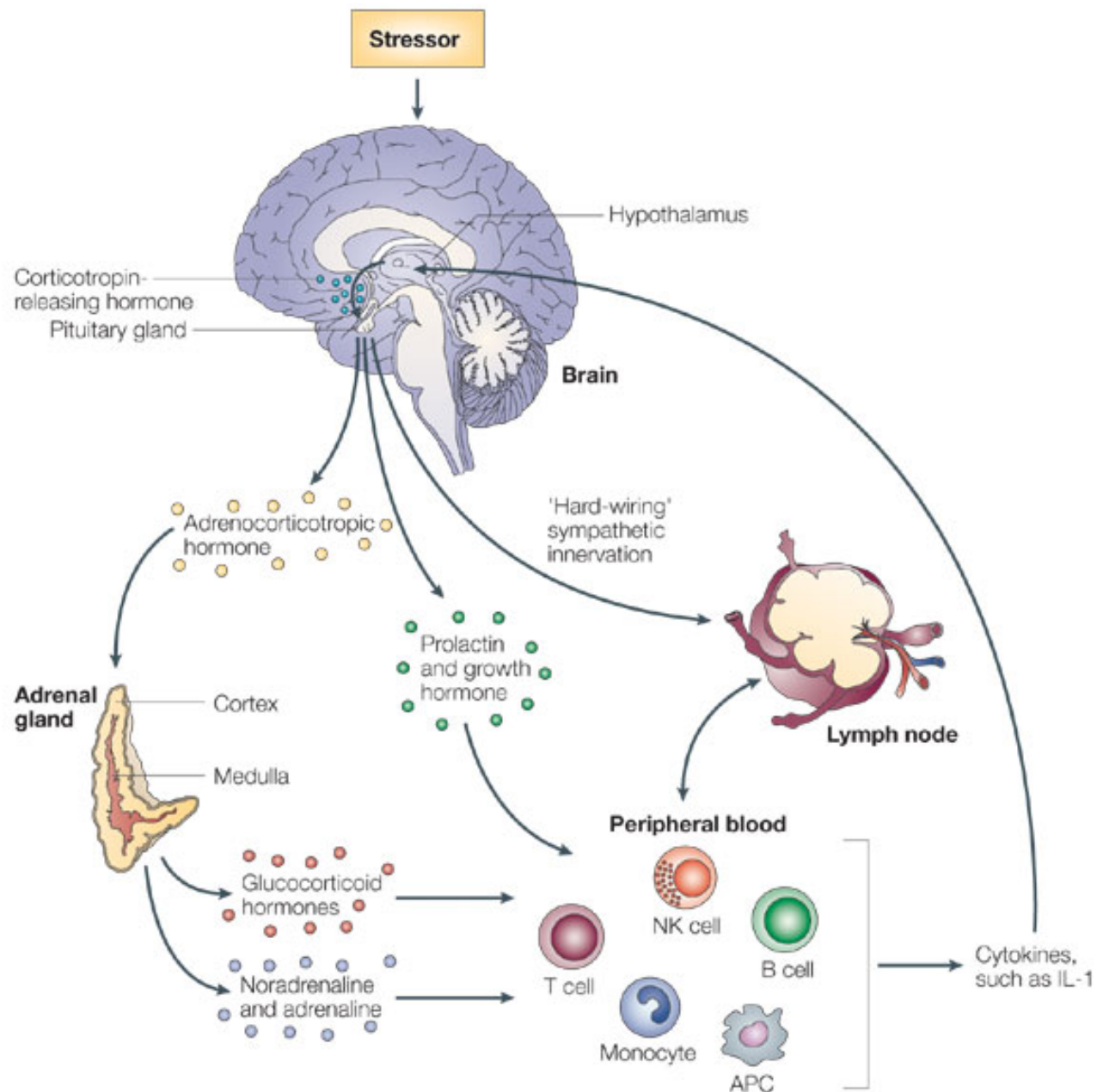


BIF 214

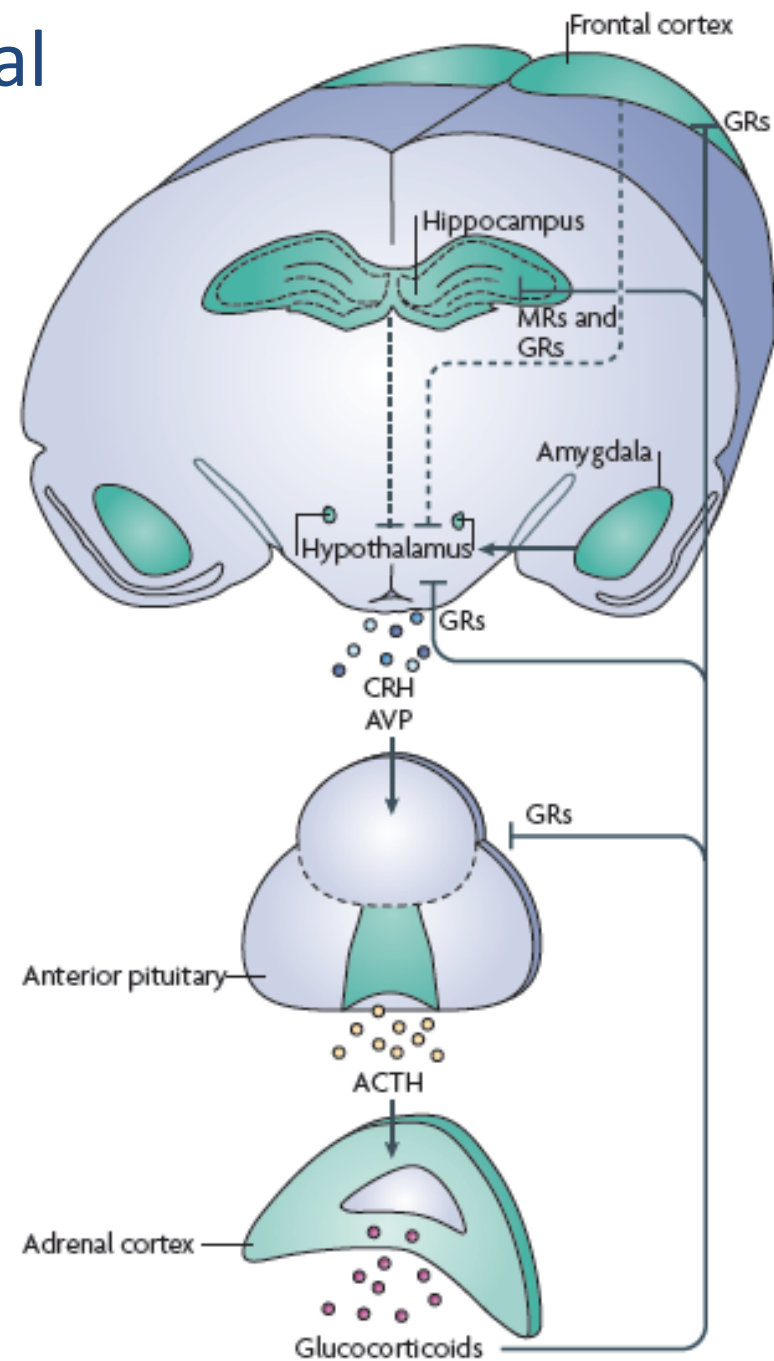
*Fisiologia Animal: Mecanismos e Adaptação do Controle Interno,
Reprodução e Defesa*

Eixo hipotálamo-hipófise-adrenal
Neuroimunoendocrinologia

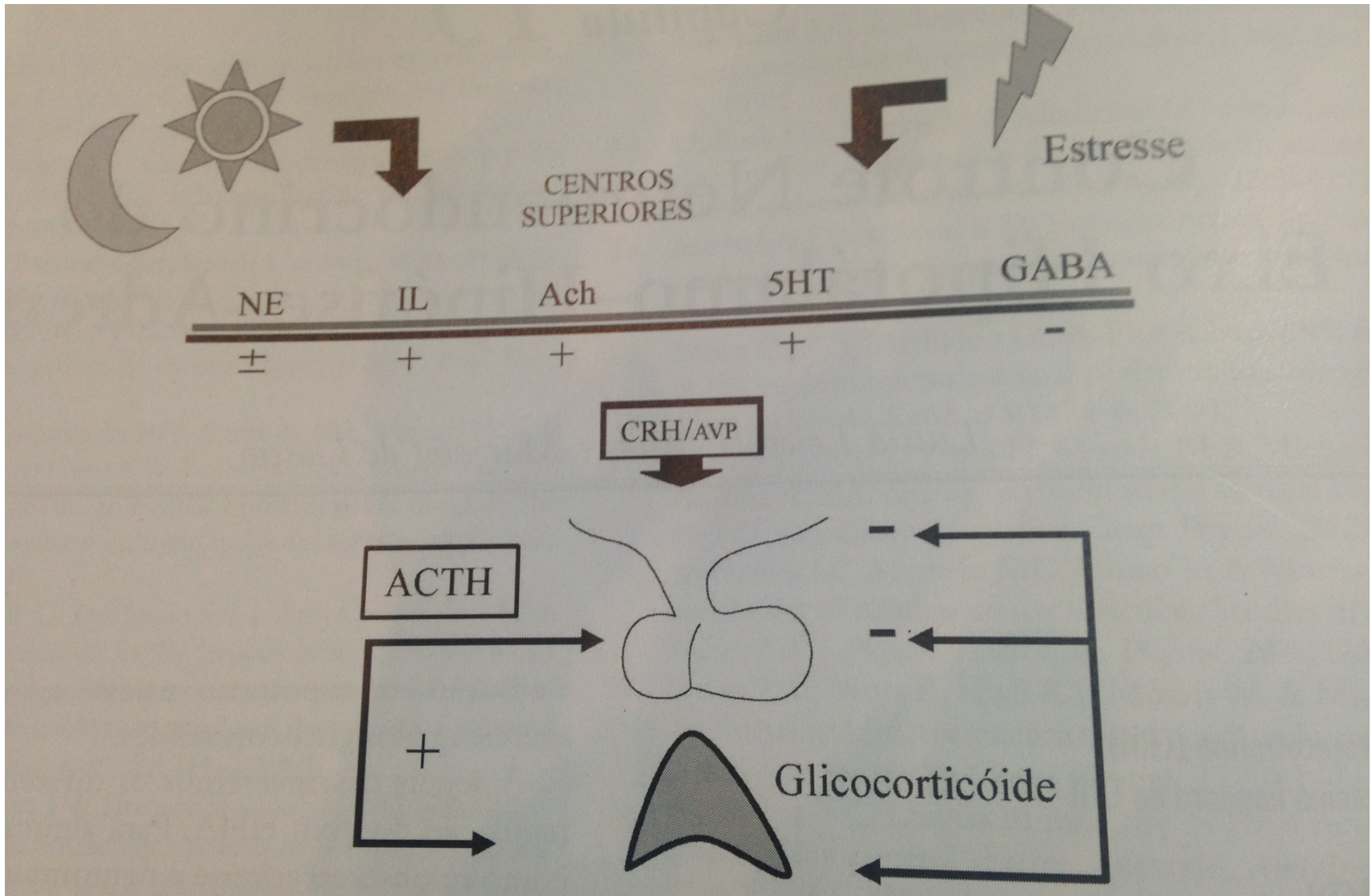
2016



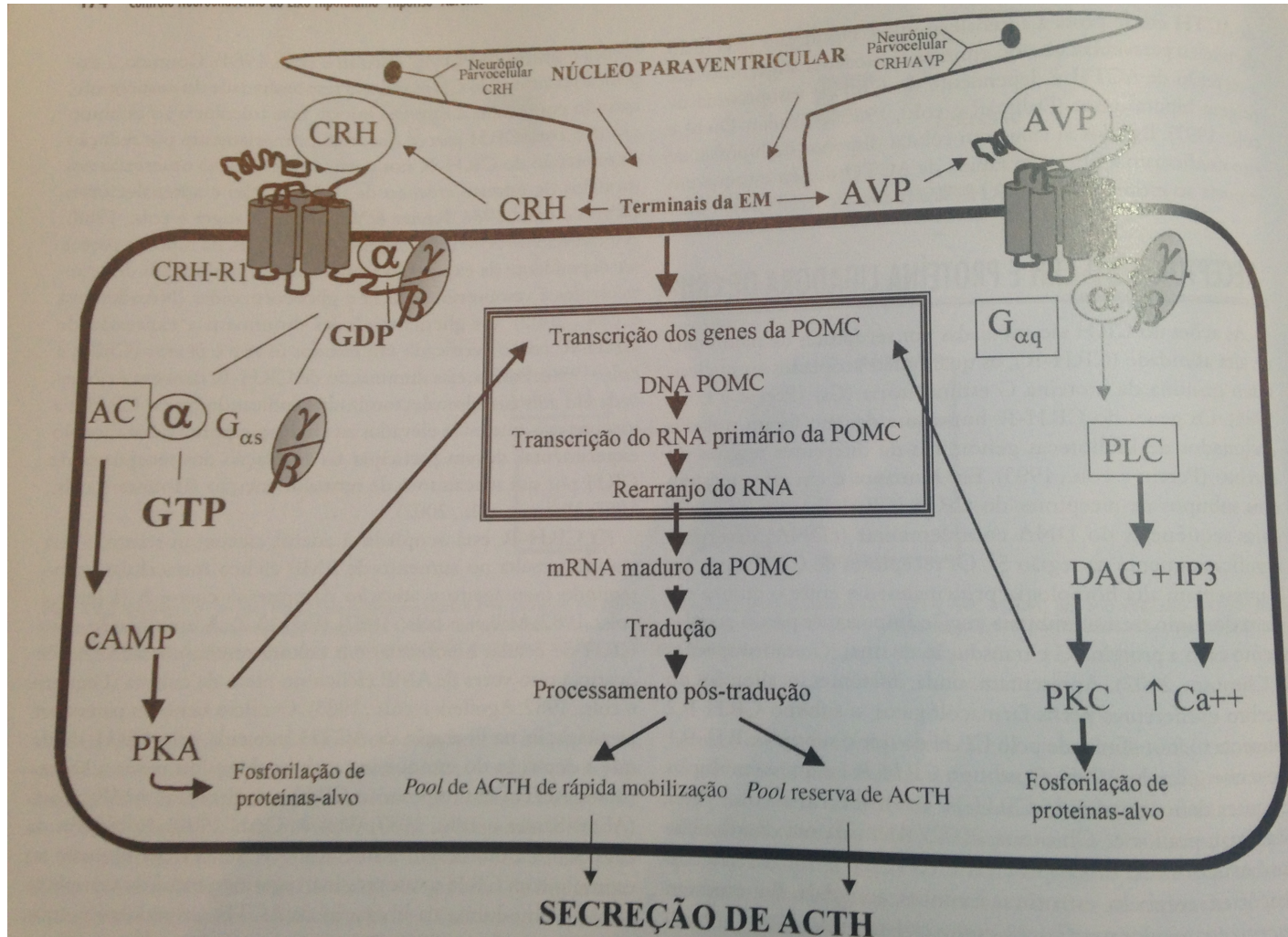
Eixo hipotálamo-hipófise-adrenal



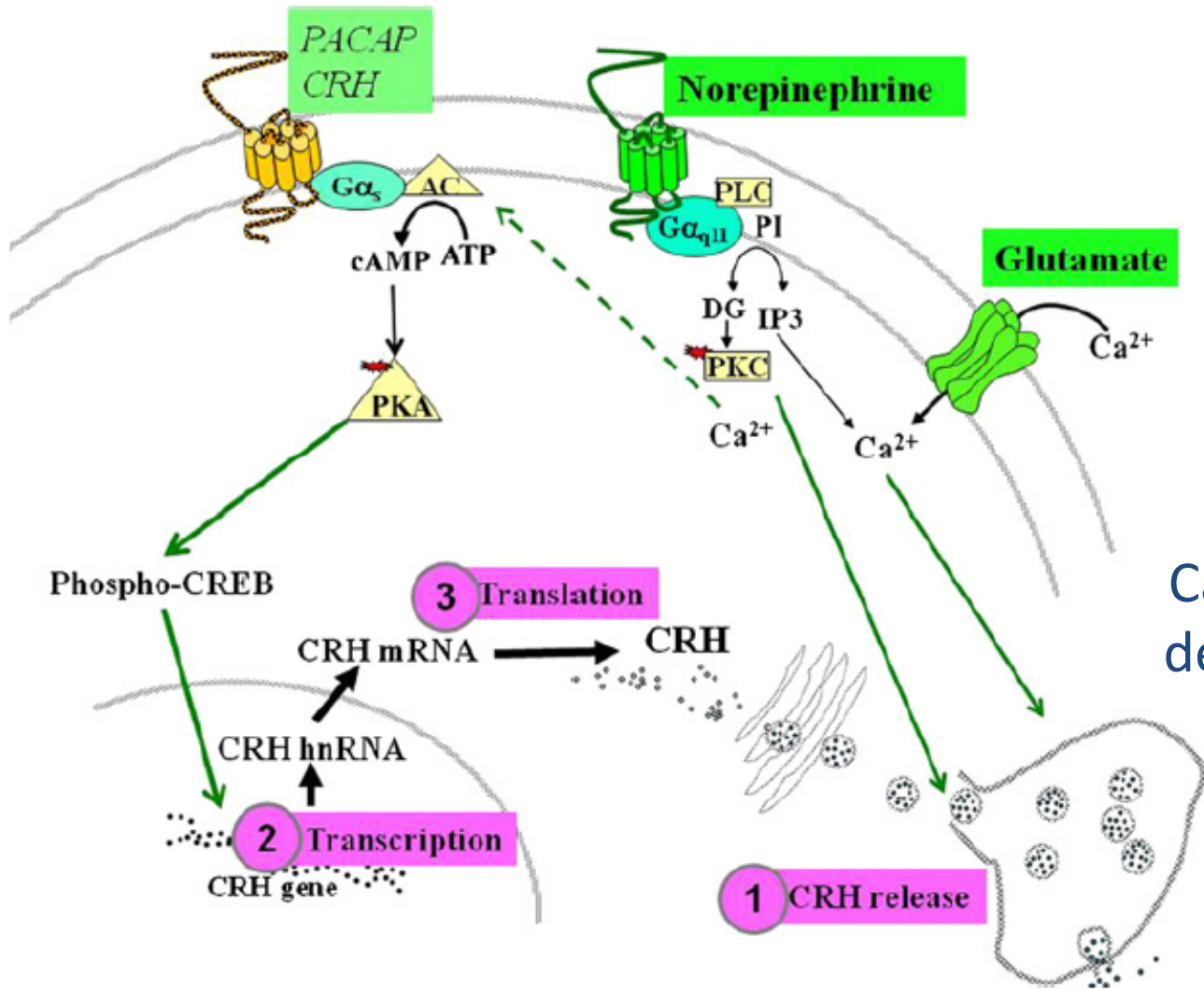
Regulação do eixo Hipotálamo-Hipófise-Adrenal



Sinalização de receptores de CRH e vasopressina na célula corticotrófica



Estimulação de neurônio liberadores de CRH

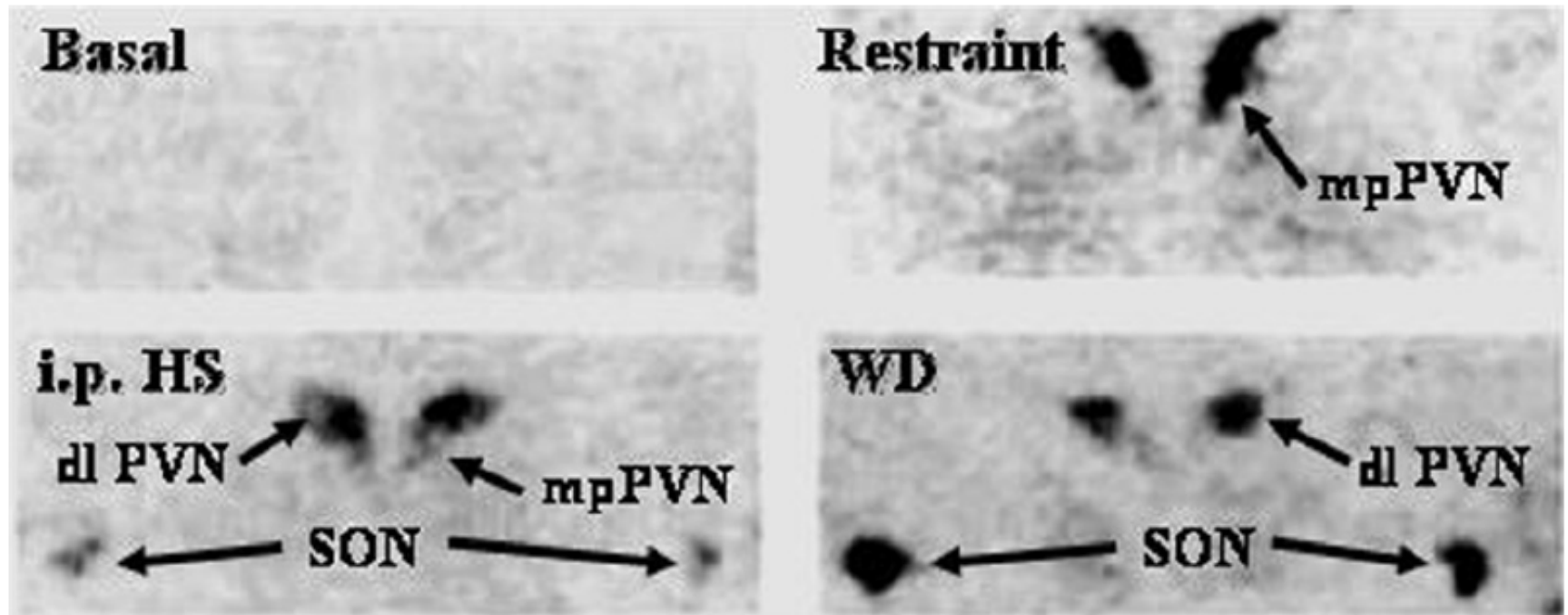


Cálcio induz liberação de vesículas contendo CRH

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 ótico dependo do tipo de estresse

Restrain: contenção

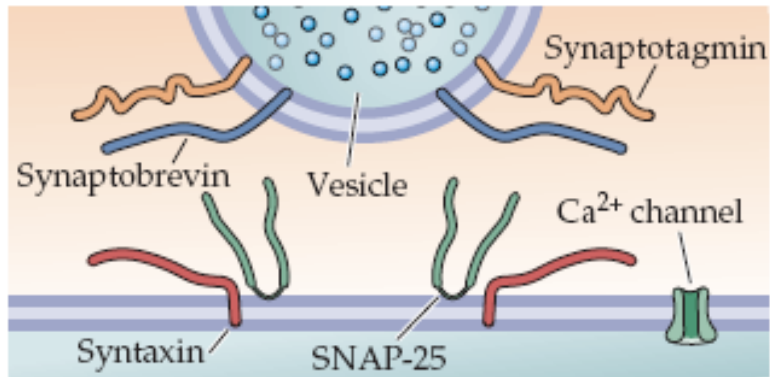
i.p. HS: hipertonic saline injection

WD: water deprivation

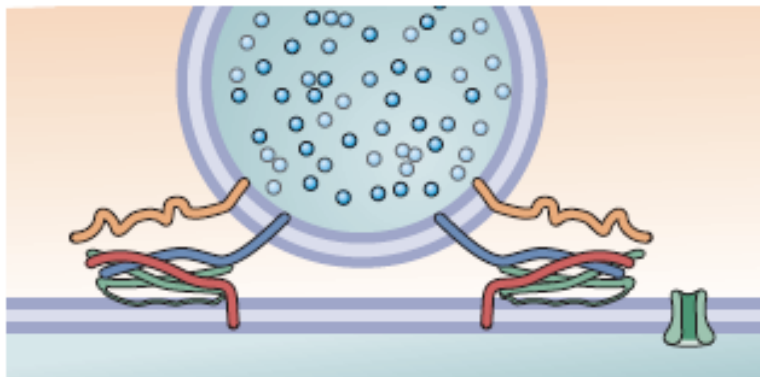
SON: liberação de ADH, controle hídrico

Cálcio induz liberação de vesículas contendo CRH

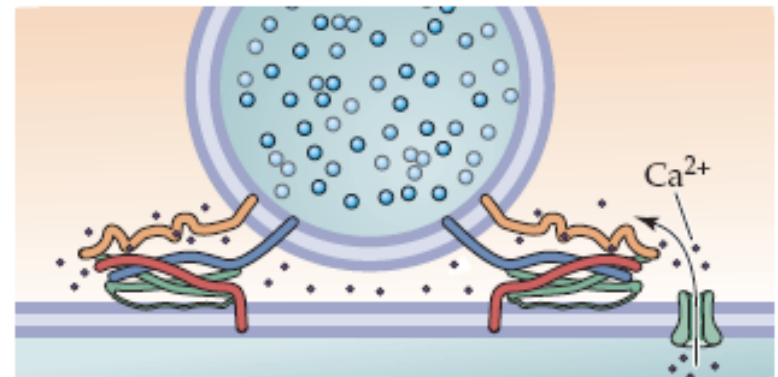
(1) Vesicle docks



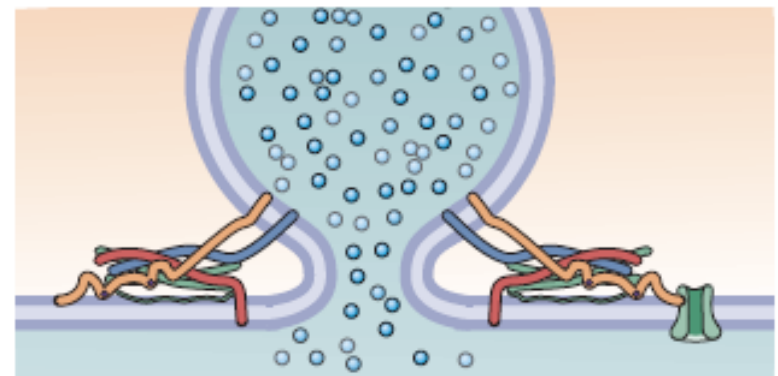
(2) SNARE complexes form to pull membranes together



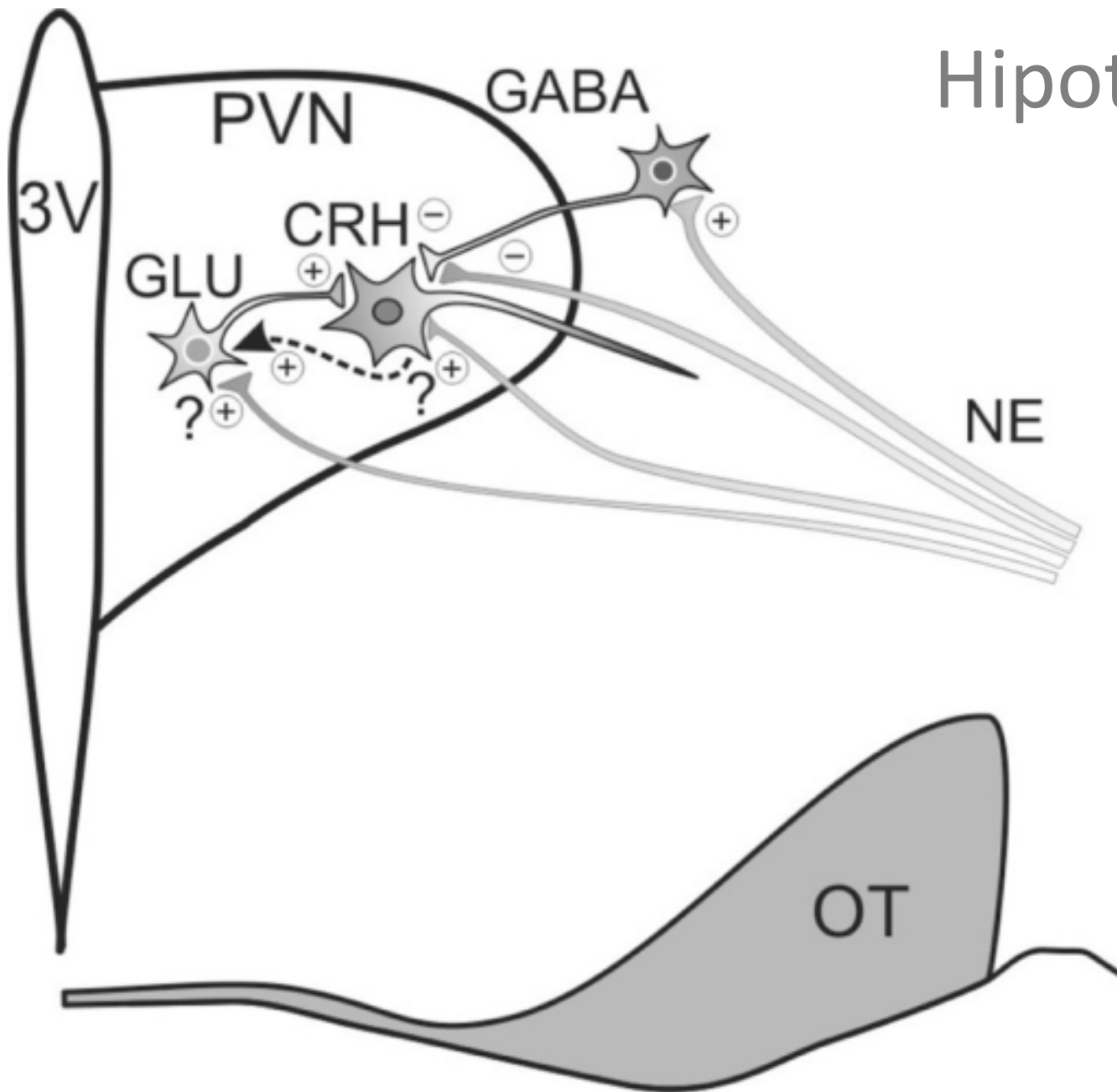
(3) Entering Ca²⁺ binds to synaptotagmin



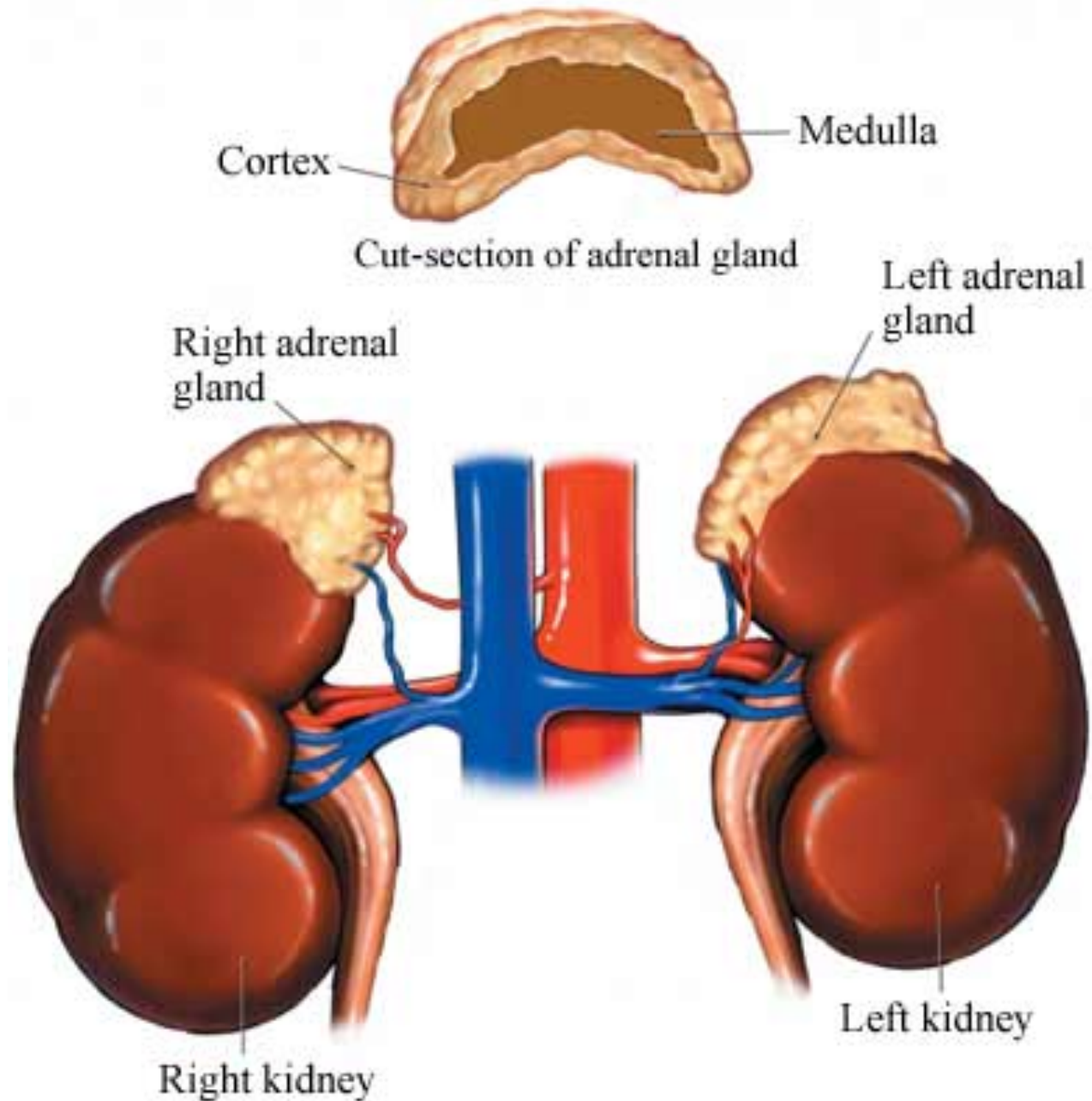
(4) Ca²⁺-bound synaptotagmin catalyzes membrane fusion



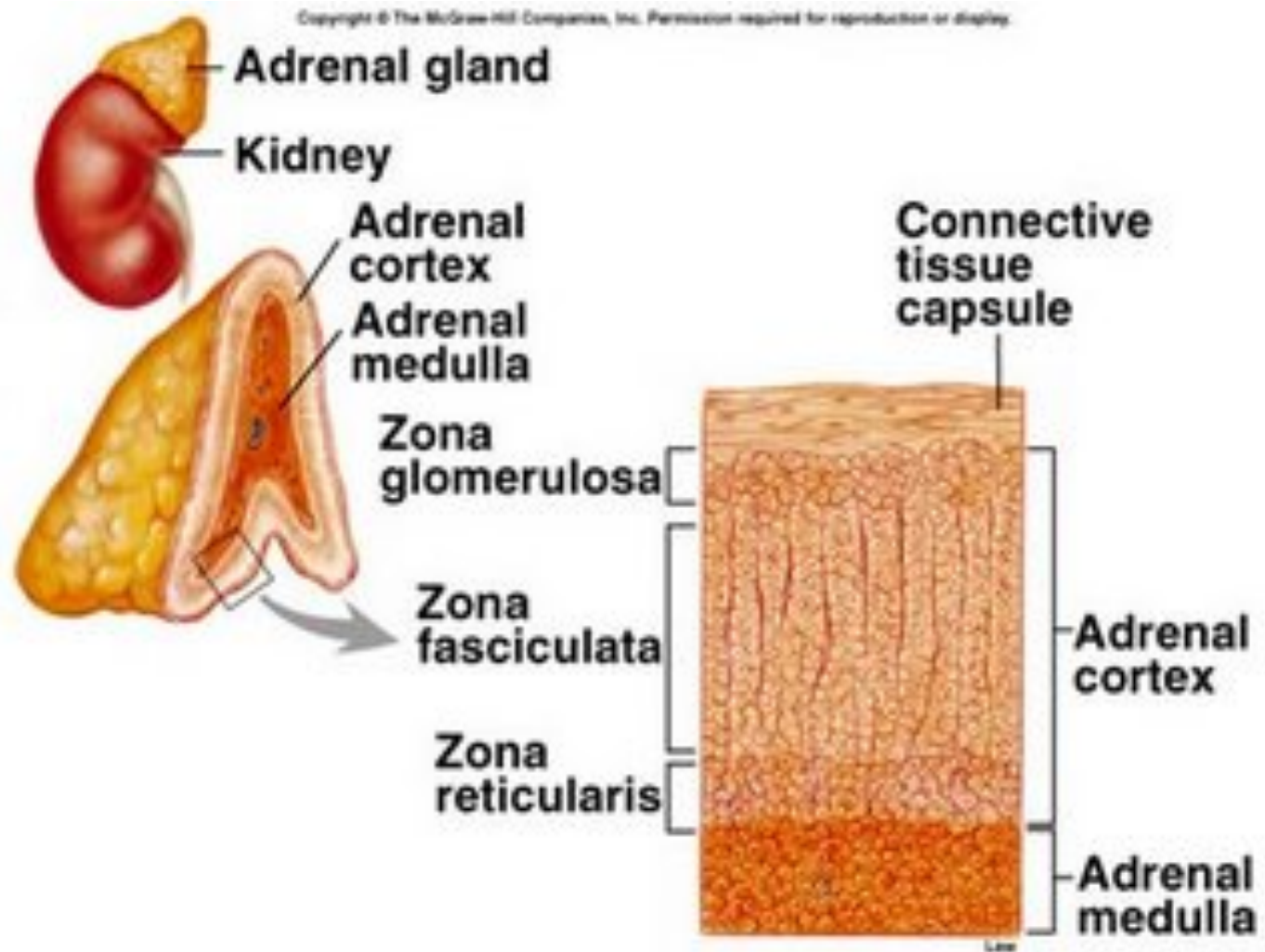
Hipotálamo



Glândulas adrenais

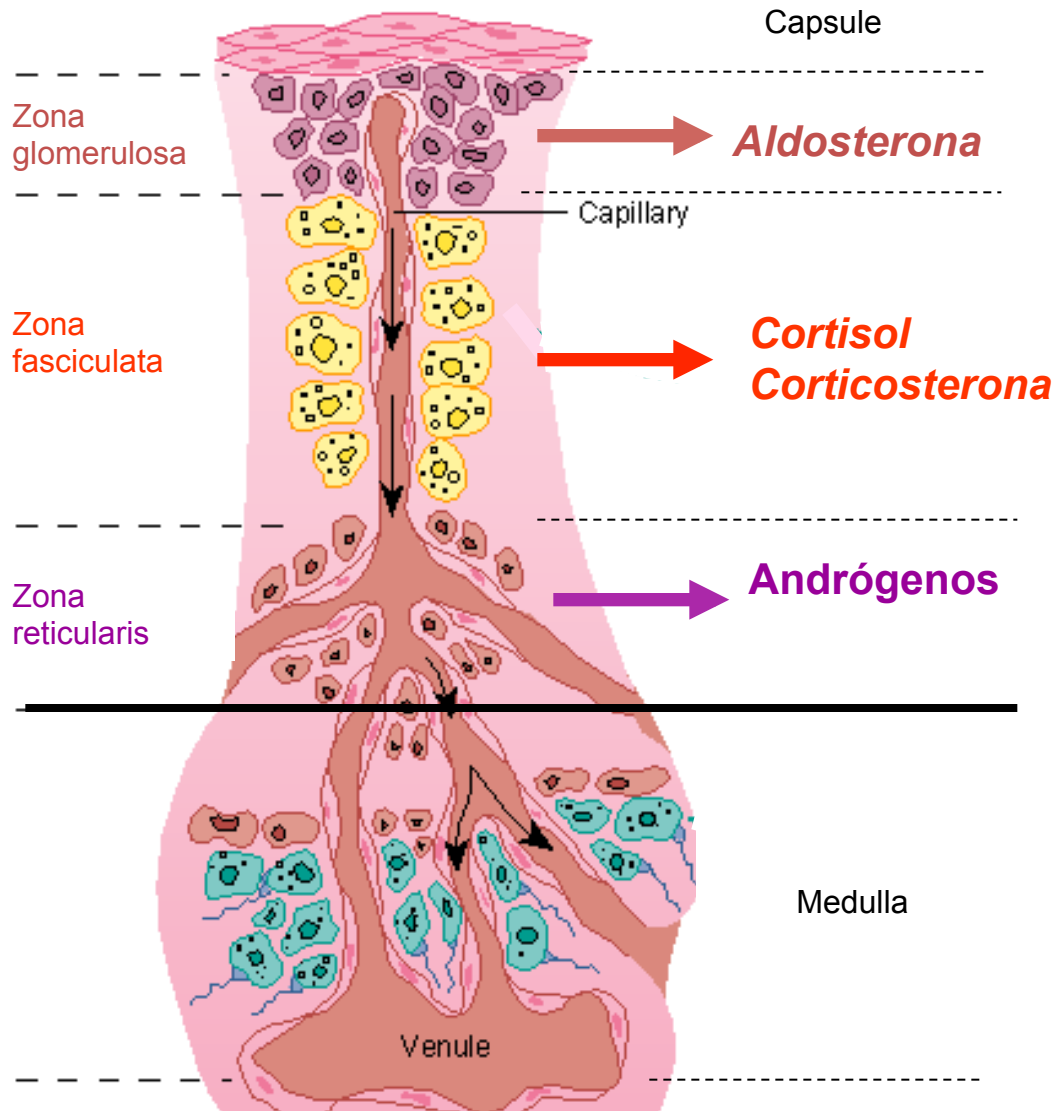


Glândulas adrenais



Córtex Adrenal - 3 camadas

3 grupos de hormônios (esteroidais)



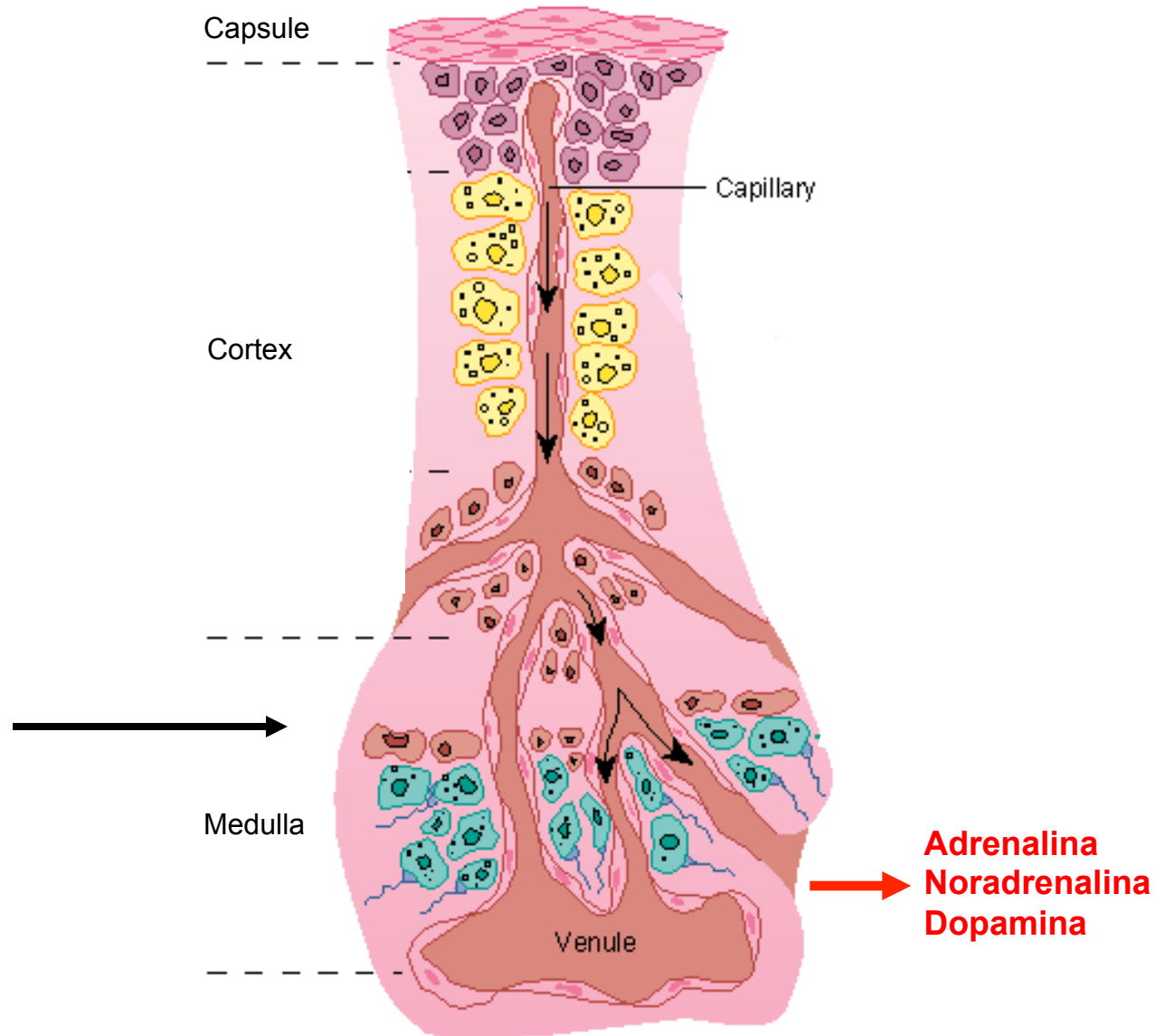
Mineralocorticóides
aldosterona

Glicocorticóides
•cortisol
•corticosterona

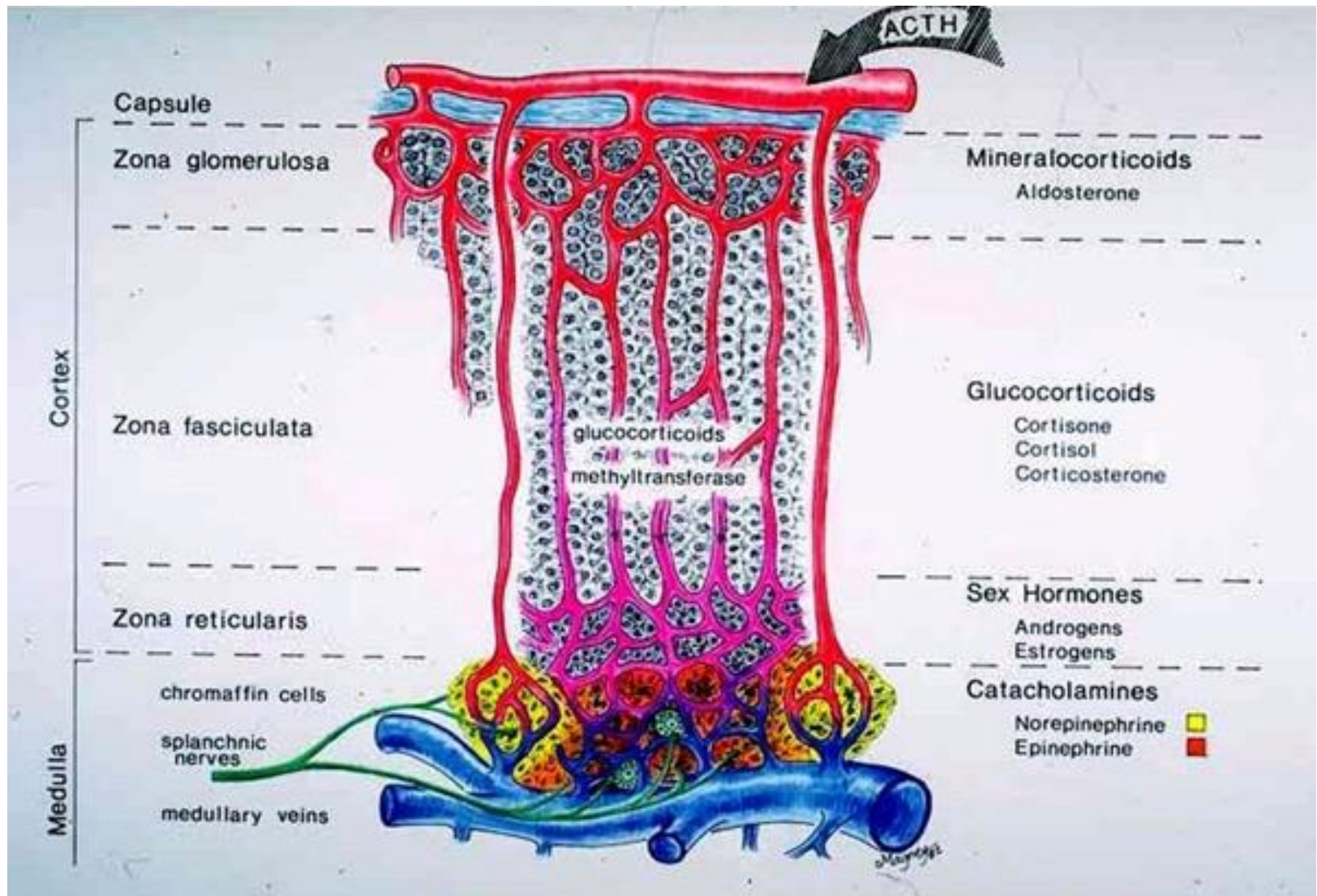
Andrógenos adrenais
androstenediona

Medula Adrenal

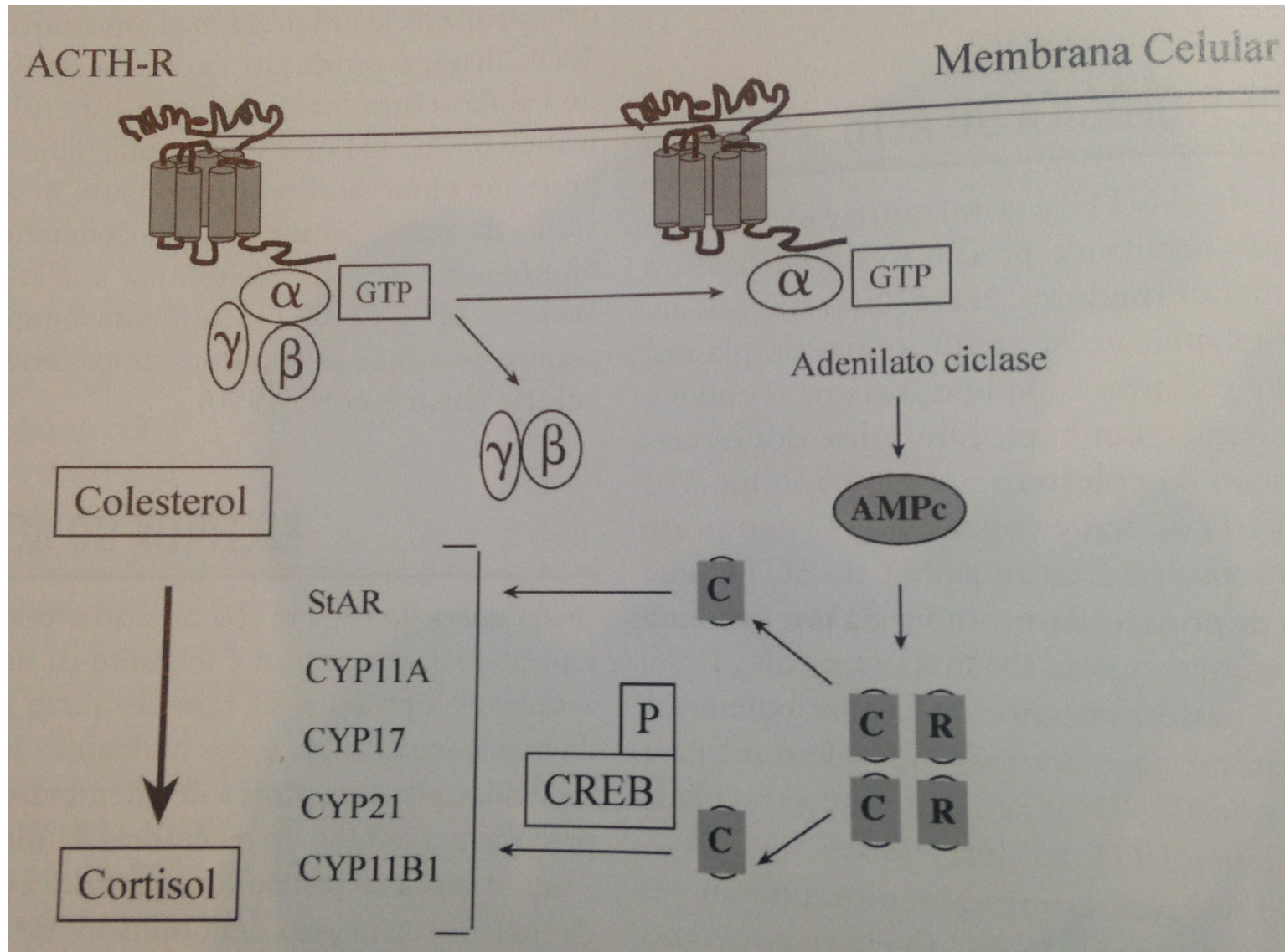
medula adrenal



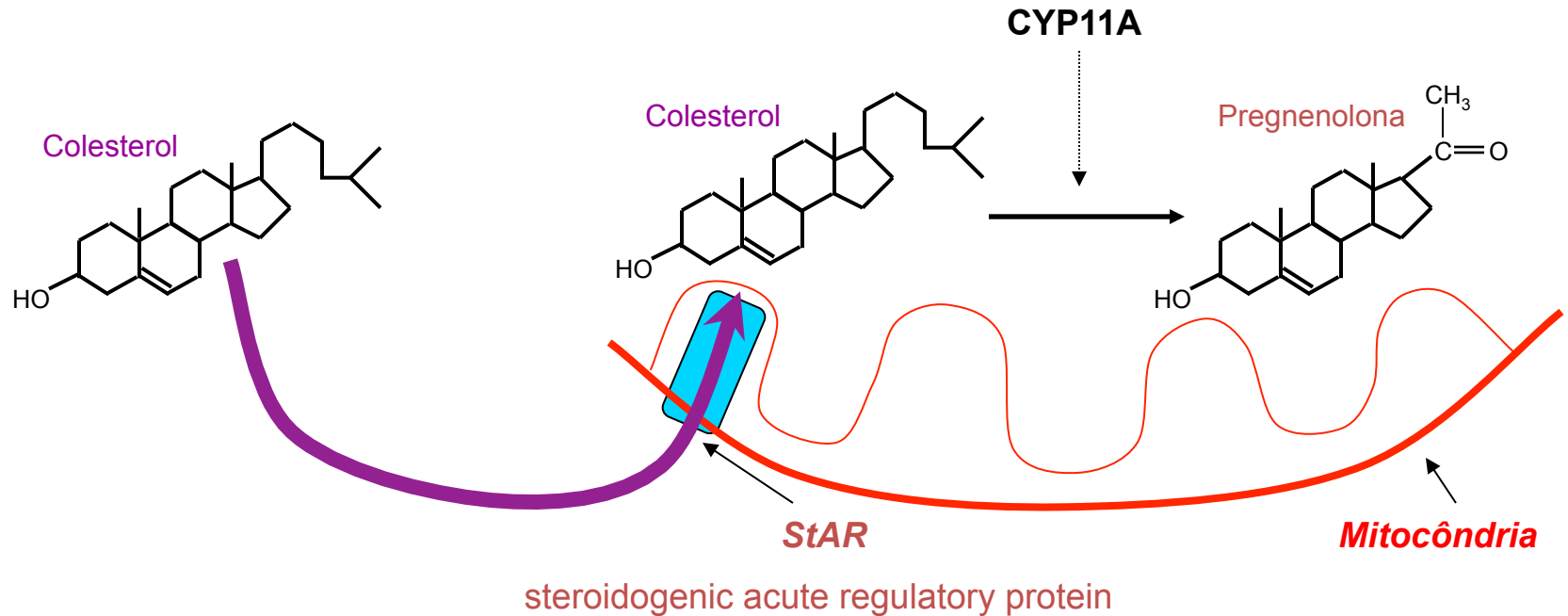
Glândulas adrenais



Sinalização do receptor de ACTH na célula adrenocortical



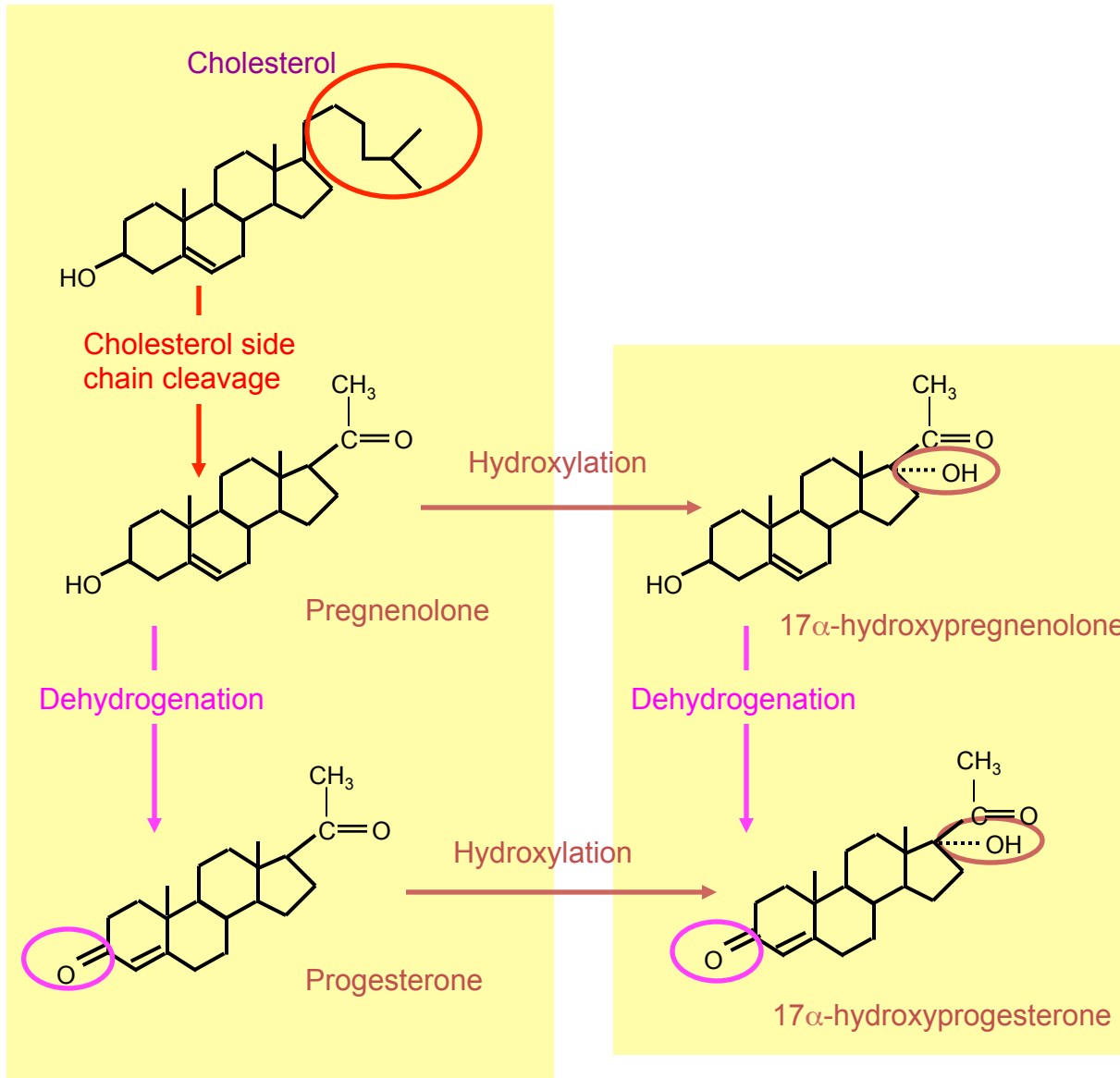
Liberação do colesterol na membrana da mitocôndria

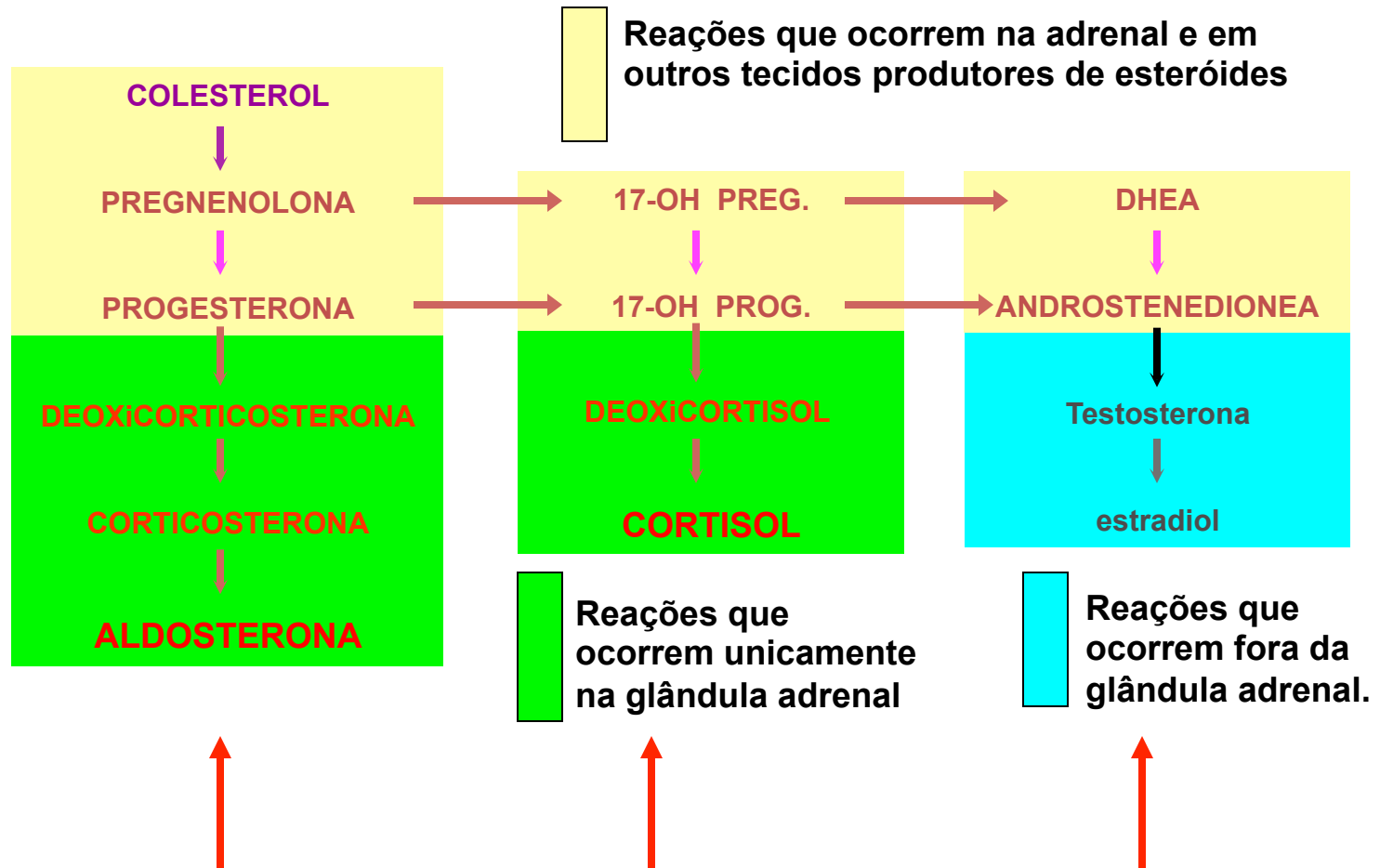


cholesterol $\Rightarrow$ pregnenolona



17- α hidroxiprogesterona
progesterona

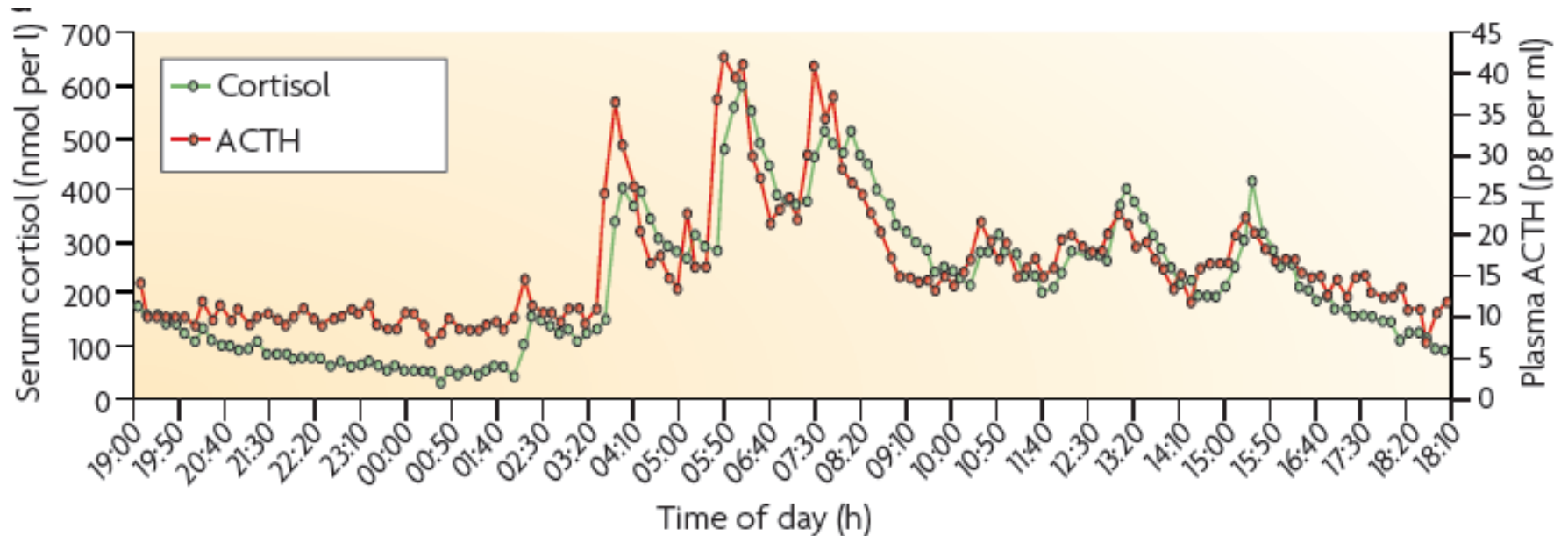




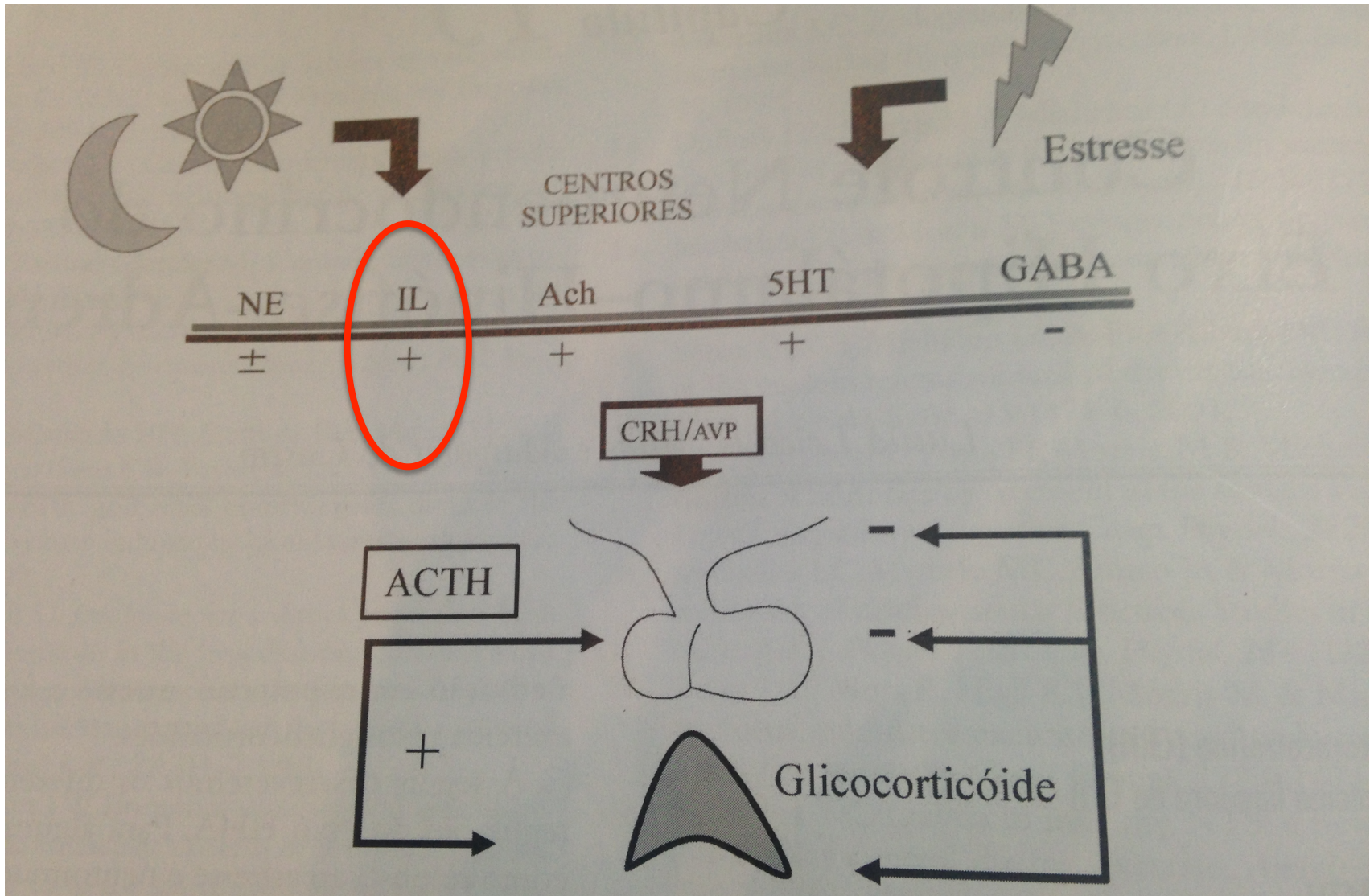
Vias biossintéticas distintas para cada hormônio

ACTH e glicocorticóide

Ritmos circadiano e ultradiano



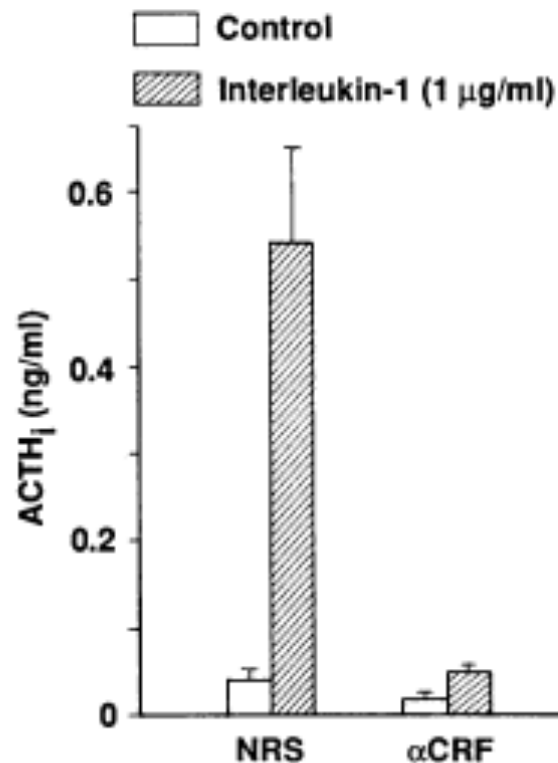
Regulação do eixo Hipotálamo-Hipófise-Adrenal



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.



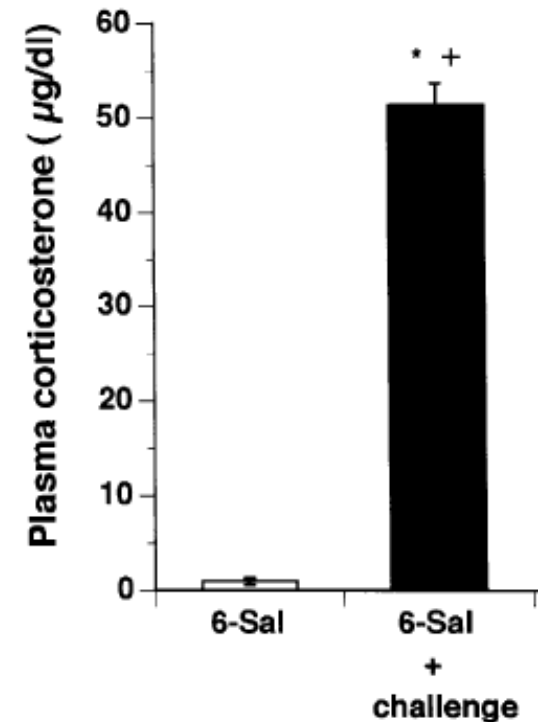
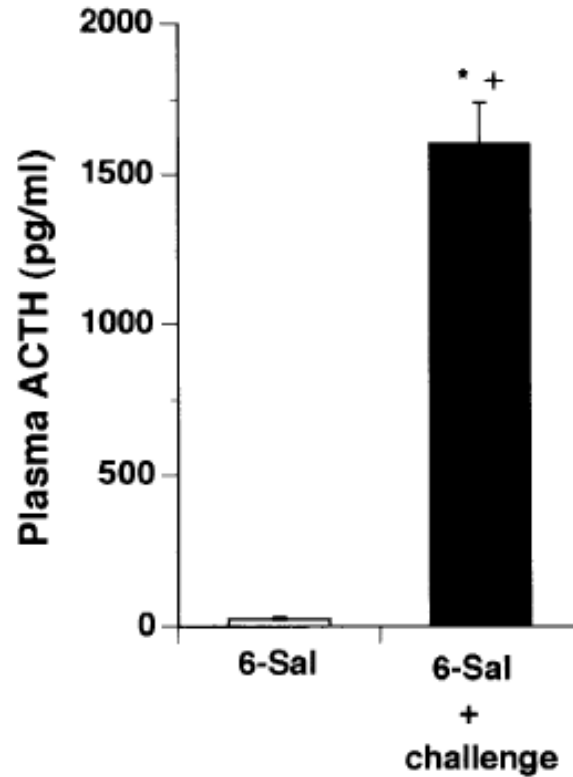
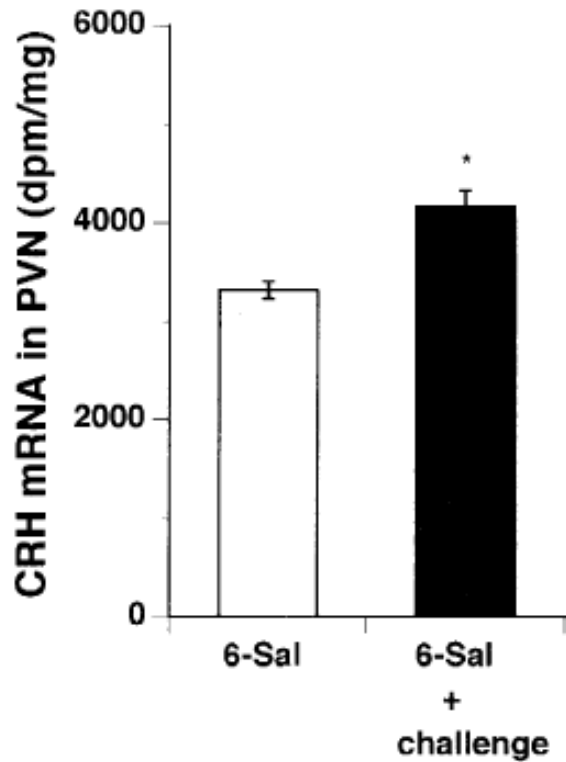
Inflamação sistêmica

CRF: corticotropin-releasing factor

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

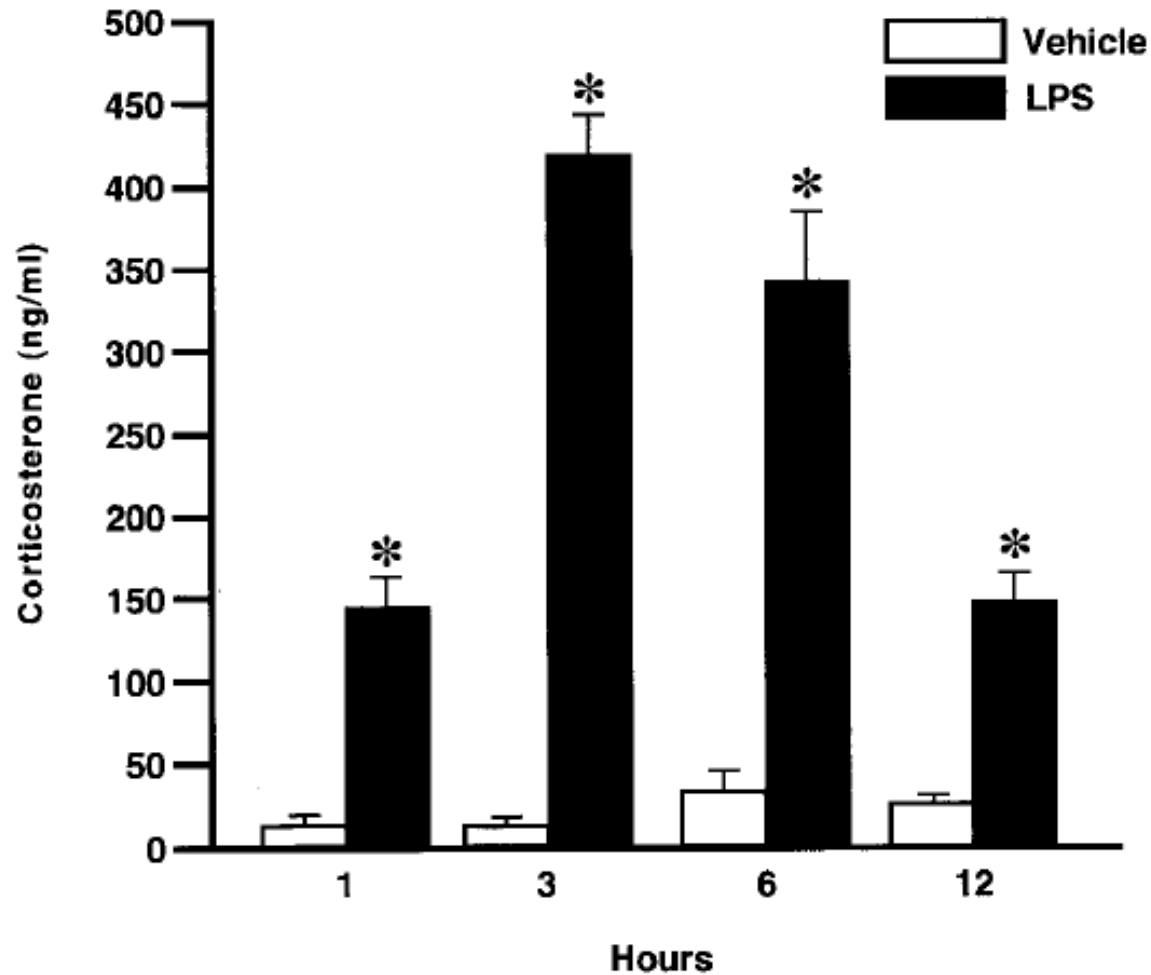
ACTH: adrenocorticotrophic hormone

Inflamação sistêmica



Aumento de CRH, aumento de ACTH, aumento corticosterona

Inflamação sistêmica



Decurso temporal na produção de glicocorticóides

Ativadores imunológicos do HPA

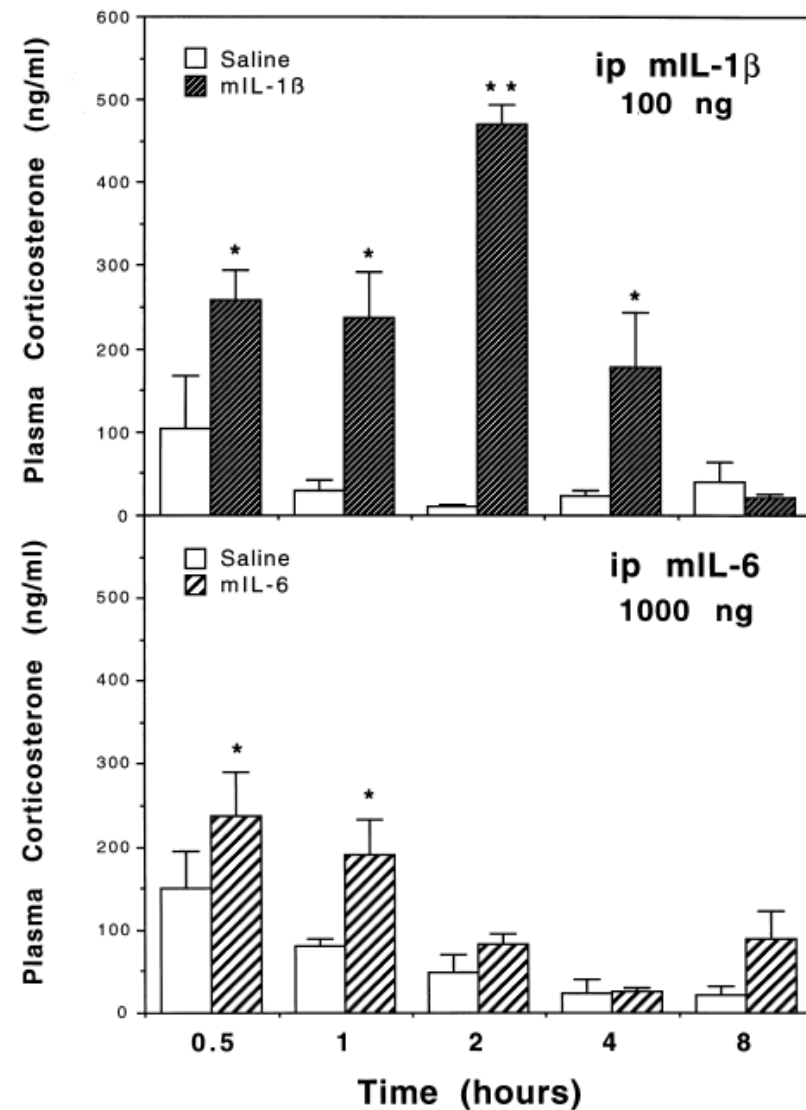


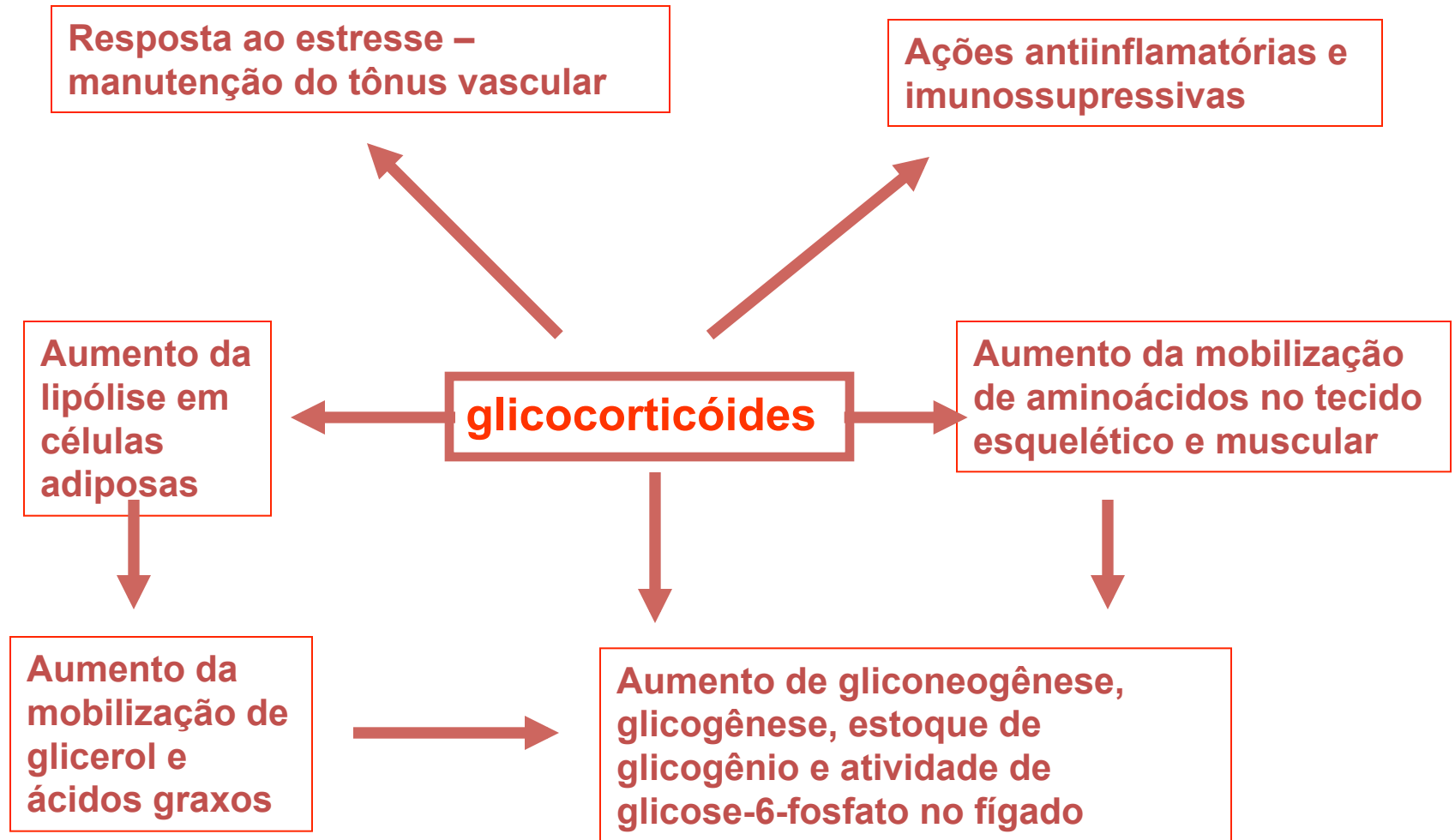
FIGURE 1. Effects of mIL-1 β and IL-6 on plasma corticosterone. Mouse IL-1 β (100 ng/mouse) (*top*) or mouse IL-6 (1 μ g/mouse) (*bottom*) was injected i.p., and samples collected at various subsequent times. Plasma corticosterone was determined by radioimmunoassay. $N = 7$. *Significantly different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

Ativadores imunológicos do HPA

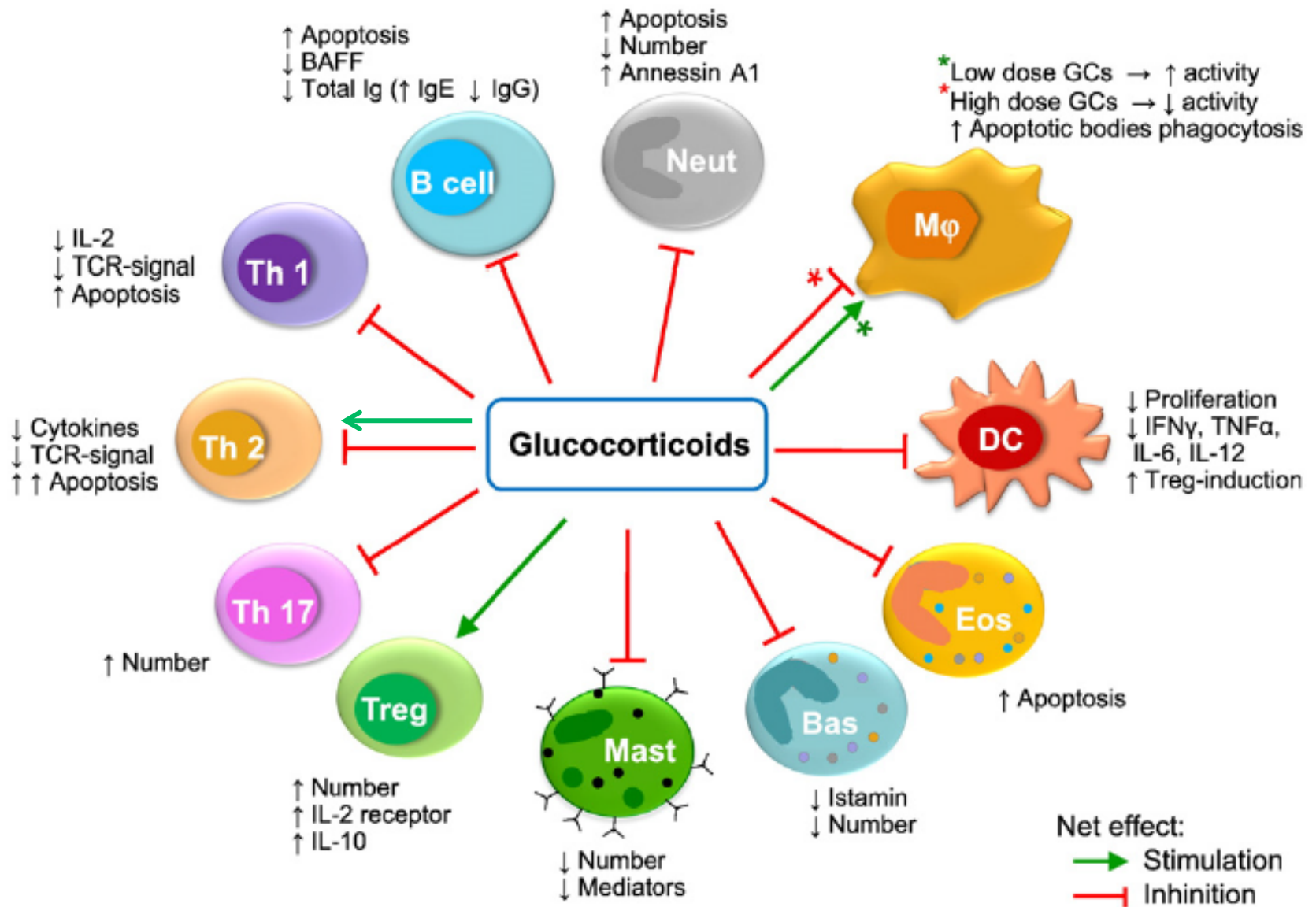
TABLE 1. HPA responses to cytokine administration in mice

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

Ações dos glicocorticóides



Efeitos dos glicocorticóides sobre células imune



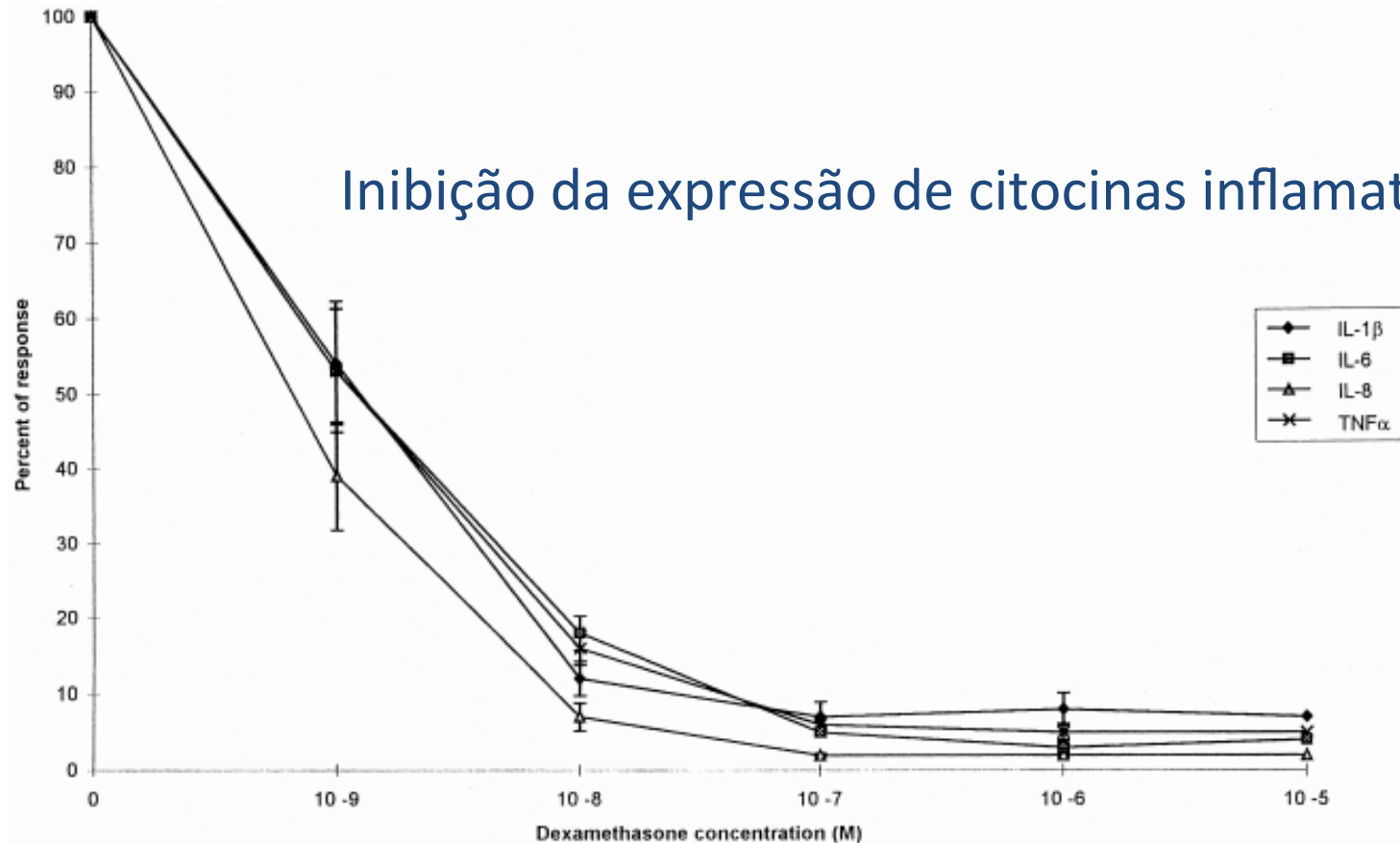
Efeitos dos Glicocorticóides nas Células Imunes

PBMCs: peripheral blood monuclear cells

Tratamento: LPS

Incubação: 24 horas

Inibição da expressão de citocinas inflamatórias

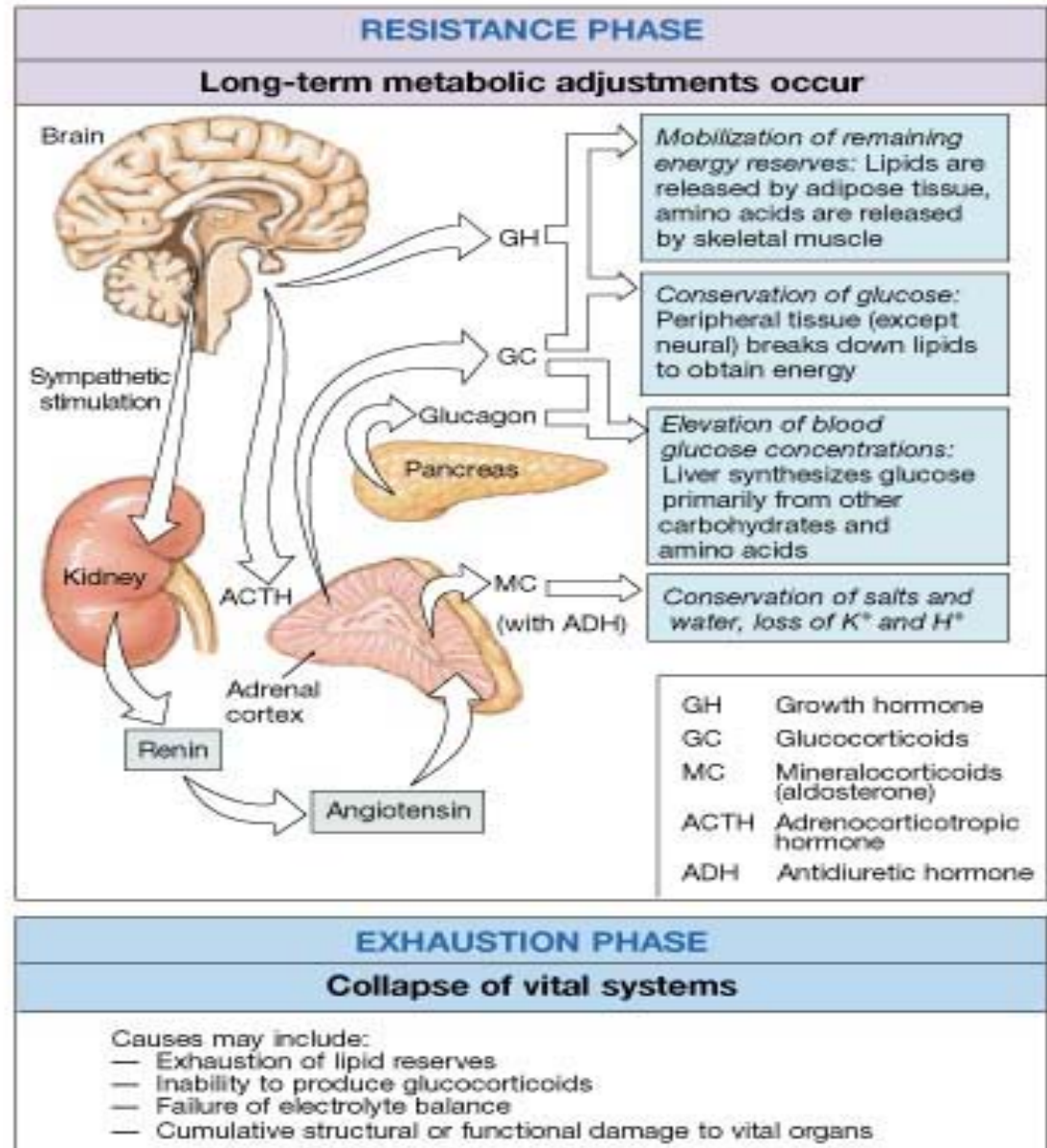


Franchimont et al 1997.

Efeitos dos glicocorticóides sobre células imune

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

Ações Biológicas de Glicocorticóides durante períodos de estresse



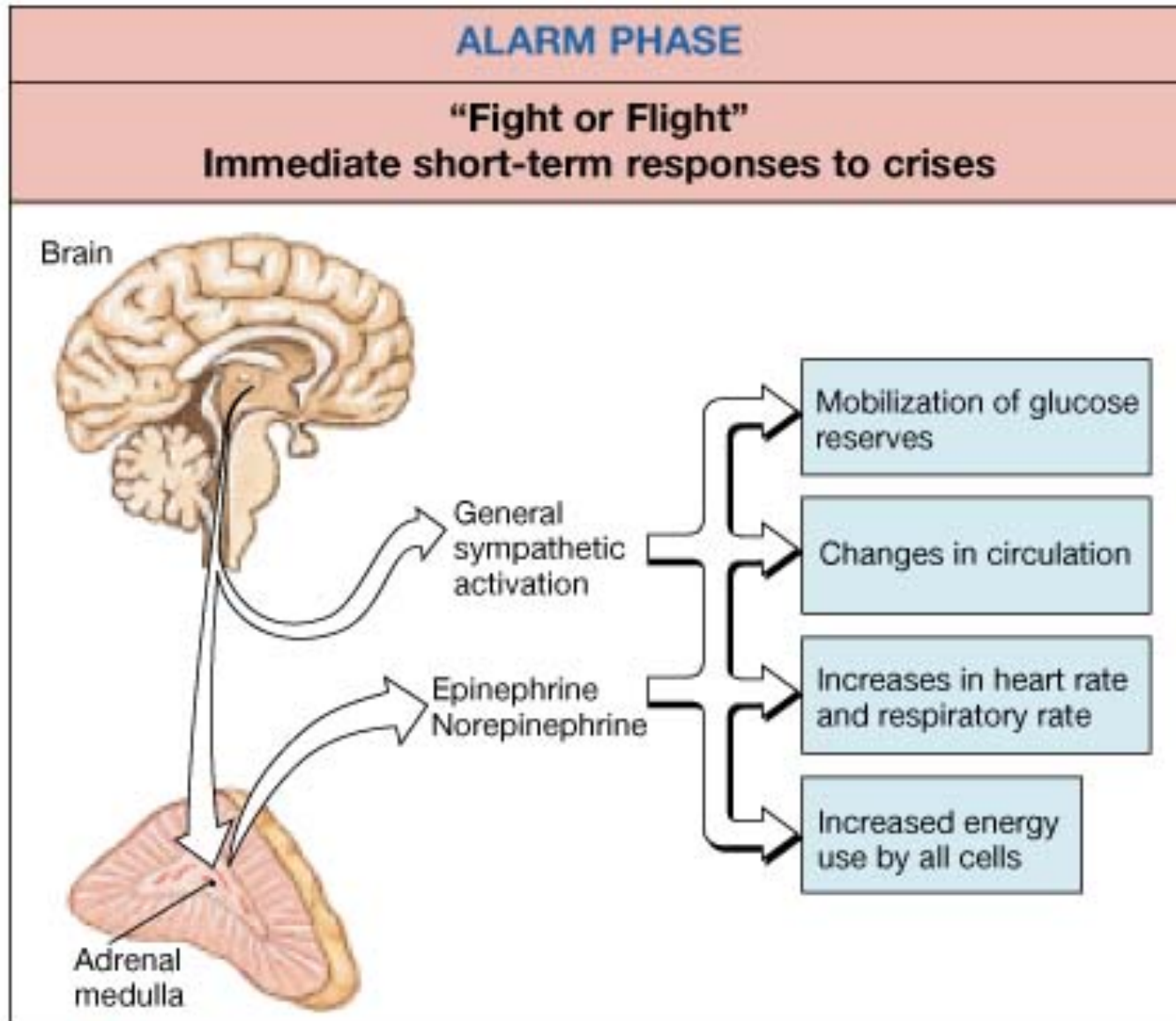
Mobilização de estoques de energia

por estimular
gliconeogênese
lipólise

The General Adaptation Syndrome

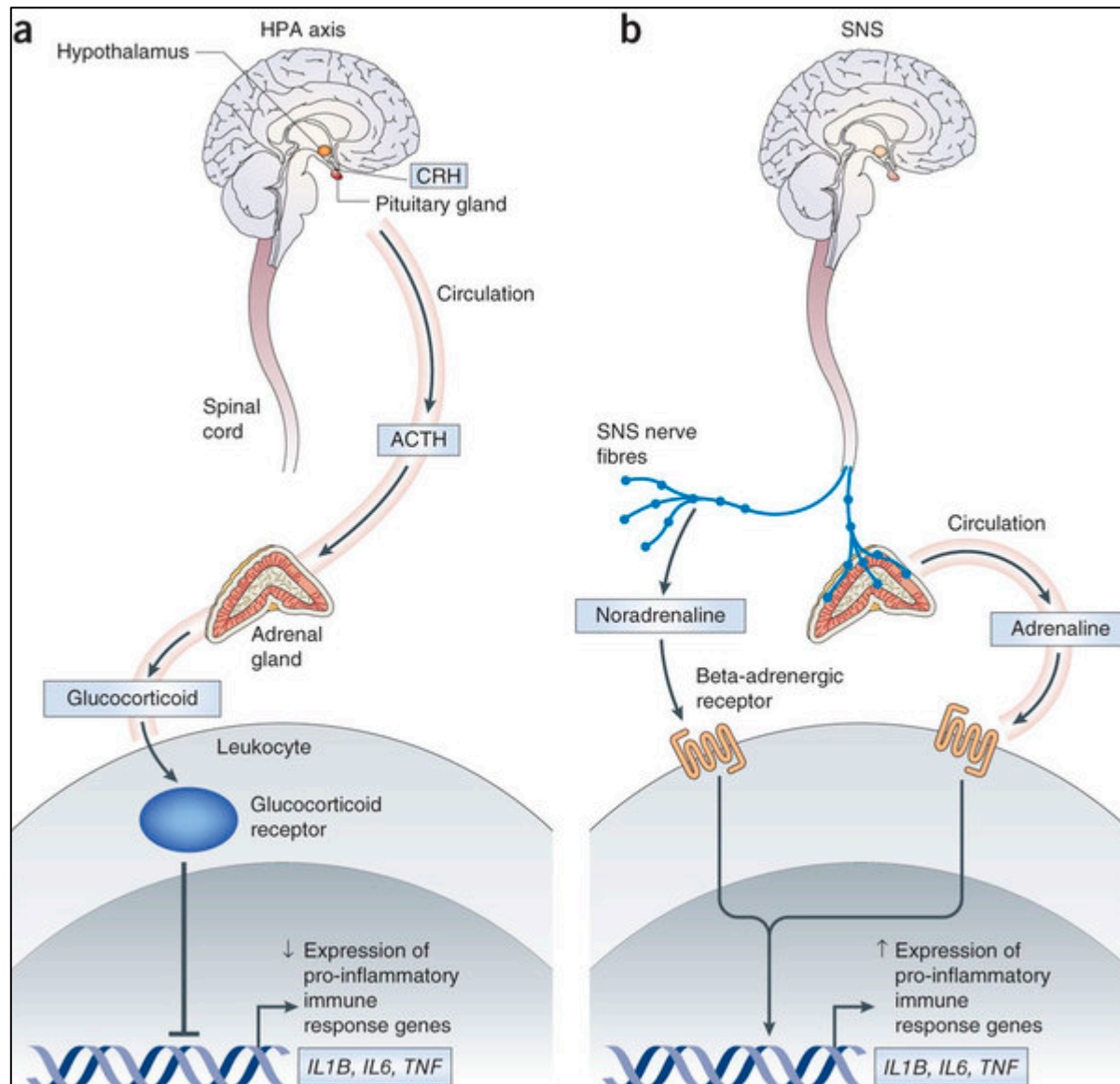
Ações Biológicas dos Hormônios da Medula da adrenal

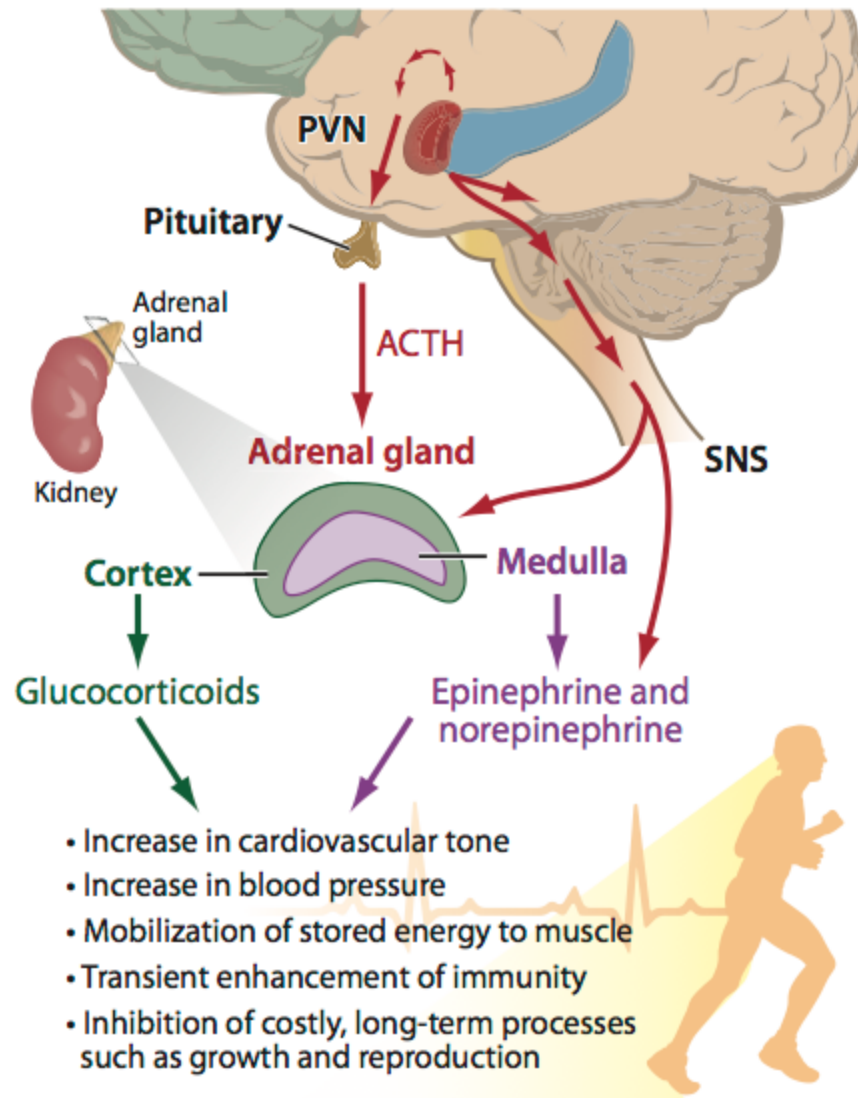
Resposta imediata ao estresse



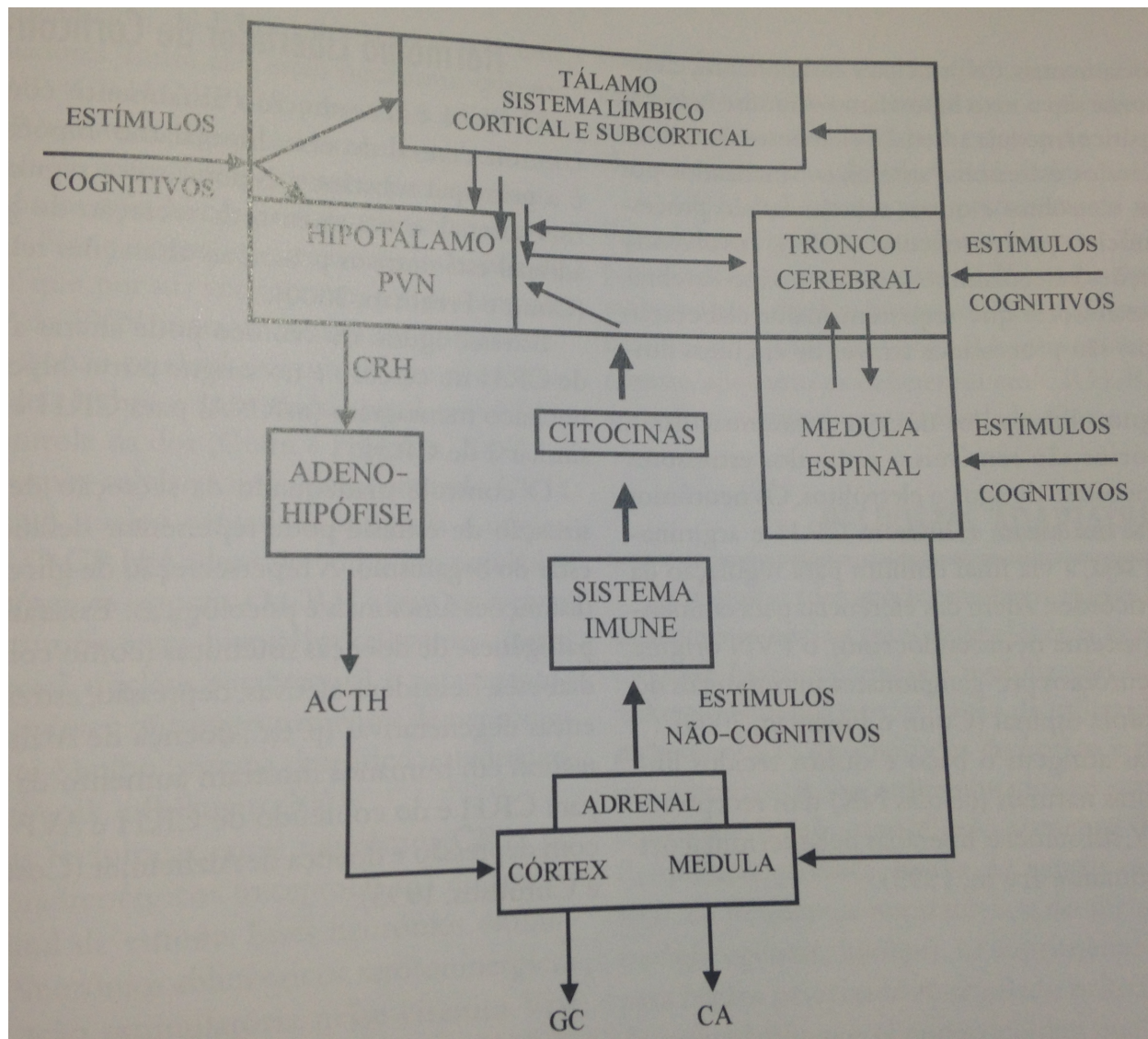
The General Adaptation Syndrome

CNS regulation of inflammatory gene expression in immune cells

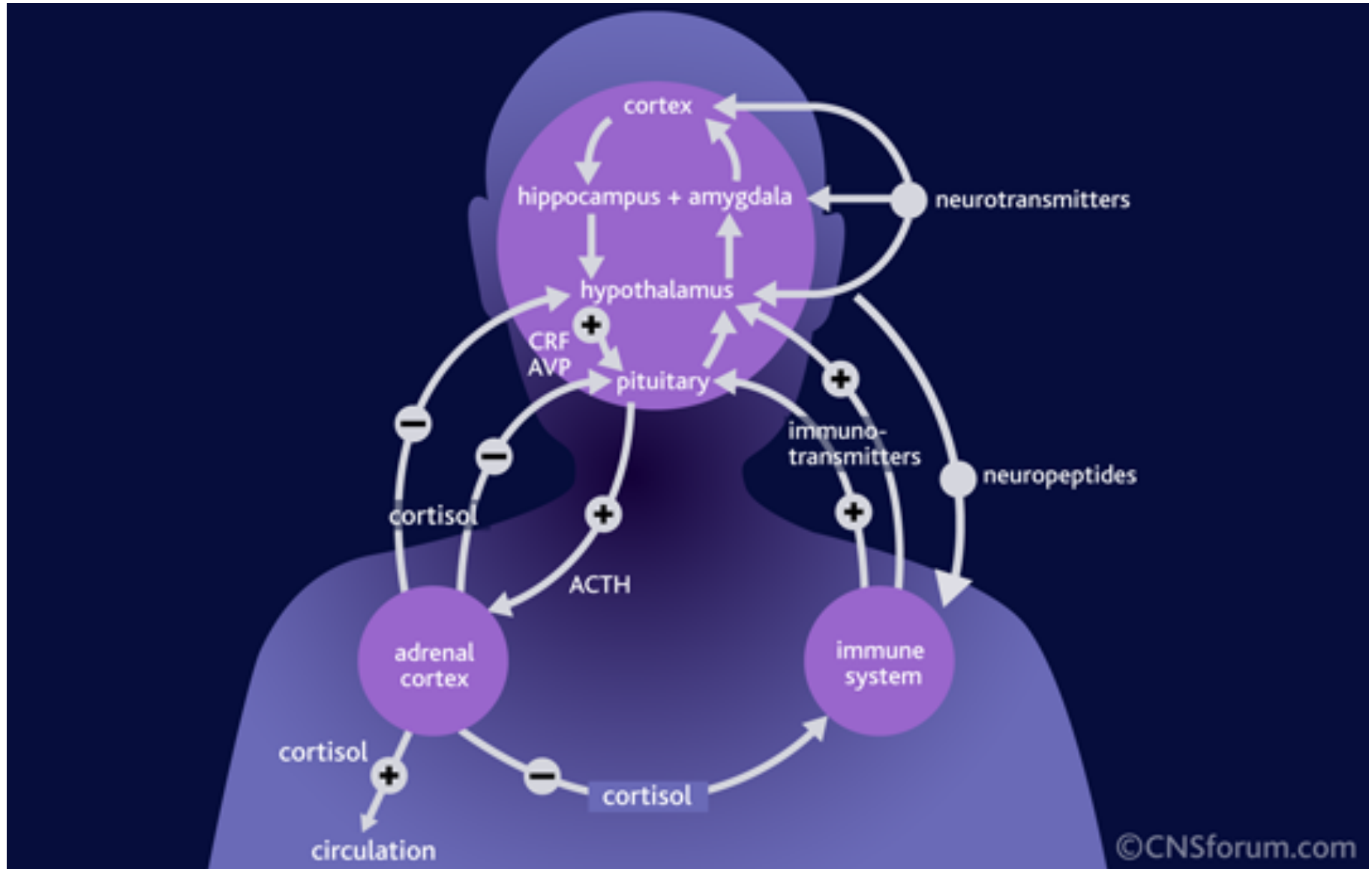




Sistema de estresse: componentes sensoriais e de integração



Funcionamento normal do eixo HPA



Alteração do funcionamento do eixo HPA pode levar a quadro fisiopatológicos

