Cortisol Awakening Response: An Ancient Adaptive Feature

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Abstract

Similar to other endocrine substances, cortisol secretion follows a pulsating rhythm. The cortisol awakening response (CAR) occurs upon awakening in the absence of any apparent stressful situation or imminent danger, which is a very intriguing feature. When confronting any stressful situation, two systems are activated. One system is regulated by the hypothalamic-pituitary-adrenal axis (HPA), and the other system is regulated by cerebral structures that control the activity of the autonomic sympathetic nervous system. Both systems receive inputs from emotional memory circuits, namely the amygdala, the hippocampus, the medial prefrontal cortex, and lateral septal nuclei, among others. This circuit integrates sensory information that comes from thalamic nuclei. The acquisition, retention, and evocation of recent and remote memories that are processed by the emotional memory circuit allow the selection of strategies for survival. The diurnal secretion of cortisol occurs near the time of awakening (i.e., after a period of rest or sleeping) and persists for several hours in the absence of any current stressful situation. The CAR seems to represent an ancient adaptive-allostatic feature that prepares an individual to face eventualities that are forthcoming during the day. The CAR is regulated by hypothalamic nuclei that modulate circadian rhythm, namely the suprachiasmatic nucleus and its connections with the paraventricular nucleus, and then activate the HPA axis. The CAR may represent a useful preparatory process that occurs before a stressful situation. The participation of emotional memory circuits may modify the CAR and contribute to resilient or vulnerable reactions when coping with threatening situations.
Keywords: Adaptive; Allostasis; Allostatic load; Ancient; Anxiety; Cortisol; Cortisol awakening response; Stress

1. Introduction

Throughout the day, plasma cortisol levels typically peak many times. A period of low plasma concentrations generally centers around midnight, with an abrupt rise that commonly occurs after awakening, independent of age, gender, and other aspects [1]. The cortisol awakening response (CAR) is an indicator of adrenocortical activity that consists of an increase in plasma cortisol within the first hour after waking. Within the first 30-40 min after awakening, free cortisol levels rise by 50-60%, remain elevated for at least 60 min [2], and decline to a nadir thereafter by about bedtime.

An approach to understanding the processes that allow individuals to adapt to their environment is called allostasis [3, 4]. This concept refers to functional changes in hormones and mediators that occur in an organism that allow the individual to confront perturbations in the internal and external milieus. These changes permit the survival of the individual and consequently the species. Allostasis depends on the activity of two main systems: (i) hypothalamic-pituitary-adrenal (HPA) axis and (ii) autonomic nervous system. During the day, cortisol levels may increase in response to emergencies, whereas the CAR may be an anticipatory response that is directed toward daily eventualities just after awakening. However, in cases in which high levels of cortisol persist for a long period of time, are inefficiently managed, or become exaggerated, allostatic load may occur [4-6], which can negatively impact health.

The organism is able to respond to emergency situations through physiological adaptive changes that permit the individual to maintain homeostasis and survive. From a psychological perspective, this response is referred to as resilience, which reflects the ability of the living organism to face and overcome stressful situations [7]. In other cases, some maladaptive processes may be related to vulnerability [8-10]. However, HPA and autonomic activity is insufficient to explain resilience and vulnerability. Increases in cortisol when confronting an emergency situation and the CAR may prepare the individual for future emotional threatening events, thus suggesting the participation of brain circuits that are involved in emotional processing.

The present review considers the participation of emotional memory circuits in the regulation of endocrine and autonomic responses both at rest and when confronting a threatening situation. Cortisol has been considered a marker of stress [11], in addition to other products of autonomic nervous system activity. Acute stressors activate the HPA axis, leading to the release of corticotropin-releasing factor into the portal circulation (Figure 1). Adrenocorticotropic hormone (ACTH) is then released into the plasma, and the cortical portion of the adrenal gland is activated to deliver cortisol into the circulation. Plasma cortisol levels reach a peak approximately 15-30 min after an environmental challenge [12].
Figure 1: A threatening situation elicits two simultaneous responses: sympathetic responses and cortisol secretion that is regulated by the HPA axis. These two systems interact with each other. The participation of cerebral nuclei that regulate emotional memory processing may explain susceptibility and resilience to stress. ACTH, adrenocorticotropic hormone; HPA, hypothalamic-pituitary-adrenal axis; PVN, paraventricular nucleus of the hypothalamus; mPFC, medial prefrontal cortex.

The cortisol response when confronting stressful situations has been extensively reviewed elsewhere; therefore, we only briefly discuss it herein. We focus mainly on the CAR, beginning with a brief overview of the brain structures that regulate emotional memory and its relationships with brain structures that regulate cortisol secretion. We then discuss the specific features of the CAR, its neural control, and the cortisol response to cope with threatening situations in other vertebrates. The hypothesis of the present treatise is that the CAR may represent a very useful ancient adaptive response.

2. Emotional Memory Circuit

Emotional memory allows an individual to recognize signs from the environment and compare them with past experiences to effectively judge and respond to the environment by choosing the best coping strategy [13, 14]. Such processes involve the hippocampus and other deep temporal lobe structures, such as the amygdala [15], the mesolimbic system [16], and interactions among these structures and the prefrontal cortex [17, 18], among other connections. Sensory inputs relies on thalamic nuclei that are connected to cortical and subcortical cerebral circuits [19] that regulate the emotional meaning of stimuli and endocrine and autonomic responses.
The neural circuits that regulate emotional memory comprise several interrelated structures that are located primarily in deep layers of the temporal and frontal lobes that project to the HPA axis and cerebral regulators of corticosterone secretion and adrenergic system activation (Figure 2).

Figure 2: Anatomical representation of emotional memory circuit. Connections between the amygdala, hippocampus, lateral septal nucleus (LSN), and medial prefrontal cortex (mPFC) modulate the utilization of emotional memories. These nuclei are also connected to the locus coeruleus and hypothalamus, which are involved in autonomic responses and cortisol secretion.

Among other temporal lobe structures, the amygdala complex is composed of many functionally heterogeneous nuclei [20]. The amygdala nuclei have been largely considered as fundamental in the process and integration of defensive and fear reactions [21-23]. Basolateral amygdala includes basal, lateral and accessory basal nuclei [24] and fear reactions [25], increased anxiety state [26], during the processes of emotional learning [27] and classic conditioning [28] relates to a higher neuronal firing rate in these regions than in absence of stimulation or resting situations. From a behavioral point of view, electrical stimulation of amygdala produces signs of fear and anxiety, accompanied by vegetative responses in both cats [29] and human beings [30]. Fear expression involves cortical association areas, and thalamic and amygdaline interconnections [31]; importantly, cortisol seems to regulate the connectivity between amygdala and at least the medial prefrontal cortex (mPFC) inclusively during rest conditions [32], while amygdala-hypothalamic connections regulate vegetative activity in response to threatening situations [33].

Among another amygdaline connections, the reciprocal innervation with hippocampus modulate the unconditioned fear, defense reactions, goal-directed behavior and emotional memory [34, 35], with the important participation of the two different portions of hippocampus [36]. Therefore, amygdala-hippocampus relations are crucial in the control and regulation of episodic memory and emotional memory, and as above mentioned, through the connections of amygdala with hypothalamus in the control of cortisol secretion. In rats, the corresponding portions are the dorsal and ventral hippocampus, which are related to memory and emotional processing, respectively [37]. The responsivity of dorsal hippocampal neurons responders to amygdala stimulation increased 48 h after a single session of stress, suggesting the formation of an emotional memory [38]. Increases in endogenous cortisol and...
norepinephrine levels in turn increase neuronal activation in the amygdala in response to threatening images [39]. In such cases, the higher levels of plasma cortisol when confronting a threatening situation may facilitate specific learning that is relevant to survival [40].

Amygdala-mPFC connections are able to regulate aggressive behavior in rodents [41-43]. In rats, the mPFC involves the cingulate, prelimbic (PL) and infralimbic (IL) subregions, each subregion possess different connections and consequently different functions. In particular PL and IL differentially regulate the expression of fear [44], among other behaviors [17], possibly due to their interconnections with amygdala [45]. mPFC subregions differentially participate in the process of acquisition and extinction of conditioned fear [46, 47] through inhibitory connections coming from amygdala [28], thus mediating distinct strategies to cope with environment. Inactivation of the PL cortex impaired the expression of fear but not extinction memory. Inactivation of the IL cortex had no effect of the expression of fear but impaired both the acquisition and extinction of conditioned fear memories [46]. Activation of the PL and IL regions has yielded consistent results. The PL cortex is active during fear conditioning, and the IL cortex becomes active during fear extinction [47].

Another structure that is connected to the amygdala, hippocampus, and mPFC is the lateral septal nucleus. Together with the aforementioned key regions, the lateral septal nucleus also participates in the control of motivational and autonomic responses [48], the antidepressant actions of drugs [49], anxiety [50], affective behavior, and autonomic activity [51].

Brain structures that are related to emotional memory appear to influence and may be influenced by the actions of cortisol secretion and sympathetic activity. In such a case, the participation of emotional memory circuits due to its function of retention of experiences related with threatening situations may account for the formation of resilience and vulnerability, and consequently modifying the vegetative responses, favoring or negatively impacting on the efficacy of allostatic processes.

### 2.1 Cortisol awakening response and sleep
The diurnal increase in cortisol secretion is associated with the sleep/wake and light/dark cycles. The CAR is a very constant feature that is modulated by circadian influences. In very young children, the level of morning cortisol is positively associated with the amount of stage-2 sleep the night before and negatively associated with total sleep time and other slow-wave-sleep stages [52].

Total sleep deprivation in healthy adults decreases the CAR in parallel with changes in the perception of energy level, concentration, and speed of thought and a reduction of cognitive functioning despite an increase in regional dopaminergic activity [53]. Chronic circadian misalignment significantly reduced cortisol levels and increased the release of inflammatory factors, including tumor necrosis factor, interleukin, and C-reactive protein [54]. The interaction between sleep and the HPA axis is complex and bidirectional. Hypothalamic-pituitary-adrenal axis hyperactivity and decreases in the duration and quality of sleep occur in insomnia, depression, Cushing’s syndrome, and sleep-disordered breathing, among other ailments [55]. Changes in sleep duration contribute to daily variations in cortisol and autonomic nervous system activity [56].
2.2 Neural regulation of the cortisol awakening response

The suprachiasmatic nucleus regulates the circadian rise in plasma ACTH [57,58]. Suprachiasmatic nucleus regulates activity on paraventricular hypothalamic nucleus and exerts a decisive action on the day/night pattern of hormonal and autonomic activity regulation [59]. This anatomical feature regulates CAR and the influence of ACTH on suprarenal cortex [60].

Sensorial stimulation produces emotional reactions and elaborated behaviors (Figure 3). The hypothalamic regulation CAR [61] is modulated by a multiple system of neurotransmission, mainly glutamatergic, aspartate, and GABAergic fibers from telencephalic and forebrain regions, which are considered limbic structures [62-64], but not from the lower brainstem. These hypothalamic nuclei control the neuroendocrine response to stress, whereas the extended amygdala controls the autonomic responses to stress [12]. Therefore, the paraventricular nucleus may be considered an integrator of neuroendocrine and autonomic nervous system responses and may also participate in the integrated emotional response. The CAR may also be involved in the activation of a negative feedback loop that results in the termination of ACTH secretion [65]. Anxiety may be a useful adaptive feature [14] that, combined with the storage of emotional memories of prior experiences, facilitates the choice of the best strategies for survival.

Figure 3: The circadian rhythm of cortisol release occurs in the absence of a threatening situation. Therefore, it may be considered a useful allostatic adaptive feature that prepares an individual for eventual emergency situations, with the fundamental participation of emotional memory circuits. PVN, paraventricular nucleus of the hypothalamus; SCH n: suprachiasmatic nucleus; CAR: cortisol awakening response.
2.3 Cortisol in other animal species

The cortisol response to threatening situations is not exclusive to humans or other mammals. Individuals that present similar HPA axis function express similar responses to threatening situations, independent of species. A rise in cortisol may indicate the development of behavioral strategies that facilitate escape from predators and functional metabolic changes that allow survival through allostasis.

In the presence of predators or threatening situations, cortisol (or corticosterone) is released by fish [66-69], amphibians [70], small mammals [71-74], goats [75], and seals [76]. This rise in cortisol (or corticosterone) allows suppressive behavioral actions (e.g., freezing) in some cases and preparative defensive actions (e.g., attack) in others [77, 78]. For example, increases in cortisol may mobilize glucose for sustained vigilance and running during periods of reduced foraging possibilities [78]. It is currently unknown whether such increases in circulating cortisol in other vertebrates follow a circadian rhythm or occur after periods of sleep or rest. The delivery of cortisol by the adrenal glands and other metabolic processes may be related to a functional preparatory reaction of the organism to a threatening situation that allows individuals to adapt to their environment.

3. Conclusion

The processes that are involved in the sequence of events that allows us to cope with stress appear to represent an adaptive process that slowly developed in our ancestral past [79]. The increase in glucocorticoid levels upon awakening prepares the body for activity, thus enabling foraging behavior by increasing the amount of energy that is available [60, 80]. Homo sapiens have not appreciably changed for a long time. As a species, we are exactly alike. One function of the CAR may be to energize people in the morning [81].

Early in the morning, a relatively high amount of cortisol is released, and cortisol levels dramatically increase after a few minutes, leading to exploratory behavior, food seeking, and the facilitation of typical behavioral patterns of each species to survive [82]. Upon awakening, our body is ready to hunt and fight, being previously prepared to support thirst and hunger by liquids retention and increased metabolic rate, ultimately some of the main cortisol functions. The CAR may be considered an ancient adaptive feature. Understanding the relationships between brain circuits that modulate emotional memory and cerebral structures that modulate endocrine and autonomic responses to stress may shed light on the processes that regulate resilience and vulnerability when coping with threatening situations.

4. Conflict of Interest

The authors declare that they have no competing interests and no financial support to report.

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