

The Pathophysiology of Stress

Michael D. Lumpkin, PhD

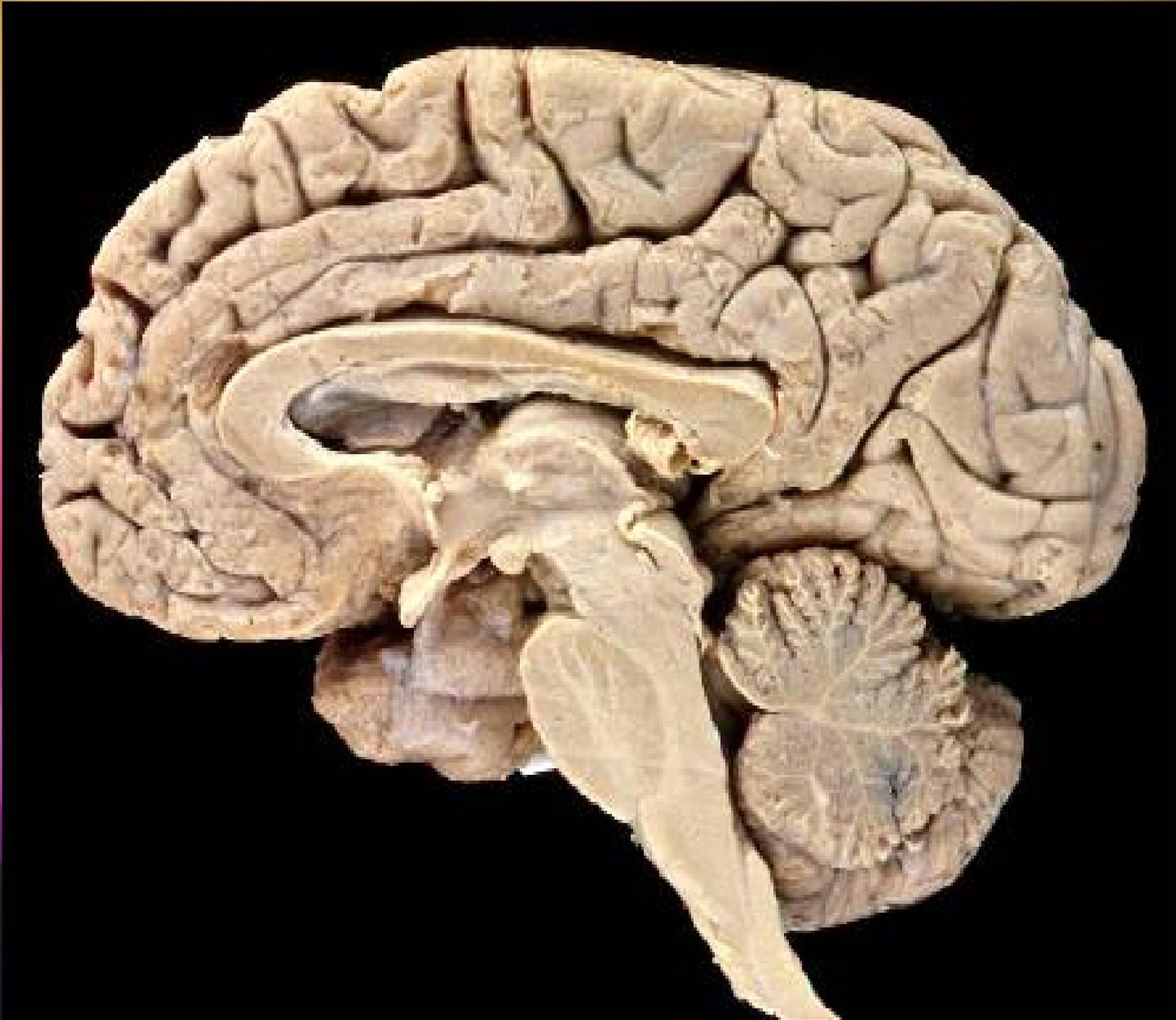
Professor

Georgetown University School of Medicine

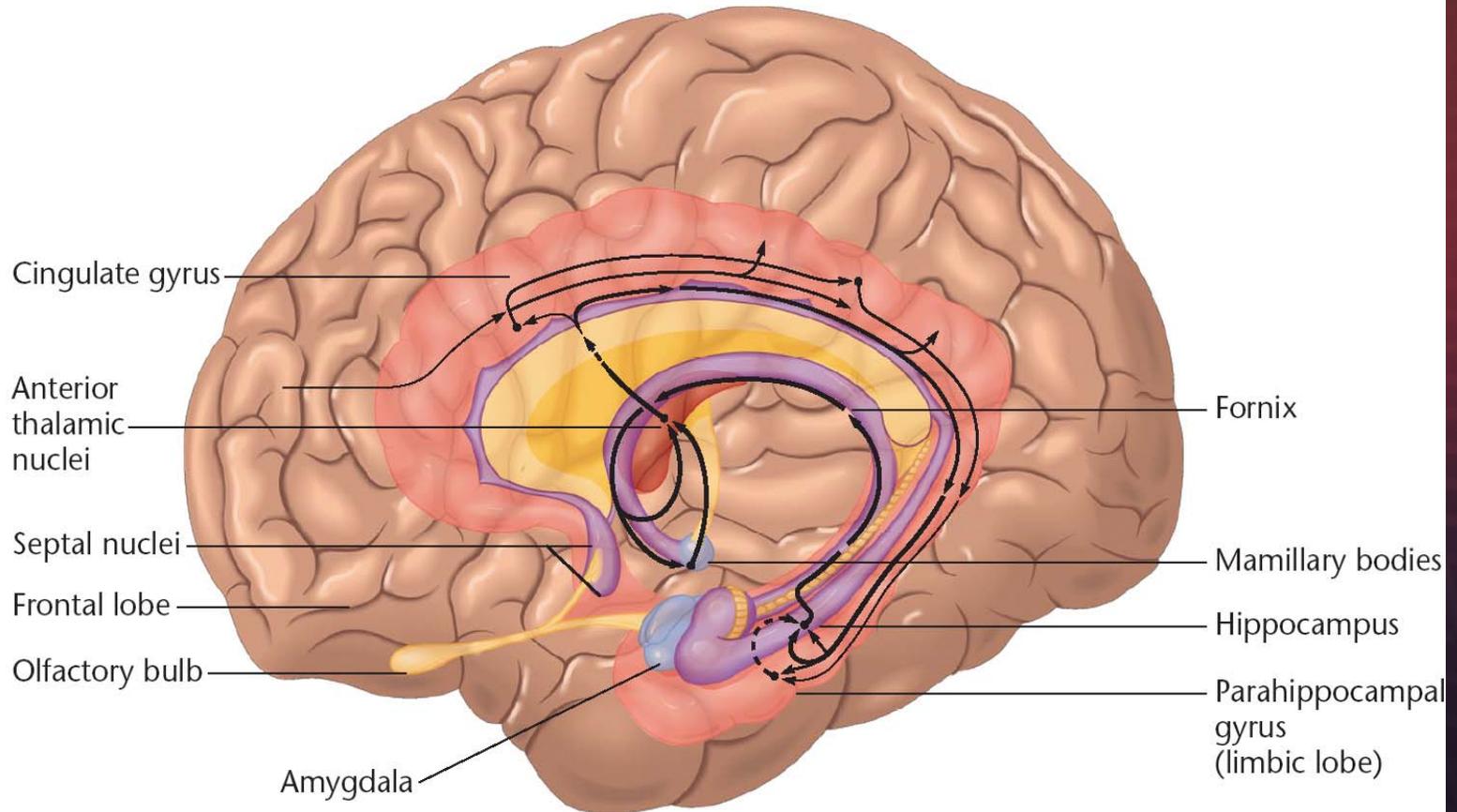
Washington, DC

Middle East Cancer Consortium

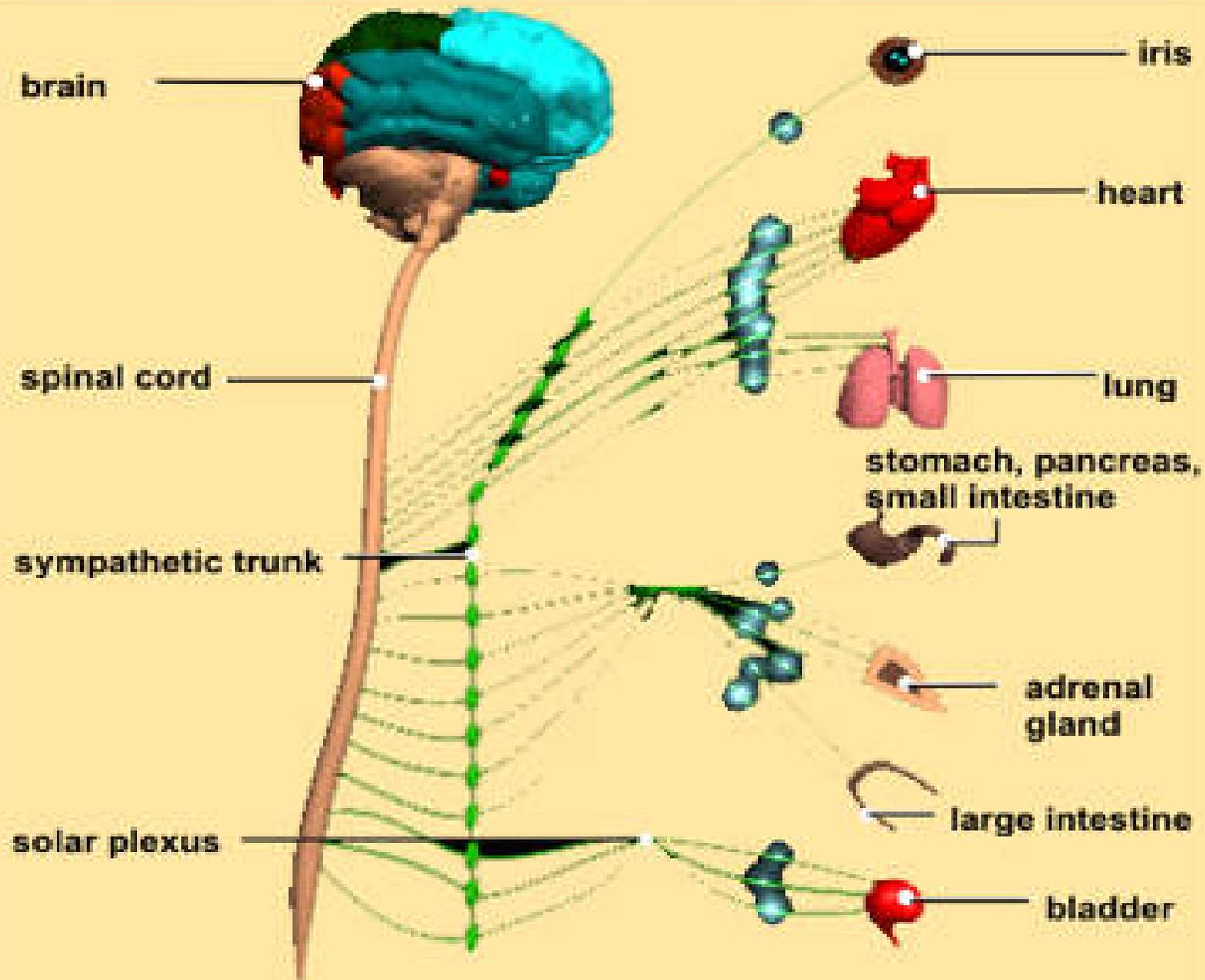
Larnaca, Cyprus, June 2007



Neural Connections: Cognitive-Emotional-Autonomic



The Sympathetic Nervous System



The Parasympathetic Nervous System

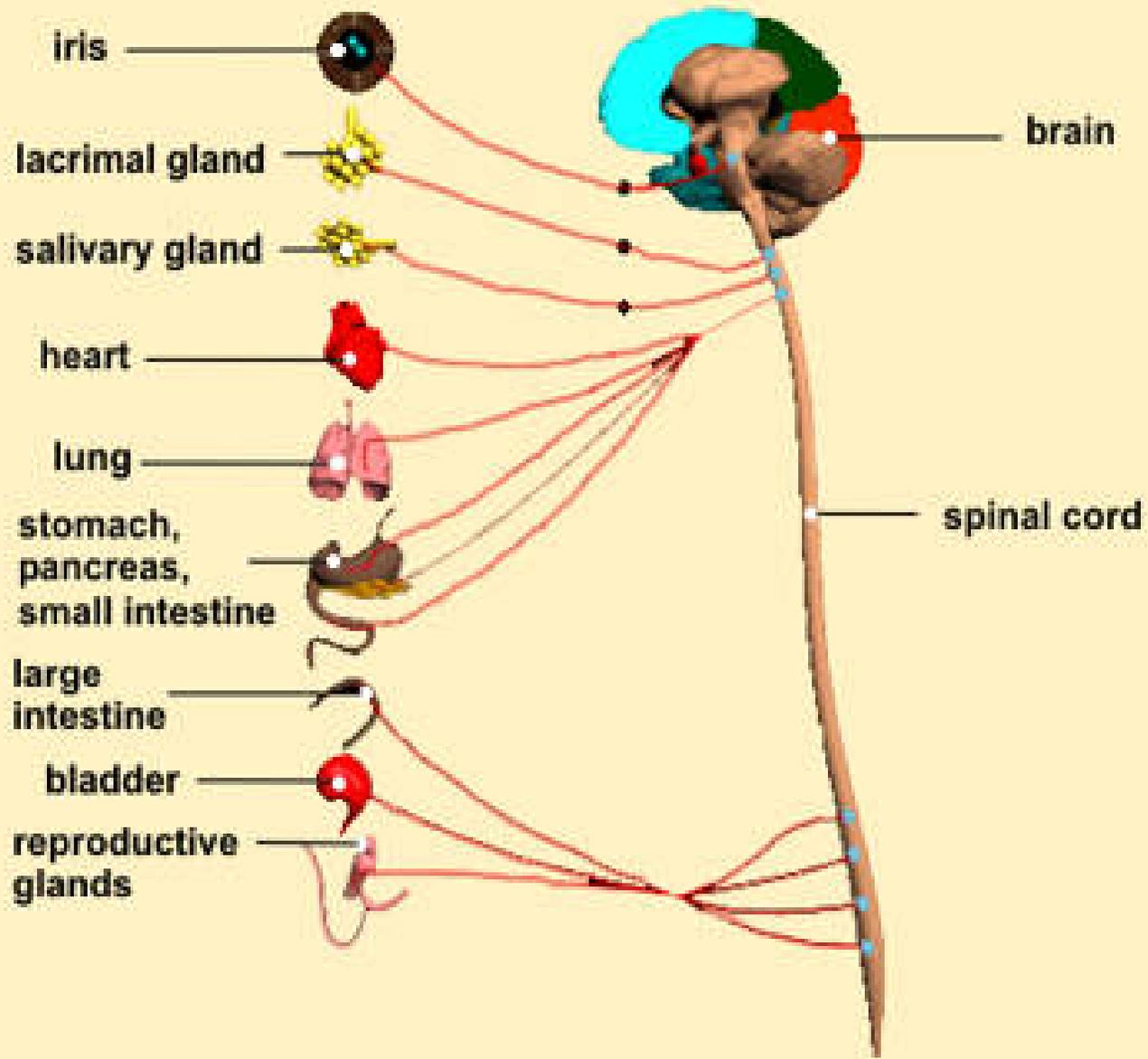
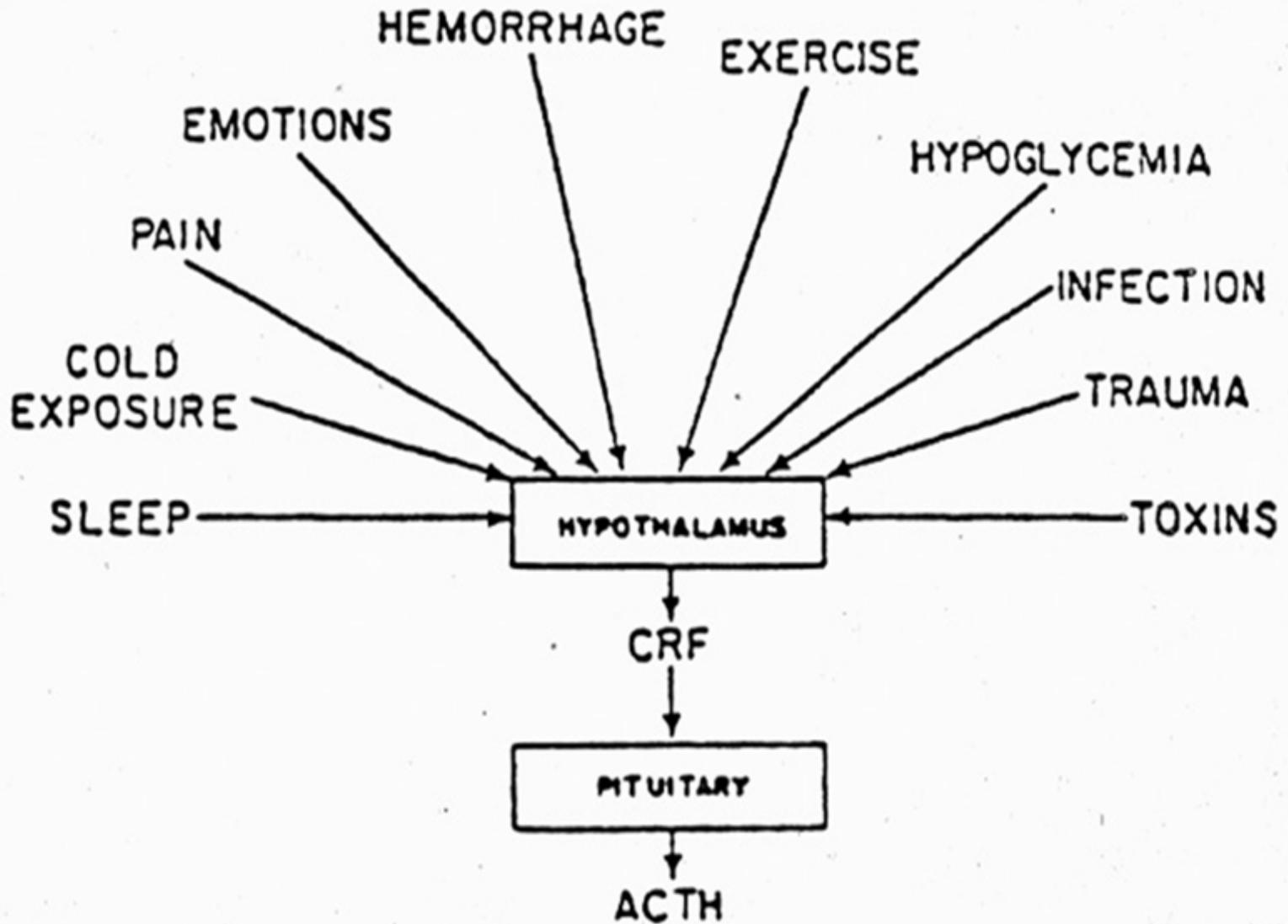


Fig 11-9.—Factors that elicit CRF secretion.



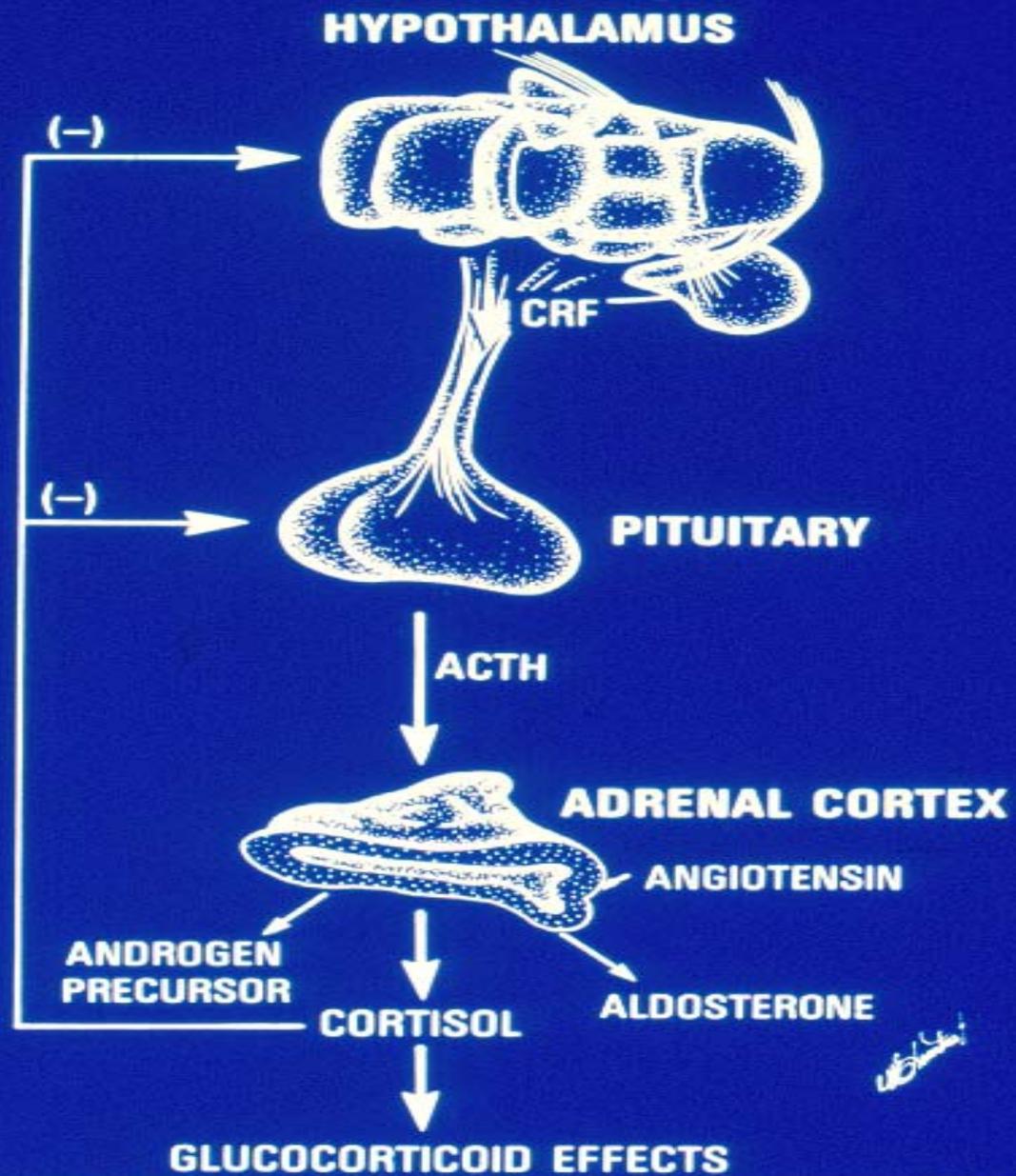
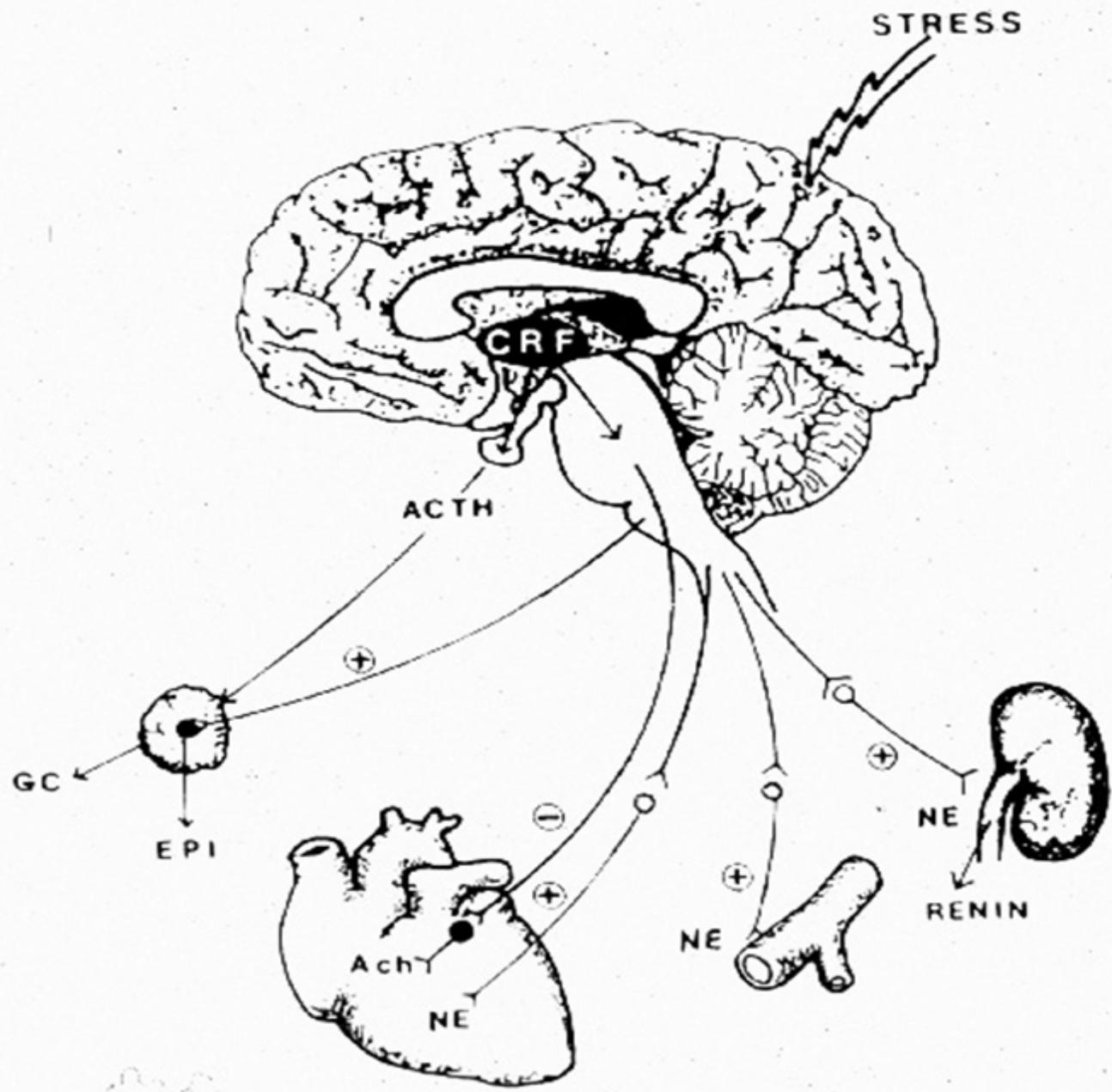
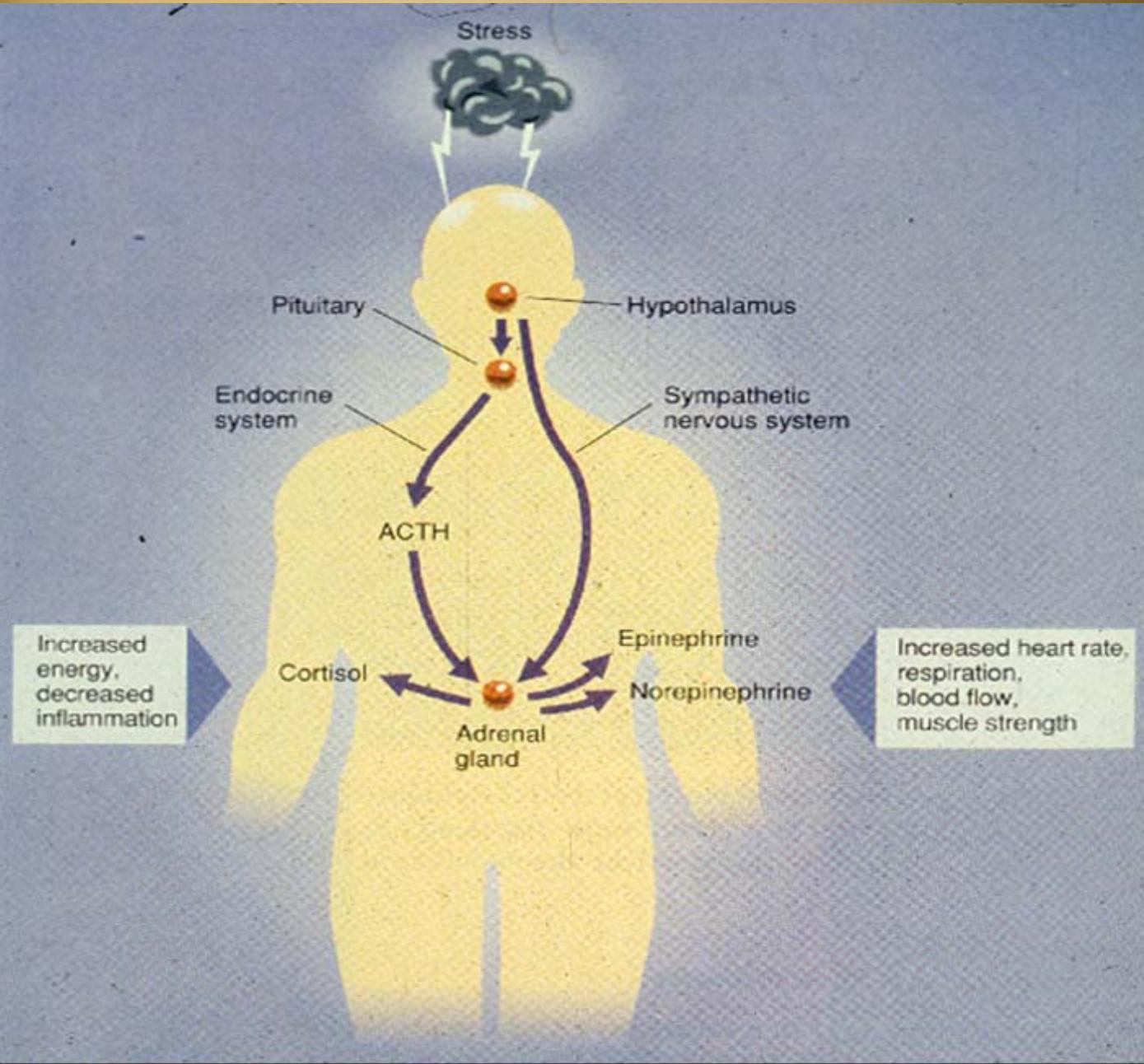


Figure 8.32. Hypothalamic:pituitary:adrenocortical axis.





Behavioral Effects of Corticotropin-Releasing Factor

1. CRF injected intracerebroventricularly increases locomotor activity in a familiar photocell environment
2. CRF facilitates the acoustic startle response
3. CRF produces increased responsiveness to "stress" in an open field test
4. CRF has an "anxiogenic-like" effect in the operant conflict test
5. CRF produces enhanced suppression of responding in conditioned emotional response test
6. CRF produces a dose-dependent facilitation of stress-induced fighting
7. CRF produces "anxiogenic-like" response in the plus maze
8. CRF produces a dose-dependent taste aversion and place aversion

Table 1

Similarities between Signs and Symptoms of Major Depression (DSM III-R Criteria) and the Behavioral Effects of Centrally Administered CRF in Laboratory Animals

DSM III-R major depression	Effect of centrally administered CRF
1. Depressed mood (irritable mood in children and adolescents) most of day, nearly every day, as indicated either by subjective account or observations by others	1. Mimics the behavioral despair syndrome observed after maternal separation in rhesus monkey infants
2. Markedly diminished interest or pleasures in all or almost all activities most of day, nearly every day	2. Diminishes sexual behavior in male and female rats
3. Significant weight loss or weight gain when not dieting or decrease or increase in appetite nearly every day	3. Decreases food consumption in rats
4. Insomnia or hypersomnia nearly every day	4. Disrupts normal sleep patterns with concomitant EEG changes
5. Psychomotor agitation or retardation nearly every day	5. Increases locomotor activity in a familiar environment and produces "stresslike" alterations in locomotion in a novel environment
6. Fatigue or loss of energy, nearly every day	6. No data
7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day	7. No data
8. Diminished ability to think or concentrate or indecisiveness nearly every day	8. No data
9. Recurrent thoughts of death, recurrent suicidal ideation or a suicide attempt	9. No data

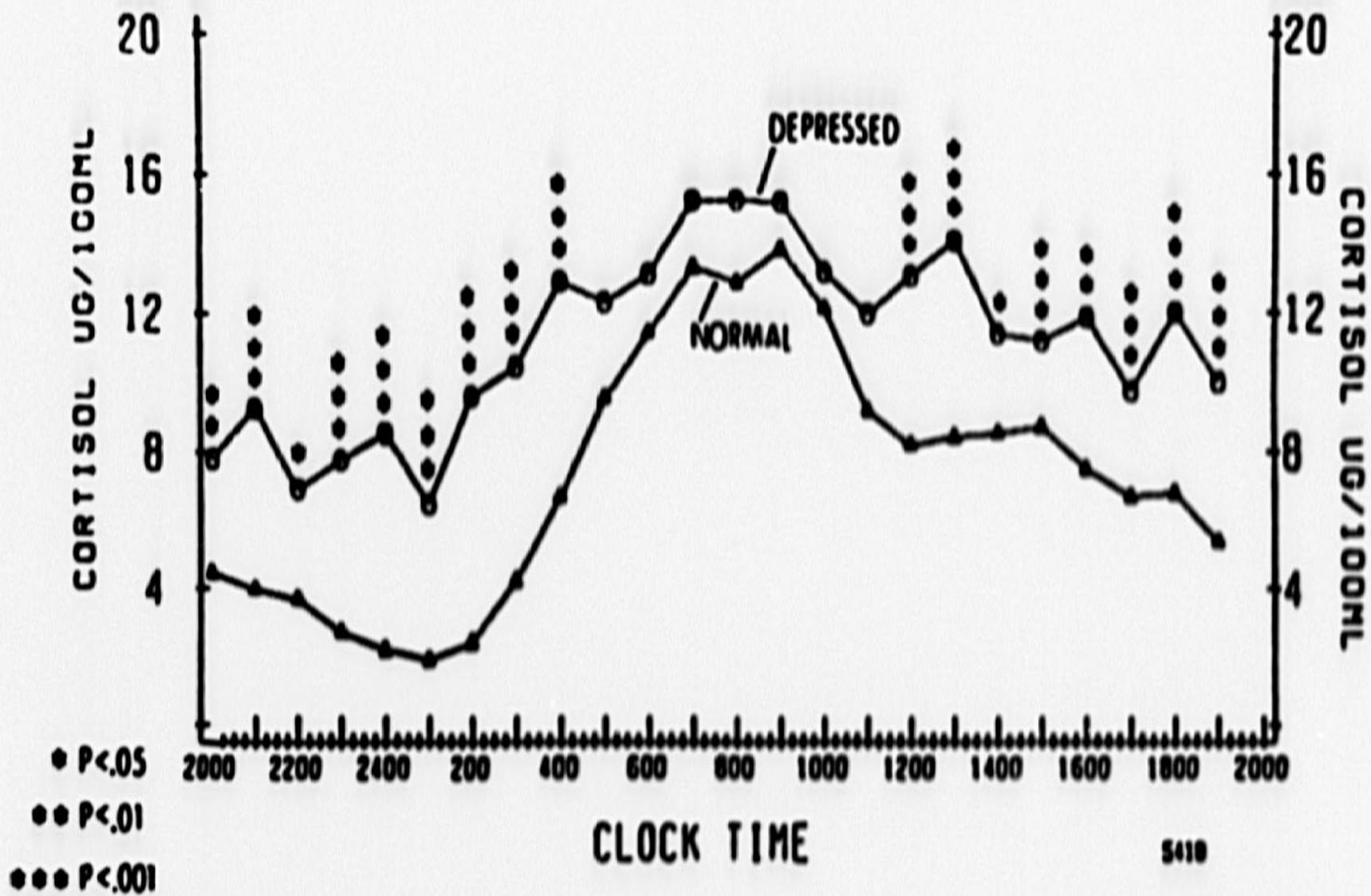


Table 2 States Associated with Altered Hypothalamic-Pituitary-Adrenal Axis Activity and Altered Regulatory or Dysregulation of Behavioral and/or Peripheral Adaptation

Increased HPA axis

Decreased HPA axis

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 X)
 Childhood sexual abuse
 Hyperthyroidism
 Premenstrual tension syndrome
 Cushing's syndrome
 Pregnancy

Adrenal insufficiency
 Atypical/seasonal depression
 Chronic fatigue syndrome
 Fibromyalgia
 Hypothyroidism
 Nicotine withdrawal
 Postglucocorticoid therapy
 Post-Cushing syndrome cure
 Postpartum period
 Postchronic stress
 Rheumatoid arthritis

Effects of Glucocorticoids in the Immune System

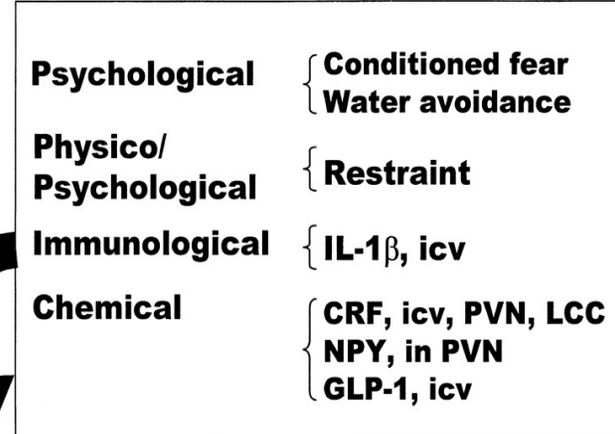
Inhibitory effects

- ◆ Decreases peripheral blood lymphocytes, eosinophils, basophils, monocytes, and neutrophils
- ◆ Inhibits production of IL-1, IL-2, IL-2 receptor, γ -interferon
- ◆ Inhibits F_c receptor expression
- ◆ Inhibits *in vitro* and *in vivo* proliferation of T lymphocytes to antigens and mitogens
- ◆ Inhibits many monocyte functions, including antigen presentation, lymphokine production, differentiation, and phagocytosis
- ◆ Inhibits immunoglobulin production *in vivo*
- ◆ Inhibits T suppressor cell function *in vivo* and *in vitro*

STRESSORS



STRESSORS

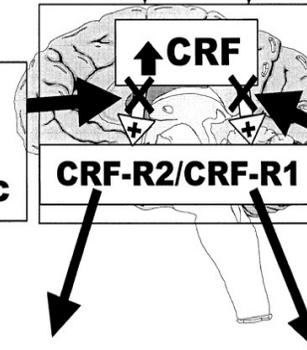


CRF Antagonists

Astressin, ic
D-Phe CRF12-41, ic
 α -Helical CRF9-41, icv, PVN, ic

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Astressin, icv
D-Phe CRF12-41, icv
 α -Helical CRF9-41, icv, PVN
NBI-27914, icv



Stomach

↓ Contractility
↓ Emptying

Colon

↑ Motility
↑ Transit
↑ Defecation

Remote control

Local control

A. Vasoconstrictor fibres

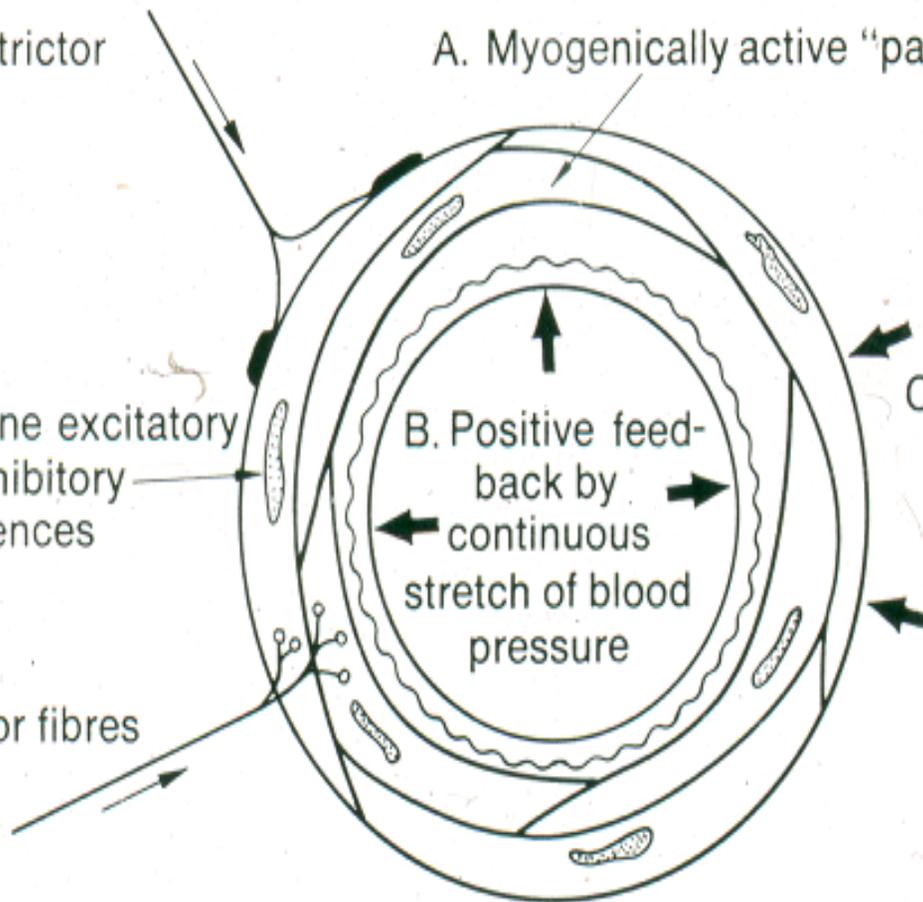
A. Myogenically active "pacemaker" cells

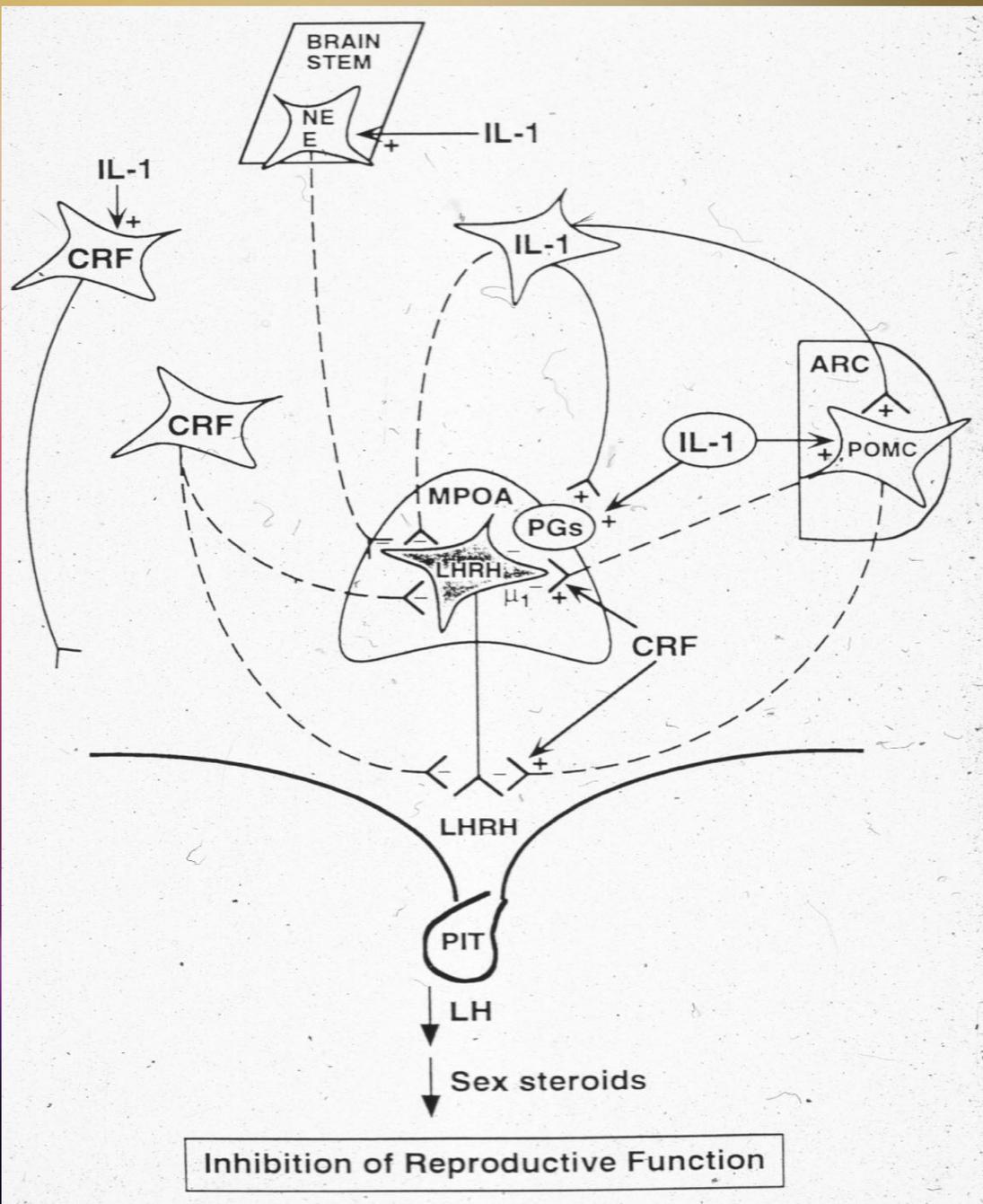
B. Blood-borne excitatory and inhibitory influences

B. Positive feedback by continuous stretch of blood pressure

C. Vasodilator fibres

C. Negative feedback by the vasodilator action of tissue metabolites





Inhibition of Reproductive Function

PHYSICAL OR PSYCHOLOGICAL STRESS

