight from there to larger and more-complex networks seems to be the most rational way to interpret the behavioral changes that are seen with fluctuations in circulating hormone levels.

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References

1 Calabrese, E.J. and Baldwin, L.A. (2003) Hormesis: the dose–response revolution. *Annu. Rev. Pharmacol. Toxicol.* 43, 175–197
2 Giraldo, J. *et al*. (2002) Assessing the (a)symmetry of concentration–effect curves: empirical versus mechanistic models. *Pharmacol. Ther.* 95, 21–45
3 Pliska, V. (1994) Models to explain dose–response relationships that exhibit a downturn phase. *Trends Pharmacol. Sci.* 15, 178–181
4 Sapolsky, R.M. *et al*. (2000) How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr. Rev.* 21, 55–89
5 Diamond, D.M. *et al*. (1992) Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. *Hippocampus* 2, 421–430
6 Joëls, M. and de Kloet, E.R. (1994) Mineralocorticoid and glucocorticoid receptors in the brain. Implications for ion permeability and transmitter systems. *Prog. Neurobiol.* 43, 1–36
7 Sandi, C. *et al*. (1997) Experience-dependent facilitating effect of corticosterone on spatial memory formation in the water maze. *Eur. J. Neurosci.* 9, 637–642
8 Kademian, S.M. *et al*. (2005) Biphasic effects of adrenal steroids on learned helplessness behavior induced by inescapable shock. *Neuropsychopharmacology* 30, 58–66
9 McEwen, B.S. *et al*. (1968) Selective retention of corticosterone by limbic structures in rat brain. *Nature* 220, 911–912
10 Hollenberg, S.M. *et al*. (1985) Primary structure and expression of a functional human glucocorticoid receptor cDNA. *Nature* 318, 635–641
11 Arriza, J.L. *et al*. (1987) Cloning of human mineralocorticoid receptor complementary DNA: structural and functional kinship with the glucocorticoid receptor. *Science* 237, 268–275
12 Edwards, C.R. *et al*. (1988) Localisation of 11 β-hydroxysteroid dehydrogenase – tissue specific protector of the mineralocorticoid receptor. *Lancet* 2, 986–989
13 Funder, J.W. *et al*. (1988) Mineralocorticoid action: target tissue specificity is enzyme, not receptor, mediated. *Science* 242, 583–585
14 Seckl, J.R. and Walker, B.R. (2004) 11β-hydroxysteroid dehydrogenase type 1 as a modulator of glucocorticoid action: from metabolism to memory. *Trends Endocrinol. Metab.* 15, 418–424
15 Reul, J.M. and de Kloet, E.R. (1985) Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. *Endocrinology* 117, 2505–2511
16 de Kloet, E.R. *et al*. (2005) Stress and the brain: from adaptation to disease. *Nat. Rev. Neurosci.* 6, 463–475
17 Joëls, M. (1997) Steroid hormones and excitability in the mammalian brain. *Front. Neuroendocrinol.* 18, 2–48
18 Joëls, M. and de Kloet, E.R. (1989) Effects of glucocorticoids and norepinephrine on the excitability in the hippocampus. *Science* 245, 1502–1505
19 Joëls, M. *et al*. (1991) Mineralocorticoid hormones suppress serotonin-induced hyperpolarization of rat hippocampal CA1 neurons. *J. Neurosci.* 11, 2288–2294
20 Beck, S.G. *et al*. (1996) Corticosterone alters 5-HT1A receptor-mediated hyperpolarization in area CA1 hippocampal pyramidal neurons. *Neuropsychopharmacology* 14, 27–33
21 Kerr, D.S. *et al*. (1992) Hippocampal glucocorticoid receptor activation enhances voltage-dependent $Ca2^{+}$ conductances: relevance to brain aging. *Proc. Natl. Acad. Sci. U. S. A.* 89, 8527–8531
22 Karst, H. *et al*. (2000) Corticosteroid actions in hippocampus require DNA binding of glucocorticoid receptor homodimers. *Nat. Neurosci.* 3, 977–978
23 Lynch, M.A. (2004) Long-term potentiation and memory. *Physiol. Rev.* 84, 87–136
24 Kim, J.J. and Diamond, D.M. (2002) The stressed hippocampus, synaptic plasticity and lost memories. *Nat. Rev. Neurosci.* 3, 453–462
25 Hesen, W. and Joëls, M. (1996) Modulation of 5HT1A responsiveness in CA1 pyramidal neurons by *in vivo* activation of corticosteroid receptors. *J. Neuroendocrinol.* 8, 433–438
26 Joëls, M. *et al*. (2003) Acute stress increases calcium current amplitude in rat hippocampus: temporal changes in physiology and gene expression. *Eur. J. Neurosci.* 18, 1315–1324
27 Mesches, M.H. *et al*. (1999) Exposing rats to a predator blocks primed burst potentiation in the hippocampus *in vitro*. *J. Neurosci.* 19, RC18
28 Joëls, M. and de Kloet, E.R. (1992) Control of neuronal excitability by corticosteroid hormones. *Trends Neurosci.* 15, 25–30
29 Sapolsky, R.M. (2003) Stress and plasticity in the limbic system. *Neurochem. Res.* 28, 1735–1742
30 Akama, K.T. and McEwen, B.S. (2005) Gene therapy to bet on: protecting neurons from stress hormones. *Trends Pharmacol. Sci.* 26, 169–172
31 Abraham, I.M. *et al*. (2001) Action of glucocorticoids on survival of nerve cells: promoting neurodegeneration or neuroprotection? *J. Neuroendocrinol.* 13, 749–760
32 Stienstra, C.M. and Joëls, M. (2000) Effect of corticosteroid treatment *in vitro* on adrenalectomy-induced impairment of synaptic transmission in the rat dentate gyrus. *J. Neuroendocrinol.* 12, 199–205
33 Joëls, M. *et al*. (2001) Effect of adrenalectomy on membrane properties and synaptic potentials in rat dentate granule cells. *J. Neurophysiol.* 85, 699–707
34 Karst, H. and Joëls, M. (2003) Effect of chronic stress on synaptic currents in rat hippocampal dentate gyrus neurons. *J. Neurophysiol.* 89, 625–633
35 Laaris, N. *et al*. (1995) Glucocorticoid receptor-mediated inhibition by corticosterone of 5-HT1A autoreceptor functioning in the rat dorsal raphe nucleus. *Neuropharmacology* 34, 1201–1210
36 Froger, N. *et al*. (2004) Neurochemical and behavioral alterations in glucocorticoid receptor-impaired transgenic mice after chronic mild stress. *J. Neurosci.* 24, 2787–2796
37 Verkuyl, J.M. and Joëls, M. (2003) Effect of adrenalectomy on miniature inhibitory postsynaptic currents in the paraventricular nucleus of the hypothalamus. *J. Neurophysiol.* 89, 237–245
38 Verkuyl, J.M. *et al*. (2004) Chronic stress attenuates GABAergic inhibition and alters gene expression of parvocellular neurons in rat hypothalamus. *Eur. J. Neurosci.* 20, 1665–1673
39 Verkuyl, J.M. *et al*. (2005) GABAergic transmission in the rat paraventricular nucleus of the hypothalamus is suppressed by corticosterone and stress. *Eur. J. Neurosci.* 21, 113–121
40 Meijer, O.C. *et al*. (1998) Penetration of dexamethasone into brain glucocorticoid targets is enhanced in mdr1A P-glycoprotein knockout mice. *Endocrinology* 139, 1789–1793
41 Karssen, A.M. *et al*. (2001) Multidrug resistance P-glycoprotein hampers the access of cortisol but not of corticosterone to mouse and human brain. *Endocrinology* 142, 2686–2694
42 Volk, H.A. *et al*. (2004) Neuronal expression of the drug efflux transporter P-glycoprotein in the rat hippocampus after limbic seizures. *Neuroscience* 123, 751–759
43 Pariante, C.M. *et al*. (2004) Do antidepressants regulate how cortisol affects the brain? *Psychoneuroendocrinology* 29, 423–447
44 Pariante, C.M. *et al*. (2003) Antidepressant fluoxetine enhances glucocorticoid receptor function *in vitro* by modulating membrane steroid transporters. *Br. J. Pharmacol.* 139, 1111–1118
45 Zhou, J. and Cidlowski, J.A. (2005) The human glucocorticoid receptor: one gene, multiple proteins and diverse responses. *Steroids* 70, 407–417
46 Pascual-Le Tallec, L. and Lombes, M. (2005) The mineralocorticoid receptor: a journey exploring its diversity and specificity of action. *Mol. Endocrinol.* 19, 2211–2221
47 Bhargava, A. and Pearce, D. (2004) Mechanisms of mineralocorticoid action: determinants of receptor specificity and actions of regulated gene products. *Trends Endocrinol. Metab.* 15, 147–153
48 Rogerson, F.M. *et al*. (2004) Mineralocorticoid receptor binding, structure and function. *Mol. Cell. Endocrinol.* 217, 203–212
49 Breslin, M.B. *et al*. (2001) Multiple promoters exist in the human GR gene, one of which is activated by glucocorticoids. *Mol. Endocrinol.* 15, 1381–1395
50 Kwak, S.P. *et al*. (1993) 5′-Heterogeneity of the mineralocorticoid receptor messenger ribonucleic acid: differential expression and regulation of splice variants within rat hippocampus. *Endocrinology* 133, 2344–2350
51 Zennaro, M.C. *et al*. (2001) A new human MR splice variant is a ligand-independent transactivator modulating corticosteroid action. *Mol. Endocrinol.* 15, 1586–1598
52 Otto, C. *et al*. (1997) Absence of glucocorticoid receptor-β in mice. *J. Biol. Chem.* 272, 26665–26668

53 Lu, N.Z. and Cidlowski, J.A. (2005) Translational regulatory mechanisms generate N-terminal glucocorticoid receptor isoforms with unique transcriptional target genes. *Mol. Cell* 18, 331–342
54 Pascual-Le Tallec, L. *et al*. (2004) Human mineralocorticoid receptor A and B protein forms produced by alternative translation sites display different transcriptional activities. *Eur. J. Endocrinol.* 150, 585–590
55 De Bosscher, K. *et al*. (2003) The interplay between the glucocorticoid receptor and nuclear factor-κB or activator protein-1: molecular mechanisms for gene repression. *Endocr. Rev.* 24, 488–522
56 Meijer, O.C. *et al*. (2000) Differential expression and regional distribution of steroid receptor coactivators SRC-1 and SRC-2 in brain and pituitary. *Endocrinology* 141, 2192–2199
57 Meijer, O.C. *et al*. (2005) Steroid receptor coactivator-1 splice variants differentially affect corticosteroid receptor signaling. *Endocrinology* 146, 1438–1448
58 Tallec, L.P. *et al*. (2003) Protein inhibitor of activated signal transducer and activator of transcription 1 interacts with the N-terminal domain of mineralocorticoid receptor and represses its transcriptional activity: implication of small ubiquitin-related modifier 1 modification. *Mol. Endocrinol.* 17, 2529–2542
59 Windle, R.J. *et al*. (1998) Ultradian rhythm of basal corticosterone release in the female rat: dynamic interaction with the response to acute stress. *Endocrinology* 139, 443–450
60 Karst, H. *et al*. (1994) Corticosteroid receptor-dependent modulation of calcium currents in rat hippocampal CA1 neurons. *Brain Res.* 649, 234–242