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Recent advances in cortisol sensing technologies for point-of-care application

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ABSTRACT

Everyday lifestyle related issues are the main cause of psychological stress, which contributes to health disparities experienced by individuals. Prolonged exposure to stress leads to the activation of signaling pathways from the brain that leads to release of cortisol from the adrenal cortex. Various biomarkers have been affected by psychological stress, but cortisol "a steroid hormone" is known as a potential biomarker for its estimation. Cortisol can also be used as a target analyte marker to determine the effect of exposure such as organophosphates on central nervous system, which alters the endocrine system, leading to imbalance in cortisol secretion. Cortisol secretion of individuals depends on day–night cycle and field environment hence its detection at point-of-care (POC) is deemed essential to provide personalized healthcare. Chromatographic techniques have been traditionally used to detect cortisol. The issues relating to assay formation, system complexity, and multistep extraction/purification limits its application in the field. In order to overcome these issues and to make portable and effective miniaturized platform, various immunoassays sensing strategies are being explored. However, electrochemical immunosensing of cortisol is considered as a recent advancement towards POC application. Highly sensitive, label-free and selective cortisol immunosensor based on microelectrodes are being integrated with the microfluidic system for automated diurnal cortisol monitoring useful for personalized healthcare. Although the reported sensing devices for cortisol detection may have a great scope to improve portability, electronic designing, performance of the integrated sensor, data safety and lifetime for point-of-care applications, This review is an attempt to describe the various cortisol sensing platforms and their potential to be integrated into a wearable system for online and continuous monitoring of cortisol rhythm at POC as a function of one's environment.

Contents

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1. Introduction

Cortisol, a steroid hormone, is a biomarker for numerous diseases and plays an important role in the regulation of various physiological processes such as blood pressure, glucose levels, and carbohydrate metabolism. It also plays an important role in homeostasis of the cardiovascular, immune, renal, skeletal and endocrine system (Ron de Kloet and Holsboer, 2005; Gatti et al., 2009; Levine et al., 2007). It is known that cortisol secretion follows a circadian rhythm through a 24 h cycle with cortisol levels highest during daybreak (30 min after awakening) and progressively lower by night sleep (Corbalan-Tutau et al., 2012; Nicolson, 2008) (Fig. 1). Apart from the day–night cycle, several controllable factors can affect cortisol levels such as eating patterns and physical activity.

Abnormal increase in cortisol levels inhibits inflammation, depresses immune system, increases fatty and amino acid levels in blood. While excess cortisol levels have been shown to contribute to the development of Cushing's disease with the symptoms of obesity, fatigue and bone fragility (McEwen, 2002), decreased cortisol levels lead to Addison's disease which is manifested by weight loss, fatigue, and darkening of skin folds and scars (Edwards et al., 1974). The most dominating effect on cortisol variation comes from psychological/emotional stress, which is why cortisol is popularly called the "stress-hormone" (Holsboer and Ising, 2010).

Increasing level of psychological stress due to the globalization, altered living style, and competition is becoming a serious concern in everyday schedule and life threatening diseases such as heart attack, depression, and brain pain are the health challenges faced by the most developed countries (Djuric et al., 2008). The potential causes of health disparities in everyday lifestyle are multiple and shown in Fig. 2, *Source*: NIH Public Access (Djuric et al., 2008). The accurate and precise detection of psychological stress is thus gaining attention for personalized health monitoring and diagnostics. The physiological effects of psychological stress on human health are shown in Fig. 2 (Djuric et al., 2008). The stress cycles (Fig. 3) in human find its ways into nervous system and upsets the chemistry of entire body (Fulford and Stone, 1997). The schematic diagram of the procedures in the body during stress full time is shown in Fig. 4.

Efforts are being made to develop wearable detection analytical devices to quantify stress and related abnormalities in environmental condition to gain useful information for timely diagnostics and treatment. Studies have linked cortisol levels with human stress and hence cortisol has emerged as a most potent biomarker for physiological stress detection (Gatti et al., 2009; Levine et al., 2007). There has been growing interest in measurement of cortisol to establish whether cortisol variation can be used as a precursor to medically and psychologically relevant events such as stress, the most recent affliction being post-traumatic stress disorder (PTSD) (Delahanty et al., 2000; Yehuda et al., 2002, 2001). Since cortisol secretion is dependent on environmental and behavioral triggers, its measurement at point-of-care has become imperative to understand behavioral patterns.

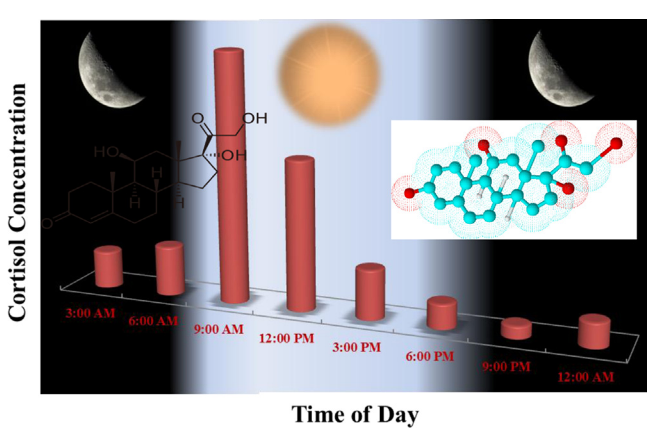

Fig. 1. Chemical structure of cortisol and typical diurnal variation of cortisol levels over a 24 h cycle.

Currently, in clinical practice, total cortisol, which is the sum of free and protein bound fractions, is measured. However, free cortisol is the only biologically active fraction (Le Roux et al., 2003) and is responsible for all cortisol-related activities in the body. Hence, in order to accurately diagnose and treat cortisol-related conditions, regular estimation of free cortisol is required. Most current strategies for the estimation of free cortisol are limited to laboratory techniques that are laborious, time-consuming, require large sample volume, expensive, and cannot be implemented at point of care (Frasconi et al., 2009; Lewis and Elder, 1985; Ruder et al., 1972; Tilden 1977; Turpeinen et al., 1997; Yaneva et al., 2009; Yang et al., 1994). Another significant shortcoming of the current set-up is that they only provide a snapshot of the cortisol levels of samples submitted in a diagnostic lab and do not provide a true representation of the cortisol variations that a specimen undergoes in an environment that triggers cortisol generation or suppression. Hence, real-time and continuous monitoring of cortisol levels is required to obtain valuable information that could assist doctors in better diagnosis and treatment of cortisol-related conditions. Detection of 24-h cortisol levels is currently a cumbersome process, which either involves admitting the patient for the time of study (Czeisler et al., 1976) or where the patient samples blood/saliva into vials at specified time intervals during the 24-h time period, and ships it to a diagnostic laboratory (Brezina et al., 2011). The typical turnaround time is 8–10 days and is still not a true representation of cortisol levels in stressful environments. Hence, there is a need to develop sensing platforms for the detection of cortisol at point-of-care. Application at point-of-care requires that the sensor be portable, have a miniaturized form factor, disposable, sterile, low power consumption, have low turnaround time and is cost effective (Ahn et al., 2004; Soper et al., 2006; Wang, 2006).

This review highlights the current efforts to develop strategies and technologies that enable detection of cortisol at POC.

2. Secretion of cortisol

Cortisol is a hormone that is secreted from the adrenal glands located above the kidneys. Cortisol is the end product of the hypothalamic–pituitary–adrenal (HPA) axis, which is the main component of the human body's adaptive system to maintain regulated physiological processes under changing environmental factors. As the name suggests, the HPA axis is a complex signaling system among the hypothalamus in the brain, the pituitary glands and the adrenal glands (Dobson and Smith, 2000; Ron de Kloet and Holsboer, 2005).

Fig. 5a presents a schematic of the HPA axis in which a typical response to an environmental trigger is initiated at the hypothalamus that releases a hormone called the CRH (corticotrophin releasing hormone) that travels to the pituitary glands. Specialized cells that work synergistically with the pituitary glands release ACTH (adrenocorticotrophic hormone) into the blood stream that travels to the adrenal cortex. The adrenal cortex responds by increasing the production of cortisol. The produced cortisol then goes to participate in all the governing physiological processes. Since the adrenal glands have no visible innervation, it can be inferred that ACTH is the sole stimulant for initiating cortisol production. The adrenal glands do not store cortisol, but they are