The Importance of Measuring Diurnal Cortisol (CAR and Beyond) -Fundamentals for Clinicians-

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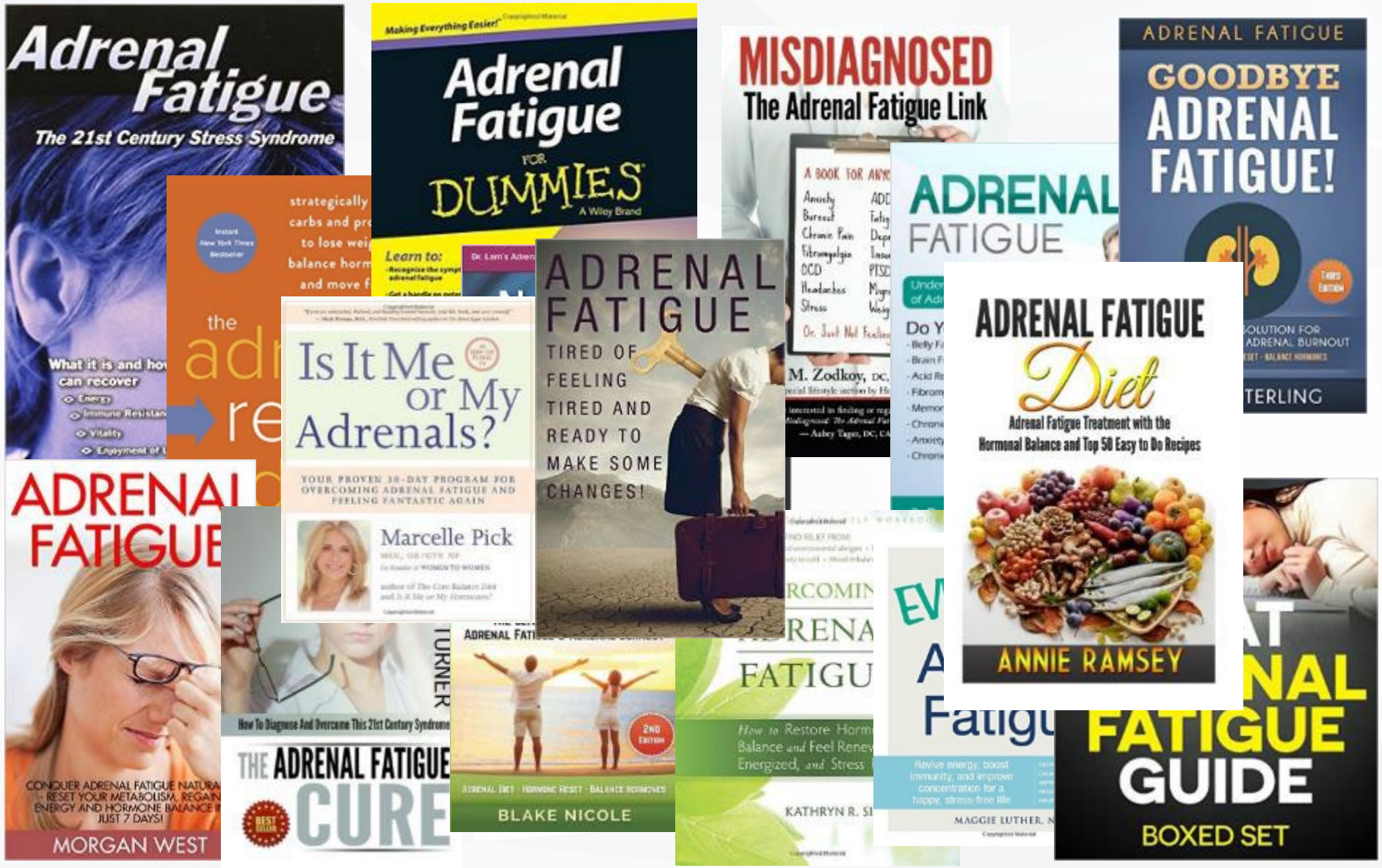
My “Stressful” Mission

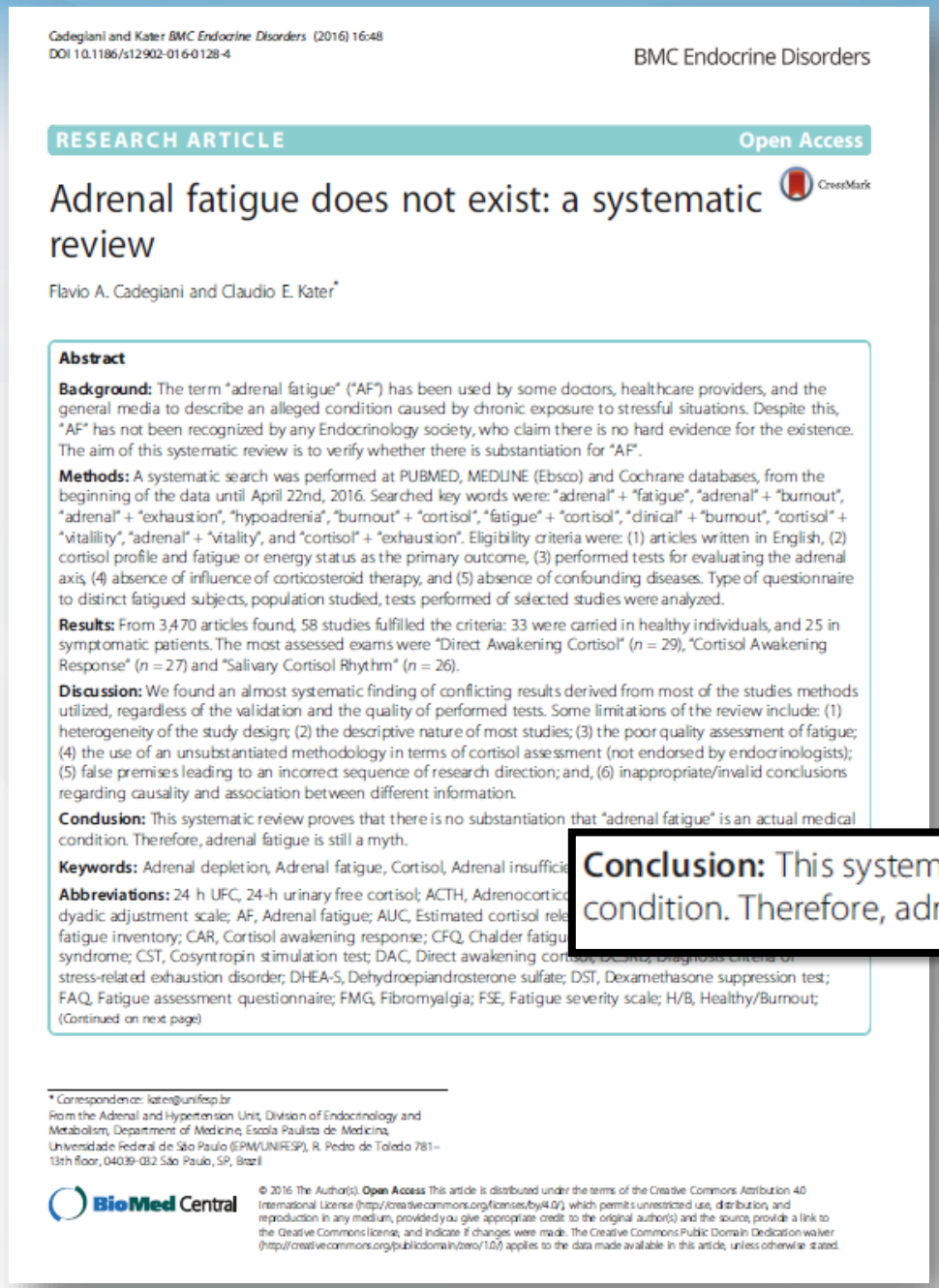
- To re-align the Functional Med. Community to the current research of HPA axis and stress dysfunction
- To expand the view of the HPA axis beyond the stress-response
- To create a common nomenclature around stress and HPA axis function that is useful and accurate for the healthcare and scientific community
- To encourage more uniformity in the laboratory testing for HPA axis function (units, nomenclature, collection timing and instructions etc.) and encourage test menu options that mirror published literature more closely.
- To promote more research related to testing and HPA axis interventions
- Help clinicians incorporate HPA axis therapies to prevent and treat stress-related chronic dysfunction

Clinicians as Researchers….N of 1+

- Clinicians that are investigating the underlying root cause(s) of complex chronic disease(s) in their patients using specialty tests need to know more than just how to “interpret” the results
  - Understand the fundamental research that undergirds the test which has been performed (what is it measuring, what does it mean)
  - Think about other implications of the test results- beyond the immediate and direct interpretation
  - Be keenly aware that how (and when) the samples were collected impact interpretation of the findings
  - Be able to explain to peers and critics the clinical benefits for specialty testing that is not common for diagnosing “diseases”

Popular Language for Stress





Cadegiani and Kater *BMC Endocrine Disorders* (2016) 16:48
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BMC Endocrine Disorders

RESEARCH ARTICLE Open Access

Adrenal fatigue does not exist: a systematic review

Flavio A. Cadegiani and Claudio E. Kater*

Abstract

Background: The term "adrenal fatigue" ("AF") has been used by some doctors, healthcare providers, and the general media to describe an alleged condition caused by chronic exposure to stressful situations. Despite this, "AF" has not been recognized by any Endocrinology society, who claim there is no hard evidence for the existence. The aim of this systematic review is to verify whether there is substantiation for "AF".

Methods: A systematic search was performed at PUBMED, MEDLINE (Ebsco) and Cochrane databases, from the beginning of the data until April 22nd, 2016. Searched key words were: "adrenal" + "fatigue", "adrenal" + "burnout", "adrenal" + "exhaustion", "hypoadrenia", "burnout" + "cortisol", "fatigue" + "cortisol", "clinical" + "burnout", "cortisol" + "vitality", "adrenal" + "vitality", and "cortisol" + "exhaustion". Eligibility criteria were: (1) articles written in English, (2) cortisol profile and fatigue or energy status as the primary outcome, (3) performed tests for evaluating the adrenal axis, (4) absence of influence of corticosteroid therapy, and (5) absence of confounding diseases. Type of questionnaire to distinct fatigued subjects, population studied, tests performed of selected studies were analyzed.

Results: From 3,470 articles found, 58 studies fulfilled the criteria: 33 were carried in healthy individuals, and 25 in symptomatic patients. The most assessed exams were "Direct Awakening Cortisol" ($n = 29$), "Cortisol Awakening Response" ($n = 27$) and "Salivary Cortisol Rhythm" ($n = 26$).

Discussion: We found an almost systematic finding of conflicting results derived from most of the studies methods utilized, regardless of the validation and the quality of performed tests. Some limitations of the review include: (1) heterogeneity of the study design; (2) the descriptive nature of most studies; (3) the poor quality assessment of fatigue; (4) the use of an unsubstantiated methodology in terms of cortisol assessment (not endorsed by endocrinologists); (5) false premises leading to an incorrect sequence of research direction; and, (6) inappropriate/invalid conclusions regarding causality and association between different information.

Conclusion: This systematic review proves that there is no substantiation that "adrenal fatigue" is an actual medical condition. Therefore, adrenal fatigue is still a myth.

Keywords: Adrenal depletion, Adrenal fatigue, Cortisol, Adrenal insuffici

Abbreviations: 24 h UFC, 24-h urinary free cortisol; ACTH, Adrenocortic dyadic adjustment scale; AF, Adrenal fatigue; AUC, Estimated cortisol rele fatigue inventory; CAR, Cortisol awakening response; CFQ, Chalder fatigu syndrome; CST, Cosyntropin stimulation test; DAC, Direct awakening cort stress-related exhaustion disorder; DHEA-S, Dehydroepiandrosterone sulfate; DST, Dexamethasone suppression test; FAQ, Fatigue assessment questionnaire; FMG, Fibromyalgia; FSE, Fatigue severity scale; H/B, Healthy/Burnout;

(Continued on next page)

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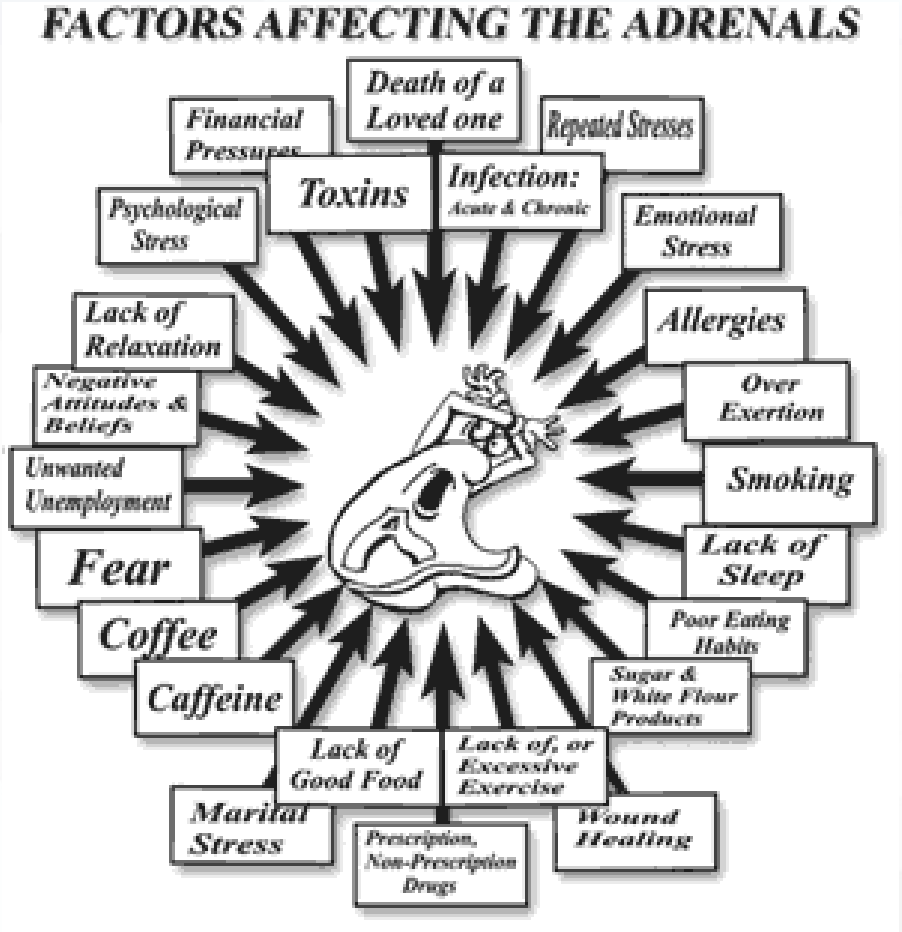
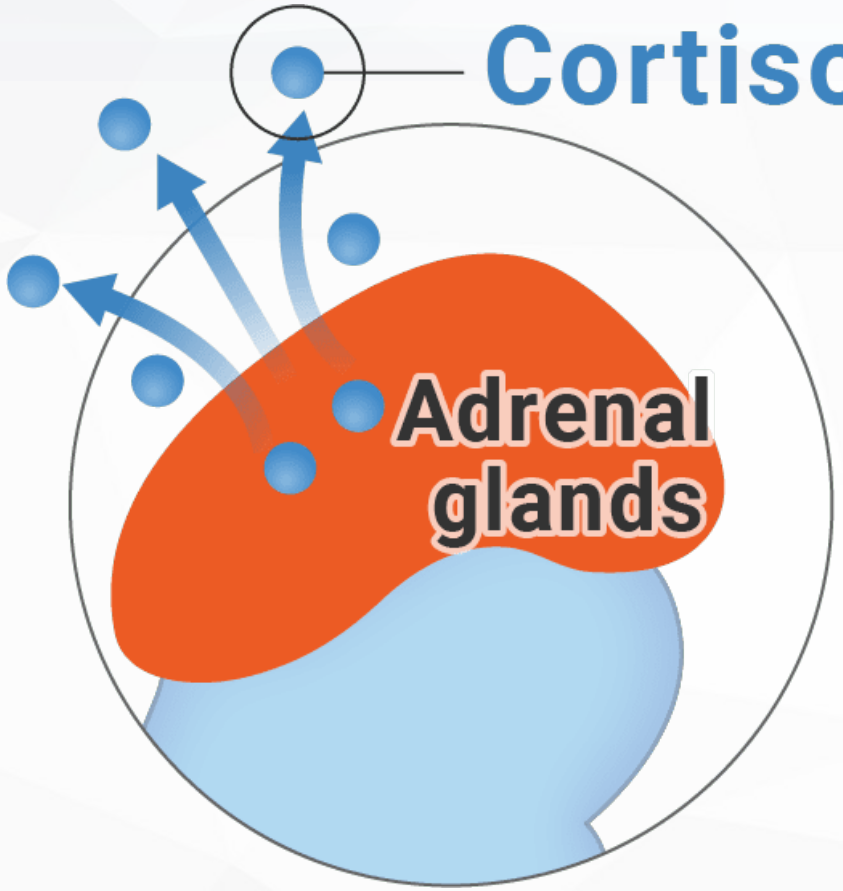
Yes- this is as ridiculous as you would imagine but, it helps to bolster the common, but incorrect, perception that investigating stress-related chronic disease in the clinic is mostly baseless. After all, it is published literature!

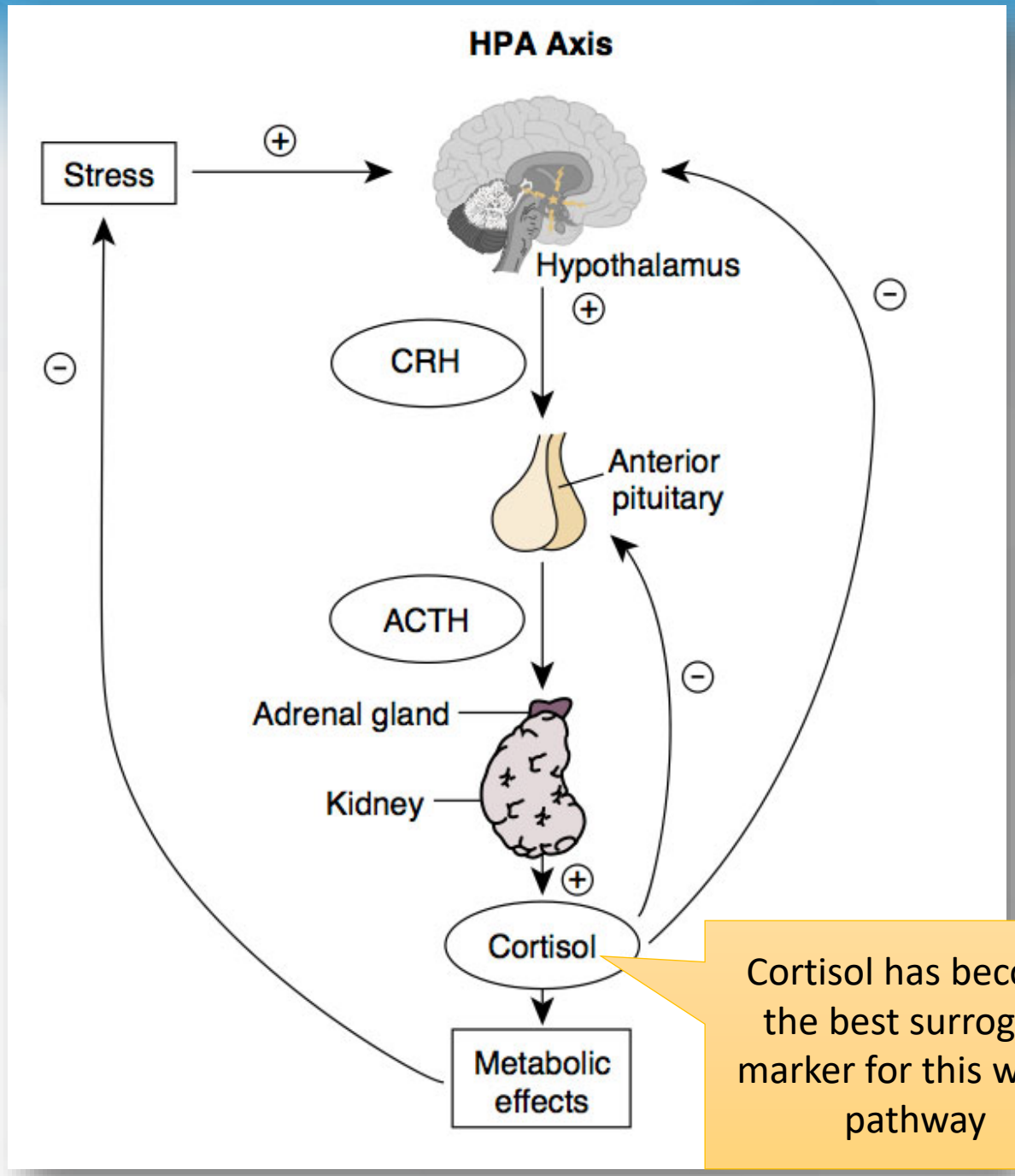
Conclusion: This systematic review proves that there is no substantiation that "adrenal fatigue" is an actual medical condition. Therefore, adrenal fatigue is still a myth.

When did "Stress" become "Adrenals"?



We think “Adrenals” because we test Cortisol

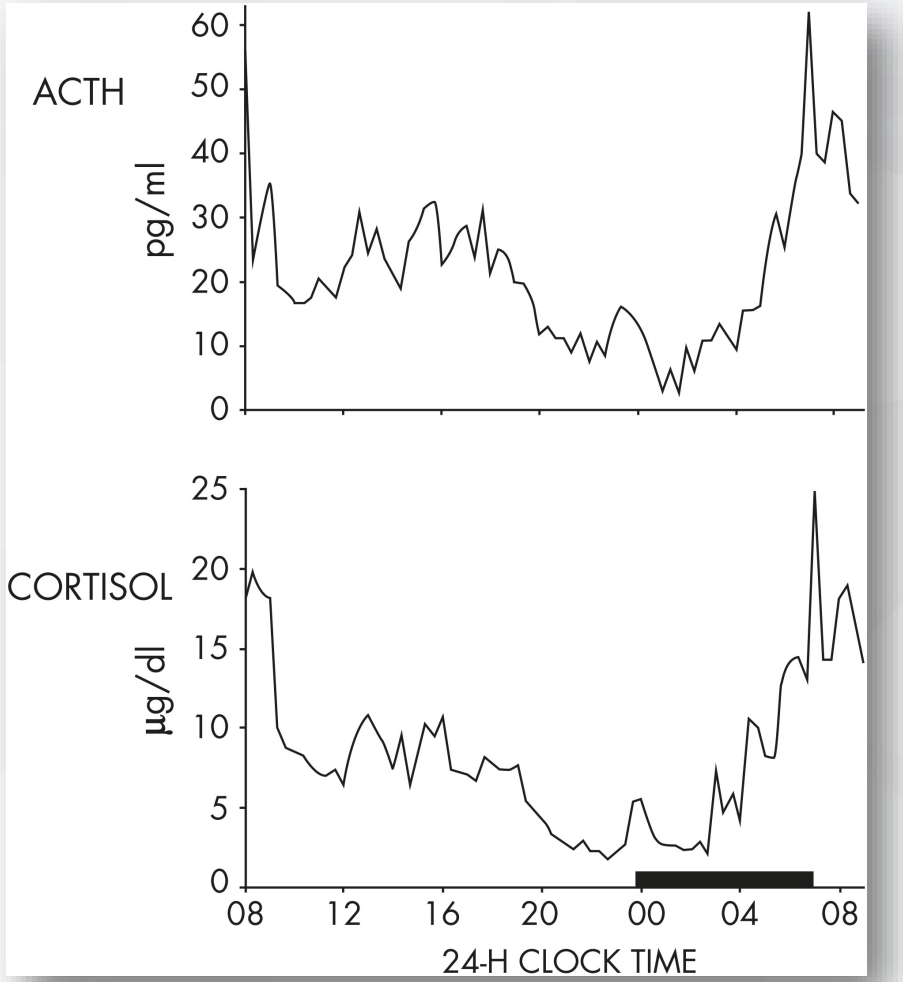




What are we Really Trying to Measure or Understand?

- The Relationship between a Stressor and its Metabolic Effects
- The Resilience of a Person's Stress Response System to withstand additional Stressors (reserve capacity)
- How Acute and Chronic Stressors have affected the Circadian nature of the HPA axis
- What are the most likely therapies or changes that can increase a person's ability to improve HPA axis mediated functions.

Cortisol as a surrogate for ACTH



Plasma ACTH and Cortisol measured every 15 minutes in a healthy young man under normal (basal) conditions.

Note the Ultradian Rhythm of ~60-90 minutes of both ACTH and Cortisol

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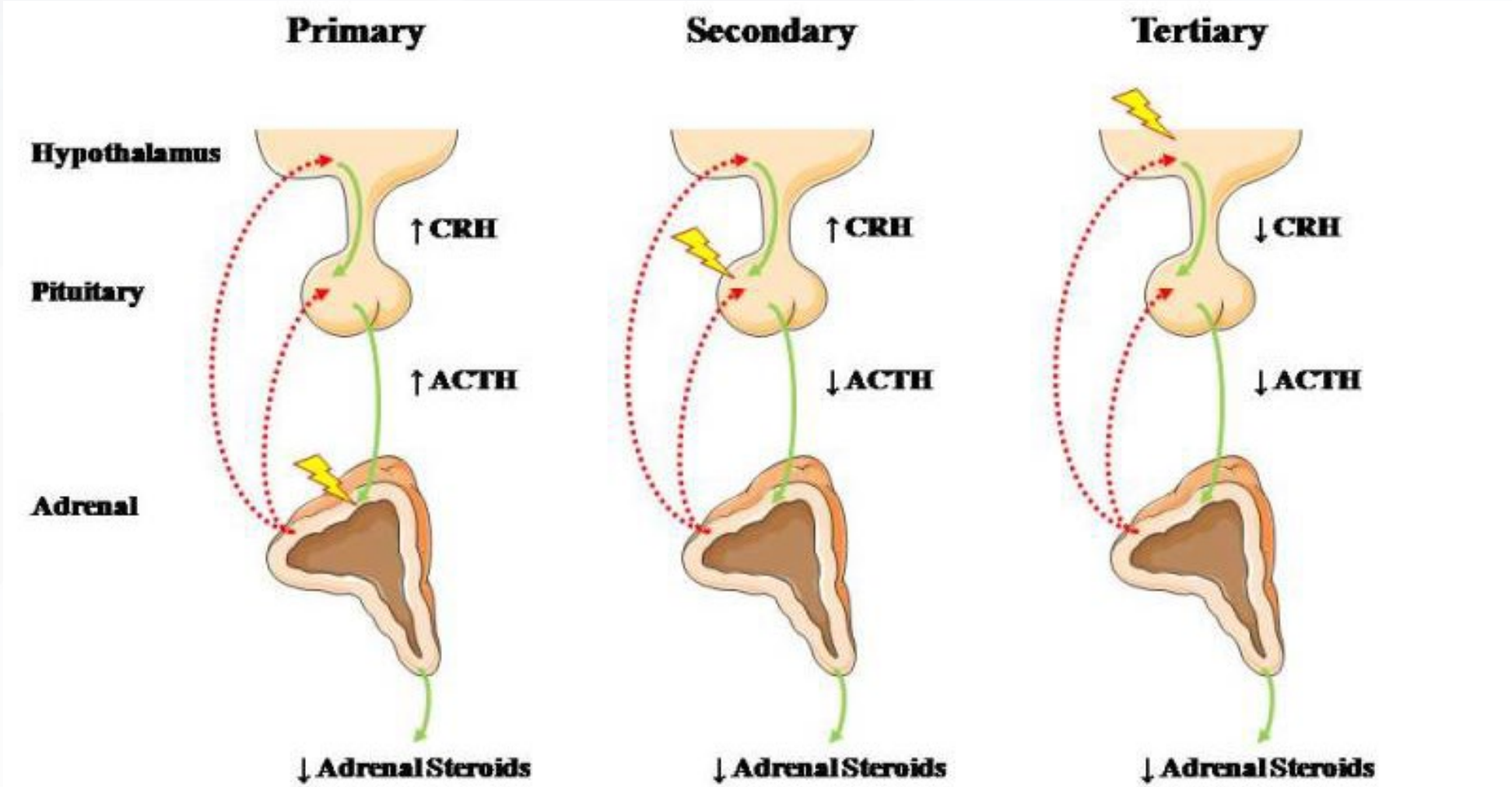
The Nomenclature of Adrenal Insufficiency



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A new view on hypocortisolism

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KEYWORDS
Hypocortisolism;
Cortisol;
Allostatic load index;
Developmental model;
Protective effects

Summary Low cortisol levels have been observed in patients with different stress-related disorders such as chronic fatigue syndrome, fibromyalgia, and post-traumatic stress disorder. Data suggest that these disorders are characterized by a symptom triad of enhanced stress sensitivity, pain, and fatigue. This overview will present data on the development, mechanisms and consequences of hypocortisolism on different bodily systems. We propose that the phenomenon of hypocortisolism may occur after a prolonged period of hyperactivity of the hypothalamic-pituitary-adrenal axis due to chronic stress as illustrated in an animal model. Further evidence suggests that despite symptoms such as pain, fatigue and high stress sensitivity, hypocortisolism may also have beneficial effects on the organism. This assumption will be underlined by some studies suggesting protective effects of hypocortisolism for the individual.

1. Introduction

Since the work of Selye (1936), stress has been associated with an activation of the hypothalamic-pituitary-adrenal (HPA) axis resulting in an increased release of cortisol from the adrenal glands. In recent years, a phenomenon has been described that is characterized by a hyporesponsiveness on different levels of the HPA axis in a number of stress-related states. This phenomenon, termed 'hypocortisolism', has been reported in about 20-25% of patients with stress-related disorders such as chronic fatigue syndrome (CFS), chronic pelvic pain (CPP), fibromyalgia (FMS), post-traumatic stress disorder (PTSD), irritable bowel syndrome (IBS), low back pain (LBP), burnout, and atypical depression (Griep et al., 1998; Heim et al., 1998, 2000; Pruessner et al., 1999; Gold and Chrousos, 2002; Gur et al., 2004; Roberts et al., 2004; Rohleder et al., 2004). When hypocortisolemic, all these disorders may share affiliated syndromes characterized by a triad of enhanced stress sensitivity, pain, and fatigue.

Suggesting a common endocrinological pathway characterized by a diminished glucocorticoid efficacy in these disorders, we will discuss the development and mechanisms of hypocortisolism based on animal and human studies. In addition, consequences of a hypocortisolemic stress response on two other bodily systems, the sympathetic nervous system (SNS) and the immune system will be addressed. Finally, we will hypothesize about

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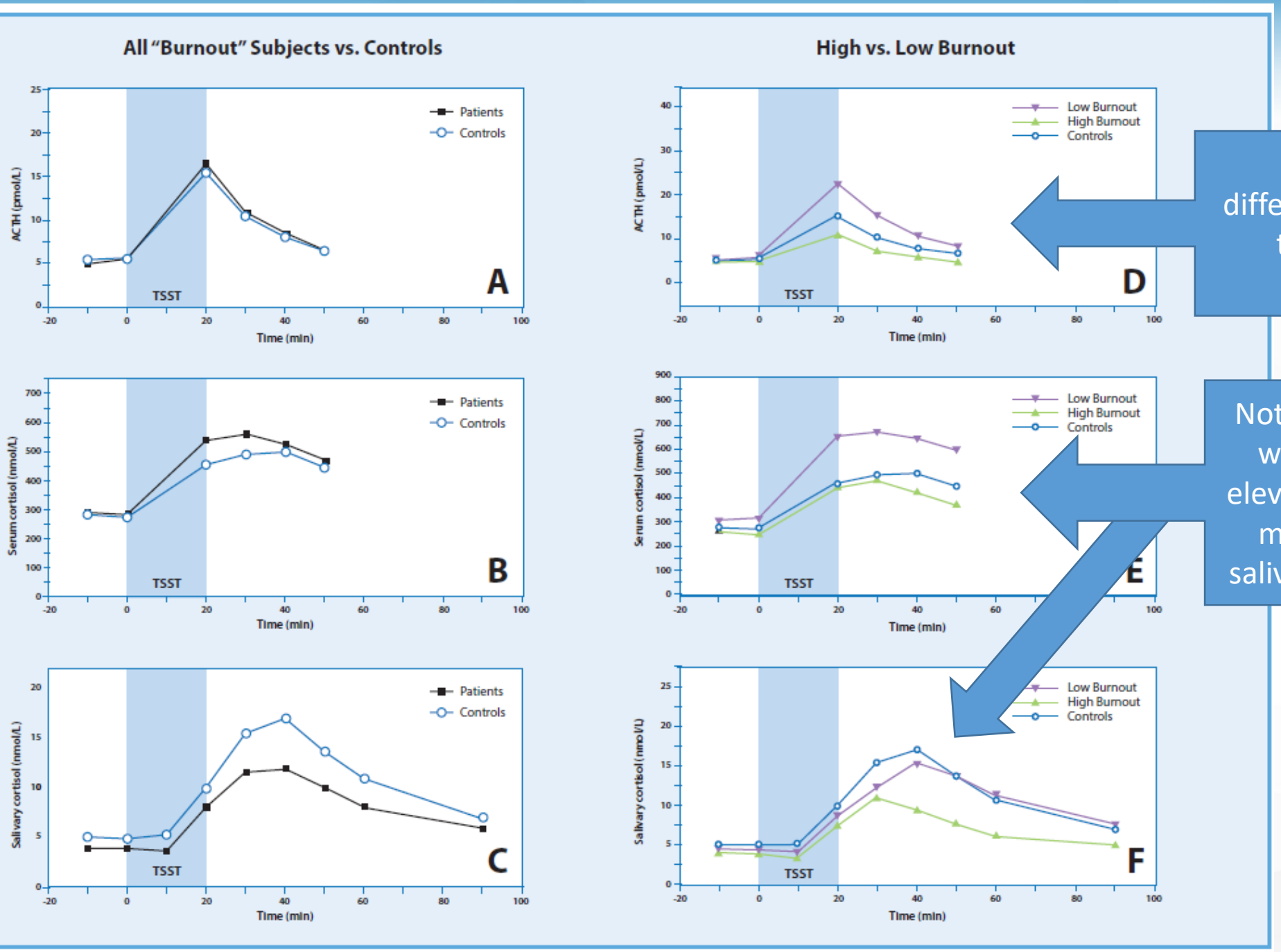
Adaptation to chronic stress: could it be viewed as secondary or tertiary "AI"?

Based on these results we propose that hypocortisolism is a protective response dampening chronic HPA axis activity and thereby reducing the damaging effects of the glucocorticoid response to daily hassles at the expense of symptoms such as high stress sensitivity, pain, and fatigue.

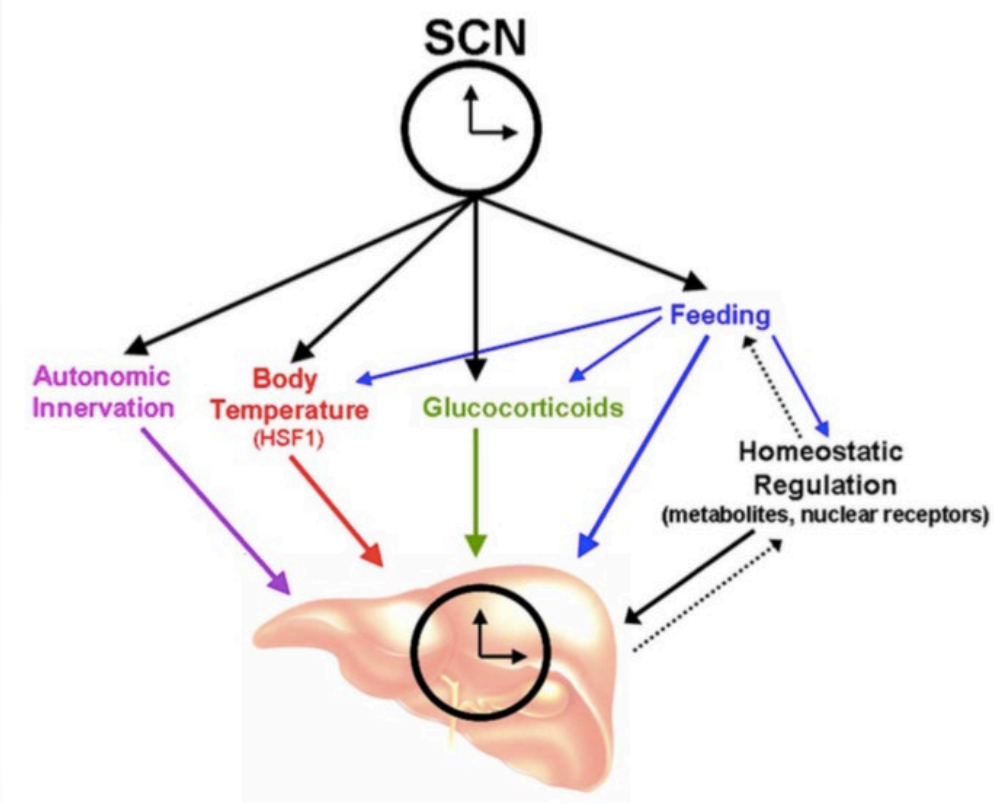
Front Psychiatry. 2015 Feb 2;6:8.

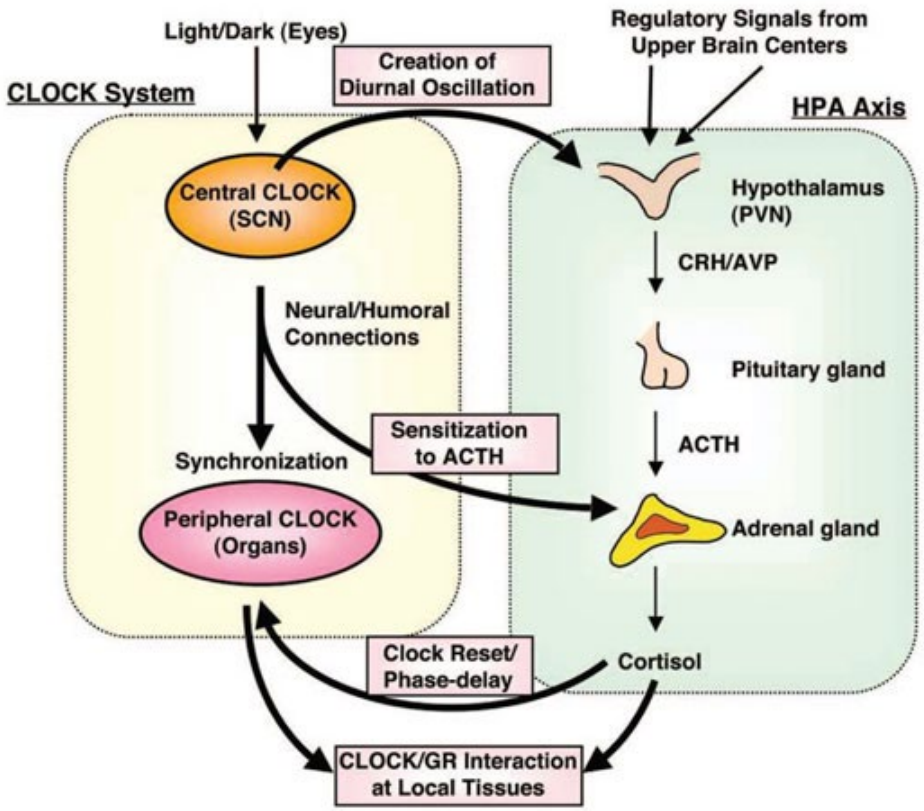


ACTH Levels differentiate those in true HPA axis "Burnout"

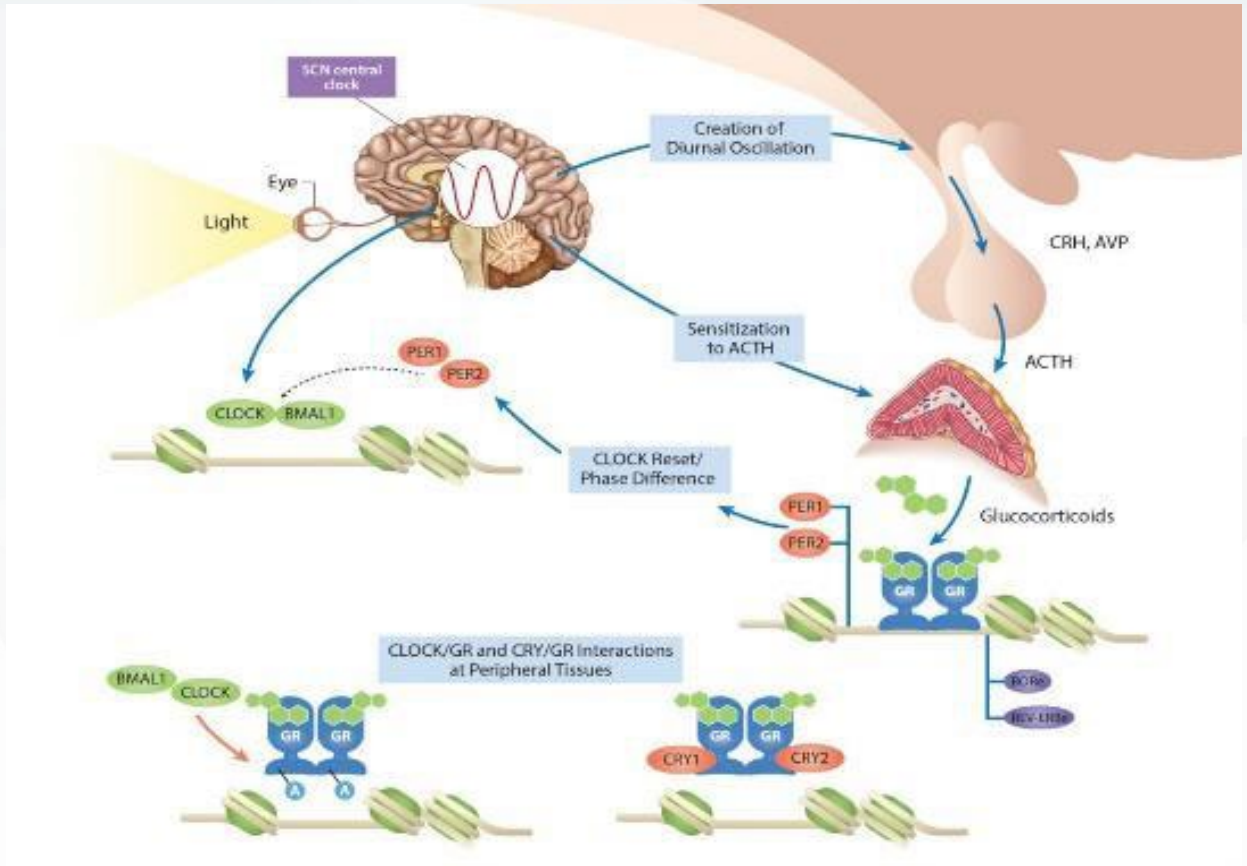
Note that in subjects with low burnout elevated total Cortisol mirrors ACTH but salivary levels do not!

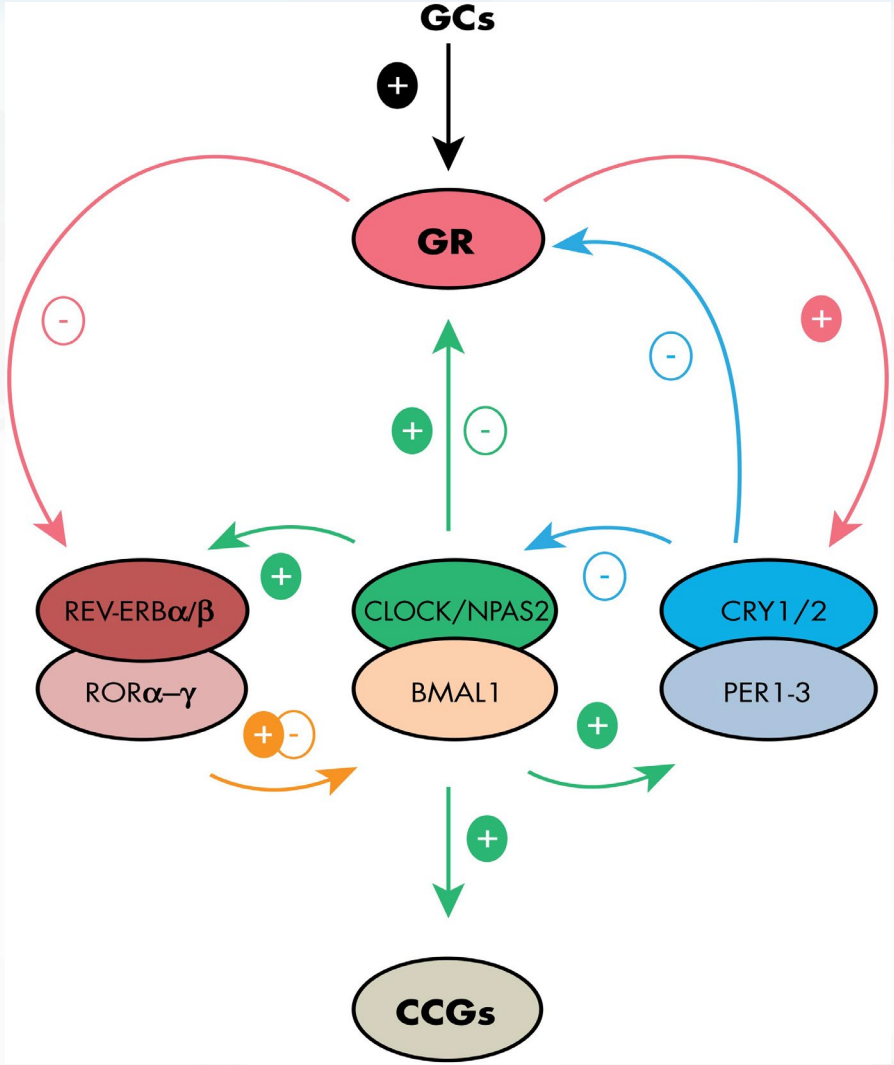
My Last Seminar for DUTCH: Circadian Function and Cortisol





Molecular feedback loops generating circadian rhythmicity in both central and peripheral tissues.





Guilliams TG, The Role of Stress and the HPA Axis in Chronic Disease Management- 2015

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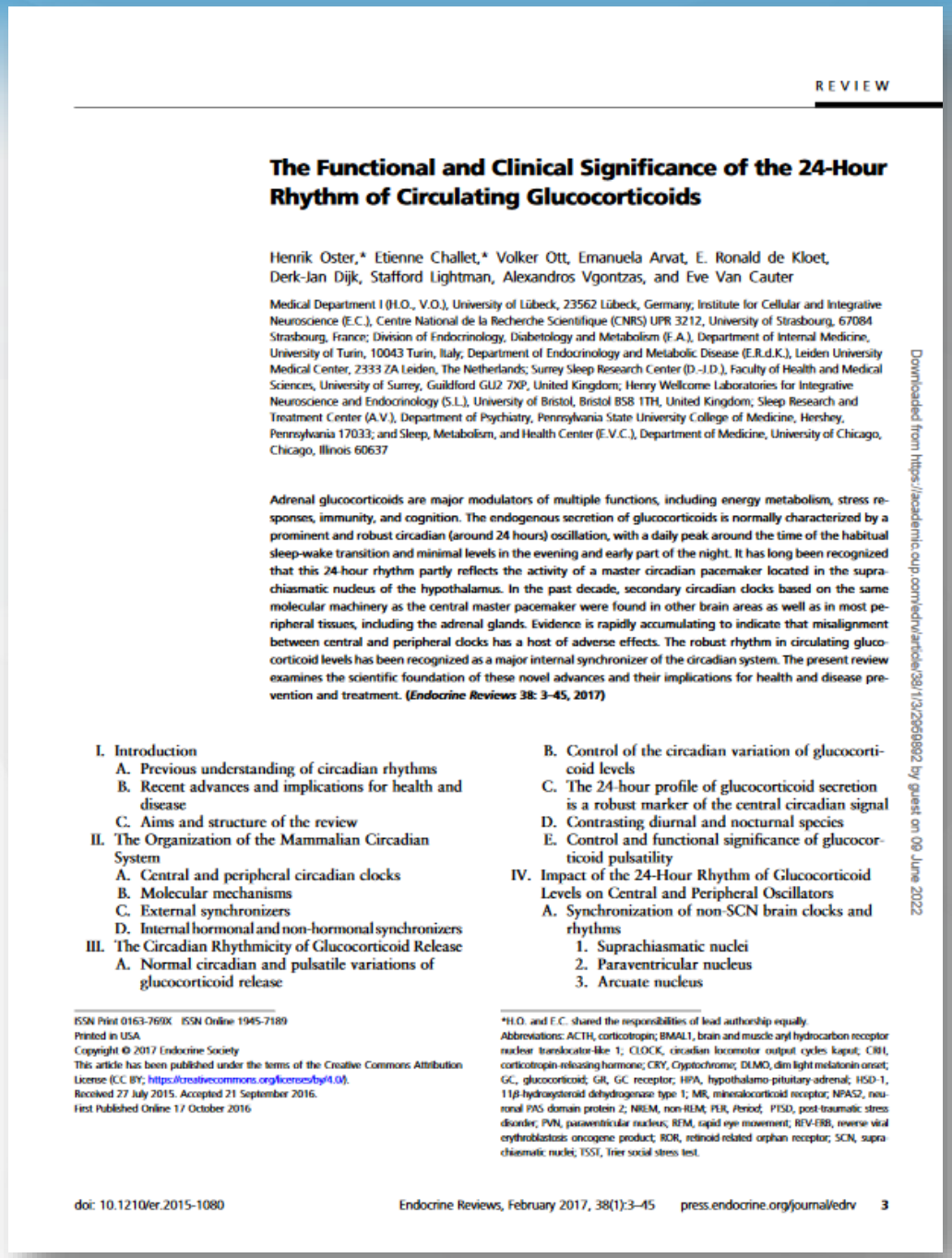

REVIEW

The Functional and Clinical Significance of the 24-Hour Rhythm of Circulating Glucocorticoids

Henrik Oster,* Etienne Challet,* Volker Ott, Emanuela Arvat, E. Ronald de Kloet, Derk-Jan Dijk, Stafford Lightman, Alexandros Vgontzas, and Eve Van Cauter

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Adrenal glucocorticoids are major modulators of multiple functions, including energy metabolism, stress responses, immunity, and cognition. The endogenous secretion of glucocorticoids is normally characterized by a prominent and robust circadian (around 24 hours) oscillation, with a daily peak around the time of the habitual sleep-wake transition and minimal levels in the evening and early part of the night. It has long been recognized that this 24-hour rhythm partly reflects the activity of a master circadian pacemaker located in the suprachiasmatic nucleus of the hypothalamus. In the past decade, secondary circadian clocks based on the same molecular machinery as the central master pacemaker were found in other brain areas as well as in most peripheral tissues, including the adrenal glands. Evidence is rapidly accumulating to indicate that misalignment between central and peripheral clocks has a host of adverse effects. The robust rhythm in circulating glucocorticoid levels has been recognized as a major internal synchronizer of the circadian system. The present review examines the scientific foundation of these novel advances and their implications for health and disease prevention and treatment. (*Endocrine Reviews* 38: 3–45, 2017)

I. Introduction
  A. Previous understanding of circadian rhythms
  B. Recent advances and implications for health and disease
  C. Aims and structure of the review
II. The Organization of the Mammalian Circadian System
  A. Central and peripheral circadian clocks
  B. Molecular mechanisms
  C. External synchronizers
  D. Internal hormonal and non-hormonal synchronizers
III. The Circadian Rhythmicity of Glucocorticoid Release
  A. Normal circadian and pulsatile variations of glucocorticoid release
  B. Control of the circadian variation of glucocorticoid levels
  C. The 24-hour profile of glucocorticoid secretion is a robust marker of the central circadian signal
  D. Contrasting diurnal and nocturnal species
  E. Control and functional significance of glucocorticoid pulsatility
IV. Impact of the 24-Hour Rhythm of Glucocorticoid Levels on Central and Peripheral Oscillators
  A. Synchronization of non-SCN brain clocks and rhythms
    1. Suprachiasmatic nuclei
    2. Paraventricular nucleus
    3. Arcuate nucleus

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*H.O. and E.C. shared the responsibilities of lead authorship equally.

Abbreviations: ACTH, corticotropin; BMAL1, brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1; CLOCK, circadian locomotor output cycles kaput; CRH, corticotropin-releasing hormone; CRY, Cryptochrome; DLMO, dim light melatonin onset; GC, glucocorticoid; GR, GC receptor; HPA, hypothalamo-pituitary-adrenal; HSD-1, 11β-hydroxysteroid dehydrogenase type 1; MR, mineralocorticoid receptor; NPAS2, neuronal PAS domain protein 2; NREM, non-REM; PER, *Period*; PTSD, post-traumatic stress disorder; PVN, paraventricular nucleus; REM, rapid eye movement; REV-ERB, reverse viral erythroblastosis oncogene product; ROR, retinoid related orphan receptor; SCN, suprachiasmatic nuclei; TSST, Trier social stress test.

- Must Read Review of How the Diurnal Rhythm of Cortisol is affected by (or diagnostic of) certain common conditions or lifestyle decisions.
- *Endocrine Reviews*, Volume 38, Issue 1, 1 February 2017, Pages 3–45, https://doi.org/10.1210/er.2015-1080

frontiers in Endocrinology

REVIEW
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Stress-Related and Circadian Secretion and Target Tissue Actions of Glucocorticoids: Impact on Health

Nicolas C. Nicolaides[1,2], Evangelia Charmandari[1,2], Tomoshige Kino[3] and George P. Chrousos[1,2]*

[1] Division of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, National and Kapodistrian University of Athens Medical School, 'Aghia Sophia' Children's Hospital, Athens, Greece, [2] Division of Endocrinology and Metabolism, Center of Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece, [3] Division of Experimental Genetics, Sidra Medical and Research Center, Doha, Qatar

Living organisms are highly complex systems that must maintain a dynamic equilibrium or homeostasis that requires energy to be sustained. Stress is a state in which several extrinsic or intrinsic disturbing stimuli, the stressors, threaten, or are perceived as threatening, homeostasis. To achieve homeostasis against the stressors, organisms have developed a highly sophisticated system, the stress system, which provides neuroendocrine adaptive responses, to restore homeostasis. These responses must be appropriate in terms of size and/or duration; otherwise, they may sustain life but be associated with detrimental effects on numerous physiologic functions of the organism, leading to a state of disease-causing disturbed homeostasis or cacostasis. In addition to facing a broad spectrum of external and/or internal stressors, organisms are subject to recurring environmental changes associated with the rotation of the planet around itself and its revolution around the sun. To adjust their homeostasis and to synchronize their activities to day/night cycles, organisms have developed an evolutionarily conserved biologic system, the "clock" system, which influences several physiologic functions in a circadian fashion. Accumulating evidence suggests that the stress system is intimately related to the circadian clock system, with dysfunction of the former resulting in dysregulation of the latter and *vice versa*. In this review, we describe the functional components of the two systems, we discuss their multilevel interactions, and we present how excessive or prolonged activity of the stress system affects the circadian rhythm of glucocorticoid secretion and target tissue effects.

Keywords: stress, stress system, hypothalamic–pituitary–adrenal axis, glucocorticoids, glucocorticoid receptor, circadian endocrine rhythms, clock system

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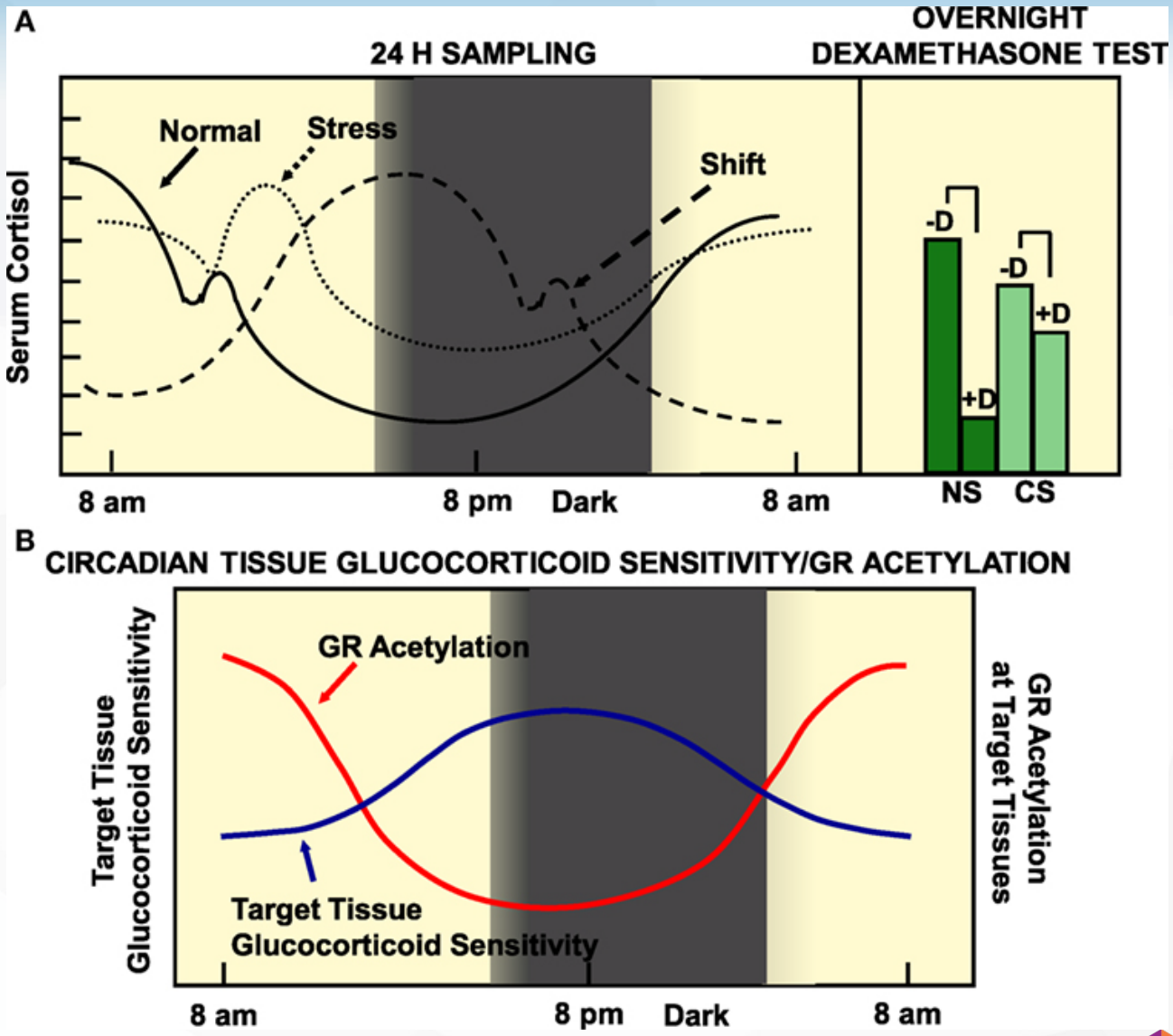
THE STRESS SYSTEM

The stress system consists of the locus caeruleus/norepinephrine autonomic nervous systems and the hypothalamic–pituitary–adrenal (HPA) axis. These two components interact with each other, as well as with other brain subsystems, such as the mesocortical and the mesolimbic dopaminergic system, which is involved in reward and motivation, the central nucleus of the amygdalae, which generate fear and/or anger, and the arcuate nucleus of the hypothalamus participating in



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The human stress response

Georgina Russell and Stafford Lightman**

Abstract | The human stress response has evolved to maintain homeostasis under conditions of real or perceived stress. This objective is achieved through autoregulatory neural and hormonal systems in close association with central and peripheral clocks. The hypothalamic–pituitary–adrenal axis is a key regulatory pathway in the maintenance of these homeostatic processes. The end product of this pathway — cortisol — is secreted in a pulsatile pattern, with changes in pulse amplitude creating a circadian pattern. During acute stress, cortisol levels rise and pulsatility is maintained. Although the initial rise in cortisol follows a large surge in adrenocorticotropic hormone levels, if long-term inflammatory stress occurs, adrenocorticotropic hormone levels return to near basal levels while cortisol levels remain raised as a result of increased adrenal sensitivity. In chronic stress, hypothalamic activation of the pituitary changes from corticotropin-releasing hormone-dominant to arginine vasopressin-dominant, and cortisol levels remain raised due at least in part to decreased cortisol metabolism. Acute elevations in cortisol levels are beneficial to promoting survival of the fittest as part of the fight-or-flight response. However, chronic exposure to stress results in reversal of the beneficial effects, with long-term cortisol exposure becoming maladaptive, which can lead to a broad range of problems including the metabolic syndrome, obesity, cancer, mental health disorders, cardiovascular disease and increased susceptibility to infections. Neuroimmunoendocrine modulation in disease states and glucocorticoid-based therapeutics are also discussed.

Zeitgebers
Cues that entrain or synchronize the body's 24-h cycle

Ultradian rhythms
Biological rhythms that occur with a frequency of <24 h

Circadian clock
A biochemical oscillator with phases synchronized with solar time

In response to a stressor, the body activates multiple coordinated and dynamic processes to restore homeostasis, preserve life and ultimately achieve evolutionary success for the species. The importance of endocrine systems in this homeostatic regulation has been known since the early studies of Hans Selye[1] in the 1930s, when activation of the sympatho–adrenomedullary (SAM) and hypothalamic–pituitary–adrenal (HPA) axes was described in response to physical injury and exertion as well as perceived psychological threats. Interestingly, anticipation of these threats is itself a very potent activator of these systems[2]. Homeostatic processes also interact with internal and external Zeitgebers such as the light–dark cycle and internal body clocks[3,4]. These internal clocks enable the body to anticipate regular changes in the environment to ensure optimal fitness across the 24 h and thus the best chance for survival[5]. The human stress response is an additional homeostatic mechanism that provides a better chance of survival when the body is under threat and mobilizes neural and hormonal networks to optimize cognitive, cardiovascular, immunological and metabolic function (FIG. 1). In this Review we discuss how the HPA axis helps achieve and maintain homeostasis. We will show how it utilizes rhythmic 24-h patterns of secretion to achieve appropriate tissue activity at different times of the day, and faster ultradian rhythms to optimize tissue-specific glucocorticoid signalling and maintain the rapid reactivity necessary for a stress response system.

Circadian clocks

In the absence of internal or external stressors, the integrity of physiological systems is maintained in a dynamic fashion over 24 h by an internal circadian clock that anticipates the changes occurring over the 24-h day. In the past, the neurocentric hierarchical view was that body rhythms were controlled from a master clock in the hypothalamic suprachiasmatic nucleus (SCN)[6]. Now, it is very clear that peripheral clocks also exist in most, if not all, tissues of the body, which have their own autonomous transcriptional autoregulatory feedback loops[7]. The core clock genes, both in the SCN and peripheral clocks, are *CLOCK* and *BMAL1*. Activation of these genes generates a heterodimer of BMAL1 with either CLOCK or NPAS2, which bind at promoter elements called E-boxes to drive genes encoding period 1–3, cryptochrome 1–2 and nuclear receptor subfamily 1–2. The resultant proteins then feedback to repress *BMAL1* by a series of feedback loops, generating a 24-h rhythm[8,9] that allows time-of-day-dependent regulation of downstream genomic pathways. This rhythmicity is crucial for homeostasis. The body can only behave optimally when all

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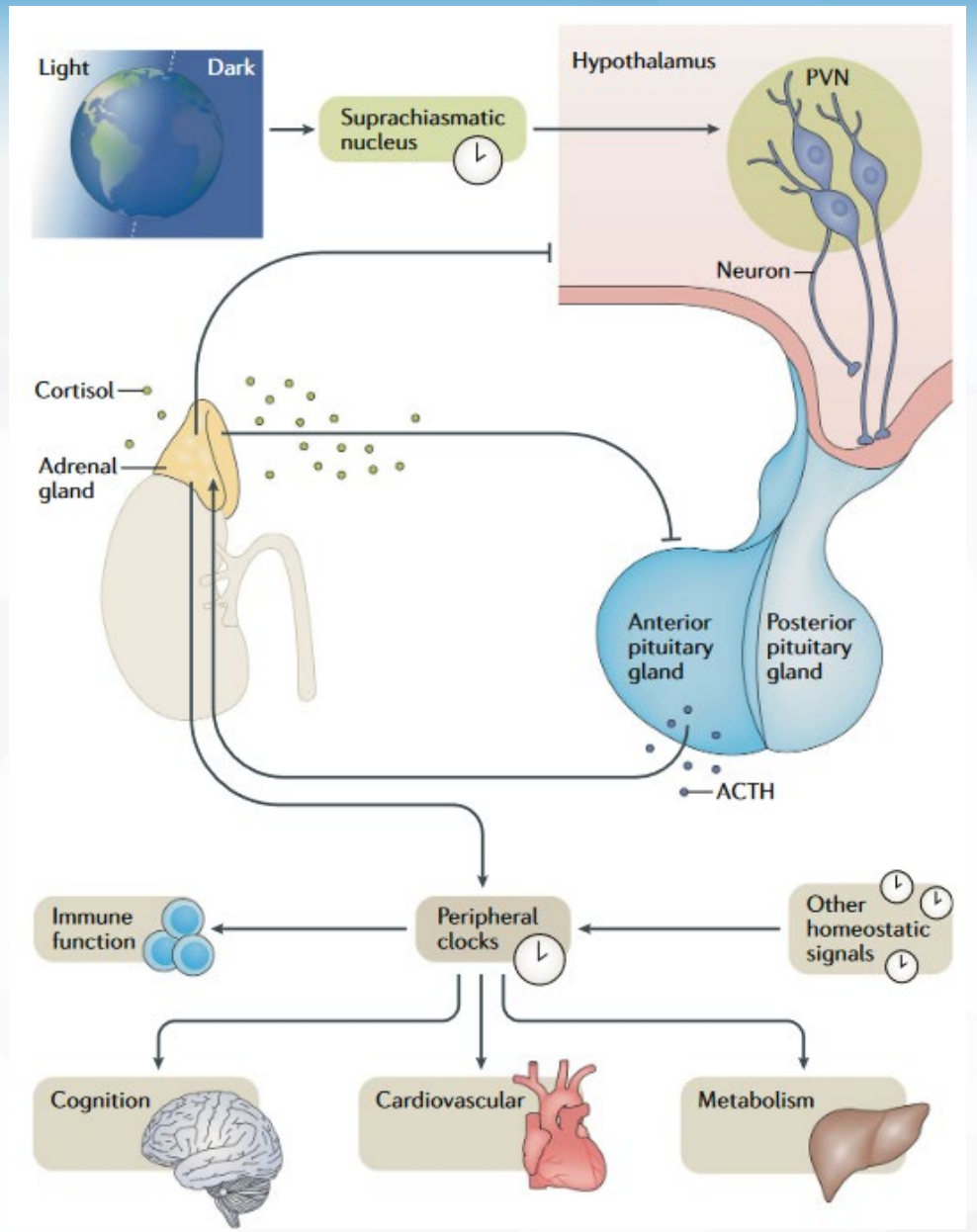

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In response to a stressor, the body activates multiple coordinated and dynamic processes to restore homeostasis, preserve life and ultimately achieve evolutionary success for the species. The importance of endocrine systems in this homeostatic regulation has been known since the early studies of Hans Selye[1] in the 1930s, when activation of the sympatho–adrenomedullary (SAM) and hypothalamic–pituitary–adrenal (HPA) axes was described in response to physical injury and exertion as well as perceived psychological threats. Interestingly, anticipation of these threats is itself a very potent activator of these systems[2]. Homeostatic processes also interact with internal and external Zeitgebers such as the light–dark cycle and internal body clocks[3,4]. These internal clocks enable the body to anticipate regular changes in the environment to ensure optimal fitness across the 24 h and thus the best chance for survival[5]. The human stress response is an additional homeostatic mechanism that provides a better chance of survival when the body is under threat and mobilizes neural and hormonal networks to optimize cognitive, cardiovascular, immunological and metabolic function (FIG. 1). In this Review we discuss how the HPA axis helps achieve and maintain homeostasis. We will show how it utilizes rhythmic 24-h patterns of secretion to achieve appropriate tissue activity at different times of the day, and faster ultradian rhythms to optimize tissue-specific glucocorticoid signalling and maintain the rapid reactivity necessary for a stress response system.

Circadian clocks

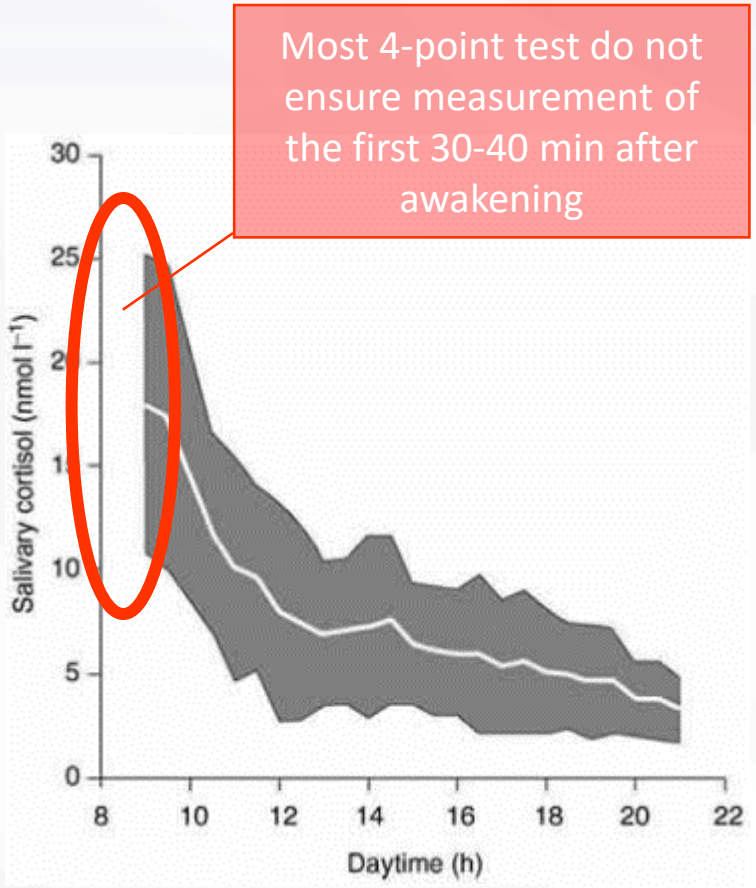
In the absence of internal or external stressors, the integrity of physiological systems is maintained in a dynamic fashion over 24 h by an internal circadian clock that anticipates the changes occurring over the 24-h day. In the past, the neurocentric hierarchical view was that body rhythms were controlled from a master clock in the hypothalamic suprachiasmatic nucleus (SCN)[6]. Now, it is very clear that peripheral clocks also exist in most, if not all, tissues of the body, which have their own autonomous transcriptional autoregulatory feedback loops[7]. The core clock genes, both in the SCN and peripheral clocks, are *CLOCK* and *BMAL1*. Activation of these genes generates a heterodimer of BMAL1 with either CLOCK or NPAS2, which bind at promoter elements called E-boxes to drive genes encoding period 1–3, cryptochrome 1–2 and nuclear receptor subfamily 1–2. The resultant proteins then feedback to repress *BMAL1* by a series of feedback loops, generating a 24-h rhythm[8,9] that allows time-of-day-dependent regulation of downstream genomic pathways. This rhythmicity is crucial for homeostasis. The body can only behave optimally when all

If we are to understand the growing epidemic of stress-related human disease, we need to go back to first principles and understand not only the mechanisms underlying the regulation of our patterns of physiological activity and hormone secretion — particularly over the important and notoriously difficult nadir period during sleep — but also why they are important for the maintenance of health. If we are going to aspire to an objective of optimal personalized medicine, we need to devise methods not only to measure dynamic basal patterns of hormonal metabolic and immune functioning over the whole day, but also novel therapeutic interventions to counteract the causes of environmental-related and/or stress-related illness.

Nature Reviews Endocrinology **volume 15**, pages 525–534 (2019)

Standard 4-point salivary test
A good start, but opportunities to expand

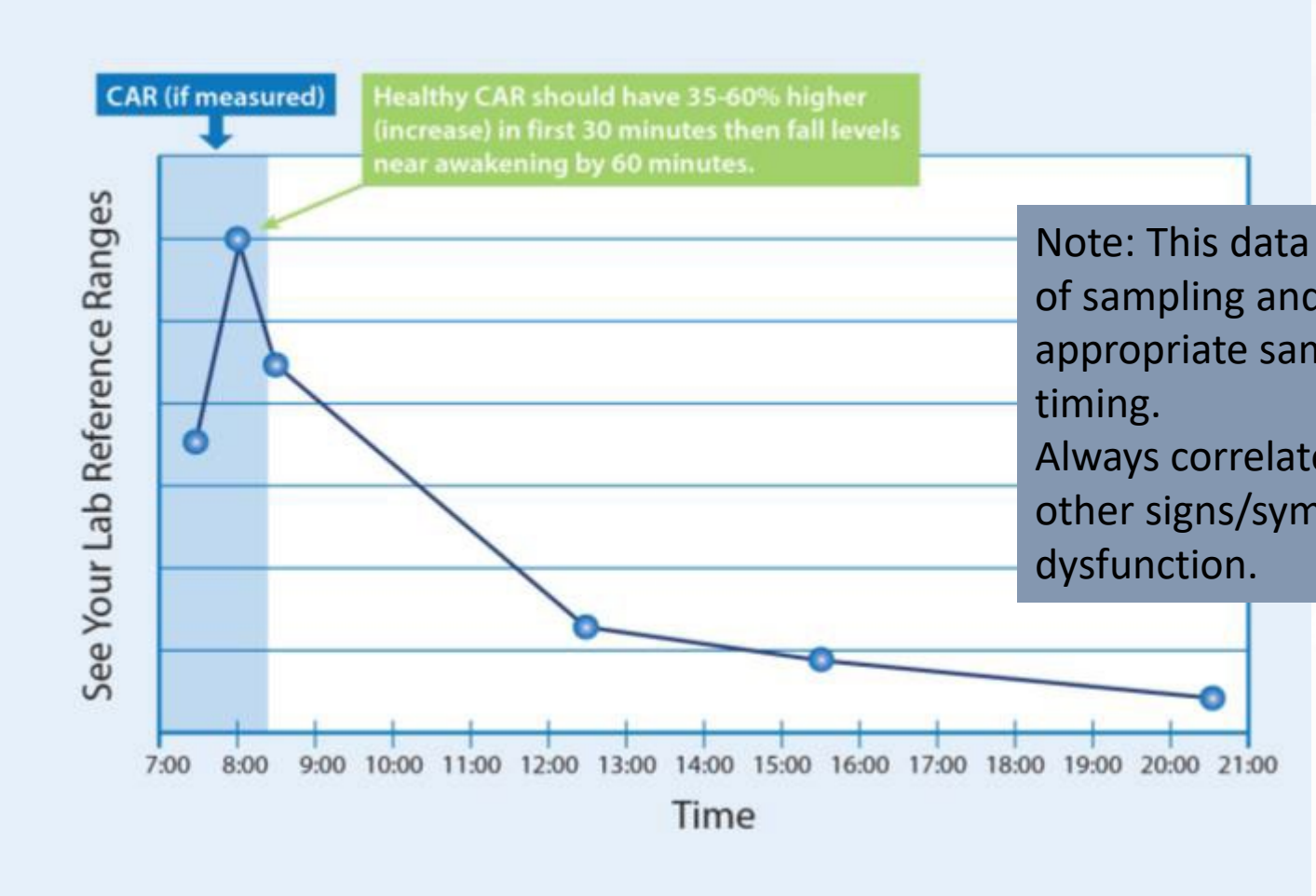
Normal (unprovoked) values of salivary cortisol during the day



C Kirschbaum and D H Hellhammer

- Cortisol is highest upon awakening (+30 min)
- Decreases rapidly until ~noon, then gradually diminishes to lowest point several hours after onset of sleep.

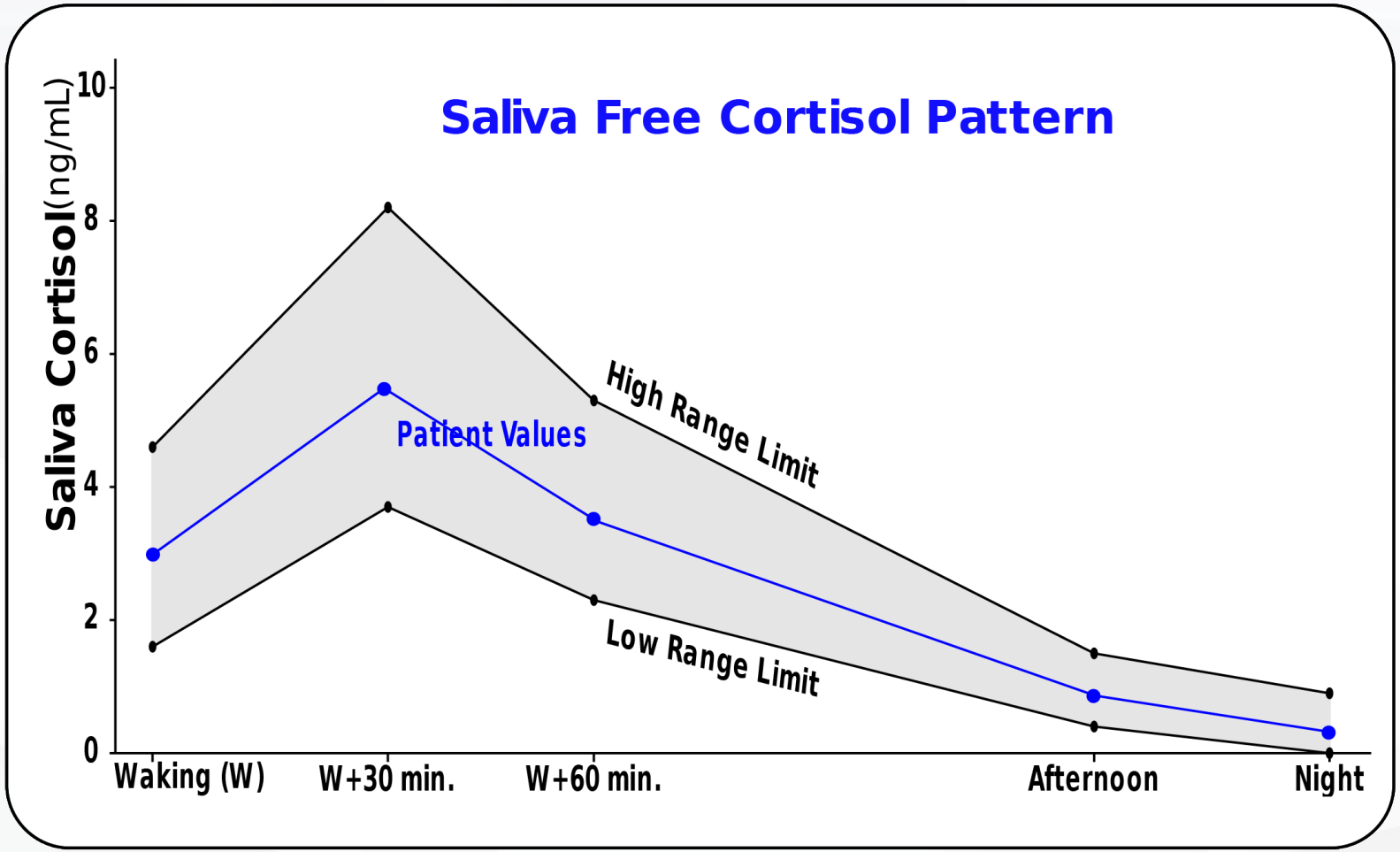
A “normal” diurnal salivary cortisol with CAR



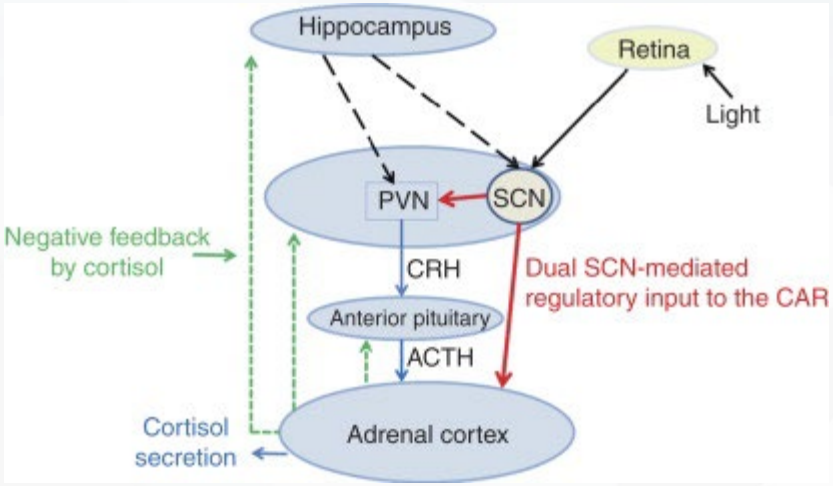
Note: This data only represents the day of sampling and is highly dependent on appropriate sampling techniques and timing.
Always correlate salivary cortisol with other signs/symptoms of HPA axis dysfunction.

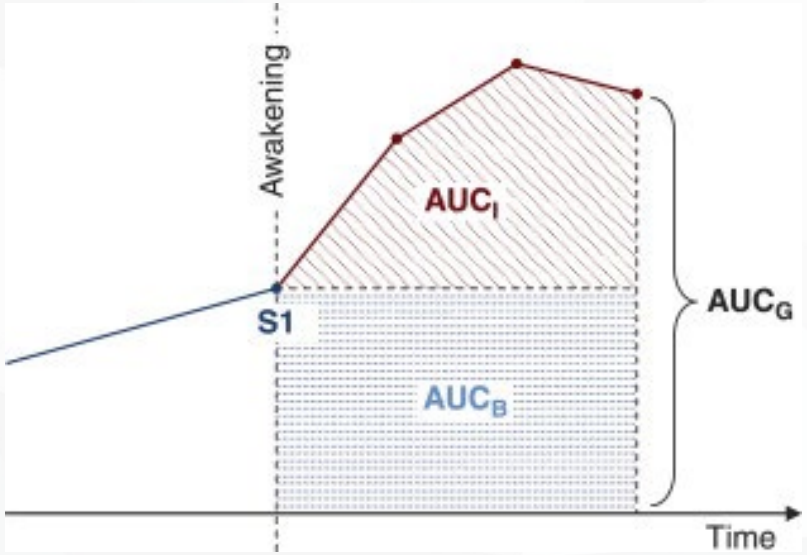
Typical Diurnal Pattern with CAR

(note chart is not to scale)



Cortisol Awakening Response (CAR): a mini HPA provocation test





- CAR is prompted by both circadian HPA activity and waking (light)
- No response to nighttime waking
- CAR is absent or blunted in most napping situations
- Surrogate marker for HPA axis plasticity/reactivity
- Affected by anticipitory stress

International Review of Neurobiology
Volume 93, 2010, Pages 153-175

Cortisol Awaking Response (CAR): The most important "single point"

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Review

Cortisol awakening response and psychosocial fac
A systematic review and meta-analysis

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Positive well-being
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Burnout and fatigue

ABSTRACT

The magnitude of the cortisol awakening respo
adrenocortical (HPA) axis activation, has been
have been inconsistent across studies. We sy
association between the cortisol awakening re
62 articles were identified. Separate analyses
waking (CARi), and the integrated volume of co
that the CARi was positively associated with job
with fatigue, burnout, or exhaustion. There wer
positive affects. The CARauc was positively related to general life stress and negatively related to
posttraumatic stress syndrome. This review concludes that different psychosocial factors are associated
with an enhanced or reduced cortisol awakenin

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4.4. Issues from sensitivity analyses
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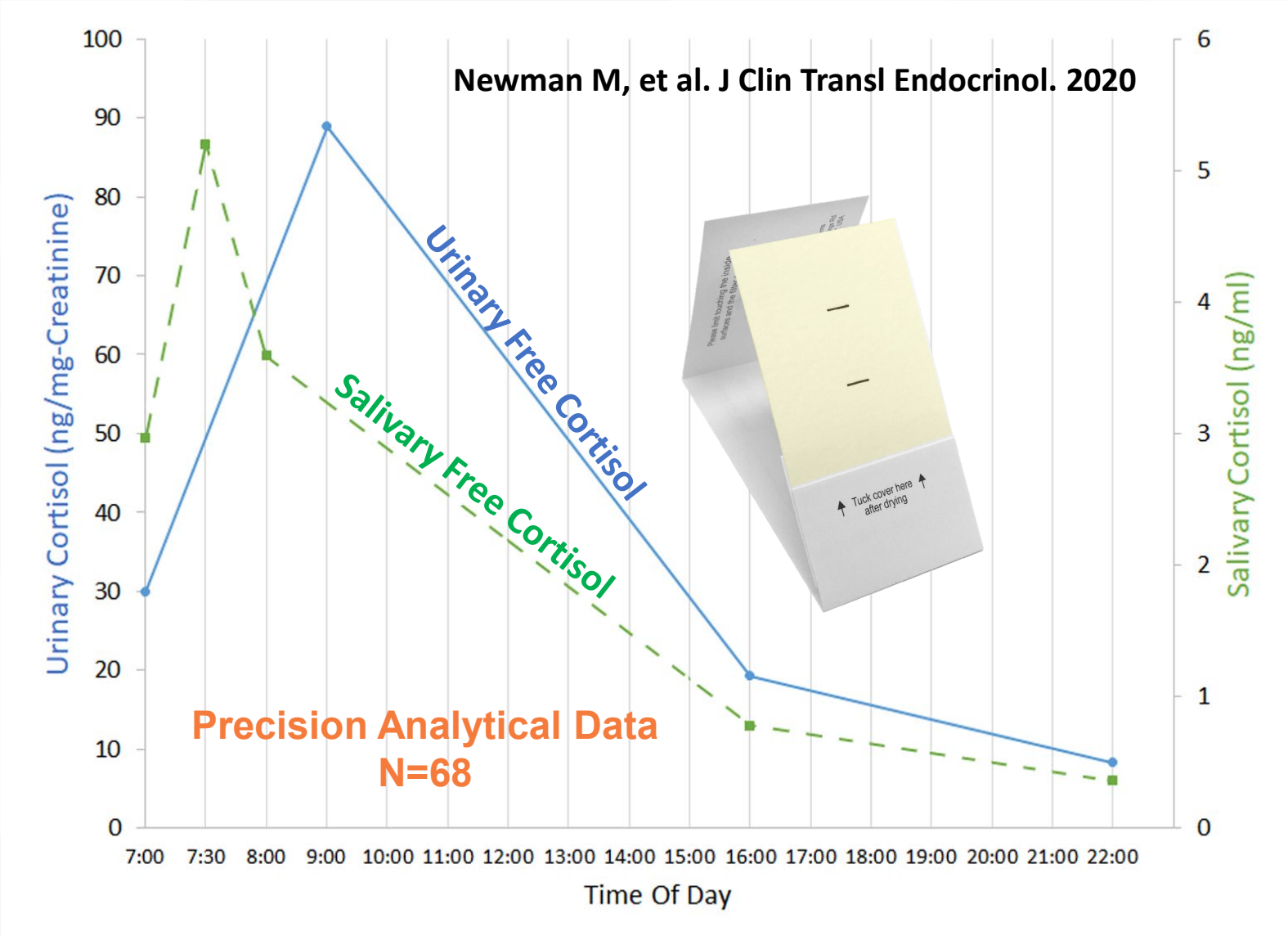
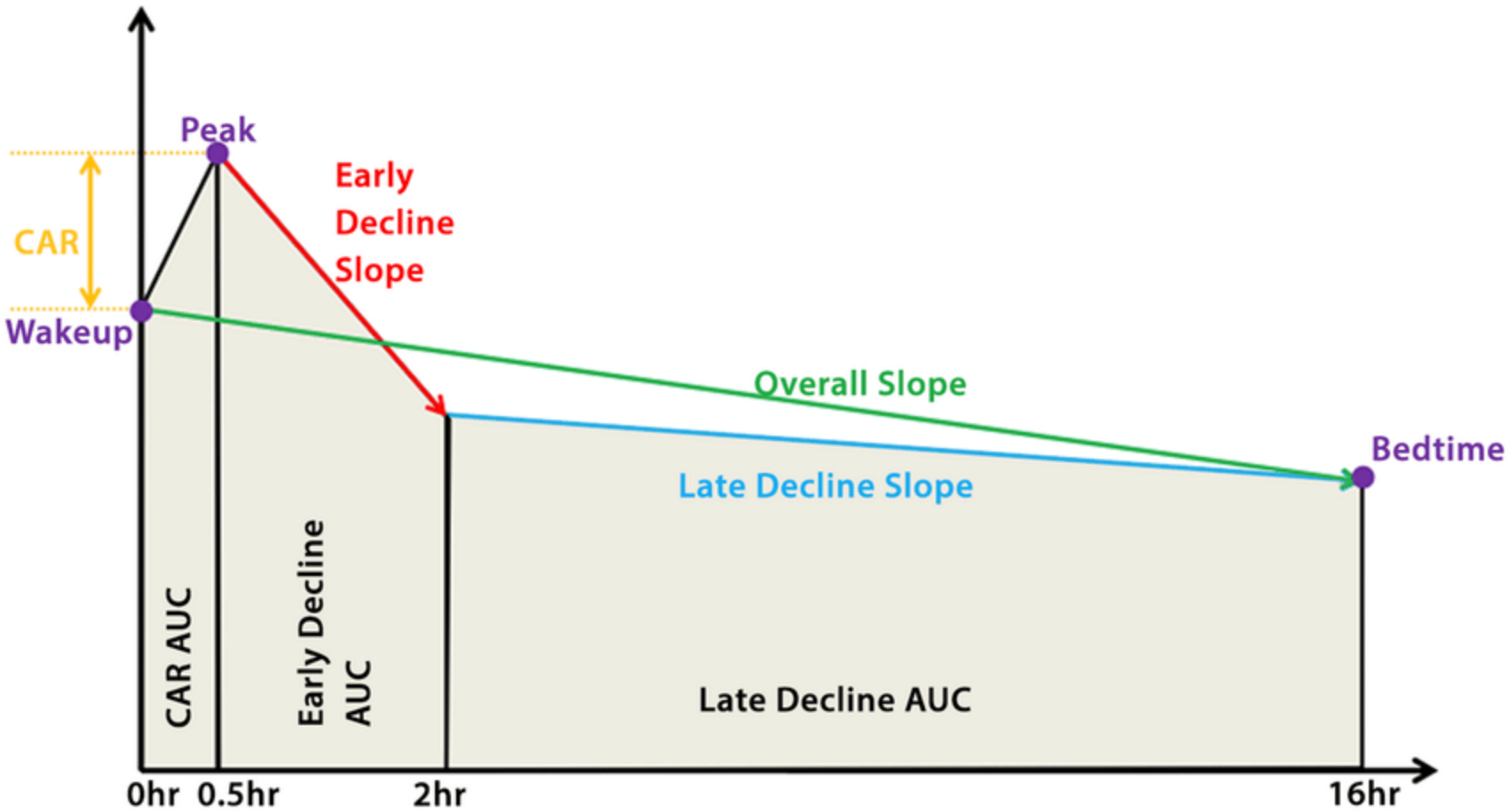
4.6. Conclusions
Acknowledgements
References

Type of analysis	No of studies	Combined effect size r (95% CI)	p value	Heterogeneity p value
(1) Job stress (overall)	22	0.061 (0.012 - 0.110)	0.015	0.43
Job stress (aggregate effect)	12	0.070 (0.002 - 0.138)	0.045	0.19
Job stress (male)	8	0.055 (-0.052 - 0.160)	0.31	0.86
Job stress (female)	9	0.067 (-0.016 - 0.148)	0.11	0.55
Job stress (quality score ≥6)	17	0.056 (0.002 - 0.110)	0.044	0.56
Job stress (AINC)	15	0.037 (-0.025 - 0.097)	0.24	0.64
Job stress (AUCi)	3	0.025 (-0.149 - 0.198)	0.78	0.46
Job stress (ACOR)	3	0.096 (-0.085 - 0.279)	0.33	0.071
Job stress (≥2 days assessed)	8	0.060 (-0.037 - 0.156)	0.23	0.071
Job stress (≥3 time points assessed)	6	0.101 (-0.007 - 0.207)	0.066	0.17
(2) General life stress (overall)	35	0.065 (0.007 - 0.123)	0.029	< 0.001
General life stress (aggregate effect)	25	0.042 (-0.026 - 0.110)	0.23	< 0.001
General life stress (male)	3	0.099 (-0.058 - 0.251)	0.22	0.53
General life stress (female)	13	0.078 (-0.057 - 0.213)	0.25	0.001
General life stress (healthy populations)	31	0.064 (0.006 - 0.122)	0.032	0.002
General life stress (quality score ≥6)	18	0.083 (-0.005 - 0.169)	0.065	0.001
General life stress (AINC)	20	0.060 (-0.015 - 0.134)	0.12	< 0.001
General life stress (AUCi)	5	0.008 (-0.196 - 0.211)	0.94	0.27
General life stress (ACOR)	9	0.103 (-0.014 - 0.216)	0.083	0.071
General life stress (≥2 days assessed)	22	0.099 (0.030 - 0.167)	0.005	0.006
General life stress (≥3 time points assessed)	14	0.103 (0.005 - 0.198)	0.039	0.13
(5) Fatigue, burnout, or exhaustion (overall)	16	-0.065 (-0.138 - 0.010)	0.089	0.067
Fatigue, burnout, or exhaustion (aggregate effect)	15	-0.054 (-0.126 - 0.019)	0.15	0.11
Fatigue, burnout, or exhaustion (male)	4	0.036 (-0.116 - 0.186)	0.64	0.94
Fatigue, burnout, or exhaustion (female)	3	0.079 (-0.045 - 0.201)	0.21	0.32
Fatigue, burnout, or exhaustion (healthy population)	12	-0.024 (-0.096 - 0.051)	0.53	0.20
Fatigue, burnout, or exhaustion (quality score ≥6)	9	-0.062 (-0.160 - 0.037)	0.22	0.027
Fatigue, burnout, or exhaustion (AINC)	7	-0.032 (-0.150 - 0.088)	0.60	0.16
Fatigue, burnout, or exhaustion (AUCi)	6	-0.148 (-0.255 - -0.037)	0.009	0.52
Fatigue, burnout, or exhaustion (MINC)	2	0.000 (-0.252 - 0.252)	1.00	1.00
Fatigue, burnout, or exhaustion (≥2 days assessed)	9	-0.033 (-0.123 - 0.058)	0.48	0.16
Fatigue, burnout, or exhaustion (≥3 time points assessed)	10	-0.144 (-0.230 - -0.060)	0.001	0.33
(6) Posttraumatic stress syndrome (overall)	3	-0.141 (-0.587 - 0.371)	0.60	< 0.001
Positive psychological states or traits (aggregate effect)	3	-0.141 (-0.587 - 0.371)	0.60	< 0.001
Posttraumatic stress syndrome (quality score ≥6)	2	-0.380 (-0.566 - -0.160)	0.001	0.89
Posttraumatic stress syndrome (AUCi)	2	-0.016 (-0.631 - 0.612)	0.97	< 0.001
Posttraumatic stress syndrome (≥3 time points assessed)	3	-0.141 (-0.587 - 0.371)	0.60	< 0.001

Dried Urine vs Saliva CAR and Diurnal Patterns



Research Component of Diurnal Cortisol



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Invited Review

Assessment of the cortisol awakening response: Expert consensus guidelines

Tobias Stalder[a,*], Clemens Kirschbaum[a], Brigitte M. Kudielka[b], Emma K. Adam[c], Jens C. Pruessner[d], Stefan Wüst[b], Samantha Dockray[e], Nina Smyth[f], Phil Evans[f], Dirk H. Hellhammer[g], Robert Miller[a], Mark A. Wetherell[h], Sonia J. Lupien[i], Angela Clow[f]

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ABSTRACT

The cortisol awakening response (CAR), the marked increase in cortisol secretion over the first 30–45 min after morning awakening, has been related to a wide range of psychosocial, physical and mental health parameters, making it a key variable for psychoneuroendocrinological research. The CAR is typically assessed from self-collection of saliva samples within the domestic setting. While this confers ecological validity, it lacks direct researcher oversight which can be problematic as the validity of CAR measurement critically relies on participants closely following a timed sampling schedule, beginning with the moment of awakening. Researchers assessing the CAR thus need to take important steps to maximize and monitor saliva sampling accuracy as well as consider a range of other relevant methodological factors. To promote best practice of future research in this field, the International Society of Psychoneuroendocrinology initiated an expert panel charged with (i) summarizing relevant evidence and collective experience on methodological factors affecting CAR assessment and (ii) formulating clear consensus guidelines for future research. The present report summarizes the results of this undertaking. Consensus guidelines are presented on central aspects of CAR assessment, including objective control of sampling accuracy/adherence, participant instructions, covariate accounting, sampling protocols, quantification strategies as well as reporting and interpreting of CAR data. Meeting these methodological standards in future research will create more powerful research designs, thus yielding more reliable and reproducible results and helping to further advance understanding in this evolving field of research.

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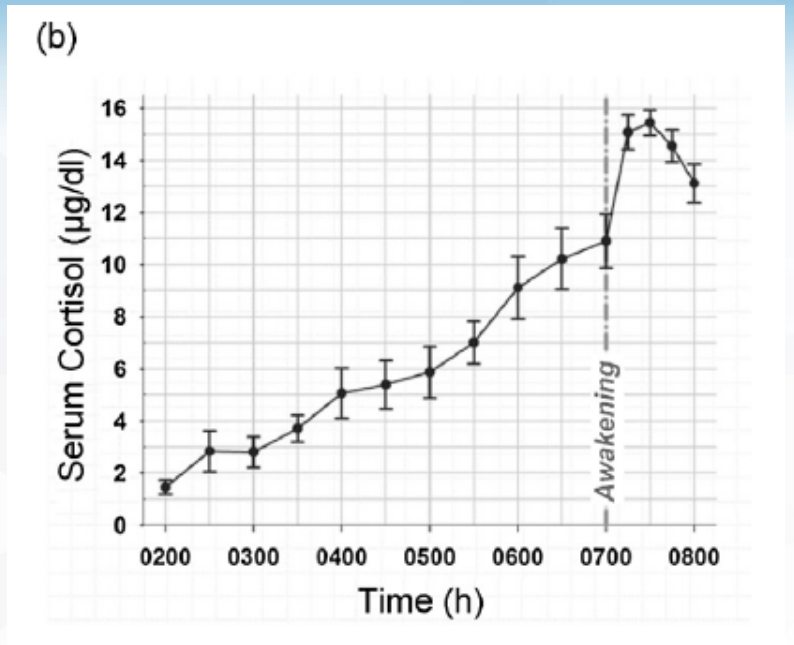
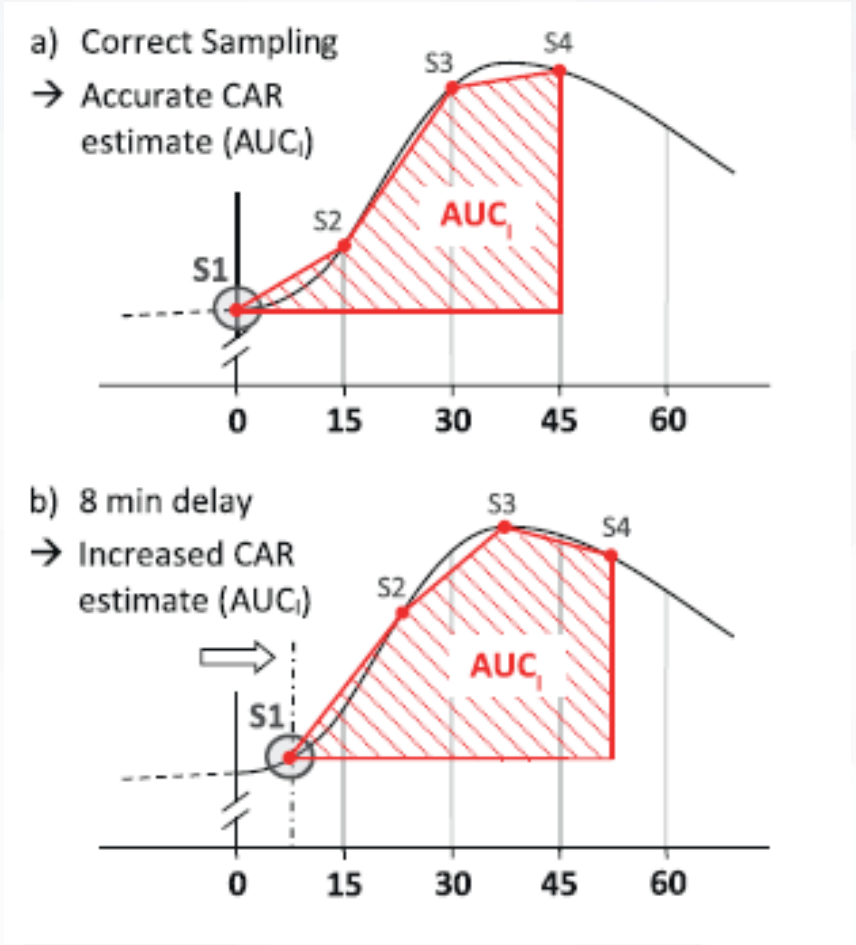
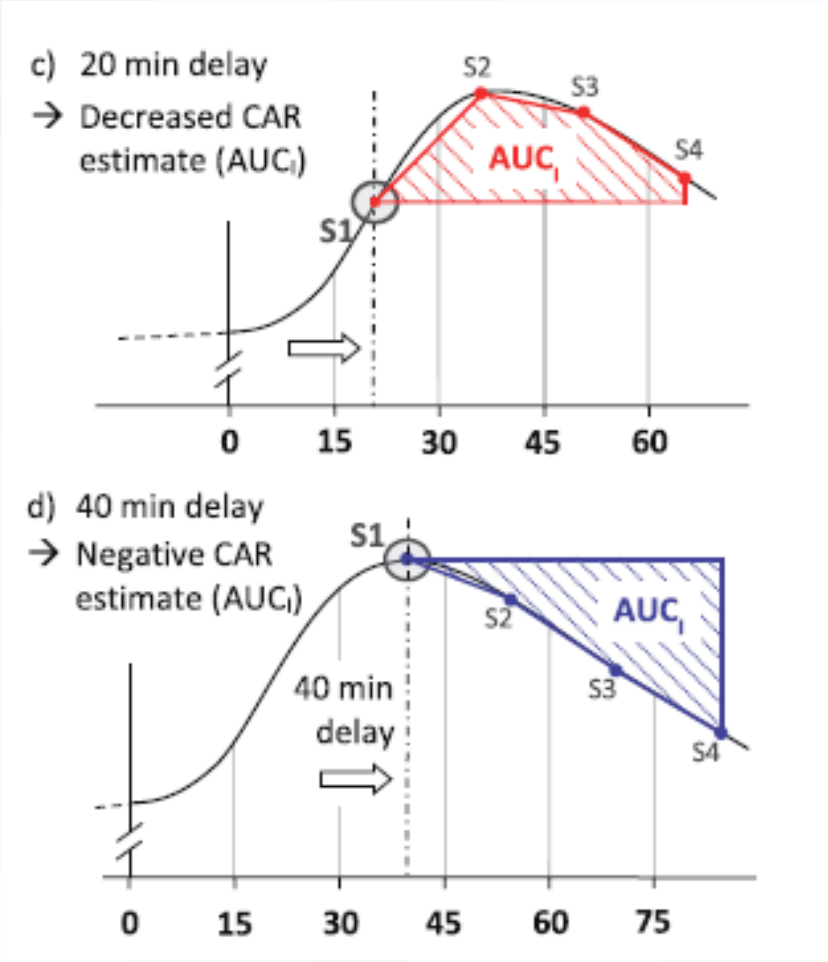


Cortisol Awakening Response is both a natural phenomena, and a biomarker (i.e., the measure of cortisol from waking to ~1 hour post awakening

Measuring this as a biomarker in the literature includes lots of issues, mostly due to sampling errors.

Timing is Critical for CAR Research





Perceived Work Overload and Chronic Worrying Predict Weekend–Weekday Differences in the Cortisol Awakening Response

Wolff Schlotz, MSc, Juliane Hellhammer, MSc, Peter Schulz, PhD, and Arthur A. Stone, PhD

Objective: The cortisol increase after awakening has been shown to be associated with work-related stress. Several studies demonstrated a moderate stability of cortisol awakening responses on subsequent days, suggesting situation-dependent variance. This study tests whether cortisol awakening responses are different on weekdays compared with weekend days and whether such differences may be explained by chronic work overload and worrying. **Methods:** Two hundred nineteen participants took saliva samples immediately after awakening and 30, 45, and 60 minutes later on 6 consecutive days starting on Saturday. Perceived chronic work overload and worrying were assessed by a standardized questionnaire. **Results:** There is a clear weekend–weekday difference in the cortisol response to awakening. This difference is associated with chronic work overload and worry. Independent of sex and weekend–weekday differences in time of awakening and sleep duration, participants who report higher levels of chronic work overload and worrying show a stronger increase and higher mean levels of cortisol after awakening on weekdays, but not on weekend days. **Conclusions:** The weekend–weekday differences in the cortisol awakening response and their association with chronic stress clearly demonstrate that the day of cortisol assessment is crucial in psychoendocrinological stress studies.
Key words: cortisol awakening response, salivary cortisol, weekend, perceived stress, work overload, worry.

ANOVA = analysis of variance; **CAR** = cortisol awakening response; **GLM** = general linear model; **HPA** = hypothalamic–pituitary–adrenal axis.

INTRODUCTION

Several studies detect a cortisol increase after awakening (1–6) that may be a marker of hypothalamic–pituitary–adrenal axis (HPA) activity, in particular of the sensitivity of the adrenal cortex (7). This cortisol awakening response (CAR) is influenced by light (8, 9), sex (4), and time of awakening (6,10,11). There is also evidence for an association of the CAR with sleep duration (4), although another study (1) failed to detect it. With regard to psychological stress measures, a relation of morning cortisol levels to self-reported chronic work-related stress is often observed (12–14). Cortisol levels after awakening are moderately stable. Wüst et al. (4) report a range in correlations of $0.37 < r < 0.66$ for single measures in the first hour after awakening on 2 consecutive days. Pruessner et al. (1) report a range of $0.39 < r < 0.67$ for individual area under the curve measures on 2 consecutive days. These correlations demonstrate a day-to-day variability that suggests situation-dependent variance in the CAR.

This study focuses on the CAR on weekdays compared with weekend days. The standard work schedule divides the week into 2 sections: 5 work days, usually the weekdays Monday through Friday, and 2 off work days, usually the weekend days Saturday and Sunday. Several studies demonstrated increased cardiovascular activity on workdays compared with nonworkdays (15–17). Differences between workdays and nonworkdays in heart rate, systolic blood pressure, and urinary epinephrine levels are more pronounced in persons facing high job demands (18), suggesting an increased work-stress-related sympathetic activation. Because of the abovementioned standard work schedule, these differences are likely to be observed in a weekend–weekday comparison of biological stress reactions.

Weekend–weekday differences may also emerge in the area of cognitive preoccupation with subjectively significant problems. This preoccupation may appear as worrying, which is a common human experience and may constitute constructive problem-solving activity, enabling the individual to cope with life problems (19,20), but may also be dysfunctional, ie, enhancing stress and anxiety instead of reducing it (21,22). Worrying may appear in anticipation of everyday demands after awakening and thus may be more pronounced on weekdays than on weekend days. On the other hand, weekdays and weekend days have been shown to differ in the amount of negative affect (23,24). These differences may also be attributable to the standard work schedule, and thus may be linked to work-related stress and worrying, respectively, as outlined above.

The objectives of this study are to test the hypothesis that the CAR is different on weekdays compared with weekend days and, if so, to determine whether these differences are linked to perceived work-related stress and worry. We hypothesize 1) that the CAR is more pronounced on weekdays compared with weekend days; 2) that this difference is independent of sex, time of awakening, and sleep duration; and 3) that this difference is attributable to perceived work overload and worry.

METHODS

Participants and Methods

Participants

Participants were recruited by newspaper announcements in the region of Trier, Germany. Because the study originally was designed with an emphasis on the influence of age on psychoneuroendocrinological systems, participants had to be between 24 and 40 years or more than 60 years old to be included in the study; those treated with corticosteroids and those with diabetes were excluded from the study. All participants provided written informed consent and they were paid DM 40 after completion of the study protocol. A subset of 219 participants (117 female [53%], 102 male [47%]) was selected from the whole sample ($N = 309$) based on the following criteria (see Study Protocol below for details): (a) No missing cortisol, bedtime, and awakening time measure, respectively, on the weekend; and (b) a maximum of 2 missing

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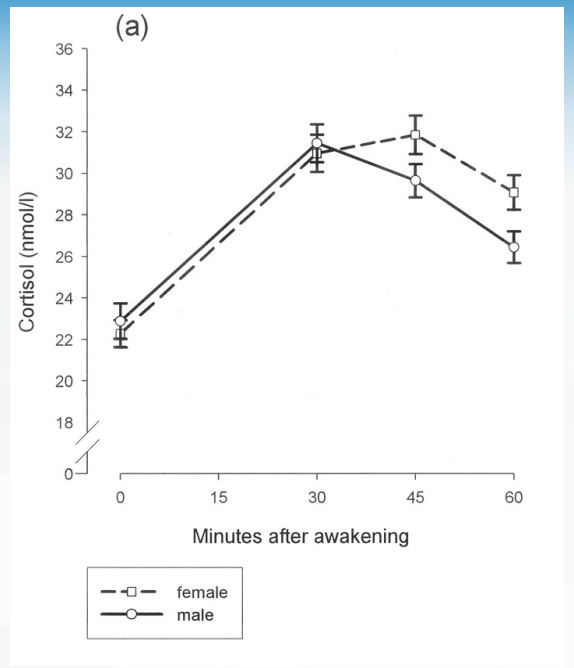

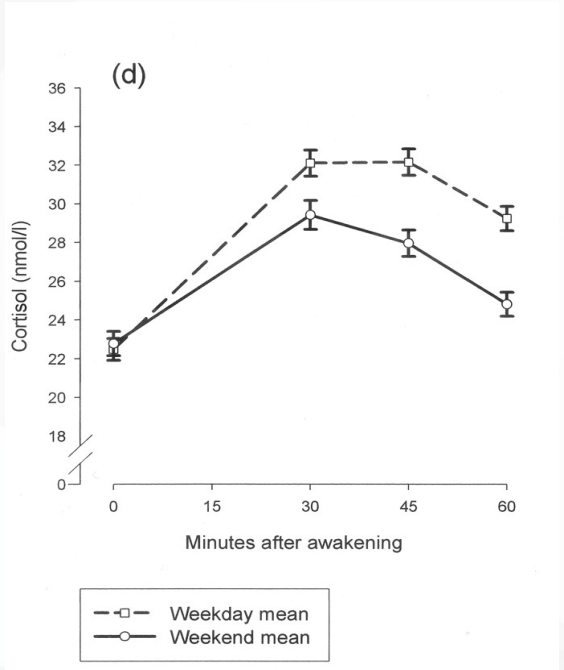

What day did your patient take their cortisol test?

How did this influence the results?

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PNEC-1893; No. of Pages 8
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Seasonal differences in the diurnal pattern of cortisol secretion in healthy participants and those with self-assessed seasonal affective disorder

Lisa Thorn [a,*], Phil Evans [a], Anne Cannon [a], Frank Hucklebridge [b], Phil Evans [a], Angela Clow [a]

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Cortisol;
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Seasonal affective disorder

Summary This study compared the daily pattern of free salivary cortisol secretion in winter and in summer between two groups; participants with self-assessed seasonal affective disorder (SAD) and age- and sex-matched healthy controls. Fifty-two participants completed the study with an equal number in each group. The diurnal pattern of cortisol secretion was assessed across two consecutive weekdays in summer, and two in winter, with conditions being counterbalanced. On each study day participants collected multiple saliva samples in the domestic setting to capture the cortisol awakening response (CAR) and declining levels across the day. In addition, perceived stress, anxiety, depression, state stress and state arousal were assessed using validated questionnaires. There was no evidence for any seasonal changes in psychological data or cortisol pattern for the healthy control population. In summer, self-assessed SAD and control participants had similar psychological and cortisol profiles. In winter however, SAD participants reported greater depression, stress and anxiety, and lower levels of arousal. Furthermore, the CAR was significantly attenuated in SAD participants during winter months. There was no difference in cortisol levels during the rest of the day between controls and SAD participants in winter. In line with the above findings and previous research, there was an inverse relationship between the increase in cortisol following awakening and a measure of seasonality in winter. Furthermore in winter, a general dysphoria construct correlated inversely with the CAR, indicating that participants reporting greater depression, stress and anxiety and lower arousal, exhibited lower CARs. In conclusion, during the shortened photoperiod in winter, the cortisol response to awakening is attenuated in participants with self-assessed SAD in comparison to controls. These findings contribute to the understanding of the physiology of SAD.

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1. Introduction

Cortisol has a well-established circadian rhythm which is synchronised with the light–dark and sleep–wake cycles.

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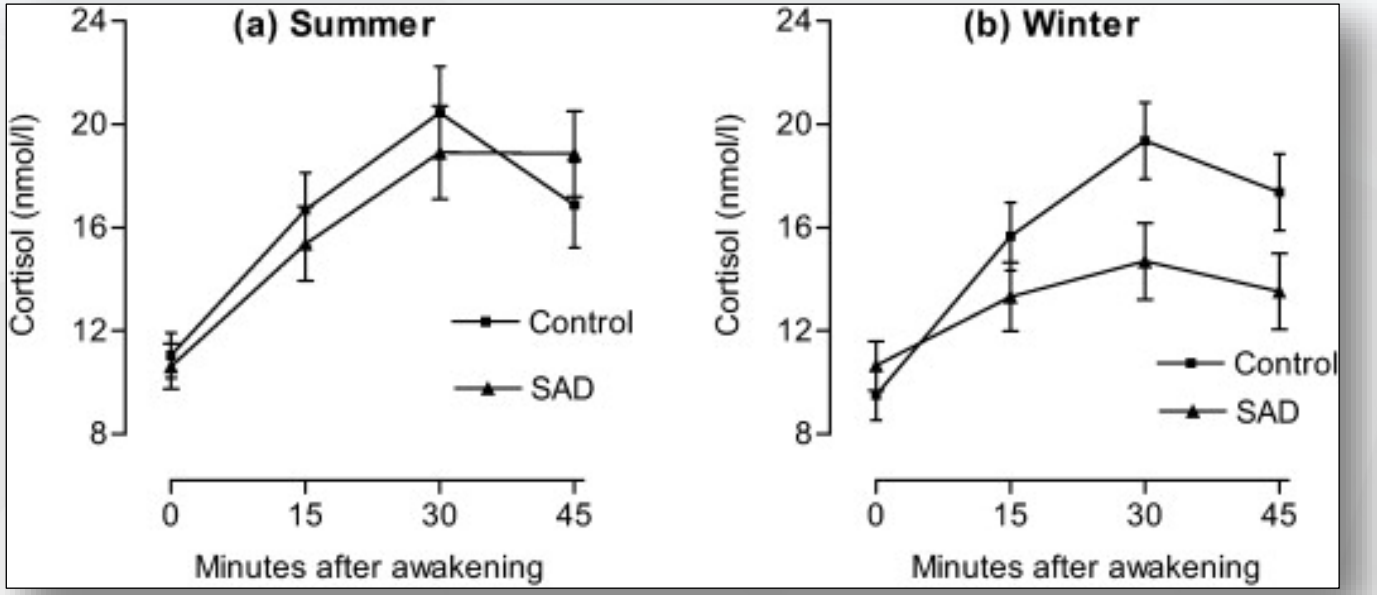

Ovulation can affects CAR

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The cortisol awakening response (CAR) across the female menstrual cycle

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KEYWORDS
Cortisol awakening response (CAR);
Salivary cortisol;
Female menstrual cycle;
Ovulation;
Hypothalamus–pituitary–adrenal (HPA) axis;
Hypothalamus–pituitary–gonadal (HPG) axis;
Gonadal steroids;
Estrogen;
Ambulatory assessment;
Chromatographic ovulation test

Summary The cortisol awakening response (CAR) has been established as a useful marker of hypothalamus–pituitary–adrenal (HPA) axis activity and has become a standard tool for stress research in ambulatory settings. Although much knowledge has been accumulated on a variety of factors modulating the CAR, the impact of the female menstrual cycle, especially during ovulation, still remains unclear. To the best of our knowledge, this is the first study that measured the CAR during menses, the follicular phase, ovulation and the luteal phase in a repeated measurement design. For this purpose, a final sample of 29 naturally cycling, healthy, non-smoking, and medication-free women collected saliva samples directly after awakening as well as 30, 45, and 60 min later during each of the four different phases. To determine the timing of ovulation, an ambulatory chromatographic ovulation test kit was applied.

A repeated measurements ANOVA resulted in a significant interaction effect sample × cycle phase ($p = 0.04$), with the highest awakening response during ovulation. While awakening cortisol levels were comparable across the four cycle phases (p = n.s.), the net increase was significantly elevated during ovulation ($p = 0.05$). Our data also confirmed earlier cross-sectional results reporting no differences in the CAR between the follicular and luteal phase. Finally, a concurrent assessment of mood applying the POMS (Profile of Mood States) yielded no differences across the four cycle phases (all p = n.s.).

In sum, the present data points to the idea that the CAR is elevated during ovulation, an effect which is presumably mediated by elevated sex steroid levels during the ovulation period.

1. Introduction

The cortisol awakening response (CAR) is a sharp and discrete burst of cortisol secretion in the first hour post-awakening that is superimposed on the continuous circadian rise occurring during the second half of the night (Wilhelm et al., 2007; Clow et al., 2010). Since its introduction as index of adre-

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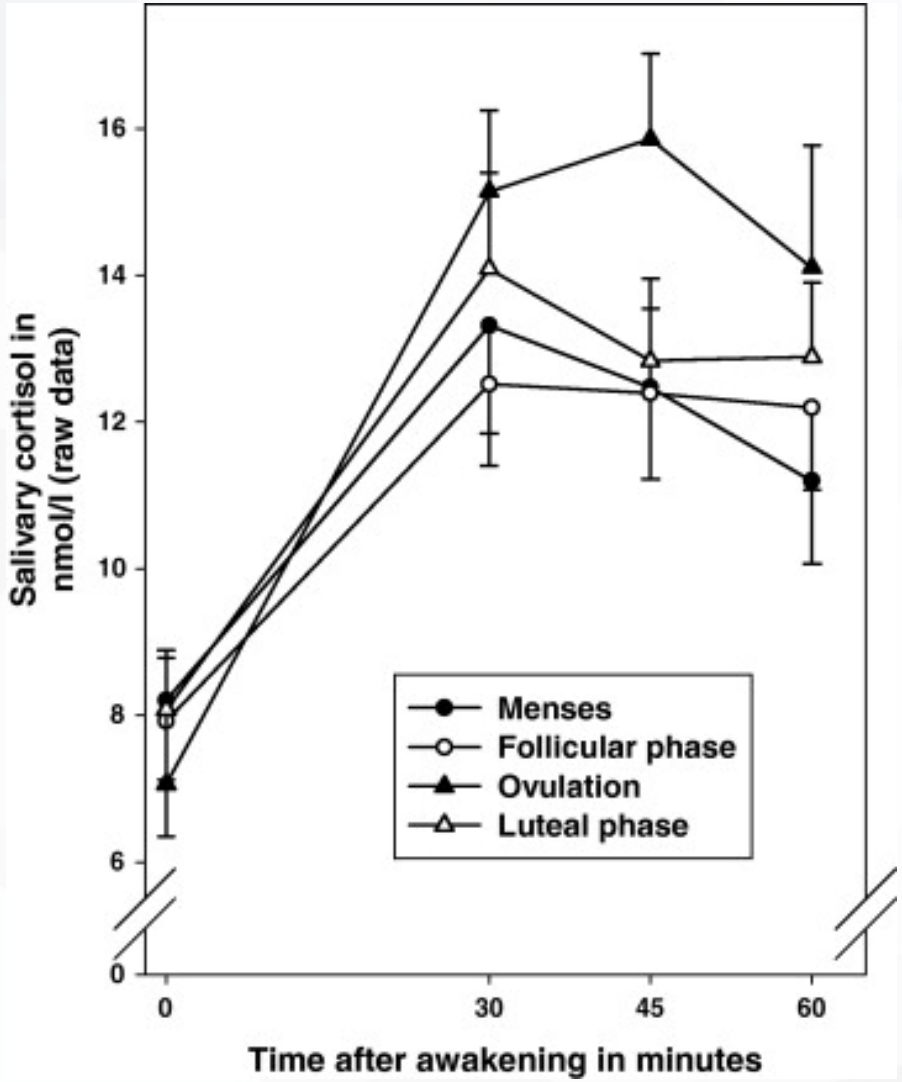

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ORIGINAL RESEARCH REPORT

Premenstrual syndrome is associated with altered cortisol awakening response

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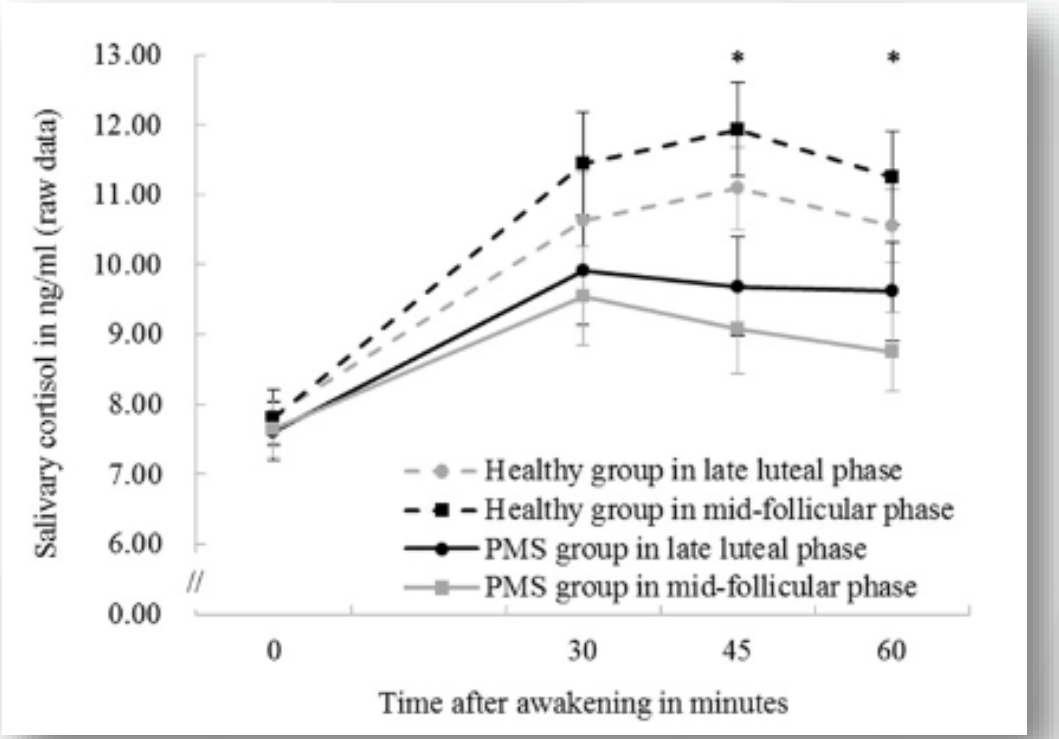
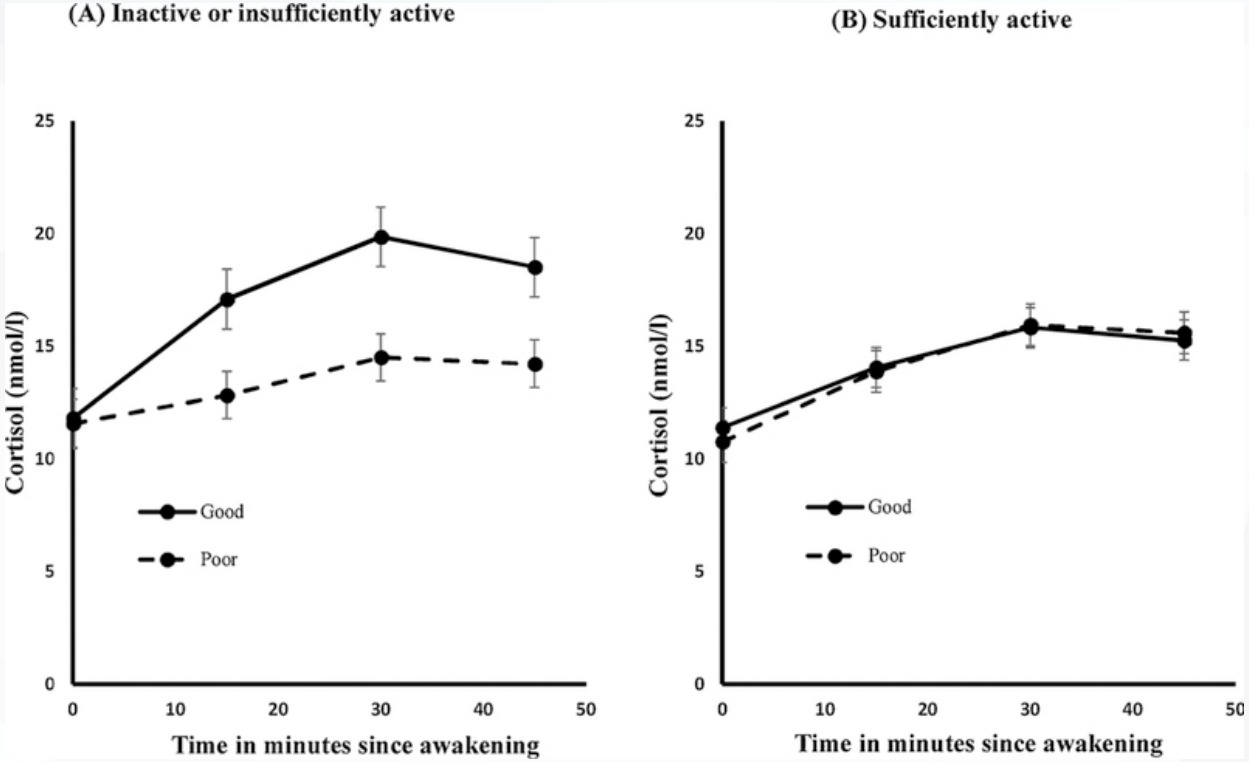
ABSTRACT

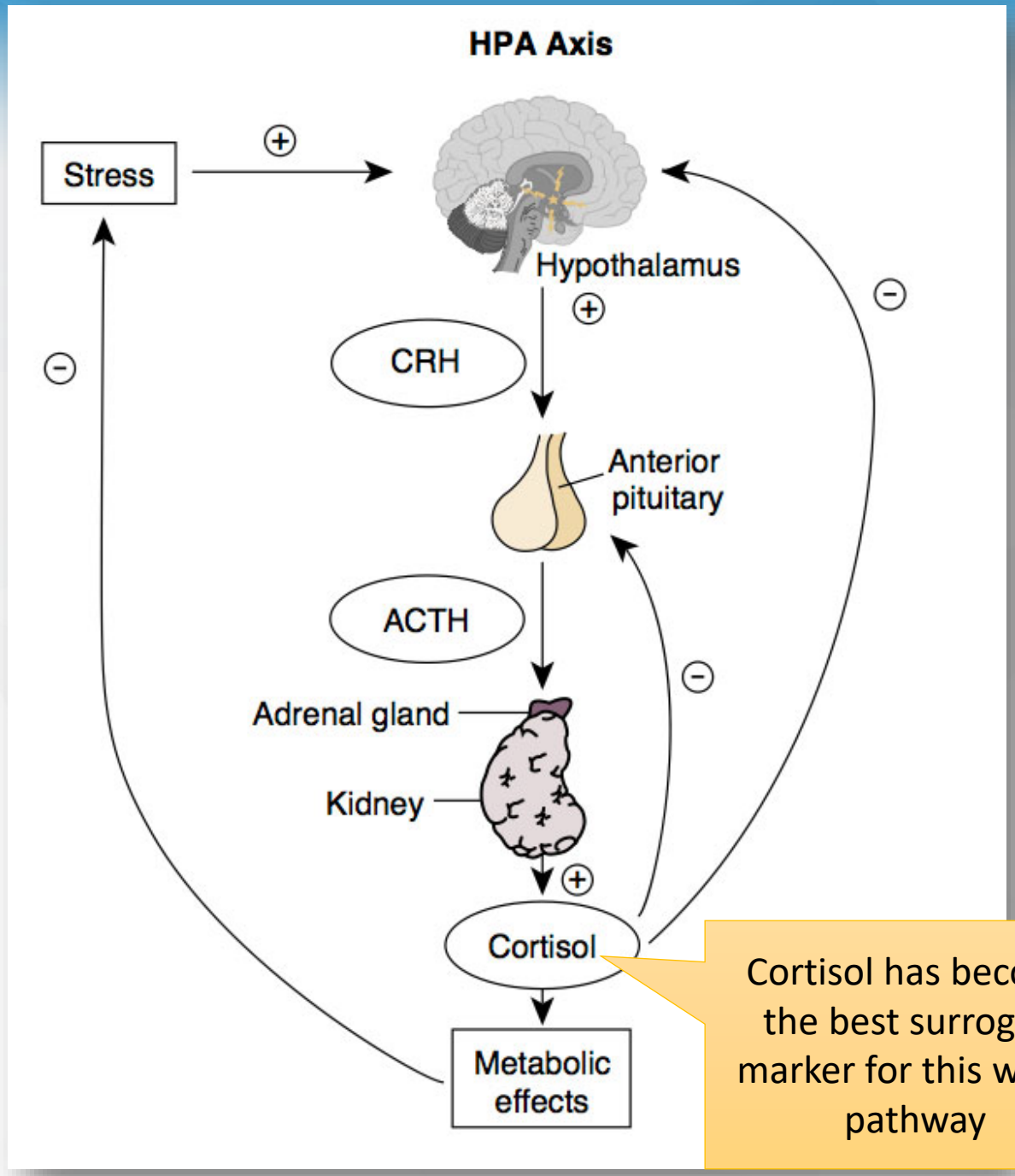
Previous studies have revealed stress-induced dysregulation of hypothalamic-pituitary-adrenal (HPA) axis in women with premenstrual syndrome (PMS). So far, however, the results about the relationship between HPA axis dysregulation and PMS are mixed. To this end, it is necessary to investigate the basal activity of the HPA axis in women with PMS instead of only assessing a certain stressor. Therefore, this study evaluated the relationship between the cortisol awakening response (CAR) and PMS. Thirty-two women with PMS (mean age 22.47 ± 2.20 years) and 36 healthy controls (mean age 22.28 ± 2.43 years) were included in this study. Saliva samples of our participants were collected successively at 0, 30, 45, and 60 min after awakening to assess CAR during each of two phases of the menstrual cycle (the mid-follicular phase and the late luteal phase). The results showed a significantly attenuated CAR in women with PMS compared with the healthy controls, especially at 45 and 60 min after awakening, regardless of the menstrual cycle phases. Furthermore, there was a significant negative correlation between PMS severity as measured by PMS scale and AUCi (i.e. the Area Under the Curve with respect to increase) in the mid-follicular phase. Our findings suggested that an attenuated CAR activity profile may be an important risk factor for the development of PMS.



Sleep quality and (CAR)
The moderating role of physical activity

- 275 police officers (age = 42 years ± 8.3, 27% women) Buffalo-NY
- Provided four salivary cortisol samples (on awakening and 15, 30, and 45 min after awakening).
- Hours of leisure time physical activity were assessed using the Seven-Day Physical Activity Recall questionnaire.
- Sleep quality (good/poor) was evaluated using the Pittsburgh Sleep Quality Index (PSQI) scale.
- Analyses were stratified by participant level of reported LTPA (sufficiently vs. insufficiently active, defined as ≥ 150 vs. < 150 min/week of moderate intensity activity, respectively).





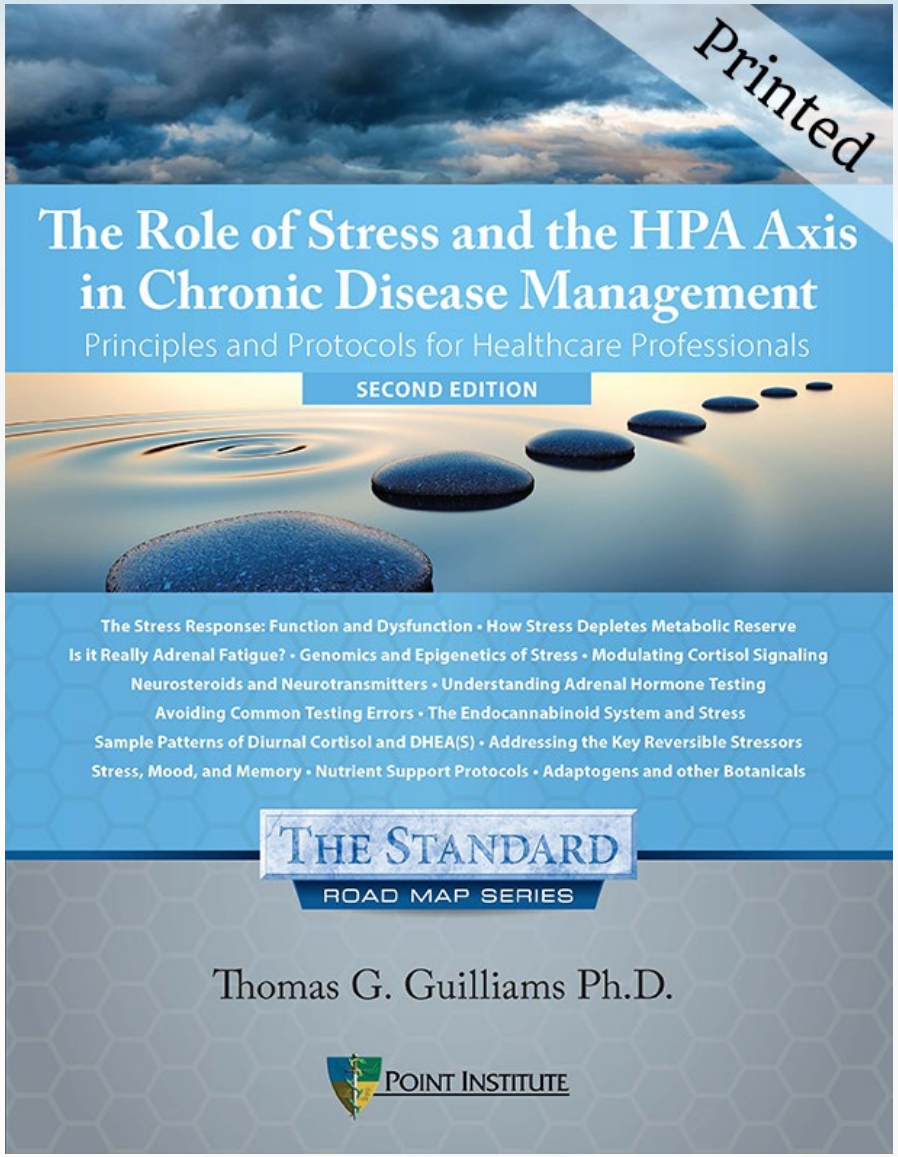
Cortisol Measured Correctly and at the Right Times can be a Window to Many Things.

- The Relationship between a Stressor and its Metabolic Effects
- The Resilience of a Person's Stress Response System to withstand additional Stressors (reserve capacity)
- How Acute and Chronic Stressors have affected the Circadian nature of the HPA axis

The most likely therapies or changes that can increase a person's ability to improve HPA axis mediated functions.

Summary for Now…

- Understand that you are not measuring “adrenals” but the HPA axis, both stress-induced alterations and the patient’s circadian rhythms.
- Timing is crucial for interpretation, ensure this was done right
- Know the research behind why diurnal measures of cortisol are so important to understand Fx rather than Dx
- There is more: Urinary metabolites, provocation tests, suppression tests, measuring status quo vs. altering parameters (light after awakening, post-therapy changes)
- We are just at the beginning of our understanding of how measuring Cortisol help us understand health and we didn’t even mention DHEA!



Second Edition- Published in November of 2020

Available in Print and eBook (PDF-format)

Expansion from our first edition includes discussion of the HPA axis and the endocannabinoid system, memory and brain function, and thyroid functions

Each section is updated with current information and references, including an expansion of therapeutic solutions

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Thank you !

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