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The salivary alpha amylase over cortisol ratio as a marker to assess dysregulations of the stress systems

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ABSTRACT

Different factors have been associated with changes in the regulation of the two major stress response systems of the human body, the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal (HPA) axis. Changes in these systems have been associated with various (psycho)pathologies across adulthood, and are thus frequently assessed within the context of allostatic load. Early Life Adversity (ELA) has been identified as one such factor. Individuals with histories of ELA show evidence of elevated basal and reactive salivary alpha amylase (sAA) levels (a marker of SNS activity), blunted cortisol levels (a marker of HPA axis activity), and an asymmetrical relationship between the two variables. However, variable methods used in the past to measure each variable, and the relationship between the two systems, prevent us from drawing firm conclusions.

This preliminary study investigated whether the ratio of reactive sAA over reactive cortisol would be more informative to investigate the relationship between the two stress systems than the ratio of cortisol over sAA, or either marker alone, and whether there is a systematic link between this marker and subjective indexes of chronic stress and depression. We studied this in a total of 37 subjects (n = 20 with signs of early life adversity and n = 17 without) exposed to the Trier social stress test. Using a specific formula to determine the ratio of sAA over cortisol, we found a systematically stronger positive relationship with indexes of chronic stress and depression when compared to cortisol over sAA, or either marker alone. Our findings suggest that the ratio of sAA over cortisol might be a better marker of stress systems dysregulation than the ratio of cortisol over sAA, sAA or cortisol alone. The usefulness of this marker for other chronic stress states as found in allostatic load is discussed.

1. Introduction

Stress is defined as a state in which an organism's internal regulatory balance (or homeostasis) is disturbed by real or perceived challenges in its external environment. These stressors can be of biological, environmental, social, emotional, or psychological nature that stimulate the body to restore its homeostatic balance, in a process called stress response.

In response to a stressor, two major biological stress systems are activated: the Sympathetic Nervous System (SNS), in the period immediately following the onset of the stressor, and with a time delay, the Hypothalamic–Pituitary–Adrenal system (HPA) axis (reviewed in [1]). Across life, the repeated or chronic activation of these systems can lead to changes in functioning, leading to impaired or inadequate responses to subsequent challenges. This change over time can be thought of as wear and tear on the stress response systems and has been named 'allostatic load'.

In normally functioning individuals, the physiological onset of the sympathetic branch of the autonomic stress response is associated with the activation of the pre-ganglionic sympathetic nerves, located in the locus coeruleus of the brain stem, which trigger the release of epinephrine and norepinephrine (NE) from the adrenal medulla. These catecholamines help facilitate the immediate physical reactions characteristic of SNS activity, such as elevated heart rate and breathing and dilation of pupils [1–3].

Methods for assessing sympathetic activity vary and include cardiovascular measures such as heart rate (HR), blood pressure (BP), the time interval between the electrical stimulation of the ventricles and the opening of the aortic valve, i.e. pre-ejection period (PEP) and urinary catecholamine concentrations. However, in recent years Chatterton et al. (1996) [4] (see also [5,6]) have associated sAA as a marker for the sympathetic component of the stress response (reviewed in [7]). Although sAA, a digestive enzyme mainly involved in breaking down starch molecules in the oral cavity, is not a direct by-product of the SNS, several studies have found elevated levels of

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sAA under physical (i.e. exercise, heat and cold stress) and psychological (i.e. written examinations) stress conditions, and further reported that these sAA levels are associated with overall changes in NE in response to stress [4]. Additionally, a number of studies have examined the activity of sAA during laboratory stress tasks such as the Trier Social Stress Test (TSST; [8]), and the Cold Pressor Task (CPT; [9]). Speirs et al. (1974) [10] found an immediate increase (from baseline) in sAA levels, peaking roughly 10 minutes after the onset of the stressor followed by a quick return to baseline levels after the termination of the stressor [11,12,13].

Whereas the SNS is characterized by instantaneous fluctuations in physiological markers of the stress response, the HPA axis is slower to respond. A situation perceived as stressful triggers the paraventricular nucleus of the hypothalamus to release Corticotropin-Releasing-Hormone (CRH), which in turn stimulates the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH). The ACTH acts on the cortex of the adrenal glands to produce glucocorticoid (GC) hormones such as corticosterone in animals, and cortisol in humans [1].

Salivary cortisol has been recognized as a reliable biological marker for the HPA axis stress response for several decades now (reviewed in [14] and [15]). Its slow profile of activation was demonstrated by Kirschbaum & Hellhammer [15], whereby following a psychosocial laboratory stressor [8], cortisol levels were shown to rise gradually until they peaked approximately 20–30 min after the onset of the stressor, and returned to baseline values within 1 h post-stress.

One of the factors associated with a dsyregulation of the stress systems is early Life Adversity (ELA). Various ELA factors such as poor parental care, childhood trauma and neglect, physical and sexual abuse have been associated with disturbances in physiological and psychological well being later in life, and as such might contribute to allostatic load. A large body of literature has identified ELA as a risk factor for the development of various psychopathologies such as depression, post-traumatic stress disorder (PTSD), schizophrenia and eating disorders later on in life [16–19].

ELA has further been associated with numerous pathological conditions, including obesity, diabetes, and cardiovascular disease. It has been speculated that this is also associated with altering the set point of physiological stress mechanisms, an important aspect in allostatic load. Developmental research has highlighted the importance of stable childhood environments and sensitive parenting in the normal development of the HPA axis [20–22]. In some of these studies, self-reported parental loss during childhood has been linked to greater HPA axis sensitivity in adulthood, and higher basal cortisol levels in response to stress [23,24]. Other studies have reported desensitization of the HPA axis, with blunted diurnal and reactive cortisol levels [13,25].

The effect of ELA on the development of the SNS has also been of recent interest, though the literature on the topic is sparse. Evidence from the few studies in existence has shown elevated heart rates and diurnal urinary catecholamines in children with history of maltreatment and neglect [26–29,30,31], and heightened sympathetic activity during acute stress situations [23,32,33]. Therefore, the evidence provided by the literature suggests that exposure to ELA during the developmental period shifts the set-point of the stress systems and increases sensitivity to stressors, acute and chronic, later on in life.

To study the effects of ELA on the development and responsiveness of the different stress systems more comprehensively, in 2002, a review by Bauer and Boyce proposed that studying the two systems concurrently would be more enlightening than examining either alone [11]. Drawing on evidence from classic theories and empirical research on arousal and performance (e.g., memory, attention), these authors proposed that the SNS and HPA systems work in alliance to generate the stress response, and that optimal adaptation requires the two systems to coordinate their response. Thus concurrent activation or deactivation of the SNS and HPA systems would be most adaptive and associated with fewer health problems, while asymmetries or dissociations between the two stress systems could be maladaptive and associated with greater number of health or behavior problems.

To date, only a few studies have examined the associations between chronic stress and SNS and the HPA regulation. Their findings provide mixed evidence about the idea of a consistent interrelationship between the two systems [13,34–36]. Gordis et al. presented the first empirical investigation of the interaction between SNS and HPA as a predictor of aggressive behavior in early adolescents. According to the findings of that study, highest levels of aggression were found among those adolescents with low levels of both cortisol and sAA (i.e. symmetrical activity), and that at high levels of sAA, lower cortisol levels were not associated with aggression [37]. Similarly, a study by El-Sheikh et al. (2008) found that children with higher basal cortisol and sAA levels were more likely to be diagnosed with internalizing and externalizing problems than children with lower SNS activity [34]. In a later study, Gordis et al. reported greater asymmetry in baseline and reactive sAA and cortisol levels in response to a laboratory stress task, in youths with histories of maltreatment and abuse than those without [13]. A recent investigation by Vigil et al. found that chronic stress resulting from material and social loses experienced by hurricane Katrina victims was associated with blunted baseline cortisol levels. Moreover, they also reported overall elevated sAA levels in their sample, which they explained were reflective of the lack of security and increased number of daily hassles encountered by victims of natural disaster. Furthermore, the dissociation between the two stress systems was found to be associated with lower self-esteem and a higher risk of developing mood problems in the future [36].

While the literature provides evidence of dissociations between the two systems in chronically stressed individuals, the studies described above have used a number of different methods to quantify the asymmetrical relationship between SNS and HPA. Gordis et al. used correlations between baseline and peak levels, area under the curve (AUC) scores and change from baseline to peak for sAA and cortisol to calculate the asymmetry [13]. Others used forms of regression analyses [36,37] and general linear modeling [35] to establish symmetrical associations between SNS and HPA axis. In an effort to better quantify, and standardize the methodology to assess the relationship between the two stress systems, we examined the ratios of sAA over cortisol, and cortisol over sAA, each as a single measurement unit. The hormonal ratio method has been widely implemented in research and medical practice as a reliable index for a variety of health and behavioral outcomes [38,39].

The goal of the current study was to investigate whether the ratio of sAA over cortisol, or cortisol over sAA amylase would be a better marker to identify possible stress system dysregulations than either marker alone. We hypothesized that the ratio method would effectively combine the discriminative capacities of the two stress markers into a single unit and could serve as a more sensitive assessment of stress system dysregulation compared to either marker alone. This study further examined whether there was a systematic link between the ratios and subjective indexes of stress and depression. Given the exploratory nature of the methodology, we had no a priori hypotheses.

Whereas the current body of literature has primarily studied the associations between SNS and HPA axis in children and youth, to our knowledge no one has examined this relationship in adults, therefore, we studied this in a sample of adults with histories of childhood abuse and poor parental care and those without. Furthermore, with the exception of Gordis et al. [13], the body of research examining the relationship between the two stress systems has mainly assessed basal levels of sAA and cortisol. Given that dissociations between the two stress systems, if any, appear to be more salient and measurable during times of stress [9,11,40] we investigated these