Hormones and Well-being

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Abstract:

The growing evidence that positive psychological functioning is linked to favorable health outcomes has led to a search for biological mechanisms that may underlie these salubrious effects. Although there is interest in biological processes that are uniquely related to positive psychological functioning, most work to this point has centered on those with known associations with adverse psychological experiences, such as stress and depression. This chapter reviews the existing literature on the ways in which psychological well-being (broadly defined) is linked to hormone systems in the body (endocrine and neuroendocrine). The chapter is structured by hormone system. Given the newness of the field, this literature is understandably limited, and conclusions about such links are consequently tentative. Nonetheless, the overall picture is promising, and links between hormone systems and psychological well-being should be a vibrant area of future research with critical implications for physical and mental health.

Keywords: well-being, optimism, HPA axis, cortisol, catecholamines, metabolic hormones, oxytocin, prolactin

Psychological well-being has been linked to a broad range of health outcomes, most notably reduced risk of diverse forms of morbidity and general mortality (Chida & Steptoe, 2008; Giltay, Geleijnse, Zitman, Hoekstra, & Schouten, 2004; Hill & Turiano, 2014; Pressman & Cohen, 2005), and there is a large and growing literature devoted to illuminating the biological mechanisms that may underlie these health effects. Although there is interest in identifying biological processes that may be unique to positive psychosocial functioning (Kubzansky, Boehm, & Segerstrom, 2015), the bulk of existing research has examined the ways in which well-being affects and is affected by well established biological responses to adversity, including those related to immune and endocrine function (Friedman, 2012; Steptoe, Dockray, & Wardle, 2009). The focus of this chapter is on connections between well-being and endocrine biology, including bi-directional influences.

The construct of well-being can be operationalized in a variety of different ways. There exists, for example, two broad categories of well-being measures – hedonic and eudaimonic – reflecting different ideas of what it means to lead a good life, a debate that stretches back to Greek philosophical disputes. While hedonic well-being comprises various elements of emotional life (such as positive and negative affect and satisfaction with life), eudaimonic well-being focuses more on the realization of individual potential through meaningful engagement (Ryan & Deci, 2001; Waterman, 1993). While the two are often correlated, they are distinct in a number of relevant ways, including how they change with age and how they relate to a range of outcomes, including health (Cole et al., 2015; Friedman, 2012; Ryff, 2014; Ryff & Keyes, 1995). There are additional indicators of positive psychological functioning, such as optimism, that do not fit neatly into one category. In this chapter we define well-being broadly and consider links between diverse endocrine systems and multiple aspects of well-being.

An important point to make at the outset is that this chapter focuses on research featuring explicit measures of well-being, not ill-being. That is, there is a large and long-standing body of research on the endocrine, neuroendocrine, and autonomic correlates of clinical and sub-clinical mental illness, chronic stress, and the like. But there is substantial evidence that well-being is not merely the absence of ill-being (Keyes, 2002; Pressman & Cohen, 2005; Ryff et al., 2006). For example, studies in which more advantageous profiles of endocrine function are observed in those with lower levels of stress or depression

have not necessarily demonstrated the biological impact on well-being. For this reason, with only a few exceptions we constrain our review to research assessing indicators of well-being. See Table 1 for an overview of the hormones, their function, and a brief summary of evidence in relation to well-being.

Table 1

Hormone function and summary of associations with well-being

	Function	Summary
Adrenal hormones		
Cortisol	Elevates blood glucose levels; activates anti-stress and anti-inflammatory pathways.	Well-being is linked to optimal daily cortisol regulation and buffering of adverse experiences.
DHEA(S)*	Androgen; intermediate in sex steroid biosynthesis; binds to neurotropin receptors.	Supplementation in older adults increases well-being
Catecholamines	Initiates cascade of physiological changes, mobilization of resources in response to stressors.	Studies linking catecholamines and well-being are mixed and inconclusive.
Sex hormones		
Testosterone	Controls expression and maintenance of male-specific characteristics; regulates sexual differentiation and behavior.	Weak evidence linking testosterone to well-being in older adults. Studies lacking in younger adults.
Estrogen	Controls expression and maintenance of female-specific characteristics; regulates sexual differentiation and behavior.	Evidence linking estrogen to well-being is largely absent. Studies across wider age ranges are needed.
Metabolic hormones		
Insulin-like growth factor	Involved in neuronal survival, neurogenesis, angiogenesis, neurotransmission, regulation of food intake, and cognition.	Inversely associated with well-being; binding protein directly linked to well-being. Associations likely age- and sex-specific.
Insulin	Regulates macronutrient metabolism by promoting absorption of glucose into tissues.	Intranasal insulin improves mood and attenuates reactivity to social stress; association may be dependent on age and ethnicity.
Thyroid hormones	Regulates physiological functions, including growth and development, metabolism, body temperature, and heart rate.	Generally positively linked to well-being, but evidence is mixed; age, sex, and thyroid function contribute to these associations.
Other hormones		
Oxytocin	Facilitates labor during pregnancy; promotes maternal bonding, sexual behavior, and affiliation	Intranasal administration has inconsistent associations with mood; links to well-being appear to be moderated by receptor genotype.

Anti-diuretic hormone	Stimulates water retention and vasoconstriction; promotes pair-bonding behavior	Limited evidence suggests positive relationship to happiness; receptor type may influence associations in a sex-specific manner.
Prolactin	Regulates water and salt balance, breast milk production, cell proliferation and differentiation, T-cell immunity, pancreatic β cell function, hematopoiesis, and adipogenesis	Limited number of studies suggest sex-specific positive associations with well-being. Positive behavior patterns during conflict were also associated with higher levels among women.
*DHEA(S) – Dehydroepiandrosterone (sulfate)		

Adrenal Hormones

The adrenal glands, located above the kidneys, are composed of an inner medulla and an outer cortex that together produce a number of hormones, including cortisol, dehydroepiandrosterone (DHEA), epinephrine and norepinephrine, among others. These hormones play key regulatory roles across multiple physiological systems. Most notably, the hormones produced by the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) axis help coordinate whole-body adaptive responses to acute and chronic stressors and other environmental challenges encountered in daily life. For a more detailed treatment of the HPA axis, the SAM axis and their role in the stress response and well-being, see DePasquale and Gunnar in this volume (Chapter 22).

Dysregulated levels of adrenal hormones have marked negative consequences for diverse physiological functions, and numerous syndromes and disorders characterized by aberrant hormone production are well-documented (Charmandari, Nicolaides, & Chrousos, 2014; Lacroix, Feelders, Stratakis, & Nieman, 2015; Zografos, Perysinakis, & Vassilatou, 2014). Conversely, the maintenance of efficient regulation of these hormones, not only day-to-day but across the life course, corresponds to optimal functioning and health. In addition, steroid hormones such as cortisol and DHEA can cross the blood-brain barrier (Banks, 2012) where they have marked influences on both neurophysiology and subjective psychological experience; these influences are observed in the context of stressors and during normal daily activity. The ability of adrenal steroids to influence the brain directly highlights bidirectional influences that are relevant for this chapter: well-being affects the regulation of adrenal hormones, and circulating adrenal hormones can affect subjective experiences of well-being.

Cortisol. The steroid hormone cortisol is the main downstream effector of the HPA axis. Cortisol serves to elevate blood levels of glucose, by liberating existing stores or initiating glucose synthesis, to be used by muscles and the brain for daily activity and responses to environmental challenges. It also activates potent anti-stress and anti-inflammatory pathways.

Cortisol is present in diverse tissues, including blood, urine, saliva, and hair, and cortisol levels from these different sources provide information on different aspects of HPA function. To illustrate, cortisol levels in blood and saliva can change over the course of minutes and hours, providing a lens into acute changes in the physical and psychological state of the organism. Levels in urine and hair, in contrast, reflect longer-term accumulation, and analysis of cortisol in these tissues can inform about chronic patterns of HPA activity. Importantly, cortisol concentrations determined from different tissues within the same person often show weak inter-correlations, emphasizing the distinct aspects of HPA functioning that different modes of assessment provide (Rector, Tay, Wiese, & Friedman, unpublished data).

In general, cortisol has been used to study the impact of negative subjective experience (e.g. stress, depression) on health via dysregulated HPA axis activation. There are, however, associations between cortisol and well-being that are distinct from these links to ill-being. To this point, cortisol is the best-studied hormonal correlate of well-being.

A currently popular mode of assessing HPA regulation involves tracking fluctuations in cortisol across the day. Cortisol has a strong diurnal pattern, with a peak soon after awakening and a nadir right before the onset of sleep. To assess diurnal cortisol, 4 samples are typically collected: one upon awakening, a second 30 minutes later, a third before lunch, and the fourth before bedtime. The timing of these samples makes it possible to capture several important parameters of the diurnal cortisol rhythm: the waking value, the cortisol awakening response (CAR) – the rise from waking to 30 minutes later, during which cortisol concentrations increase by around 50% – the decline to mid-day, which is usually the steepest part of the daily decline, and the concentration approaching the typical nadir, which both allows for calculation of the

cortisol slope, or rate of decline across the entire day, and the value of the nadir, which has been shown to be meaningful for mental health in itself. Cumulative cortisol production across the day can also be estimated as the cortisol area under the curve (AUC). Diurnal cortisol regulation is a particularly attractive focus for research as many of these parameters are stable across measurement occasions (i.e., trait-like) while also being sensitive to acute life challenges (i.e., state-like).

There are at least two major features of the diurnal cortisol profile that show distinct patterns in relation to positive psychosocial functioning: the CAR and the slope (of cortisol levels over the day). In a study of 80 healthy Chinese adults aged 19-55 years, greater positive affect was associated with a steeper diurnal slope, but was unrelated to the CAR (Lai et al., 2005). Conversely, a later study using participants from the Family Heart Study (mean age: 31 years) found that greater positive affect was associated with a less pronounced CAR, but was unrelated to the diurnal decline (Brummett, Boyle, Kuhn, Siegler, & Williams, 2009). Notably, the Chinese study used median splits to determine high and low positive affect, suggesting that the relationship between positive affect and diurnal cortisol slope may not be linear across all levels of positive affect. That is, associations with the cortisol slope within the high positive affect group may be stronger than in those in the low positive affect group. Moreover, positive affect comprises dimensions of both emotional valence and degree of arousal. Calm and excitement, for example, are both positive emotions, but the latter is associated with higher levels of arousal. Along these lines, Hoyt, Craske, Mineka, and Adam (2015) found that high but not low arousal positive affect was associated with a steeper cortisol slope (and lower bedtime cortisol levels) among adolescents. The steeper slope seems to have been in part a function of lower levels of bedtime cortisol in those with the highest levels of high arousal positive affect (Hoyt et al., 2015). These results suggest a multi-dimensional representation of positive affect, which captures both valance and arousal, may be critical for a precise account of the relationship between positive affect and cortisol, and possibly help to explain prior mixed results.

There are more consistent findings for dispositional optimism. For example, among 543 healthy adults aged 53-76 years from the Whitehall II cohort study, a more robust CAR – a larger increase in cortisol from waking to 30 minutes later – was associated with lower optimism, but not the diurnal decline (Endrighi, Hamer, & Steptoe, 2011). A similar pattern of associations between optimism and the CAR was reported in Chinese adults. However, this relationship may be sex- and/or ethnicity-specific, as some associations were found only among men in the Chinese sample (Lai et al., 2005).

Smyth and colleagues (2017) assessed the relationship between global life satisfaction, measured by a single item, momentary affect (from ecological momentary assessment), stress, and diurnal cortisol slopes among 115 working aged adults (aged 19-63). Multi-level models revealed a trend ($p<.10$) towards greater global life satisfaction and steeper slopes, indicating a stronger diurnal rhythm, on each of the 3 sampling days. Interestingly, after averaging the slopes across the days, life satisfaction was actually associated with flatter cortisol slopes (Smyth, Zawadzki, Juth, & Sciamanna, 2017). The authors note that the initial measurements of cortisol did not begin until a few hours after waking, and likely missed important information from the early hours of the day needed to adequately assess the daily slope. However, Ryff and associates (2006) also reported an association between flatter cortisol slope and higher scores on the eudaimonic well-being domains of personal growth and purpose in life in 52 women aged 75 and older. These authors note that upon further examination, those with higher personal growth and purpose in life started the day with lower levels of salivary cortisol and stayed lower across the day, compared to those with lower scores on these domains (Ryff et al., 2006). These observations underscore the importance of considering absolute levels of cortisol and diurnal slope in tandem; flat slopes may result in different absolute levels of cortisol exposure depending on waking levels. Thus, one should also consider interactions between components in associations with well-being.

Well-being has also been studied as a buffer against the impact of stress on HPA responses. For example, in 135 community-dwelling adults aged 61 or older, Jobin and colleagues (2014) assessed stress perceptions and four indicators of diurnal cortisol (AUC, awakening, afternoon/evening, and CAR levels) on 12 different days over six years. When considering absolute levels of stress across participants, optimism was associated with a reduced CAR among those experiencing high stress levels. Compared to pessimists, optimists were protected against elevations in cortisol AUC, awakening levels, and afternoon/evening levels on days they perceived higher-than-average stress levels (Jobin, Wrosch, & Scheier, 2014). Conversely, in a double-blind, randomized study, Koelsch et al. (2016) exposed 143 participants to a CO_2 stress test (inhalation of 35% CO_2) and measured the impact of positive mood-inducing music on cortisol recovery. They found that compared to a neutral music control group the music intervention was associated with more positive mood and stronger cortisol responses to the acute stressor. The authors suggest that the lower cortisol among those with more negative mood is associated with a suboptimal (i.e. less robust) stress response, similar to HPA hypoactivity observed in patients with depression (Koelsch et al., 2016). The differences in the results of these two studies also illustrate the

nuances associated with different types of analyses. In the context of acute stressors, a robust response is often linked to favorable outcomes, whereas in the context of daily function higher levels of cortisol typically indicate greater ongoing stress and poorer outcomes.

Overall, cortisol is a sensitive biomarker of psychological experience. Although a relatively recent line of work, research on positive psychological functioning and cortisol suggests that cortisol regulation may be one biological pathway by which well-being has its beneficial effects on health. This effect is seen in direct links between markers of positive psychological functioning (e.g. positive affect; optimism) and daily cortisol regulation. Well-being also buffers the impact of adverse experiences.

Dehydroepiandrosterone (DHEA). The steroid hormone DHEA (and its longer lived sulfated form, DHEA-S) is one of the most abundant circulating steroids. Like cortisol, the majority of DHEA is produced and secreted by the adrenal cortex under the control of adrenocorticotropic hormone (ACTH). In addition to functioning as a metabolic intermediate in the synthesis of sex steroids and as an androgen in its own right, DHEA binds to and activates receptors of neurotrophins like nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) with high affinity, and is thus capable of signaling neurons to survive, differentiate and grow (Lazaridis et al., 2011; Prough, Clark, & Klinge, 2016). DHEA levels begin to decline in the early thirties at a rate of about 5% per year – DHEA is sometimes referred to as the "anti-aging" hormone – although the decline is highly variable and is driven by unknown factors. The various negative effects of this age-related decline are particularly robust in women, since DHEA is their only source of sex steroids after menopause. Such a decrease in DHEA-derived sex steroid availability could be partially responsible for numerous symptoms of hormone deficiency observed after menopause, including vaginal atrophy, bone loss, fat accumulation, type 2 diabetes, skin atrophy, cognition problems, memory loss, and possibly Alzheimer's disease (Labrie, 2007, 2010).

Observational studies associating DHEA(S) levels with various measures of well-being have been conducted primarily among older adults (Berr, Lafont, Debuire, Dartigues, & Baulieu, 1996; Lebrun et al., 2006; Petros, Opacka-Juffry, & Huber, 2013). Along with other physiological outcomes, Berr and colleagues (1996) found that among 622 community-dwelling adults aged over 65 years, DHEA levels were significantly lower in females with depressive symptoms, poor subjective health, and poor life satisfaction. A later study involving 402 post-menopausal women aged 56-73 years found that none of the hormonal parameters measured, including DHEA and DHEA-S, were related to quality of life (Lebrun et al., 2006). In an opportunistic sample of 32 individuals (63% women; mean age 29), Petros and associates (2013) found that salivary DHEA-S and resilience were positively associated after adjustment for age and sex. However, well-being was not significantly correlated with DHEA-S, cortisol, or the DHEA-S/cortisol ratio (Petros et al., 2013). These studies suggest that lower levels of DHEA(S) may be indicative of lower levels of well-being, although the results to this point are limited and mixed.

The potential importance of DHEA to health in older age has led to a number of studies aimed at boosting DHEA levels by supplementation. These studies provide the opportunity to examine the consequences of the manipulation of DHEA for well-being. The duration of administration in most placebo-controlled supplementation studies range from 7 days to 4 months. A 3-month randomized, double-blind placebo cross-over DHEA replacement trial among 30 men and women (aged 40-70 years) resulted in restoration of DHEA levels to those of young adults, a 2-fold increase in androgens in women and a small rise in androstenedione for men. These were accompanied by increased perceptions of physical and psychological well-being in men (67%) and women (84%) after 12 weeks, including improved sleep quality, feeling more relaxed, and having increased energy to better handle stress, as reported in open-ended questions (Morales, Haubrich, Hwang, Asakura, & Yen, 1998). Another randomized double-blind cross-over trial in men aged 62-76 found no significant differences in well-being between treatment and control groups in a 13-week DHEA supplementation trial. However, correlation analyses showed that higher morning DHEA levels were associated with lower confusion, while higher evening levels were associated with lower anxiety and lower current negative mood in the morning (van Niekerk, Huppert, & Herbert, 2001). These are relatively short administration periods, and studies assessing the impact of DHEA supplementation across longer periods of time are rare. As part of a 1-year DHEA supplementation trial in 225 men and women aged 55-85, cognitive functioning, life satisfaction, and quality of life were measured at 3, 6, and 12 months. This study found increases in cognitive function in the treatment group compared to the placebo control. Depression scores also decreased in both men and women. Women additionally showed increases in life satisfaction (Kritz-Silverstein, von Muhlen, Laughlin, & Bettencourt, 2008).

DHEA supplementation also has effects on brain regions relevant for well-being. A study involving 24 healthy young men (aged between 18 and 40 years), examined the impact of 7 days of DHEA supplementation on episodic memory and assessed potential neural correlates for its effects, specifically event-related potentials (ERPs). DHEA administration led to reduced evening cortisol and improved mood

and memory. The authors linked these results to neuronal recruitment in the steroid-sensitive anterior cingulate cortex (ACC) that may be involved in pre-hippocampal memory processing (Alhaj, Massey, & McAllister-Williams, 2006). This neuronal recruitment by DHEA may be of particular importance to the issue of well-being, as the ACC as well as the prefrontal cortex and insula have been implicated in the regulation of happiness and well-being (Berridge & Kringelbach, 2011; Lewis, Kanai, Rees, & Bates, 2014; Suardi, Sotgiu, Costa, Cauda, & Rusconi, 2016).

In addition to the direct effects of DHEA supplementation on well-being, researchers have also examined the role of DHEA supplementation as a buffer against the adverse effects of stress exposure. For example, in a study by Kudielka et al. (1998), 75 healthy older males and postmenopausal women participated in a 2-week double-blind, placebo-controlled study of DHEA supplementation. Afterwards, they underwent an acute psychosocial stressor, the Trier Social Stress Test (TSST). Women treated with DHEA showed similar ACTH stress responses to men, but they were significantly enhanced compared to women on the placebo. As noted above, robust responses to acute stressors are considered markers of health.

There may also be a 3-way association among stress, well-being, and DHEA-S. A recent study focusing on caregivers of individuals with dementia and use of adult daycare services examined salivary levels of DHEA-S and their relationships to positive mood and depressive symptoms in the caregivers. This study found that DHEA-S levels in caregivers were significantly higher on the days after the individuals for whom they were caring used daycare services. These results suggest potential restorative effects of a brief respite from providing care and thereby protection against the physiological effects associated with caregiving stress. Furthermore, DHEA-S levels co-varied with daily positive mood, but not with depressive symptoms (Zarit et al., 2014).

Overall, observational studies suggest that DHEA links specifically to well-being are more readily discernible among older adults than their younger counterparts. Randomized control trials involving DHEA supplementation generally suggest a positive impact of DHEA supplementation on well-being, although null findings have also been reported. One difficulty in comparing study results is variability in the experimental protocols used: DHEA dosage protocols and well-being measures assessed vary from study to study. Studies with comparable dosages of DHEA covering longer supplementation durations and wider age ranges may provide further information about age- and sex- and dose-specific associations. Likewise, a common set of well-being measures to compare across studies would be informative. Evidence also points to DHEA(S) acting as a buffer against acute stress or as a restorative agent during recovery from chronic stress, although the range of well-being measures assessed in these studies has been limited.

Catecholamines. Norepinephrine and epinephrine are the two main chemical messengers released from the adrenal medulla via sympathetic nervous system activation, and they are responsible for the so-called 'fight-or-flight' response to threatening environmental stimuli. [Note: While the adrenal medulla is the sole source of epinephrine in the periphery, norepinephrine is released in multiple other parts of the body from sympathetic neurons]. Generally their release initiates a cascade of physiological changes and mobilization of resources needed to respond to a stressor, including elevations in heart rate, cardiac output, blood pressure and blood glucose levels. Not surprisingly, given this role in the stress response, studies of links between well-being and catecholamines tend to focus on well-being as a modifier of hormonal reactivity and recovery following stressors.

A range of measures has been used to assess well-being in the context of autonomic function, the latter usually in response to an experimental stressor. For example, in participants of the Family Heart Study mentioned above, Brummett et al. (2009) found that during a sadness and anger recall protocol, positive affect was inversely related to the mean level of norepinephrine. However, positive affect was unrelated to reactivity or recovery after. The study of 90 newlywed couples focused on behaviors during a real-time marital conflict as predictors of epinephrine and norepinephrine responses, measured as the composite of hourly blood samples across the day. The tendency of husbands to withdraw from the conflict ('negative-withdrawal' pattern) was associated with higher norepinephrine levels in the wives, whereas more positive behaviors ('validation-facilitation' pattern) were associated with lower epinephrine levels (Kiecolt-Glaser et al., 1996). In the study by Koelsch and colleagues (2016), norepinephrine exhibited the fastest and strongest response to the CO_2 stress test. However, norepinephrine was not significantly different in the positive mood-inducing music stimulus group compared to the neutral control group. Further analyses, comparing those who increased and decreased mood in response to the stress, showed that positive mood did not affect norepinephrine response to or recovery from the CO_2 stress.

Cancer tumors are able to synthesize and release hormones, and one interesting area of study is the impact of the host environment on tumor hormone processes. In a clinical sample of 353 adult ovarian cancer patients, Davis et al. (2015) used latent factors to represent eudaimonic well-being (personal growth,

purpose in life and self-acceptance), positive affect, and psychological distress, and assessed their relationship with norepinephrine levels in tumor samples. Increased eudaimonic well-being was related to reduced tumor norepinephrine levels (Davis et al., 2015).

Taken together, the studies associating epinephrine and norepinephrine with measures of well-being are mixed, although there have been few such studies, and larger epidemiological studies that could provide information about broad, population-level patterns of association between circulating or experimentally-induced levels of catecholamines and diverse measures of well-being are lacking.

Sex Hormones

Steroidal sex hormones, also called gonadal hormones, are produced in the gonads, i.e. the testes and ovaries of males and females, respectively. Their synthesis is under the control of the hypothalamic-pituitary-gonadal (HPG) axis, and is crucial for the proper development and function of the body. Testosterone and estrogens, present at higher levels in males and females, respectively, control the expression and maintenance of secondary sex-specific characteristics, and regulate sexual differentiation and sexual behavior patterns.

Some studies have measured the psychological impact of testosterone replacement (usually to restore sexual function) in males with abnormally low levels of testosterone, for reasons of hypogonadism or marked declines with age (e.g. adrenopause). Such studies have documented increases in anger, hostility, and aggressive behavior, with variable effects (Bassil, Alkaade, & Morley, 2009). Among those with normal functioning (eugonadal) additional testosterone administration may have a minor impact on mood (O'Connor, Archer, & Wu, 2004). In females, the rise and fall of levels of estrogen with the menstrual cycle have been suggested to play a major role in the fluctuation of mood and emotions. Over the life cycle, the decline in estrogen levels among women (e.g. perimenopause and menopause) has been suspected to modulate the increased rate of depression and mood disorders, compared to men. While the underlying mechanisms are not known, evidence points to the neurological effects of estrogen, which are directly relevant to mood symptomotology (Wharton, Gleason, Olson, Carlsson, & Asthana, 2012). Varying levels of testosterone and estrogen are often examined in conjunction with sexually dimorphic phenomena. However, few studies have directly investigated their relationship with well-being. The following section discusses findings relevant to the correspondence of levels of these hormones and various measures of well-being.

Testosterone. Studies relating testosterone to well-being have focused on older adults, in part because there is a gradual, age-related decline of serum levels after age 30 (Bassil et al., 2009), and generally these studies have not found links between testosterone and well-being. Castanho et al. (2014), studying 120 Portuguese community-dwelling adults aged 51-87 years, identified four participant clusters based on performance in cognitive functioning (executive functioning, memory), depressive mood and well-being. These clusters were compared for their serum concentrations of various hormones, including testosterone. In males, higher testosterone was generally associated with lower odds of membership in the poorest performance cluster, characterized by poor cognitive functioning, low well-being, and high depression, although testosterone was not significantly associated with the well-being or quality of life measures for either sex (Castanho et al., 2014). An earlier study by Lebrun and associates (2006) among 402 post-menopausal women aged 56-73 years did not find an association between testosterone levels and health-related or general life satisfaction. Similarly, in 466 men aged 64-97 years from the Lieto Study, Eskelinen and associates (2007) found that total testosterone and free testosterone levels were associated with higher self-rated health after adjustment for age; however, these associations were no longer significant after further adjustment for body mass index (Eskelinen, Vahlberg, Isoaho, Kivela, et al., 2007).

In general, given the above studies, the evidence that testosterone is related to well-being among older adults is weak. Importantly though, there are relatively few studies of testosterone that have assessed well-being. There are also few studies involving younger samples (e.g. around the time when testosterone levels first begin their decline). Well-being might, for example, affect trajectories of changes in testosterone over time. In addition, other measures of well-being, such as eudaimonic well-being, positive affect, and optimism, have not been investigated thoroughly.

Estrogen. Changes in estrogen levels occur naturally throughout the life course, and fluctuations, sudden withdrawal, or sustained deficits in estrogen have been linked with significant mood disturbance. Studies specifically examining the link between estrogen and well-being are inconsistent and appear to implicate lower estrogen levels in the progression of negative mental health instead of improvements associated with higher levels.

In their study of Portuguese community-dwelling adults, Castanho and colleagues (2014) found that in males lower levels of estradiol (a major form of estrogen) predicted significantly higher odds of

membership in the poorest performance cluster, characterized by poor cognitive functioning, low well-being, and high depression. In the individual linear regression analysis, estrogen was not significantly associated with the well-being or quality of life measures (Castanho et al., 2014). Lebrun and associates (2006) failed to find an association between estrogen and health-related or general life satisfaction in post-menopausal women. However, there was a negative relationship between estrogen and health, seen only in the highest quintile of estrogen. This association was no longer significant after adjustment for fat mass (Lebrun et al., 2006).

Estrogen appears, at least in older adults, not to be directly related to well-being. There may a sex-dependent association, whereby males generally perform worse than females with lower levels of estradiol. However, this association does not appear to be specific to well-being, but more likely reflects an overall reduction in mental functioning. There have been few observational studies of estrogens that include measures of eudaimonic well-being, optimism, or positive affect; such efforts would complement existing findings and allow for meaningful comparisons across studies.

Metabolic Hormones

Metabolism refers to a complex network of continuous biochemical processes that allow for the efficient breakdown of food into energy for carrying out activities of daily life (catabolism) or for conversion into usable components for building and repairing the body (anabolism). In addition to age, sex, body composition, diet, and physical activity, metabolism is greatly influenced by hormone function. Metabolic hormones, such as growth hormone, insulin, insulin-like growth factor, and thyroid hormones, provide signals that regulate catabolic and anabolic processes within the body. The structure provided by anabolic processes supports the proper functioning of the body. Consequently, dysregulation of metabolism can be associated with a wide range of diseases and disorders. For example, abnormal cellular structure and function of neuronal circuits in the brain has been implicated in the development and progression of neuropsychiatric disorders, including neurodegenerative diseases like Alzheimer's. Importantly, these disorders frequently co-occur with metabolic disturbances, such as insulin resistance, diabetes, and obesity (McIntyre, Mancini, & Basile, 2001). Individuals with major mental illnesses, such as schizophrenia and bipolar disorder, also have an increased prevalence of metabolic syndrome (Newcomer, 2007). Although, associations among these populations may be due to non-disease-related factors such socioeconomic status or adverse metabolic side effects from medications. In non-clinical populations, these metabolic hormones are likewise suggested to have an impact on cognitive functioning and mood. These observations highlight the potential role of metabolism in general well-being.

Insulin-like growth factor 1 (IGF-I). Insulin-like growth factor is a hormone whose production is regulated by growth hormone, nutrition, and insulin. These insulin-like peptides are involved in a variety of biological activities, including neuronal survival, neurogenesis, angiogenesis, excitatory and inhibitory neurotransmission, regulation of food intake, and cognition (Werner & LeRoith, 2014). Across the life course, IGF-I follows an age-dependent pattern with serum levels peaking around puberty and declining thereafter with increasing age. Most IGF-I in the blood is produced by the liver (Roelfsema & Clark, 2001). The majority of studies involving IGF-I and well-being are among individuals with growth hormone deficiency undergoing growth hormone replacement therapy. The few studies in non-deficient populations suggest an association between IGF-I (and its binding proteins) and well-being.

In a study of individuals aged 20-74, Unden and associates (2002) measured several domains of well-being (social well-being, mental well-being, self-esteem, social support, and self-rated health) and found that they were positively correlated to IGF-I in those aged 20-44 years. Overall, age was found to account for 40% of the variation in IGF-I levels. In multivariate analyses controlling for this decline with age, social well-being was important in predicting IGF-I concentrations in the younger age group. In the older two age groups (i.e., 45-59 years and 60-74 years), associations were limited to physical factors, such as sex hormone binding globulin, low density lipoprotein, and lipoprotein(a), as well as education and physical health (Unden, Elofsson, Knox, Lewitt, & Brismar, 2002). These results suggest that in older adults age-related changes in health and physical function may dominate and diminish the potential links between psychosocial factors and IGF-I. Of note, these analyses were completed using stepwise selection of independent variables for the linear regression model. This variable selection method has since been found to have inherent reliability issues (Whittingham, Stephens, Bradbury, & Freckleton, 2006). However, this null association was also observed in the above study by Lebrun and colleagues (2006) that found no consistent associations of well-being with IGF-I, nor with two major binding proteins, among the post-menopausal women. More recently, Emeny et al. (2014) found that among 985 Cooperative Health Research in the Region Augsburg (KORA) study participants aged 64-93 years, IGF-I was inversely associated with well-being and directly linked to depressive symptoms in women. On the other hand, the binding protein IGFBP-3 was positively associated with well-being in women. IGFBP-3 serves to shuttle IGF-I around the body, but its affinity for the IGF receptor means that it may also act as an antagonist,

preventing IGF from binding and causing changes within the cell (hence the opposing effects of IGF-I and IGFBP-3 in this study). There were similar trends in men, but not statistically significant (Emeny et al., 2014). This study suggests that the previous studies may have failed to observe an association in older adults because it may be sex-specific. Further studies using the quality of life instruments utilized in these earlier studies with stratification by sex would be needed to confirm this possibility.

Overall, these findings show that in older adults, IGF-I may be inversely associated with well-being, while levels of its binding protein (IGFBP-3) were directly related to well-being. Importantly, these associations may be limited to older females. The menopausal status of these women may also be an important discriminating factor for these associations.

Insulin. Insulin is a peptide hormone produced by beta (β) cells of the pancreatic islets. Insulin helps to regulate the metabolism of carbohydrates, fats, and protein by promoting the absorption of glucose from the blood into fat, liver, and skeletal muscle cells. Under normal physiological functioning, the release of insulin into the circulation is closely linked to glucose concentrations in the blood. High glucose concentrations stimulate β cells to secrete insulin. Conversely, low glucose levels inhibit the secretion of insulin (Sonksen & Sonksen, 2000). Like steroid hormones, insulin can cross the blood-brain barrier where it appears to play an important role in neuronal survival (Werner & LeRoith, 2014). Research linking insulin levels and well-being has largely investigated the effect of insulin therapy either directly on mood or as a buffer of stress. These studies have generally found that intranasal insulin improves mood and attenuates HPA reactivity to social stress (Lee, Zabolotny, Huang, Lee, & Kim, 2016).

Observational studies have generally reported inverse associations between insulin levels and well-being. Oreskovic and Goodman (2013) investigated the relationship between dispositional optimism and insulin levels measured 6-7 years later among adolescents aged 12-19 years. In bivariate analyses, insulin was negatively correlated to scores on optimism and positively correlated with scores on pessimism. In analyses adjusted for a range of potential confounders, an inverse association was found among non-Hispanic black, but not white adolescents, whereby a one unit increase in unidimensional optimism corresponded to 2.2% lower insulin levels (Oreskovic & Goodman, 2013). A study of 402 post-menopausal women found that insulin was not related to health-related life satisfaction. There were negative associations between insulin and life satisfaction which were present only in the highest quintile of insulin, but these were attenuated by adjustment for fat mass (Lebrun et al., 2006).

Lee et al. (2016) recently summarized the results of numerous experimental studies involving insulin administration to human and animal subjects. A set of four studies specifically examined the impact of intranasal insulin on well-being and psychological responses to stressors, including social evaluative stress. The studies have generally found that intranasal insulin improved mood and attenuated HPA reactivity to social stress (Lee et al., 2016).

Thyroid hormones (TSH/T_4/T_3). Thyroid stimulating hormone (TSH) is an integral part of the hypothalamic-pituitary-thyroid axis. Specifically, the hypothalamus releases thyrotropin-releasing hormone (TRH) to stimulate the anterior pituitary to produce TSH. TSH then stimulates the thyroid gland to produce thyroxine (T_4), which is in turn converted to active triiodothyronine (T_3). T_3 affects almost every physiological process in the body, including growth and development, metabolism, body temperature and heart rate. T_3 and T_4 levels provide negative feedback to the hypothalamus and pituitary gland to regulate the release of TRH and TSH, respectively.

Alterations in the levels of thyroid metabolites occur normally with age and are also present in conditions that often result in lower levels of thyroid hormones (hypothyroidism), such as Hashimoto's Thyroiditis, thyroidectomy, or other thyroid deficiency. In non-patient populations, subclinical hyperthyroidism is characterized by lower-than-normal TSH in the presence of normal levels of free thyroxine (fT_4). Subclinical hypothyroidism is characterized by elevated TSH in the presence of normal fT_4. Subclinical hypothyroidism is often accompanied by increased levels of thyroid autoantibodies (thyroid peroxidase; anti-TPO).

Thyroid hormone status has predominantly been studied in relation to depression. Whereas most of the patients with primary depression have normal thyroid function, some patients with hypothyroidism or hyperthyroidism manifest features of depression, the latter presenting with a wider spectrum of neuropsychiatric symptoms (Hage & Azar, 2012). However, some studies have investigated the relationship of thyroid hormones with health-related quality of life (HR-QOL) and well-being, though not all studies are in agreement. Comparing 93 Hashimoto's Thyroiditis patients with 31 euthyroid (normally functioning thyroid) controls, Yalcin et al. (2017) found that depression and anxiety scores were higher and scores on subscales of the SF-36 (physical functioning, general health, and mental health) were lower in the

patients. Larger studies outside of clinical populations tend not to find any associations of TSH and T_4 levels with life satisfaction, self-rated health, and quality of life in healthy control populations, nor any differences in those with hypothyroidism undergoing thyroxine replacement therapy (Eskelinen, Vahlberg, Isoaho, Lopponen, et al., 2007; Kelderman-Bolk, Visser, Tijssen, & Berghout, 2015). In a large study of 9,491 individuals of the LifeLines Cohort Study aged 18-90 years old, Klaver et al. (2013) compared to euthyroid individuals, there was no difference between those with elevated or suppressed TSH or fT_4 levels in HR-QOL. There was a sex-specific effect whereby women with suppressed TSH scored significantly lower on domains of 'physical functioning' and 'general health' compared to euthyroid women (Klaver et al., 2013). Similarly, a later study among 8,214 Danish General Suburban Population Study participants aged 20 or older (55 years on average) found no difference in well-being between subclinical hypothyroidism and euthyroid individuals with or without high levels of anti-TPO. One exception is that euthyroid women with high anti-TPO had better well-being than euthyroid women with anti-TPO in the reference range; although this association may have arisen by chance (Fjaellegaard, Kvetny, Allerup, Bech, & Ellervik, 2015).

The literature on links between thyroid hormones and well-being generally show associations in the expected directions, but as with catecholamines, more large-scale studies are needed to document population-level associations.

Other Hormones

The hormones discussed below include posterior pituitary hormones, oxytocin and vasopressin, and prolactin. These hormones are important messengers that potently influence inter-personal interactions, including in-group affiliation and out-group discrimination, mating preferences and pair-bonding, parental behavior, and pro-social behavior (Olff et al., 2013; Shamay-Tsoory & Abu-Akel, 2016; Sobrinho, 1991; Walum et al., 2008), and as such may have considerable bearing on social well-being. These hormones also coordinate a number of other processes important for physiological and mental health, such as pain perception, wound healing, and reward circuits in the brain. Thus, these hormones may work across multiple levels to impact the subjective experiences of the individual.

Oxytocin. Oxytocin is a neuropeptide produced by the hypothalamus and stored in the posterior pituitary where it is released into the circulation. It can also be released from specific neural projections to other structures in the brain where it modulates the activity of other neurochemical systems. In addition to its physiological role during pregnancy – increasing uterine tone, promoting uterine contractions, and inducing labor – oxytocin is also involved in maternal bonding, sexual behavior, and affiliation (Ishak, Kahloon, & Fakhry, 2011). Recently, oxytocin administration has gained increased attention for its ability to promote positive social behavior and stress regulation, and for its potential as a therapeutic intervention for alleviating symptoms of various psychiatric disorders. However, the observed effects are not uniformly beneficial. Accumulating evidence suggests that contextual and inter-individual factors, such as presence of a stranger versus a friend, sex, attachment style, or the presence of psychiatric symptoms, moderate the effects of oxytocin, as well as absolute levels in the periphery (Olff et al., 2013). Specifically, these factors are thought to interact with oxytocin to influence the salience of social and environmental cues. Depending on the context, oxytocin can induce pro-social, anti-social or even aggressive behavior (De Dreu, 2012; De Dreu, Greer, Van Kleef, Shalvi, & Handgraaf, 2011; Shamay-Tsoory & Abu-Akel, 2016). Thus, oxytocin effects are not uniformly pro-social, as has been thought (it has been popularly referred to as the "cuddle" hormone), but rather is highly sensitive to social context.

Studies specifically relating oxytocin to well-being are rare. Those that have been done have tended to focus on the potential beneficial effects of intranasal administration. There is also interest in the oxytocin receptor, which has a number of polymorphisms that may be linked to well-being to different degrees. Barraza et al. (2013) studied the impact of 10 daily doses of intranasal oxytocin on mood among 41 residentially housed older adults (mean age of 80) in a randomized, double-blind, placebo-controlled study. No changes in mood were observed across the 10-day period. However, dispositional gratitude improved in the treatment group compared to controls. Saphire-Bernstein and colleagues (2011) investigated the link between the oxytocin receptor genotypes (with or without the A allele) and psychosocial resources (optimism, mastery, self-esteem) among 344 university students and employees aged 18-36 years. This study found that carriers of the A allele had lower levels of these resources, compared to G/G homozygotes. These resources were also found to mediate the relationship between oxytocin receptor type and depression (Saphire-Bernstein, Way, Kim, Sherman, & Taylor, 2011). These findings are in line with an earlier study by Lucht et al. (2009) among 285 adults that found individuals with the oxytocin receptor A/A genotype had lower scores for positive affect. However, this effect was only observed in males (Lucht et al., 2009).

Oxytocin has also been suggested to predict positive affective responses to acute socio-evaluative

stress. Using the TSST among 172 participants aged 18-35 years, Moons, Way, and Taylor (2014) found that post-stress oxytocin levels interacted with oxytocin receptor polymorphisms to predict positive affective responses to the stressor. This effect was sex-specific whereby higher levels of oxytocin in females with the G/G genotype had more positive affect compared to the carriers of the A allele (Moons et al., 2014).

Anti-diuretic hormone/arginine vasopressin (ADH/AVP). Vasopressin is a hormone released from the posterior pituitary gland. Release of vasopressin in the blood increases water retention in the body, and in higher concentrations, produces vasoconstriction. Vasopressin also acts on reward circuits in the brain to promote pair-bonding behavior during partner preference formation in prairie voles. Similar effects of vasopressin receptor activation have been found in studies of marital discord in men (Walum et al., 2008). Studying the impact of intranasal vasopressin administration on musical working memory, Granot and associates (2013) found that compared to those in the placebo group, those receiving vasopressin had higher scores on happiness (Granot, Uzefovsky, Bogopolsky, & Ebstein, 2013). Moons et al. (2014) found an interaction between vasopressin and its receptor in predicting anger responses to the TSST. This effect was gender-specific whereby men, but not women, with high post-stressor vasopressin levels who were also carriers of a particular vasopressin receptor polymorphism had more post-stressor anger compared to non-carriers (Moons et al., 2014).

Prolactin. Prolactin is a potent hormone secreted mainly from the anterior pituitary gland with a broad range of biological effects, including water and salt balance, breast milk production, cell proliferation and differentiation, T-cell immunity, pancreatic β cell function, hematopoiesis, and adipogenesis. It acts via binding to prolactin receptors and cytokine-like receptors located in many tissues throughout the body (Bole-Feysot, Goffin, Edery, Binart, & Kelly, 1998). Creative approaches have been used in the study of prolactin responses to stressors. In one study, for example, women with anger responses to hypnosis-evoked experiences of humiliation showed elevated prolactin (Sobrinho, 2003). Additionally, more passive coping mechanisms in real-life situations have been associated with chronic elevations in prolactin (Sobrinho, 1991, 2003).

Studies assessing levels of prolactin and measures of well-being are limited. Castanho et al. (2014) found sex-specific associations among 120 Portuguese participants aged 51-87 years. In males, higher prolactin was associated with higher odds of membership in the poorest performance cluster, characterized by poor cognitive function, higher depression and lower well-being, compared to the best performance cluster. Similarly, in males only, linear regression analyses showed that higher prolactin predicted less depressive mood and greater well-being (Castanho et al., 2014). Kiecolt-Glaser et al. (1996) also measured prolactin among 90 newlywed couples during marital conflict and found that the more positive 'validation-facilitation' behavior pattern, but not the 'negative-withdrawal' pattern, was associated with higher prolactin levels, in women only. No such associations between the behavior patterns and endocrine responses during marital conflict were observed in the men.

Conclusion

The existing literature points to associations of some, but not all, hormones with well-being that are not merely the mirror image to those of ill-being. There are some features of the current literature that limit the conclusions we can draw about the relationship between hormones and well-being. First, the measures of well-being used across the above studies are diverse – some focused on emotions, others on meaningful engagement with life pursuits, others on optimism – and not all are used in any single study. Null findings in particular are thus difficult to interpret: is there no association with well-being, or with the specific measure of well-being used in a specific study? Second, the impact of basic but influential characteristics, such as age and sex, has not been considered explicitly in most studies and may have marked consequences for the outcomes studied. Even if there is a robust association between a particular hormone and well-being, it may change with age, for example, along with normative changes in biological functioning. Moreover, for many of the hormones considered here there has been evidence of sex-specific associations that should be clarified and replicated in future studies. Third, there are still open questions regarding the nature of the hormones themselves. In particular, the complexity of diverse cortisol assessments (c.f. Clow, Hucklebridge, Stalder, Evans, & Thorn, 2010) necessitates the systematic testing of the links between positive functioning and these measures. It may not be reasonable to expect that all of these different measures of cortisol will be linked to the same aspects of well-being to the same degree. Lastly, this chapter has considered studies looking specifically at the association of single isolated hormones with well-being. It is well-known that these hormones all have some degree of stimulatory or inhibitory function in relation to other hormones. For example, testosterone has been found to enhance the effects of growth hormone (Meinhardt & Ho, 2006) and norepinephrine to strongly inhibit insulin release (Nakaki, Nakadate, & Kato, 1980). There are practical reasons that no studies have included measures of all these various hormones and investigated their interactive associations with well-being, but the existence of such complexity must

be acknowledged and assessed wherever possible. The few studies that did assess multiple hormones in a single sample did not specifically investigate their interactions in predicting well-being, but the results nonetheless suggest that complex interactions may exist with sex-specific effects (Castanho et al., 2014; Kiecolt-Glaser et al., 1996; Lebrun et al., 2006).

In sum, research on the associations between hormones and well-being appears to be in its infancy compared to the vast body of work characterizing hormone associations with ill-being (e.g., depression, stress). Thus, this represents a fertile area of research with great promise to illuminate the physiological pathways by which well-being affects physical and mental health.

References

Alhaj, H. A., Massey, A. E., & McAllister-Williams, R. H. (2006). Effects of DHEA administration on episodic memory, cortisol and mood in healthy young men: A double-blind, placebo-controlled study. *Psychopharmacology (Berl), 188*(4), 541-551. doi: 10.1007/s00213-005-0136-y

Banks, W. A. (2012). Brain meets body: The blood-brain barrier as an endocrine interface. *Endocrinology, 153*(9), 4111-4119. doi: 10.1210/en.2012-1435

Barraza, J. A., Grewal, N. S., Ropacki, S., Perez, P., Gonzalez, A., & Zak, P. J. (2013). Effects of a 10-day oxytocin trial in older adults on health and well-being. *Exp Clin Psychopharmacol, 21*(2), 85-92. doi: 10.1037/a0031581

Bassil, N., Alkaade, S., & Morley, J. E. (2009). The benefits and risks of testosterone replacement therapy: A review. *Ther Clin Risk Manag, 5* (3), 427-448.

Berr, C., Lafont, S., Debuire, B., Dartigues, J. F., & Baulieu, E. E. (1996). Relationships of dehydroepiandrosterone sulfate in the elderly with functional, psychological, and mental status, and short-term mortality: A French community-based study. *Proc Natl Acad Sci U S A, 93* (23), 13410-13415.

Berridge, K. C., & Kringelbach, M. L. (2011). Building a neuroscience of pleasure and well-being. *Psychol Well Being, 1*(1), 1-3. doi: 10.1186/2211-1522-1-3

Bole-Feysot, C., Goffin, V., Edery, M., Binart, N., & Kelly, P. A. (1998). Prolactin (PRL) and its receptor: Actions, signal transduction pathways and phenotypes observed in PRL receptor knockout mice. *Endocr Rev, 19*(3), 225-268. doi: 10.1210/edrv.19.3.0334

Brummett, B. H., Boyle, S. H., Kuhn, C. M., Siegler, I. C., & Williams, R. B. (2009). Positive affect is associated with cardiovascular reactivity, norepinephrine level, and morning rise in salivary cortisol. *Psychophysiology, 46*(4), 862-869. doi: 10.1111/j.1469-8986.2009.00829.x

Castanho, T. C., Moreira, P. S., Portugal-Nunes, C., Novais, A., Costa, P. S., Palha, J. A., . . . Santos, N. C. (2014). The role of sex and sex-related hormones in cognition, mood and well-being in older men and women. *Biol Psychol, 103* , 158-166. doi: 10.1016/j.biopsycho.2014.08.015

Charmandari, E., Nicolaides, N. C., & Chrousos, G. P. (2014). Adrenal insufficiency. *Lancet, 383*(9935), 2152-2167. doi: 10.1016/S0140-6736(13)61684-0

Chida, Y., & Steptoe, A. (2008). Positive psychological well-being and mortality: A quantitative review of prospective observational studies. *Psychosom Med, 70*(7), 741-756. doi: 10.1097/PSY.0b013e31818105ba

Clow, A., Hucklebridge, F., Stalder, T., Evans, P., & Thorn, L. (2010). The cortisol awakening response: More than a measure of HPA axis function. *Neuroscience and Biobehavioral Reviews, 35* (1), 97-103. doi: 10.1016/j.neubiorev.2009.12.011

Cole, S. W., Levine, M. E., Arevalo, J. M. G., Ma, J., Weir, D. R., & Crimmins, E. M. (2015). Loneliness, eudaimonia, and the human conserved transcriptional response to adversity. *Psychoneuroendocrinology, 62*, 11-17. doi: 10.1016/j.psyneuen.2015.07.001

Davis, L. Z., Slavich, G. M., Thaker, P. H., Goodheart, M. J., Bender, D. P., Dahmoush, L., . . . Lutgendorf, S. K. (2015). Eudaimonic well-being and tumor norepinephrine in patients with epithelial ovarian cancer. *Cancer, 121*(19), 3543-3550. doi: 10.1002/cncr.29516

De Dreu, C. K. (2012). Oxytocin modulates cooperation within and competition between groups: An integrative review and research agenda. *Horm Behav, 61*(3), 419-428. doi: 10.1016/j.yhbeh.2011.12.009

De Dreu, C. K., Greer, L. L., Van Kleef, G. A., Shalvi, S., & Handgraaf, M. J. (2011). Oxytocin promotes human ethnocentrism. *Proc Natl Acad Sci U S A, 108* (4), 1262-1266. doi: 10.1073/pnas.1015316108

DePasquale, C. E. & Gunnar, M. R. (2018). Stress, development, and well-being. In E. Diener, S. Oishi, & L. Tay (Eds.), *e-handbook of well-being*. NobaScholar.

Emeny, R. T., Bidlingmaier, M., Lacruz, M. E., Linkohr, B., Peters, A., Reincke, M., & Ladwig, K. H.

(2014). Mind over hormones: Sex differences in associations of well-being with IGF-I, IGFBP-3 and physical activity in the KORA-Age study. *Exp Gerontol, 59*, 58-64. doi: 10.1016/j.exger.2014.08.001

Endrighi, R., Hamer, M., & Steptoe, A. (2011). Associations of trait optimism with diurnal neuroendocrine activity, cortisol responses to mental stress, and subjective stress measures in healthy men and women. *Psychosom Med, 73*(8), 672-678. doi: 10.1097/PSY.0b013e31822f9cd7

Eskelinen, S. I., Vahlberg, T. J., Isoaho, R. E., Kivela, S. L., & Irjala, K. M. (2007). Associations of sex hormone concentrations with health and life satisfaction in elderly men. *Endocr Pract, 13*(7), 743-749. doi: 10.4158/EP.13.7.743

Eskelinen, S. I., Vahlberg, T. J., Isoaho, R. E., Lopponen, M. K., Kivela, S. L., & Irjala, K. M. (2007). Associations of thyroid-stimulating hormone and free thyroxine concentrations with health and life satisfaction in elderly adults. *Endocr Pract, 13*(5), 451-457. doi: 10.4158/EP.13.5.451

Fjaellegaard, K., Kvetny, J., Allerup, P. N., Bech, P., & Ellervik, C. (2015). Well-being and depression in individuals with subclinical hypothyroidism and thyroid autoimmunity - a general population study. *Nord J Psychiatry, 69*(1), 73-78. doi: 10.3109/08039488.2014.929741

Friedman, E. M. (2012). Well-being, aging, and immunity. In S. C. Segerstrom (Ed.), *The Oxford handbook of psychoneuroimmunology* (pp. 37-62). New York: Oxford University Press.

Giltay, E. J., Geleijnse, J. M., Zitman, F. G., Hoekstra, T., & Schouten, E. G. (2004). Dispositional optimism and all-cause and cardiovascular mortality in a prospective cohort of elderly dutch men and women. *Arch Gen Psychiatry, 61*(11), 1126-1135. doi: 10.1001/archpsyc.61.11.1126

Granot, R. Y., Uzefovsky, F., Bogopolsky, H., & Ebstein, R. P. (2013). Effects of arginine vasopressin on musical working memory. *Front Psychol, 4* , 712. doi: 10.3389/fpsyg.2013.00712

Hage, M. P., & Azar, S. T. (2012). The link between thyroid function and depression. *J Thyroid Res, 2012* , 590648. doi: 10.1155/2012/590648

Hill, P. L., & Turiano, N. A. (2014). Purpose in life as a predictor of mortality across adulthood. *Psychol Sci, 25*(7), 1482-1486. doi: 10.1177/0956797614531799

Hoyt, L. T., Craske, M. G., Mineka, S., & Adam, E. K. (2015). Positive and negative affect and arousal: cross-sectional and longitudinal associations with adolescent cortisol diurnal rhythms. *Psychosom Med, 77*(4), 392-401. doi: 10.1097/PSY.0000000000000178

Ishak, W. W., Kahloon, M., & Fakhry, H. (2011). Oxytocin role in enhancing well-being: A literature review. *J Affect Disord, 130* (1-2), 1-9. doi: 10.1016/j.jad.2010.06.001

Jobin, J., Wrosch, C., & Scheier, M. F. (2014). Associations between dispositional optimism and diurnal cortisol in a community sample: When stress is perceived as higher than normal. *Health Psychol, 33*(4), 382-391. doi: 10.1037/a0032736

Kelderman-Bolk, N., Visser, T. J., Tijssen, J. P., & Berghout, A. (2015). Quality of life in patients with primary hypothyroidism related to BMI. *Eur J Endocrinol, 173*(4), 507-515. doi: 10.1530/EJE-15-0395

Keyes, C. L. (2002). The mental health continuum: From languishing to flourishing in life. *J Health Soc Behav, 43*(2), 207-222.

Kiecolt-Glaser, J. K., Newton, T., Cacioppo, J. T., MacCallum, R. C., Glaser, R., & Malarkey, W. B. (1996). Marital conflict and endocrine function: Are men really more physiologically affected than women? *J Consult Clin Psychol, 64* (2), 324-332.

Klaver, E. I., van Loon, H. C., Stienstra, R., Links, T. P., Keers, J. C., Kema, I. P., . . . Wolffenbuttel, B. H. (2013). Thyroid hormone status and health-related quality of life in the LifeLines Cohort Study. *Thyroid, 23*(9), 1066-1073. doi: 10.1089/thy.2013.0017

Koelsch, S., Boehlig, A., Hohenadel, M., Nitsche, I., Bauer, K., & Sack, U. (2016). The impact of acute stress on hormones and cytokines, and how their recovery is affected by music-evoked positive mood. *Sci Rep, 6*, 23008. doi: 10.1038/srep23008

Kritz-Silverstein, D., von Muhlen, D., Laughlin, G. A., & Bettencourt, R. (2008). Effects of dehydroepiandrosterone supplementation on cognitive function and quality of life: The DHEA and Well-Ness (DAWN) Trial. *J Am Geriatr Soc, 56* (7), 1292-1298. doi: 10.1111/j.1532-5415.2008.01768.x

Kubzansky, L. D., Boehm, J. K., & Segerstrom, S. C. (2015). Positive psychological functioning and the biology of health. *Social and Personality Psychology Compass, 9* (12), 645-660.

Kudielka, B. M., Hellhammer, J., Hellhammer, D. H., Wolf, O. T., Pirke, K. M., Varadi, E., . . . Kirschbaum, C. (1998). Sex differences in endocrine and psychological responses to psychosocial stress in

healthy elderly subjects and the impact of a 2-week dehydroepiandrosterone treatment. *J Clin Endocrinol Metab, 83*(5), 1756-1761. doi: 10.1210/jcem.83.5.4758

Labrie, F. (2007). Drug insight: breast cancer prevention and tissue-targeted hormone replacement therapy. *Nat Clin Pract Endocrinol Metab, 3* (8), 584-593. doi: 10.1038/ncpendmet0559

Labrie, F. (2010). DHEA, important source of sex steroids in men and even more in women. *Prog Brain Res, 182*, 97-148. doi: 10.1016/S0079-6123(10)82004-7

Lacroix, A., Feelders, R. A., Stratakis, C. A., & Nieman, L. K. (2015). Cushing's syndrome. *Lancet, 386*(9996), 913-927. doi: 10.1016/S0140-6736(14)61375-1

Lai, J. C., Evans, P. D., Ng, S. H., Chong, A. M., Siu, O. T., Chan, C. L., . . . Chan, C. C. (2005). Optimism, positive affectivity, and salivary cortisol. *Br J Health Psychol, 10* (Pt 4), 467-484. doi: 10.1348/135910705X26083

Lazaridis, I., Charalampopoulos, I., Alexaki, V. I., Avlonitis, N., Pediaditakis, I., Efstathopoulos, P., . . . Gravanis, A. (2011). Neurosteroid dehydroepiandrosterone interacts with nerve growth factor (NGF) receptors, preventing neuronal apoptosis. *PLoS Biol, 9*(4), e1001051. doi: 10.1371/journal.pbio.1001051

Lebrun, C. E., van der Schouw, Y. T., de Jong, F. H., Pols, H. A., Grobbee, D. E., & Lamberts, S. W. (2006). Relations between body composition, functional and hormonal parameters and quality of life in healthy postmenopausal women. *Maturitas, 55*(1), 82-92. doi: 10.1016/j.maturitas.2006.01.008

Lee, S. H., Zabolotny, J. M., Huang, H., Lee, H., & Kim, Y. B. (2016). Insulin in the nervous system and the mind: Functions in metabolism, memory, and mood. *Mol Metab, 5* (8), 589-601. doi: 10.1016/j.molmet.2016.06.011

Lewis, G. J., Kanai, R., Rees, G., & Bates, T. C. (2014). Neural correlates of the 'good life': Eudaimonic well-being is associated with insular cortex volume. *Soc Cogn Affect Neurosci, 9* (5), 615-618. doi: 10.1093/scan/nst032

Lucht, M. J., Barnow, S., Sonnenfeld, C., Rosenberger, A., Grabe, H. J., Schroeder, W., . . . Rosskopf, D. (2009). Associations between the oxytocin receptor gene (OXTR) and affect, loneliness and intelligence in normal subjects. *Prog Neuropsychopharmacol Biol Psychiatry, 33* (5), 860-866. doi: 10.1016/j.pnpbp.2009.04.004

McIntyre, R. S., Mancini, D. A., & Basile, V. S. (2001). Mechanisms of antipsychotic-induced weight gain. *J Clin Psychiatry, 62 Suppl 23* , 23-29.

Meinhardt, U. J., & Ho, K. K. (2006). Modulation of growth hormone action by sex steroids. *Clin Endocrinol (Oxf), 65*(4), 413-422. doi: 10.1111/j.1365-2265.2006.02676.x

Moons, W. G., Way, B. M., & Taylor, S. E. (2014). Oxytocin and vasopressin receptor polymorphisms interact with circulating neuropeptides to predict human emotional reactions to stress. *Emotion, 14*(3), 562-572. doi: 10.1037/a0035503

Morales, A. J., Haubrich, R. H., Hwang, J. Y., Asakura, H., & Yen, S. S. (1998). The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. *Clin Endocrinol (Oxf), 49*(4), 421-432.

Nakaki, T., Nakadate, T., & Kato, R. (1980). Alpha 2-adrenoceptors modulating insulin release from isolated pancreatic islets. *Naunyn Schmiedebergs Arch Pharmacol, 313* (2), 151-153.

Newcomer, J. W. (2007). Metabolic syndrome and mental illness. *Am J Manag Care, 13* (7 Suppl), S170-177.

O'Connor, D. B., Archer, J., & Wu, F. C. (2004). Effects of testosterone on mood, aggression, and sexual behavior in young men: a double-blind, placebo-controlled, cross-over study. *J Clin Endocrinol Metab, 89*(6), 2837-2845. doi: 10.1210/jc.2003-031354

Olff, M., Frijling, J. L., Kubzansky, L. D., Bradley, B., Ellenbogen, M. A., Cardoso, C., . . . van Zuiden, M. (2013). The role of oxytocin in social bonding, stress regulation and mental health: An update on the moderating effects of context and interindividual differences. *Psychoneuroendocrinology, 38* (9), 1883-1894. doi: 10.1016/j.psyneuen.2013.06.019

Oreskovic, N. M., & Goodman, E. (2013). Association of optimism with cardiometabolic risk in adolescents. *J Adolesc Health, 52* (4), 407-412. doi: 10.1016/j.jadohealth.2012.09.011

Petros, N., Opacka-Juffry, J., & Huber, J. H. (2013). Psychometric and neurobiological assessment of resilience in a non-clinical sample of adults. *Psychoneuroendocrinology, 38* (10), 2099-2108. doi: 10.1016/j.psyneuen.2013.03.022

Pressman, S. D., & Cohen, S. (2005). Does positive affect influence health? *Psychol Bull, 131*(6), 925-971. doi: 10.1037/0033-2909.131.6.925

Prough, R. A., Clark, B. J., & Klinge, C. M. (2016). Novel mechanisms for DHEA action. *J Mol Endocrinol, 56*(3), R139-155. doi: 10.1530/JME-16-0013

Rector, J. L., Tay, L., Wiese, C. W., & Friedman, E. M. (unpublished data). Assessing the relative sensitivity of cortisol indices to psychosocial and physical health factors.

Roelfsema, V., & Clark, R. G. (2001). The growth hormone and insulin-like growth factor axis: its manipulation for the benefit of growth disorders in renal failure. *J Am Soc Nephrol, 12*(6), 1297-1306.

Ryan, R. M., & Deci, E. L. (2001). On happiness and human potentials: A review of research on hedonic and eudaimonic well-being. *Annu Rev Psychol, 52*, 141-166. doi: 10.1146/annurev.psych.52.1.141

Ryff, C. D. (2014). Psychological well-being revisited: Advances in the science and practice of eudaimonia. *Psychother Psychosom, 83*(1), 10-28. doi: 10.1159/000353263

Ryff, C. D., Dienberg Love, G., Urry, H. L., Muller, D., Rosenkranz, M. A., Friedman, E. M., . . . Singer, B. (2006). Psychological well-being and ill-being: Do they have distinct or mirrored biological correlates? *Psychotherapy and Psychosomatics, 75*(2), 85-95. doi: 10.1159/000090892

Ryff, C. D., & Keyes, C. L. (1995). The structure of psychological well-being revisited. *Journal of Personality and Social Psychology, 69*(4), 719-727.

Saphire-Bernstein, S., Way, B. M., Kim, H. S., Sherman, D. K., & Taylor, S. E. (2011). Oxytocin receptor gene (OXTR) is related to psychological resources. *Proc Natl Acad Sci U S A, 108*(37), 15118-15122. doi: 10.1073/pnas.1113137108

Shamay-Tsoory, S. G., & Abu-Akel, A. (2016). The social salience hypothesis of oxytocin. *Biol Psychiatry, 79*(3), 194-202. doi: 10.1016/j.biopsych.2015.07.020

Smyth, J. M., Zawadzki, M. J., Juth, V., & Sciamanna, C. N. (2017). Global life satisfaction predicts ambulatory affect, stress, and cortisol in daily life in working adults. *Journal of Behavioral Medicine, 40*(2), 320-331. doi: 10.1007/s10865-016-9790-2

Sobrinho, L. G. (1991). Neuropsychiatry of prolactin: Causes and effects. *Baillieres Clin Endocrinol Metab, 5*(1), 119-142.

Sobrinho, L. G. (2003). Prolactin, psychological stress and environment in humans: Adaptation and maladaptation. *Pituitary, 6*(1), 35-39.

Sonksen, P., & Sonksen, J. (2000). Insulin: Understanding its action in health and disease. *Br J Anaesth, 85*(1), 69-79.

Steptoe, A., Dockray, S., & Wardle, J. (2009). Positive affect and psychobiological processes relevant to health. *Journal of Personality, 77*(6), 1747-1776. doi: 10.1111/j.1467-6494.2009.00599.x

Suardi, A., Sotgiu, I., Costa, T., Cauda, F., & Rusconi, M. (2016). The neural correlates of happiness: A review of PET and fMRI studies using autobiographical recall methods. *Cogn Affect Behav Neurosci, 16*(3), 383-392. doi: 10.3758/s13415-016-0414-7

Unden, A. L., Elofsson, S., Knox, S., Lewitt, M. S., & Brismar, K. (2002). IGF-I in a normal population: relation to psychosocial factors. *Clin Endocrinol (Oxf), 57*(6), 793-803.

van Niekerk, J. K., Huppert, F. A., & Herbert, J. (2001). Salivary cortisol and DHEA: Association with measures of cognition and well-being in normal older men, and effects of three months of DHEA supplementation. *Psychoneuroendocrinology, 26*(6), 591-612.

Walum, H., Westberg, L., Henningsson, S., Neiderhiser, J. M., Reiss, D., Igl, W., . . . Lichtenstein, P. (2008). Genetic variation in the vasopressin receptor 1a gene (AVPR1A) associates with pair-bonding behavior in humans. *Proc Natl Acad Sci U S A, 105*(37), 14153-14156. doi: 10.1073/pnas.0803081105

Waterman, A. S. (1993). Two conceptions of happiness: Contrasts of personal expressiveness (eudaimonia) and hedonic enjoyment. *J Pers Soc Psychol, 64*(4), 678-691. doi: 10.1037/0022-3514.64.4.678

Werner, H., & LeRoith, D. (2014). Insulin and insulin-like growth factor receptors in the brain: Physiological and pathological aspects. *Eur Neuropsychopharmacol, 24*(12), 1947-1953. doi: 10.1016/j.euroneuro.2014.01.020

Wharton, W., Gleason, C. E., Olson, S. R., Carlsson, C. M., & Asthana, S. (2012). Neurobiological underpinnings of the estrogen - mood relationship. *Curr Psychiatry Rev, 8*(3), 247-256. doi: 10.2174/157340012800792957

Whittingham, M. J., Stephens, P. A., Bradbury, R. B., & Freckleton, R. P. (2006). Why do we still use stepwise modelling in ecology and behaviour? *J Anim Ecol, 75*(5), 1182-1189. doi: 10.1111/j.1365-2656.2006.01141.x

Yalcin, M. M., Altinova, A. E., Cavnar, B., Bolayir, B., Akturk, M., Arslan, E., . . . Balos Toruner, F. (2017). Is thyroid autoimmunity itself associated with psychological well-being in euthyroid Hashimoto's thyroiditis? *Endocr J, 64*(4), 425-429. doi: 10.1507/endocrj.EJ16-0418

Zarit, S. H., Whetzel, C. A., Kim, K., Femia, E. E., Almeida, D. M., Rovine, M. J., & Klein, L. C. (2014). Daily stressors and adult day service use by family caregivers: Effects on depressive symptoms, positive mood, and dehydroepiandrosterone-sulfate. *Am J Geriatr Psychiatry, 22* (12), 1592-1602. doi: 10.1016/j.jagp.2014.01.013

Zografos, G. N., Perysinakis, I., & Vassilatou, E. (2014). Subclinical Cushing's syndrome: Current concepts and trends. *Hormones (Athens), 13*(3), 323-337. doi: 10.14310/horm.2002.1506