

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,

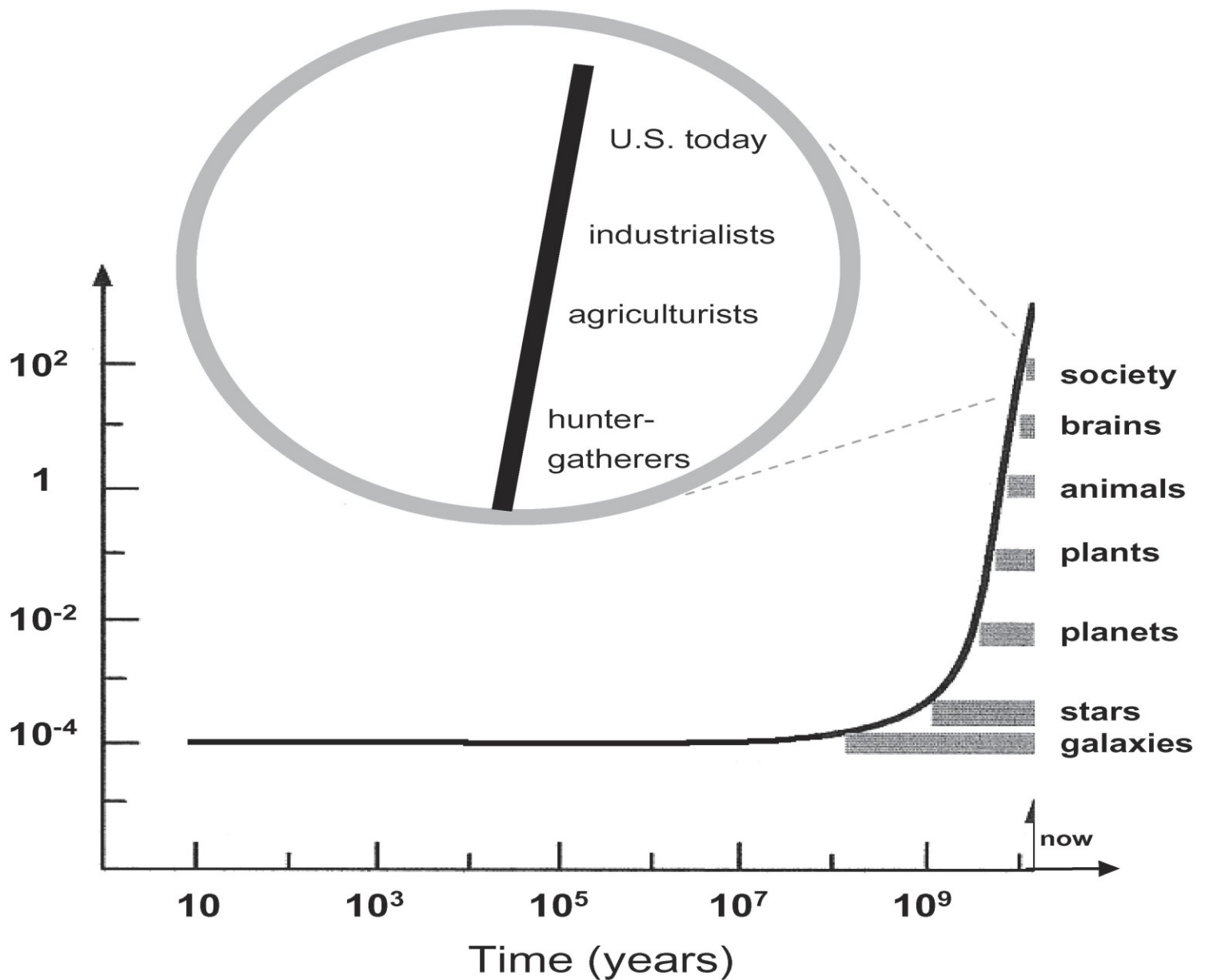
EPIGENETICS/EPIMUTATIONS

HUMAN COMPLEXITY: SOME HUMAN BRAIN NUMBERS

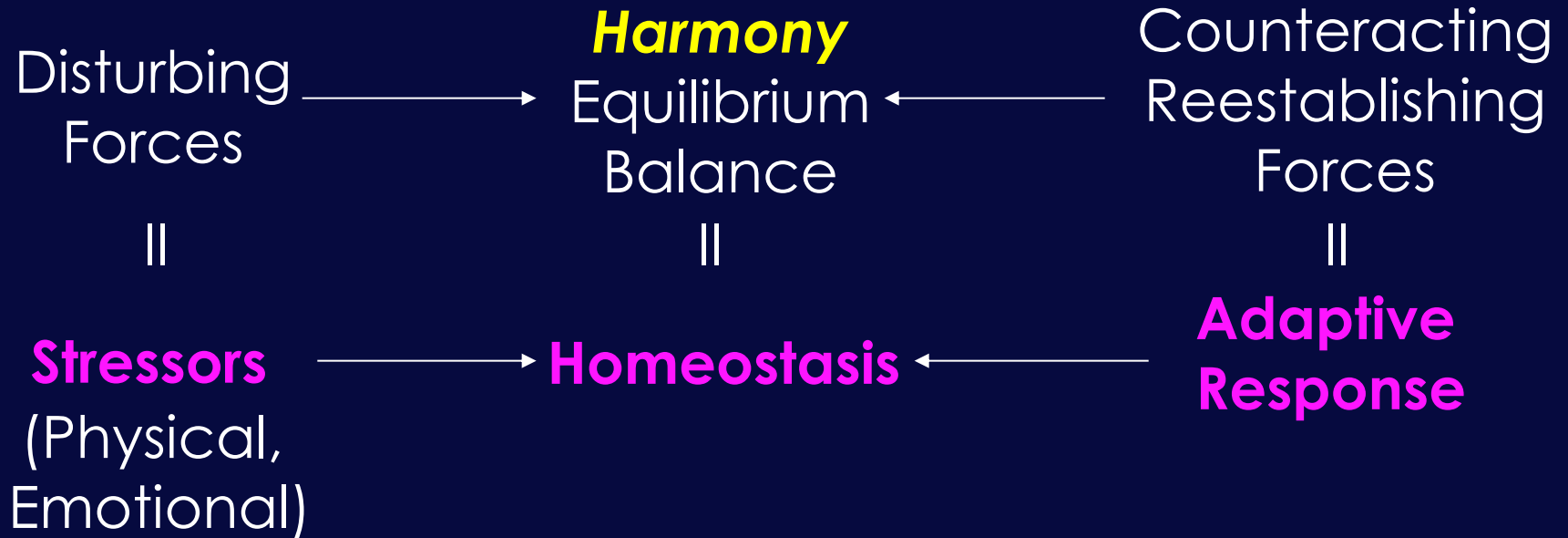
- ~ 100 billion neurons (100×10^{12}) x >10.000 synapses per neuron = **>10¹⁸ synapses**
- ~ 100.000 km of fibers
- ~ 1 trillion or more glial cells
- ~ 1.25 terabytes
- ~ 15 Watt lamp (2% of BW uses 20% energy)

Plasticity

Power density
(W/kg)



Complex Systems Theory



Pythagoras= *Harmony*

Alcmaeon= *Iso-nomia*

Epicurus= *Eustatheia*

Walter Cannon= *Homeostasis*

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

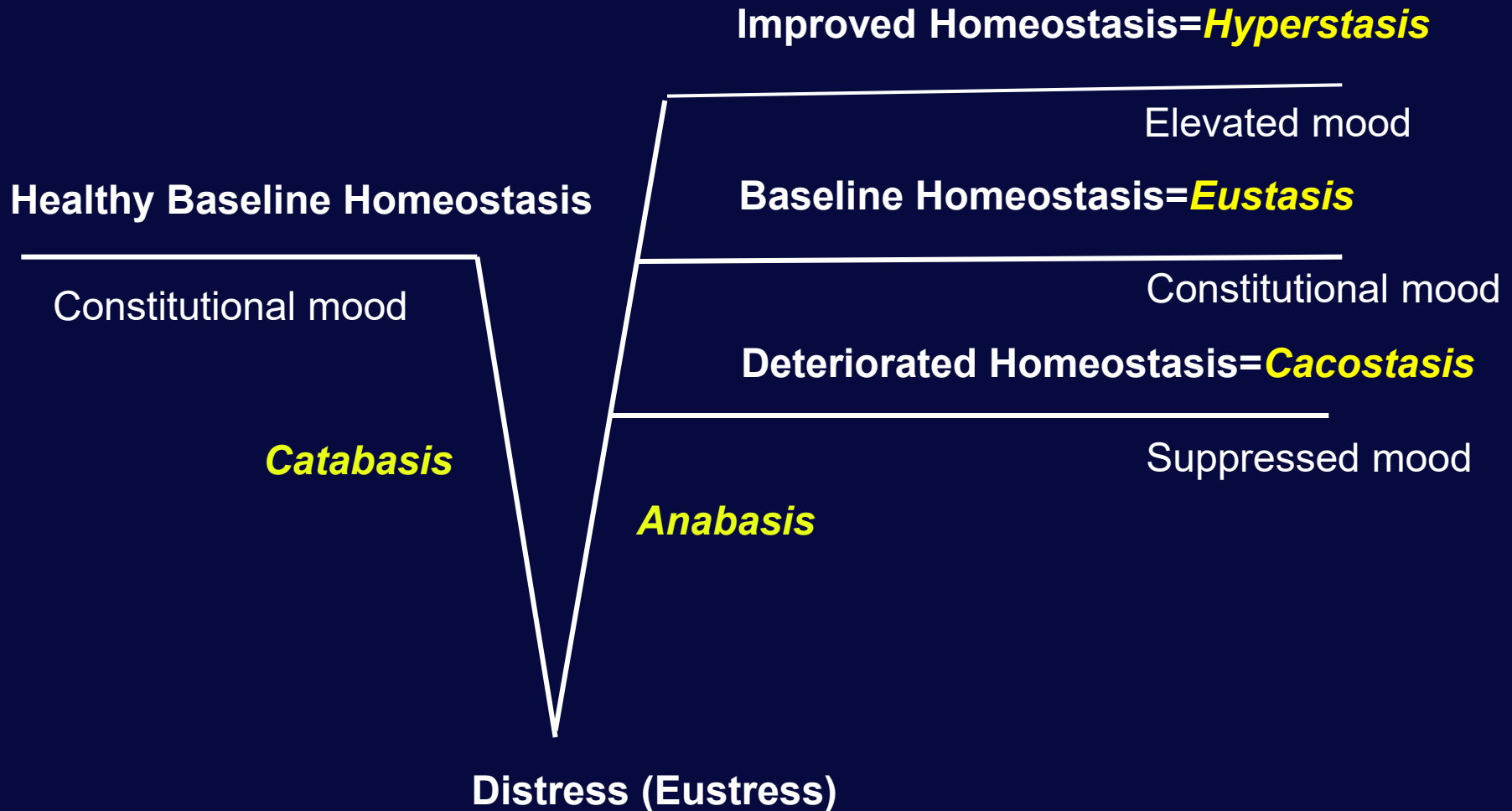
STRESS ETYMOLOGY

Indoeuropean root:

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

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

Homeostasis over Time



Homeostasis over Time

Resilience=
-Small disturbance
-Quick recovery

Improved Homeostasis=**Hyperstasis**

Healthy Baseline Homeostasis

Baseline Homeostasis=**Eustasis**

Constitutional mood

Elevated mood

Constitutional mood

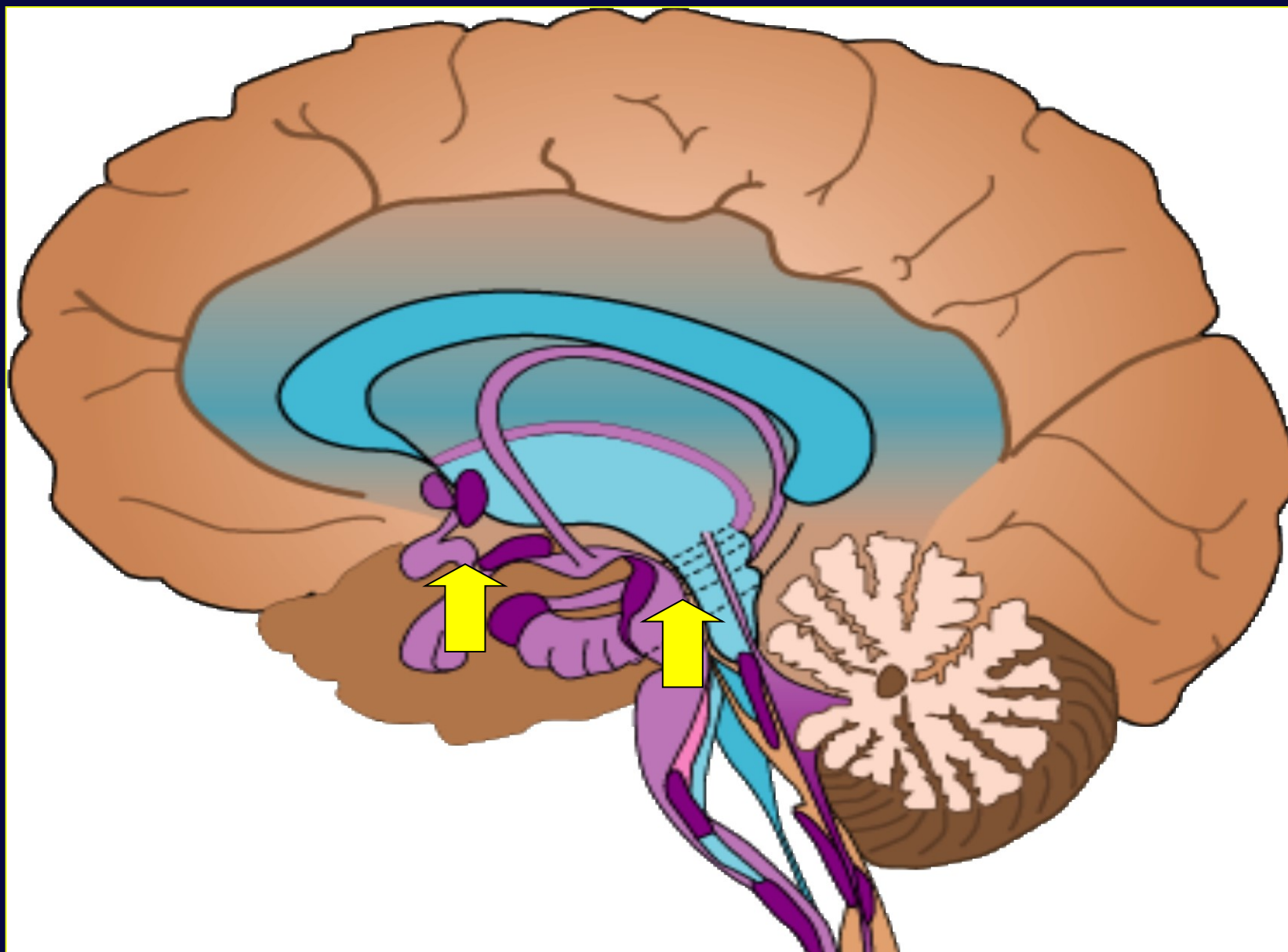
Deteriorated Homeostasis=**Cacostasis**

Suppressed mood

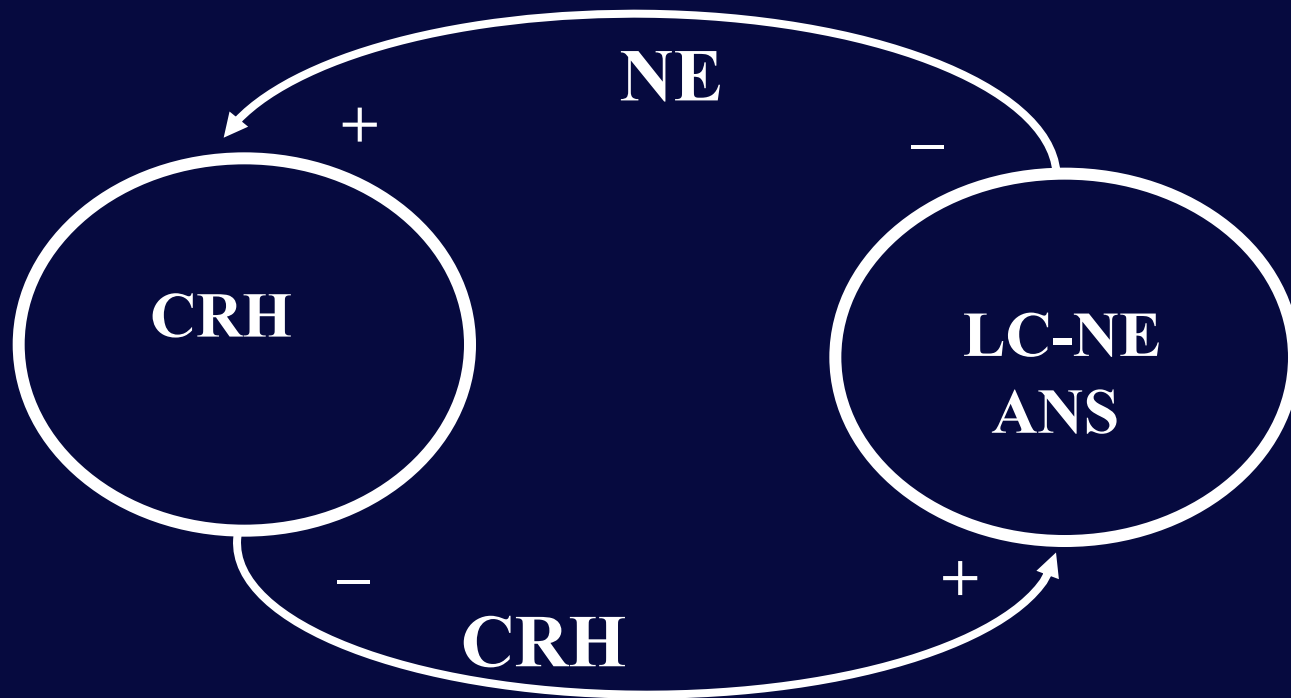
Catabasis

Anabasis

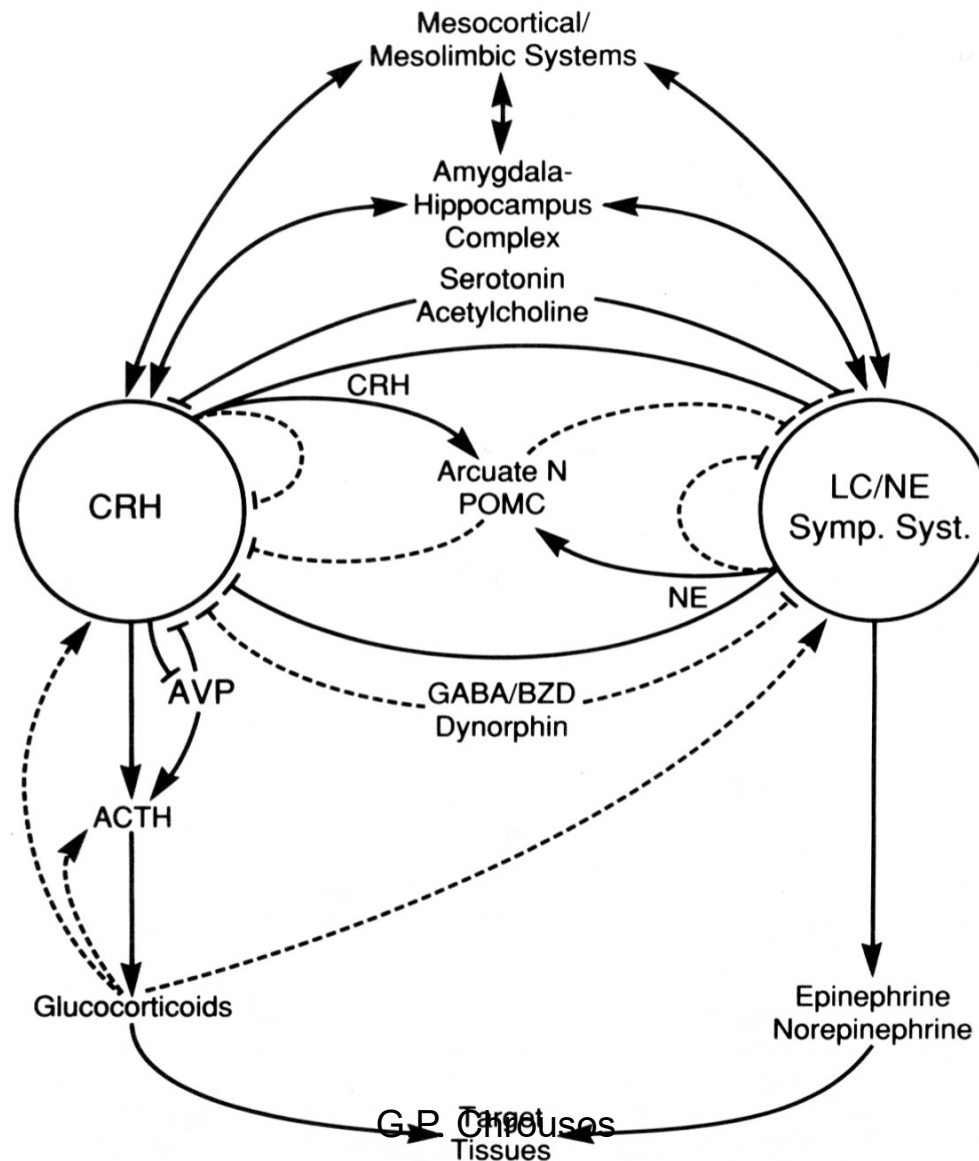
Distress/Eustress



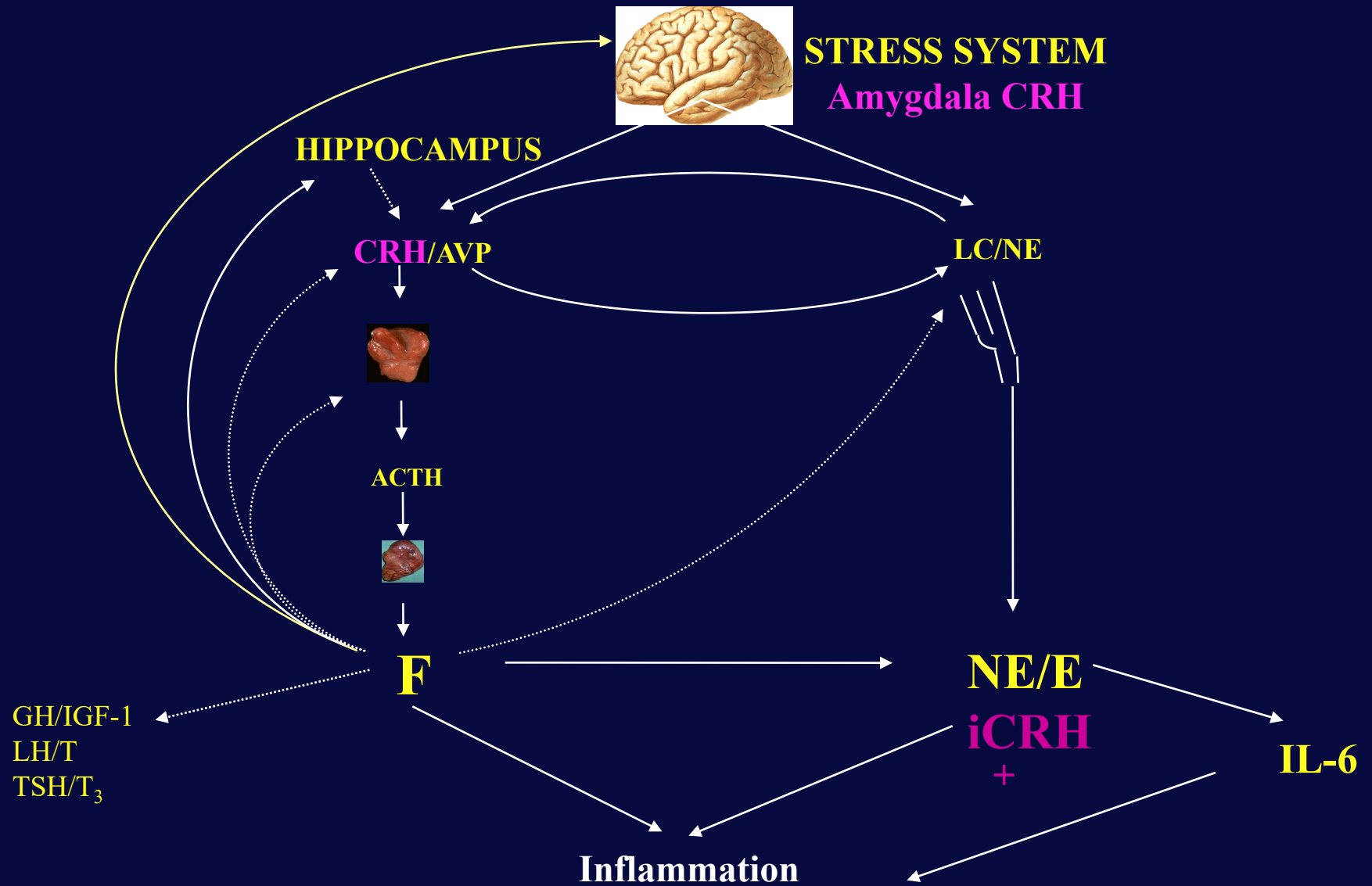
Stress System



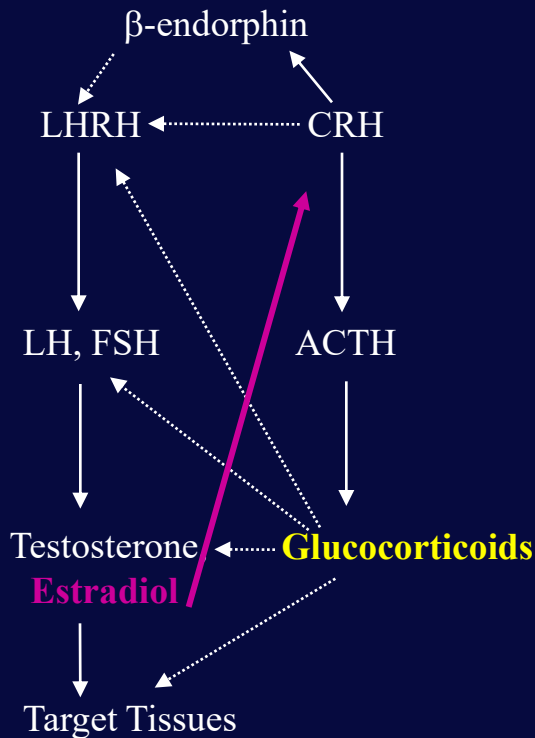
Stress System



Chrousos
JAMA 1992

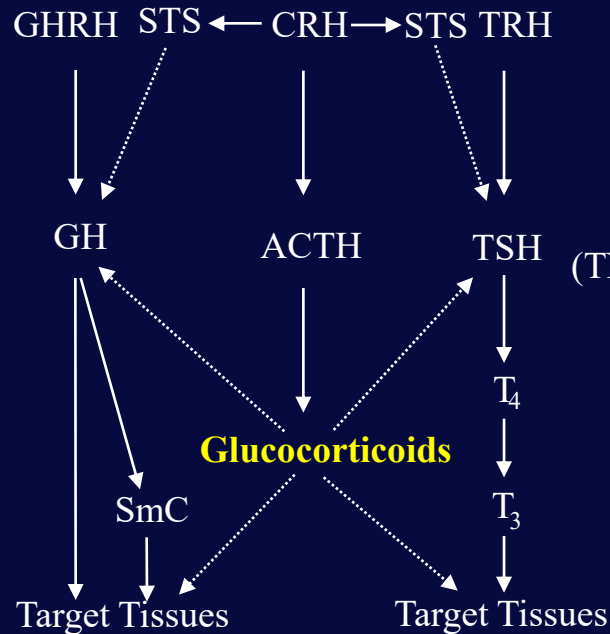


Reproduction



HYPOGONADISM

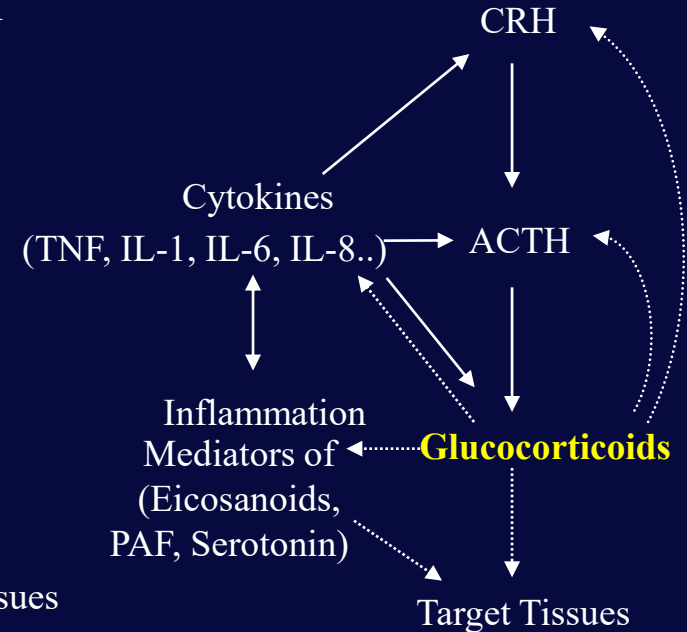
Growth and Thyroid Function



POOR GROWTH

“EUTHYROID SICK”

Immune Function



**INFLAMMATION,
ANTI-INFLAMMATION,
Th1 to TH2 SHIFT
PARAINFLAMMATION**

Ligand

Cell Membrane

Ligand Binding

GR

HSPs/FKBPs

Import

Nucleus

Transactivation /Transrepression

Assembly

Export

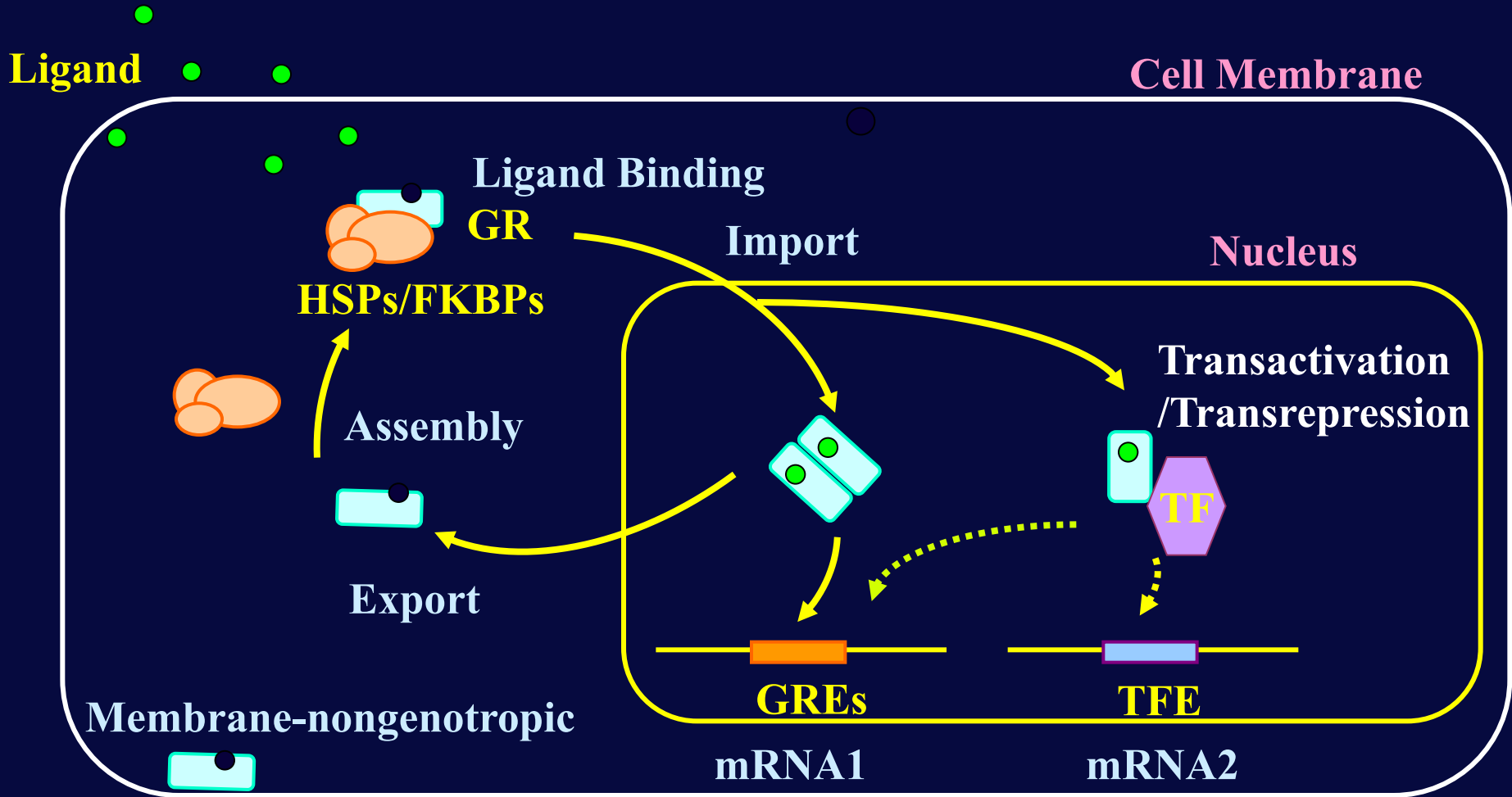
Membrane-nongenotropic

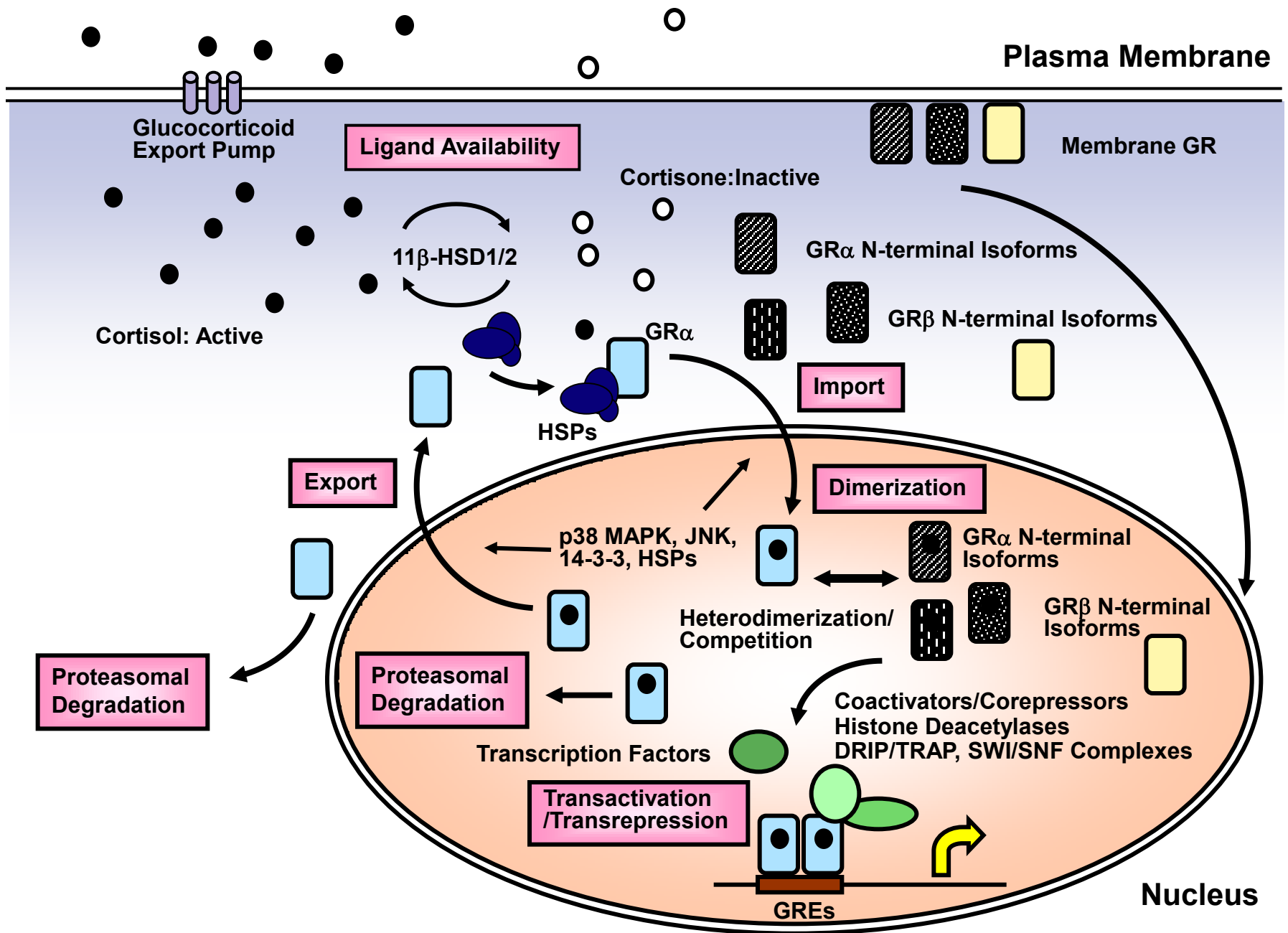
GREs

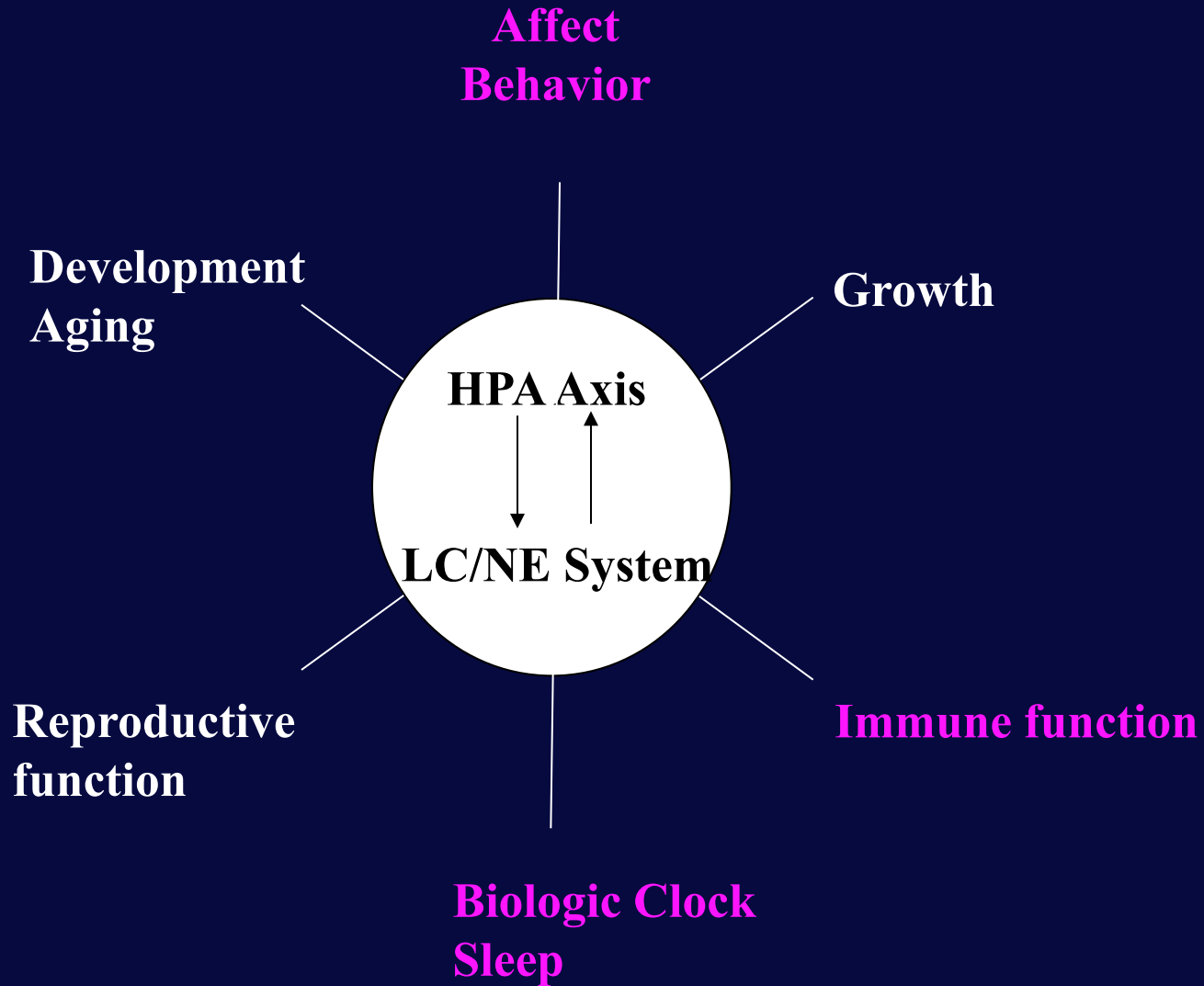
TFE

mRNA1

mRNA2



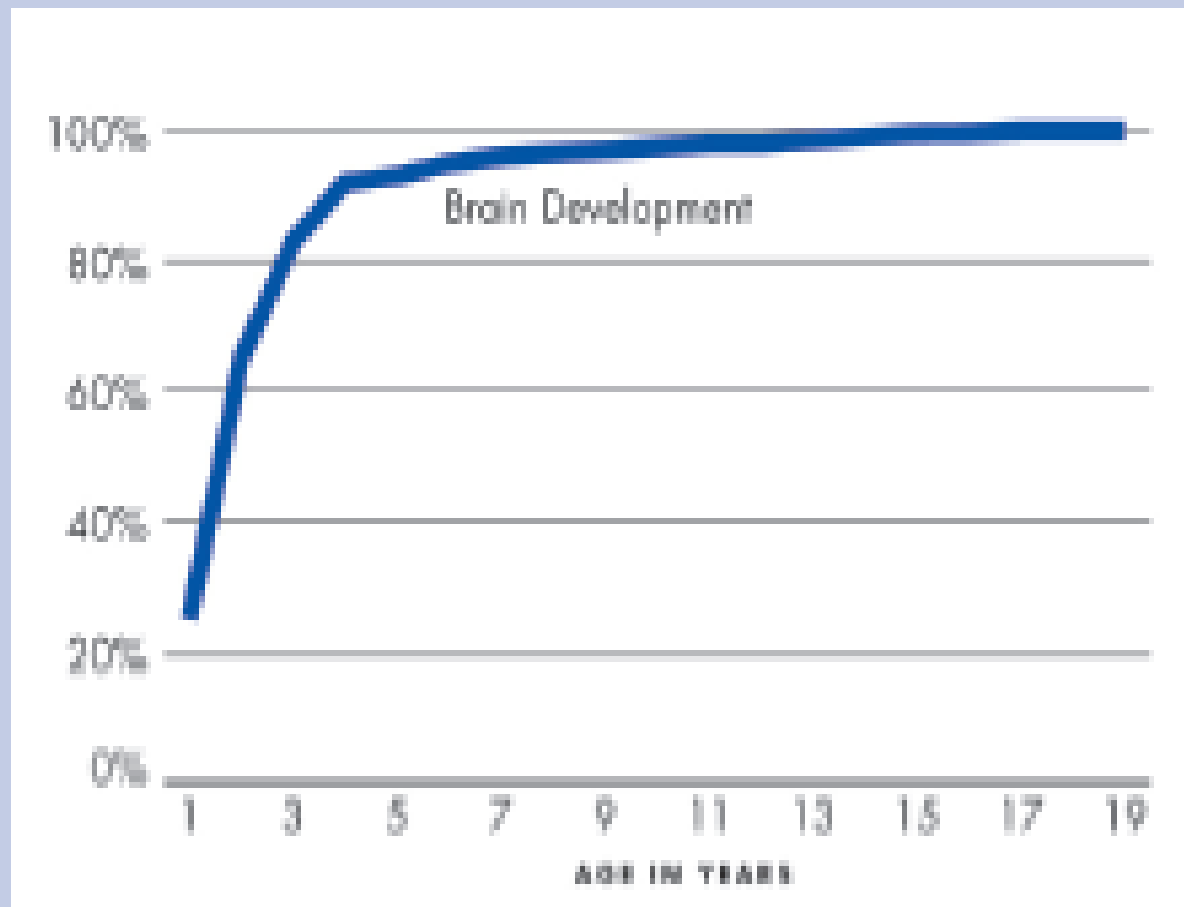




Physical and Emotional Stress Pathophysiology

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

Brain Growth and Child Age



Source: RAND Corporation

THE DEVELOPING BRAIN



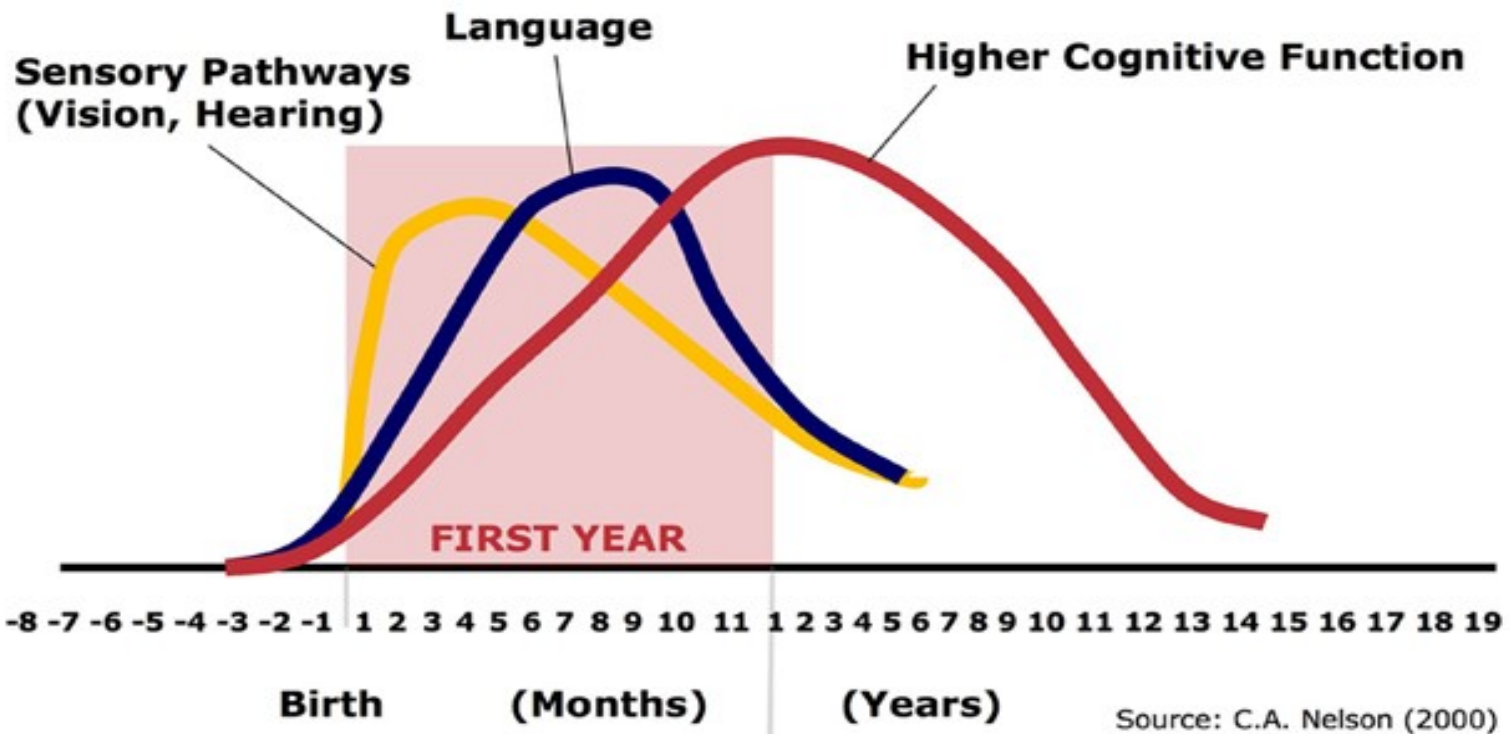
Cognitive and Language Development



Center on the Developing Child
HARVARD UNIVERSITY

Human Brain Development

Neural Connections for Different Functions Develop Sequentially



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

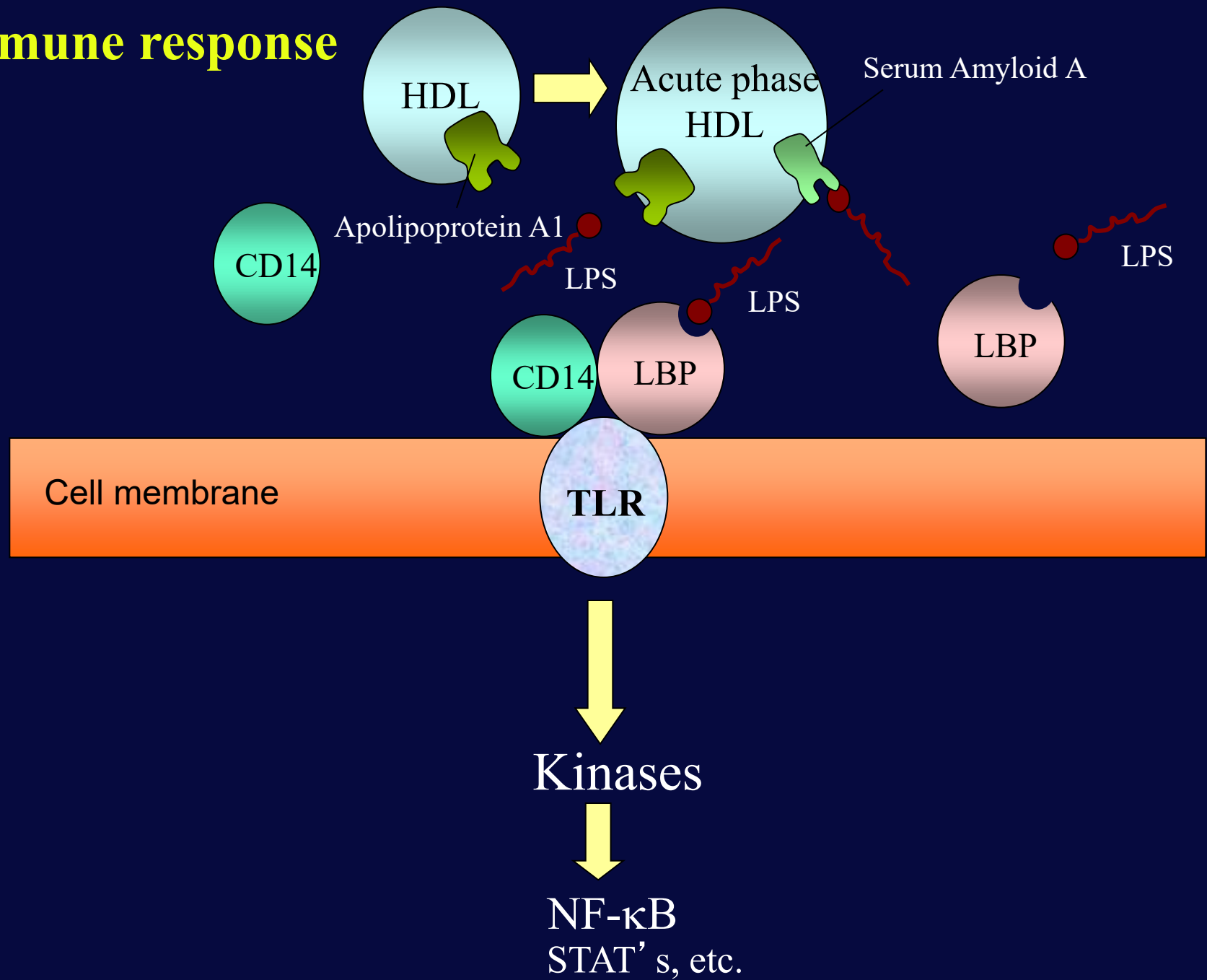
- Toll-like Receptors (TLRs)
- RIG-1-like Receptors
- C-Type Lectin Receptors
- Nod-like Danger Receptors (NLDRs)



NF-KB NFAT STATs MAPKs

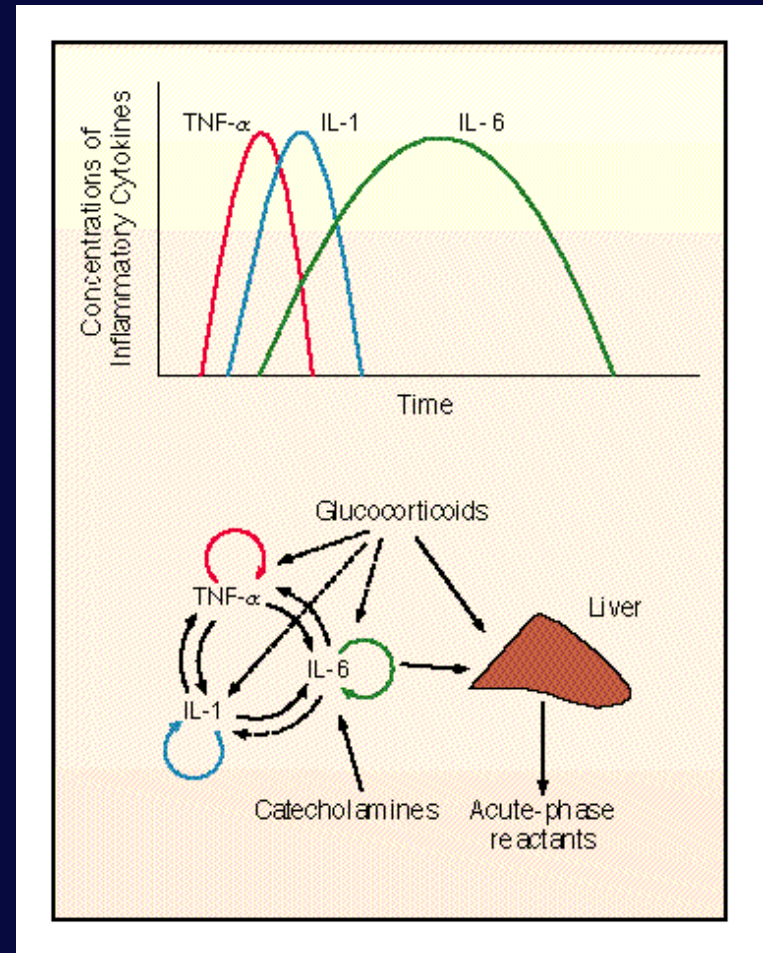
Inflammasome, caspase1, IL-1beta, IL-18

Immune response

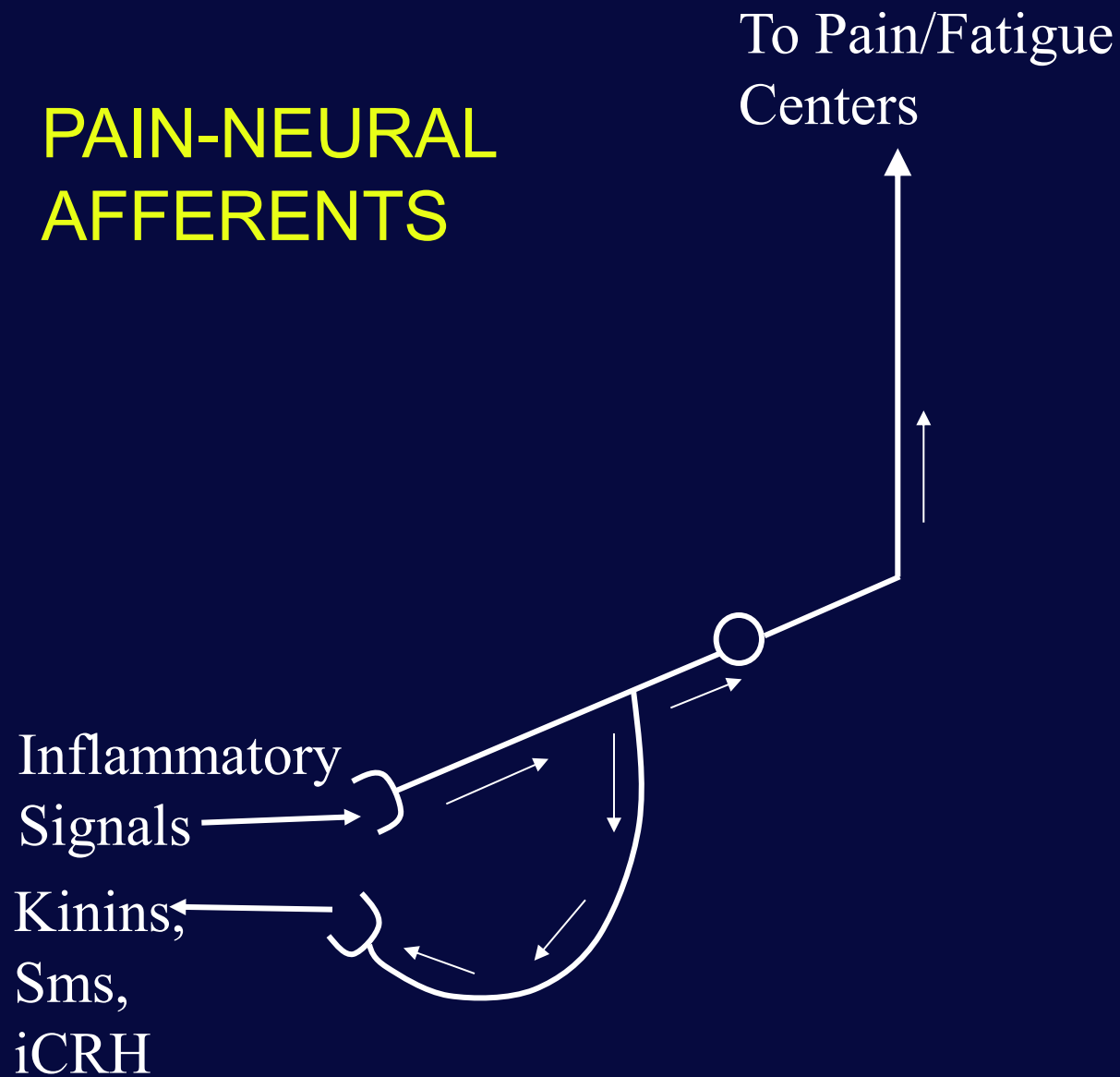


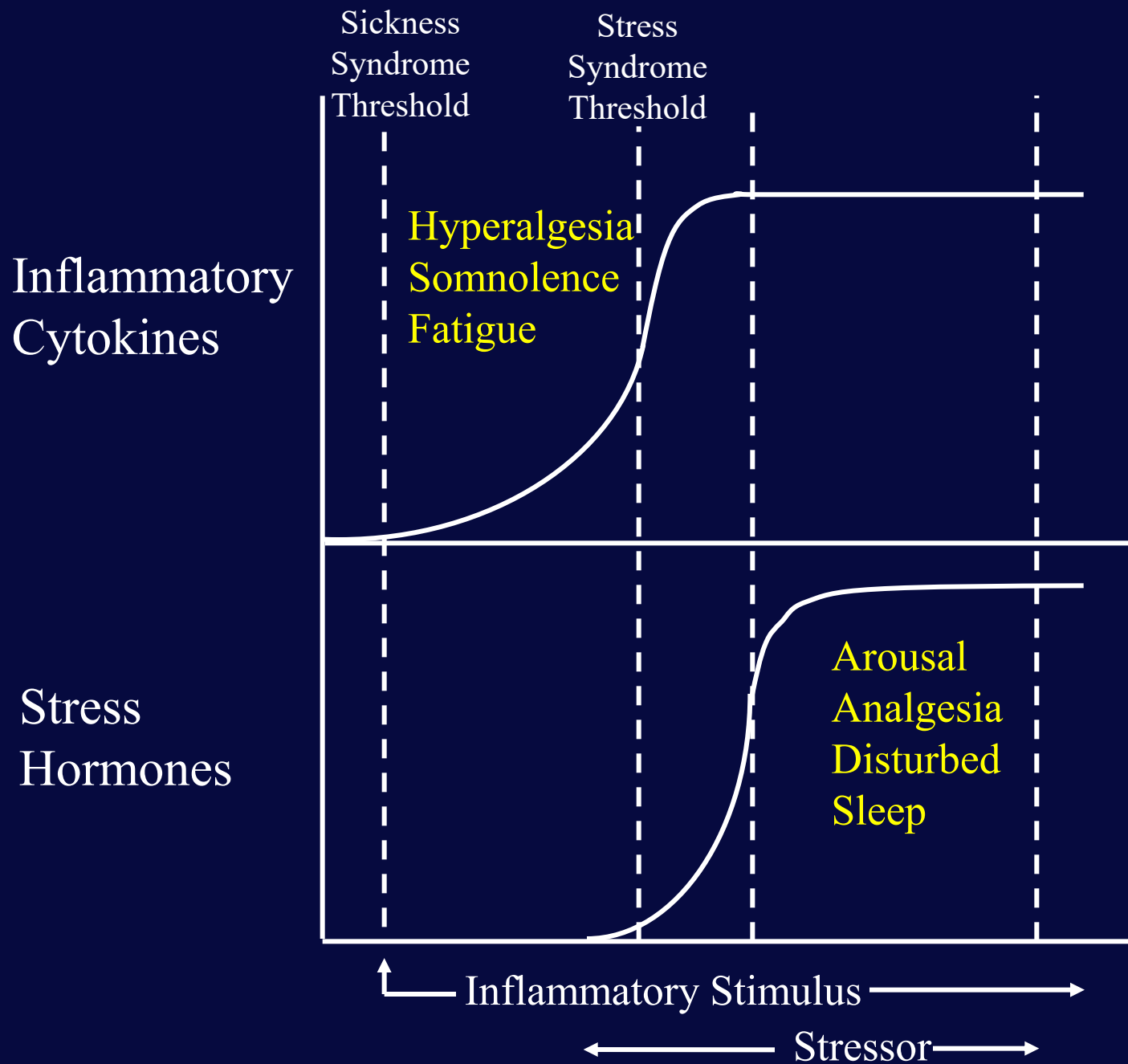
ACTIVATION OF IMMUNE AND IMMUNE ACCESSORY CELLS

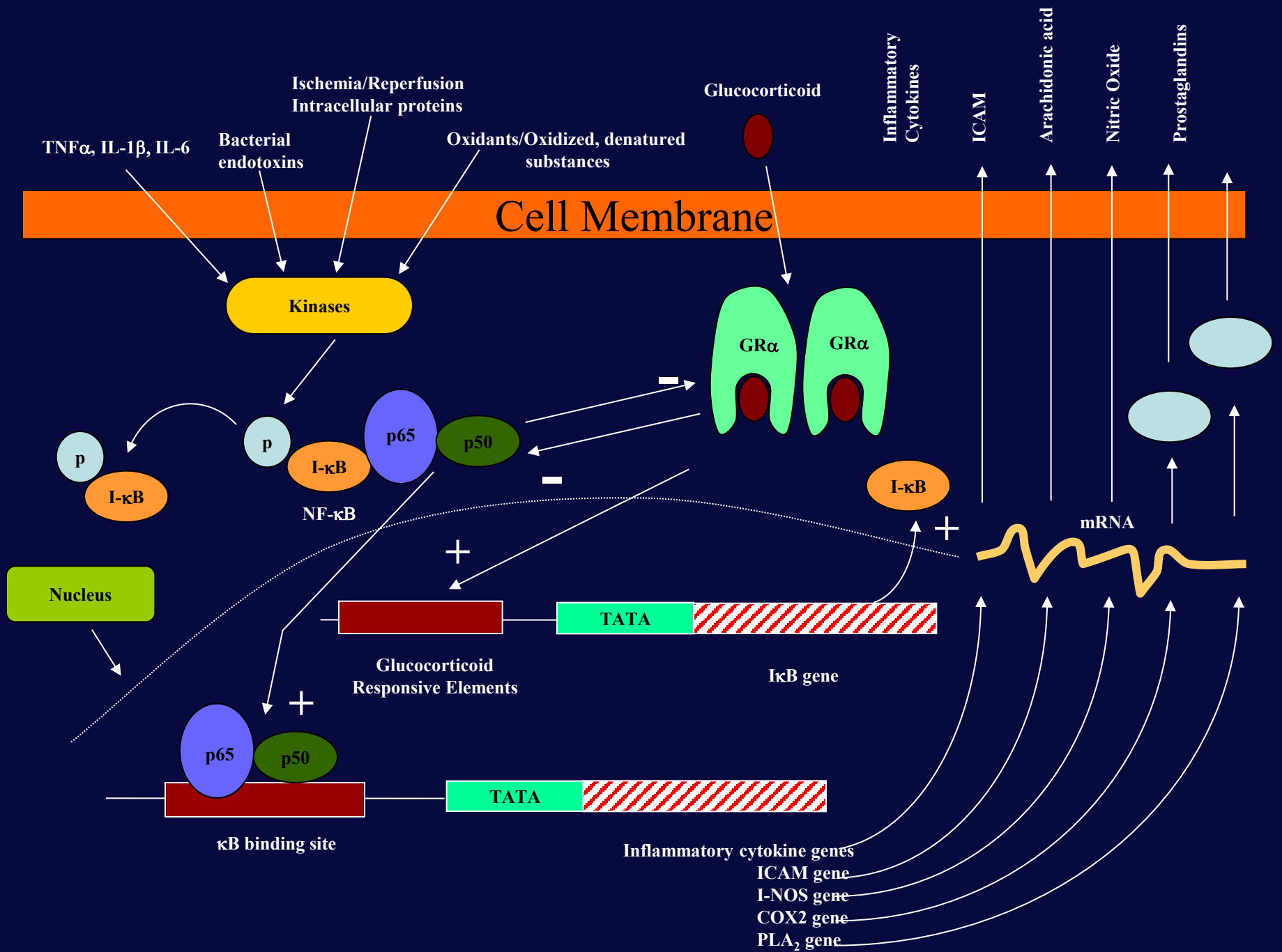
- INFLAMMATORY CYTOKINES: $\text{TNF}\alpha$, IL-1, IL-6, IL-8
- OTHER MEDIATORS OF INFLAMMATION:
- Prostanoids, PAF



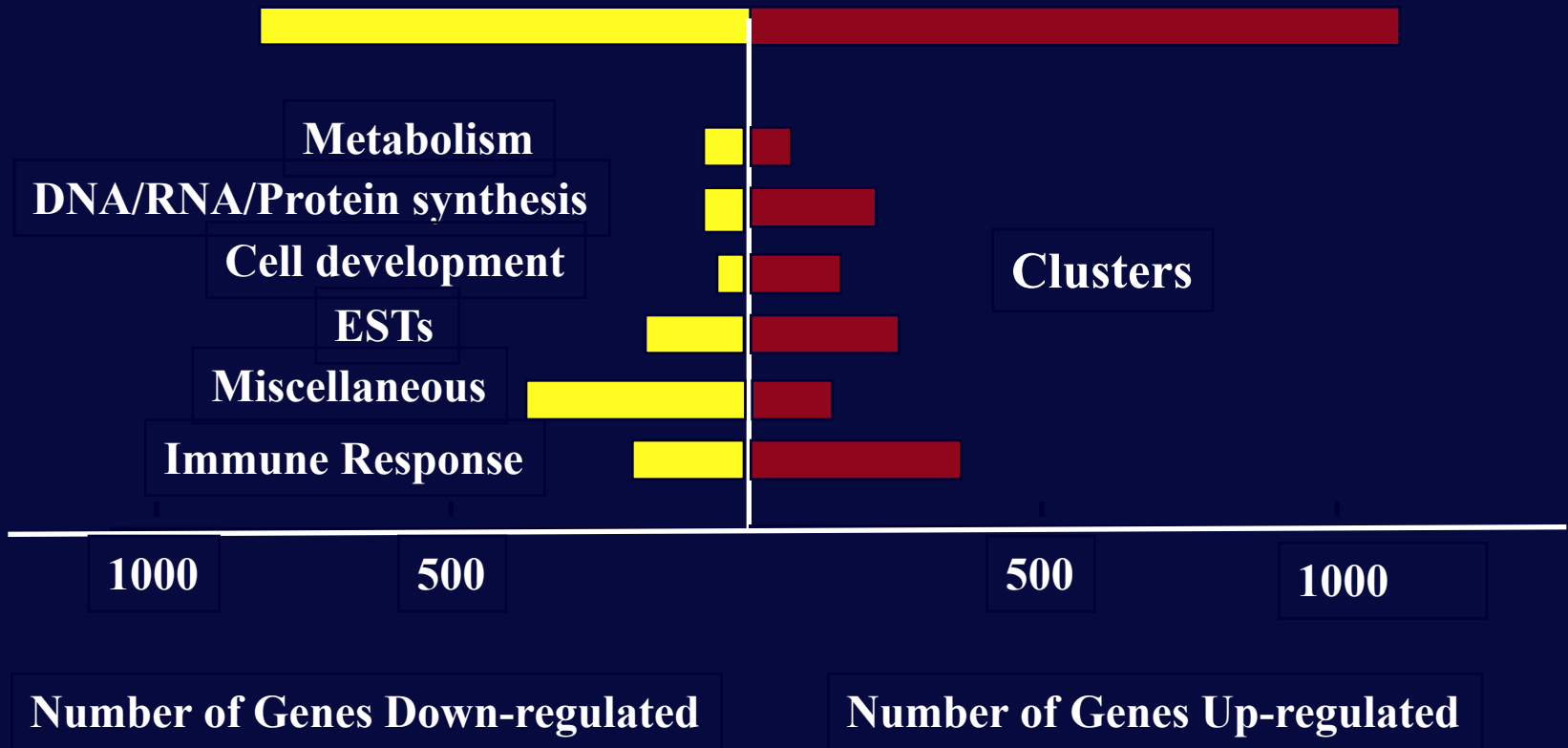
PAIN-NEURAL AFFERENTS





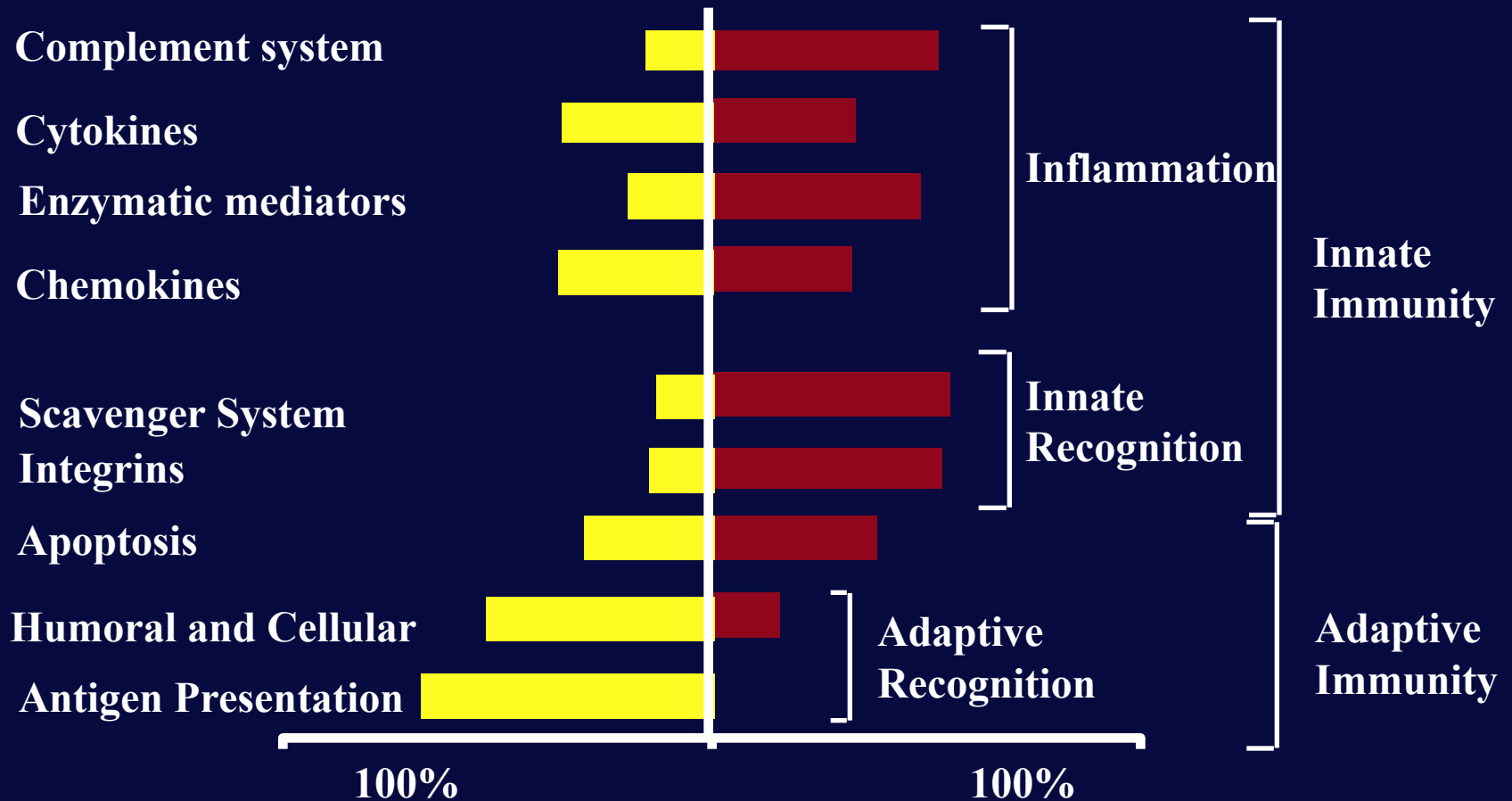


Regulated genes



Subcategories

Subclusters



Peripheral Immune
Activation and
Cytokine Secretion

Central Secretion
of Cytokines
($\text{TNF}\alpha$, IL-1,
IL-6, etc.)

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

**Stress +/-
Sickness Syndrome
Manifestations**

Peripheral
Infections

Post
Partum
Period

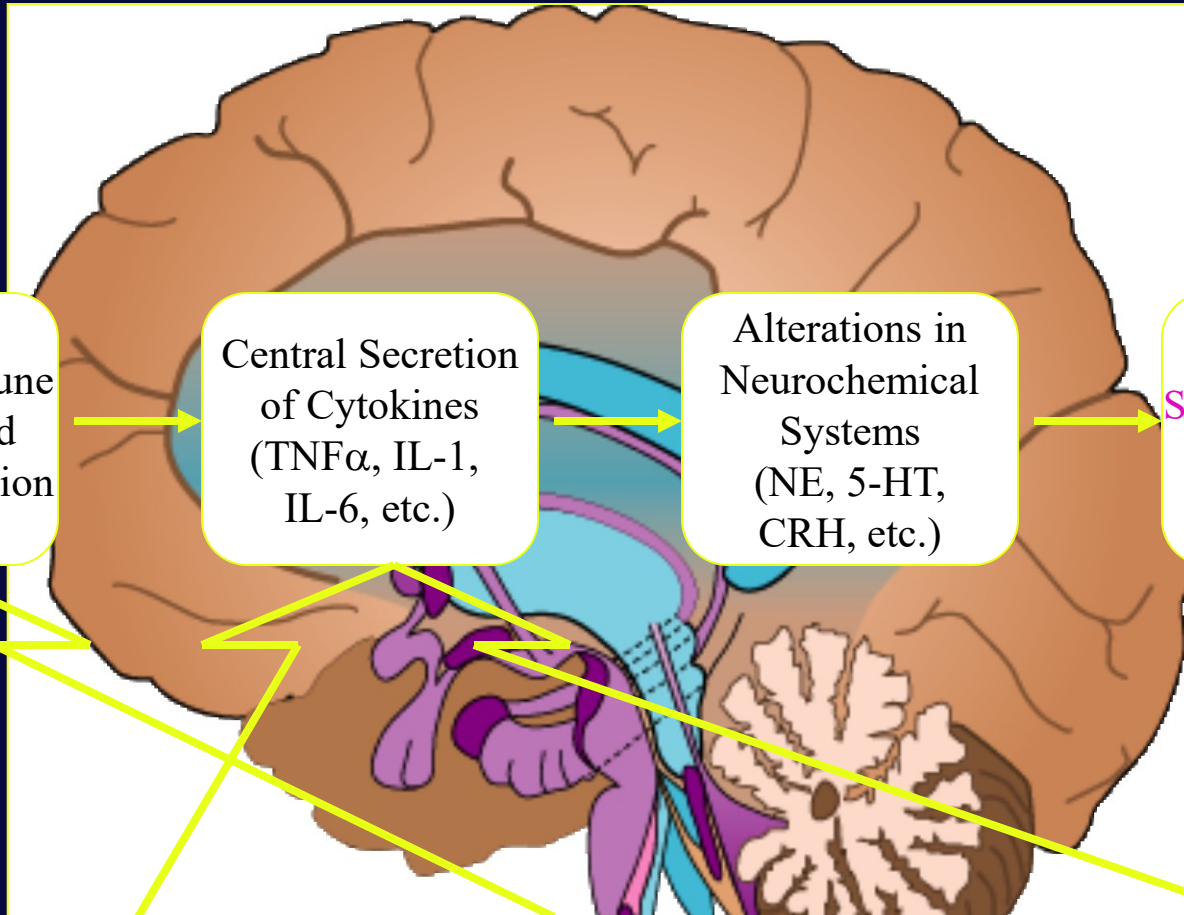
Stress

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:

stress behavior MUS) fatigue, pain (sickness behavior,

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

GENETIC VARIATION

STRESS

Real or perceived

NUTRITION

AGING



Stress system
CRH/AVP-LC/NE

HPA axis

**Systemic Sympathetic
Adrenomedullary Systems**

↓ GH/IGF-1
↓ LH, T, E2
↓ TSH, T₃

↑ **Cortisol**

Target Tissues

NE, E, IL-6 ↑

**Sickness
Syndrome**

PCOS

Endothelial Dysfunction

Para-Inflammation/immune Dysfunction/Th1 to Th2

**Atherosclerosis
Cardiovascular Disease**

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

↑ **TG**
↑ **LDL**
↓ **HDL**

ABP ↑

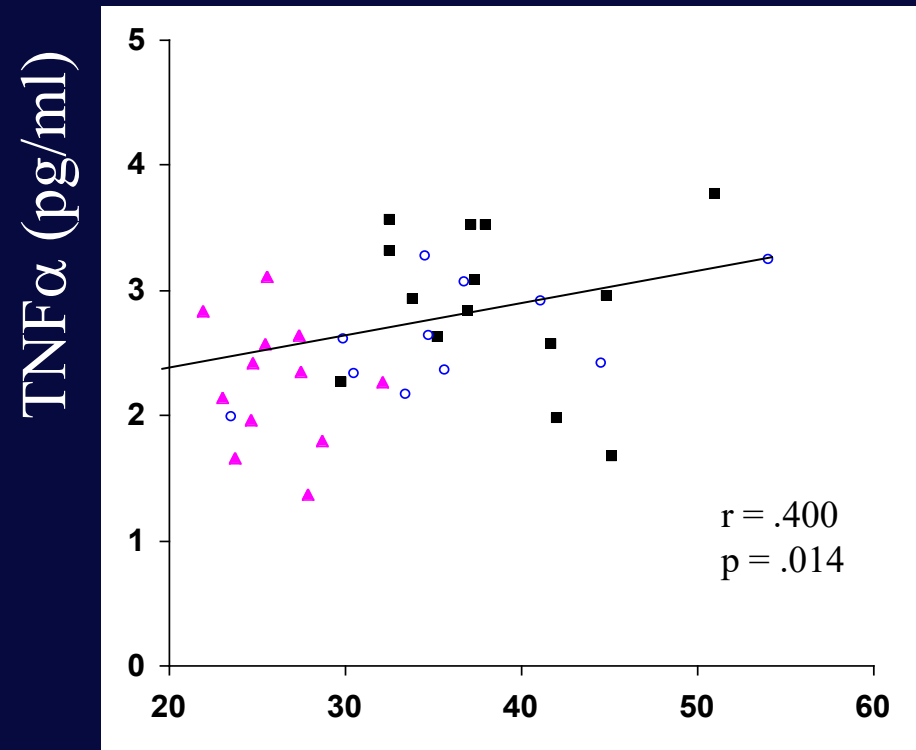
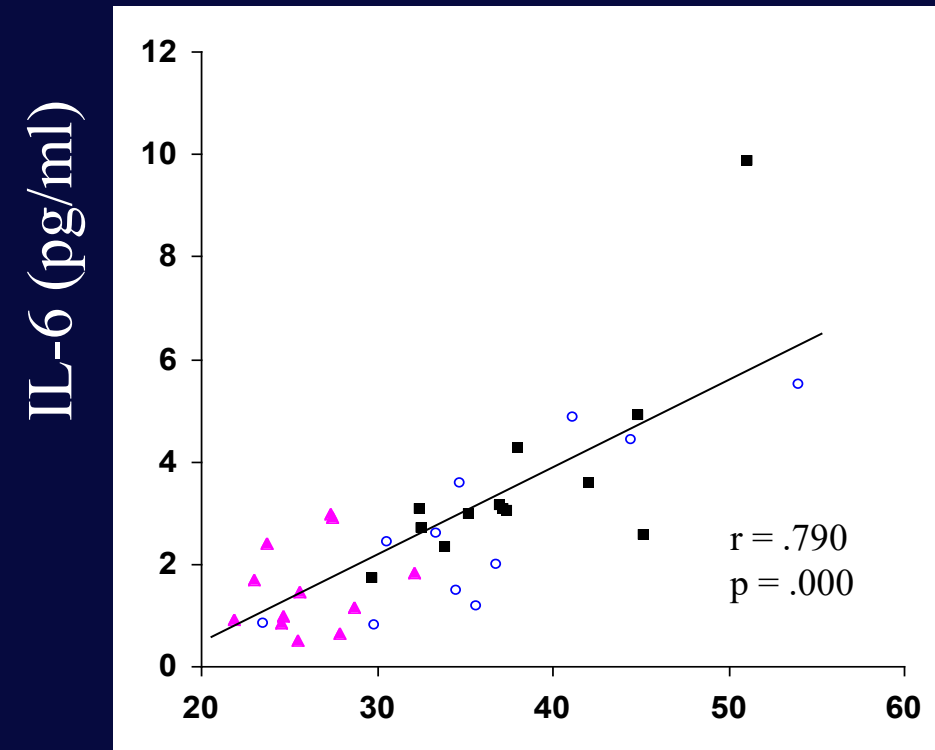
APR ↑
Cytokines ↑

Dyscoagulation

Sleep Apnea

Osteoporosis

Both IL-6 and TNF α correlate with BMI



BMI

Vgontzas *et al.* JCEM 1997

HYPERCYTOKINEMIA

TRAUMA/ BURNS

INFECTIOUS ILLNESSES

AUTOIMMUNE INFLAMMATORY DISEASES

ALLERGIC INFLAMMATIONS

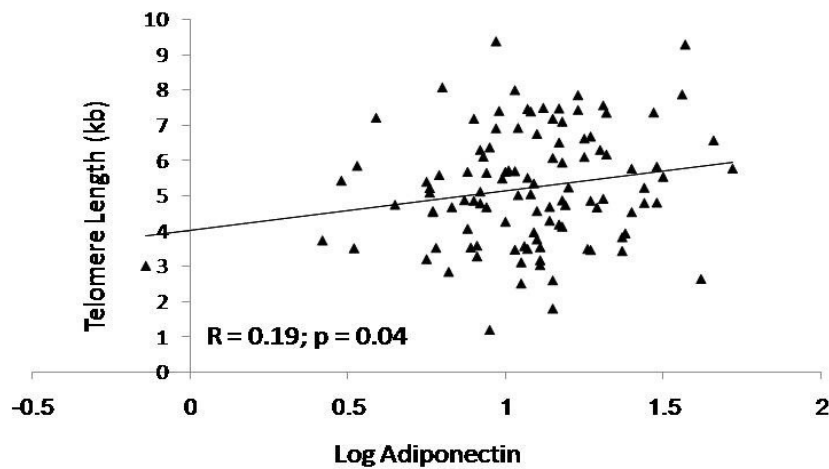
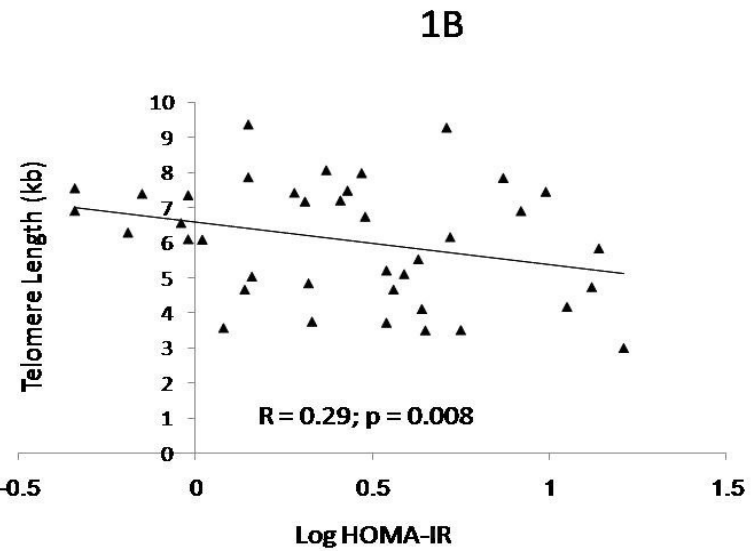
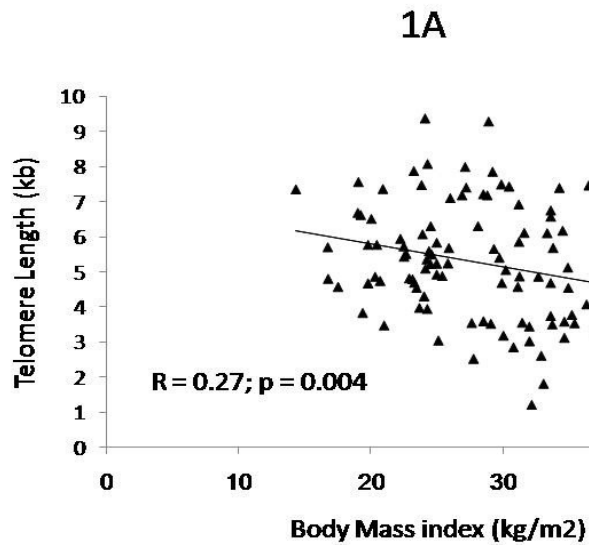
CNS INFLAMMATIONS

NONINFLAMMATORY STRESS

OBESITY/VISCERAL OBESITY

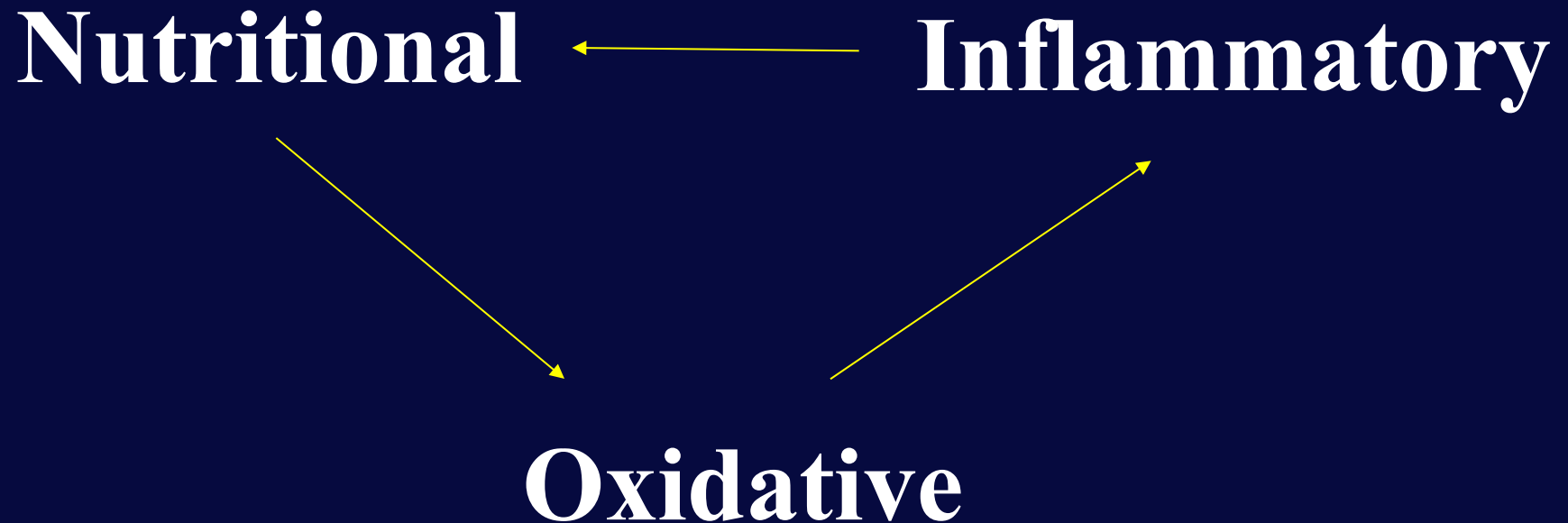
AGING



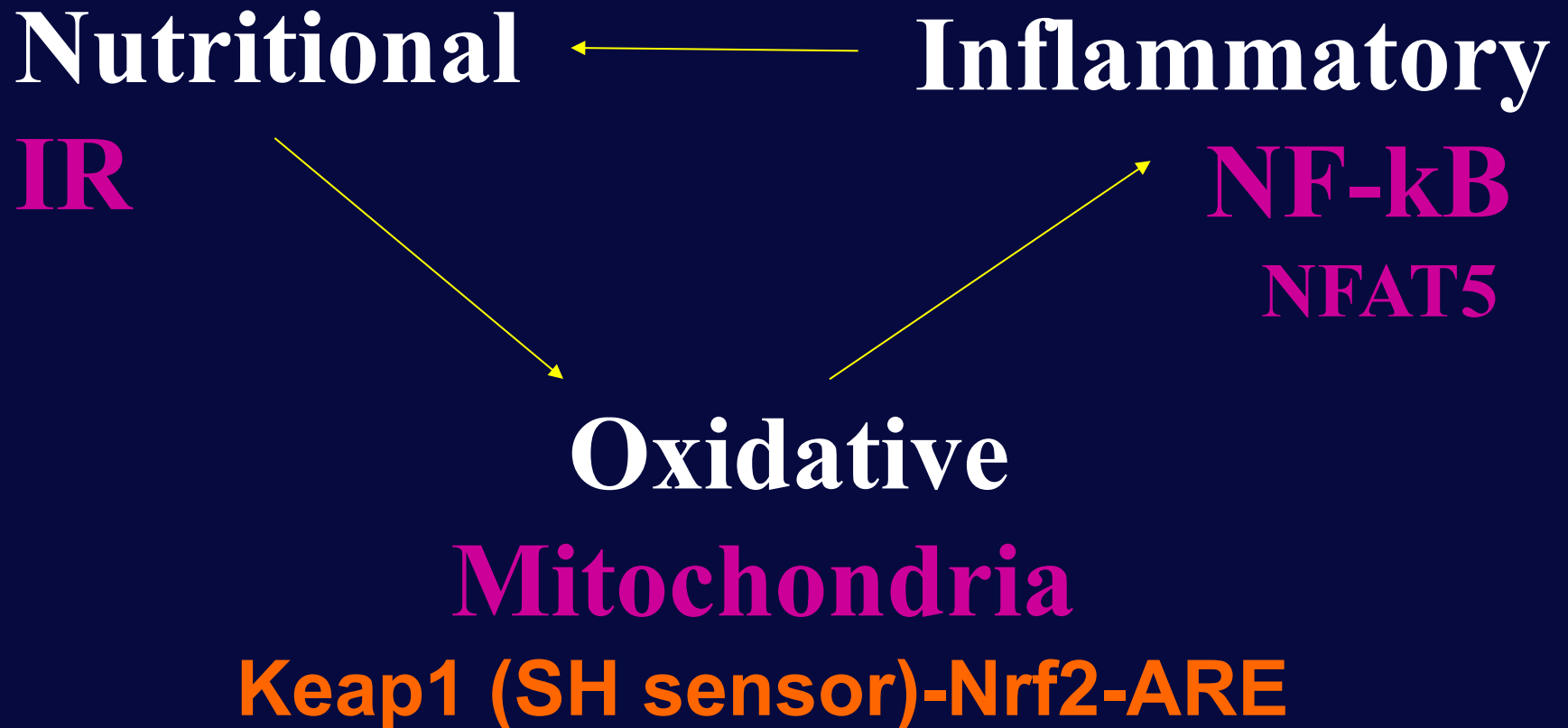


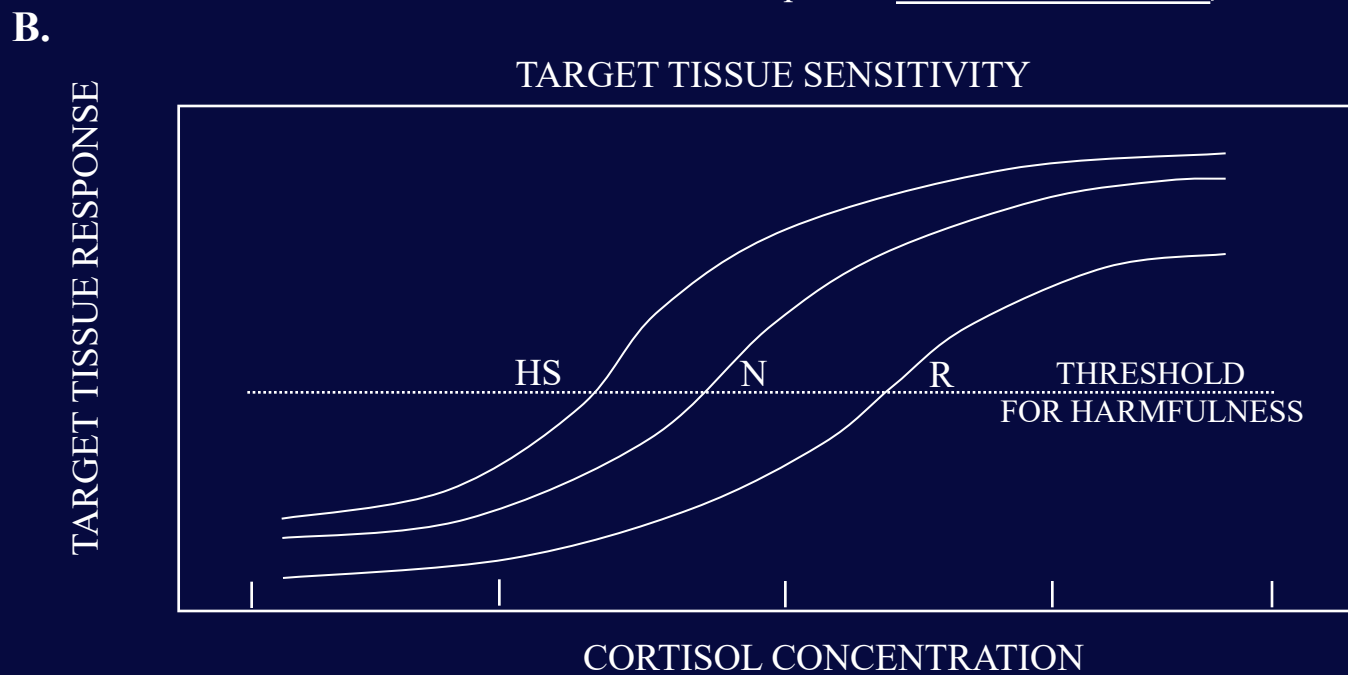
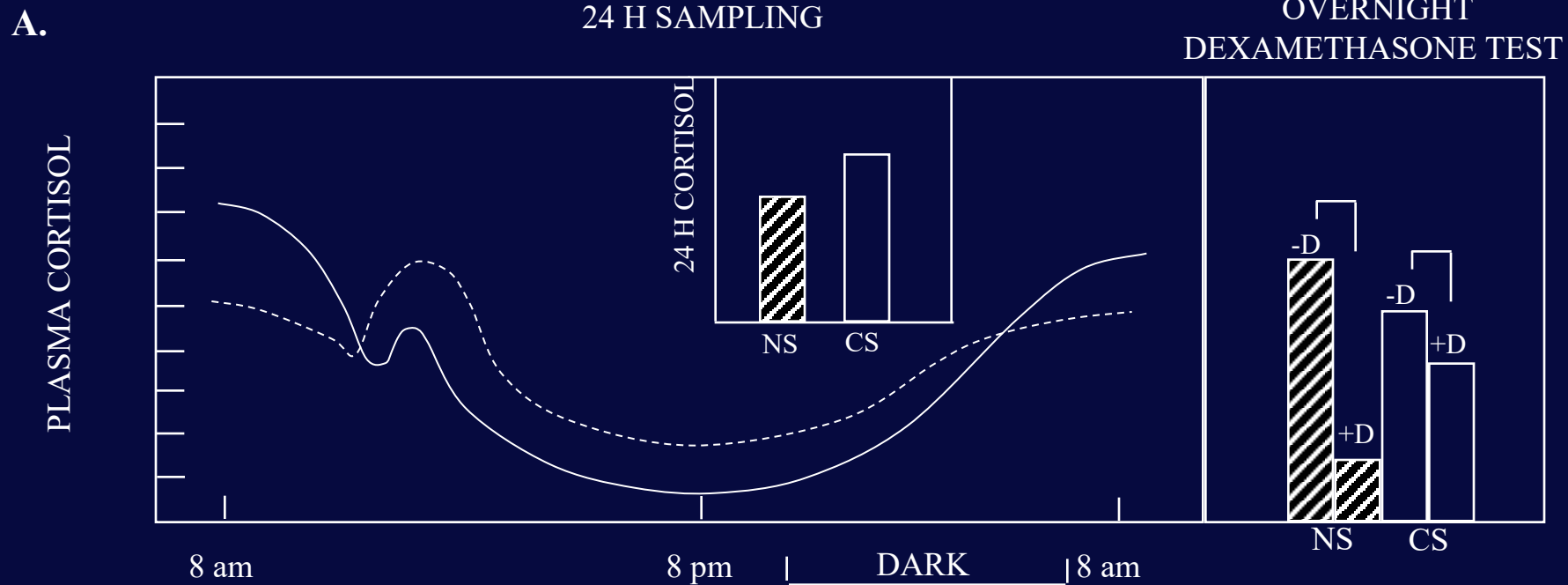
1C

Cellular Stress



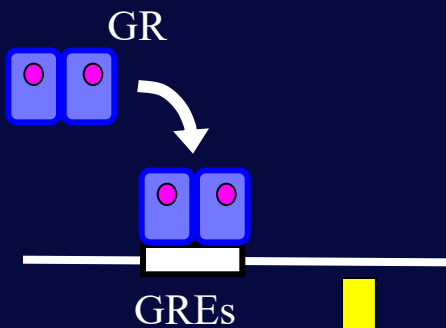
Cellular Stress





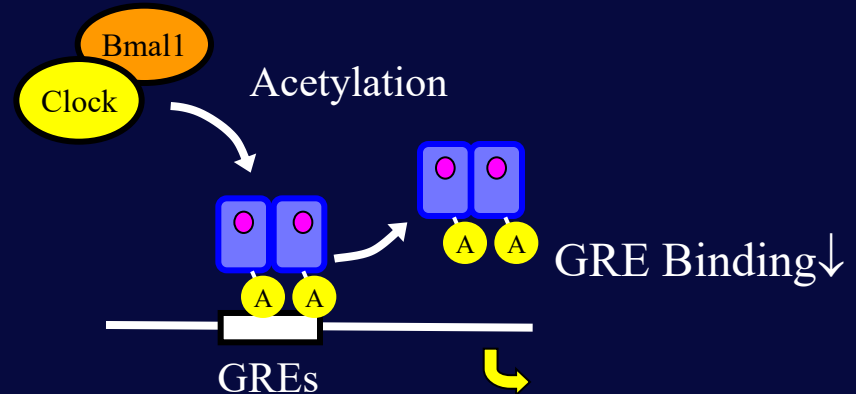
Results #1: Clock/Bmal1 Represses GR Transcriptional Activity through Acetylation

In the Absence of Acetylation by CLOCK

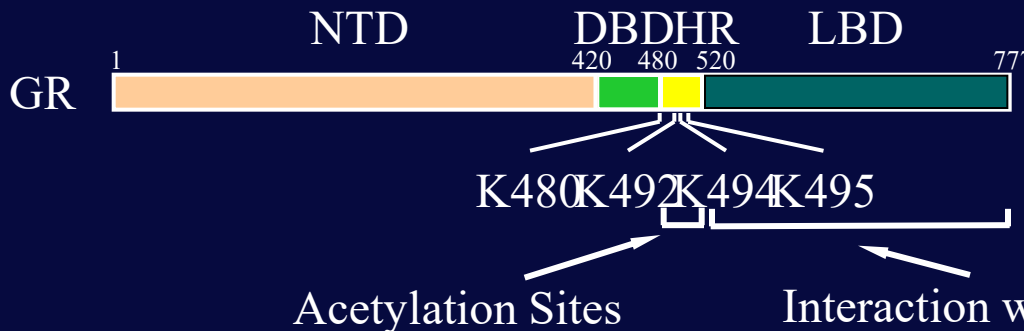


GR-induced Transcriptional Activity

In the Presence of Acetylation by CLOCK



GR-induced Transcriptional Activity↓



Uncoupling between Circadian Rhythm of Serum Cortisol and Tissue Glucocorticoid Sensitivity

