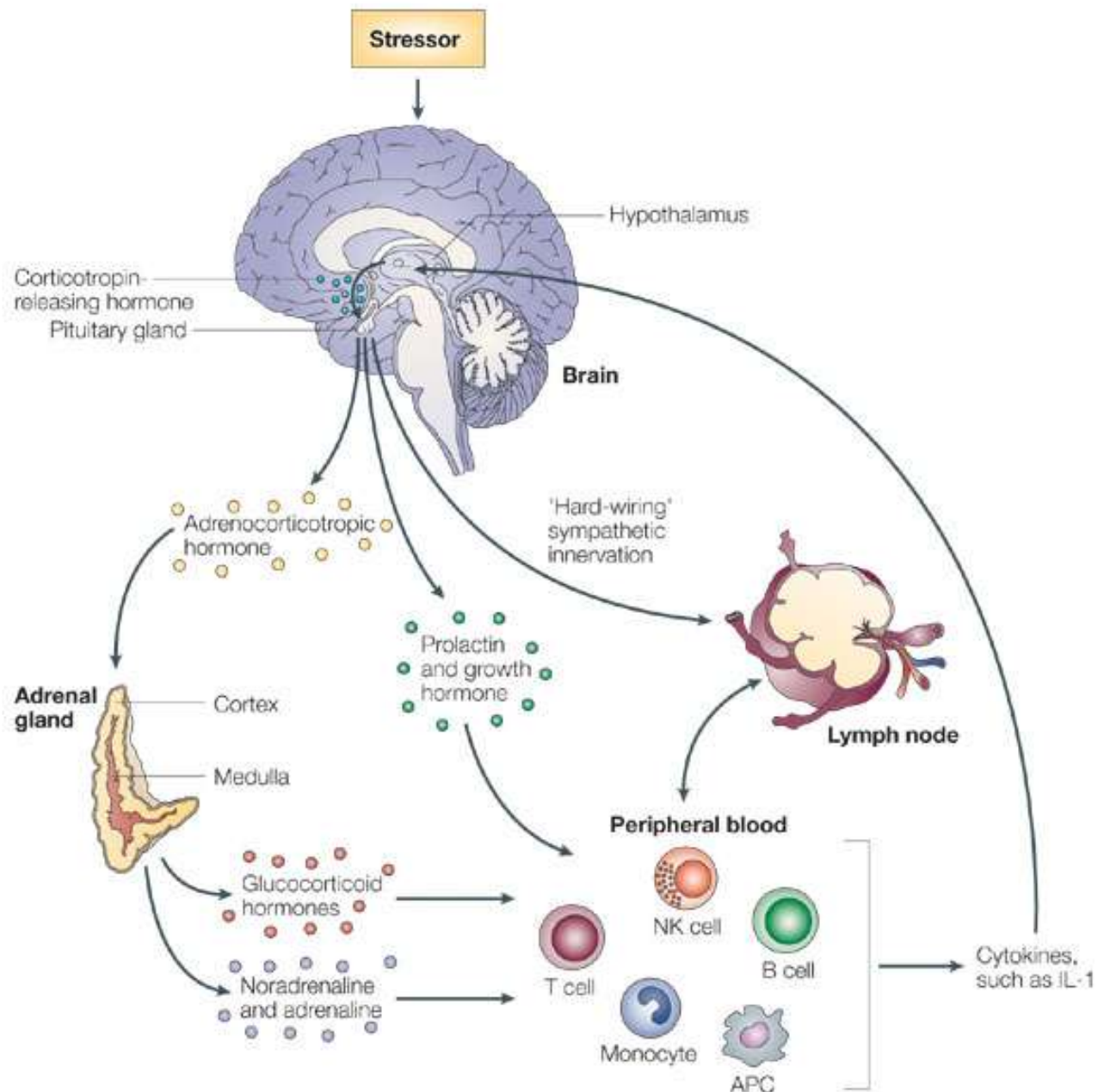


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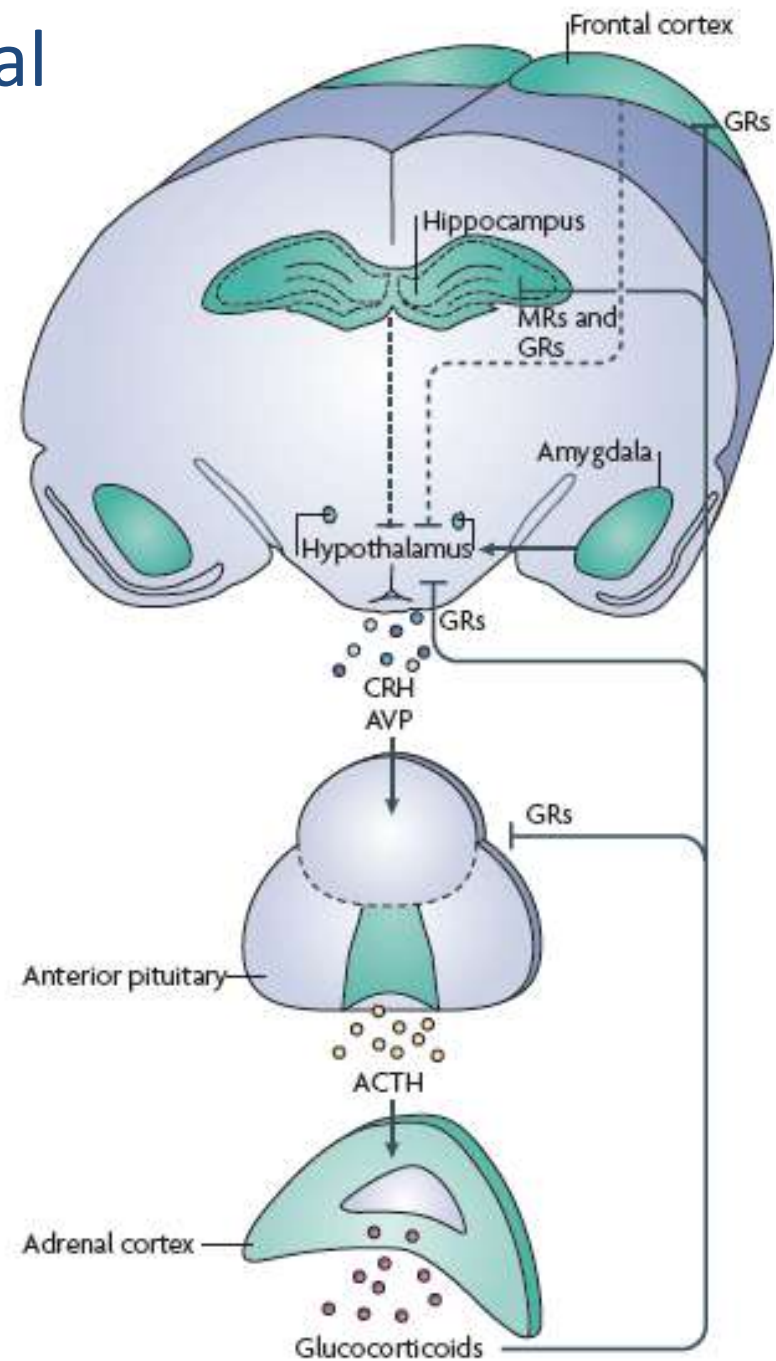
*Fisiologia Animal: Mecanismos e Adaptação do Controle Interno,  
Reprodução e Defesa*

Eixo hipotálamo-hipófise-adrenal  
Neuroimunoendocrinologia

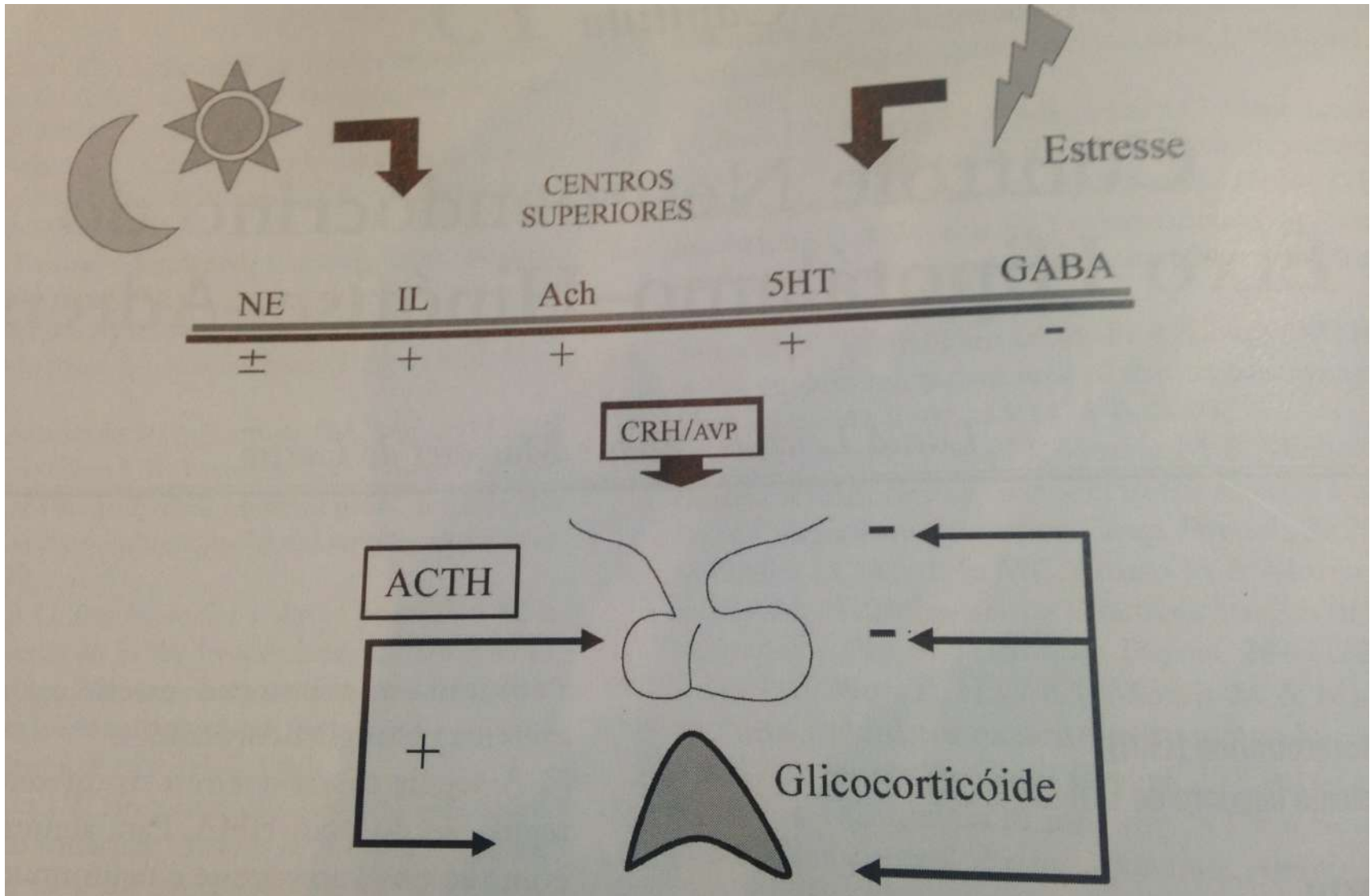
2017



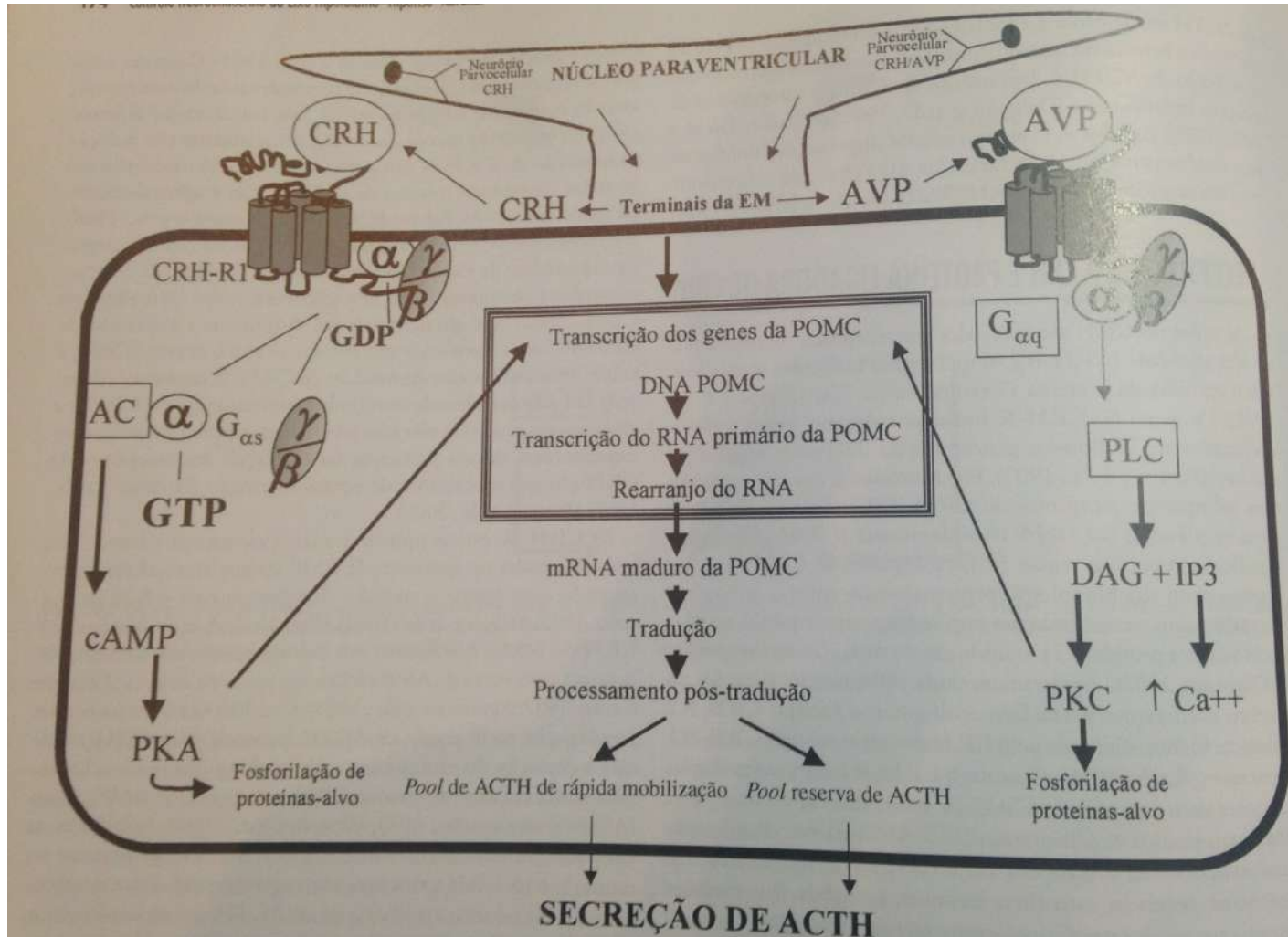
# Eixo hipotálamo-hipófise-adrenal



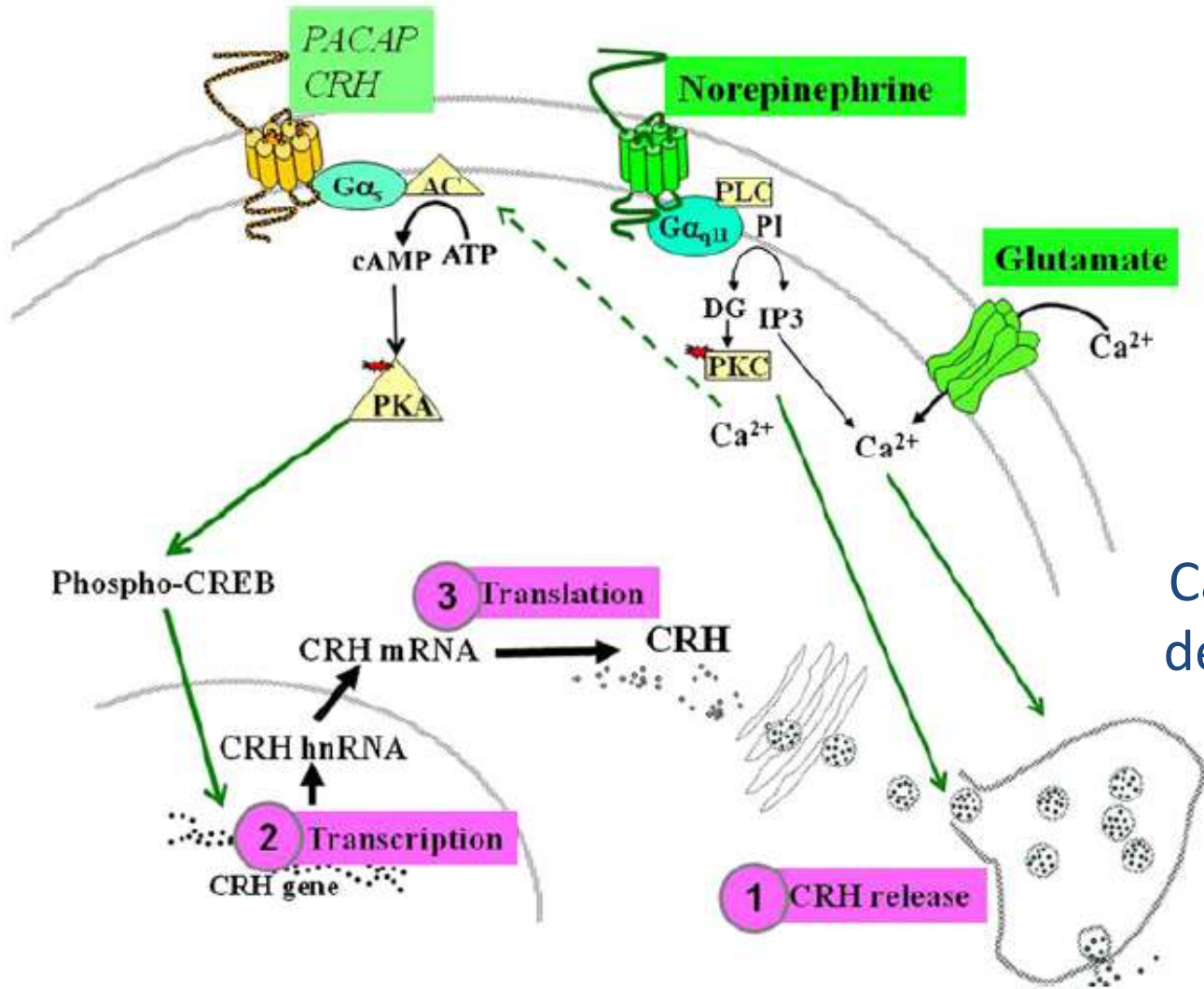
# Regulação do eixo Hipotálamo-Hipófise-Adrenal



# Sinalização de receptores de CRH e vasopressina na célula corticotrófica



# Estimulação de neurônios liberadores de CRH

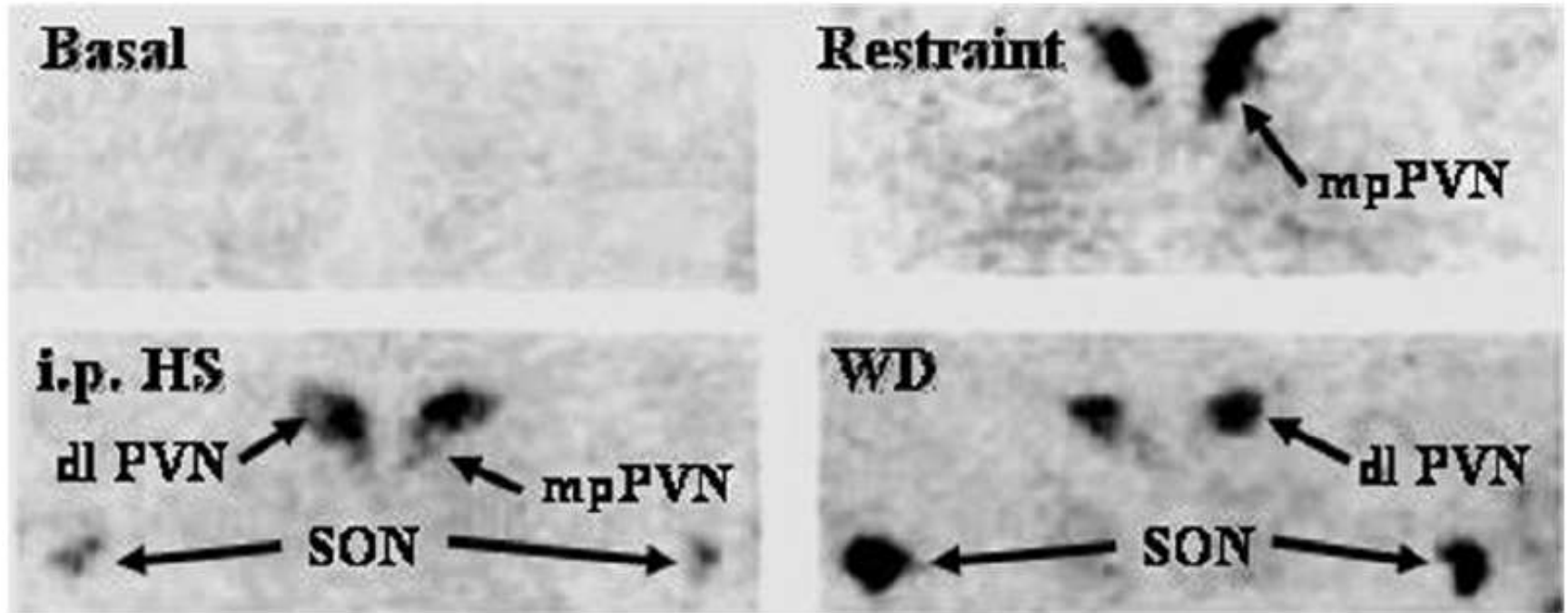


Cálcio induz liberação de vesículas contendo CRH

CRH induz a transcrição de mais CRH

# Estresse

## Especificidade da Resposta



Expressão de receptores de CRH no PVN dorsomedial (neurônios CRH) e no núcleo supra óptico dependo do tipo de estresse

Restrain: contenção

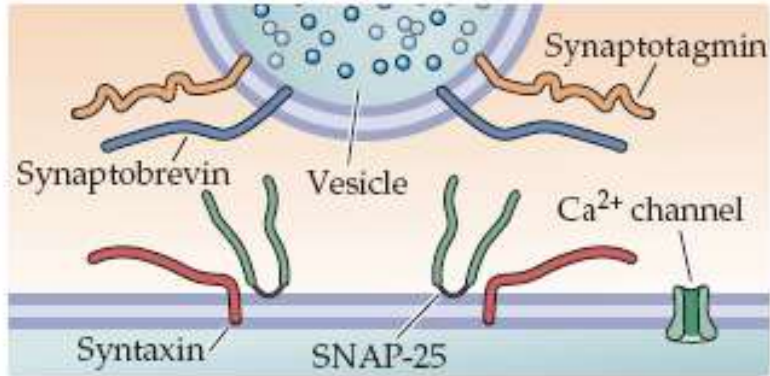
i.p. HS: hipertonic saline injection

WD: water deprivation

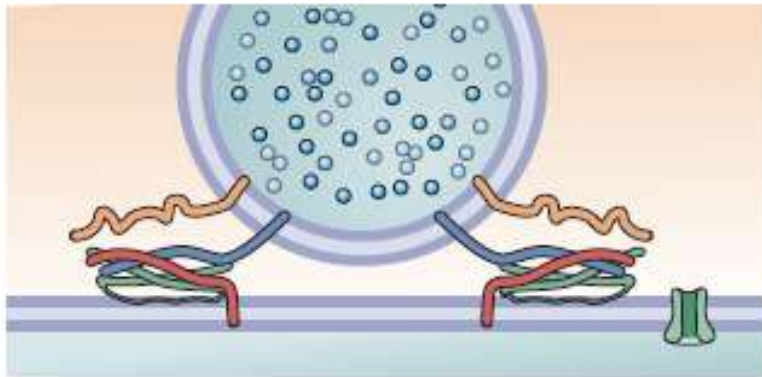
SON: liberação de ADH, controle hídrico

# Cálcio induz liberação de vesículas contendo CRH

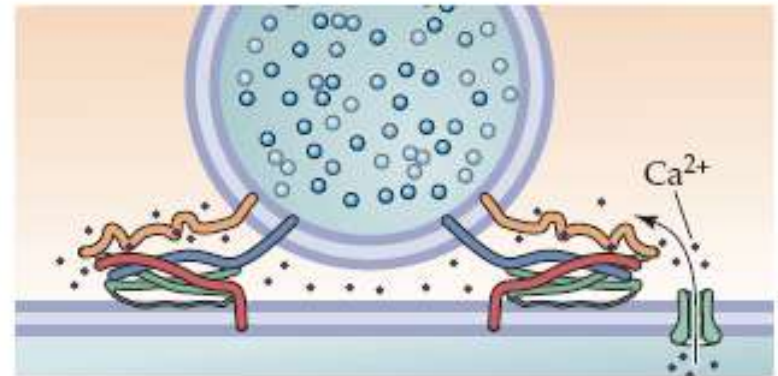
(1) Vesicle docks



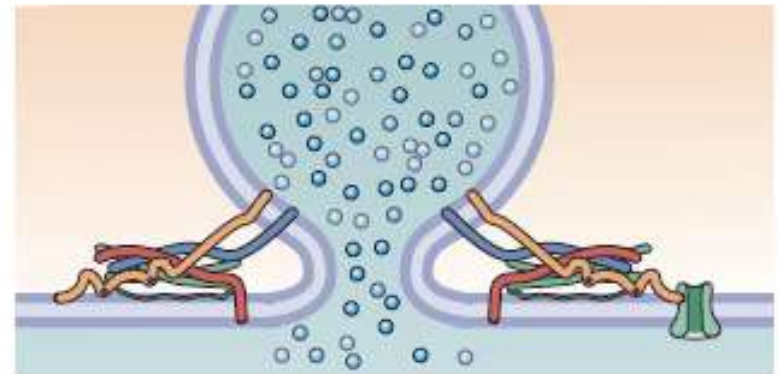
(2) SNARE complexes form to pull membranes together



(3) Entering  $Ca^{2+}$  binds to synaptotagmin

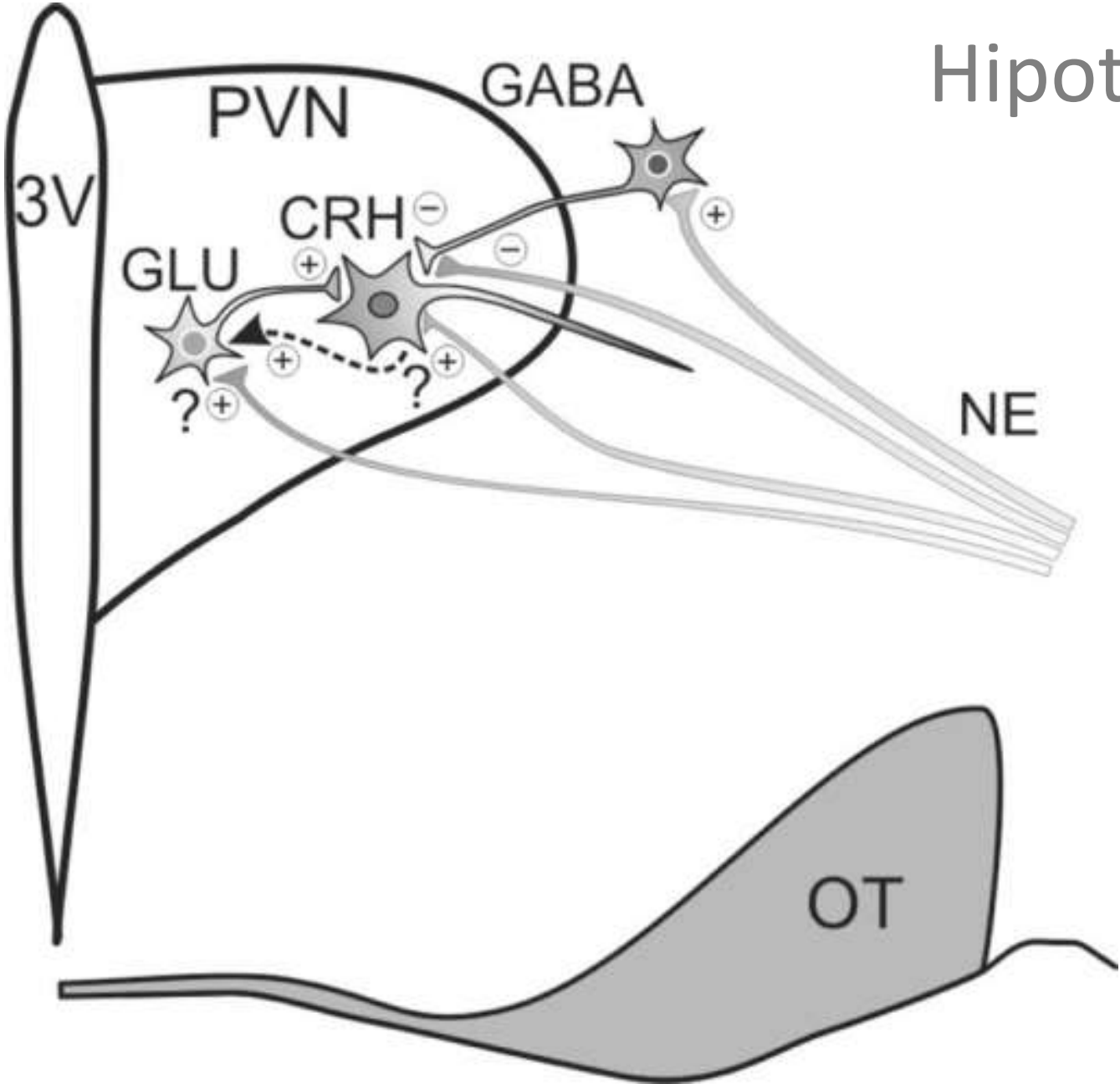


(4)  $Ca^{2+}$ -bound synaptotagmin catalyzes membrane fusion

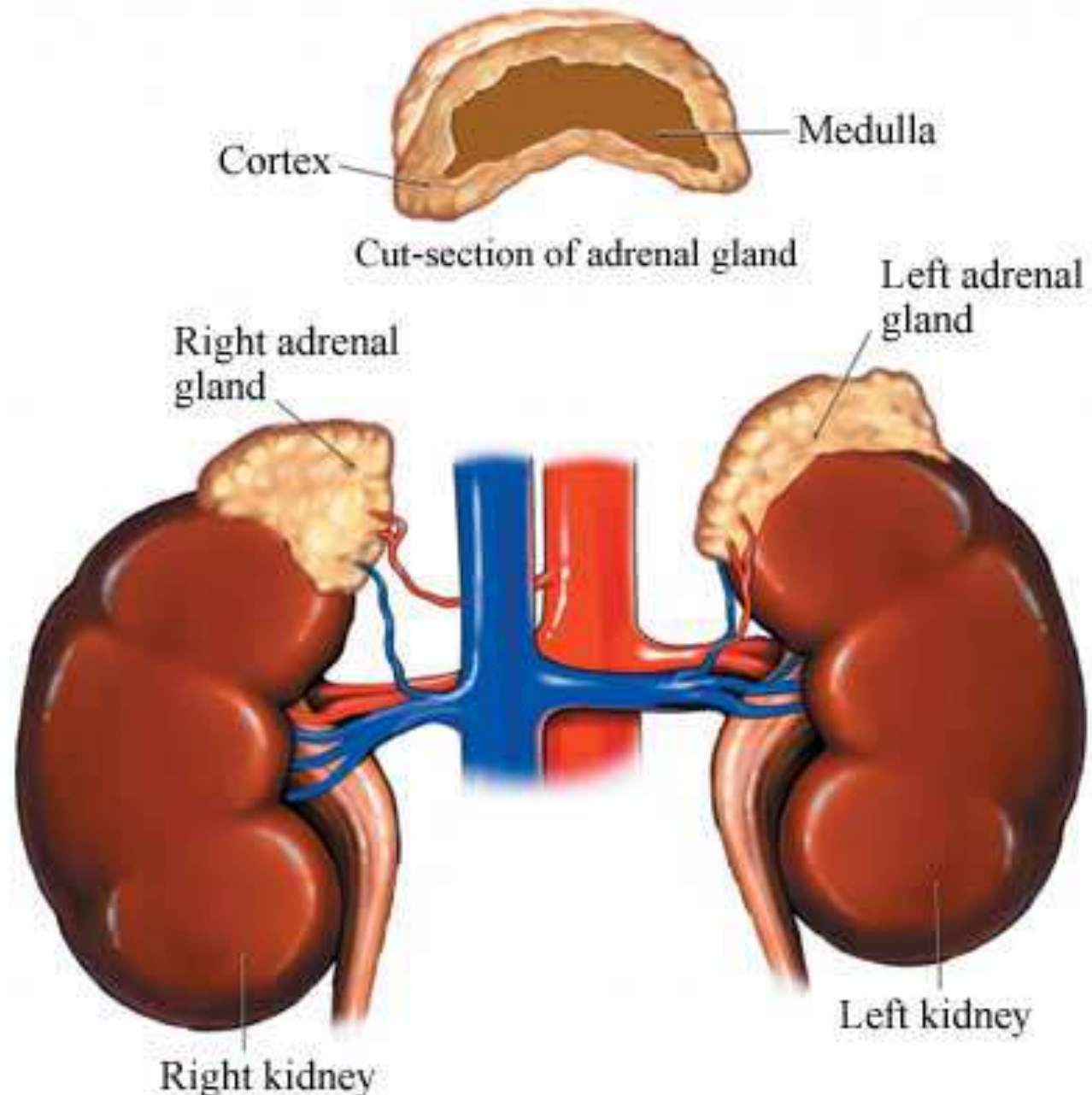




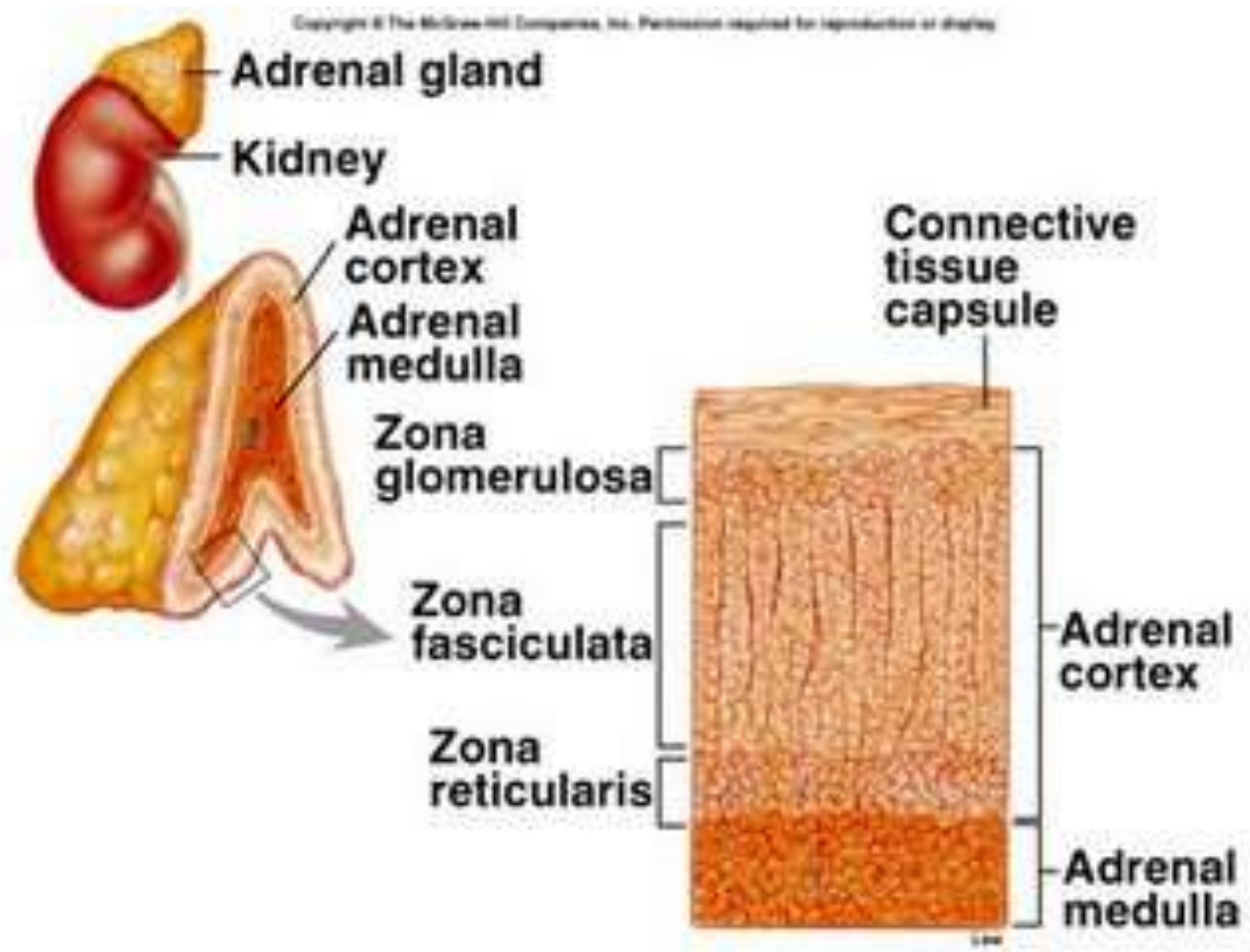
# Hipotálamo



# Glândulas adrenais

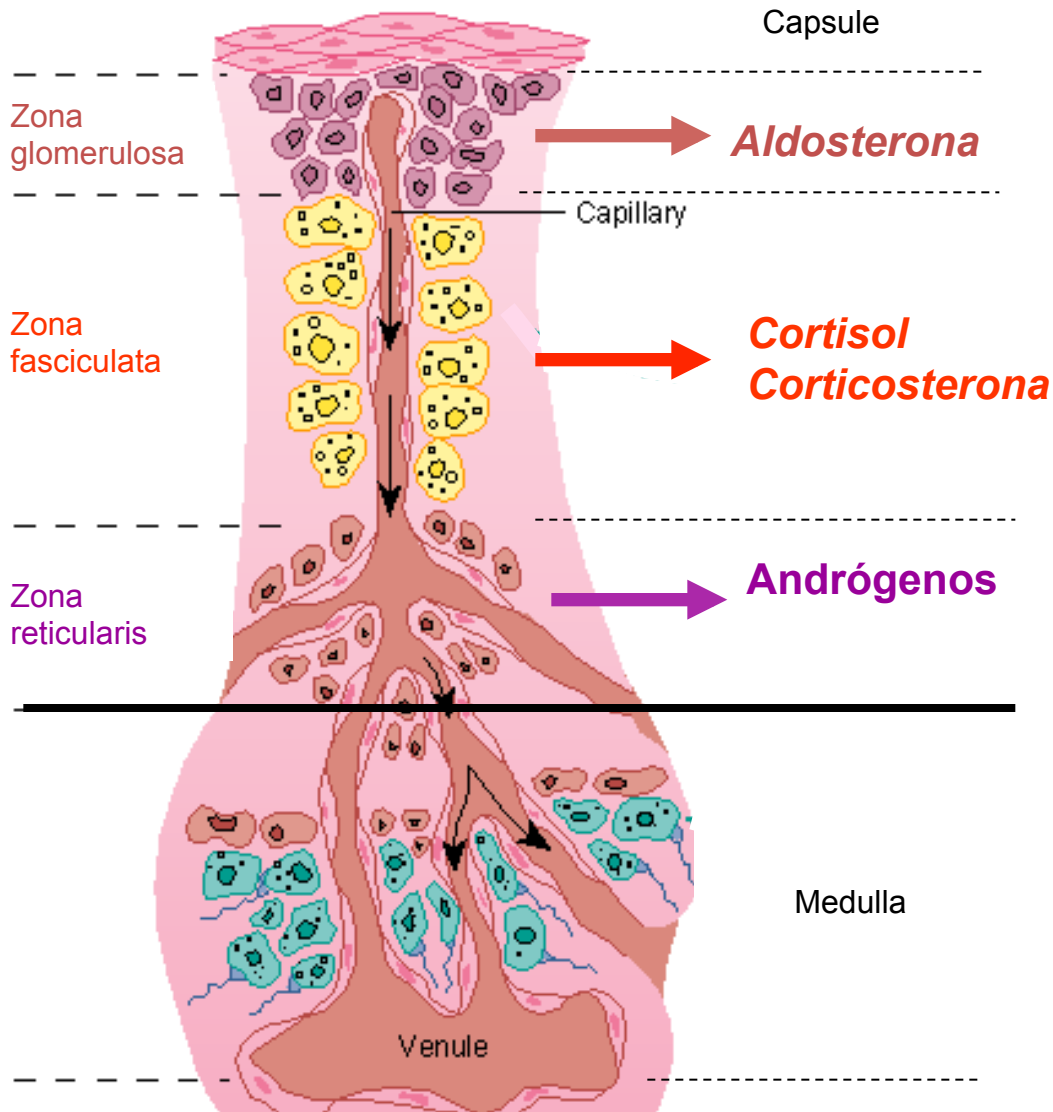


# Glândulas adrenais



# Córtex Adrenal - 3 camadas

## 3 grupos de hormônios (esteroidais)

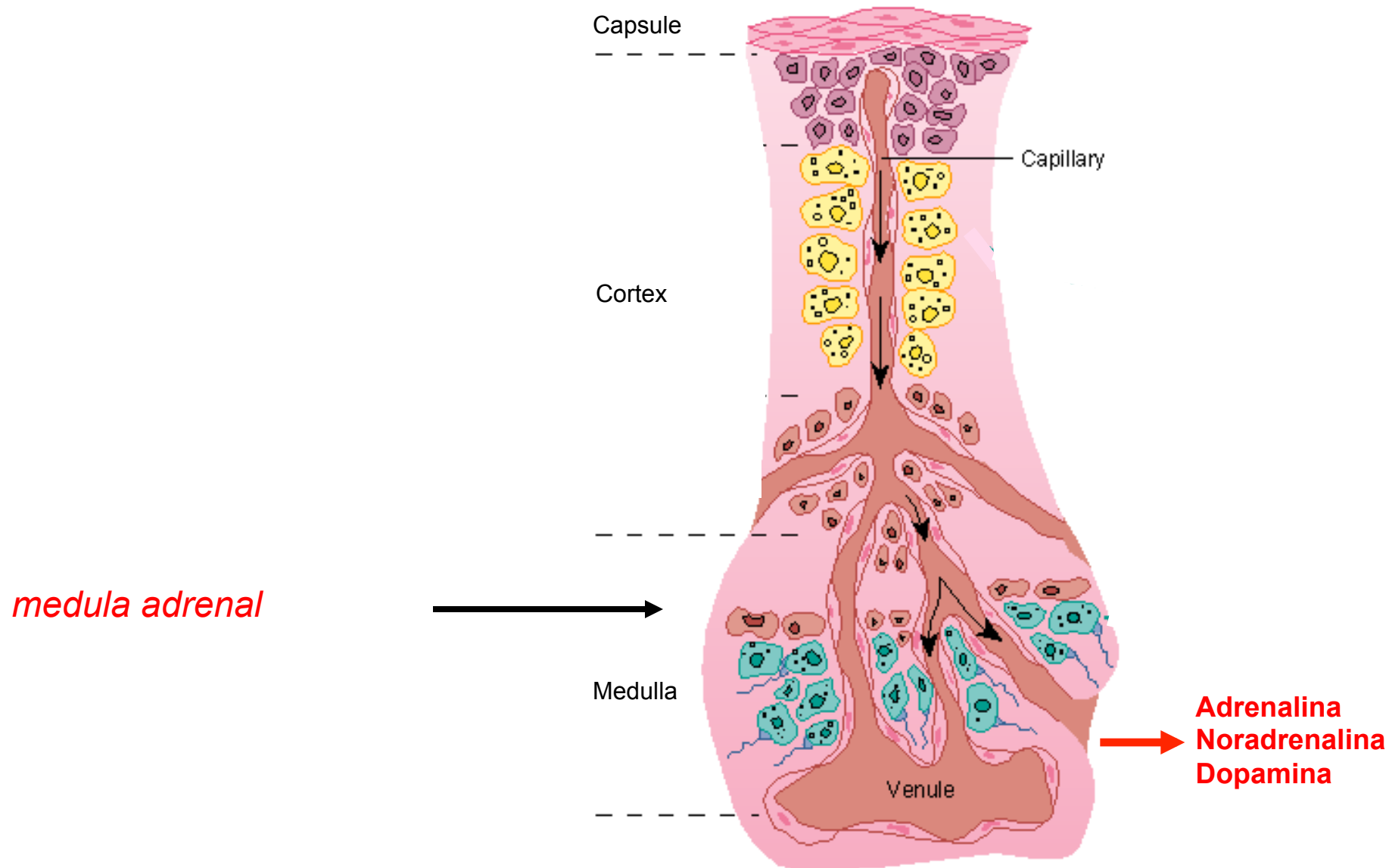


**Mineralocorticóides**  
aldosterona

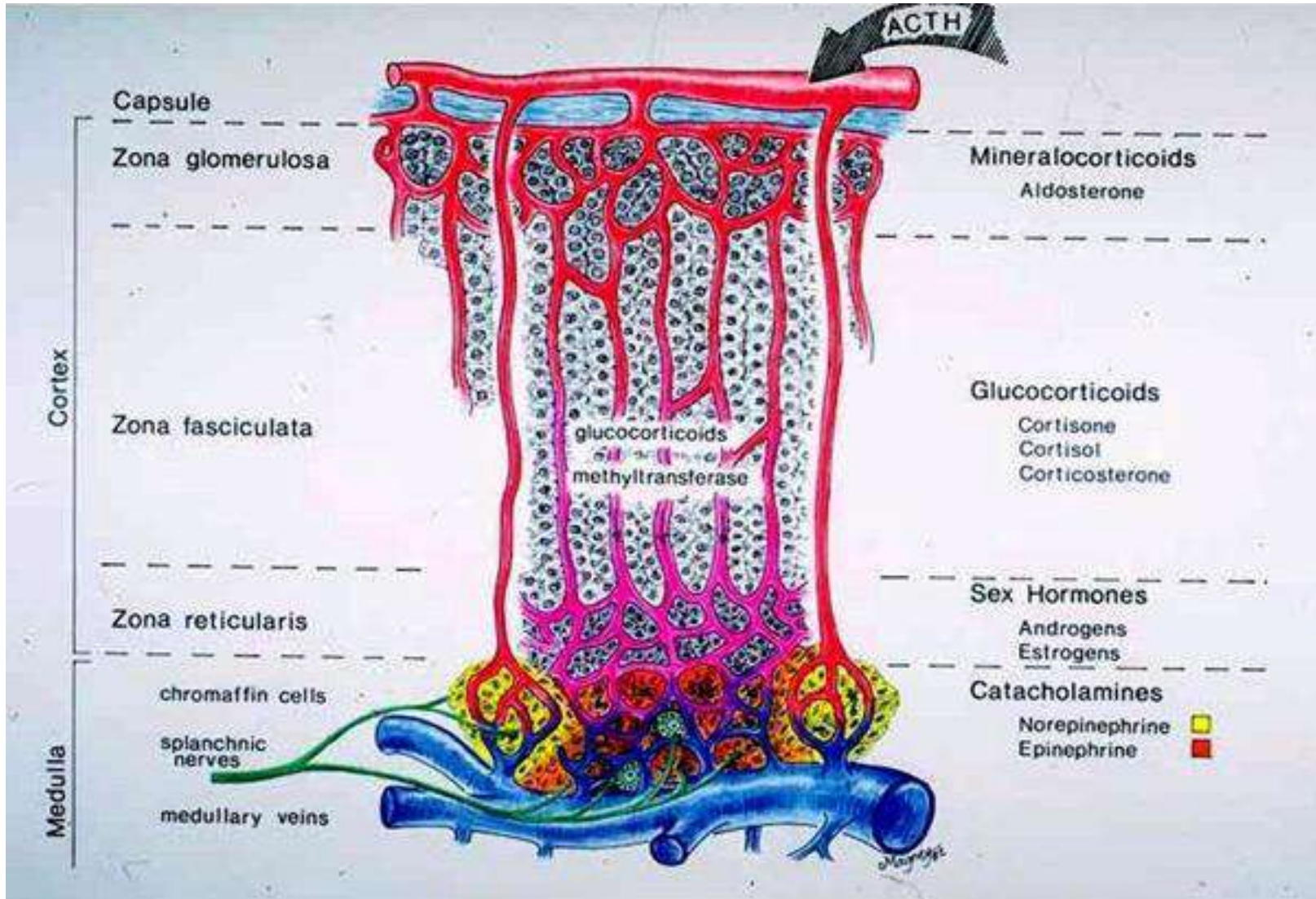
**Glicocorticóides**  
• cortisol  
• corticosterona

**Andrógenos adrenais**  
androstenediona

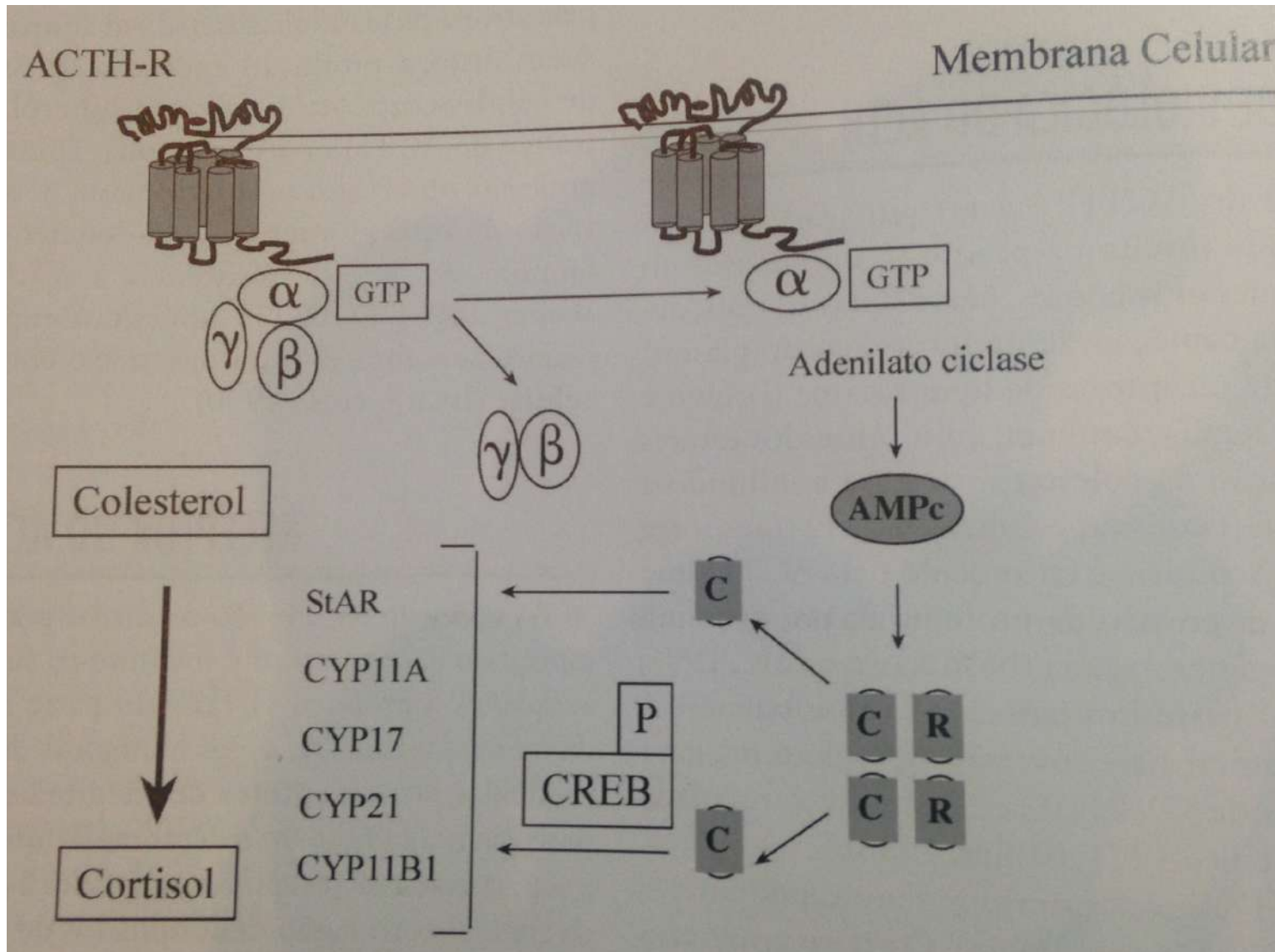
# Medula Adrenal



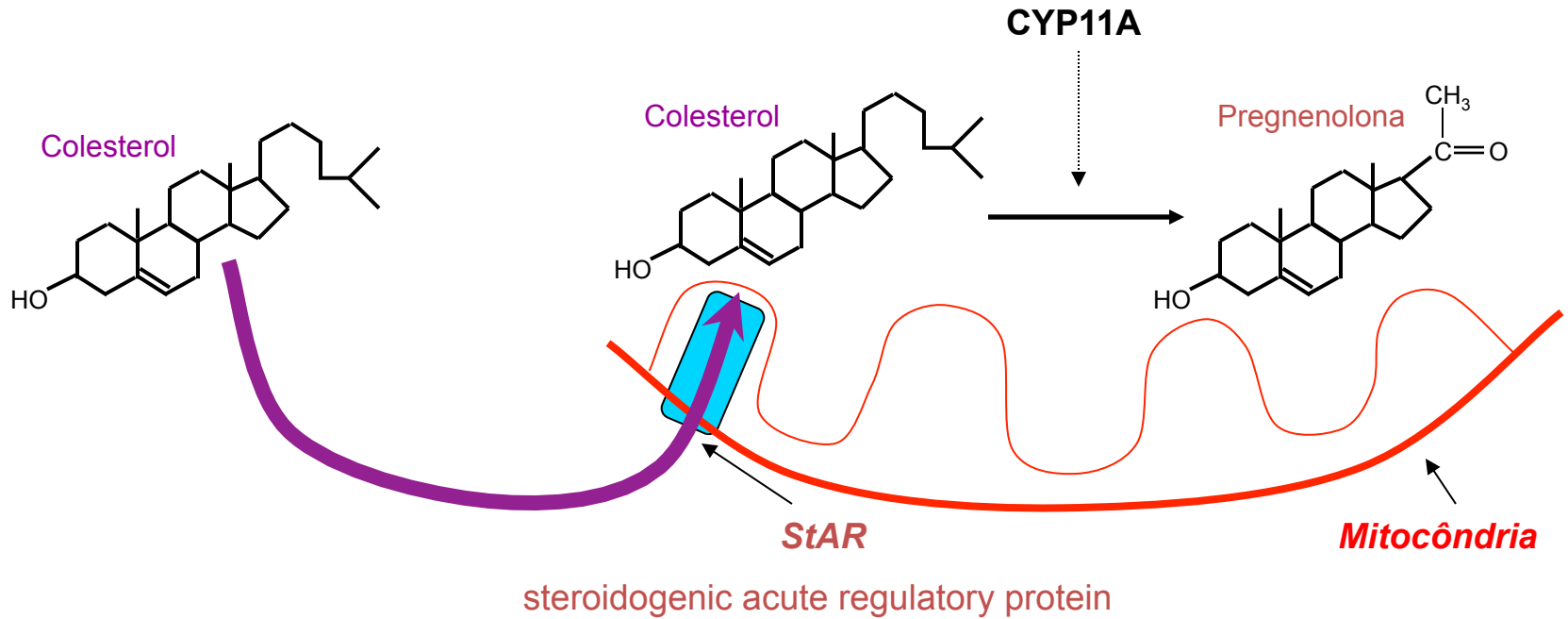
# Glândulas adrenais



# Sinalização do receptor de ACTH na célula adrenocortical



# Liberação do colesterol na membrana da mitocôndria



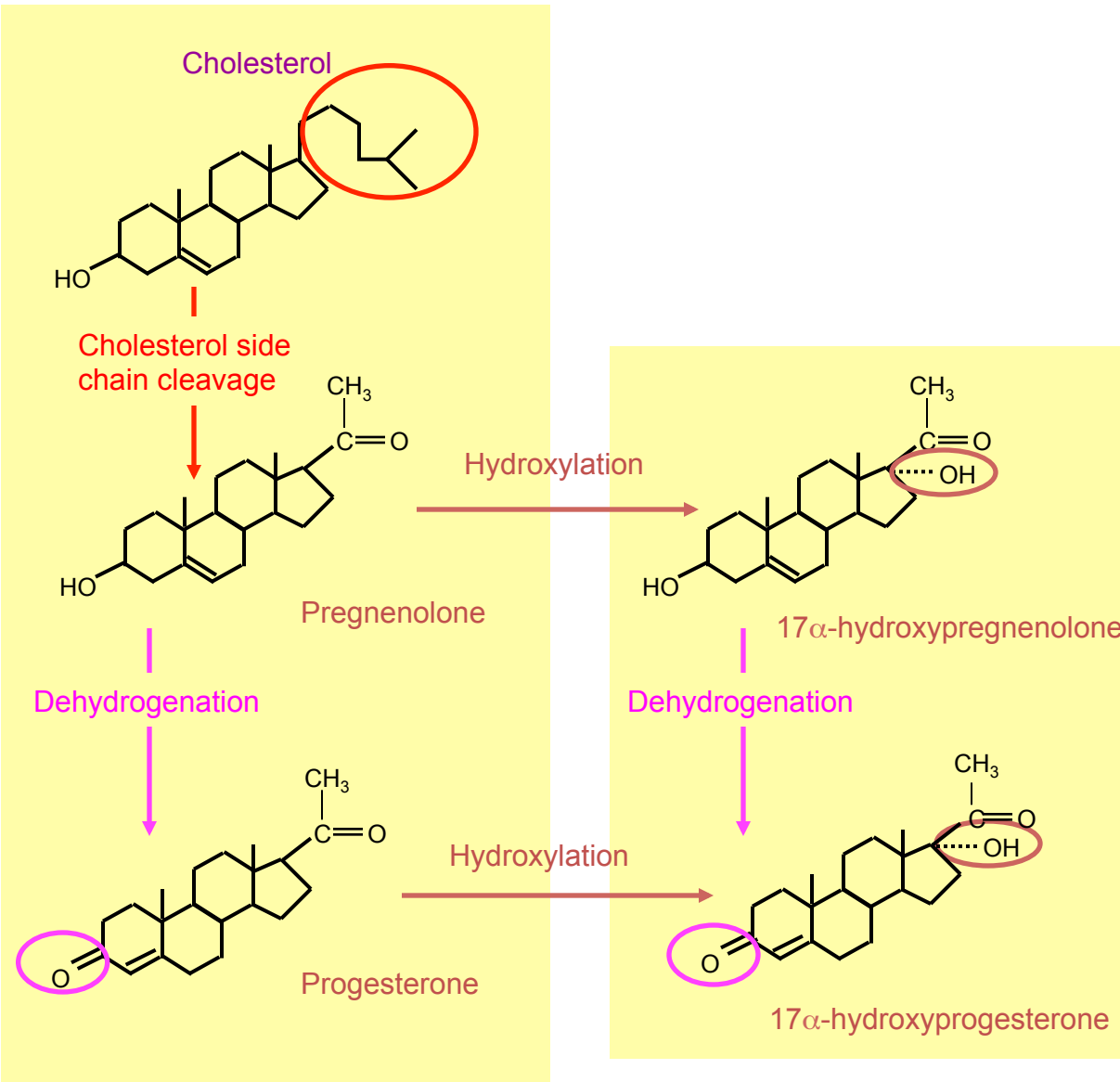


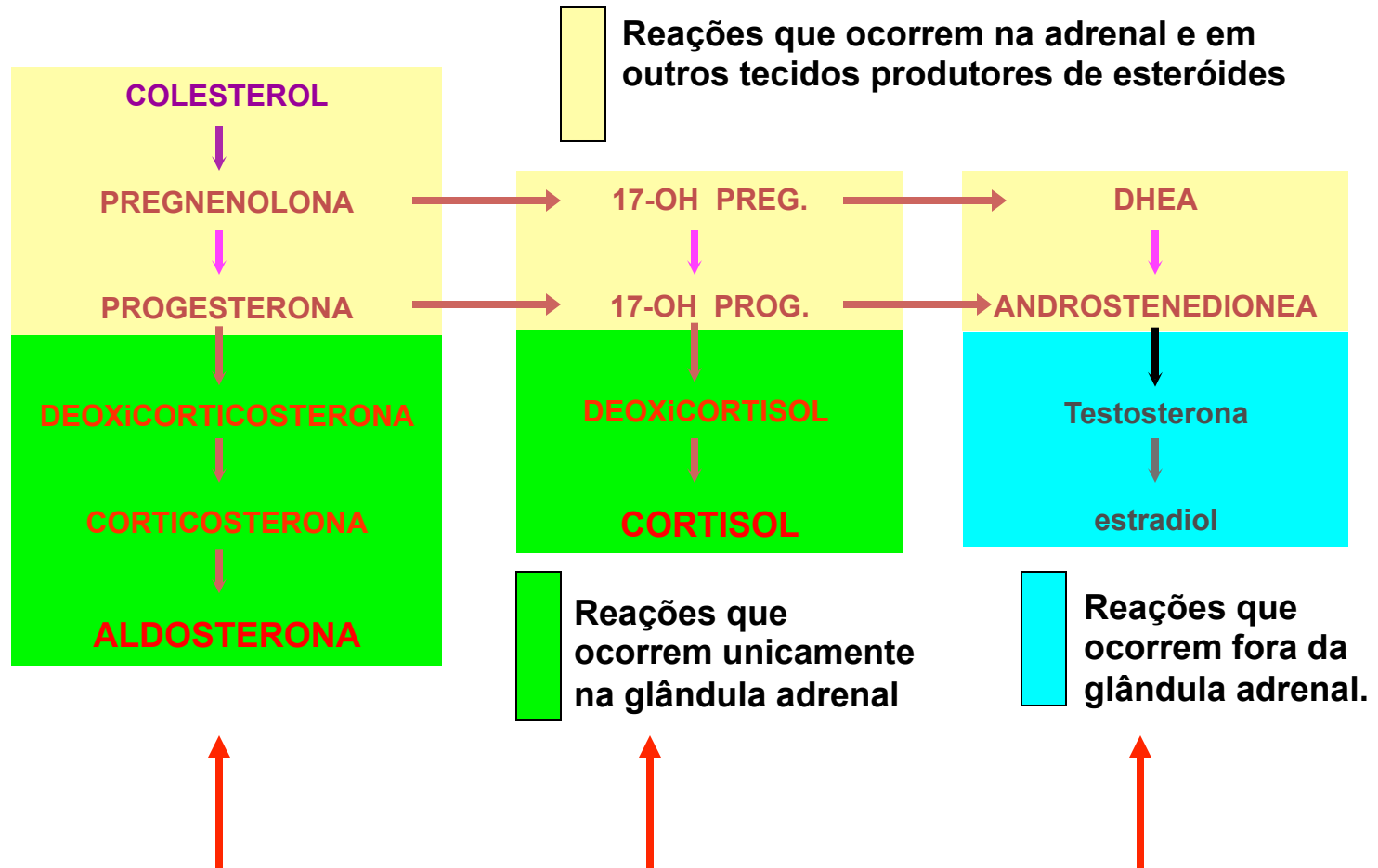
colesterol  $\Rightarrow$  pregnenolona



17- $\alpha$ hidroxiprogesterona

progesterona

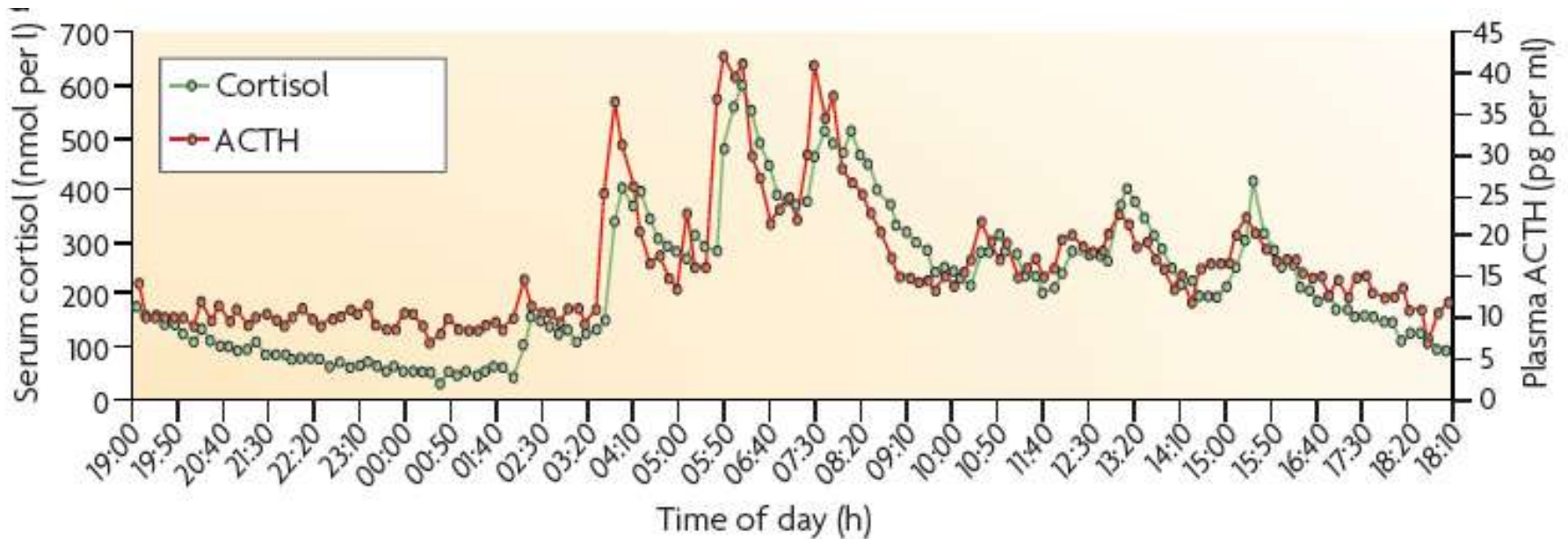




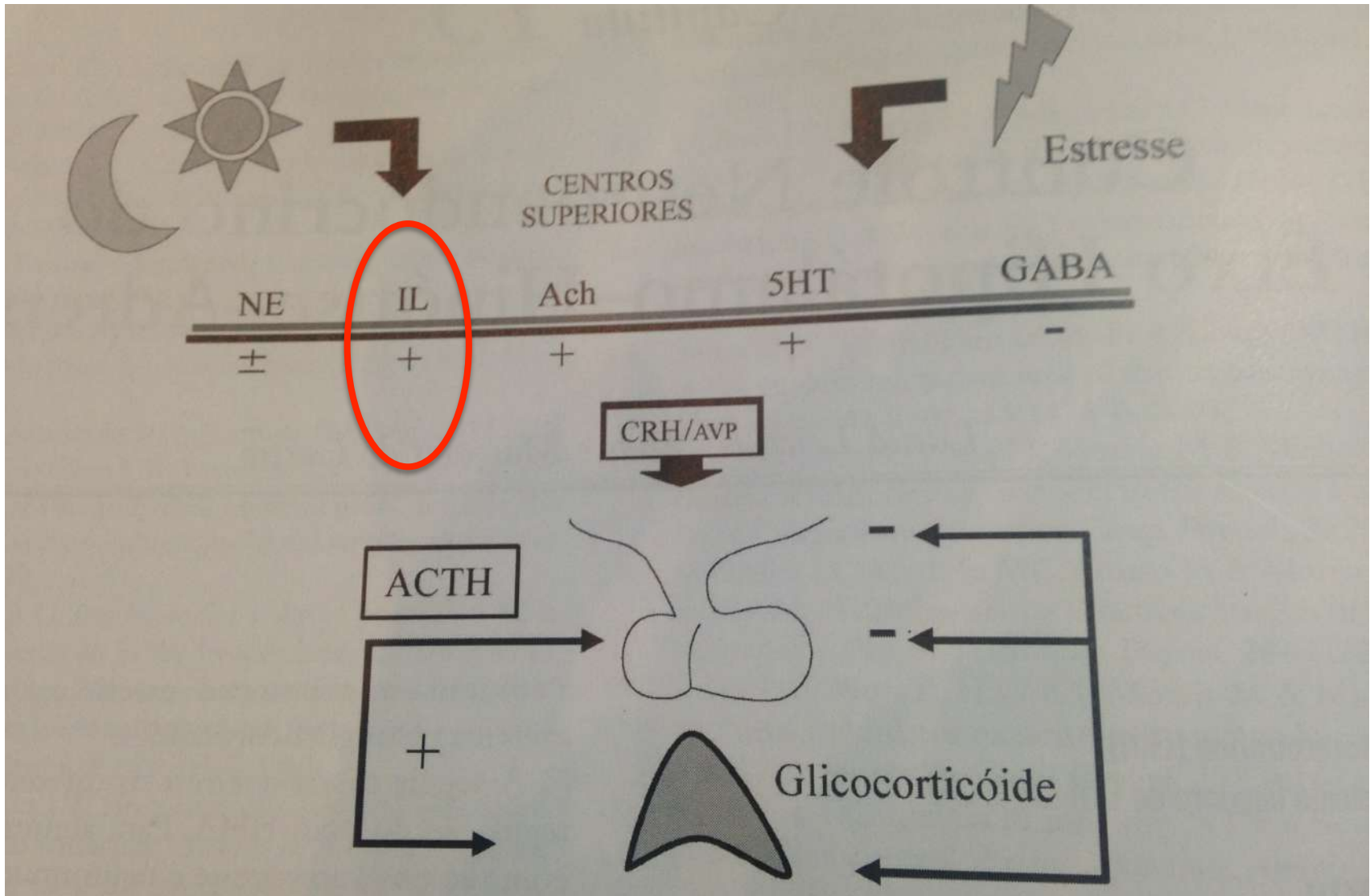
Vias biossintéticas distintas para cada hormônio

# ACTH e glicocorticóide

## Ritmos circadiano e ultradiano



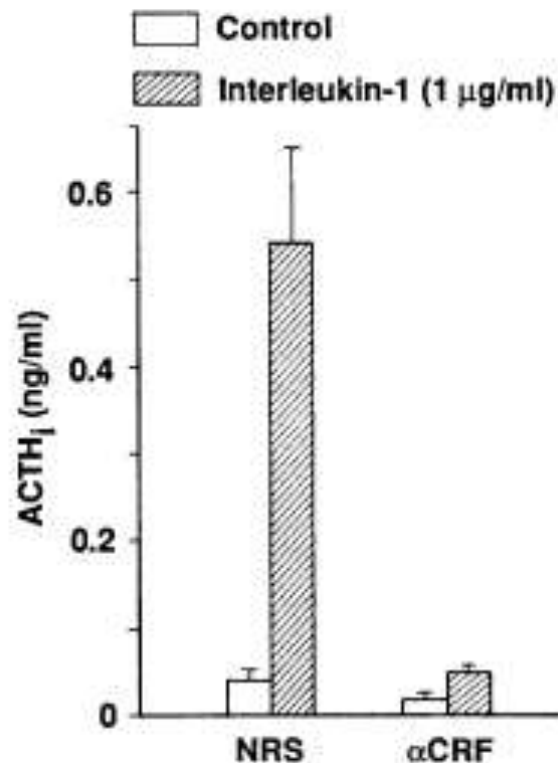
# Regulação do eixo Hipotálamo-Hipófise-Adrenal



# Corticotropin-Releasing Factor–Producing Neurons in the Rat Activated by Interleukin-1

FRANK BERKENBOSCH, JOEP VAN OERS, ADRIANA DEL REY, FRED TILDERS, HUGO BESEDOVSKY

Intraperitoneal administration of human recombinant interleukin-1 (IL-1) to rats can increase blood levels of corticosterone and adrenocorticotrophic hormone (ACTH). The route by which IL-1 affects pituitary-adrenal activity is unknown. That the IL-1-induced pituitary-adrenal activation involves an increased secretion of corticotropin-releasing factor (CRF) is indicated by three lines of evidence. First, immunoneutralization of CRF markedly attenuated the IL-1-induced increase of ACTH blood levels. Second, after blockade of fast axonal transport in hypothalamic neurons by colchicine, IL-1 administration decreased the CRF immunostaining in the median eminence, indicating an enhanced release of CRF in response to IL-1. Third, IL-1 did not stimulate ACTH release from primary cultures of anterior pituitary cells. These data further support the notion of the existence of an immunoregulatory feedback circuit between the immune system and the brain.



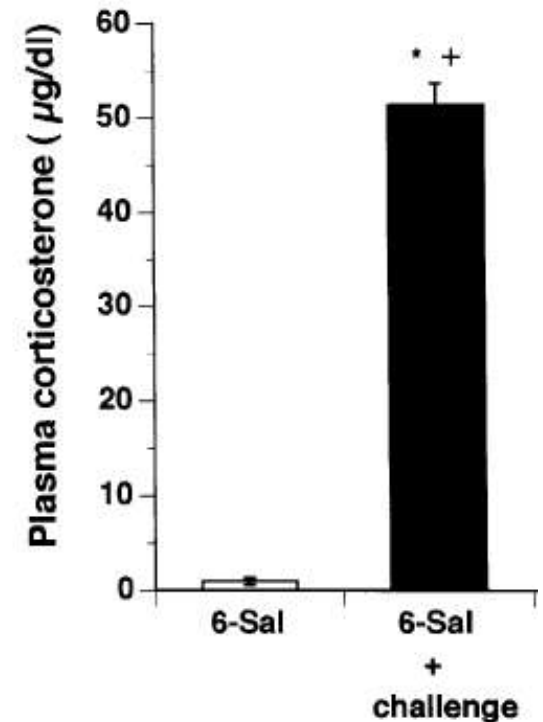
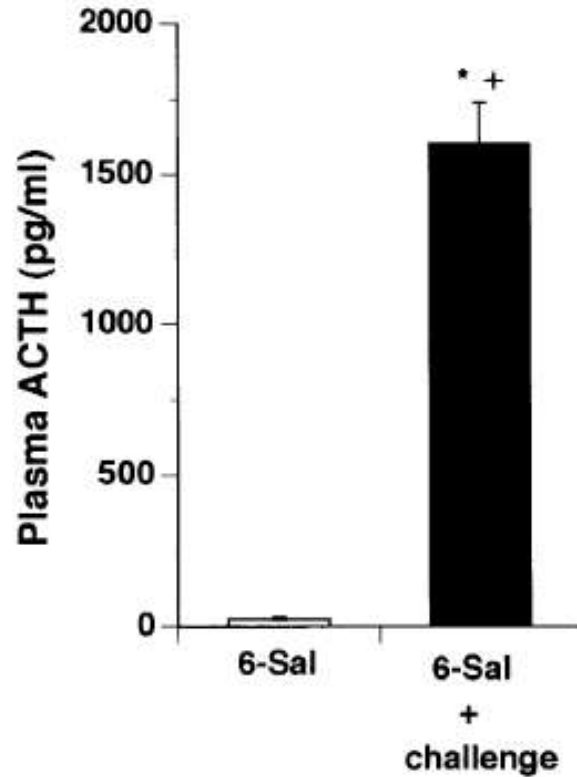
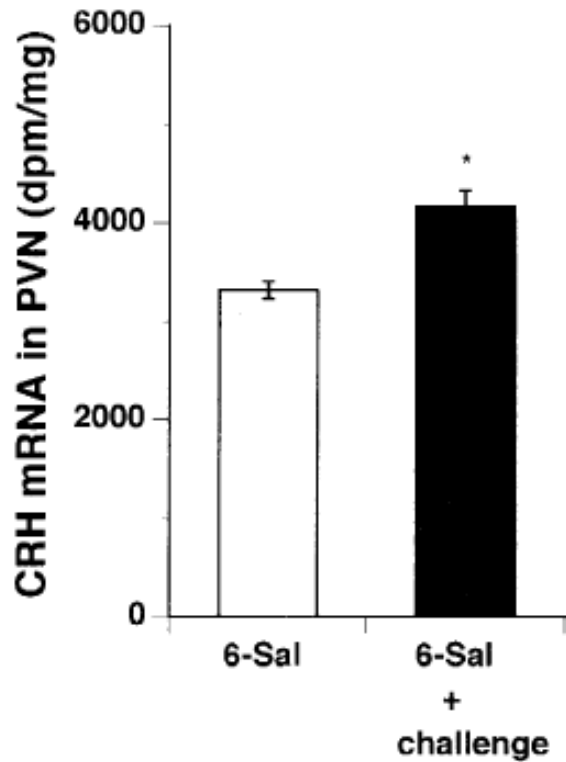
Ratos tratados com soro normal de coelho ou com anticorpo contra CRF de coelho, injetados ou não com IL-1 de humano.

ACTH: adrenocorticotrophic hormone

## Inflamação sistêmica

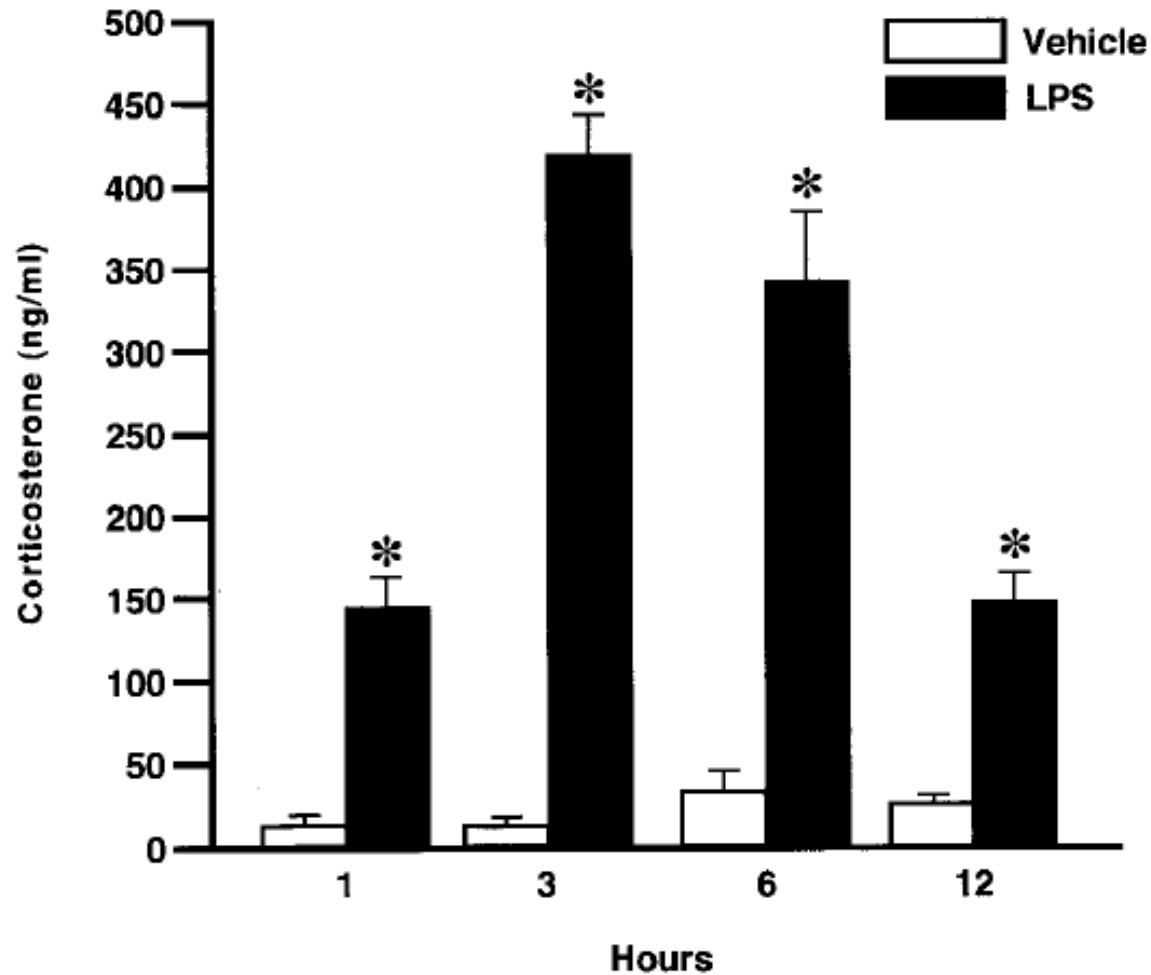
CRF: corticotropin-releasing factor

# Inflamação sistêmica



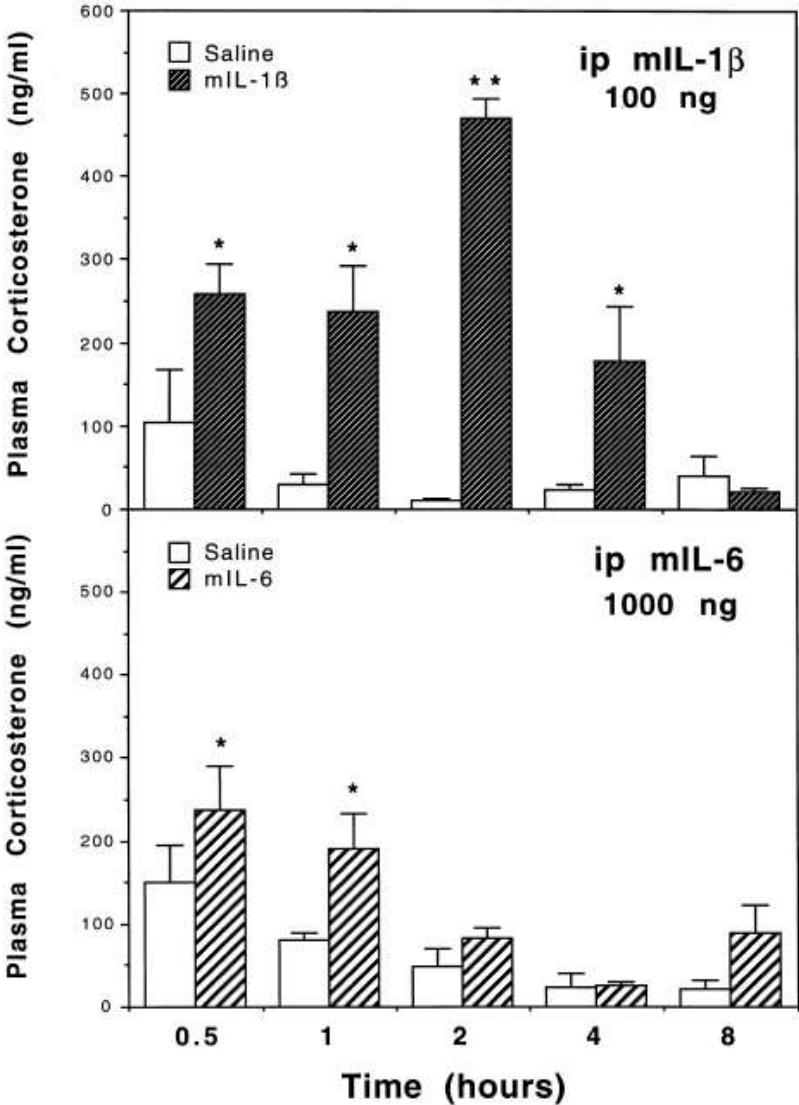
Aumento de CRH, aumento de ACTH, aumento corticosterona

# Inflamação sistêmica



Decurso temporal na produção de glicocorticóides

# Ativadores imunológicos do HPA



**FIGURE 1.** Effects of mIL-1 $\beta$  and IL-6 on plasma corticosterone. Mouse IL-1 $\beta$  (100 ng/mouse) (*top*) or mouse IL-6 (1  $\mu$ g/mouse) (*bottom*) was injected i.p., and samples collected at various subsequent times. Plasma corticosterone was determined by radioimmunoassay.  $N = 7$ . \*Significantly different from the corresponding saline groups (\* $p < 0.05$  or \*\* $p < 0.01$ , respectively). Data from the bottom figure are from Wang and Dunn.<sup>27</sup>



# Ativadores imunológicos do HPA

**TABLE 1. HPA responses to cytokine administration in mice**

Cytokine	
IL-1 $\alpha$ /IL-1 $\beta$	Potent and prolonged (see FIG. 1)
IL-2	No effect
IL-6	Weak, short-lived response (see FIG. 1)
TNF $\alpha$	Weak, but slower than IL-6
IFN $\alpha$	No effect

# Glicocorticóides - Funções

## Metabolismo energético

- Aumento de disponibilidade energética
- Quebra de proteínas para serem transformadas em glicose no fígado;
- Quebra de gordura corporal – disponibilização de energia par o corpo

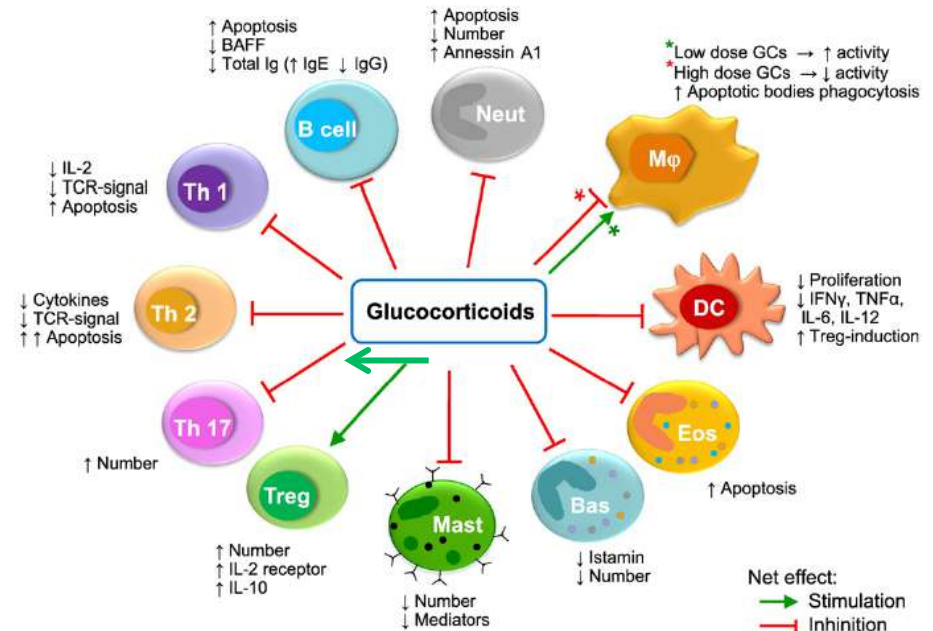
## Balanço hídrico

- Aumenta a reabsorção de sódio e água pelos rins . Atua em sinergismo com a aldosterona.

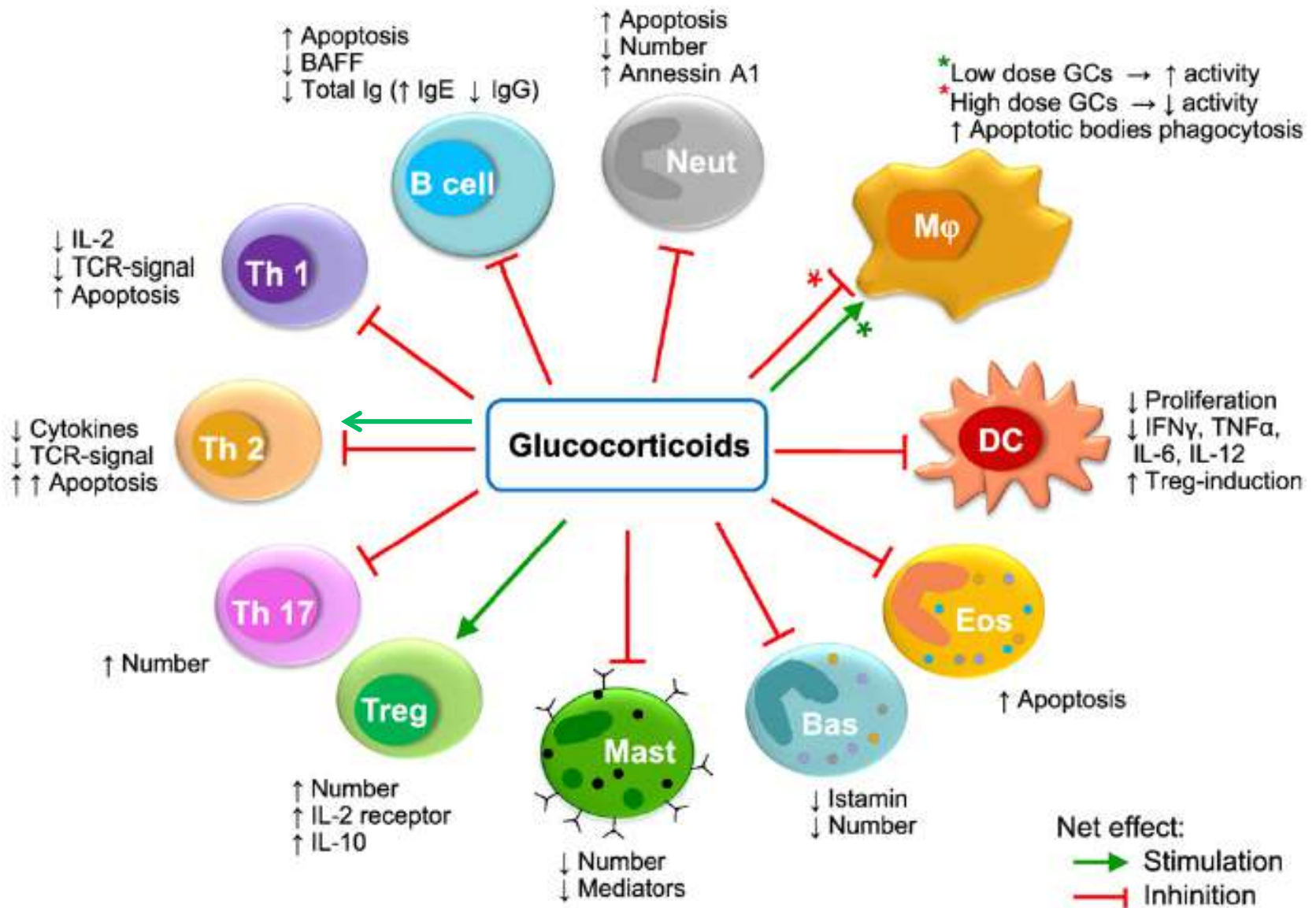
## Manutenção do tônus muscular dos vasos sanguíneos

- Melhor circulação sanguínea

## • CONTROLE IMUNOLÓGICO



# Efeitos dos glicocorticóides sobre células imune

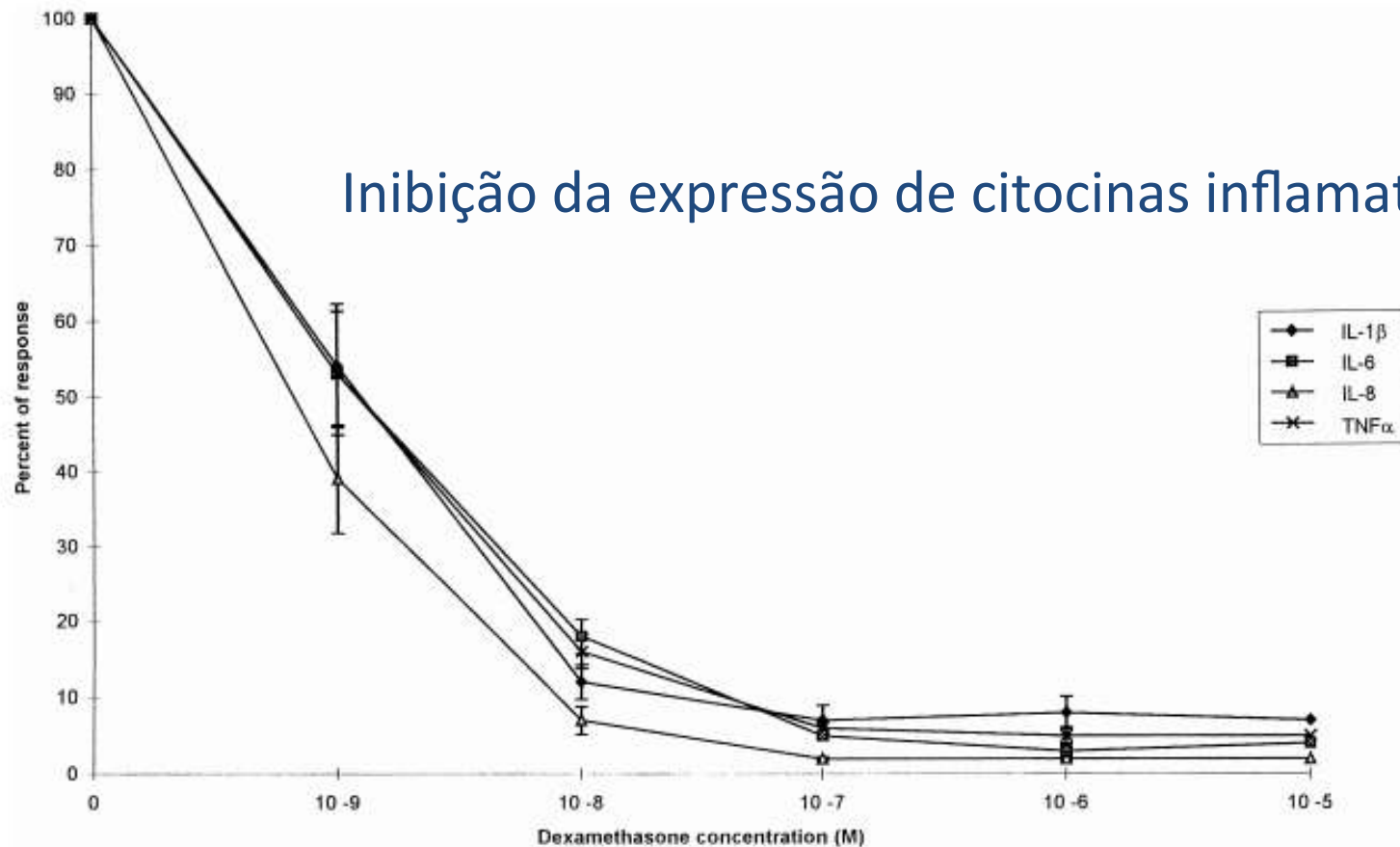


# Efeitos dos Glicocorticóides nas Células Imunes

PBMCs: peripheral blood monuclear cells

Tratamento: LPS

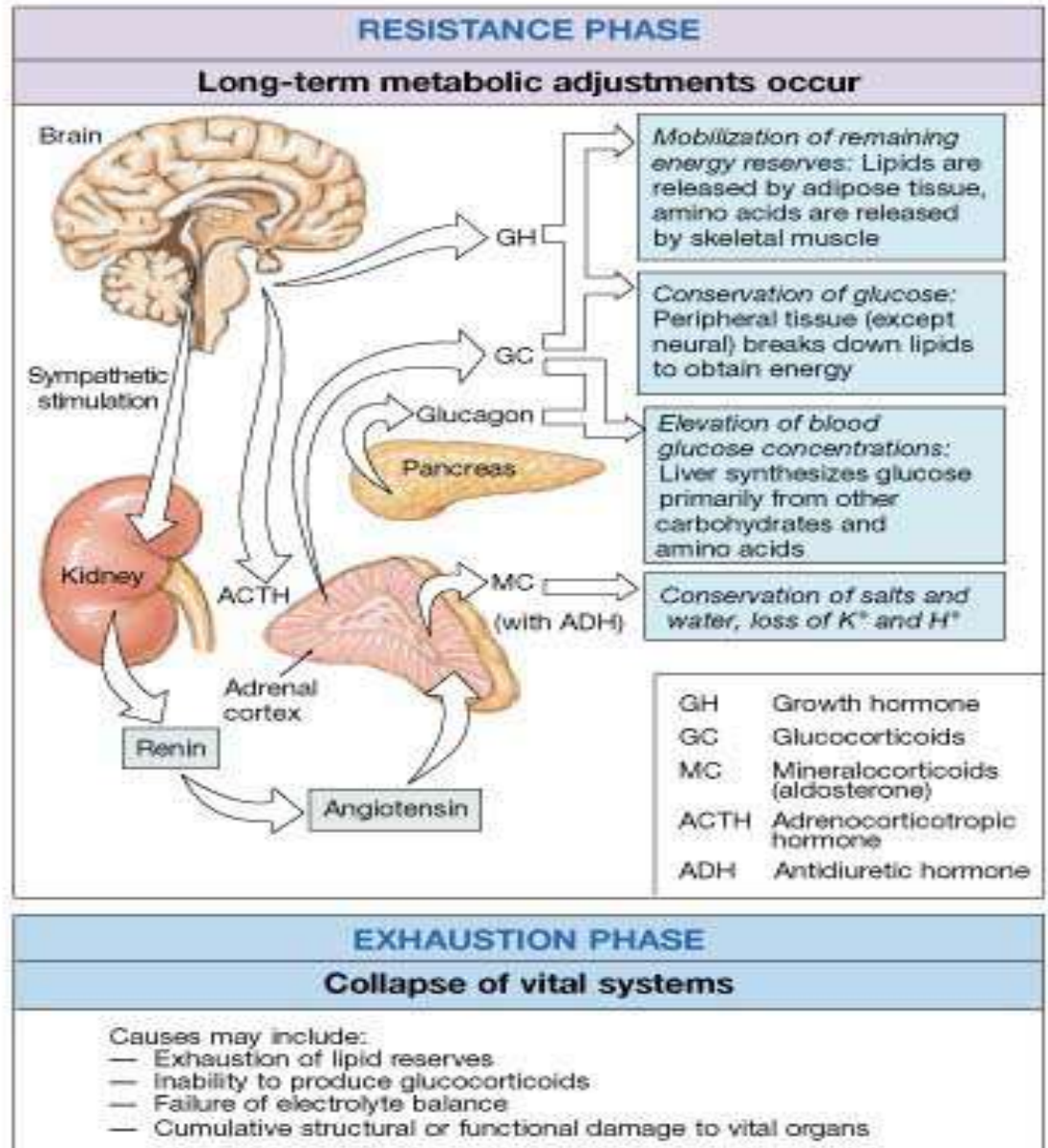
Incubação: 24 horas



# Efeitos dos glicocorticóides sobre células imune

<b>Células</b>	<b>Efeitos</b>
<b>Linfócitos</b>	<b>Reduz número de células circulantes</b> <b>Inibe a ativação/proliferação (inibindo IL-2)</b> <b>Induz apoptose</b> <b>Suprime a ativação das células NK</b>
<b>Monócitos</b>	<b>Reduz número de células circulantes</b> <b>Inibe secreção de IL-1, IL-6, TNF-<math>\alpha</math> e quimiocinas</b> <b>Reduz síntese de colagenase, elastase ativador de plasminogem no tecido</b>
<b>Eosinófilos</b>	<b>Reduz número de células circulantes</b> <b>Reduz sobrevivência (diminuição na liberação de GM-CSF endotelial)</b> <b>Reduz a aderência ao endotélio (inibição IL-1)</b>
<b>Basófilos</b>	<b>Reduz número de células circulantes</b> <b>Diminui a liberação de histamina e leucotrienos</b> <b>Inibe a expansão de mastócitos</b>
<b>Neutrófilos</b>	<b>Aumenta número de células circulantes</b> <b>Reduz quimiotaxia (diminuição de IL-1, IL-8 e leucotrieno B4)</b> <b>Reduz a aderência ao endotélio</b>

# Ações Biológicas de Glicocorticóides durante períodos de estresse

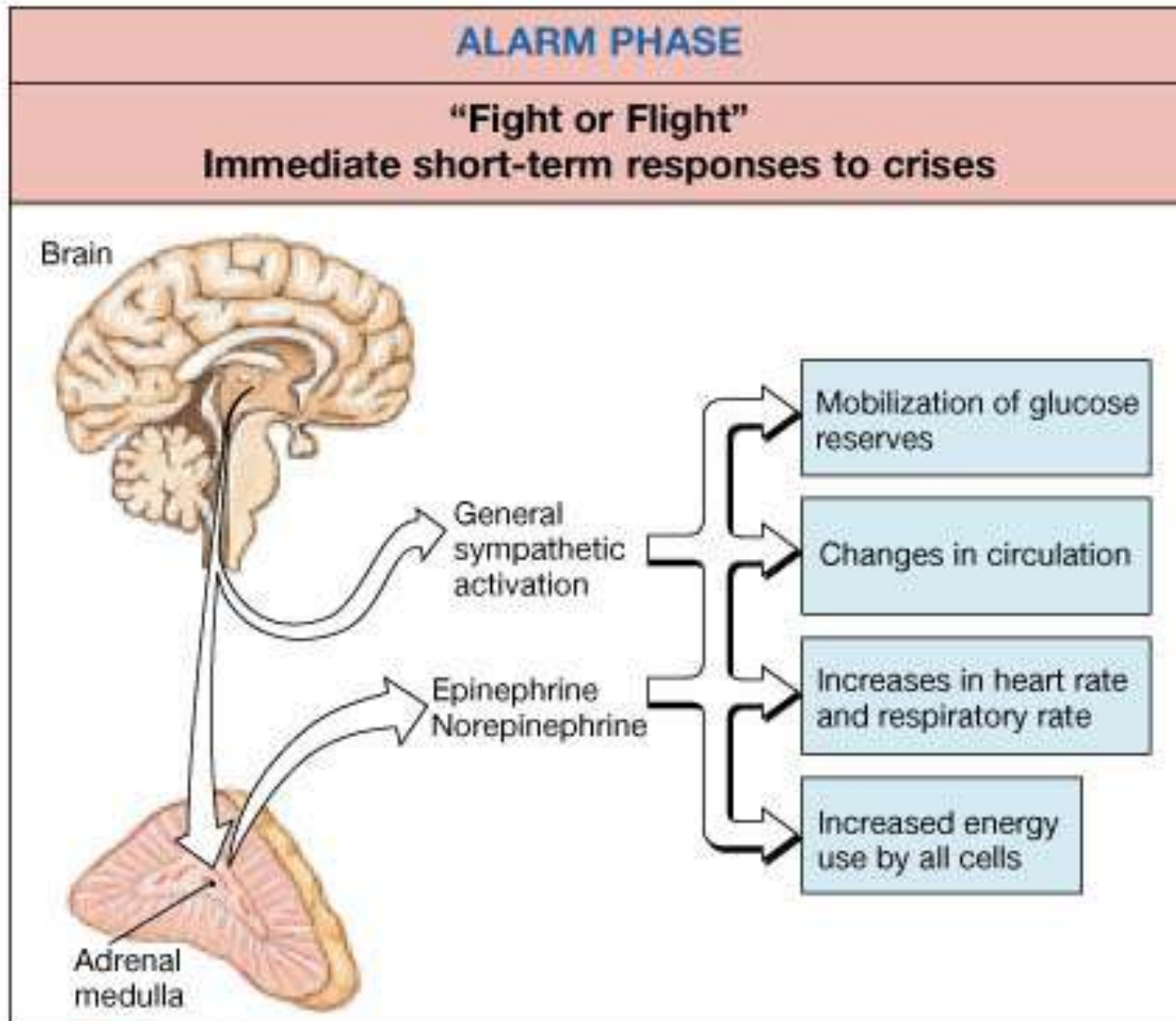


Mobilização de estoques de energia

↓  
por estimular gliconeogênese lipólise

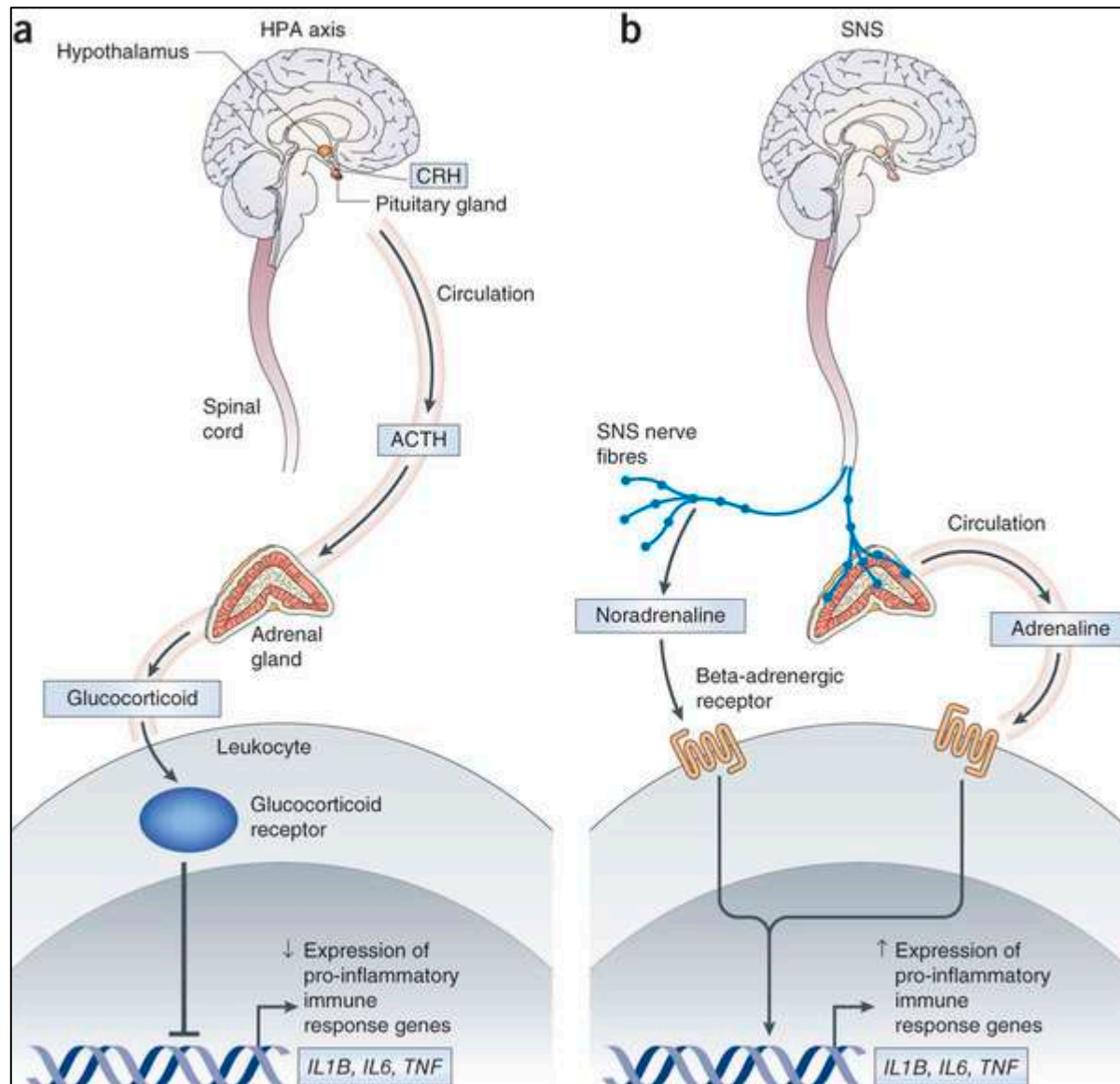
# Ações Biológicas dos Hormônios da Medula da adrenal

## Resposta imediata ao estresse

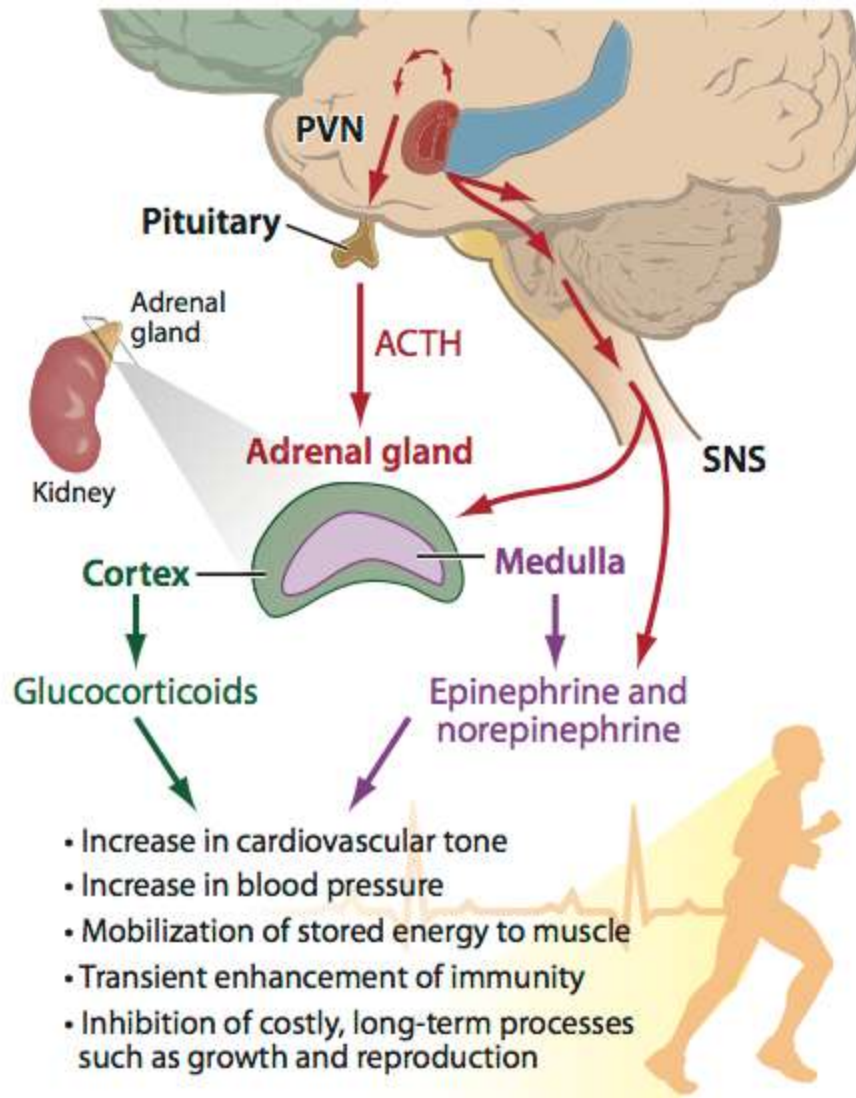


**The General Adaptation Syndrome**

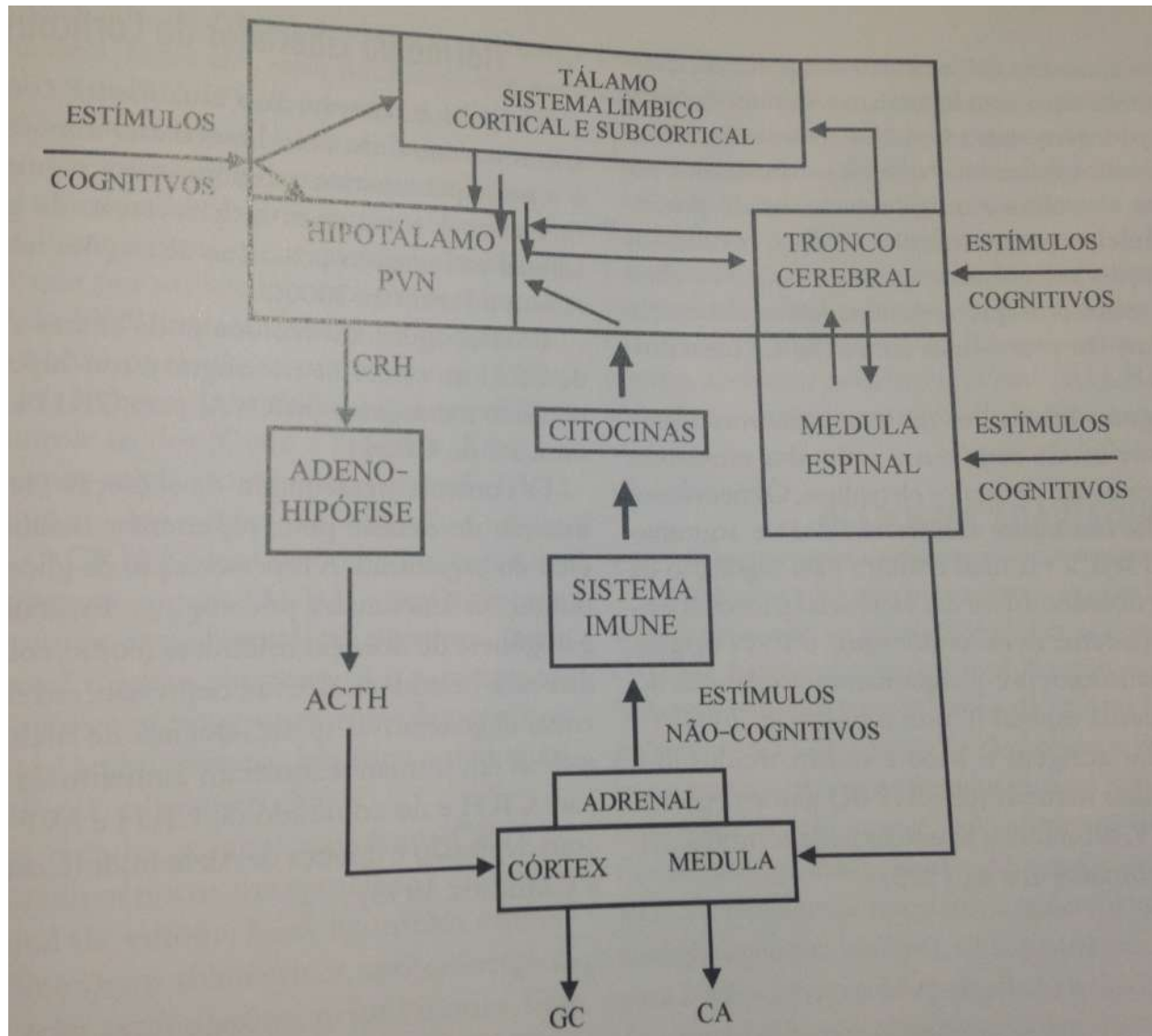
# CNS regulation of inflammatory gene expression in immune cells



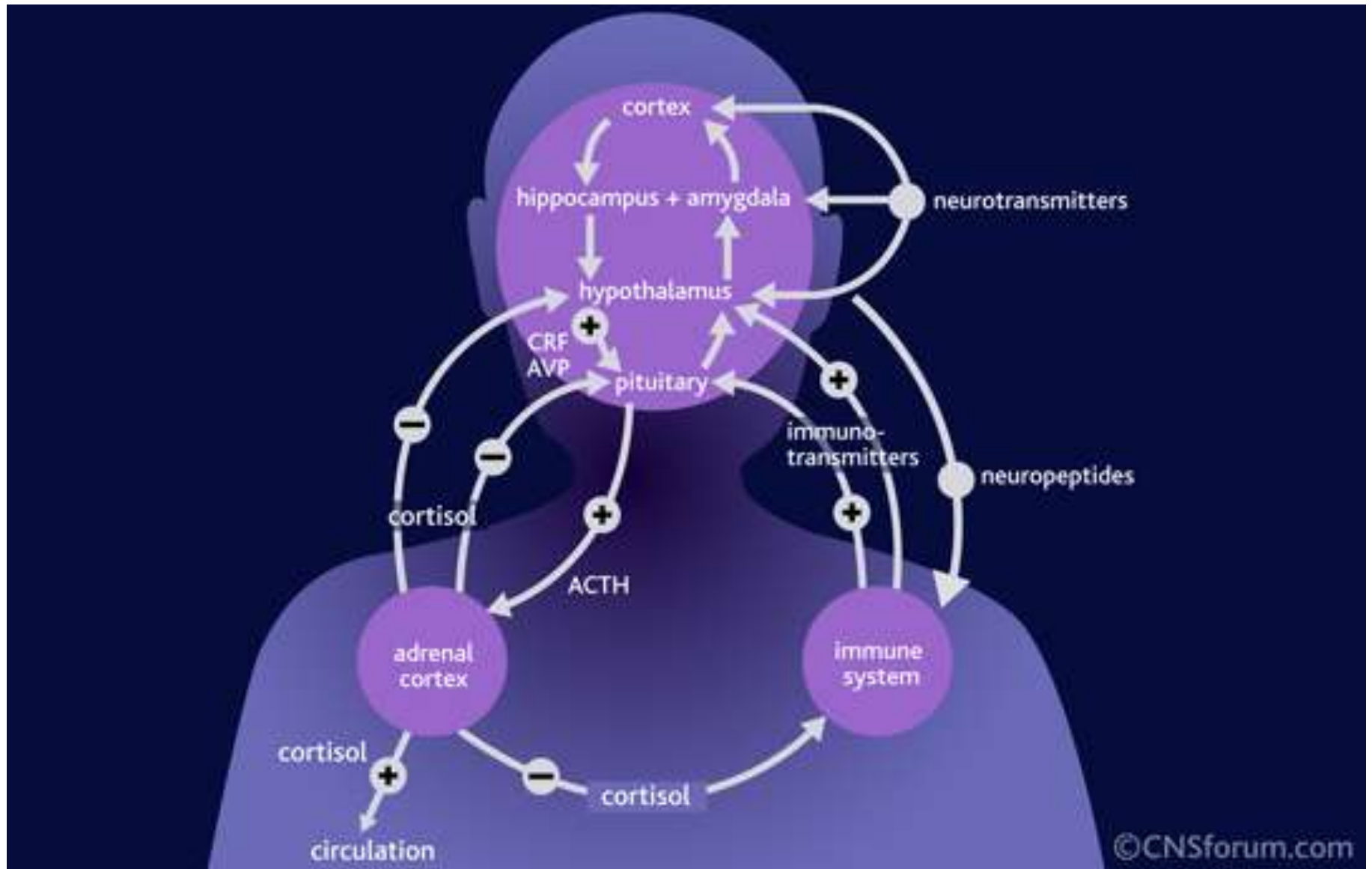




# Sistema de estresse: componentes sensoriais e de integração



# Funcionamento normal do eixo HPA



# Alteração do funcionamento do eixo HPA pode levar a quadro fisiopatológicos

