Cortisol as a biomarker of stress

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Summary

This review focuses on the use of salivary cortisol concentrations as a convenient and non-invasive biomarker of stress.

Acute stress causes an increase in cortisol concentration and beneficial interventions such as CBT and meditation can attenuate this rise.

The impact of repeated life stress in susceptible individuals can be detected by a disrupted cortisol circadian cycle (eg high evening cortisol levels). Holistic healthcare can be evaluated in relation to recovery of normal cortisol cycles.

Investigations into holistic healthcare could use salivary cortisol concentrations as a convenient biomarker of change.

I am a founder member of the Psychophysiology and Stress Research Group (PSRG) at the University of Westminster. The PSRG has an international reputation in the study of salivary cortisol and the secretory immune system in relation to mood and susceptibility to infection. As both a health psychologist and researcher I have a strong belief in the mind-body link and through my research I seek to find the mechanisms that underpin this phenomenon. Recently I participated as an on-screen expert in the BBC TV series The Stress Test.

Introduction

The consequences of psychological stress are increasingly being taken seriously by health professionals, legislators and the public alike. The Health Executive estimates that one in five employees suffer from high levels of stress, costing UK industry more than £3.7 billion per year in lost production. Yet these figures, striking as they are, undoubtedly underestimate the scale of personal anguish, relationship problems and deterioration in physical and psychological wellbeing caused by stress. This increasingly talked-about problem remains controversial as it has not been possible to subjectively measure the effect of stress upon an individual.

The experience of stress is complex and subjective. The problem of quantification is complicated by large individual differences in the extent to which stressors illicit stress responses: the experience of stress is not directly proportional to the stressful event that causes it. For humans, feelings of stress can be moderated by aspects of personality (eg self-esteem) the individual's perception of an event (interpretation and meaning) as well as the ability to cope. However the importance of the problem has led psychophysiologists to search for an objective biological marker for the impact of stress. A reliable biomarker would also enable evaluation of a range of interventions and the demonstration of quantifiable benefit. It is the aim of this article to review current knowledge about stress measurement and how this can be utilised in future research in the area of holistic healthcare.

Biological markers of stress reactivity

Most work that seeks to identify a reliable biological marker of stress responding is focused upon the hormone cortisol. The brain has a chemical 'hotline' to the adrenal gland which secretes cortisol (known as the hypothalamic-pituitary-adrenal or HPA axis). Following perception of a stressor,

higher brain centres signal to the more primitive hypothalamus to release corticotrophic-releasing hormone (CRH) which stimulates the pituitary gland to release adrenocorticotrophic hormone (ACTH) into the blood which, in turn, stimulates the adrenal cortex to release cortisol into the circulation. It takes about 15 minutes to illicit this response and individual differences in the size of this response have been the subject of much research. In particular it has been shown that large cortisol responders are more likely to have low self-esteem[1, 2] and are less likely to habituate following repeated exposure to the same stressor.[2] Importantly it has been demonstrated that the size of the cortisol response to a standard stressor can be attenuated by interventions like transcendental meditation and cognitive behavioural therapy.[3, 4, 5]

The size of the cortisol response to a standardised stressor (such as the Trier Social Stress Test[6] is an excellent way to measure acute stress reactivity (see **Figure 1**). This type of work has increased in popularity since the validation of salivary measures of cortisol as a reliable index of circulating levels of cortisol.[7] Salivary measurement has many advantages over blood and urine sampling as it is non-invasive, immediate and allows multiple sampling at frequent intervals (eg every 10–15 minutes if desired, as in **Figure 1**). Such techniques could be used to evaluate a range of holistic healthcare interventions although care would need to be taken about time of day (see below) and to use a counterbalanced experimental design to ensure that the results could not be attributed to order effects (ie the intervention always being evaluated second).

Acute stress-induced cortisol secretion (which takes about 15 minutes to reach its peak) is much slower than adrenaline release. There is a direct neural input to the adrenal medulla which regulates adrenaline release; it does not (like cortisol) rely upon slower chemical messengers. However, use of adrenaline levels as an accurate and direct indicator of stress is not commonplace as this hormone is released in response to positive (arousal and excitement) and negative (stress) events and as such is unable to discriminate between these two different types of emotions. More straightforward measures of heart rate and blood pressure do have a place in stress psychophysiology but like adrenaline also suffer from the disadvantage of being sensitive to both negative and positive emotional changes. Indeed it has been shown that the neuroendocrine (cortisol) response to a stressor can be dissociated from the sympathetic-adrenal-medullary response (adrenaline).[8] Although these two response systems work in harmony they are not equivalent.

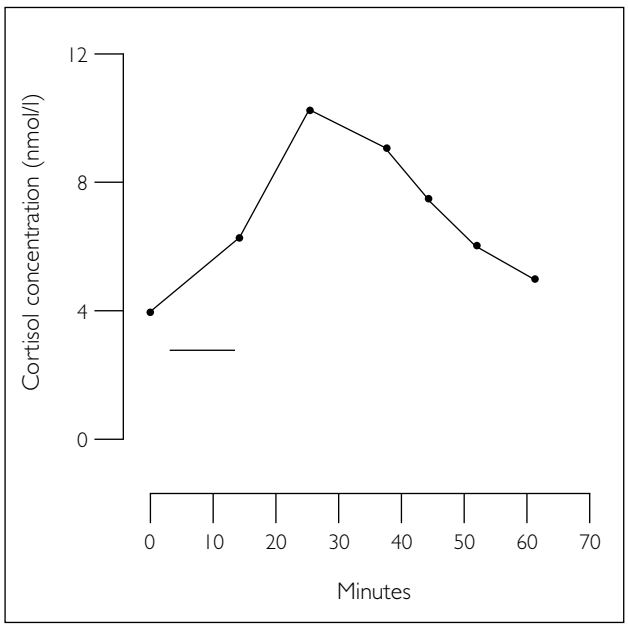


Figure 1: A typical salivary cortisol response to a standard stressor, in this case the TSST.[6] The solid bar represents the duration of the stressor.

The circadian pattern of cortisol secretion

The hormone cortisol is the only hormone we cannot live without. In addition to its key role in the stress response it is vital for normal body functioning. Cortisol has a very diverse set of actions ranging from effects on blood pressure, stored reserves of energy and the balance of the immune system. The core characteristic of healthy cortisol secretion, and the one that complicates its use as a biological marker, is that under normal circumstances levels are carefully regulated to give very different concentrations at different times of the day. This marked circadian cycle, changing levels by up to 20 times over the day (see **Figure 2**) is vital for informing other body systems when it

is night and day. Levels of cortisol in the morning rise partly in response to light[10, 11] so cortisol performs the role of being the 'eyes' for the rest of the body – just as melatonin is sensitive to dark and signals night. The role of healthy cortisol is to orchestrate (along with melatonin) the rest of the body so that its many functions are synchronised around the 24 hour light/dark cycle. The immune system is an excellent example of this: at night it goes into cell-mediated mode patrolling for damaged or diseased cells in the body, eg viral infection or cancer, and in the day it swings into humoral mode searching for invading pathogens within the blood.[12, 13] It is believed that one key role for healthy cortisol is to promote the swing towards daytime immunity soon after waking up.[14] If this healthy cycle of cortisol secretion were shown to be sensitive to the effects of stress, then in addition to affording a biomarker of stress it would provide a mechanism by which stress and health could be linked: a disrupted cortisol cycle would negatively impact upon a range of other body systems.

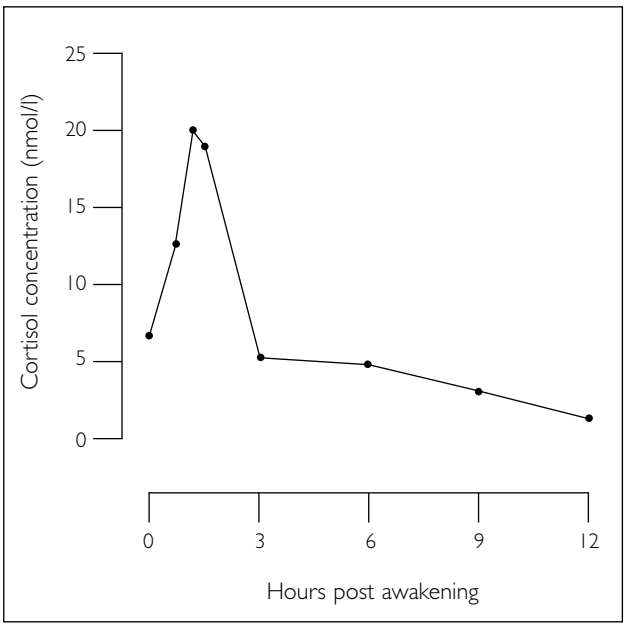
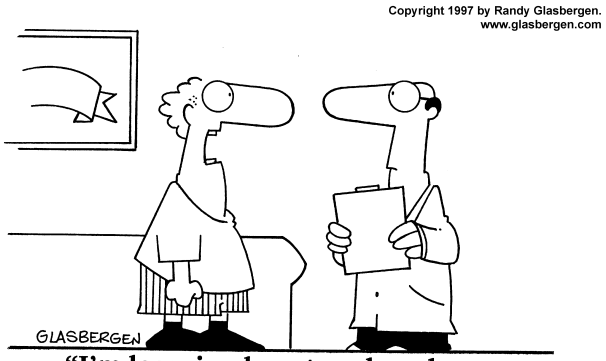


Figure 2: A typical healthy diurnal profile of salivary cortisol concentrations synchronised to awaking time. Notice the marked awakening cortisol response in the first 45 minutes post-awakening and the underlying diurnal decline.



**"I'm learning how to relax, doctor—
but I want to relax *better* and *faster!*
*I want to be on the cutting edge of relaxation!"***

There is evidence that normal ageing is associated with a flattening of the cortisol circadian pattern – most notably older people present with higher levels of cortisol in the evening than their younger counterparts.[15] Furthermore, clinical depression has also been associated with hypersecretion of cortisol and flattened diurnal cortisol profiles.[16, 17] It seems that these changes in the slope of the cortisol profile may have real significance as survival from serious disease such as cancer has been linked with the rate of cortisol decline over the day.[18, 19] Evidence that stress may be a mediating factor in the disruption of the cortisol circadian pattern has been derived from studies on animals. For example, pigs exposed to isolation stress exhibited unstable cortisol circadian rhythms[20] and social stress in rodents caused disruption in the expression in a range of circadian rhythms.[21] There are receptors in the brain and pituitary that detect circulating cortisol concentrations and these receptors are largely responsible for regulating the decline in cortisol levels over the day.[22] Repeated stress activation of cortisol secretion can lead to desensitisation of these receptors and this is thought to result in disrupted circadian cycles.[23, 24, 25]

Normative values for the diurnal pattern of cortisol secretion in healthy undergraduate students are available.[9] Although it is always necessary to incorporate control groups into any experimental paradigm investigating cortisol secretion, these values provide a guide against which populations and interventions can be evaluated. In addition this paper[9] discusses the best way to measure the diurnal pattern of cortisol secretion with strict reference to waking time.

More recently research has focused on a discrete and very interesting aspect of the cortisol circadian cycle: the awakening cortisol response (ACR). There is clear evidence that the first 30–45 minutes post-awakening are very sensitive to the effects of stress and burnout.[25] However, methodological difficulties associated with sample collection[26, 27] have meant that, as yet, there is no clear agreement about the reason for these relationships. What is clear from the literature is that burnout and exhaustion are associated with reduced cortisol secretion in the first 45 minutes after awakening.[28] It is early days in the research validating the ACR as an accurate biomarker of stress, but I am confident that this may become the most sensitive and useful marker of stress that we can have.

In summary, research into cortisol measurement has found it to be a useful biomarker for stress. There are two alternative approaches: measurement of the cortisol response to an acute stress challenge or measurement of the basal levels of cortisol over the day. Without doubt the hormone cortisol, which is easy to sample in saliva samples, could be a useful tool in holistic healthcare research.

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