

## THE IMPACT OF STRESS AND GLUCOCORTICOIDS ON MEMORY

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### Abstract

*Responses to stress are mediated by a complex network of the nervous and endocrine systems. Glucocorticoids, which are among the most important “players” in stress resilience, may have important implications in the cognitive functions, particularly in the modulation of memory. Declarative memory, the memory for facts, events and word meaning is the most studied type of memory on which glucocorticoids exert an influence, both positively through consolidation and negatively through impairment. These effects depend on the receptor type, dose, time of exposure, memory component and the salience of stimuli, retrieval being generally affected and storage being facilitated, especially for emotionally relevant events. Glucocorticoids also induce hippocampal atrophy, which is a hallmark seen in various diseases accompanied by a chronic high level of cortisol, such as the Cushing syndrome, major depression, post-traumatic stress disorder. Also, chronic stress might be a risk factor for the development of Alzheimer's disease, especially when a genetic background and other environmental influences are present.*

**Keywords:** glucocorticoids, memory, hippocampus.

### Introduction

The effects of stress on human health are well documented in medicine and psychology. Stress is a common ingredient in our day-to-day life, a continuous challenge we have to face in an unceasingly changing world. Due to the enormous impact that stress has on health and quality of life, an interdisciplinary approach arose in the last decades in the form of psychoneuroimmunology, incorporating various aspects from psychology, immunology, endocrinology and neuroscience.

Responses to stress are mediated by a complex network of nervous and endocrine systems. There are several neural structures directly involved in stress coping. When encountering a stressful event, the nervous system processes the information and compares it with the organism's actual state and long term goals. If the event is perceived as potentially contextual changing or threatening, both nervous and endocrine systems harmonize in developing a response in order to cope properly, both mentally and emotionally [1]. Higher cortical structures, like the prefrontal cortex are involved in cognitive processing, e.g. trying to make the best decision, staying calm or thinking of solutions, whereas limbic - related subcortical areas like the amygdala are important

in emotional responses, e.g. being afraid, anxious or angry and, in conjunction with the hippocampal formation, playing a role in memory formation. But it is of crucial importance to adapt the organism's internal state and maintain the homeostasis unchanged (e.g. vital respiratory and cardio-vascular functions). This task is accomplished especially by a complex network of nervous and endocrine structures that form the so-called hypothalamic-pituitary-adrenal (HPA) axis [2].

A primary role of the HPA axis is the induction of glucocorticoids (GC), the main stress hormones, with major roles in our survival. Apart from their notorious implications in the immune system, studies in neuroendocrinology also point out important implications for GC in cognitive functions, particularly in the modulation of memory. In this review, we discuss about the effects of GC on memory impairment, with special emphasis on situations where the person experiences a stressful situation that triggers an acute change in the neurohormonal status, as well as the implications of memory and neurohormonal status in severe brain diseases (such as Alzheimer's disease and depression) or brain alterations (such as hippocampal atrophy) linked to long-term stress exposure.

### Glucocorticoid-induced memory impairment

Acting on the amygdala, GC help enhance the memory of emotionally relevant events through its connections with the

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hippocampus [3,4]. This process seems also to be dose-dependent: intermediate levels of GC enhance memory consolidation, whereas extremely low or high levels tend to impair it. However, GC appear to have negative effects on memory retrieval, regardless of their blood levels [5]. The effects of GC on memory are also supported by the wide distribution of GC within the central nervous system, with the existence of two types of receptors with affinity for glucocorticoids: type I, also called mineralocorticoid receptors, and type II, or glucocorticoid receptors. Type I receptors are highly expressed in limbic areas like the hippocampus and entorhinal cortex and seem to be associated with memory enhancement, whereas type II receptors are distributed both in limbic areas (hypothalamus and hippocampus) and cortical areas, especially the prefrontal cortex and their preferential activation has been associated with memory impairment [6].

Increased levels and activity of GC could result in memory impairment through an alteration of brain circuits and biochemical processes responsible for memory formation and storage. A number of case control studies revealed detrimental effects of GC on declarative memory, including decreased memory performance in asthmatic children treated with high doses of prednisone, or a correlation between the levels of cortisol, ACTH and memory impairment in patients with Cushing's disease, as well as a decrease in verbal memory performance (word list recall) following a low-dose dexamethasone administration in normal adults [7].

In addition to impairment of previously learnt information, there is evidence that another type of episodic memory, the autobiographic memory (remembering episodes of one's own past) is impaired. In a double-blind, placebo-controlled study on 22 healthy male students, Buss *et al.* observed that the students receiving 10 mg hydrocortisone had a worse performance in an autobiographic memory test than those who were on placebo. It has been suggested that acute glucocorticoid administration is probably not responsible for causing significant hippocampal atrophy, such as the one produced by chronic elevated glucocorticoid levels, but temporary memory impairment could be due to a specific interplay of receptor activation and non-genomic pathways. Moreover, in these subjects, GC impaired the retrieval of neutral events, whereas positive and negative events (emotionally relevant experiences) were only mildly affected, possibly because such events were better consolidated. The authors reasoned that the observed depression-associated hypercortisolemia could be responsible for the impairment of autobiographic memory retrieval observed in these patients [8]. However, Wingenfeld *et al.* reported an enhancement of autobiographic memory retrieval in patients with post traumatic stress disorder (PTSD) following the administration of hydrocortisone as compared with healthy controls treated with the same dose, where an impairment of neutral information was observed [9].

High GC levels induced by acute stress seem to have a variable impact on spatial memory. For instance, de Quervain *et al.* observed an impairment of spatial memory retrieval in stressed rats compared to control rats during platform searching in a water-maze test [5]. Conrad *et al.* showed a similar spatial memory retrieval impairment in chronically-stressed rats during spatial tasks in the Y maze [10]. On the other hand, Sandi *et al.* found that acute corticosterone exposure facilitated the storage of information in rats during tasks in Morris water maze. Stress-exposed rats (trained at 19°C) or injected with corticosterone were able to learn faster and consolidate memory better than non-stressed rats, trained at 25°C [11].

Social memory, a type of memory for person recognition, is mediated by the hippocampus and is also impaired by GC exposure. Social stress is the stress response during social interactions with other persons and the subsequent acutely elevated cortisol levels could disrupt social memory through a non-genomic pathway involving membrane-associated glucocorticoid receptors [12].

### **The effects of glucocorticoid exposure on the hippocampus**

The hippocampus is highly influenced by increased levels of GC, either stress-induced or after exogenous administration. It has been evidenced that both age-related increase in GC levels [13-17] and diseases associated with a chronic increase in cortisol levels, such as Cushing's syndrome [18,19], major depressive disorder [20] and post-traumatic stress disorder [21], are linked with hippocampal atrophy and dysfunction in humans.

Hippocampal atrophy is the result of several cellular and molecular events, which include downregulation of receptors, shrinkage of dendritic arborization, alteration of synapses, inhibition of LTP, impairment of energy metabolism, activation of NMDA-dependent excitotoxicity. Neuronal atrophy could be induced in part by a reduction of brain-derived neurotrophic factor (BDNF), a factor involved in the survival and trophicity of neurons and synapses. Also, there is evidence of interactions between GC and serotonergic system by 5-HT1A serotonin receptor modulation. Pharmacological decrease of serotonin in the hippocampus resulted in a blockade of stress effects on memory, suggesting that serotonin could be involved in hippocampal damage during stress [7,21]. However, Malberg *et al.* reported a reversal of downregulation of neurogenesis in animals exposed to stress following treatment with a selective serotonin reuptake inhibitor [22]. In fact, both *in vivo* and *in vitro* results showed that GC tend to inhibit neurogenesis through type II receptor activation, while type I activation led to a mixed effect, some studies suggesting a decrease in neurogenesis and others actually an increase [23]. Moreover, it is worth noting that hippocampal atrophy is not only the consequence of high cortisol level, but also a cause. The hippocampal damage disrupts the normal inhibitory control on the HPA axis, leading to an

excess of CRH secretion and eventually to increased glucocorticoid levels, worsening the hippocampal atrophy. Chronic exposure to GC results in a preferential activation of type II receptors and induces neuronal death and attenuation of neurogenesis [16].

Using magnetic resonance imaging (MRI), hippocampal atrophy was described in patients with Cushing's syndrome. Resmini *et al* found that only patients with severe memory impairments showed a reduction of the hippocampal volume and identified older age as the only predictor of hippocampal reduction in both patients and controls matched for age, gender and years of education. However, both verbal and spatial memory were impaired in patients as compared to controls, even after cure [19].

In experimental models, Ohl *et al* showed in a study on male tree shrews that hippocampal reduction occurred in both cortisol-treated animals as well as in psychosocial stress-exposed group [24]. In patients with unipolar depression, studies of hippocampal volume showed mixed results. While some demonstrated a clear reduction in hippocampal volume, others have failed to find significant changes [20]. Recently, Kohler *et al* suggested that cerebrovascular disease-induced white matter abnormalities are more important than the cortisol level for cognitive impairment in people with depression [25].

Despite the huge amount of evidence for GC-induced hippocampal damage, there are opinions against this concept. Some studies revealed low levels of cortisol in patients with PTSD, arguing against the role of high cortisol levels in hippocampal damage. Regarding this issue, it is possible that cortisol levels are elevated at the onset of this disease, and decreasing chronically. Others have speculated that people who were born with a small hippocampus and a lower intelligence rather than stress itself are at risk for developing PTSD. This theory was criticized by observations that people with PTSD showed a decrease of their IQ after the traumatic event [21].

A reduction of the hippocampal volume was also found in metabolic disorders, such as type-2 diabetes mellitus, however this reduction was not correlated with diurnal cortisol level, but with a blunting of cortisol awakening response (CAR), a rise in cortisol post wake-up. While the reduction of hippocampal volume would be the cause of this ablated HPA axis response to awakening, knowing that hippocampal integrity is crucial for cortisol regulation, the actual hippocampal atrophy seems to be caused by hyperglycemia itself, through the formation of glycated end-products, generation of oxygen species and endothelial damage [26].

#### **Alzheimer's disease – a neurological disease with endocrine components?**

Alzheimer's disease (AD) is the most common neurodegenerative disease and the most common dementing illness. It affects primarily hippocampus-related memory, leading to a progressive loss of memory and other cognitive

functions. While there are some theories regarding the neurobiology of this disease, no cure is known in present.

Clinical studies demonstrated that chronic stress and glucocorticoid levels can be a risk factor for AD and are associated with early hippocampal atrophy and cognitive decline [27-31]. Experiments on transgenic mice elucidated the pathophysiology of GC in AD-spectrum dementias, showing that GC influenced both amyloid deposition and tau hyperphosphorylation, chronic stress being a trigger for APP misprocessing. Hyperphosphorylation is induced by two kinases, glycogen synthase kinase 3 (GSK3) and cyclin-dependent kinase 5 (CDK5), both of them being stimulated by GC. On the other hand, GC appear to increase tau levels. Moreover, GC stimulates  $\beta$ -secretase, the enzyme starting the so-called amyloidogenic pathway and increase APP levels by increasing the transcription of APP gene [32-34]. An important thing to keep in mind is that transgenic rat neural cells expressing human tau gene (htau) are more vulnerable to GC-induced A $\beta$  pathology than cell lines with rat tau gene [33].

The identification of an enzyme involved in cortisol metabolism, 11 $\beta$ -hydroxysteroid dehydrogenase type 1 as a genetic susceptibility for AD further increased the evidence for GC role in molecular biology of this disease. A haplotype of this gene is associated with high levels of cortisol and an increased risk for developing AD. In addition, there are findings suggesting that high CSF levels of cortisol are associated with the presence of apoE4, one of the three isoforms of apolipoprotein E involved in lipid circulation in central nervous system. ApoE4 is at present the most studied genetic risk factor in the sporadic form of AD because of its role in A $\beta$  deposition [32]. Regarding the link between altered neurosteroidogenesis and AD, MacKenzie *et al.* found no evidence of cortisol synthesis in the hippocampus and cerebellum in post-mortem samples from AD patients, despite high levels of cortisol in the blood and CSF [35].

#### **Conclusions**

Stress adaptation and resilience are critical conditions for the organism's welfare and depend on highly complex nervous and endocrine networks, centered on the HPA axis. When a person's resources and stress-adapting mechanisms are affected, a series of biological and neuropsychological consequences develop. Glucocorticoids are one of the most important "players" in stress resilience and have both beneficial and detrimental effects on declarative memory in a time-dependent, dose-dependent and receptor type-dependent fashion. Chronic stress induces dysfunction of the HPA axis, leading to increased levels of glucocorticoids and impairment of different aspects of declarative memory (verbal memory, social memory, spatial memory) mainly through hippocampal damage. While chronic exposure to glucocorticoids results in hippocampal atrophy, in the amygdala, especially the baso-lateral complex, the effect is the opposite, namely an increase in dendritic arborization and spinogenesis of neurons. Also, chronic stress can be a risk

factor for the development of Alzheimer's disease, especially when a genetic background and other environmental influences are present.

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