Adrenals and Role of Stress in Chronic Disease Management

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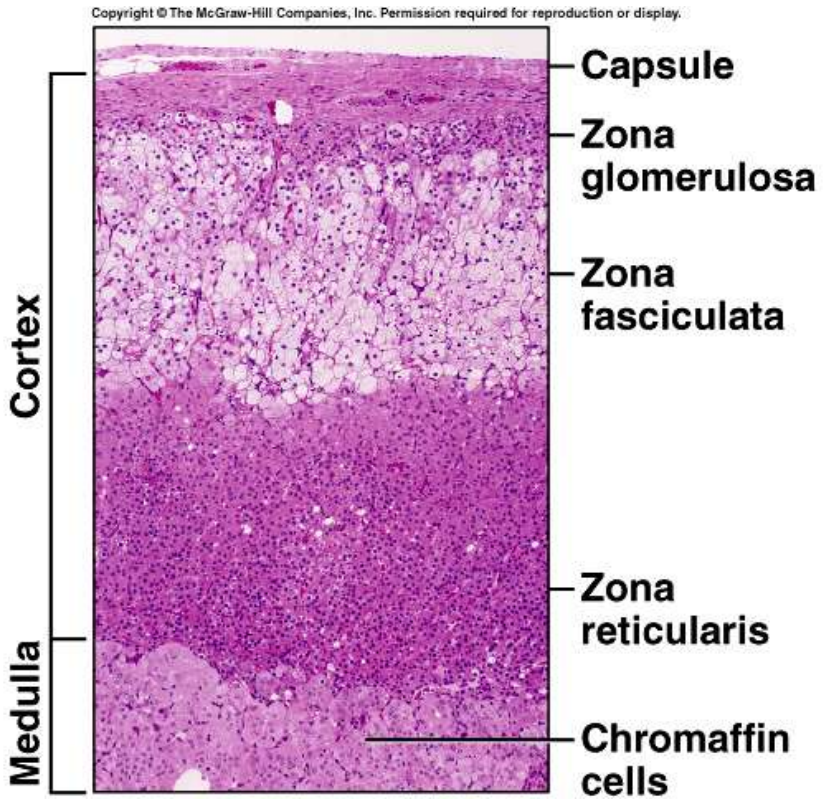
2009
2014

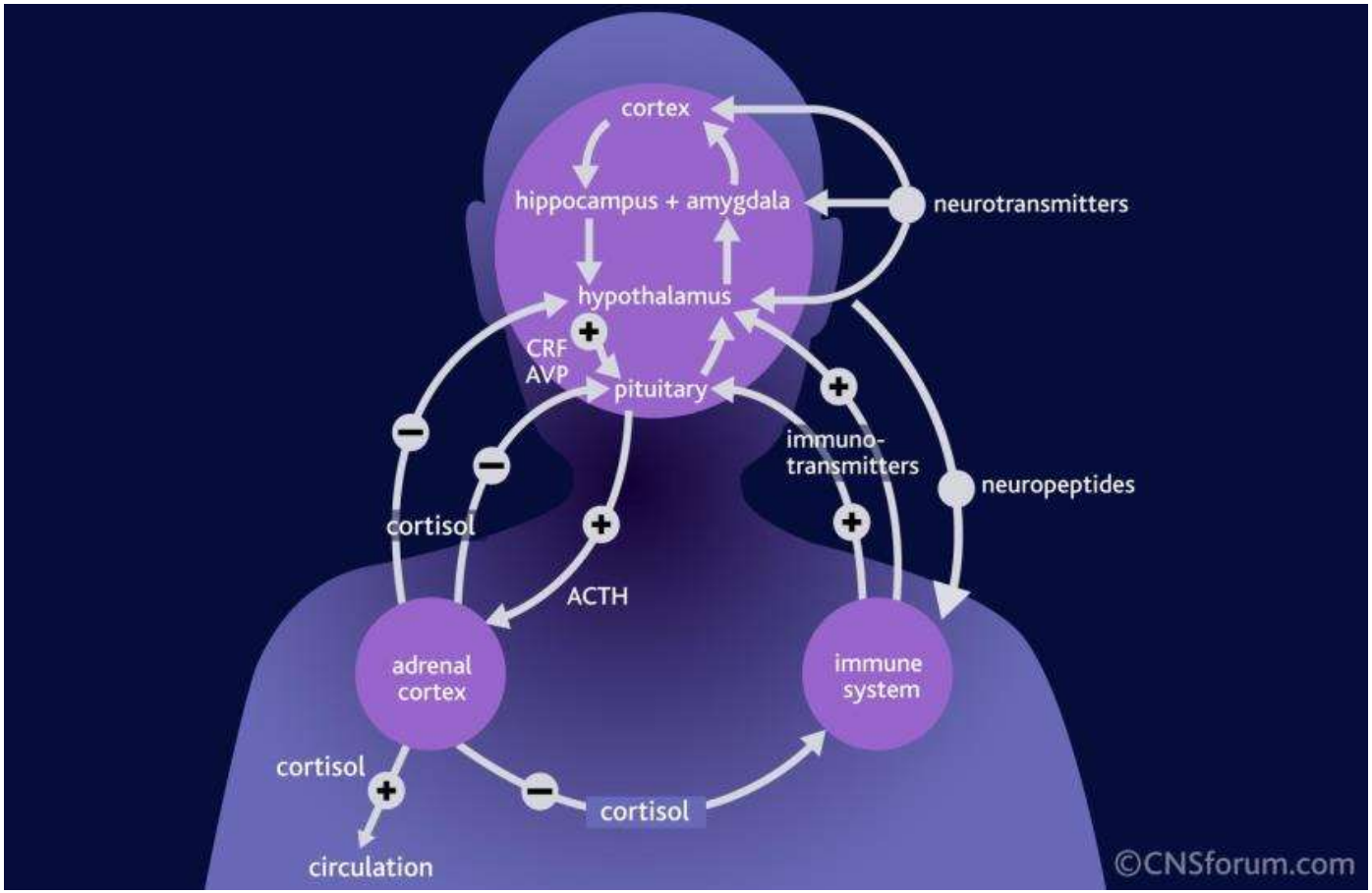
Learning objectives

- To learn to confidently diagnose subclinical and clinical thyroid and adrenal disorders and describe them
- To be aware of the scientific literature on HPA and thyroid axis dysfunction
- To learn the common environmental and nutritional factors contributing to these conditions and common investigations
- To understand the physiology and stages of HPA axis dysfunction and subclinical thyroid disease
- To develop a holistic protocol for treatment of HPA axis dysfunction and subclinical thyroid disease

Adrenals


Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.
Capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Chromaffin cells
Cortex
Medulla

The HPA axis


cortex
hippocampus + amygdala
neurotransmitters
hypothalamus
CRF
AVP
pituitary
immuno-
transmitters
neuropeptides
cortisol
ACTH
adrenal
cortex
immune
system
cortisol
cortisol
circulation
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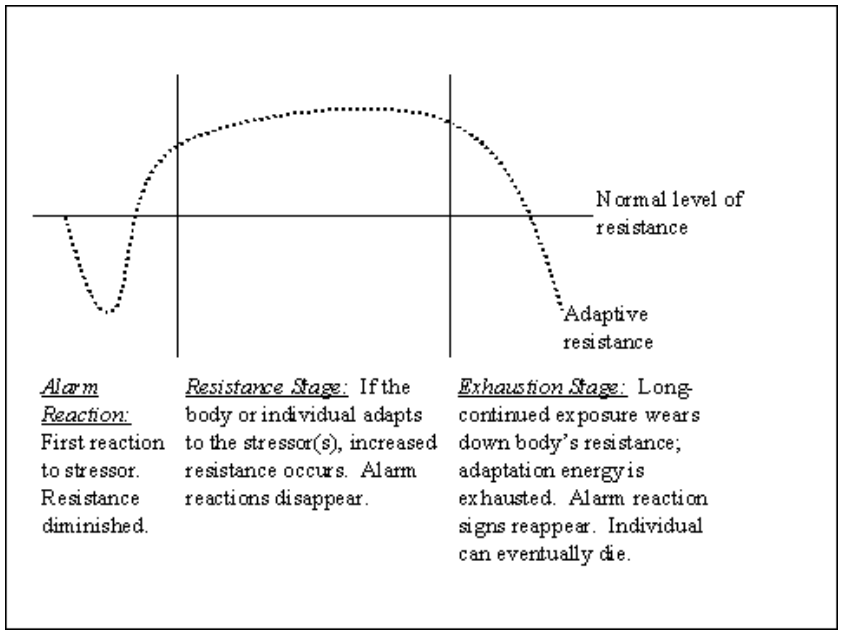
Adrenal disorders

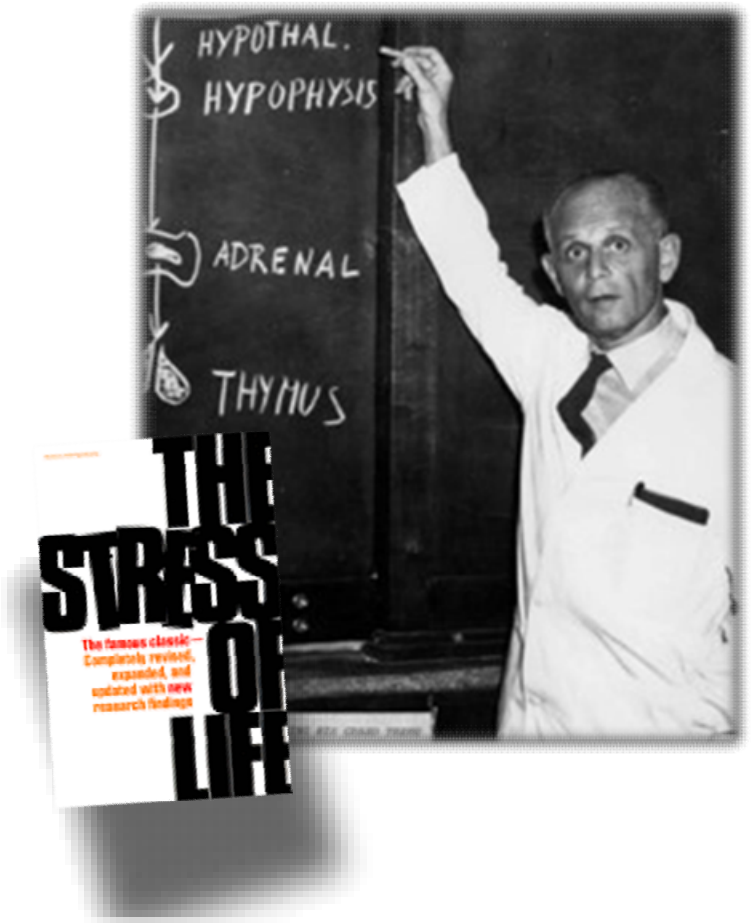
- Overactivity
  - Cushing's disease
  - Phaeocromocytoma
  - Hyperaldosteronism

- Underactivity
  - Addison's Disease
  - HPA axis dysfunction (previously labelled as adrenal fatigue)

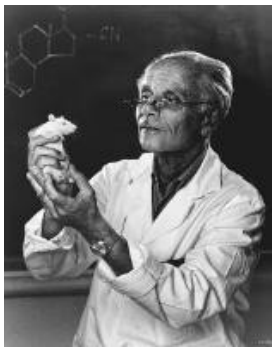
Selye's contribution

General Adaptation Syndrome (G.A.S)

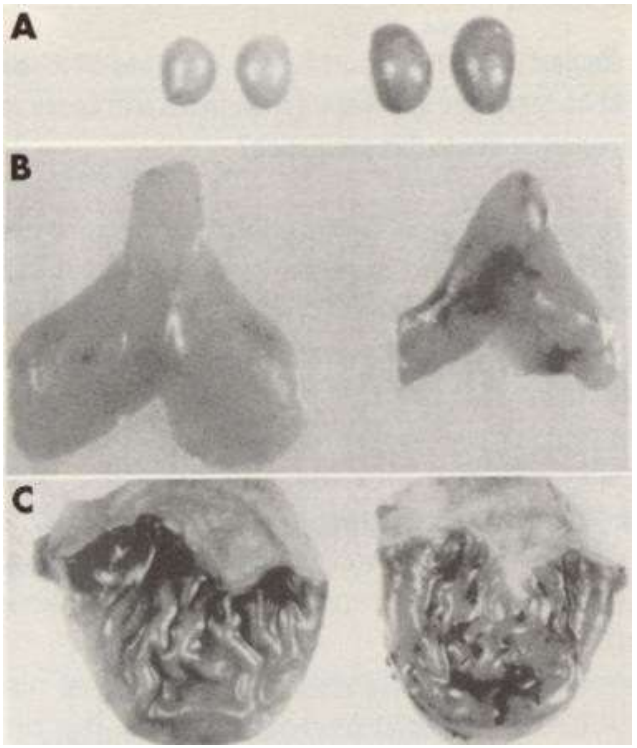




Selye and the pathophysiology of stress



Control **"Stress"**



Hypertrophy of Adrenal Gland (HPA)

Atrophy of the thymus and other lymphatic glands (Immune system)

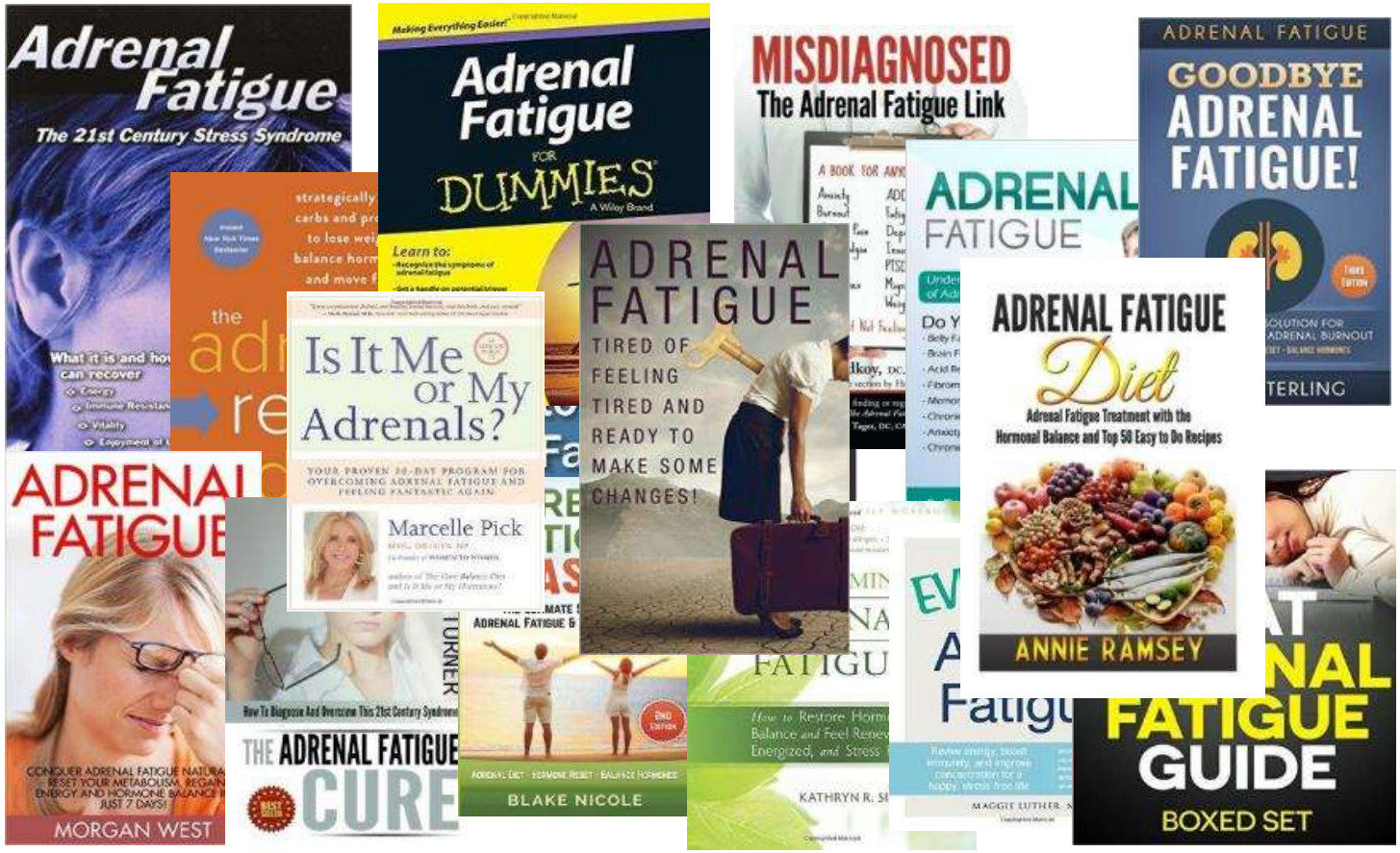
Erosions and ulcers in the duodenum (GI-system)

Hans Selye

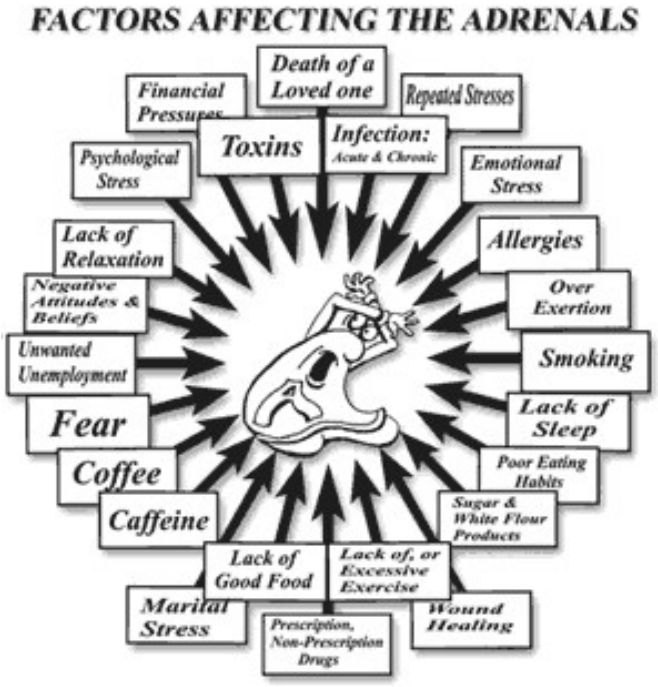
Preface "The Stress of Life" (1956)

"*Stress is essentially reflected by the rate of all the wear and tear caused by life*. …For instance, we are just beginning to see that many common diseases are largely due to errors in our adaptive response to stress, rather than to direct damage by germs, poisons, or life experiences. In this sense many nervous and emotional disturbances, high blood pressure, gastric and duodenal ulcers, and certain types of sexual, allergic, cardiovascular, and renal derangement appear to be essentially *diseases of adaptation*."

Popular language for stress



When did “Stress” become “Adrenals”



Is it adrenal fatigue?

According to the Hormone Foundation/Endocrine Society:

"Adrenal fatigue" is not a real medical condition. There are no scientific facts to support the theory that long-term mental, emotional or physical stress drains the adrenal glands and causes many common symptoms. There is no test that can detect adrenal fatigue. Supplements and vitamins made to "treat" adrenal fatigue may not be safe. Taking these supplements when you don't need them can cause your adrenal glands to stop working and may put your life in danger."

"Doctors urge you not to waste precious time accepting an unproven diagnosis such as "adrenal fatigue" if you feel tired, weak, or depressed."

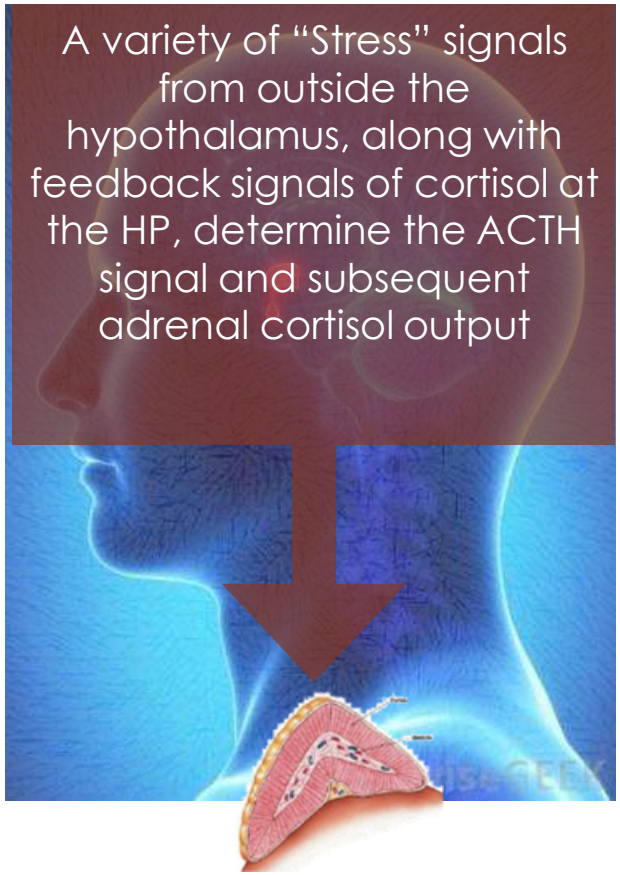
Nomenclature matters!

- Primary Adrenal insufficiency is real (though uncommon) and is not a stress-related chronic disease phenomenon.

- Stress-Related changes in adrenal hormone output are regulated by HPA axis- adaptations primarily in the brain, and are not caused by "fatigue" or the inability to produce hormones by the adrenal gland.

The adrenals respond to the brain

(Feedback inhibition alters cortisol output)



N Engl J Med 2002; 346:108-114

Is the Endocrine Society right?

Well sort of…..

- The term "Adrenal Fatigue" does not properly describe the stress response that leads to changes in adrenal hormone output or a sense of "fatigue"

So we should stop using this terminology

- But, they are **incorrect** in their assertions that long term stress has no affect on adrenal hormone output, or that no test is capable of assessing the effects of stress on human physiology.

So we need to re-think how we discuss 'adrenals' and… start using different terminology

Physiological resilience

- It is the immediate capacity of the cell/tissue and organ to respond to changes in physiological need

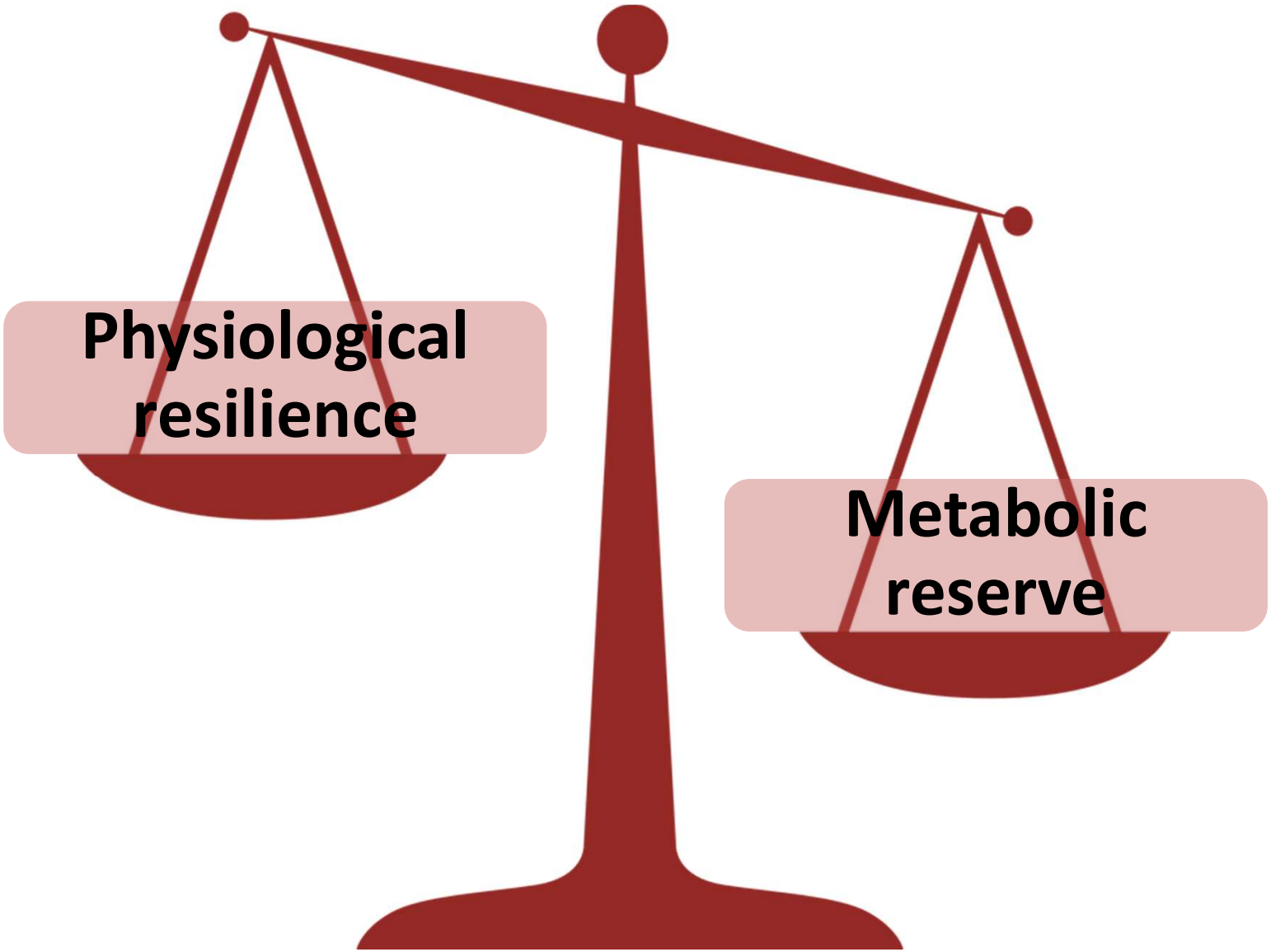
Metabolic reserve

- Long-term capacity of tissues and organ systems to withstand ongoing and repeated challenges to physiological needs

Physiological resilience and metabolic reserve

- Capacity of each cell/organ to withstand necessary changes that create the rhythm of a healthy organism

- When inappropriate or overwhelming signals begin to overpower physiological resistance, the stretching of that system does not resolve immediately and leads to long term chronic dysfunction and disease


Physiological resilience
Metabolic reserve

Chronic stress depletes metabolomic reserve

- The stress response system allocates resources and changing metabolic function to allow the best chance of survival for the immediate future
- This is often at the cost of reducing the organism's buffer against long term metabolic dysfunction
- This leads to depletion of essential nutrients
- This reserve capacity is vulnerable to depletion but managed by being resupplied and strengthened

Stress response and daily functions

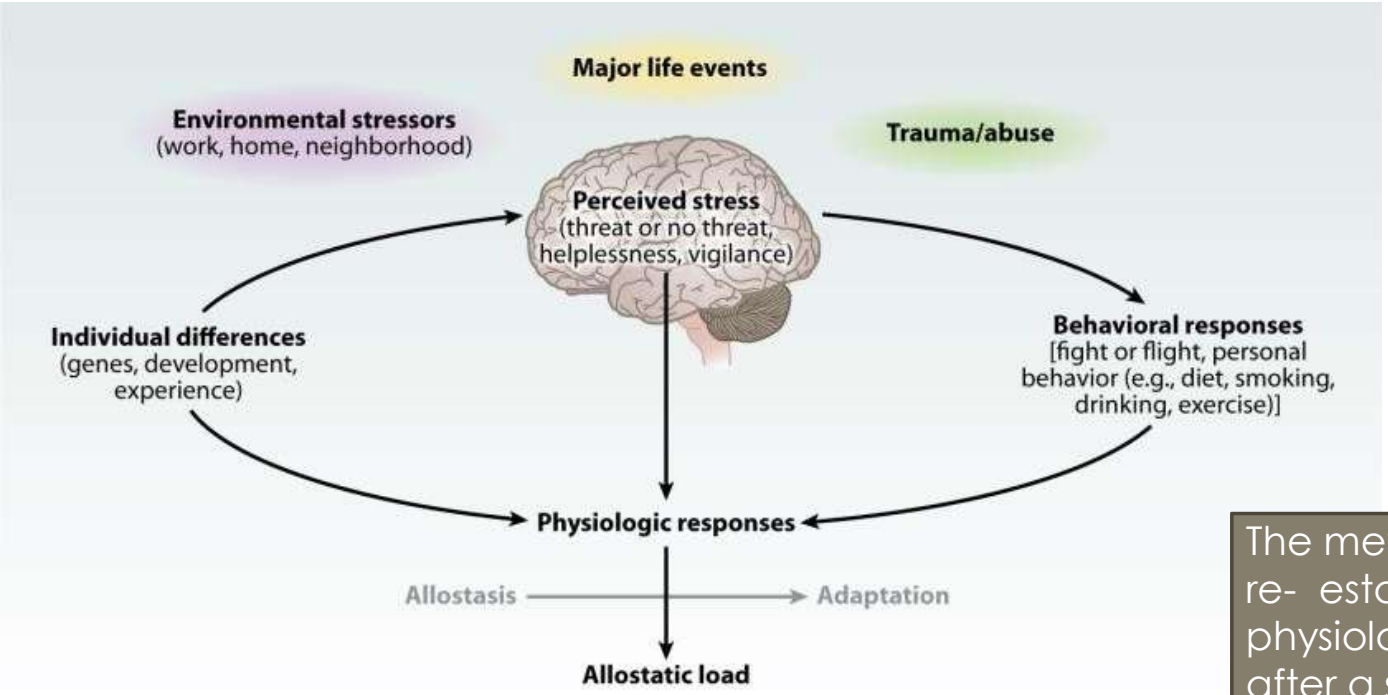
Just like emergency vehicles need to use the same roads used for non-emergency functions, the stress response system uses the same organs, cells, metabolites and signaling mechanisms that the body uses to maintain non-stress metabolic functions

What is the correct terminology?

- Most appropriate overall term:
  - HPA Axis Dysfunction
  - Maladaption to Stress or Stress-response dysfunction, Adaptation to Stress……with consequences.

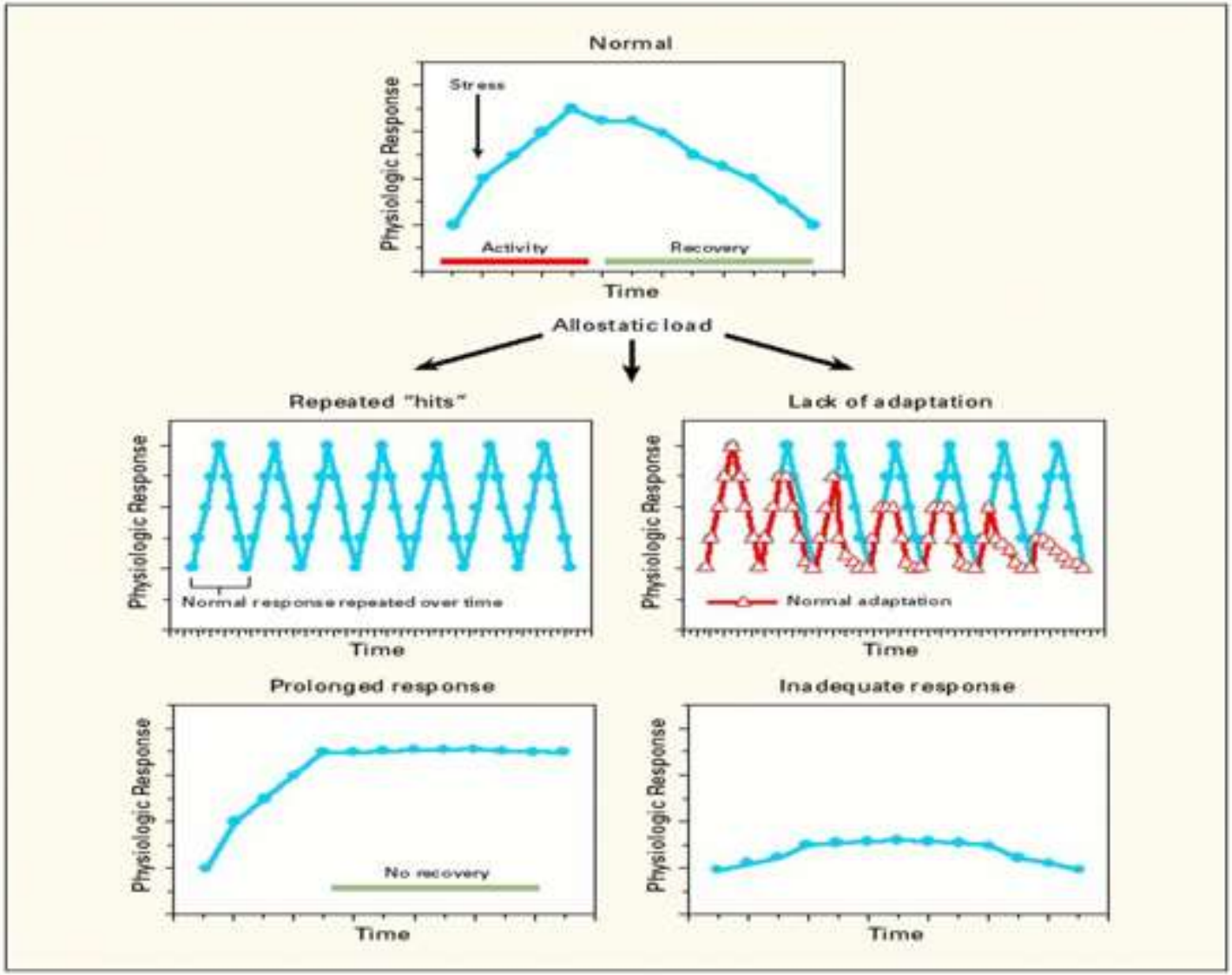
- Specific Terms (where appropriate)
  - Hypocortisolism/Hypercortisolism
  - Low DHEA or DHEA-S
  - High Allostatic Load, or Burnout (properly defined)

Newer stress nomenclature: Allostatic load



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

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



Bruce S. McEwen, Ph.D. Protective and Damaging Effects of Stress Mediators. NEJM. Jan 2008: Volume 338:171-179

Stress

- ***Allostasis*** - the ability to achieve stability through change — is critical to survival.

- Stress system - protect the body by responding to internal and external stress.
  - Autonomic nervous system
  - Hypothalamic–pituitary–adrenal (HPA) axis
  - Cardiovascular and metabolic systems
  - Immune systems

- ***Allostatic load*** - the price of accommodation to stress, (wear and tear) that results from chronic overactivity or underactivity of allostatic systems.

Bruce S. McEwen, Ph.D. Protective and Damaging Effects of Stress Mediators. NEJM. Jan 2008: Volume 338:171-179

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)

Some disorders associated with the stress-response system

Increased activity of the HPA axis

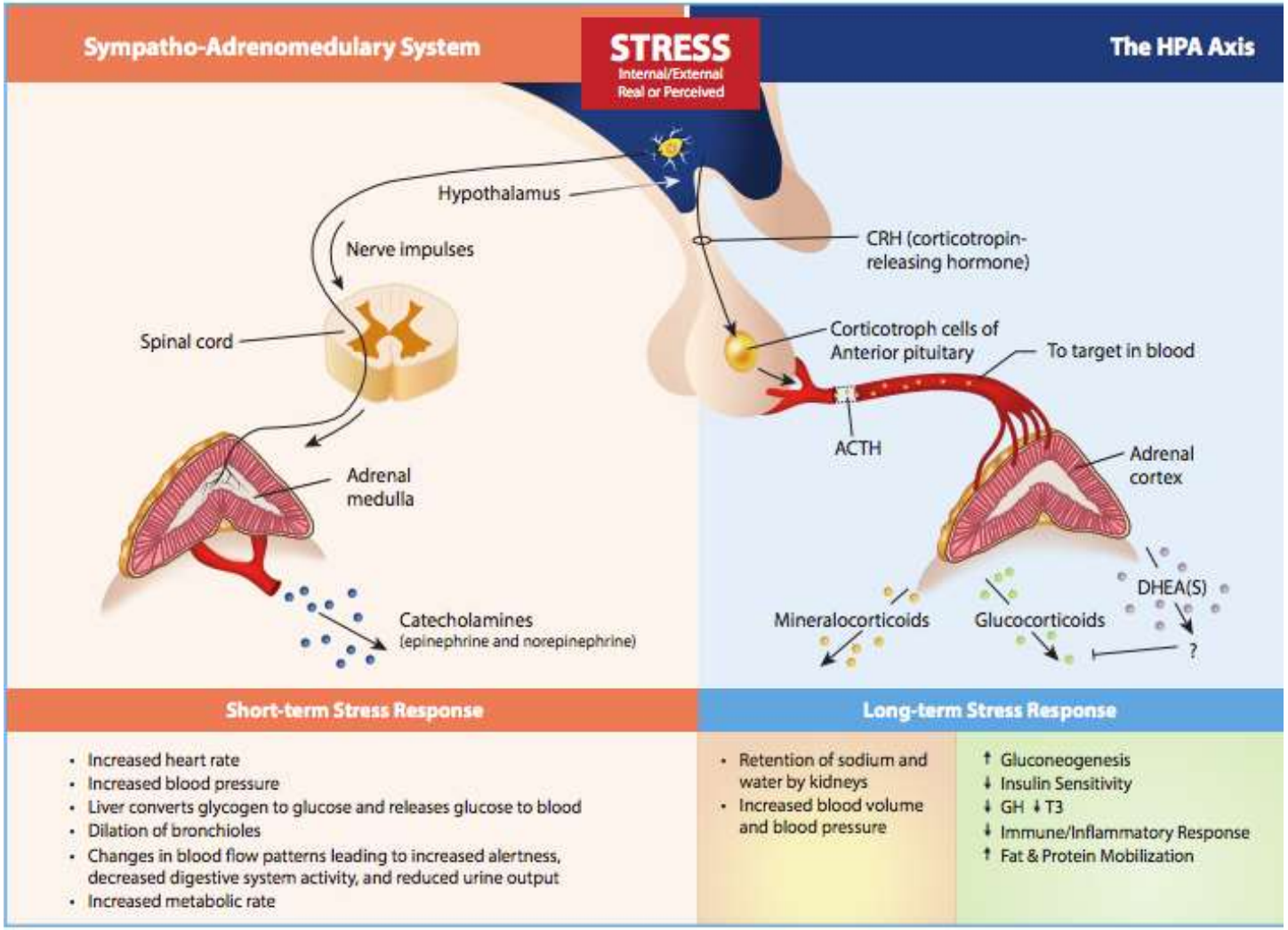
- Cushing syndrome
- Chronic stress
- Melancholic depression
- Anorexia nervosa
- Obsessive–compulsive disorder
- Panic disorder
- Excessive exercise (obligate athleticism)
- Chronic, active alcoholism
- Alcohol and narcotic withdrawal
- Diabetes mellitus
- Central obesity (metabolic syndrome)
- Post-traumatic stress disorder in children
- Hyperthyroidism
- Pregnancy

Decreased activity of HPA axis

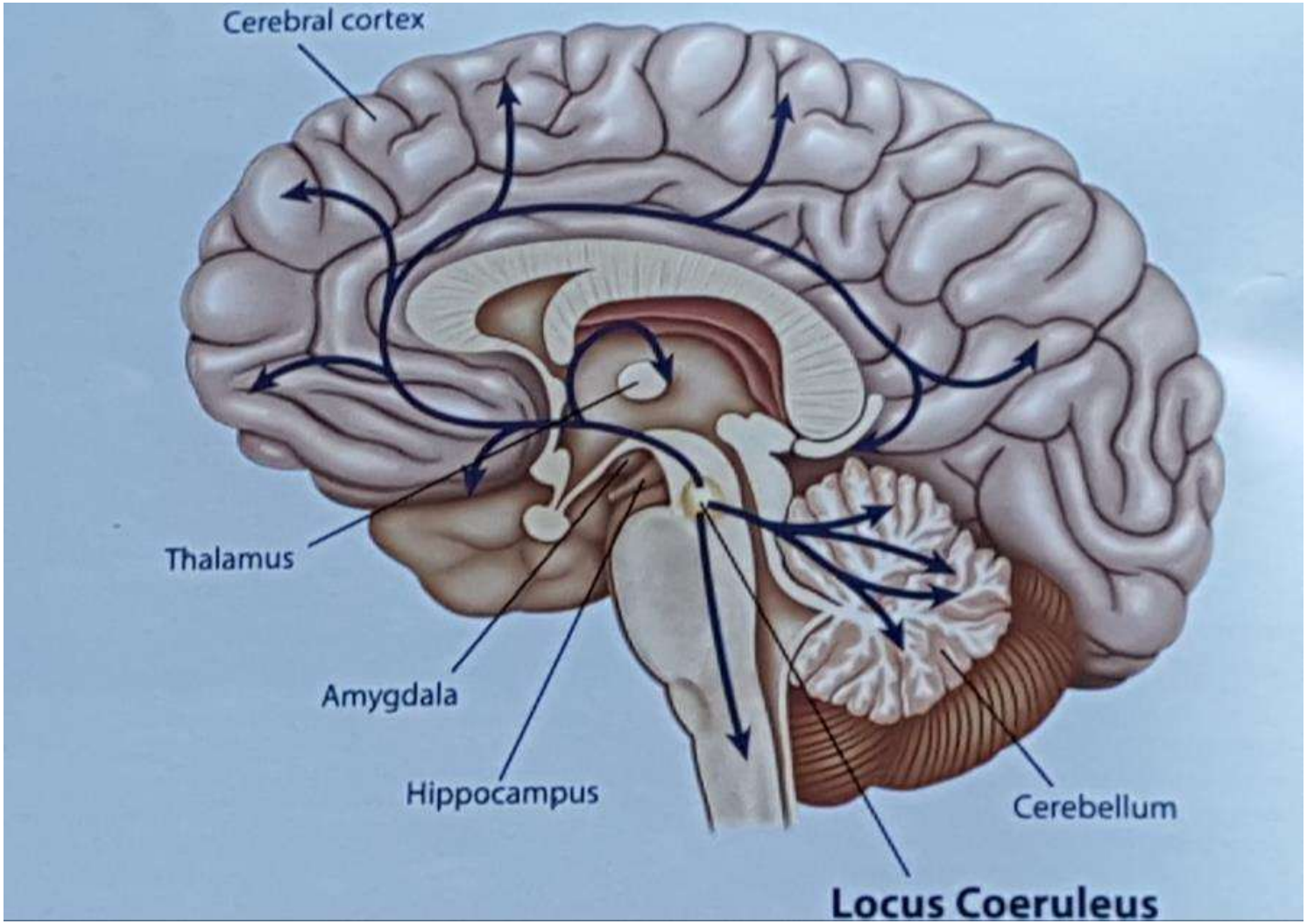
- Adrenal insufficiency
- Atypical/seasonal depression
- Chronic fatigue syndrome
- Fibromyalgia
- Premenstrual tension syndrome
- Climacteric depression
- Nicotine withdrawal
- Following cessation of glucocorticoid therapy
- Following Cushing syndrome cure
- Following chronic stress
- Postpartum period
- Adult post-traumatic stress disorder
- Hypothyroidism
- Rheumatoid arthritis
- Asthma, eczema

Chrousos, G. P. (2009) Stress and disorders of the stress system
Nat Rev Endocrinol doi:10.1038/nrendo.2009.106

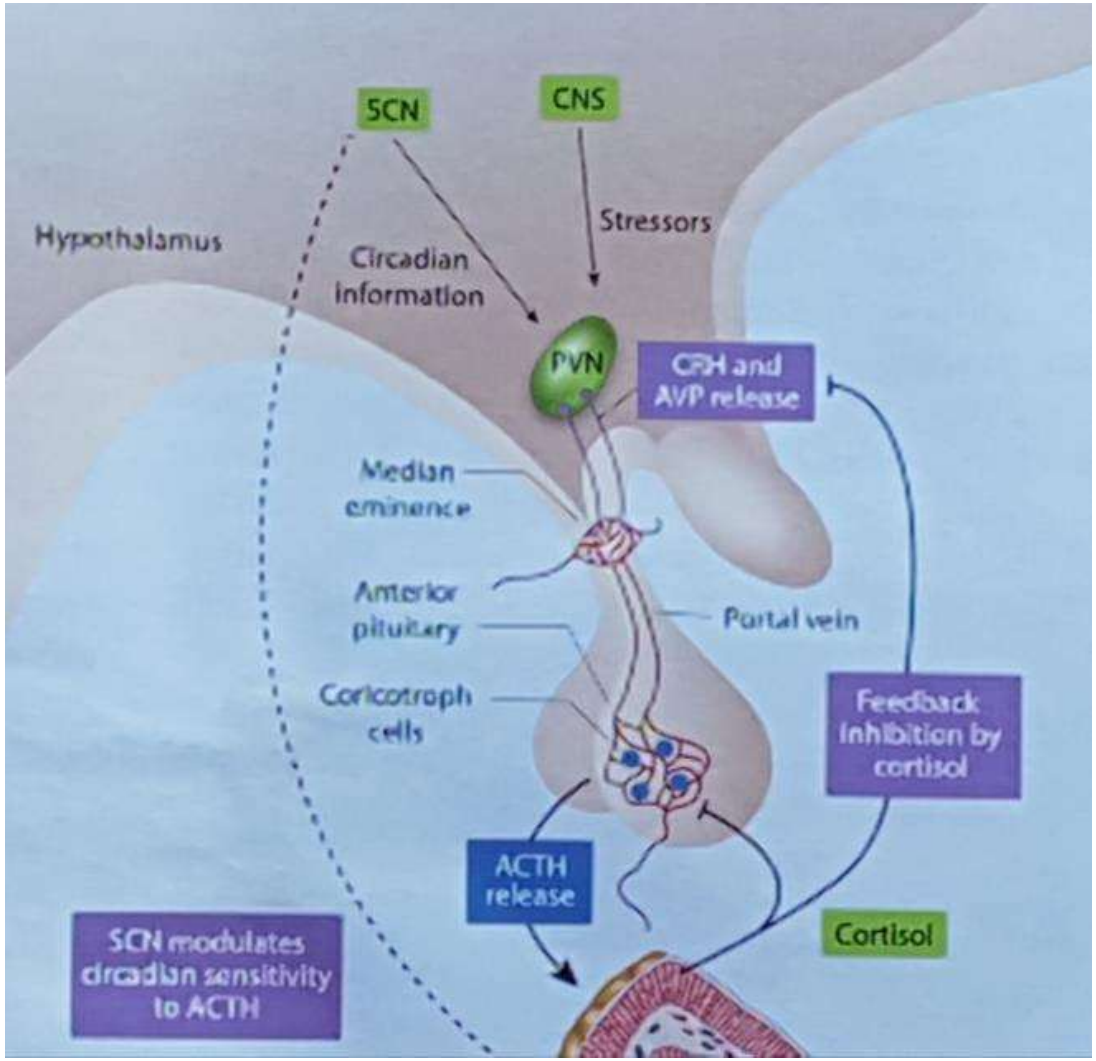
Stress response system



Sympatho adrenal system

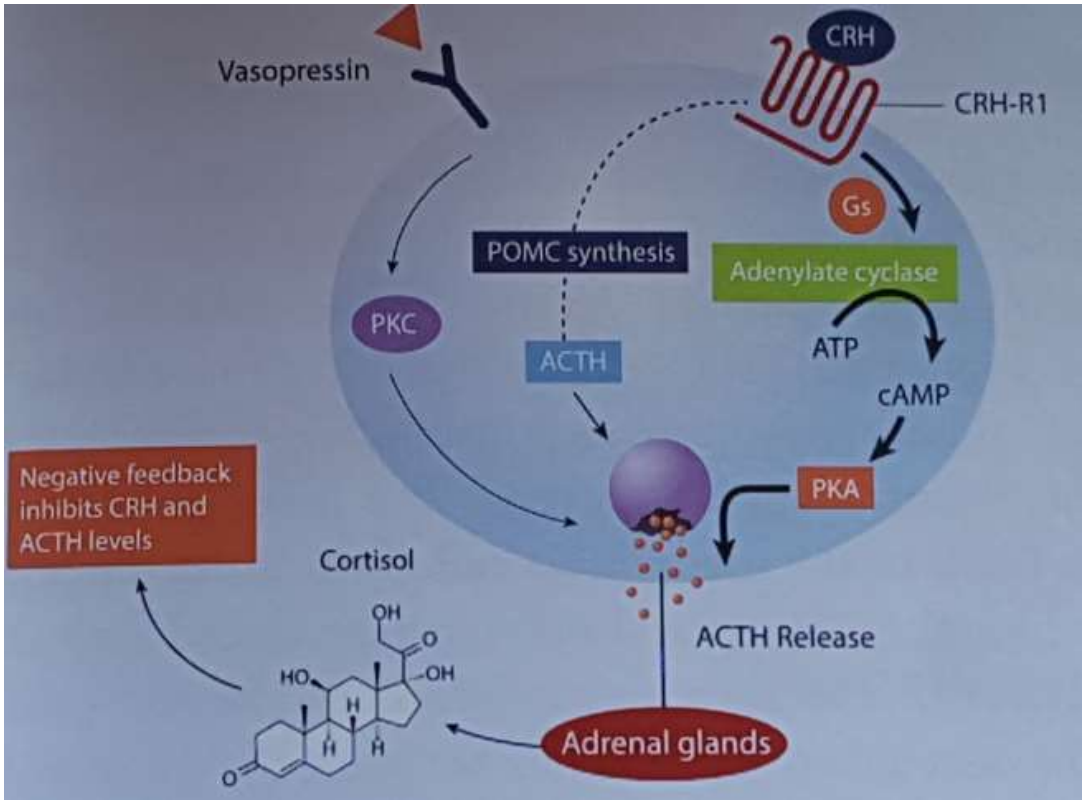


HPA axis

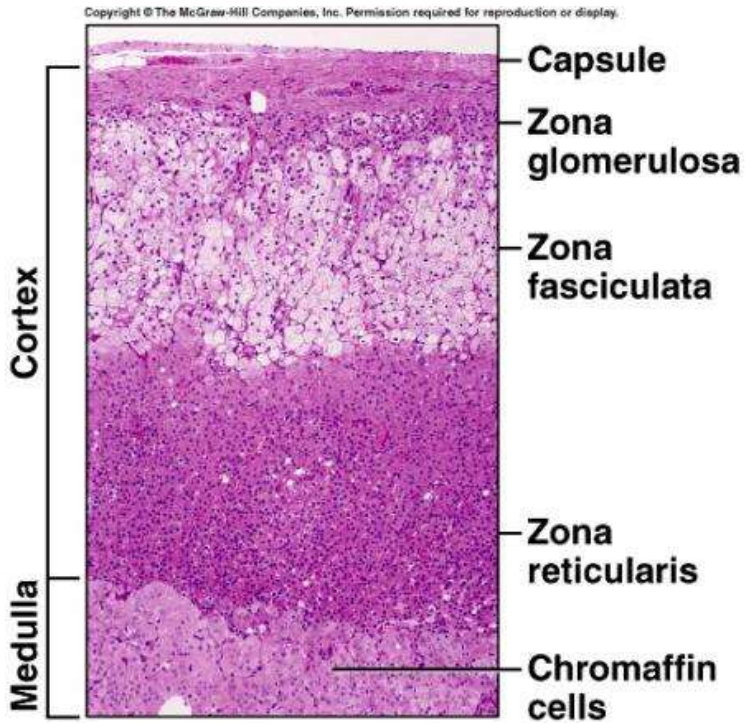

SCN
CNS
Hypothalamus
Circadian information
Stressors
PVN
CRH and AVP release
Median eminence
Anterior pituitary
Portal vein
Corticotroph cells
Feedback inhibition by cortisol
ACTH release
Cortisol
SCN modulates circadian sensitivity to ACTH

The pituitary controlling HPA signals

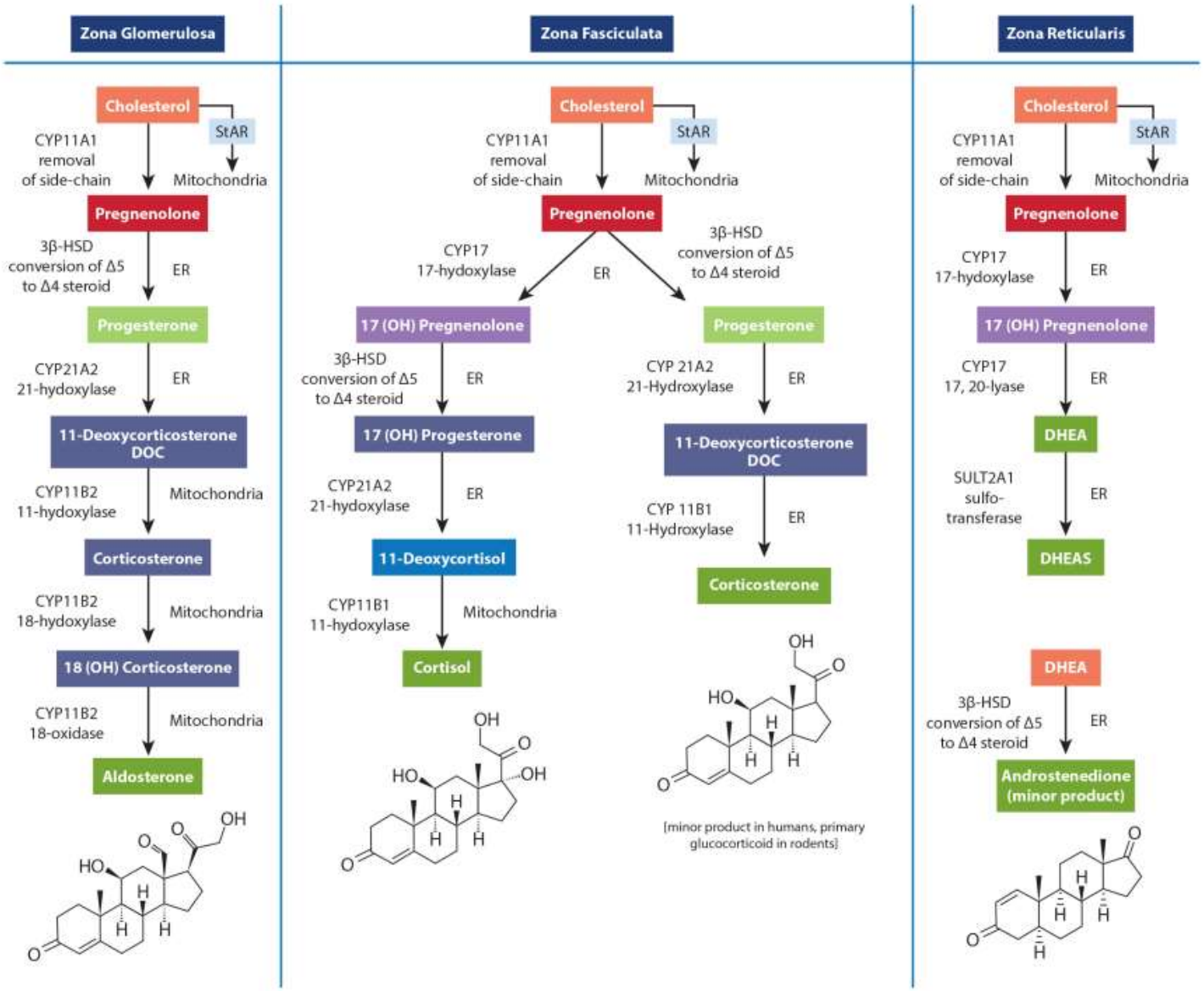
- Relay station that converts neuroendocrine outputs from the hypothalamus into hormone signals from other endocrine organs
- As person ages the signaling and endocrine functions within the pituitary are altered
- Stress affects all endocrine functions with HPA dysfunction, leading to thyroid dysfunction, reproductive cycle dysfunction and pigmentation issues of skin



Adrenal gland



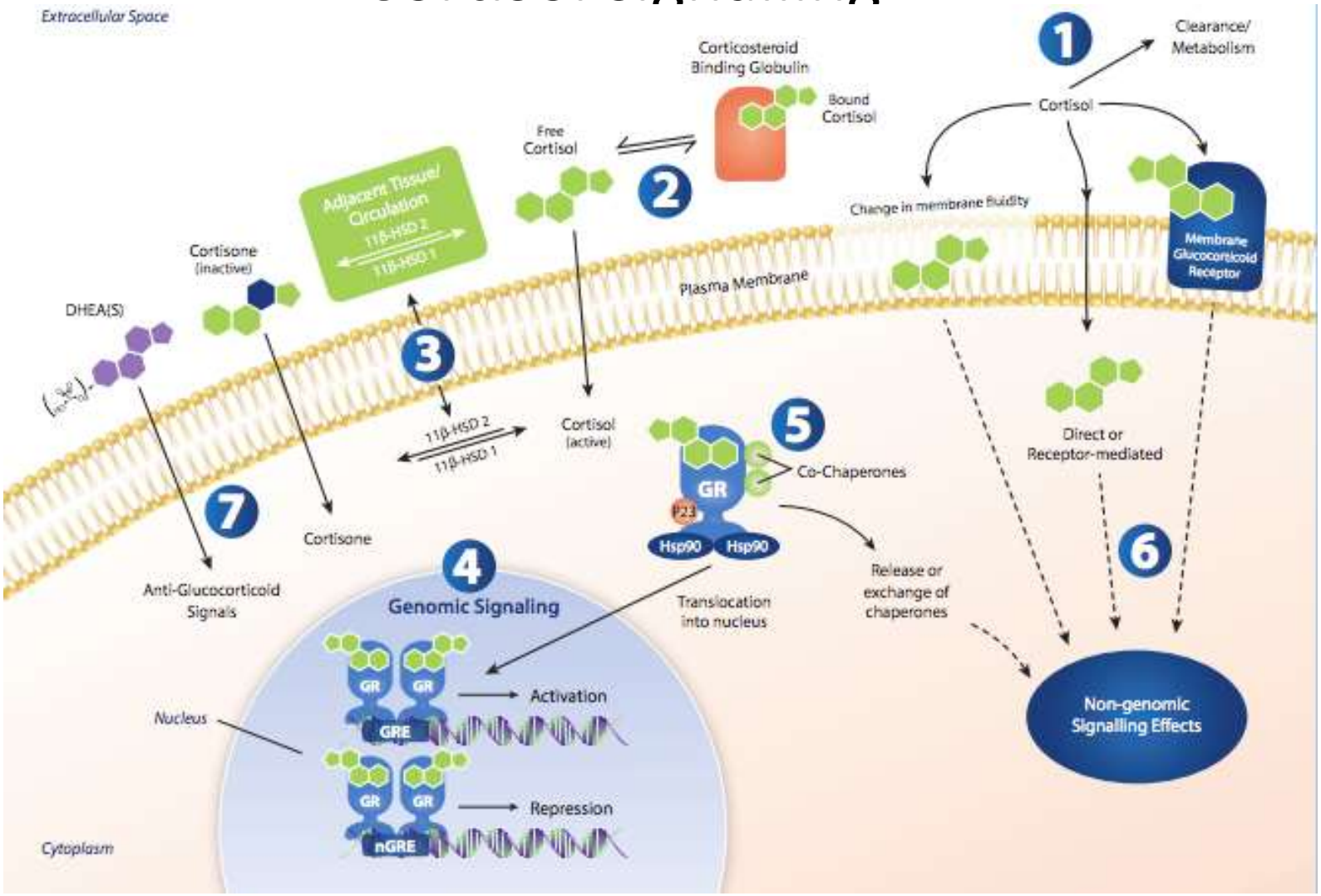
Note: There is no 'pregnenolone steal'

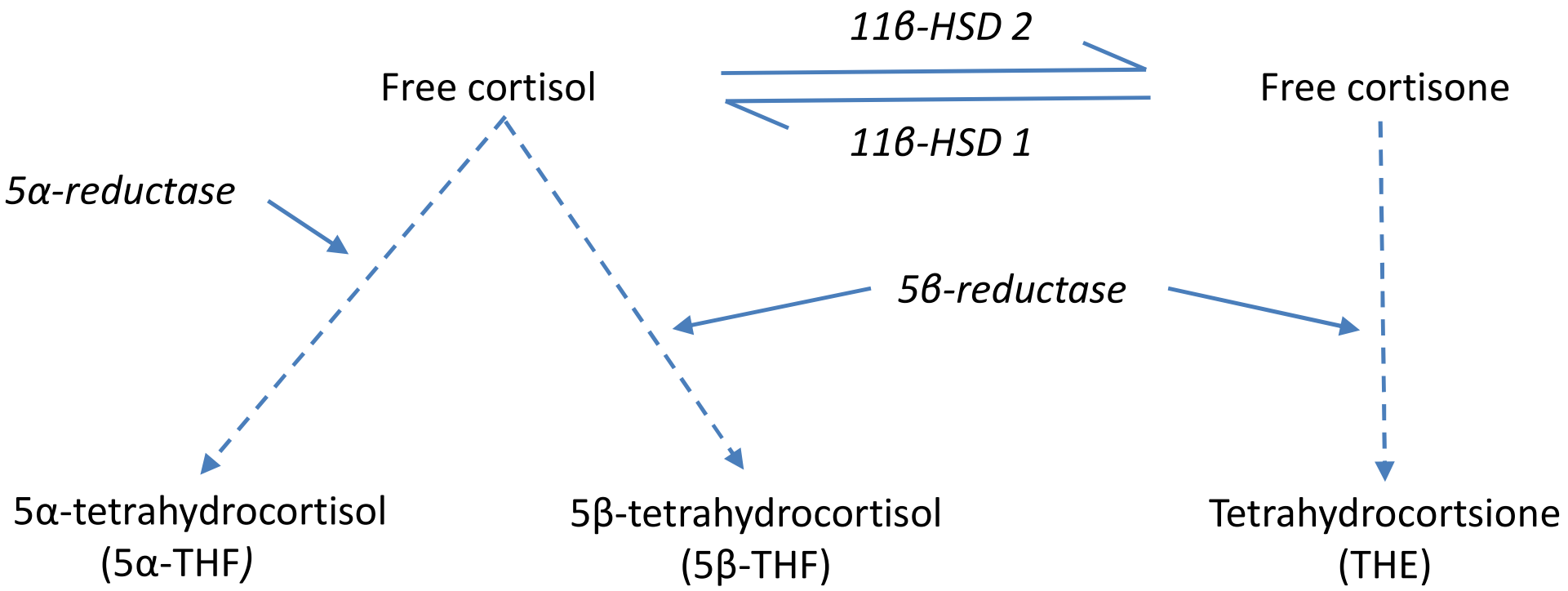

Zona Glomerulosa
Cholesterol
StAR
CYP11A1
removal
of side-chain
Mitochondria
Pregnenolone
3β-HSD
conversion of Δ5
to Δ4 steroid
ER
Progesterone
CYP21A2
21-hydoxylase
ER
11-Deoxycorticosterone
DOC
CYP11B2
11-hydoxylase
Mitochondria
Corticosterone
CYP11B2
18-hydoxylase
Mitochondria
18 (OH) Corticosterone
CYP11B2
18-oxidase
Mitochondria
Aldosterone
Zona Fasciculata
Cholesterol
StAR
CYP11A1
removal
of side-chain
Mitochondria
Pregnenolone
CYP17
17-hydoxylase
ER
3β-HSD
conversion of Δ5
to Δ4 steroid
17 (OH) Pregnenolone
3β-HSD
conversion of Δ5
to Δ4 steroid
ER
17 (OH) Progesterone
CYP21A2
21-hydoxylase
ER
11-Deoxycortisol
CYP11B1
11-hydoxylase
Mitochondria
Cortisol
Progesterone
CYP 21A2
21-Hydroxylase
ER
11-Deoxycorticosterone
DOC
CYP 11B1
11-Hydroxylase
ER
Corticosterone
[minor product in humans, primary glucocorticoid in rodents]
Zona Reticularis
Cholesterol
StAR
CYP11A1
removal
of side-chain
Mitochondria
Pregnenolone
CYP17
17-hydoxylase
ER
17 (OH) Pregnenolone
CYP17
17, 20-lyase
ER
DHEA
SULT2A1
sulfo-
transferase
ER
DHEAS
DHEA
3β-HSD
conversion of Δ5
to Δ4 steroid
ER
Androstenedione
(minor product)

Hormones and adrenal medula

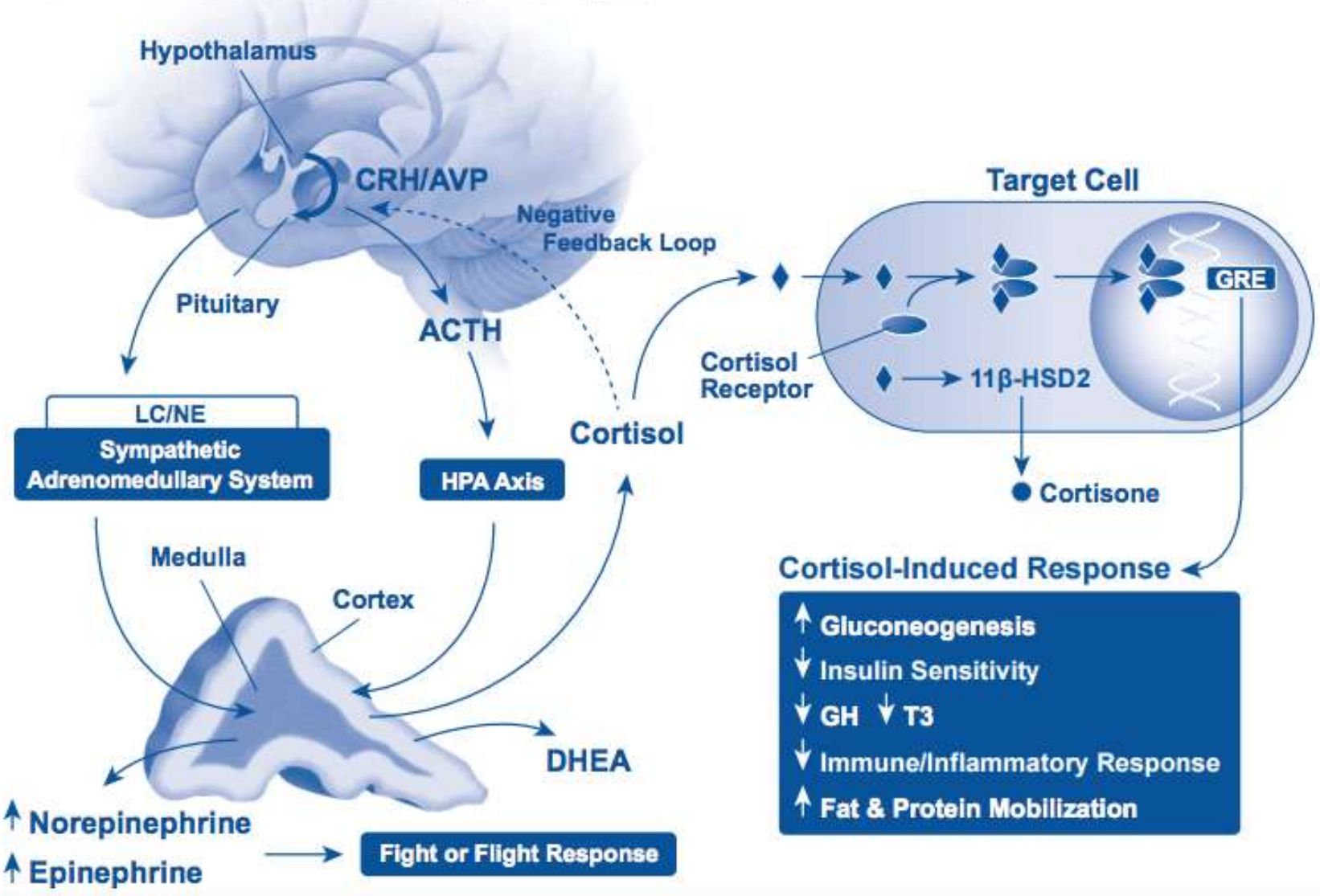
- Extension of CNS secretes two important catecholamines, epinephrine and norepinephrine
- Acetylecholine from sympathetic neurons trigger a release of epinephrine and norepinephrine almost instantaneously upon encountering a stressor (10 minutes prior to HPA axis cortisol response)
- Biosynthesis of NE from tyrosine occurs like other adrenergic neurons like LC/NE (via tyrosine hydroxylase and dopamine decarboxylase)
- Adrenal medula expresses uniquely PNMT enzyme to allow production of epinephrine (80% E and 20% NE)
- Half life is only a few minutes till degraded by methylation via COMT or deamination by MAO

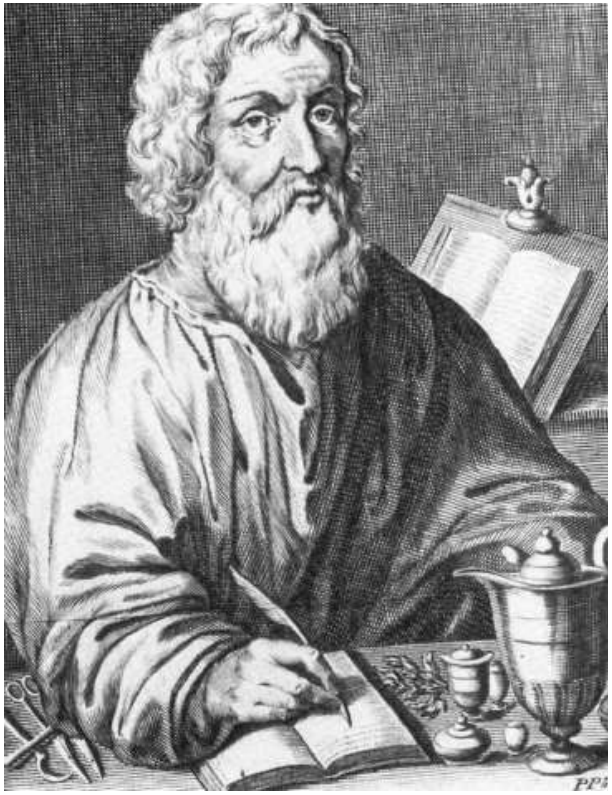
Cortisol signalling




11β-HSD 2
Free cortisol
Free cortisone
11β-HSD 1
5α-reductase
5β-reductase
5α-tetrahydrocortisol
(5α-THF)
5β-tetrahydrocortisol
(5β-THF)
Tetrahydrocortsione
(THE)

The HPA Axis and Stress Response System

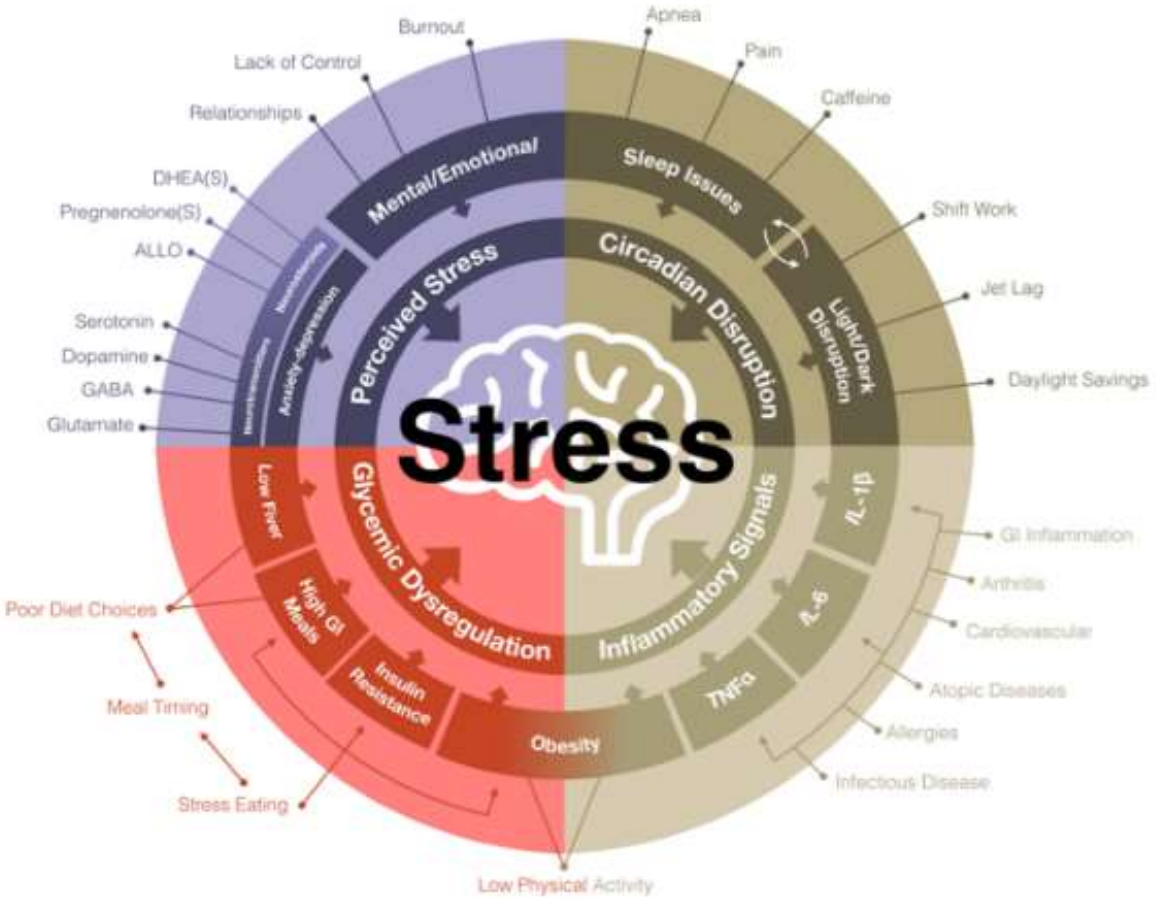




Everyone has a doctor in him or her; we just have to help it in its work. The natural healing force within each one of us is the greatest force in getting well.

~ Hippocrates, 400 BC

What makes the brain stressed?



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

HPA axis + circadian control

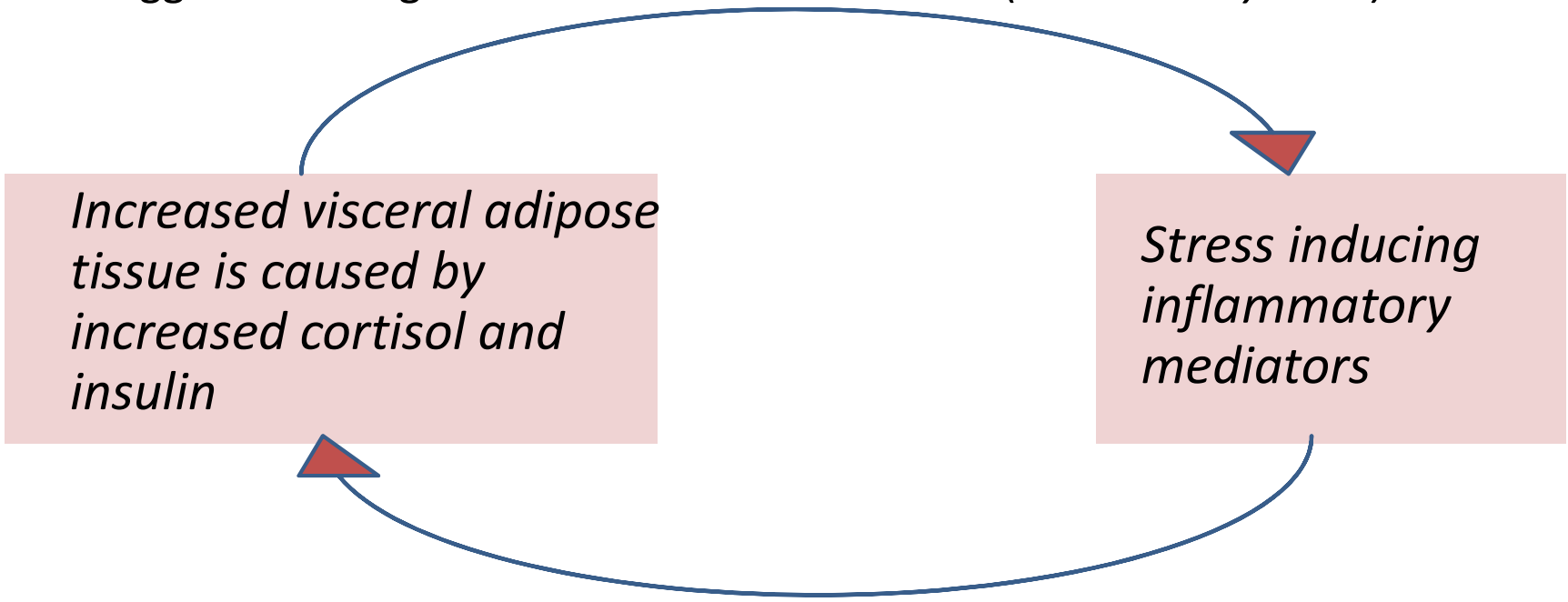
- HPA axis is intermittently tied with controlling circadian rhythm that are entrained by light and dark cycles of day and night
- Lifestyle choices or needs result in HPA axis dysfunction, leading to metabolic dysfunctions like IR, obesity and neurotransmitter dysregulation
- Good sleep of 7.5 hours is the greatest ‘reset button’ of the HPA axis

Dysglycemia + HPA axis

- One of the main functions of HPA axis is glucose regulation, insulin sensitivity and overall energy balance
- Hypoglycaemia is a potent HPA axis activation
- Most chronic stressors operate at low levels and go unrecognised by the patient

Obesity

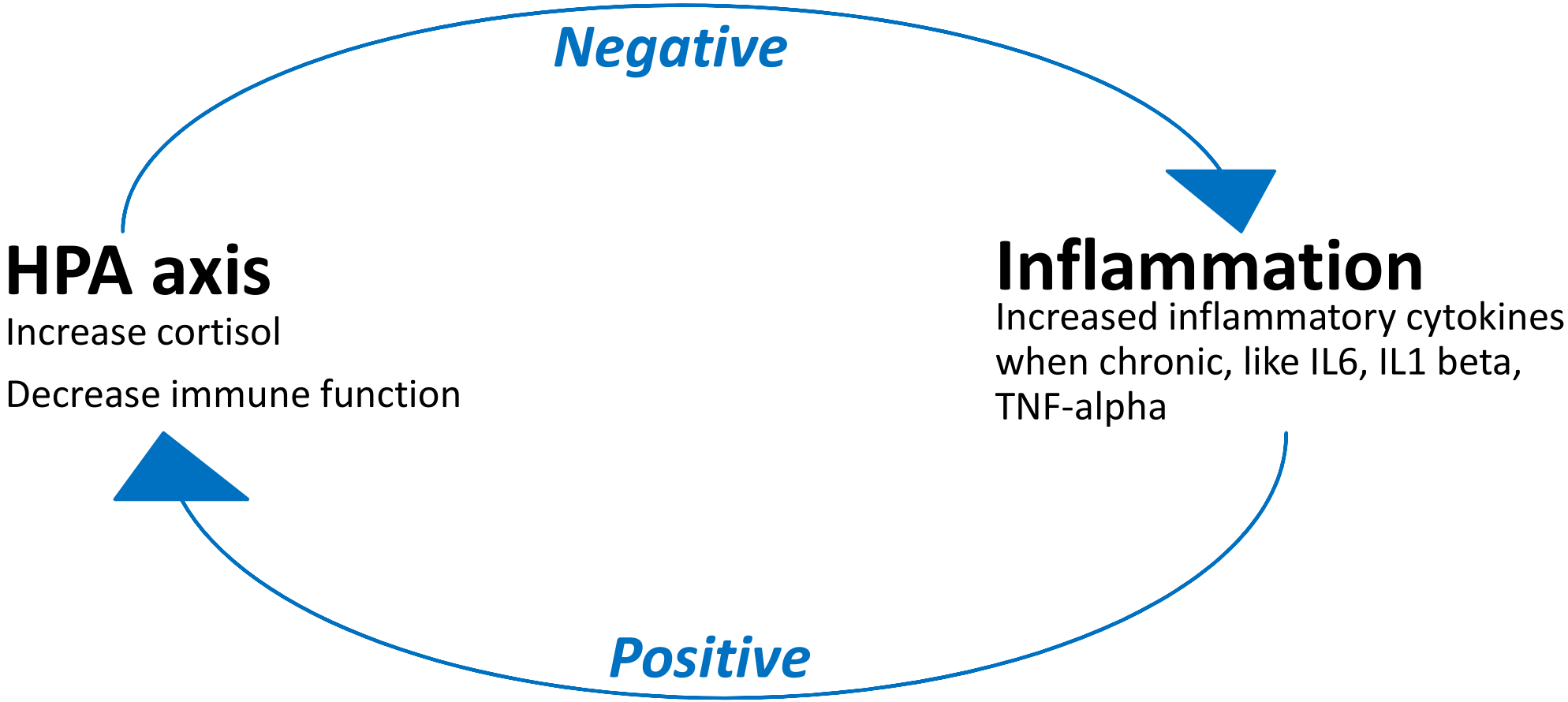
- Stress increases consumption of comfort foods. *Nat Acad of Sciences USA 2003*
- Aggressive weight loss is an HPA axis stressor. (*Int J. Obesity 2012)*



Hippocampus + metabolic function + HPA axis

- Hypothalamus is very sensitive to falling ghrelin levels as main source of energy

- Chronic hyperinsulinemia as in obesity/MS leads to impairment in glucose sensing by the hypothalamus, leading to further underrated metabolic dysfunction



There is strong relationship between HPA axis and inflammatory signalling

Inflammation + HPA axis

- Chronic elevations of inflammation induce cortisol will eventually downregulate the HPA axis + cortisol production

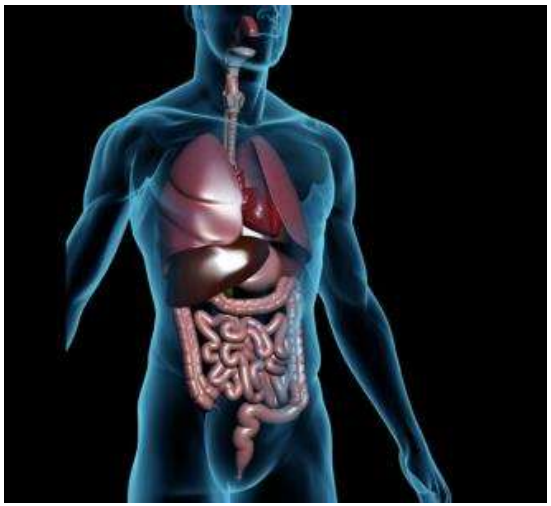
- Also there is a factor of cortisol resistance in key tissues + immune cells, which block the anti-inflammatory affect of cortisol

Inflammation + HPA axis

- Inflammation anywhere is a HPA stressor
- Can be from GI tract (food allergies or IBD (leaky gut))
- Inflammatory condition Rh diseases
- Chronic low level inflammation (obesity, cardiometabolic)
- Chronic infection (sinusitis, fungal etc)
- Toxin load creating autoimmune reactions

HPA axis + gastrointestinal system

- ‘A troubled intestine can send signals to the brain, just as a troubled brain can send signals to the gut. Hence a person’s gut distress can be the cause or the product of anxiety, stress or depression. They are intermittently connected and for all practical purposes they should be viewed as one system.’



Coordinated surveillance systems, protecting ‘self’ at the interfaces

Stress + gastrointestinal system

- Alterations in gastrointestinal irritability
- Increase in visceral perception
- Changes in gastrointestinal secretion
- Negative effect on GI mucosa blood flow and repair, and increase in IB
- Negative effect on intestinal flora, neurotransmitter and cytokine levels

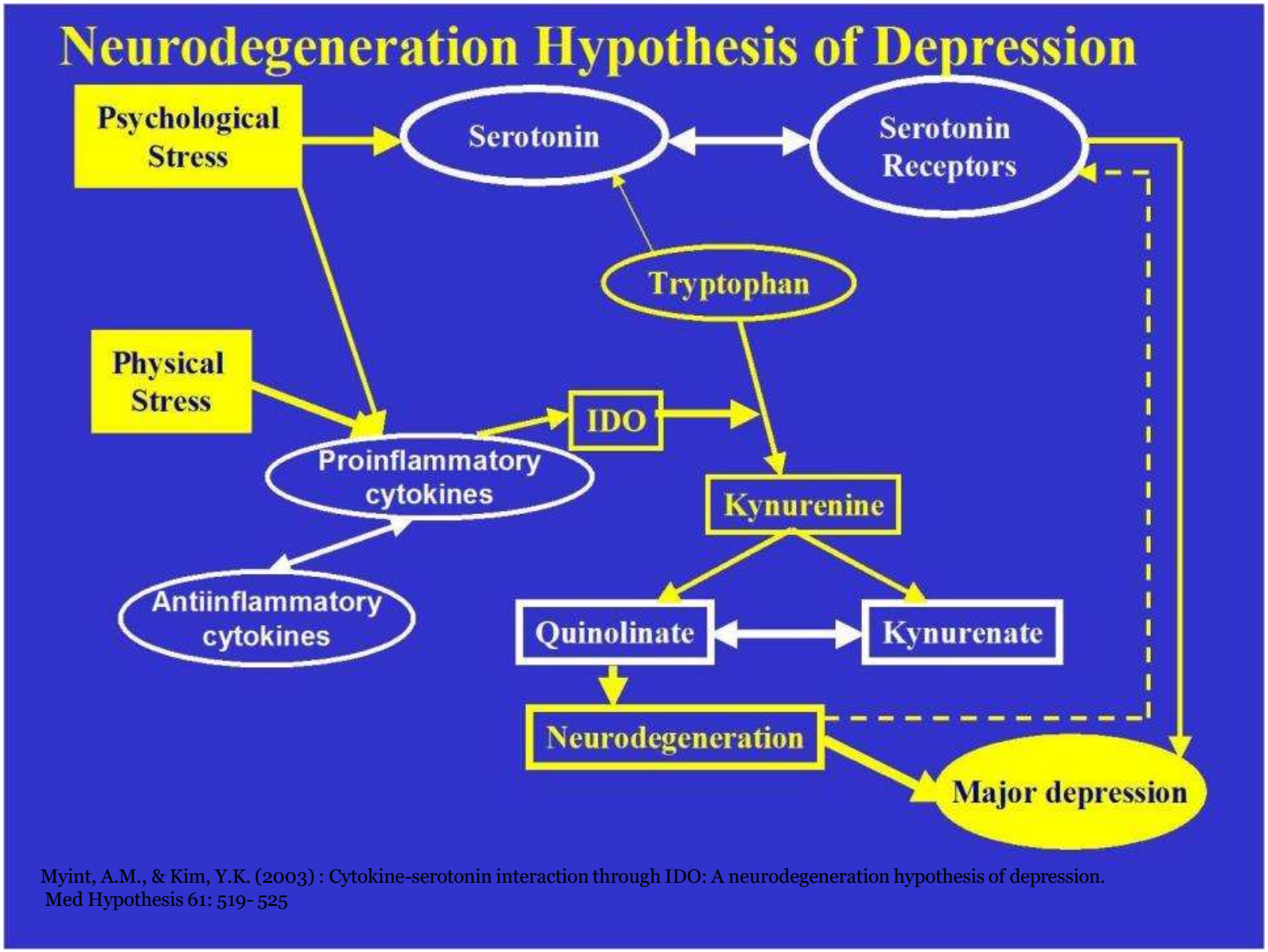
Cortisol and the hippocampus

- Repeated stress affects brain function, especially hippocampus.
- High concentrations of cortisol and NMDA receptors.
- Participates in verbal memory and memory context
- Impairment decreases the reliability and accuracy of contextual memories.
- Damage may exacerbate stress by preventing access to the information needed to decide that a situation is not a threat
- Regulates the stress response and acts to inhibit the response of the HPA axis to stress

Bruce S. McEwen, Ph.D. Protective and Damaging Effects of Stress Mediators. NEJM. Jan 2008: Volume 338:171-179

Hippocampal changes in chronic stress

- Hippocampus alterations in both structure and function have been identified in long term stress
- Volume loss demonstrated in PTSD, depression, cushing's syndrome
- Functional changes include reduction in hippocampal excitability, long-term potentiation and memory.



Myint, A.M., & Kim, Y.K. (2003) : Cytokine-serotonin interaction through IDO: A neurodegeneration hypothesis of depression. Med Hypothesis 61: 519- 525

A new view on hypocortisolism

Eva Fries, Judith Hesse, Juliane Hellhammer, Dirk H. Hellhammer*

Department for Psychobiology, University of Trier, Johanniterufer 15, 54290 Trier, Germany

Received 18 November 2004; received in revised form 6 April 2005; accepted 6 April 2005

KEYWORDS
Hypocortisolism;
Cortisol;
Allostatic load index;

Summary Low cortisol levels have been observed in patients with different stress-related disorders such as chronic fatigue syndrome, fibromyalgia, and post-traumatic stress disorder. Data suggest that these disorders are characterized by a symptom triad of enhanced stress sensitivity, pain, and fatigue. This overview will

Raison and Miller (2003) assume that prolonged or repeated exposure to immune stimuli might predispose an individual to reduced glucocorticoid signaling as a means of freeing bodily defenses from inhibitory control in the face of an ongoing infectious threat. Thus, an enhanced release of

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may be beneficial for health and survival. Most strikingly, the demonstration of a low allostatic load index in hypocortisolemic subjects suggests that a down-regulation of the HPA axis in chronically stressed subjects protects those subjects against the harmful effects of a high allostatic load index.

Hypocortisolism may be an adaptive mechanism to liberate the immune system or protect the nervous system

Investigations

- Serum cortisol - for excluding Addison's Disease
- Short Synacthen test –for excluding Addison's Disease
- Urinary 24-hr free cortisol – possibly helpful
- Serum DHEA(S) – possibly helpful
- Urinary cortisol/DHEA – possibly helpful

Saliva tests for adrenal function

- “Salivary cortisol measurements are an excellent index of plasma free cortisol concentrations”

J Clin Endocrinol Metab. 1988 Feb;66(2):343-8.

- Adrenal Cortex Hormone Tests
  - Salivary cortisol (4 times daily)
  - DHEA-S
  - progesterone
  - estrogens
  - testosterone

dutch

Dried Urine Test for Comprehensive Hormones

Advanced Adrenal Assessment

Accession # 00216507
Sample Female Report
123 A Street
Sometown, CA 90266

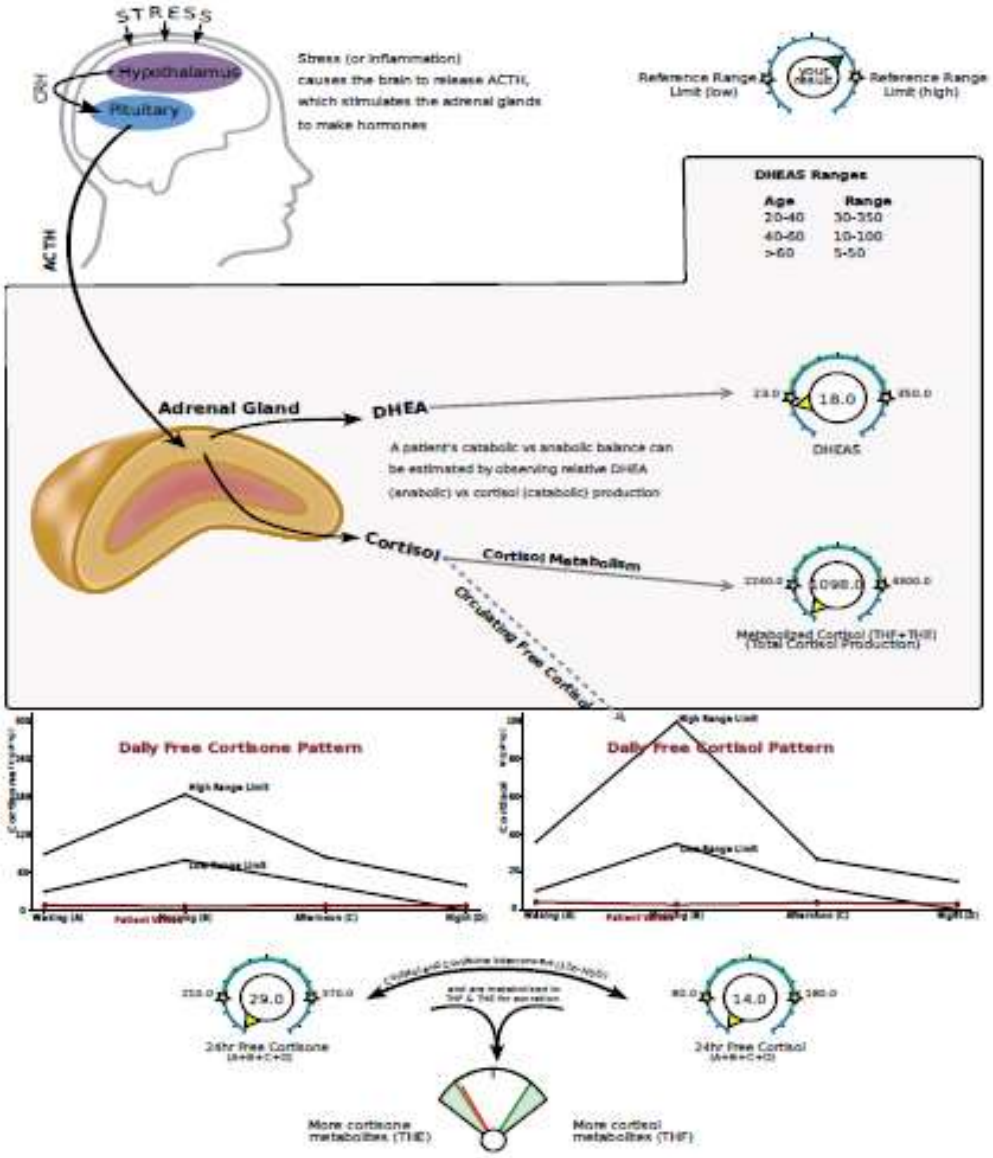
PRECISION ANALYTICAL
Consulting & Laboratory

Ordering physician:
Research Only

DOB:1976-01-01
Gender: Female

Collection Times:
2015-11-10 03:00PM
2015-11-10 04:00AM
2015-11-10 08:00AM
2015-11-10 08:00PM

Category	Test		Result	Units	Normal Range
Creatinine					
	Creatinine A (Waking)	Within range	0.49	mg/ml	0.3 - 3
	Creatinine B (Morning)	Within range	0.33	mg/ml	0.3 - 3
	Creatinine C (Afternoon)	Within range	0.55	mg/ml	0.3 - 3
	Creatinine D (Night)	Within range	0.3	mg/ml	0.3 - 3
Daily Free Cortisol and Cortisone					
	Cortisol A (Waking)	Below range	4.0	ng/mg	10 - 36
	Cortisol B (Morning)	Below range	2.8	ng/mg	35 - 100
	Cortisol C (Afternoon)	Below range	3.7	ng/mg	12 - 27
	Cortisol D (Night)	Within range	3.0	ng/mg	0 - 15
	Cortisone A (Waking)	Below range	8.0	ng/mg	30 - 90
	Cortisone B (Morning)	Below range	6.4	ng/mg	80 - 185
	Cortisone C (Afternoon)	Below range	7.5	ng/mg	40 - 85
	Cortisone D (Night)	Low end of range	7.4	ng/mg	0 - 40
	24hr Free Cortisol	Below range	14.0	ug	80 - 180
	24hr Free Cortisone	Below range	29.0	ug	210 - 370
Cortisol Metabolites and DHEAS					
	b-Tetrahydrocortisol (b-THF)	Below range	346.0	ng/mg	750 - 1450
	a-Tetrahydrocortisol (a-THF)	Below range	41.0	ng/mg	90 - 320
	b-Tetrahydrocortisone (b-THE)	Below range	710.0	ng/mg	1300 - 2560
	Metabolized Cortisol (THF+THE)	Below range	1098.0	ng/mg	2240 - 4300
	DHEAS	Below range	18.0	ng/mg	23 - 350


STRESS
CNS
Hypothalamus
Pituitary
ACTH
Stress (or inflammation) causes the brain to release ACTH, which stimulates the adrenal glands to make hormones
Reference Range Limit (low)
Your result
Reference Range Limit (high)
DHEAS Ranges
Age Range
20-40 30-350
40-60 10-100
>60 5-50
Adrenal Gland
DHEA
A patient's catabolic vs anabolic balance can be estimated by observing relative DHEA (anabolic) vs cortisol (catabolic) production
18.0
DHEAS
Cortisol
Cortisol Metabolism
Circulating Free Cortisol
1098.0
Metabolized Cortisol (THF+THE)
(Total Cortisol Production)
Daily Free Cortisone Pattern
High Range Limit
Low Range Limit
Daily Free Cortisol Pattern
High Range Limit
Low Range Limit
29.0
24hr Free Cortisone
14.0
24hr Free Cortisol
More cortisone metabolites (THE)
More cortisol metabolites (THF)

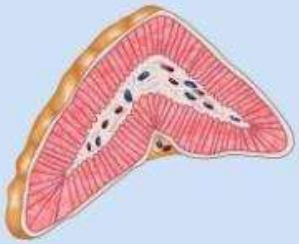
Strategies for Supporting HPA Axis Function

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 (?)

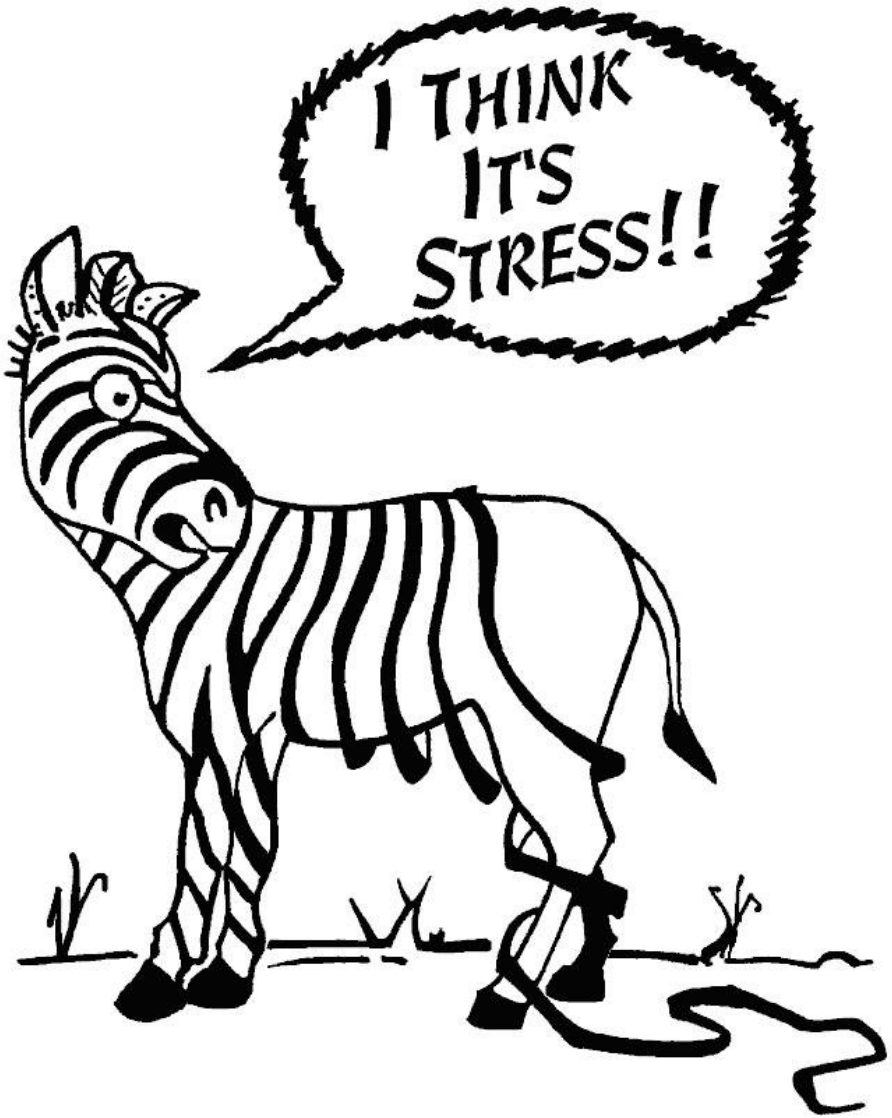
Nutrient Support for Adrenal Steroidogenesis
- Vitamin C
- B-Vitamin (general)
  - Pantothenic Acid
  - Niacin
- Minerals (general)
  - Magnesium/Zinc
- Glandulars (Adrenal)

Target-tissue Cortisol Modulation

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

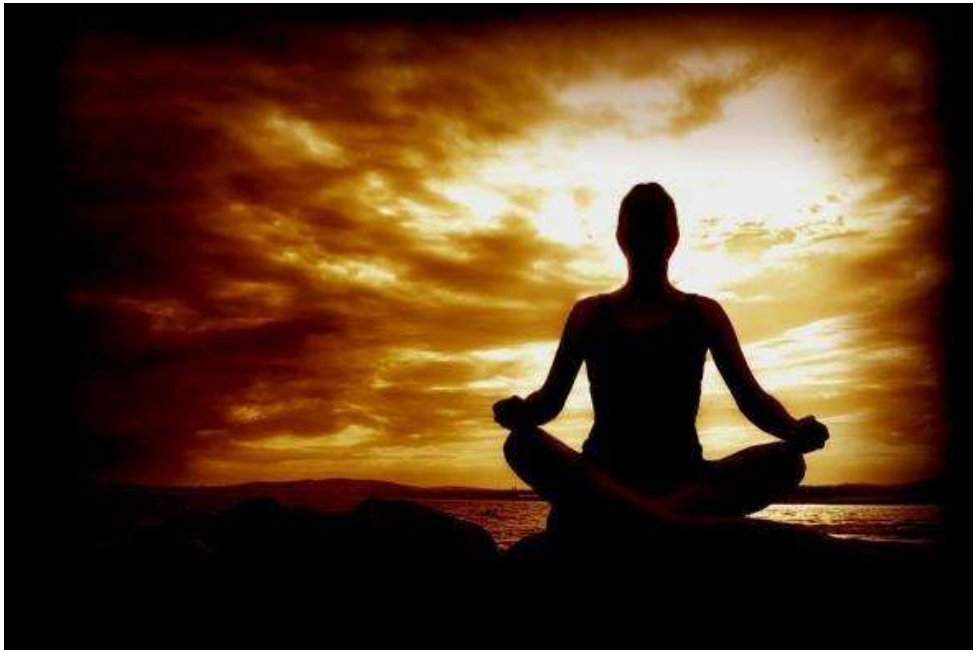
↑ HSP Modulation of GR
- Consider Adaptogens
- Consider Physical Activity (not intense)

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


I THINK
IT'S
STRESS!!

Management

- The ultimate goal is to discover the route cause of the imbalance related to the stress response and to regain physiological balance, while slowly reversing the chronic manifestations caused by stress



The art of medicine consists of amusing the patient while nature cures the disease

~ Voltaire, 18th Century

**"I'm finally learning how to relax.
Unfortunately, relaxation makes me tense."**