CIRCADIAN RHYTHMS IN HEALTH AND DISEASE

DR ALLISON SMITH
DR KATE PLACZEK

ZRT LABORATORY

Today's Presenters

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Cortisol Dysregulation in Metabolic Syndrome

Presenter: Allison Smith, ND

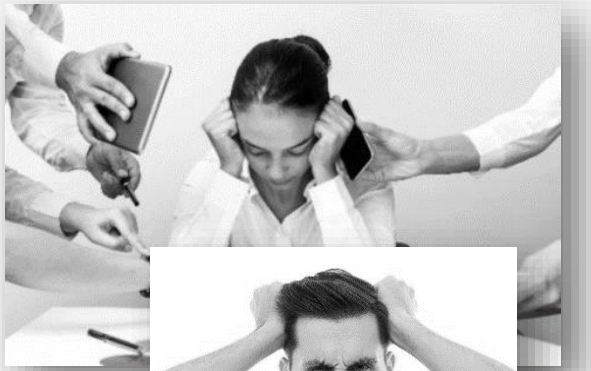
This webinar is designed for practitioners who are either new to thinking about cortisol outside of Addison's and Cushing's, or who have experience running diurnal tests but have gotten away from cortisol testing over the years. During this presentation, Dr. Allison Smith discusses:

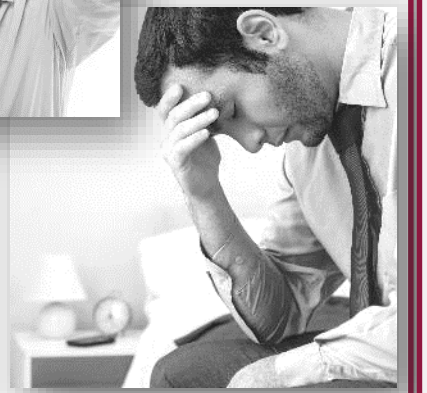
- The basis for cortisol's many impacts on a metabolic syndrome diagnosis
- Some of the recent research on cortisol dysregulation and the link with metabolic disease
- How monitoring diurnal cortisol levels during treatment provides valuable insights that lead to better outcomes

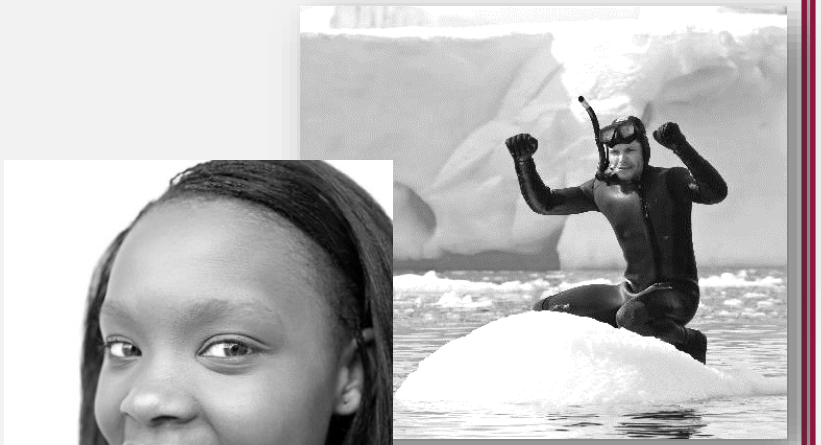
Related Resources

- **Blog**: Avoiding 3 Common Interpretation Pitfalls for Salivary Cortisol Tests
- **Web**: Stress & Adrenal Hormones
- **Listen** to the webinar: MP3 DOWNLOAD

https://www.zrtlab.com/webinars/cortisol-dysregulation-in-metabolic-syndrome/







EMOTIONAL

PHYSIOLOGICAL

ENVIRONMENTAL

OUR STRESS EXPOSURE

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Stress Response

INSTINCT

VS

CULTURE

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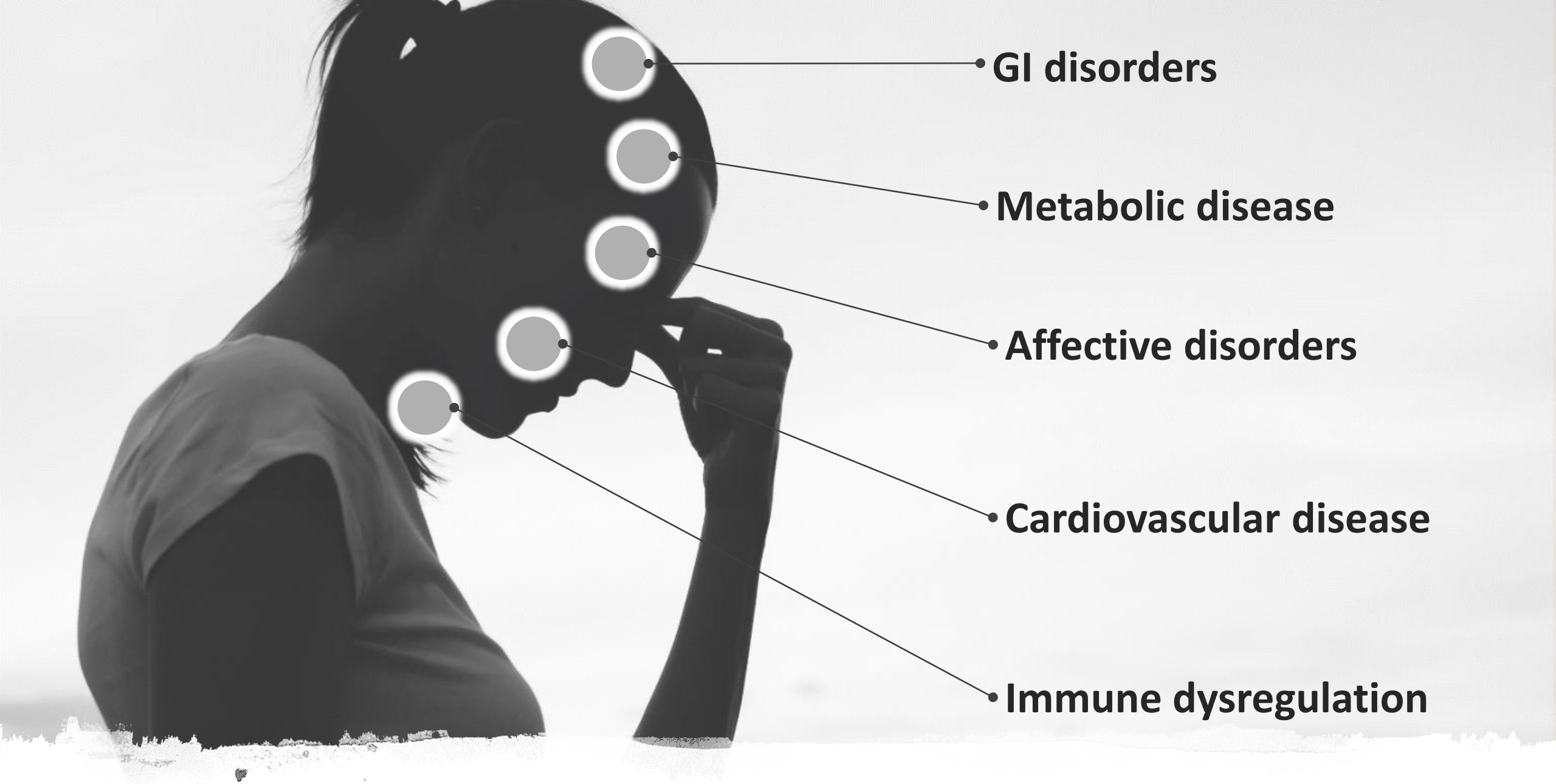
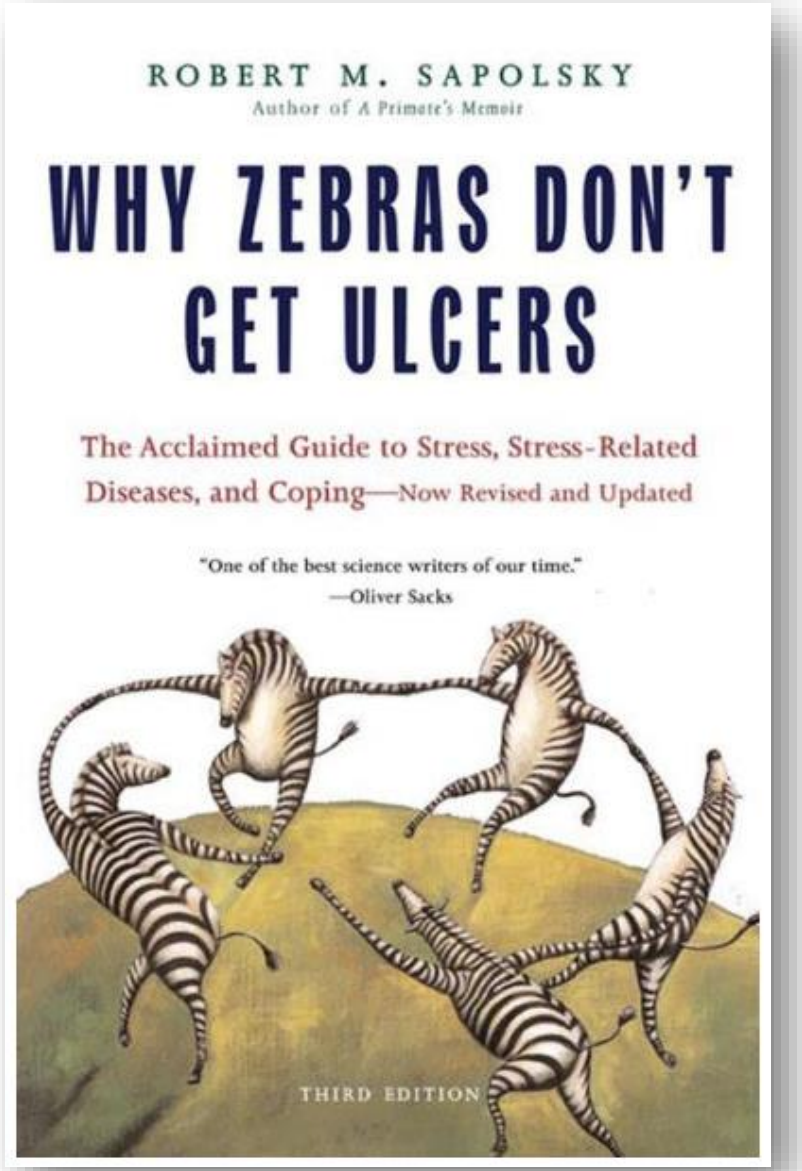
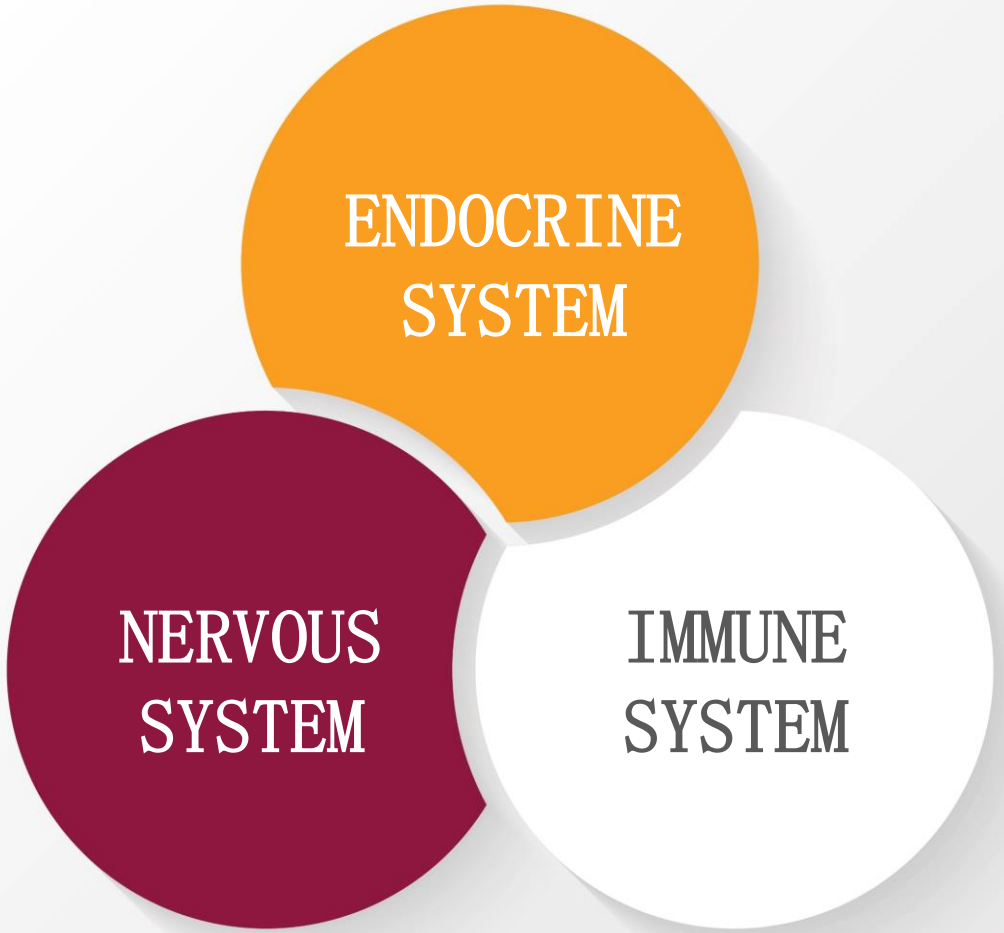
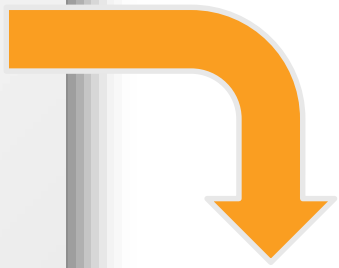




Morey et. al. (2015) *Curr Opin Psychol* 1 5
Elenkov et. al. (2000) *Pharmacological Reviews* 52(4)

AUTONOMIC NERVOUS SYSTEM





HPA AXIS

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Morey et. al. (2015) *Curr Opin Psychol* 1 5
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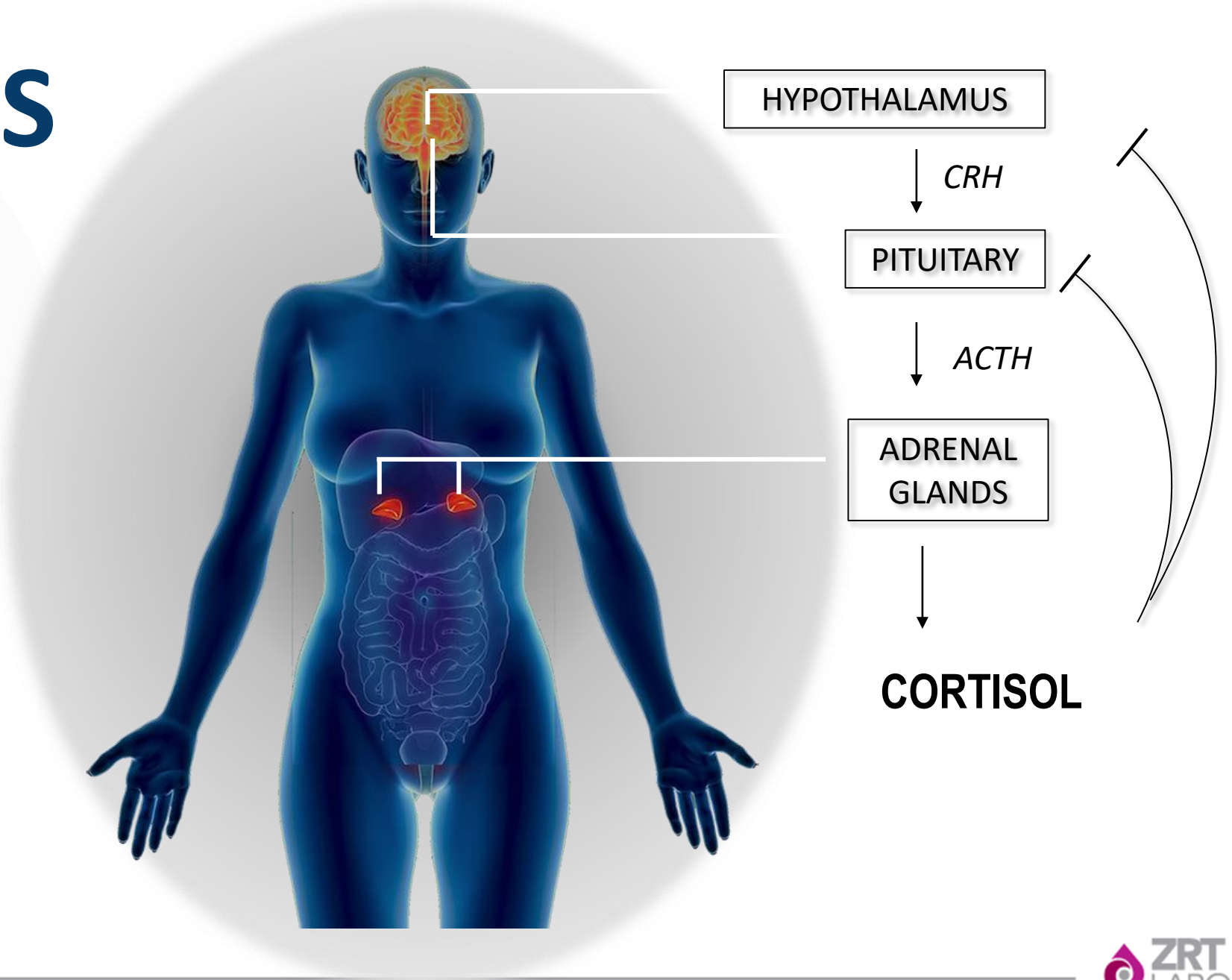
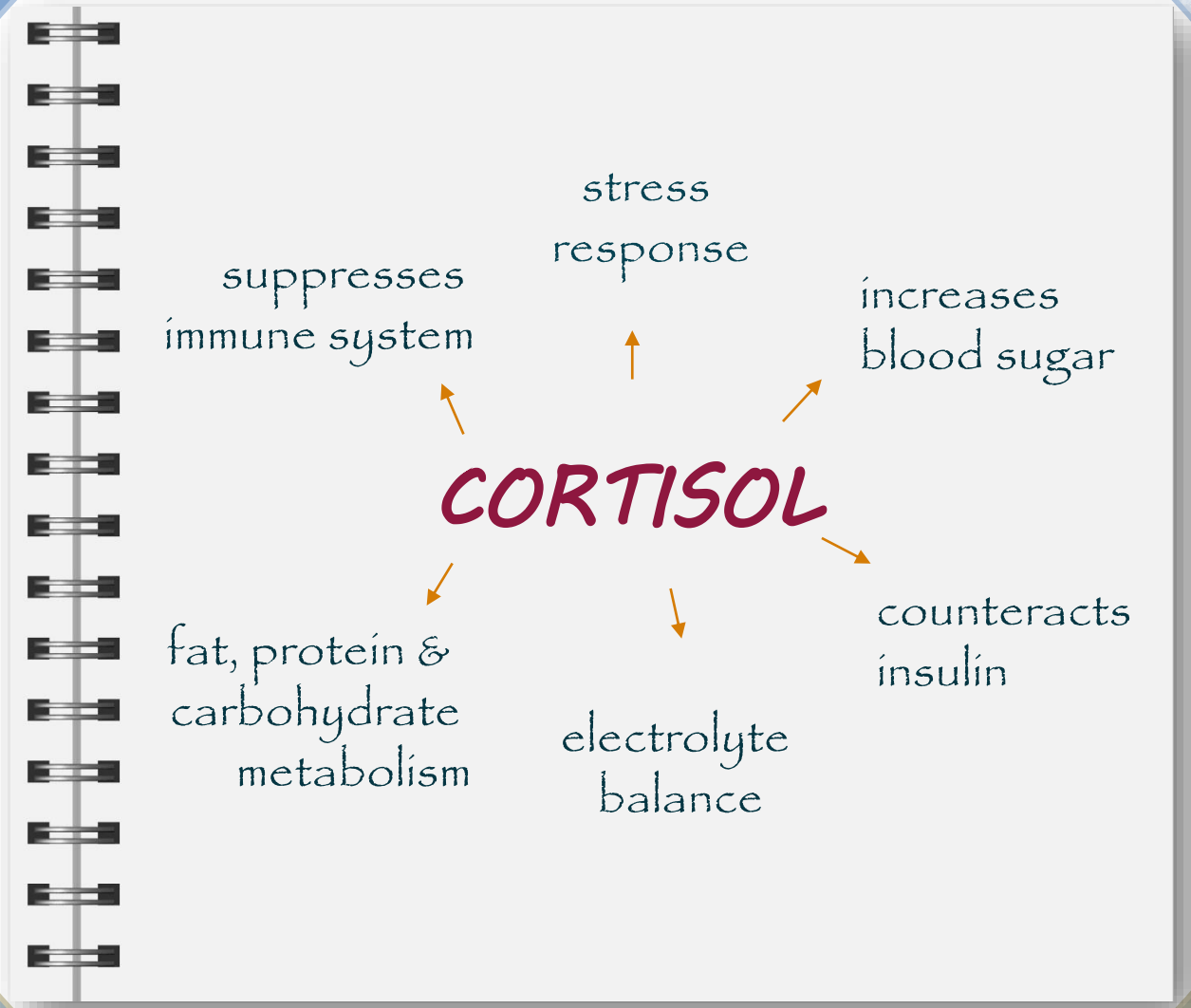
HPA AXIS





https://www.sciencedirect.com/topics/neuroscience/cortisol

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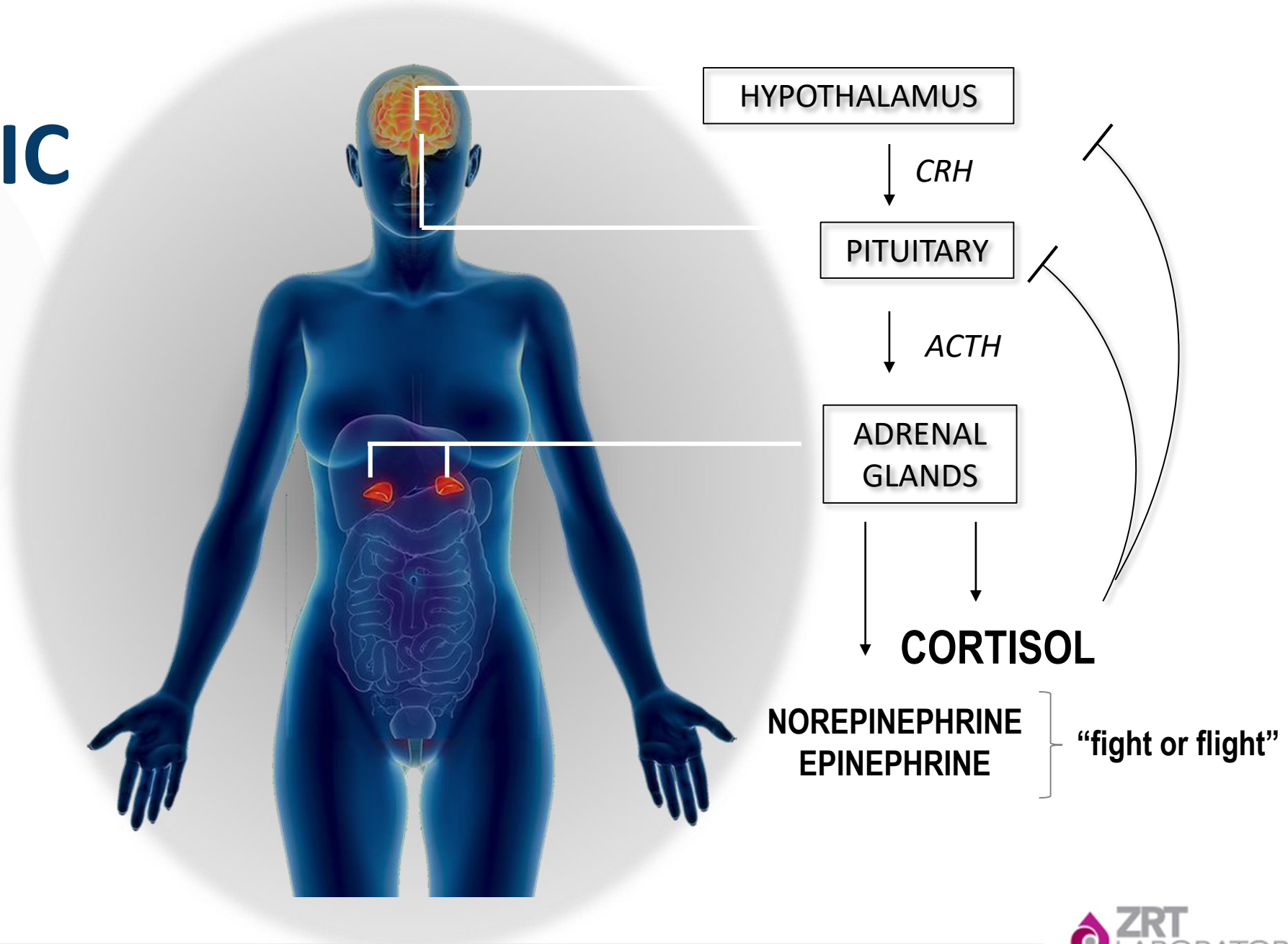
HPA AXIS & SYMPATHETIC NERVOUS SYSTEM



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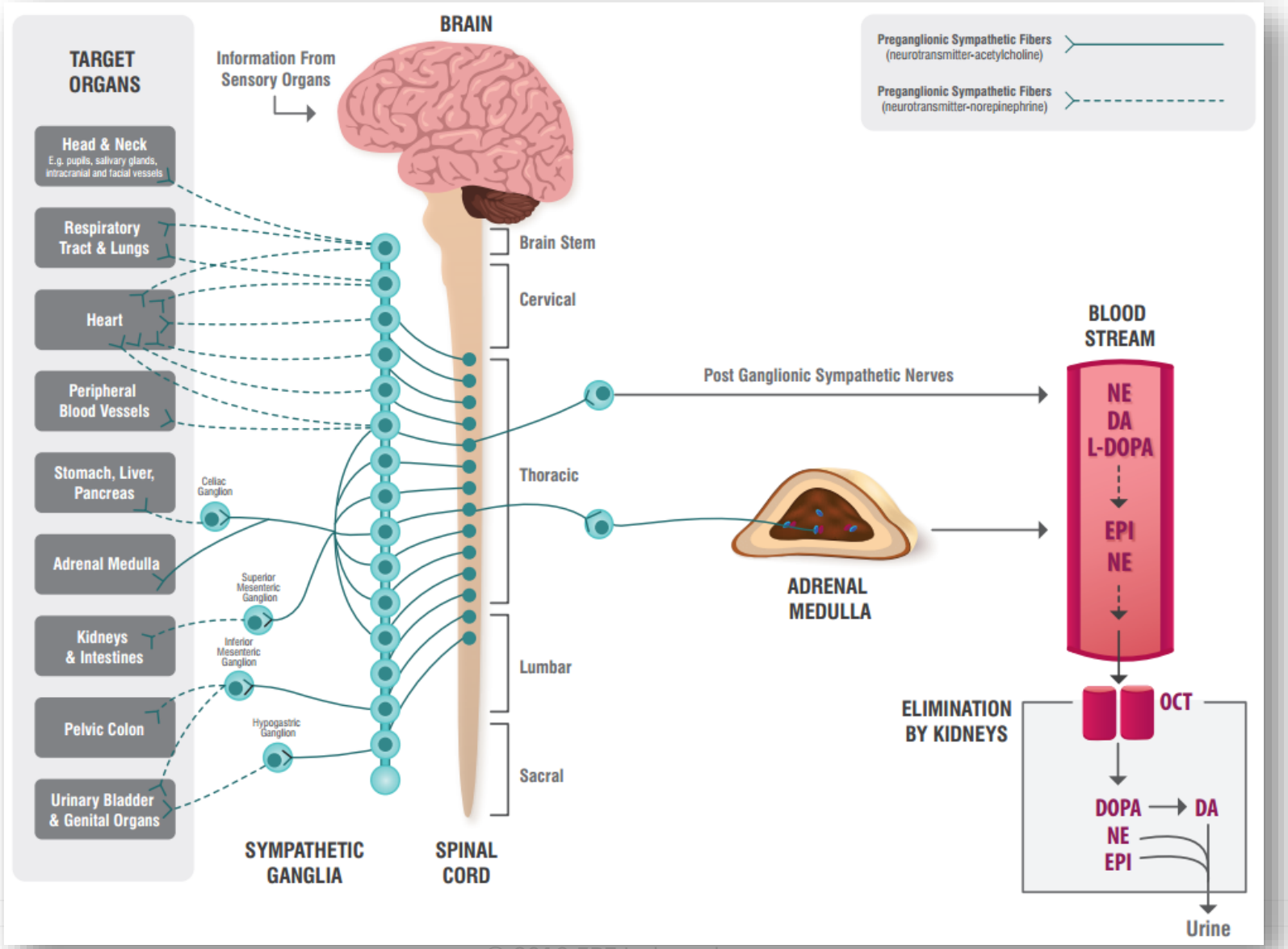
SYMPATHO-ADRENAL SIGNALING



ADRENAL ANATOMY

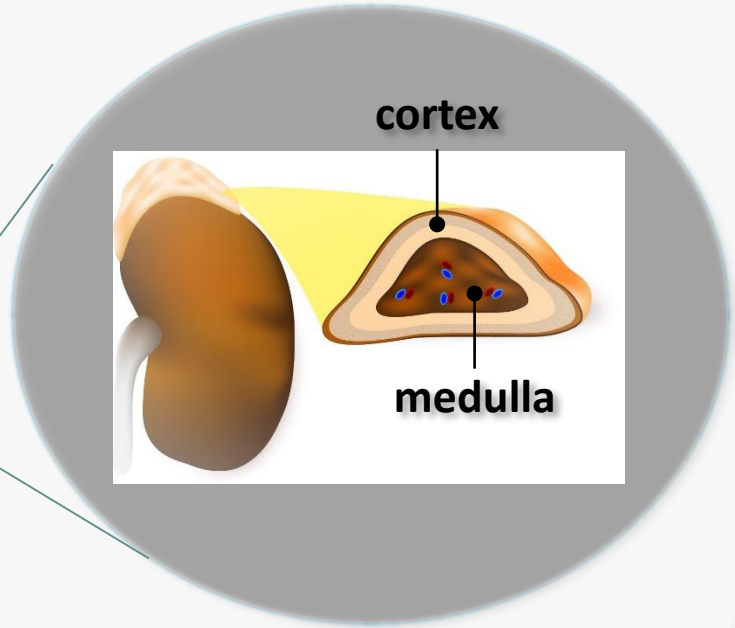
HYPOTHALAMUS

CRH

PITUITARY

ACTH

ADRENAL GLANDS



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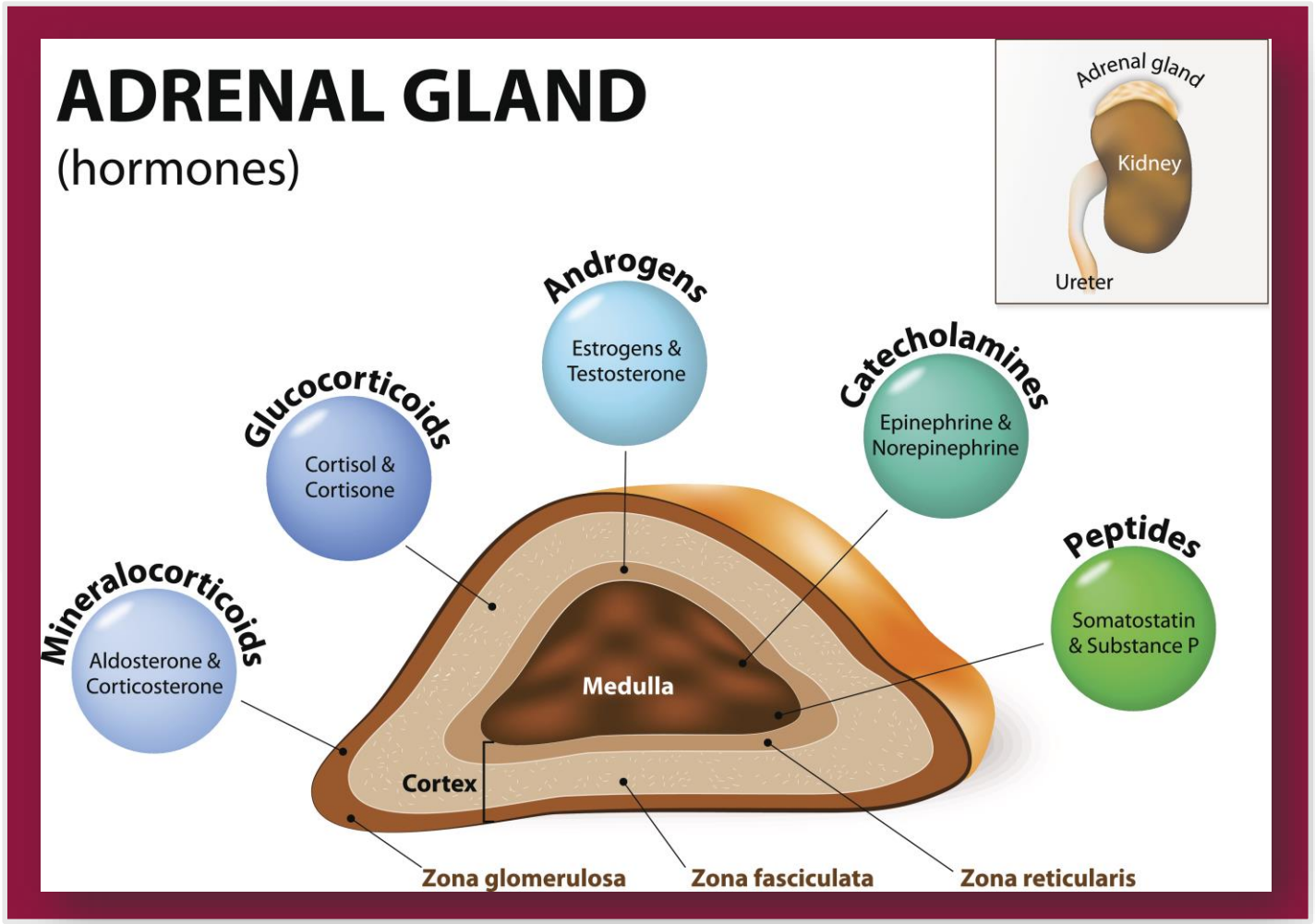
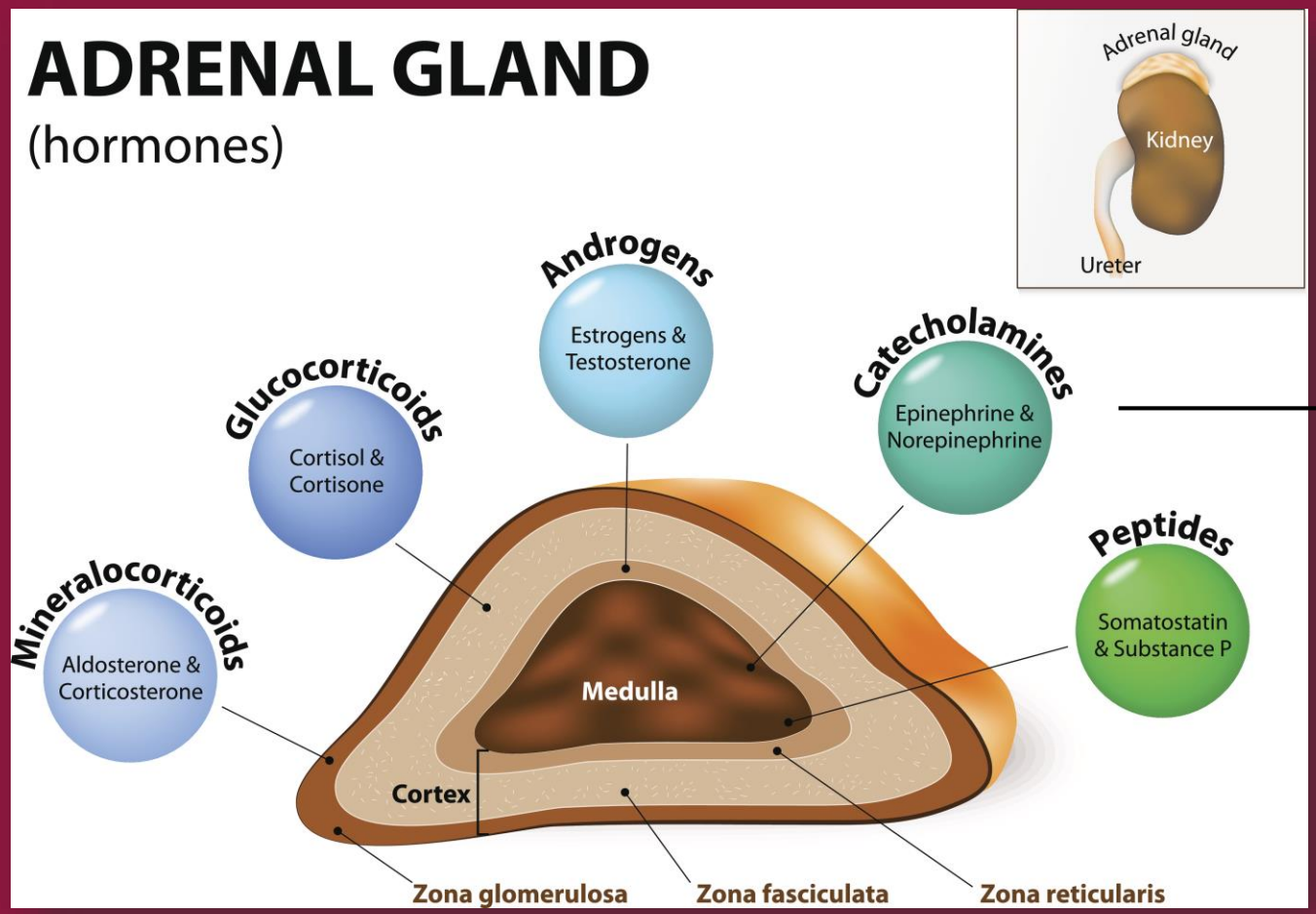
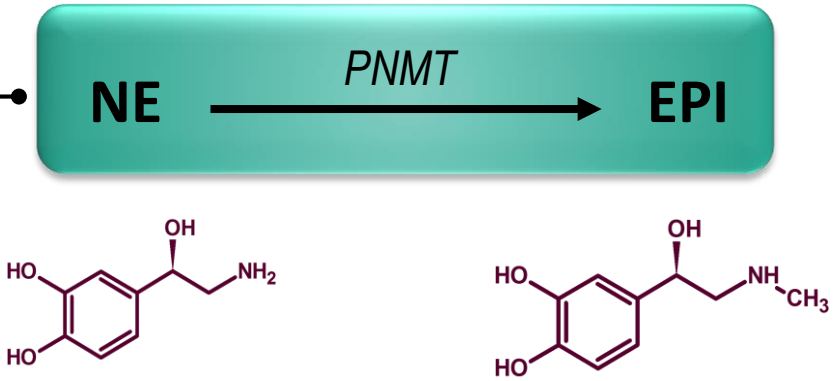


ADRENAL GLAND

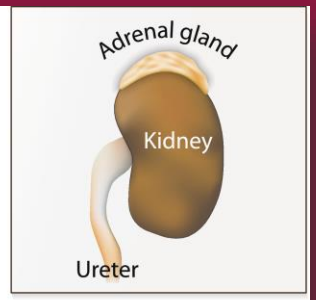
(hormones)

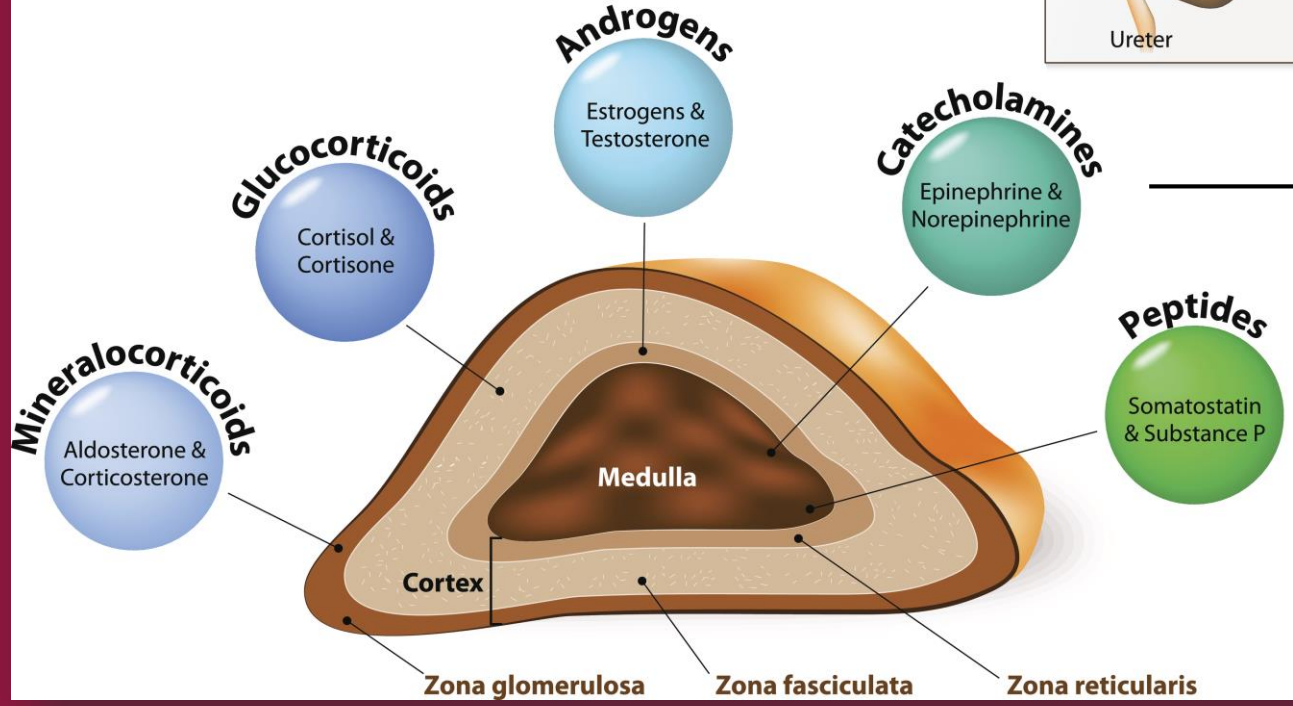




ADRENAL GLAND

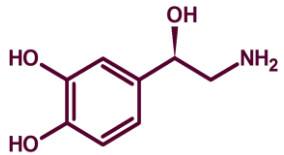
(hormones)

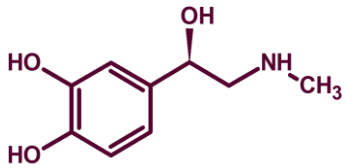




cortisol

NE —*PNMT*→ **EPI**





HPA AXIS – CORTISOL

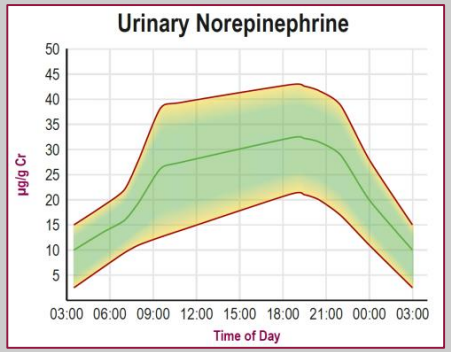
Sympatho - adrenal nervous system – NE & EPI

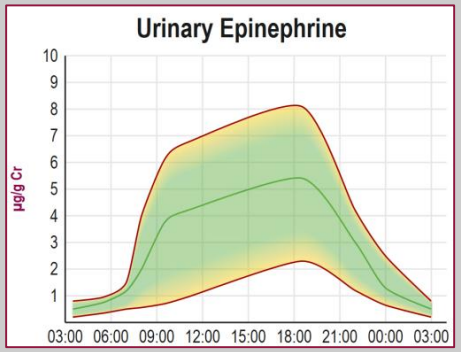
Sympathetic nervous system

FAST

SYMPATHETIC NERVES & ADRENAL MEDULLA

DIURNAL PATTERN





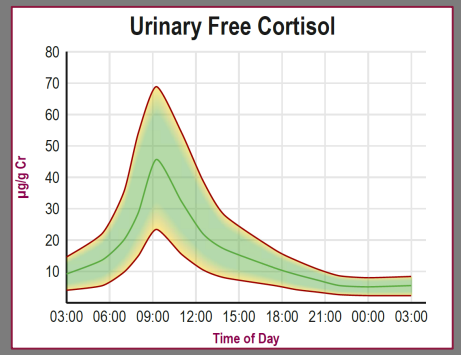
VS

HPA AXIS - CORTISOL

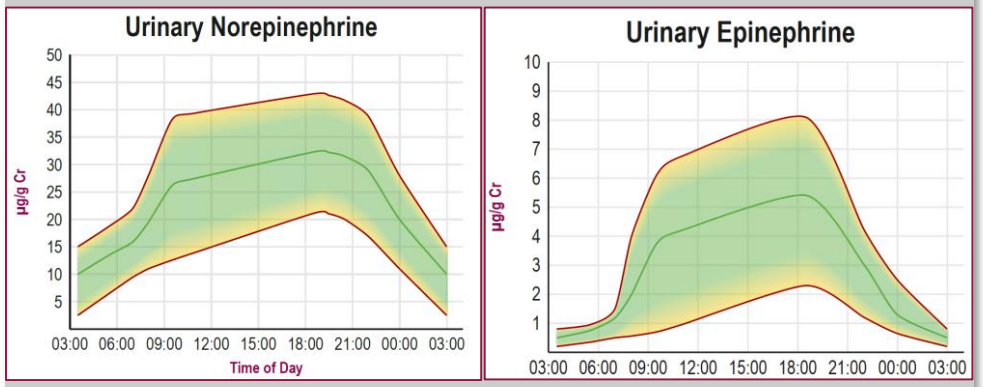
SLOW, SUSTAINED

ADRENAL CORTEX

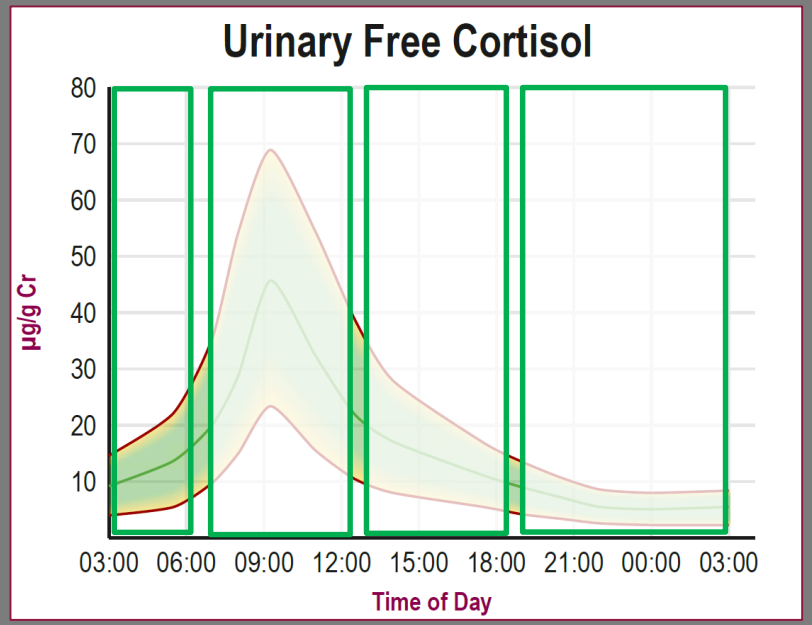
CIRCADIAN REGULATION



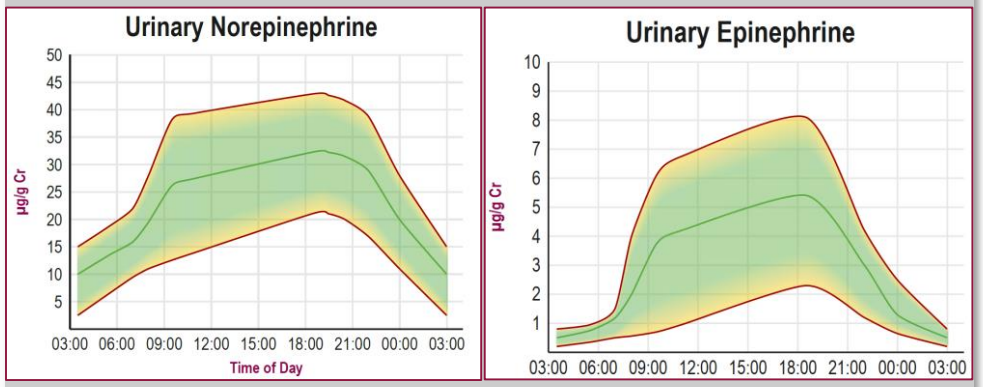
Sympathetic nervous system



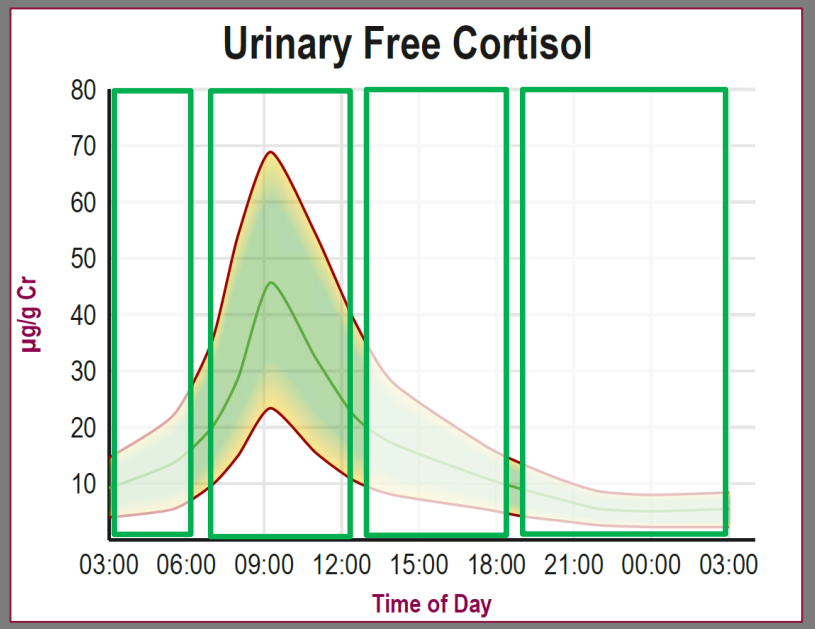
HPA AXIS - CORTISOL



Sympathetic nervous system



HPA AXIS - CORTISOL



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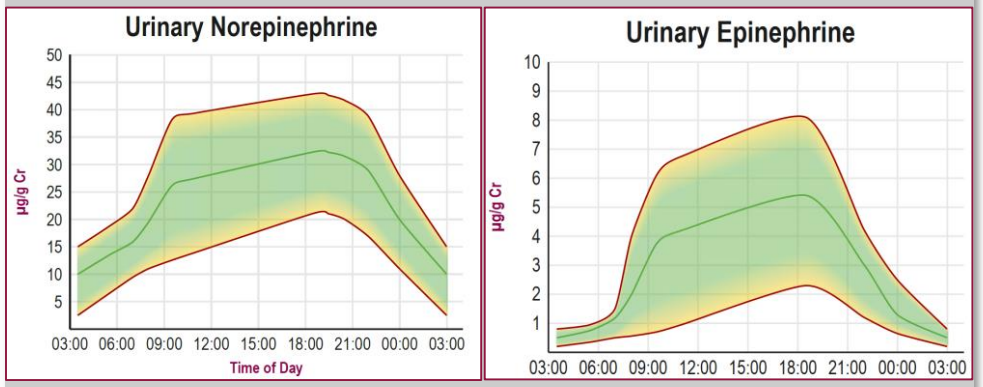
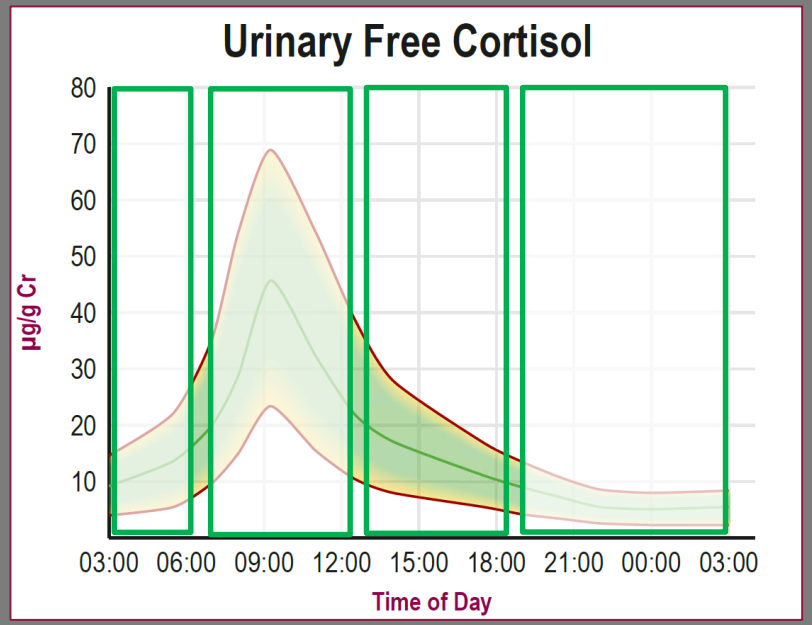


HPA AXIS - CORTISOL



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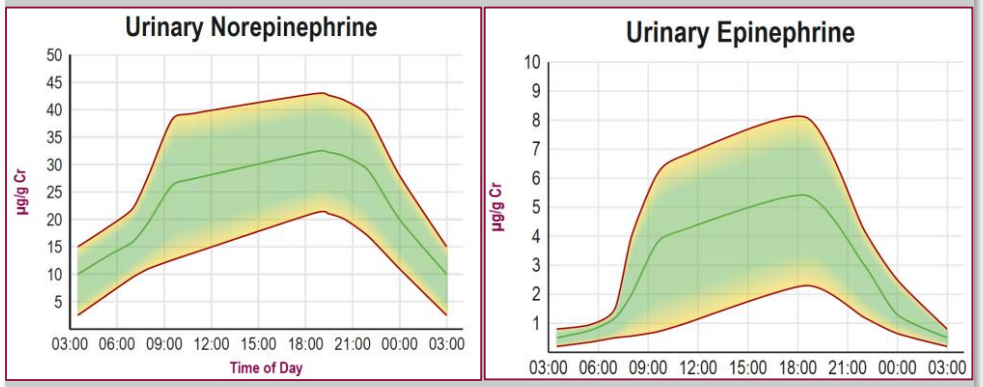
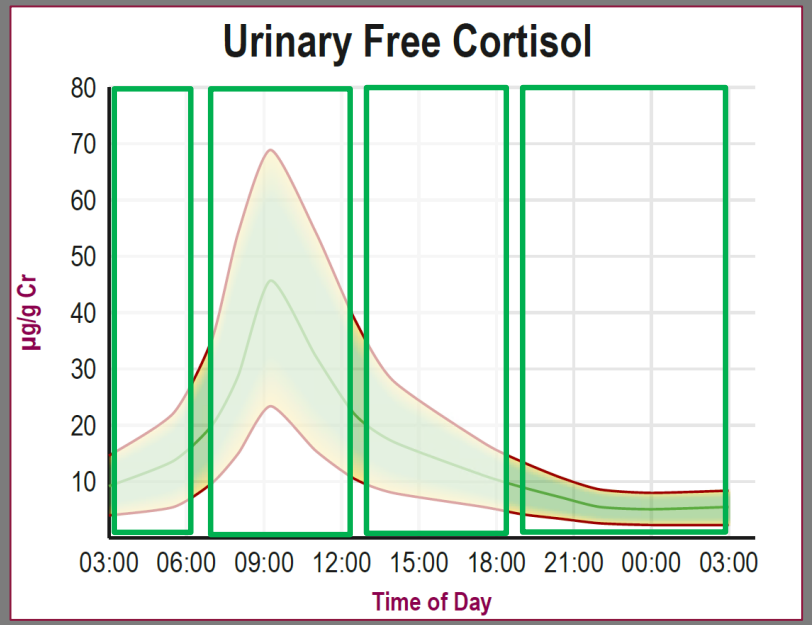
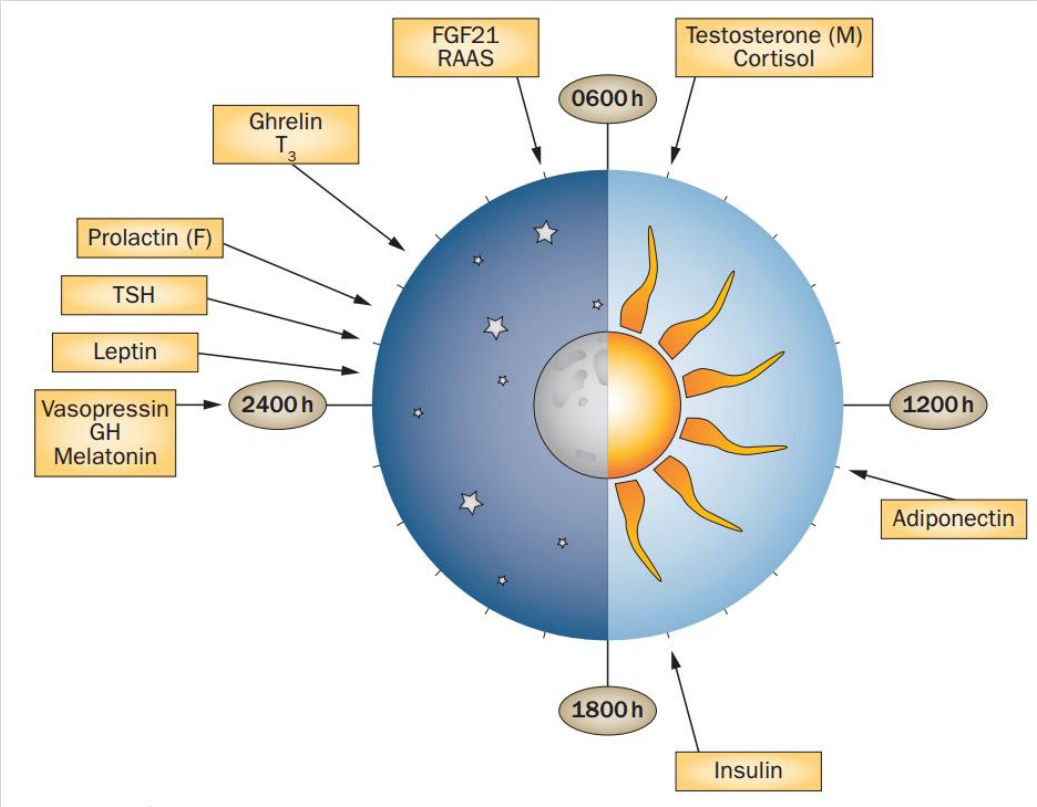


HPA AXIS - CORTISOL



CIRCADIAN ALIGNMENT



CIRCADIAN MISALIGNMENT

STRESS

- Disrupted sleep
- Irregular feeding times
- Decreased exercise
- Artificial light

HYPERACTIVATION OF HPA AXIS

LOSS OF CORTISOL PULSATILITY

MALADAPTATION OF HPA AXIS

INAPPROPRIATE INFLAMMATION RESPONSE

Gamble, et. al. 2014 *Nat. Rev. Endocrinol.* 10

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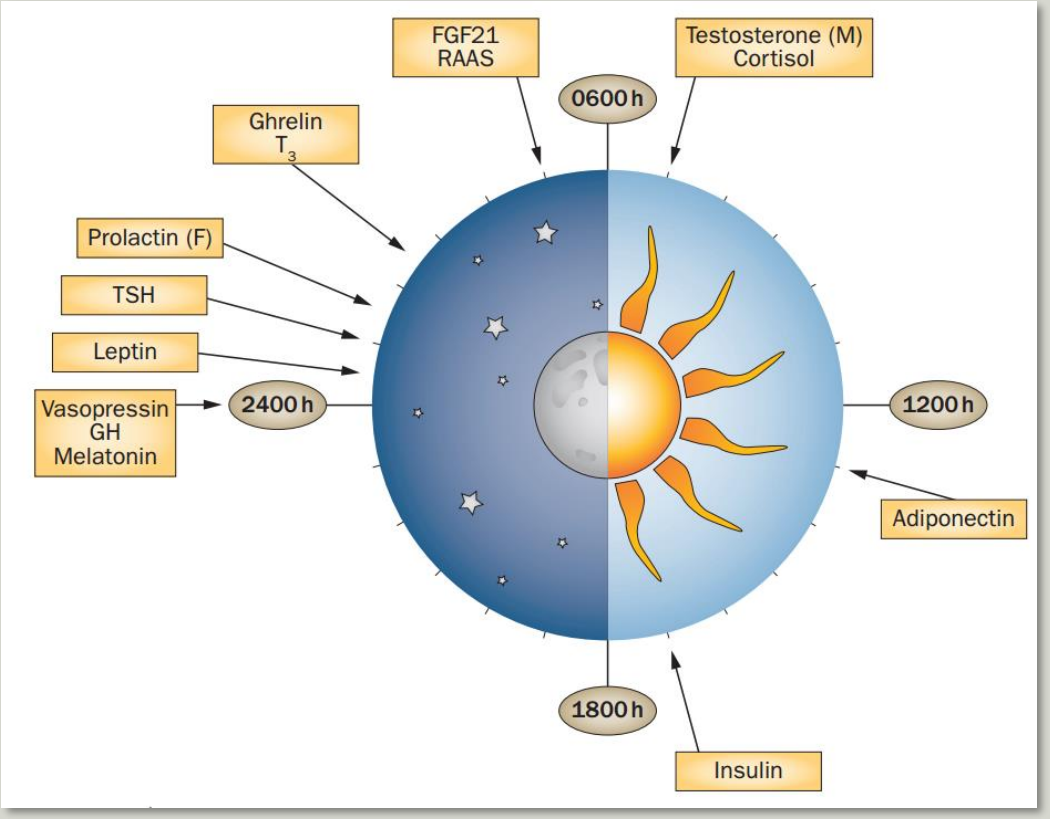
CIRCADIAN ALIGNMENT



CIRCADIAN MISALIGNMENT

STRESS

- Disrupted sleep
- Irregular feeding times
- Decreased exercise
- Artificial light

HYPERACTIVATION OF HPA AXIS

TOO MUCH CORTISOL @ INAPPROPRIATE TIMES

MALADAPTATION OF HPA AXIS

INAPPROPRIATE INFLAMMATION RESPONSE

Gamble, et. al. 2014 *Nat. Rev. Endocrinol.* 10

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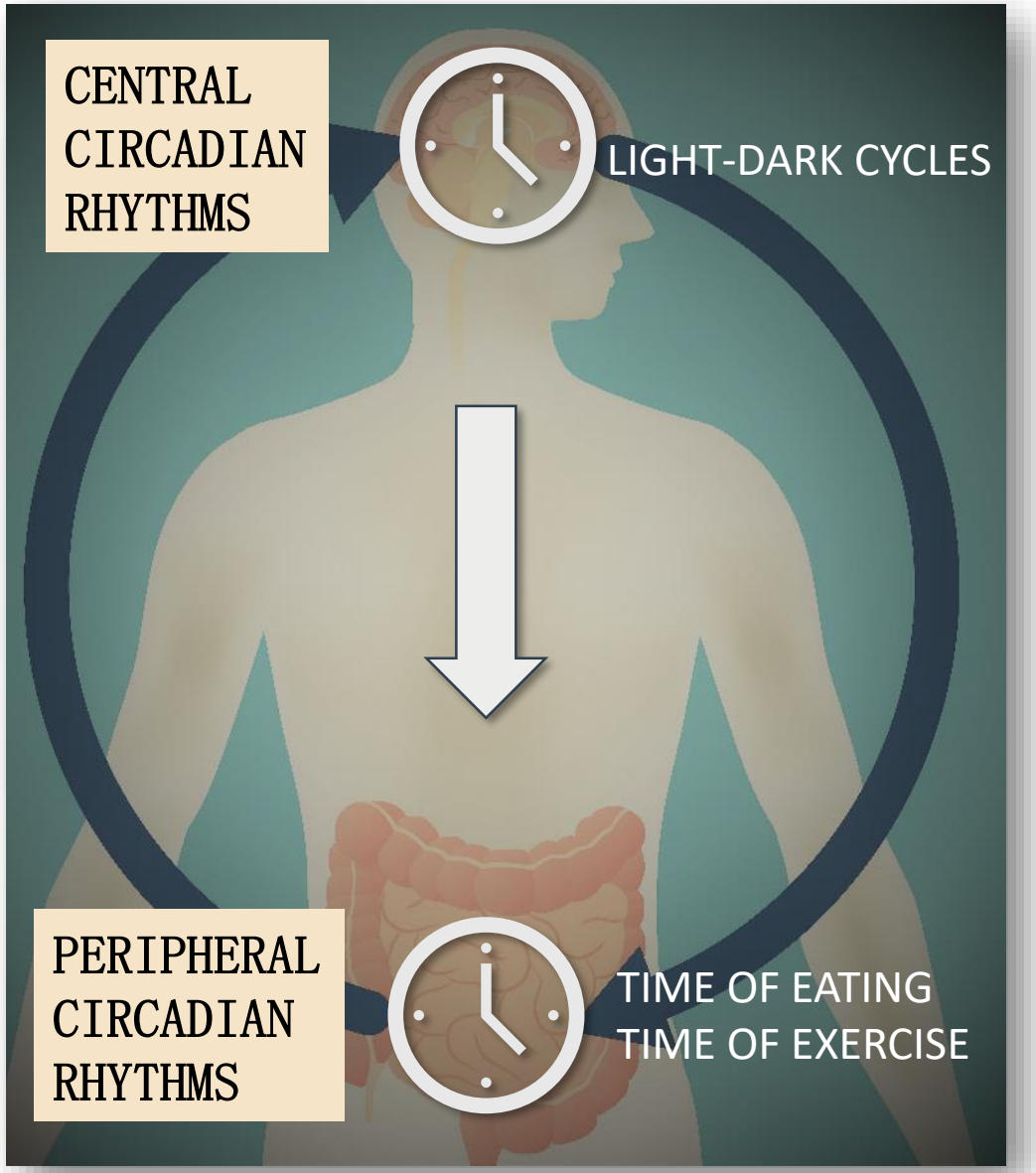

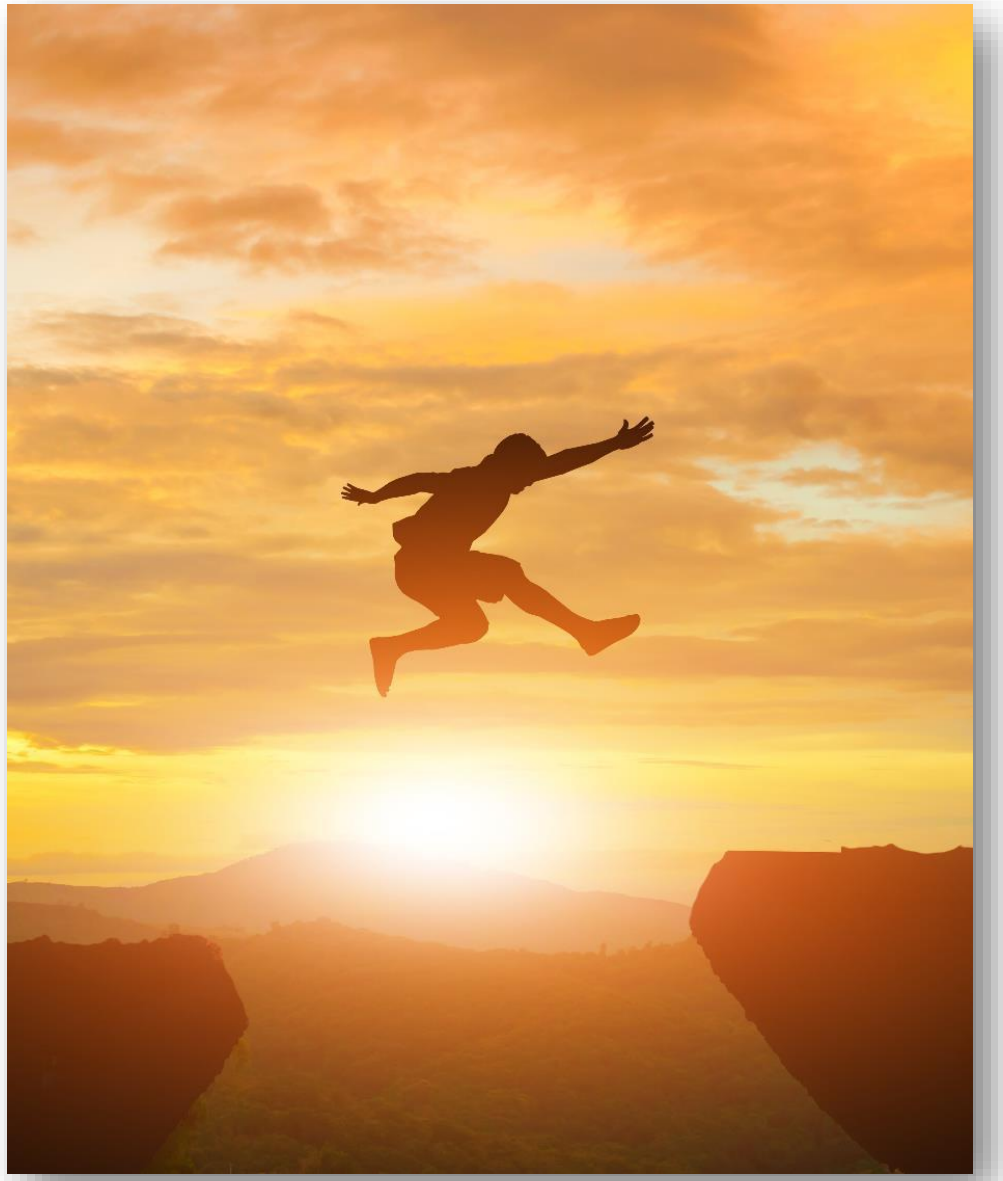

Adapted from Voigt, et. al. 2016 *International Reviews of Neurobiology* 131

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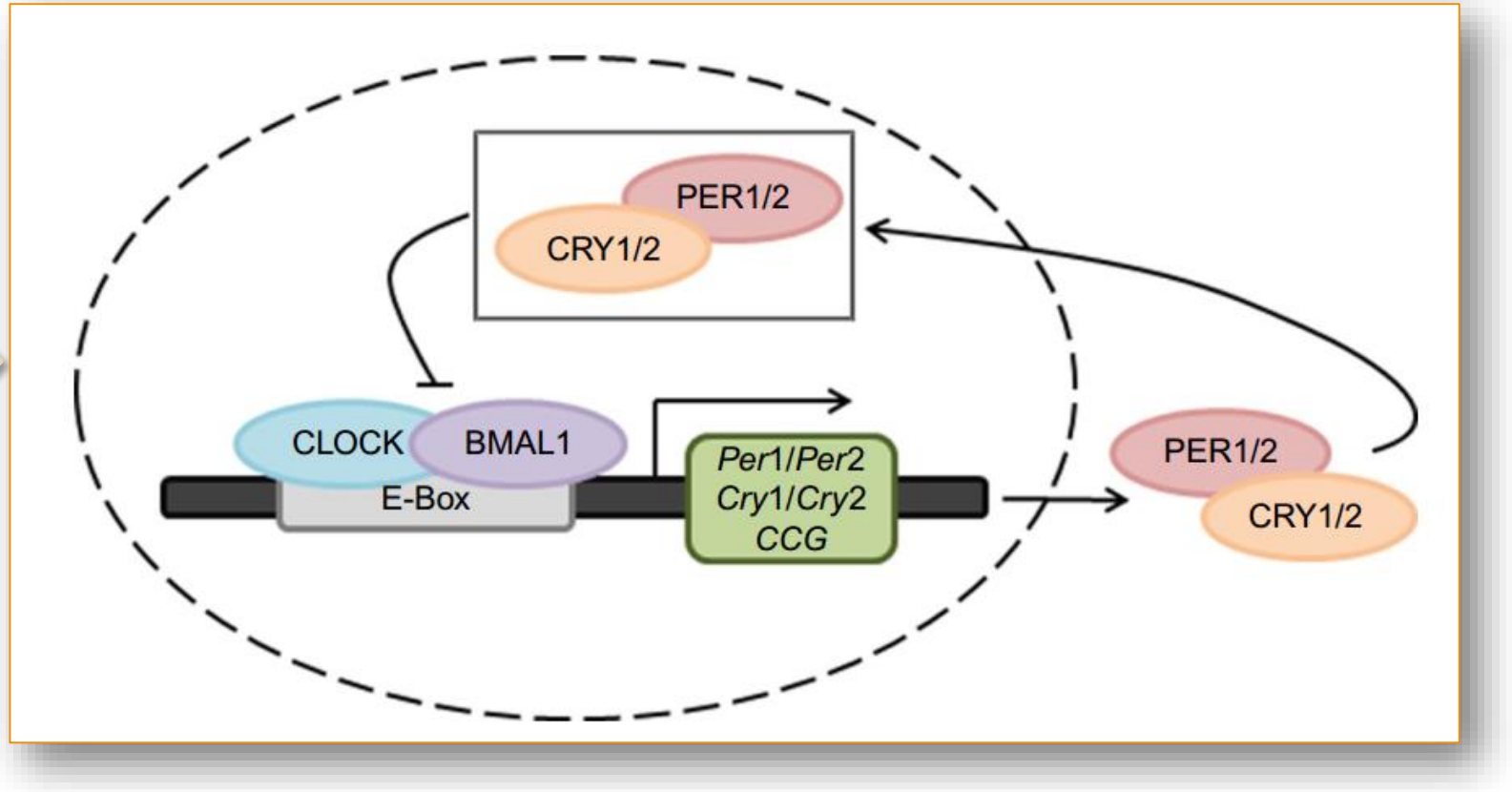
THE MOLECULAR CIRCADIAN CLOCK

SCN IN THE HYPOTHALAMUS



Voigt, et. al. 2016 *International Reviews of Neurobiology* 131

THE MOLECULAR CIRCADIAN CLOCK

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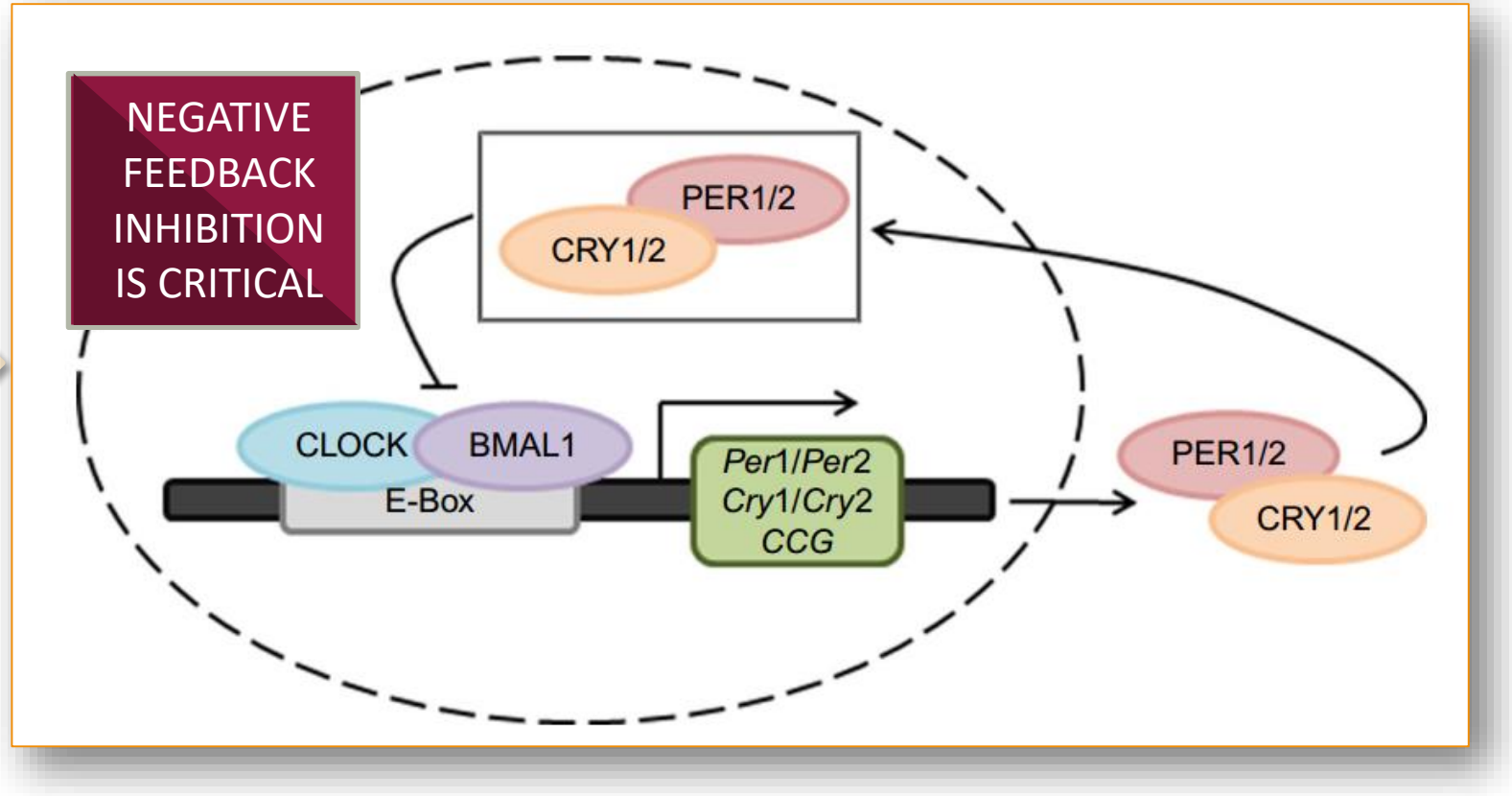
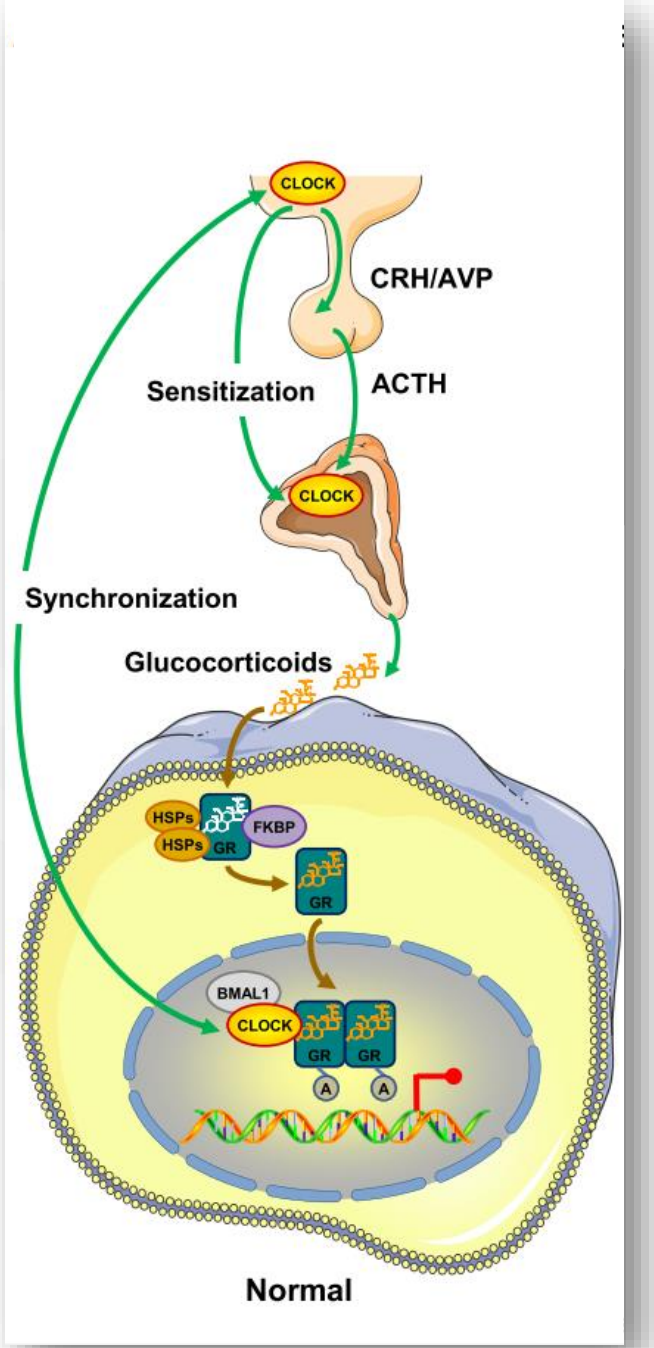
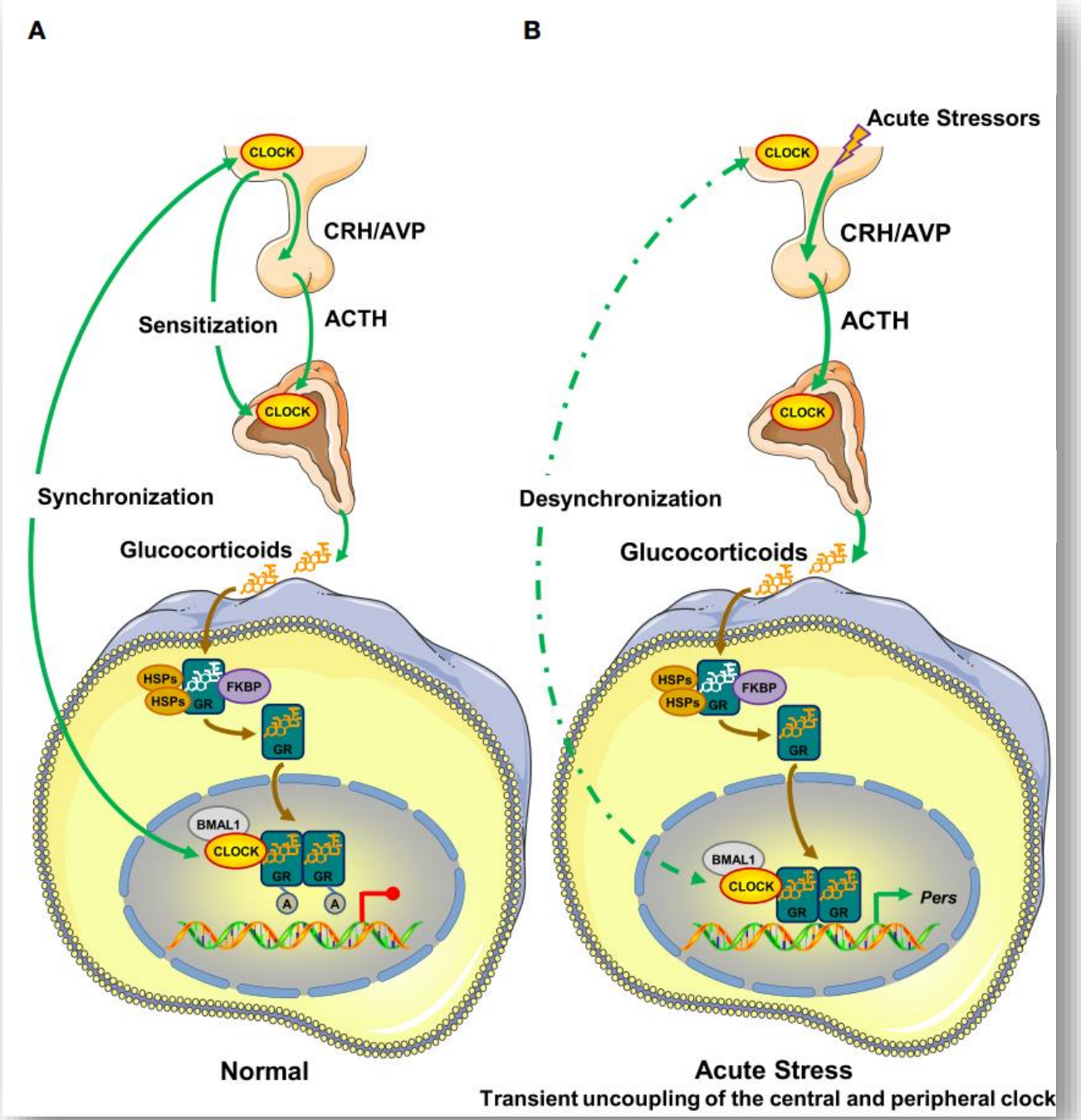


Voigt, et. al. 2016 *International Reviews of Neurobiology* 131



Nicolaides, et. al. 2017 *Frontiers in Endocrinology* 8 (70)



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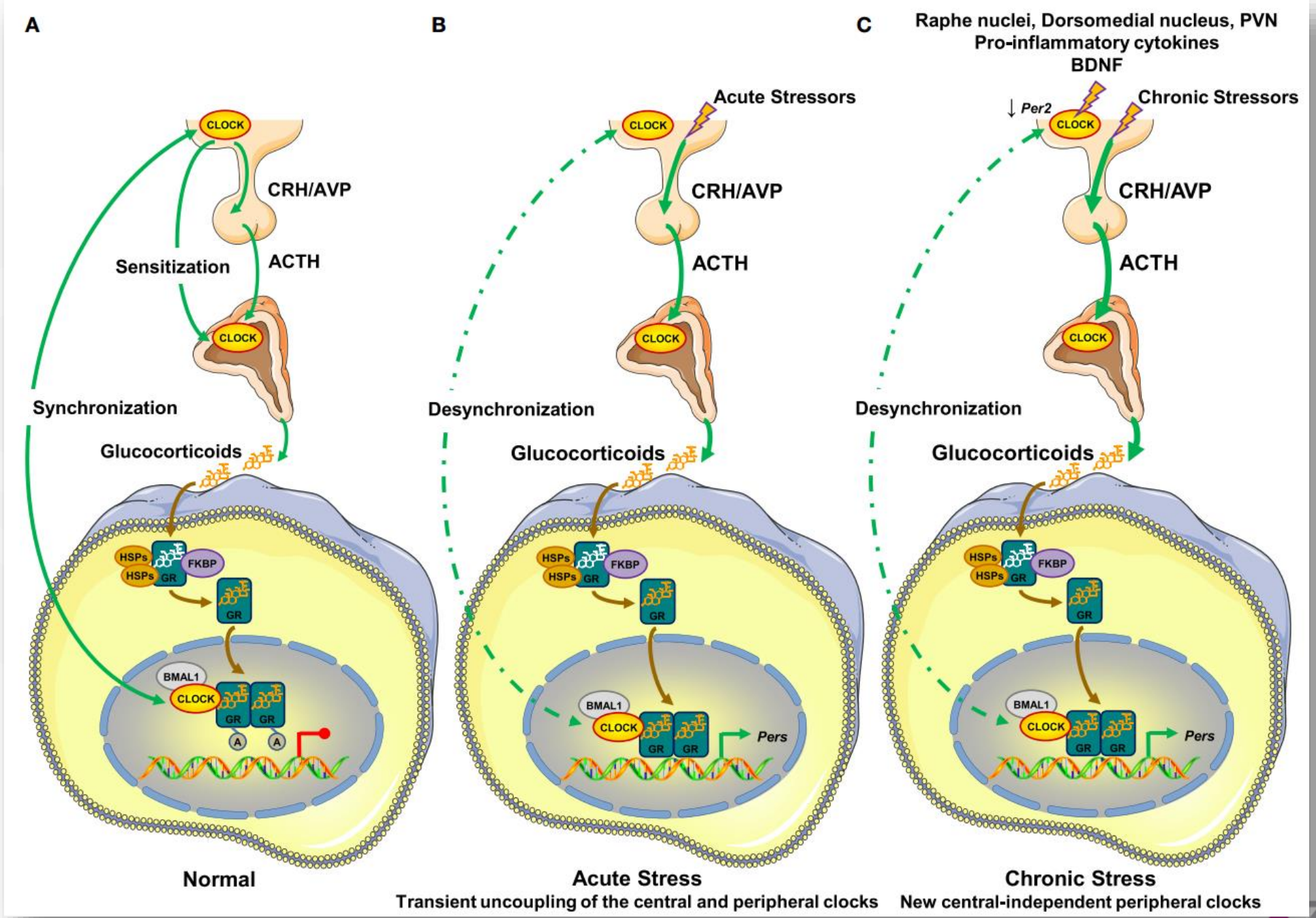
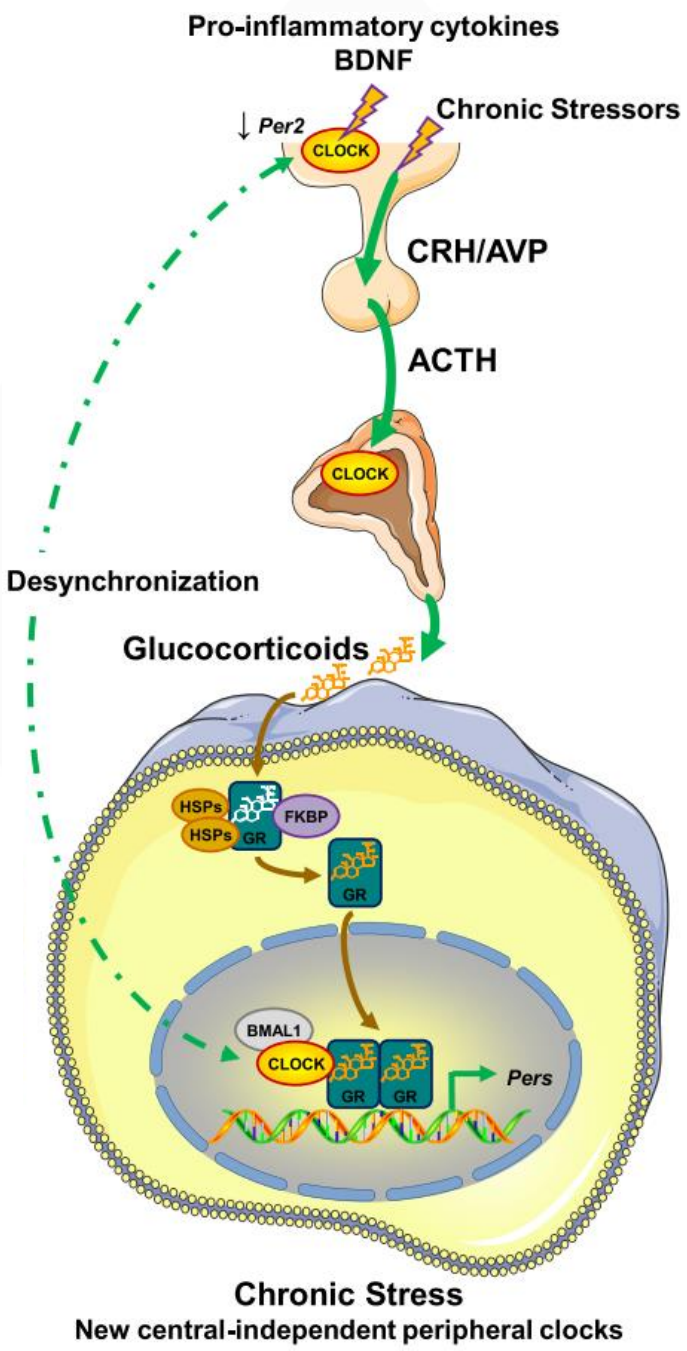


Nicolaides, et. al. 2017 *Frontiers in Endocrinology* 8 (70)

CHRONIC STRESS LEADS TO DESYNCHRONIZATION



↑↑ CORTISOL → GLUCO-CORTICOID RECEPTOR DESENSITIZATION → LOSS OF NEGATIVE FEEDBACK → ↑↑↑↑ CORTISOL → LOSS OF CORTISOL PULSATILITY → DESYNCHRONIZATION

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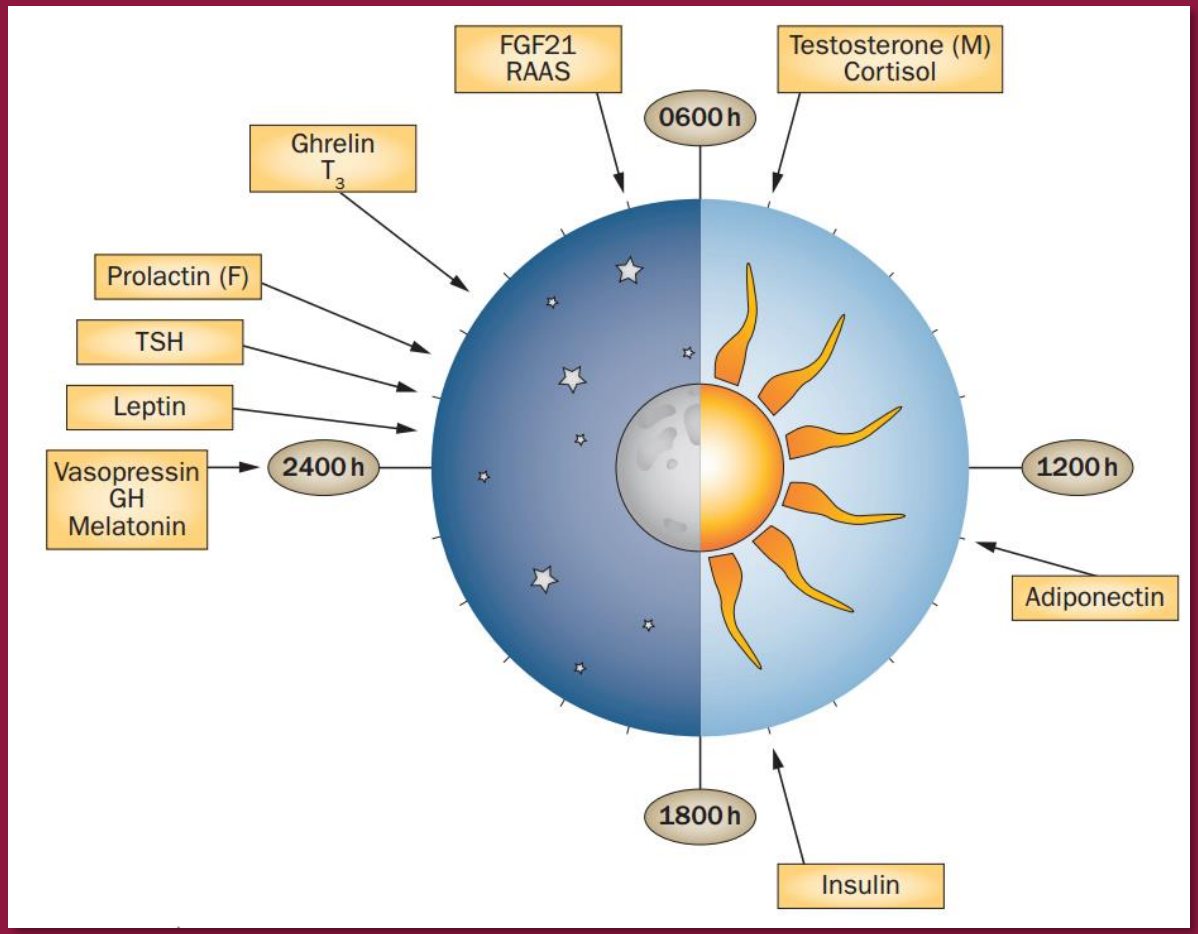
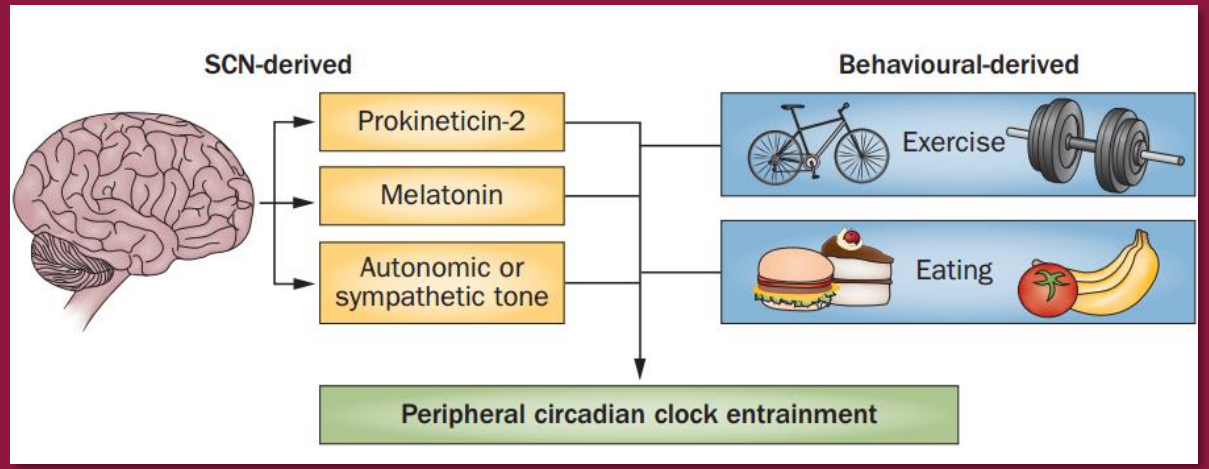
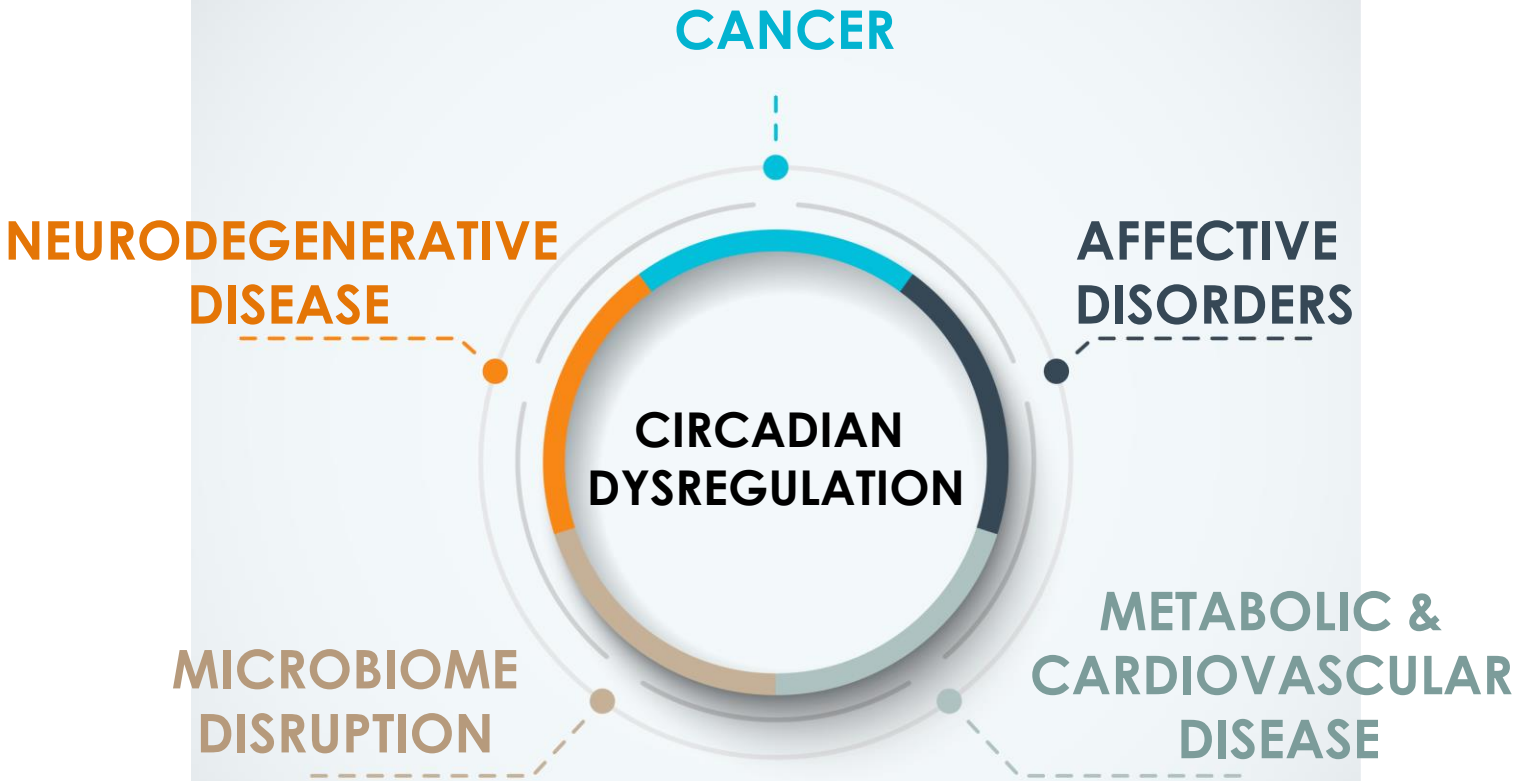




Key points

- Various endocrine factors are known to exhibit time-of-day-dependent oscillations in both humans and animals
- Endocrine factor rhythms are driven not only by environmental and behavioural influences, but also by intrinsic circadian clocks
- Circadian dyssynchrony is associated with multiple pathologic states, including cardiometabolic diseases and cancer
- Reinstatement of circadian synchrony through time-of-day-restricted feeding and pharmacologic strategies improves metabolic homeostasis

Gamble, et. al. 2014 *Nat. Rev. Endocrinol.* 10



Bunney 2015 *Mol Psychiatry* 20(10)
Maury 2010 *Circ Res* 106(3)
Lin 2018 *Front Endocrinol* 9(219)
Voigt 2016 *Int Rev of Neurobiol* 131
Abbott 2016 Nature and Science of Sleep 8

CLINICAL APPLICATION

Circadian Rhythms –
Assessment to Treatment

Chronodisrupted States

- Alzheimer's
- Bipolar
- Cancer
- Cardiovascular Disease (and ↑ events)
- Depression
- Diabetes (Type 2)
- GI Problems (IBS, IBD, etc)
- Hypertension (non-dippers, esp)
- Insomnia (+ other sleep problems)
- Liver Diseases (NASH, NAFLD, HCC)
- Obesity
- Parkinson's
- Sleep Apnea

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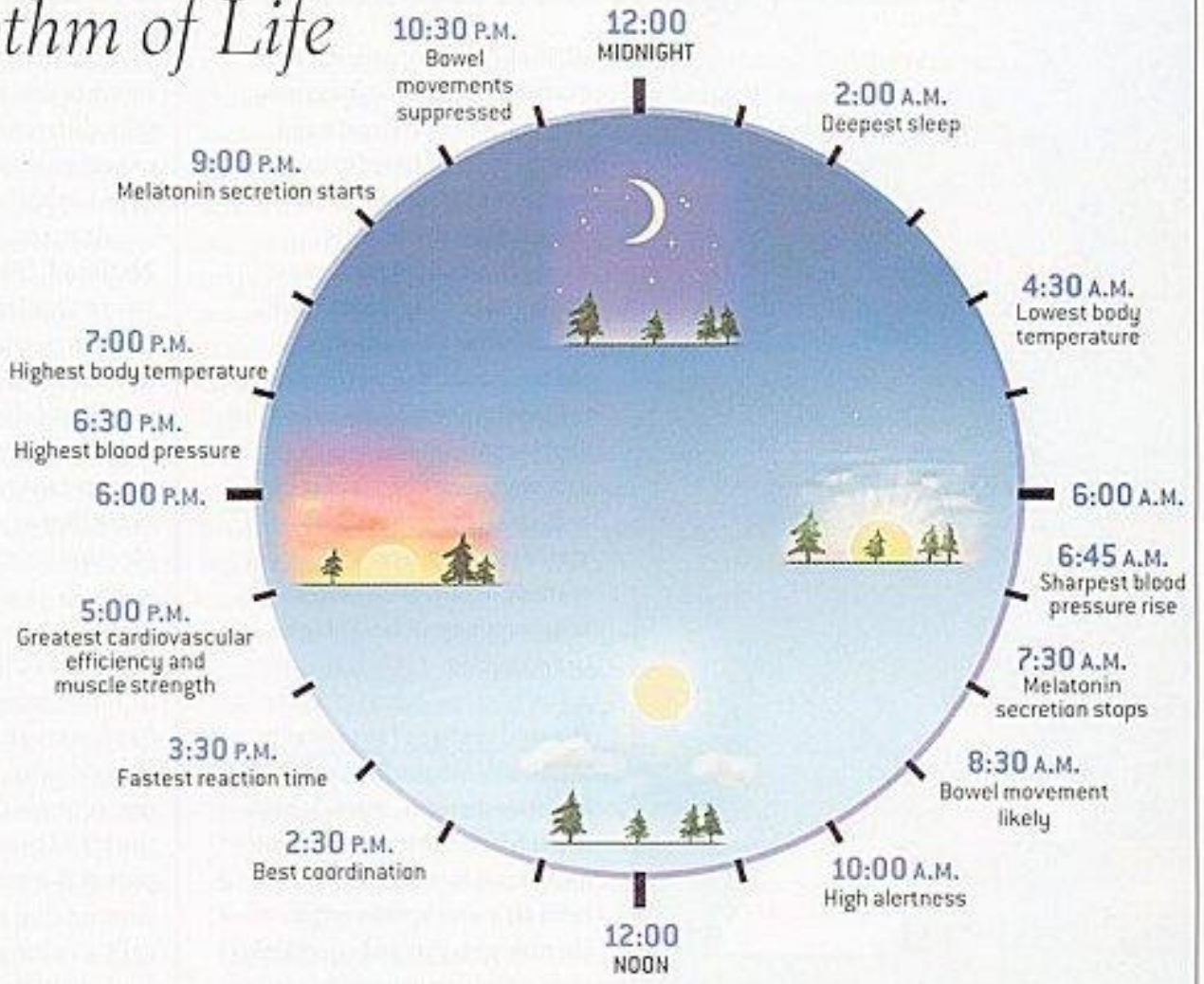
Symptoms of Chronodisruption

- Anxiety
- Depression
- Emotional disturbances
- Fatigue
- Foggy thinking “brain fog”
- Metabolic syndrome constellation
- Pain
- Perceived stress
- Sleep problems
- Weight gain

CYCLIC EVENTS

The Rhythm of Life

THE CIRCADIAN CLOCK affects the daily rhythms of many physiological processes. The diagram at the right depicts the circadian patterns typical of someone who rises early in the morning, eats lunch around noon and sleeps at night. Although circadian rhythms tend to be synchronized with cycles of light and dark, other factors—such as ambient temperature, meal times, stress and exercise—can influence the timing as well. —*K.W.*

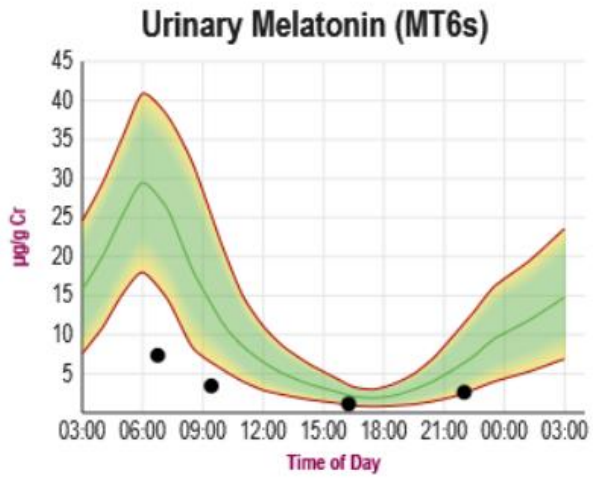


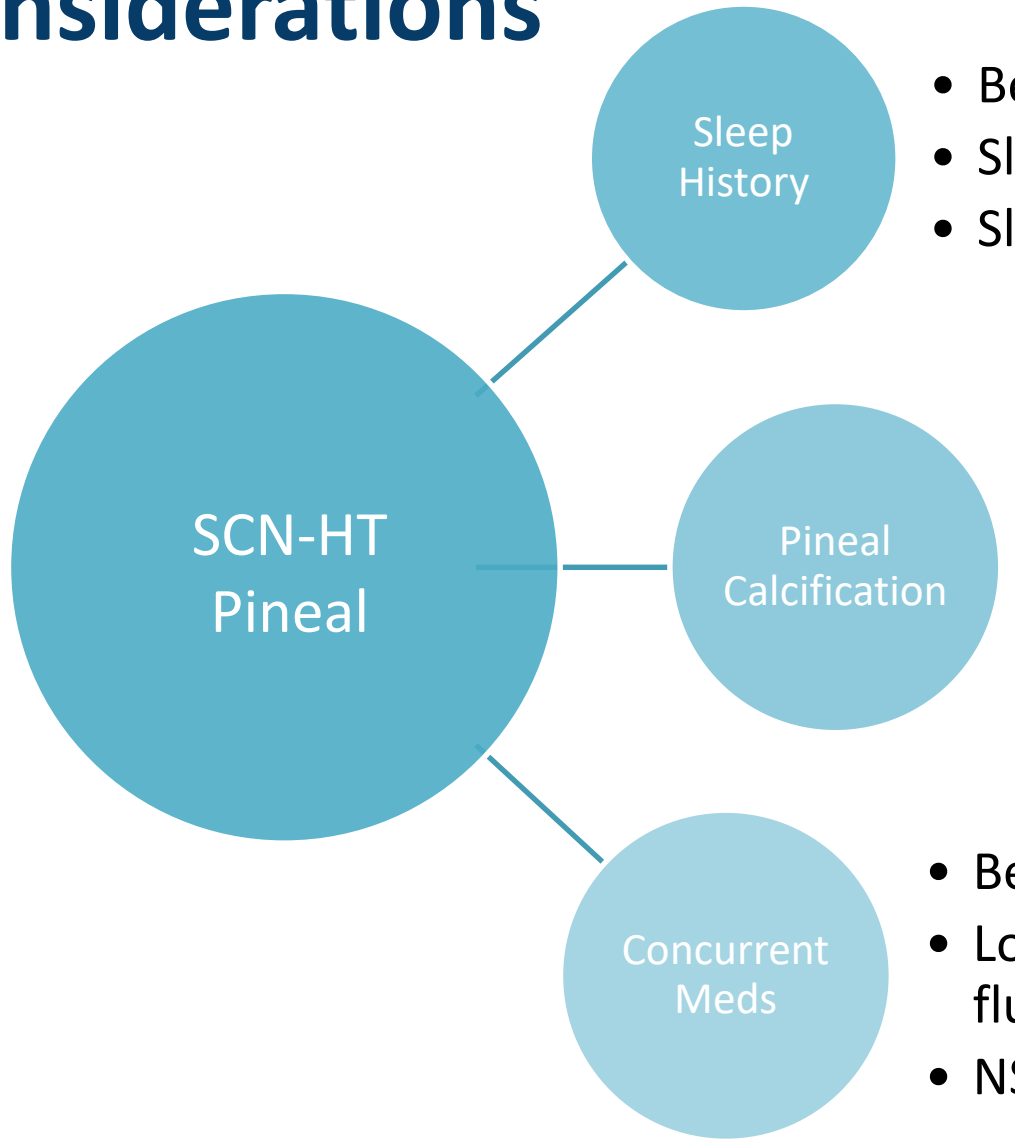
SOURCE: The Body Clock Guide to Better Health, by Michael Smolensky and Lynne Lamberg. Henry Holt, 2000

Central Clock Considerations

Light/Dark

Melatonin





- Bedtime practices
- Sleep hygiene
- Sleep latency

- Assess likelihood
- Pt age, HTN, renal dz, history of chemo or radiation, schizophrenia….

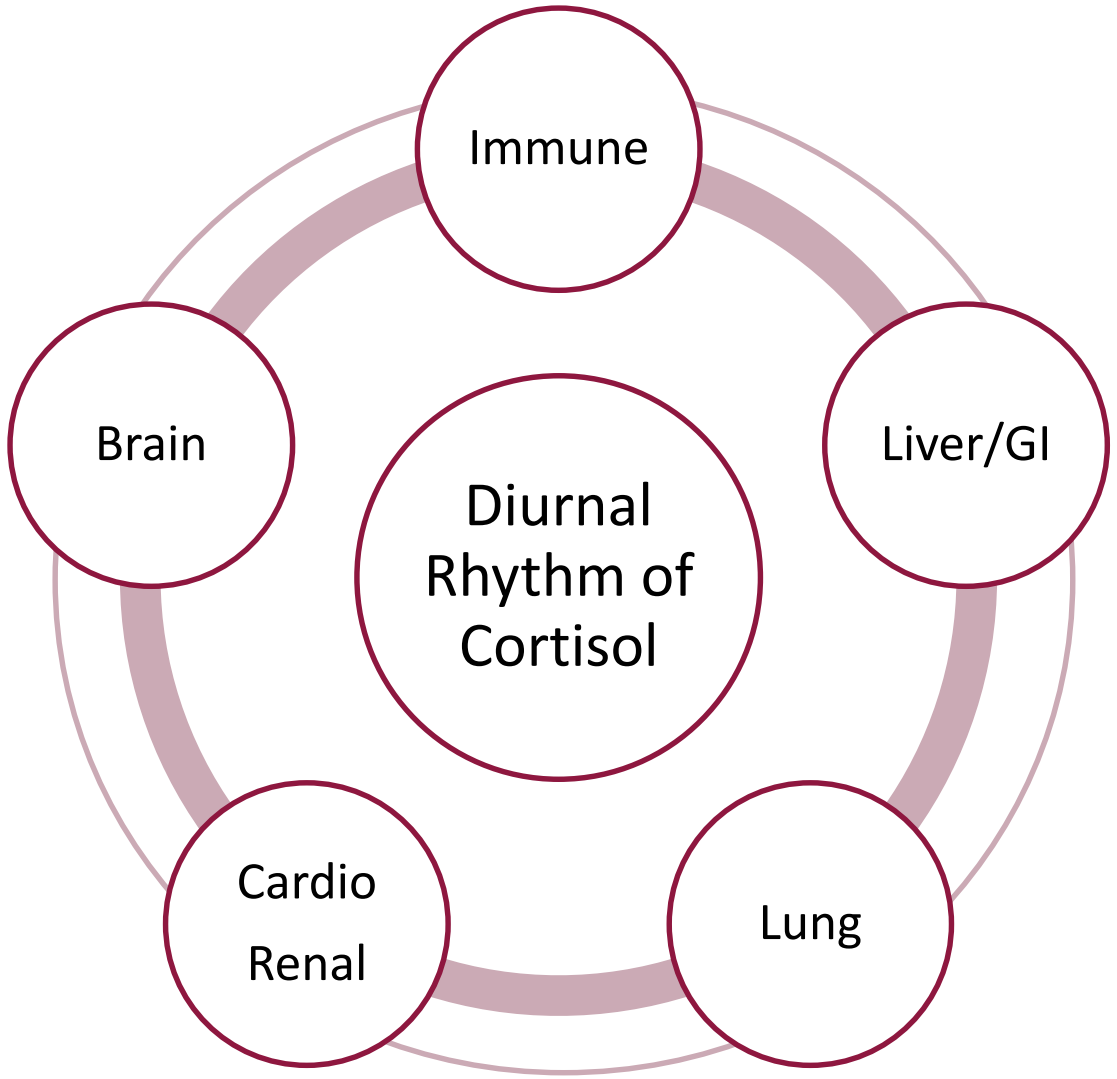
- Beta blockers
- Long term fluoxetine
- NSAIDs

Melatonin Roles

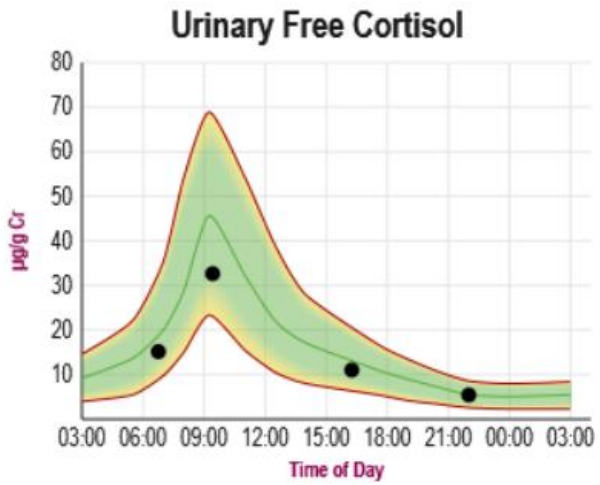
- Anti-inflammatory
- Anti-oxidant
- Centrally sedating (melatonin comes up, NE and cortisol come down)
- Gut immune modulator
- ↑ Insulin sensitivity/ Hypoglycemic
- Maintain leptin sensitivity

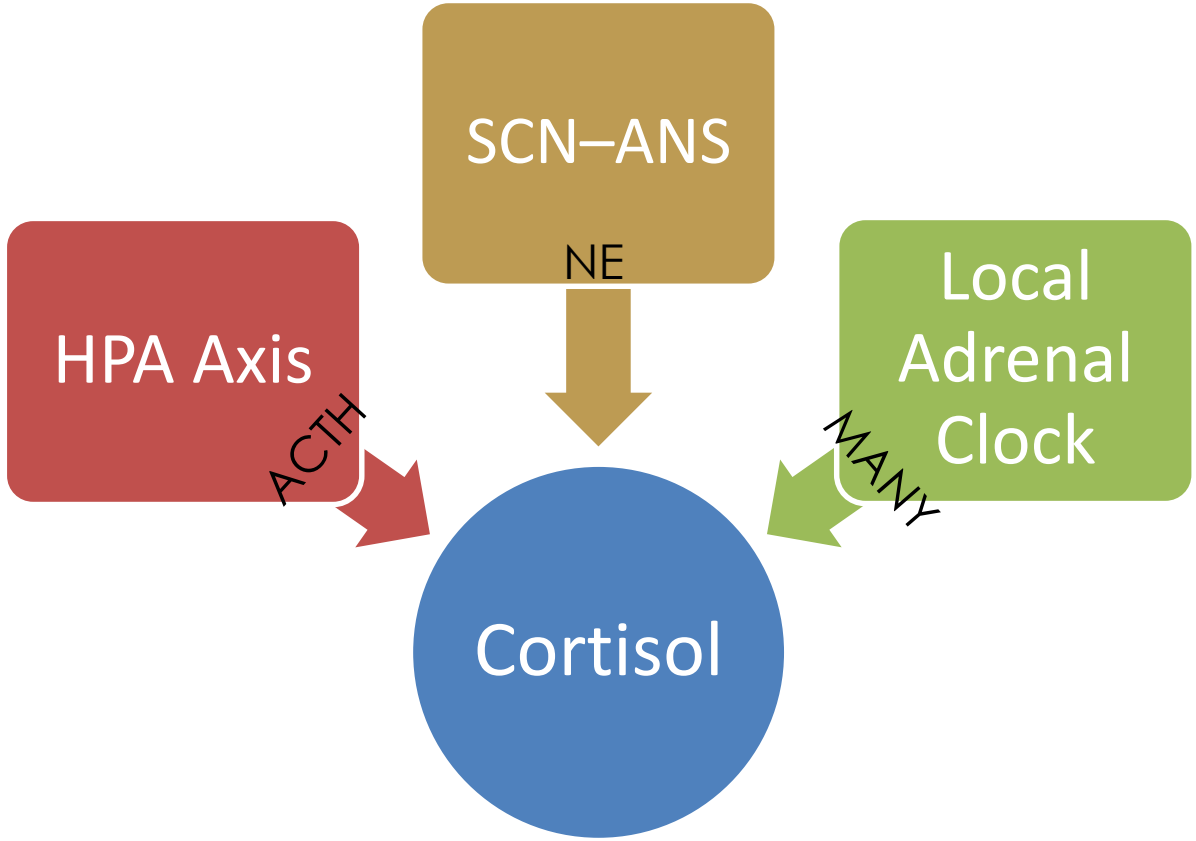
Why doesn't melatonin monotherapy always work?

Peripheral Clocks Synchronize Around Cortisol Rhythm



Peripheral Clocks - Adrenal





Local Adrenal Clock Mediators

Immune/Inflammation
(TNFα, IL-6, VIRUSES)

Dysglycemia
(Insulin, Glucose
Glucagon)

NOT UNDER HPA AXIS CONTROL

MAINTAINED BY SCN-ANS

FOOD ENTRAINABLE

Sympathetic
NS Activity
(NE + EPI)

Assessing Sympathetic Activity

- Urinary NE → sympathetic tone/activity
- Urinary Epi → adrenal activity in response to sympathetic activity
- AND disrupted daily rhythms of NE and/or Epi desynchronize peripheral clocks
  - Through cortisol

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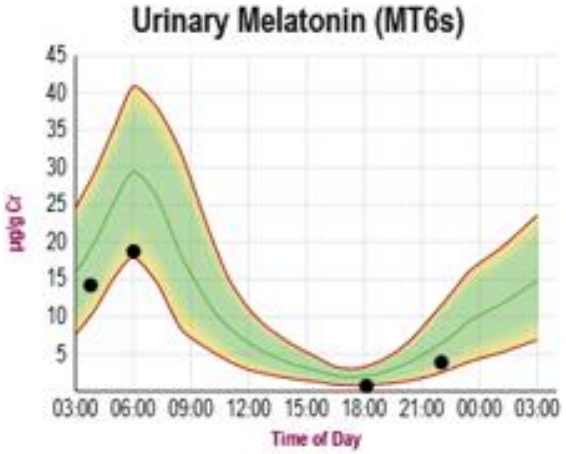
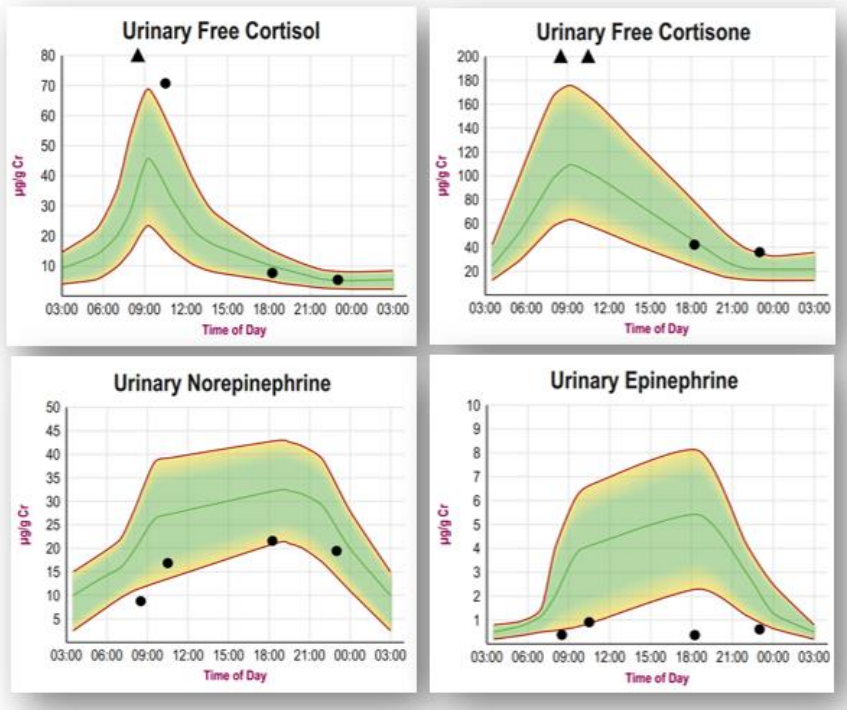
Testing for Synchronization

- Central Clock
  - Diurnal Melatonin (urine or saliva*)
- Peripheral Clocks
  - Diurnal Cortisol (urine or saliva)
  - Diurnal Norepinephrine (urine)
  - Diurnal Epinephrine (urine)
- Dried Urine: 4 samples collected
  - Waking, waking + 2hr, evening, bed

*Possible problems with sampling during sleeping hours





Diverse Approach

Protect clock synchrony

- Reprogram stress response (adaptogens, nervines, meditation, neurofeedback)
- Reinforce conscious, habitual, diurnal schedule if possible with respect to light/dark cycle (sleep hygiene, melatonin, BLT, exercise)
- Eat with intention (breakfast, shorten feeding hrs, high fiber)
- Control inflammatory responses (COX/LOX/Cytokines - polyphenols, ginsenosides, berberine, curuminoids, etc)
- Support immune activity (TH1/TH2 balance, antiviral therapies)
- Protect the microbiome and maintain gut health (fiber, pre- and probiotics. Antimicrobials, motility)

CASES

Shifting Circadian Rhythms –
Create a Foundation for Health

Breast Cancer

63 YO POST-MENOPAUSAL FEMALE

THERAPIES:
None

SYMPTOMS:
BREAST CANCER
Aches and pains
Anxious
Depressed
Foggy thinking
Fatigue
Tearful
Panic attacks
Weight gain
Constipation

SYMPTOM CATEGORIES	RESULTS | 02/22/18
Estrogen / Progesterone Deficiency	46%
Estrogen Dominance / Progesterone Deficiency	51%
Low Androgens (DHEA/Testosterone)	53%
High Androgens (DHEA/Testosterone)	29%
Low Cortisol	49%
High Cortisol	56%
Hypometabolism	49%
Metabolic Syndrome	60%

frontiers in Endocrinology

MINI REVIEW
published: 04 May 2018
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Altered Circadian Rhythms and Breast Cancer: From the Human to the Molecular Level

*Hui-Hsien Lin and Michelle E. Farkas**

Department of Chemistry, University of Massachusetts, Amherst, MA, United States

Circadian clocks are fundamental, time-tracking systems that allow organisms to adapt to the appropriate time of day and drive many physiological and cellular processes. Altered circadian rhythms can result from night-shift work, chronic jet lag, exposure to bright lights at night, or other conditioning, and have been shown to lead to increased likelihood of cancer, metabolic and cardiovascular diseases, and immune dysregulation. In cases of cancer, worse patient prognoses and drug resistance during treatment have also been observed. Breast, colon, prostate, lung, and ovarian cancers and hepatocellular carcinoma have all been linked in one way or another with altered circadian rhythms. Critical elements at the molecular level of the circadian system have been associated with cancer, but there have been fairly few studies in this regard. In this mini-review, we specifically focus on the role of altered circadian rhythms in breast cancer, providing an overview of studies performed at the epidemiological level through assessments made in animal and cellular models of the disease. We also address the disparities present among studies that take into account the rhythmicity of core clock and other proteins, and those which do not, and offer insights to the use of small molecules for studying the connections between circadian rhythms and cancer. This article will provide the reader with a concise, but thorough account of the research landscape as it pertains to altered circadian rhythms and breast cancer.

Keywords: altered circadian rhythms, shift work, breast cancer, molecular mechanism, hormone pathways, small molecule modulators

OPEN ACCESS

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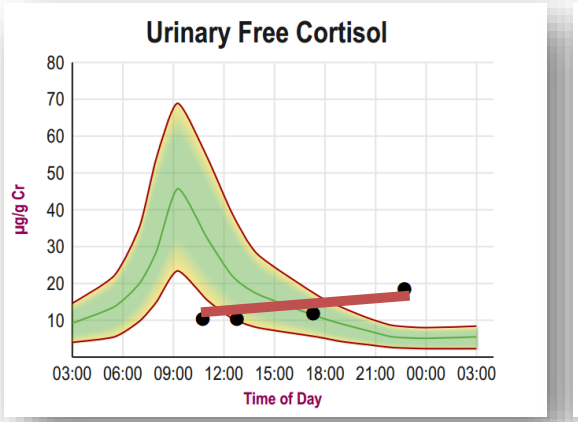
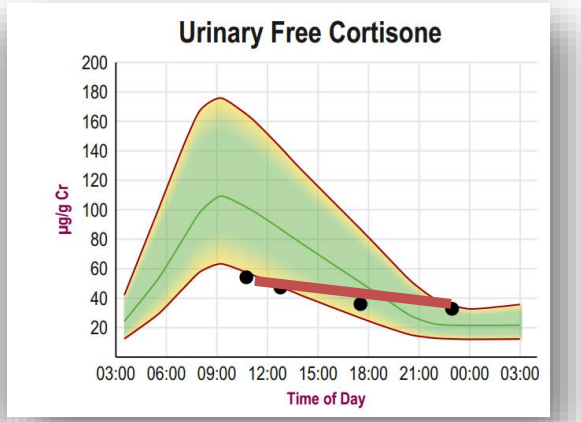
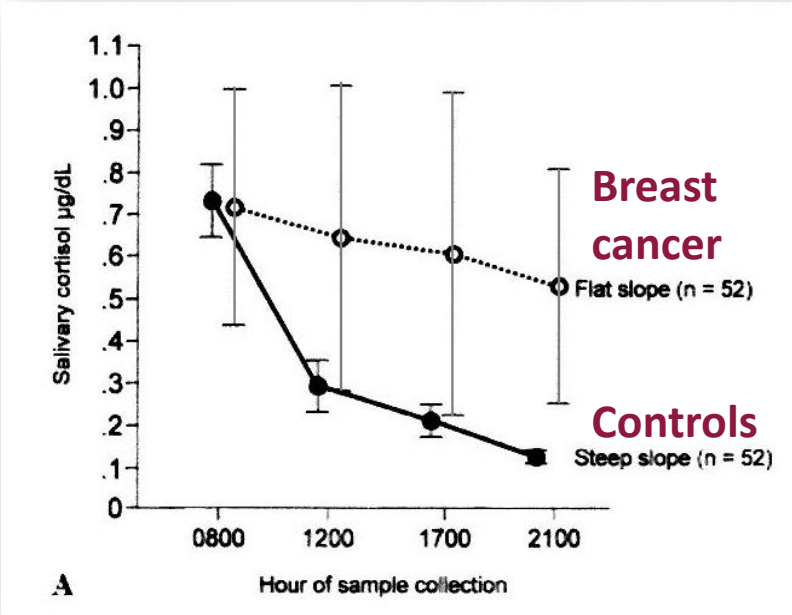






Sephton et. al. 2000 J Natl Cancer Inst Jun 21; 92(12)

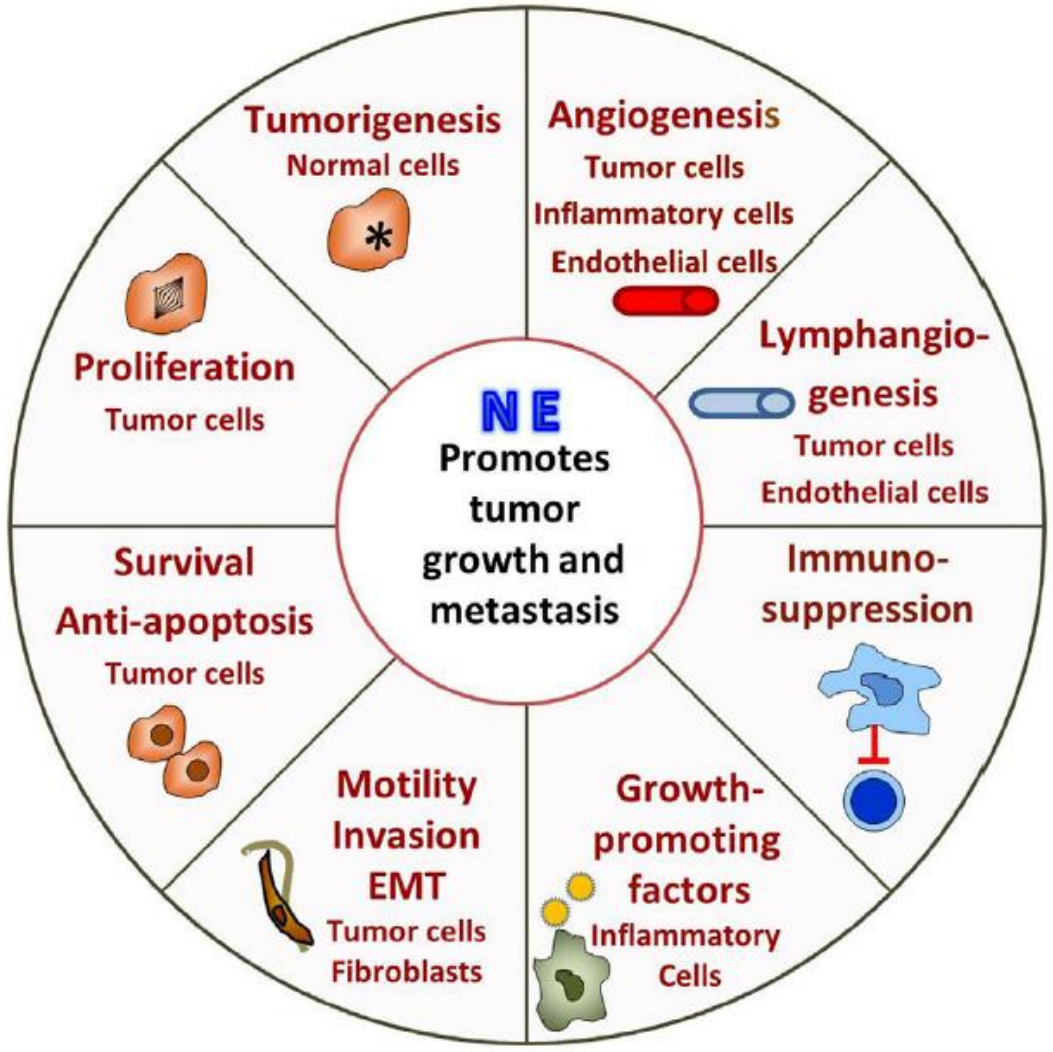
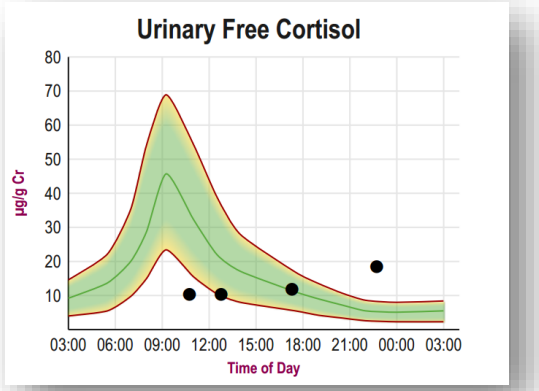
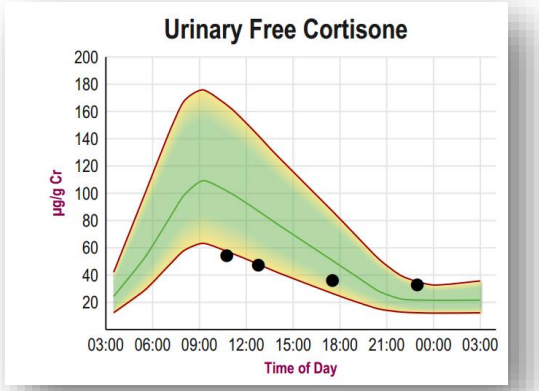
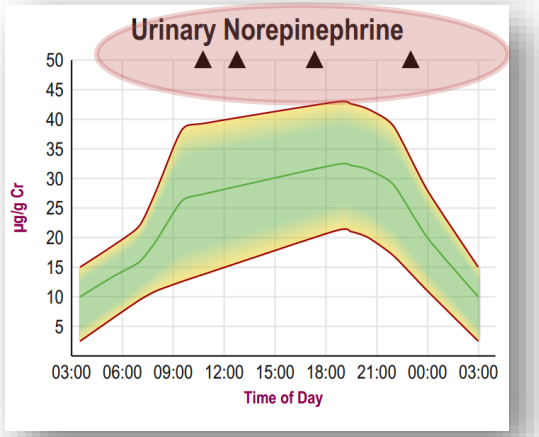
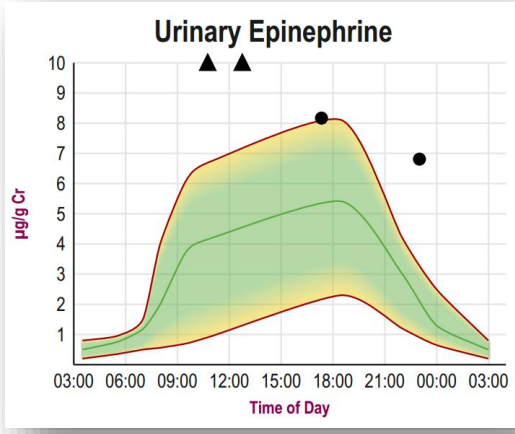


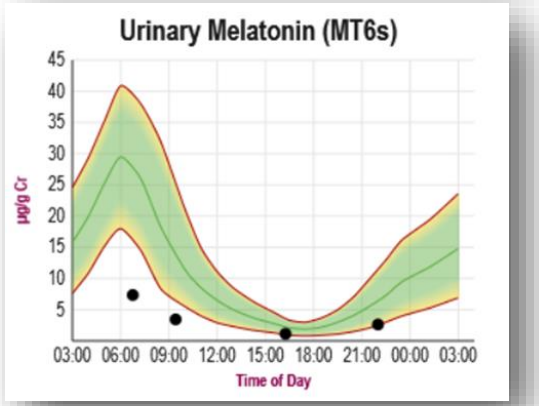
FIGURE 1 | Adrenergic signaling promotes tumor survival, growth, and metastasis. The tumor is innervated by postganglionic nerves of the sympathetic nervous system and, in response to stress, these nerves secrete norepinephrine (NE). Many cells in the tumor microenvironment express adrenergic receptors, and their responses support tumor growth. See text for discussion.











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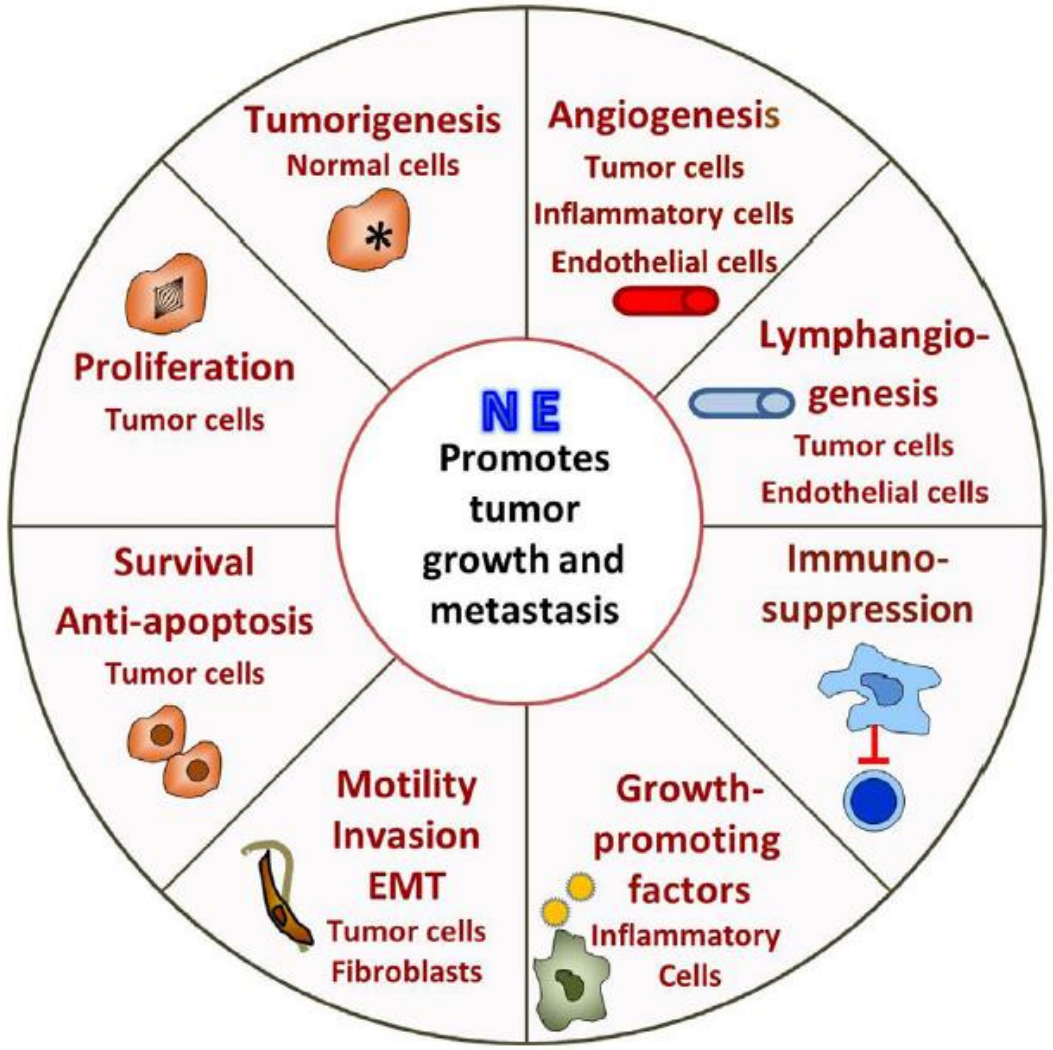

FIGURE 1 | Adrenergic signaling promotes tumor survival, growth, and metastasis. The tumor is innervated by postganglionic nerves of the sympathetic nervous system and, in response to stress, these nerves secrete norepinephrine (NE). Many cells in the tumor microenvironment express adrenergic receptors, and their responses support tumor growth. See text for discussion.

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Beta Blockers and Breast Cancer Mortality: A Population-Based Study

Thomas I. Barron, Roisin M. Connolly, Linda Sharp, Kathleen Bennett, and Kala Visvanathan

See accompanying editorial on page 2612 and article on page 2645

From Trinity College, University of Dublin, Dublin; National Cancer Registry Ireland, Cork, Ireland; and Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Centre; Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/11/2919-2635/$20.00

DOI: 10.1200/JCO.2010.33.5422

ABSTRACT

Purpose
Preclinical studies have demonstrated that antagonism of β_2-adrenergic signaling inhibits several pathways necessary for breast tumor progression and metastasis. A series of population-based observational studies were conducted to examine associations between beta blocker use and breast tumor characteristics at diagnosis or breast cancer–specific mortality.

Patients and Methods
Linked national cancer registry and prescription dispensing data were used to identify women with a diagnosis of stage I to IV invasive breast cancer between January 1, 2001, and December 31, 2006. Women taking propranolol (β_1/β_2 antagonist; n = 70) or atenolol (β_1 antagonist; n = 525), in the year before breast cancer diagnosis were matched (1:2) to women not taking a beta blocker (n = 4,738). Associations between use of propranolol or atenolol and risk of local tumor invasion at diagnosis (T4 tumor), nodal or metastatic involvement at diagnosis (N2/N3/M1 tumor), and time to breast cancer–specific mortality were assessed.

Results
Propranolol users were significantly less likely to present with a T4 (odds ratio [OR], 0.24, 95% CI, 0.07 to 0.85) or N2/N3/M1 (OR, 0.20; 95% CI, 0.04 to 0.88) tumor compared with matched nonusers. The cumulative probability of breast cancer–specific mortality was significantly lower for propranolol users compared with matched nonusers (hazard ratio, 0.19; 95% CI, 0.06 to 0.60). There was no difference in T4 or N2/N3/M1 tumor incidence or breast cancer–specific mortality between atenolol users and matched nonusers.

Conclusion
The results provide evidence in humans to support preclinical observations suggesting that inhibiting the β_2-adrenergic signaling pathway can reduce breast cancer progression and mortality.

J Clin Oncol 29:2635-2644. © 2011 by American Society of Clinical Oncology

CrossMark

β-Blockers Reduce Breast Cancer Recurrence and Breast Cancer Death: A Meta-Analysis

W. Kurtis Childers,[1] Christopher S. Hollenbeak,[2] Pramil Cheriyath[3]

Abstract

The normal physiologic stress mechanism, mediated by the sympathetic nervous system, causes a release of the neurotransmitters epinephrine and norepinephrine. Preclinical data have demonstrated an effect on tumor progression and metastasis via the sympathetic nervous system mediated primarily through the β-adrenergic receptor (β-AR) pathway. In vitro data have shown an increase in tumor growth, migration, tumor angiogenesis, and metastatic spread in breast cancer through activation of the β-AR. Retrospective cohort studies on the clinical outcomes of β-blockers in breast cancer outcomes showed no clear consensus. The purpose of this study was to perform a systematic review and meta-analysis of the effect of β-blockers on breast cancer outcomes. A systematic review was performed using the Cochrane library and PubMed. Publications between the dates of January 2010 and December 2013 were identified. Available hazard ratios (HRs) were extracted for breast cancer recurrence, breast cancer death, and all-cause mortality and pooled using a random effects meta-analysis. A total of 7 studies contained results for at least 1 of the outcomes of breast cancer recurrence, breast cancer death, or all-cause mortality in breast cancer patients receiving β-blockers. In the 5 studies that contained results for breast cancer recurrence, there was no statistically significant risk reduction (HR, 0.67; 95% confidence interval [CI], 0.39-1.13). Breast cancer death results were contained in 4 studies, which also suggested a significant reduction in risk (HR, 0.50; 95% CI, 0.32-0.80). Among the 4 studies that reported all-cause mortality, there was no significant effect of β-blockers on risk (HR, 1.02; 95% CI, 0.75-1.37). Results of this systematic review and meta-analysis suggest that the use of β-blockers significantly reduced risk of breast cancer death among women with breast cancer.

Clinical Breast Cancer, Vol. 15, No. 6, 426-31 © 2015 Elsevier Inc. All rights reserved.
Keywords: Breast cancer metastasis, Breast cancer recurrence, Meta-analysis, β-adrenergic receptors, β-blockers

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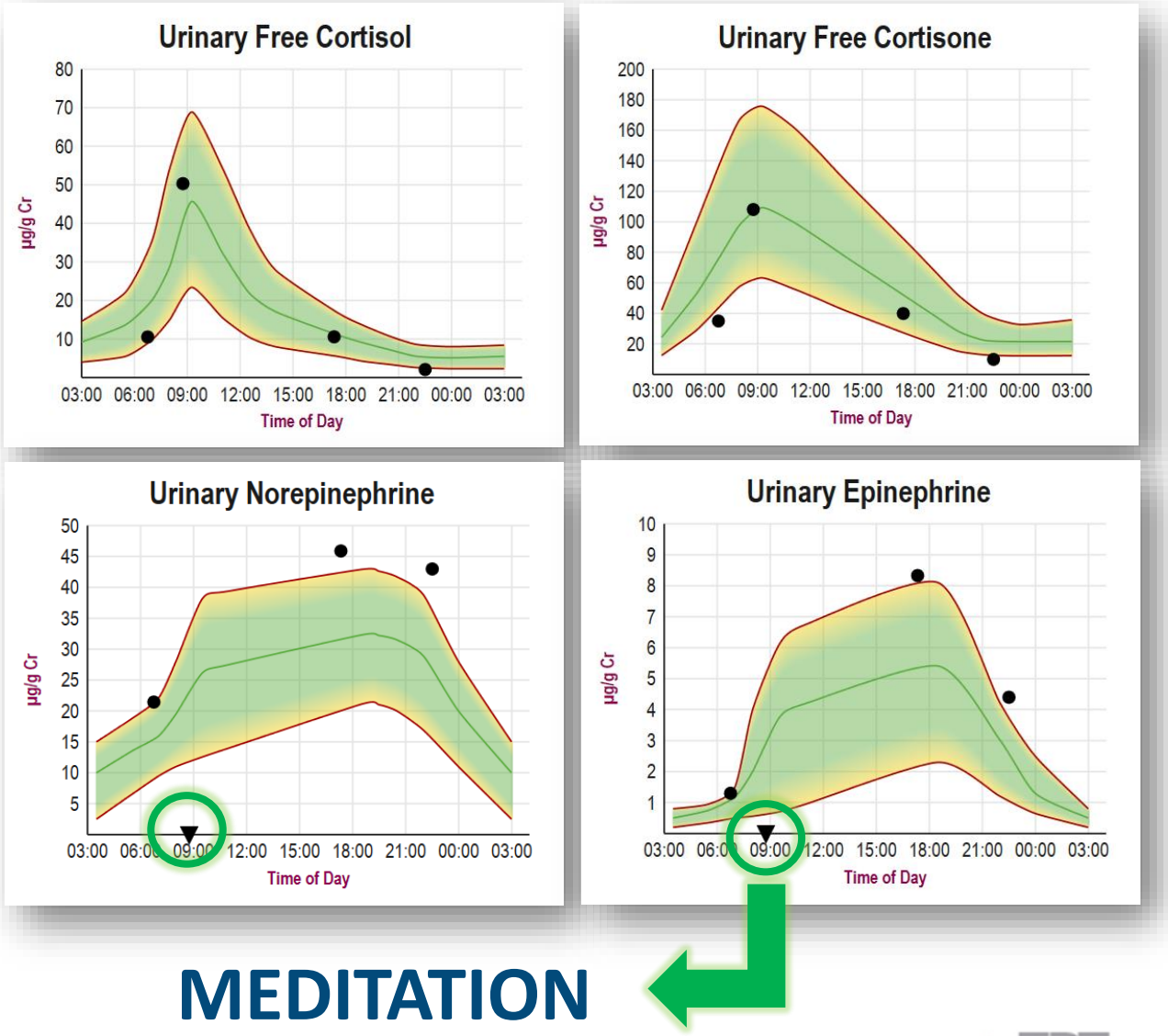
What else can lower NE levels?

MEDITATION

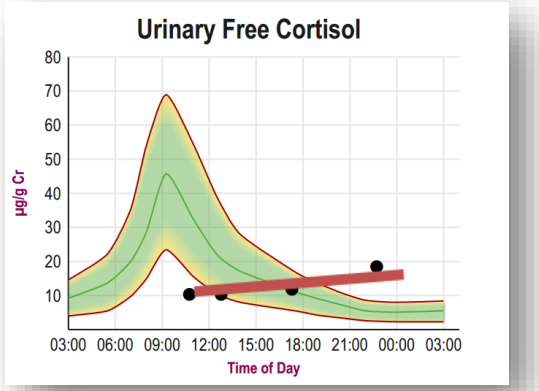
Meditation between the first and second voids creates a predictable and precipitous drop in both NE and EPI

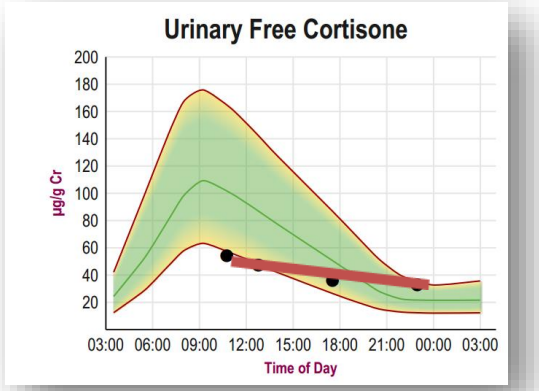
They then appear to resume their typical diurnal pattern (hyper)

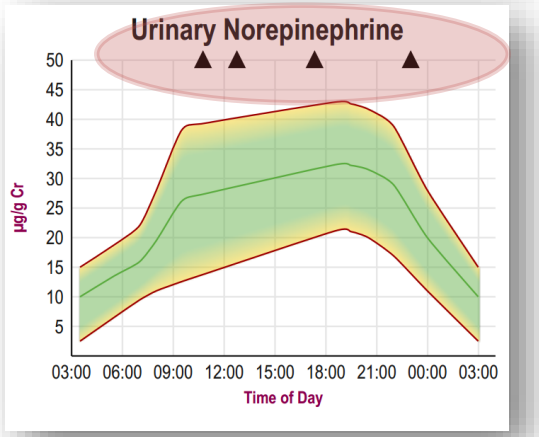


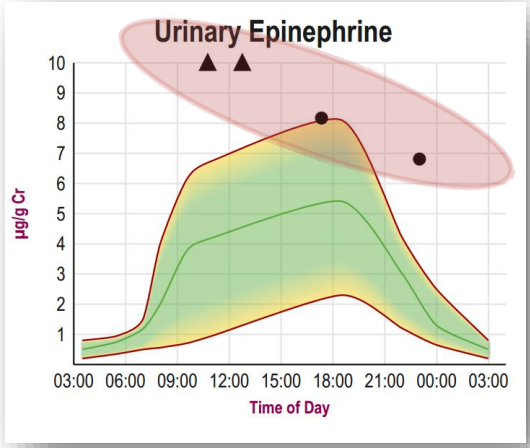
Review of Findings

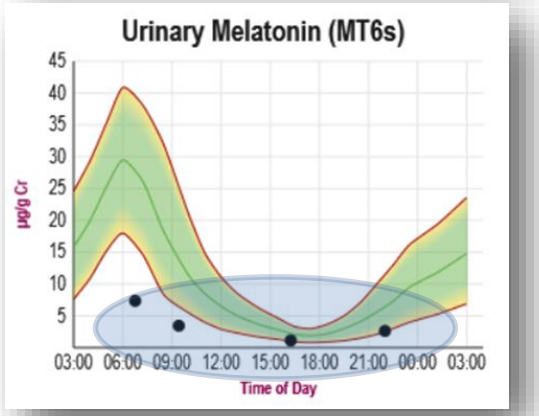
- Peripheral Clock
  - Flattened Cortisol Rhythm
  - Elevated NE with loss of curve
  - Elevated Epi with loss of curve
- Central Clock
  - MT6s low with flattened curve











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Phytochemicals: Current strategies for treating breast cancer (Review)

BRIDG'ETTE B. ISRAEL[1*], SYREETA L. TILGHMAN[1*], KITANI PARKER-LEMIEUX[2] and FLORASTINA PAYTON-STEWART[3]

[1]Division of Basic Pharmaceutical Sciences, College of Pharmacy and Pharmaceutical Sciences, Florida A&M University, Tallahassee, FL 32307; [2]Division of Basic Pharmaceutical Sciences, College of Pharmacy; [3]Division of Mathematical and Physical Sciences, College of Arts and Sciences, Xavier University of Louisiana, New Orleans, LA 70125, USA

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Abstract. Females with early-stage metastatic, estrogen-dependent breast cancer are generally treated with surgery, radiation and chemotherapy, or with more targeted approaches such as aromatase inhibitors (anastrozole or letrozole) or anti-estrogens (tamoxifen). Despite widespread successful usage of these agents for the trea… relapse and metasta… for patients with br… made major contrib… of resistance mecha… the most critical pa… the inability to adeq… outcomes in femal… including triple ne… investigation of nov… reveal previously u… to treat metastatic… phytochemicals ha… therapeutic breast… estrogen-dependent… cell proliferation, p… cell populations. W… exhibited promise,… Therefore, to effecti… tumors, it is critica… agents for effective… literature on the current state of phytochemicals is reviewed, including their limitations and potential as targeted therapies for breast cancer.

- Phytochemicals
  - Isoflavones
  - Epigallocatechin gallate (EGCG)
  - Resveratrol
  - Lignans
  - Curcumin
  - Carotenoids

Correspondence to: Dr Florastina Payton-Stewart, Division of Mathematical and Physical Sciences, College of Arts and Sciences, Xavier University of Louisiana, 1 Drexel Drive, New Orleans, LA 70125, USA
E-mail: flpayton@xula.edu

*Contributed equally

Key words: phytochemicals, breast cancer, anti-estrogens, aromatase inhibitors

Contents

…of cancer mortality …w cases and 40,450 …d States in 2016 (1). … breast cancer (1). …tation report in 2012, …ncer is projected to increase (2). There are four stages of breast cancer: Cancer in the earliest state is designated stage 0 (carcinoma *in situ*) and ranges from stage I through IV. Stage IV is the most aggressive stage of the disease. A higher stage implies a more advanced metastatic cancer. Some of the stages are further divided into sub-stages designated A, B and C. When detected early, (i.e., stage I, localized breast cancer), the 5-year survival rate is 100% (3). It is common for cancer to spread to other organs; breast cancer typically spreads to the lungs, bones, liver or brain (3).

Breast cancer is classified into three main subtypes based on the molecular profiles: i) Hormone receptor-positive [estrogen receptor (ER)+]; ii) human epidermal growth factor receptor (EGFR) 2 (HER2)-positive; and iii) triple negative tumors (4). Hormone receptor-positive is a subtype of breast cancer in which the ER is expressed. HER2-positive is a subtype of breast cancer that contains HER2, a member of

Breast Cancer

- Melatonin + Bright Light Therapy
  - Continuous replacement
- Decrease Sympathetic Tone
  - Biofeedback
  - Meditation, Mindfulness, etc
  - Vitamin D3 (tx to 50-80)
  - Bacopa 200 mg BID
  - Beta-blockers (tissue fx)
- Adaptogens
  - DHA (450 mg)
  - Rhodiola (200 – 600mg)

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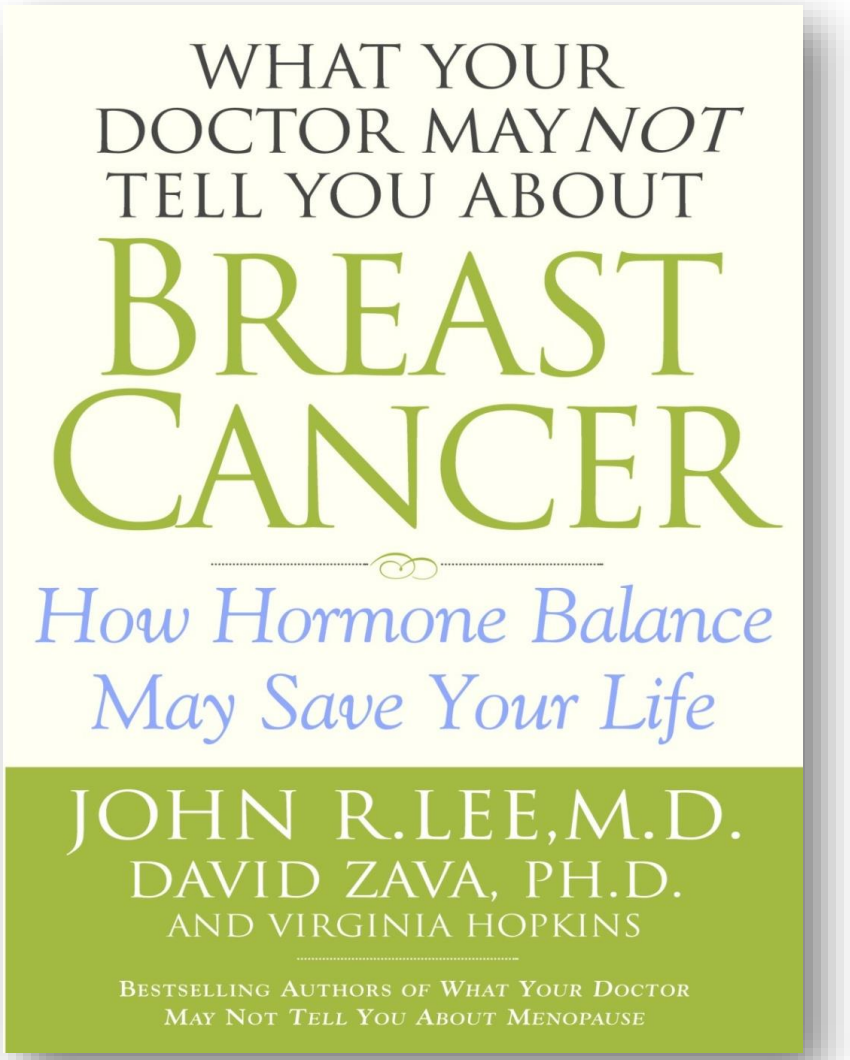


Insomnia

25 YO MALE

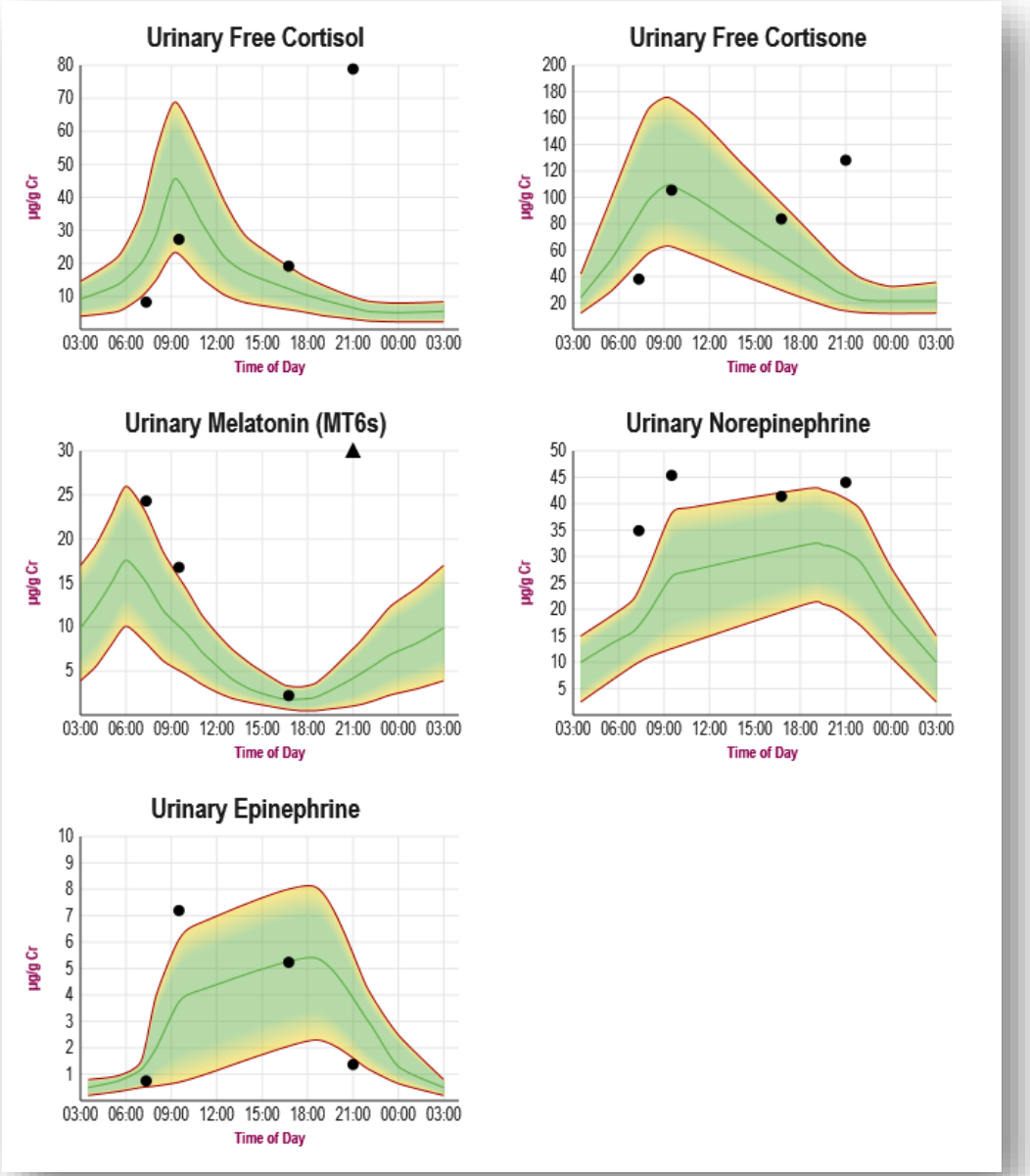
THERAPIES:
Duloxetine
Nicotine patch

SYMPTOMS:
Sleeping difficulty
Depressed
Anxious
Mental fatigue
Physical fatigue AM/PM
Panic attacks
Burned out feeling
Decreased stamina

SYMPTOM CATEGORIES	RESULTS | 11/07/17
Estrogen / Progesterone Deficiency	29%
Estrogen Dominance / Progesterone Deficiency	2%
Low Androgens (DHEA/Testosterone)	33%
High Androgens (DHEA/Testosterone)	17%
Low Cortisol	36%
High Cortisol	29%
Hypometabolism	30%
Metabolic Syndrome	12%

Review of Findings

- Peripheral Clock
  - Cortisol and cortisone elevated at bed
  - NE elevated throughout
  - Epi curve intact, high am
- Central Clock
  - Duloxetine may increase MT6s excretion



Yang et al. BMC Psychiatry (2018) 18:279
https://doi.org/10.1186/s12888-018-1845-1

BMC Psychiatry

STUDY PROTOCOL Open Access

N-acetylcysteine as add-on to antidepressant medication in therapy refractory major depressive disorder patients with increased inflammatory activity: study protocol of a double-blind randomized placebo-controlled trial

Chenghao Yang[1,2,3], Fokko J. Bosker[2,3], Jie Li[1*] and Robert A. Schoevers[2,3]

Abstract

Background: A subgroup of depressed patients with increased inflammatory activity was shown to be more susceptible to develop Treatment Resistant Depression (TRD). Earlier studies with anti-inflammatory drugs have shown benefits in the treatment of major depressive disorder (MDD), but the effects are expected to be higher in patients with increased inflammatory activity. Supplementation of N-acetylcysteine (NAC) to ongoing antidepressant therapy may positively influence outcome of depression treatment in these patients. Therefore, this study aims to investigate the efficacy of NAC supplementation in patients with insufficient response to standard antidepressant treatment, and to explore potential roles of inflammation and oxidative stress involved in the alleged pathophysiological processes of TRD.

Methods/design: A double-blind randomized placebo-controlled study comparing NAC versus placebo as add-on medication to antidepressant treatment with 12-week treatment and 8-week follow up in patients with TRD and increased inflammatory activity. Apart from clinical efficacy defined as the change in Hamilton Depression Rating Scale (HAMD)-17 score, secondary outcomes include changes in pathophysiological mechanisms related to depression as well as changes in local brain activity (functional Magnetic Resonance Imaging, fMRI) and white matter integrity (Diffusion Tensor Imaging, DTI). Importantly, sole patients with CRP levels with values between 0.85 and 10 mg/L will be included.

Discussion: This is the first clinical trial taking both TRD and increased inflammatory activity as inclusion criteria. This study will provide reliable evidence for the efficacy of NAC in patients with TRD displaying increased inflammatory activity. And this study also will help explore further the roles of inflammation and oxidative stress involved in the alleged pathophysiological processes of TRD.

Trial registration: The trial protocol has been registered on "ClinicalTrials.gov"with protocol ID "NAC-2015-TJAH" and ClinicalTrials.gov ID "NCT02972398".

Keywords: N-acetylcysteine, Treatment resistant depression, Inflammatory activity, Biomarkers, Brain activity

Treatment Considerations

- Add 30 minutes Bright Light Therapy am + good sleep hygiene practices QHS + Brkfst
- Decrease Sympathetic Tone
  - Biofeedback for at-home use BID
  - Meditation or mindfulness practice
  - GABA 200 mg TID
  - Nervines
    - Valerian Root 200 -600 mg daily
    - Chamomile 500 – 1500 mg daily
- N-acetylcysteine 1200 mg upon waking
- Adaptogens
  - Ashwagandha 500mg QHS
  - Phosphatidylserine 100 – 500mg QHS

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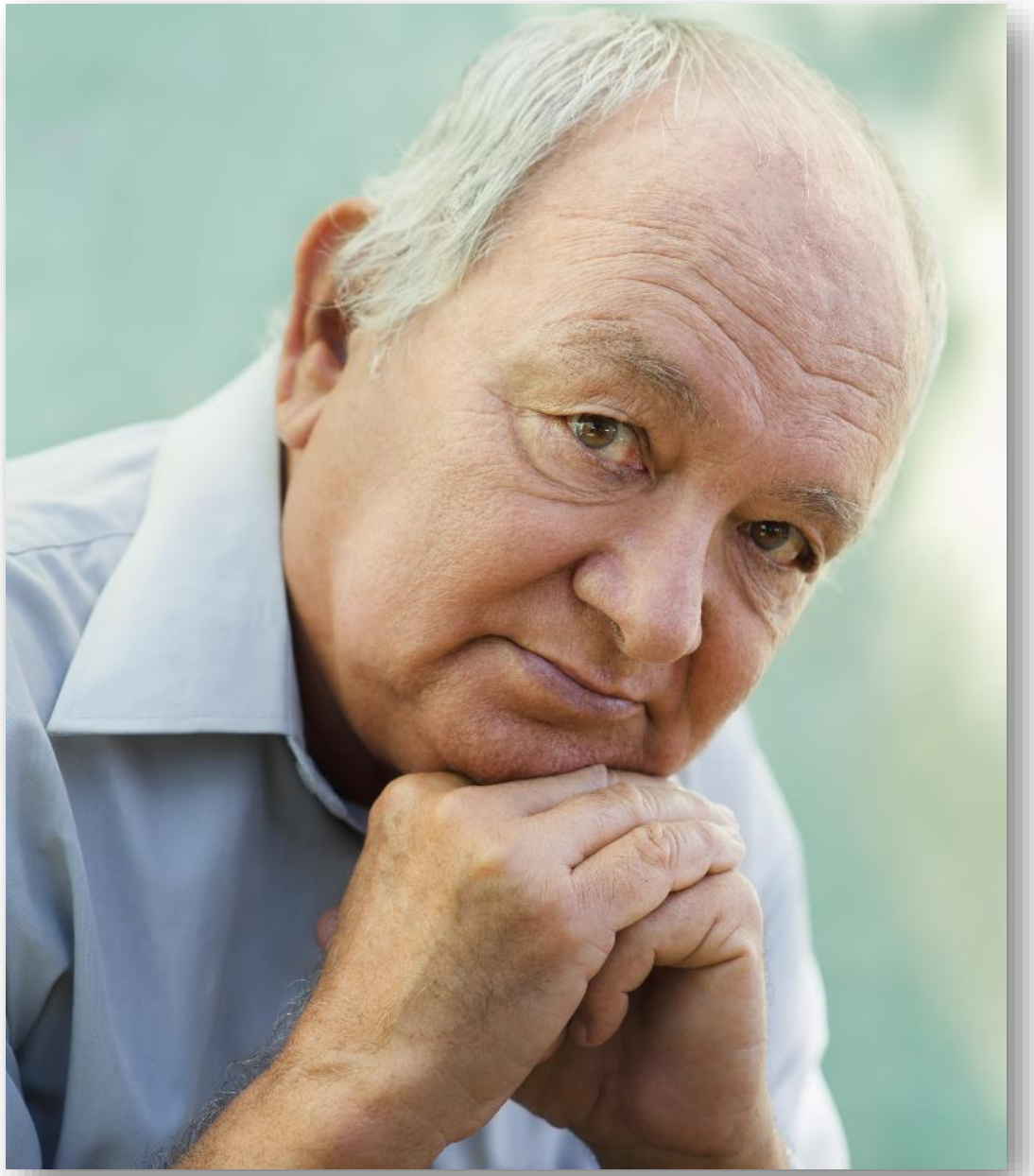


Chronic Pain

61 YO MALE

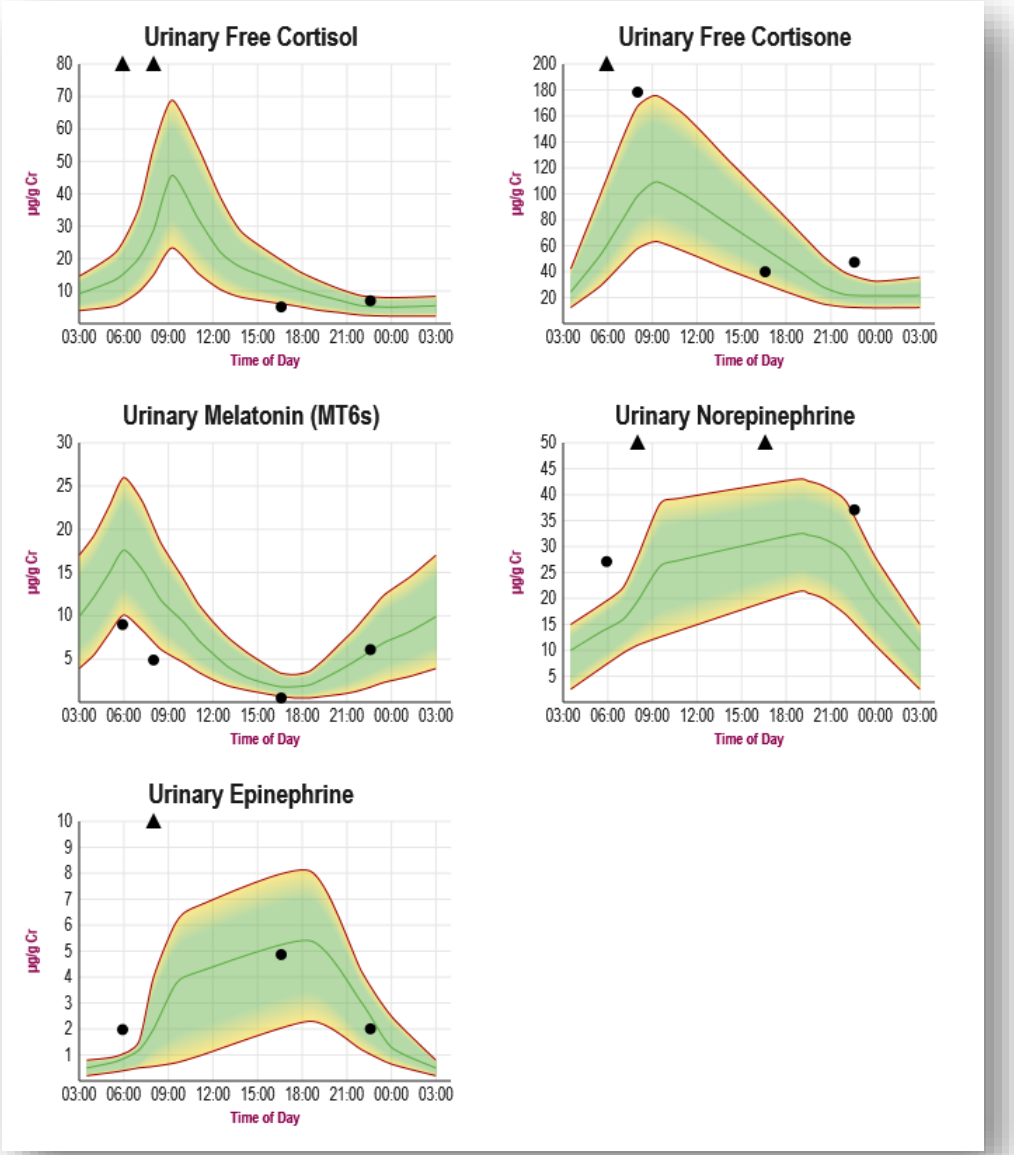
THERAPIES:
Simvastatin
Calcium
Vitamin D3

SYMPTOMS:
Joint pain
Back/knee pain
Weight gain
Muscle soreness
Hot flashes/night sweats
Fatigue am/pm
Sleep disturbed
High cholesterol
Forgetful
↓ stamina

SYMPTOM CATEGORIES	RESULTS | 10/17/17
Estrogen / Progesterone Deficiency	90%
Estrogen Dominance / Progesterone Deficiency	75%
Low Androgens (DHEA/Testosterone)	54%
High Androgens (DHEA/Testosterone)	31%
Low Cortisol	46%
High Cortisol	54%
Hypometabolism	27%
Metabolic Syndrome	58%

Review of Findings

- Peripheral Clock
  - Hypercortisol am and pm, low during day
  - Elevated NE through day
  - Elevated EPI through am
- Central Clock
  - Low melatonin, curve preserved somewhat



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REVIEW

Melatonin in Chronic Pain Syndromes

Andrei Danilov · Julia Kurganova

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ABSTRACT

Melatonin is a neurohormone secreted by epiphysis and extrapineal structures. It performs several functions including chronobiotic, antioxidant, oncostatic, immune modulating, normothermal, and anxiolytic functions. Melatonin affects the cardiovascular system and gastrointestinal tract, participates in reproduction and metabolism, and body mass regulation. Moreover, recent studies have demonstrated melatonin efficacy in relation to pain syndromes. The present paper reviews the studies on melatonin use in fibromyalgia, headaches, irritable bowel syndrome, chronic back pain, and rheumatoid arthritis. The paper discusses the possible mechanisms of melatonin analgesic properties. On one hand, circadian rhythms normalization results in sleep improvement, which is inevitably disordered in chronic pain syndromes, and activation of melatonin adaptive capabilities. On the other hand, there is evidence of melatonin-independent analgesic effect involving melatonin receptors and several neurotransmitter systems.

Keywords: Chronic pain; Fibromyalgia; Headache; Irritable bowel syndrome; Low back pain; Melatonin; Migraine; Rheumatoid arthritis

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INTRODUCTION

The role of the circadian rhythm in human life has been well known for a long time. The notion of the circadian rhythm introduced by Franz Halberg in 1959 overturned researchers' understanding of many processes in the human body. It was found that circadian rhythms are involved in several physiological processes, such as the sleep–wake cycle, body temperature regulation, hormone secretion, cell division and proliferation, gastro-intestinal tract function, etc. Circadian rhythm disorders may result in several pathological conditions, while most diseases may cause circadian

Treatment Considerations

- Melatonin 5mg QHS (mb + bright light therapy)
- "Eat breakfast" rx + Yoga practice 4 days a wk
- Inflammation
  - Polyphenols – quercetin, curcumin
  - EPA w/ DHA – 1200/800 or higher
- Pregnenolone and CoQ10 (Simvastatin)
- Adaptogens and Nervines
  - Liposomal Curcumin 2g daily
  - Passion flower, Hops, Valerian, etc
  - Bacopa monnieri 200mg BID (cognitive)

Thank you!
Questions?

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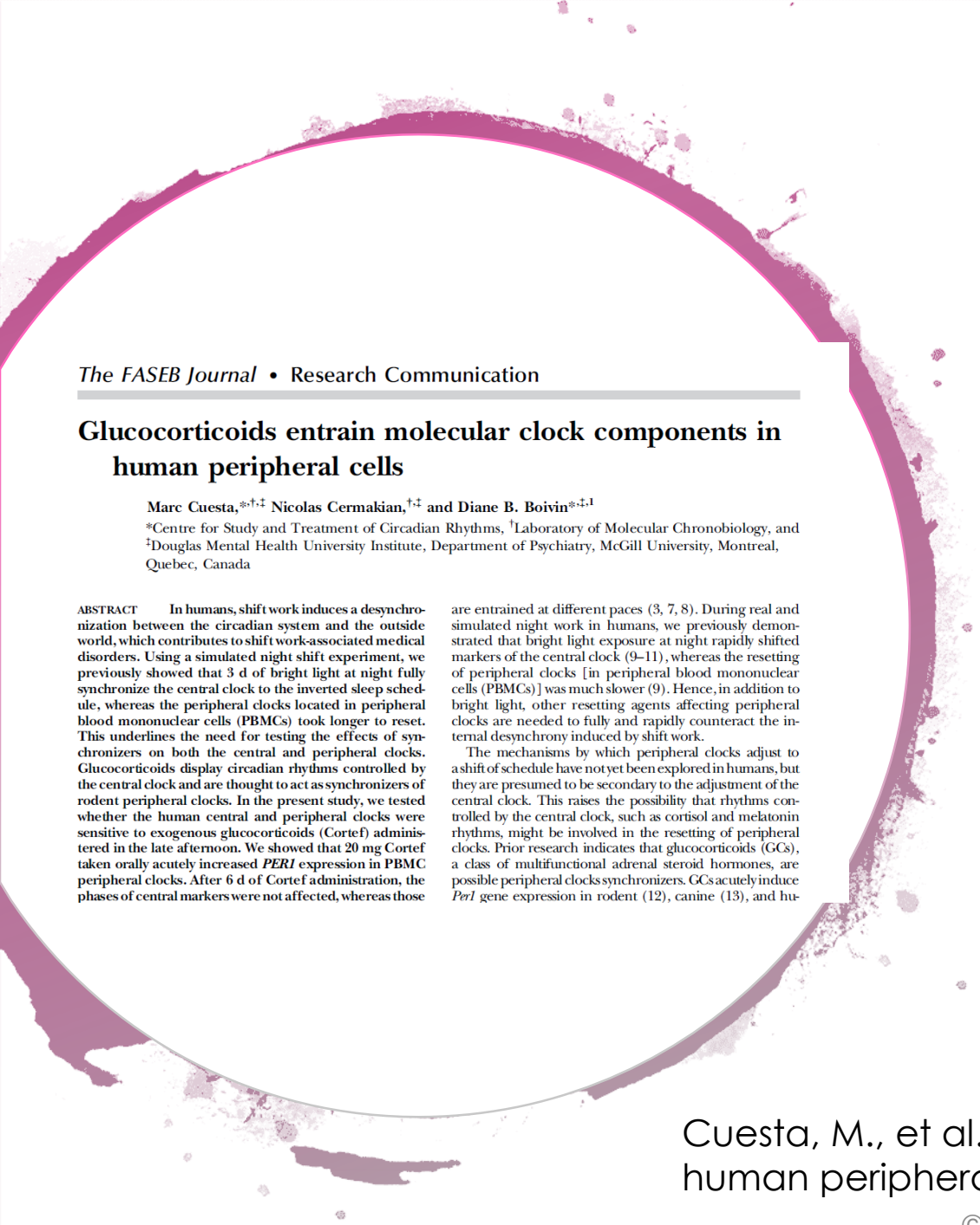
Appendix

Using Melatonin to Entrain the Clock

- Replacement – 0.3 – 1 mg an hour before sleep is desired
- Phase advancing – 0.3 – 2mg 6 hours before baseline bedtime +30 min bright light therapy after waking (1.5hr advance)
- Phase delaying – dose melatonin early in the day, bright light therapy at night
- Much higher doses used in condition-specific studies

Using Light Therapy to Entrain Central and Peripheral Clocks

Bright Light Therapy (BLT)	5,000 – 10,000 lux 30-60 minutes at desired waking
Narrow Spectrum Blue Light Therapy	470 nm 45 minutes at desired waking



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Glucocorticoids entrain molecular clock components in human peripheral cells

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ABSTRACT **In humans, shift work induces a desynchronization between the circadian system and the outside world, which contributes to shift work-associated medical disorders. Using a simulated night shift experiment, we previously showed that 3 d of bright light at night fully synchronize the central clock to the inverted sleep schedule, whereas the peripheral clocks located in peripheral blood mononuclear cells (PBMCs) took longer to reset. This underlines the need for testing the effects of synchronizers on both the central and peripheral clocks. Glucocorticoids display circadian rhythms controlled by the central clock and are thought to act as synchronizers of rodent peripheral clocks. In the present study, we tested whether the human central and peripheral clocks were sensitive to exogenous glucocorticoids (Cortef) administered in the late afternoon. We showed that 20 mg Cortef taken orally acutely increased *PER1* expression in PBMC peripheral clocks. After 6 d of Cortef administration, the phases of central markers were not affected, whereas those**

are entrained at different paces (3, 7, 8). During real and simulated night work in humans, we previously demonstrated that bright light exposure at night rapidly shifted markers of the central clock (9–11), whereas the resetting of peripheral clocks [in peripheral blood mononuclear cells (PBMCs)] was much slower (9). Hence, in addition to bright light, other resetting agents affecting peripheral clocks are needed to fully and rapidly counteract the internal desynchrony induced by shift work.

The mechanisms by which peripheral clocks adjust to a shift of schedule have not yet been explored in humans, but they are presumed to be secondary to the adjustment of the central clock. This raises the possibility that rhythms controlled by the central clock, such as cortisol and melatonin rhythms, might be involved in the resetting of peripheral clocks. Prior research indicates that glucocorticoids (GCs), a class of multifunctional adrenal steroid hormones, are possible peripheral clocks synchronizers. GCs acutely induce *Per1* gene expression in rodent (12), canine (13), and hu-

Using Cortef to Entrain Peripheral Clocks

- 6 days of 20 mg Cortef in the afternoon shifted peripheral clocks 9.5 – 11.5 hours
- Acute admin ↑cortisol and PER1 activity and 6 days adjusted BMAL1 and PER 2-3 activity in immune cells
- Melatonin (central clock) was not affected by Cortef

Cuesta, M., et al. Glucocorticoids entrain molecular clock components in human peripheral cells. FASEB, 2015.

Using Diet to Entrain Clock

- High fat and CHO (SAD) Diet
  - Associated with phase delay and metabolic syndrome
- Ketogenic Diet
  - Associated with phase advance
- Intermittent Fasting
  - Mixed in humans – but seems to affect circadian rhythm
- Early Time Restricted Feeding (eTRF)
  - 6-7 hours of eating per day only – front loaded toward brkfst
  - Fast the rest of the day and night
- Daily breakfast
  - Research on breakfast skippers → obesity, HTN

Using Biofeedback to Control Peripheral Clocks

- WELLBE bracelet
- Oura ring
- HeartMath
- Equisync
- Elite HRV