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Psychosocial Stress and Salivary Cortisol in Older People: A Brief Review

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Abstract

The Hypothalamic–Pituitary–Adrenal (HPA) axis is crucial for homeostatic and allostatic adjustments to internal and external challenges. However, how aging affects this neuroendocrine axis is still incompletely understood. Being the end-product of the HPA axis, cortisol has been extensively studied for the last two decades because an increased cortisol response to psychosocial challenge has been hypothesized to be a risk factor for developing a number of age-related disorders in humans. This hypothesis has been addressed by separate lines of research focusing on the impact of acute laboratory stressors and chronic natural stressors on cortisol secretion in the elderly. This paper summarizes major findings generated by the aforementioned lines of research with a focus on studies examining salivary cortisol. It is concluded that although age does not have a consistent effect on cortisol response to acute laboratory stressors, evidence supporting an age effect on basal cortisol secretion is emerging. Moreover, the age-cortisol relationship is modulated by chronic stress and other psychosocial factors. Further research is warranted to throw more light on these preliminary findings.

Keywords: Salivary cortisol; Older people; Cortisol awakening response (CAR); Trier Social Stress Test (TSST); Hypothalamic-pituitary-adrenal (HPA) axis; Stress

Introduction

Aging has been assumed to be associated with a decline in the capacity to adapt to stressful forces in life, which is marked by an increase in cortisol response to stressful challenges [1-3]. This assumption has been one of the main driving forces of research on psychosocial stress and cortisol secretion in aging populations. Being the end-product of the HPA axis, cortisol has been studied extensively because loss of diurnal regulation has been seen as crucial to the aging process and the onset of frailty [4-6]. Recent evidence suggests that increase in cortisol secretion is a key factor determining immuosenescence [7] and a lower level of cortisol is associated with longevity [8].

However, findings generated in the last two decades fail to provide unequivocal support to the aforementioned assumption. Mixed findings may partly reflect the remarkably heterogeneous responses of the aged population to stressful challenges, which remain to be delineated more clearly. It is possible that some old people may age more successfully than others such that they are able to remain biologically younger than their peers [9,10]. Keeping the aforementioned issues in mind, I review recent findings on the relationship between psychosocial stress and cortisol regulation in aging so as to arrive at a better understanding of the multitude of factors that determine reactivity of the HPS axis in the aged populations. Although there are already a handful of recent reviews on psychosocial stress and cortisol [11,12], none of these focuses specifically on the elderly and age effect. This review is expected to fill this gap in the literature. The focus of this paper will be on studies examining salivary cortisol for two reasons. First, as cortisol in saliva does not bind to corticosteroid binding globulins as it does in the blood, salivary cortisol can be considered as a more reliable indicator of free or active cortisol than serum cortisol [13]. Second, the use of salivary cortisol as a biomarker of stress has become increasingly common in geriatric research. Therefore, focusing on studies examining salivary cortisol is more likely to lead to conclusions that reflect the current knowledge accurately.

Control of cortisol secretion

Cortisol has profound effects on glucose metabolism, helps to make fat available for energy, and modulates the immune responses, among other physiological functions that it serves [14]. The role cortisol plays in physiologic function is so crucial that as pointed out by Clow, Thorn, Evans, and Hucklebridge (2004) [15], we cannot survive without this hormone. The age-related increase in cortisol secretion has also been hypothesized to be a key determinant of the decline in immune function associated with aging [7].

The release of cortisol into the bloodstream is a result of a cascade initiated in the hypothalamus. Specifically, the corticotropin-releasing-hormone (CRH) is synthesized in and released by the paraventricular nucleus (PVN) of the hypothalamus into the portal blood circulation. When the CRH reaches the anterior pituitary gland, it stimulates the secretion of adrenocorticotropic hormone (ACTH). ACTH enters the systemic blood circulation, and stimulates the adrenal cortex to synthesize and secret glucocorticoids, with cortisol being the main glucocorticoid in humans [16]. Exposure to psychosocial stress intensifies the activity of the HPA axis, which results in an increase in the secretion of cortisol to maintain homeostasis. This increase in cortisol secretion is controlled by a negative feedback mechanism which detects increased cortisol level by receptors located in multiple brain regions such as the hippocampus, the hypothalamus, and the pituitary gland [17,18]. As successful adaptation involves both the mounting of a cortisol response to stressors and an appropriate control of this response, deficiencies in either one of the two mechanisms may have pathogenic consequences.

Measuring cortisol secretory activity

One of the major challenges of studying the effect of psychosocial stress on cortisol secretion is the establishment of reliable indices of cortisol secretory activity. The basal level of HPA axis activity follows a well-documented diurnal rhythm with several episodes of high-amplitude secretion. Cortisol secretion peaks within 60 minutes after waking and declines thereafter until reaching the nadir around midnight [17]. Recent evidence suggests that the cortisol awakening response (CAR), which is marked by an increase from 50% to 150% within the first 30 minutes after waking up in the morning [19], is a reliable marker of HPA axis activity [15]. This distinct component of the cortisol diurnal rhythm has been shown to have a salient genetic component in twin studies [20,21], and is sensitive to chronic stress in the elderly [22,23]. Recent evidence suggests that in addition to being a measure of the activity of the HPA axis, the CAR also involves in the mobilization of energy for the transition from sleep to wakefulness, which is partly mediated by the suprachiasmatic nucleus [24].

The CAR can be divided into two separate components: the area under the curve with respect to ground (AUC_G) and the area under the curve with respect to increase (AUC_I) [25]. The former captures the overall concentration whereas the latter indexes the increase from after post-awakening. However, a number of researchers have argued that CAR should restrictively refer to the increase in cortisol from awakening and be operationalized by the AUC_I or similar indices [14].

Other reliable markers of the activity of the HPA axis that have been adopted in geriatric research are (1) the total diurnal secretion or cortisol exposure throughout the day, and (2) the diurnal decline. The former refers to the overall concentration of cortisol over the course of a day, and has been operationalized as area under the concentration-time curve (AUC) [26]. The second marker, diurnal decline has been operationalized in prior research as a decrease in the cortisol levels measured at different times during the day [27]. For example, the diurnal slope which is computed by dividing the difference between the cortisol level at 30 minutes and 12 hours post-awakening by the time interval between these two samples [28].

Cortisol response to laboratory stressors

The Trier Social Stress Test

A number of studies have examined the difference in cortisol response to laboratory stressors between younger and older participants [11,12]. Being the most commonly used laboratory stressor, the Trier Social Stress Test (TSST) consists of a preparation period, a public speaking and a mental arithmetic task in front of an audience [29]. Lasting for about 15 minutes, the TSST has been shown to reliably elicit the strongest cortisol response in comparison to other protocols [30,31] a two- to three-fold rise in cortisol is observed in 70% to 85% of participants exposed to the stressor. The cortisol response to the TSST exhibits a prototypical pattern of change over time: increases steadily from the onset of stressor, peaks at about 20 minutes, and returns to pre-stress level within 45 minutes [11]. This is most commonly operationalized as area under the concentration–time curve (Figure 1), which implies that saliva or blood samples must be collected at multiple time points to fully capture the entire stress response. The cortisol response to TSST is determined by genetic factors as shown in twin studies [31] as well as gene studies on polymorphisms in HPA axis related genes [32].

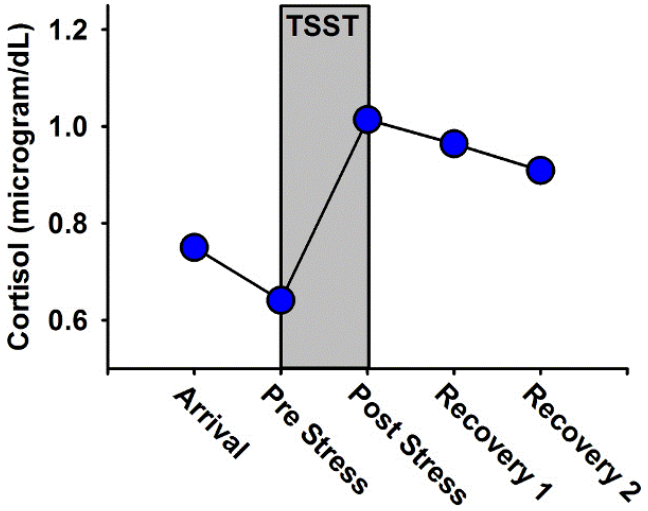

Figure 1: Hypothetical Cortisol Data in Response to the TSST

Note: TSST = Trier Social Stress Test. Adapted from Birkett (2011) [57]. The Trier Social Stress Test Protocol for inducing psychological stress. *Journal of Visualized Experiments,* 56, e3238. (doi: 10.3791/3238)

Age difference in cortisol response to the TSST

On the basis of findings reported in prior studies, a significantly greater increase in cortisol response was not observed consistently in the older group. In particular, in studies using a younger group whose mean age was below 30 yrs [33,34], the hypothesized age effect was not demonstrated, which is consistent with data reported by two earlier studies [35,36]. However, when the older group was compared to an older younger group (mean age=50 yrs) [37], an accentuated cortisol response was observed in the younger instead of the older group. Apparently, the conclusions that can be drawn from these cross-sectional findings are very limited, given the small effect sizes of the age effect (the absolute sizes of d ranged from .29 to .42) [2].

The interpretability of the aforementioned findings is further curtailed by the absence of a proper control condition in prior studies. A proper control group is one that requires participants to engage in the public speaking and mental math task without being evaluated by a panel of judges. Any cortisol responses to this condition could only be attributed to the cognitive demand of the tasks. This point is important because cognitive tasks without explicit social-evaluative threat have been found to induce higher cortisol response in older participants [38]. In other words, without a control group, researchers cannot attribute observed age differences in cortisol response specifically to the uncontrollable social-evaluative threat that constitutes the major source of stress of the TSST [39].

Factors modifying the cortisol response to TSST

As pointed out in recent reviews, age is only one of the numerous factors that determine the cortisol response to TSST [11,12,40]. Genetic and psychological factors could play a more important role in explaining the variation of cortisol response to TSST in older people. Findings from a recent study with 97 healthy older participants (mean age=61.15 years) point clearly to the significant influence of

polymorphism in the HTR1A gene encoding serotonin receptor 1A (5-HT1A) on cortisol response to TSST: the G allele is associated with an attenuated response [41]. It has also been shown in the same study that stressful events experienced during childhood and adolescence are associated negatively with the cortisol response to the TSST. These recent findings suggest that the cortisol response to the TSST in the elderly cannot be accurately assessed without taking into account the effects of the aforementioned factors.

Chronic stress and diurnal cortisol rhythms in aging

The conjecture that aging is associated with elevated diurnal cortisol seems to be supported by available evidence. A number of cross-sectional studies have shown a positive association between age and diurnal secretion of cortisol [42-44]. Following a group of 51 healthy older participants over 6 years, Lupien et al. (1996) [45] observed an increase in 24-hour plasma cortisol concentrations over 6 years in participants. In line with this, in a recent longitudinal study with a larger sample of older participants (N=157), diurnal cortisol concentrations were found to increase significantly over a period of 4 years [46]. Impairment in the negative feedback of the HPA axis in old age may explain this observation because an elevation of CRH has been observed in older people in response to the dexamethasone suppression test [47,48]. Taken together, these findings can be taken to imply that aging is associated with an increase in tissue exposure to cortisol.

With respect to aging and CAR, although it has been reported that there is a trend for age to be associated with a lower CAR in older participants [49], age has also been found to be associated with a greater CAR [50-52], or have no significant relationship with CAR [9,53]. The reasons for mixed findings are not immediately apparent but can be attributed to differences in operationalization of CAR, ages of participants, influences of state-dependent variables, and compliance with the study protocol. Compliance becomes particularly important for accurate assessment of the CAR because delays greater than 5 minutes between awakening and collection of the first saliva sample can lead to inaccurate estimation [18]. The compliance issue becomes most problematic when awakening and saliva sample collection times are monitored by self-reports instead of objectively with electronic devices as being done in most studies.

A limited amount of data shows that chronic stressors such as bereavement or caregiving in older people lead to a blunted cortisol concentrations [23]. Older people with anxiety disorders have been found to exhibit a blunted CAR in comparison to their healthy peers [22]. In line with this, Holocaust survivors with PTSD also exhibit a blunted morning cortisol response compared to those survivors without PTSD [54].

The more critical issue of whether age-related changes in the diurnal cortisol secretion are modified by chronic stress and other factors has been addressed in a handful of recent studies. In particular, the positive association between age and nocturnal cortisol levels has been shown to become stronger with increasing anxiety levels in participants [43]. Moreover, low self-esteem accentuates the negative association between age and CAR [49] whereas longer sleep duration in older people tends to counteract the elevated diurnal secretion in aging [46]. These findings imply that the age effect on basal cortisol is moderated by psychosocial factors. Further research to throw more light on this pattern of relationships is warranted.

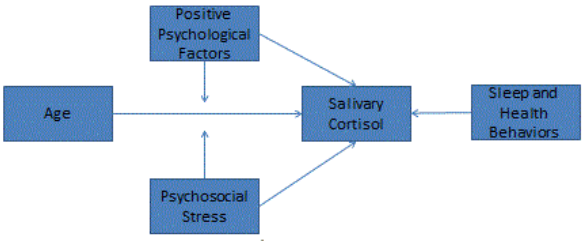

Figure 2: A Conceptual Framework Relating Age and Psychosocial Factors to Salivary Cortisol in Older People

Note: The hypothesized longitudinal effect of age on salivary cortisol is exacerbated by psychosocial stress and mitigated by positive psychological factors. Aging is expected to have negative neuroendocrine effects when older individuals are exposed to high level of stress without sufficient protection conferred by positive psychological factors. Sleep and other health behaviors are treated as confounding variables in the model.

Conclusions

Findings reviewed earlier suggest that age does not significantly affect cortisol response to acute laboratory stressors. Although aging is associated with complex changes in the HPA axis [1], these changes do not seem to manifest in the cortisol response to acute psychosocial stress in laboratory settings. In other words, alterations in the cortisol response to acute psychosocial stress is not necessary a consequence of aging. Further pursuit along this line of research does not seem to be promising.

On the other hand, available evidence tends to suggest a positive association between age and diurnal cortisol secretion and moderating effects of stress and other factors on this relationship. However, as the amount of supporting data is still limited, further research is warranted to arrive at more concrete conclusions. Future research will be benefited by adopting a conceptual framework that is informed by some of the most recent findings. As illustrated in Figure 2, the focus of the framework is on the longitudinal impact of age on different indices of the diurnal cortisol profile in the elderly. Special attention is given to the potential moderating effect of psychosocial factors. Moderators are not restricted to stress but include factors that confer resilience to stressful encounters because data showing the beneficial neuroendocrine effects of the resilience factors in the elderly are mounting [9,10,53,55]. As sleep and health behaviors exert detectable effects on cortisol secretion [46,56], these confounding variables must be properly controlled for accurate assessment of the effects of age and psychosocial stress.

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