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Physiological and molecular mechanisms of stress-induced memory impairment

Heba Essam El-din El-sayed Ali, Ahmad Bahaa El-din Abd-Allah, Akmal Ahmed Hassan Diab, Radwa Mahmoud Al-sayed

Medical Physiology Department, Faculty of Medicine - Zagazig University, Egypt

Corresponding author: Heba Essam El-din El-sayed Ali

Email: haelnouary@medicine.zu.edu.eg, hebaessam921@gmail.com

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Abstract: Stress profoundly impacts memory, manifesting as both acute and chronic impairments. The physiological and molecular mechanisms underlying this are complex and interconnected, involving multiple brain regions and signaling pathways. Acute stress, characterized by the activation of the hypothalamic-pituitary-adrenal (HPA) axis, leads to a surge in glucocorticoids like cortisol. Elevated cortisol levels can interfere with memory consolidation and retrieval by modulating synaptic plasticity in the hippocampus, a crucial brain region for learning and memory. This modulation occurs through glucocorticoid receptor (GR) binding, affecting processes like long-term potentiation (LTP) and dendritic spine morphology. Excessive cortisol can also impair neurogenesis in the hippocampus, further contributing to memory deficits. Beyond glucocorticoids, the sympathetic nervous system, activated concurrently with the HPA axis, releases norepinephrine, influencing amygdala activity and potentially disrupting memory encoding through its effects on stress hormone release and modulation of attentional processes. Chronic stress, however, leads to more persistent and potentially irreversible changes. Prolonged exposure to elevated glucocorticoids can result in hippocampal atrophy and neuronal damage, contributing to long-term memory impairments. Furthermore, chronic stress is associated with dysregulation of the HPA axis itself, leading to a hyperactive response to subsequent stressors and exacerbating memory deficits. At the molecular level, stress impacts numerous signaling pathways. Increased levels of pro-inflammatory cytokines, like IL-1β and TNF-α, contribute to neuroinflammation, damaging neuronal structures and disrupting synaptic function. Furthermore, chronic stress can lead to oxidative stress, resulting in the accumulation of reactive oxygen species (ROS) and neuronal damage. These molecular changes contribute to impairments in synaptic plasticity, neurogenesis, and ultimately, memory function. Understanding the intricate interplay of these physiological and molecular mechanisms is crucial for developing effective interventions to mitigate stress-induced memory impairment, potentially targeting specific pathways such as GR signaling, neuroinflammation, or oxidative stress. Further research is needed to clarify the precise temporal dynamics and interactions among these mechanisms to optimize therapeutic strategies..

Keywords: *Physiological and molecular mechanisms, stress-induced, memory impairment*

Introduction.

Stressful events can impact memory and reasoning and activate both the sympathetic nervous system (SNS), leading to the release of noradrenaline and adrenaline (NA) into the bloodstream by the adrenal medulla, and also the hypothalamic-pituitary-adrenal (HPA) axis, leading to the secretion of glucocorticoids (cortisol) into the blood by the adrenal cortex [1, 2].
Stress-induced cortisol release can have a direct impact on the hippocampus and the amygdala, brain structures involved in memory and emotional processes [3]. Cortisol can cross the blood-brain barrier and bind to glucocorticoid receptors in the hippocampus, thus modulating hippocampal function, and consequently, modulating encoding and retrieval of long-term memories [3]. A considerable amount of research has investigated the impact of stress-related cortisol release on memory processing [4, 5].
The fast stress response occurs seconds after the stressor and involves the release of adrenaline, which increases alertness and facilitates memory encoding [6]. The slow stress response involves the release of cortisol, which impairs the retrieval of consolidated memories [6].

Cellular and molecular mechanisms of stress-induced memory impairment:

Stress is an adaptive neurobiological response that enables the body to adjust to internal and external environmental challenges [7]. The stress-responsive system is a complex adaptive system that seems to be highly conserved across species [8]. It is well established that two different but interconnected systems, including the hypothalamic-pituitary-adrenocortical (HPA) and the sympathetic-adrenomedullary (SAM), have significant roles in the coordination of both physical and psychological responses to stress situations [9]. The SAM system is a component of the sympathetic division of the autonomic nervous system. It is responsible for the first phase of the stress response, which leads to a short-term reaction to provide appropriate responses [10]. Following the activation of the SAM system, the adrenal gland center releases epinephrine into the blood circulation, then facilitates rapid mobilization of metabolic resources to induce fight/flight fast responses [11, 12]. Exposure to a stressor increases the secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from the paraventricular nucleus (PVN) of the hypothalamus to stimulate the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH) into the blood circulation [13, 14].
The ACTH, in turn, induces glucocorticoid synthesis and release from the cortex of adrenal glands, which are cortisol in humans and corticosterone in rodents [15].
Evidence suggests that endogenous synthesis of corticosteroids is not limited to the adrenal cortex. Using messenger RNA (mRNA) and immunogold electron microscopic analysis, it has been shown that the hippocampal neurons express the specific enzymes, including P450 (c21), P450 (2D4), P450 (11β1), and 3β-hydroxysteroid dehydrogenase to produce a low nanomolar level of corticosterone in rats [16]. The glucocorticoids are responsible for long-term responses and help the body adapt to stress. Circulating glucocorticoids seem necessary for brain development, neuronal survival and neurogenesis, psychophysiological adaptation to stress conditions, and adaptive immune responses [17, 18].

The secretion of glucocorticoids from the HPA axis is tightly regulated by endocrine and neuronal systems [19]. The rate of glucocorticoid release and the level of glucocorticoid release could determine 'fast' and 'delayed' negative feedback regulation, respectively, to protect the body from prolonged activities [20]. Glucocorticoid negative feedback may be mediated at multiple levels via glucocorticoid receptors (GRs) located in the hypothalamus and the anterior pituitary gland. The HPA axis is also modulated through a glucocorticoid-independent neuronal mechanism [19]. Both direct and indirect pathways have a central role in controlling the end product of the HPA axis (Figure 1) [21].

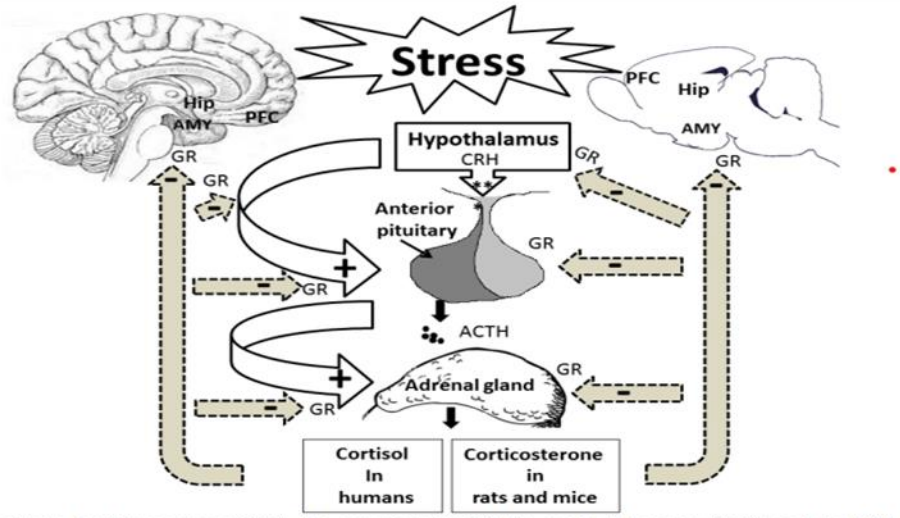

Figure 1. Stress affects the hippocampus (Hip), the amygdala (AMY), the prefrontal cortex (PFC), and the HPA axis. Following stress exposure, the hypothalamus is activated to release CRH into the bloodstream to stimulate the pituitary gland for producing ACTH. The bloodstream delivers ACTH to the adrenal glands to release cortisol in humans and corticosterone in rodents. Stress hormones via GRs affect memory-related brain regions. +: stimulation; –: inhibition

The limbic brain structures, including the hippocampus (Hip), the amygdala (AMY), and the prefrontal cortex (PFC), control the PVN activity via the glutamatergic and gamma-aminobutyric acidergic (GABAergic) innervations [22]. Glutamatergic projections of the Hip and the PFC indirectly inhibit the PVN neurons in the hypothalamus. Thus, they play an essential role in terminating the HPA axis-induced stress response and have a negative feedback modulation on this axis [23].

Effects of stress on memory

Stress impairs memory formation

The end product of neuroendocrine stress cascades, glucocorticoids, plays a critical role in brain processes, including neural plasticity, synaptic transmission, and cognitive functions such as learning and memory [24]. Glucocorticoids exert their cellular effects by acting on MRs, and GRs in the brain regions, which are essential for memory performance [6, 25]. The elevation of cortisol under a stressful situation or exogenous glucocorticoid administration affects memory consolidation [24].

The exposure to the acute stressful stimulus affected the consolidation of object recognition task memory in mice and resulted in long-term memory impairment without any adverse effect on short-term memory. Blocking cannabinoid receptors (CBs) of adrenergic neurons improved stress-induced memory loss [26], indicating the role of the cannabinoid system in the modulation of cognitive function. In line with these findings, human research has shown that acute stress in pre-encoding information enhances the recall of emotional memories [27], also memory impairment is dependent on cortisol level, for example, exposure to acute stress leads to a decrease in cortisol level leading to a loss of memory recall [28].

Long-term memory was negatively affected by acute stress during memory consolidation and before memory reactivation [29]. Recalling a memory under stress is state-dependent, and memory enhancement occurs in a similar stressful state that happens during the consolidation of information. Stress-induced robust changes in structural and functional neuronal plasticity [29] eventually altered glutamatergic-mediated synaptic transmission via N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, which are essential components in synaptic plasticity; therefore, they could affect memory storage [30].

Experiments prove that stress changes dendritic arborization and alters dendritic spine density in different brain regions. Chronic stress results in spine density loss and retraction of apical dendritic branches in the hippocampal regions [31]. Moreover, acute stress potentiates glutamatergic transmission in the PFC [32], facilitating working memory through glucocorticoid-inducible kinase signaling [33]. In contrast, chronic stress causes the impairment of prefrontal-dependent memory formation [34] by acting on suppressing glutamatergic transmission.

Stress affects long-term potentiation and long-term depression

The activation of the HPA axis and SAM system following exposure to a stressful event could modulate cognitive and emotional memory through changes in synaptic strength [35]. Some studies reported that stress induces alterations in synaptic plasticity through cellular mechanisms, including long-term potentiation (LTP) and long-term depression (LTD). The neuro-cognitive processes contain multicomponent stages, including encoding, consolidation, and retrieval. The most intensive studies showed that stress might affect all three specific phases involved in memory formation and directly is dependent on many factors such as the stressor's timing, which in turn, causes improvement or impairment of memory performance [6].

The animal examination has indicated that elevation of cortisol under stressful situations or exogenous glucocorticoid administration affects memory consolidation. The exposure to the acute stressful stimulus affected the consolidation of object recognition memory in mice and resulted in long-term memory impairment without any adverse effect on short-term memory. Interestingly, stress-induced memory loss is reversed by blocking CBs of adrenergic neurons [26].

Neurotransmitters are involved in the effects of stress on memory

Different stressors affect various neurotransmitter systems' molecular and cellular functions, including GABAergic, cholinergic, glutamatergic, serotonergic, dopaminergic, and endocannabinoid system (ECS). The changes in neurotransmitters' release and synaptic concentrations are associated with the type of stress and brain regions [36].

GABAergic system

Gamma-aminobutyric acid (GABA) receptors, including GABA subtype A (GABAA), GABA subtype B (GABAB), and GABA subtype C (GABAC), are ionotropic receptors that control and manage cognitive functions broadly expressed in the central nervous system (CNS). Metabotropic GABAB receptors bind to G protein inhibitors (Gi/o) to mediate prolonged slow inhibitory action. Both pre- and post-synaptic GABAA and GABAB receptors inhibit the excitatory and inhibitory neuronal functions. Hence, activation of these receptors modulates long-lasting potentiation in the different brain regions [37, 38].

Dopaminergic system

Dopamine-induced effects are mediated via G-protein-coupled receptors classified into two subclasses: D1- and D2-like receptors. Stimulation of dopaminergic D1 or D2 receptors enhances or inhibits the adenylyl cyclase activity to change cyclic adenosine monophosphate (cAMP) concentration, respectively [39]. Dopamine receptors are highly expressed in different brain areas, including the (VTA), the nucleus accumbens (NAc), the substantia nigra, the hippocampus, and the amygdala. Dopamine receptors are involved in the formation of different types of learning and memory, such as passive avoidance learning [40], spatial memory, and reward-related learning and memory [41]. Exposure to acute or chronic stress increases dopamine release in the nucleus accumbens, the ventral tegmental area, and the prefrontal cortex [42]. In general, acute stress increases the amount of dopamine in the brain to increase the risk of an adult's desire to use addictive substances [43].

Serotonergic system

Serotonin is mainly produced in the raphe nuclei of the brain stem. There are seven types of serotonergic receptors. Based on the chemical structure of serotonin, these receptors are called 5-hydroxytryptamine (5-HT). The serotonergic receptors are a combination of metabotropic and ionotropic receptors that have excitatory and inhibitory roles in the CNS [44]. The 5-HT receptors regulate the release of different neurotransmitters, including glutamate, GABA, and acetylcholine. The serotonergic heteroreceptors are therapeutic targets for treating depression, Alzheimer's diseases (AD), and Parkinson's diseases [45]. Serotonin plays a role in chronic stress-induced cognitive dysfunction. [46] found that exposure to chronic stress caused cell death in the interfascicular nucleus of the dorsal raphe, which results in decreased serotonergic innervation of the medial prefrontal cortex.

Stress changes the number and structure of astrocytes

Astrocytes are the most abundant glial cells in the CNS. They contribute to the blood-brain barrier formation [47], neurotrophin secretion [48], neurotransmitter recycling [49], and regulation of neuronal synaptogenesis [50]. Additionally, the activation of the astrocytic cAMP enhances the lactate shuttle from astrocytes to neurons, serving as energy for synaptic plasticity and memory formation processes [51].
Interestingly, astrocytes undergo structural plasticity during memory formation. With the elevation of the stress hormones and extracellular glutamate after HPA axis activation, astrocytes are one of the critical cells that respond to stress's physiological consequences and are influenced structurally and functionally by stress conditions. Stress induces the hypertrophy of astrocytes and a reduction in gap junction coupling between cells in the Hip and the neocortex. The latter effects reduce functional coupling between hippocampal and neocortex astrocytes, which is associated with the attenuation of astrocytes' capacity to supply neurons with L-lactate [52]. Exposure to chronic stress also reduces the volume fraction of fine astrocytic protrusions and the number of astrocytes in the amygdala, which may affect AMY-related memory formation [53].

Astrocytes' specific elimination of glucocorticoid receptors in mice results in impairment of fear memory and aversive memory formation, which suggests that the signaling of the astrocytic glucocorticoid receptors regulates stress-induced-aversive memory formation [54]. In general, it can be suggested that astrocytes should be considered a cellular target for therapies for stress-induced memory impairment.

Stress-induced significant changes in microglia may be involved in memory impairment

Exposure to stressful conditions and activation of signaling pathways of stress receptors leads to the inhibition of the production of proinflammatory cytokines such as interleukin-1β (IL-1β), IL-18, IL-6, or tumor necrosis factor-α (TNF-α) in the CNS [55]. However, the immune system function disrupts and leads to the overactivation of inflammatory pathways under severely stressful conditions. Microglia cells, the CNS macrophage cells, express the stress hormone receptors, including the glucocorticoid (GC), MR, and norepinephrine (NE) receptors. Therefore, these cells are one kind of the key cells in regulating stress-associated outcomes [56]. Severe and intense stress over-activates the microglia cells and thereby enhances the release of inflammatory cytokines, leading to neuroinflammation. The morphology of microglial cells changes due to stress, and they show fewer branches and an enlarged soma called ameboid microglia [57].
Besides, as a danger signal, stress triggers the formation and activation of microglia inflammasomes. The inflammasomes are intracellular protein structures that involve the formation of proinflammatory cytokines in cells and play a critical role in innate immunity [58], leading to impaired function of neuronal synapses and deficits of synaptic plasticity that underlie cognitive dysfunction. Exposure to stressors dysregulates the microglia function, negatively affecting the neurogenesis and neuronal functions, and may have long-lasting consequences over the lifespan [59].

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