Targeting the Root Causes of Stress

Thomas G. Guilliams, Ph.D.
Founder/Director- Point Institute
Adj. Asst. Prof. University of Wisconsin School of Pharmacy
Senior Scientific Advisor- Ortho Molecular Products

GENOVA DIAGNOSTICS®

Lahnor Powell, ND, MPH

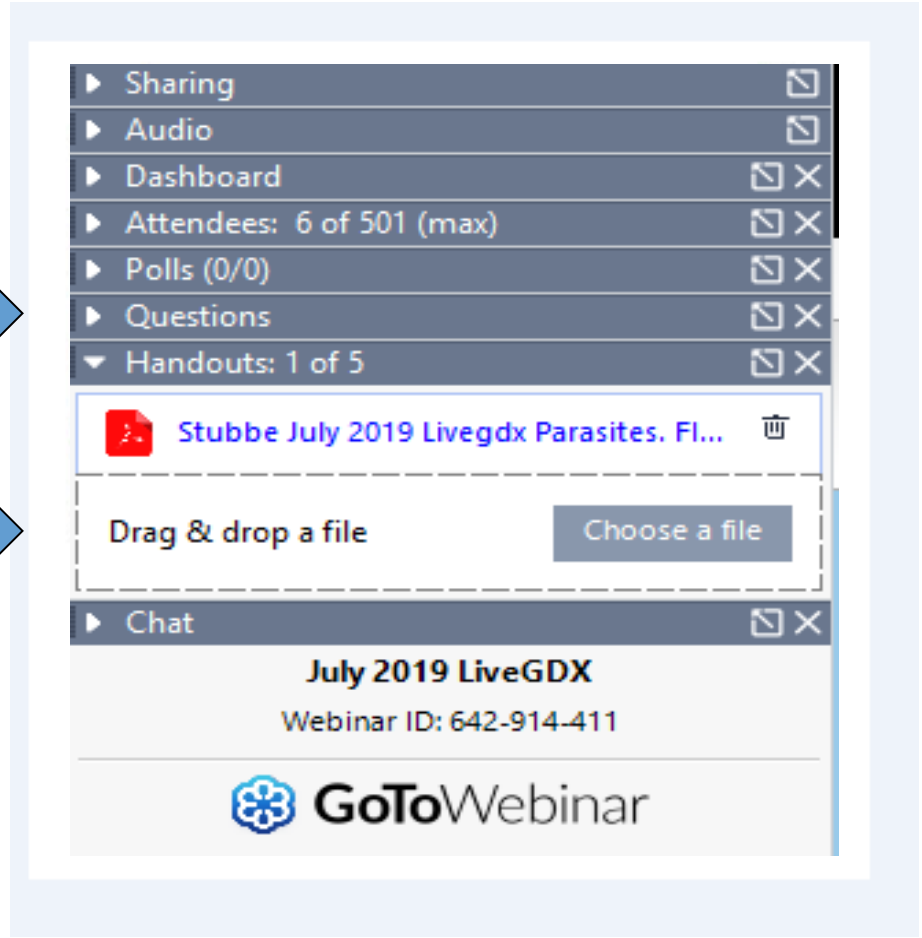
Medical Education Specialist | Department of Medical Affairs | Genova Diagnostics

GENOVA DIAGNOSTICS

Technical Issues & Clinical Questions

Please type any technical issue or clinical question into either the “Chat” or “Questions” boxes, making sure to send them to “Organizer” at any time during the webinar.

We will be compiling your clinical questions and answering as many as we can the final 15 minutes of the webinar.



DISCLAIMER: *Please note that any and all emails provided may be used for follow up correspondence and/or for further communication.*

GENOVA DIAGNOSTICS

Need More Resources?

Explore

WWW.GDX.NET

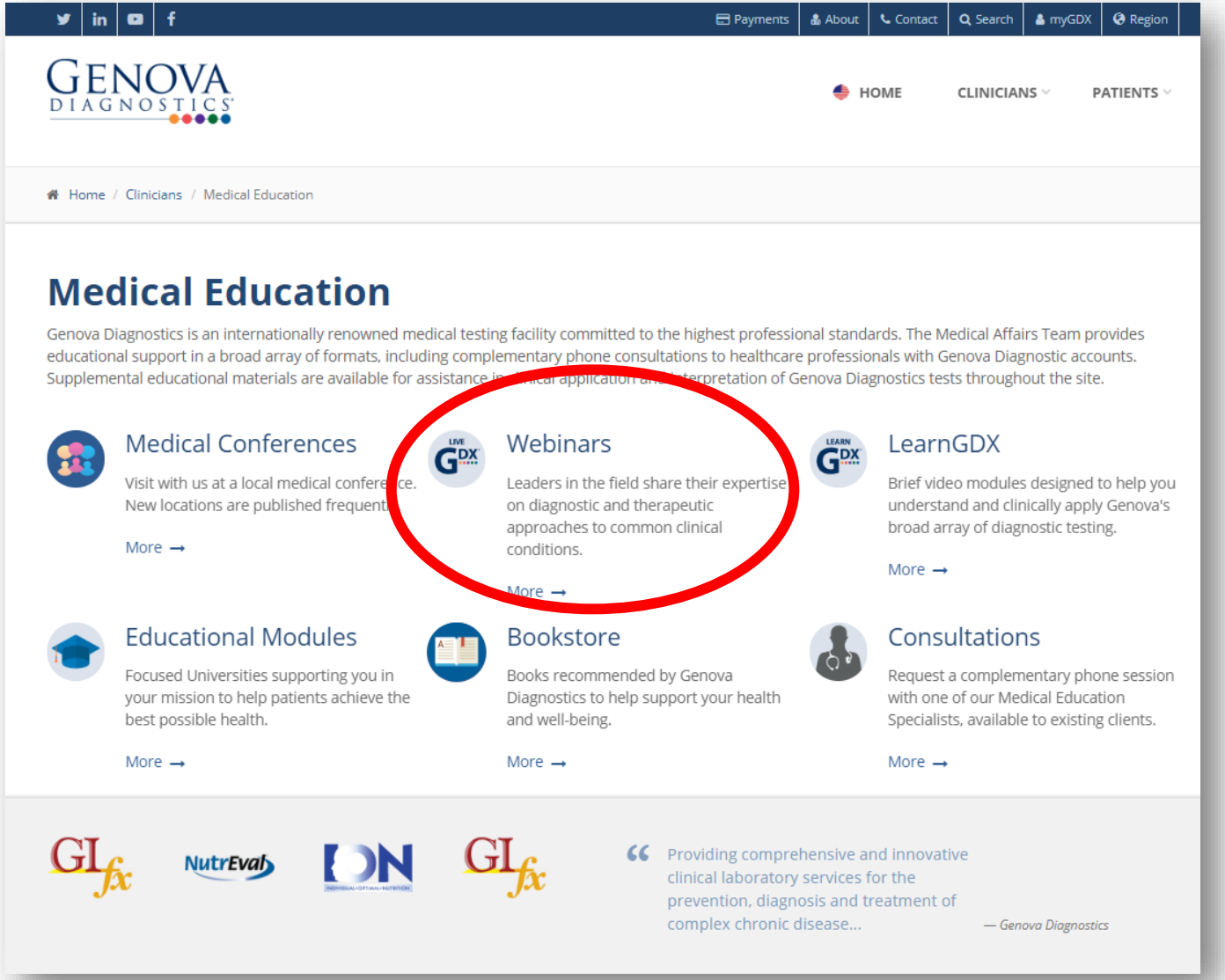
for more information and educational resources, including…

LEARN **GDX** – Brief video modules

LIVE **GDX** – Previous webinar recordings

GI University – Focused learning modules

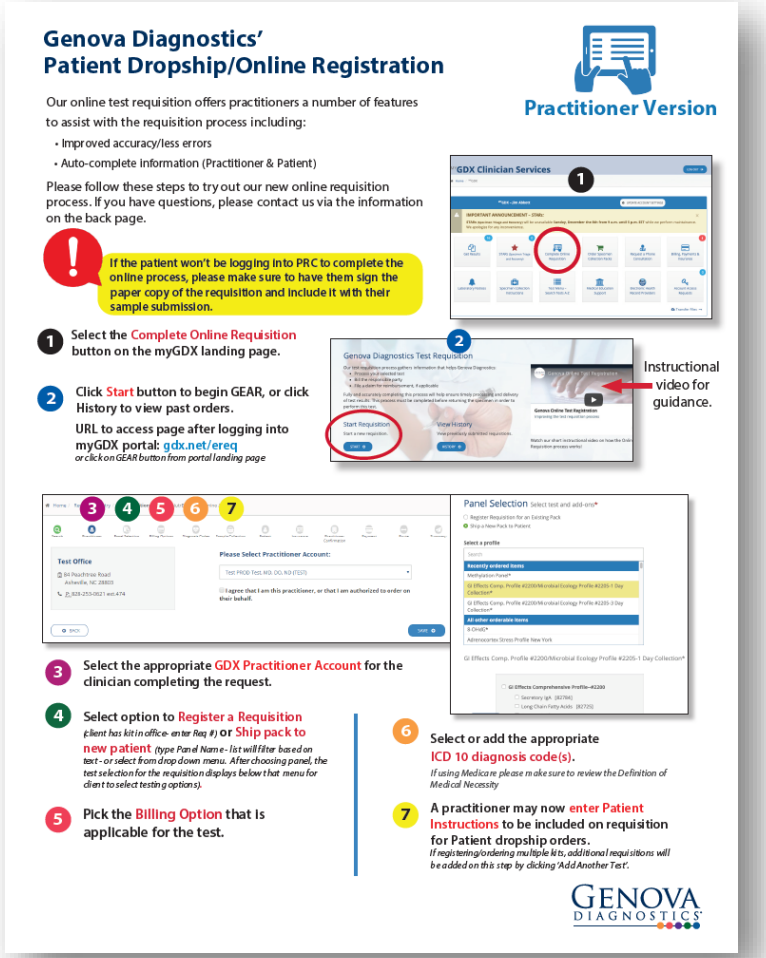
MY **GDX** – Order materials and get results



GENOVA DIAGNOSTICS

Patient Dropship/Online Registration

https://youtu.be/YHd0lD9GVG4



Genova Diagnostics' Patient Dropship/Online Registration

Practitioner Version

Our online test requisition offers practitioners a number of features to assist with the requisition process including:

- Improved accuracy/less errors
- Auto-complete information (Practitioner & Patient)

Please follow these steps to try out our new online requisition process. If you have questions, please contact us via the information on the back page.

If the patient won't be logging into PRC to complete the online process, please make sure to have them sign the paper copy of the requisition and include it with their sample submission.

1 Select the Complete Online Requisition button on the myGDX landing page.

2 Click Start button to begin GEAR, or click History to view past orders.

URL to access page after logging into myGDX portal: gdx.net/ereq
or click on GEAR button from portal landing page

Instructional video for guidance.

3 Select the appropriate GDX Practitioner Account for the clinician completing the request.

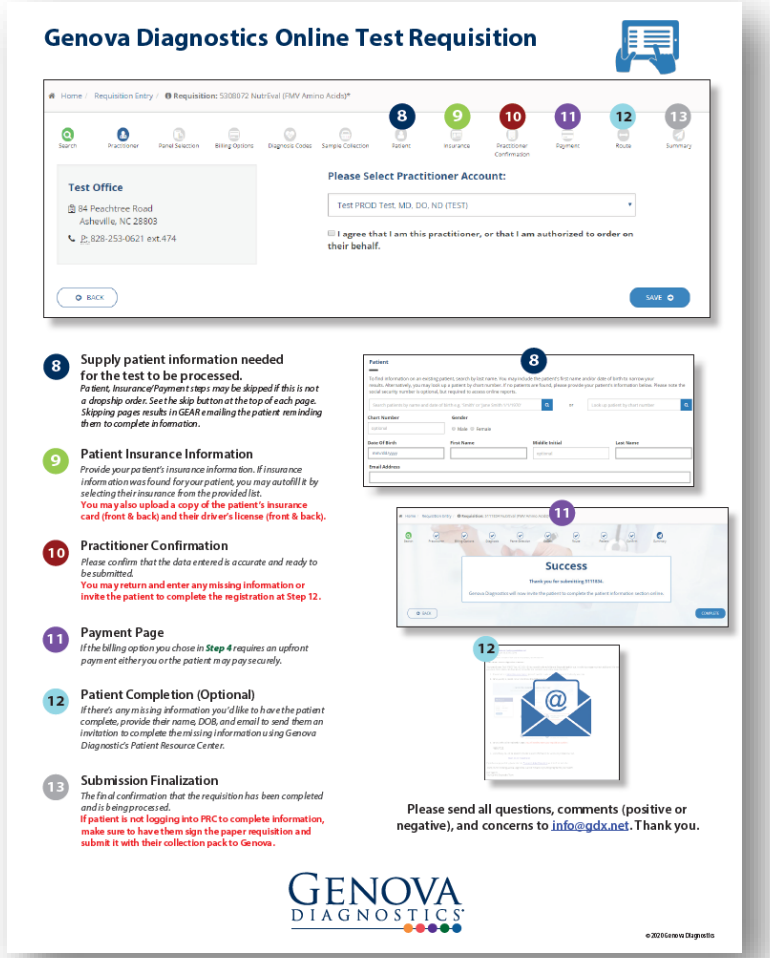
4 Select option to Register a Requisition *(client has kit in office- enter Req #)* or Ship pack to new patient *(type Panel Name - list will filter based on text - or select from drop down menu. After choosing panel, the test selection for the requisition displays below that menu for client to select testing options).*

5 Pick the Billing Option that is applicable for the test.

6 Select or add the appropriate ICD 10 diagnosis code(s).
If using Medicare please make sure to review the Definition of Medical Necessity

7 A practitioner may now enter Patient Instructions to be included on requisition for Patient dropship orders.
If registering/ordering multiple kits, additional requisitions will be added on this step by clicking 'Add Another Test'.

GENOVA DIAGNOSTICS



Genova Diagnostics Online Test Requisition

8 Supply patient information needed for the test to be processed.
Patient, Insurance/Payment steps may be skipped if this is not a dropship order. See the skip button at the top of each page. Skipping pages results in GEAR emailing the patient reminding them to complete information.

9 Patient Insurance Information
Provide your patient's insurance information. If insurance information was found for your patient, you may autofill it by selecting their insurance from the provided list.
You may also upload a copy of the patient's insurance card (front & back) and their driver's license (front & back).

10 Practitioner Confirmation
Please confirm that the data entered is accurate and ready to be submitted.
You may return and enter any missing information or invite the patient to complete the registration at Step 12.

11 Payment Page
*If the billing option you chose in **Step 4** requires an upfront payment either you or the patient may pay securely.*

12 Patient Completion (Optional)
If there's any missing information you'd like to have the patient complete, provide their name, DOB, and email to send them an invitation to complete the missing information using Genova Diagnostics Patient Resource Center.

13 Submission Finalization
The final confirmation that the requisition has been completed and is being processed.
If patient is not logging into PRC to complete information, make sure to have them sign the paper requisition and submit it with their collection pack to Genova.

Please send all questions, comments (positive or negative), and concerns to info@gdx.net. Thank you.

GENOVA DIAGNOSTICS

GENOVA DIAGNOSTICS

Targeting the Root Causes of Stress

Thomas G. Guilliams, Ph.D.
Founder/Director- Point Institute
Adj. Asst. Prof. University of Wisconsin School of Pharmacy
Senior Scientific Advisor- Ortho Molecular Products

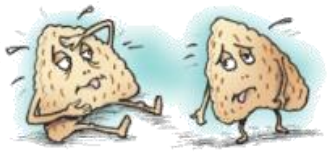
GENOVA DIAGNOSTICS®

Overview of this Presentation

- Review the root, influences, and goal of HPA Axis Stress Response
- Looking at the HPA Axis differently; beyond cortisol control
- Discuss strategies for supporting the HPA Axis Function

The Root of HPA Axis Stress is Not Adrenal Fatigue!

- Adrenal function (or dysfunction) is rarely a **defining feature or root cause** of a Stress Response System (HPA axis) dysfunction; this oversimplification often misses the most common root causes of HPA axis and Stress-related phenomena
- The most powerful therapies that clinicians can use to support the Stress-Response and the HPA axis are not directly related to “Adrenal Support”, and they are often overlooked or underleveraged



GENOVA DIAGNOSTICS

What Influences the HPA axis Response to "Stress" A Simplified Approach

Response to Homeostatic Metabolic Needs

- Energy Needs (hypoglycemia)
- Inflammation
- Metabolic Dysregulation
- Circadian Disruption

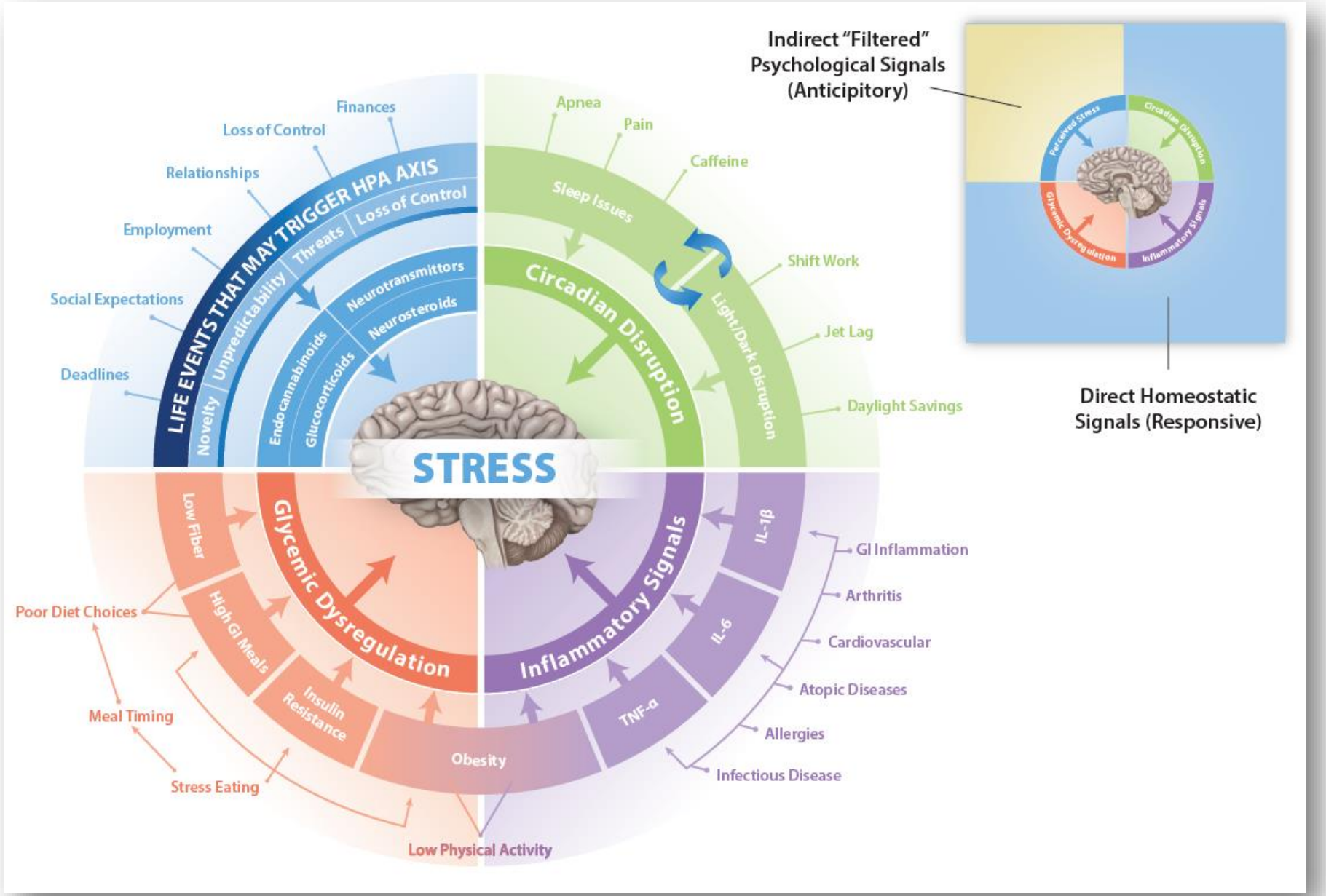
Anticipation of Metabolic Needs

- Psychosocial anticipation of dysregulation
- Circadian anticipation of metabolic functions

Adaptations from All Prior HPA axis Activations

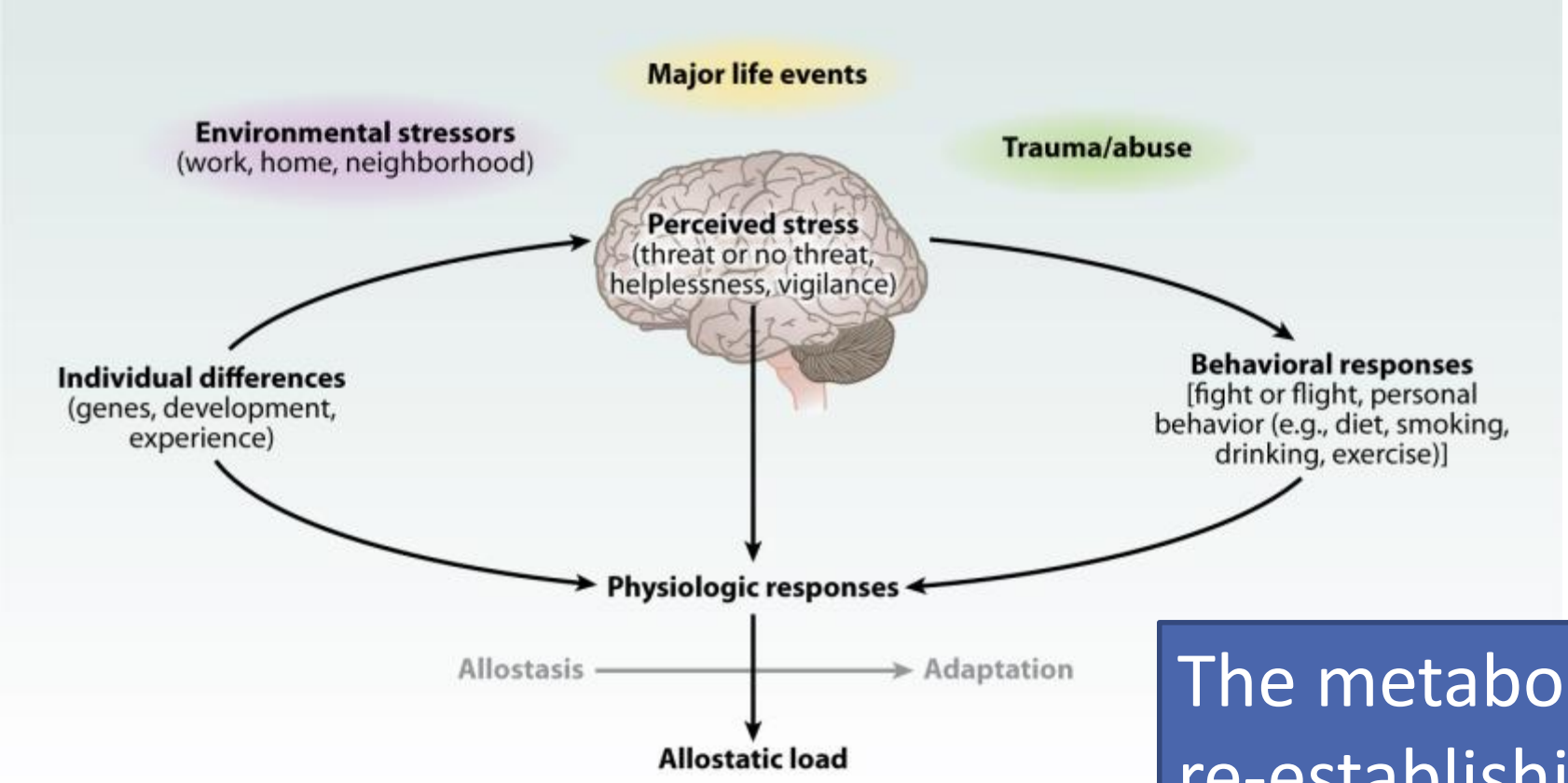
- Early Life Stress
- Cortisol sensitivity
- Feedback Loops
- Epigenetics
- Chaperones
- Neuro-steroids
- Learned Responses

GENOVA DIAGNOSTICS



Guilliams TG, The Role of Stress and the HPA Axis in Chronic Disease Management (2nd Ed- 2020).

Allostatic Load: The Cost of Adaptation



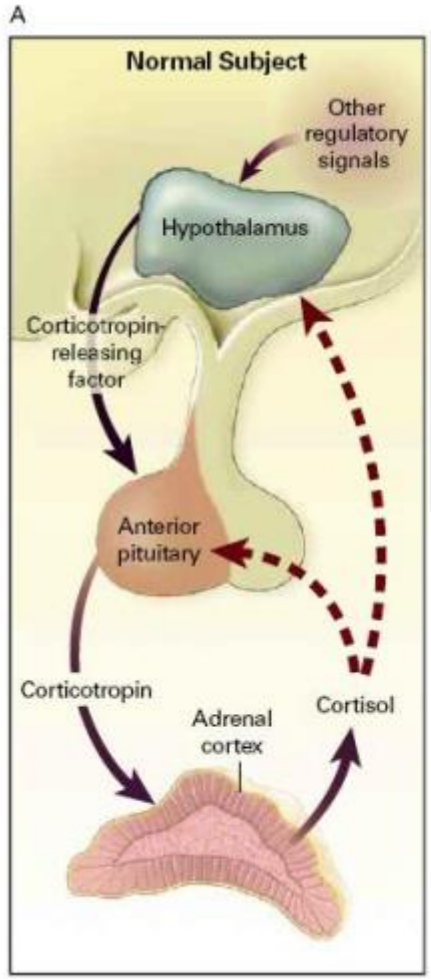
McEwen BS, Gianaros PJ. 2011.
Annu. Rev. Med. 62:431–45

The metabolic cost of re-establishing physiological integrity after a stressor

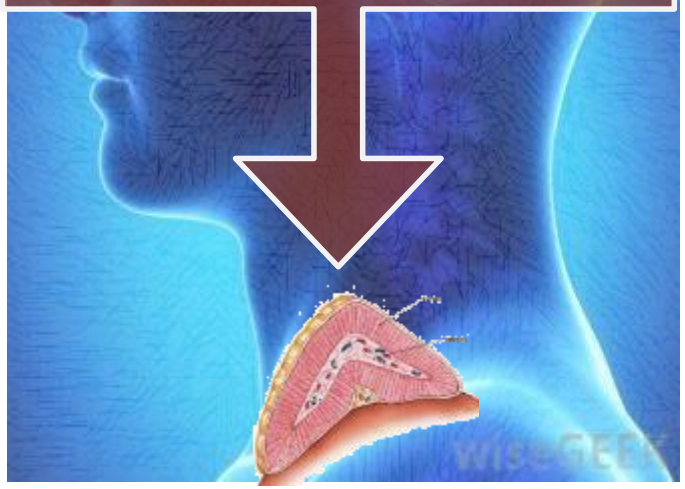
GENOVA DIAGNOSTICS

The Adrenals respond to the Brain

(Feedback inhibition alters cortisol output)



A variety of "Stress" signals from outside the hypothalamus, along with feedback signals of cortisol at the HP, determine the ACTH signal and subsequent adrenal cortisol output



GENOVA DIAGNOSTICS

Yehuda R. *N Engl J Med* 2002; 346:108-114.

The “Goal” of the Stress Response

- Maintain effective blood supply (O_2/nutrition) to brain, heart, skeletal muscle for immediate survival
- Increase energy production by recruiting substrates (glucose, FA, AA) from body stores and enhance gluconeogenesis
- Optimize ATP production for vital short-term needs at the expense of long-term metabolic functions
- Achieving Physiological Reliance at the Expense of Metabolic Reserve (akin to Ames’ Triage theory)

Stress Drives on the Same Road!

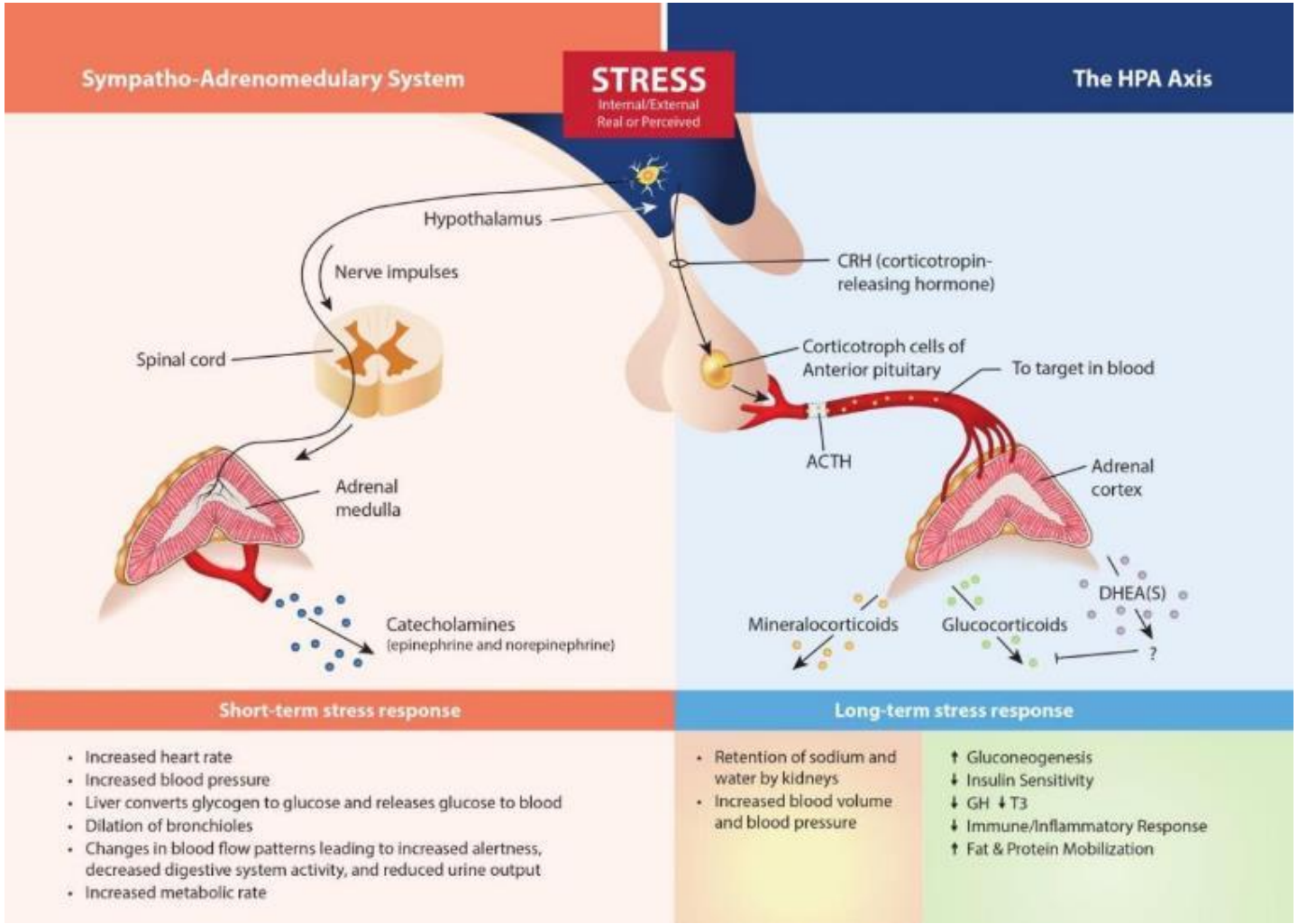
- Just like emergency vehicles need to use the same roads used for non-emergency functions;
- The stress-response system uses the same organs, cells, metabolites and signaling mechanisms that the body uses to maintain non-stress metabolic functions

GENOVA DIAGNOSTICS

Thinking Differently About the HPA Axis: Beyond Stress!

- An Energy Management System that:
  - Upregulates metabolic systems to coincide with diurnal activities and energy needs
  - Modulates cell metabolism in anticipation of energy availability
  - Prepares immune functions for increased vulnerabilities- tied to anticipated activity
  - In an emergency- overrides metabolic systems to ensure energy availability to survive the crisis

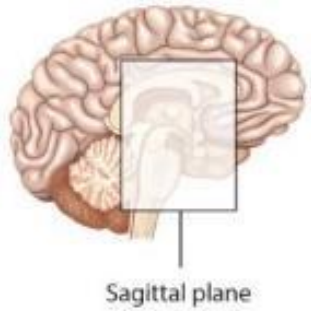
The HPA Axis is More than Just Cortisol Control

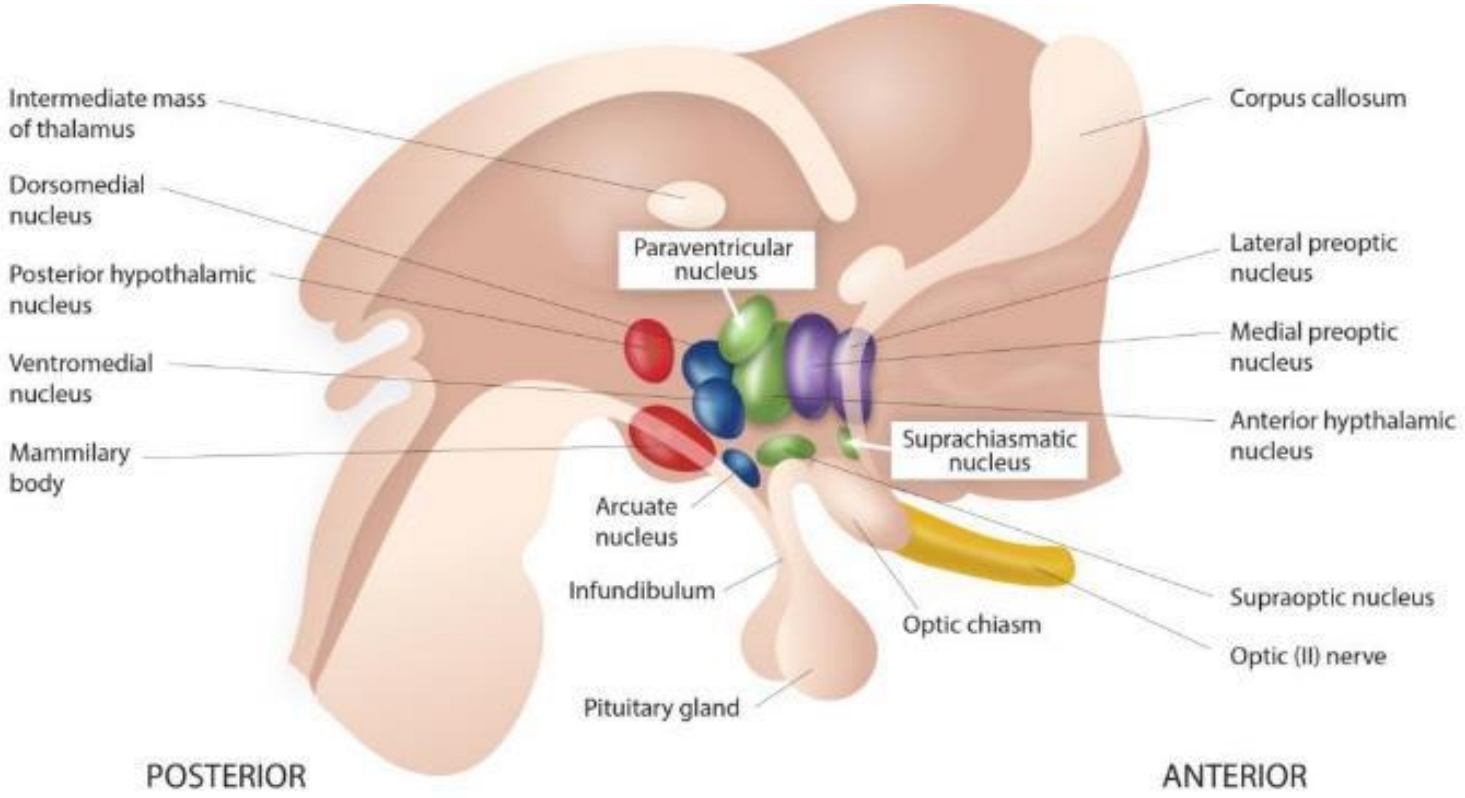


GENOVA DIAGNOSTICS

Guilliams TG, The Role of Stress and the HPA Axis in Chronic Disease Management (2nd Ed- 2020).

The Hypothalamus Nuclei: Defining “Stress”

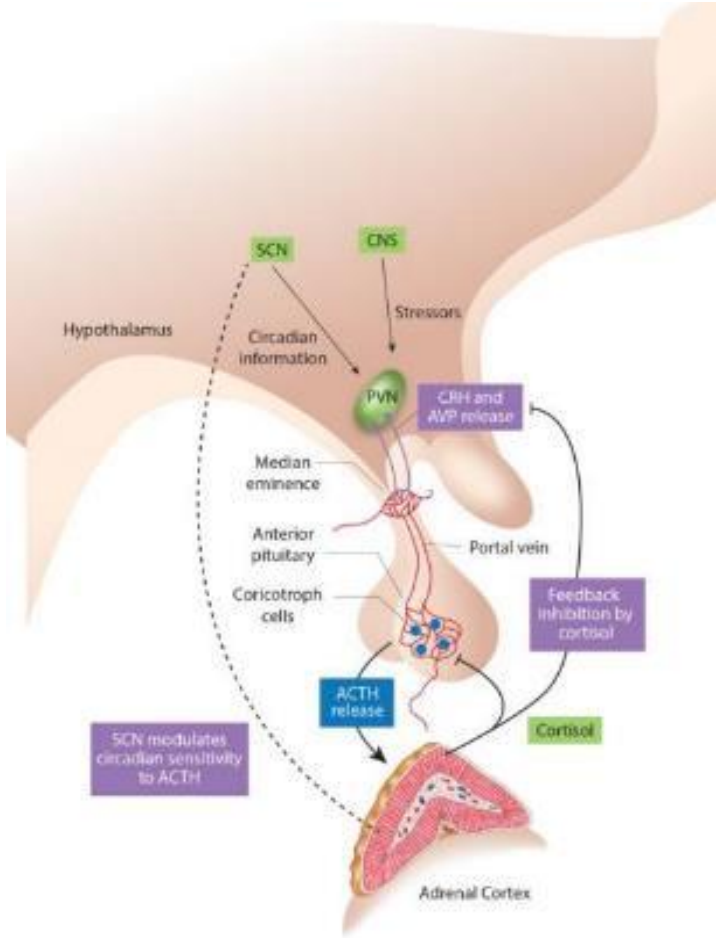


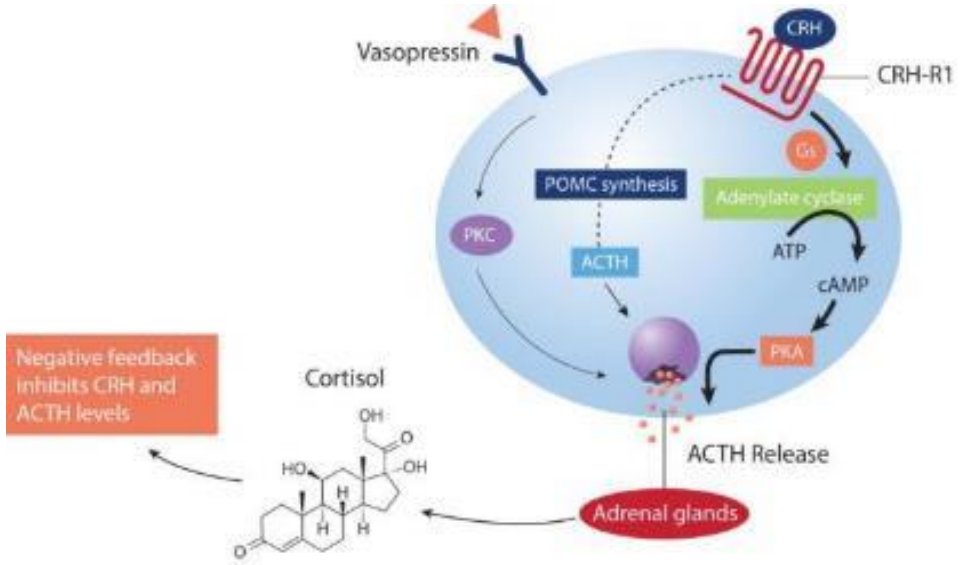


GENOVA DIAGNOSTICS

Guilliams TG, The Role of Stress and the HPA Axis in Chronic Disease Management (2nd Ed- 2020).

PVN Consolidates Signal



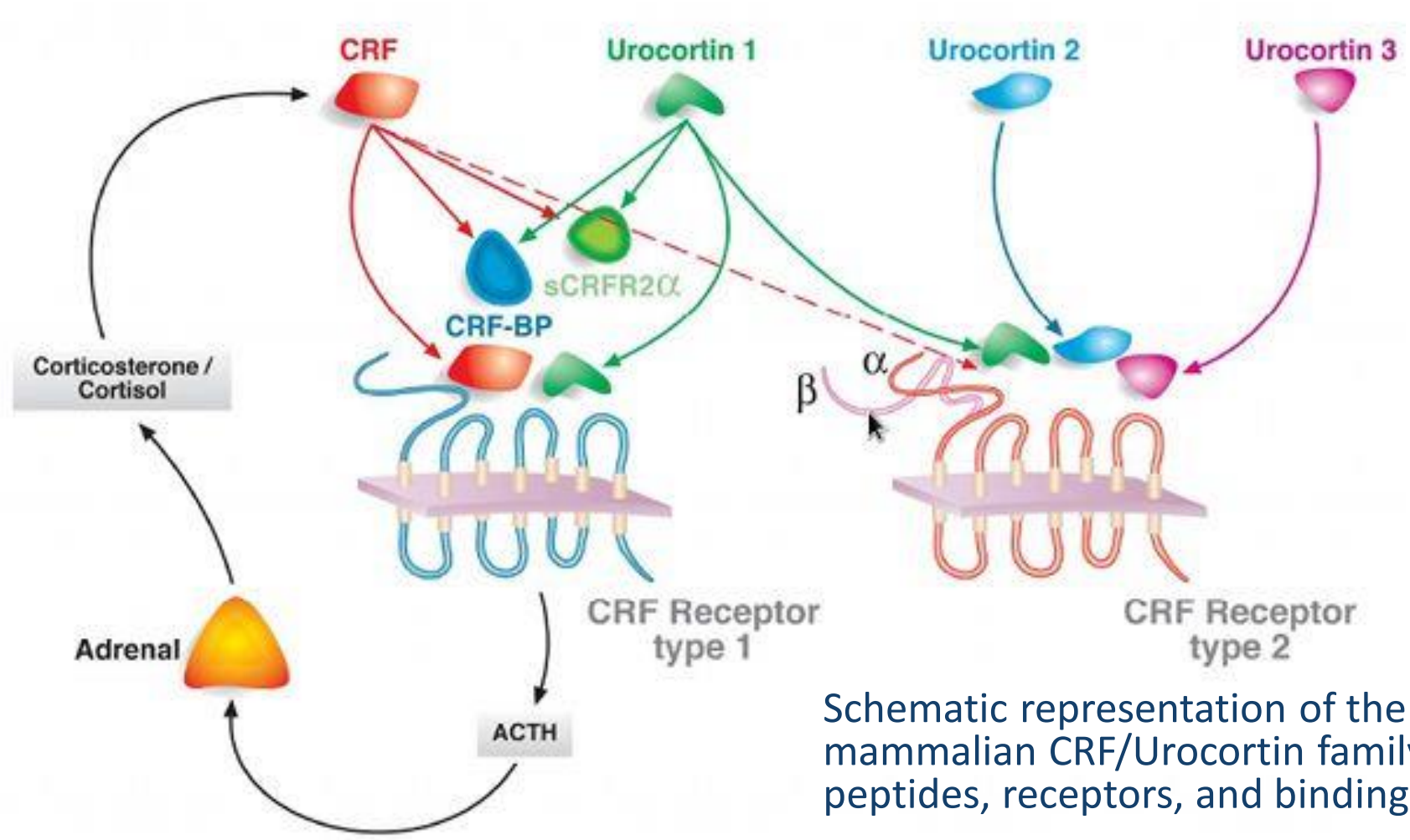


- Pre-formed ACTH is released upon CRH and/or arginine vasopressin (AVP) interaction with their respective receptors. AVP is a much weaker signal compared to ACTH

GENOVA DIAGNOSTICS

Guilliams TG, The Role of Stress and the HPA Axis in Chronic Disease Management (2nd Ed- 2020).

CRF (CRH) and Urocortins



Schematic representation of the mammalian CRF/Urocortin family of peptides, receptors, and binding proteins

GENOVA DIAGNOSTICS

Kuperman Y & Chen A. *Trends Endocrinol Metab*. 2008.

CRF/CRH Receptors: Beyond signaling ACTH

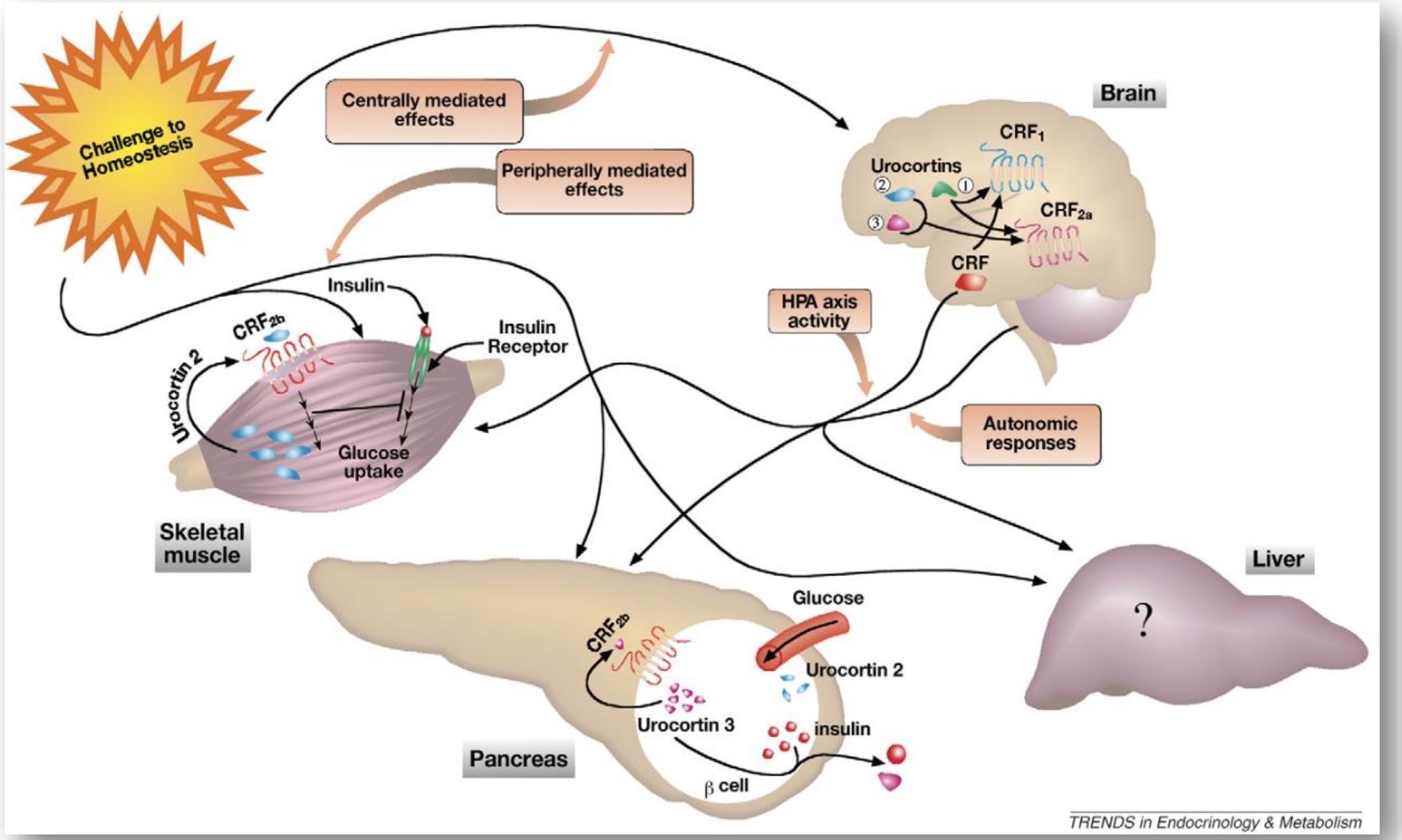
- CRH and urocortins bind to two receptors
- CRH Receptors are found in many areas of the brain and also in many peripheral tissues
- CRH is also produced by other tissues (i.e. some immune cells)

	CRH-R1	CRH-R2
Chromosome	17q21.31	7p14.3
Amino acids	415-446	397-438
Splice Variants	CRH-R1a CRH-R1c, e, h: (N-terminal variants) CRH-R1b, f: (intracellular variants) CRH-R1g, d: (transmembrane variants)	CRH-R2a CRH-R2b: (N-terminal variant) CRH-R2c: (N-terminal variant)
Central Distribution	Anterior pituitary Lateral hypothalamic nuclei Locus ceruleus Hippocampus/amygdala Thalamus Neocortex Cerebellum	Ventromedial hypothalamic nuclei Amygdala Bed nucleus Stria terminalis Lateral septum Dorsal raphe Brain stem
Peripheral Distribution	Adrenal gland Ovary/testis Skin	Peripheral vasculature Heart/skeletal muscles Gastrointestinal tract
Endogenous ligands	CRH Urocortin 1	Urocortin 1 Urocortin 2 and 3

GENOVA DIAGNOSTICS

Kassi et al. EndoText.com Stress, Endocrine Physiology and Pathophysiology.

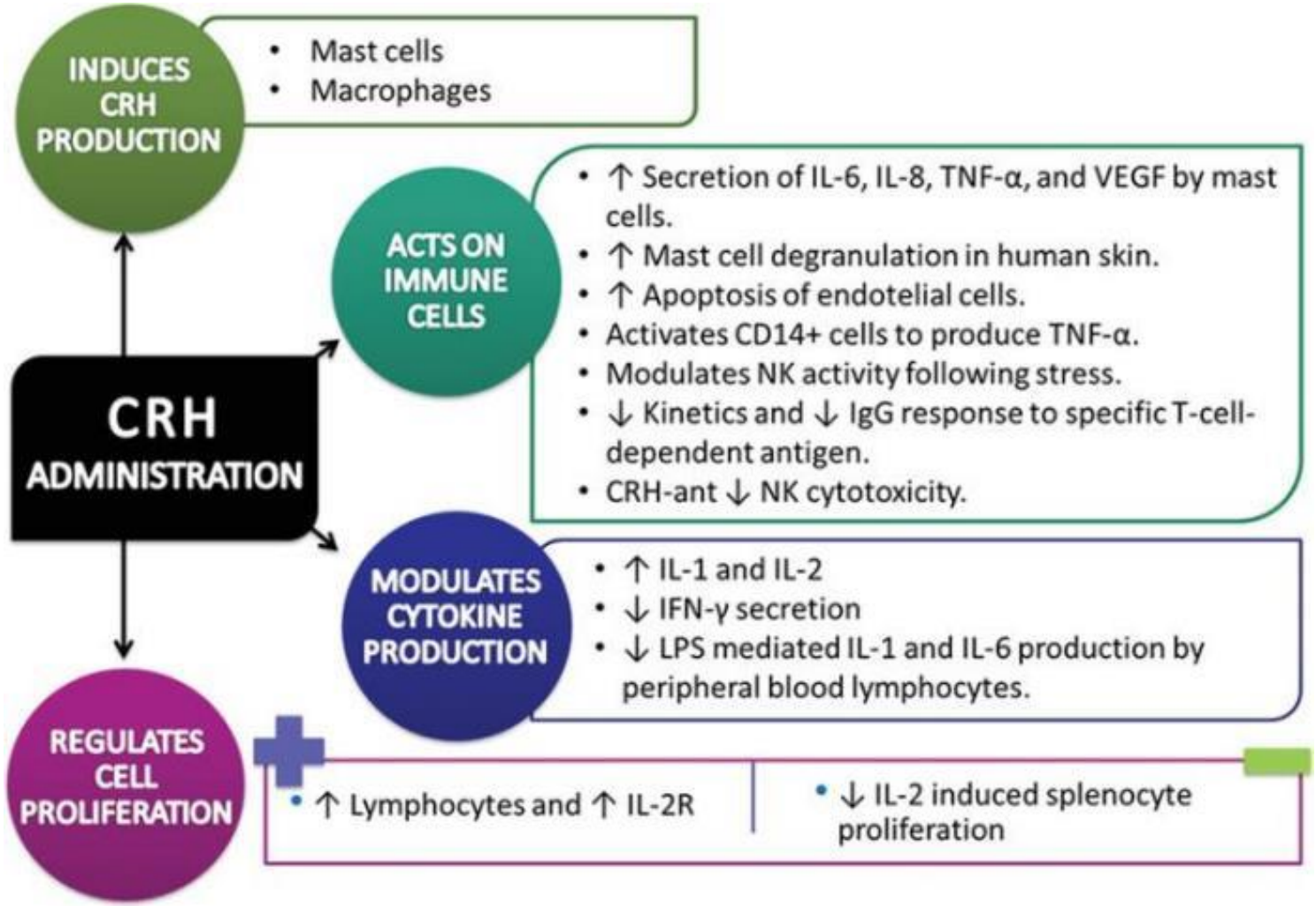
CRH/CRH Receptors in Metabolism



GENOVA DIAGNOSTICS

Kuperman Y & Chen A. *Trends Endocrinol Metab*. 2008.

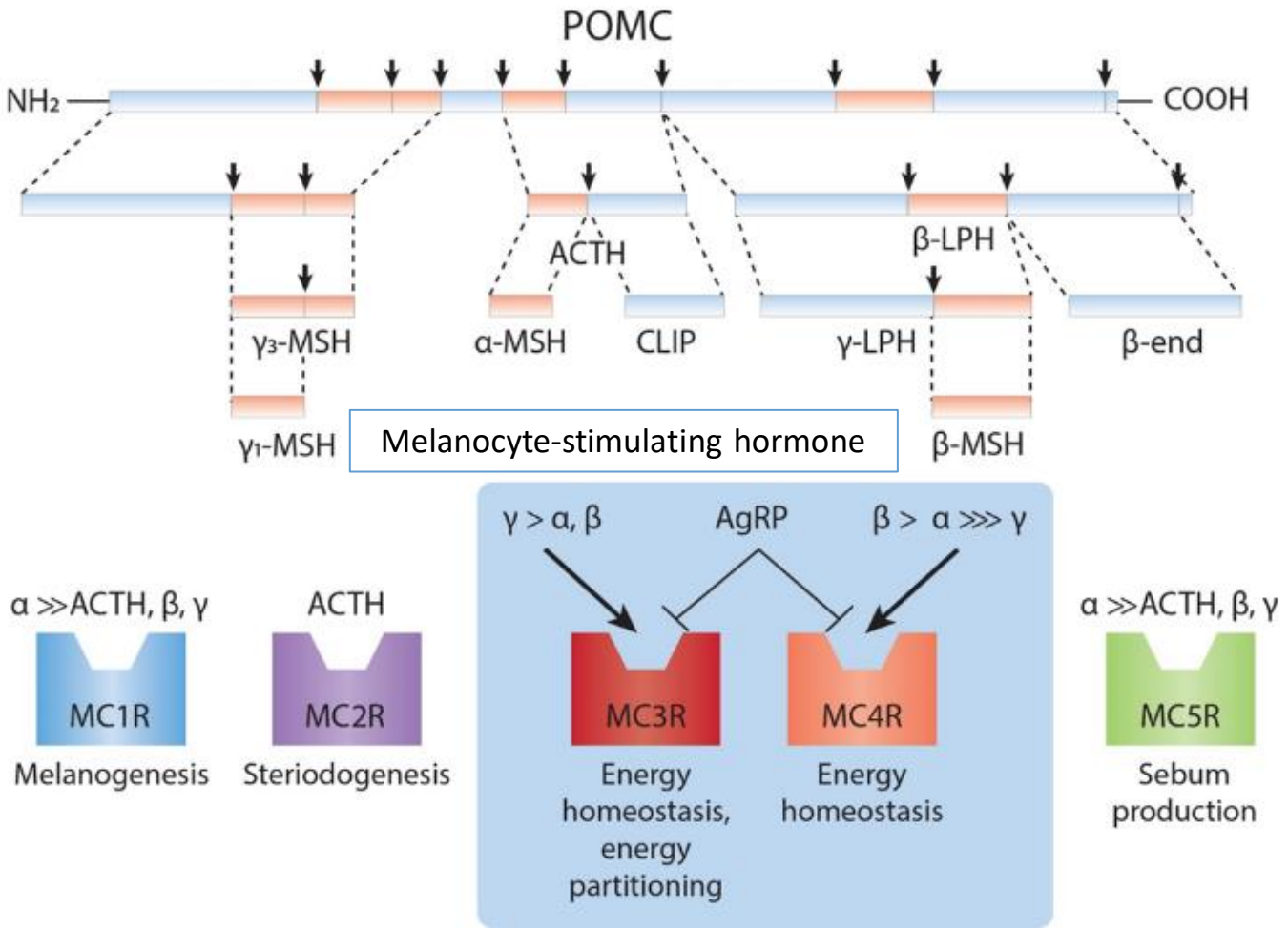
CRH and Immune Cells



GENOVA DIAGNOSTICS

Front Integr Neurosci., 13 August 2013 http://dx.doi.org/10.3389/fnint.2013.00056.

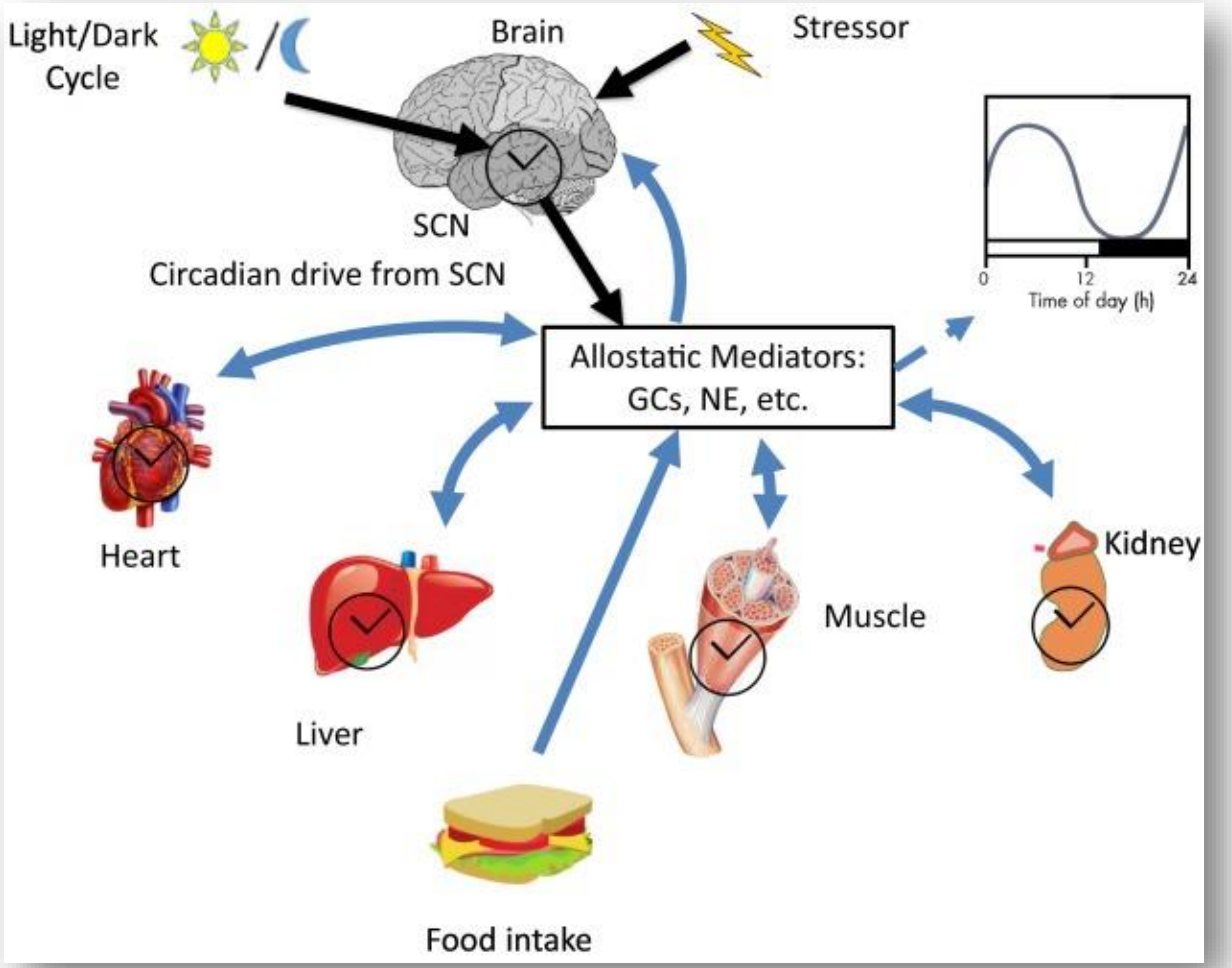
ACTH and POMC Pro-opiomelanocortin



GENOVA DIAGNOSTICS

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

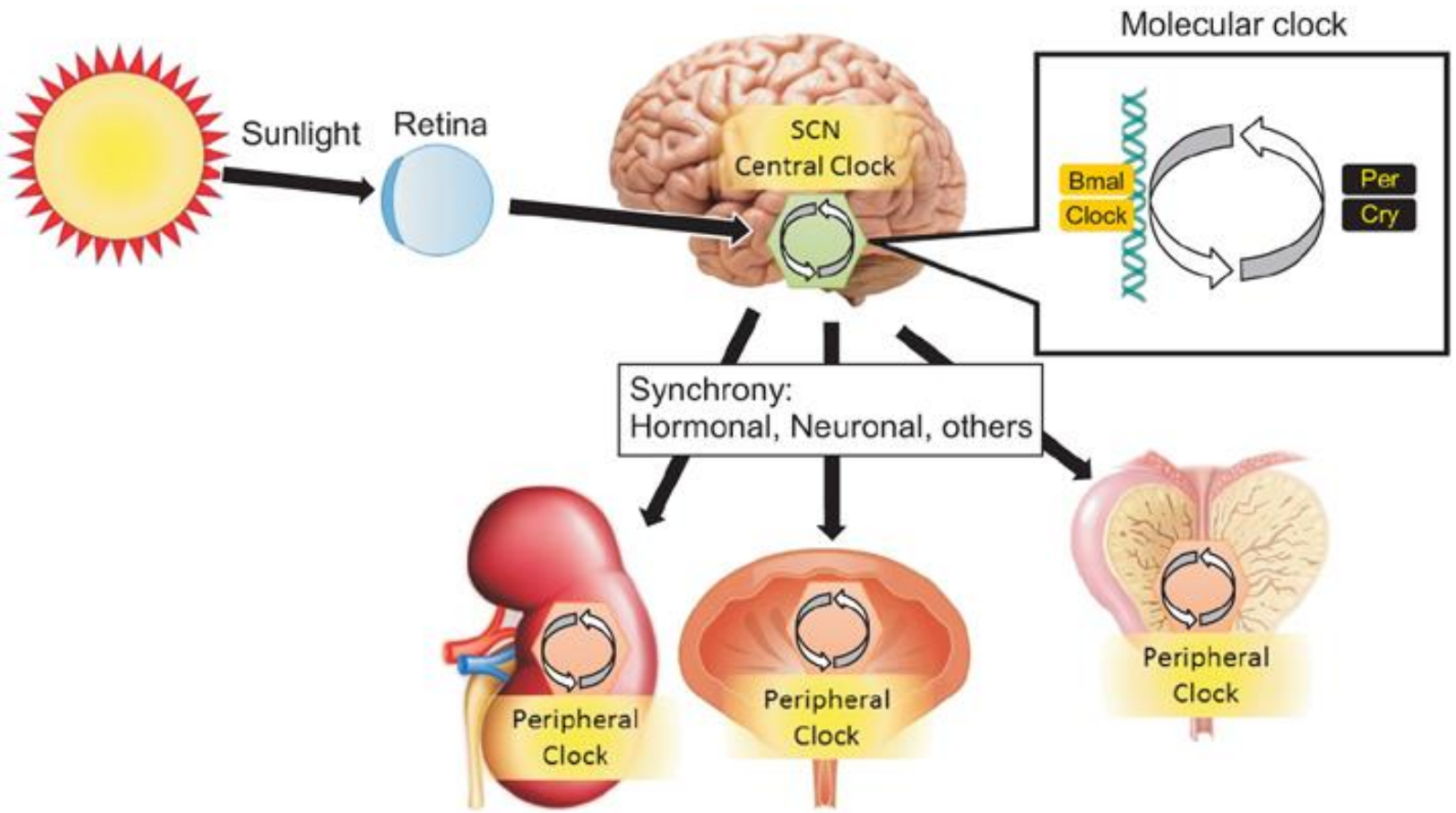
The HPA Axis-Circadian-Metabolism Connection



GENOVA DIAGNOSTICS

Rao R, Androulakis IP. *Horm Behav*. 2019 Apr;110:77-89.

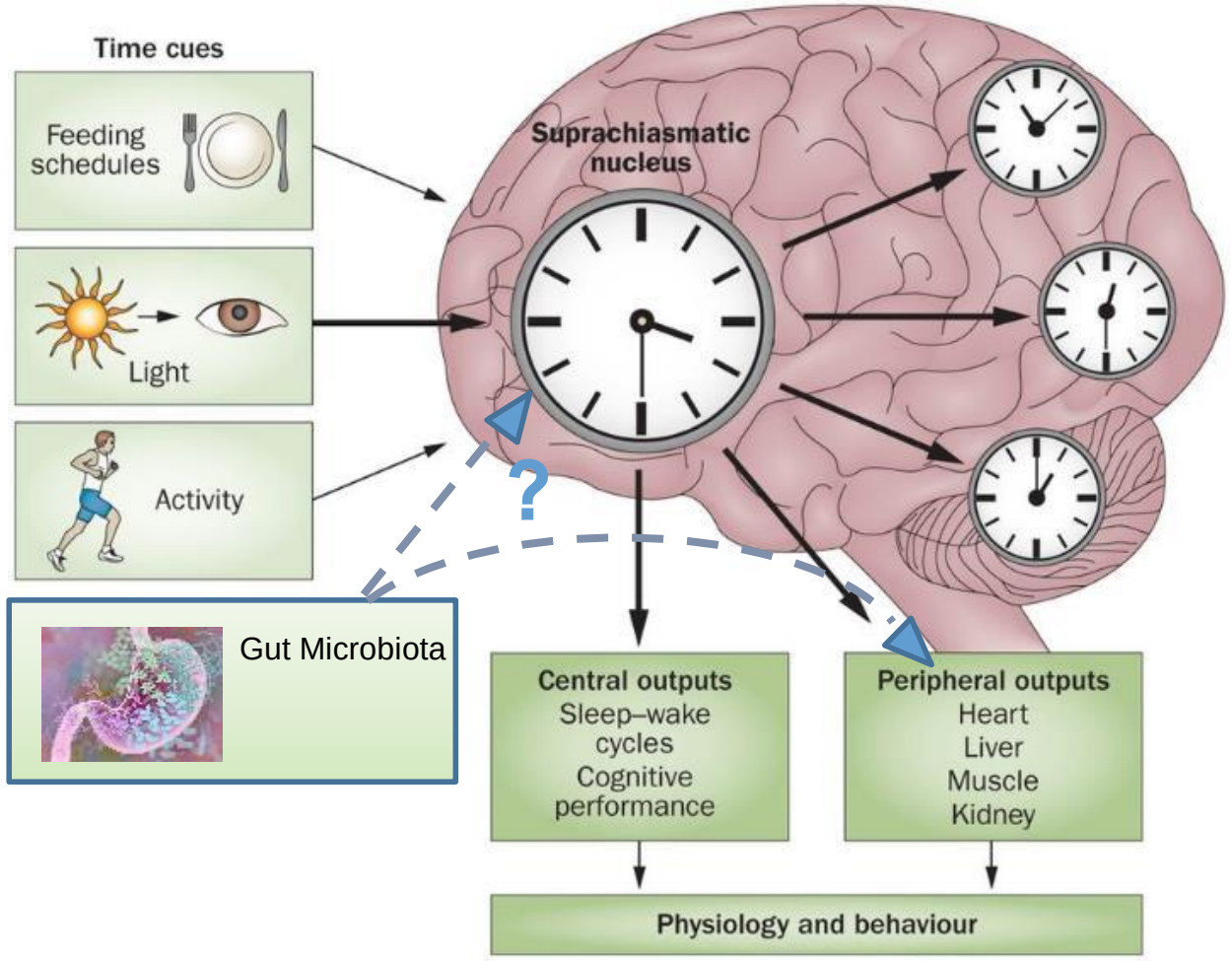
Synchronizing Peripheral Clocks via the Suprachiasmatic Nucleus (SCN)



GENOVA DIAGNOSTICS

Investig Clin Urol. 2016 May;57(3):165-173. https://doi.org/10.4111/icu.2016.57.3.165.

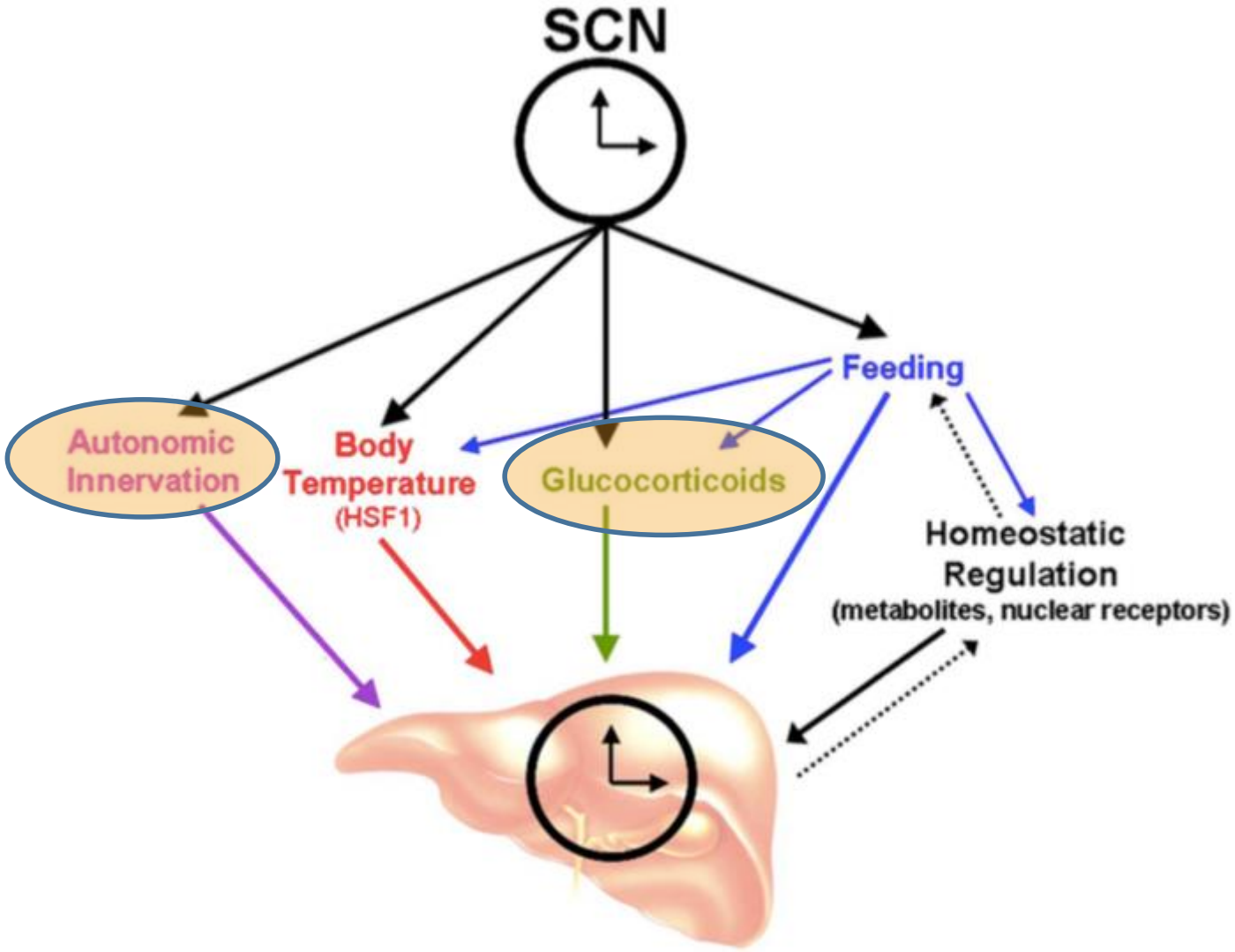
Time Cues: Zeitgebers



GENOVA DIAGNOSTICS

Nature Reviews Neurology **volume 10**, pages 683–693 (2014).

Major Signals from SCN to Peripheral Clocks

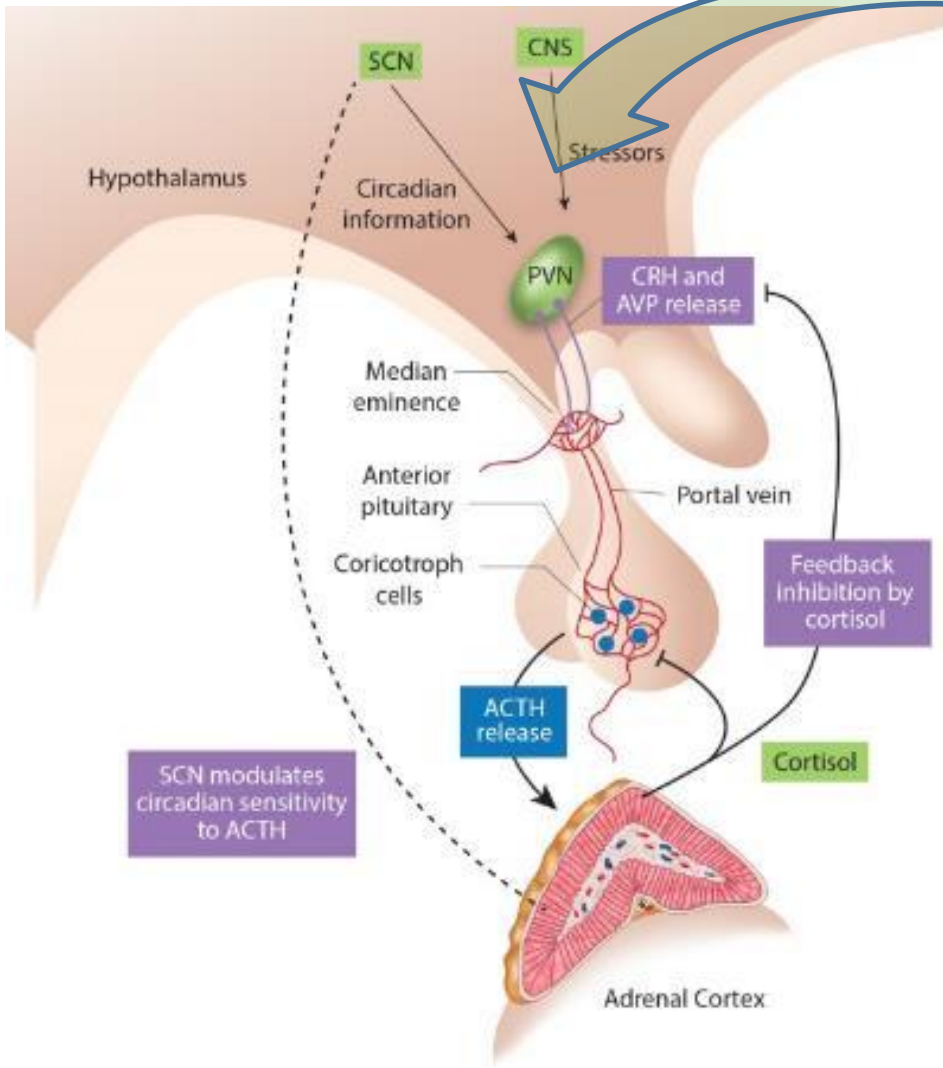


GENOVA DIAGNOSTICS

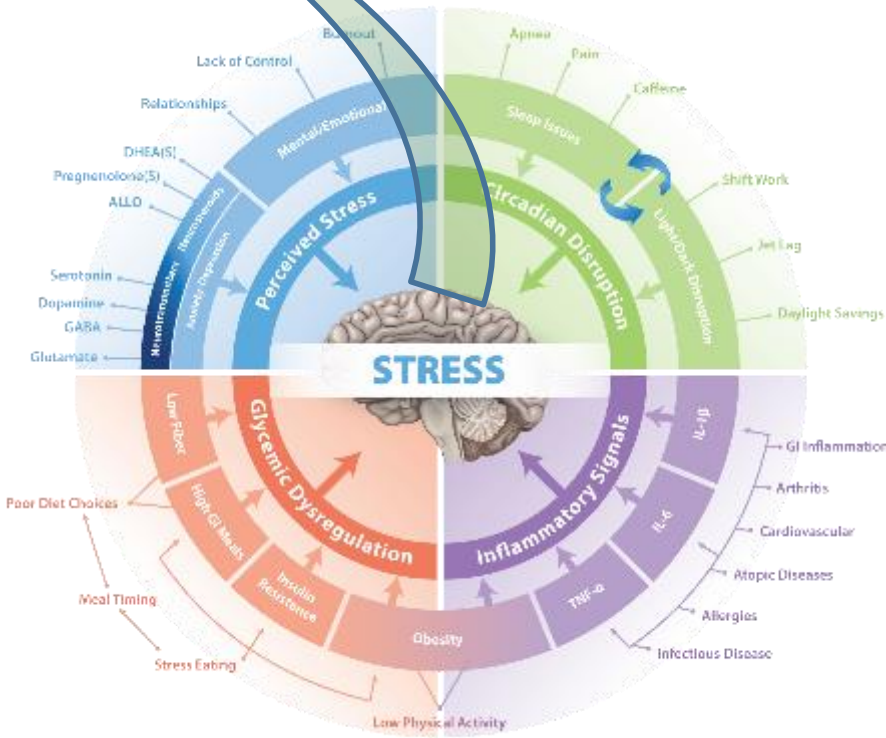
Mohawk JA, et al. *Annu Rev Neurosci*. 2012;35:445-62.

Two Major signals: Surveillance of “Stress” and Circadian Re-synchrony

SCN acts as the body’s main zeitgeber to synchronize circadian rhythm to light

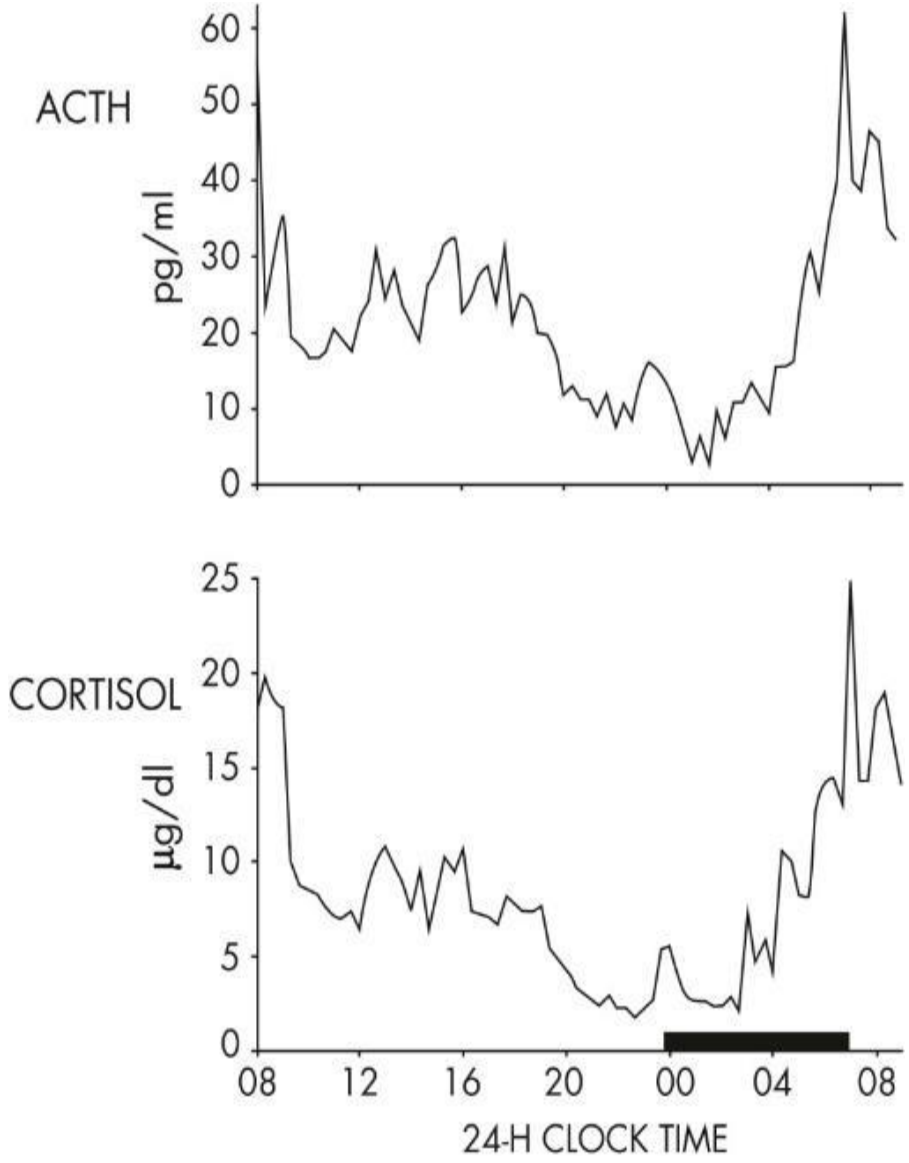


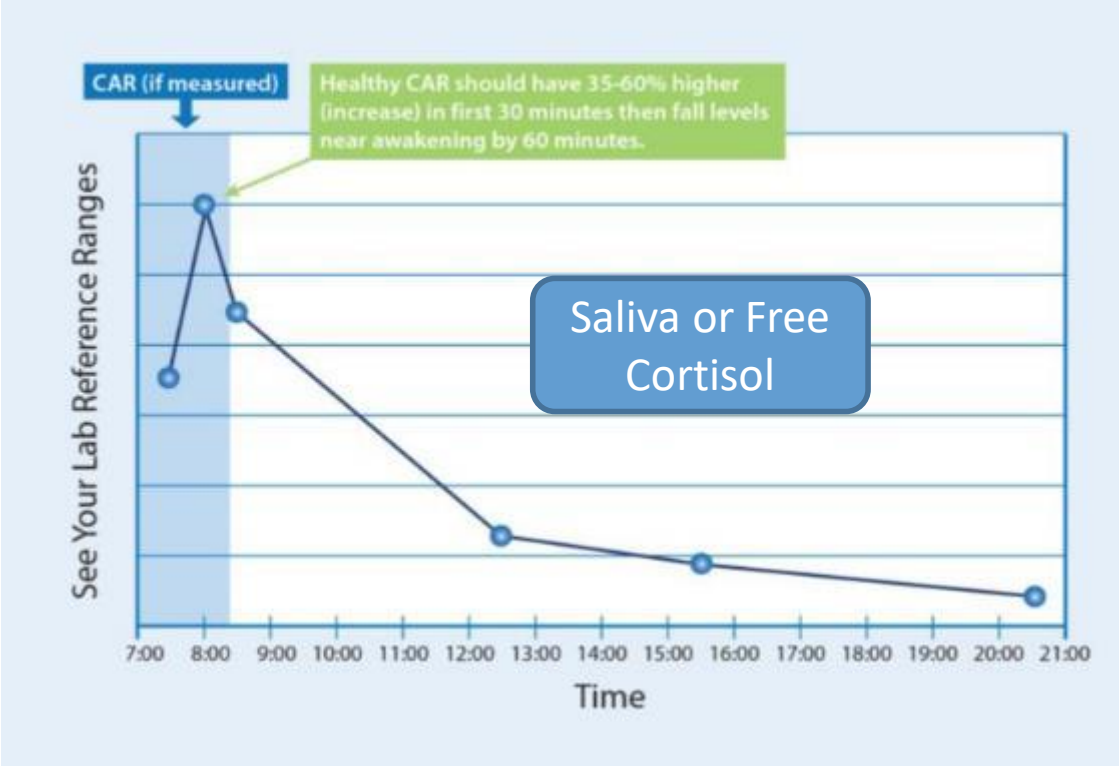
PVN consolidates the Stress Signal



GENOVA DIAGNOSTICS

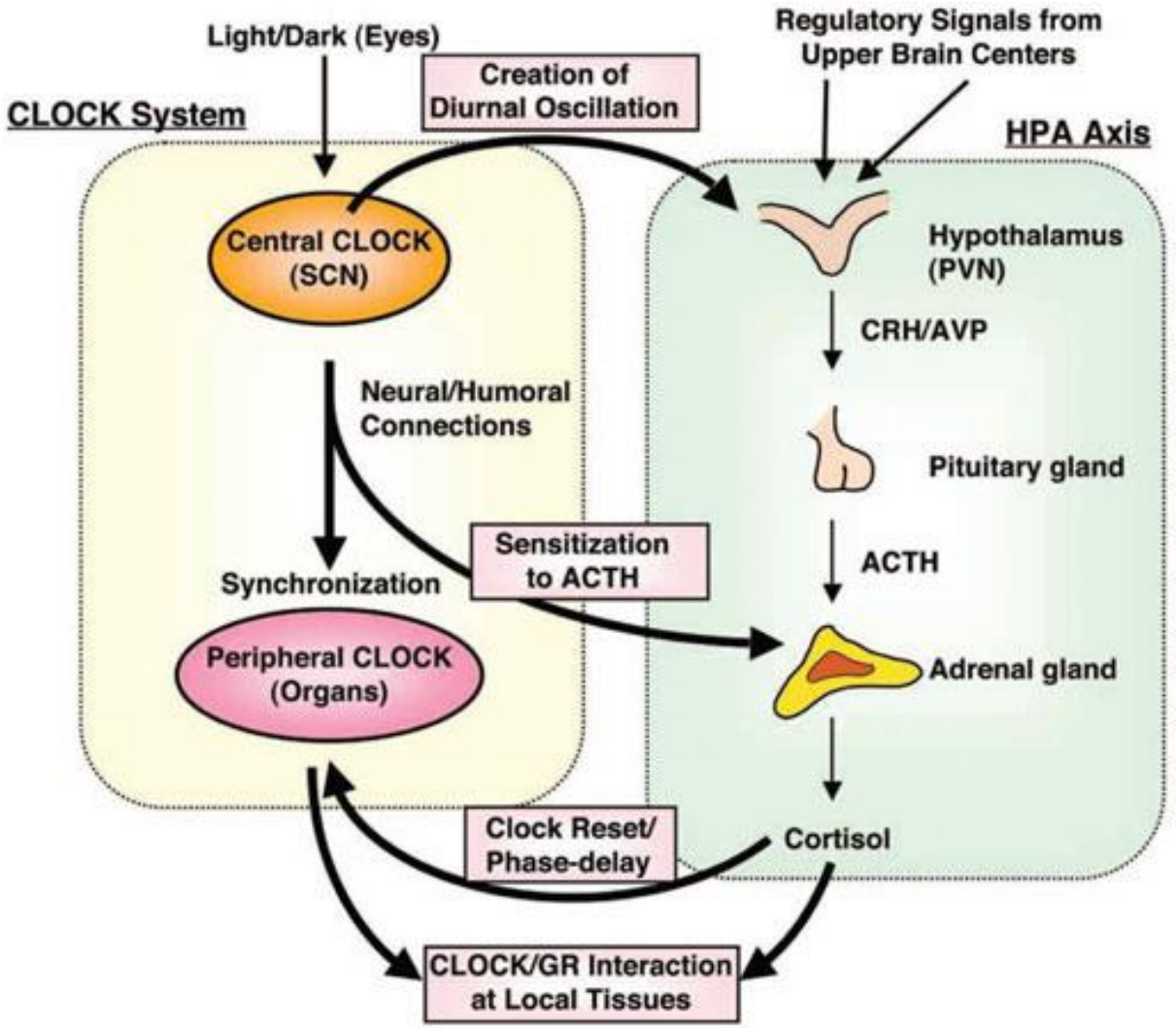
Circadian and Ultradian Rhythm of ACTH and Cortisol





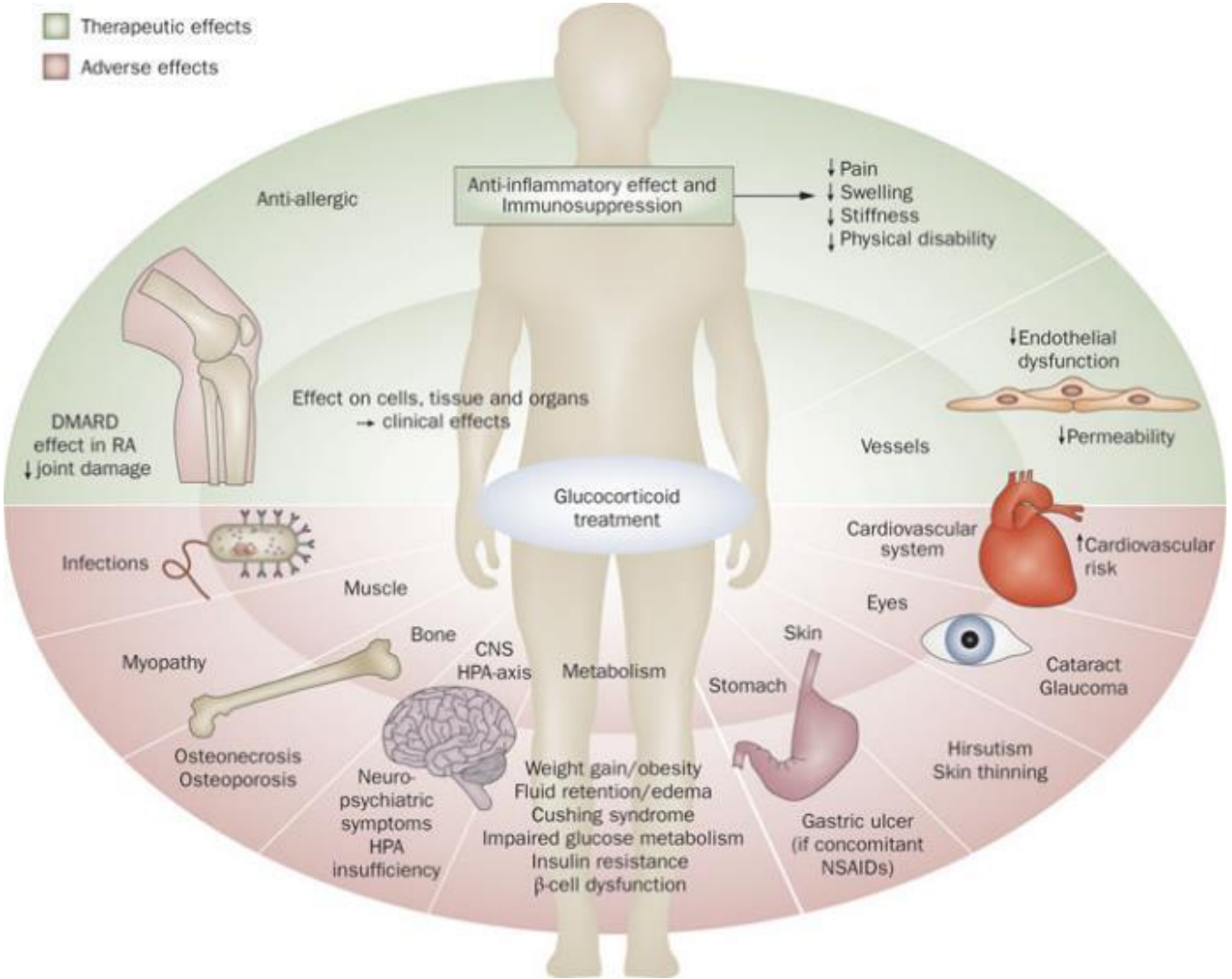
GENOVA DIAGNOSTICS

The HPA Axis and Clocks (Central and Peripheral)



GENOVA DIAGNOSTICS

Cortisol: A Major Signal for Cellular Transcription



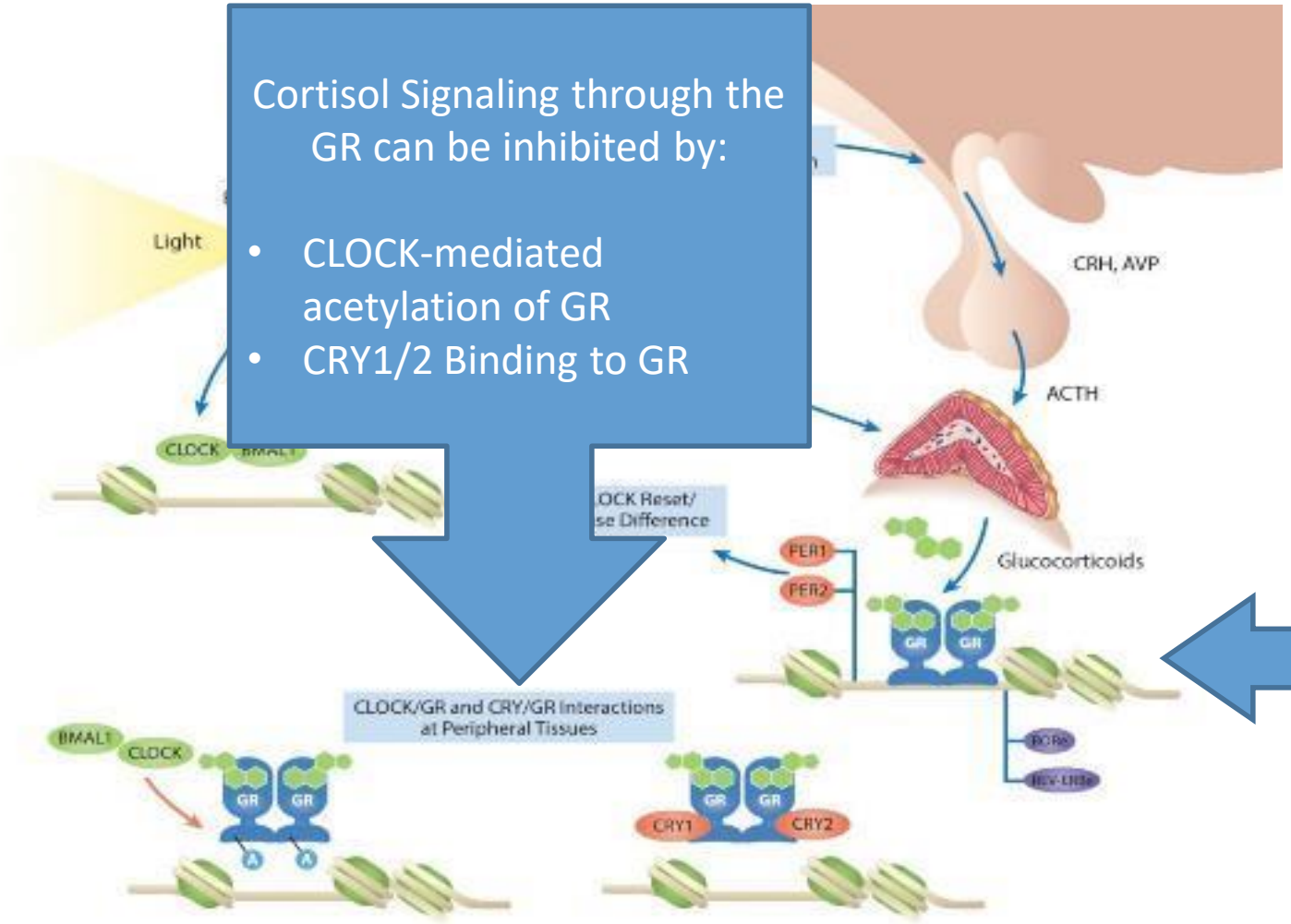
GENOVA DIAGNOSTICS

Cells **2013**, *2*(2), 202-223; doi:10.3390/cells2020202 .

Cortisol/GR and Clock Gene Interactions

Cortisol Signaling through the GR can be inhibited by:

- CLOCK-mediated acetylation of GR
- CRY1/2 Binding to GR



GR/Cortisol modulates the peripheral clock by

- Increasing or phase-shifting the expression of PER1/2.
- Reducing the expression of RORα and Rev-ERBα

GENOVA DIAGNOSTICS

DNA Research 12, 191–202 (2005) doi:10.1093/dnares/dsi003

Genome-wide Expression Analysis Reveals 100 Adrenal Gland-dependent Circadian Genes in the Mouse Liver

Katsutaka Oishi,[1] Noriko Amagai,[1] Hidenori Shirai,[1,2] Koji Kadota,[3,4] Naoki Ohkura,[5] and Norio Ishida[1,2,*]

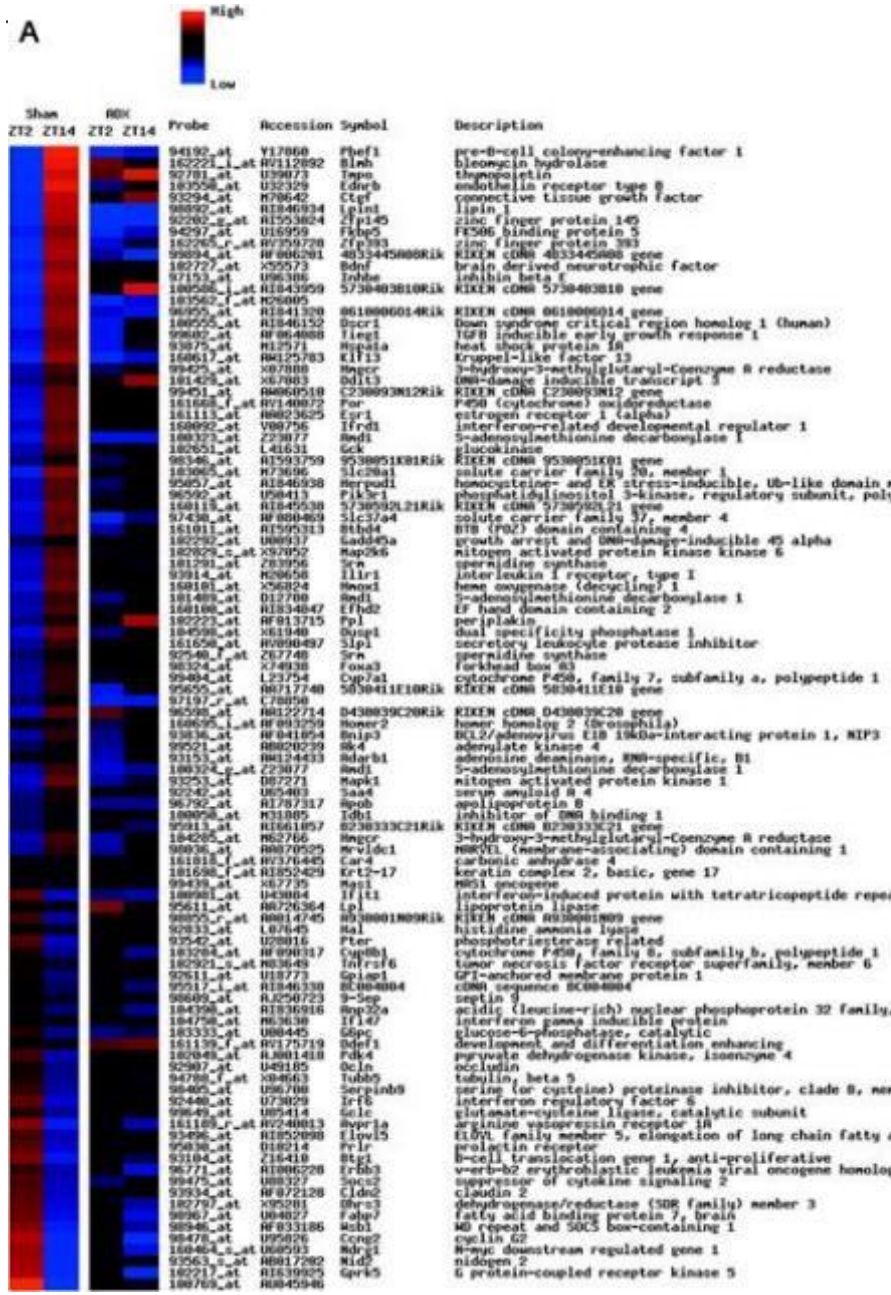
Clock Cell Biology Research Group, Institute for Biological Resources and Functions, National Institute of Advanced Industrial Science and Technology (AIST), Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki 305-8566, Japan[1], Graduate School of Life and Environmental Sciences, University of Tsukuba, Tsukuba, Ibaraki 305-8502, Japan[2], Computational Biology Research Center, National Institute of Advanced Industrial Science and Technology, Aomi Frontier Bldg 17F, 2-43 Aomi, Koto-Ku, Tokyo 135-0064, Japan[3], Transcriptome Research Center, National Institute of Radiological Sciences (NIRS), 4-9-1 Anagawa, Chiba, Chiba 263-8555, Japan[4] and Clinical Molecular Biology, Faculty of Pharmaceutical Sciences, Teikyo University, 1091-1 Suarashi, Sagamiko, Tsukui, Kanagawa 199-0195, Japan[5]

(Received 9 February 2005; revised 28 April 2005)

Abstract

Recent progress in genome-wide expression analysis has identified hundreds of circadian genes not only in the suprachiasmatic nucleus (the mammalian master clock) but also in peripheral tissues, such as heart, liver and kidney of mammals. Glucocorticoid is thought to be a circadian time cue for mammalian peripheral clocks. To identify the genes of which the circadian expression is regulated by endogenous glucocorticoids, we performed DNA microarray analysis using hepatic RNA from adrenalectomized (ADX) and sham-operated mice. We identified 169 genes that fluctuated between day and night in the livers of the sham-operated mice. Among these, 100 lost circadian rhythmicity in ADX mice. These included the genes for key enzymes of liver metabolic functions, such as *glucokinase*, *HMG-CoA reductase* and *glucose-6-phosphatase*. The circadian expression of *Lpin1*, *FKBP51* and S-*adenosyl methionine decarboxylase* was also abolished in the ADX mice. On the other hand, although the circadian expression of clock or clock-related genes, such as *mPer2*, *DBP*, *E4BP4*, *mDec1*, *Usp2* and *Wee1* remained almost totally intact in the liver of ADX mice, it was extremely damped in homozygous *Clock* mutant mice. The present findings suggested that one type of hepatic circadian genes in mice is transcriptionally regulated by core components of the circadian clock, such as CLOCK and BMAL1, and that the other depends on the adrenal gland.

Key words: circadian rhythm; glucocorticoids; *Clock*; DNA microarray; liver



For those who want the details!

Tissue Cortisol Sensitivity Fluctuates Diurnally

Nicolaides et al. BMC Endocrine Disorders 2014, 14:71
http://www.biomedcentral.com/1472-6823/14/71

BMC Endocrine Disorders

REVIEW Open Access

Recent advances in the molecular mechanisms determining tissue sensitivity to glucocorticoids: novel mutations, circadian rhythm and ligand-induced repression of the human glucocorticoid receptor

Nicolas C Nicolaides[1,2*], Evangelia Charmandari[1,2], George P Chrousos[1,2,3] and Tomoshige Kino[4]

Abstract

Glucocorticoids are pleiotropic hormones, which are involved in almost every cellular, molecular and physiologic network of the organism, and regulate a broad spectrum of physiologic functions essential for life. The cellular response to glucocorticoids displays profound variability both in magnitude and in specificity of action. Tissue sensitivity to glucocorticoids differs among individuals, within tissues of the same individual and within the same cell. The actions of glucocorticoids are mediated by the glucocorticoid receptor, a ubiquitously expressed intracellular, ligand-dependent transcription factor. Multiple mechanisms, such as pre-receptor ligand metabolism, receptor isoform expression, and receptor-, tissue-, and cell type-specific factors, exist to generate diversity as well as specificity in the response to glucocorticoids. Alterations in the molecular mechanisms of glucocorticoid receptor action impair glucocorticoid signal transduction and alter tissue sensitivity to glucocorticoids. This review summarizes the recent advances in our understanding of the molecular mechanisms determining tissue sensitivity to glucocorticoids with particular emphasis on novel mutations and new information on the circadian rhythm and ligand-induced repression of the glucocorticoid receptor.

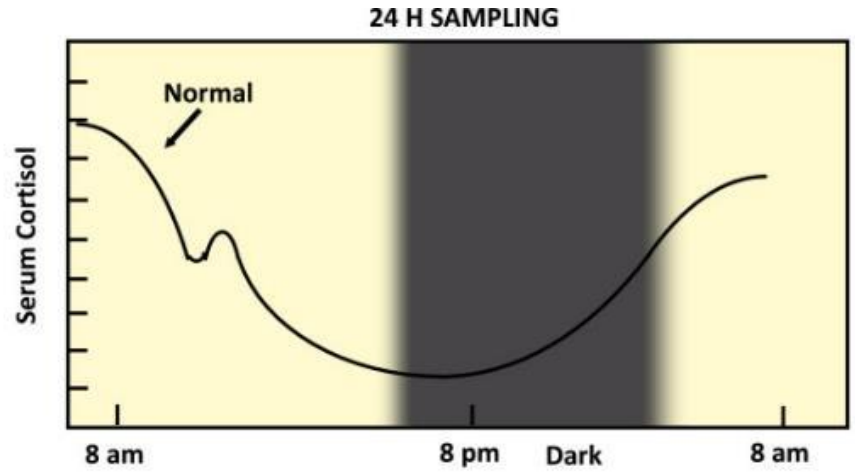
Keywords: Glucocorticoid receptor, Glucocorticoid resistance, Glucocorticoid hypersensitivity, Glucocorticoid signal transduction

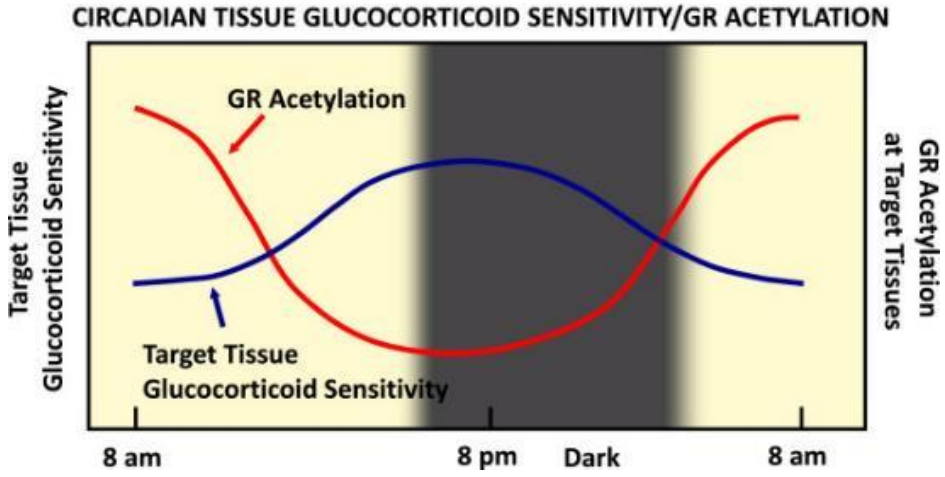
Background

In humans, glucocorticoids are synthesized by the adrenal cortex and released following activation of the hypothalamic-pituitary-adrenal (HPA) axis, and play an important role in the maintenance of resting and stress-related homeostasis. Named for their effects on glucose metabolism, glucocorticoids are involved in almost every cellular, molecular and physiologic network of the organism, and regulate a broad spectrum of physiologic functions essential for life, including growth, reproduction, cognition, behavior, cell proliferation and survival, as well as immune, central nervous system (CNS) and cardiovascular functions [1-3]. Given their powerful anti-inflammatory and immunosuppressive actions, synthetic glucocorticoids represent one of the most widely used therapeutic compounds employed in the treatment of acute and chronic inflammatory/autoimmune and lymphoproliferative disorders [1,3]. However, chronic exposure to glucocorticoids in patients with such disorders leads to multiple adverse effects. Sometimes glucocorticoid resistance of the affected organ or tissue may develop, representing a major challenge for the treatment of these conditions [4].

At the cellular level, the actions of glucocorticoids are mediated by the human glucocorticoid receptor

* Correspondence: nnicolaides@bioacademy.gr
[1]Division of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, University of Athens Medical School, 'Aghia Sophia' Children's Hospital, Athens 11527, Greece
[2]Division of Endocrinology and Metabolism, Clinical Research Center, Biomedical Research Foundation of the Academy of Athens, Athens 11527, Greece
Full list of author information is available at the end of the article





GENOVA DIAGNOSTICS

BMC Endocrine Disorders201414:71.

HSP and Chaperones Influence GR and Circadian Function

HSP90 Affects the Stability of BMAL1 and Circadian Gene Expression

Rebecca Schneider,* René M. Linka,* and Hans Reinke*,†,1

*University of Düsseldorf, Medical Faculty, Institute of Clinical Chemistry and Laboratory Diagnostics, Düsseldorf, Germany, and †IUF—Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany

International Journal of *Molecular Sciences*

MDPI

Review

Hsp90 Heterocomplexes Regulate Steroid Hormone Receptors: From Stress Response to Psychiatric Disease

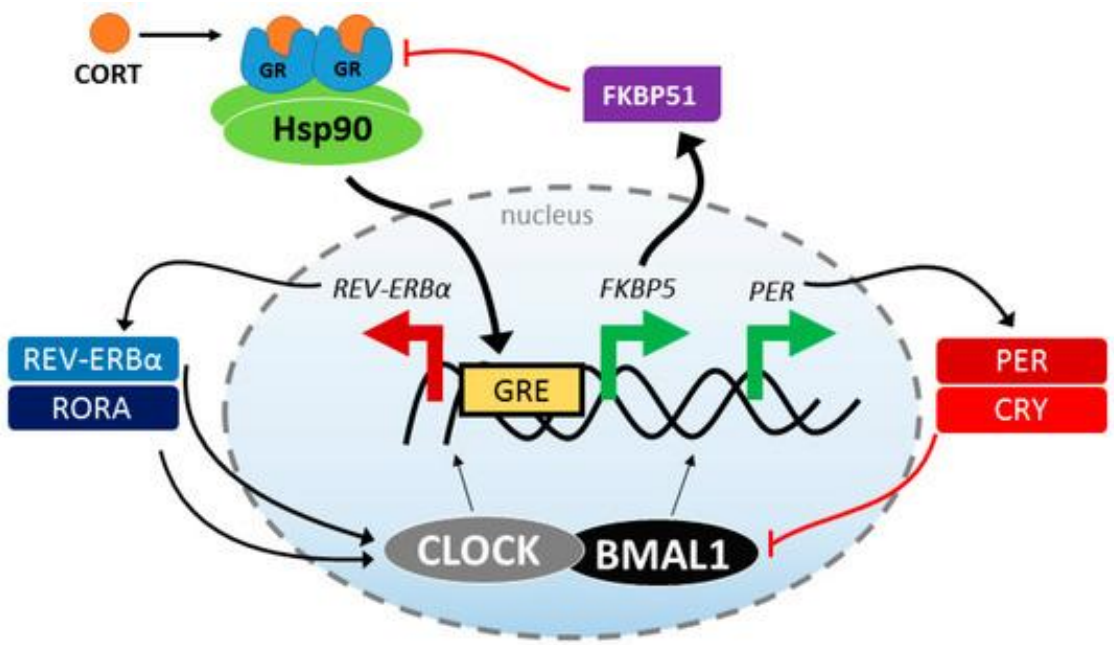
Jeremy D. Baker, Ilayda Ozsan, Santiago Rodriguez Ospina, Danielle Gulick and Laura J. Blair *

USF Health Byrd Institute, Morsani College of Medicine, Department of Molecular Medicine, University of South Florida, 4001 East Fowler Ave, Tampa, FL 33613, USA; jeremyb@health.usf.edu (J.D.B.); iozsan@health.usf.edu (I.O.); santiago3@health.usf.edu (S.R.O.); dgulick@health.usf.edu (D.G.)

* Correspondence: lblair@health.usf.edu; Tel.: +1-813-396-0639

Received: 17 November 2018; Accepted: 17 December 2018; Published: 25 December 2018

check for updates



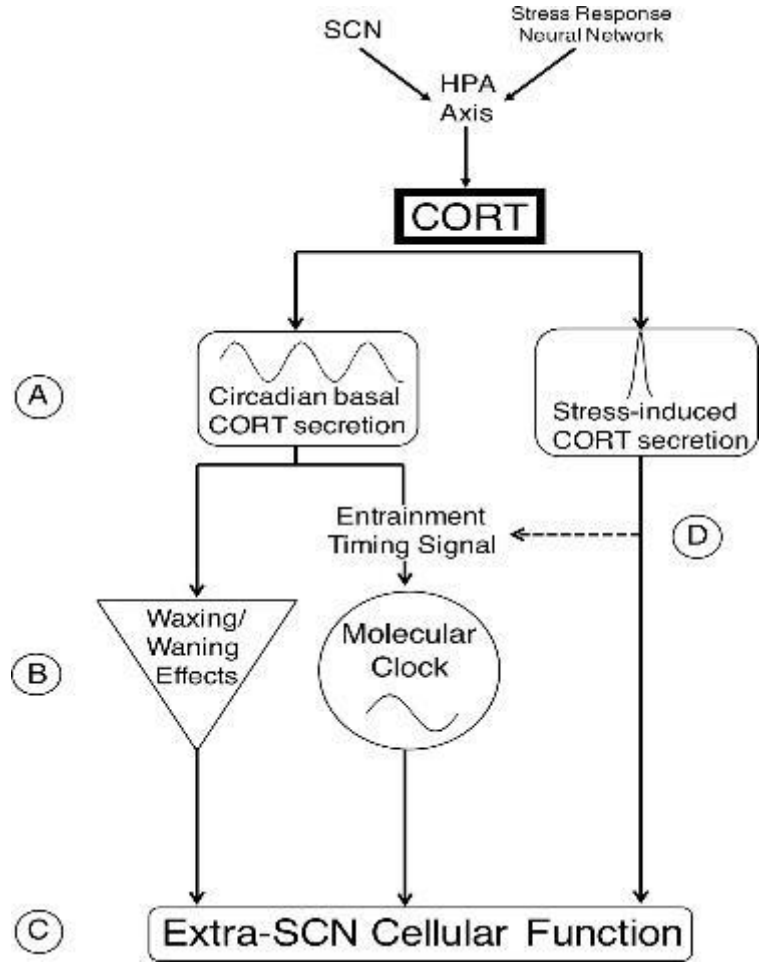
GENOVA DIAGNOSTICS

Int. J. Mol. Sci. 2019, 20(1), 79; https://doi.org/10.3390/ijms20010079.

Why Use the Stress Response to Help Manage the Circadian Rhythm?

- A large number of stressors can generate extreme fluctuations of cortisol (outside the normal diurnal rhythm) on any given day....wouldn't this create havoc on the circadian rhythm of each cell? What about chronic stress?

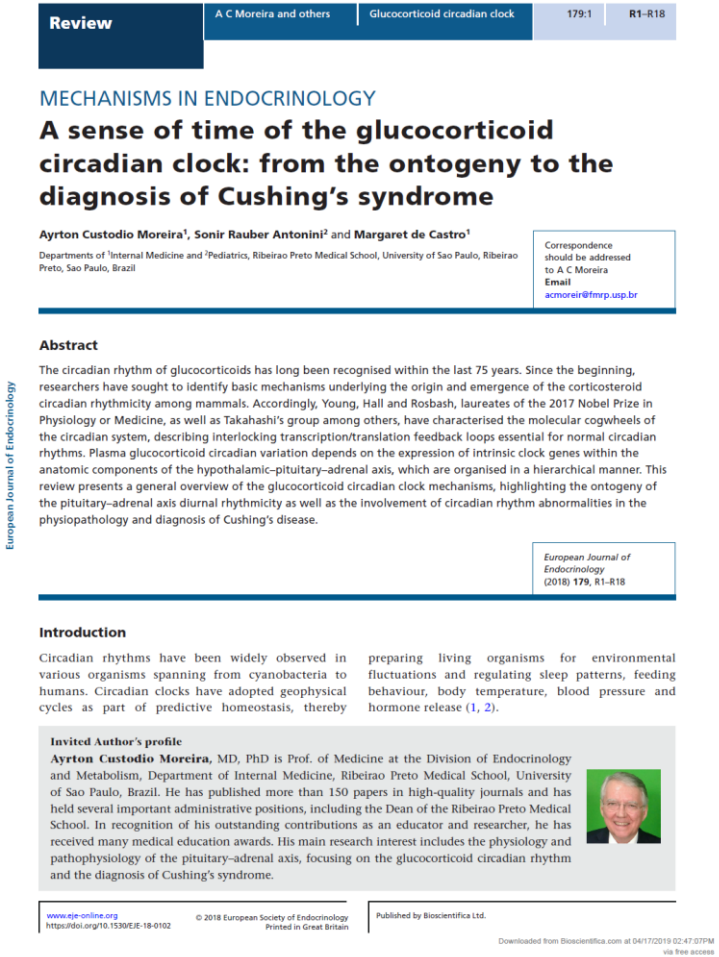
Important Note: The Suprachiasmatic Nucleus and the Pineal Gland Do Not Have Glucocorticoid Receptors- Preventing them from being directly influenced by Stress-Related Cortisol Output



GENOVA DIAGNOSTICS

Front Neuroendocrinol. 2018 Apr;49:52-71.

Chronic HPA Axis Dysregulation Affects Circadian Metabolism



Review | A C Moreira and others | Glucocorticoid circadian clock | 179:1 | R1–R18

European Journal of Endocrinology

MECHANISMS IN ENDOCRINOLOGY

A sense of time of the glucocorticoid circadian clock: from the ontogeny to the diagnosis of Cushing's syndrome

Ayrton Custodio Moreira[1], **Sonir Rauber Antonini**[2] and **Margaret de Castro**[1]

Departments of [1]Internal Medicine and [2]Pediatrics, Ribeirao Preto Medical School, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil

Correspondence should be addressed to A C Moreira
Email
acmoreir@fmrp.usp.br

Abstract

The circadian rhythm of glucocorticoids has long been recognised within the last 75 years. Since the beginning, researchers have sought to identify basic mechanisms underlying the origin and emergence of the corticosteroid circadian rhythmicity among mammals. Accordingly, Young, Hall and Rosbash, laureates of the 2017 Nobel Prize in Physiology or Medicine, as well as Takahashi's group among others, have characterised the molecular cogwheels of the circadian system, describing interlocking transcription/translation feedback loops essential for normal circadian rhythms. Plasma glucocorticoid circadian variation depends on the expression of intrinsic clock genes within the anatomic components of the hypothalamic–pituitary–adrenal axis, which are organised in a hierarchical manner. This review presents a general overview of the glucocorticoid circadian clock mechanisms, highlighting the ontogeny of the pituitary–adrenal axis diurnal rhythmicity as well as the involvement of circadian rhythm abnormalities in the physiopathology and diagnosis of Cushing's disease.

European Journal of Endocrinology (2018) **179**, R1–R18

Introduction

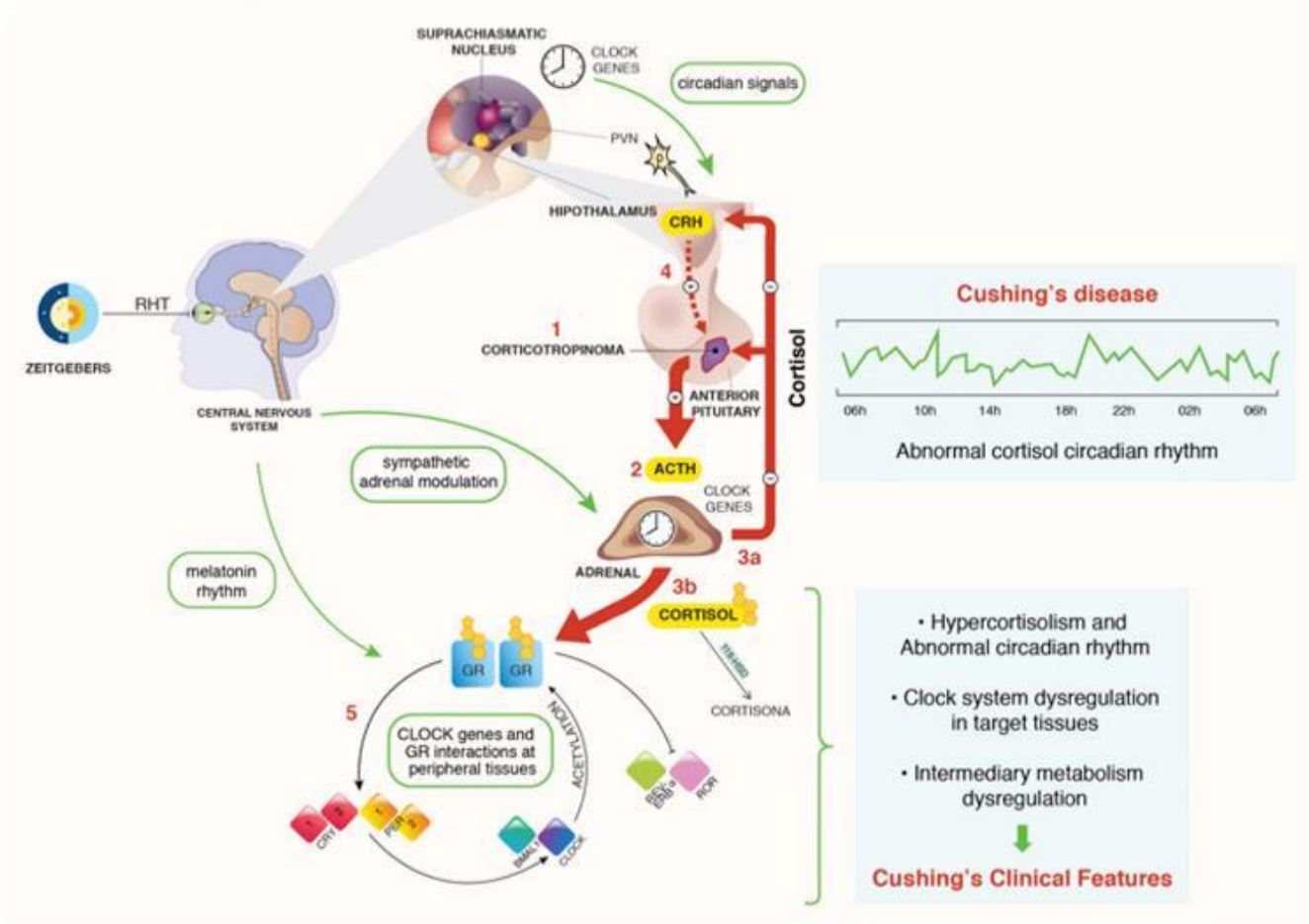
Circadian rhythms have been widely observed in various organisms spanning from cyanobacteria to humans. Circadian clocks have adopted geophysical cycles as part of predictive homeostasis, thereby preparing living organisms for environmental fluctuations and regulating sleep patterns, feeding behaviour, body temperature, blood pressure and hormone release (1, 2).

Invited Author's profile

Ayrton Custodio Moreira, MD, PhD is Prof. of Medicine at the Division of Endocrinology and Metabolism, Department of Internal Medicine, Ribeirao Preto Medical School, University of Sao Paulo, Brazil. He has published more than 150 papers in high-quality journals and has held several important administrative positions, including the Dean of the Ribeirao Preto Medical School. In recognition of his outstanding contributions as an educator and researcher, he has received many medical education awards. His main research interest includes the physiology and pathophysiology of the pituitary–adrenal axis, focusing on the glucocorticoid circadian rhythm and the diagnosis of Cushing's syndrome.

www.eje-online.org
https://doi.org/10.1530/EJE-18-0102

Published by Bioscientifica Ltd.



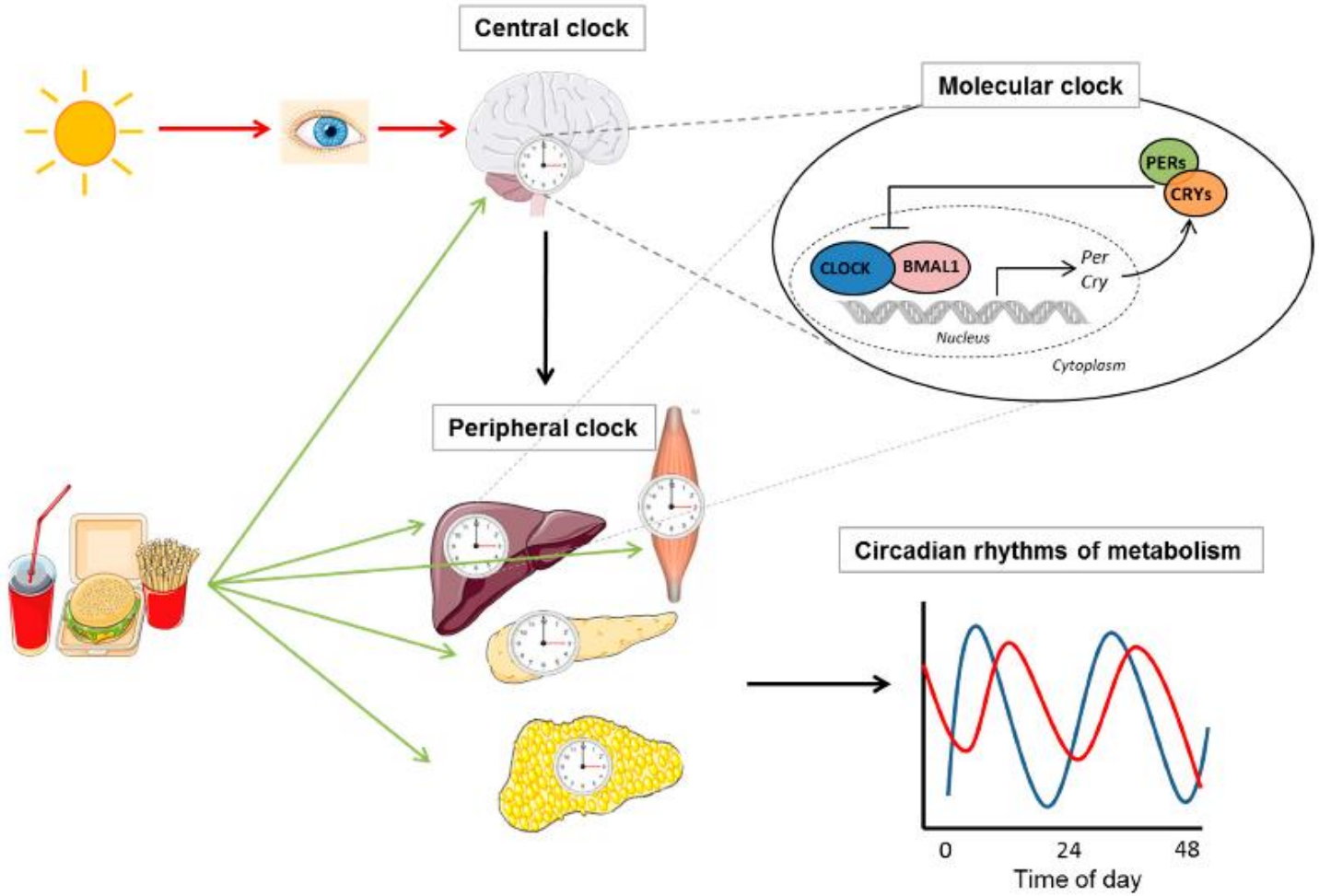
GENOVA DIAGNOSTICS

Eur J Endocrinol. 2018 Jul;179(1):R1-R18. doi: 10.1530/EJE-18-0102. Epub 2018 Apr 16.

What is the Purpose of Biological Rhythms?

- Properly Time Basic Metabolic Activities to Reduce their Metabolic “Cost”
  - Modify heart rate, blood pressure, glucose availability, and alertness for activity cycle
  - To coordinate the efficiency of nutrient transport and metabolism with nutrient availability- including mitochondrial activity and ROS/Antioxidants
  - To upregulate detoxification to coordinate with anticipated intake of foods
  - To modify immune system functions with activity and feeding cycles
  - Seasonally- to coordinate mating activity with safe birthing season, to coordinate metabolic efficiency with food source availability and differences, to stimulate migratory changes if necessary, etc.

Food is a Powerful “Zeitburger”



- Feeding and Fasting is recognized as a major signal synchronizing peripheral clocks, second only to light
- Rodent Studies suggest that dual system of circadian control exist when altering feeding to daytime
- Synchrony is linked to:
  - Meal timing or time of food access
  - Meal Contents

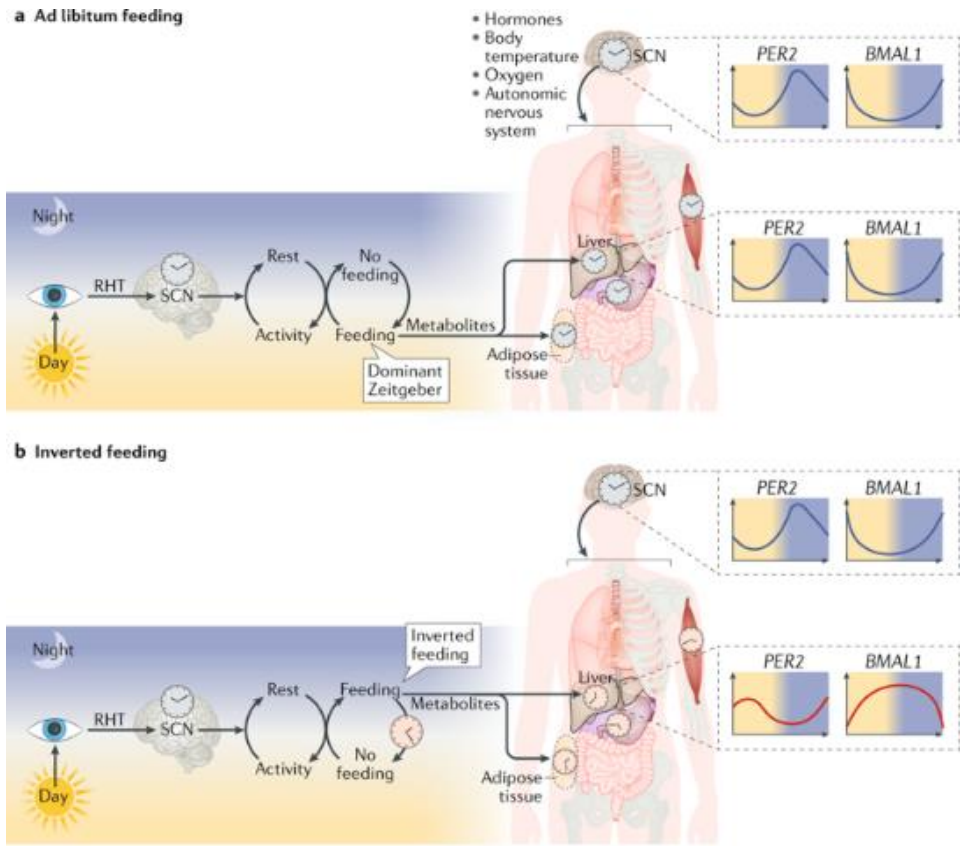
GENOVA DIAGNOSTICS

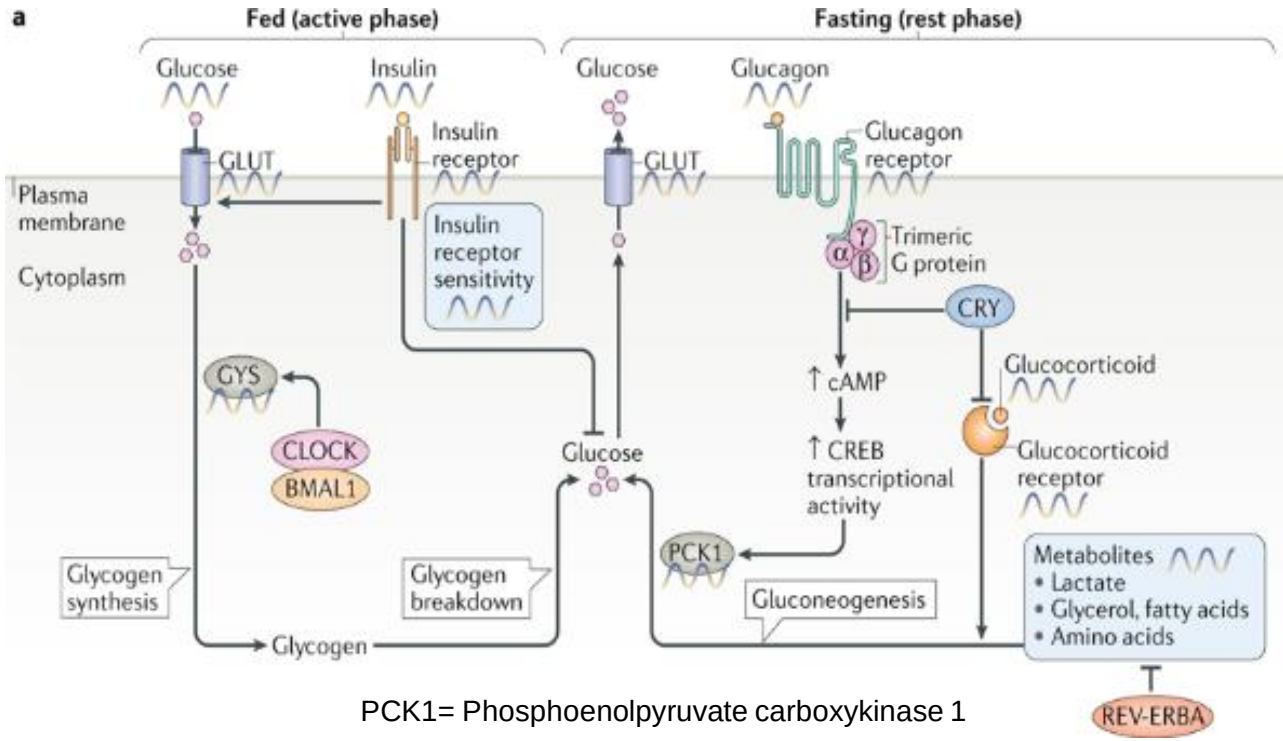
Int. J. Mol. Sci. 2019, 20(8), 1911.

METABOLIC SIGNALLING

Crosstalk between metabolism and circadian clocks

Hans Reinke[1,2]* and Gad Asher[2]*





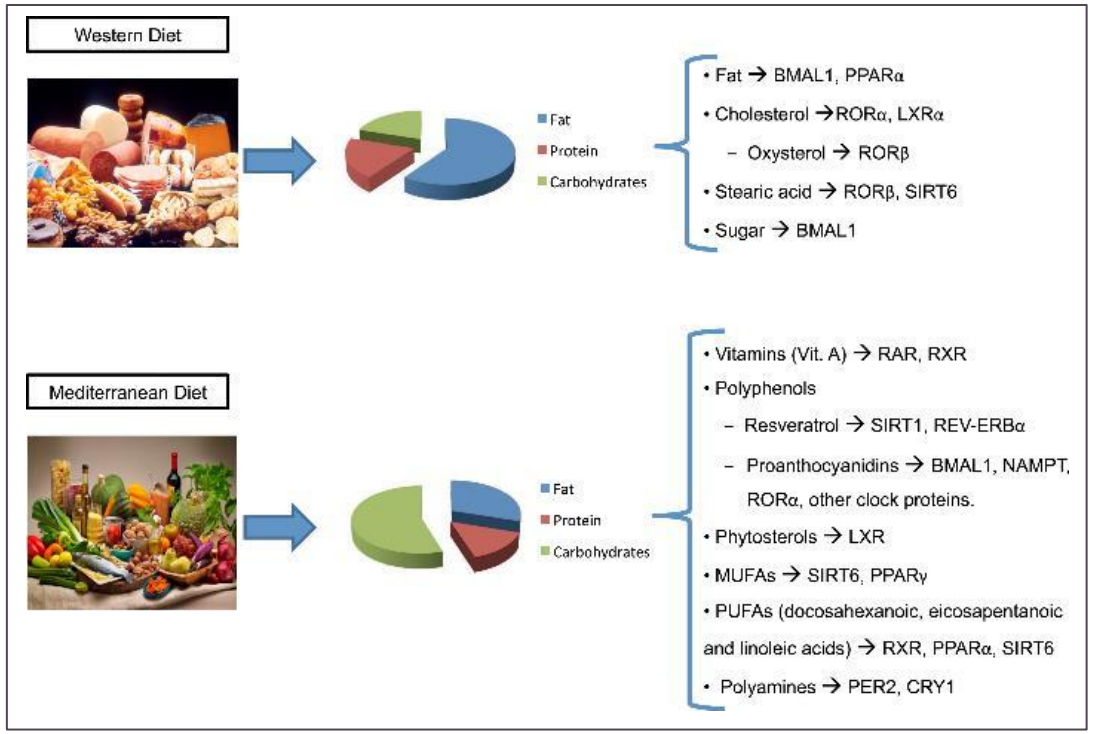
PCK1= Phosphoenolpyruvate carboxykinase 1

GENOVA DIAGNOSTICS

Nature Reviews Molecular Cell Biology **volume 20**, pages227–241(2019).

Diet Composition Produces Diverse Zeitgebers for the Clock

"Different diets produce macromolecules and metabolites known to function as zeitgebers for the circadian clock in various tissues and cell types. While lipids and cholesterol are known to modulate PPARγ, RORα, LXR, and RORβ, fats and high glucose likely modulates BMAL1 activity in a GSK3β-dependent manner. Stearic acid has been observed to modulate the sirtuin protein SIRT6 (which binds directly to CLOCK:BMAL1). Under different dietary conditions, there is an increase in potential clock zeitgebers including vitamin A (known to activate RAR and RXR), polyphenols such as resveratrol (activator of SIRT1) and proanthocyanidins (regulators or modulators of Bmal1, Nampt, and several other clock genes)."

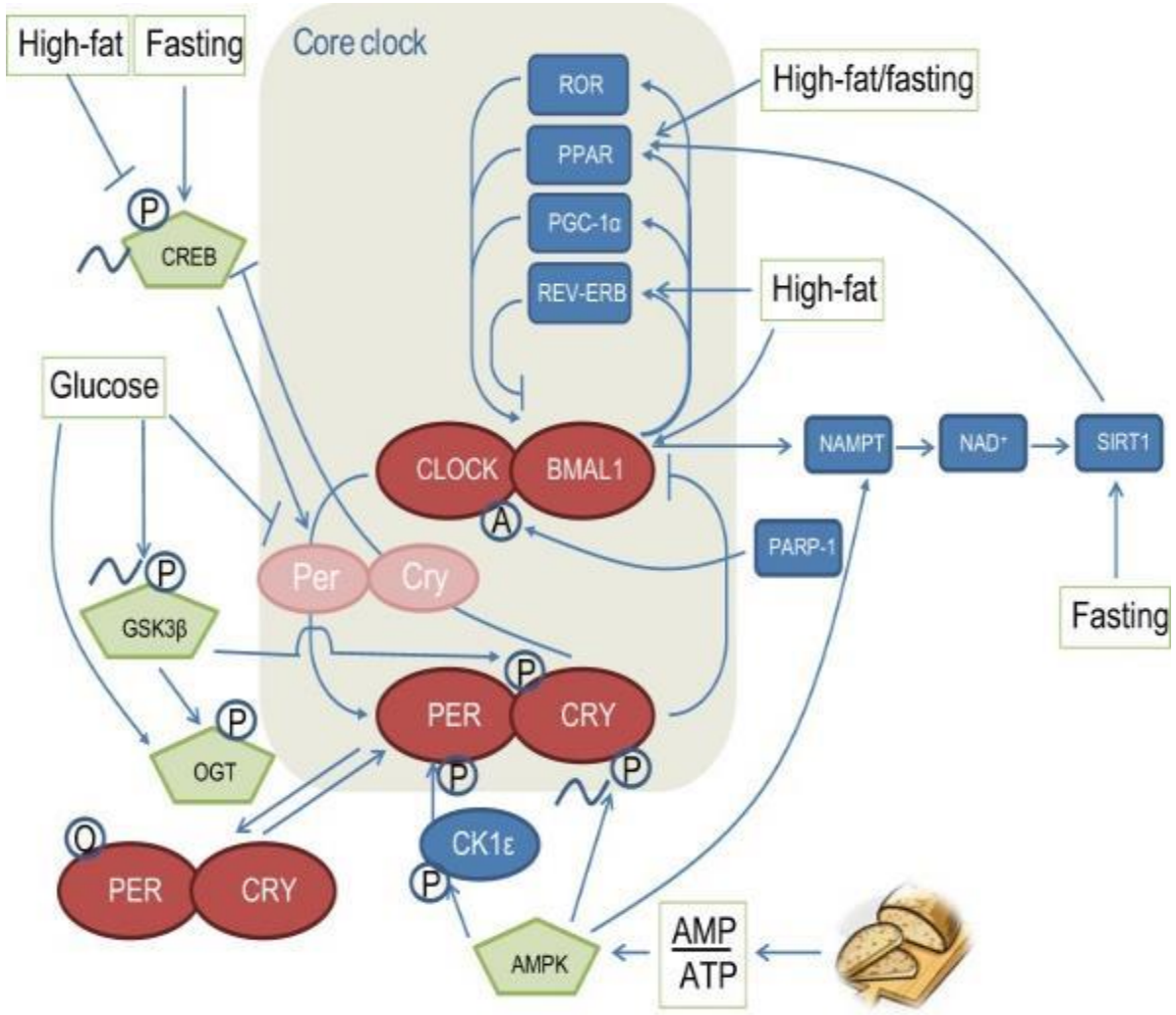


GENOVA DIAGNOSTICS

Ribas-Latre A, et al. *Molecular Mteabolism.* 2016;5(3):133-152.

What are the Important “Signals” at the Molecular Level?

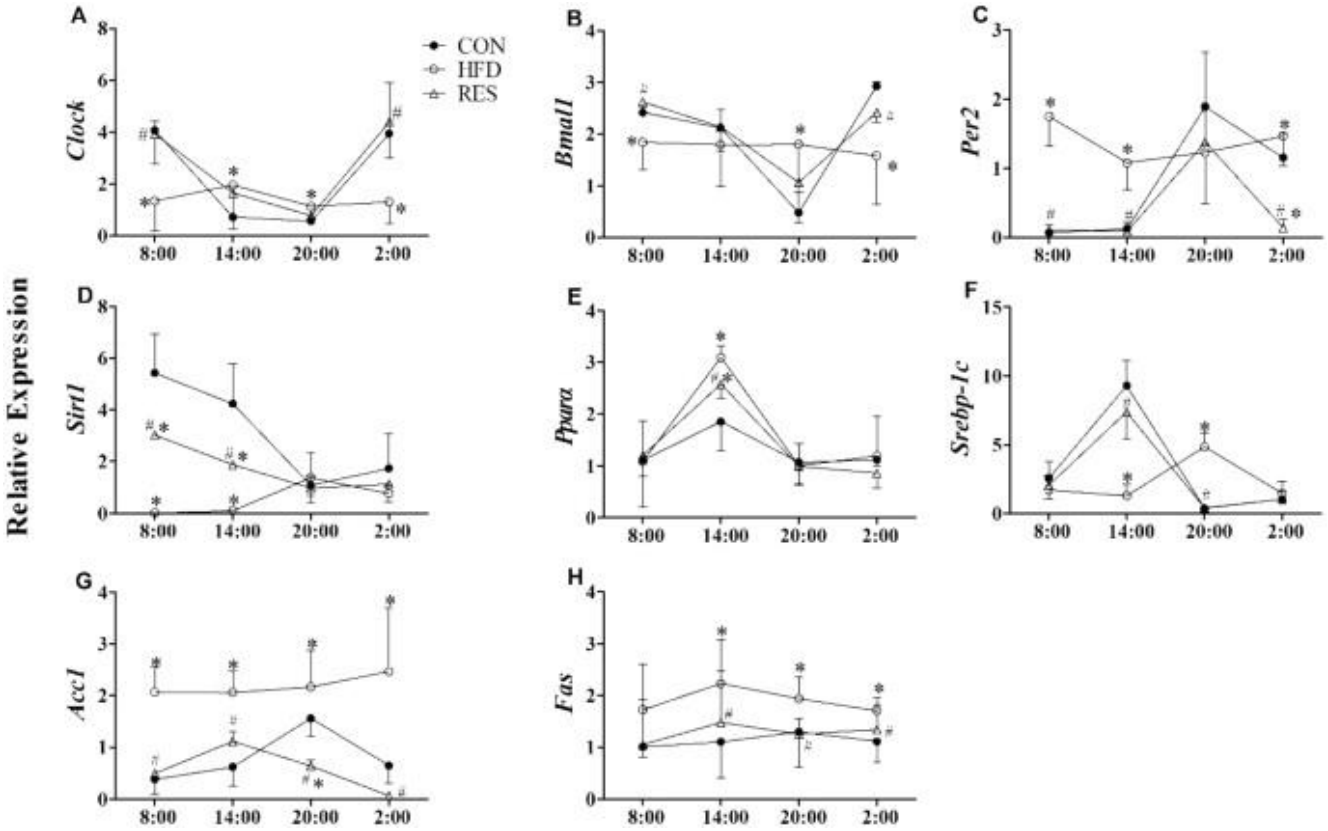
- AMPK- Energy Sensor- Triggered when ATP is low
  - Can phosphorylate Clock-related genes
- CREB (cAMP-response element binding protein) is also a nutrient sensor and clock regulator
  - Phosphorylation of CREB is increased during fasting
- Glycogens Synthase Kinase: GSK activity is circadian acts to regulate CRY
  - Elevated glucose increases GSK phosphorylation (inactivating it)
  - Lithium is a GSK inhibitor
- Sirtuins (SIRT): NAD-dependent HDACs. SIRT1 binds to CLOCK/BMAL1 and PER2 in circadian fashion
  - As NAD(P)+ fluctuates (high-fasting, low fed)- this cycle triggers SIRT activities



Am J Physiol Regul Integr Comp Physiol. 2015 Mar 1; 308(5): R337–R350.

Could SIRT1 Modulators Help Resynchronize the Clock?

- Resveratrol ameliorates the metabolic and clock-gene changes seen in mice given a HFD
- These data have not yet been repeated in humans



GENOVA DIAGNOSTICS

Sun L, et al. *Biochem and Biophys Research Comm.* (2015);458(2015):86-91.

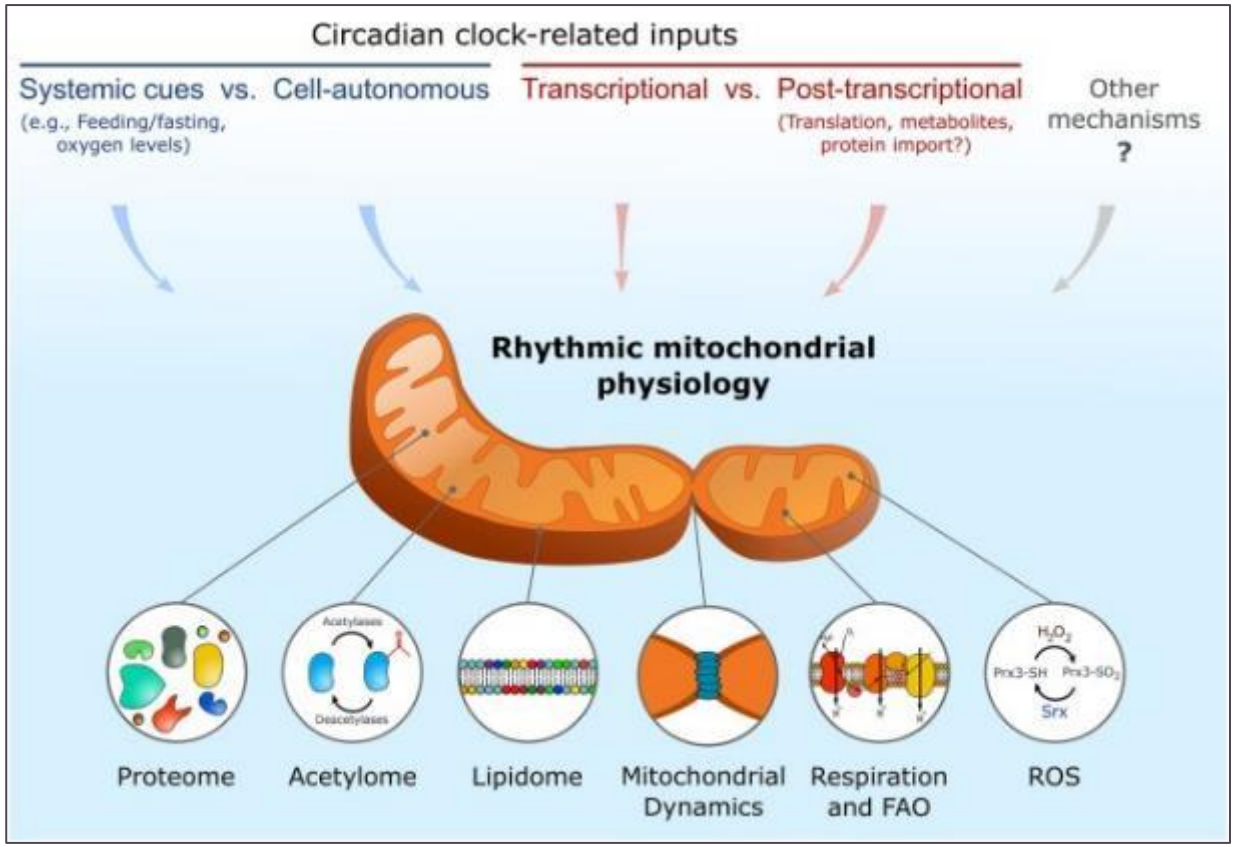
Table 1. Nutrients and food factors that modulate circadian clocks.

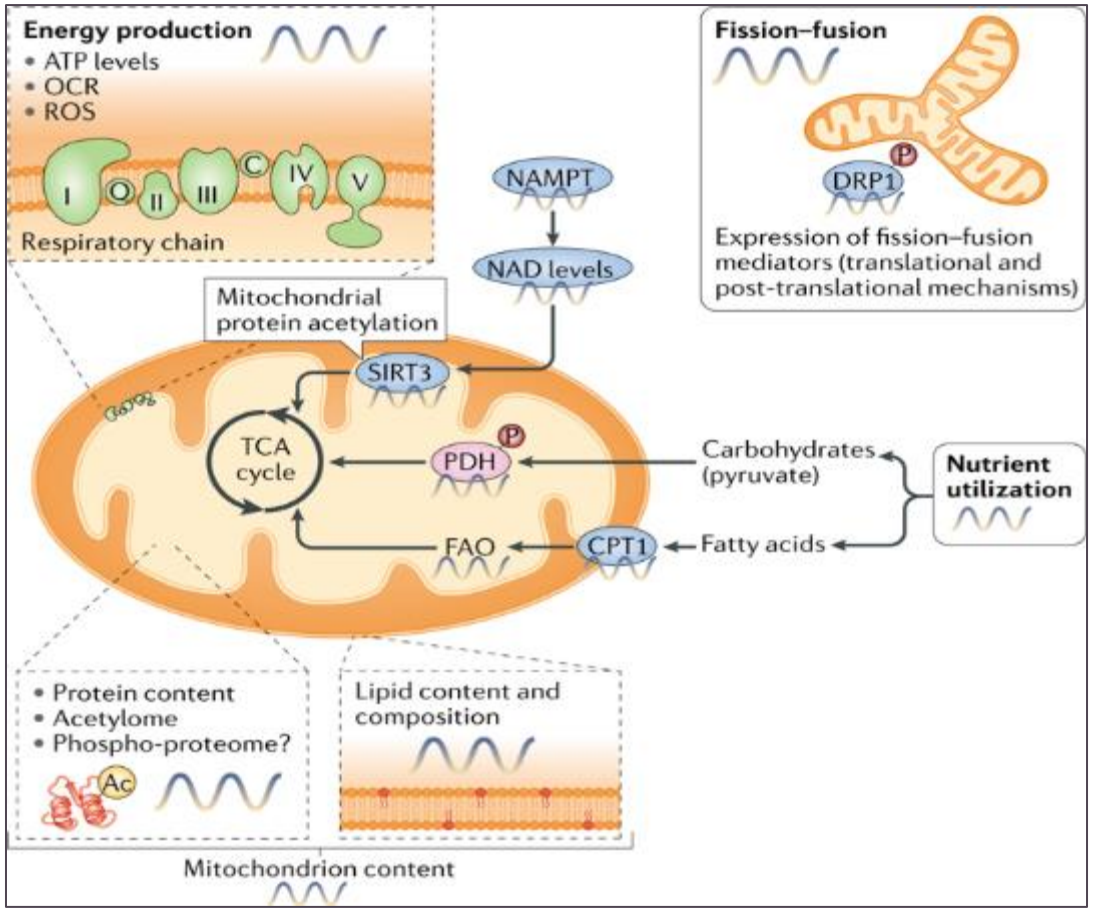
Factor	Effect	Organism	Reference No.
Caffeine	Period extension	Neurospora	[63]
	Period extension	*Chlamydomonas reinhardtii*	[64]
	Phase delay	Mouse SCN slices	[58]
	Period extension	*Drosophila*	[62]
	Period extension	Human U2OS cells, Mouse NIH3T3 cells, Mouse liver slices, Mice	[59]
	Period extension, Phase shift	Mouse MEF cells, Mice	[60]
	Period extension, Phase delay of melatonin rhythm	Human U2OS cells, Humans	[61]
Cinnamic acid	Period shortening	Mouse differentiated neuronal cells, Mice	[69]
DHA, EPA	Enhancement of food entrainment	Mice	[55]
Forskolin	Phase shift	Rat-1 cells, Mouse fibroblasts	[72,73]
Harmine	Period extension	Mouse NIH3T3 cells	[66]
	Period extension	Mouse MEF cells, Mouse differentiated neuronal cells, Mouse SCN slices	[67]
Lithium	Period extension of locomotor rhythm	Rats	[85]
	Period extension of locomotor rhythm	Hamsters	[86]
	Period extension	Mouse fibroblasts, Mouse lung and SCN slices, Mice	[87]
Nobiletin	Enhancement of amplitude	Mouse immortalized fibroblasts, Mice	[84]
Ornithine	Phase advance of melatonin rhythm	Rats	[88]
	Phase advance	Mice	[56]
Palmitate	Period extension, Phase shift	Mouse fibroblasts, Mouse differentiated adipocytes	[68]
Resveratrol	Phase shift	Rat-1 cells	[57]
Theophylline	Period extension	*Chlamydomonas reinhardtii*	[64]
	Period extension	*Trifolium repens* L.	[89]
High-fat diet	Period extension	Mice	[43]
High-salt diet	Phase advance of peripheral clocks	Mice	[53]
Ketogenic diet	Phase advance of locomotor onset	Mice	[51]
Rapidly digested starch	Enhancement of food entrainment	Mice	[54]

GENOVA DIAGNOSTICS

Biosci Biotechnol Biochem. 2017 May;81(5):863-870.

Metabolism and Circadian Clock



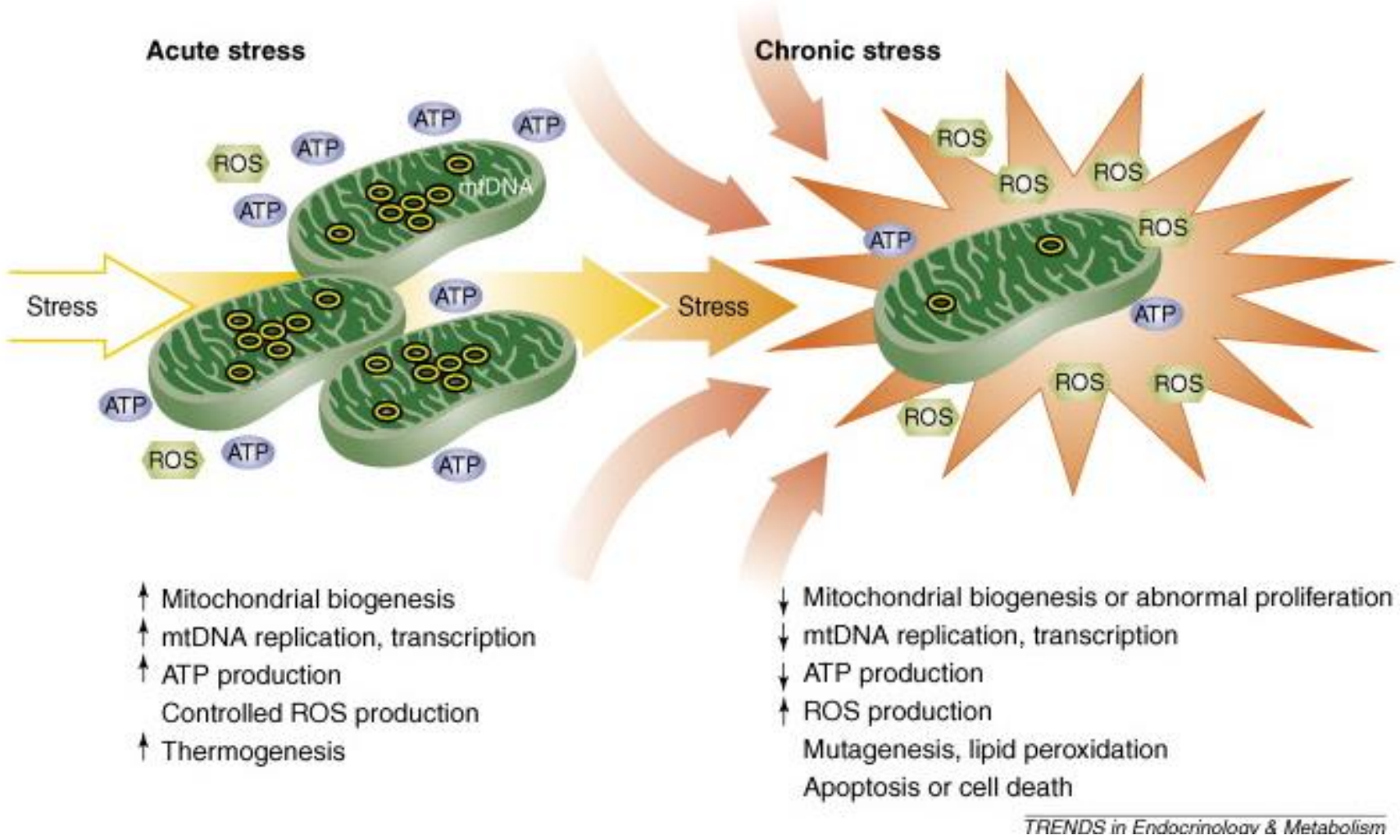


GENOVA DIAGNOSTICS

Manella, et al. *Front. Endocrinol.* 2016:https://doi.org/10.3389/fendo.2016.00162.

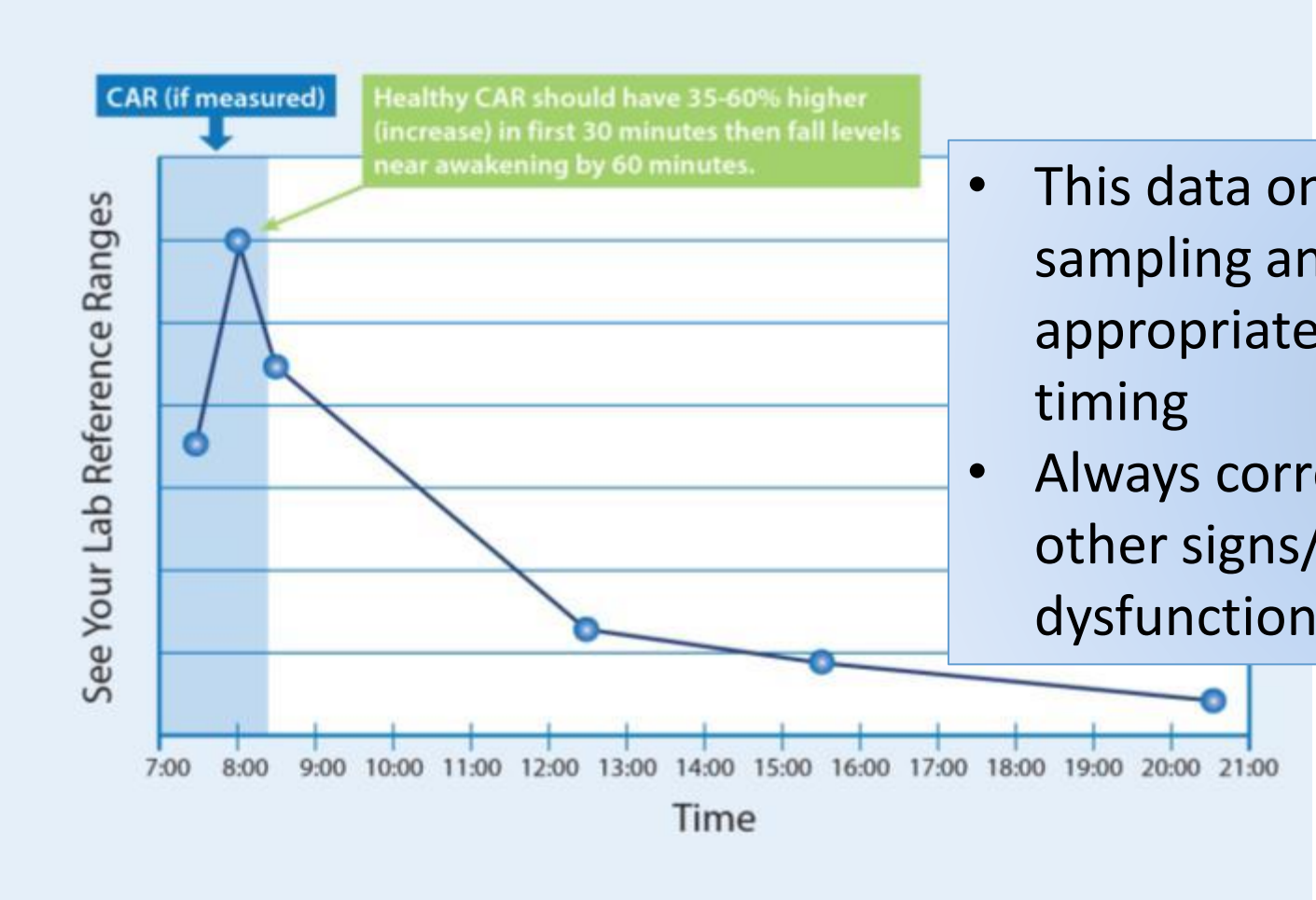
Reinke H, et al. *Natur Reviews Mole Cell Bio.* 2019;20:227-241.

Biphasic response to Cortisol



GENOVA DIAGNOSTICS

Measuring HPA Axis Response- Circadian Dynamic



- 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

GENOVA DIAGNOSTICS

What Influences the HPA axis Response to "Stress" A Simplified Approach

Response to Homeostatic Metabolic Needs

- Energy Needs (hypoglycemia)
- Inflammation
- Metabolic Dysregulation
- Circadian Disruption

Anticipation of Metabolic Needs

- Psychosocial anticipation of dysregulation
- Circadian anticipation of metabolic functions

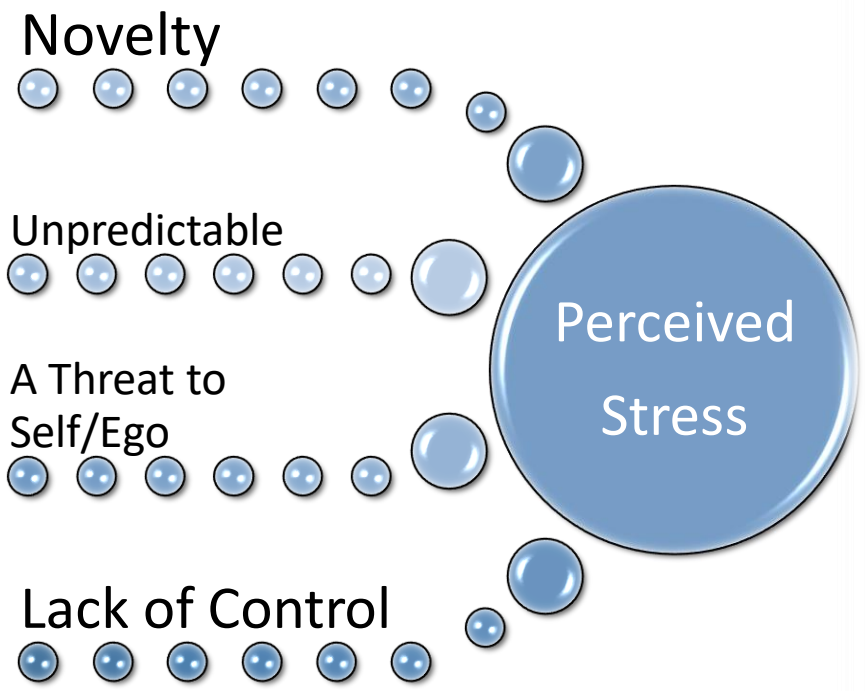
Adaptations from All Prior HPA axis Activations

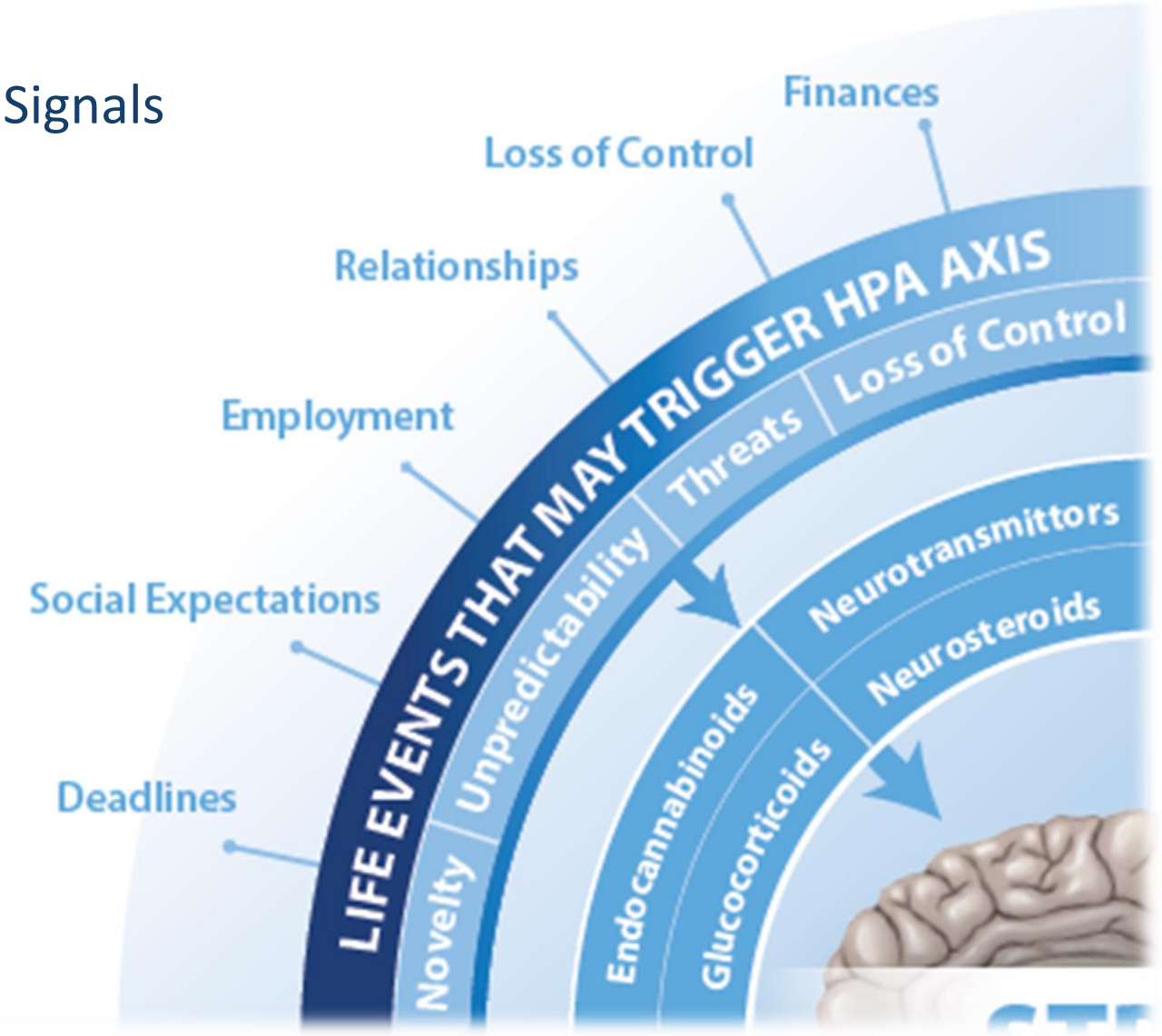
- Early Life Stress
- Cortisol sensitivity
- Feedback Loops
- Epigenetics
- Chaperones
- Neurosteroids
- Learned Responses

GENOVA DIAGNOSTICS

Perceived Stress

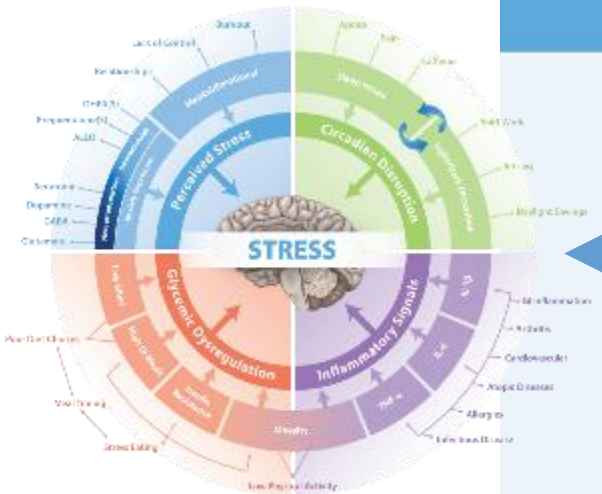
- Converting External Events into Internal Signals

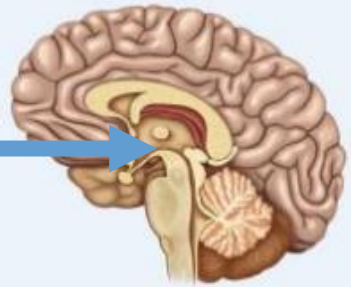




GENOVA DIAGNOSTICS

Strategies for Supporting HPA Axis Function



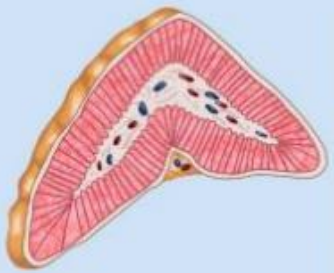


CNS Support

Maintain Appropriate Hypothalamus Response to Stressors
- ↓ Glycemic Dysregulation
- ↓ Perceived Stressors
- ↓ Inflammatory Signals
- ↑ Circadian Signals
  - Sleep Therapy
  - Light/Dark Entrainment
  - Meal Timing

Balance Neurotransmitters/ Neurosteroids
- Consider Supplementing Precursors and Cofactors for Neurotransmitter Synthesis
- Consider Supplemental DHEA & Pregnenolone

Balance Cortisol Feedback Mechanisms
- Consider Phosphotidyl Serine
- Consider Adaptogens



Adrenal Support

Protect Zone Reticularis
- Antioxidants
- Adaptogens (?)

Nutrient Support for Adrenal Steroidogenesis
- Vitamin C
- B-Vitamin (general)
  - Pantothenic Acid
  - Niacin
- Minerals (general)
  - Magnesium/Zinc
- Glandulars (Adrenal)

Target-tissue Cortisol Modulation

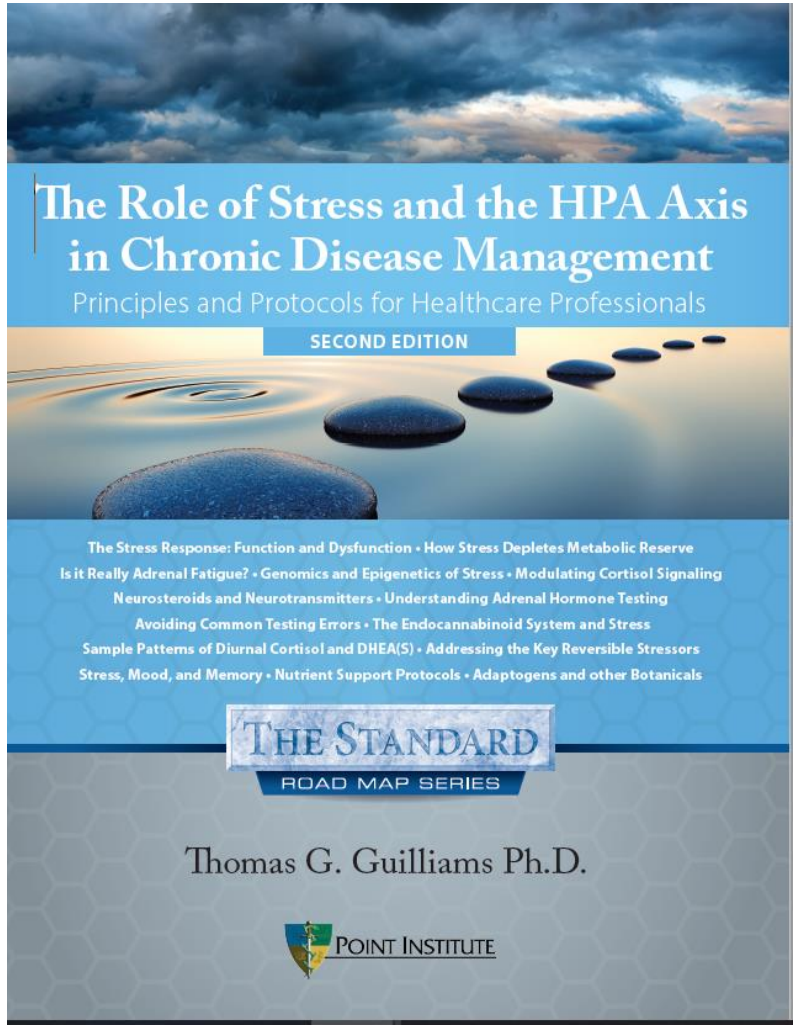
↓ 11β-HSD1 Activity
- Reduce Inflammation
- Reduce Insulin Resistance/Insulin
- Reduce Central Adiposity
- Consider Physical Activity (not intense)

↑ HSP Modulation of GR
- Consider Adaptogens
- Consider Physical Activity (not intense)

↑ DHEA's Anti-Glucocorticoid Activity
- Consider Suplemental DHEA

GENOVA DIAGNOSTICS

The Second Edition of the Stress Roadmap is Available



Available in Print or eBook (PDF) format

www.pointinstitute.org

GENOVA DIAGNOSTICS

Presenter:
Thomas G. Guilliams, Ph.D.
t.guilliams@pointeinstitute.org

US Client Services: 800-522-4762

UK Client Services: 020.8336.7750

We look forward to hearing from you!

Questions?

GENOVA DIAGNOSTICS

Upcoming LIVE GDX Webinar Topics

Register for upcoming LIVE GDX Webinars online at WWW.GDX.NET

Patient Dropship/Online Registration: https://youtu.be/YHd0lD9GVG4

Subscribe to our weekly Podcast at WWW.GDX.NET/THE-LAB-REPORT

LIVE GDX

GENOVA DIAGNOSTICS

Targeting the Root Causes of Stress

Thomas G. Guilliams, Ph.D.
Founder/Director- Point Institute
Adj. Asst. Prof. University of Wisconsin School of Pharmacy
Senior Scientific Advisor- Ortho Molecular Products

GENOVA DIAGNOSTICS®