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Stress and cognition: are corticosteroids good or bad guys?

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Corticosteroid hormones secreted by the adrenal cortex protect the brain against adverse events and are essential for cognitive performance. However, in recent literature, the central action of corticosteroids has mostly been portrayed as damaging and disruptive to memory formation. We argue that this paradox can be explained by appreciating the specific role of both mineralocorticoid and glucocorticoid receptors in the various stages of information processing. In addition, the context in which corticosteroid-receptor activation takes place is crucial in determining steroid-mediated effects. These effects generally favour adaptive behaviour that is most relevant to the situation. Corticosteroid effects on cognition can, however, turn from adaptive into maladaptive, when actions via the two corticosteroid-receptor types are imbalanced for a prolonged period of time.

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CORTICOSTEROIDS secreted by the adrenal cortex readily enter the brain, where they coordinate, together with other components of the stress system, the organism's ability to cope with stress. They divert energy supply to challenged tissues and control the excitability of neuronal networks that underlie learning and memory processes. The corticosteroid hormones promote the interpretation and storage of novel information while facilitating extinction of behaviour that is no longer relevant. Despite the obvious importance of the stress hormones for mental health and homeostasis[1], the potentially disruptive effects of corticosteroids in the control of brain function and behaviour have recently received much attention[2–6].

Why is the action of corticosteroid hormones necessary and positive at some times while regarded as disruptive for memorizing specific tasks at other times? In this article, we argue that two issues are of extreme importance when considering this paradox. First, the effect of corticosteroid hormones on memory performance can only be fully appreciated when considering the specific role of the two receptor types for these hormones in the brain. Corticosterone (in rodents) and cortisol (in humans) bind to mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs), with a tenfold difference in affinity[7] (see Box 1). These receptors are found together in abundance in hippocampal neurones[8,9]. Second, the consequences of corticosteroid-receptor activation largely depend on the context, that is, the environmental input during the various stages of information processing: acquisition, consolidation and retention[10]. For example, corticosteroid receptors mediate, in a coordinate manner, the network function of hippocampal circuits that underlie complex learning paradigms, such as spatial learning. However, if a novel experience interferes with acquisition or retrieval of behaviour, MRs and GRs can operate in another context, apparently extinguishing learned responses but actually favouring the switch to a more-opportune response[11,12].

Role of mineralocorticoid and glucocorticoid receptors

Recent studies have shown that MRs have a role in behavioural reactivity during novel situations, whereas GRs are involved in consolidation of learned information (see Fig. 1). This is based partly on studies that have used the Morris water maze. Intracerebroventricular administration of selective GR antagonists before or immediately after the first training session in a water maze results in impaired retention of the task 24 h later[10,15]. As treatment before the retrieval test is ineffective, GR inhibition apparently interferes with the consolidation rather than the retrieval of acquired spatial information. Inhibiting MRs does not influence the

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Box 1. Corticosteroid receptors in the brain

Two types of corticosteroid receptors are found in the brain: mineralocorticoid receptors (MR), which bind corticosterone and cortisol with high affinity; and glucocorticoid receptors (GR), which have approximately one tenth the affinity of MRs (Ref. a). Neurones in the hippocampus contain both receptor types. Cells in most other brain regions mainly contain GRs. Owing to the high affinity of MRs, these receptors are already occupied to a large extent when corticosteroid levels are low, that is, at rest. Under these conditions, GRs are only partially occupied. They become fully activated when corticosteroid levels rise considerably, for example, after stress.

After the binding of corticosteroids, phosphorylation and dissociation of the steroid-receptor complex takes place, followed by translocation of the complex to the nuclear compartment[b]. Classically, homodimers of MRs or GRs were thought to bind to hormone-responsive elements in the DNA, thus affecting the transcription of specific genes. Meanwhile it has become clear that many steroid actions might, in fact, be due to protein–protein interactions between corticosteroid-receptor monomers and other transcription factors[c]. This is probably also true for steroid actions in the brain. If indeed such crosstalk occurs, the effect of steroids on brain cells crucially depends on the timing and nature of inputs that activate other transcription factors such as cAMP-response-element-binding protein or immediate–early genes.

A great variety of the cellular actions of corticosteroids have been described, particularly for hippocampal cells[d,e]. In general, situations where mostly MRs but few GRs are activated are associated with small Ca^{2+} currents, and, thus, reduced spike-frequency accommodation, stable responses to repeated stimulation of glutamatergic pathways and relatively small responses to biogenic amines. Activation of MRs, therefore, seems to guarantee a stable background of neuronal firing and might, thus, contribute to its 'pro-active' role in maintaining homeostasis[f]. Activation of GRs in addition to MRs, as is seen, for example, after exposure to a stressor, results in enhanced Ca^{2+} influx, stronger spike-frequency accommodation and marked responses to biogenic amines, such as 5-HT-induced hyperpolarization (Refs g–k). Such activation, thus, seems to reduce cellular activity after acutely stressful situations, which agrees with the 'reactive' mode by which corticosteroids facilitate recovery of disturbed homeostasis[f]. Interestingly, in the absence of corticosteroids, cellular properties and synaptic plasticity resemble the situation seen with simultaneous MR and GR activation, revealing either U-shaped or bell-shaped dose dependency for the steroid actions[d]. Recent observations regarding effects of stress exposure on synaptic plasticity follow essentially the same pattern[l]. These network properties might either change in parallel with or result from the steroid-mediated effects on cellular characteristics, such as Ca^{2+} influx and responsiveness to glutamatergic input.

The effects of steroids on the properties of hippocampal cells and circuits reveal several features that are relevant to steroid modulation of learning and memory processes. First, it is evident that predominant MR activation results in completely different actions from concomitant MR and GR activation. The relative activation of MR and GR, therefore, seems to be an important determinant of limbic activity. The MR and GR contribution is, of course, not a static figure, but is influenced by many factors, such as regulation of receptor synthesis, affinity of the receptors and circulating levels of corticosteroids. Second, in neurones that participate in elaborate networks, corticosteroid actions might be influenced largely by the nature of prior or concomitant activation of specific afferent pathways. This phenomenon could contribute to the contextual dependence observed in behavioural tests.

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latencies to find the platform, irrespective of the time of treatment. However, it does change the search pattern in the free swim trial significantly (see Fig. 1). The rats still head directly to the former platform location (hence retention is undisturbed) but explore other areas of the pool subsequently rather than remaining there as the controls do. It is known that processing of information depends crucially on hippocampal functions associated with the recognition of goals and the evaluation of the outcome of action[16,17]. Behavioural reactivity towards stimuli[16], evinced by approaching and investigating, also relates to hippocampal function. Therefore, Oitzl *et al.*[14] have addressed specifically the role of MR activation in behavioural reactivity. It appears that behavioural reactivity is increased inappropriately in the absence of corticosteroids (adrenalectomy), as well as with high doses of corticosterone that lead to the occupation of both MR and GR. We detected a U-shaped dose–response curve, as predominant MR activation, produced by a low dose of corticosterone, normalized this behaviour.

Studies on inhibitory avoidance responses of day-old chicks further illustrate the crucial role of the two steroid-receptor systems in memory formation. In this test, MR and GR antagonists both appeared to be amnestic but influenced different aspects of learning and memory[18]. The MR antagonist altered the bird's pecking pattern and, thus, its reactivity to stimuli. A primary interference with memory processes takes place only when the animals are treated with a GR antagonist. In rats too, MR-mediated effects could be discerned on perception and behavioural reactivity in light–dark inhibitory avoidance tasks. Rats readily enter a dark environment; generally, application of an aversive electric foot-shock prolongs the time to enter the dark environment when tested 24 h later. Inhibition of MRs appears to impair retention of this behaviour but is effective only before[19] and not immediately after[19,20] training, which, again, excludes the implication of MRs in consolidation processes. These examples show that even if performance during retrieval appears to be the same after MR and GR inhibition, the former is related to the initial behavioural response and the latter to storage processes.

The MR- and GR-mediated effects can be disentangled by administration of selective agonists and antagonists for each receptor type, at specific stages of information

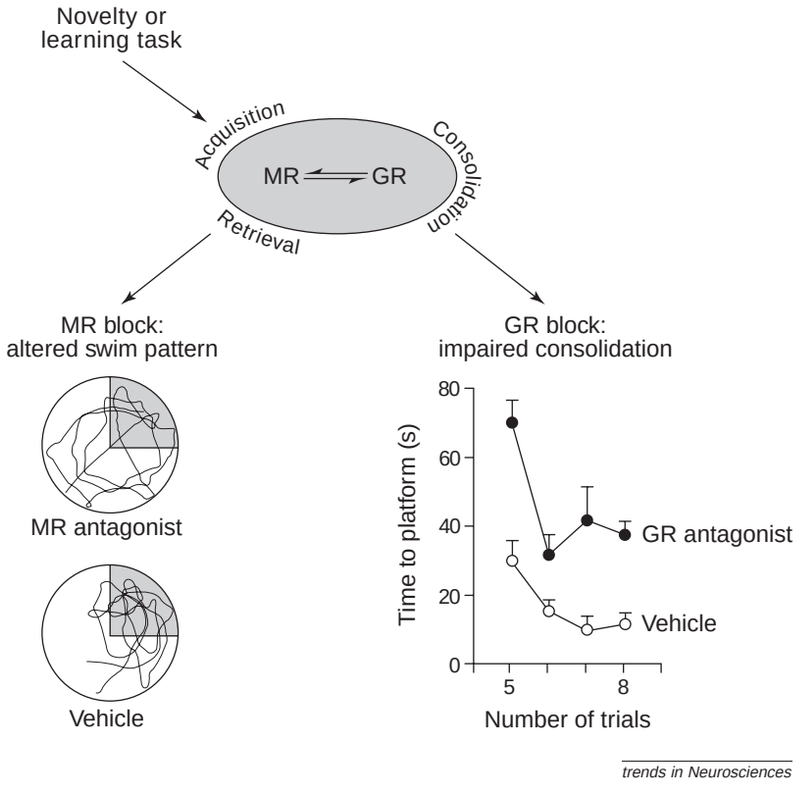

Fig. 1. ***Mineralocorticoid (MR) and glucocorticoid receptors (GR) affect different aspects of information processing.*** *Following exposure to a learning task, for example, the Morris water maze, MR block 30 to 45 min before retrieval on day 2, changed the swim pattern. Latencies to reach the platform represent the spatial-learning capacity. Rats approach the location of the platform directly but spend less time searching in the vicinity of the platform (mean percentage of time ± SEM in platform quadrant: MR antagonist 27.8 ± 1.2; vehicle 35.4 ± 2.3). Inhibition of GR immediately after acquisition on day 1 results in impaired performance 24 h later (shown in the graph). These MR- and GR-mediated effects on information processing facilitate behavioural adaptation.* Based on data taken from Refs 10, 13 and 14.

processing. This should be done with care, as synthetic steroids are poorly transported across the blood–brain barrier[21]. For example, the use of dexamethasone, a potent GR agonist, has an interesting caveat: the steroid effectively suppresses stress-induced pituitary–adrenal activity (and, thus, corticosterone production), but it hardly substitutes for the depleted endogenous hormone in brain, particularly with respect to MR. This fact explains why systemic administration of corticosterone to adrenalectomized rats, which activates MRs and GRs, and not dexamethasone, can reinstate contextual fear conditioning[22,23]. In conclusion, these behavioural studies underscore the idea that MR activation is essential for interpretation of environmental stimuli and selection of a behavioural response. Activation of GRs (in addition to already activated MRs) within the context of a behavioural task is a prerequisite for optimal memory.

Importance of context

The consequence of MR or GR activation, or both, strongly depends on the context of the learning task. In accordance, environmental inputs that activate specific neuronal pathways are likely to influence steroid-receptor-mediated changes in limbic activity (see Box 1). For example, in the inhibitory avoidance response of day-old chicks, corticosterone enhances memory for a weak aversant, while the same dose of the steroid impairs memory that results from a strong aversant[24]. Correspondingly, exogenous corticosterone given immediately after training facilitates memory performance in the Morris water maze. A decrease in the water temperature that produces a similar large corticosterone response also improves cognitive performance[25]. In addition to the amount of corticosterone, the timing and contextual input during the various stages of information processing has been found to be relevant[12]. Memory in a radial maze is impaired when an unrelated stressor, which was accompanied by increase in corticosterone level, interrupt the task. These examples show that although GRs are necessary for consolidation of information, subsequent GR activation, when triggered by a distracting stressor that is out of context with respect to the original learning task, disrupts ongoing consolidation and apparently influences retrieval of previously stored information.

This raises the question of whether exposure to an unrelated stressor, which is removed from the context of a learning task, affects cognitive function primarily via GRs. The answer to this question can be derived from a study showing that stress or corticosterone administration prior to the retrieval test in the Morris water maze reduced swim time spent in the former platform quadrant[5]. At first sight this could be interpreted as a deficit that was due entirely to altered GR function. Yet, the unrelated stressor led to a change in exploratory behaviour and the behavioural response to the novel situation (no platform) that was very similar to the previously observed pattern seen after the block of MRs in the brain[10]. In our view, the GR activation that is due to an unrelated stressor disrupts the function of MRs during the retrieval process. Studies using mice that are homozygous or heterozygous for a targeted disruption of the gene encoding GRs, support this interdependency of MRs and GRs (Refs 13,26). It has been found that the homozygous mutants exhibited impairment in GR-related long-term memory processes but, in addition, also failed to display MR-dependent platform-directed search strategies. These experiments clearly demonstrate that MR- and GR-mediated effects are different, but interact and proceed in a coordinate manner: linked in time to the particular stage in information processing.

LTP and LTD

Recent electrophysiological studies have indicated an attractive neurobiological substrate for the stress-induced beneficial or disruptive effects on memory formation. These studies focus on the role of corticosteroids in LTP and LTD, two phenomena that refer to the strengthening and weakening, respectively, of synaptic contacts by repeated stimulation[27,28]. The rapid induction, specificity, associativity and long-lasting nature of LTP have led to the suggestion that it contributes to the storage of information. This is supported by the fact that compounds that prevent induction of LTP in hippocampal areas also interfere with hippocampus-associated learning tasks. A strict link between LTP and memory formation, however, is still disputed[29,30]. In naïve, unstressed animals, LTP can be elicited readily, while homosynaptic LTD is usually not seen.

Studies where LTP is examined *in vitro* under specific conditions of MR and GR activation have shown that LTP is induced optimally when corticosteroid levels are mildly elevated, that is, when MRs and some of the GRs are activated (see Fig. 2)[31–33]. In fact, activation of MRs, seems to be a prerequisite for optimal LTP, as poor LTP is observed in the absence of adrenal steroids. Also, when GRs were occupied extensively (in addition to

MRs), for example, because of extremely high corticosteroid levels or the presence of a selective GR agonist, it was hard to obtain LTP while LTD was robust[31,34]. These data point to a bell-shaped dose-dependency for LTP in the hippocampus[31]. This has also been observed for nearly all of the cellular effects of corticosteroids in the hippocampus, such as Ca^{2+} influx and responsiveness to transmitters (see Box 1)[35,36].

Mildly stressful conditions in the context of a learning paradigm, which result in the activation of MRs and some of the GRs, could induce LTP-like synaptic plasticity in the hippocampus[37], although experimental proof for this still awaits careful studies that monitor both neuroendocrine activity and hippocampal plasticity in animals exposed to a learning situation. Subjecting animals to a novel situation, which is out of the context of the behavioural paradigm, prevents the induction of LTP (Ref. 38) and even reverses earlier elicited LTP (Ref. 39). The depotentiation could provide the means to erase synaptic strengthening installed by information that is no longer relevant to the new situation, and to allow the storage of new information. At present, we can only speculate about the mechanism underlying depotentiation that follows the subjection of an animal to a novel situation, which is, after all, not associated with extensive GR activation. One explanation is that the likelihood of inducing LTP could depend on the presence of an activity-dependent sliding threshold for LTP–LTD formation[6,34,40]. According to this theory, recently elicited LTP increases the threshold for subsequent induction of LTP and lowers the threshold for LTD. A shift in LTP–LTD induction might not merely depend on the prior history of synaptic potentiation, but generally more on the recent activity in the circuit and might, for example, involve the recruitment of particular transcription factors (see Fig. 2 and Box 1).

When animals are subjected to more-severe and unpredictable stressful situations, where GRs are activated to a large extent (in addition to MRs), subsequent LTP induction has been found to be impaired while LTD induction is facilitated[41–45]. A prominent role of GRs in this phenomenon is supported by the fact that pretreatment with a GR antagonist prevents the appearance of LTD (Ref. 46). In accordance, the treatment of animals with the GR agonist RU28362 allows induction of LTD (Ref. 47). The role of MRs has so far not been investigated under these conditions. It cannot be excluded that, similar to behavioural studies, extensive GR occupation that is not produced by a learning paradigm interferes with natural MR function, that is, the promotion of LTP. In addition, as some of the severe stressors that are used, for example, tail-shock, involve physical components that are likely to activate aminergic pathways through the brainstem, as well as limbic circuits[48], it is possible that compounds other than corticosteroids contribute to the impaired LTP formation.

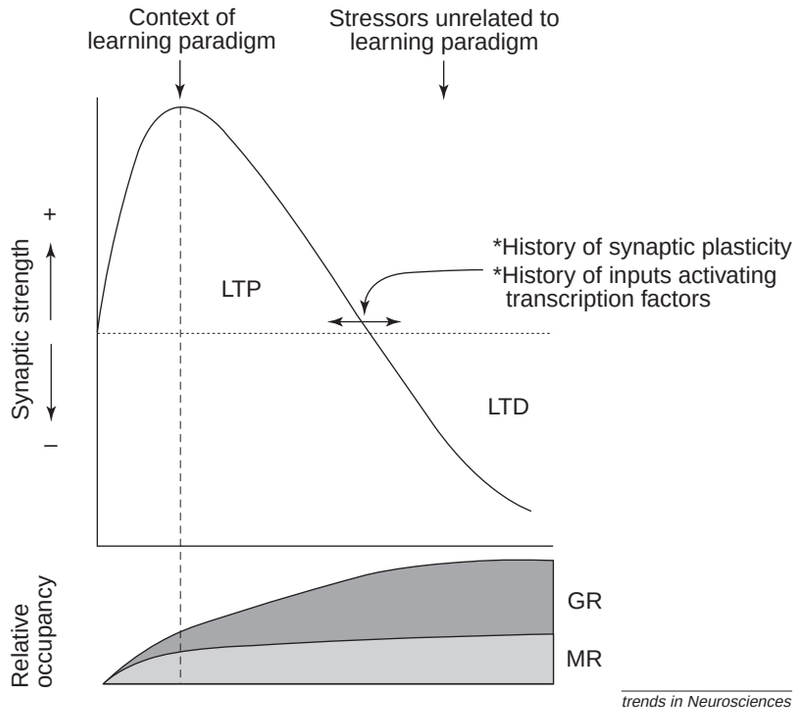

Fig. 2. ***Synaptic strength and corticosteroid receptors.*** *Synaptic strength is enhanced (LTP) when most of the mineralocorticoid receptors (MRs) and only part of the glucocorticoid receptors (GRs) are activated, for example, during mildly stressful conditions in the context of a learning paradigm. When animals are subjected to a severe stressor, which results in extensive GR activation, subsequent LTP induction is impaired, while LTD is robust. The point where LTP is impaired and LTD facilitated does not merely depend on corticosteroid-receptor occupancy: the recent history of synaptic plasticity and of other inputs activated during earlier events (asterisks) could shift this point to the left or right. This could explain why even during mildly stressful situations that are unrelated to the learning paradigm, for example, exposure to a novel environment, synaptic strength can be decreased.* Based on data taken from Refs 6 and 31.

Concluding remarks

The objective of this article has been to highlight that the co-localized hippocampal corticosteroid receptor types mediate, in a coordinated manner, the action of corticosteroids on distinctly different aspects of cognitive function. In order to aid understanding of the role of these receptors it is important to emphasize that the hormones themselves do not cause behavioural changes, but influence the information-processing systems conditionally, so that specific internal and external stimuli are more likely to elicit responses in the appropriate context. Thus, the hormone is, during each stage of information processing, required for activation of MR-responsive networks that underlie retrieval of previously learned tasks or behavioural responses to novelty. If hormone levels rise in response to novelty, GR-responsive networks promote the consolidation of new information. In this way, MR and GR functioning is linked in time to bias information processing towards adaptive behaviour that is most relevant to the situation. If such corticosteroid-mediated actions occur out of context in learning tasks, it does not imply that memory is impaired, but rather that behaviour is switched to a more-opportune response that is adapted to the actual condition[11,12].

In humans, corticosteroids have been mostly found to disrupt memory formation[4,49,50]. This can be explained partly by the limitations in experimental design, which do not allow differential receptor manipulation locally in the human brain. In order to assess the role of circulating corticosteroids in human cognition correctly, however, studies where the effects of endogenous corticosteroids are attenuated rather than those in which the subjects are exposed to high amounts of exogenous corticosteroids will be indispensable. Methods for delivery and targeting the steroid-responsive sites in the human brain, therefore, need to be developed for selective synthetic steroid-receptor antagonists that overcome the problem of the blood–brain barrier[21]. With the use of these tools, the coordinated MR- and GR-mediated actions occurring in the context of a particular event in information processing can be discerned.

The coordinated MR- and GR-mediated effects on cognition that serve to select the most-opportune response to the actual situation of the organism can turn into maladaptation, when animals are chronically exposed to stressful conditions. Thus, severe conditions, those that are capable of producing hypercorticism, have been found to impair spatial memory in adult animals, for example, after exposure to restraint stress for 6 h a day, for at least 3 weeks[51,52]. Accordingly, long-term treatment with very high doses of exogenous corticosteroids produces disruptive effects in water-maze performance[53]. Long-term effects that are beyond the direct modulatory actions of corticosteroids have been observed with chronic psychosocial stress in the tree shrew[54].

These maladaptive corticosteroid effects might evolve via differential changes in corticosteroid-receptor-mediated actions. Generally, impairments of learning and memory processes are thought to involve disturbed GR-mediated effects. However, MRs rather than GRs are markedly reduced in number when corticosteroid levels are elevated[55–58]. It is likely, therefore, that defective MR-mediated processes, those that are normally involved in flexible interpretation of novel stimuli, also contribute to the memory impairment seen with chronic stress exposure. If imbalance in MR- and GR-mediated actions on crucial neuronal networks that underlie behavioural adaptation persist, a condition of neuroendocrine dysregulation, which results in altered stress-hormone levels might develop. When it surpasses a specific threshold, this imbalance might contribute to deterioration of cognitive function and enhance vulnerability to disease in genetically predisposed individuals[1,59]. We hypothesize that by repairing the imbalance in MR- and GR-mediated actions one could potentially promote the restorative capacity that is still present in the diseased brain.

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