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Stress-linked cortisol concentrations in hair: what we know and what we need to know

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Abstract

Cortisol has major impacts upon a range of physiological homeostatic mechanisms and plays an important role in stress, anxiety and depression. Although traditionally described as being solely synthesised *via* the hypothalamic-pituitary-adrenal (HPA) axis, recent animal and human studies indicate that cortisol may also be synthesised *via* a functionally-equivalent ‘peripheral’ HPA-like process within the skin, principally within hair follicles, melanocytes, epidermal melanocytes and dermal fibroblasts. Current data indicate that basal levels of cortisol within hair vary across body regions, show diurnal variation effects, respond to the onset and cessation of environmental stressors, and may demonstrate some degree of localisation in those responses. There are conflicting data regarding the presence of variability in cortisol concentrations across the length of the hair shaft, thus challenging the suggestion that hair cortisol may be used as a historical biomarker of stress and questioning the primary origin of cortisol in hair. The need to comprehensively ‘map’ the hair cortisol response for age, gender, diurnal rhythm and responsivity to stressor type is discussed, plus the major issue of if, and how, the peripheral and central HPA systems communicate.

Keywords

hair follicles; HPA axis; skin

Introduction

Although generally thought of as the ‘stress hormone’, cortisol is vital to life under non-stressful conditions, but becomes elevated during times of stress (Sapolsky et al., 2000). Cortisol is synthesised by the adrenal cortex as an outcome of several upstream processes which assist the organism to adjust to environmental demand. Once secreted by the adrenal glands, cortisol binds to cytosolic glucocorticoid receptor proteins present in most tissues and enters the cell nucleus, acting as transcriptional regulator. Cortisol assists the organism to cope effectively with threat by enhancing the organism’s ability to respond to homeostatic challenge and by assisting the body to defend itself against infectious agents (Weissmann and Thomas, 1962 ; Weissmann, 1967 ; Persellin and Ku, 1974). Cortisol also has a major role in moderating the harmful effects of inflammation (Kessler, 1992).

The consequences of dysregulation of cortisol production

Hypercortisolaemia—Although circulating cortisol concentrations feed back to the hypothalamus and inhibit corticotropin releasing hormone (CRH) secretion there [and thus adrenocorticotropin hormone (ACTH) in the pituitary and cortisol production in the adrenals], this moderating mechanism may be insufficient when the organism is under chronic stress (Fries et al., 2005), leading to the diseases of hypercortisolaemia. These may include fibromyalgia, early over-activation of the immune system that is followed by depressed activation, susceptibility to stress, pain and fatigue (Fries et al., 2005), muscle wastage and hyperglycaemia (Aron et al., 2007). Prolonged and elevated expression of cortisol leads to increased serum lipids, endothelial damage and resultant incidence of coronary heart disease (CHD) (Koertge et al., 2002 ; Smith et al., 2005) and acute respiratory failure (Jantz and Sahn, 1999). Hypercortisolaemia has also been shown to cause atopic dermatitis (Amano et al., 2008) and suppressed skin immunity (Chrousos, 2009). Other outcomes of excessively high levels of cortisol expression include decreased immunocompetence (Segerstrom and Miller, 2004), increased risk of infection, osteoporosis, steroid diabetes and destruction of hippocampal neurons leading to cell loss, depression and chronic distress (Chrousos, 2009 ; Rao et al., 2009). Chronic stress and major elevations of circulating cortisol may also be accompanied by alteration to the structure and function of brain regions (Ulrich-Lai and Herman, 2009), which may contribute to the development of anxiety, depression (Holsboer, 2004 ; Gillespie and Nemeroff, 2005 ; Yuan, 2008) and other psychiatric conditions (Roozendaal et al., 2009). Thompson and Craighead (2008) reported that up to 80% of depressed patients have elevated cortisol levels, although this may be more likely with patients suffering from psychotic depression than non-psychotic depression (Gillespie and Nemeroff, 2005).

Hypocortisolaemia—Although most attention has been paid to the adverse consequences of over-production of cortisol, hyporesponsiveness of the hypothalamic-pituitary-adrenal (HPA) axis is also associated with physical diseases which have concomitant psychopathological states. About one-quarter of patients with stress-related disorders such as chronic pain, fibromyalgia, irritable bowel syndrome, posttraumatic stress disorder and low back pain also suffer from hypocortisolism (Fries et al., 2005). It has been suggested that hypocortisolism develops after a prolonged period of hyperactivity of the HPA axis (Hellhammer and Wade, 1993) *via* (a) reduced biosynthesis or release of CRH, AVP or ACTH or cortisol itself; (b) hypersecretion of one of these, followed by a consequent down-regulation of target receptors; (c) increased sensitivity to negative glucocorticoid feedback; (d) lowered free cortisol; and (e) decreased effects of cortisol on its receptors and the target cells/tissues (Fries et al., 2005). Hypocortisolaemia may also have negative effects upon overall health by inhibiting the negative feedback effect of cortisol on catecholamine synthesis and secretion and by over-activating the immune system because of the reduced anti-inflammatory effects of cortisol (Raison and Miller, 2003; Fries et al., 2005).

Both hyper- and hypocortisolaemia can therefore be associated with adverse consequences for the organism. Chrousos (2009) listed the comparative effects of each of these dysregulations of cortisol synthesis, arguing that ‘malfunction of the stress response might impair growth, development, behaviour and metabolism, which might potentially lead to various acute and chronic disorders’ (p. 380). Thus, the investigation of cortisol (over-)production remains a potentially rewarding focus for research in general and mental health in particular. Bearing this in mind, it is of interest that cortisol may also be synthesised in a ‘peripheral’ HPA axis located in the skin, including hair; that this source of cortisol may influence the overall cortisol supply, as well as its local areas; and that there is only limited knowledge at this stage regarding the linkages between adrenal and peripheral cortisol.

Cortisol in skin

Although the overwhelming proportion of attention regarding cortisol production and responsiveness to environmental stimuli (and its sequelae) has been on the HPA axis (i.e., ‘centrally’), evidence has accumulated over several decades that demonstrates the existence of a parallel CRH-ACTH-cortisol production system within skin, including its epidermal and dermal compartments, as well as hair follicles (Slominski and Mihm, 1996; Slominski et al., 1996a, 2000b, 2007; Slominski and Wortsman, 2000; Ito et al., 2005), referred to as the ‘peripheral HPA axis’ (Slominski and Mihm, 1996; Slominski et al., 2007). Relatively fewer reports have been published about the links between peripheral cortisol and health issues, or even how the peripheral cortisol system functions. Mammalian skin expresses all the necessary enzymes for the production of steroids, which can start with local production of pregnenolone (Slominski et al., 1996a, 2000a, 2002, 2004b, 2005b, 2006a, 2007, 2008; Rogoff et al., 2001; Thiboutot et al., 2003; Ito et al., 2005; Zouboulis et al., 2007; Makrantonaki et al., 2010). Production of corticosterone has been demonstrated in normal and malignant melanocytes and dermal fibroblasts (Slominski et al., 1999b, 2005a,b). In addition, cortisol has been shown to be produced in melanocytes and dermal fibroblasts (Ito et al., 2005; Slominski et al., 2005b, 2006a) and non-malignant keratinocytes which have all the enzymes necessary for cortisol synthesis (Hannen et al., 2011), and it has been hypothesised that dermal cortisol may be involved in the regulation of wound healing (Vukelic et al., 2011). Thus, within the skin all the elements of a ‘peripheral HPA axis’ can be shown to be present and functional and, as shown in Figure 1, CRH can be shown to stimulate ACTH secretion which in turn can stimulate cortisol production by melanocytes.

In contrast, reports about hair cortisol are more recent, fewer in number and cover less detail than for skin cells in general. In order to elucidate the role of hair follicles in the production of peripheral cortisol, this review describes those reports presented to date, discusses issues that have yet to be addressed and suggests possible targets for future research.

Methods

To elucidate the current state of knowledge of peripheral cortisol in hair, the rest of this review focuses upon the extant data on that topic, describes the findings in animal and human studies, discusses several major issues with regard to the role of peripheral cortisol and raises several topics for further investigation. In order to achieve this review of the current literature, online searches were conducted in May 2010 and again in August 2011 using the terms ‘cortisol’ and ‘hair’. In addition, each study that was identified by this search was then checked for citations via Google Scholar, plus hand searches were conducted of the reference list in each of the articles identified from this procedure.

Results

Cortisol in hair

The earliest papers to report the presence of CRH and of proopiomelanocortin (POMC)-derived ACTH, as well as of the corresponding receptors in hair follicles, were based on studies using the C57BL/mouse model (Slominski et al., 1992, 1996b, 1998, 1999a; Ermak and Slominski, 1997; Roloff et al., 1998; Mazurkiewicz et al., 2000; Kauser et al., 2006). Those studies defined the hair follicle as both a prominent source and a potential target for the bioactivity of POMC products, suggesting a role for POMC-derived peptides in maintaining the immune privilege properties of the anagen hair follicle (Paus, 1999; Slominski et al., 2000b). Expression of the above elements has also been reported in the human hair follicle (Slominski et al., 1993, 2001, 2004a, 2006b; Kono et al., 2001; Quevedo et al., 2001; Ito et al., 2004, 2005; Kauser et al., 2006).

Hair grows in cycles, with periods of new growth (anagen), transition (catagen) and quiescence (telogen), when the hair stops growing and may be easily removed by pulling. On the scalp, hair growth rate is between 0.2 mm/day and 1.12 mm/day, or 6 to 33.5 mm/month (Giovanoli-Jakubczak and Berg, 1974 ; Harkey, 1993). Scalp hair grows faster than pubic hair, which is faster than beard hair (Harkey, 1993), with some racial [Caucasian hair growth is faster than Asian hair growth (Harkey, 1993)] and gender influences [women's scalp hair grows faster than that on men (Saitoh et al., 1969)], as well as a general slowing of growth rate with age (Myers and Hamilton, 1951). Hair grows fastest on the vertex region of the scalp, with the largest percent (85%) of follicles in the anagen stage (Harkey, 1993).

Ito and colleagues (2005) presented data showing that the hair follicle contained a complete HPA-like system, producing CRH, ACTH and cortisol with no necessary connection to the overall blood supply (and thence by-passing the HPA axis), confirming an original hypothesis that the skin represents an equivalent 'peripheral' HPA-like system to locally manage responses to stress (Slominski and Mihm, 1996 ; Slominski et al., 1999a ; Slominski and Wortsman, 2000). Ito et al. (2005) used scalp hair follicles that had been removed from patients undergoing face-lift surgery and found that in the hair follicles they studied: (a) stimulation with CRH up-regulated ACTH production; (b) ACTH stimulation up-regulated cortisol production; and (c) hair follicles displayed regulatory feedback similar to that noted in the central HPA axis. Of perhaps major importance were demonstrations that the production of cortisol in hair could be independent of central HPA influences in similar ways to its production in cultured melanocytes (Slominski et al., 2005b) and dermal fibroblasts (Slominski et al., 2005a, 2006a). Those studies established the hair follicle as an independent source of cortisol, thereby justifying further investigation of hair cortisol as a separate peripheral system that could act independently from the central HPA axis.

Animal studies

Although other steroid concentrations have been measured in animal hair (e.g., progesterone, oestradiol and testosterone in cattle), the first identified report of cortisol measurement in animal hair was by Koren et al. (2002), who plucked between 7 and 20 mg of fur from 10 male rock hyrax, *Procavia capensis*, that had been trapped and were later released in their wild environment. Hair was taken while the animals were anaesthetised, and later weighed, chopped with scissors and placed in a glass vial for assay for both cortisol and testosterone (Koren et al., 2002). Koren and colleagues (2002) reported a significant positive correlation between hair testosterone and social rank of the male hyrax (assessed by the ratio of aggressive:evasive actions taken by each animal), but no significant relationship for hair cortisol and social rank. However, the principal value of Koren et al.'s (2002) study was in showing that animal hair could be used to measure cortisol and the authors argued that this was particularly valuable for providing a measure that can 'represent (cortisol) accumulations over time' (p. 405), rather than using blood, saliva, urine or faeces, which all represent cortisol concentrations relating to the animal's immediate state rather than a longer period of time (as is possible with hair).

In a later study, Koren et al. (2008) also collected hair from another sample of 89 male rock hyraxes and this time measured social rank by the presence of 'singing' behaviour, as well as the ratio of aggressive:evasive actions in males. Only 25% of males engaged in singing and these singers were involved in 24 of the 25 sexual copulation events observed within the entire sample over the period of observation. Among singers, hair cortisol was significantly, and directly, associated with social rank, as defined by aggressive:evasive actions.

Hair cortisol has also been used as an indicator of longer-term stress levels induced by relocation of habitat in 11 rhesus macaques, *Macaca mulatta* (Davenport et al., 2006). Hair was shaven from the posterior vertex of the neck 13 weeks and a few days prior to

relocation, and then 14 weeks and 35 weeks after relocation. Hair cortisol concentrations following relocation were significantly higher than before relocation. An unexpected result of this study was the lack of a significant difference in cortisol concentrations between the proximal (i.e., near the scalp) and the distal (furthest from the scalp) ends of the hair samples collected. Davenport et al. (2006) argued against this being a function of cortisol having been diffused along the hair shaft *via* water (the typical hair shaft is 15–35% water, but most of this water is in the section of hair shaft that is below the scalp surface).

Although a side issue to the main purpose of their study, Chun-Lu (2009) noted a significant correlation between hair cortisol concentrations and instances of received intense aggression among a sample of 16 rhesus macaques, supporting the findings of Koren et al. (2002, 2008) and Davenport et al. (2006) that social stress increases concentrations of cortisol in hair. Similar data were reported by Clara et al. (2007) for the correlation between hair cortisol collected from captive-born common marmosets (*Callithrix jacchus*) and stress associated with presentation of a model snake. On a slightly different theme, Dettmer et al. (2009) collected hair from the posterior vertices of 32 infant rhesus macaques over a 5.5-month period (at 2 weeks and again at 6 months) and compared this to performance on a test of object permanence that was used as an index of cognitive development. There was a significant positive correlation between hair cortisol concentration and age when criterion was reached on the test of cognitive development, suggesting that infant rhesus macaques that showed what those researchers called chronic integrated HPA activity, had relatively poorer cognitive performance than infants with less HPA activity, as measured *via* hair cortisol concentrations. A further study of hair cortisol was undertaken by Accorsi et al. (2008), who compared hair and faecal cortisol concentrations from 27 cats and 29 dogs. Hair was shaven, new growth collected about 90 days after initial shaving and faeces were collected soon after defecation during this period. Faecal and hair cortisol concentrations were statistically positively correlated for both cats and dogs.

Together, these seven reports of the measurement of cortisol in the hair of various animals establish that: (a) cortisol may be reliably assayed from animal hair and fur; (b) there is a direct relationship between level of cortisol in hair/fur and the animal's experience of stress; (c) cortisol may be transmitted along the hair shaft; but (d) no data have been reported which clarify the origin of the cortisol found in animal hair/fur (i.e., whether it comes from the hair follicle or from the bloodstream). On this last point, several of these papers have discussed their data from the perspective of hair cortisol representing serum cortisol that has been transmitted from the bloodstream to the hair follicle (Davenport et al., 2006, 2008 ; Accorsi et al., 2008 ; Koren et al., 2008 ; Dettmer et al., 2009), thus suggesting that hair cortisol is an index of central HPA axis activity. However, Ito et al.'s (2005) report of the independence of the hair follicle as a producer of cortisol challenges that perspective and leaves open the future resolution of the original source of hair cortisol as systemic or of local origin. Its local production from cholesterol was substantiated by independent studies on human skin and cultured skin cells (Slominski et al., 1996a, 2004c, 2005a,b, 2006a). This issue is central to an understanding of the function of hair cortisol and will be discussed in detail later.

Human studies

Several studies have shown that steroids may be assayed from human hair. For example, Wheeler et al. (1998) described assay procedures for extracting testosterone from human hair, compared male and female concentrations, and established that the assay procedures used may also be applied to other steroids. Cirimele et al. (2000) developed similar assays for detecting 10 corticosteroids (including cortisol) in human hair, suggesting that they may be more efficient than traditional urine analysis for detecting the presence of corticosteroids in sporting, clinical and forensic settings, a comment echoed by Raul et al. (2004), who reported on the use of liquid chromatography and mass spectrometry to identify cortisol in

human hair. Yang et al. (1998) extended the use of assays of human hair to include the reproductive hormones estradiol and progesterone from the hair of 22 females. As well as demonstrating that these procedures were valid (hair data were significantly correlated with those from serum), Yang et al. also showed that there was no significant difference in cortisol concentrations from washed and unwashed hair. Further, by analysing hair collected at three points during the menstrual cycle of women in the sample, Yang et al. were able to show that oestradiol and progesterone concentrations varied similarly in hair, as they did in serum, across the three sampling occasions during these women's menstrual cycles. Finally, the hair of the women in that study was between 200 and 450 mm long, and was divided into three segments (top, middle and basal – the latter being closest to the scalp) and tested for differences in oestradiol and progesterone. Although there were minor differences across the hair shaft segments (up to 14% between adjacent segments), these were not statistically significant – a finding similar to that reported by Davenport et al. (2006) in macaque hair and further raising the issue of how cortisol and other steroid hormones travel along the hair shaft. Yang et al. (1998) also commented that they had detected the same reproductive steroids in fingernails and testosterone in the beards of the male subjects. Further to this, a recent study showed that cortisol may also be assayed from fingernails (Warnock et al., 2010).

Following the initial exploration studies mention above, several papers have examined the concentration of cortisol in human hair under various stress conditions, principally chronic or acute pain. Klein et al. (2004) compared hair cortisol concentrations between six healthy and six hospitalised infants who were undergoing painful medical procedures. Cortisol levels were higher in the latter than the former group of infants, thus linking elevated hair cortisol with the presence of pain. A similar report also showed that hospitalised infants had significantly higher hair cortisol than non-hospitalised infants (Yamada et al., 2007). Pain has also been shown to produce significantly higher hair cortisol concentrations (collected from the posterior vertex) in nine female and six male adult severe chronic pain patients compared with 20 female and 19 male non-patient control subjects (Van Uum et al., 2008).

Three studies have reported hair cortisol data from pregnant women, used as examples of people experiencing stress but at a less intense level than the acute or chronic pain of those studies reviewed in the preceding paragraph. In the first of these studies of pregnant women, Kalra et al. (2005) collected scalp hair from 25 pregnant women who also completed self-report questionnaires on their level of depression (Centre for Epidemiological Studies-Depression scale: CES-D) and chronic stress (Perceived Stress Scale: PSS). Those data were compared to hair cortisol, CES-D and PSS results from 25 pregnant women who were not depressed. Contrary to expectations, the women who were depressed showed a significant negative correlation between hair cortisol and their (high) CES-D scores and the women who were not depressed showed a significant positive correlation between hair cortisol and their (low) CES-D scores, leading those authors to conclude that women who were most stressed and depressed had the lowest levels of hair cortisol. However, in a subsequent study conducted by some of the previous authors, Kalra et al. (2007) reported a significant direct correlation between perceived chronic stress (PSS) and hair cortisol among 25 healthy pregnant women.

Recently, Kirschbaum et al. (2009) examined hair cut from the posterior vertices of 103 mothers of neonates, 19 mothers of infants aged 3–9 months old, and 20 non-pregnant nulliparous women. Overall, hair cortisol levels were significantly higher among women with children than among nulliparous women. This hypothesis was supported by data reported from the same laboratory by Tietze et al. (2010) in which hair was collected from 31 unemployed and 28 employed persons. As expected, unemployed persons had significantly higher hair cortisol concentrations than employed persons.

In a study of the relative concentration of cortisol in hair from different regions of the scalp, Sauve et al. (2007) cut hair from the posterior vertex, anterior vertex, nape, temporal and frontal sections of the head from 14 ‘volunteers’ (p. E185) of non-described age or gender. No significant differences were found in the cortisol concentrations in human hair collected from these five sites. In addition, there was a significant correlation between hair cortisol and a 24-h urine cortisol ($r = 0.33$).

The effects of age, gender, body site and time

Apart from the studies by Davenport et al. (2006), Kirschbaum et al. (2009), Tietze et al. (2010) and Webb et al. (2010), which examined hair in segments representing growth periods, little has been reported on the ‘mapping’ of hair cortisol concentration distribution according to gender, age, hair shaft length, or responsiveness to short-term stressors (pregnancy is a relatively long experience). Similarly, apart from Sauve and colleagues (2007), who compared cortisol concentrations from various sections of the scalp, little research attention has been shown to the presence of variability in hair cortisol concentrations across body sites, although a pilot study of this issue conducted in our own laboratory found that young males’ forearm hair concentrations were higher than those in their scalps or lower legs (Sharpley et al., 2010a).

It is commonly reported that central cortisol shows a diurnal rhythm effect (Weitzman et al., 1971), typically a ‘morning elevation-evening drop’ pattern (Smyth et al., 1997), although up to 20% of participants show different patterns in their diurnal cycle from day to day (Smyth et al., 1997), and up to 50% show depression of that cycle owing to a range of influences (Stone et al., 2001). The precise points of maximum and minimum cortisol concentrations also vary across some individuals (Smyth et al., 1997), although the former is usually early in the morning and the latter later in the afternoon. This diurnal fluctuation has been described as adaptive (Yates and Urquhart, 1962), in the same way that other circadian-driven physiological variations influence survival behaviour by maximising the use of physiological resources (Minors and Waterhouse, 1981), and it may be that the same kinds of diurnal variations also exist within hair cortisol concentrations. There were no studies found in the literature regarding the presence of a diurnal rhythm in hair cortisol, although our own early investigations of this phenomenon (Sharpley et al., 2010b) with a pilot sample of four participants who collected hair and saliva over 15 h during a single day, suggested that hair cortisol may mirror the central diurnal rhythm. These data need extensive replication with larger samples and across longer periods of time (including during sleep) to enable the same kind of reliability to be applied to diurnal variations in hair cortisol, as is reported for central cortisol (even allowing for the wide inter-subject differences in the presence and form of the central cortisol diurnal rhythm reported above).

Responsiveness of hair cortisol concentrations to brief and transitory stressors

Because most of the kinds of stressors that have been used to study changes in hair cortisol concentrations are relatively lengthy (e.g., pregnancy, moving habitat, medical procedure pain), it is relevant to enquire if cortisol in hair responds to relatively brief stressors in the same way as central cortisol. Studies of this issue have the propensity to also illuminate the issue of localisation of hair cortisol effects. In a small pilot study (Sharpley et al., 2009) using three healthy males who underwent a brief, 1-min cold pressor test on their preferred hand, all showed significant increases in hair concentrations to this pain, as shown in Figure 2. Moreover, those increases were immediate (i.e., they occurred during hand immersion); short-lived (hair cortisol concentrations reduced to pre-stressor levels within 5 min after the end of the cold pressor test), and localised (there were no changes in hair cortisol

concentrations in the opposite lower leg). Although replicated with a further five male participants (Sharpley et al., 2010c), these data are not yet robust enough to constitute conclusive findings. Replication with more participants, a wider range of physical stressors (both pain and non-pain), psychological stressors, measures of hair cortisol concentrations that are local vs. distal to the site of the stressor, using stressors of varying length, and measuring any 'lag' between stressor onset and hair cortisol concentration increase, may provide the kinds of data that will enable a model of hair cortisol responsiveness to stress to be compiled. These findings may also contribute to a better understanding of the next issue – the relationship between central and peripheral cortisol.

Independence of *in vivo* hair cortisol responses *vis-à-vis* central cortisol

The presence of direct communication between central and peripheral cortisol-production systems may appear logical, but may not be necessary, or present, when they are performing different functions. The agreed functions of central cortisol are fairly global in that cortisol is transferred to most cells in the body *via* the bloodstream (some of these functions are described in the introductory section of this article). However, these functions are unlikely to be also instigated by cortisol that is synthesised in the periphery, simply because cortisol produced by the adrenal glands is likely to reach the majority of body areas faster and more easily than cortisol produced in hair follicles and/or skin melanocytes, and the relative amounts of cortisol produced by hair and skin are much smaller than those produced by the adrenal glands (Slominski et al., 2005b ; Sharpley et al., 2009). In addition, there are no data, as yet, which show that cortisol produced in fibroblasts, melanocytes or hair follicles enters the bloodstream in quantities that could be of significance to overall body performance. Although no conclusive measure has been taken of the amount of cortisol that a single hair follicle can produce *in vivo*, individual hair follicles and skin cells (or even localised groups of these agents) are unlikely to secrete the same quantities of cortisol that can be rapidly transmitted into the circulation for dissemination around the body, as can be produced by the adrenal glands. Further, as described above, there are some initial data (Sharpley et al., 2009, 2010c) that may indicate that hair cortisol is produced by local hair follicles in response to local stressors in ways that suggest that hair cortisol is independent of central cortisol and that local hair cortisol is independent of hair cortisol from other regions. Thus, the presence and nature of intercommunication systems between different areas of the skin across the body need to be determined to understand if, and how, central-peripheral cortisol systems communicate. As a corollary from this point, the multiple diseases that arise from hypercortisolaemia as a result of cortisol synthesised in the adrenal glands may be exacerbated if cortisol concentrations in melanocytes or hair dramatically increase during chronic stress and contribute to the central cortisol in the bloodstream, hence affecting all cells with cortisol receptors. The role of peripheral cortisol in central cortisol-related illness therefore needs to be determined.

In summary, there is no doubt that central cortisol permeates all body cells and may account for at least some of the cortisol found in hair follicles. The effects of long-term stressors such as alcoholism and Addison disease upon hair cortisol may reflect a combination of central and peripheral cortisol production; this important issue requires further investigation. However, to date, there is no evidence that hair cortisol permeates other target organs of the body and thus contributes to overall hypercortisolaemia – that issue remains a major target for future investigations.

Is cortisol is secreted into hair as it grows and washed out over time?

Although Yang et al. (1998) showed that progesterone and oestradiol concentrations did not vary across the hair shaft, which ranged in length from 20 to 45 cm, cortisol concentration in hair may be more complicated, particularly as the hair follicle can synthesise cortisol itself.

A number of studies have examined the concentration of cortisol in different segments of the hair shaft but the results from those studies are contradictory.

Based on the assumption that hair grows at about 10 mm/month (Harkey, 1993), Kirschbaum and colleagues (2009) collected hair from women with young children <12 months old and women who did not have children (as a control group). The hair was divided into 'time passed' segments according to its length from the base. Moreover, hair close to the scalps of mothers with a neonate had double the cortisol concentration of hair from the non-mothers, as did hair further from the scalps of those mothers of children aged 3–9 months old. Kirschbaum et al. (2009) found that there was a monotonic drop of about 30–40% per 3-month period in hair cortisol concentrations from the nulliparous women, declining from the segments taken closest to the scalp (and therefore most recently grown) to a stable low level after 12 months (i.e., when the hair shaft was about 120 mm long). The researchers attributed this decline from about 63.5 pM/g to about 13.8 pM/g of cortisol in hair to be a function of 'washout' of cortisol from the hair segment over time. This hypothesis was supported by data reported from the same laboratory by Tietze et al. (2010) in which hair from 31 unemployed persons had significantly higher concentrations of cortisol than hair from 28 employed persons. Additionally, hair segments longer than 60 mm also showed the washout effect previously reported.

However, these data and the hypothesis of washout of cortisol from hair are challenged by several findings. One of the first studies to examine the issue of hair cortisol concentration along the hair shaft directly was by Davenport and colleagues (2006), whose comprehensive study of cortisol in rhesus monkey hair demonstrated no difference in concentration between proximal and distal ends of the hair shaft. Similarly, Manenschijn et al. (2011) reported no decline in the cortisol concentrations of six consecutive hair segments in 195 healthy, nine hypercortisolaemic and one hypocortisolaemic individuals. Our own data also indicated no significant difference in cortisol concentrations across the length of hair shafts of up to 500 mm long that were taken from 12 healthy young women (Sharples et al., 2010a).

Perhaps encompassing the underlying contradiction and possible causes of variability (or lack of) along the hair shaft, a recent study (Thomson et al., 2009) reported that hair from patients with Cushing's Syndrome (which is accompanied by an elevation in cortisol) that was divided into 10 mm segments, showed a variation in hair cortisol concentration in direct accordance with the clinical course of the patients' symptoms for periods of up to 18 months. In contrast, eight out of nine control participants (non-Cushing's syndrome patients) showed no significant difference in cortisol concentration along the hair shaft, while the ninth control subject showed a pattern of rising cortisol from the proximal to distal ends of the hair shaft.

As suggested by these reports, some studies have suggested that cortisol is relatively consistent in concentration along the hair shaft, and others have reported that concentrations dropped off after about 60 mm length of hair shaft, leaving this issue open to further investigation. There may also be a possible distinction between participants who are undergoing an ongoing stressor with clear biological links to hypercortisolaemia (such as Cushing's syndrome) compared with participants who are not undergoing such a powerful cortisol-linked stressor.

That cortisol remains in hair over time is dramatically demonstrated by the examination of hair samples from the bodies of 10 deceased persons from five different archaeological sites in Peru who had been dead for between 500 and 1500 years and whose hair had concentrations of cortisol ranging between 91 and 717 ng/g (Webb et al., 2010). Further, when analysed according to length of the hair shaft (and therefore the time that the hair had

grown), several person's samples were of lengths representing periods longer than 12 months and showed no significant difference in cortisol concentration between the proximal and distal ends of the hair.

Thus, there are data that support variability in cortisol concentrations along the hair shaft (perhaps reflecting the degree of stress the subject was under at the time the hair was germinated within the scalp) and other data which suggest that hair cortisol concentrations remain fairly stable over time. There are also data which show that cortisol concentrations in hair remain detectable over centuries. However, in most studies, cortisol concentrations were always detectable, suggesting that there is a basal or underlying concentration of cortisol within the hair shaft. Therefore, it is possible that cortisol is laid down within the hair shaft as it grows and that it also penetrates from the blood or surrounding skin cells, but that this cortisol is transitory and reflects the organism's current immediate stress status. The mechanism underlying this transitory transport system remains to be determined but appears not to be surface-mediated *via* sebum as it cannot be washed off, even with solvents.

Discussion

Summary of findings to date and directions for future research

Several findings emerge from this review of the small literature on hair cortisol as a contribution to an overall understanding of how the peripheral HPA axis works. In terms of 'what we know': first, cortisol is produced by the hair follicle or epidermal and dermal skin cells; second, cortisol may be assayed from human and some animal hair; third, cortisol concentrations in human hair show the same kind of elevation owing to severe pain or stress that has been reported in cortisol that is produced by the adrenal glands; fourth, there are data which suggest that cortisol concentrations may vary according to changing stressor demands, whether they be relatively long (e.g., pregnancy) or brief (1-min cold pressor pain), and may return to basal levels after the cessation of the stressor; fifth, human hair cortisol concentrations appear to have an overall positive correlation with central HPA-produced cortisol measured in urine or serum; and sixth, cortisol concentrations from sites on the human scalp appear to be fairly consistent.

However, there are several points that 'we need to know'. The first of these is resolution of the confusion as to whether cortisol concentrations in human hair decrease over time to reach a stable low or 'basal' level, or whether they continue to react immediately and frequently to environmental threats of long or short duration. While there are data from three studies showing a lack of variability in hair cortisol concentrations over time periods greater than about 6–12 months, plus a general 'washout' of cortisol after that period, other data show retention of cortisol concentrations in hair over very long periods (several hundred years), plus the suggestion that the concentrations found therein may reflect the individual's experiences of stressors during at least the last 18 months of life. Further, our data showing dramatic elevations in hair cortisol following only 1 min of pain challenge the suggestion that hair cortisol is 'set' at follicle growth concentrations and then gradually decreases over time. The issue of whether hair cortisol concentration is a dynamic or static entity needs to be investigated. Data from studies that, for example collect hair cortisol concentration data over several weeks or months and compare it to participants' daily experiences of stressful events may clarify this issue.

Second (and probably more important), the studies reviewed above reveal no data which conclusively show that *in vivo* hair cortisol concentrations are the *sole* product of the peripheral cortisol-synthesis system in the hair follicle rather than also reflecting concurrent activity in the epidermis and dermis, or the central HPA axis activity that is transmitted to hair follicles *via* the bloodstream. Investigation of the relative fluctuations in 'central'

cortisol and hair cortisol over short and long periods of stressful and non-stressful experiences could provide some answers to this question, as could examination of the links between melanocytes, fibroblasts and hair follicles as co-producers of cortisol.

Third, although some data exist regarding the ‘mapping’ of hair cortisol across genders, scalp and body sites, under different types of stressors, and during typical diurnal rhythm periods, these are only basic and cannot provide definitive information regarding the ways in which hair cortisol responses fluctuate (if they do) according to these variables. Of primary interest in understanding how the whole peripheral HPA axis functions, is the link (if it exists) between hair and other skin cells. In addition, there are no convincing data regarding age-related differences in hair cortisol, nor whether the experience of illness influences concentrations of cortisol in hair. Until these ‘mapping’ studies have been reported, the issue of whether hair cortisol may be used as an ‘historical’ stress biomarker remains open to conjecture.

Conclusion

There are sufficient data to conclude there is a HPA-like axis within the hair follicle and that cortisol can be synthesised directly by the hair follicles. However, the regulation of this axis and sources of cortisol within the hair shaft are likely to be complex as illustrated in Figure 3. Further, cortisol concentrations in hair appear (to some extent) to reflect one aspect of peripheral HPA-like responses to general and localised stressors, although the differentiation between these two sets of stressors and their effects upon hair cortisol needs to be reliably determined. Some initial data appear to suggest that cortisol concentrations along the hair shaft represent a dynamic process that is counter to traditional definitions of the hair shaft as being dead; this challenge to conventional wisdom is also supported by data on other steroids in the hair shaft. Perhaps the key issue that needs attention is the link between central and peripheral cortisol synthesis processes, as this may define the function and independence of hair cortisol in respect to adrenal cortisol.

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Biographies

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Figure 1. Cortisol production in skin

(A) CRH significantly stimulates ACTH production by melanocytes over 24 h, while cAMP (insert) increases in a dose responsive manner to CRH stimulation within 1 h. (B) ACTH and forskolin (insert) stimulate cortisol production by melanocytes over 24 h in a dose responsive manner. (Modified from Slominski et al., 2005b). * $p < 0.05$; ** $p < 0.01$.

Figure 2. Hair cortisol responses to a brief pain stressor

Cortisol concentration in hair and saliva before and after a cold pressor test. The independent rise in cortisol concentration in the hair or blood strongly suggests that cortisol in hair is not derived from the blood or stimulated centrally *via* ACTH. (In Sharpley et al., 2009.)

Figure 3. Pathways for secretion of cortisol in the hair shaft

Diagram illustrating the possible pathways cortisol may be secreted into the hair shaft. The hair shaft appears to have two repositories of cortisol. Firstly, one which is imbedded within the shaft and may reflect historical cortisol concentrations, and another which is transitory and reflects current cortisol concentrations. The source of the cortisol in either compartment remains unclear with possible sources being the skin, blood or the hair follicle. If the source is the skin or the hair follicle, it is also unknown whether the stimulus for cortisol production is central (*via* the sympathetic nervous system) or induced by the direct effects of a local stressor.