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HPA axis and memory

O. T. Wolf * PhD

Senior Research Fellow

Department of Experimental Psychology II, University of Düsseldorf, Geb. 23.02, Ebene 01, Raum 43, Universitätsstraße 1, D-40225, Düsseldorf, Germany

The hormones of the hypothalamus–pituitary–adrenal (HPA) axis influence memory in situations of acute and chronic stress. The present review tries to summarize the current state of knowledge by describing the enhancing as well as the impairing effects of stress or glucocorticoid (GC) treatment documented in animals and humans. GCs secreted during the acquisition of a stressful task facilitate consolidation. However, acute stress (or GC treatment) unrelated to the task impairs performance. The effects of acute stress are additionally modulated by gender, age and the emotional valence of the learning material. Chronic stress in rodents has mostly impairing effects on memory and hippocampal integrity. However, other regions of the brain, such as the prefrontal cortex, are also sensitive to stress. In humans, similar observations have been reported in several patient populations as well as in older subjects. The potential to reverse these effects using behavioural or pharmacological approaches needs to be explored.

Key words: glucocorticoids; memory; HPA axis; hippocampus.

Everyone knows from subjective experience that stress influences memory. Some stressful events might be remembered for a lifetime while other things are forgotten, or not stored in the first place, because of stress. Reviewed here is the current knowledge, derived from both animal and human studies, on how memory is influenced by the glucocorticoids (GCs) secreted during stress. Several important modulatory variables are discussed—among which are the length of exposure to stress (acute or chronic), the type of memory investigated and the age and sex of the experimental subjects.

Animals, including humans, react in multiple ways to physical or psychological stress. A first rapid reaction is activation of the autonomous nervous system (ANS) leading to enhanced catecholamine activity. Adrenalin (epinephrine) and noradrenalin (norepinephrine) from the adrenal medulla produce the typical stress symptoms (e.g. increased heart rate, sweat gland activation). A second, slower response is activation of the hypothalamus–pituitary–adrenal (HPA) axis. Corticotrophin-releasing hormone (CRH) from the hypothalamus reaches the pituitary, which thereafter secretes adrenocorticotrophin (ACTH). Both CRH and ACTH have cognition-modulating properties of their own; these properties, which are not the focus of this chapter, have

* Tel.: +49-211-811-1799; Fax: +49-211-811-2019.
E-mail address: oliver.wolf@uni-duesseldorf.de (O. T. Wolf).

been reviewed elsewhere.[1–4] ACTH, in turn, stimulates the adrenal cortex to secrete glucocorticoids (corticosterone in the rodent, cortisol in the human). Glucocorticoids are lipophilic hormones and can therefore readily pass the blood–brain barrier, where they influence multiple regions of the brain. The effects of GCs are mediated either via specific intracellular receptors or via the interaction of the hormone with neurotransmitter receptors on the cell surface.[5] Glucocorticoid receptors have been found in multiple areas of the brain which are relevant to cognition, namely, the hippocampus, the amygdala and the prefrontal cortex. The hippocampus is especially important for declarative or spatial memory[6,7], while the amygdala is critical for emotional memory[8] as well as for the emotional modulation of other types of memory.[9] The prefrontal cortex is crucial for working memory (this term, used in the human neuropsychological context, refers to active, short-term storage[10]). Those regions of the brain mentioned above are not only target regions of GC action but are actively involved in the feedback regulation of the HPA axis. GCs exert negative feedback (leading to reduced HPA activity) at the level of the pituitary, hypothalamus and hippocampus. In contrast to this is the positive feedback they create at the level of the amygdala, the prefrontal cortex and the brain stem (locus coeruleus), leading to enhanced HPA activity or reactivity.[5,11,12]

ACUTE EFFECTS

Neurophysiological effects

The stress-induced secretion of GCs has multiple acute effects in the central nervous system (CNS). In vitro studies, for example, have demonstrated that GCs inhibit the transport of glucose into neurones.[13] In line with these findings is a reduction in hippocampal glucose uptake as demonstrated by positron-emission tomography (PET).[14] Most of the effects in the CNS are mediated via interaction with the two intracellular receptors known as mineralocorticoid receptor (MR or type I) and glucocorticoid receptor (GR or type II). The GR has a much lower affinity for cortisol and is therefore heavily occupied only when there are high levels of GC (stress or GC treatment), whereas the MR is already occupied to a great extent under basal conditions.[5] Electrophysiological studies have revealed that high levels of GCs reduce neuronal excitability[15] and impair synaptic plasticity via a GR-mediated mechanism.[16,17] In addition, even short episodes of stress reduce the number of newly generated neurones in the dentate gyrus[18] and modulate the synaptic spine density in the CA1 region.[19] However, the effects of stress are by no means limited to the hippocampus. In the prefrontal cortex, for example, stress enhances dopaminergic activity[20] and increases extracellular glutamate levels.[21]

Animal studies

Enhancing effects

If an animal learns a stressful task, the consolidation of this task is enhanced by GCs (in the case of the rat, corticosterone) secreted during the task.[5,22] This is true for simple conditioning paradigms, avoidance learning and for spatial tasks thought to rely on the hippocampal formation. Indeed, if the learning is made more stressful (e.g. by decreasing the water temperature in a water maze), the performance of the animal is enhanced. It is noteworthy that this enhancement is associated with a more pronounced secretion of

corticosterone.[23,24] Similarly, memory-enhancing effects can be obtained if GCs are given immediately after training, thereby mimicking a stronger corticosterone response to the initial learning of the task.[9] Studies by Roozendaal and McGaugh have demonstrated, elegantly, that GCs interact via a GR-mediated mechanism in the basolateral nucleus of the amygdala with noradrenalin (norepinephrine)-stimulated alpha 1 and beta adrenoreceptors, thereby producing the memory-enhancing effect.[9,25] Studies in receptor knockout mice have further supported the notion that GR-mediated transcriptional activity is required for these results.[26] The actual information (or the memory trace) does not seem to be stored in the amygdala, but the amygdala gives the memory trace an 'emotional stamp' and thereby enhances its consolidation in other brain structures.[9,25] The stress-enhanced memory consolidation is an important adaptive process which helps the animal to adjust to a changing environment.[5,22] This process is in line with the beneficial and adaptive effects of the acute HPA response to stress observed in multiple systems in the periphery.[5,27]

Impairing effects

The previous section has summarized the memory- or consolidation-enhancing properties of stress and GCs. However, stress can also have detrimental effects on memory. If the animal is placed in a stressful environment during the delay phase (between the learning and the subsequent delayed recall), the performance in hippocampal-mediated spatial memory forms is impaired. Moreover, this event is paralleled by a reduction in hippocampal plasticity.[16,28] de Quervain et al showed that the poor memory performance is caused by the impairing effect of stress or GCs on delayed memory retrieval.[29] In contrast, stress before the initial learning seems to have only a small effect, or no effect, on spatial memory[28,29], while it has enhancing or impairing effects on several forms of conditioning, depending on the sex of the animal[30,31] (see discussion of modulatory variables below).

Studies in the non-human primate are especially valuable in the context of stress–memory research because they allow to test hypotheses based on observations in rodents without the strict ethical limitations of human research. Impairing effects of physical stress (loud noise) on prefrontal-mediated memory functions were observed in one study.[20] Most interestingly, the authors reported evidence that this effect is mediated via the dopaminergic system of the prefrontal cortex.

Human studies

Enhancing effects

The majority of studies in humans have focused on the impairing properties of stress or GC treatment (see below). The recently published study by Buchanan and Lovallo is the first to demonstrate that cortisol can enhance memory consolidation for emotional material, in this case, emotional slides.[32] Similar results have been obtained in studies investigating the effects of beta receptor blockers on memory for emotional events[33], suggesting that the model outlined by McGaugh and Roozendaal (see above) is transferable to the human.[9]

In addition to the enhancing effect on the consolidation of emotional material, cortisol administration also enhances learning of neutral material when given in the presence of very low basal levels of cortisol—due either to metyraphone treatment or to naturally occurring low basal levels in the late afternoon.[34,35] These observations support the notion of an inverted U-shaped function between cortisol levels and memory, as has been suggested by electrophysiological experiments.[16,17]

Impairing effects

Two recent studies in young subjects have shown that, as in the stress results from monkeys, administration of cortisol can interfere with the performance of prefrontal-mediated working memory[36,37], a finding in line with the high density of the GR in this area of the brain (see Ref. 38 for a review on this topic). In addition, de Quervain et al extended their work in rodents[29] to the human and were the first to show that cortisol impaired retrieval of words learned 24 h earlier, while having no effect on the initial learning or on the consolidation of these (neutral) words.[39] The impairing effect of cortisol on delayed recall was replicated in another study using a different delay interval.[37] The empirical picture is less clear for the effects of cortisol given before the learning of a declarative task. Some studies report acute impairing effects[40,41], while other studies fail to find similar effects using only slightly different experimental approaches.[36,37,39,42,43] The studies by Newcomer et al suggest that prolonged (several days) GC treatment is needed before the impairing effects on learning occur.[42,43] Indeed, negative effects of subchronic GC treatment have also been reported by other groups.[44,45]

Studies using psychosocial stressors found that those subjects showing a pronounced cortisol increase in response to the stressor (high responders) performed poorer in declarative memory tasks than subjects showing only a mild response[40,46,47]—but see Ref. 48 for an exception. Another experiment observed that psychosocial stress especially increased the amount of false memories produced[49], an observation in line with earlier studies using synthetic GCs.[41] In addition, high stress responders also appear to be impaired in working memory functions.[50]

Recent research on sleep has been able to highlight the role of certain sleep phases for memory consolidation. Declarative memory consolidation is enhanced during the early phase of sleep, characterized by a large portion of slow wave sleep and low endogenous cortisol levels. GC treatment blocks this effect, while treatment with an MR antagonist has no effect, suggesting that low occupancy of the GR during the first phase of the night is crucial for declarative memory consolidation.[51,52]

Modulating variables

Sex

The animal and human studies summarized above were conducted mainly with male subjects; it is therefore unclear whether or not these results are transferable to female subjects. Indeed, those studies looking explicitly at sex differences found striking differences. Woods and Shors reported that stress enhanced conditioning in male rats, while it impaired it in female animals. The authors were able to show that the impairing stress effect occurred only when there were high levels of oestradiol (pro-oestrus) and, surprisingly, seemed to be relatively independent of the secretion of adrenal corticosterone.[30,31] In the human studies from our group, it was observed that, in young subjects exposed to stress, male high responders exhibited poorer memory performance after the stressor, while no such association was observed in women.[47] Clearly, more research on this topic is needed in animals and humans.

Age

In addition to the sex, the age of the subject also seems to influence the response to acute stress or GC treatment. Interestingly, older subjects appear to be less sensitive for some of the acute effects of the steroid. For example, while cortisol treatment

impaired the performance of working memory in young subjects, it had no effects on working memory in older subjects.[37] Lupien et al observed, further, that the response to treatment-induced low (metyraphone) or high (cortisol) levels of cortisol in older subjects varied as a function of the development of their endogenous cortisol secretion over the last years. Subjects having stable low (or normal) levels of cortisol showed impaired declarative memory performance after metyraphone treatment, but not after cortisol treatment, while the opposite picture (no response to metyraphone, but impairment after cortisol treatment) was observed in those older subjects showing elevated basal cortisol levels.[34] Finally, our laboratory was the first to show evidence that sex and age effects might interact. While older women were more impaired in their memory performance after psychosocial stress compared with older men[53], the opposite picture emerged in younger subjects.[47]

Research agenda (acute effects)

- research investigating the enhancing properties of GCs in humans is still sparse
- the influence of modulatory variables, such as age and sex, needs to be studied more intensively
- functional neuroimaging should be used to highlight the specific areas of the brain which mediate acute stress and GC effects

CHRONIC EFFECTS

Neurophysiological effects

Chronic stress has multiple effects in the CNS. One of the best documented effects is atrophy of the apical dendrites of the CA3 region of the hippocampus.[54] The idea of a stress-induced neuronal death in the hippocampus, as suggested by some studies in rats and monkeys[12,55], has been challenged recently using more objective neuronal counting methods and studying several species (rats, tree shrews, monkeys [56–58]). In the dentate gyrus, chronic as well as acute stress leads to reduced neurogenesis.[18,59] However, the effects are again by no means restricted to the hippocampus. For example, chronic stress influences several neurotransmitters in the forebrain as well as in the amygdala.[60,61] In addition, chronic corticosterone treatment modulates dendritic organization in the prefrontal cortex.[62] Moreover, chronic stress can lead to increased HPA activity and reactivity (in the sense of a positive feedback) via mechanisms involving the CRH system in the amygdala and the noradrenergic system in the brainstem.[11,63]

Animal studies

Enhancing effects

While acute stress has enhancing as well as impairing properties on memory (see above), a different situation emerges when it comes to chronic stress. Here, the negative consequences are much more dominant; however, some forms of emotional conditioning are enhanced, even under conditions of chronic stress.[64]

Impairing effects

There are abundant rodent studies demonstrating the negative effects of chronic stress or chronic GC treatment on spatial as well as on working memory.[65–70] Similar

impairing consequences were demonstrated in tree shrews and monkeys.[71,72] These results suggest that chronic stress has negative effects on prefrontal as well as hippocampal functioning. Interestingly, some of these negative effects can be prevented by treating the animal with antidepressants or anticonvulsants.[59,67,73] The other extreme, namely, the complete absence of GCs as the result of adrenalectomy, also causes memory impairment which is associated with damage to the dentate gyrus.[74]

Human studies

The experimental induction of chronic stress, or chronic GC treatment, in humans is, of course, not feasible for ethical reasons. Researchers interested in the effects of chronic stress or chronic GC elevations therefore have to refer to clinical groups (endocrine or psychiatric patients) or special populations (e.g. older subjects) which are exposed to elevated levels of cortisol over a longer period of time due to medical or environmental conditions. Obviously this kind of study does not have the scientific power of real experiments, but rather provides correlational evidence.

Cushing patients are exposed to very high levels of cortisol until they are treated successfully, and these patients are therefore an ideal model for studying the effects of prolonged exposure to elevated GCs. Several studies have observed that these patients show deficits in attention and memory—and also have depressed mood.[75,76] In addition, there is evidence from structural neuroimaging studies that these patients have a reduction in hippocampal volume and/or more global cerebral atrophy, which appears to be, in part, reversible after correction of hypercortisolaemia.[77–79] Whether or not these brain changes are accompanied by changes in performance remains to be established.[80–82] Patients receiving GC treatment for a medical condition (e.g. arthritis) also show evidence of cognitive impairment[83]; however, the literature regarding this topic is still sparse—which is unfortunate given the fact that GCs are often prescribed in very high doses over a long period of time. There are several psychiatric conditions, which are characterized by HPA hyperactivity. Best documented are elevated CRH and cortisol levels in depressed patients, even though these observations are not made in all patients.[11,84] Some theories suggest that HPA hyperactivity is causally related to depression. It is debated whether the primary cause is a central CRF hyperactivity[85] or a GR deficit resulting in poor feedback.[86] A few small studies[87] have suggested that antiglucocorticoid therapy is effective in reducing depressive symptoms, even though neuropsychological measures have usually not been used in these studies. In addition, associations between HPA hyperactivity and poor cognitive performance have been reported in these patients.[88,89] Finally, reduced hippocampal volumes have been observed in several studies[90,91], even though few studies have tried to link HPA activity to hippocampal atrophy in depressed patients.[92,93] Moreover, observations of prefrontal as well as amygdala changes in depression argue for a combined investigation of these regions in future neuroendocrine studies.[11]

Dementia of the Alzheimer type (AD) is also characterized by HPA hyperactivity[94] and this has been related to hippocampal atrophy.[93,95] Even though these dysregulations are not the primary event in the disease, it is possible that elevated levels of cortisol enhance or accelerate the structural damage to the CNS observed in these patients.

Memory deficits and hippocampal atrophy have also been observed in post-traumatic stress disorders (PTSD). However, this psychiatric condition is characterized by lower basal cortisol levels, even though HPA hyperactivity has been observed after challenge tests. Other mediators [e.g. CRH or adrenalin (epinephrine)] have to be considered in this condition.[96,97]

Ageing, in both humans and animals, is accompanied by increases in basal cortisol levels and reductions in feedback sensitivity of the HPA axis.[98–100] Furthermore, increased levels of GC during ageing are associated with a worsening of declarative or spatial memory and hippocampal damage/atrophy in animals[101,102] as well as in humans.[100,103,104] In addition, studies in rodents strongly suggest that behavioural or pharmacological manipulations aimed at preventing the age-associated HPA hyperactivity also successfully prevent the memory impairments.[105,106] So far, most research has focused on the hippocampus; however, other sites in the brain, for example, the prefrontal cortex, also seem to be influenced by GCs in the human but these sites have not been sufficiently studied.[37,38,100]

In sum, several conditions exist in which elevated levels of cortisol and memory impairments coincide, and there is evidence that structural alterations in the hippocampus are responsible, in part, for these effects. However, the question of cause and effects remains. In Cushing's disease, the demonstration of structural reversibility of brain atrophy after correction of the hypercortisolism argues that the high levels of cortisol were indeed responsible for the atrophic changes. In the other conditions, the situation is less clear. In depression, for example, HPA hyperactivity resulting from a central hypersecretion of CRH could lead to elevated levels of cortisol and, in turn, to reduced hippocampal volumes. However, other scenarios could postulate that a small hippocampus is the primary event (maybe a genetically determined risk factor) which, in turn, leads to insufficient control of the HPA axis.[107] Similar explanations can be given for the relationships seen in ageing. Again, it is unknown whether the age-associated reduction in hippocampal volume is the primary event leading to elevated levels of cortisol—or the other way around, elevated levels of cortisol causing hippocampal atrophy. It is also possible that both events reflect a broader metabolic syndrome, often observed during ageing, called the metabolic syndrome or syndrome X; this syndrome is characterized by reduced glucose tolerance, hypertension, obesity and elevated levels of cortisol.[108,109]

Modulating variables

Sex

Striking sex differences have been observed regarding some of the acute stress effects discussed in the first part of this chapter, and there is also some evidence that sex differences exist in the effects of chronic stress. Spatial memory performance of male rats is impaired after 3 weeks of restrained stress, but it is enhanced in female rats. Moreover, the authors present evidence that this gender difference is, in part, mediated by oestradiol.[110] In a human study investigating the associations between basal cortisol levels and memory in ageing, negative associations between cortisol levels and memory performance were detected only for the female study participants, no such associations being found in the male participants.[104] Again, there is a clear need for additional research explicitly looking at sex differences.

Age

There is some evidence that older animals are more susceptible to chronic stress or chronic elevation of corticosterone.[65] However, most of the studies conducted to date have used only young animals. Older human subjects appear to show a diminished response to acute elevation of cortisol (see above); however, whether or not they are more susceptible than younger subjects to chronically elevated levels of cortisol is not

Research agenda (chronic effects)

- potential memory-enhancing effects of antiglucocorticoid treatment in hypercortisolaemic psychiatric patients have to be explored in larger placebo-controlled studies
- the relationship between hypercortisolism and hippocampal atrophy in psychiatric patients or older subjects needs to be evaluated in longitudinal studies
- the potential to reverse hippocampal atrophy should be studied in ageing and in psychiatric conditions
- other areas of the brain, namely, the prefrontal cortex and the amygdala (in its function and structure), need to be evaluated

known. It would be important to study whether older depressed patients or older Cushing patients are more susceptible than their younger counterparts to elevated levels of cortisol.

SUMMARY

This chapter has shown that GCs, as the end products of the HPA axis, influence memory. The acute effects depend on the time of GC secretion or administration, with both enhancing and impairing outcomes possible. In addition, the stress effects are influenced not only by the specific memory task but also by the age and sex of the subjects tested. Chronic stress, or chronically elevated levels of cortisol, have mostly negative effects on memory as well as on those brain structures responsible for these operations, namely, the hippocampus and also parts of the prefrontal cortex. Little research has been done on humans in an attempt to prevent the negative acute, as well as chronic, effects of high levels of cortisol on the brain—even though there is sufficient encouraging data from rodents.

This chapter has focused especially on GCs. Clearly, a more complete understanding of how stress influences cognition can be achieved only if the multiple hormonal systems influenced by stress are investigated in parallel. Finally, as an outlook for future research, questions on the influence of the genetic background of an individual (e.g. polymorphisms of the GR receptor gene[111]) on its CNS reaction to acute or chronic GC elevations need to be investigated.

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