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Saliva Cortisol and Yawning as a Predictor of Neurological Disease

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***Abstract*—**Cortisol is important to our immune system, regulates our stress response, and is a factor in maintaining brain temperature. Saliva cortisol is a practical and useful non-invasive measurement that signifies the presence of the important hormone. Electrical activity in the jaw muscles typically rises when the muscles are moved during yawning and the electrical level is found to be correlated with the cortisol level. In two studies using identical paradigms, a total of 108 healthy subjects were exposed to yawning-provoking stimuli so that their cortisol levels and electrical nerve impulses from their jaw muscles was recorded. Electrical activity is highly correlated with cortisol levels in healthy people. The Hospital Anxiety and Depression Scale, Yawning Susceptibility Scale, General Health Questionnaire, demographic, health details were collected and exclusion criteria applied for voluntary recruitment: chronic fatigue, diabetes, fibromyalgia, heart condition, high blood pressure, hormone replacement therapy, multiple sclerosis, and stroke. Significant differences were found between the saliva cortisol samples for the yawners as compared with the non-yawners between rest and post-stimuli. Significant evidence supports the Thompson Cortisol Hypothesis that suggests rises in cortisol levels are associated with yawning. Ethics approval granted and professional code of conduct, confidentiality, and safety issues are approved therein.

***Keywords*—**Cortisol, Diagnosis, Neurological Disease, Thompson Cortisol Hypothesis, Yawning.

I. Introduction

CORTISOL is a naturally occurring hormone in humans that is considered important for immune protection and stress regulation [Fig. 1] [1], [2]. Measuring the levels of cortisol is useful for monitoring several medical conditions including cases where high levels of stress are known, adrenal insufficiency, and possibly for certain neurological diseases, such as multiple sclerosis [3]. The link between assay levels obtained via invasive blood collection and non-invasive, simple saliva sampling has been documented. For example, salivary cortisol concentration has been shown to be directly proportional to the serum unbound cortisol concentration both in normal women and men [4].

It is recommended that salivary cortisol collection is more appropriate as a measure of adrenocortisol function than serum cortisol. Dynamic tests of adrenal function, such as dexamethasone suppression and adrenocorticotropic hormone (ACTH), were highly correlated in normals with adrenal insufficiency, in tests of circadian variation and in randomly collected samples [4].

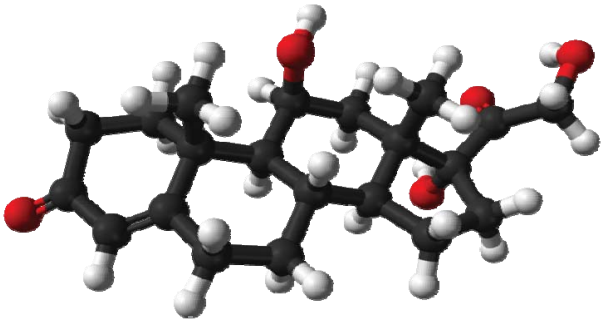

Fig. 1 Cortisol hormone showing atoms and bonds [5]

Aardal-Eriksson et al. [6] conclude that the more pronounced cortisol response in saliva than in serum and its closer correlation with ACTH offers advantages over serum cortisol. The satisfactory precision of analysis and the simple non-invasive sampling used in saliva cortisol collection makes it a viable procedure and a practical approach [7], especially when blood sampling is difficult or not an option [8].

The importance of cortisol has been recognized for some time in both psychological and physical situations involving stress and perceived stress [9]-[11]. Cushing's syndrome was named after Harvey Cushing, a neurosurgeon at Johns Hopkins Hospital, who first described it [Fig. 2]. It is manifested by too much cortisol or steroid in the blood, and can occur from taking prescribed steroid for a long period of time for inflammatory purposes, when it is then termed "iatrogenic".

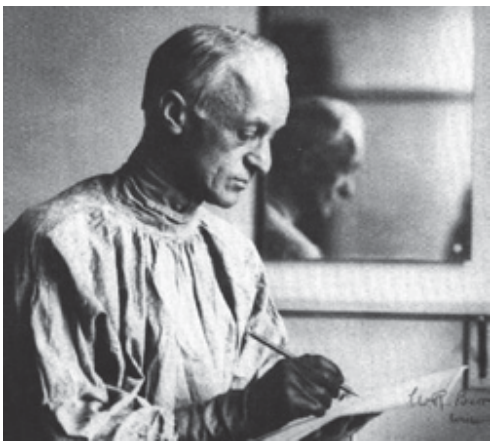

Fig. 2 Harvey Cushing [12]

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There are three possible causes of "endogenous" Cushing's syndrome (caused, other than by taking prescribed steroids) [12] [Fig 3]:

(i) A small tumor in the pituitary gland causes too much adrenocorticotropic hormone or ACTH to be secreted. ACTH controls the activity of the adrenal glands. This makes up about 70 per cent of cases and is usually termed "Cushing's disease" rather than "Cushing's syndrome".
(ii) A tumor in one of the adrenal glands produces too much cortisol and occurs in the presence of a normal pituitary gland. This accounts for about 30 per cent of cases.
(iii) The rarest syndrome, called "Ectopic ACTH Syndrome" accounts for about 1 per cent of cases and is due to a tumor lying outside of the pituitary gland (often in the thymus or lung) that causes too much ACTH to be produced. In turn, this causes the adrenal glands to produce too much cortisol. Other rare locations for tumors are in the thyroid, ovary, adrenal gland, and liver.

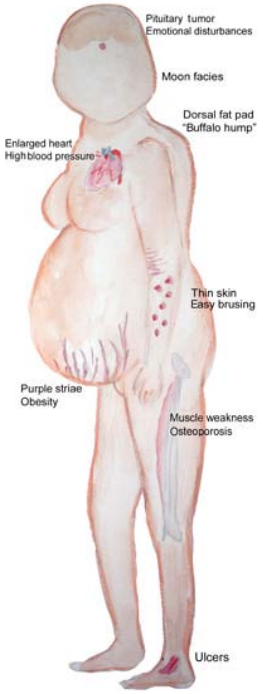

Fig. 3 Signs and symptoms of Cushing's disease. Artwork by Elizabeth Chabot [12]

The effects of producing too much cortisol are weight gain, "moon face", easy bruising (arms and legs are frequently covered), abnormal hair growth (face and near belly button in women), "Buffalo hump" (mound of fat located at the base of the back of the neck), edema (leg swelling, hypertension, purple striae (stretch marks which tend to have a pink, red or purple color), diabetes, thinning of the skin, mood changes, plethora (reddening of face and cheeks), muscle weakness (often causing thinning of the legs), and menstrual disturbances (such as amenorrhoea or irregular periods). Some of these effects can lead to other medical problems such as polycystic ovarian syndrome.

Despite the knowledge and understanding about the effects of too much cortisol in the blood, the connection between cortisol and yawning has only recently been established by the Thompson Cortisol Hypothesis (TCH) [13]. The yawn reflex was previously little understood by neurologists and neuroscientists and, despite Hippocrates in 400 BC describing the yawn reflex [14], the yawn had not been represented and reported until 2013 in terms of the electromyography emanating from the jaw-line muscles during the yawn phase [15].

Expansion of the TCH in 2014 [16], has enabled further exploration of the pathways involved during yawning [17] [18], [19], with the proposal that cortisol, in conjunction with the yawning reflex, might provide a potential biomarker for the early detection of neurological disease [20].

Predictors of disease are not new and bio-informatics is increasingly important to our understanding of disease progress and for early detection and treatment. Disease prevalence rates [21], moderating factors and early identifiers [22], [23] together with clinical case histories [24] all contribute to our scientific knowledge of the importance and roles that genes, neurotransmitters and hormones play in disease presence and prognosis.

Whilst still presenting as a conundrum, the mechanism behind yawning is becoming clearer with evidence of a strong link between cortisol, yawning, and fatigue. In multiple sclerosis, fatigue is a common symptom, together with excessive yawning due to exertion, both physically and mentally. Scientists have discovered that brain temperature rises with fatigue and particularly, in people with multiple sclerosis [25]-[27].

It is now thought that rises in cortisol elicit the yawning response which in turn regulate brain temperature and prevent the brain from over-heating [18], [20]. A series of studies led by the author and his team at Bournemouth University, UK, have determined that yawning is significantly correlated with cortisol and that the electrical nerve impulses generated from jaw-line muscles, upon yawning, are also correlated with the yawning reflex. Excessive yawning is proposed as an early indicator of underlying neurological disease, and together with cortisol, may be a potential biomarker in detection techniques.

II. Method and Materials

A. Procedure

Study 1: In a randomized controlled trial, 11 male and 15 female volunteers, aged 18-53 years, were exposed to conditions that provoked a yawning response during which saliva samples were collected at the start and again after yawning, or at the end of stimuli presentations in the case of those participants who did not yawn [Fig. 4].

The electrical nerve impulses were additionally collected during rest and at yawning phases, or after the stimuli presentation, for the non-yawners [Fig. 5]. The Hospital Anxiety and Depression Scale, Yawning Susceptibility Scale, General Health Questionnaire, demographic, and health details were collected for all participants as well as consent and ethics

permission according to standardized protocols. Exclusion criteria: chronic fatigue, diabetes, fibromyalgia, heart condition, high blood pressure, hormone replacement therapy, multiple sclerosis, and stroke.

Fig. 4 Kit for collecting saliva cortisol samples [5]

Study 2: Using an identical paradigm, a further 28 male and 54 female volunteers, spanning a slightly larger age range of 18-69 years, were randomly allocated to experimentally controlled conditions of provoked yawning as before. Electrical nerve impulses were again compared between those who yawned and those who did not yawn in the experiment.

Fig. 5 Measuring electrical nerve impulses using surface-placed electrodes along jaw-line muscles [5]

III. Results

Study 1: There was a significant difference between the saliva cortisol samples for the yawners, $t(11) = -3.115$, $p = 0.010$, and for the non-yawners, $t(14) = -2.658$, $p = 0.019$. However, for the yawners, the cortisol levels after yawning were significantly higher than for the non-yawners. There was a significant difference in EMG readings between yawners and non-yawners, $t(7) = -2.959$, $p = 0.021$.

Study 2: There was a significant difference between the saliva cortisol samples for the yawners, $t(37) = 2.842$, $p = .007$, but not for the non-yawners. For the yawners, at rest, the electrical nerve impulse value was -100 rising to 200 millionth of a volt (mean=182.2) and -60 000 to 18 000 (mean=3 897.4), after yawning. For the non-yawners, at rest, the value was -80 rising to 120 (mean=37.2) and -400 to 800 (mean=57.5), after stimuli presentation. Yawners showed a larger peak following the yawn compared with post-stimuli for the non-yawners.

IV. Conclusion

Clear evidence in support of the Thompson Cortisol Hypothesis was found together with representation of the yawn reflex in terms of the electrical nerve impulses obtained from the jaw-line muscles during the yawn phase. It is postulated that in neurological disease, such as in multiple sclerosis, where fatigue and yawning is a common symptom, cortisol may affect the hypothalamus in a positive sense so as to lower brain temperature.

The hypothalamus is implicated in the hypothalamus-pituitary-adrenal (HPA-axis) since it regulates brain temperature [Fig. 6]. By raising cortisol levels, yawning is elicited and signals the reduction in hypothalamic-regulated brain temperature. Conversely, lowering cortisol levels stops yawning and signals a rise in hypothalamic-regulated brain temperature.

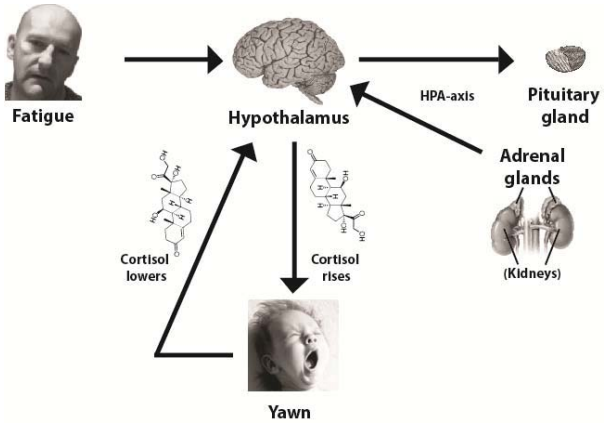

Fig. 6 Pathways explaining the Thompson Cortisol Hypothesis [20]

The author is leading a team of neuroscientists in the UK and in France that are investigating cortisol, yawning, and induced fatigue in people with multiple sclerosis. It is hoped that findings from fMRI studies on mental and physical fatigue employed in this new series of investigations may determine the best combination of biomarkers for early diagnosis.

Using cortisol and excessive yawning as a potential biomarker for the early detection of disease is unique and it is possible that several medical conditions that are dependent upon cortisol level regulation and that manifest with signs of fatigue could possibly benefit; for example, Addison's disease (adrenal insufficiency), chronic fatigue, Cushing's syndrome, multiple sclerosis, myalgic encephalomyelitis (M.E.), and stress-related conditions.

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