Stress, Memory and Aging: Relevance for the Peri- and Post-menopausal Woman

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All of us have, at some time or another, been confronted with examples of how stress influences memory. For example, being unable to retrieve well-learned information (a friend's phone number) is an example of how stress might interfere with our memory. In contrast, we have no trouble remembering specific embarrassing, shameful or frightening events from the past. This is an example of how stress can enhance our memory. In addition to the effects of acute stress on memory, there are situations of chronic stress, metabolic dysfunctions associated with aging, or stress-related psychiatric disorders, which are characterized by memory distortions.

The goal of this review is to provide a brief and selective overview of what is known about the role of glucocorticoids (GCs) in mediating some of these effects. The relevance of these alterations for aging women is discussed in some detail. Evolving behavioral and pharmacologic interventions will be summarized and future perspectives outlined.

What is Stress?

Even though the term "stress" is excessively used these days, its definition remains a challenge. The interested reader is referred to recent reviews on this topic.[1-3] A commonly used working definition states that stress occurs when a person perceives a real or anticipated challenge to internal or external balance (homeostasis).[4,5] Thus, a discrepancy between what should be and what actually exists leads to stress.[3] A stressor is the specific event that induces the stress. Stressors can be physical (eg, heat, pain) or psychological (eg, work overload, marital problems) in nature. In addition, a stressor can be acute (an upcoming job interview) or chronic (constant work overload, inadequate housing conditions, abusive relationships, etc.). Especially in humans, the subjective evaluation of the stressor, as well as the evaluation of available coping resources, is crucial in determining the impact of a stressor on the individual.[6,7] What is an exciting challenge for one person could be a substantial threat for another.

Interaction with a stressor leads to a cascade of neuroendocrine responses designed to facilitate adaptation. The hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system are the most important systems in this respect. The hypothalamus activates the HPA axis in response to input from several brain regions.[4] Corticotropin-releasing hormone (CRH) and vasopressin reach the

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pituitary through the portal blood system, where they initiate the secretion of adrenocorticotropic hormone (ACTH) in the bloodstream. In response to ACTH the adrenal glands secrete GCs. In most laboratory rodents (rats and mice) corticosterone dominates, whereas in humans cortisol is the main adrenal GC. As lipophilic steroid hormones, GCs enter the brain easily and exert multiple effects in regions throughout the brain. Of interest for the present review is the fact that GCs influence brain regions that are important for memory (eg, the amygdala, the hippocampus and the prefrontal cortex). These effects are mediated through the two receptors for the hormones; the mineralocorticoid receptor (MR) and the glucocorticoid receptor. These receptors differ in their affinity for cortisol (with the MR having a much higher affinity) and in their localization throughout the brain. In addition, GCs can exert rapid non-genomic effects by influencing ion channels or neurotransmitter receptors at the membrane level.[4,8]

Acute Stress and Memory

There is overwhelming literature on stress and memory. Here, I will focus only on declarative long-term memory, which refers to the explicit storage of facts and events that can later be intentionally retrieved.[9,10] This type of memory is tested in human studies with word lists, paired associates or short stories. In daily life it corresponds to remembering items from your grocery list, or recalling the name of a person you have met at a recent exhibition. Long-term memory can be further divided into different memory phases, namely acquisition (or initial learning), consolidation (or storage) and retrieval (or recall). An intact medial temporal lobe (hippocampus and surrounding cortical structures) is essential for the successful completion (acquisition and consolidation) of a declarative long-term memory task. The role of the hippocampus in memory retrieval is debated.[11,12] For intentional retrieval the prefrontal cortex is very important.[13] The literature regarding the effects of stress on declarative memory has been confusing, with groups reporting enhancing as well as impairing effects; however, it has become apparent that this is largely due to the fact that the different memory phases are influenced by GCs in an opposing fashion.[14]

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The stress-associated increase in GCs enhances memory consolidation, and this aspect represents the adaptive and beneficial effect of stress on memory. Elevated cortisol levels potentiate the enhancing effect of emotional arousal on memory consolidation[14-16] (The Figure depicts the chain of events underlying this phenomenon). Basically, a

Stress enhances memory consolidation: Chain of events

Stressful learning episode → activation of the HPA axis and the SNS → elevated GC levels during consolidation → enhanced consolidation → enhanced retrieval hours and days afterward (when GC levels are no longer elevated)

Stress impairs memory retrieval: Chain of events

Learning episode → consolidation → stress shortly prior to retrieval → activation of the HPA axis and the SNS → elevated GC levels during retrieval → (transiently) impaired retrieval

HPA= hypothalamus-pituitary-adrenal
SNS= sympathetic nervous system
GC=glucocorticoid

Figure. Acute positive and negative effects of stress on long-term memory. Schematic diagram of the cascade of events underlying the positive effects of glucocorticoids (GCs) on long-term memory consolidation and the negative effects of GCs on long-term memory retrieval.

stressful episode is remembered (retained) better than a non-stressful episode; this could help the individual to avoid a similar aversive event in the future. This effect is mediated by the action of GCs on the amygdala (the fear center of the brain) and the hippocampus (the memory center of the brain).[14-16] Although the enhanced memory consolidation is adaptive and beneficial, the process appears to occur at the cost of impaired retrieval (Figure). In animals, as well as humans, acute stress or GC treatment at the time of retrieval leads to impaired retrieval of previously learned information.[14,17] Thus, in a stressful situation we are less able to remember the name of a certain medication, the phone number of a friend or the description of the location of a new store in our neighborhood.

In line with these laboratory studies, there are observational studies showing that self-reported stress is associated with memory problems in older adults.[18] Roozendaal and colleagues[14] have summarized their findings on stress and long-term memory as indicative that stress puts the brain into a "consolidation mode," which is accompanied by impaired retrieval. Taken together, studies in animals and humans converge on the idea that acute stress or elevated GCs at the time of encoding (initial learning or acquisition) enhance memory consolidation, while acute events at the time of recall impair memory retrieval (Figure).

Chronic Stress and Memory

In the previous section beneficial as well as detrimental effects of acute stress were discussed. In this section the effects of chronic stress will be summarized.

Under chronic stress the brain seems to shift from a cognitive rational mode to a more affective (fearful) and automated response style.

Chronic stress or chronic GC treatment is associated with memory impairments.[8,19] In animals it has been shown repeatedly that chronic stress (over several weeks) results in impaired spatial memory. Stress-induced dendritic atrophy in the hippocampus and the prefrontal cortex is one possible underlying mechanism.[8,19] However, reduced neurogenesis and dysregulation of several neurotransmitter systems have to be considered as well.[8] Recent studies demonstrate substantial plasticity in the adult rodent brain. For example, stress-induced dendritic atrophy is reversible once the stress has ceased for a while.[19] In contrast to the negative effects of chronic stress on the hippocampus and the prefrontal cortex are the stimulatory effects on the amygdala.[20,21] Under chronic stress the brain seems to shift from a cognitive rational mode to a more affective (fearful) and automated response style (Table).

Interestingly, the negative effect of chronic stress on spatial memory might occur only in male rats, and not in female rats.[22] Similarly, in fact, acute stress impairs spatial memory only in males.[23] However, female rodents are more impaired by stress than their male counterparts with regard to other memory domains (eg, working [short-term] memory or classic [Pavlovian] eyelid conditioning).[24,25] Thus, gender differences in how stress influences

Table. Chronic Effects of Stress

Structural alterations in the brain induced by chronic stress	Possible memory correlates of these alterations
Dendritic atrophy and reduced neurogenesis in the hippocampus	Impaired hippocampal-based spatial and declarative long-term memory
Dendritic atrophy in parts of the prefrontal cortex	Impaired working (short-term) memory
Increased dendritic spines and increased corticotropin-releasing hormone in the amygdala	Increased fearfulness, proneness to depression, enhanced fear conditioning

memory are task-specific, which most likely translates to different sensitivities of specific brain regions to stress.[16]

GC treatment. In humans the effects of chronic long-term GC treatment can, of course, not be studied experimentally due to ethical considerations. The studies in which GCs (hydrocortisone, prednisone or dexamethasone) were administered in an experimental fashion for several days involved observation of declarative memory impairments.[26] Moreover, in studies involving patients receiving GC therapy (eg, due to rheumatoid arthritis) and in studies of hypercortisolemic patients with Cushing's syndrome[27] investigators observed reduced declarative memory performance.[28,29] In some of these studies a reduced hippocampal volume was observed when the patients were compared with a control group.[27,30] Initial pilot follow-up studies in patients with Cushing's syndrome suggest that hippocampal atrophy in the disorder is reversible once the hypercortisolemia has been successfully treated.[31] This would correspond to observations of preserved plasticity in rodents, as mentioned above.

Depression. Several psychiatric disorders are associated with enhanced activity of the stress hormone system. Most notably a major depressive disorder is often characterized by elevations in basal cortisol levels, increased CRH in the cerebrospinal fluid and impaired negative feedback, as demonstrated with the dexamethasone suppression test.[8,32] Patients with depression show cognitive impairments, and these have been linked in some studies with the patients' observed HPA hyperactivity.[33,34] In addition, these patients show signs of hippocampal atrophy[35,36] even though the role of HPA hyperactivity in inducing this atrophy has not been established. Finally, successful pharmacologic treatment is associated with a normalization of the stress system.[8,32]

While more research in this area is clearly needed, PTSD effectively illustrates that stress-associated psychiatric disorders are not always associated with HPA hyperactivity.

PTSD. While patients with major depression exhibit signs of HPA hyperactivity, the situation is different in patients with post-traumatic stress disorder (PTSD). Here, lower basal cortisol levels have been observed in several studies, and this has been interpreted as evidence for an enhanced negative feedback, even though this issue is still debated.[37,38] Recent small pilot studies have provided support for the hypotheses that cortisol treatment might be able to prevent[39] or treat[40] PTSD. It is thought that the ability to reduce negative memory retrieval is among other factors crucial for this beneficial effect. While more research in this area is clearly needed, PTSD effectively illustrates that stress-associated psychiatric disorders are not always associated with HPA hyperactivity. In addition, the small but promising cortisol-treatment studies conducted to date illustrate that cortisol might have unrecognized therapeutic potential.

Stress, Cortisol and Memory in Aging

Aging leads to alterations of the HPA axis, even though there is substantial variability among individuals. Basal activity increases[41] and negative feedback is less efficient.[42] Thus, the exposure to endogenous cortisol increases with aging.[41,43] These alterations can have a negative impact on fat deposition and bone density, as well as on the aging brain (see below). There is evidence that the HPA alterations during aging are more pronounced in women. This has been reported in studies measuring cortisol levels over the course of the day (eg, in a sleep laboratory setting) as well as in studies using pharmacologic or psychological challenges in order to investigate changes in the responsivity of the HPA axis.[41,43]

Animal studies have documented that memory impairment is associated with enhanced HPA activity.[44] Similarly, in older otherwise healthy humans, observational studies have reported associations between elevated cortisol levels and declarative memory impairments; this has been observed in cross-sectional studies as well as in longitudinal studies.[45-47]

Whether these associations are specific for hippocampal-based declarative memory or are, in fact, broader (also including working memory or attention) is debated. Obviously, none of these human studies allow a clear cause-and-effect interpretation, but instead represent observed associations. The possible neuroanatomical correlate of these hormone performance associations in humans remains to be established. Here, the possible association between rising cortisol levels and atrophy of the hippocampus or the prefrontal cortex (measured with magnetic resonance imaging) is insufficiently understood and the current empirical evidence is heterogeneous.[46,48]

The reader might wonder whether the above-mentioned associations are large enough to be of any clinical relevance. Thus, the question is whether or not stress contributes in a relevant way to cognitive decline or the occurrence of dementia in aging. There is some evidence to suggest that this is the case. For example, one large epidemiologic study (Religious Orders Study[49]) found that older participants who reported in a brief questionnaire that they were more prone to psychological distress had a significantly stronger decline in memory over the follow-up period of almost 5 years, and had a substantially higher risk for Alzheimer's disease. Another large genetic study[50] found that a rare polymorphism in the gene encoding an enzyme involved in regional GC metabolism in the brain (11 beta hydroxysteroid dehydrogenase type 1 [11bHSD1]) was associated with a six-fold increased risk for Alzheimer's disease. This polymorphism influenced tissue levels of biologically active GCs. Taken together, there is emerging evidence from multiple sources to suggest that chronically elevated stress hormone levels can contribute to cognitive decline in older women and men.

Another potential beneficial effect of estradiol could be a direct protective effect within brain regions sensitive to GC-induced damage.

Stress, Aging and Memory: A Role for Estrogens?

As mentioned earlier, there is evidence that cortisol levels increase with age more in women than in men.[41,43] Moreover, recent evidence suggests that basal urinary cortisol levels increase during the menopausal transition.[51] In this context questions have been raised about the potential role of estrogens in preventing age-associated HPA hyperactivity in women. As of today, the empirical situation is unsatisfying. A few small, placebo-controlled, randomized intervention studies have reported that estradiol treatment in postmenopausal women leads to a reduced cortisol response to a laboratory stressor[52] or a reduced response to a pharmacologic challenge of the HPA system.[53] In addition, an observational study reported that women on postmenopausal estrogen therapy had basal cortisol levels comparable to those in young women, and also showed a less pronounced cortisol stress response to a laboratory stressor.[54] However, since all of these studies tested only a small number of subjects, more evidence-based information on this important topic is needed.

Another potential beneficial effect of estradiol could be a direct protective effect within brain regions sensitive to GC-induced damage. For example, stress in laboratory rodents leads to memory impairments and dendritic atrophy within the hippocampus in male rats only.[55] Female rats appear to be protected, and there is evidence that this is due, in part, to their higher estradiol levels.[19,22] In older animals these gender differences are no longer apparent.[56] Based on these promising findings, the potential anti-stress properties of estradiol treatment in these rodent models need to be further explored. This could be followed by initiating similar studies in humans.

In sum, there is initial evidence from several lines of research that estradiol might prevent age-associated HPA hyperactivity, and may also be able to reduce the negative impact of chronic stress on some parts of the brain. Having said this, current empirical evidence is not strong enough to allow clinical recommendations for the practitioner. Hopefully, HPA measures will be included in some future estrogen treatment trials in order to fill this empirical gap.

Possible Strategies for Interventions

While the potential of estradiol as a stress-protective agent remains to be further explored, several other pharmacologic interventions should be briefly mentioned. These concern physiologic states in which HPA hyperactivity is often observed.

Chronic stress due to work overload has been associated with increased HPA axis activity in several studies.[57,58] Here, psychological intervention—such as social competence training, relaxation techniques, social support or active leisure activities (exercise)—should be recommended.[59-62] Only a few studies have investigated the impact of these interventions on the activity and reactivity of the stress hormone system, but existing evidence suggests that they are able to reduce the stress responsivity of the HPA axis.[63-65]

As already stated, major depression is often associated with HPA hyperactivity.[8,32] In this situation, antidepressant treatments or psychotherapeutic interventions are indicated.[66] Clinicians should be sensitive to mood alterations in their age-advanced patients, and should refer such patients for psychiatric workup if the occurrence of a depressive episode is suspected. The clinical relevance of these interventions is highlighted by the fact that depression in older adults is associated with a higher dementia risk.[67] This effect might, in part, be due to the depression-associated HPA hyperactivity. Successful antidepressant treatment, in contrast, leads to a normalized HPA axis.[8,32] In addition, antidepressants are able to prevent stress-induced dendritic atrophy in several animal models of chronic stress.[8,19,68] In humans, clinical evidence on this topic is still scarce. One recent study observed that treatment with a selective serotonin-reuptake inhibitor improved memory and reduced basal cortisol levels in depressed patients.[69] Clearly, more research in this area is warranted.

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Also often associated with increased HPA activity are the metabolic syndrome and type 2 diabetes. There is a close link between the stress system and the glucoregulatory system. Several authors have suggested that chronic stress facilitates the occurrence of the metabolic syndrome by influencing visceral fat deposition, by impairing insulin sensitivity or by changing eating habits (less healthy "comfort foods").[70,71] Here, lifestyle modifications (eg, diet and exercise) are often successful if started early enough.[72] If lifestyle changes alone are not sufficient to prevent or treat type 2 diabetes, several pharmacologic approaches are currently available.[72,73] Such interventions are important, since the metabolic syndrome and, even more so, type 2 diabetes are associated with memory impairment, hippocampal atrophy and an increased dementia risk.[74,75]

In addition to the rather indirect approaches mentioned above, there is very promising initial evidence that drugs aimed at influencing local GC concentrations within the brain might be effective agents for the prevention of cortisol-induced memory decline in aging. Local steroid concentrations are, in part, determined by the activity of the 11bHSD1 enzyme, which regenerates active GCs from their inactive 11-keto derivatives. Thus, the enzyme increases tissue levels of corticosterone and cortisol. Removal of this enzyme in transgenic mice results in lower intrahippocampal corticosterone levels and reduces GC-associated cognitive decline during aging in these animals.[76,77] In humans, two small, pharmacologic, placebo-controlled crossover intervention studies in older subjects or age-advanced patients with type 2 diabetes showed that 11bHSD1-inhibition with the drug carbenoxolone for 4 to 6 weeks was able to improve some aspects of memory.[78] More research is needed in order to establish the benefits and potential harm of this interesting intervention strategy. A cautious comment on this approach has been provided by Chrousos.[79]

Summary and Conclusions

The present review has highlighted how stress acutely enhances memory consolidation but impairs memory retrieval. In contrast, chronic stress is associated mostly with memory dysfunctions, and animal studies suggest that structural alterations in specific brain regions are responsible for these effects. Activity of the HPA axis increases with aging, and these alterations are more pronounced in women. Thus, the aging female brain is exposed to elevated levels of cortisol. Several studies suggest that this increase is associated with memory impairments. Animal studies and preliminary small-scale experimental studies in humans illustrate that several pharmacologic or behavioral interventions will, in the future, be able to protect aging women in a more targeted fashion from the negative impact of chronically elevated stress hormone levels. Nevertheless, more research is needed in the near future to permit evidence-based recommendations for the clinical practitioner.

In the meantime, patients complaining of chronic stress should be encouraged to participate in psychological anti-stress training (eg, relaxation, meditation, social competence training) and to use social support networks. These interventions should lead to an enhanced feeling of control. If signs of psychiatric disorders (depression, anxiety, PTSD) are present, a referral for a psychiatric work-up might be indicated. Depending on the outcome, pharmacologic treatments in combination with psychotherapy should be initiated.

Finally, evidence for chronic stress and a hyperactive HPA axis in the context of the metabolic syndrome should be initially addressed with lifestyle interventions. Often, a change in diet and increased physical activity will lead not only to a healthier life, but also to a happier one. In more serious cases of full-blown metabolic syndrome, pharmacologic agents targeted against specific features of the syndrome (eg, elevated blood pressure or glucose intolerance) are required.

In sum, while a neuroendocrine stress response is needed to cope with daily challenges, we have to be aware of the negative consequences of chronic stress. Promoting successful adaptation and preventing stress-associated diseases will remain challenges for clinicians and patients alike. ■

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This article includes discussion of off-label use of medication.

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