BIF0214
Fisiologia Animal
Mecanismos e Adaptação do Controle Interno e Reprodução

Sistemas de controle da produção e liberação de hormônios.

Controle Neuroendócrino da Homesostase III

Função do Sistema Endócrino

Homeostase

- Manutenção das condições corpóreas em estado de equilíbrio.

Walter Cannon (1929)

Ex.: Temperatura: ~ 37 °C; pH sanguíneo: 7,4; Pressão arterial: ~120/80 mmHg

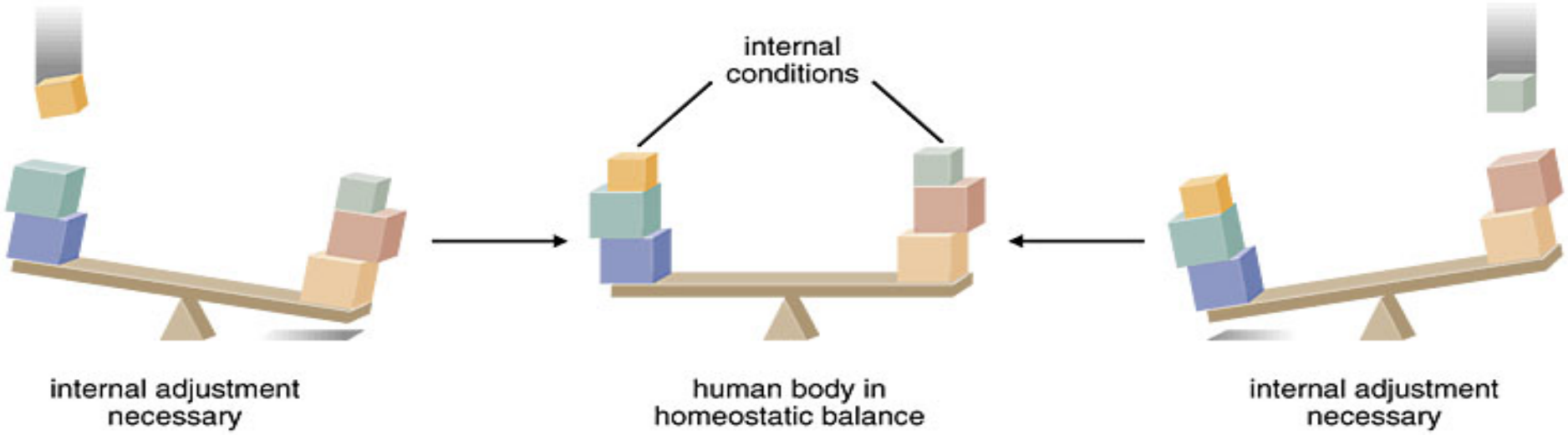
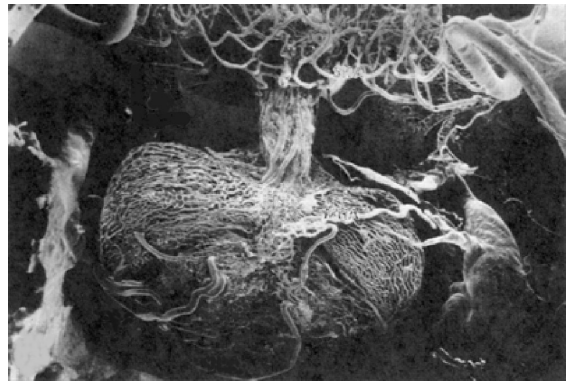


Figure 1.14 Homeostasis. The human body is maintained in a state in which the internal conditions remain within normal limits. When this balance is disturbed, the body adjusts its internal conditions, restoring balance.

Organismos Multicelulares

Regulação e integração de funções de diferentes células

Sistema nervoso
Sinais eletroquimicos



Sistema endócrino
agentes químicos

Sistema imune
citocinas

Interações neuroimunoendócrinas

Função do Sistema Endócrino

Regular, pela liberação e ação de hormônios,
a função de vários órgãos, tecidos e células

Processos fisiológicos controlados por hormônios

- Reprodução
  - crescimento e integridade estrutural de órgãos reprodutivos
  - produção de gametas
  - padrões de comportamento sexual
  - diferença fenotípica entre os sexos
  - continuação das espécies (ovulação, espermatogênese, gravidez, lactação)

- Regulação do crescimento e desenvolvimento

  Papel primário e permissivo no inicio e progressão do crescimento
  - organismo como um todo
  - tecidos individuais

- Manutenção da homeostase
  - controle do volume de fluido extracelular e pressão sanguínea
  - composição de fluidos do organismo
  - regulação plasmática e tecidual dos níveis de cálcio e fosfato
  - manutenção dos ossos, músculos e estoques de gordura corporal

Table 1-1 Classical Endocrine Glands and Their Hormones

Gland		Hormone
Pituitary	Anterior lobe	Luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), growth hormone (GH), adrenocorticotropin (ACTH), β-lipotropin, β-endorphin, thyroid-stimulating hormone (TSH)
	Intermediate lobe	Melanocyte-stimulating hormone (MSH), β-endorphin
	Posterior lobe	Vasopressin (AVP) or antidiuretic hormone (ADH), oxytocin
Thyroid		Thyroxine (T_4), 3,5,3′-triiodothyronine (T_3), calcitonin
Parathyroid		Parathyroid hormone (PTH)
Adrenal	Cortex	Cortisol, aldosterone, dehydroepiandrosterone, androstenedione
	Medulla	Epinephrine, norepinephrine
Gonads	Testis	Testosterone, estradiol, androstenedione, inhibin, activin, müllerian-inhibiting substance
	Ovary	Estradiol, progesterone, testosterone, androstenedione, inhibin, activin, FSH-releasing peptide, relaxin, follistatin
Placenta		Human chorionic gonadotropin (hCG), human placental lactogen (hPL), progesterone, estrogen
Pancreas		Insulin, glucagon, somatostatin, pancreatic polypeptide, gastrin, vasoactive intestinal peptide (VIP)
Pineal		Melatonin, biogenic amines, several peptides

Table 1-2 Nonclassical "Endocrine Organs" and Their Hormones

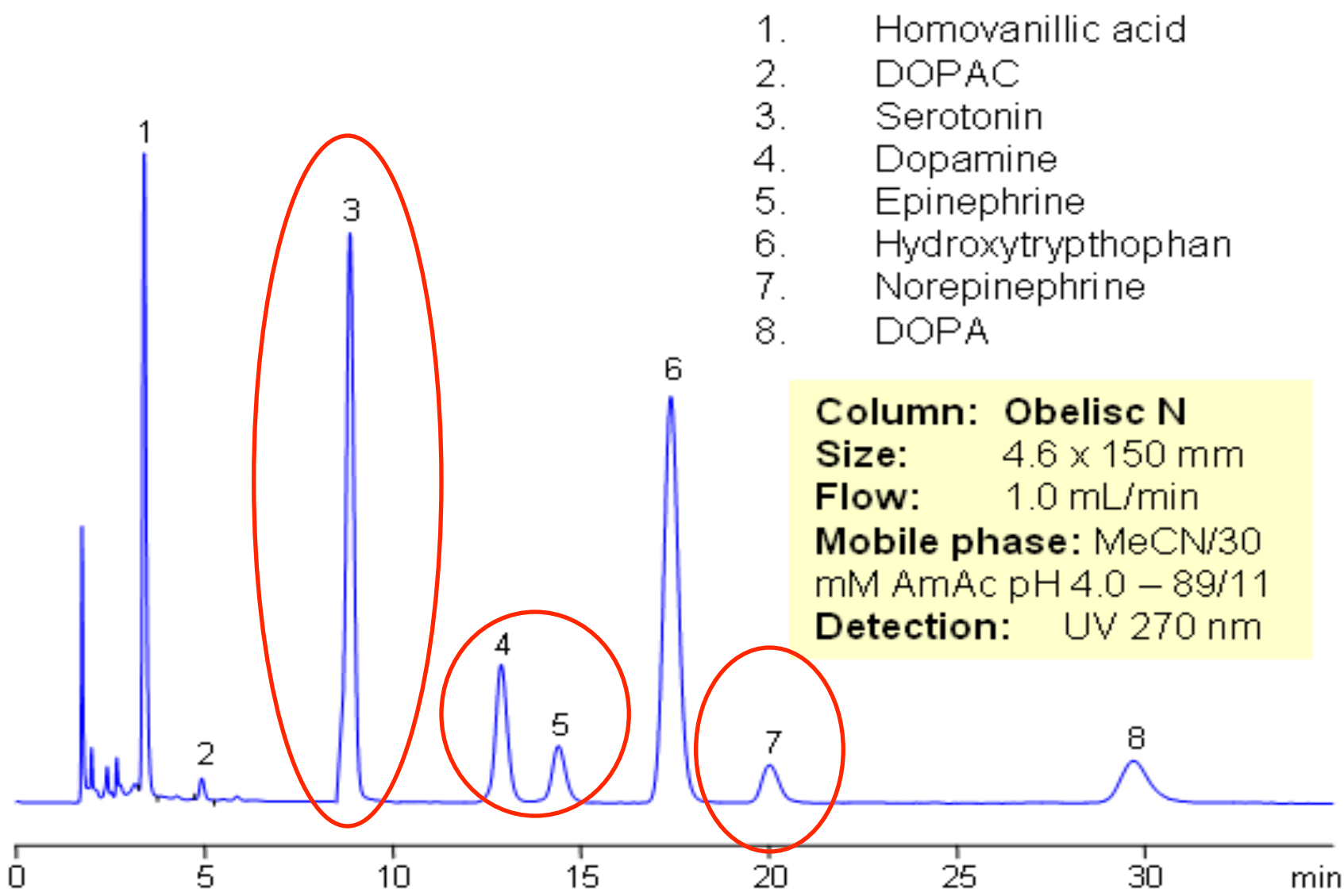
Organ	Hormone
Brain (especially hypothalamus)	Corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone TRH), luteinizing hormone-releasing hormone (LHRH), growth hormone-releasing hormone (GHRH), somatostatin, growth factors[a] (fibroblast growth factors, transforming growth factor-α (TGF-α), transforming growth factor-β (TGF-β), insulin-like growth factor I (IGF-I)
Heart	Atrial natriuretic peptides
Kidney	Erythropoietin, renin, 1,25-dihydroxyvitamin D
Liver, other organs, fibroblasts	IGF-I
Adipose tissue	Leptin
Gastrointestinal tract	Cholecystokinin (CCK), gastrin, ghrelin, secretin, vasoactive intestinal peptide (VIP), enteroglucagon, gastrin-releasing peptide
Platelets	Platelet-derived growth factor (PDGF), TGF-β
Macrophages, lymphocytes	Cytokines, TGF-β, pro-opiomelanocortin (POMC)-derived peptides
Various sites	Epidermal growth factor (EGF), TGF-α, neuregulins, neurotrophins

[a]Not considered to be hormones, but they can act as such.

Métodos de estudo em endocrinologia

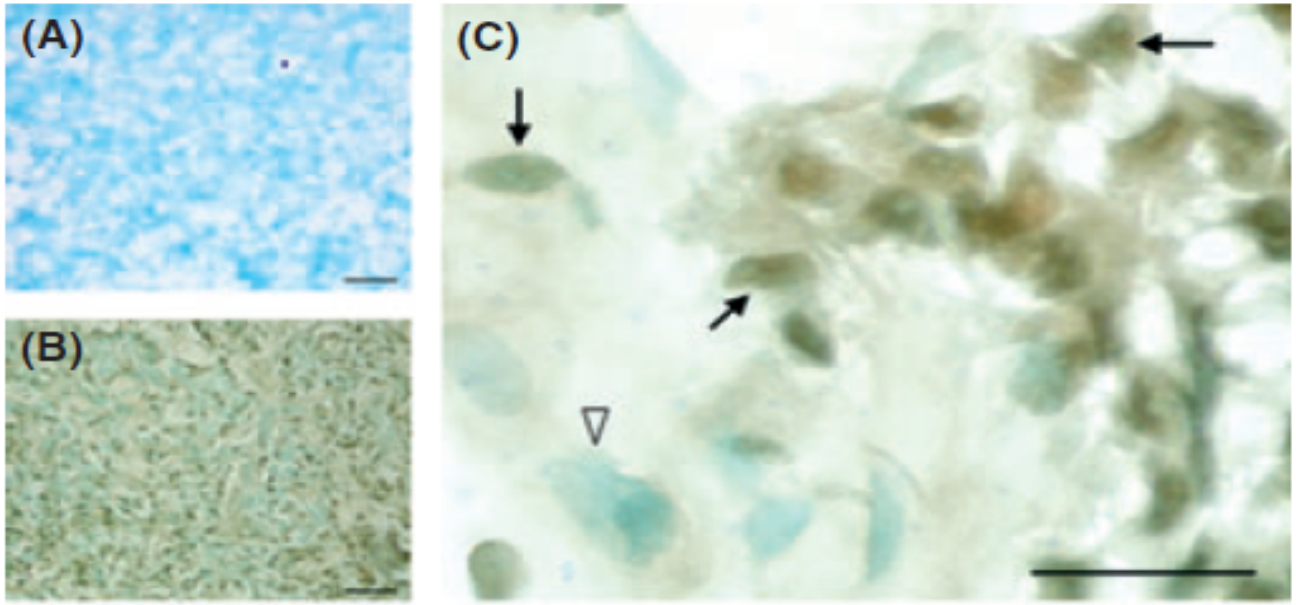
1. Ablação (remoção) / lesão
2. Terapia de reposição – implante glândula (Berthold), hormônio sintético
3. Histologia / citologia
   - Microscopia celular para atividade endócrina
   - visualização de células produtoras de hormônios e receptores
4. Técnicas Instrumentais
   - Cromatografia – técnica de separação – características da molécula – tamanho, polaridade, etc
   - Reação de Polimerase em cadeia – expressão gênica
   - Bioensaio – efeito biológico de um hormônio numa resposta biológica especifica (sistema: célula, tecido ou órgão)
     - ✓ efeito da insulina nos níveis de glicose sanguínea (in vivo)
     - ✓ noradrenalina na produção de melatonina (pineal em cultura)
5. Imunoensaios – RIA, ELISA
6. Estudos farmacológicos - Receptores/Sinal de transdução

Separação cromatográfica - HPLC

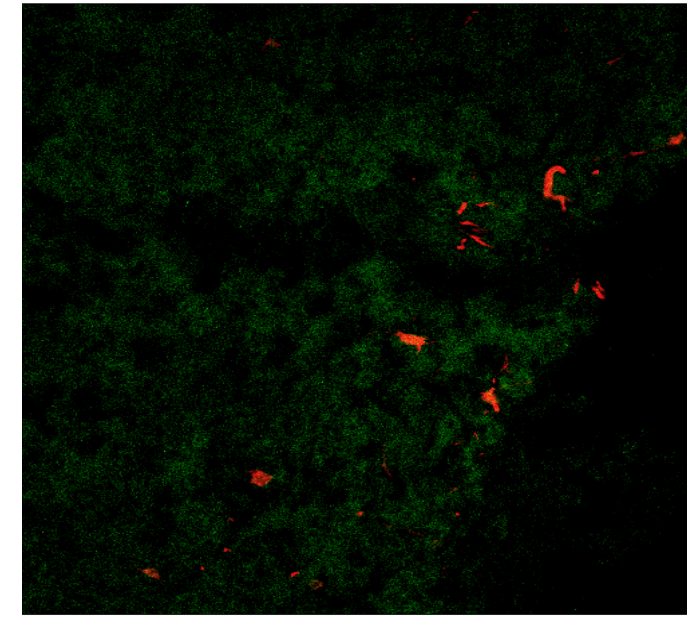


Imunohistoquímica de receptores na glândula pineal de ratos

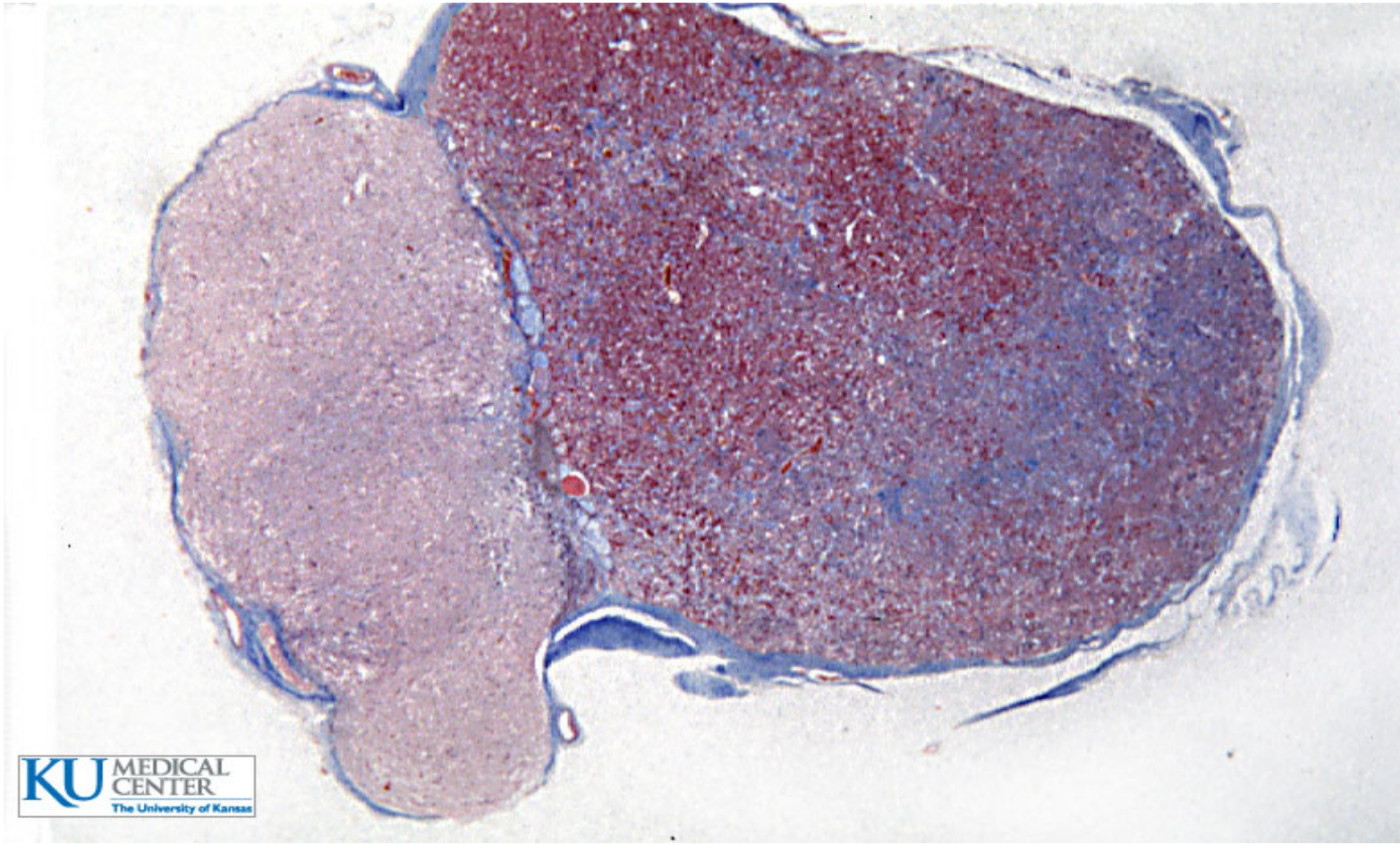
LPS



ATP



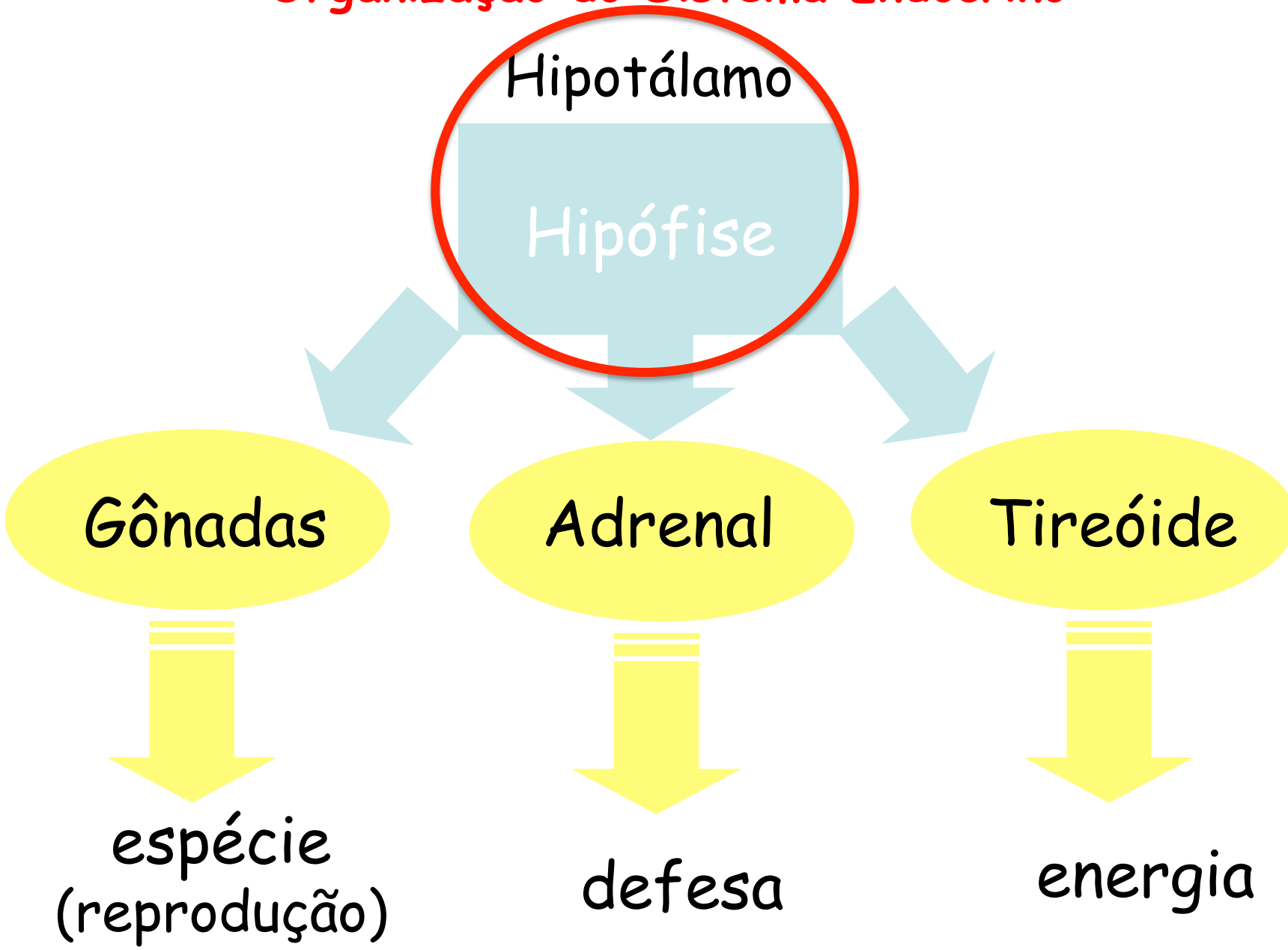
Laboratorio de Cronofarmacologia
IB - USP



Pituitary

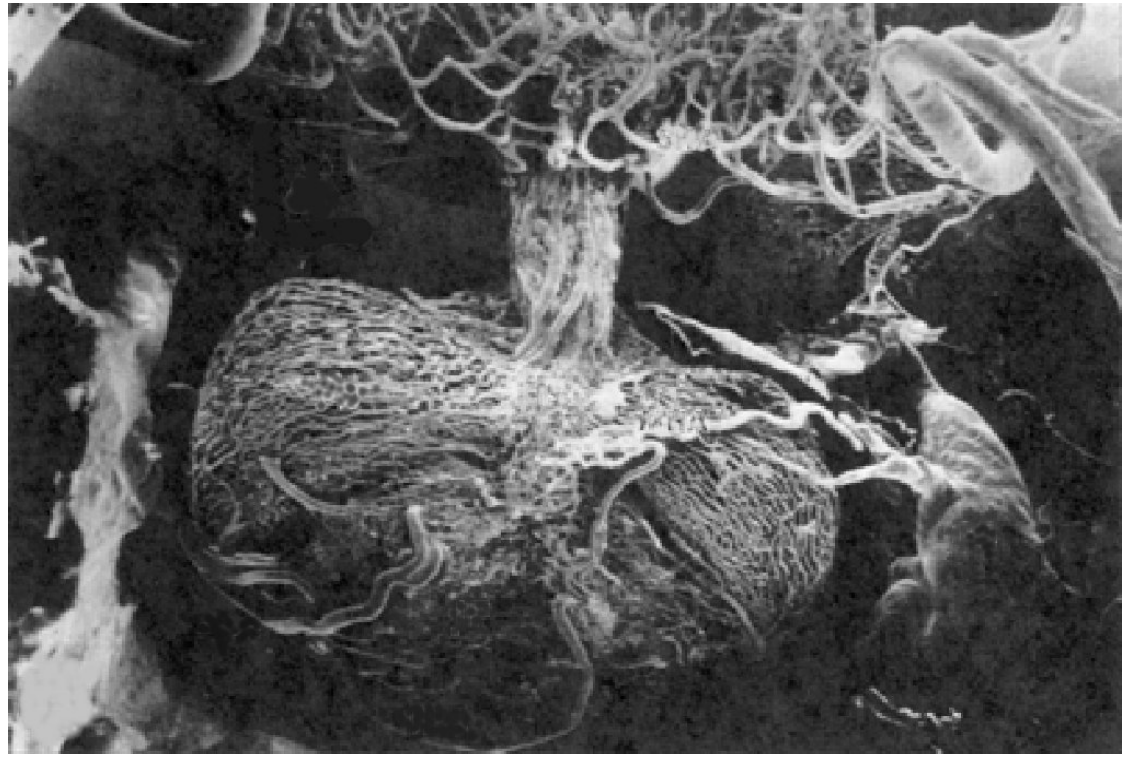
Macro view of the pituitary gland. This and the following pituitary slides are stained with Masson's trichome wherein nuclei and other basophilic structures (may include cytoplasm) are blue, collagen is green or blue, and cytoplasm (nonbasophilic) are red. Notice the lightly-stained neurohypophysis and darker-stained adenohypophysis.

Organização do Sistema Endócrino



Relações anatomo-funcionais entre o hipotálamo e a hipófise anterior

Galeno (sec XI DC); Lewi e Greving (1920); Popa e Fileding (1930); Green e Harris (1946)

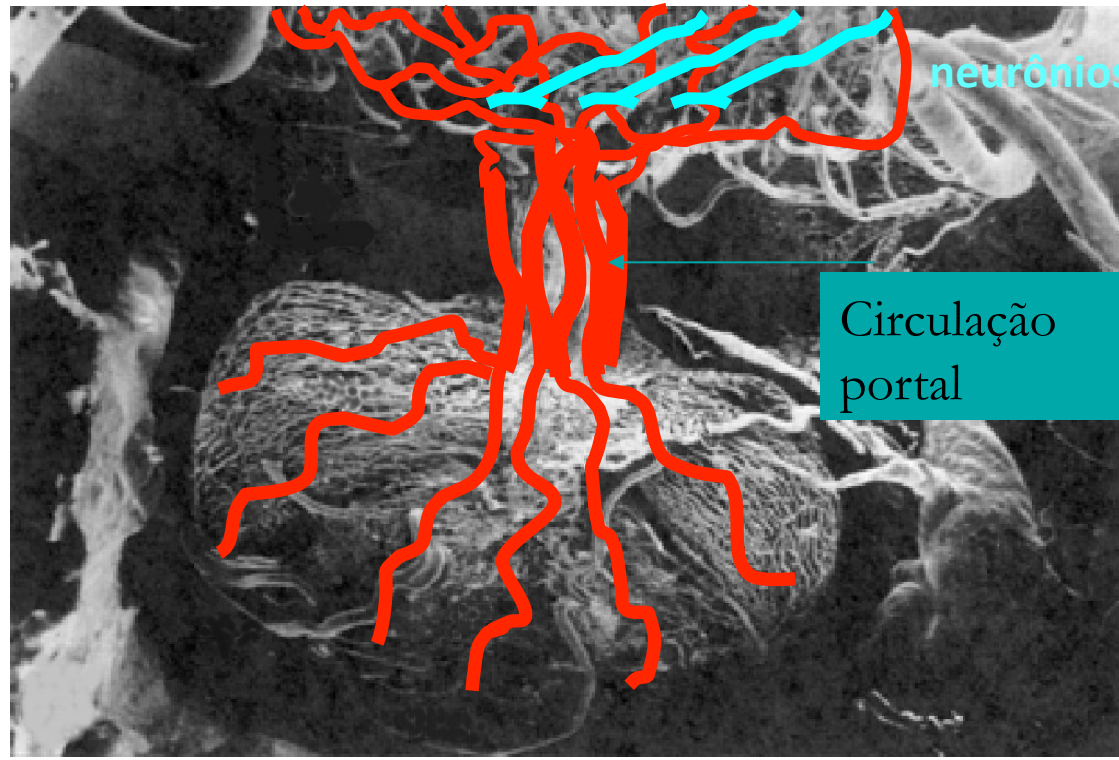


J. D. Green and G. W. Harris. The Neurovascular link between the neurohypophysis and adenohypophysis.
Journal of Endocrinology 5: 136 (1946).

"There is little doubt that the secretory activity of the adenohypophysis is to some extent under the control of the nervous system [see Marshall, 1936, 1942; Brooks, 1939]. Two hypotheses have been advanced by various authors to explain this neural control: first, that the glandular cells possess a direct secretor-motor nerve supply, or secondly, that a humoral relay transmits the nervous stimuli from the hypothalamus by means of the hypophysial portal vessels."

Journal of Endocrinology

Relações anatomo-funcionais entre o hipotálamo e a hipófise anterior



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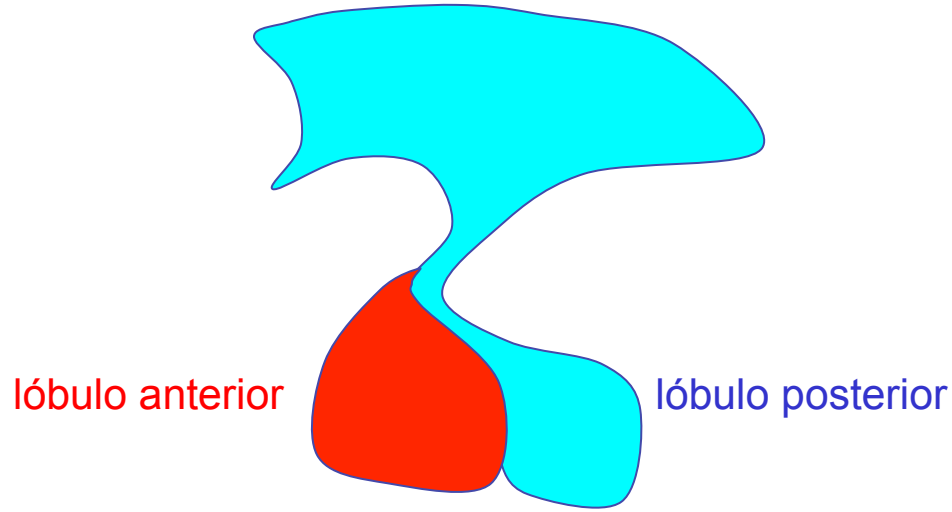
Formação da hipófise durante o desenvolvimento

à partir de diferentes tecidos embrionários.



- *tecido epitelial*
- torna-se uma protuberância do céu da boca.

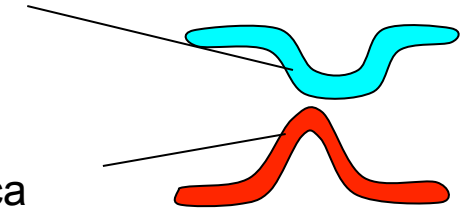
- *tecido neural*
- derivado da ectoderme
- Se desenvolve a partir do hipotálamo (downgrowth).

Desenvolvimento embrionário da hipófise

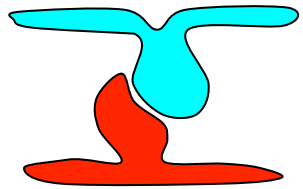
1. Protuberâncias do tecido aparecem do hipotálamo e do céu da boca.

Crescimento do Infundíbulo à partir do hipotálamo

Crescimento de células epiteliais do céu da boca



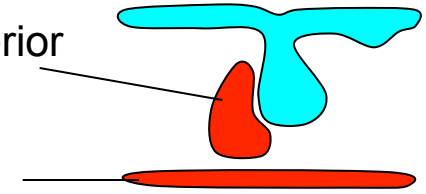
2. As duas protuberâncias de tecido fundem-se



3. A lóbulo da hipófise anterior ainda imatura separa-se do céu da boca

hipófise anterior imatura

Céu da boca

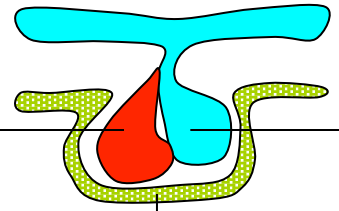


4. Maturação dos lóbulos anterior e posterior. Formação da sela túrcica óssea

lóbulo anterior

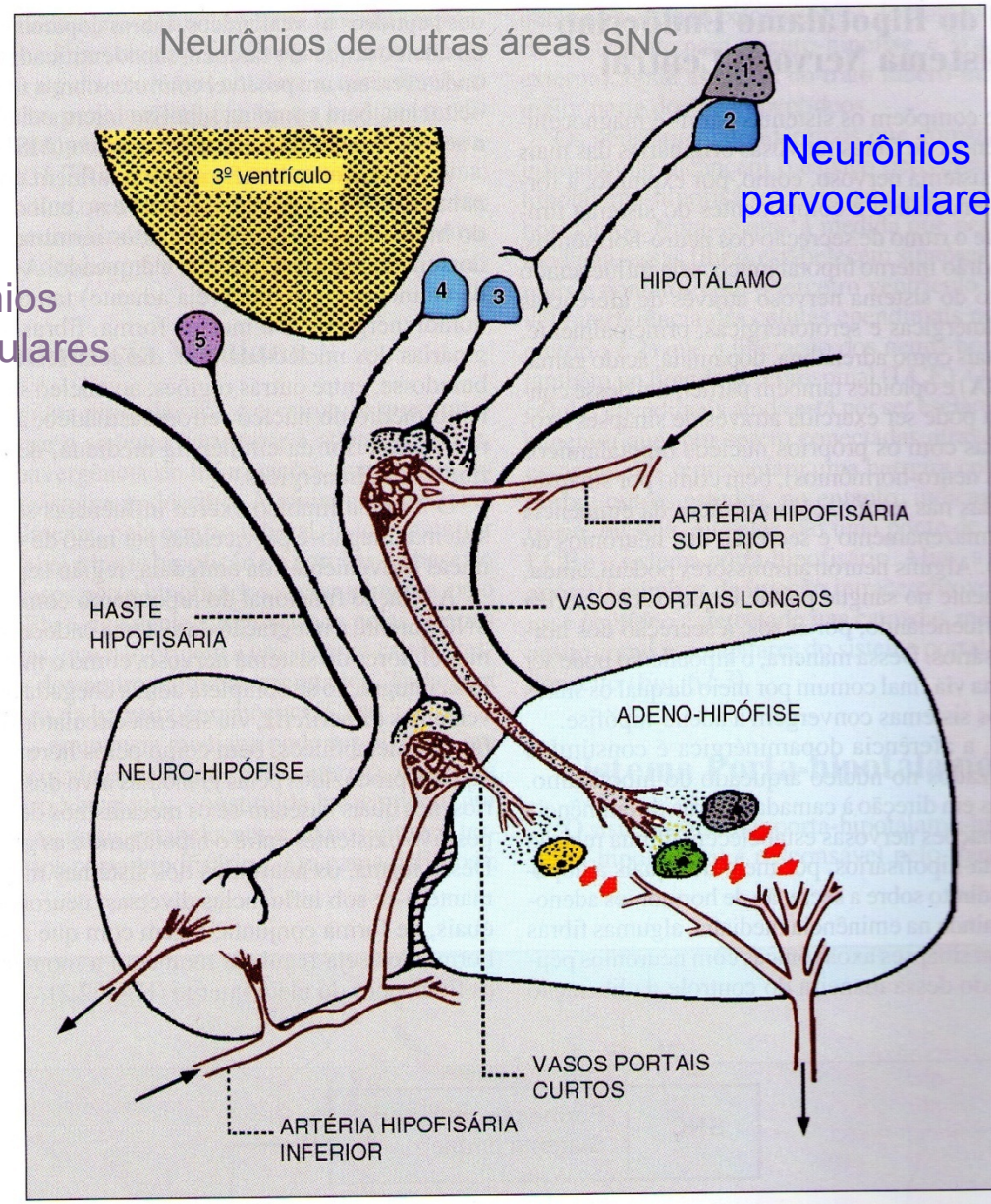
lóbulo posterior

sela túrcica

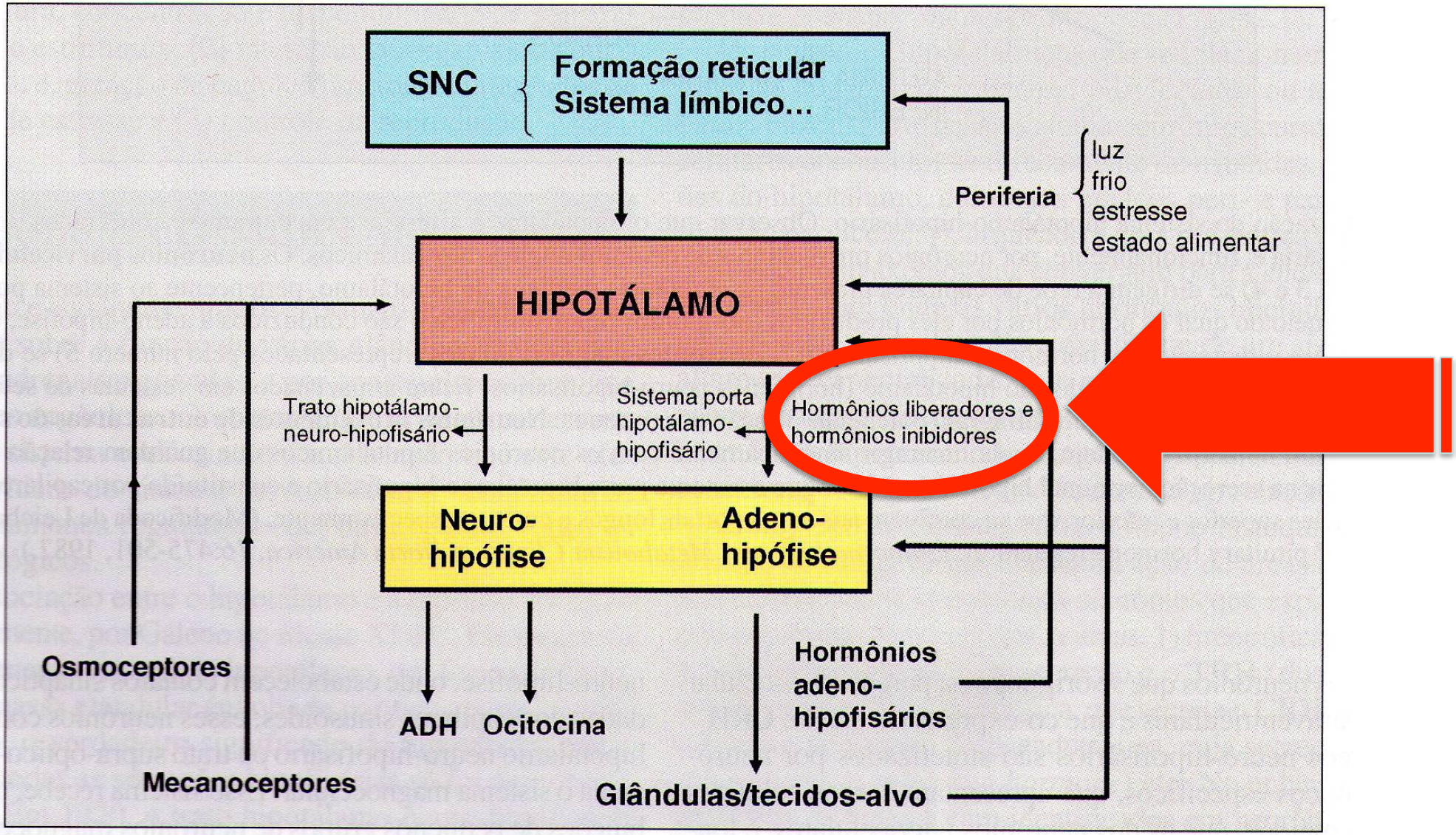


Hipotálamo – Interface entre os sistemas nervoso e endócrino

Organização do complexo hipotálamo-hipófise



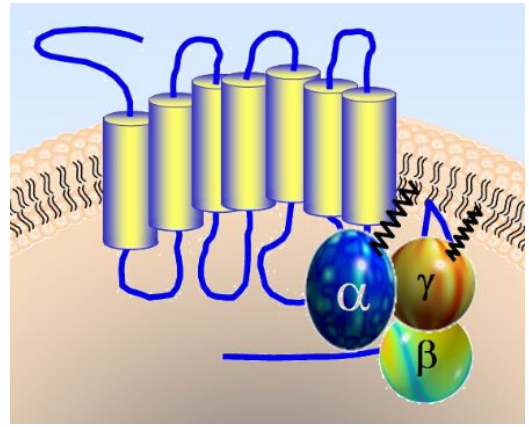
Controle da atividade do sistema hipotálamo-hipófise



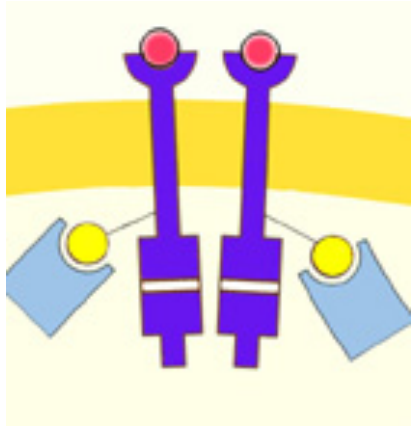
Sinais hormonais e neuronais o integram com a periferia gerando respostas endócrinas apropriadas para a manutenção da homeostase

Tipos de receptores

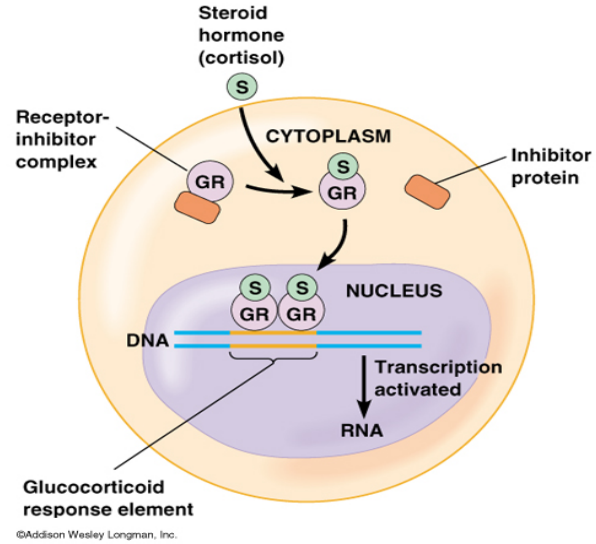
- Receptores acoplados à proteína G



- Receptores ligados à enzima – proteína quinases

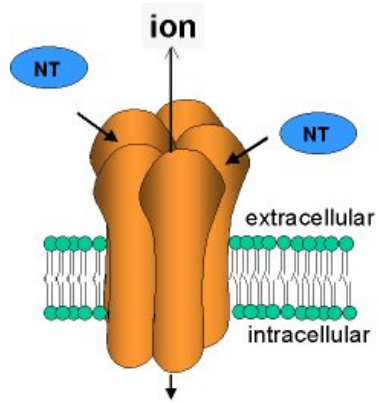


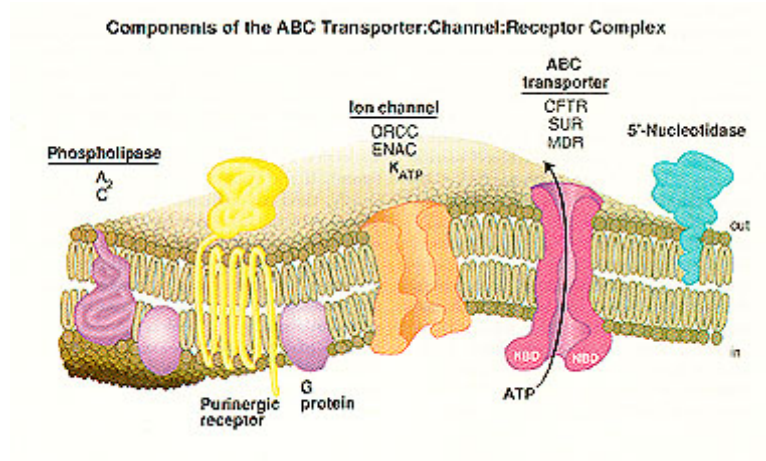
- Receptores intracelulares



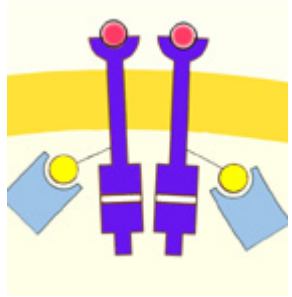
Receptores de Membrana

- Canais iônicos

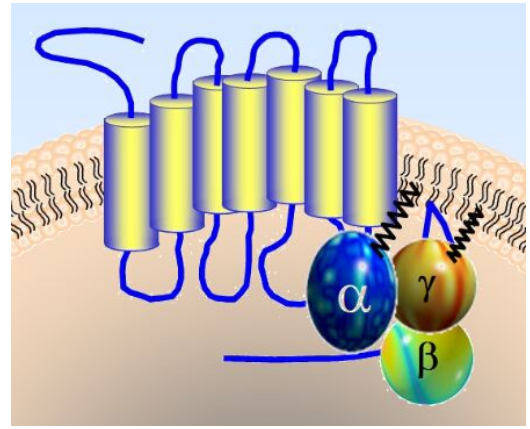




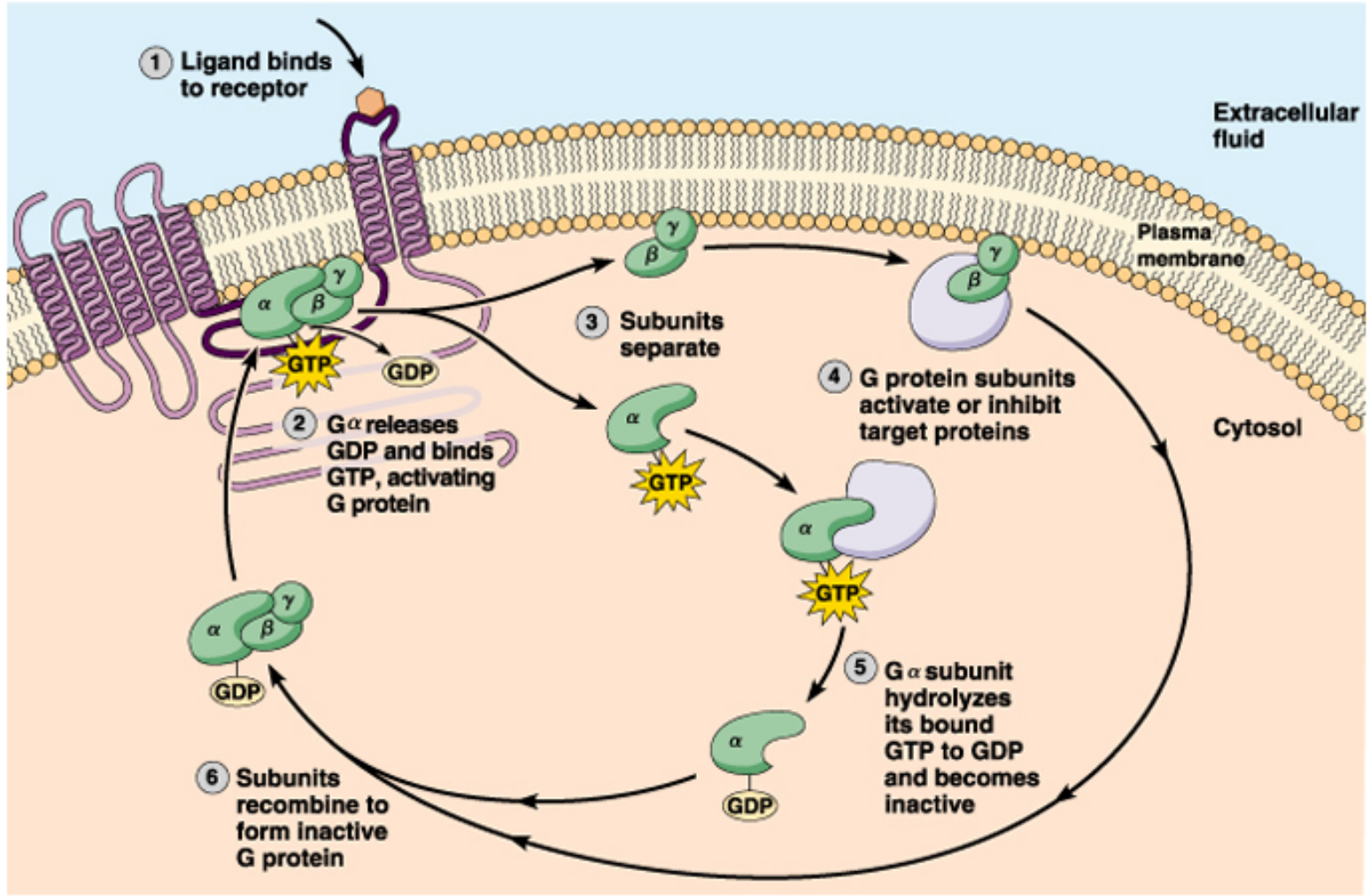
- Receptores ligados à enzima – proteína quinases



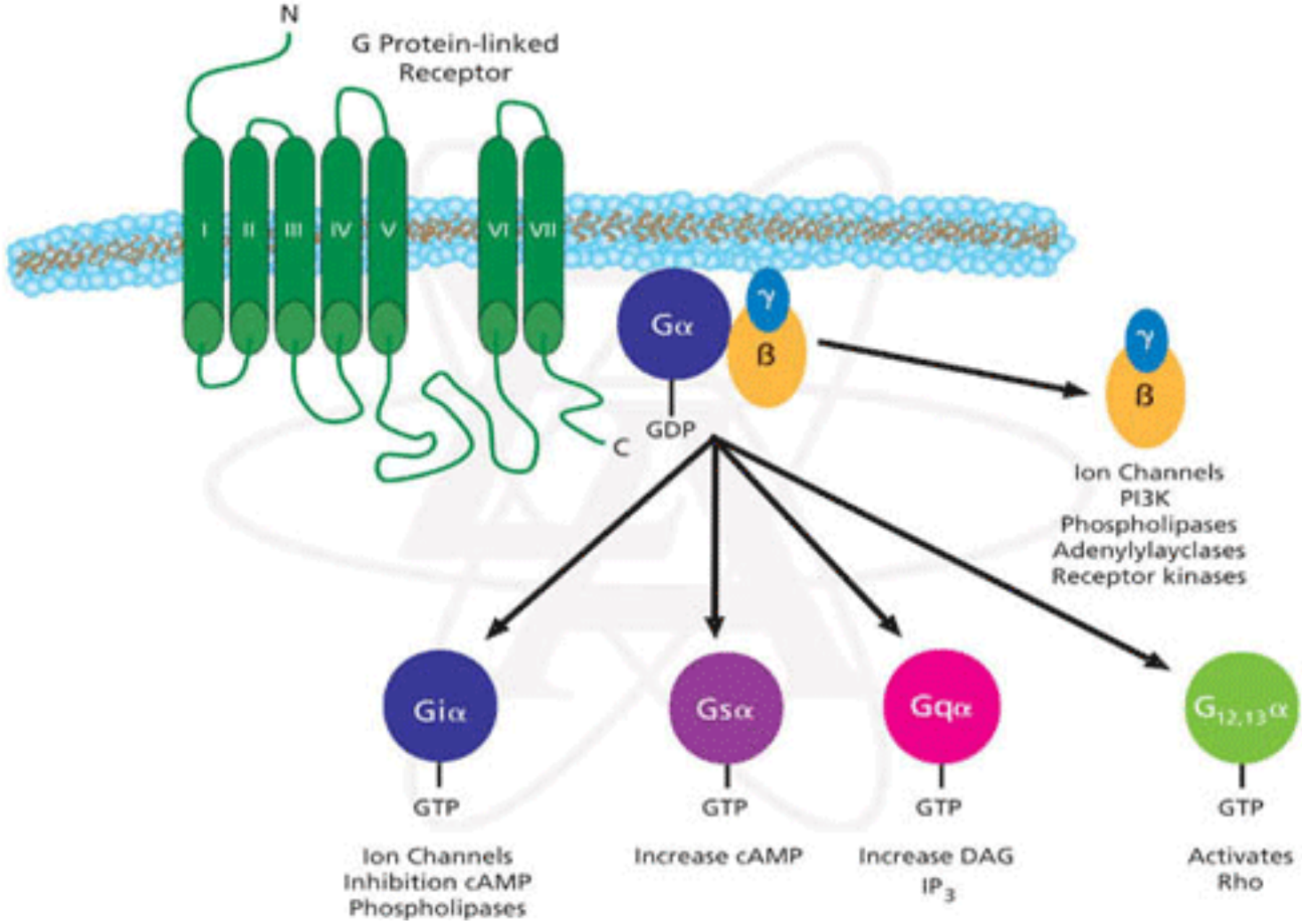
- Receptores acoplados à proteína G



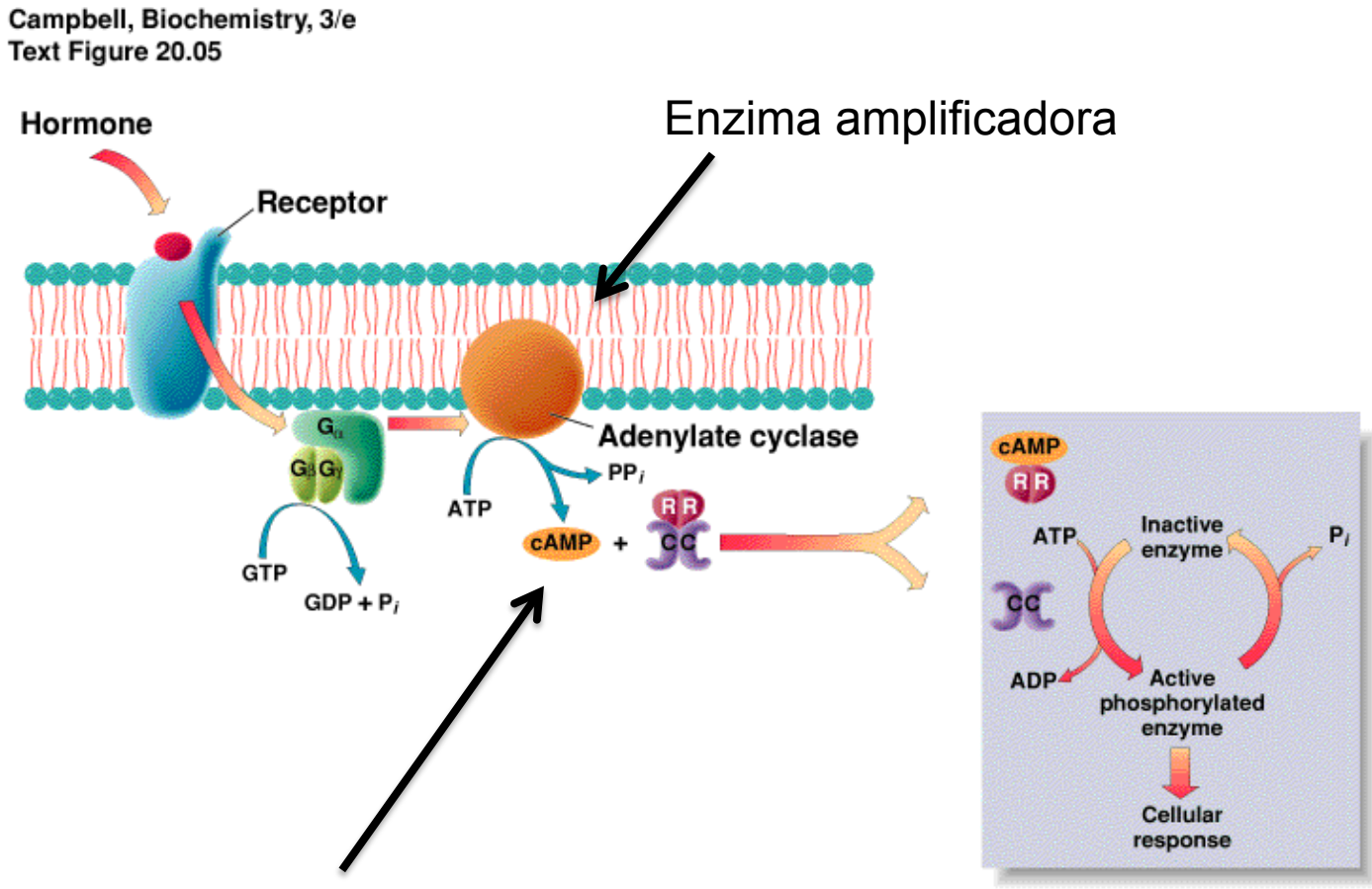
Receptores acoplados à Proteína G



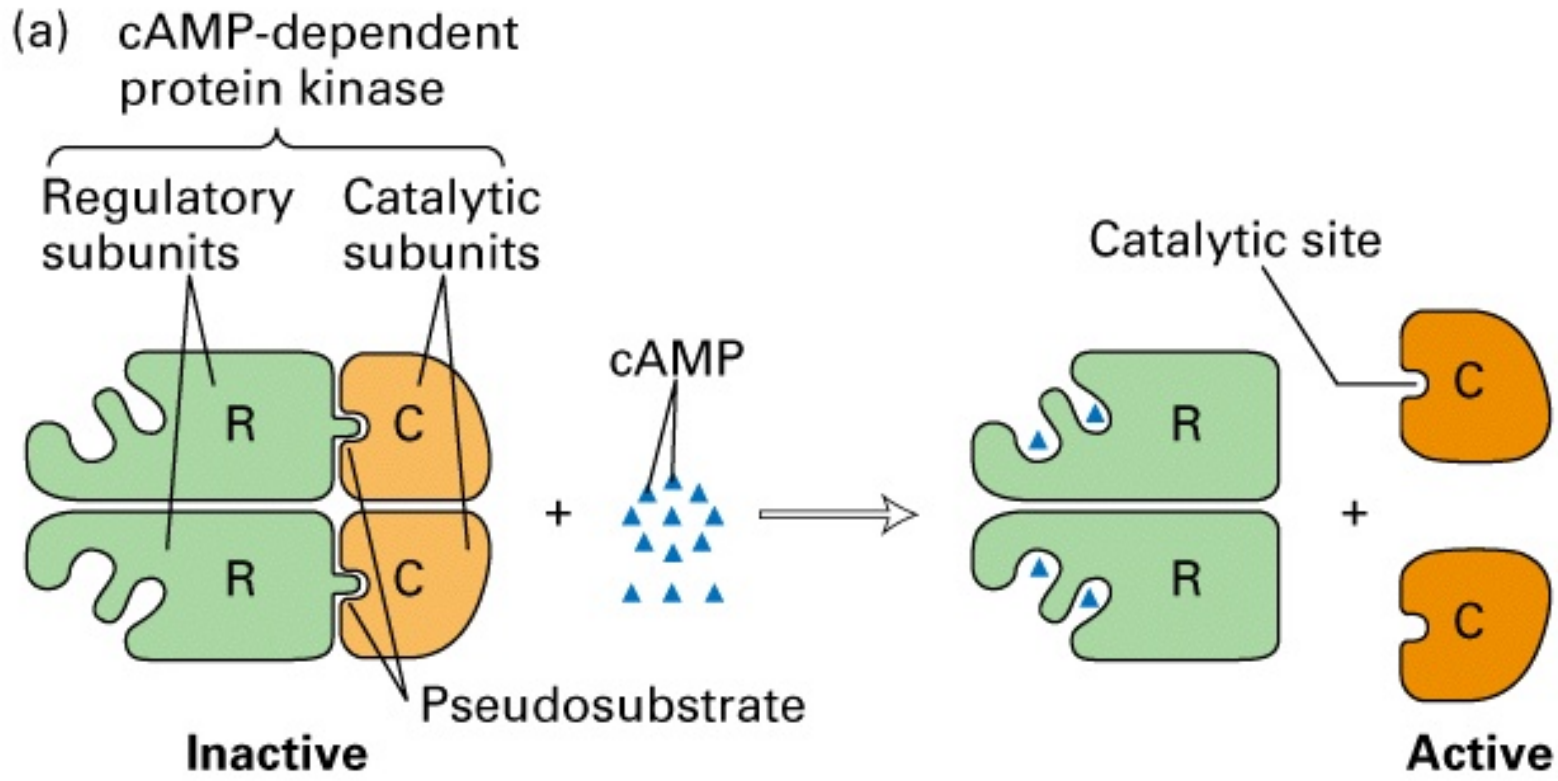
Diversidade de vias de transdução do sinal de receptores acoplados à proteína G



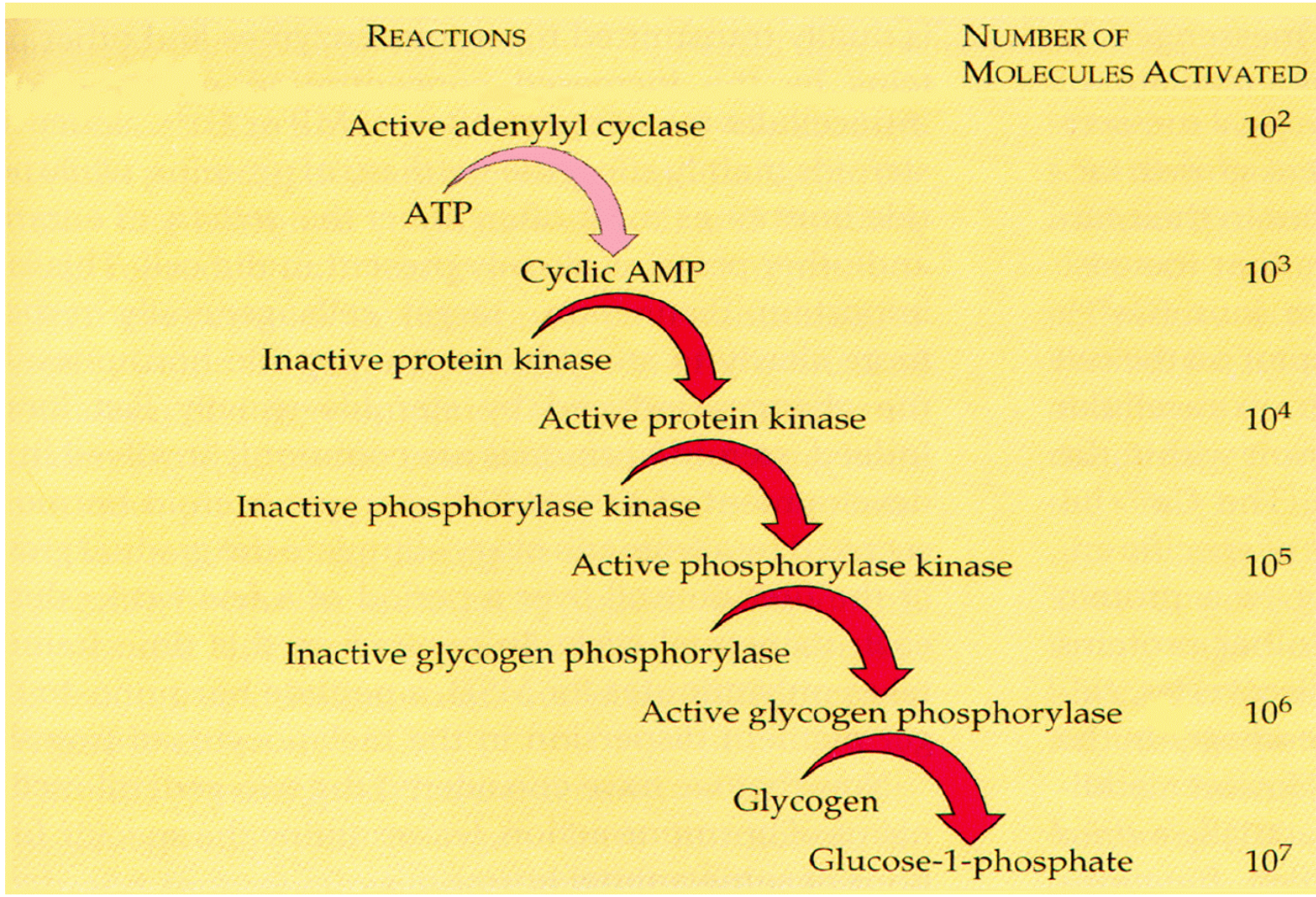
Via de transdução – Gs/AMPc



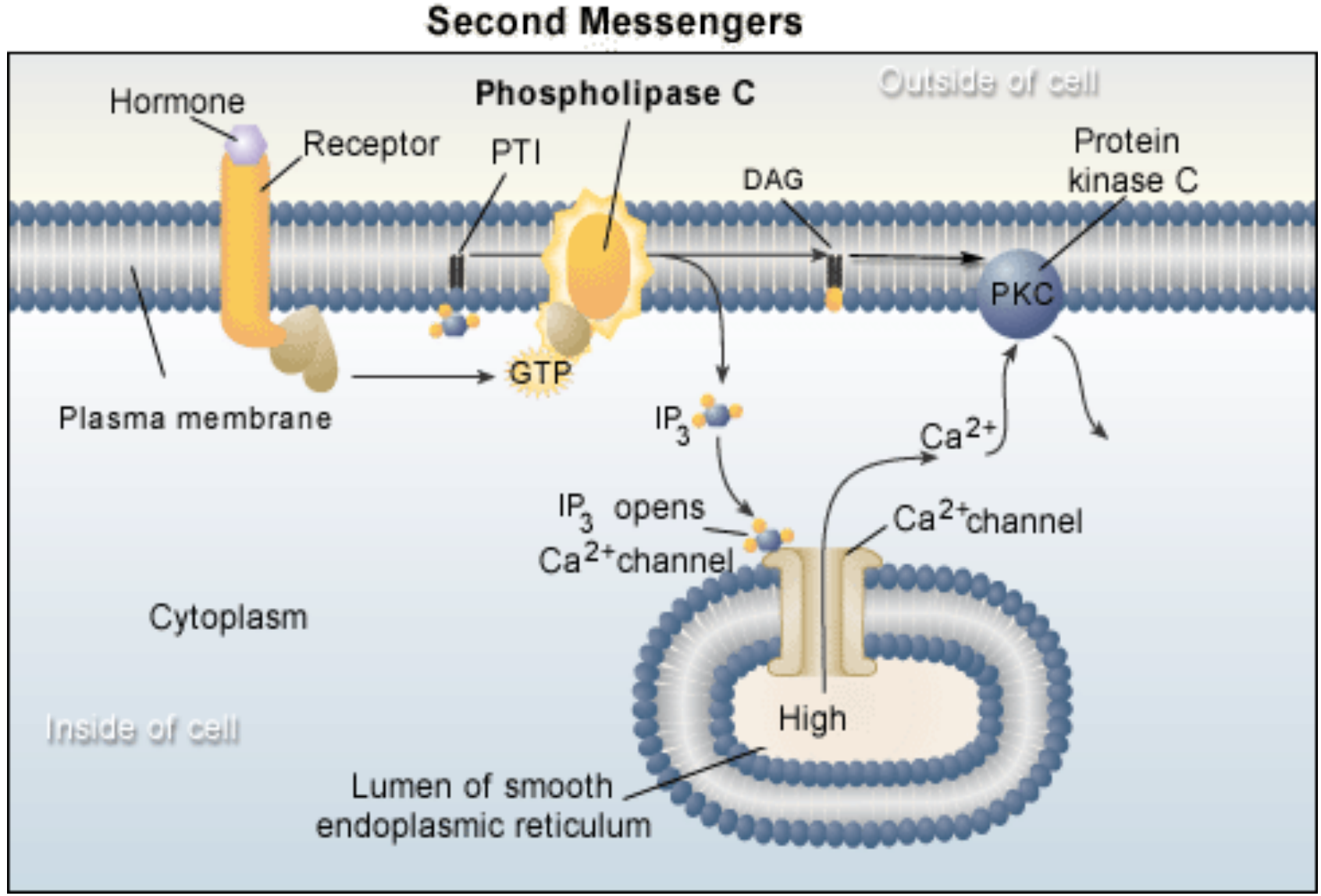
Ativação da PKA



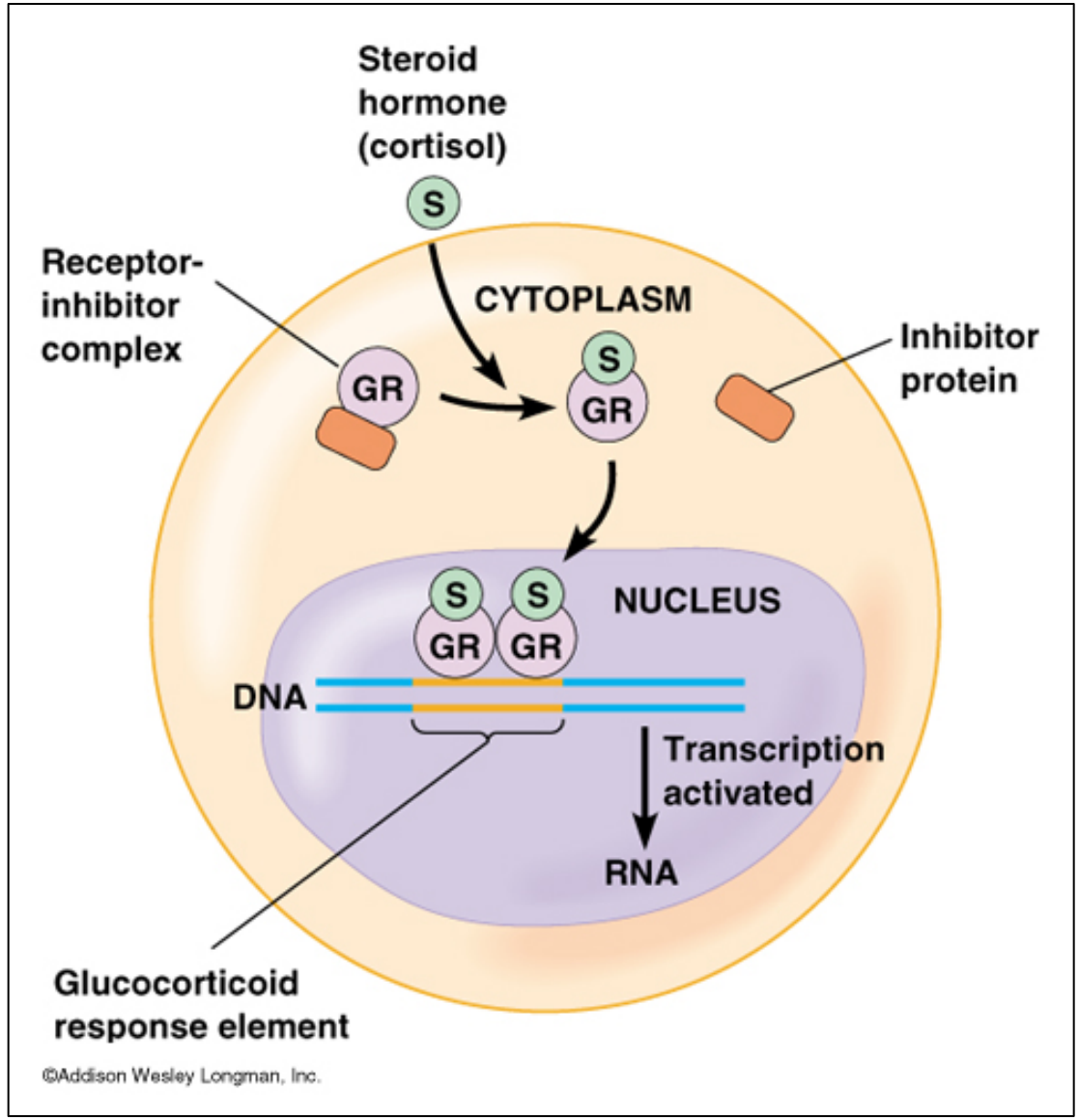
Amplificação do sinal



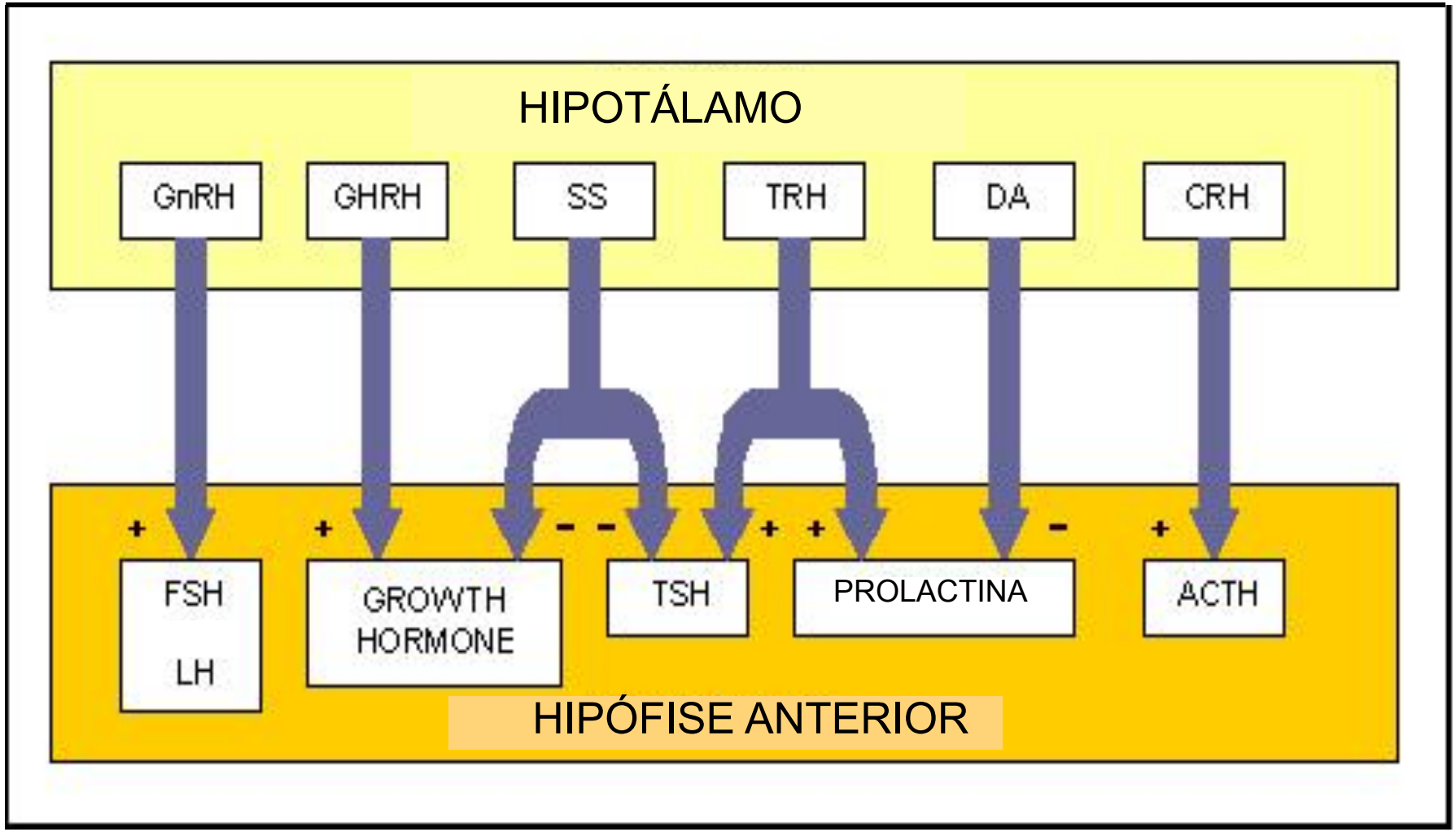
Ativação da enzima Fosfolipase C



Receptores intracelulares



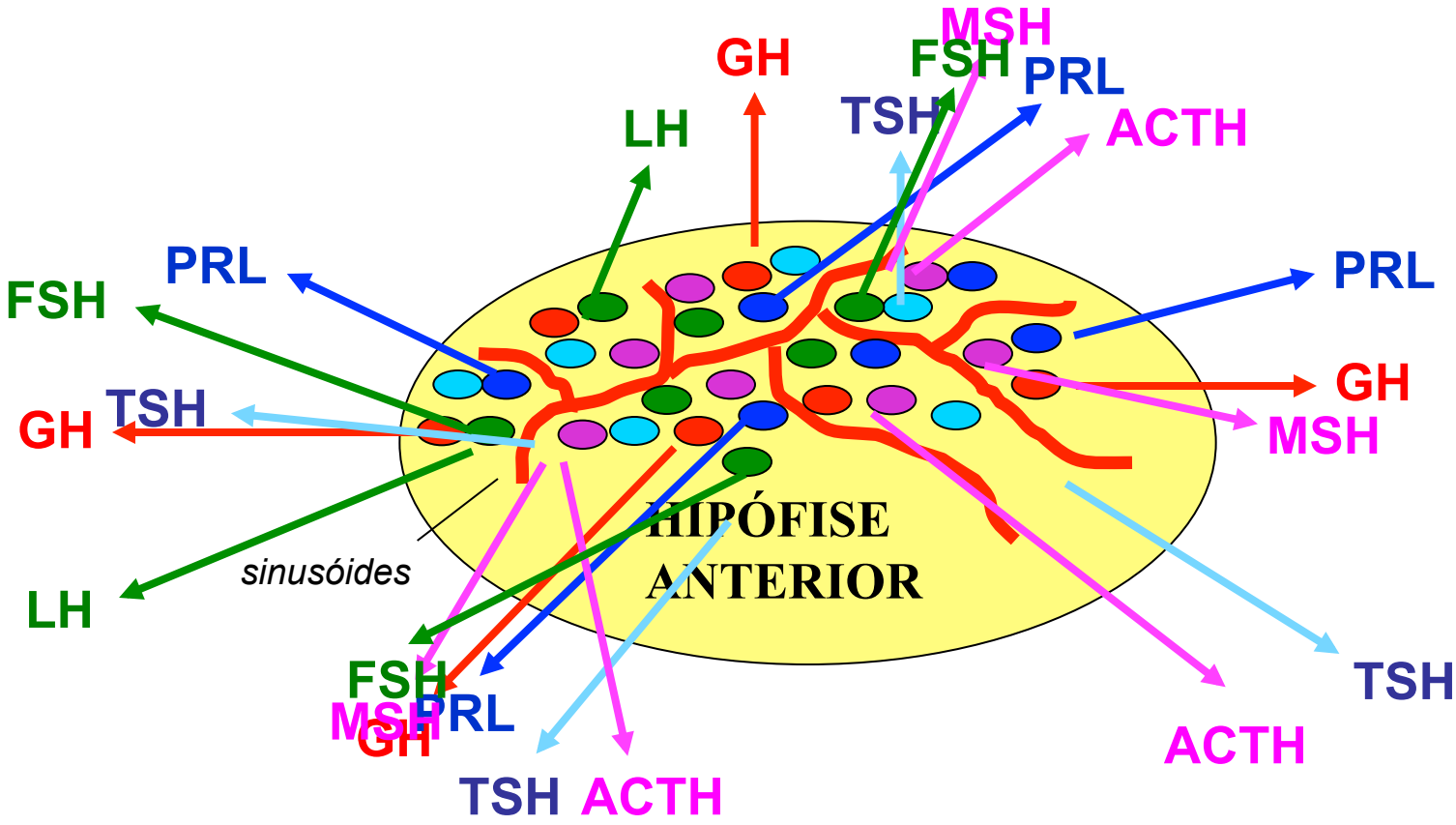
Controle hipotalâmico da hipófise anterior



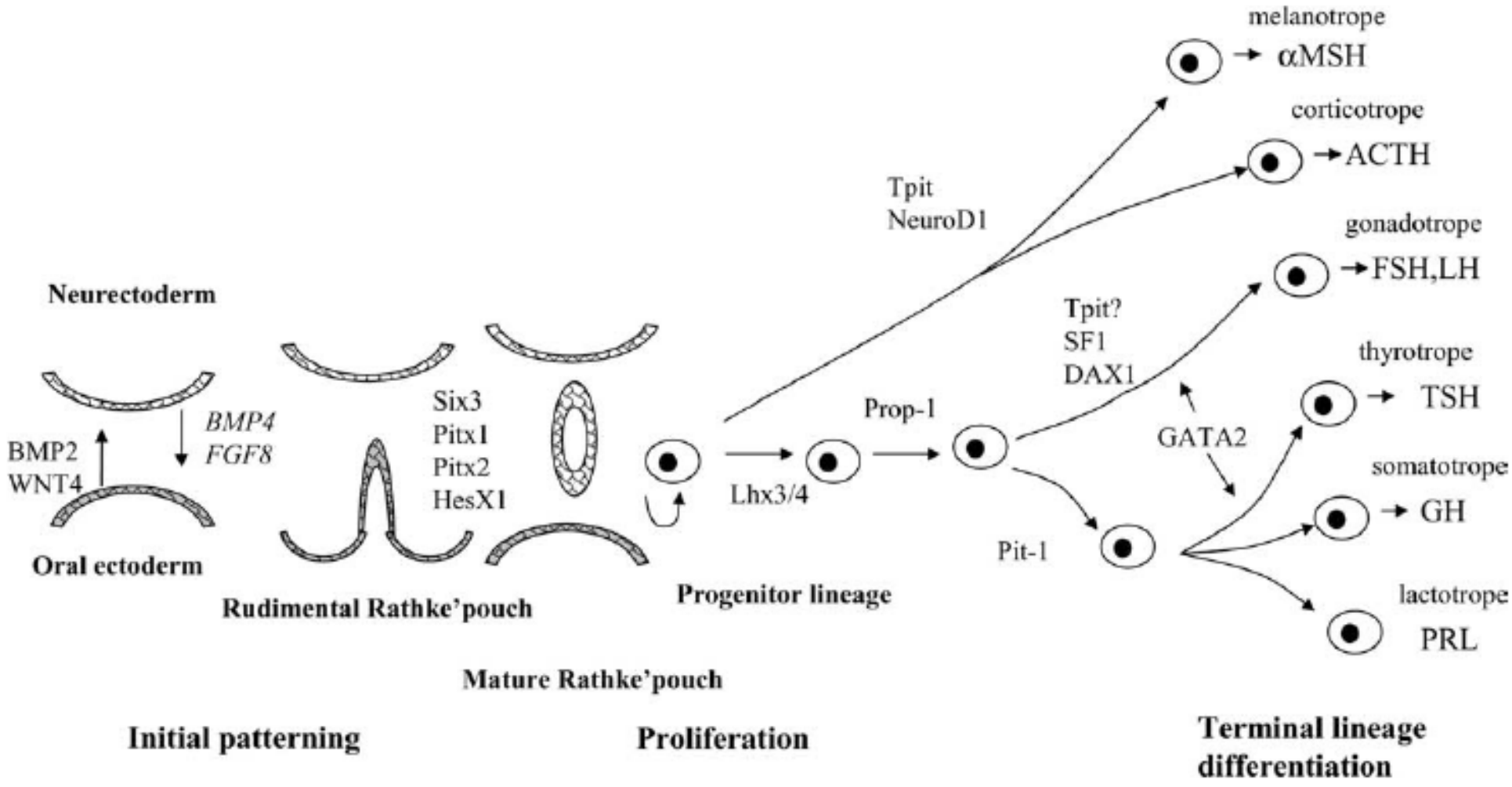
O que controla a secreção diferencial dos hormônios da hipófise anterior ?

Hipófise anterior - estrutura celular

- células epiteliais circundadas por grandes capilares - *sinusóides*.
- diferentes populações de células produzem diferentes hormônios.



Desenvolvimento da hipófise anterior

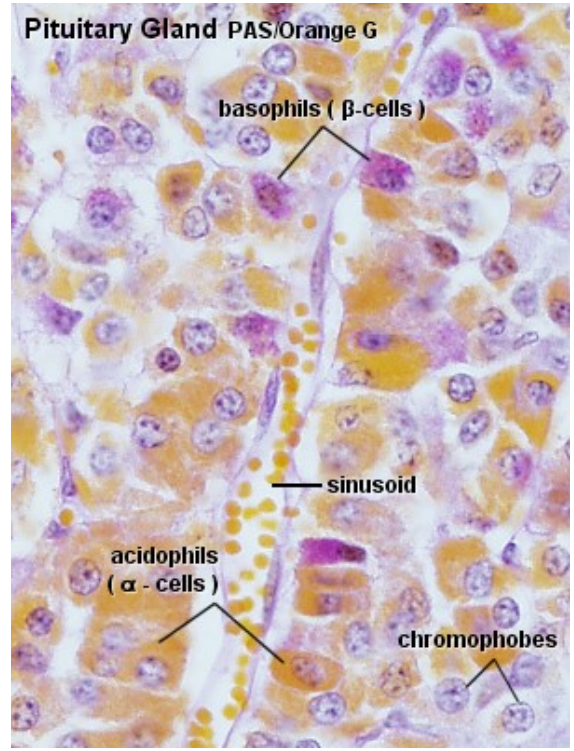


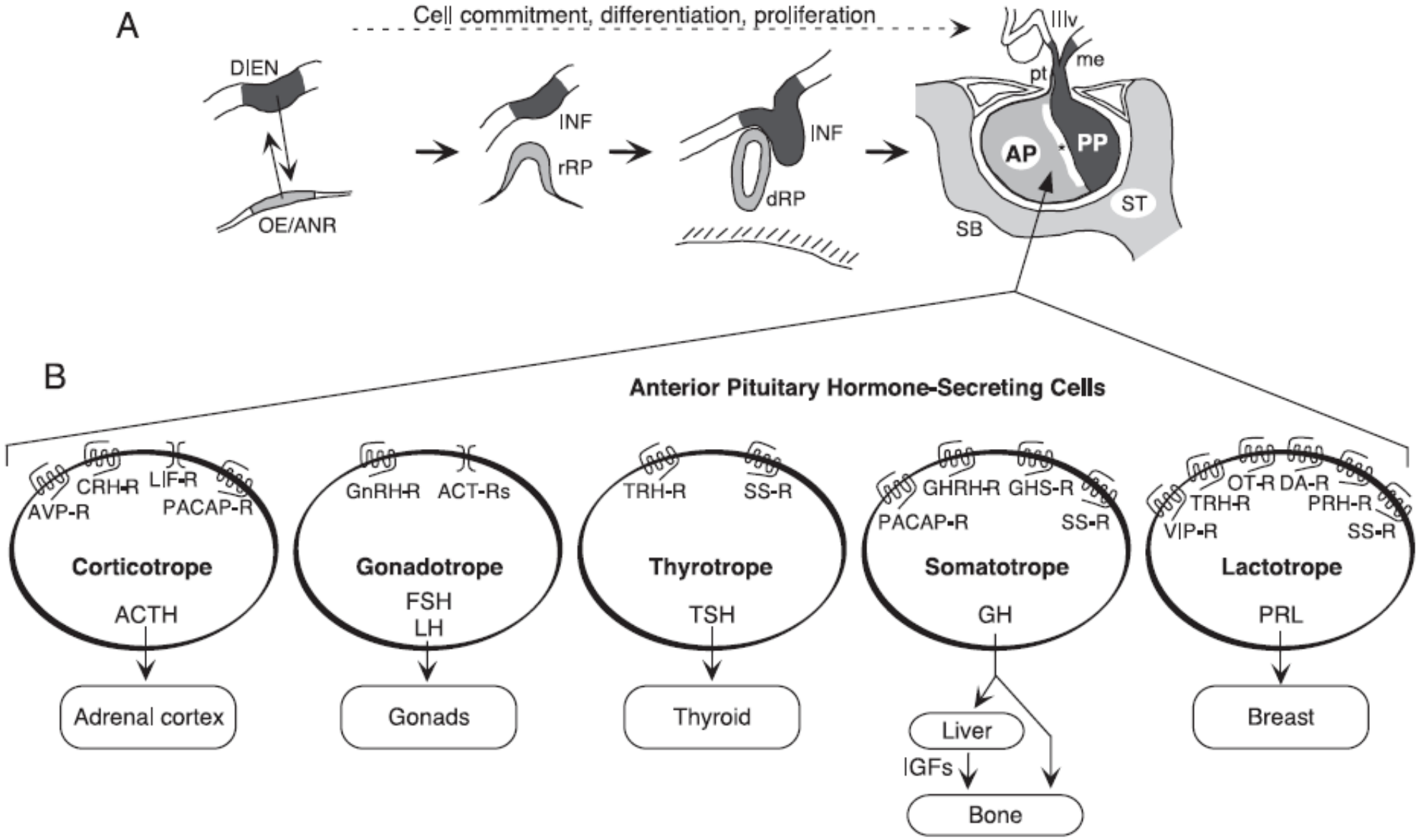
Hipófise anterior

✓ 1. Estrutura celular

Em geral há um tipo celular para cada hormônio formado na glândula

1- Somatotrópicas (30-40 % - GH) - acidófilas
2- Corticotrópicas (20 % - ACTH)
3- Tireotrópicas (TSH)
4- Gonadotrópicas (LH e FSH)
5- Lactotrópicas (PRL)




A
Cell commitment, differentiation, proliferation
DIEN
OE/ANR
INF
rRP
INF
dRP
IIIv
pt
me
AP
PP
ST
SB
B
Anterior Pituitary Hormone-Secreting Cells
CRH-R
LIF-R
AVP-R
PACAP-R
Corticotrope
ACTH
Adrenal cortex
GnRH-R
ACT-Rs
Gonadotrope
FSH
LH
Gonads
TRH-R
SS-R
Thyrotrope
TSH
Thyroid
GHRH-R
GHS-R
PACAP-R
SS-R
Somatotrope
GH
Liver
IGFs
Bone
OT-R
DA-R
TRH-R
PRH-R
VIP-R
SS-R
Lactotrope
PRL
Breast

Hormônio liberador de Tireotrofina (TRH) – Regulação e Síntese

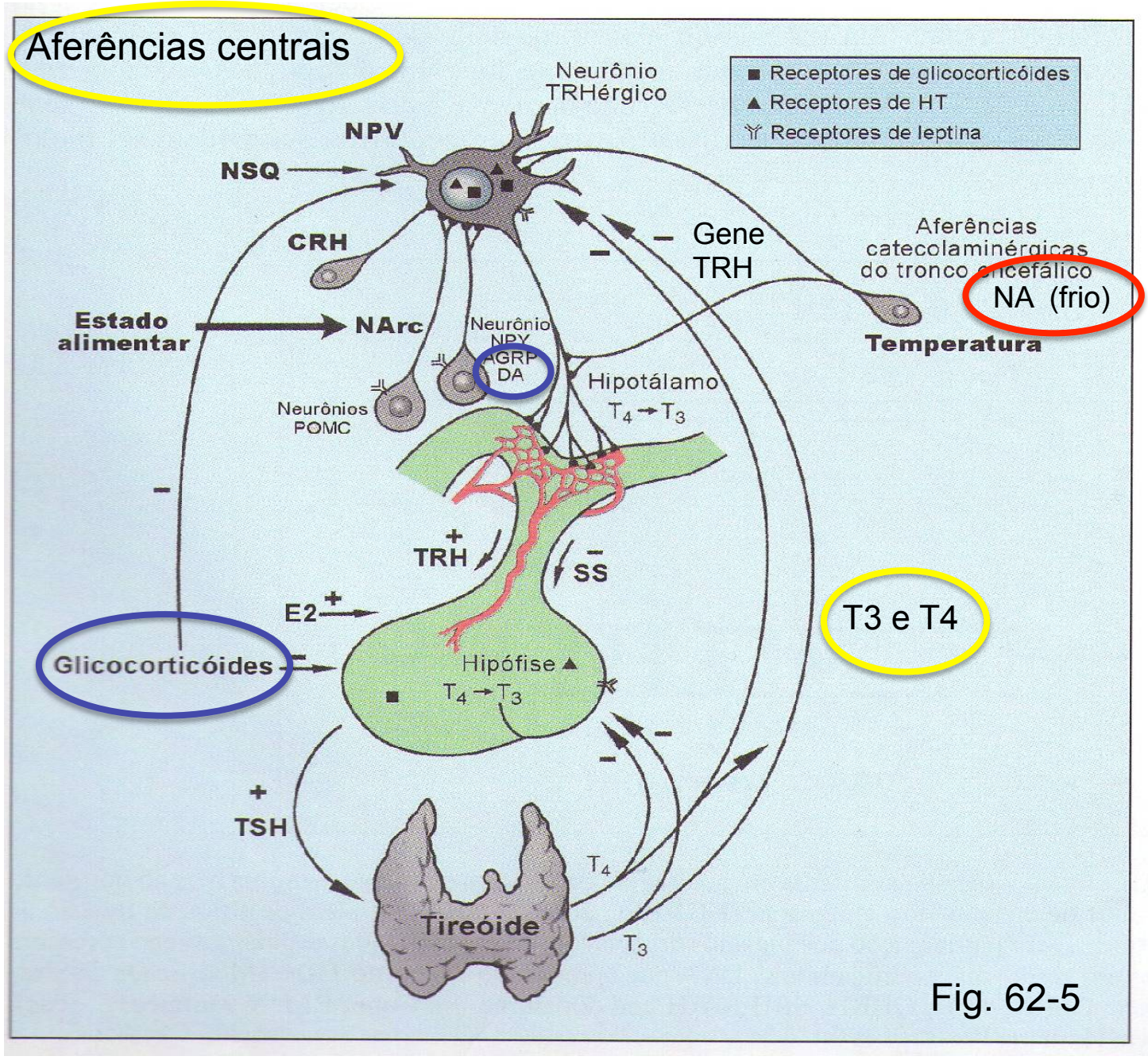
hipotálamo

↓

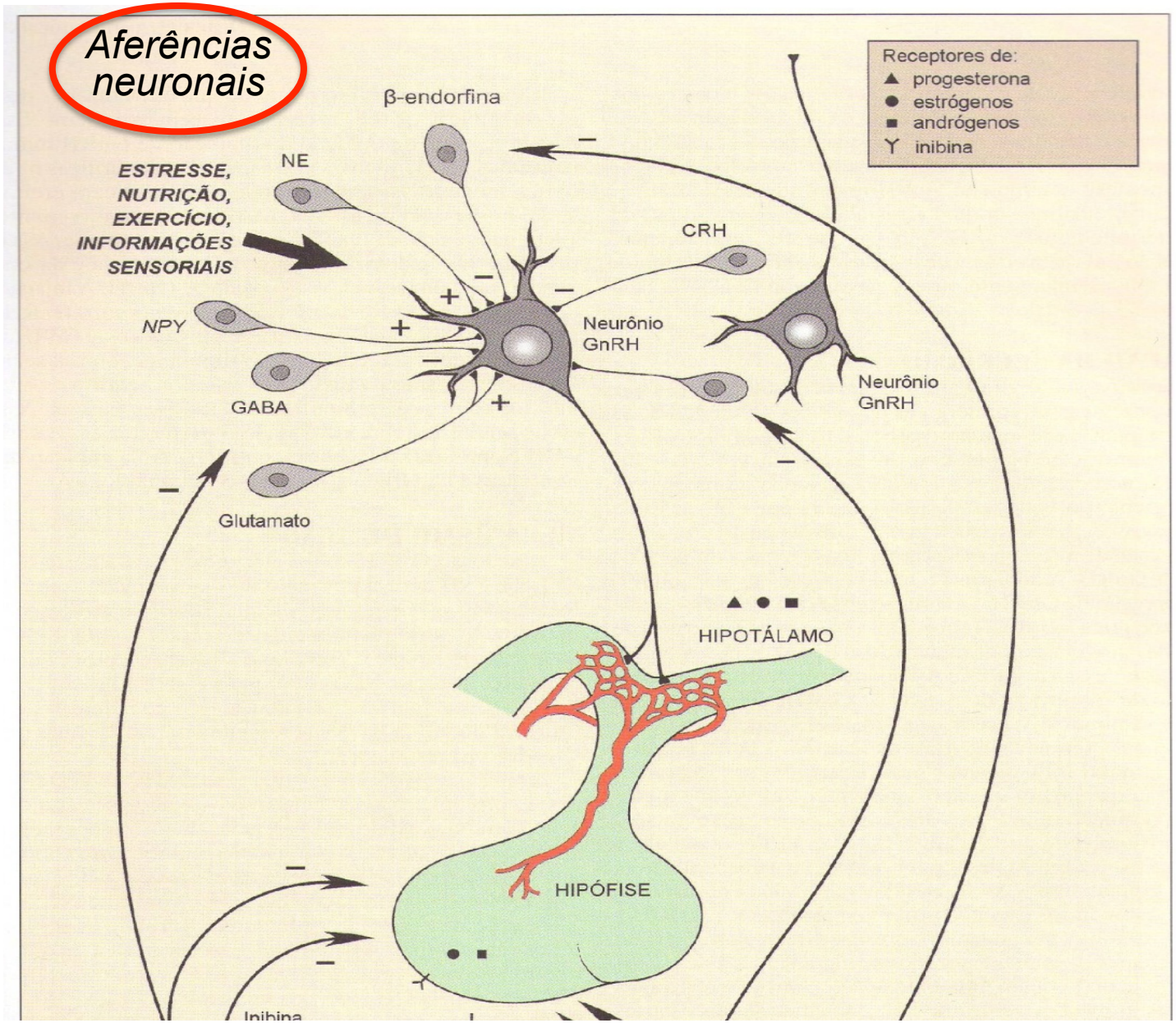
hipófise

↓

tireóide



Regulação neuroendócrina - Hormônio Liberador de Gonadotrofinas (GnRH)
Atividade do sistema hipotálamo-hipófise-gônadas



Regulação neuroendócrina - Hormônio Liberador de Gonadotrofinas (GnRH)
Atividade do sistema hipotálamo-hipófise-gônadas

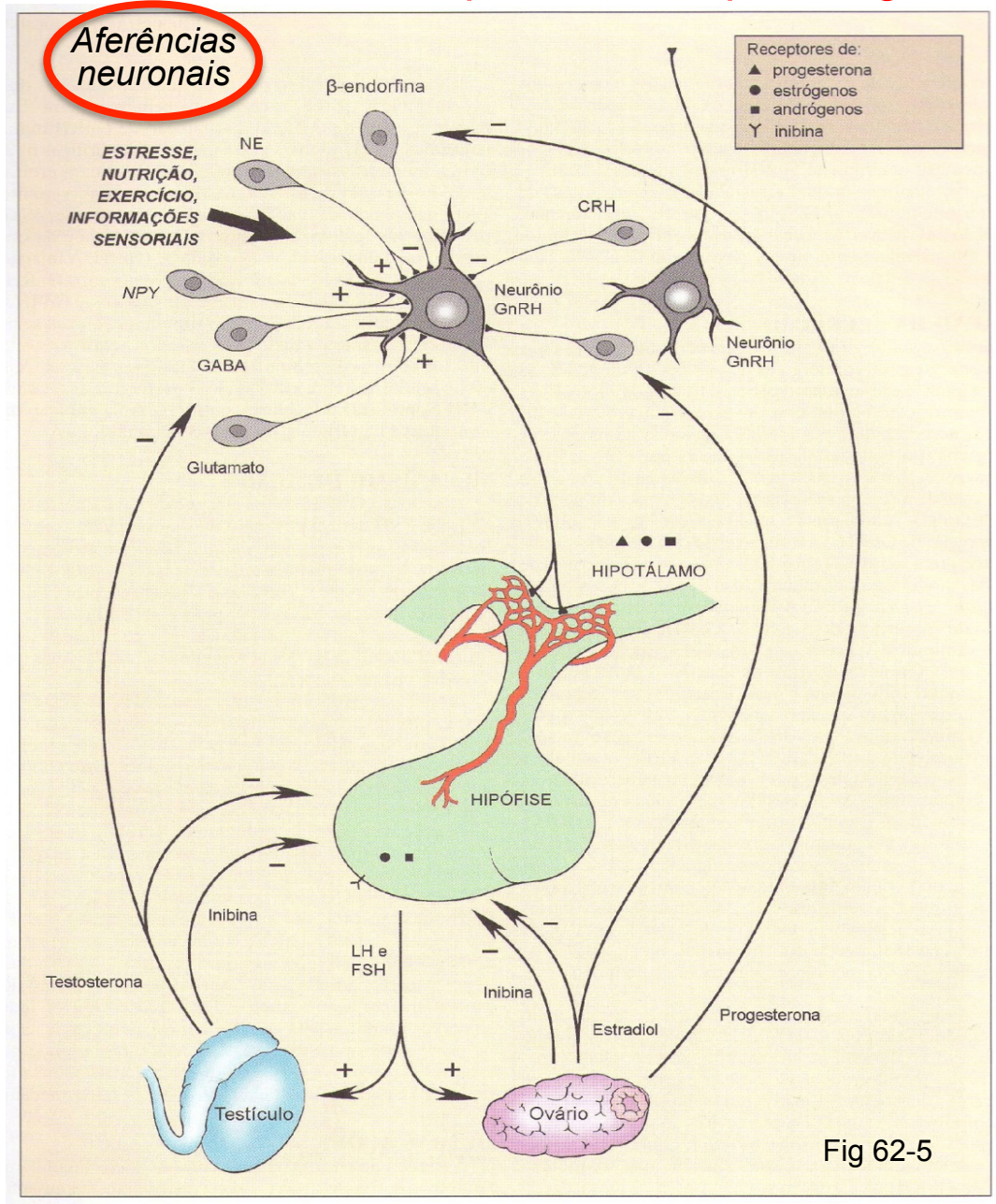


Fig 62-5

Hormônio liberador do hormônio do crescimento - GHRH

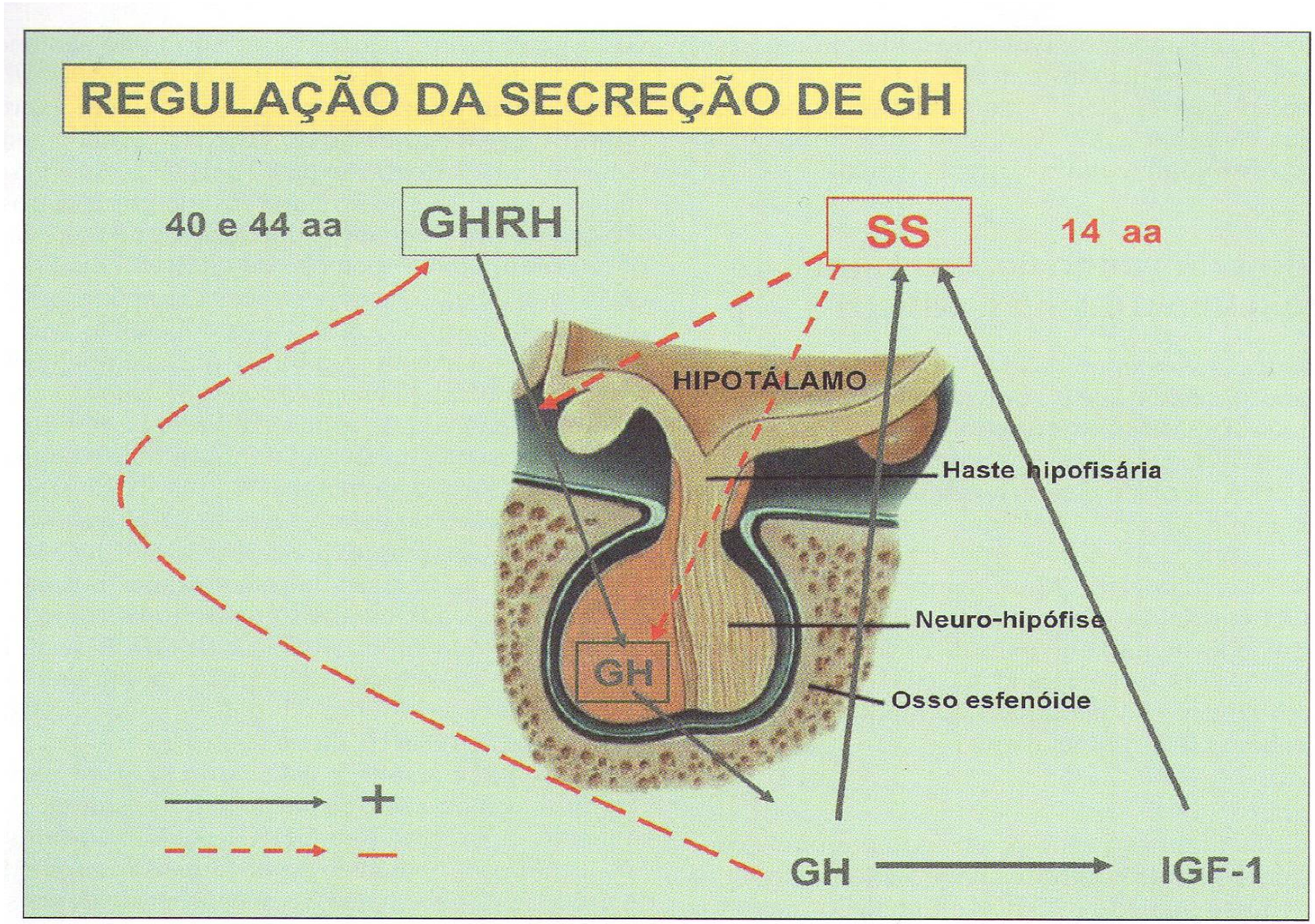


Fig 62-7

Controle da secreção de GHRH e Somatostina (SS)
Mecanismos neurais

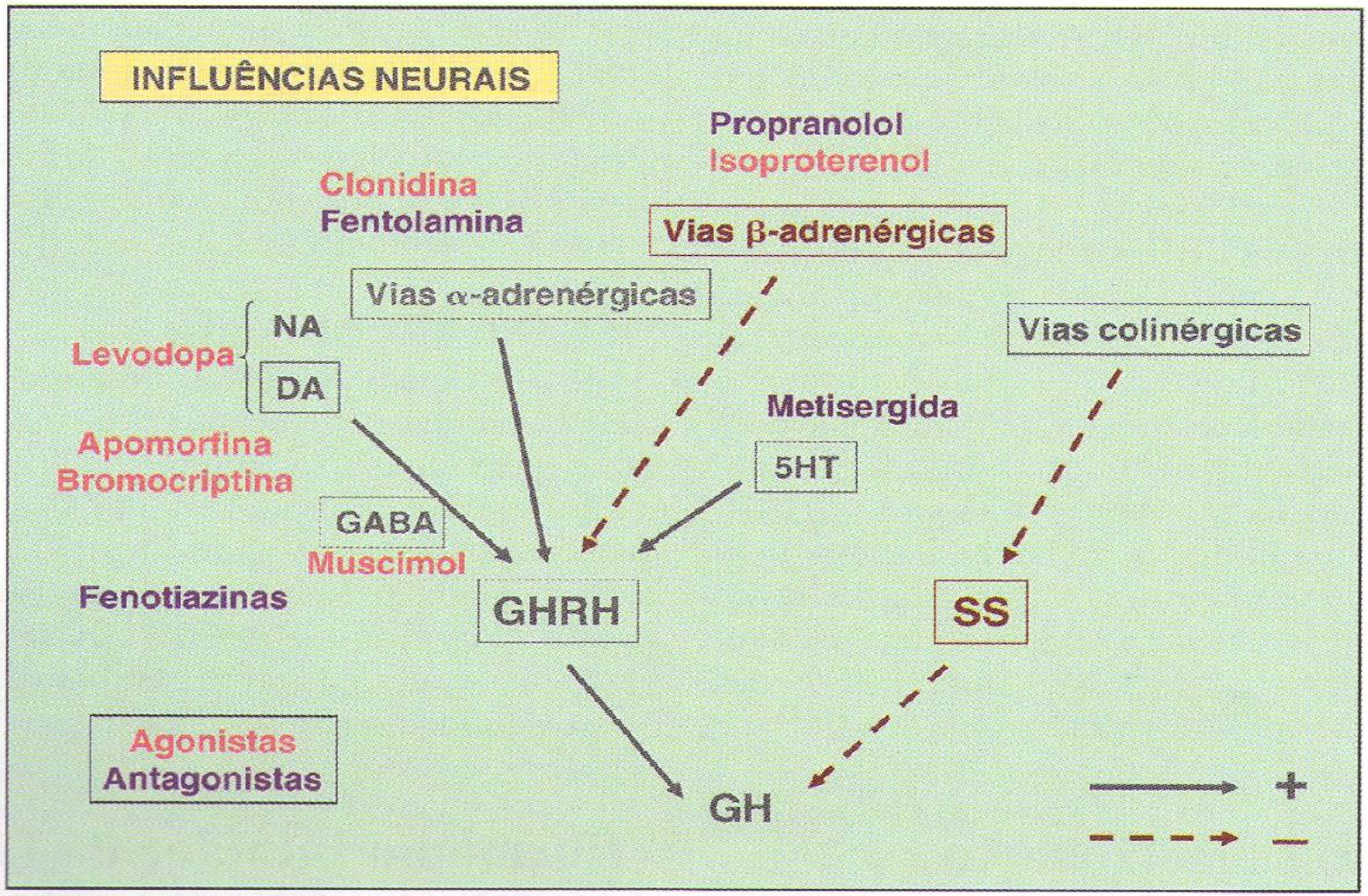
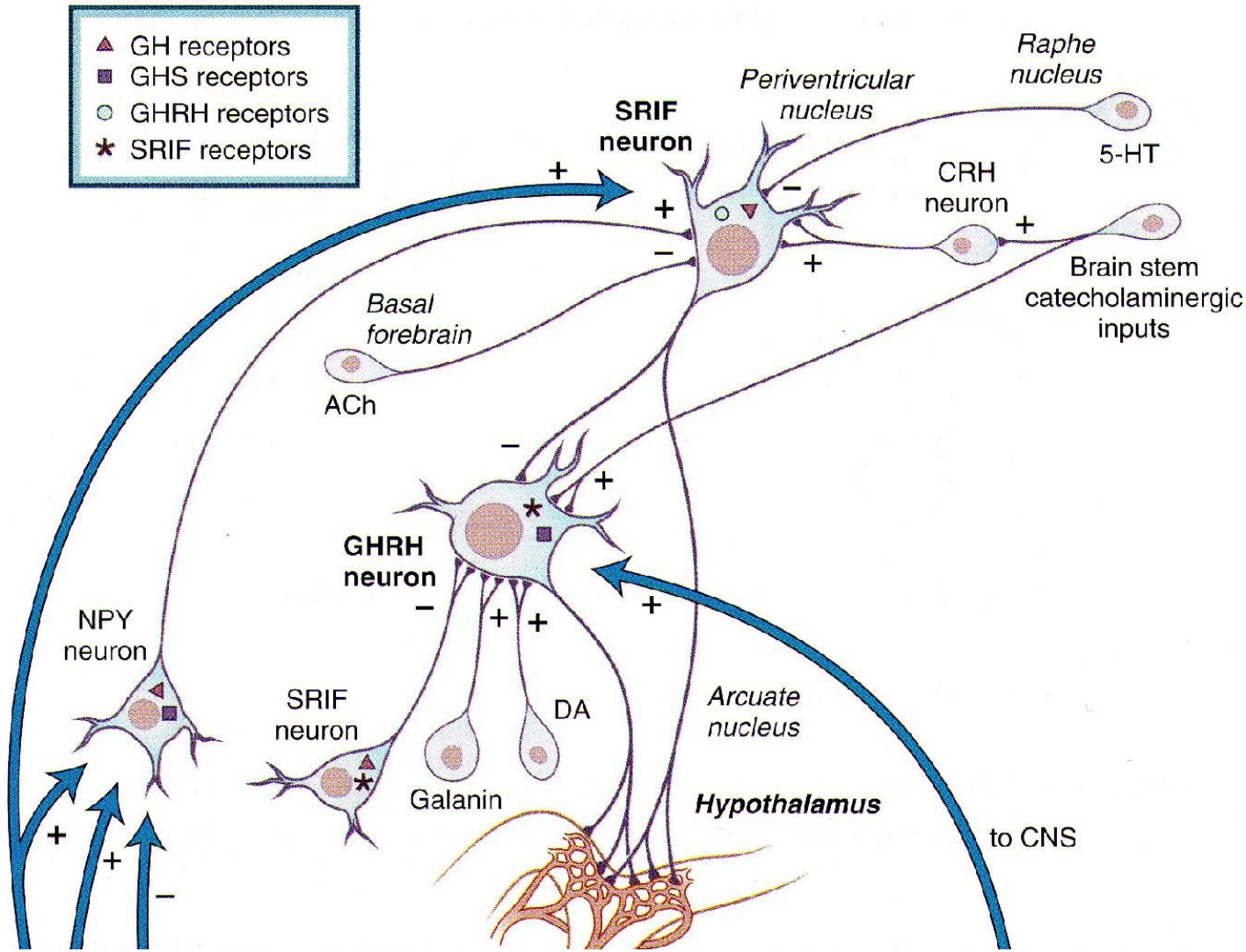


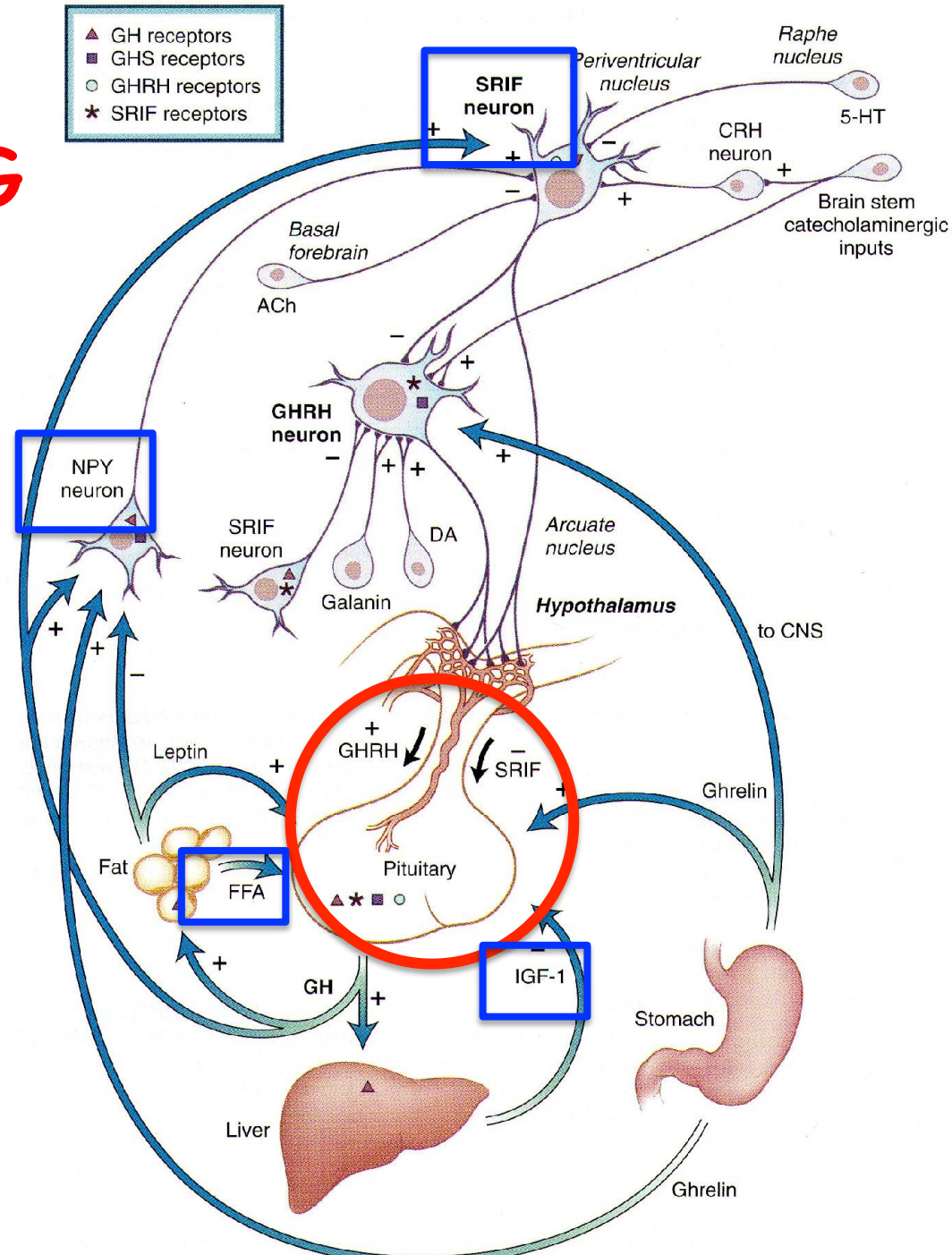
Fig 62-7

Regulação do eixo hipotálamo-hipófise-hormônio do crescimento

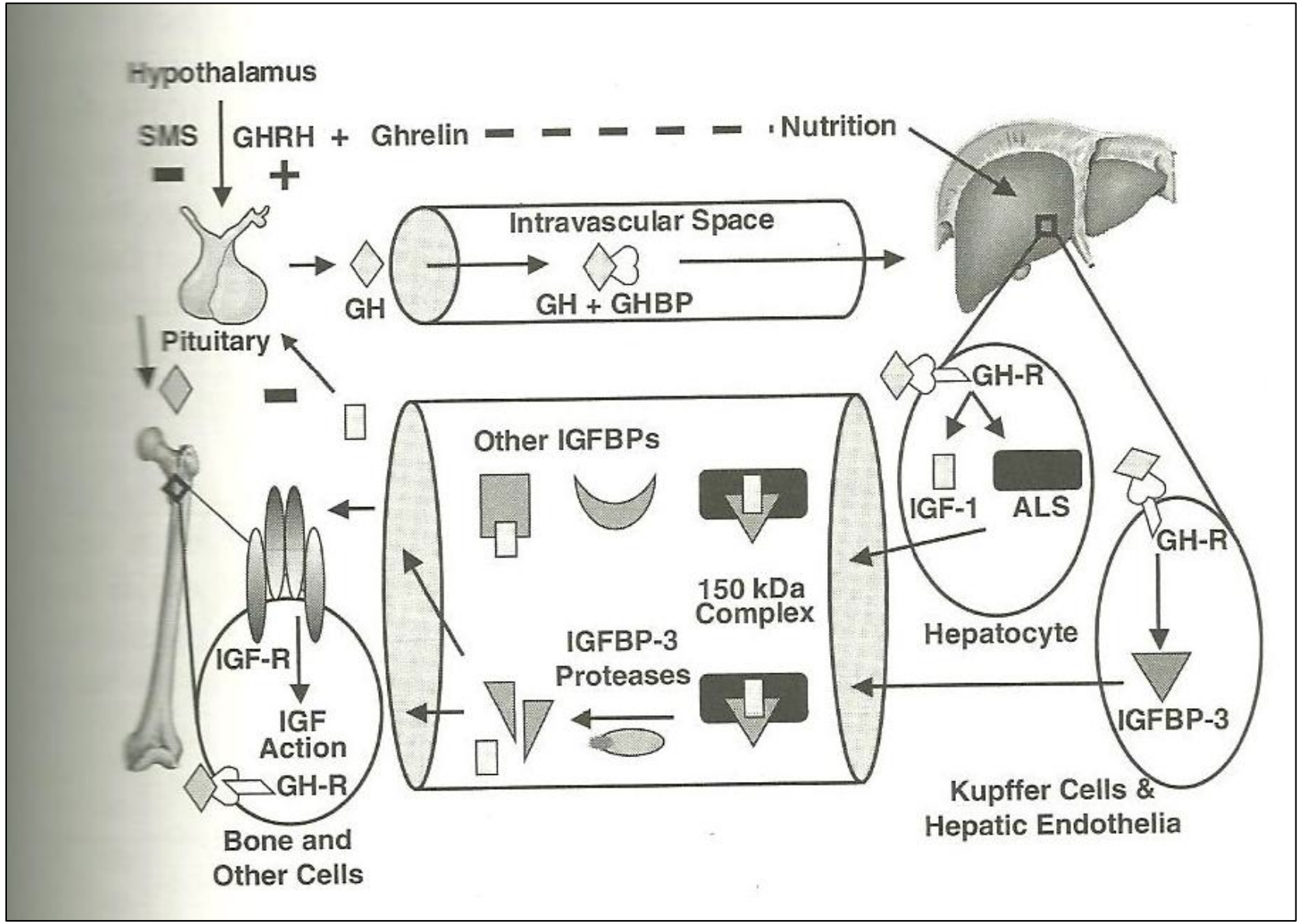


Eixo hipotálamo-hipófise-HG

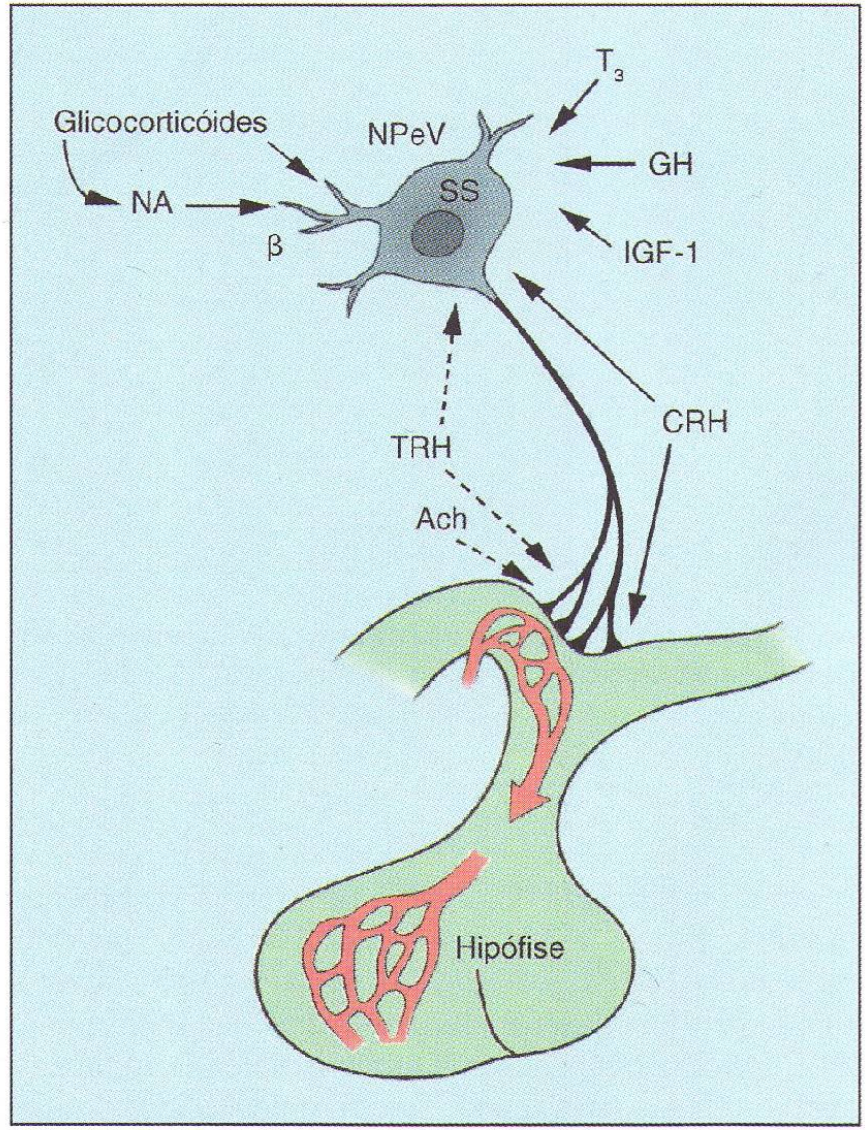
Indiretamente integrando sinais periféricos…



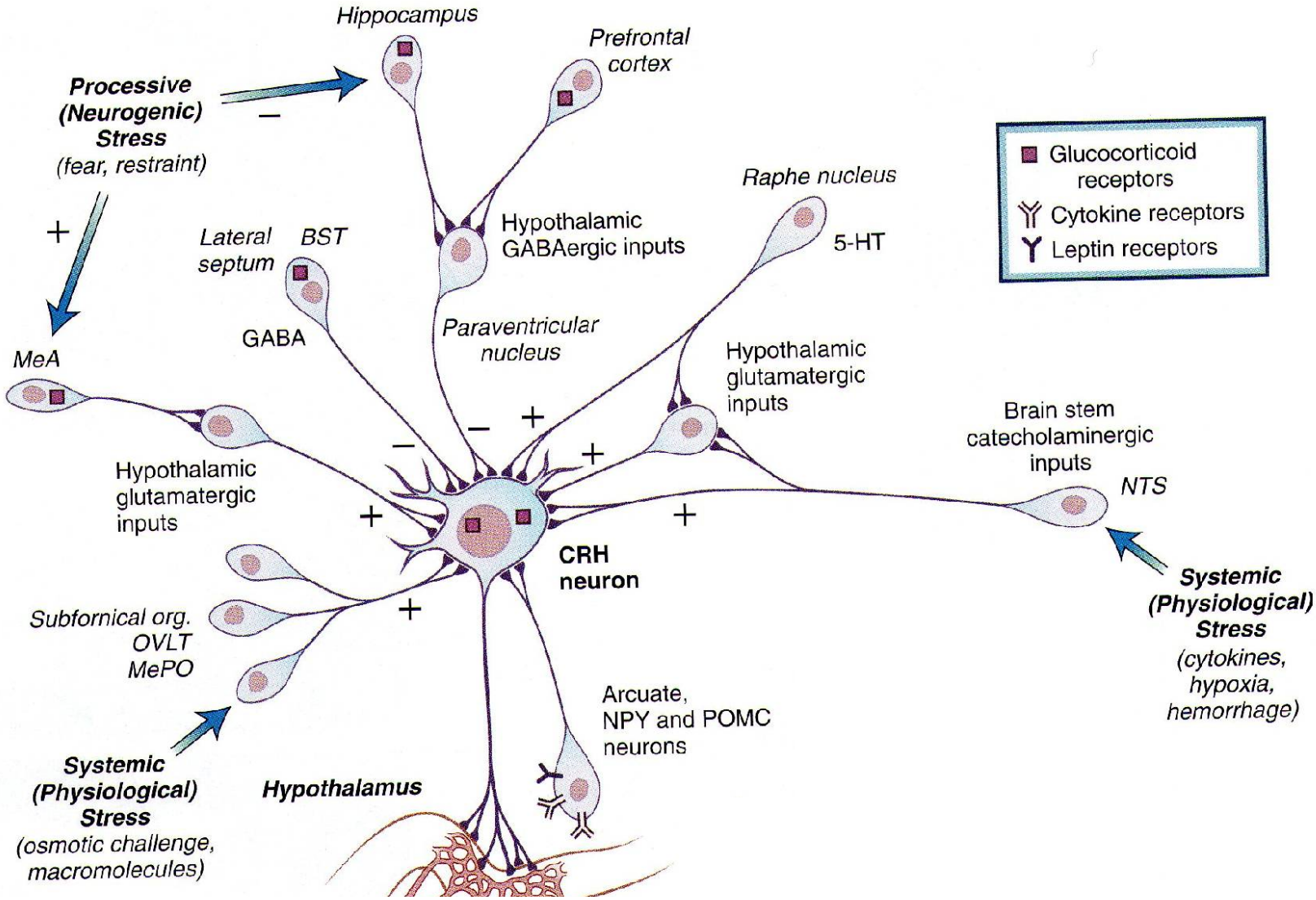
Regulação do crescimento



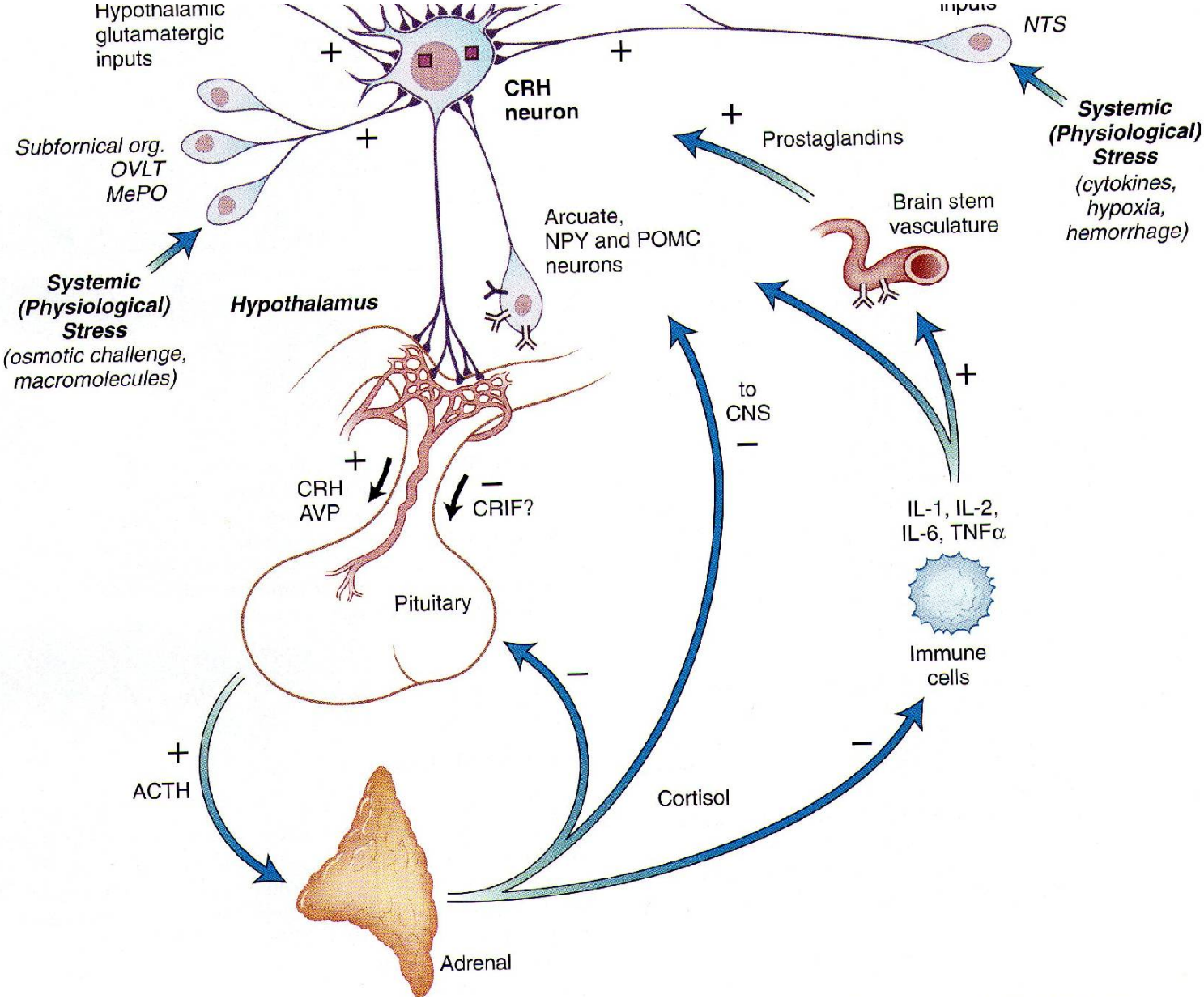
Regulação neuroendócrina da síntese e secreção de somatostatina (SS) pelo núcleo paraventricular hipotalâmico (PVN)



Regulação neuroendócrina da secreção de hormonio liberador de corticotrofina (CRH)



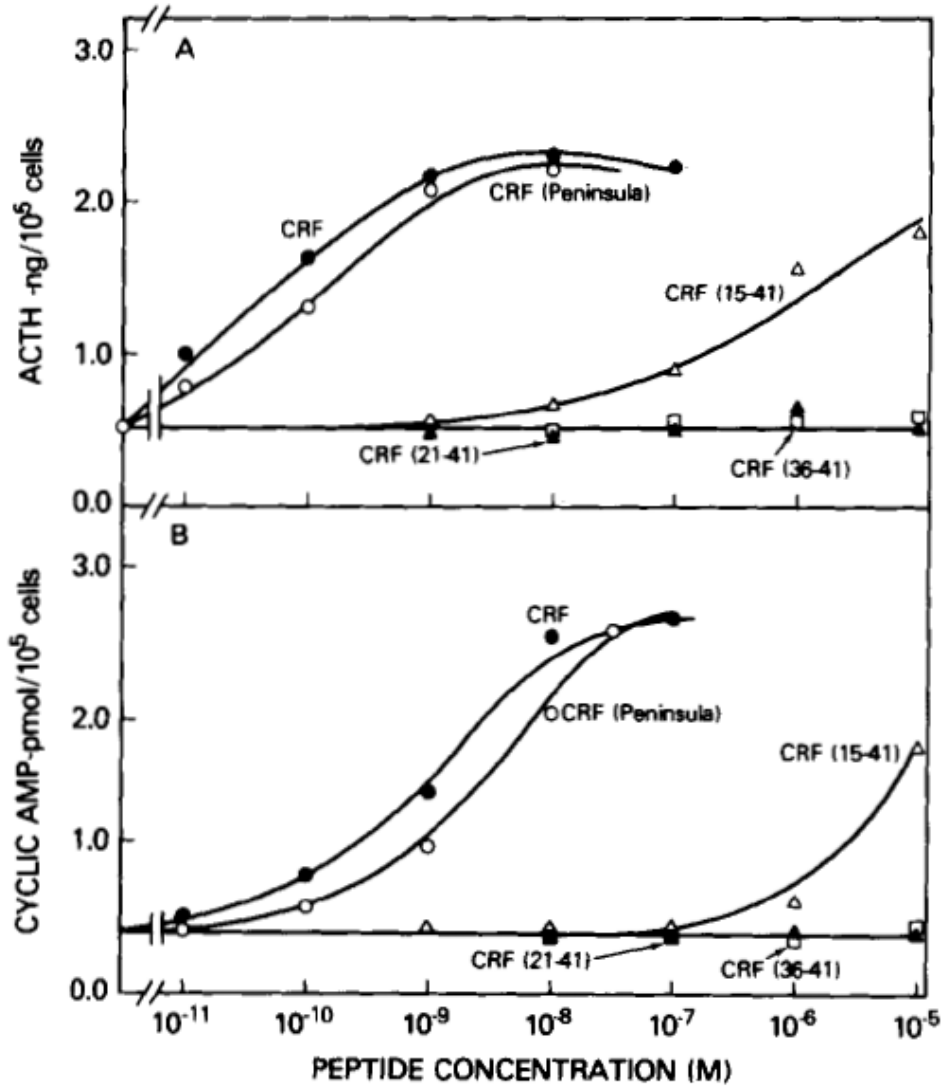
Regulação neuroendócrina da secreção de hormonio liberador de corticotrofina (CRH)

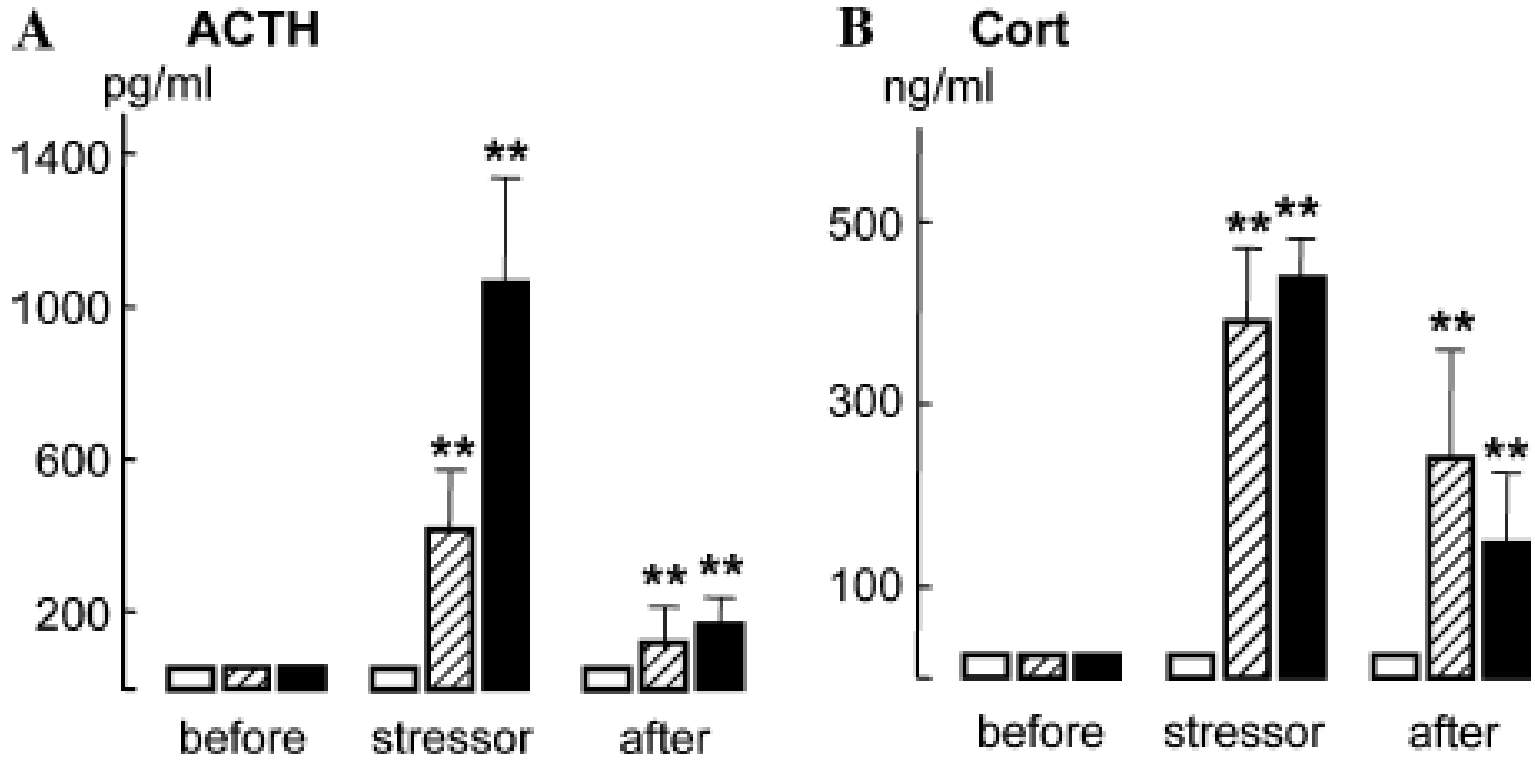


2 Regulatory hormones of the hypothalamic-pituitary axis

Hypothalamic Hormone	**Anterior Pituitary Hormone**	**Target Gland and Hormone**
Gonadotrophin Releasing Hormone (GnRH)	Follicle Stimulating Hormone (FSH) Luteinizing Hormone (LH)	Reproductive organs *Sex Steroids*
Growth Hormone Releasing Hormone (GHRH)	Growth Hormone (GH)	Liver and various tissues *Somatomedin C (IGF I)*
Thyrotrophin Releasing Hormone (TRH)	Thyroid Stimulating Hormone (TSH)	Thyroid *Thyroxine*
Corticotrophin Releasing Hormone (CRH)	Adrenocorticotropic Hormone (ACTH)	Adrenal Cortex *Cortisol*
Dopamine (Inhibitory)	Prolactin	Breasts
Somatostatin (Inhibitory)	TSH and GH	

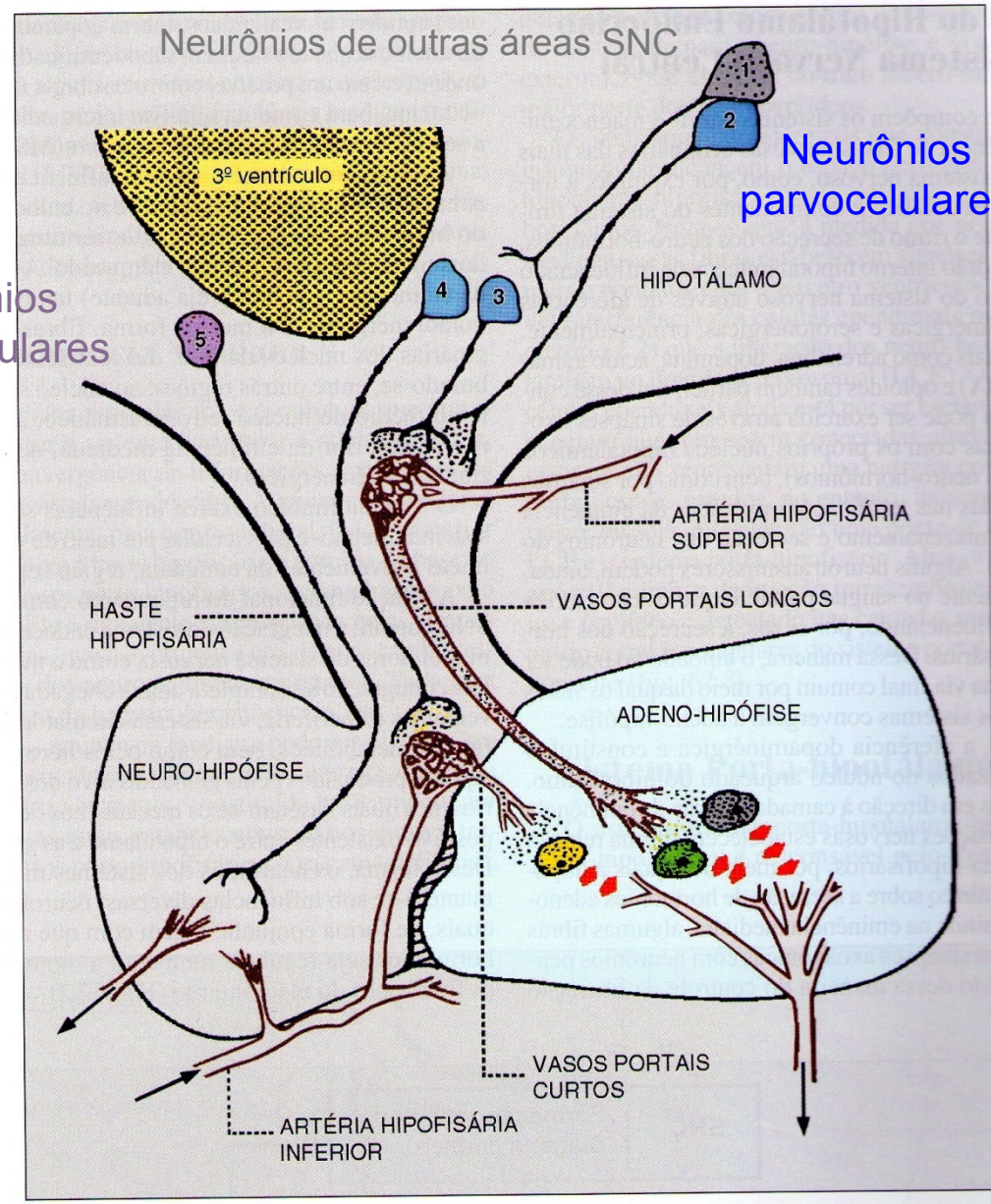
Liberação de ACTH e produção de AMPc estimulada por CRH



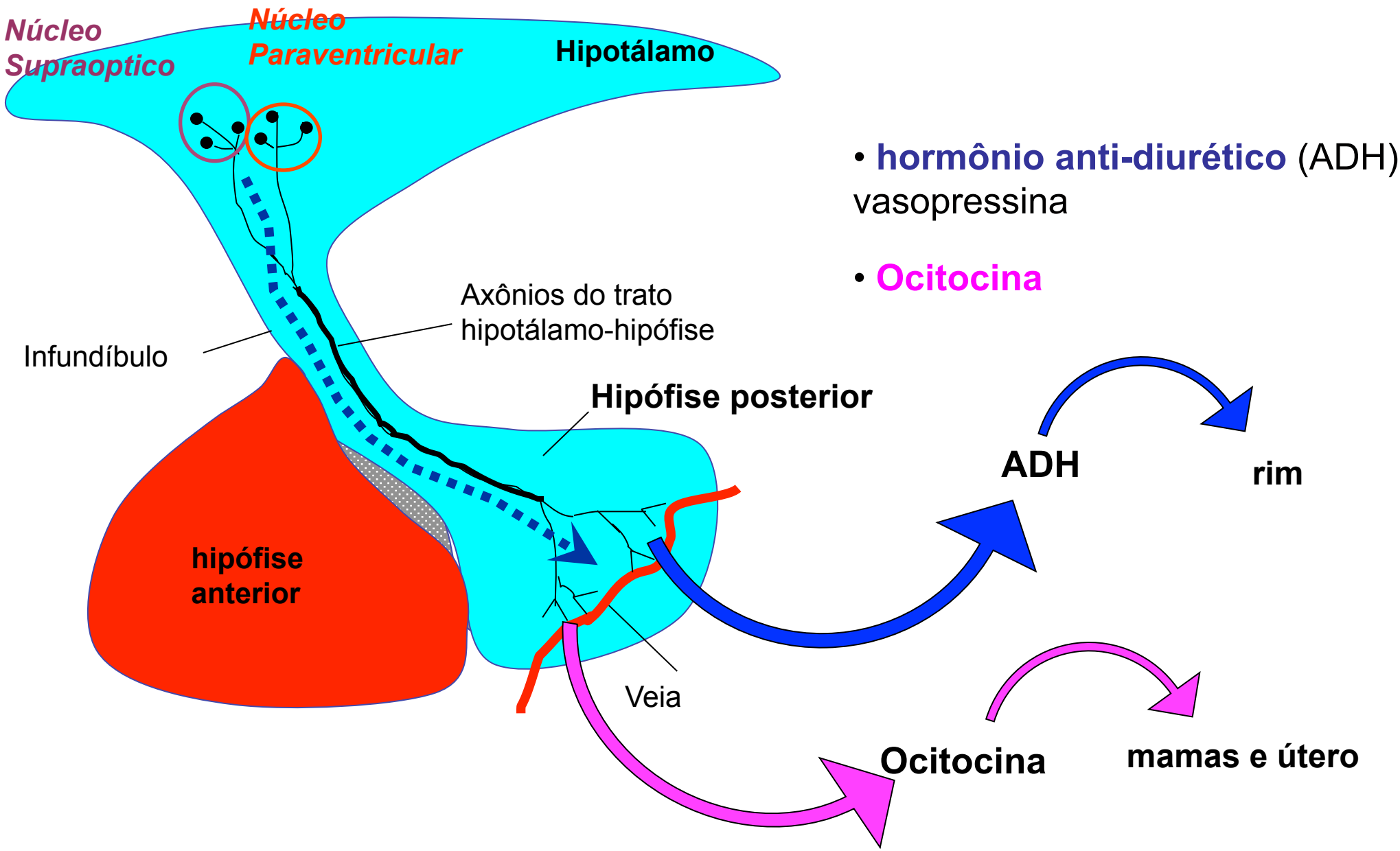

A
ACTH
pg/ml
1400
1000
600
200
**
**
**
**
before
stressor
after
B
Cort
ng/ml
500
300
100
**
**
**
**
before
stressor
after

Hipotálamo – Interface entre os sistemas nervoso e endócrino

Organização do complexo hipotálamo-hipófise

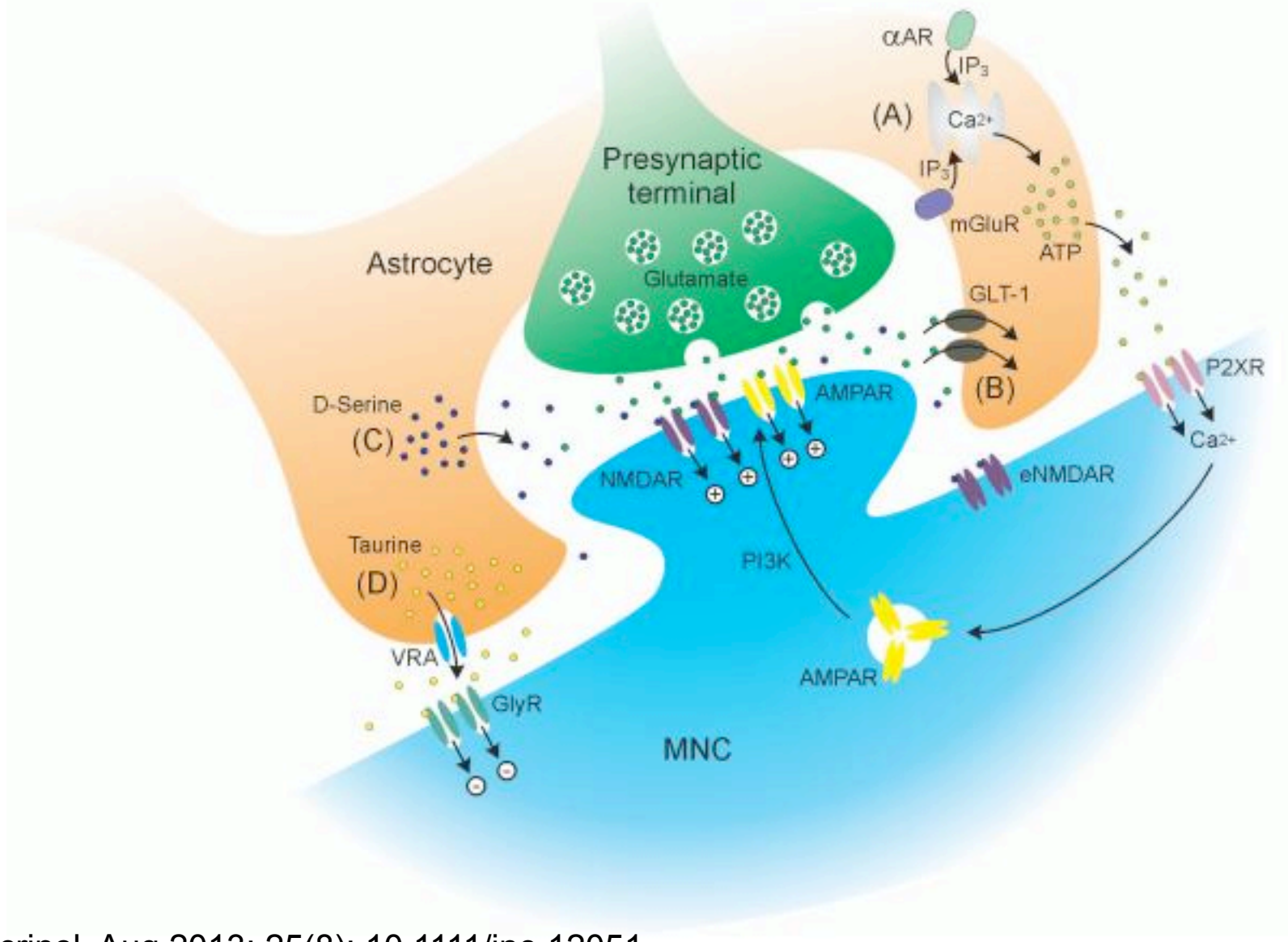


Hipófise posterior



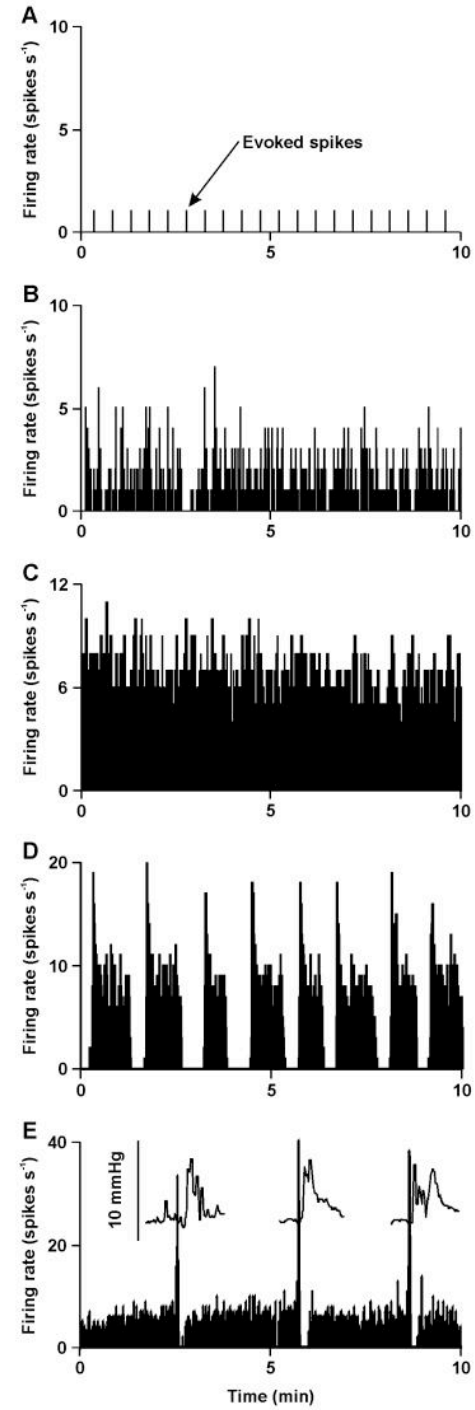
- **hormônio anti-diurético** (ADH), vasopressina
- **Ocitocina**

Glial regulation of magnocellular neurosecretory cell activity under basal conditions



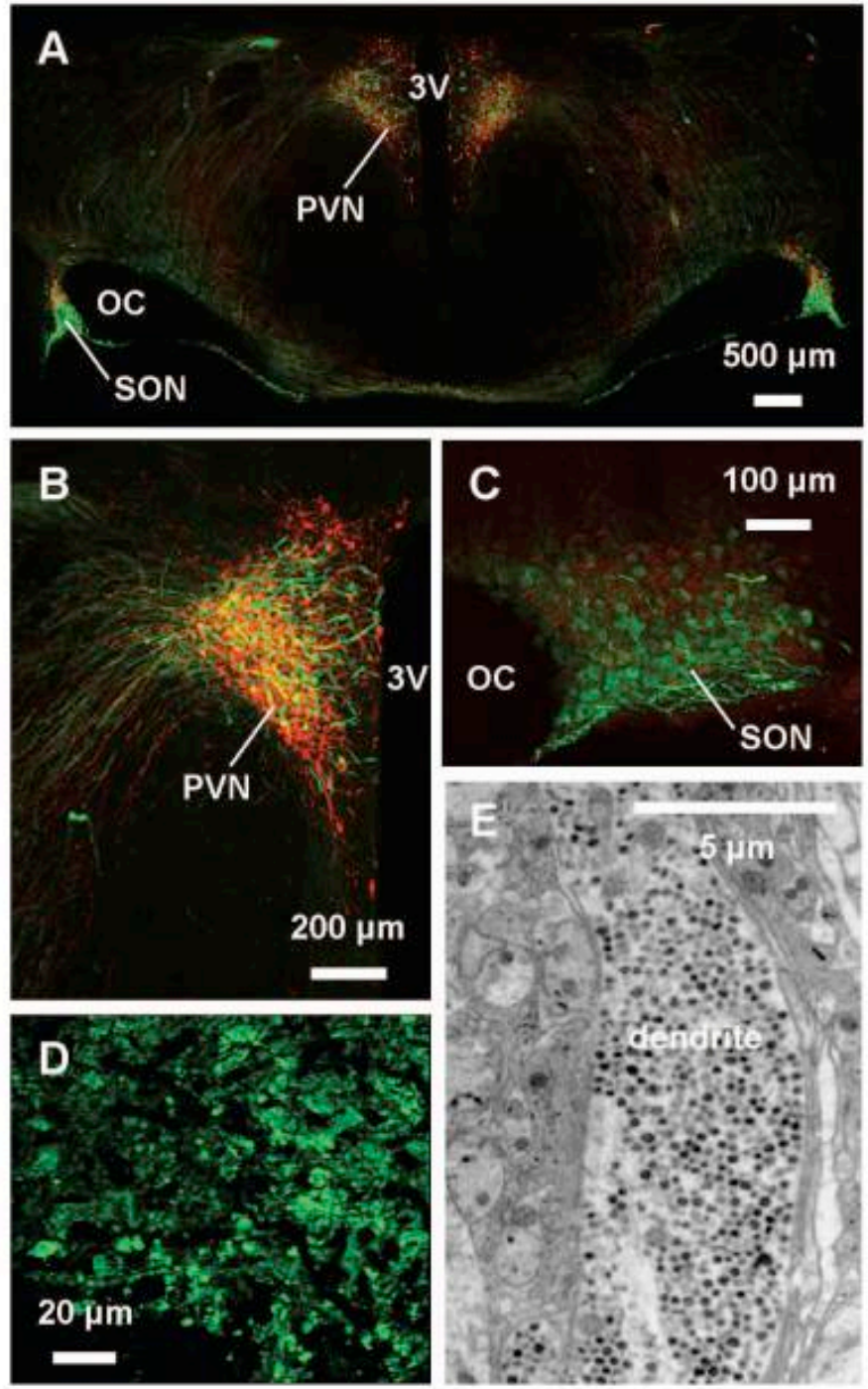
J Neuroendocrinol. Aug 2013; 25(8): 10.1111/jne.12051.
doi: 10.1111/jne.12051

Atividade espontânea de cél. neurosecretoras magnocelulares "*in vivo*"



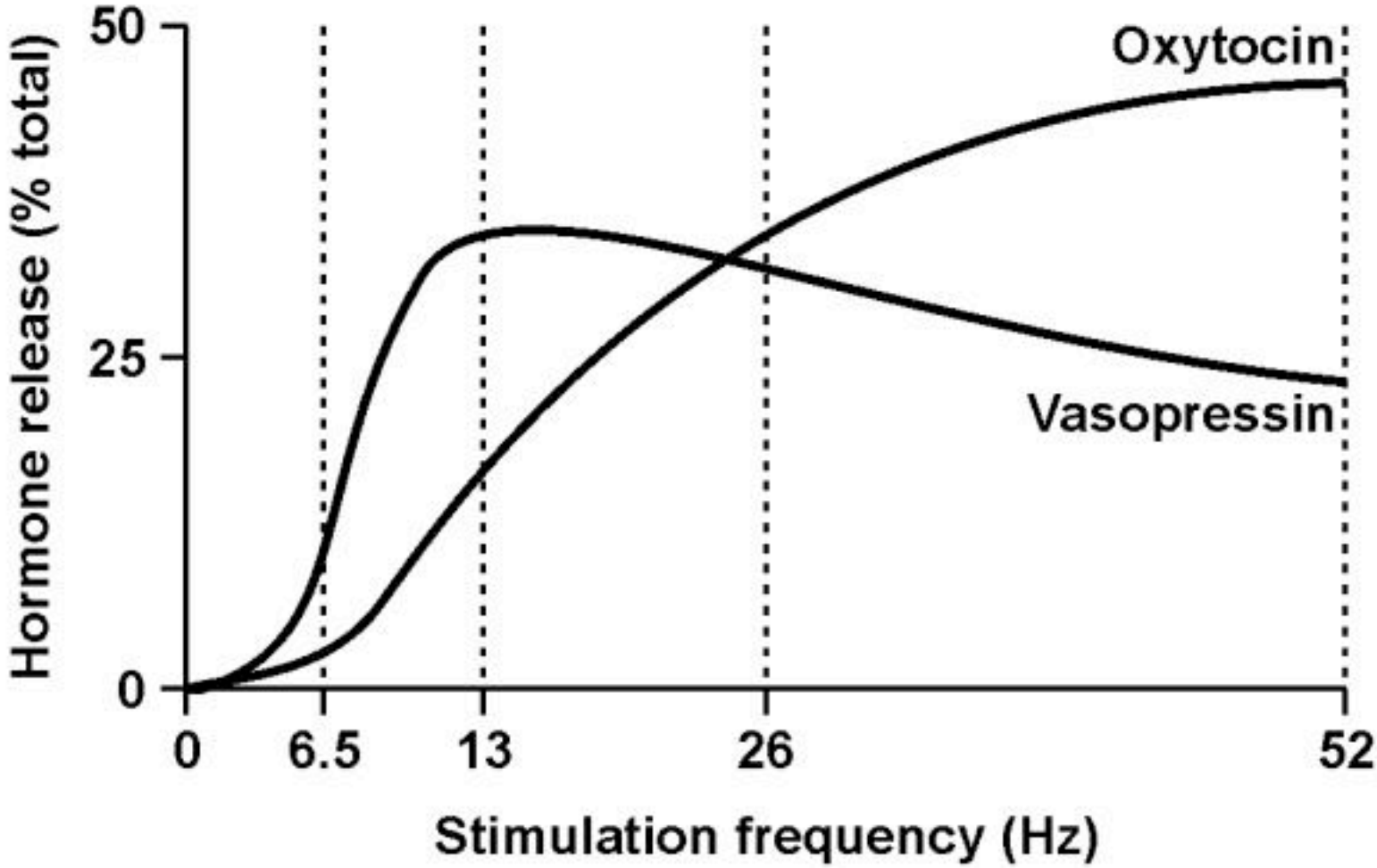
J Neuroendocrinol. Aug 2013; 25(8): 10.1111/jne.12051.
doi: 10.1111/jne.12051

Sistema neurosecretor magnocelular



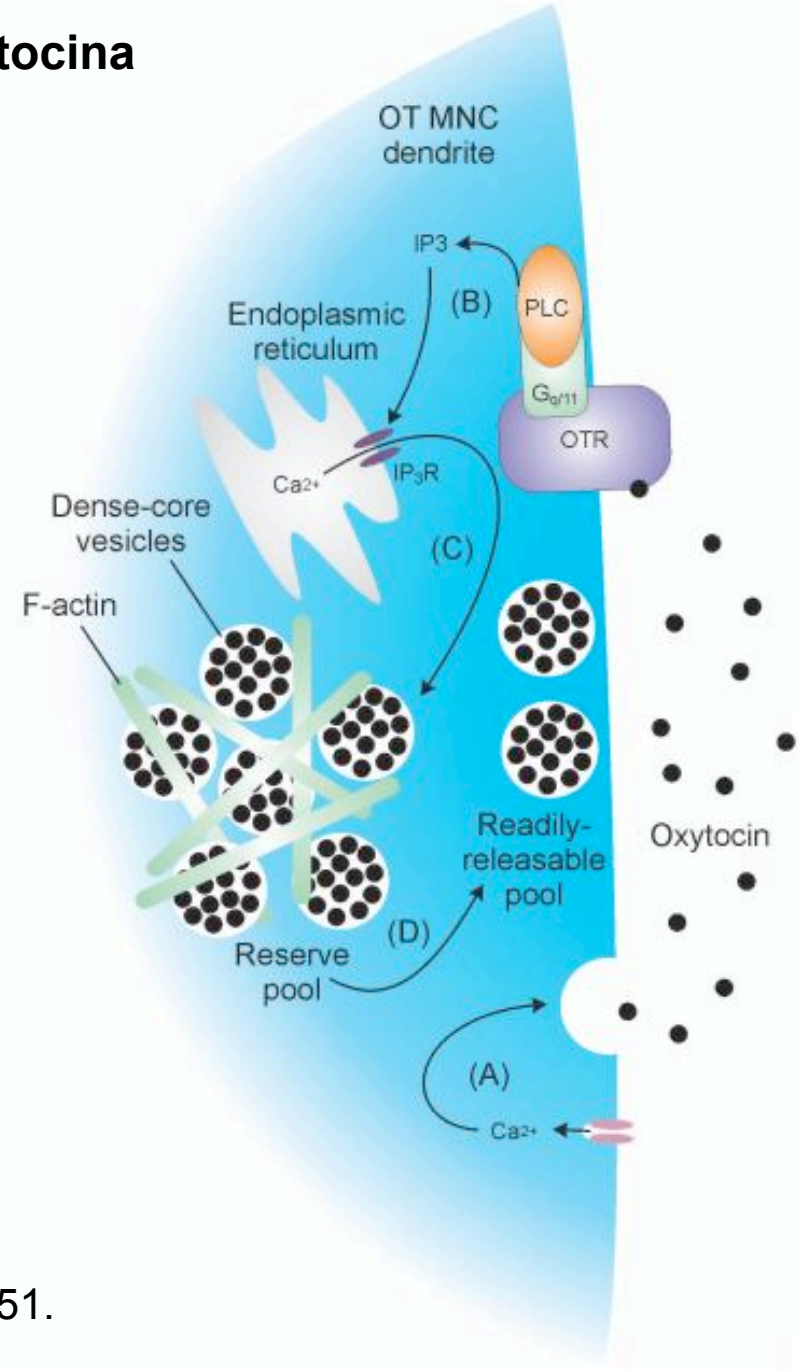
J Neuroendocrinol. Aug 2013; 25(8): 10.1111/jne.12051.
doi: 10.1111/jne.12051

Frequencia de facilitação da liberação de ocitocina e vasopressina por células neurosecretoras magnocelulares



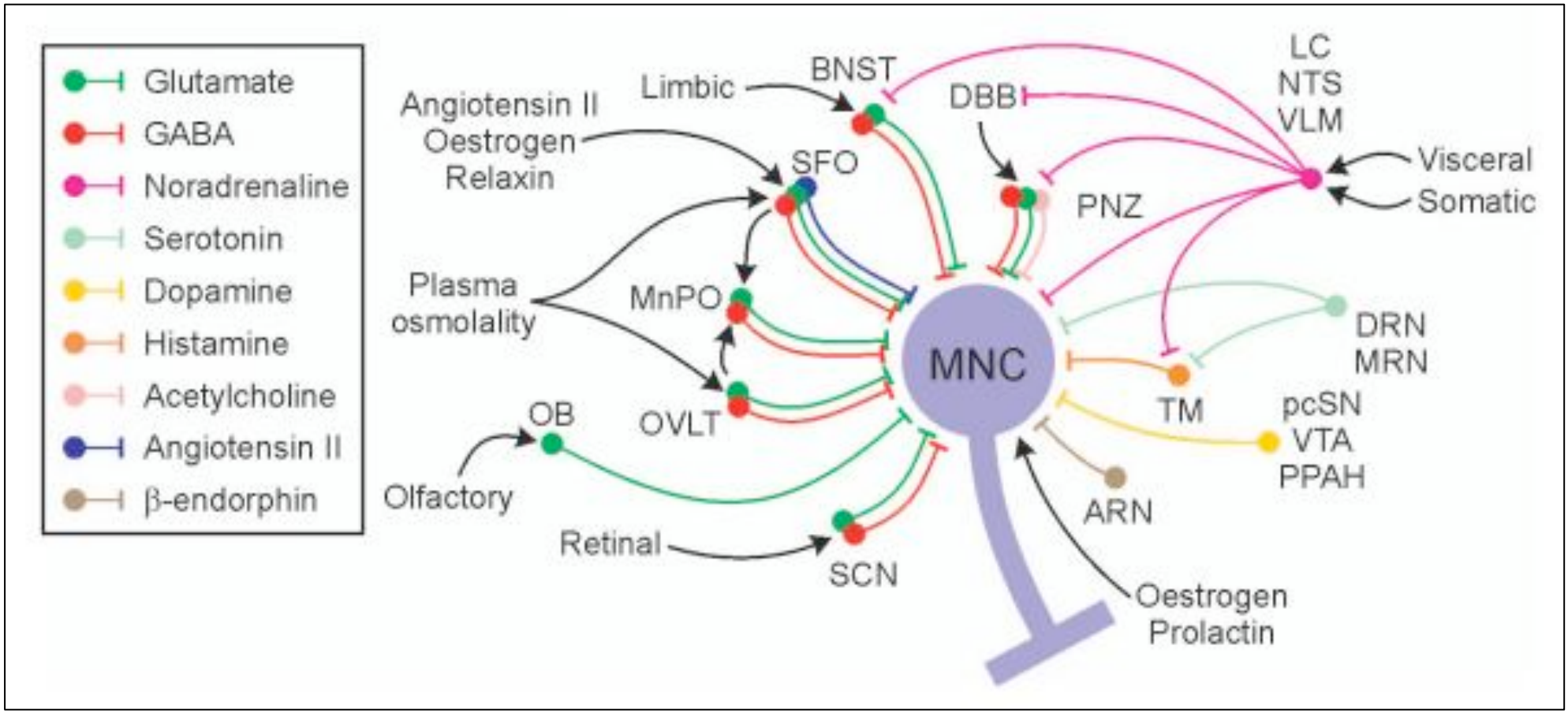
J Neuroendocrinol. Aug 2013; 25(8): 10.1111/jne.12051.
doi: 10.1111/jne.12051

Influxo de Ca^{2+} dispara a liberação de ocitocina



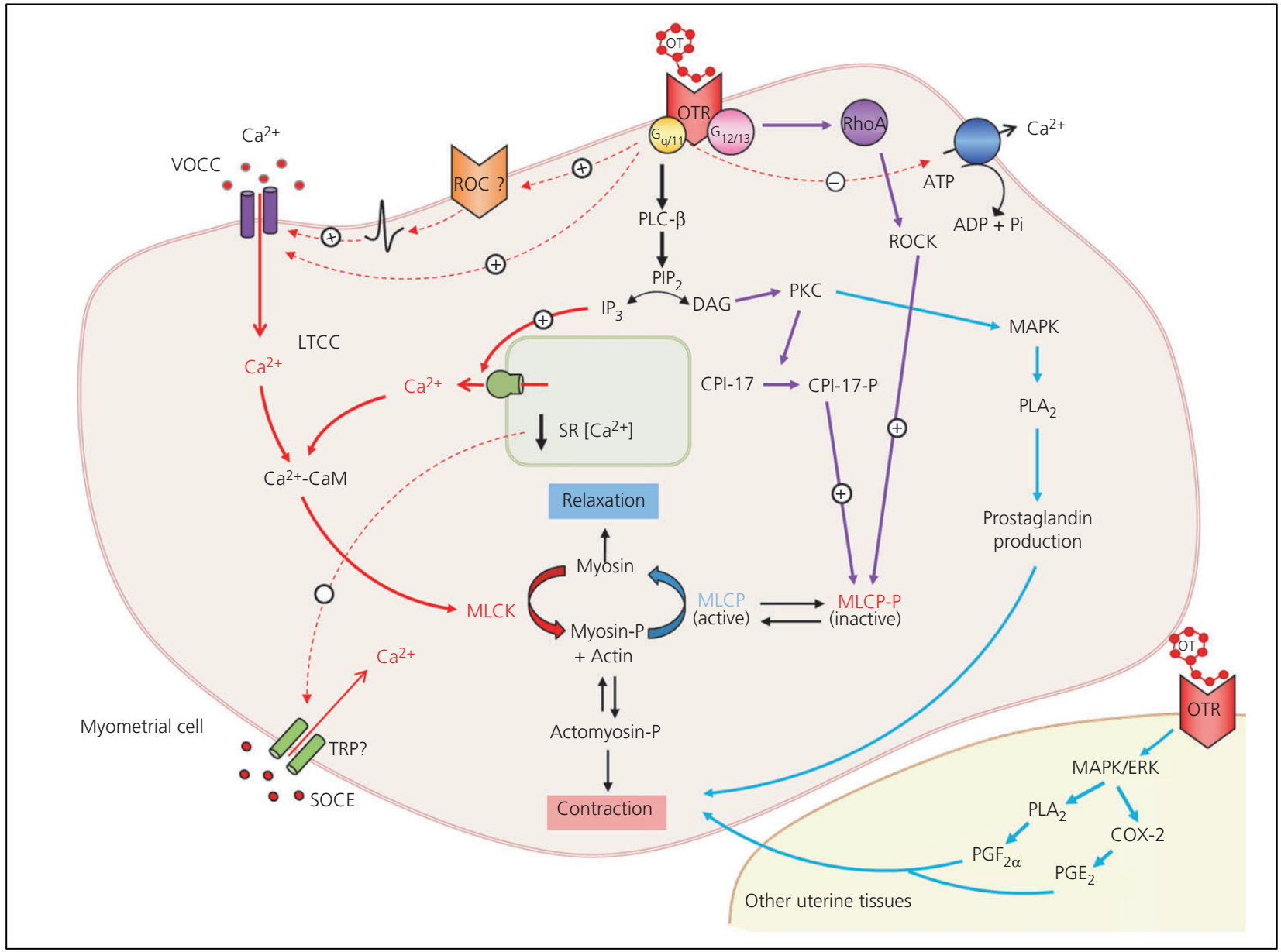
J Neuroendocrinol. Aug 2013; 25(8): 10.1111/jne.12051.
doi: 10.1111/jne.12051

Peripheral and afferent inputs to magnocellular neurosecretory cells



J Neuroendocrinol. Aug 2013; 25(8): 10.1111/jne.12051.
doi: 10.1111/jne.12051

Ocitocina – Mecanismo de ação na contração do miométrio



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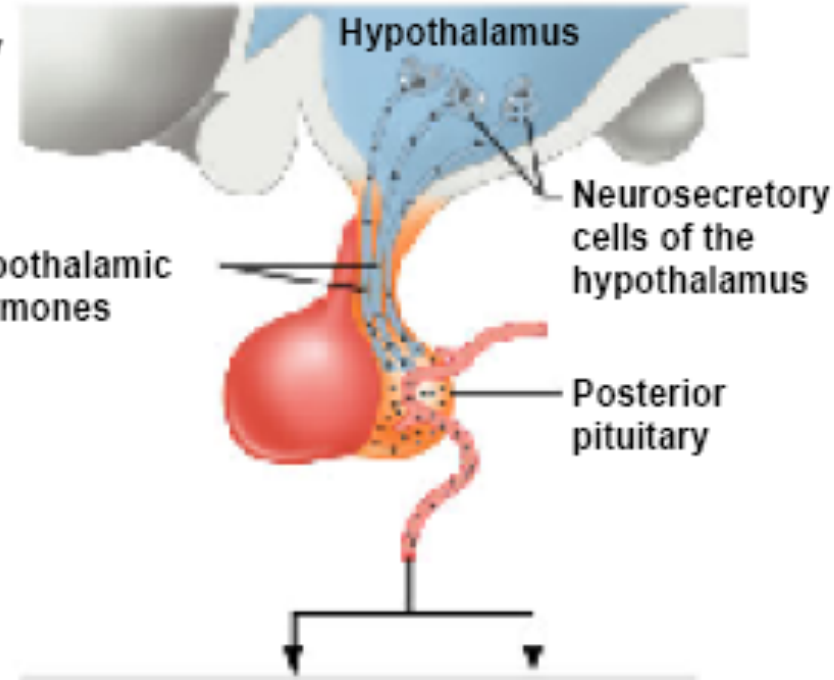
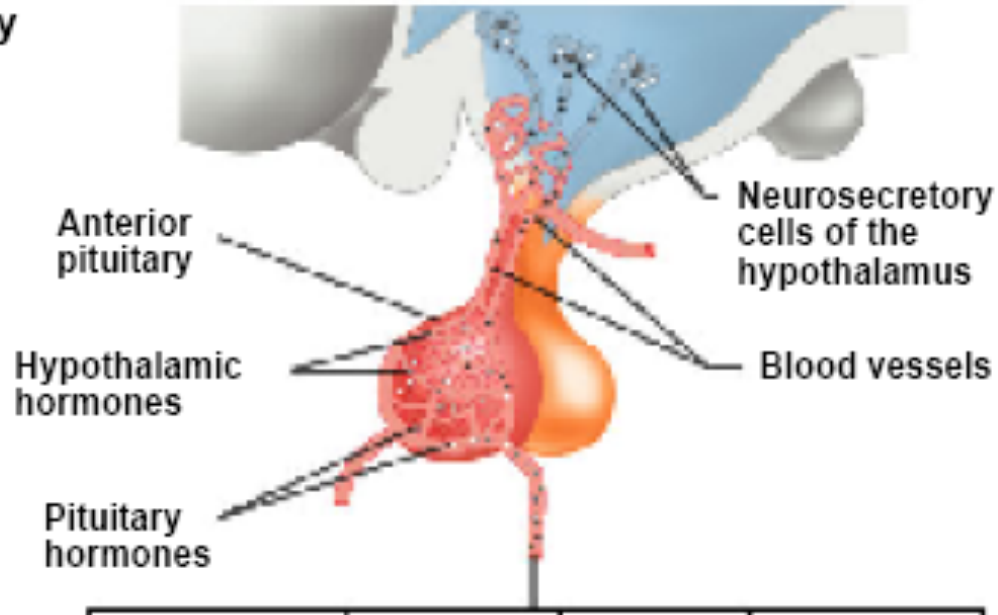
The posterior pituitary



Hormone	ADH	Oxytocin
Target	Kidney tubules	Mammary glands, uterine muscles
Response	Aquaporins activated; H_2O reabsorbed	Eject milk during nursing; contraction during labor

The anterior pituitary



Hormone	ACTH	Follicle-stimulating hormone (FSH) and luteinizing hormone (LH)	Growth hormone (GH)	Prolactin (PRL)	Thyroid-stimulating hormone (TSH)
Target	Adrenal cortex	Testes or ovaries	Bones	Mammary glands	Thyroid
Response	Production of glucocorticoids	Production of sex hormones; control of menstrual cycle	Growth	Mammary gland growth; milk production	Production of thyroid hormones