Stress and Endocrine Disruptors

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(No disclosures)

HUMAN COMPLEXITY: POST(EPI)GENOMIC ERA

Human genome:

About 3+3 billion bases ("Non-junk" DNA 98 *vs.* 2 %)
About 60%retroviral origin
About 20 thousand protein-coding genes
About 22 thousand ncRNA-coding genes
About 200 thousand transcripts
(mRNA, ncRNA)
About 200-260 thousand proteins

Single nucleotide polymorphisms (snp's or snv's),
microsatellites or copy number variants : (0.9% difference)

About >25 million snp's (snv's), 1.5 million indels
About 20 million microsatellites
>5000 cnv's (many million bases)
> 100 k disease-related mutations
>1 million reg sequences

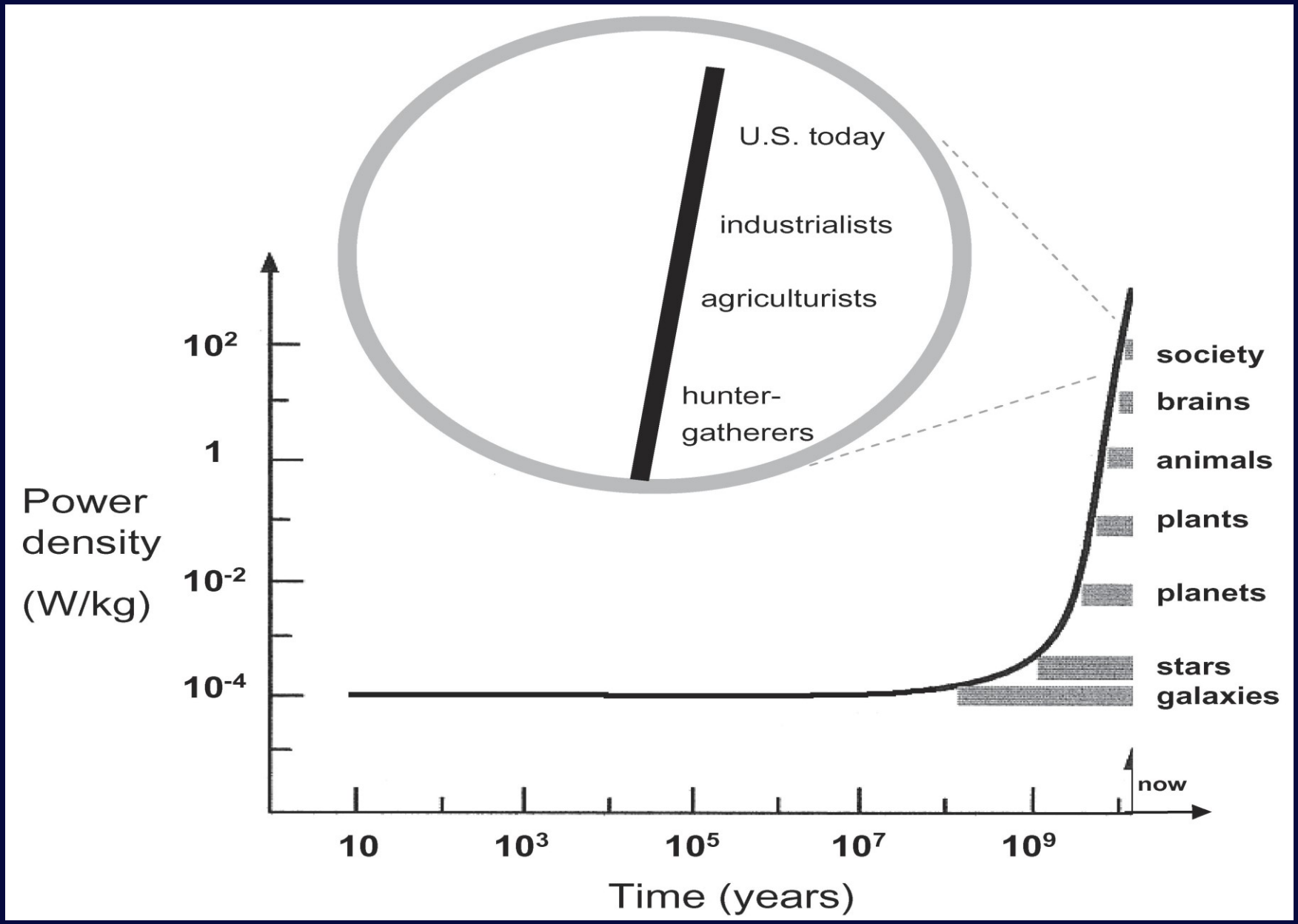
>60% of promoters have CpG islands,

EPIGENETICS/EPIMUTATIONS

HUMAN COMPLEXITY: SOME HUMAN BRAIN NUMBERS

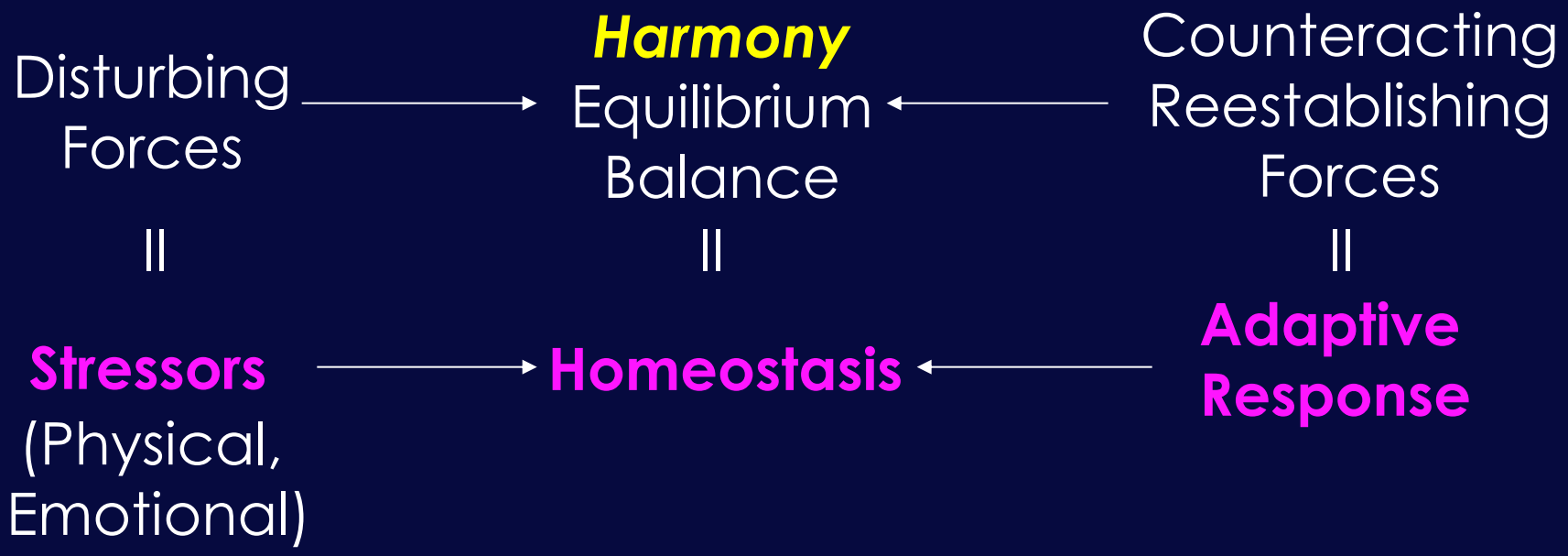
- ~ 100 billion neurons ($100x10^{12}$) x >10.000 synapses per neuron = $>10^{18}$ synapses)
- ~ 100.000 km of fibers
- ~ 1 trillion or more glial cells
- ~ 1.25 terabytes
- ~ 15 Watt lamp (2% of BW uses 20% energy)

Plasticity



Chaisson E, New Scientist 2009

Complex Systems Theory



Pythagoras= *Harmony*
Alcmaeon=*Iso-nomia*
Epicurus= Eustatheia
Walter Cannon= Homeostasis

Stress is the State of Threatened (or Perceived as Threatened) Homeostasis

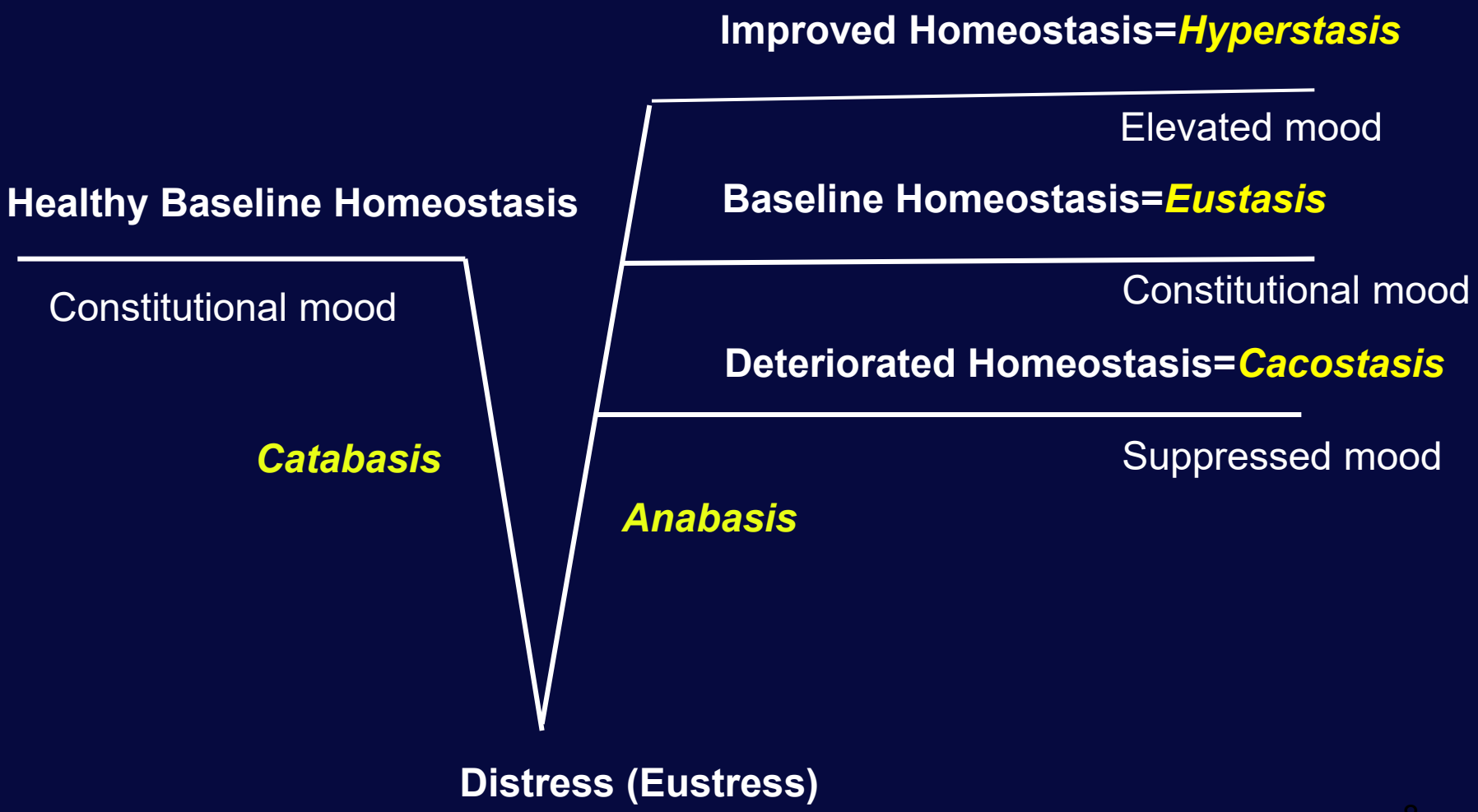
STRESS ETYMOLOGY

Indoeuropean root:

Gk: *Strangaleuin* = to strangle, also *Catastrophe,* and *Strabismus*

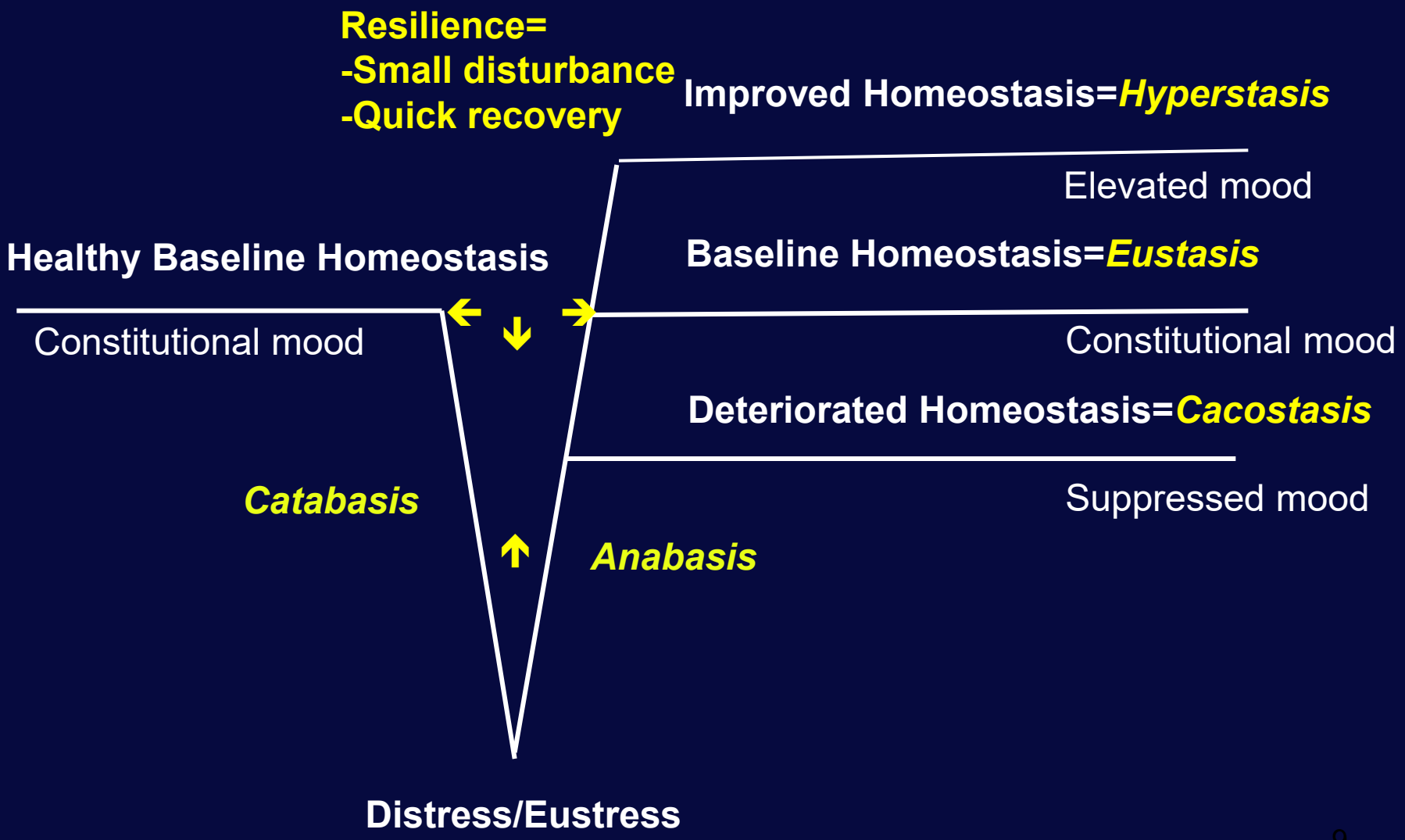
Lt: *Stringere* = to draw tight, to press

Homeostasis over Time



G.P. Chrousos

Homeostasis over Time



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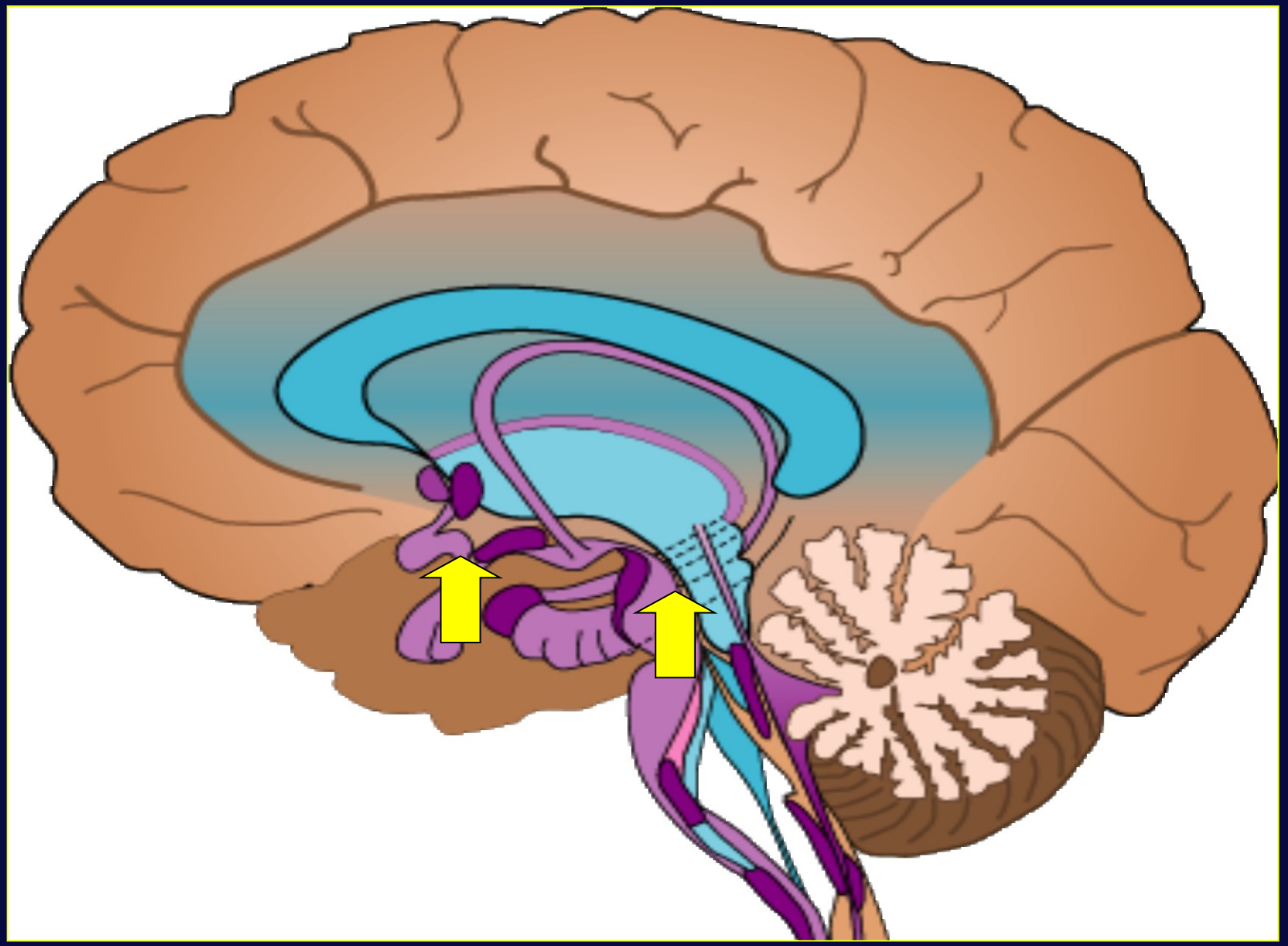
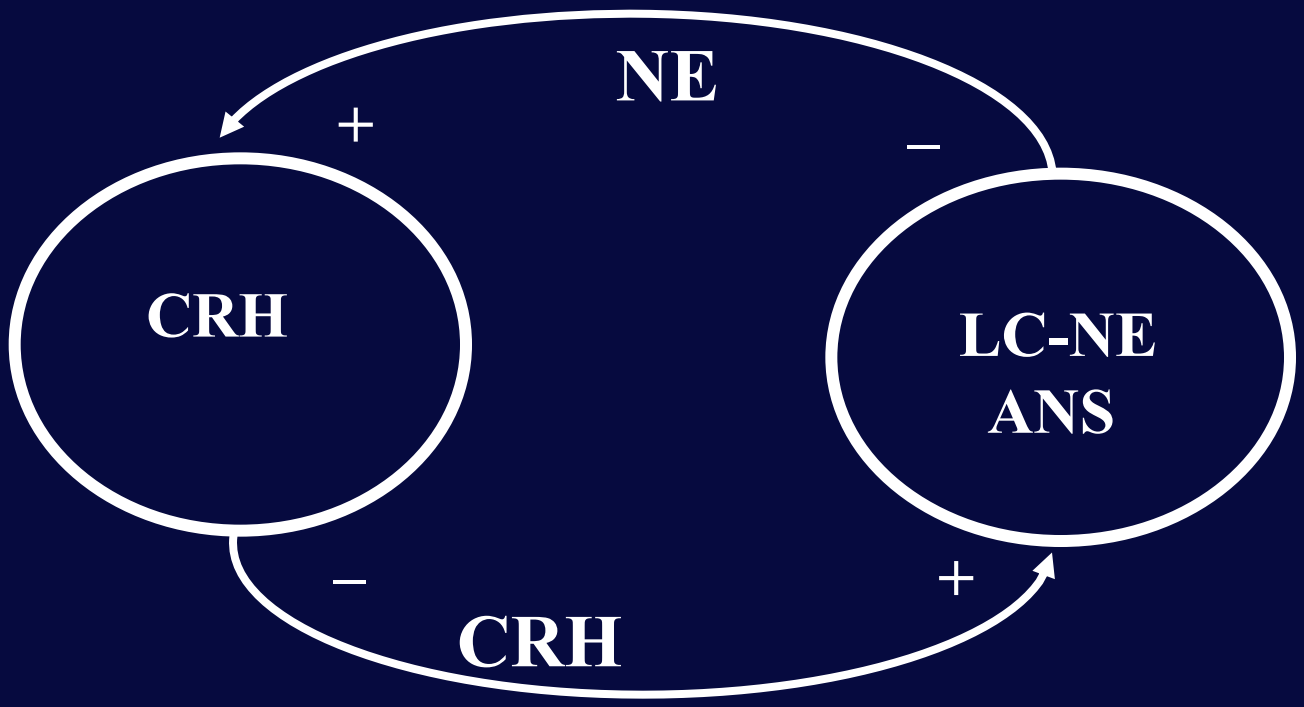
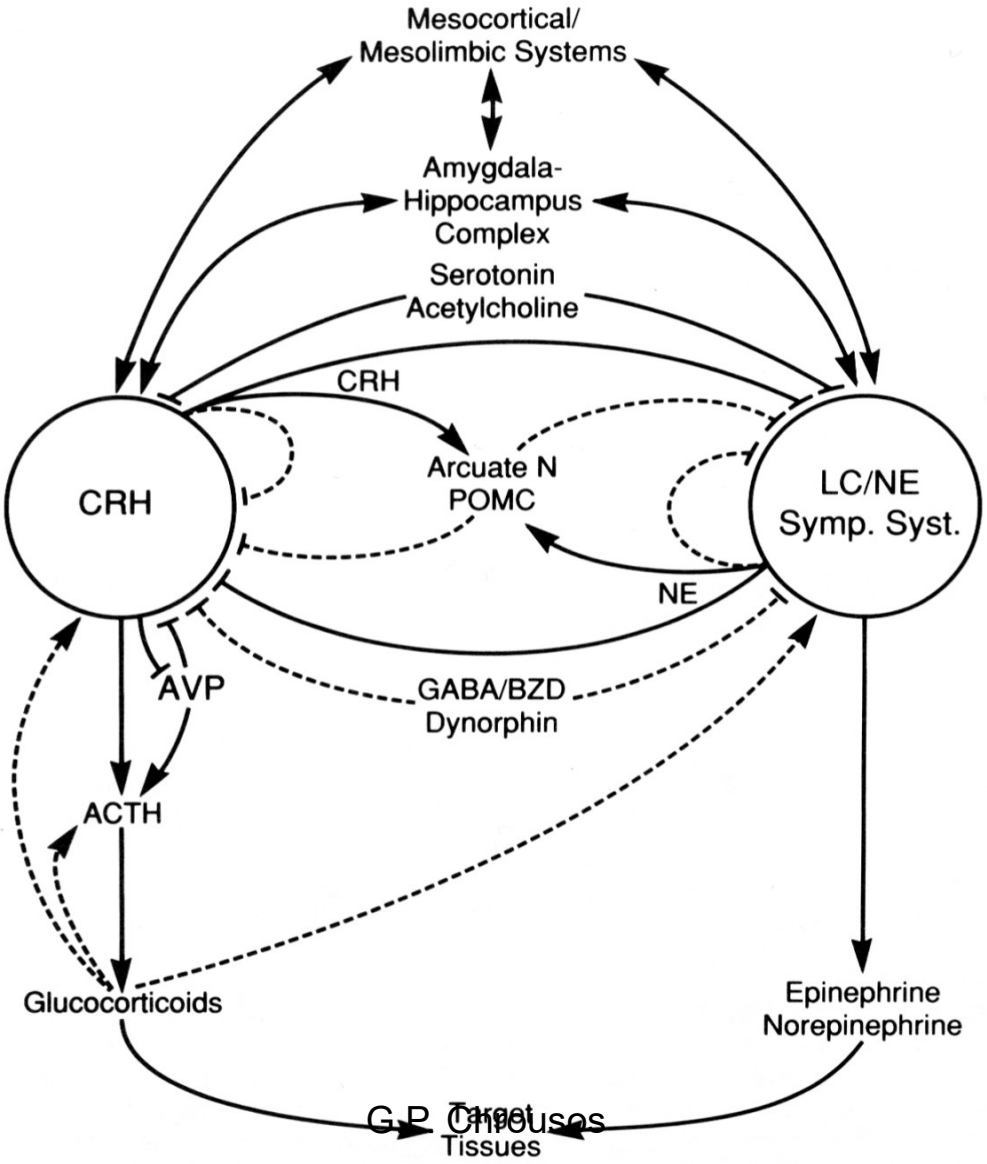


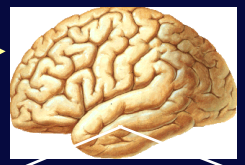
Stress System



Stress System



Chrousos
JAMA 1992



STRESS SYSTEM
Amygdala CRH

HIPPOCAMPUS

CRH/AVP

LC/NE

ACTH

F

NE/E
iCRH
+

IL-6

GH/IGF-1
LH/T
TSH/T_3

Inflammation

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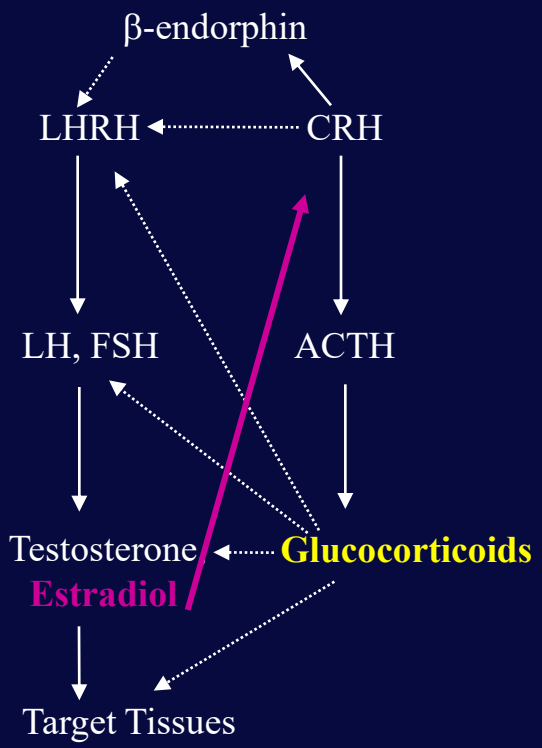
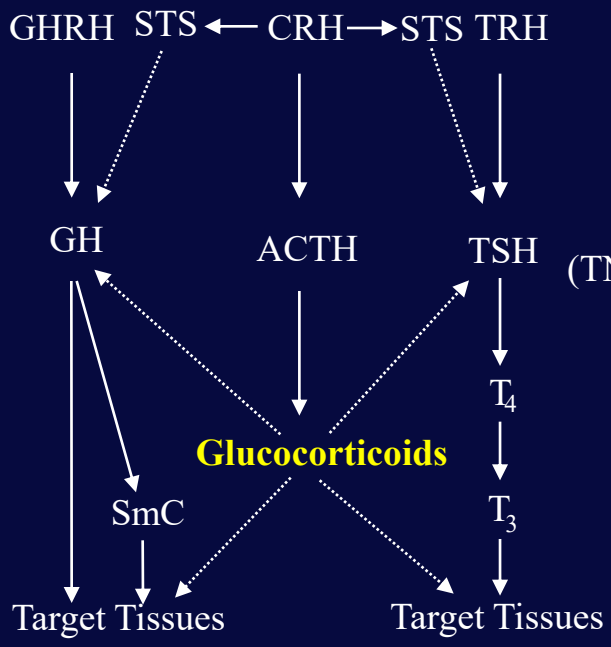
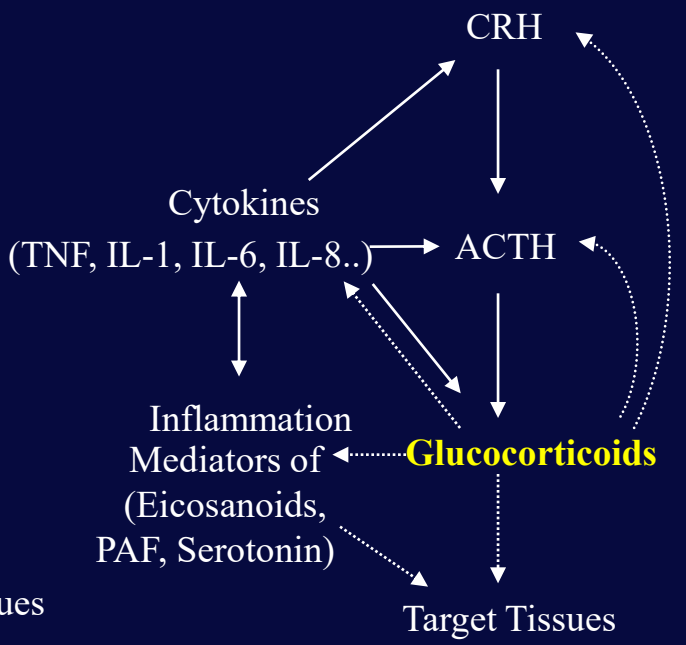
Reproduction



Growth and Thyroid Function



Immune Function



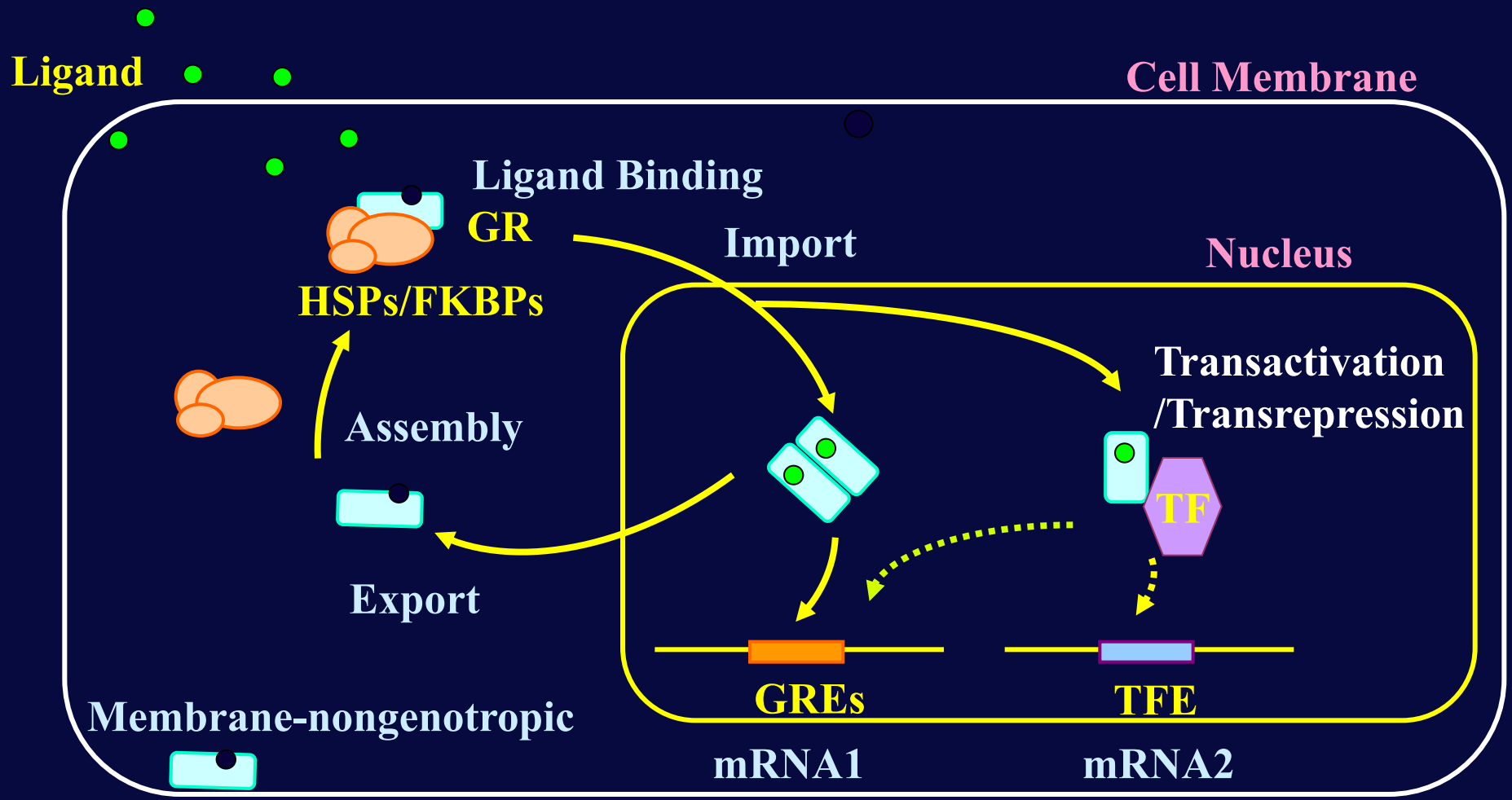
HYPOGONADISM

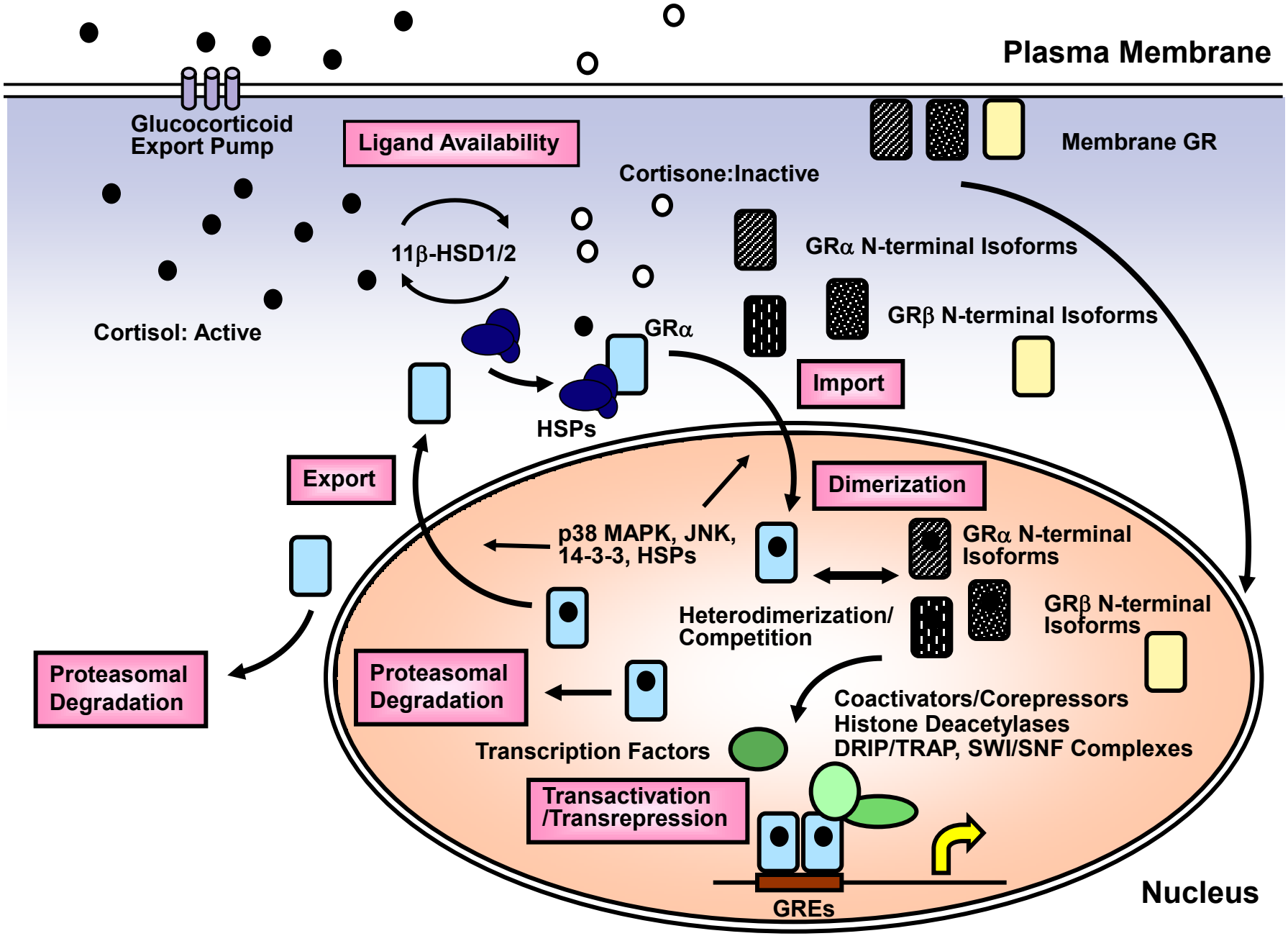
POOR GROWTH

"EUTHYROID SICK"

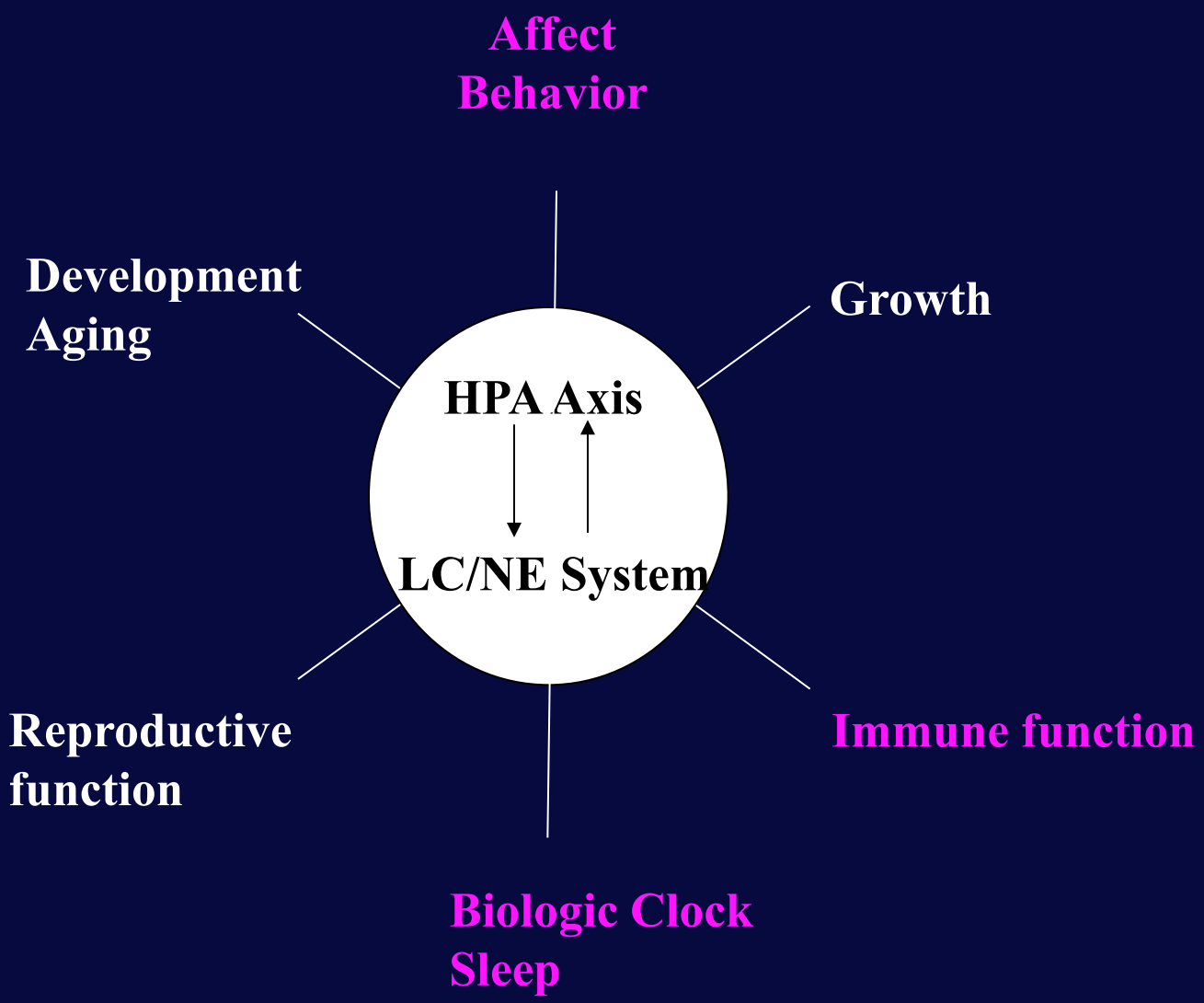
INFLAMMATION, ANTI-INFLAMMATION, Th1 to TH2 SHIFT PARAINFLAMMATION

Glucocorticoid Receptor Signaling





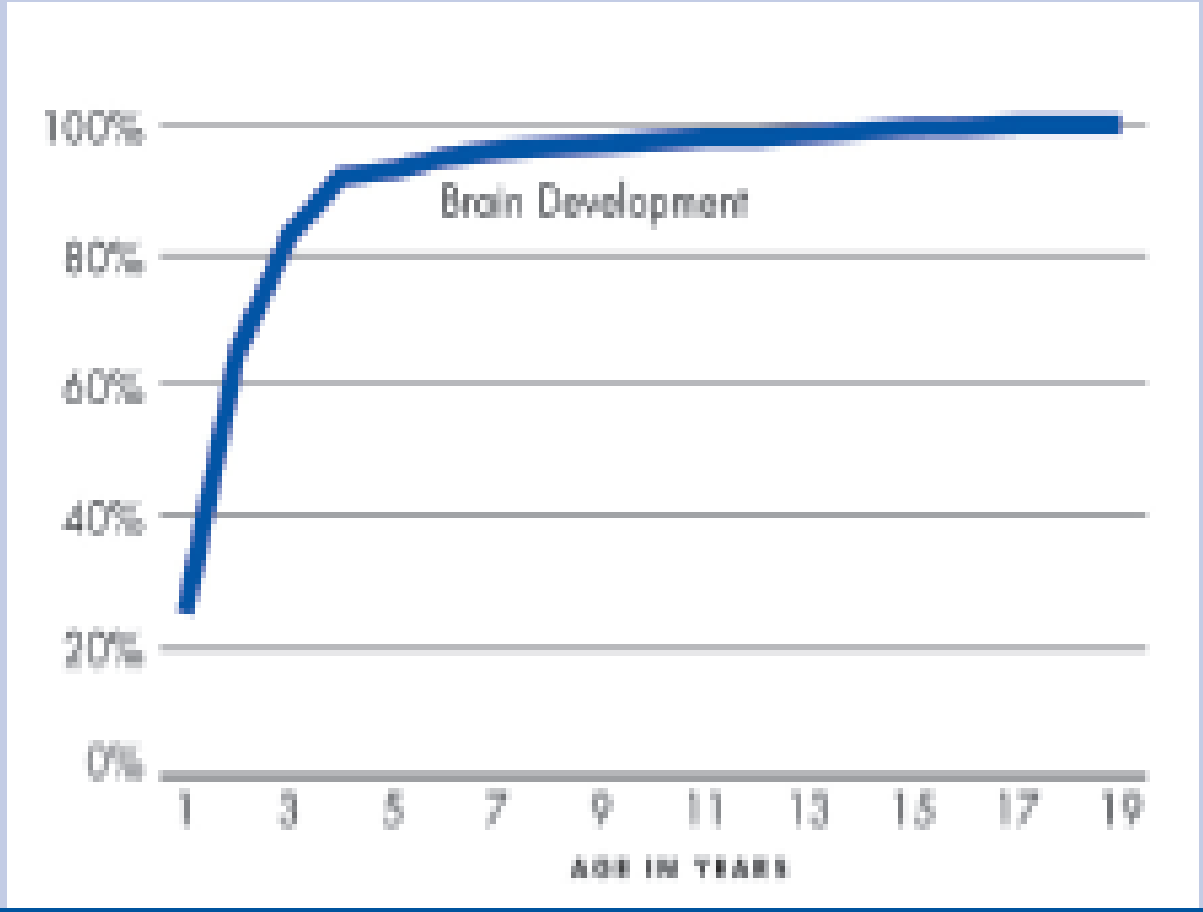
Chrousos & Kino Science STKE 2005


Affect
Behavior
Development
Aging
Growth
HPA Axis
LC/NE System
Reproductive
function
Immune function
Biologic Clock
Sleep

Physical and Emotional Stress Pathophysiology

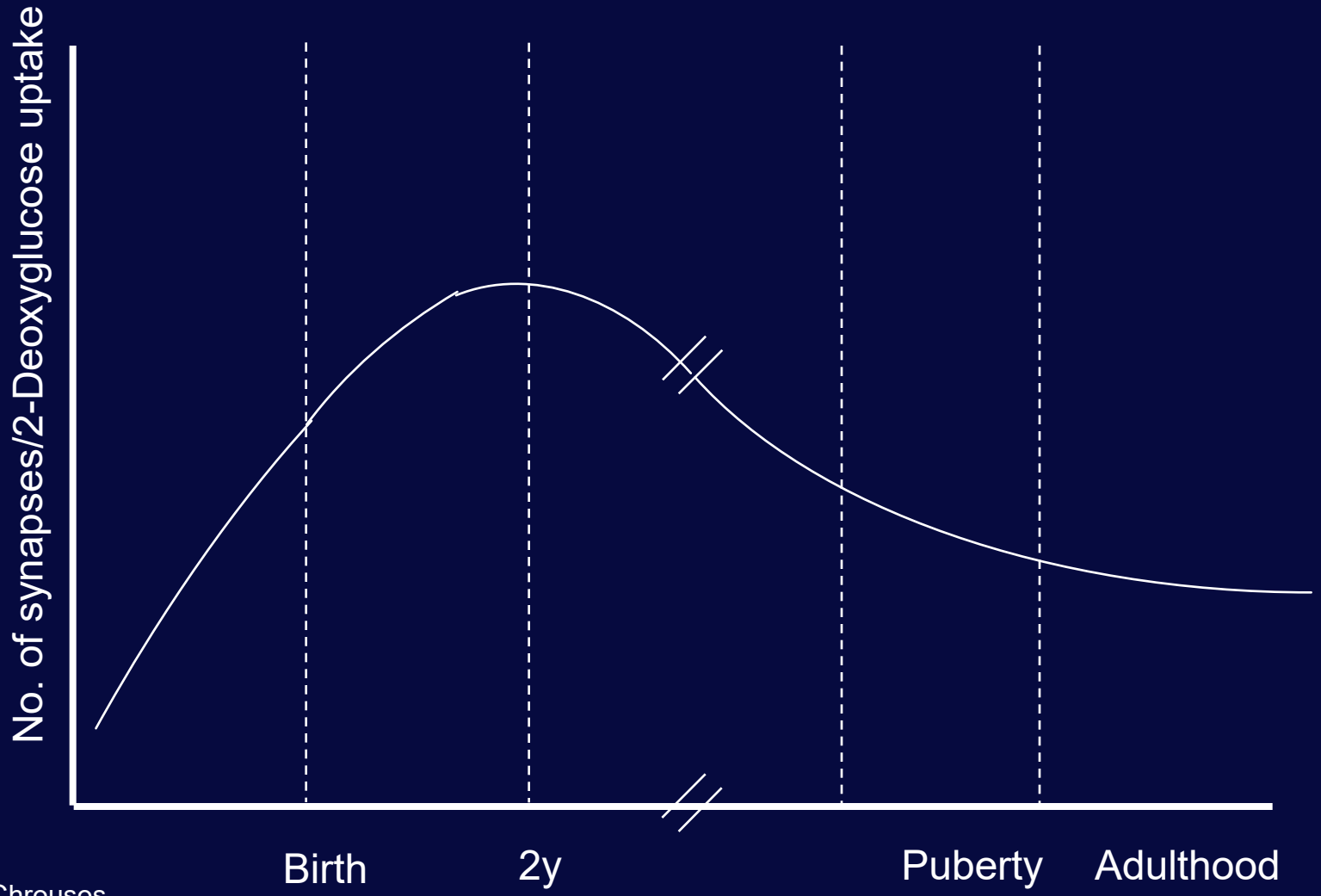
- **Timing** (Critical periods=prenatal, first 5 y and adolescence)
- **Acuity**
- **Chronicity**

Brain Growth and Child Age



Source: RAND Corporation

THE DEVELOPING BRAIN



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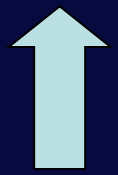
Cognitive and Language Development

Prefrontal/Frontal Lobe "Higher Functions"

- Interpretation of the environment, social cues
- Problem solving
- Planning for the future
- Proper control of impulses (emotional auto-regulation)

"CRITICAL" PERIODS OF LIFE

Prenatal, Early Childhood, Puberty
(Human brain ontogeny complete at 25-27 y)



"Organizational" Effects of Hormones, Epigenetics, "Predictive programming"

(CRH, glucocorticoids, sex steroids, cytokines)

Inflammatory Injurious Agents

- Microbial products
- Intracellular molecules (proteins, lipids, carbohydrates, nucleic acids)
- Denatured molecules (proteins, lipids, nutrients)

  Oxidation, nitrosylation, misfolding, etc.
- O and NO radicals
- Adducts
- Xenobiotics/Toxins

INNATE IMMUNITY-First Line of Defense-PRRs

Activated by engagement of germ-line encoded PRRs (Pattern Recognition Receptors)

PRRs recognize the presence of:

Microbial PAMPs (Pathogen-Associated Molecular Patterns)

Endogenous DAMPs (Danger-Associated Molecular Patterns)

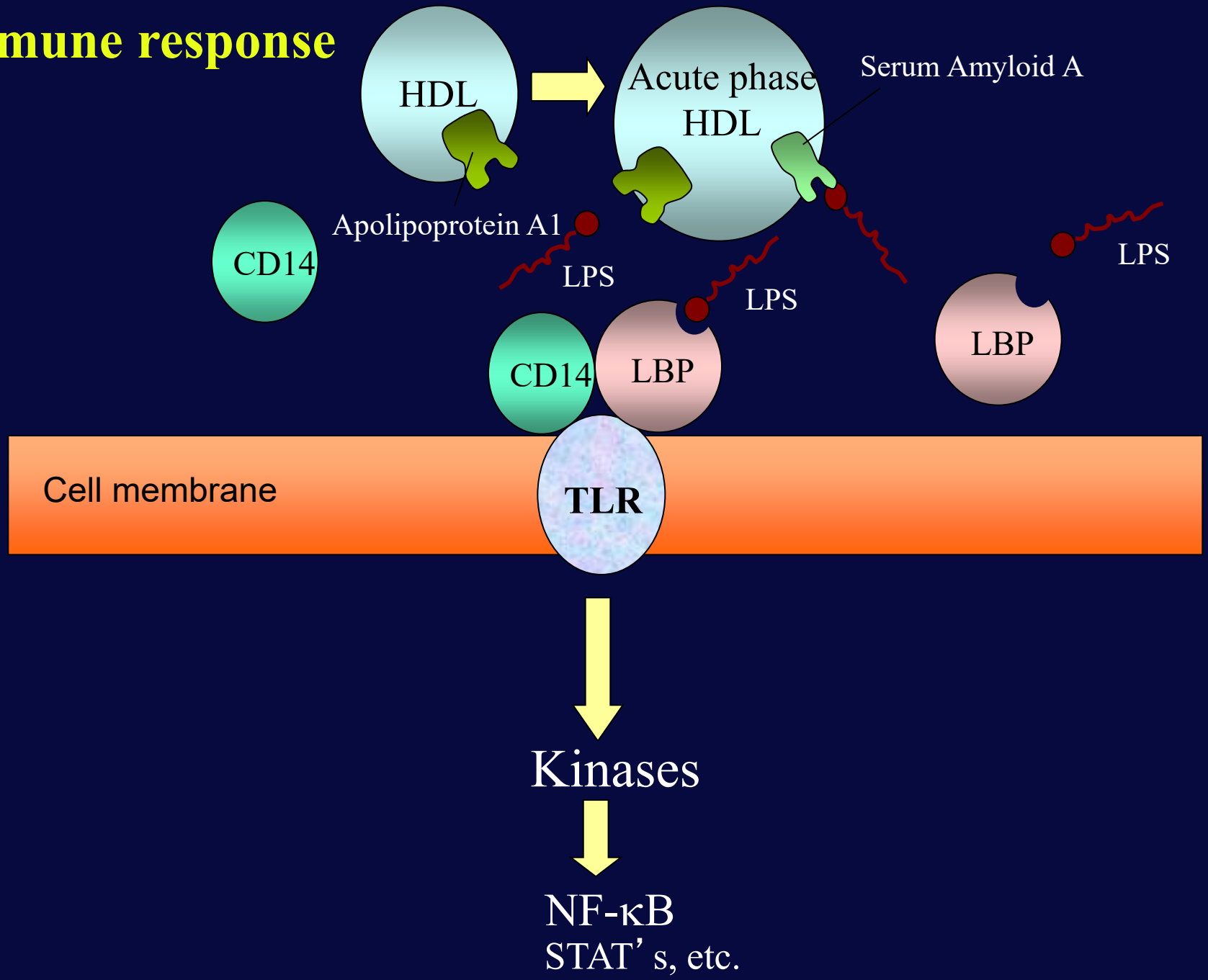
Pattern Recognition Receptors

- Toll-like Receptors (TLRs)
- RIG-1-like Receptors
- C-Type Lectin Receptors
- Nod-like Danger Receptors (NLDRs)

NF-KB NFAT STATs MAPKs

Inflammasome, caspase1, IL-1beta, IL-18

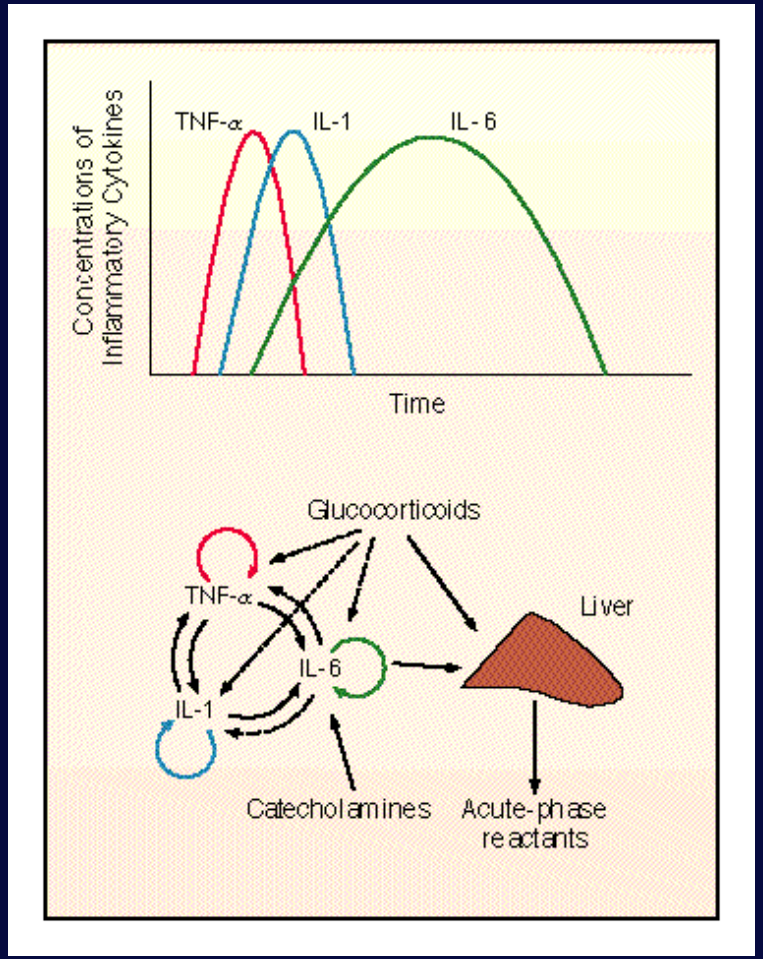
Immune response



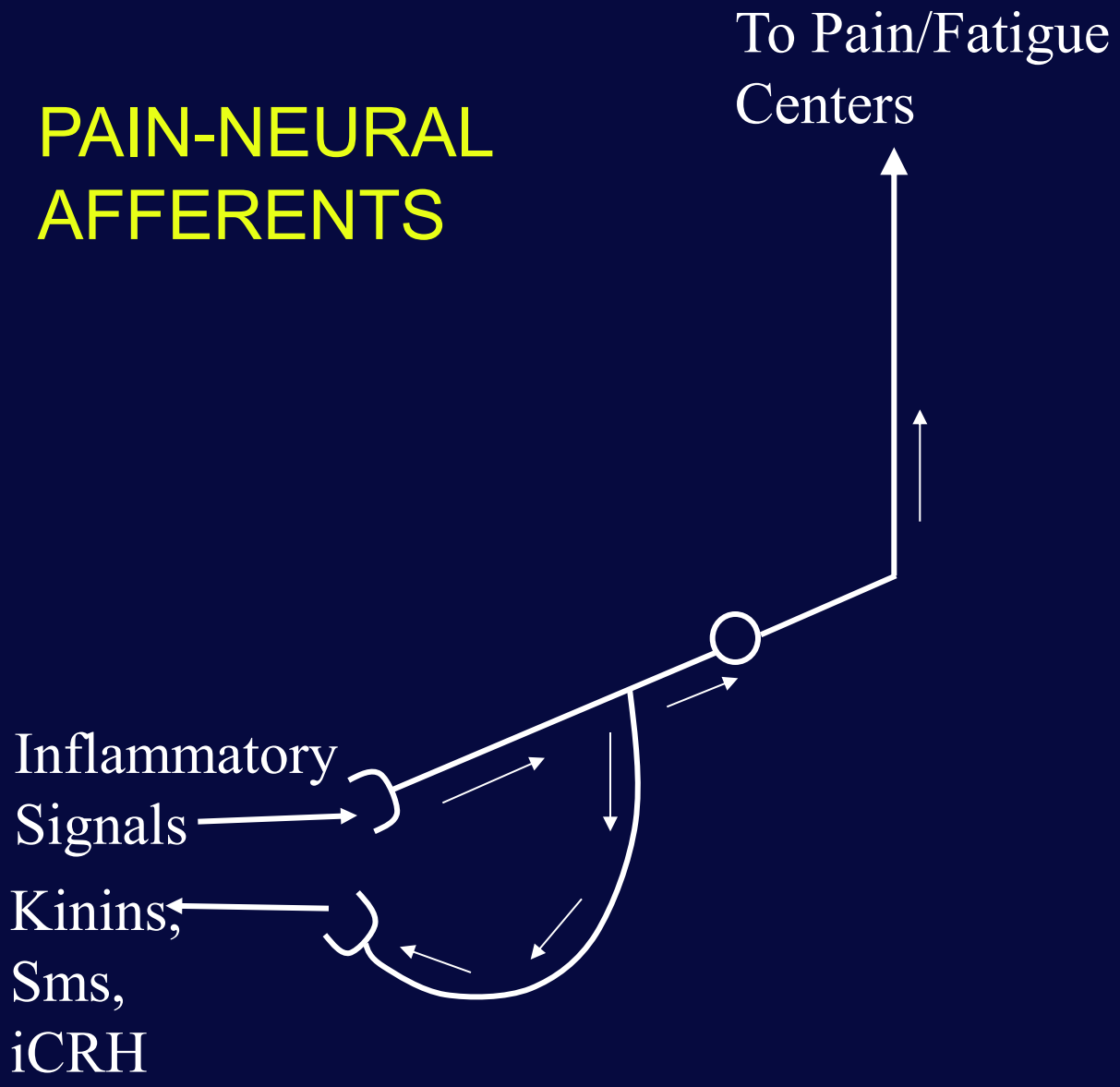
ACTIVATION OF IMMUNE AND IMMUNE ACCESSORY CELLS

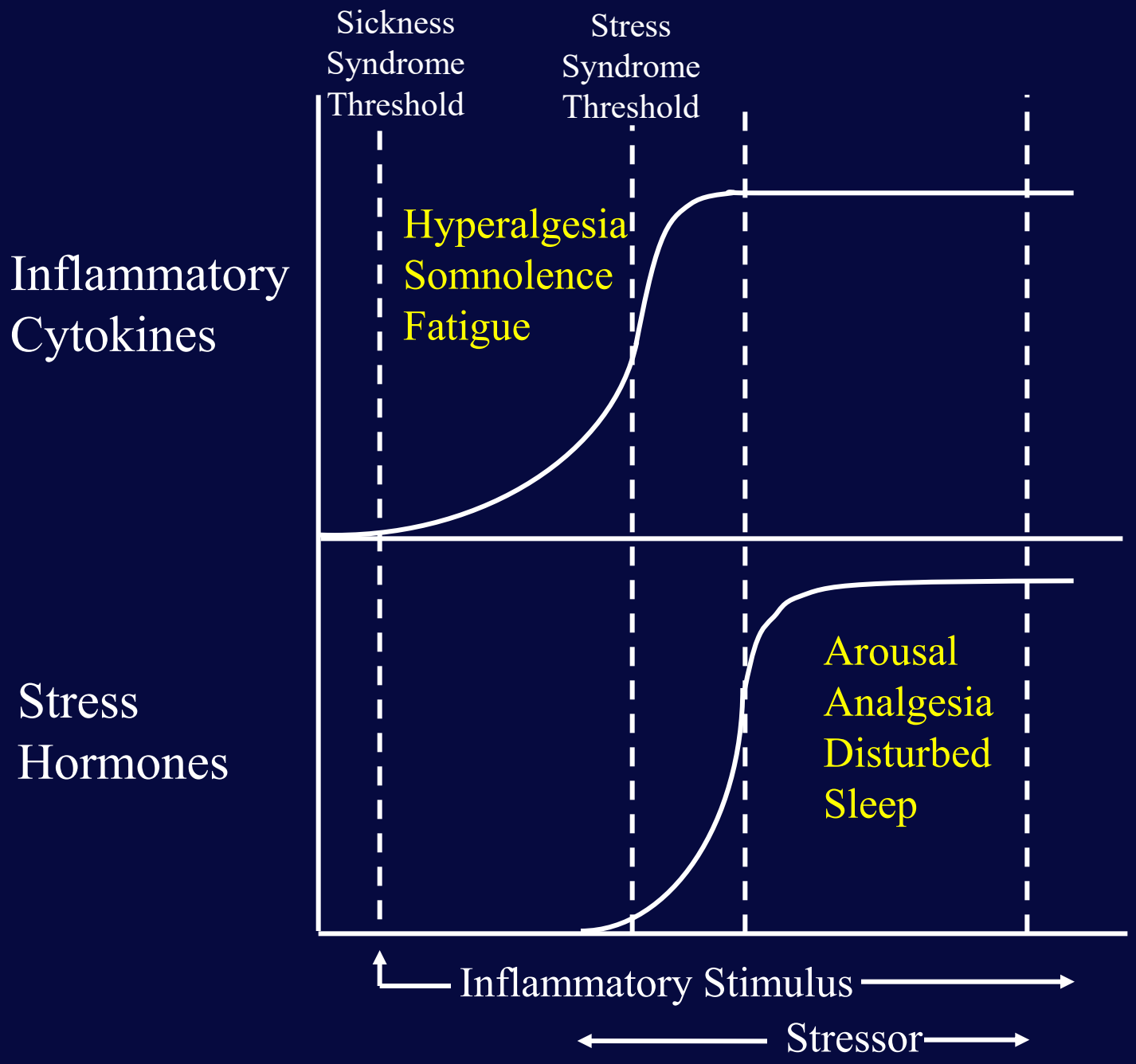
- INFLAMMATORY CYTOKINES: TNFα, IL-1, IL-6, IL-8 ....

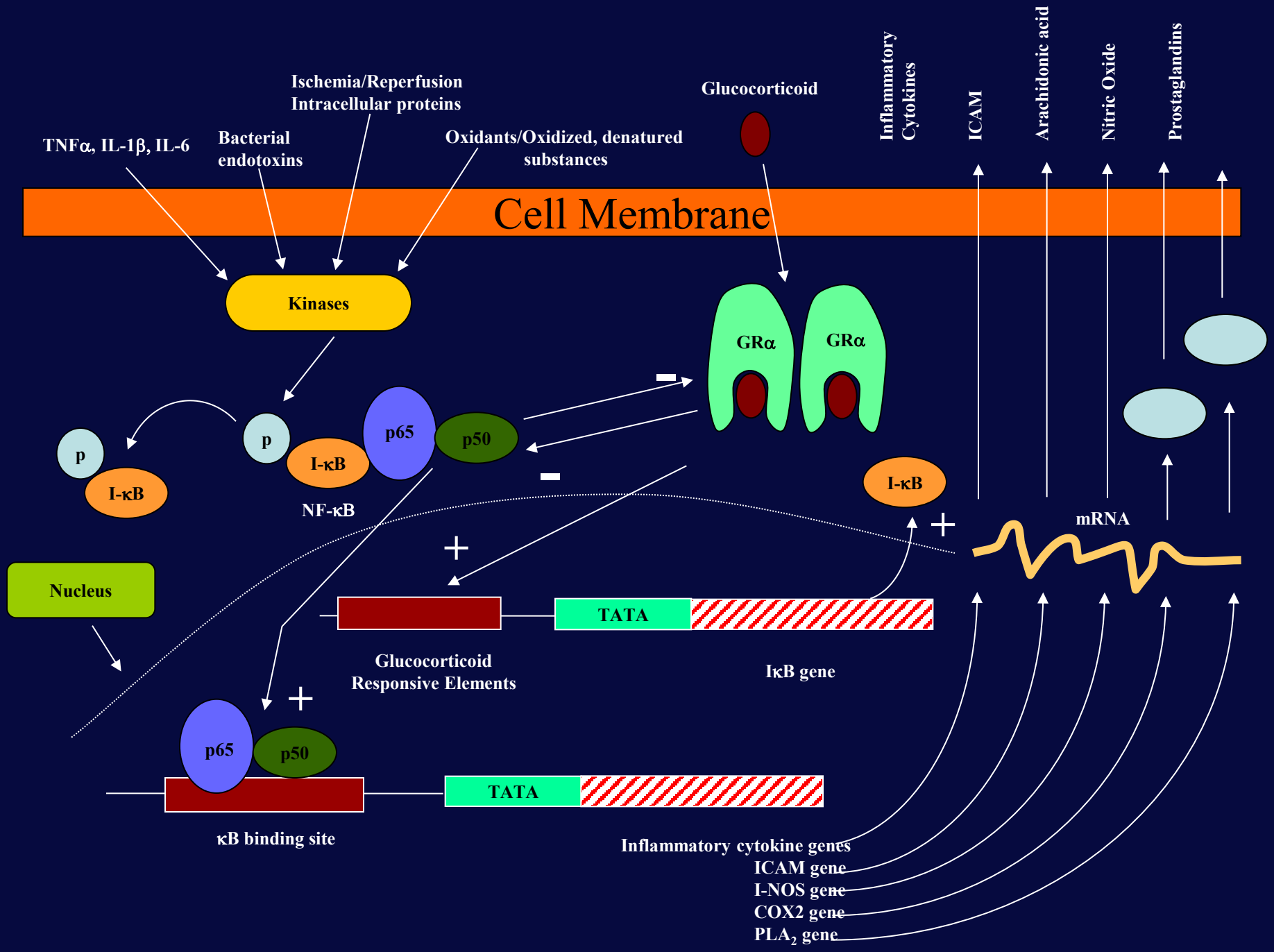
- OTHER MEDIATORS OF INFLAMMATION:
- Prostanoids, PAF ....



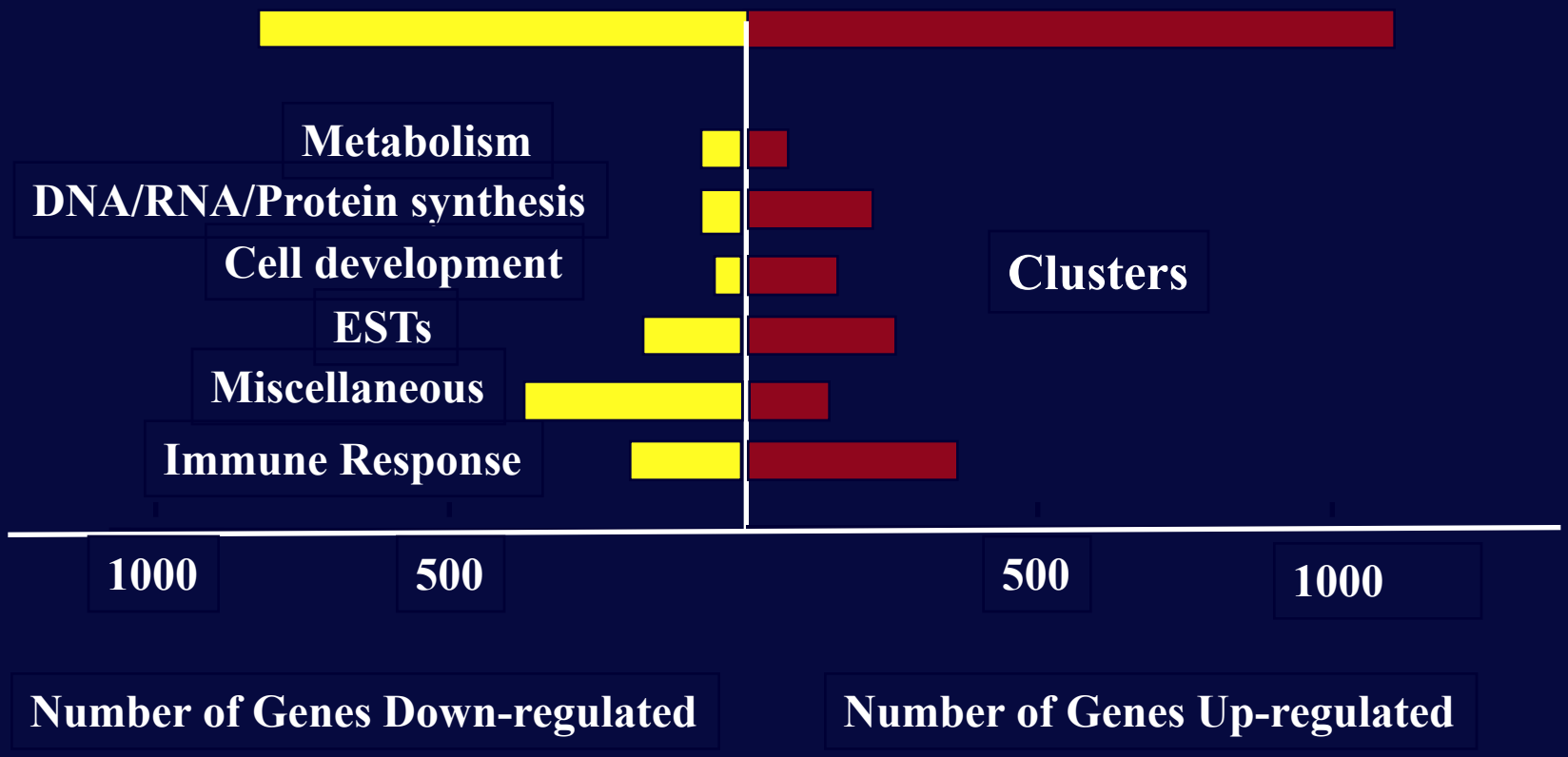
PAIN-NEURAL AFFERENTS

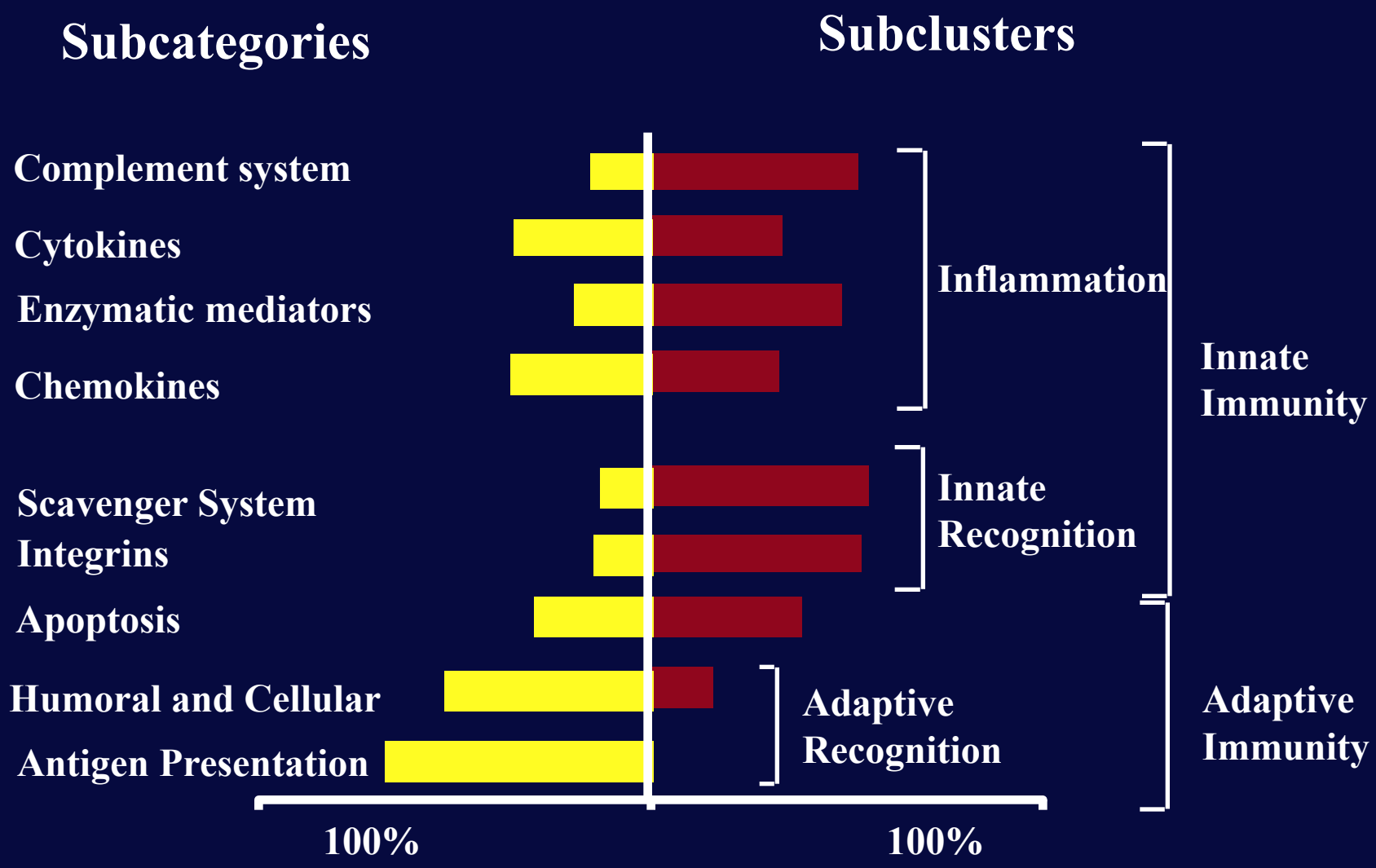



Sickness Syndrome Threshold
Stress Syndrome Threshold
Inflammatory Cytokines
Hyperalgesia
Somnolence
Fatigue
Stress Hormones
Arousal
Analgesia
Disturbed Sleep
Inflammatory Stimulus
Stressor

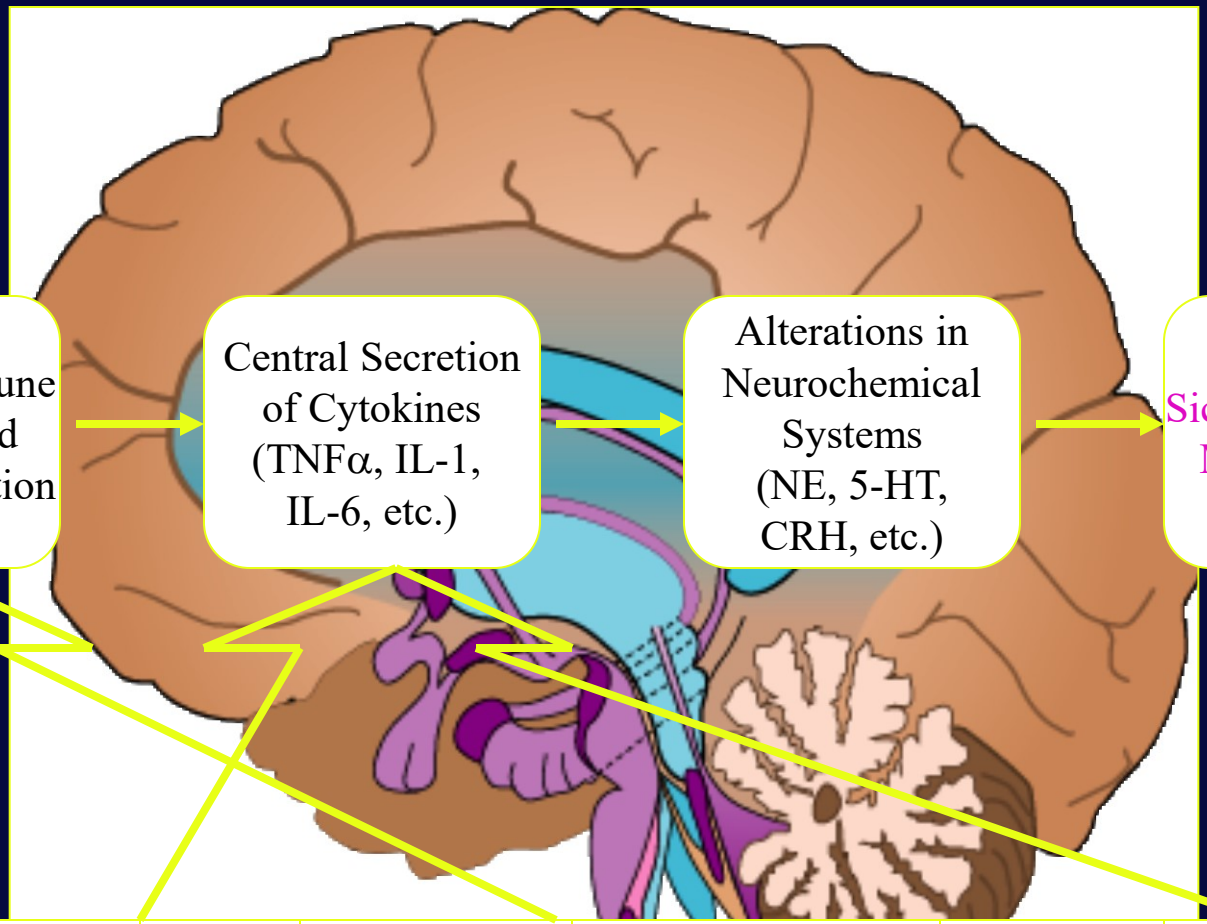

Inflammatory Cytokines
ICAM
Arachidonic acid
Nitric Oxide
Prostaglandins
Ischemia/Reperfusion Intracellular proteins
Glucocorticoid
TNFα, IL-1β, IL-6
Bacterial endotoxins
Oxidants/Oxidized, denatured substances
Cell Membrane
Kinases
GRα
GRα
p
I-κB
p65
p50
NF-κB
I-κB
mRNA
Nucleus
TATA
Glucocorticoid Responsive Elements
IκB gene
p65
p50
TATA
κB binding site
Inflammatory cytokine genes
ICAM gene
I-NOS gene
COX2 gene
PLA2 gene

Regulated genes





Galon ..Chrousos… FASEB 2002



Peripheral Immune Activation and Cytokine Secretion

Central Secretion of Cytokines (TNFα, IL-1, IL-6, etc.)

Alterations in Neurochemical Systems (NE, 5-HT, CRH, etc.)

Stress +/-
Sickness Syndrome Manifestations

Peripheral Infections

Post Partum Period

Stress

Autoimmune Disease

Neurodegenerative Disease

Stroke, Trauma

Intracerebral Infections

Epigenetics of Retrotransposons (Piwi protein-associated ncRNAs called piRNAs)

- *~60% of genome of retroviral origin*
- *10% of genome consists of Alu repeats*
- *10,000 HERV-K retrotransposons*
- *3,000-5,000 SVA retrotransposons*

The Piwi protein-piRNA pathway provides an adaptive defense in the transposon + viral arms race

Increasingly complex networks of small RNAs act through RNA-interference (RNAi) pathways to:

- restrain the spread of "selfish" genetic elements
- mediate antiviral responses
- regulate gene expression
- organize chromosomal domains

Chronic effects of stress system activation:

fatigue, pain (sickness behavior, stress behavior MUS)

smoldering para-inflammation, immune dysfunction, Th1 to Th2 shift, certain autoimmune disorders,

Vulnerability to certain infections and certain cancers

CHRONIC NONCOMMUNICABLE DISEASES

Chronic effects of stress system activation:

- **Vulnerability to certain infections**

  Viral: Common cold viruses

  Bacterial: Tuberculosis, Leprosy

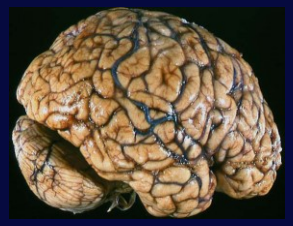
  Saprophytic infections

  Fungal

DEVELOPMENTAL HISTORY

STRESS
Real or perceived

GENETIC VARIATION



NUTRITION

AGING

Stress system
CRH/AVP-LC/NE

HPA axis

Systemic Sympathetic
Adrenomedullary Systems

↓GH/IGF-1
↓LH, T, E2
↓TSH, T_3

↑Cortisol

Target Tissues

NE, E, IL-6 ↑

Insulin resistance
Visceral Obesity/Sarcopenia
=Metabolic
Syndrome, DM type2

↑TG
↑LDL
↓HDL

ABP ↑

APR↑
Cytokines↑

Dyscoagulation

Sickness
Syndrome

Sleep Apnea

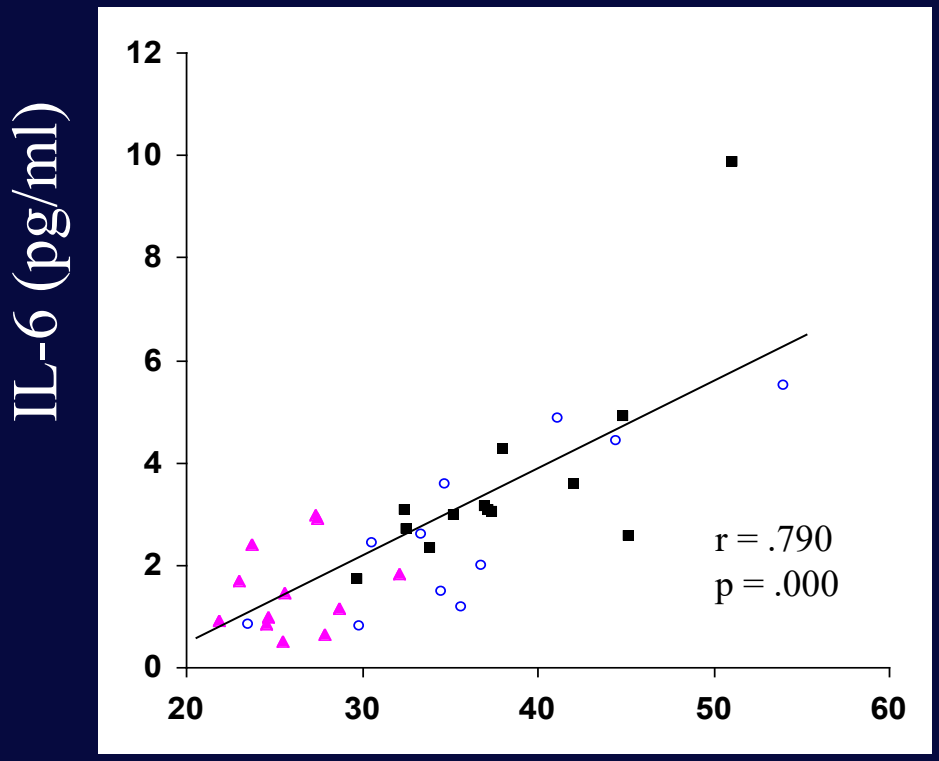
Osteoporosis

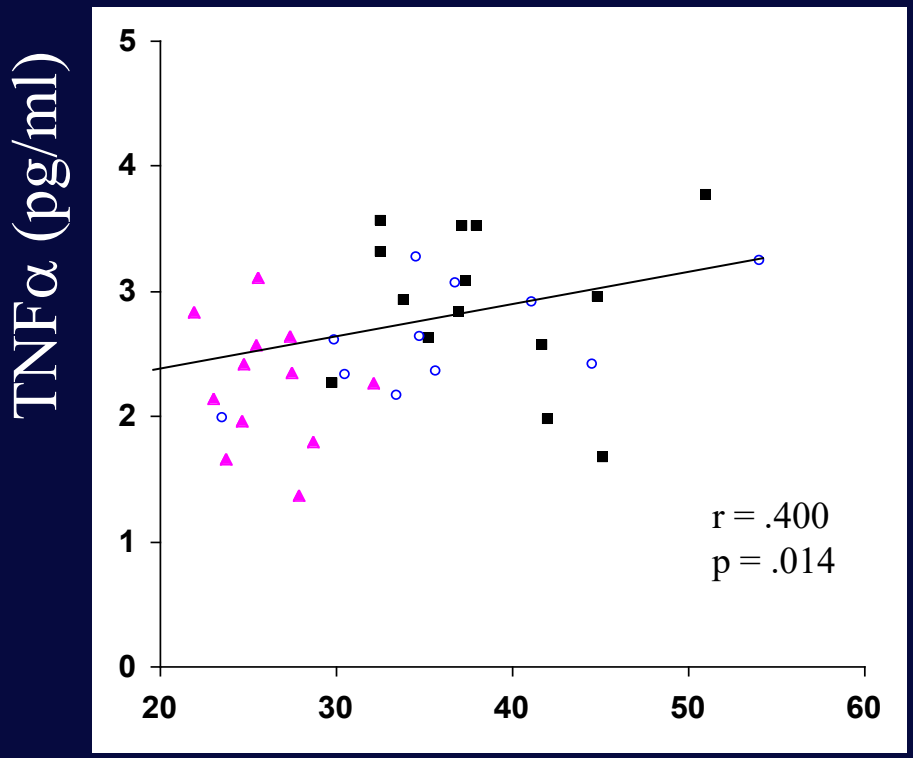
PCOS

Endothelial Dysfunction
Para-Inflammation/immune Dysfunction/Th1 to Th2

Atherosclerosis
Cardiovascular Disease

Both IL-6 and TNFα correlate with BMI





BMI

Vgontzas *et al.* JCEM 1997

HYPERCYTOKINEMIA

TRAUMA/ BURNS

INFECTIOUS ILLNESSES

AUTOIMMUNE INFLAMMATORY DISEASES

ALLERGIC INFLAMMATIONS

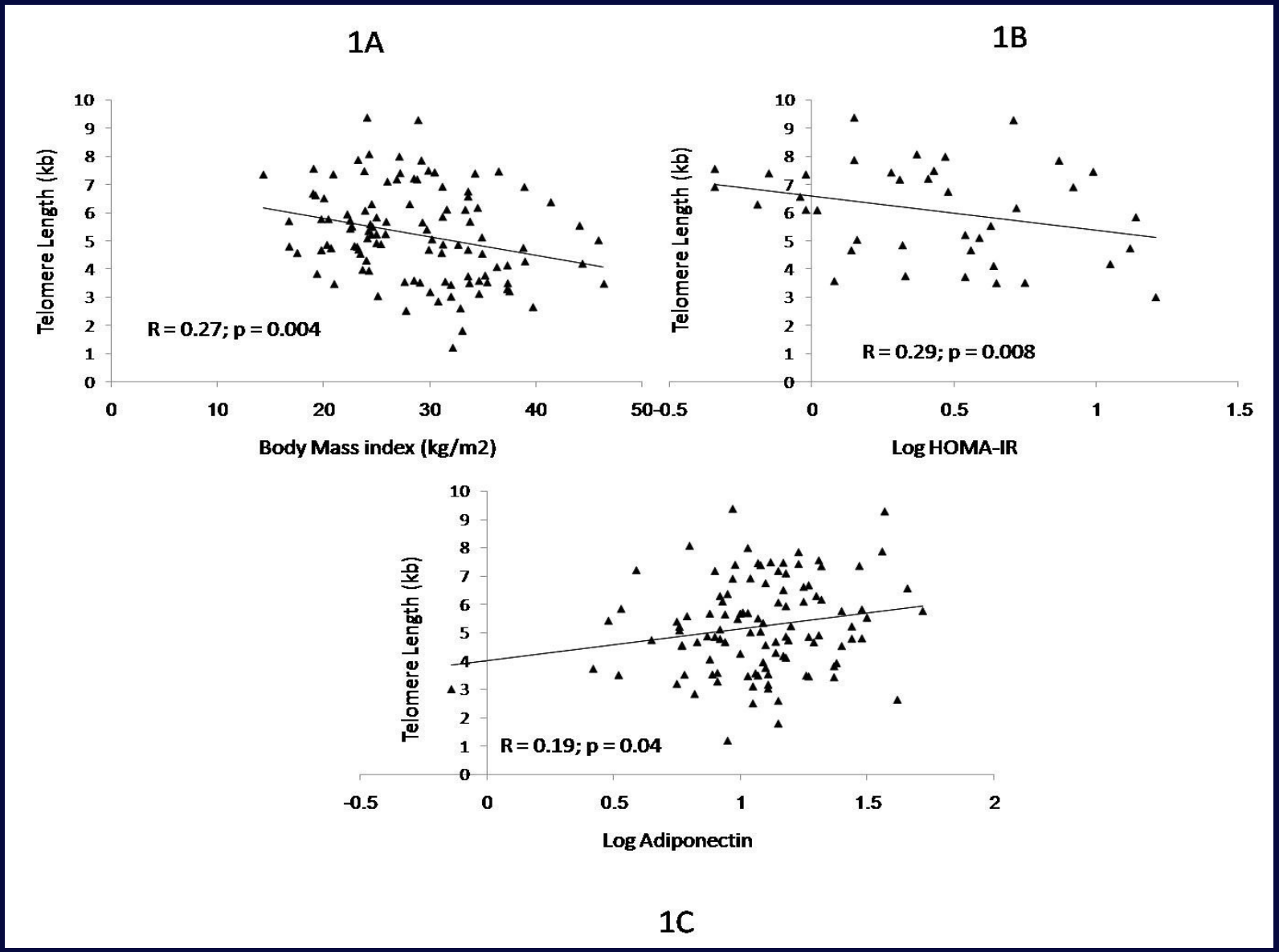
CNS INFLAMMATIONS

NONINFLAMMATORY STRESS

OBESITY/VISCERAL OBESITY

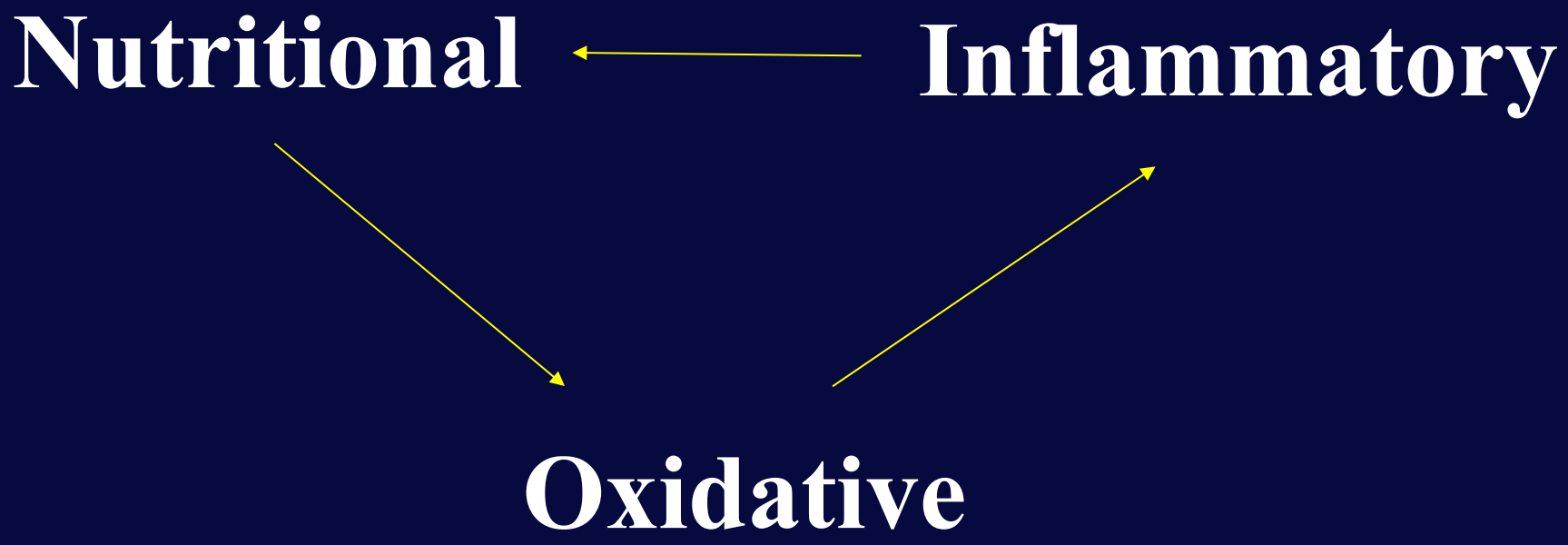
AGING


SPL

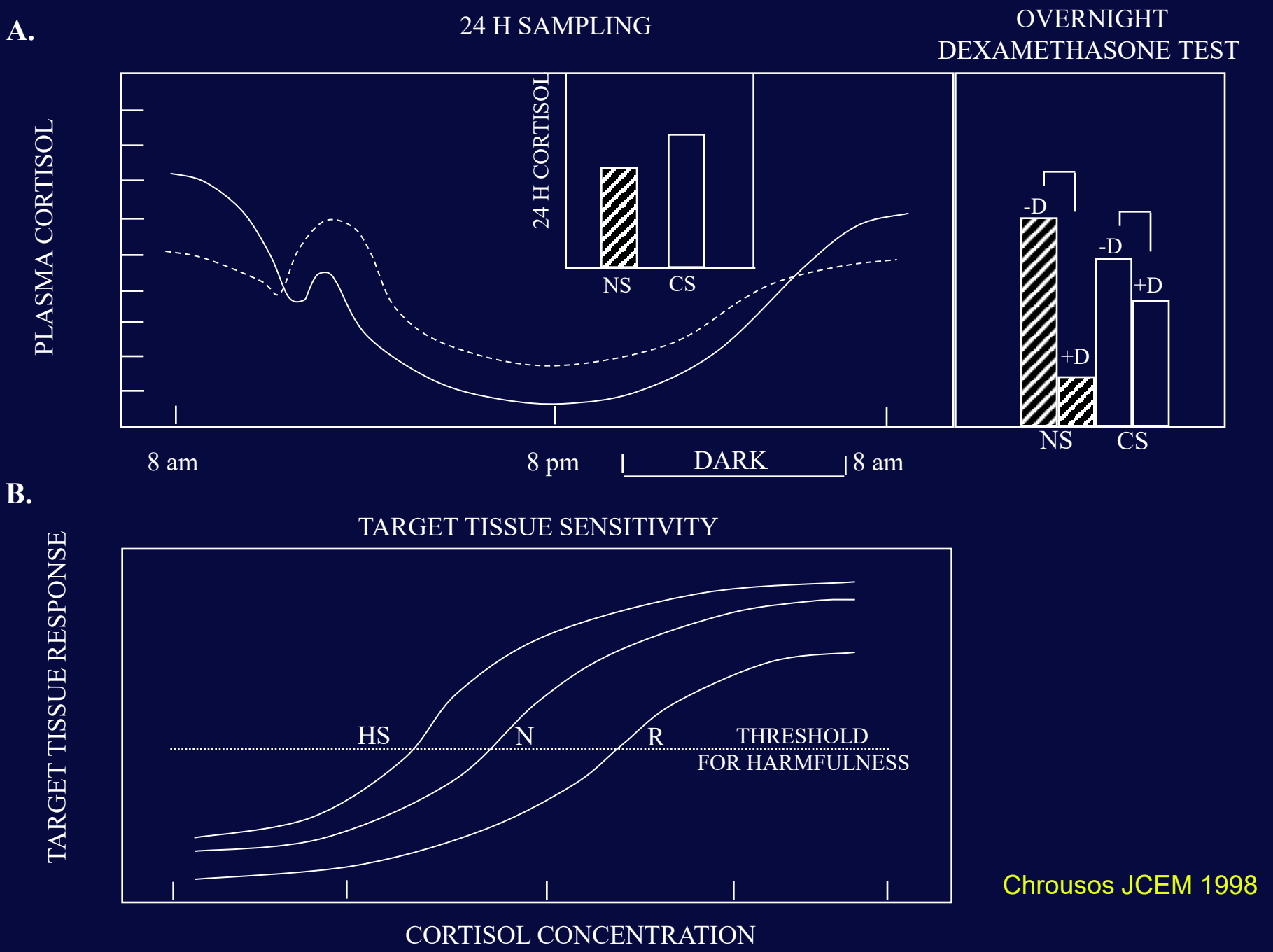


Al-Attas et al. 2010

Cellular Stress

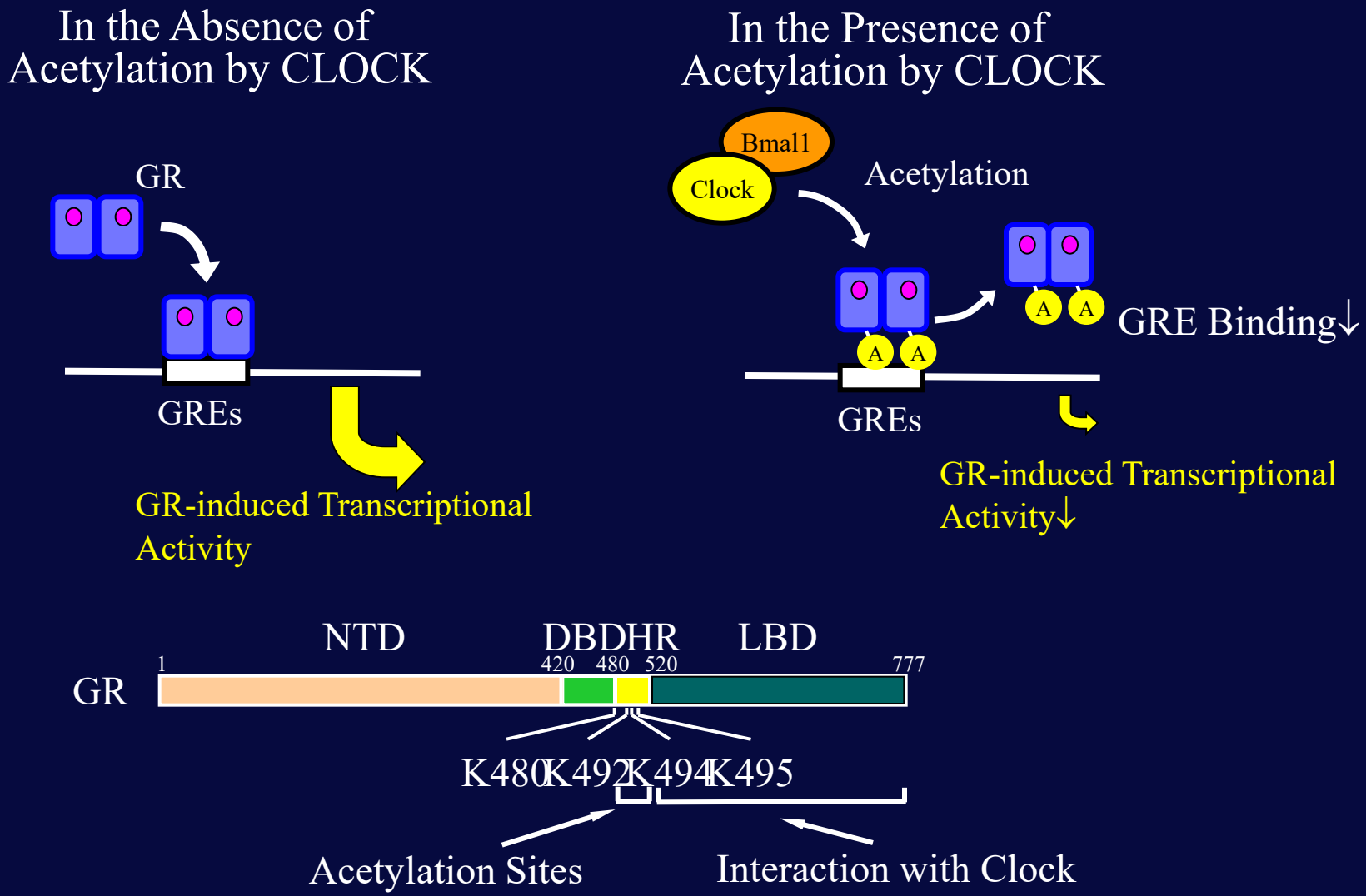


Cellular Stress

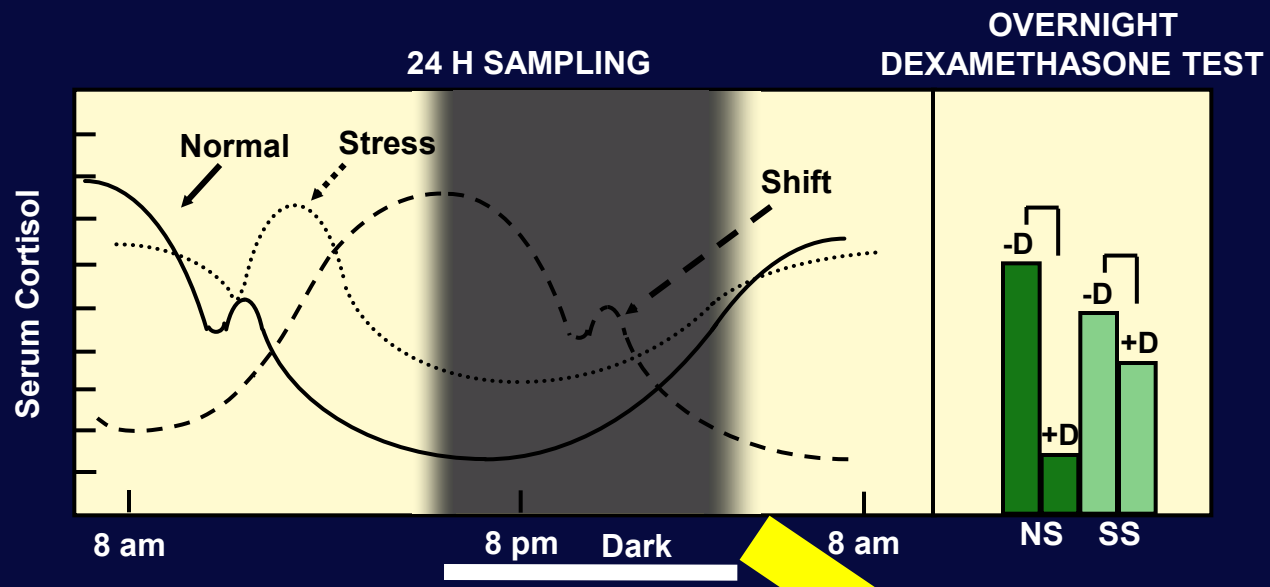


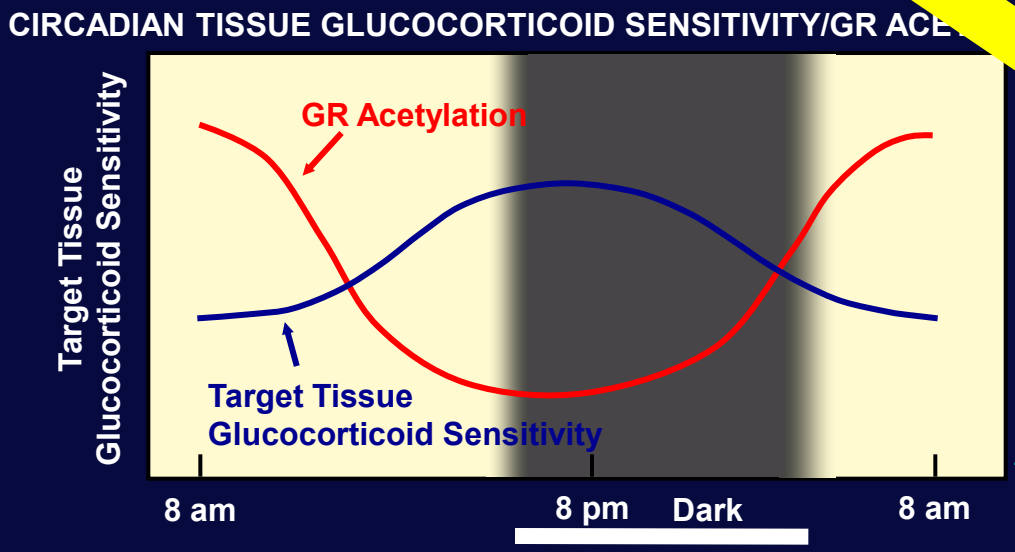
Chrousos JCEM 1998

Results #1: Clock/Bmal1 Represses GR Transcriptional Activity through Acetylation



Uncoupling between Circadian Rhythm of Serum Cortisol and Tissue Glucocorticoid Sensitivity





Functional Glucocorticoid Hypersensitivity

Pathologic Consequences