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Review

Stress, health and ageing: a focus on postmenopausal women

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Abstract

Stress influences health and disease and this might be of special relevance for ageing. The present review starts with the description of age-associated changes of the hypothalamic-pituitary-adrenal axis. In this context, the possible modulatory role of estradiol is discussed. Later, the influence of rising stress hormone levels for the ageing brain is illustrated and a few intervention strategies are outlined. At the end, the concept of allostatic load (AL) is described, which aims at a broader assessment of the impact of stress on the individual. The strengths and also the current limitations of the AL concept are highlighted.

Keywords: Ageing, allostatic load, hippocampus, hypothalamic-pituitary-adrenal axis, memory

Introduction

It is now well accepted that psychological factors substantially influence health and disease.[1,2] The present review will describe the recent progress in our understanding of how stress impacts the target systems in the periphery as well as in the brain through specific stress-related hormonal signals. Special attention will be given to the relevance of these alterations in ageing women.

Stress

Stress occurs when a person perceives a challenge to its internal or external balance (homeostasis).[1,2] Thus, a discrepancy between what should be and what actually exists leads to stress.[3] A *stressor* is a specific event that induces the stress. Stressors can be physical (e.g. cold, thirst) or psychological (e.g. work overload, marital problems, neighbourhood violence) in nature. In addition, a stressor can be acute (an upcoming surgery) or chronic (constant work overload, inadequate housing conditions and so on). Especially in humans, the subjective evaluation of the stressor and the availability of coping resources determine the impact of a stressor on the individual.[4] What is a welcomed challenge for one person might be a threat for another.

The neuroendocrinology of stress

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. HPA axis activity is increased in response to input from several brain regions.[1] Corticotrophin-releasing hormone (CRH) reaches the pituitary through the portal blood system, where it initiates the release of adrenocorticotropic hormone (ACTH) in the bloodstream. In response to ACTH, the adrenal glands secrete glucocorticoids (GCs). In humans, cortisol is the main adrenal GC. Under basal conditions, cortisol shows a marked circadian rhythm with typically lowest secretion during the first half of night-time sleep (=nadir), an abrupt elevation during the second half of sleep, peak levels shortly after awakening (=cortisol awakening response; CAR[5]) and continuously decreasing levels over the remainder of the day. Stress-related cortisol surges are superimposed on the normal circadian rhythm.[1,6]

GCs influence multiple target systems in the periphery. For example, chronically elevated cortisol levels lead to osteoporosis, diabetes and muscular atrophy.[2] In contrast, conditions characterized by unusually low cortisol levels (hypocortisolism) often go along with autoimmune diseases, chronic fatigue and chronic pain.[7] In addition, several psychiatric disorders are characterized by HPA axis alterations. Whereas major depression is typically associated with increased cortisol levels and impaired negative feedback functioning of the HPA axis, post-traumatic stress disorder often goes along with lower basal cortisol levels and an increased feedback sensitivity.[6,8]

HPA axis and ageing

Because HPA axis alterations are a close correlate or even a determining factor of the onset of different diseases,[7,9,10] the assessment of the integrity and functioning of HPA

axis regulation appears to be of major interest, especially in elderly individuals.

Evidence shows that with ageing, nocturnal nadir levels are increased and the duration of the quiescent period during the night is shortened.[11] Thus, older people are exposed to higher levels of cortisol during the night. In contrast, the data regarding age-associated changes in the cortisol awakening response have led to mixed findings.[5,12] Longitudinal studies indicate that not all older participants show an increase in cortisol levels over the years. A substantial interindividual variance exists with increasing, stable or even decreasing levels.[13] To summarize, existing data point to potentially altered basal cortisol concentrations during the period of the nocturnal trough, whereas cortisol levels remain mainly unchanged or are only slightly changed across the day; although, the large interindividual variation and the low reliability of single cortisol measurements must be acknowledged.

In the earlier decades, several studies investigated whether ageing affects the responses of the HPA axis to stress. It was assumed that differences between younger and older individuals might be more likely observed under challenge. Although earlier studies rendered very mixed results reporting either higher or lower HPA axis stress responses with advanced age, or no age-related differences.[14,15] We did not observe any age effects in salivary cortisol responses to psychosocial stress in healthy younger women compared with older women.[16] Also, in men, we found no, or only marginally higher, responses in the elderly.[17]

Pharmacological stimulation studies of the HPA axis with CRH with or without dexamethasone premedication or administration of CRH combined with vasopressin, the majority of studies showed elevated HPA axis responses in elderly subjects, and here, especially in elderly women.[16,18,19] At the level of the adrenal cortex, direct stimulation with synthetic or extracted ACTH does not indicate a generally altered adrenal cortex capacity or sensitivity with progressive age. Furthermore, studies point to a reduced HPA axis feedback sensitivity in older age that is especially pronounced in women.[20] In a recent meta-analysis, Otte *et al.*[21] concluded that the HPA axis response to a challenge increases significantly with ageing and that this effect is three times stronger in older women compared with older men.[21]

It remains poorly understood which factors are causing HPA axis hyperactivity observed during ageing in some individuals. Possible candidates are metabolic alterations associated with glucose intolerance or type 2 diabetes.[22] Alternatively, a central starting point of age-associated HPA axis alterations might be the underlying cause, since it is known that degeneration of suprathalamic control centres of the HPA axis (e.g. the hippocampus) lead to HPA axis hyperactivity.[6] Of course, these explanations are not exclusive and might interact at multiple levels.[22,23]

HPA axis alterations in ageing women: A role for estradiol?

The observation that, at least in some studies, basal HPA axis alterations and/or HPA axis responses to a pharmacological challenge are more pronounced in older postmenopausal women led to the speculation that gonadal steroids (estradiol and/or progesterone) could be involved in this effect. Unfortunately, very few studies have addressed this important issue as of today.

Studies investigating the effects of estrogen treatment on basal cortisol levels have led to mixed findings. In this context, it is important to consider the fact that oral estrogen treatment leads to an increase in corticosteroid-binding globulin (CBG). As a compensatory response, cortisol production is increased, leading to higher levels of total serum cortisol. In contrast, the biological active free fraction of the hormone appears to remain stable.[24] These changes (increase in CBG and total cortisol) do not occur in response to transdermal estradiol treatment.[24]

A few studies have investigated the effects of estrogen treatment on the HPA axis response to a challenge in menopausal women. In a small observational study, it was observed that women on postmenopausal estrogen therapy showed a less pronounced cortisol stress response to a laboratory stressor.[25] Randomized treatment studies are better suited to demonstrate a causal influence of estradiol on HPA axis reactivity in older women. In one small study, transdermal estradiol treatment resulted in a reduced HPA axis response to a psychological stressor.[26] Similarly, Lindheim *et al.*[15] observed that transdermal estradiol, when compared with a placebo, led to a blunted HPA axis response to a psychological stressor. However, in our study using a more powerful laboratory stressor transdermal estradiol treatment had no effect on the HPA axis response.[16] A discussion on the methodological problems of some of the earlier studies can be found elsewhere.[27] In our study,[16] an additional pharmacological challenge test was employed. In the combined Dex/CRH test, older women treated with placebo showed evidence of an exaggerated HPA axis response compared with younger women, which is in-line with other studies on this topic.[21] In contrast, participants treated with estradiol for two weeks showed a response pattern that was highly similar to that of a young control group.[16] Thus, this study provides the initial evidence for a beneficial effect of estradiol treatment on their HPA axis response to a pharmacological challenge in postmenopausal women. Supporting evidence comes from a study that tested the stimulatory influence of an endotoxin on the HPA axis response. Here, transdermal estradiol treatment again led to a blunted HPA axis response to this challenge.[28]

Taken together, while the existing literature is suggestive of a beneficial effect of estradiol on the HPA axis response to a challenge in older women, more research is needed before any firm conclusions can be drawn.[27] In addition, the possible impact of progesterone has not received the needed attention. It is hoped that the future sex hormone intervention trials will include markers of the HPA axis (re)activity.

Stress, ageing and the brain

In addition to their effects in the periphery, GCs influence the human brain. Of interest for the present review is the fact that GCs influence brain regions that are important for memory (e.g. the amygdala, the hippocampus and the prefrontal cortex[29]). These effects are mediated through the two receptors for the hormone. In addition, GCs can exert rapid non-genomic effects by influencing ion channels or neurotransmitter receptors at the membrane level.[1,6]

One of the best investigated areas is the modulatory effect of stress on long-term memory, a process mediated

by the hippocampus. Animal and human studies have convincingly supported a model, which postulates that stress enhances the emotional memory consolidation, but at the same time impairs the memory retrieval.[29,30] Thus, while we will remember a stressful episode for a long time, we are less able to retrieve previously learned information when we are under stress. This might explain why we have difficulties remembering material during an oral exam. Similarly, during the visit to a doctor we might find it difficult to remember the name of a medication.[29,30]

In contrast to the acute effects of stress that are temporary and from a clinical perspective not something of great concern, are chronic stress effects on the brain. Animal studies have illustrated that chronic stress leads to multiple structural and functional alterations in the central nervous system. In the hippocampus, neuronal atrophy and a reduction in neurogenesis occur. These structural changes directly or indirectly lead to memory deficits. Initially, it had been suspected that chronic stress leads to a vicious feed forward cycle causing neuronal death and a further increase of stress hormones.[31] Newer results, however, pinpoint to a preserved plasticity, suggesting that irreversible stress-induced structural damage is a rare event.[6,32,33]

In humans, several cross-sectional studies reported that higher endogenous cortisol levels were associated with impaired cognitive functions in general or impaired memory in particular. Similar findings have been obtained in cross-sectional studies.[13,34] A few studies additionally observed that rising cortisol levels were associated with smaller hippocampal volumes (suggestive of hippocampal atrophy), but here, the data are somewhat conflicting.[34,35]

Moreover, there is also evidence that patients with Alzheimer's dementia (AD) show signs of HPA axis hyperactivity when compared with healthy older control subjects.[36,37] This could just reflect the damage to HPA axis feedback centres in the brain, but might also be causally involved in disease progression.[38] The recent work in transgenic mice has documented that HPA axis hyperactivity can negatively influence amyloid metabolism as well as tau phosphorylation.[39,40] In AD patients, a placebo-controlled randomized double-blind trial revealed that treatment with the synthetic GC prednisone resulted in an accelerated memory loss.[41] Finally, an epidemiological study found that self-reported stress susceptibility was associated with an increased dementia risk.[42] Taken together, there is emerging evidence from multiple sources to suggest that chronically elevated cortisol levels can contribute directly as well as indirectly to cognitive decline in older women and men.

Having said this, when trying to interpret the findings of an association between higher cortisol levels and impaired memory in older subjects, one has to keep in mind that it is possible that older subjects feel more stressed when undergoing a memory task. It is thus possible that some of the effects observed might not reflect the chronic effects but rather acute stress effects induced by the testing situation.[35]

Intervention strategies

The present review has summarized age-associated HPA axis alterations and has shown that these changes might lead to negative health consequences. Although the potential of estradiol as a stress-protective agent remains to be explored further, several other interventions should be briefly mentioned. These concern physiological states in which the HPA axis hyperactivity is often observed.

Chronic stress due to work overload has been associated with increased HPA axis activity in several studies.[1,2] Here, psychological intervention – such as social competence training, relaxation techniques, social support or active leisure activities (exercise) – should be recommended.[43] Several psychiatric disorders are associated with the HPA axis hyperactivity, most notably major depression.[6] In this situation, antidepressant treatments or psychotherapeutic interventions are indicated. Clinicians need to be sensitive to mood alterations in their age-advanced patients. The clinical relevance of this is highlighted by the fact that depression in older adults is associated with a higher dementia risk.[44]

Another condition often associated with increased HPA axis activity is the metabolic syndrome and type 2 diabetes. The prevalence of both conditions increases substantially with age. There are close links between the stress system and the glucoregulatory system. It has been suggested that chronic stress facilitates the occurrence of the metabolic syndrome by influencing the visceral fat deposition, impairing insulin sensitivity or by changing eating habits towards unhealthier (comfort) food.[23,45] Alternatively, the negative impact of glucose intolerance on the brain might lead to HPA axis hyperactivity and in turn, elevated cortisol levels.[22] Against the metabolic syndrome, lifestyle modifications (e.g. diet and exercise) alone or in combination with pharmacological approaches can be successful.[46]

In addition to these somewhat indirect approaches mentioned above, there is a very promising initial evidence that drugs aimed at influencing the local GC concentrations within the brain might be effective agents for the prevention of cortisol-induced memory decline in ageing.[47] More research is needed in order to establish the benefits and potential harm of this interesting intervention strategy.

How to measure stress: the concept of allostatic load and its relevance for ageing

Physiological changes after stress help the organism to adapt to the increased demands and maintain homeostasis after a challenge, and can protect the body in the short run. In contrast, they can cause damage in the long run and finally promote development of stress-related diseases. The present review so far has focused on the important impact of the HPA axis stress system in influencing health and disease. However, since stress leads to multiple neuroendocrine alterations, this view is certainly too narrow. Moreover, due to the substantial intra- as well as interindividual variability of currently used HPA axis markers, their usefulness at the level of an individual patient is still limited. Thus, in order to obtain a better view on the impact of stress on an organism, a broader assessment is indicated.

Following a model introduced by McEwen and Stellar the biological 'costs' of short-term adaptation to stress are described as allostatic load (AL). AL is conceptualized as a summary measure capturing the cumulative physiological burden exacted on the body through attempts to adapt to life's demands.[48] AL is thought to reflect the

wear-and-tear on the body and brain resulting either from chronic overactivity or inactivity of physiological systems that are involved in the adaptation to environmental challenge.[2] Seeman and McEwen proposed a composite AL index consisting of measurement of the metabolic syndrome in combination with measurements of specific-stress markers (e.g. cortisol and norepinephrine). A list of the proposed AL indices is presented in Box 1.

Box 1 The 10 biological markers used to create the Allostatic Load score

(1) Waist-to-hip circumference ratio
(2) Systolic blood pressure
(3) Diastolic blood pressure
(4) Urinary cortisol
(5) Urinary norepinephrine
(6) Urinary epinephrine
(7) Serum dehydroepiandrosterone sulfate (DHEA-S)
(8) Glycosylated haemoglobin
(9) Serum high-density lipoprotein cholesterol
(10) Total serum cholesterol

It has been shown that this index increases with age and has proved useful in predicting the various physiological changes that precede the disease manifestation. Several reports based on the MacArthur studies of successful ageing have shown that this comprehensive measure predicts future cognitive, physical and functional decline as well as the increased health risks and all-cause mortality in elderly men and women better than any single factor on its own.[49,50]

We recently investigated AL in younger as well as older female school teachers in respect to chronic stress at the work place.[51] We found that higher levels of exhaustion and effort–reward imbalance (ERI) were associated with higher AL sum scores, reflecting the cumulative wear-and-tear that results from repeated efforts to adapt to stressors over time. It is noteworthy that, in this study, significant associations between chronic stress and AL could even be uncovered in a sample comprising fully functioning women, independent of age effects. These observations underline the idea that the AL composite might have high predictive power for the onset or progression of a variety of stress-related health problems in individuals in subclinical states. From a practical point of view, an AL summary measure may play a role in monitoring health states over time or in the prevention of stress-related health impairments in the future.

In sum, such findings further underline the potential advantage of a composite AL score that incorporates multiple stress-sensitive systems instead of focusing on single biological risk factors in quantifying disease risk in stressed but yet healthy individuals especially of older age.

Having said this, it has to be acknowledged that while clear diagnostic definitions of the metabolic syndrome are available,[46] diagnostic definitions for the remaining AL markers are currently not available. Moreover, for some of the AL markers (e.g. cortisol or epinephrine), the relationship to disease might not be linear but rather quadratic. Thus, very low as well as very high levels should be a concern for the clinician. Therefore, much work needs to be done before the concept of AL can be used by the general practitioner for diagnostic purposes.

Conclusion

Alterations of the HPA axis occur during ageing and they appear to be of relevance for health and disease. There is some evidence that these changes are more pronounced in older women. The potential role of the menopause related decline in gonadal steroids remains insufficiently understood. A combined AL measure is superior in predicting stress-associated disease, but currently this index can only be used for research purposes. Thus, while substantial advances have been made over the years, stress-associated diseases continue to remain a challenge for researchers and clinicians alike.

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