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Salivary cortisol as a biomarker in stress research.

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Over the last decade the use of salivary cortisol as a biomarker for the study of stress and related diseases has become increasingly common. Researchers have found that salivary hormone measurement is convenient and non-invasive, and that it makes possible studies that would be difficult with other methods. Their work has also revealed, however, that dissociations can sometimes be observed between salivary cortisol levels and other measures of HPAA-related endocrine activity. This review examines various factors that can lead to dissociation and considers the implications for various research areas.

Dissociations of salivary cortisol from CRF/AVP activity and from ACTH

Neurons that produce corticotrophin-releasing factor (CRF–also known as CRH) and arginine vasopressin (AVP) in the hypothalamus are activated by psychological events, but the degree of activation can vary based on the nature of the event. The relationships that exist between CRF and AVP neurons, ACTH and other peptides, and noradrenergic and sympathetic activation are complex, and it is likely that the dissociation observed between psychological measures of stress and salivary cortisol levels can be linked to a number of these interacting factors.

Glucocorticoid release can be affected independently from ACTH release in a number of ways: Prolonged physical and psychological stresses are known to result in augmented or diminished responses, respectively. Study of the cortisol awakening response also provides additional evidence that dissociation from ACTH may exist. It is clear that sex steroids can serve as important modulators of HPAA activity, but these relationships are complex and only partially understood. Additionally, it is now known that hair follicles can synthesize CRF, ACTH, and cortisol on their own; the degree of contribution to total cortisol levels is not yet clear.

Dissociations of salivary cortisol with blood cortisol levels

It has generally been accepted that cortisol levels measured in saliva are an excellent correlate of the free, active cortisol in blood, and that cortisol bound to blood proteins is not biologically active. There is now some thought, however, that bound cortisol may have some physiological effects on target tissues, which would mean that some degree of dissociation should be expected between salivary cortisol levels and the effective cortisol levels in blood.

Because the relationship between bound and free cortisol changes once the cortisol binding globulin (CBG) is saturated, salivary cortisol levels can respond in a non-linear fashion when blood cortisol levels are in the high range. Furthermore, in humans it is known that use of oral contraceptives can alter levels of CBG, which can in turn affect the levels of free cortisol in the blood, and ultimately in saliva. Salivary cortisol levels should therefore be scrutinized carefully for subjects whose levels of CBG may be elevated due to use of oral contraceptives, or to changes tied to menstrual cycle or pregnancy.

Studies have reported dissociation that is linked to other factors such as the circadian cycle or response to challenge. There is also evidence suggesting that CBG may be present in saliva and binding a portion of the cortisol present, which would contribute to dissociation.

Dissociations of salivary cortisol with urinary cortisol

Overnight or 24-hour measures of urinary cortisol have the advantage of offering longer-term measures of HPAA activity than that provided by serum or saliva. However, because cortisol is largely metabolized before being excreted in urine, both cortisol and its metabolites should be measured in order for urinary analysis to be a valid assessment of glucocorticoid secretion. Free cortisol measurement in blood, and correspondingly in saliva, depends both on cortisol production and on its rate of metabolism in the liver. For example, in the case of patients with chronic fatigue syndrome, low salivary cortisol levels have been reported to be associated with faster clearance of cortisol.

Dissociations of salivary cortisol with effects on target tissues

It has been well established that there is considerable variability in the sensitivity to glucocorticoids among individuals, and even from one organ to another within patients. Recent research has been exploring genetic variants in glucocorticoid receptors to explain these

differences. Another mechanism leading to differences in target tissue specificity is thought to involve the presence or absence of the enzyme 11ß-hydroxysteroid dehydrogenase type 1, which converts inert forms (cortisone, 11-dehydrocorticosterone) into active forms (cortisol, corticosterone). Taken together, these variations could help explain dissociation observed between tissue-specific sensitivity and cortisol levels measured in saliva.

Conclusions

The authors summarize by saying that "Salivary cortisol is a useful biomarker in stress research, as long as the researcher is aware of possible sources of variance, which may affect this measure. Whether these modulating factors are considered as confounders or as important part of the information certainly depends on the research question." Certain studies might benefit from the measurement of ACTH and total blood cortisol in addition to salivary cortisol, but in many cases this will not be practical or even desirable. Because of the complex interactions that exist between stress and the activation of the HPA axis, it is important that careful consideration be given to the best experimental design for each investigation.