

# Cronobiologia

Ramo da Biologia que trata de eventos biológicos repetitivos ou cíclicos.

## Ritmos Biológicos

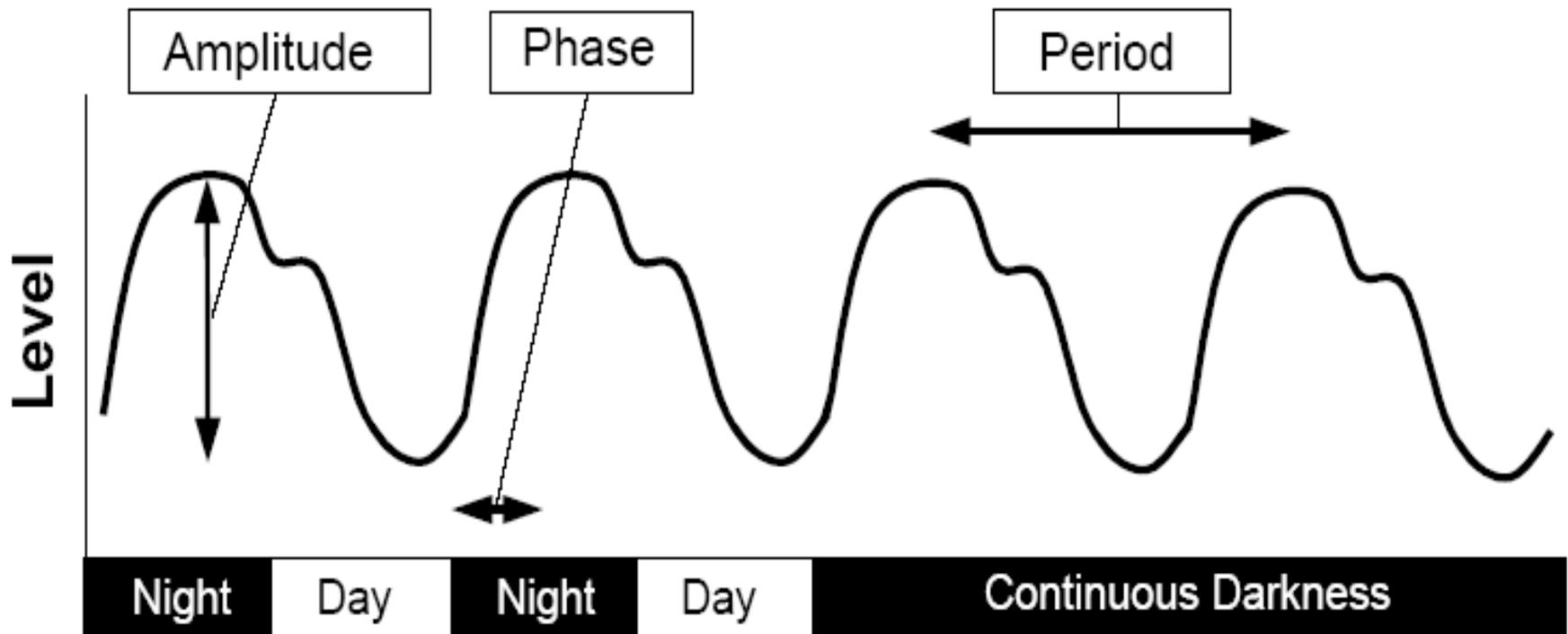
Circadianos - períodos de ~ 24 h  
atividade locomotora

Infradianos - baixa frequência  
período > 28 h

Ultradianos - batimentos rápidos  
período < 20 h

Circannual

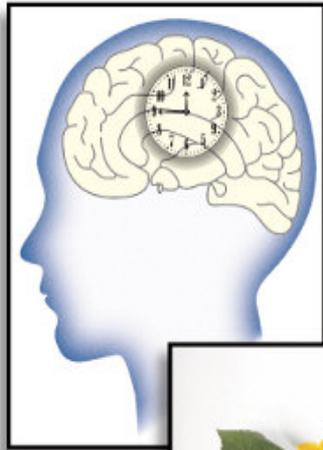
# Parâmetros de um Ritmo Circadiano



***Demonstração de ritmo por Jean Jacques d'Ortous de Mairan em 1729***



# Por que ter um relógio endógeno?



## Permite antecipação

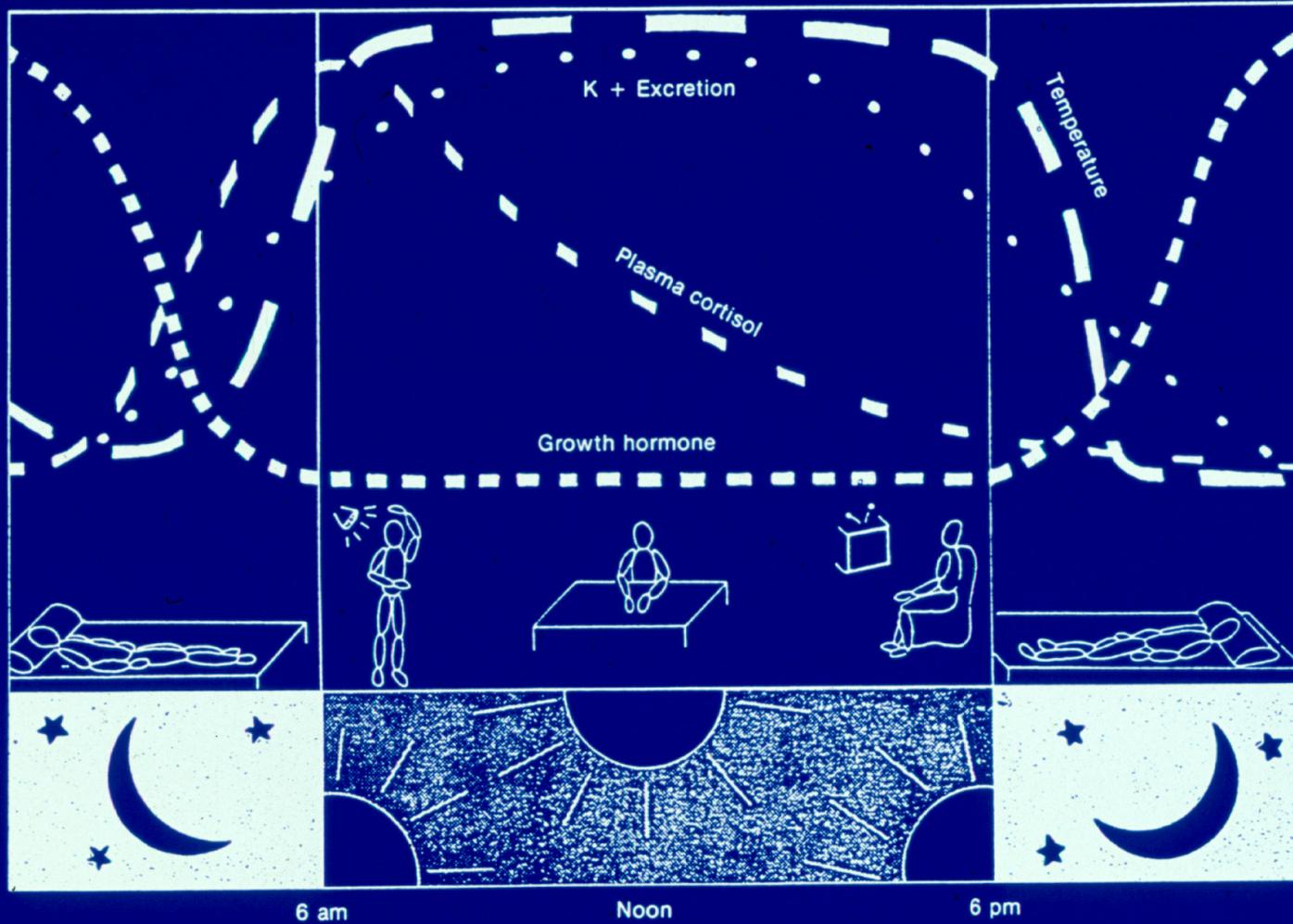
- preparação fisiológica do organismo para responder de forma adequada a eventos recorrentes.

## Confere vantagem seletiva

- otimizam o crescimento e desenvolvimento
- minimizando a susceptibilidade à predação e competição.

ex. cianobactérias

## Human Circadian Rhythms



Circadian rhythms of sleep, body temperature, growth hormone, cortisol, and urinary potassium in a human subject.

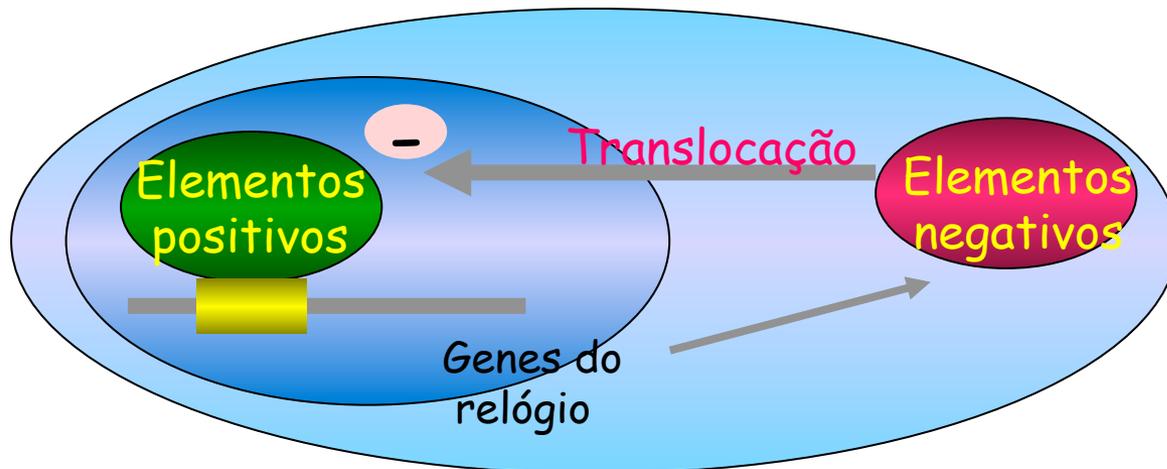
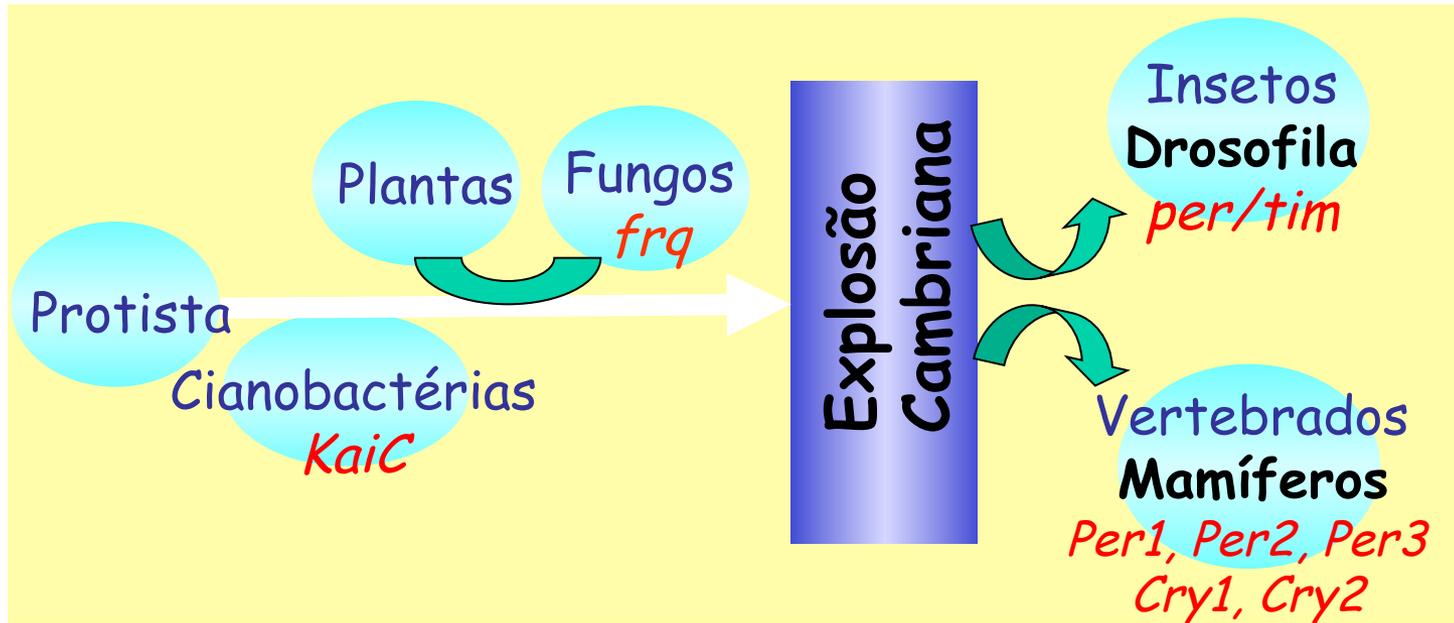
SOURCE: Adapted from G.S. Richardson and J.B. Martin, "Circadian Rhythms in Neuroendocrinology and Immunology: Influence of Aging," *Progress in NeuroEndocrinImmunology* 1:16-20, 1988.

# Significado adaptativo do relógio circadiano em cianobactérias

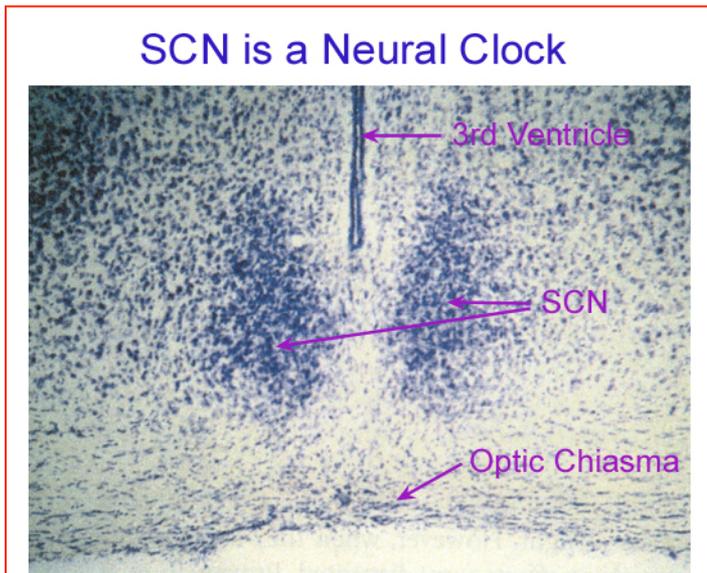
Cianobactérias mutantes com períodos endógenos próximos ao da variação ambiental levam vantagem na competição com bactérias com diferentes períodos endógenos.

(Yan et al., 1998)

# Ritmos Circadianos são gerados por genes do relógio

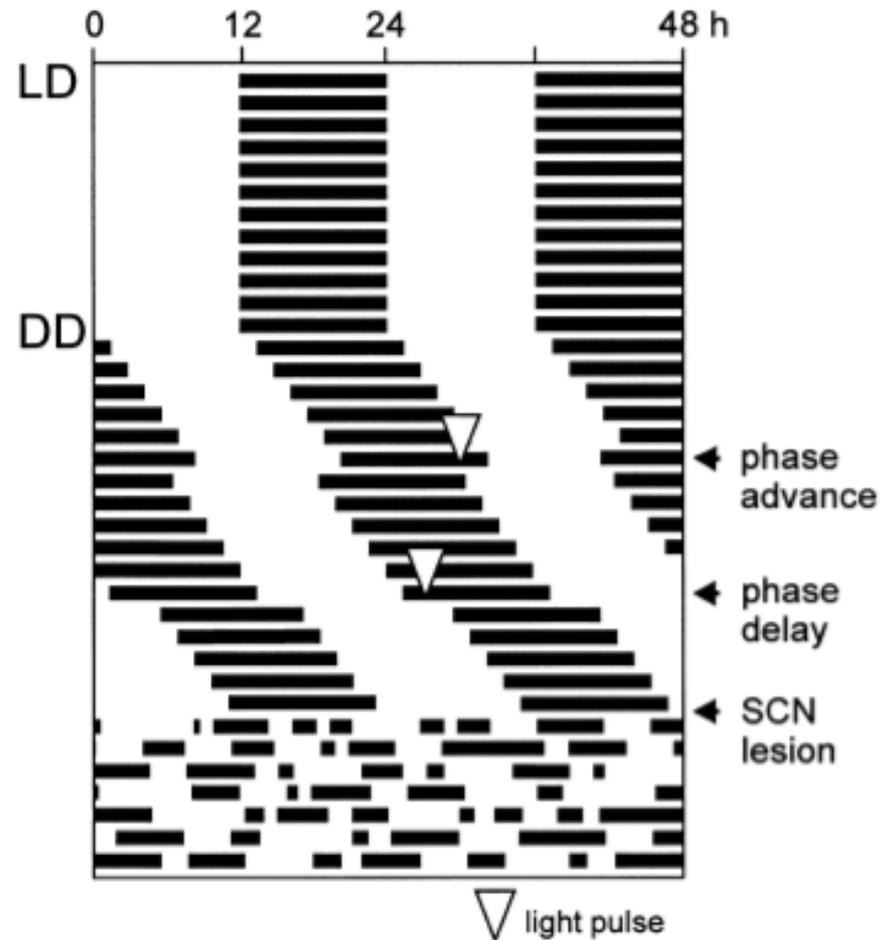


# Núcleos Supraquiasmáticos - Principal relógio em mamíferos

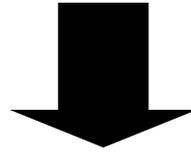


## Características

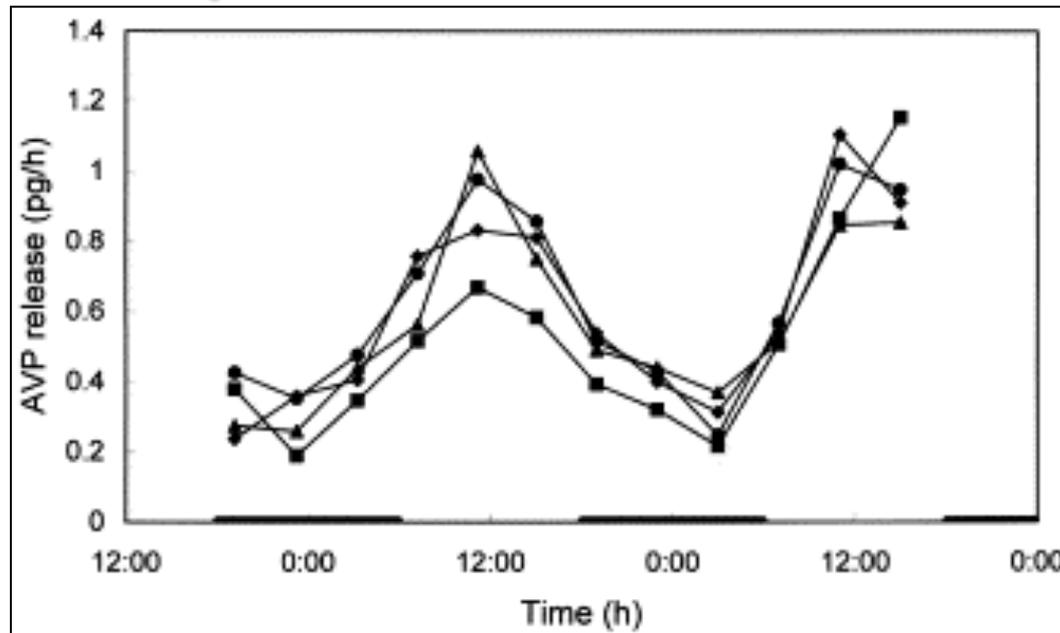
- mantido em condições constantes continua ciclando.
- sincronização entre o meio ambiente e o meio interno



O relógio pode funcionar fora do organismo

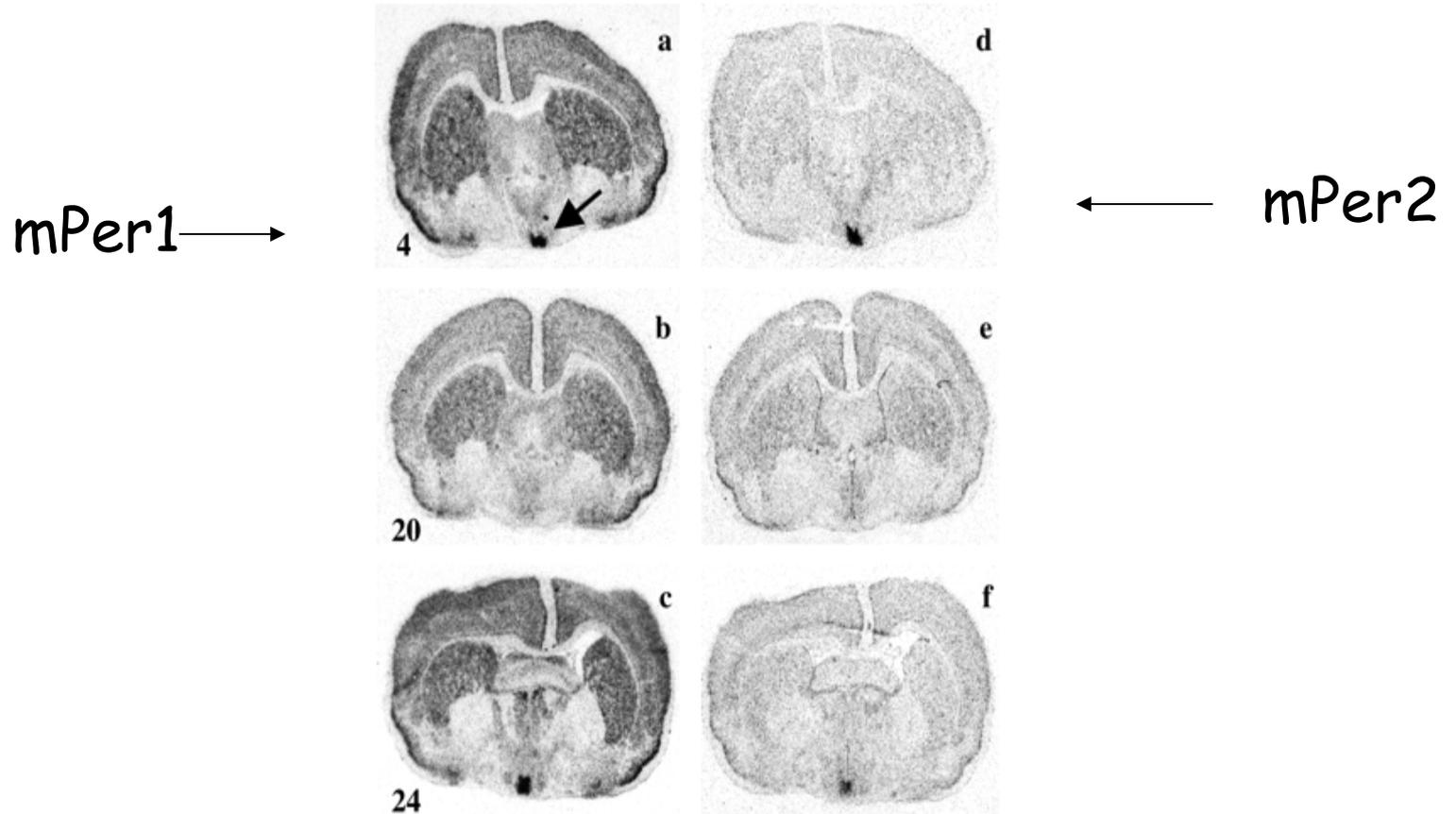


**NSQ** "in vitro" também cicla



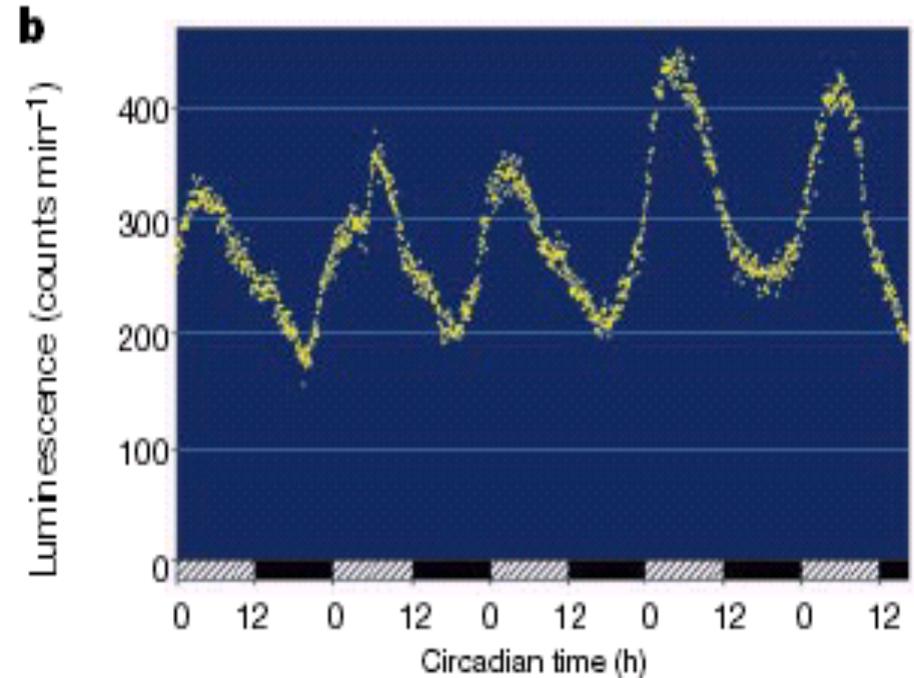
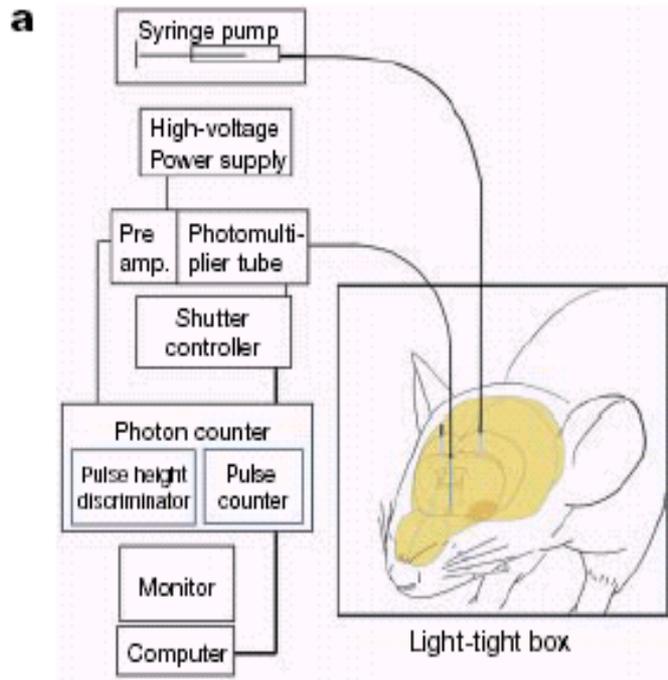
Oscilação circadiana da liberação de AVP de neurônios vasopressinérgicos localizados na porção dorso-medial do NSQ. Células isoladas de animais mantidos em 12:12 - medidas iniciadas logo após início da cultura

# Expressão rítmica de mPer1 e mPer2



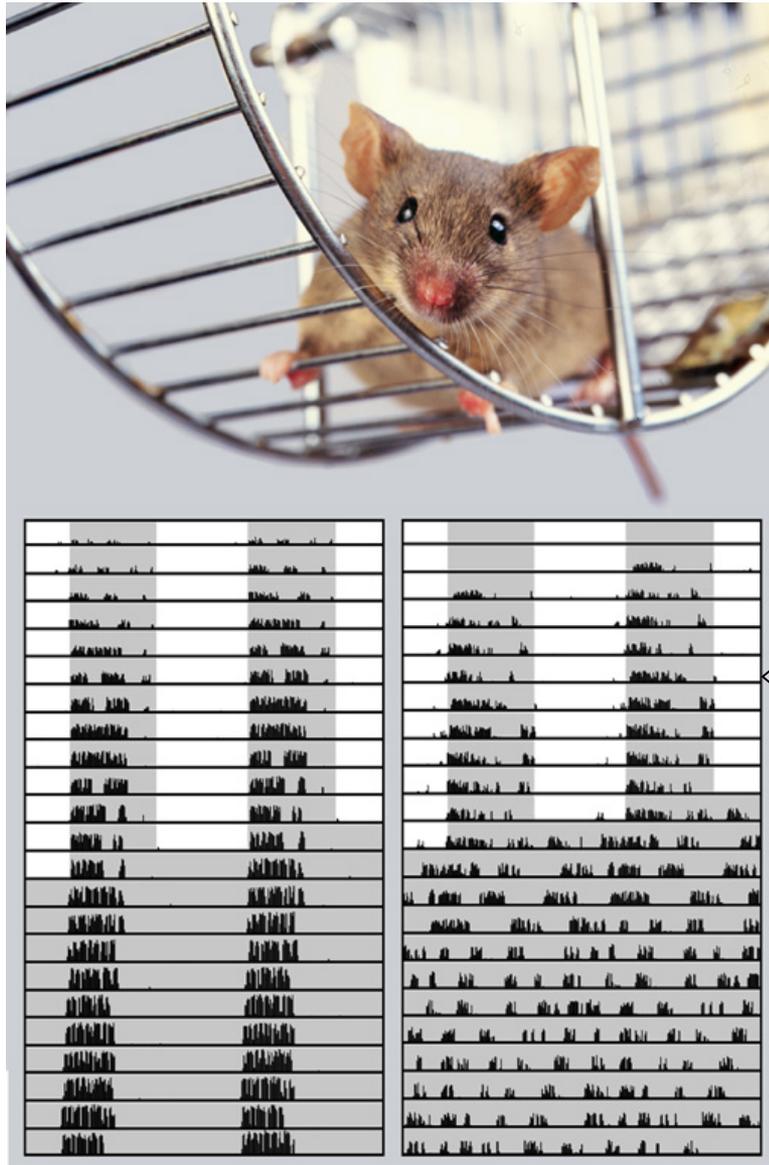
NSQ - Secção coronal

# Expressão rítmica de mPer1 “in vivo”



transgênico que expressa mPer1-luc

Flutuação circadiana da bioluminescência no NSQ

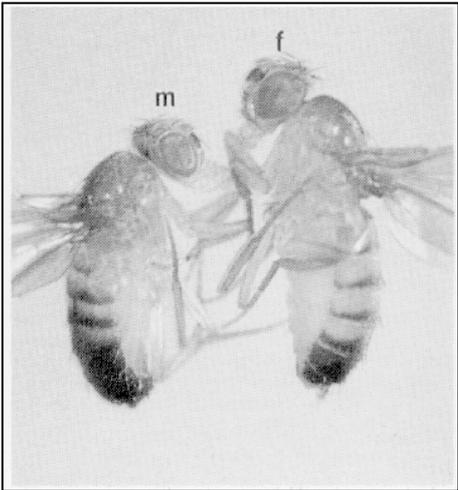
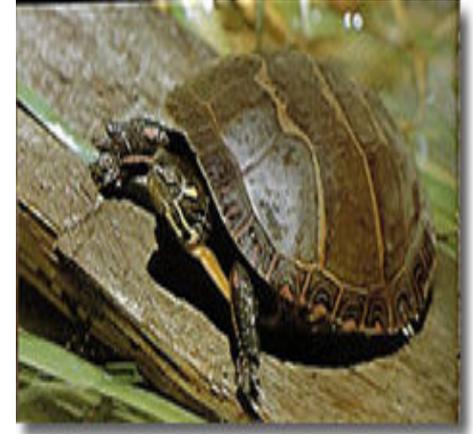


normal

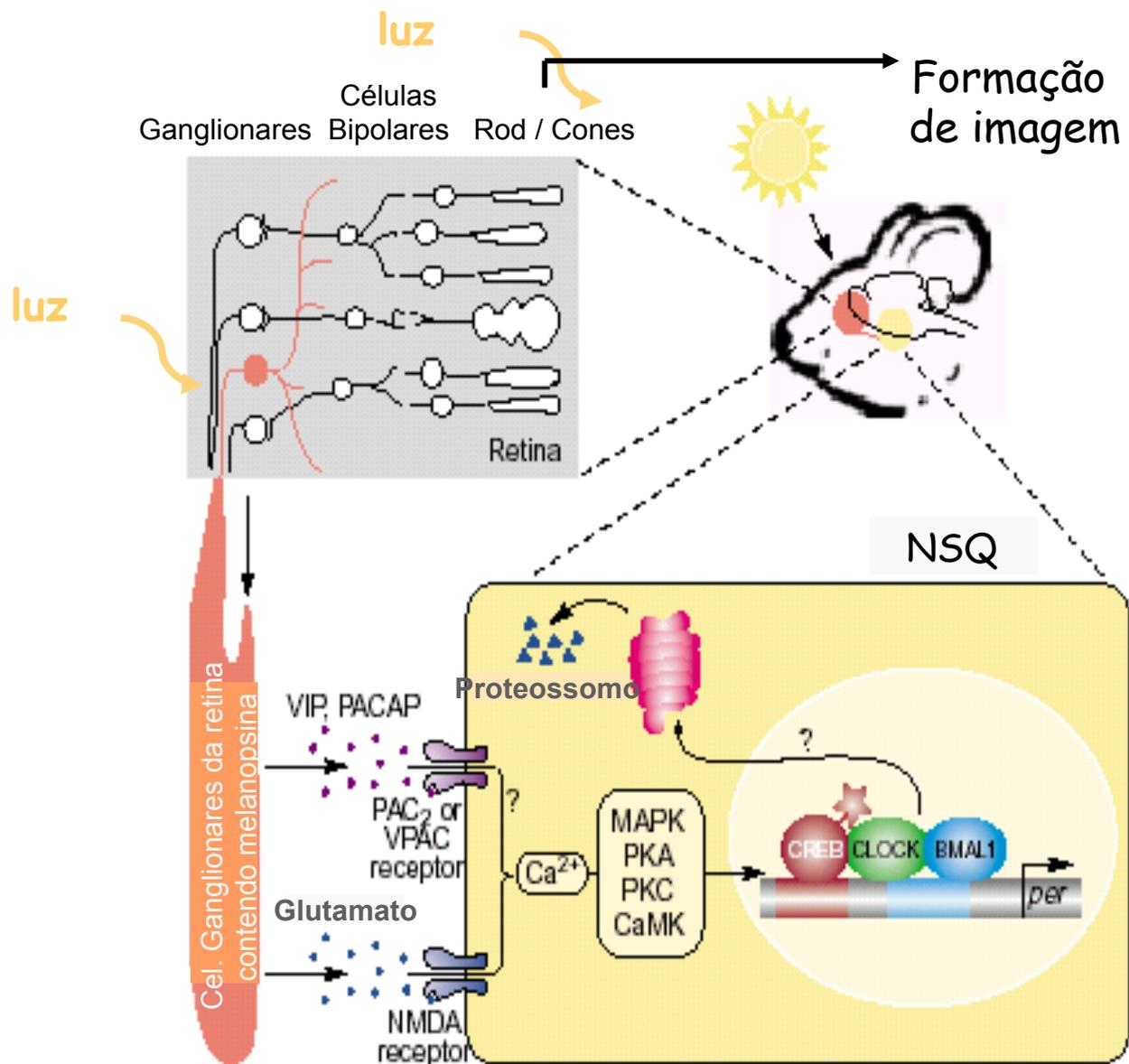
~~cry1 e cry2~~

# Interface entre o Ambiente e o Relógio - Fotorrecepção

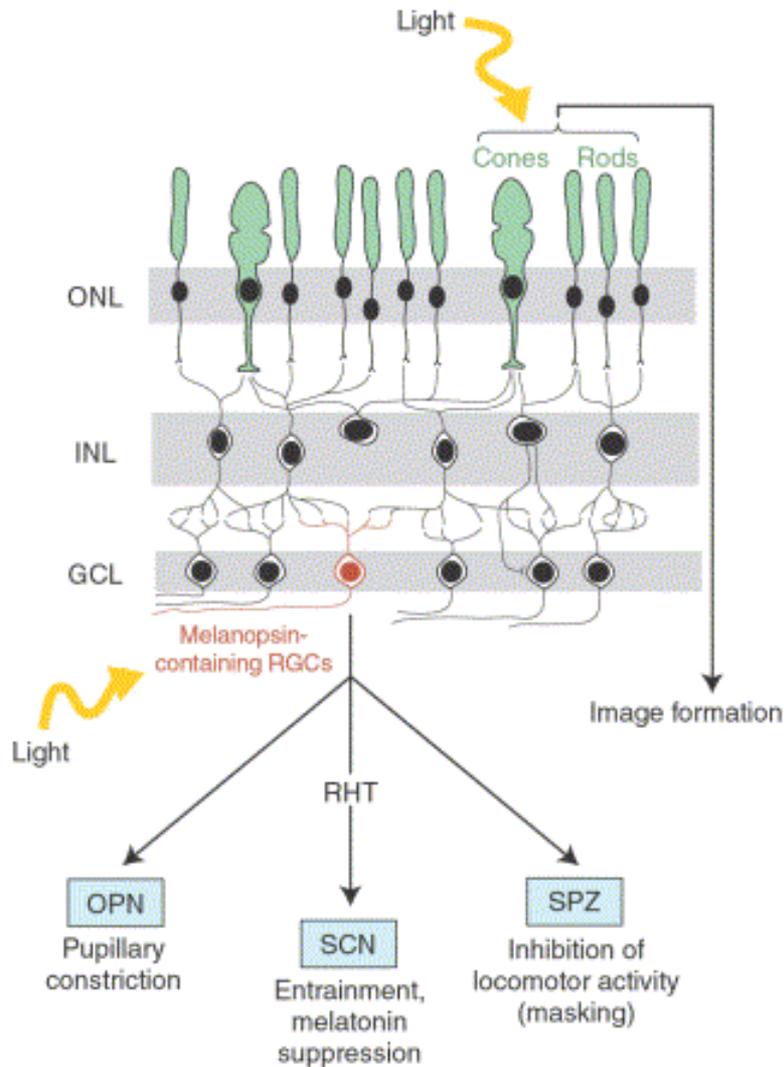
- Retina
- Pineal
- Regiões encefálicas profundas
- Órgão Frontal/Parietal (extracranianos)



# Distintos fotorreceptores na retina de mamíferos



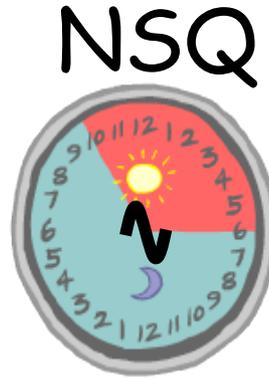
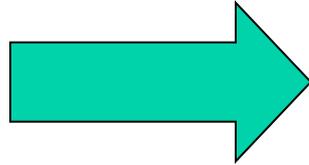
# Distintos fotorreceptores na retina de mamíferos



Current Opinion in Neurobiology

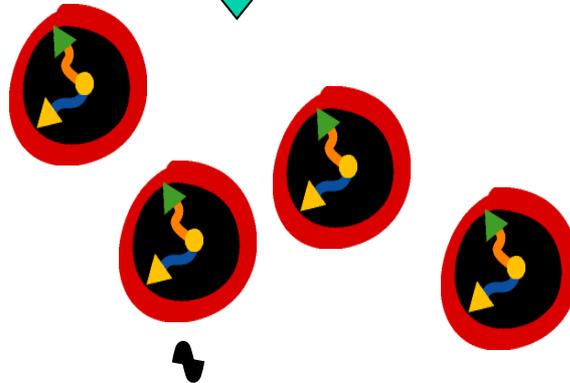
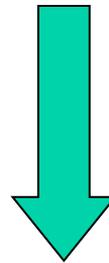
Fig. 2. Distinct photoreceptors in the mammalian retina for vision and non image-forming tasks. Cones and rods mediate light perception for image formation. Other light-regulated processes depend on different photoreceptors within the retina. These non image-forming processes are thought to involve a small subset of RGCs that express melanopsin and are light sensitive (in contrast to other RGCs). Melanopsin-containing RGCs innervate the SCN through the RHT, thus allowing entrainment of the pacemaker. Pineal melatonin suppression may also depend on this RHT/SCN-dependent pathway. Melanopsin cells also project to the olivary pretectal nucleus (OPN), allowing pupillary reflex, and to the subparaventricular zone (SPZ), thus possibly mediating the light-dependent inhibition of locomotor activity. GCL, ganglion cell layer; INL, inner nuclear layer; ONL, outer nuclear layer.

# Estrutura Molecular do Relógio - Presente em todos os tecidos



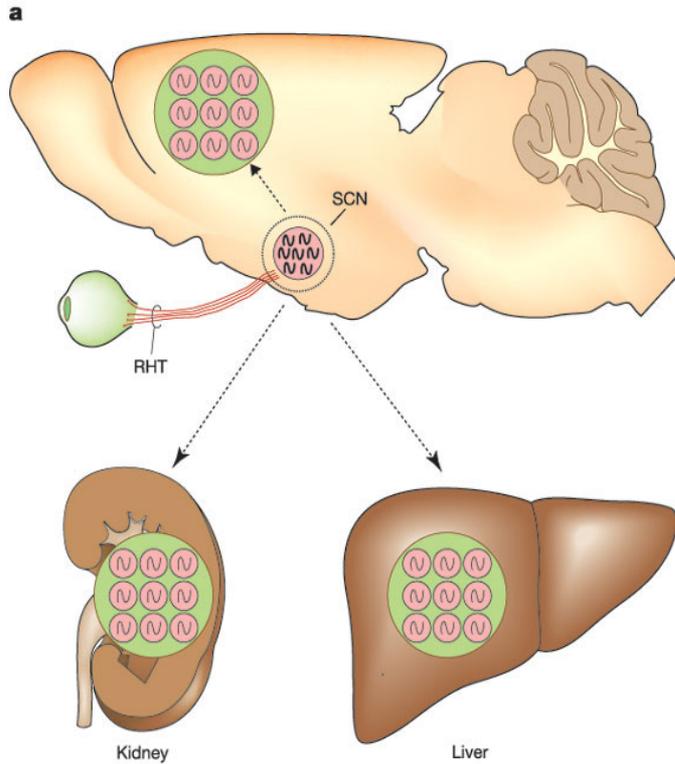
Neural

Humoral

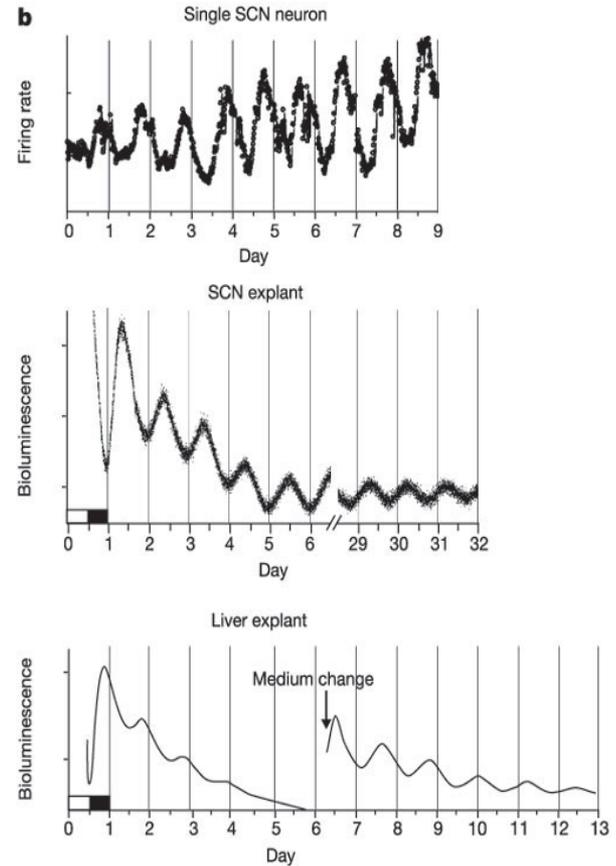


# Distribuição hierárquica de relógios

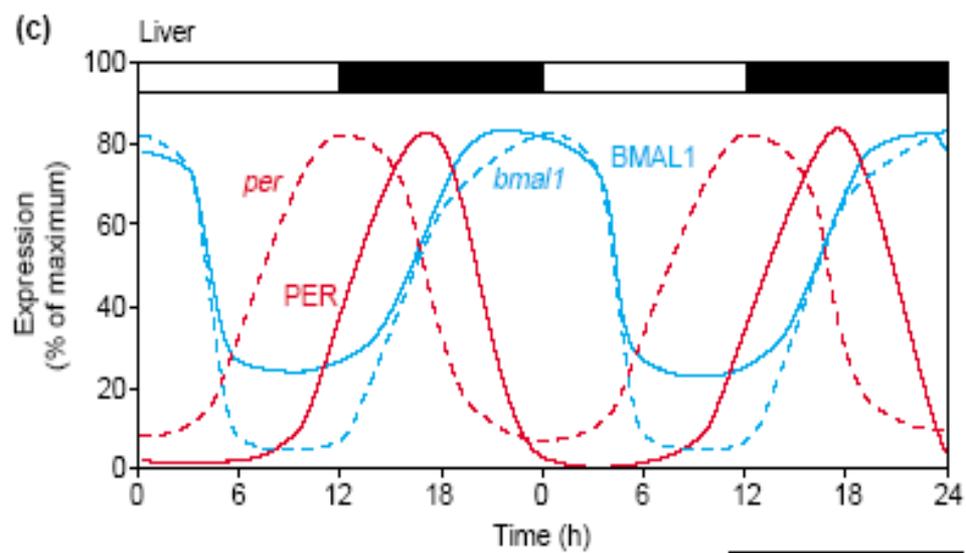
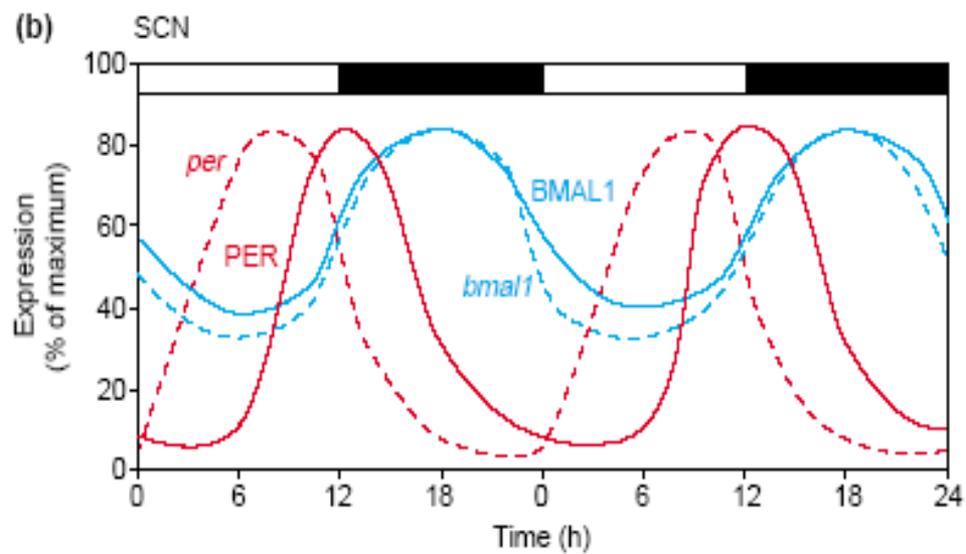
Múltiplos osciladores circadianos hierárquicos



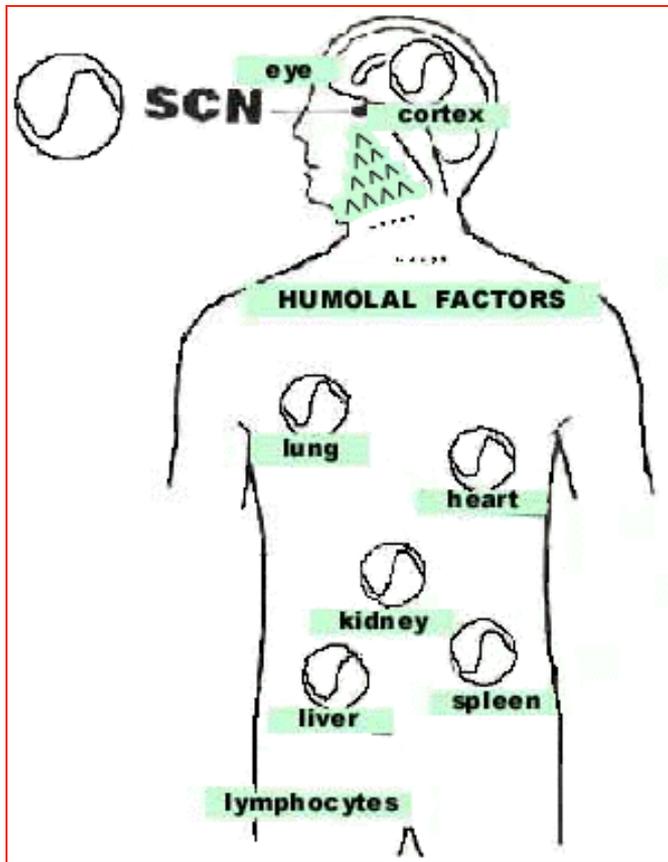
cada célula é o oscilador



Componentes bioquímicos responsáveis pelos servo-osciladores e pelo oscilador principal são muito semelhantes



# O SCN é responsável por vários ritmos fisiológicos

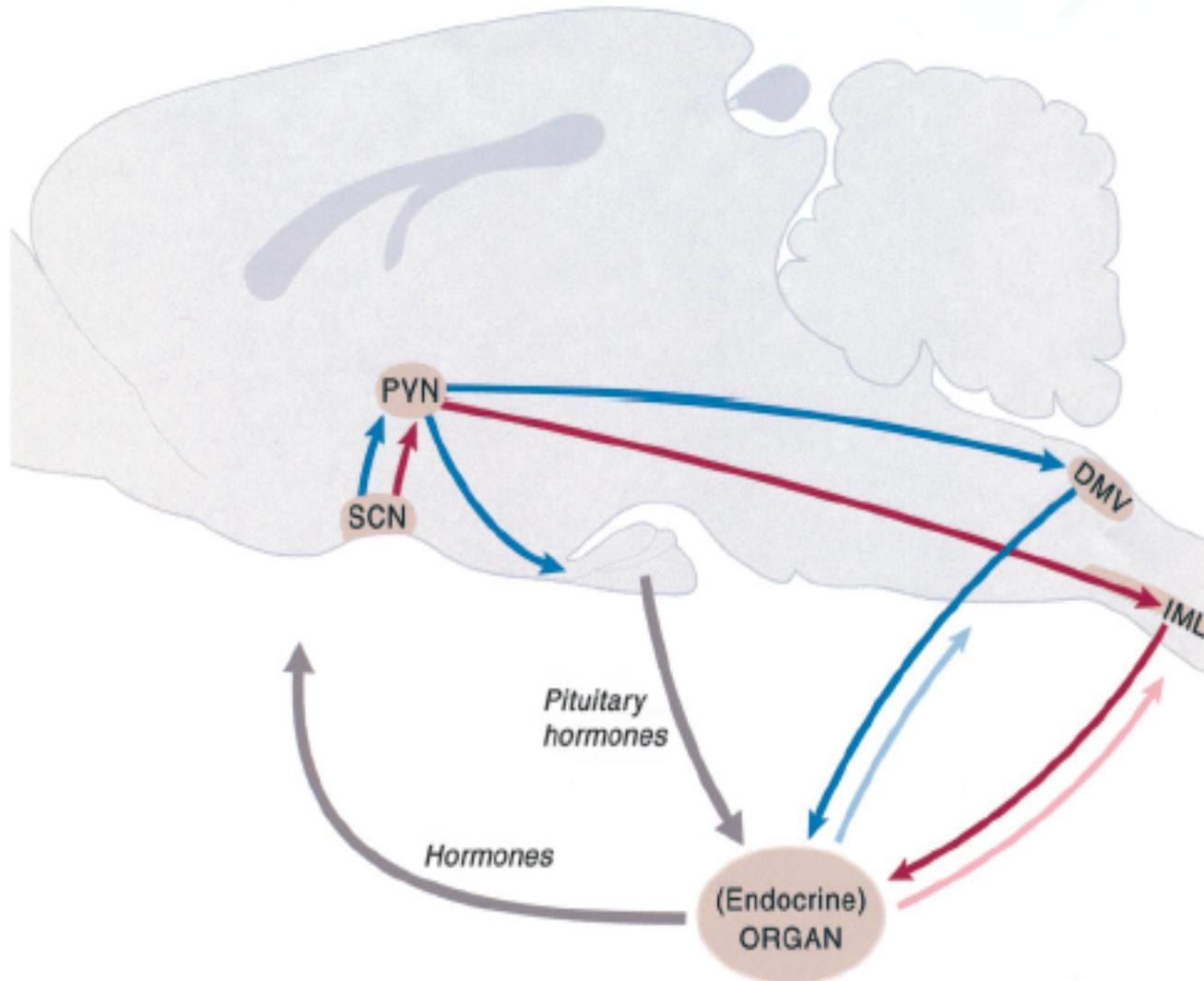


Lesão dos SCN afetam:

- 1 – locomoção (Rusak, 1977)
- 2 – ingesta (Boulos et al., 1980)
- 3 – comportamento sexual (Eskes et al., 1983, Sodersten et al., 1981)
- 4 – temperatura corporal (Eastman et al., 1983)
- 5 – ciclo sono-vigília (Eastman et al., 1983)
- 6 – produção hormonal - (corticosterona pela adrenal de ratos (Moore & Elchler, 1972); melatonina pela pineal (Moore & Klein, 1974))

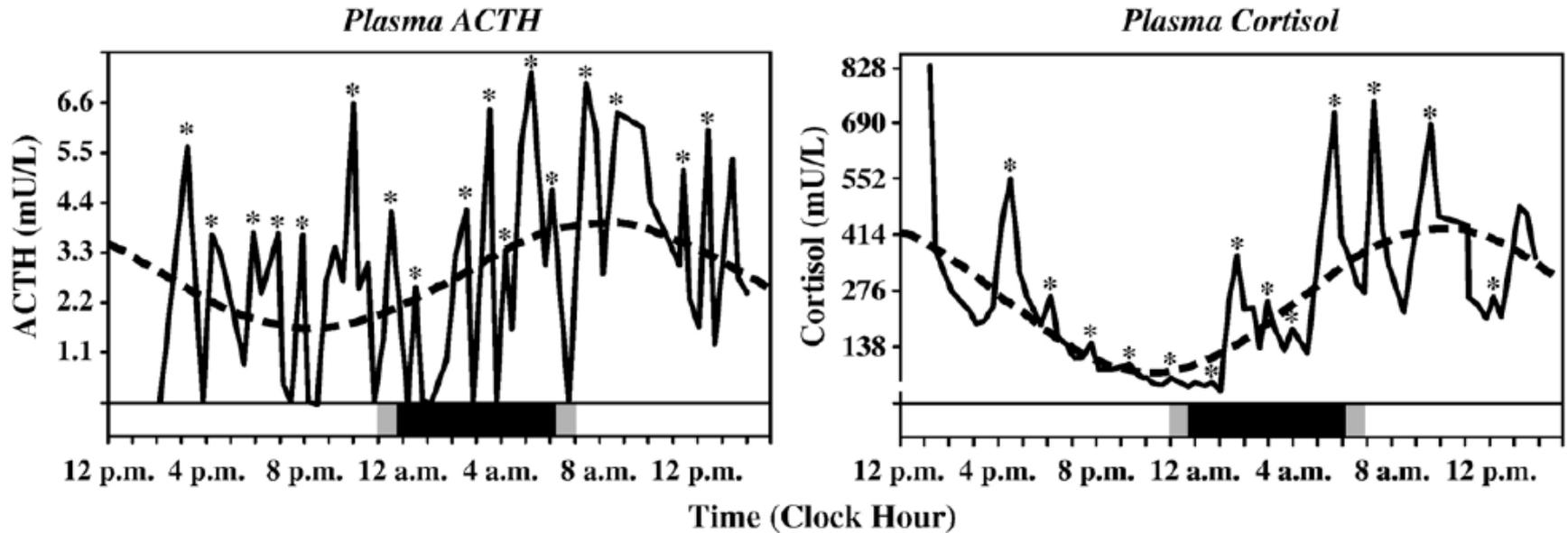
# NSQ - Sistema oscilatório endógeno

## Comunicação circadiana para o organismo



Neurônios neuroendócrinos - projeções parassimpáticas - projeções simpáticas

# Variação circadiana e pulsátil de ACTH e cortisol

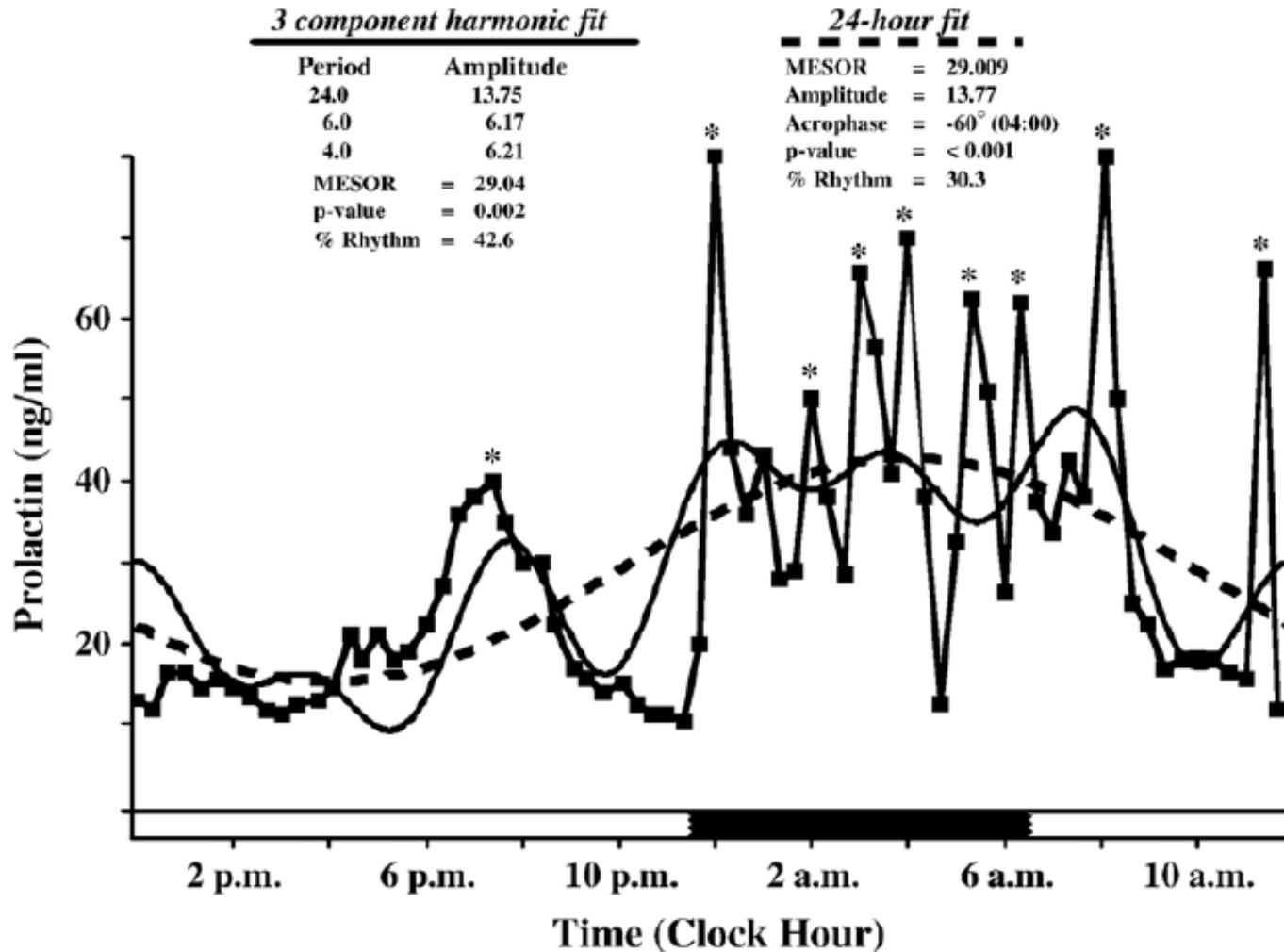


- ◆ Secreção pulsátil superimosta e modulada por um ritmo circadiano
- ◆ Aumento do pico no final da noite e começo da manhã I



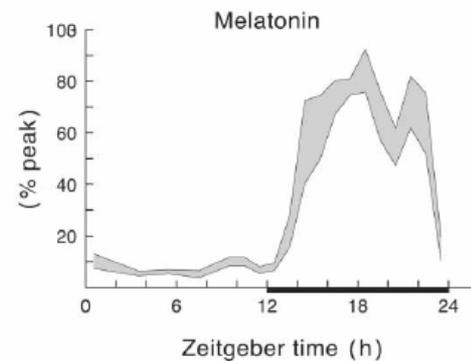
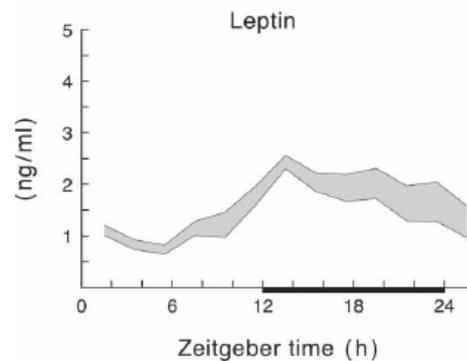
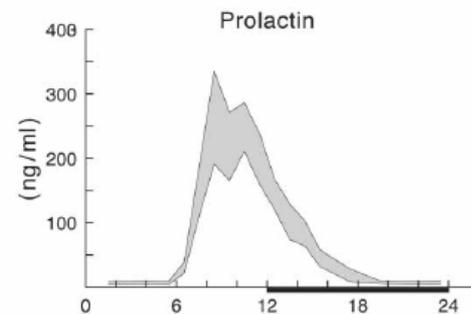
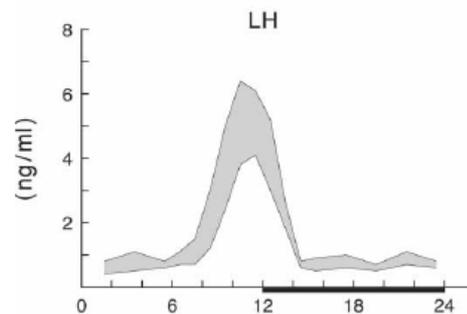
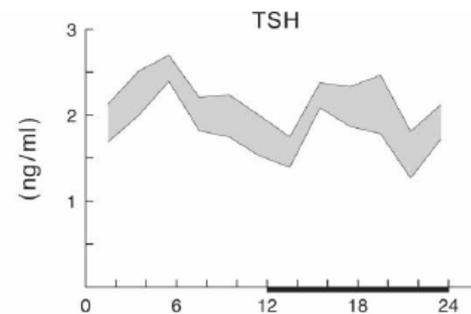
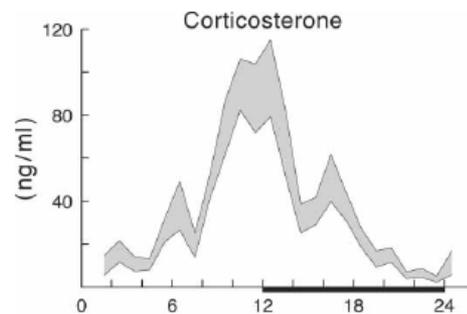
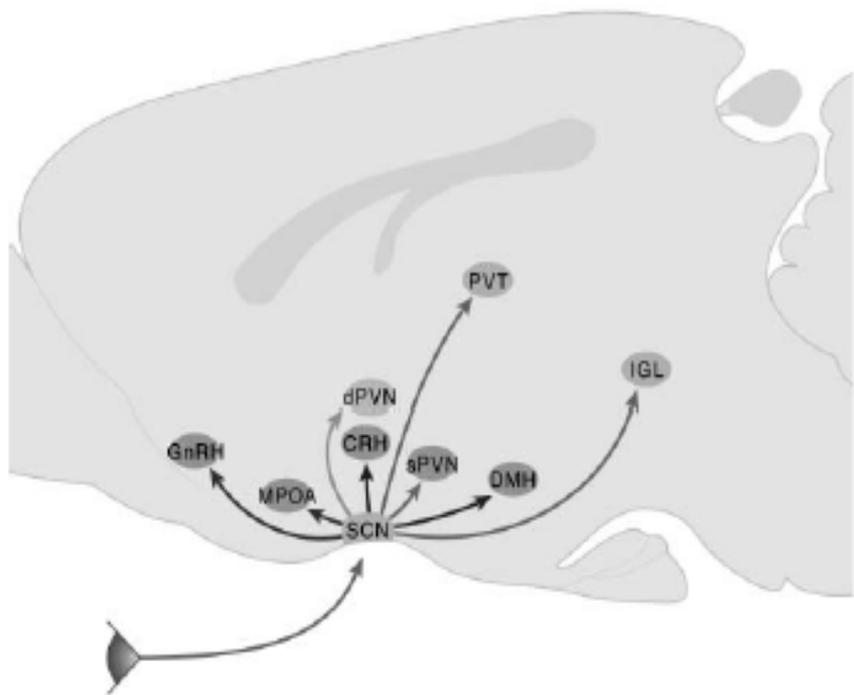
variação circadiana da concentração hormonal

# Prolactina - variação ritmica e secreção pulsátil



# Alvos do NSQ

## Ritmos hormonais de mamíferos de habito noturno

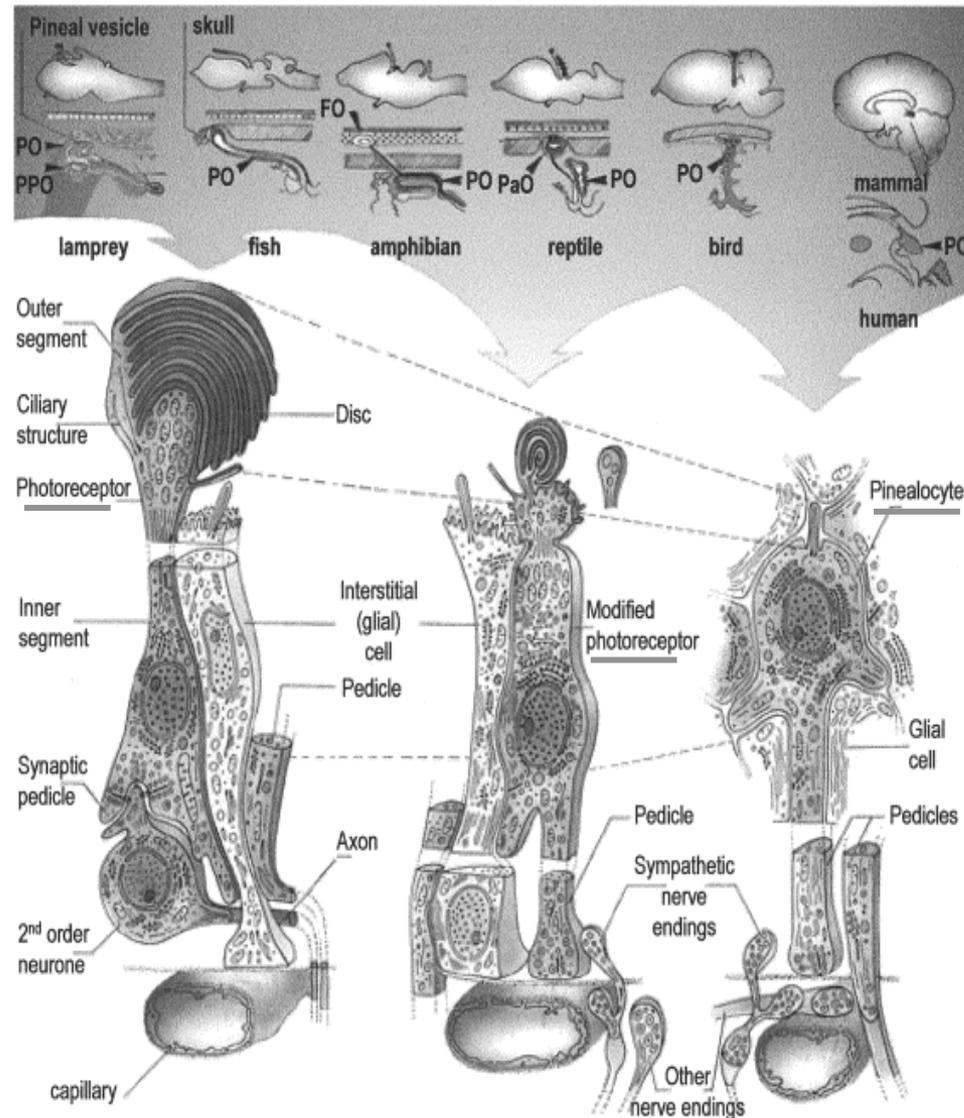


# Morfologia Comparativa da Pineal

Órgão fotossensível

Transformação Funcional  
Transformação Estrutural

Órgão neuroendócrino

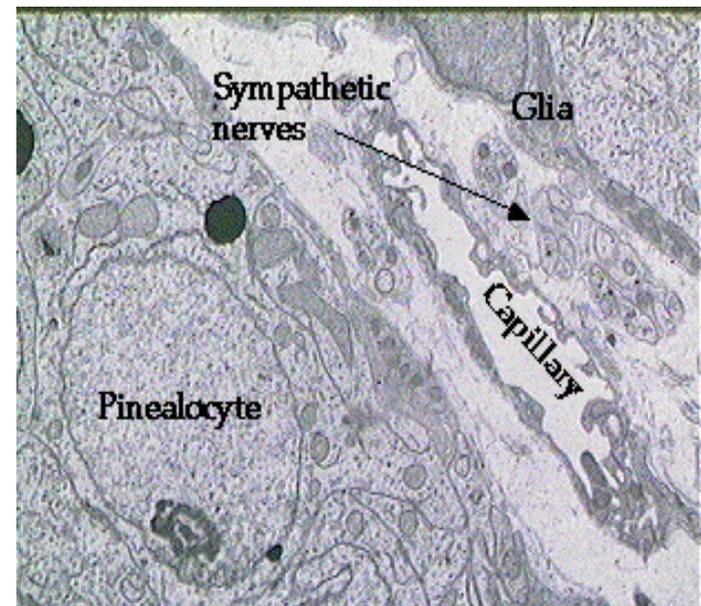
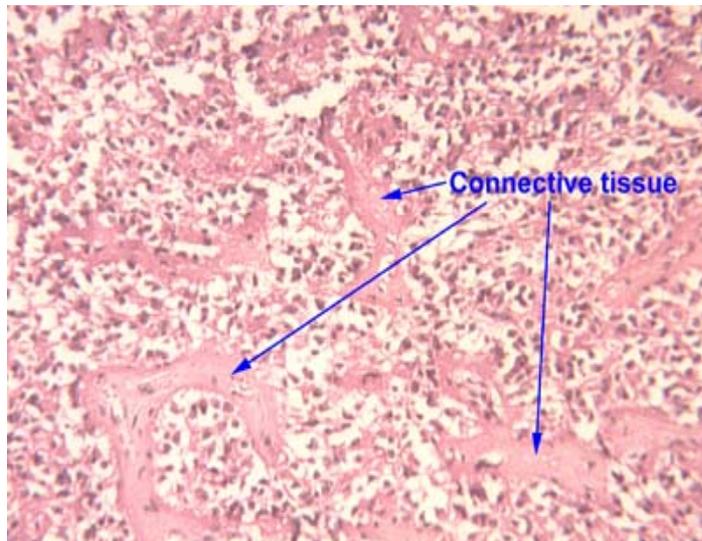
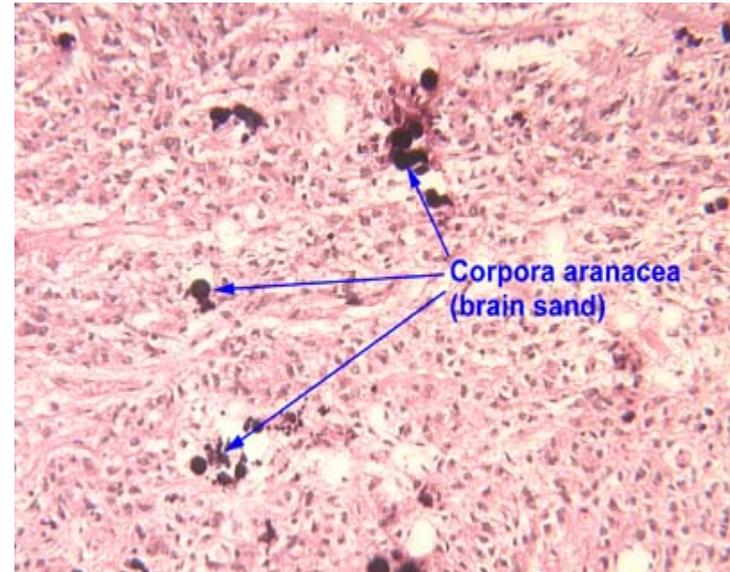
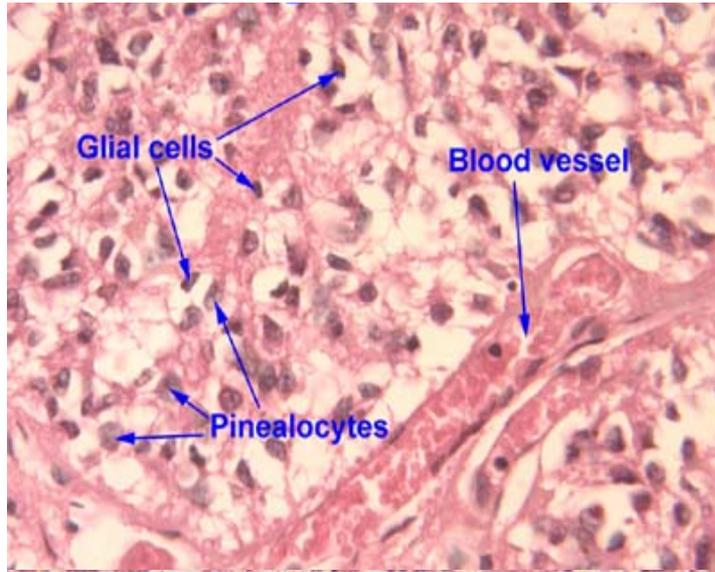


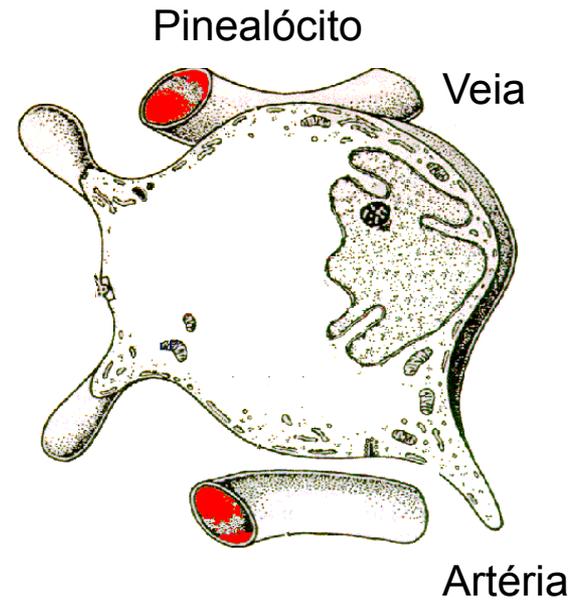
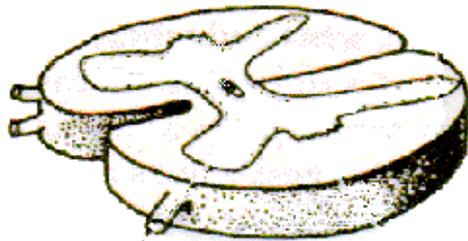
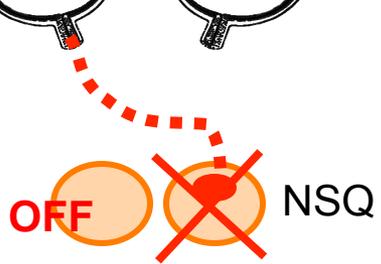
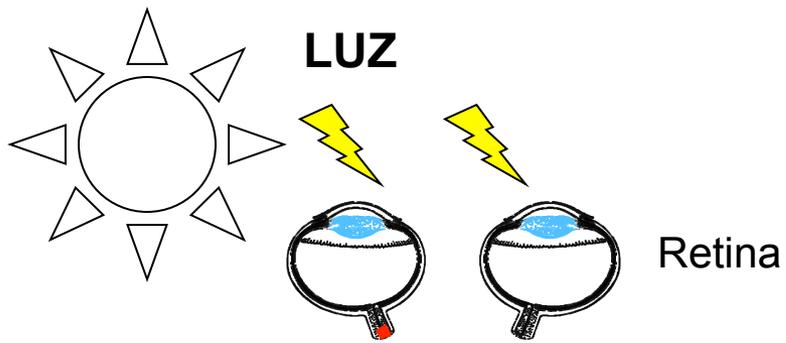
# Diversidade Anatômica e Funcional da Pineal

Reflexo das funções às quais está implicada:

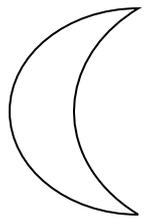
- Pigmentação da pele
- Fototaxia
- Orientação
- Locomoção
- Respostas metabólicas e termoregulatórias
- Outros eventos ritmicos

# Glândula Pineal





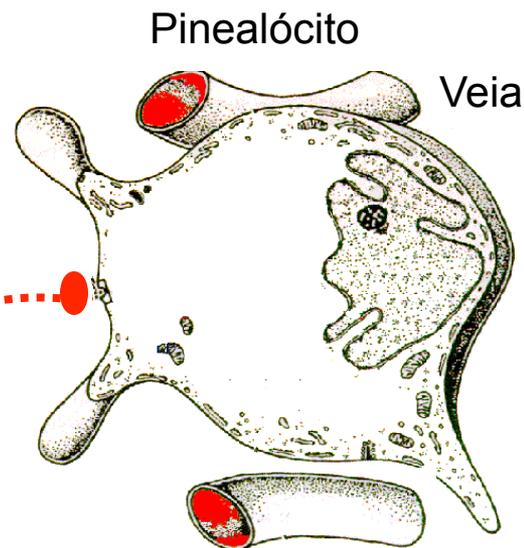
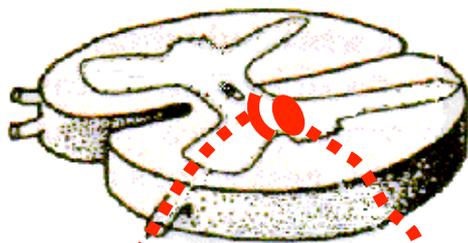
**ESCURO**



Retina



NSQ



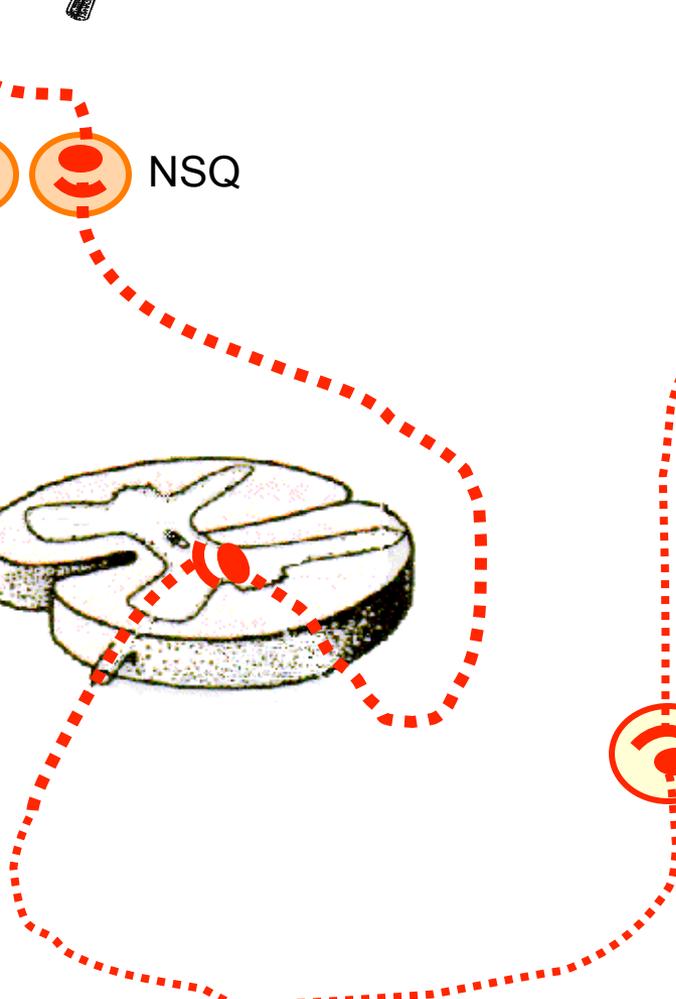
Pinealócito

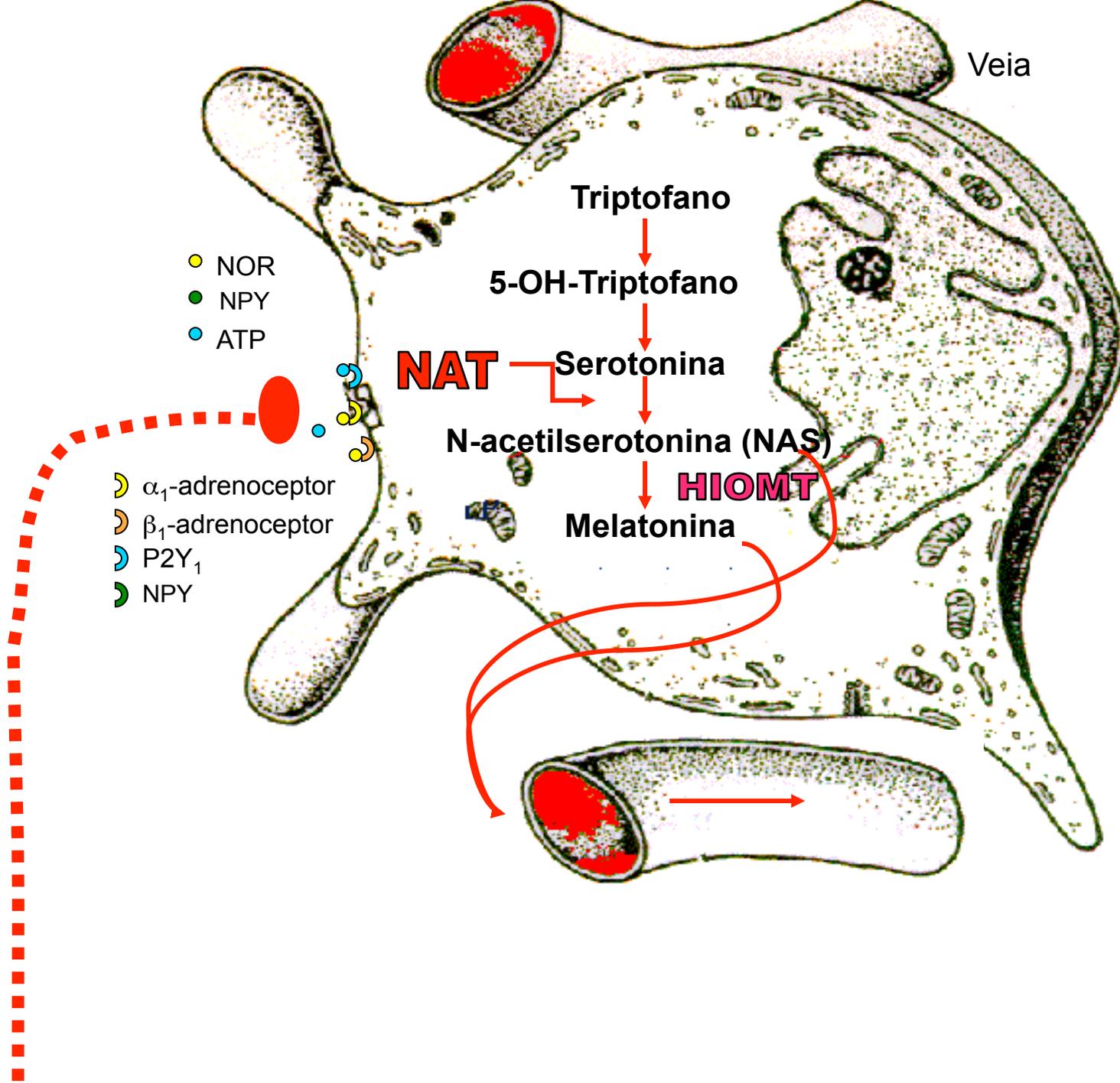
Veia

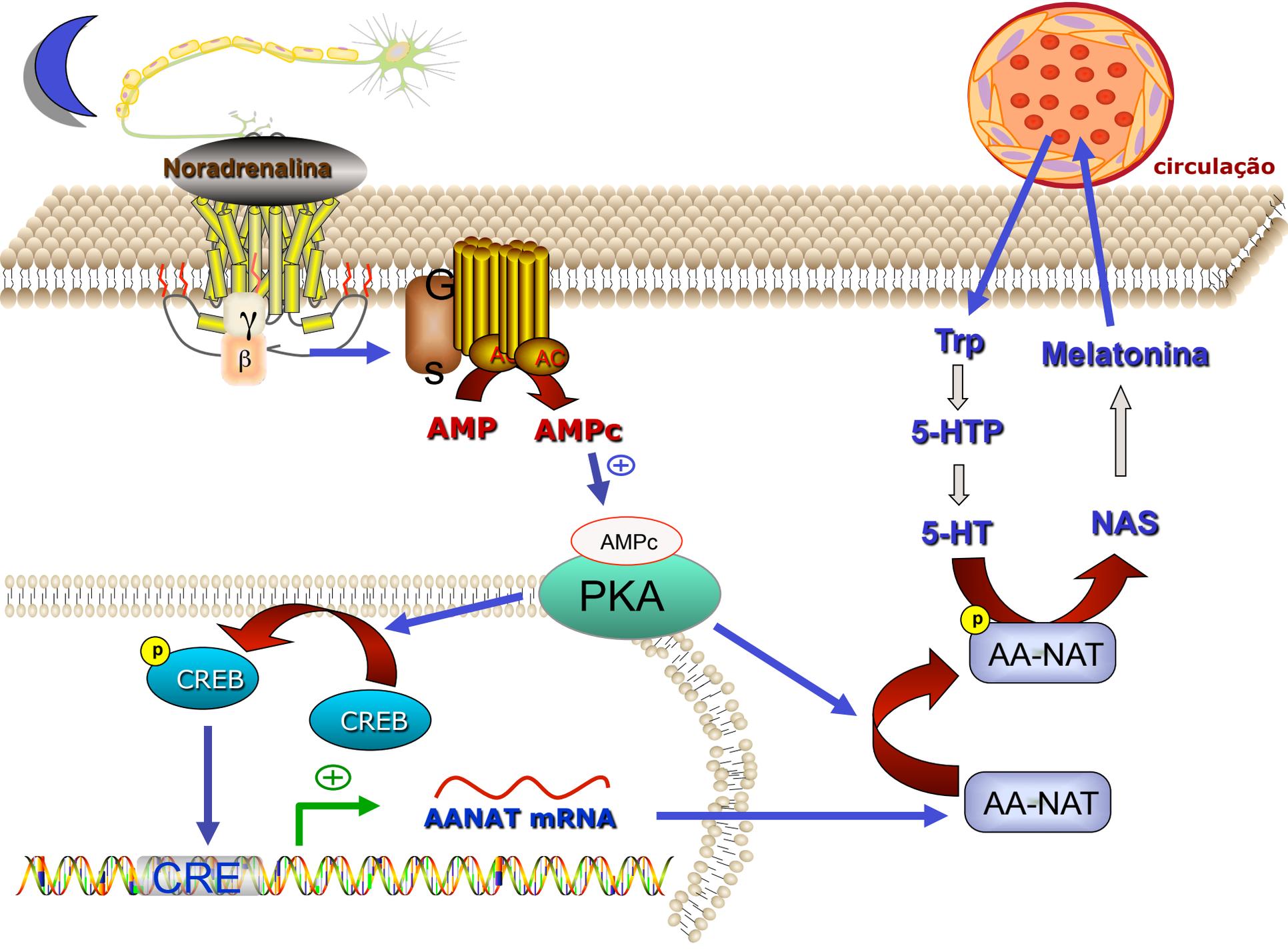
Artéria



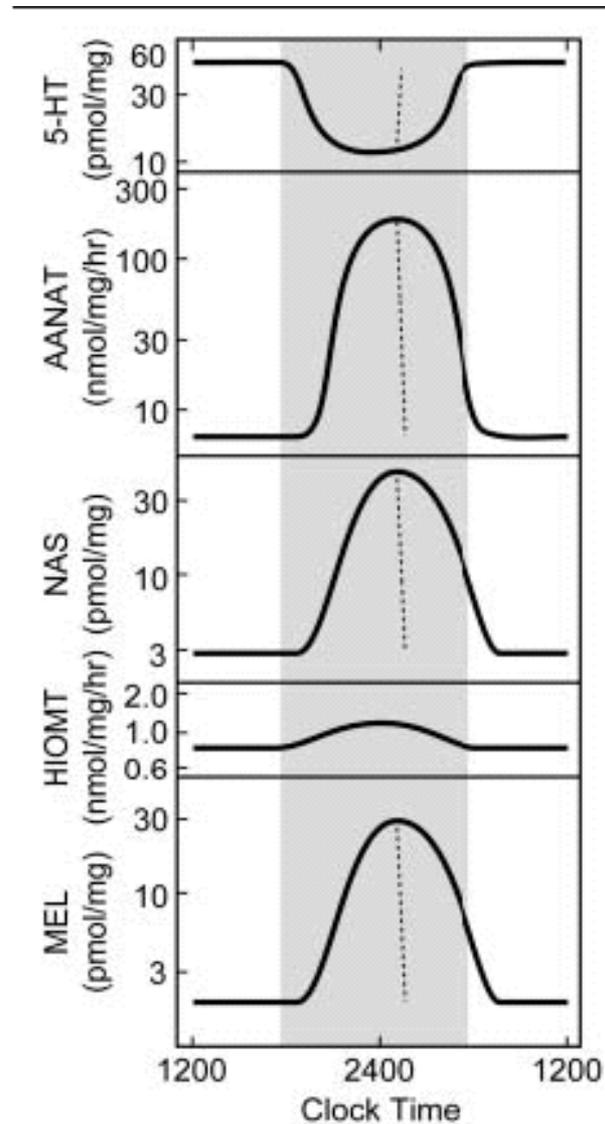
GCS



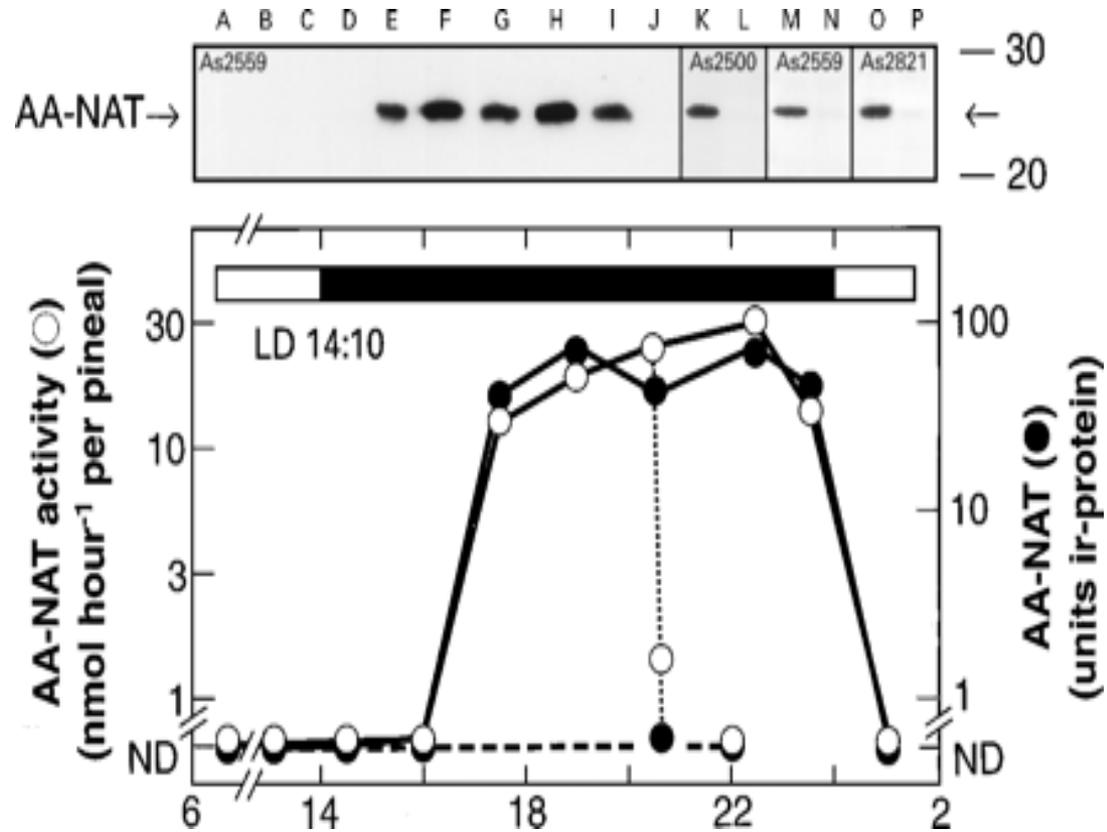




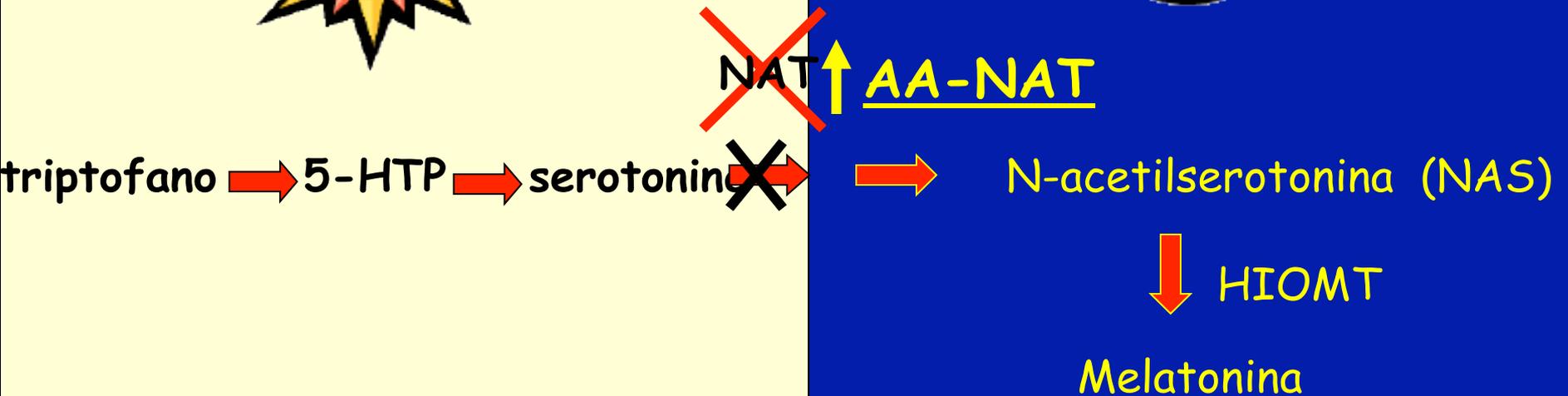
# Ritmos no metabolismo da glândula pineal



# AA-NAT na glândula pineal de ratos



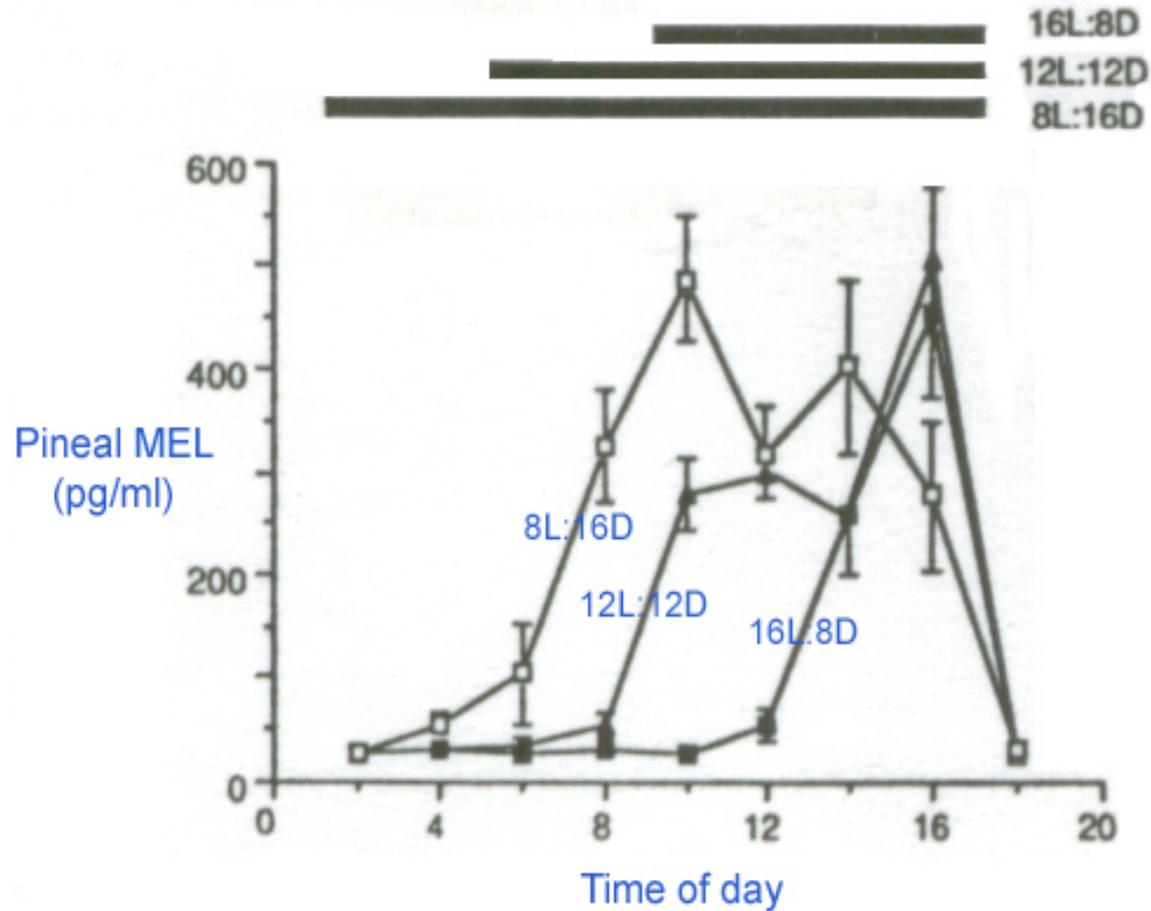
# Controle da produção de melatonina pela pineal



Produção de melatonina inibida

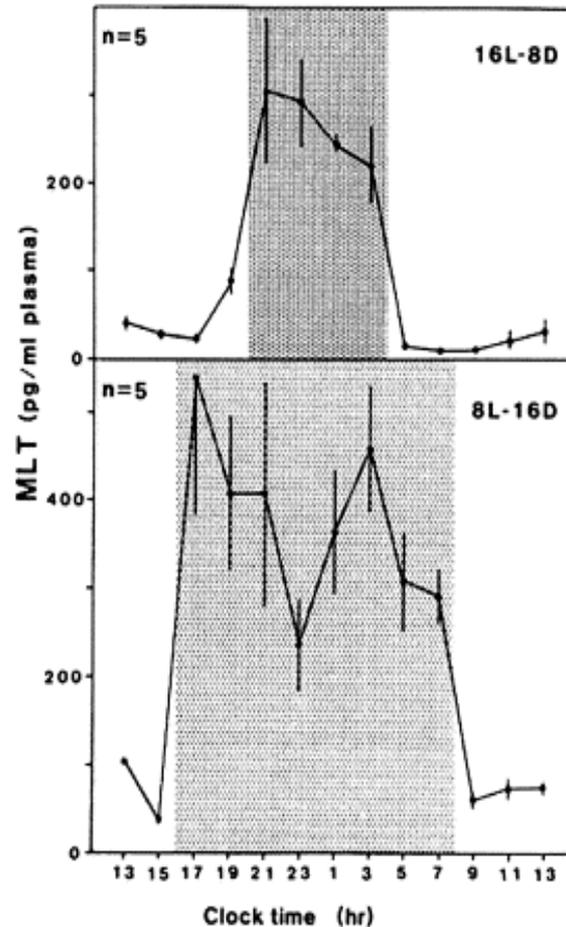
NAS e Melatonina produzidas e liberadas

## Melatonina - o hormônio marcador do escuro



# Importância do Fotoperíodo

adaptação para as estações do ano





## Verão

Dias longos, Noites curtas

↓ melatonina



## Outono



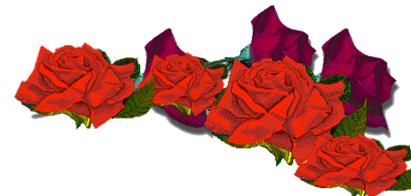
## Inverno

Dias curtos, Noites longas

↑ melatonina



## Primavera

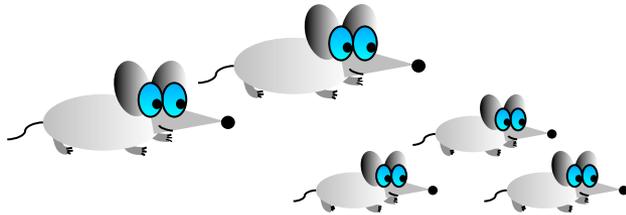




## Verão

Dias longos, Noites curtas

↓ melatonina



## Outono



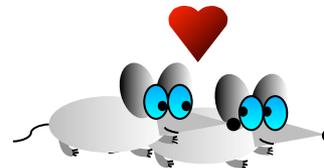
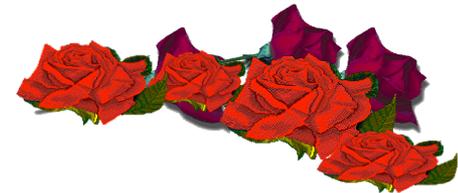
## Inverno

Dias curtos, Noites longas

↑ melatonina



## Primavera



# *Melatonina - o Hormônio do escuro*

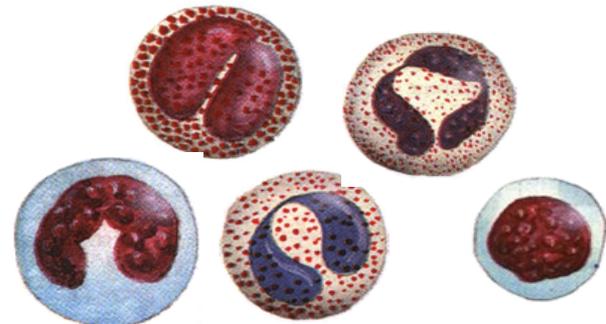
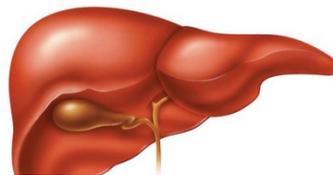
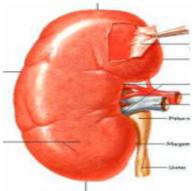
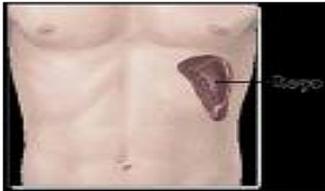
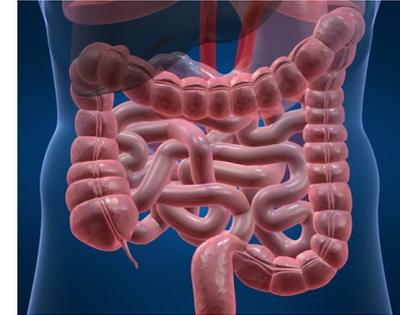
- *Transdutor endócrino da informação fotoperiódica*
- *Importante papel modulador na imunidade inata e adquirida*
  - *periférica*
  - *pineal*



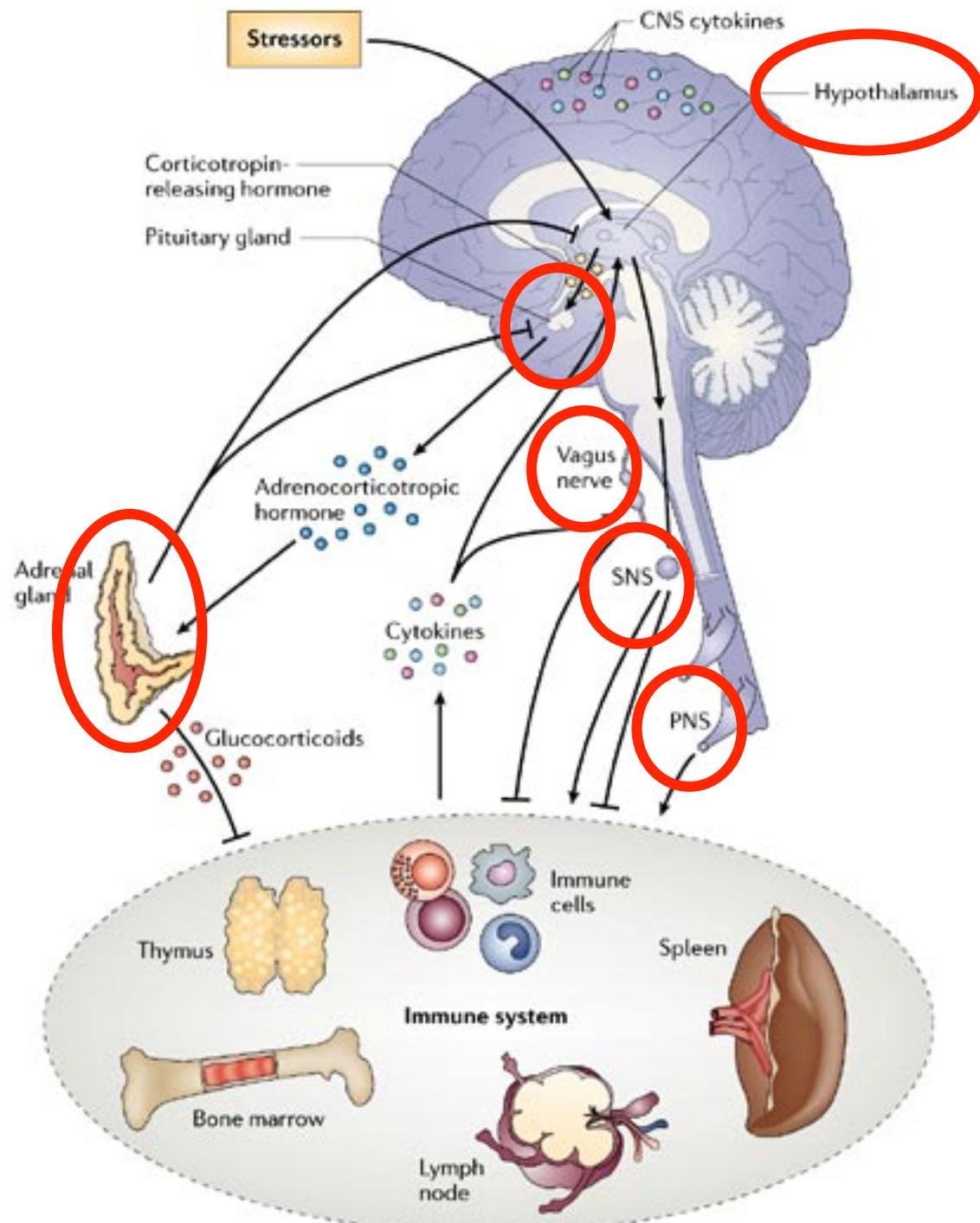
*Variação diária de respostas imunes*

# Locais de produção da melatonina

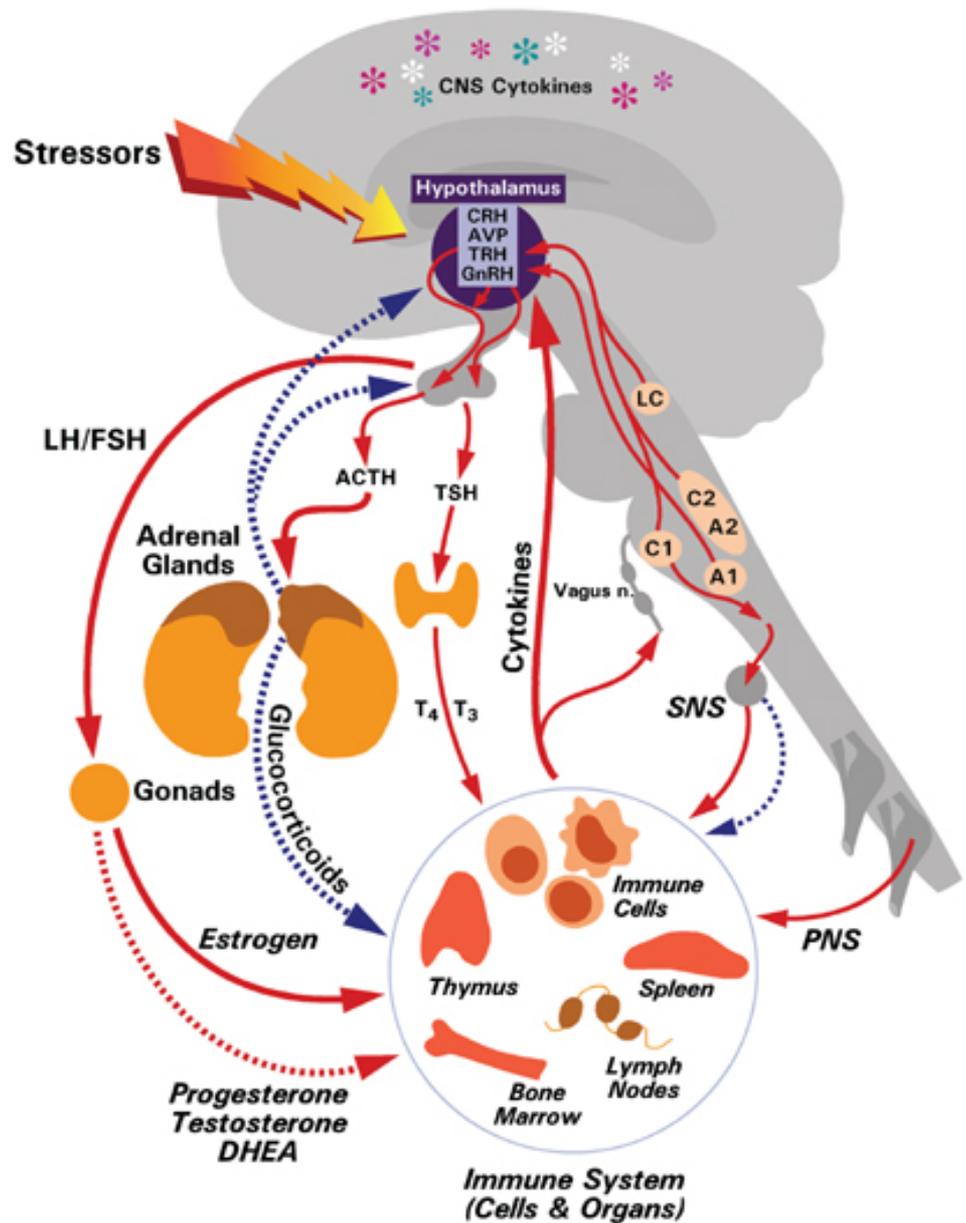
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# Conexões entre os sistemas nervoso, sistema endócrino e sistema imune

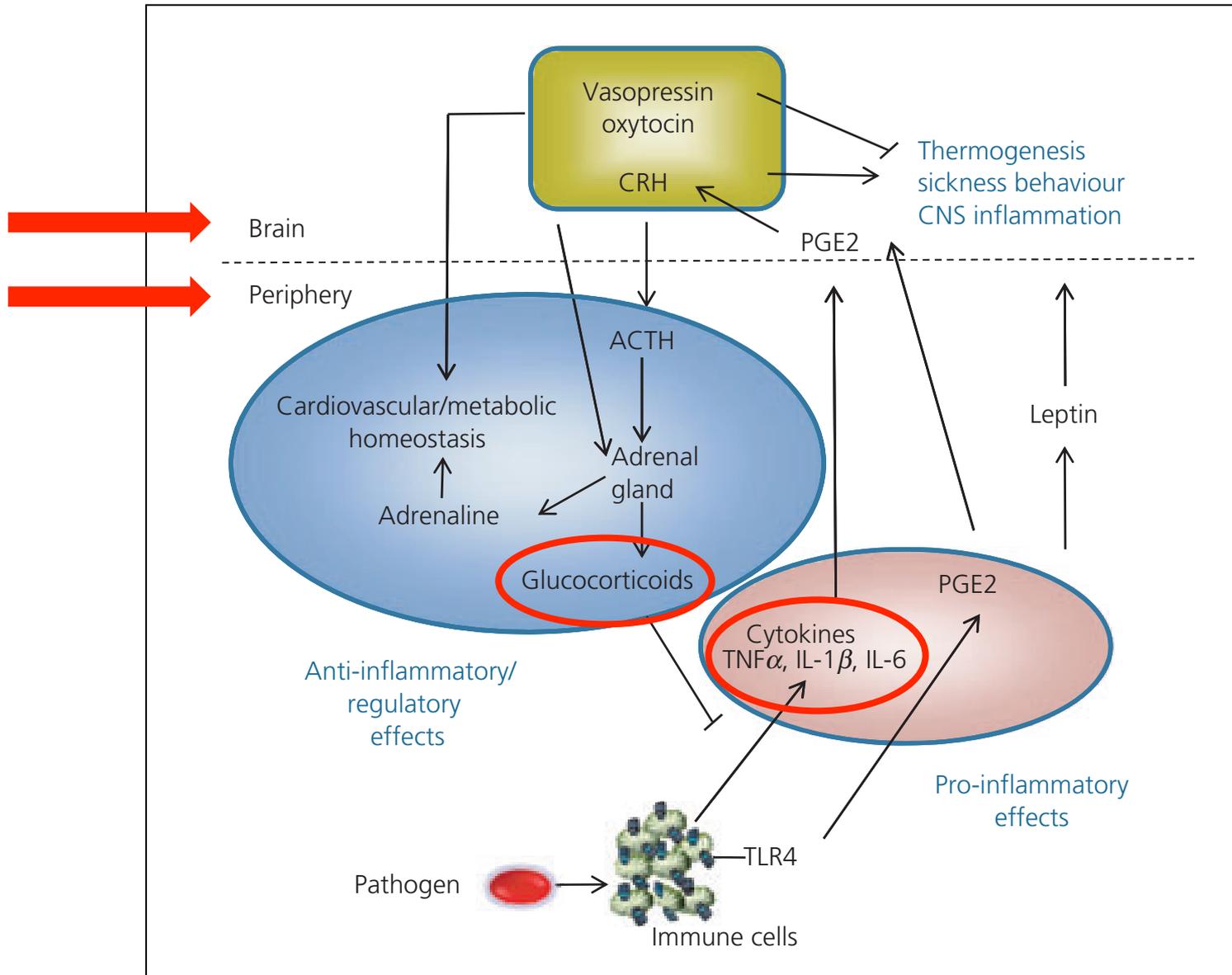


# Comunicação bidirecional entre os sistemas imune e neuroendócrino

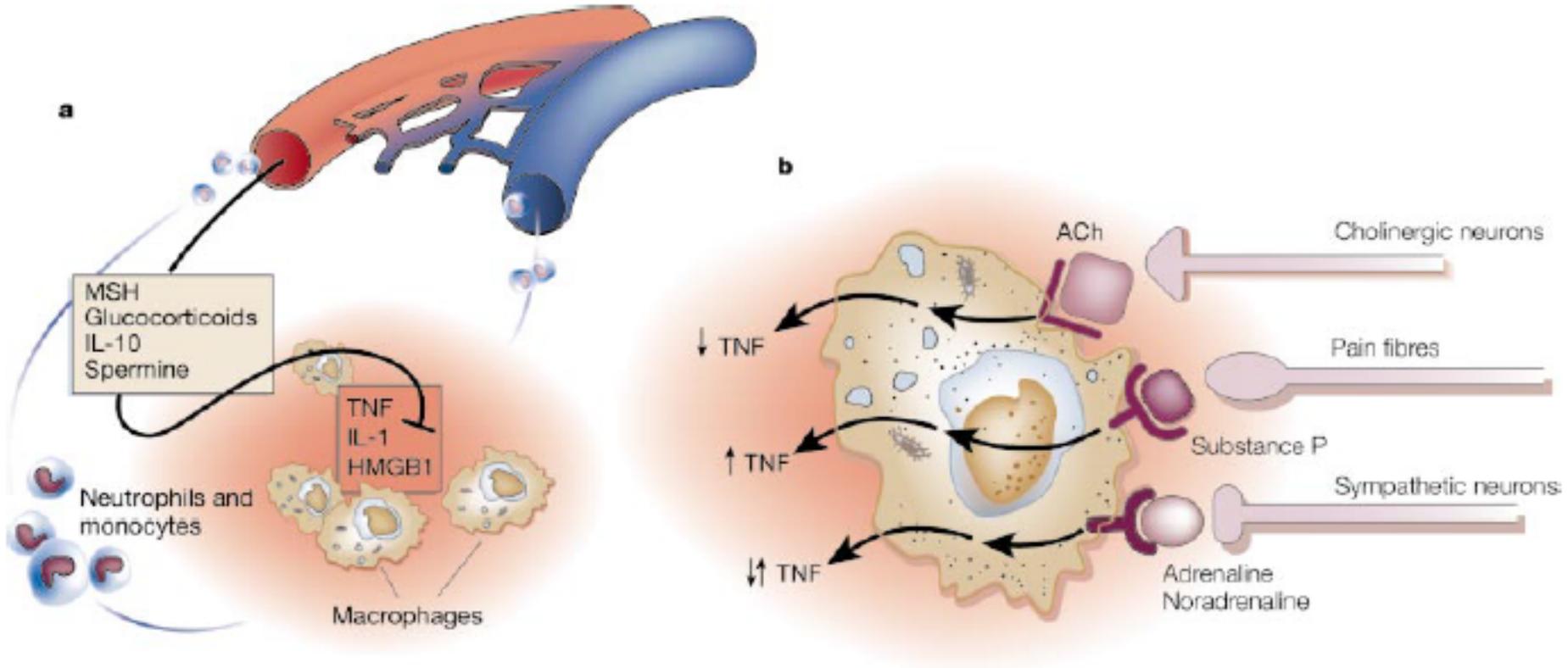




# Interações Imuno-neuroendócrinas

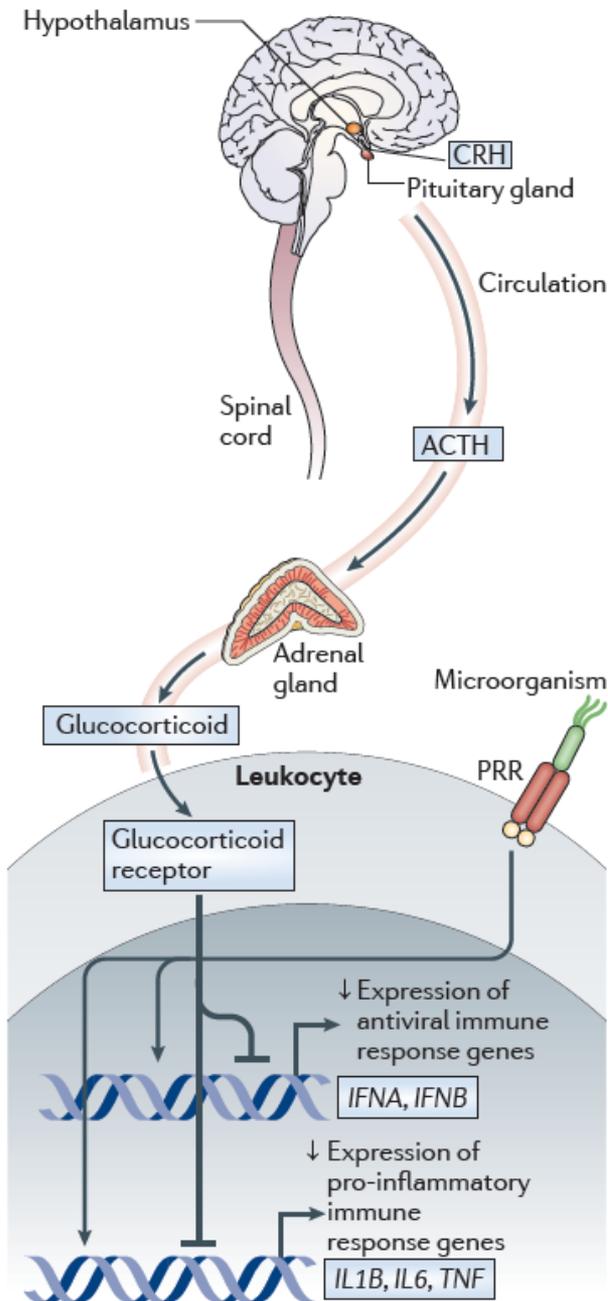


# Resposta local e sistêmica



Comunicação bidirecional permite que o sistema nervoso coordene o sistema imunológico por meio de vias de ação sistêmicas e locais

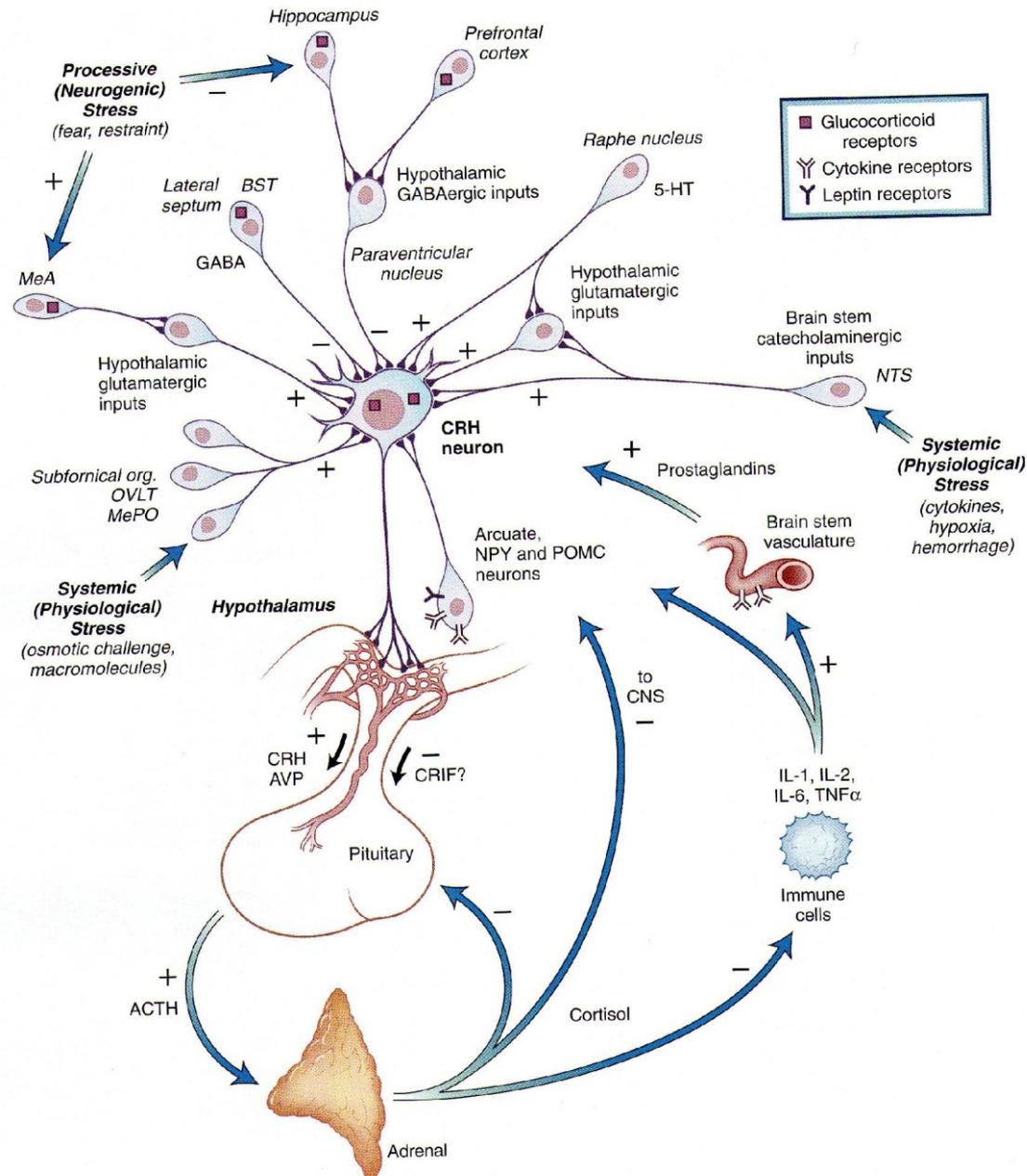
## a Hypothalamic-pituitary-adrenal axis



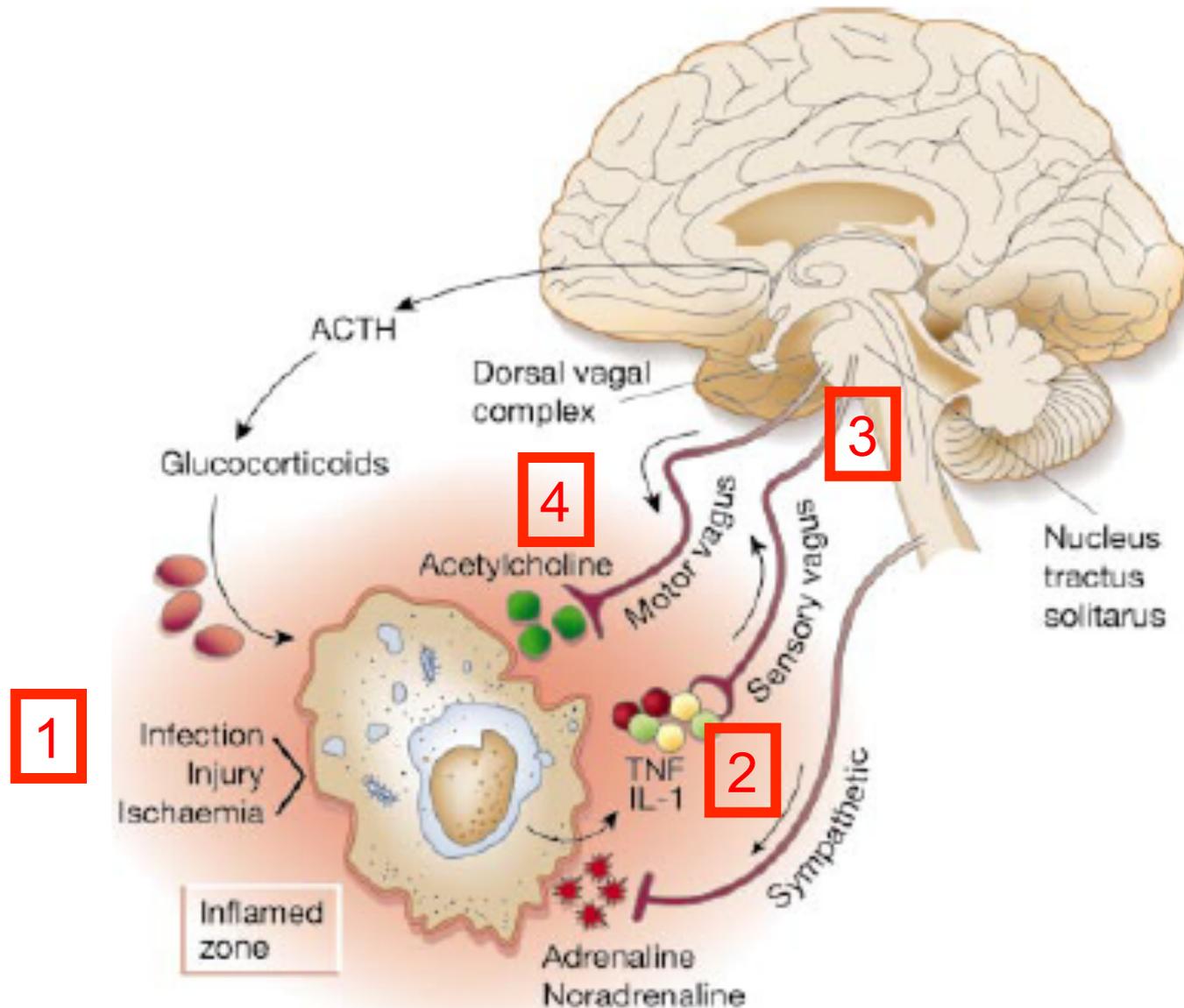
# Eixo HPA

Glicocorticóides elevados pela ativação do eixo HPA ativam receptores nucleares para glicocorticóides e controlam expressão gênica

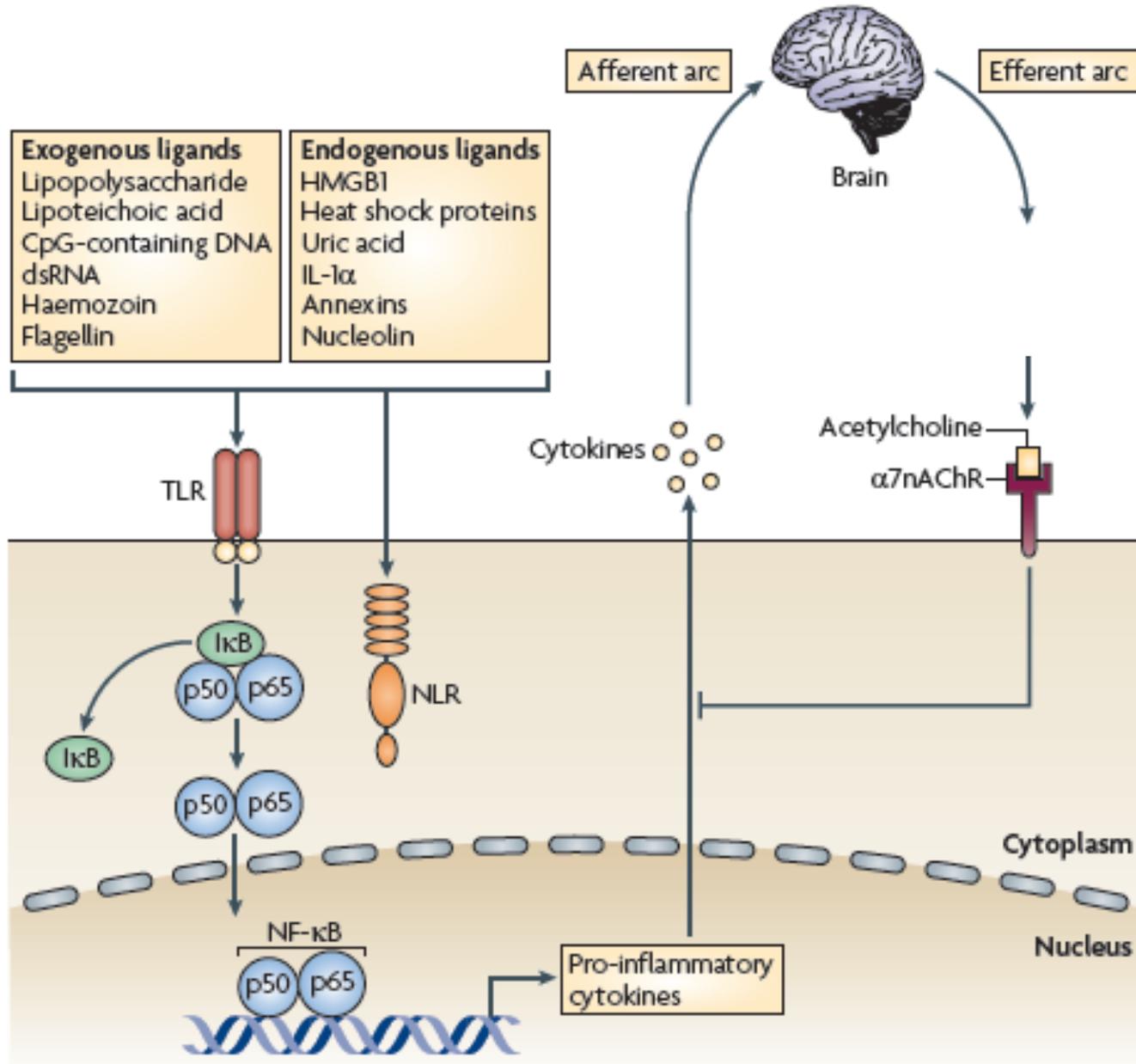
# Regulação neuroendócrina da secreção de hormônio liberador de corticotrofina (CRH)



# Sistema inmunológico - Reflexo vagal



# Inibição vagal da produção de citocinas



< Nervo vago  
Nervo esplênico

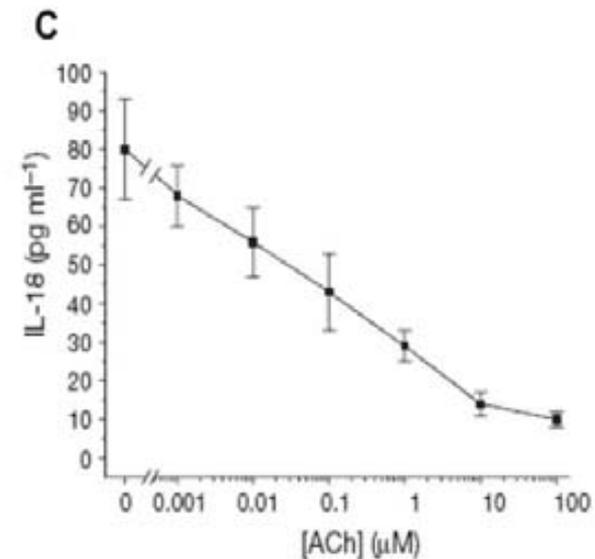
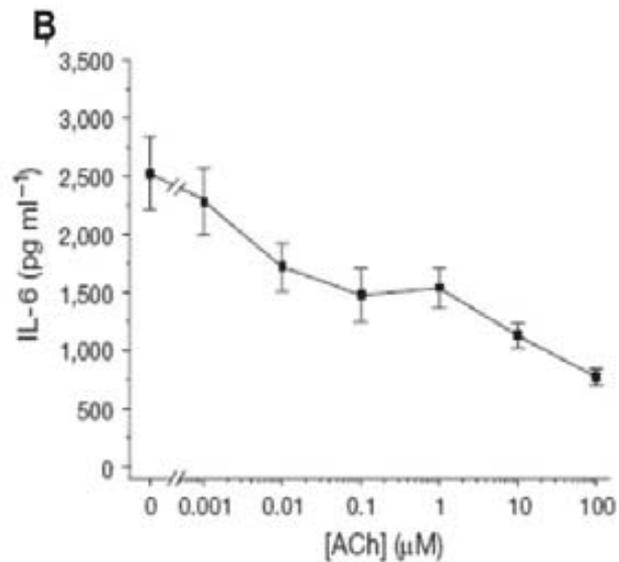
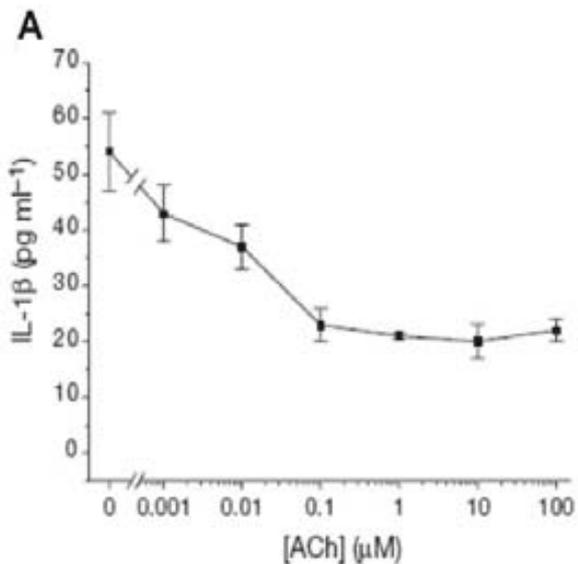
Macrófagos

Cytoplasm  
Nucleus

Pro-inflammatory cytokines

# Sistema imunológico - Reflexo vagal

Acetilcolina inibe a produção de mediadores pró-inflamatórios por macrófagos estimulados com LPS



Portanto ...

## SISTEMA NEUROIMUNOENDÓCRINO

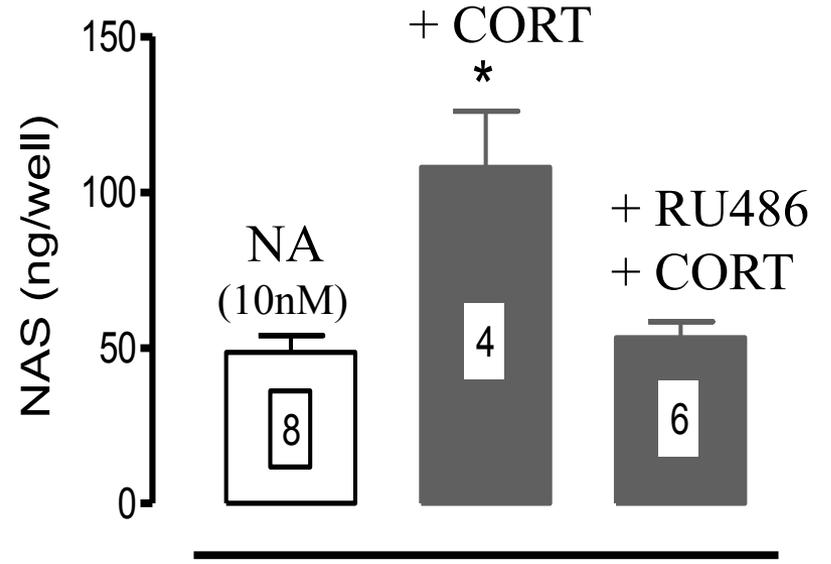
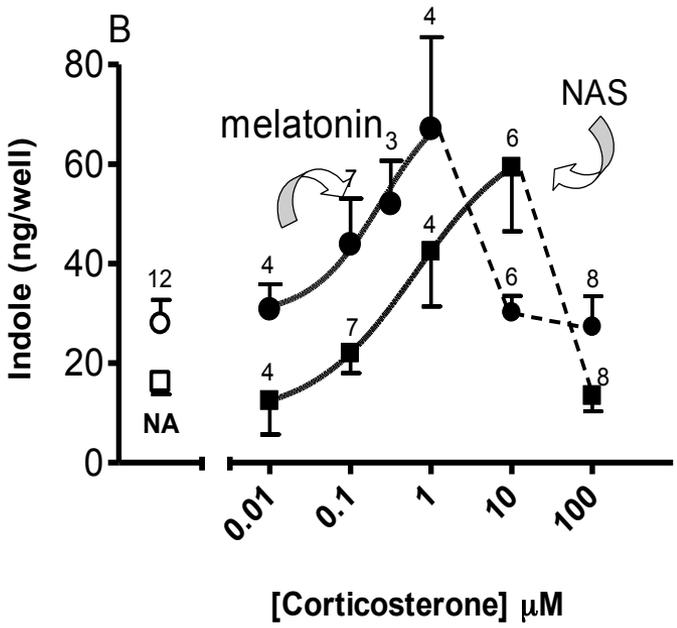
Área do conhecimento que busca compreender as diversas formas de **comunicação** entre os sistemas nervoso, endócrino e imunológico que garantem o funcionamento dinâmico e apropriado do organismo na **saúde** e na **doença**.

**Um exemplo ...**

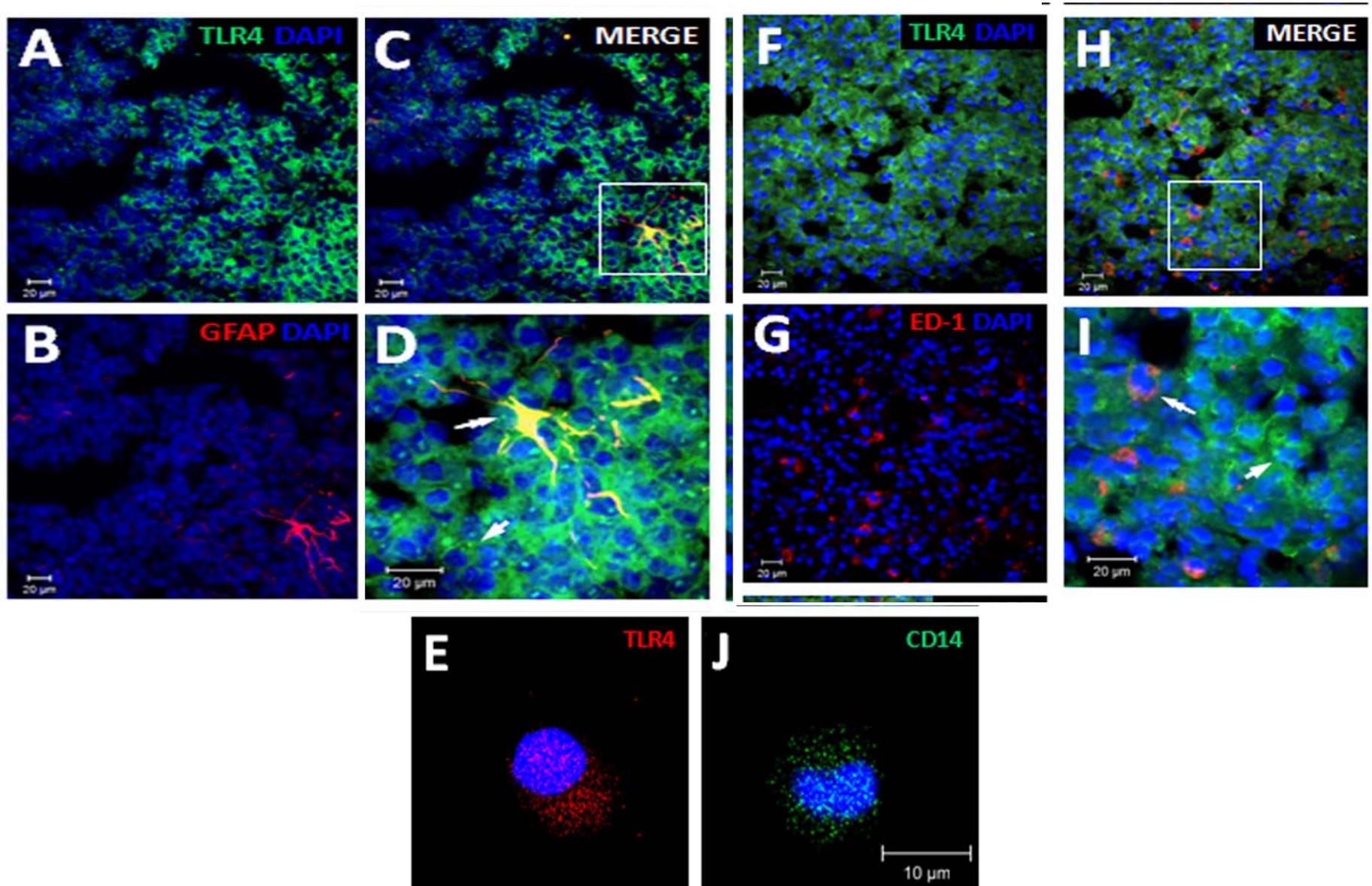
**Interações imuno-neuroendócrinas  
na glândula pineal**

# Corticosterone

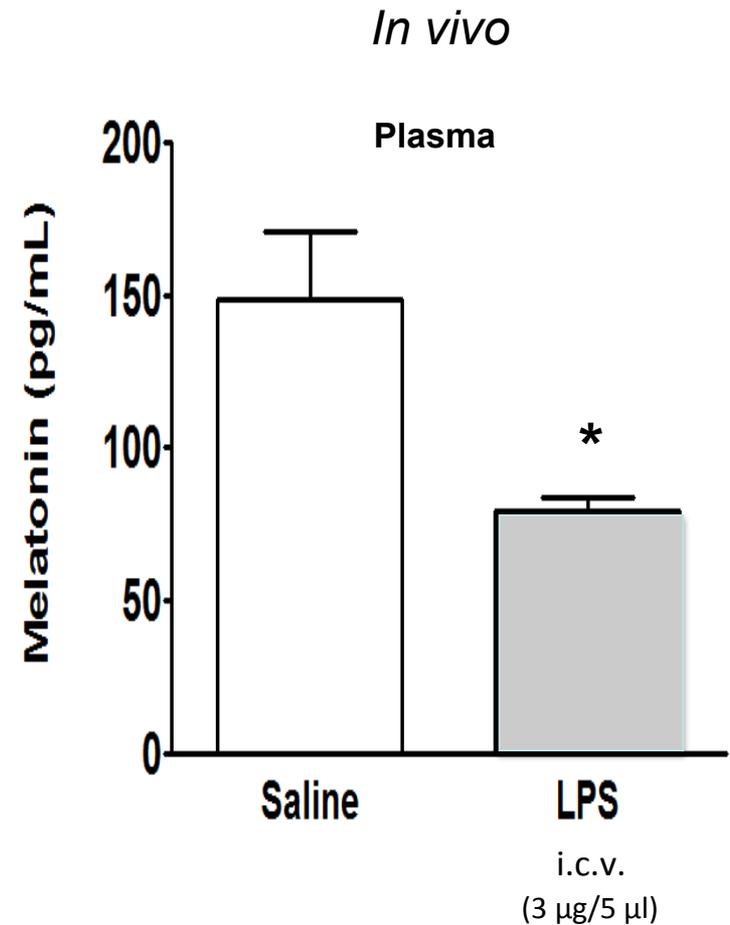
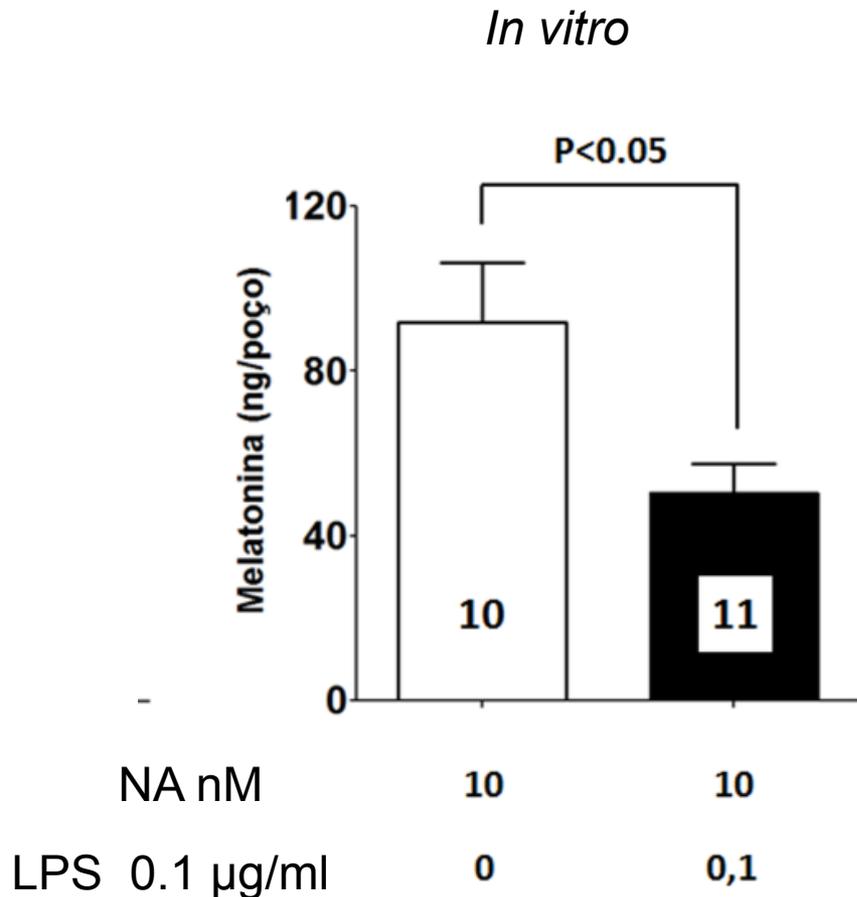
- 1. potentiates noradrenaline-induced melatonin synthesis
- 2. through an intracellular glucocorticoid receptor



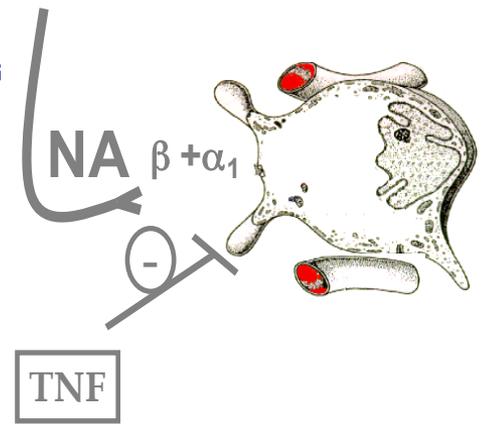
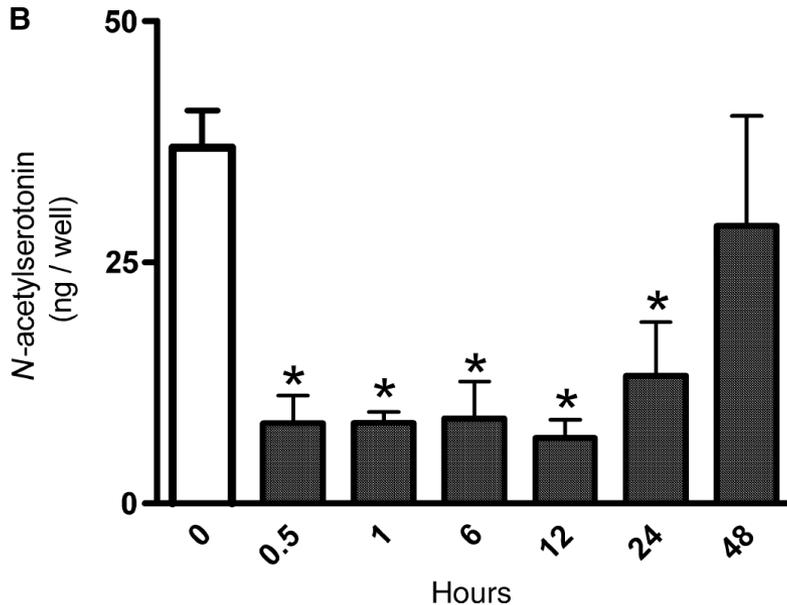
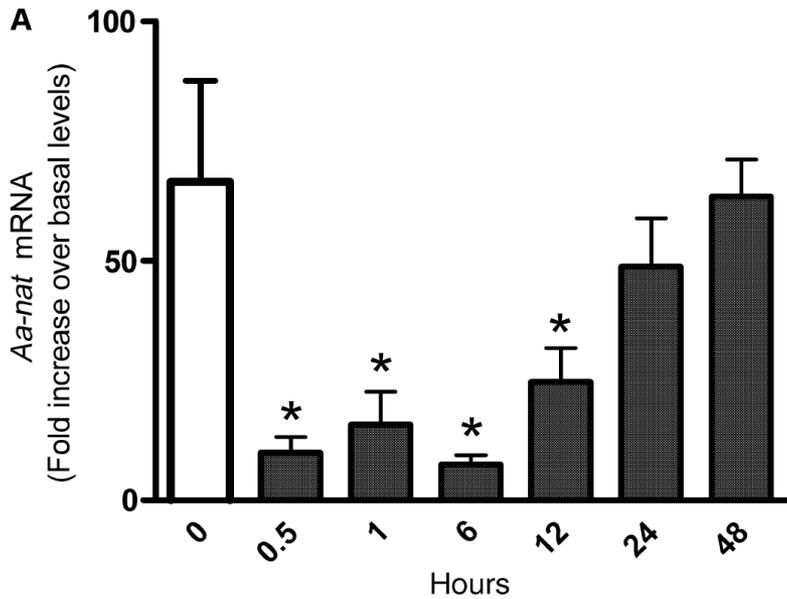
# Cellular expression of TLR4 in the rat pineal gland.



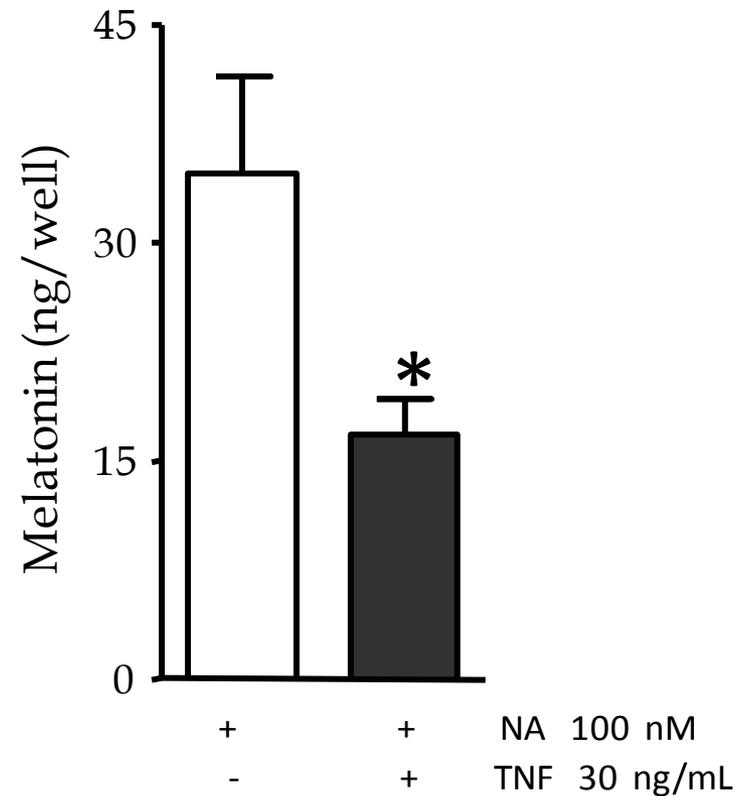
# LPS inhibits nocturnal pineal melatonin production



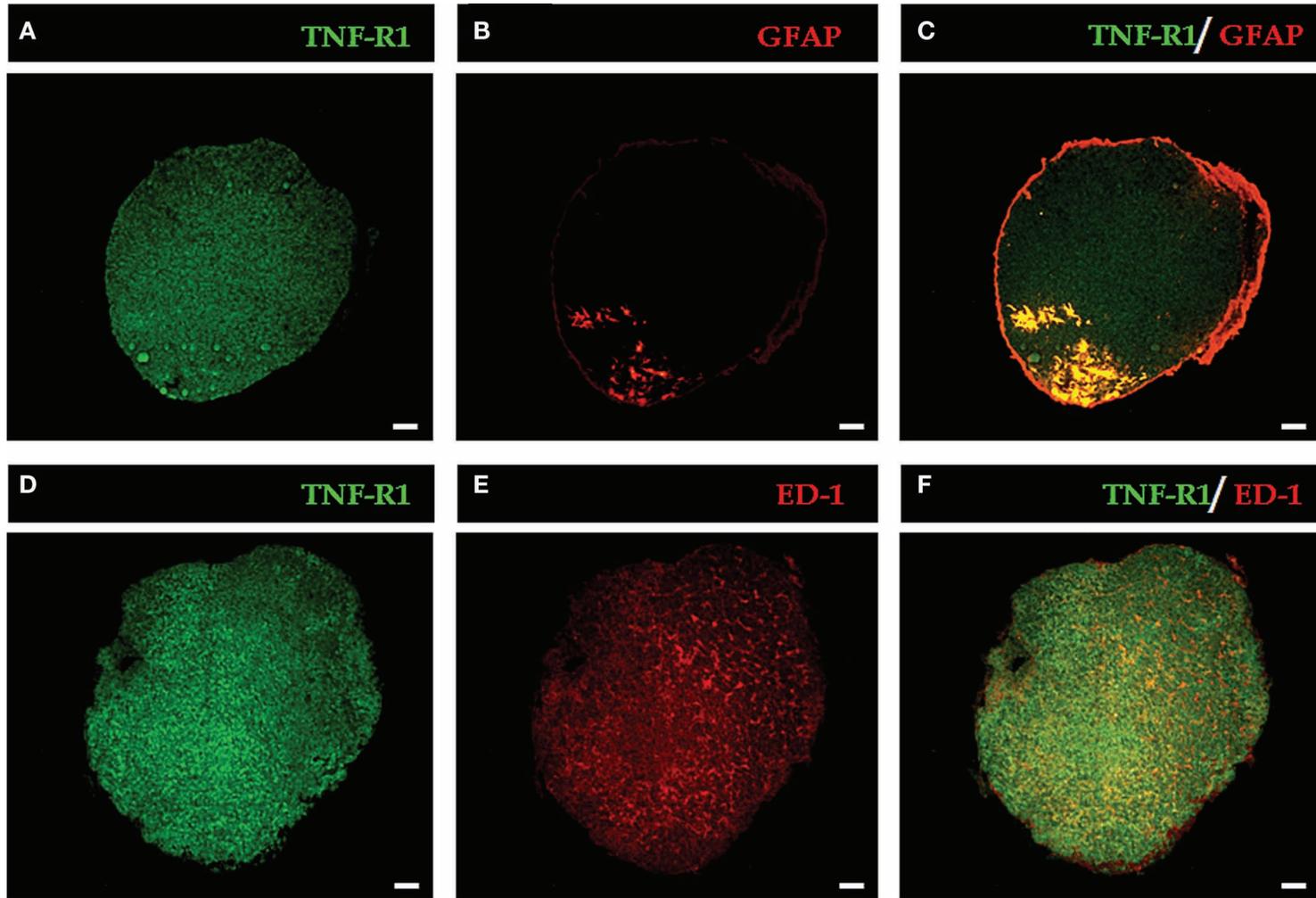
# A citocina TNF atuando na pineal



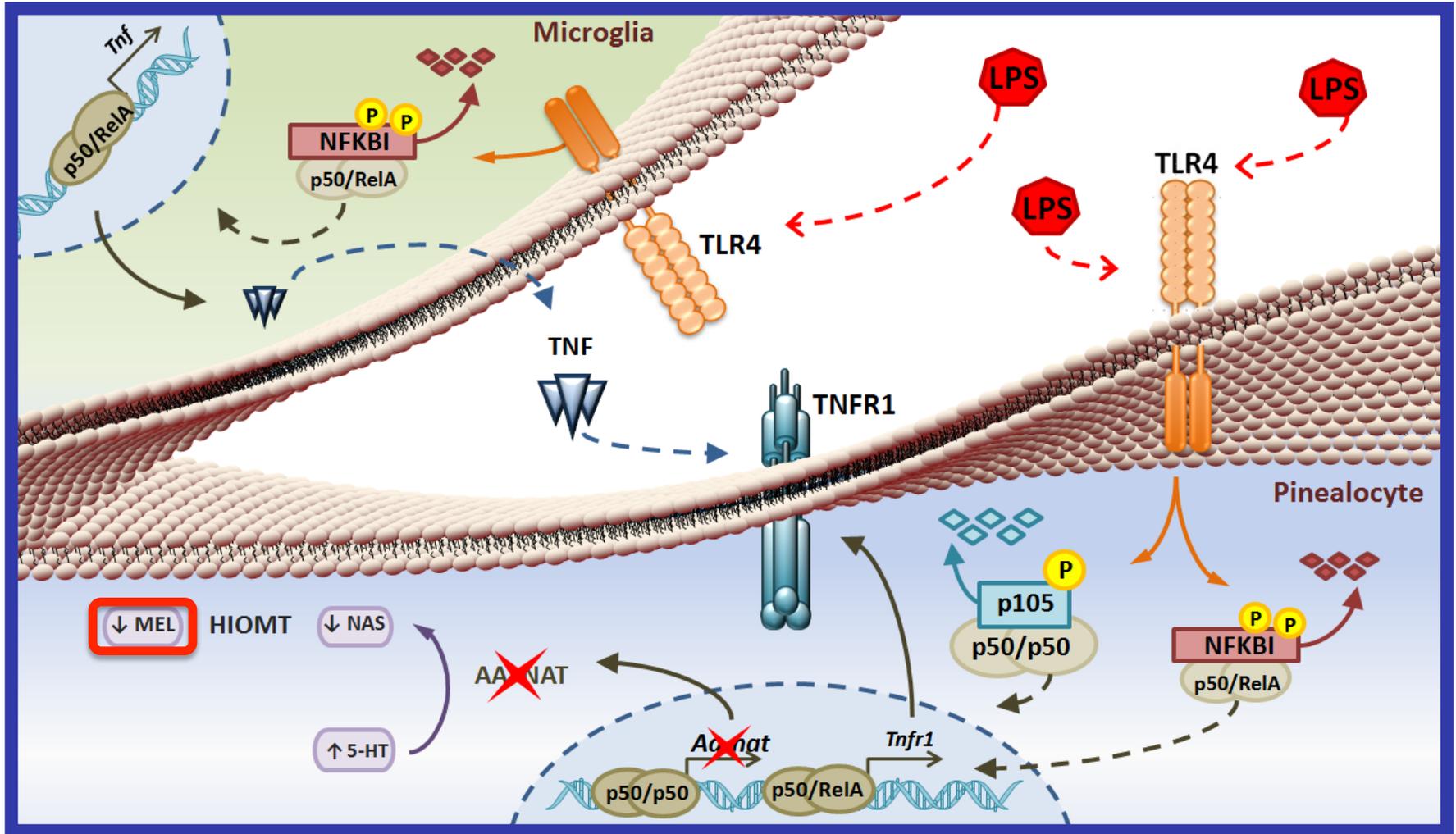
Fernandes *et al.*, 2006



# TNF-R1 DISTRIBUTION IN THE DIFFERENT CELL TYPES IN PINEAL PARENCHYMA



# LPS effect on rat pineal gland: TNF production



# TNF-R1 em pinealócitos

## TNF afeta diretamente a produção de melatonina

- ◆ *in vitro*

- ◆ dados clínicos (altos níveis de TNF circulante)

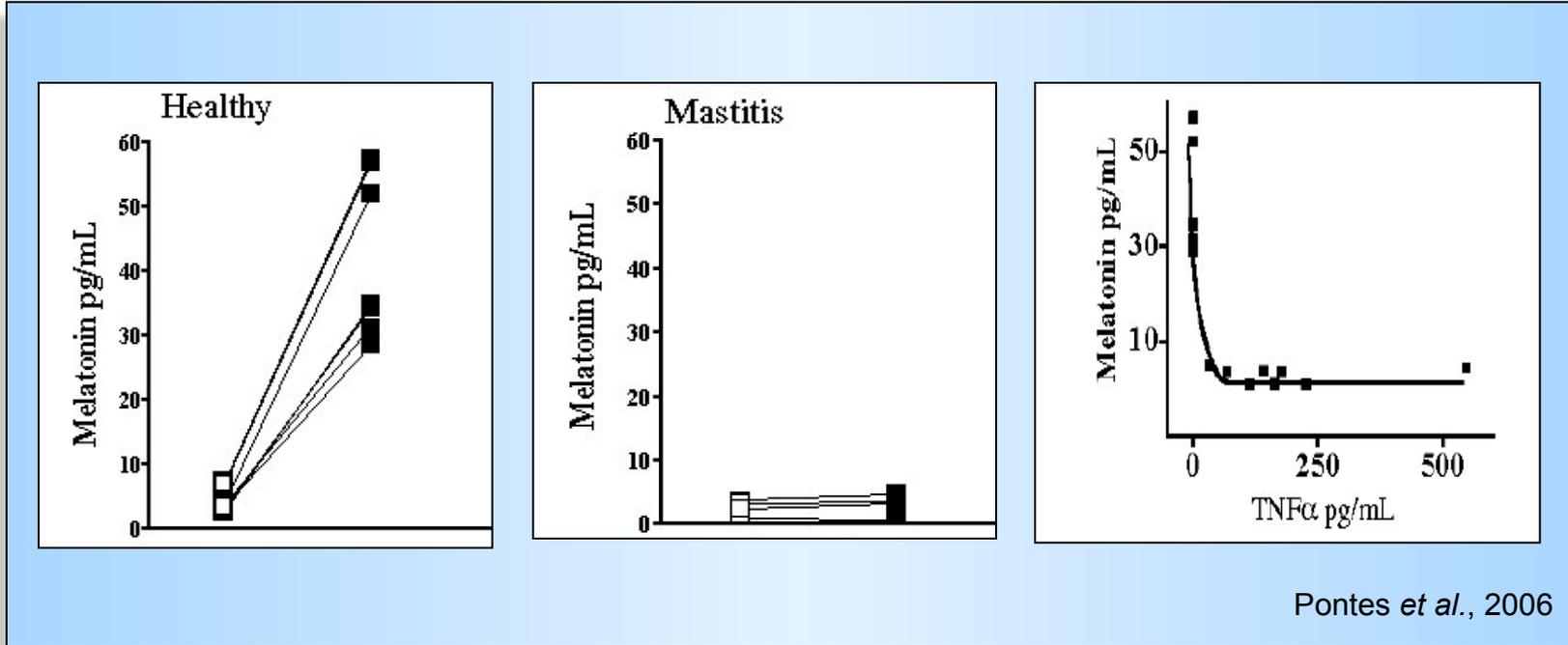
  - sepsis (Mundigler et al., 2002),

  - Infarto agudo do miocárdio (Domínguez-Rodríguez et al., 2002)

  - mastite (Pontes et al., 2006).

# TNF – controlling the nocturnal melatonin surge in humans

Mastitis → suppresses nocturnal MEL surge



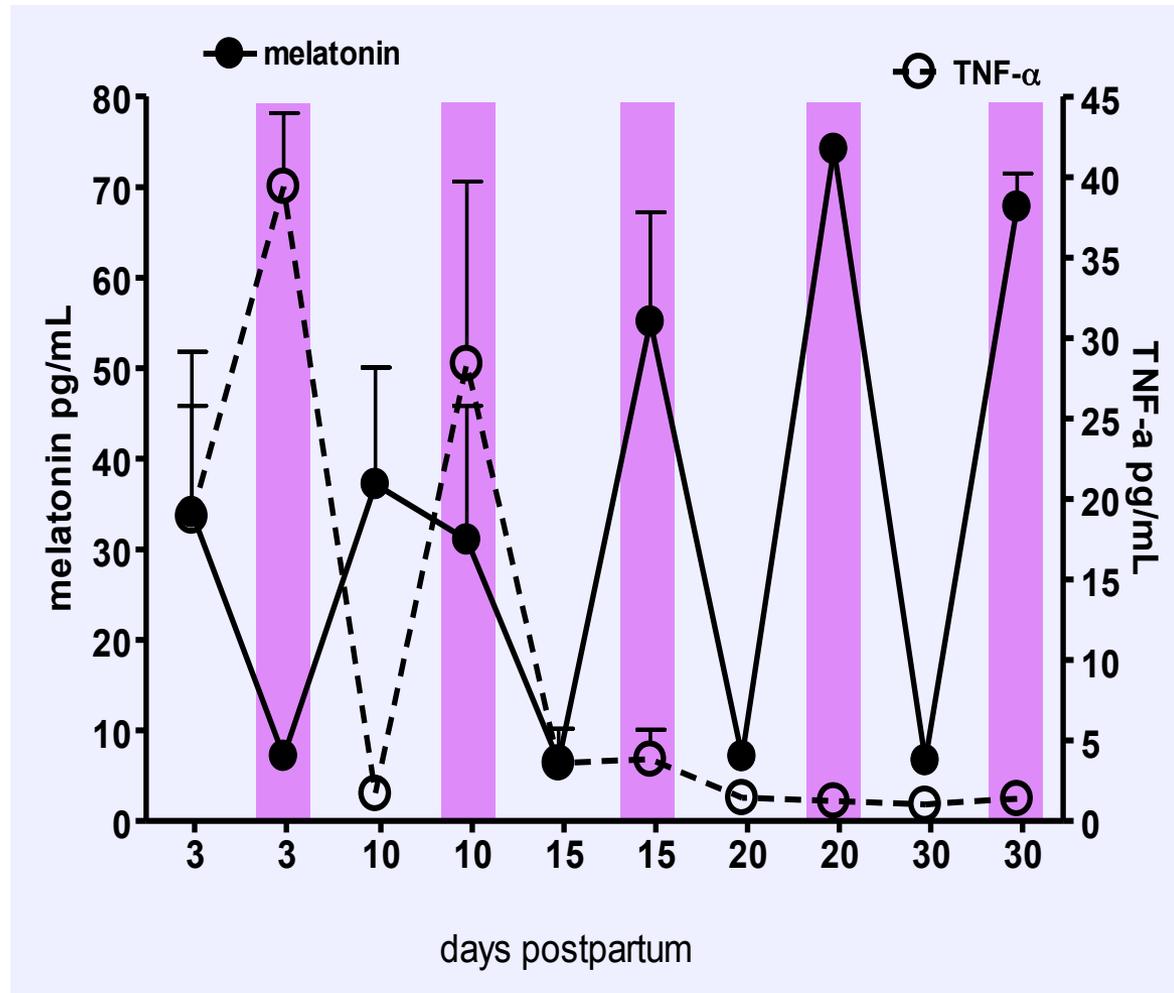
Pontes *et al.*, 2006

**Colostrum** (milk of the first days after delivery; contains cells) → day 3

Maternity Unit at the Obstetric Clinics – USP, Br.

The criteria for recently delivered mothers were: age (18–40), gestational age (37 weeks or more). All the mothers had given birth to healthy term babies.

# Restoration of daily rhythm of melatonin



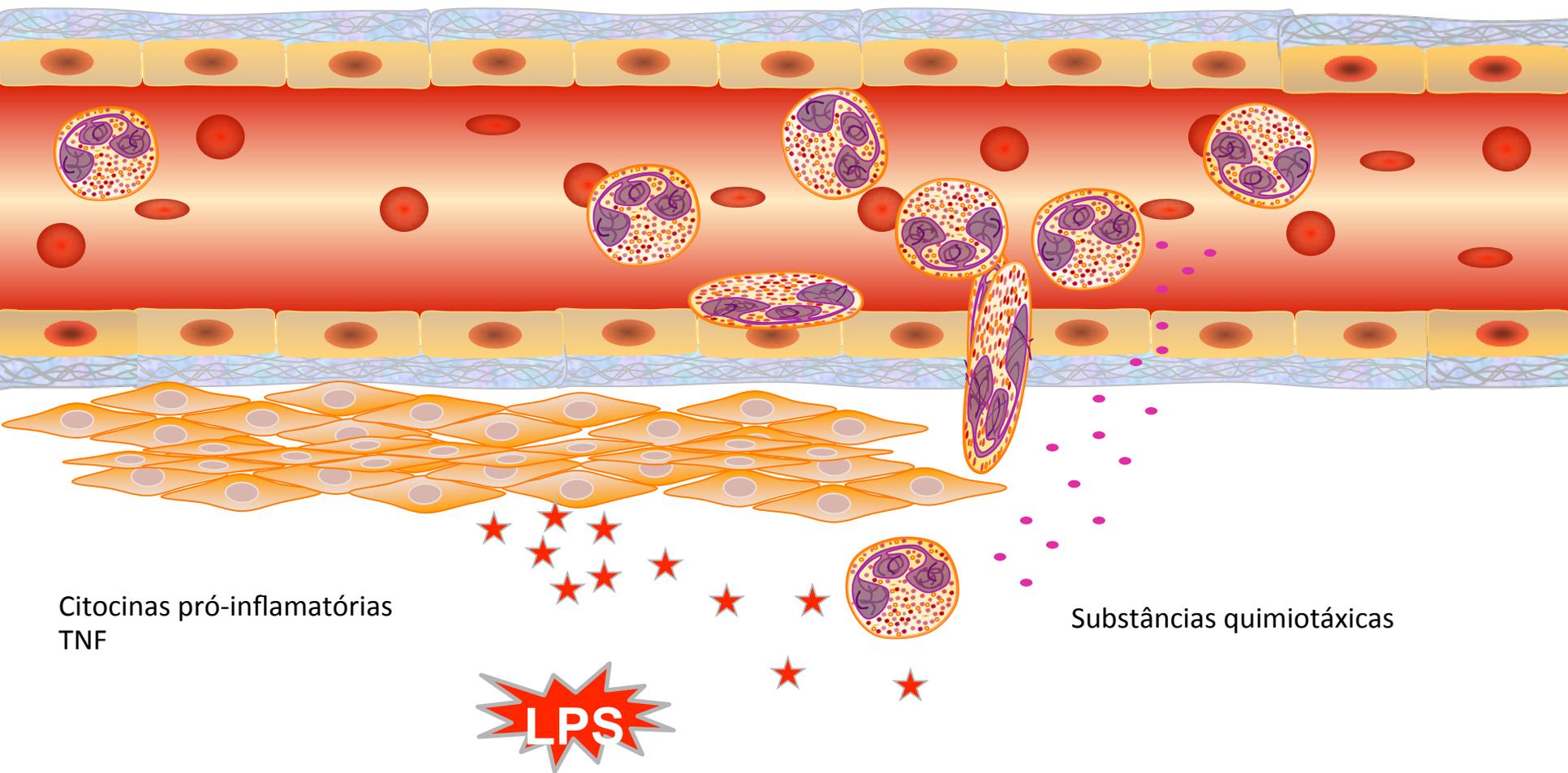
obtained after a great reduction in the levels of TNF- $\alpha$ .

# Supressão e/ou potenciação da síntese de melatonina

Quando ?

Por que ?

# Eventos que ocorrem em processos inflamatórios



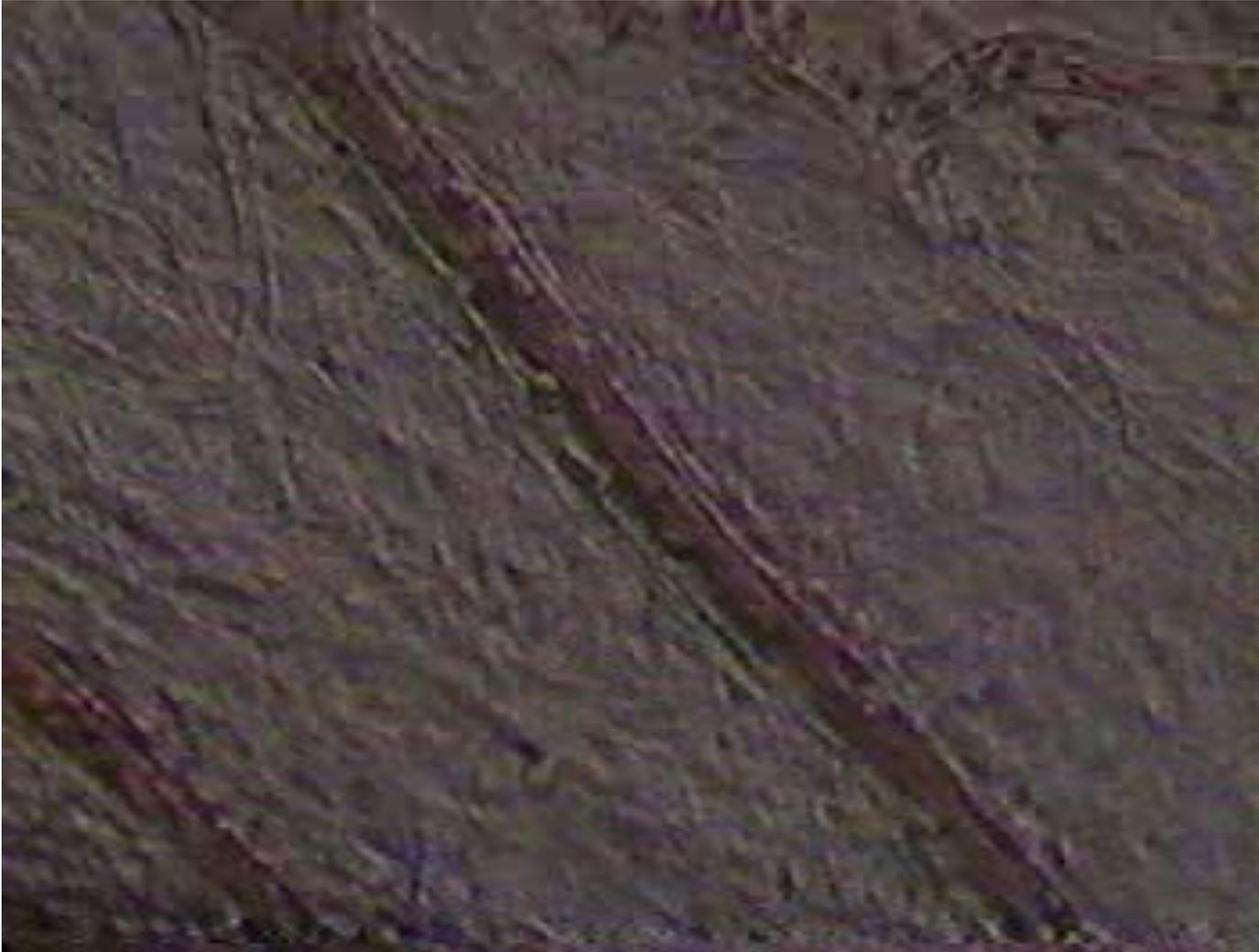
Citocinas pró-inflamatórias  
TNF

Substâncias quimiotáticas

**LPS**

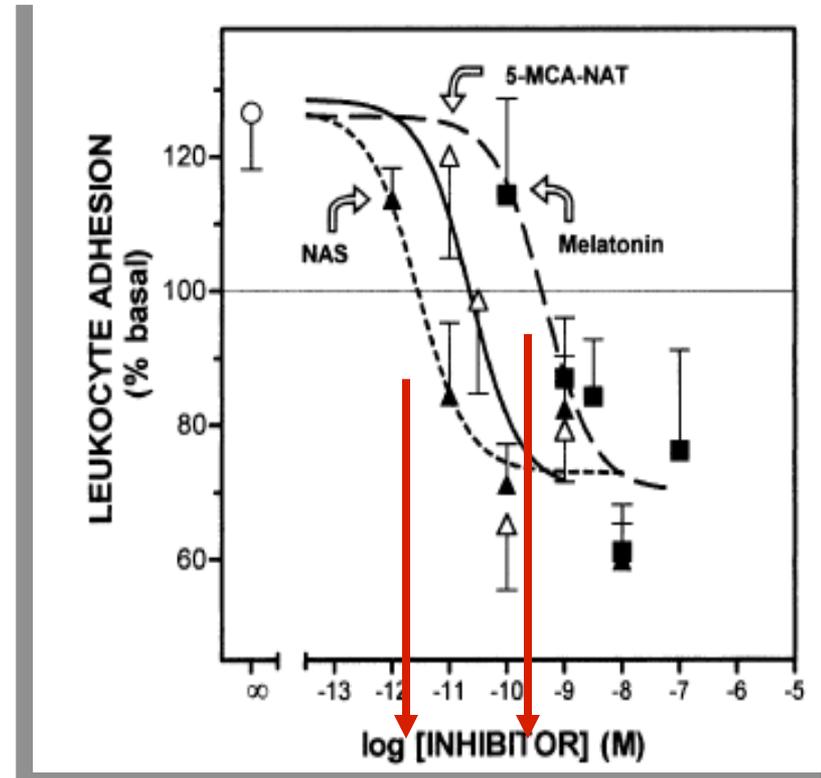
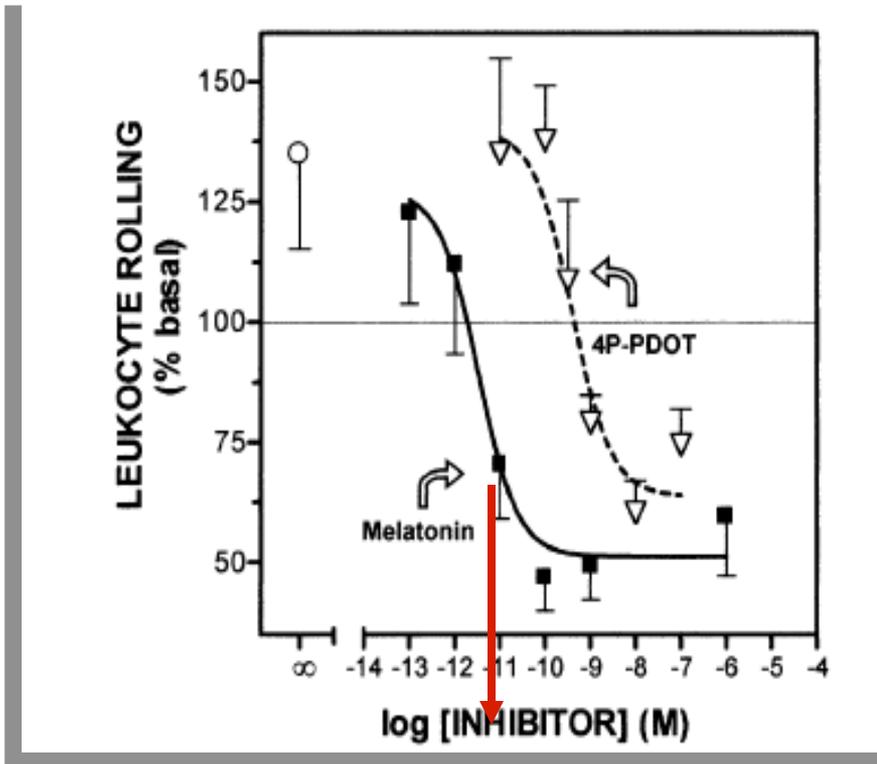
Processo Inflamatório

# Melatonina atua no rolamento e adesão de leucócitos

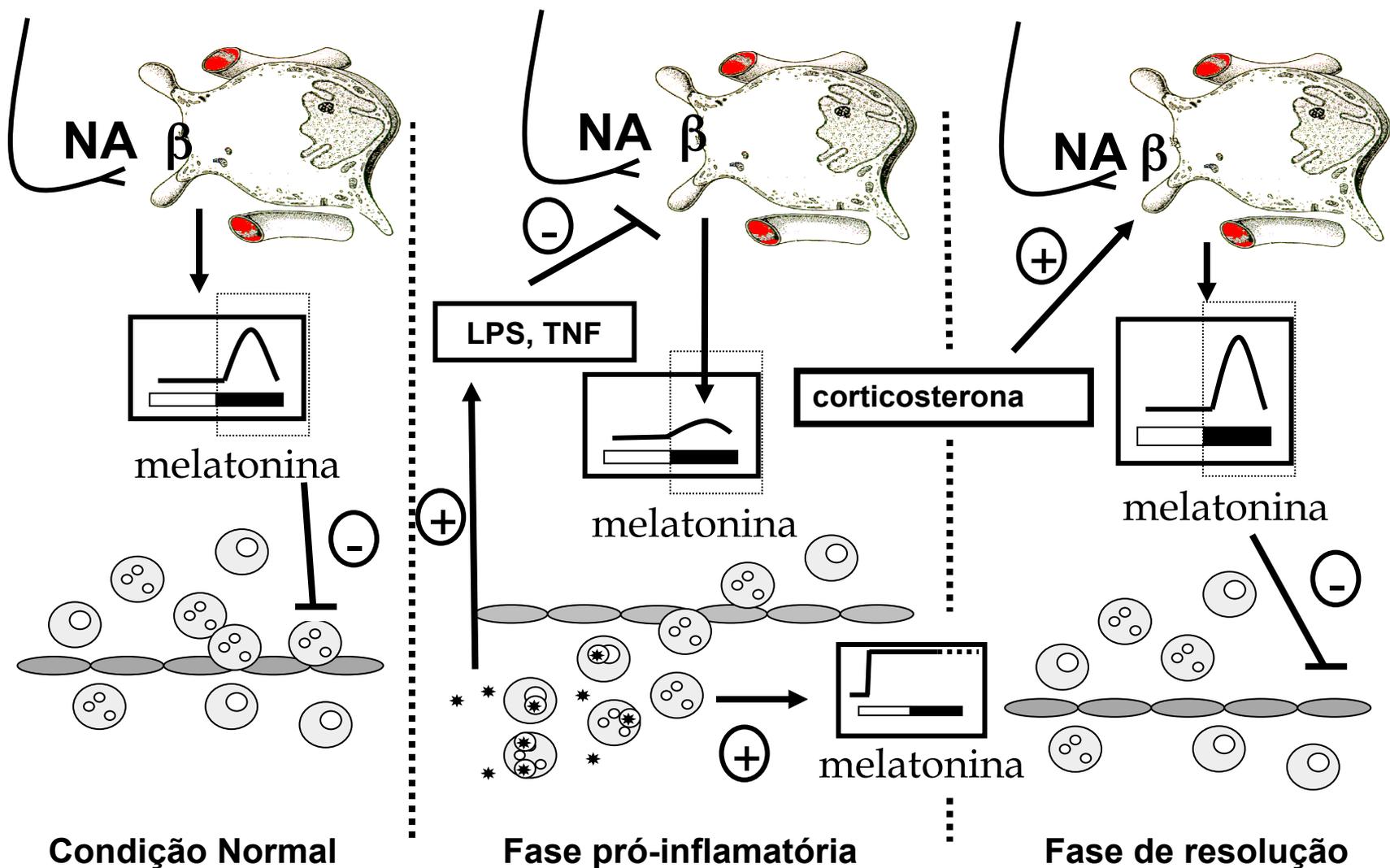


# Melatonina

## Inibição do rolamento e adesão de leucócitos



# Eixo Imune-pineal



# SISTEMA NEUROIMUNOENDÓCRINO

## Comunicação bidirecional

