

BIF 214

Fisiologia Animal:

*Mecanismos e Adaptação do Controle Interno,
Reprodução e Defesa*

Cronobiologia no sistema endócrino

Cronobiologia

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

Ritmos Biológicos

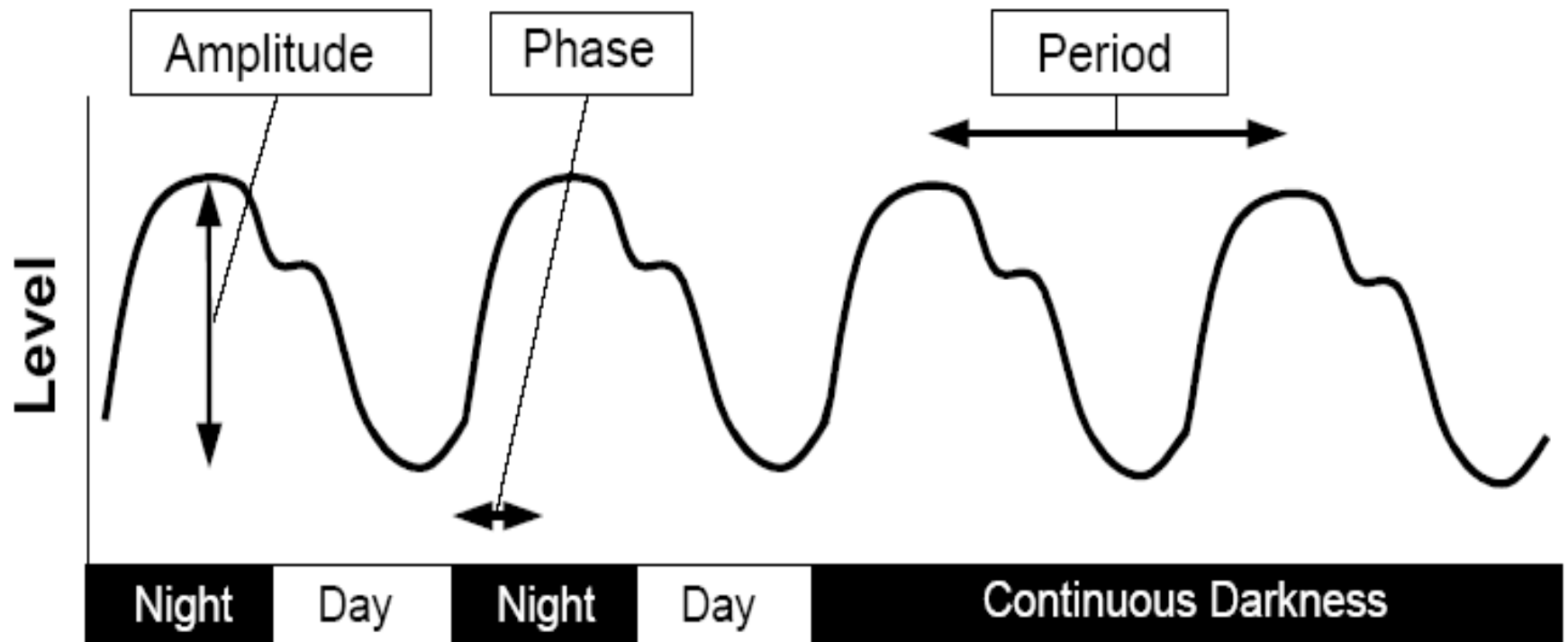
Circadianos - períodos de ~ 24 h
atividade locomotora

Infradianos - baixa frequência
período > 28 h

Ultradianos - batimentos rápidos
período < 20 h

Circanual

Parâmetros de um Ritmo Circadiano



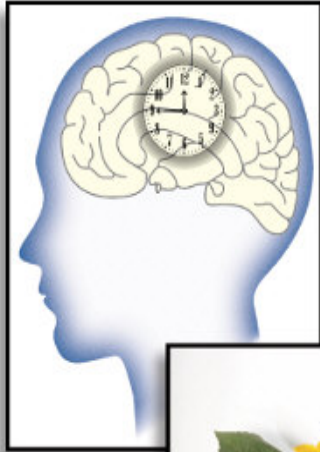
Demonstração de ritmo por Jean Jacques d'Ortous de Mairan em 1729



Por que ter um relógio endógeno?

Permite antecipação

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

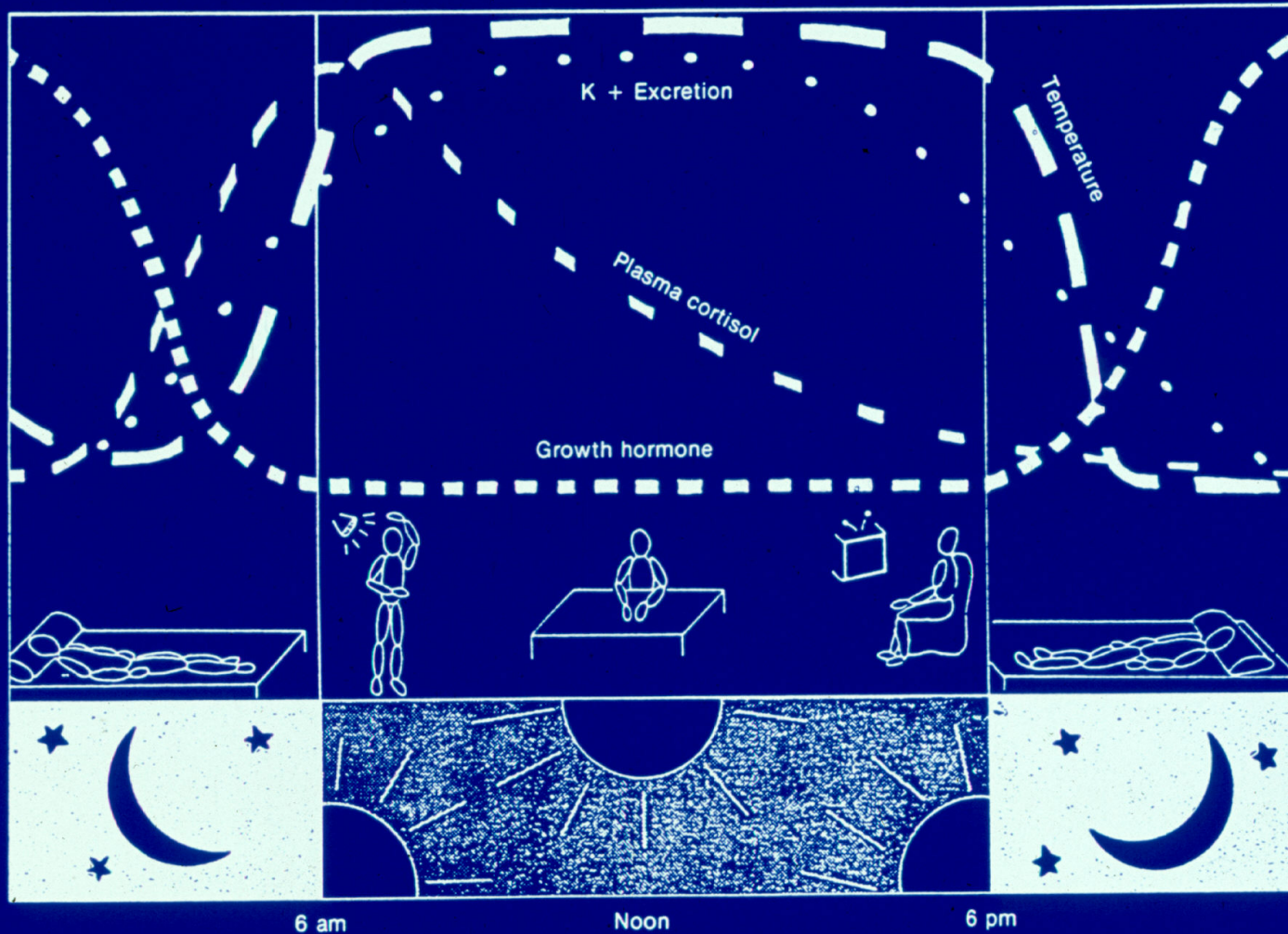


Confere vantagem seletiva

- 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.

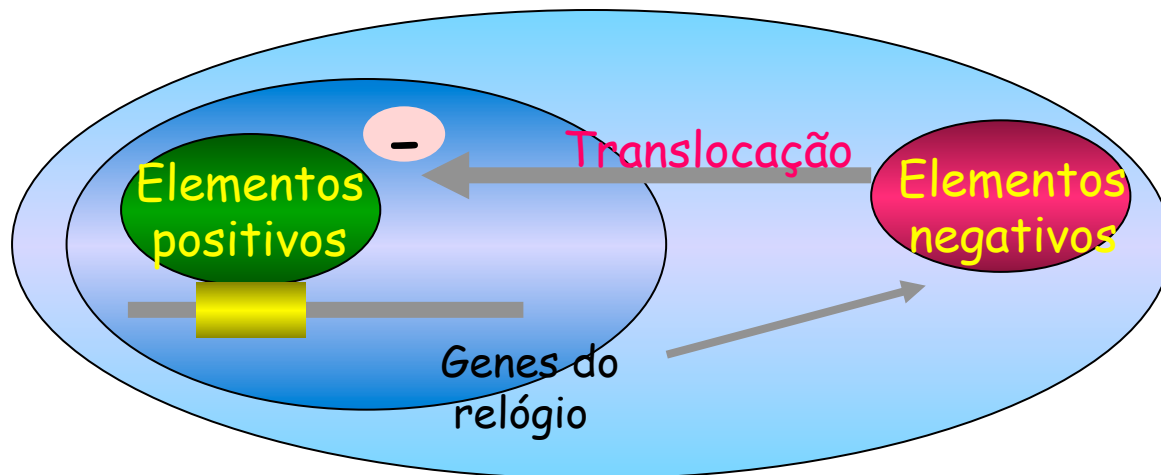
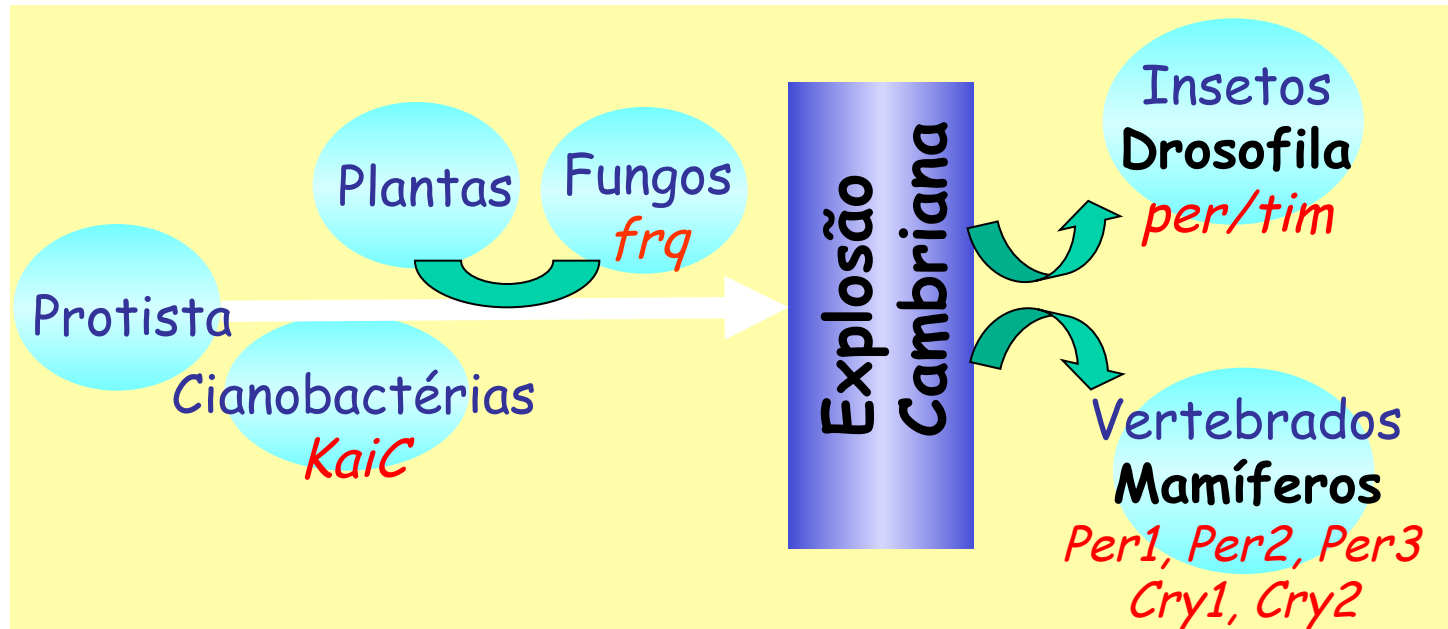
SOURCE: Adapted from G.S. Richardson and J.B. Martin, "Circadian Rhythms in Neuroendocrinology and Immunology: Influence of Aging," *Progress in NeuroEndocrinImmunology* 1:16-20, 1988.

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.

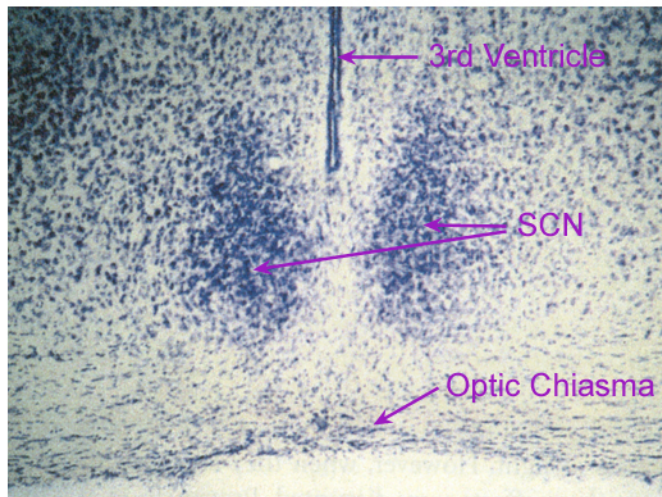
(Yan et al., 1998)

Ritmos Circadianos são gerados por genes do relógio



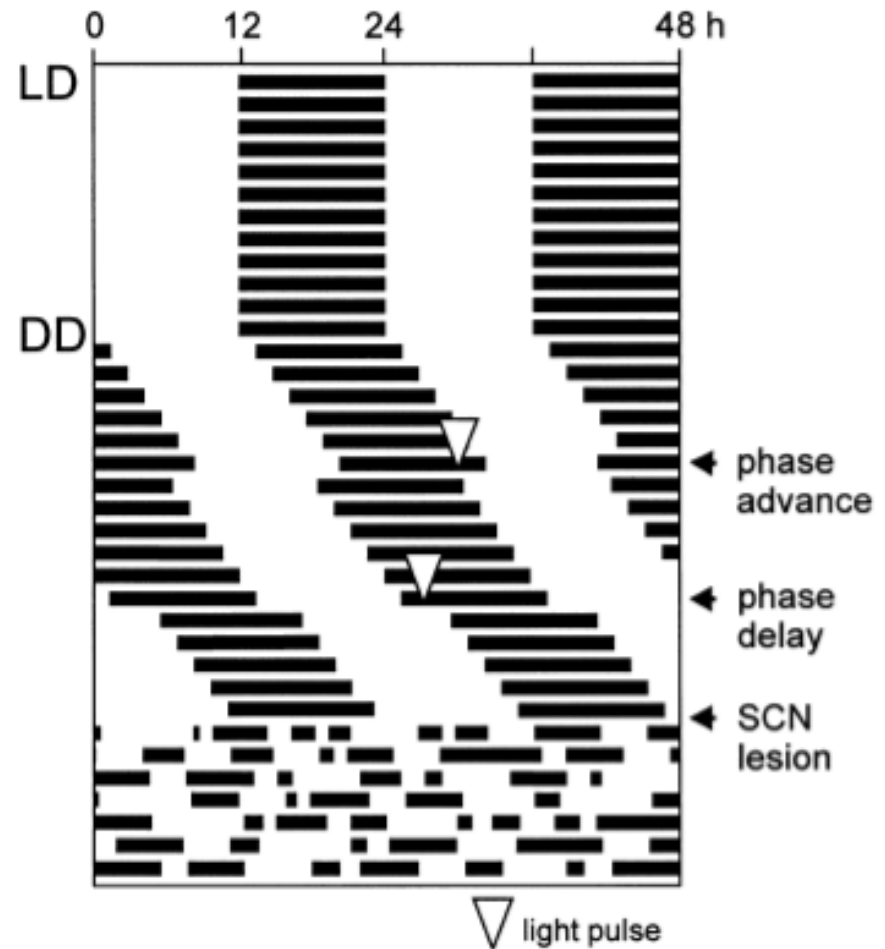
Núcleos Supraquiasmáticos - Principal relógio em mamíferos

SCN is a Neural Clock

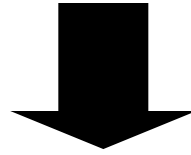


Características

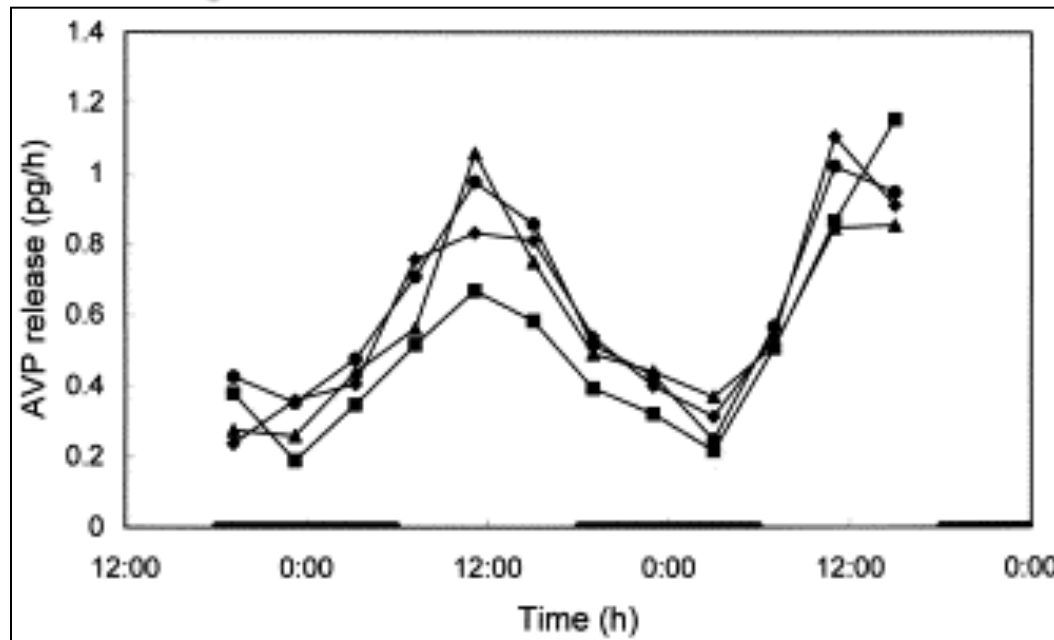
- mantido em condições constantes continua ciclando.
- sincronização entre o meio ambiente e o meio interno



O relógio pode funcionar fora do organismo

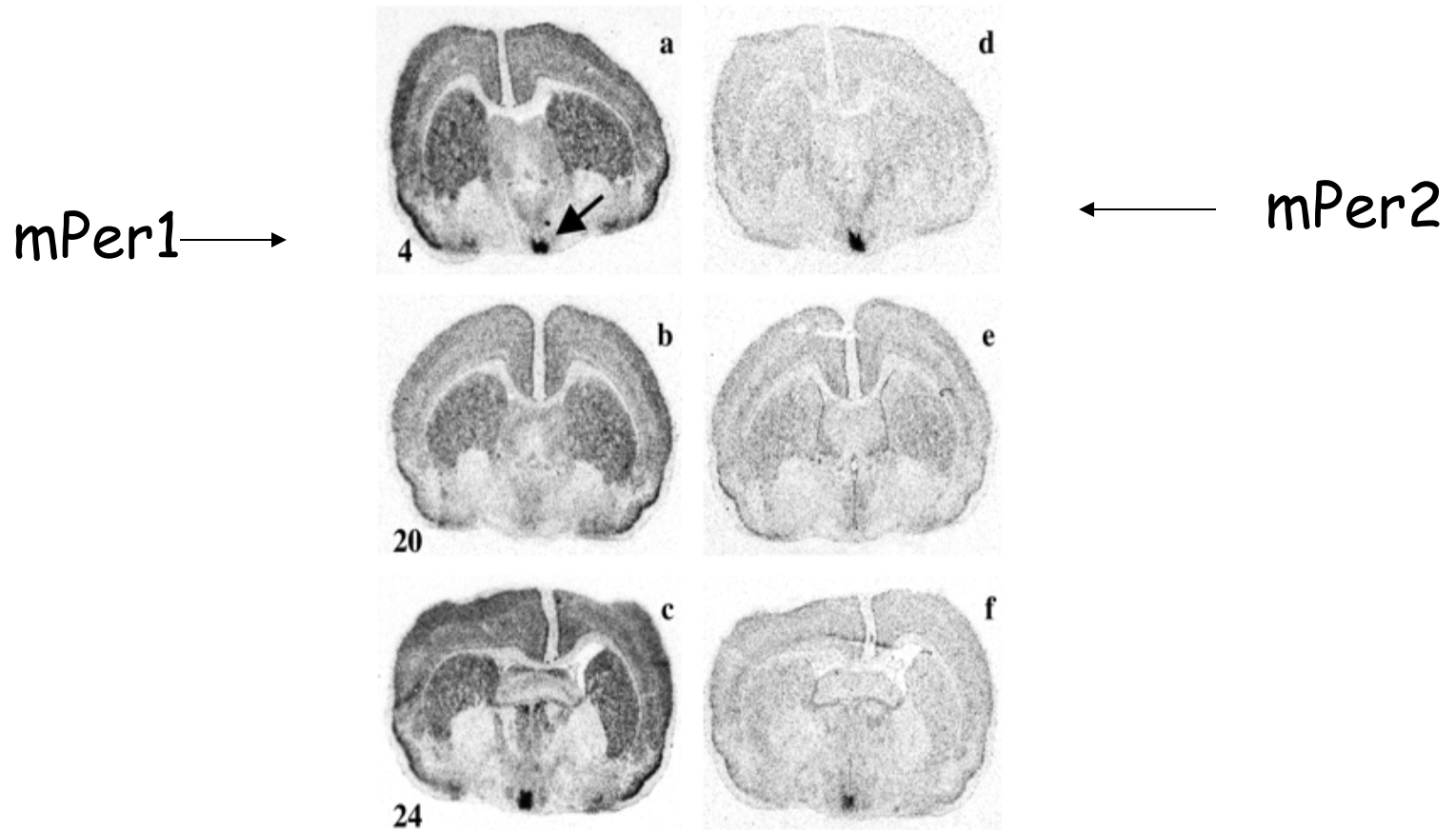


NSQ "in vitro" também cicla



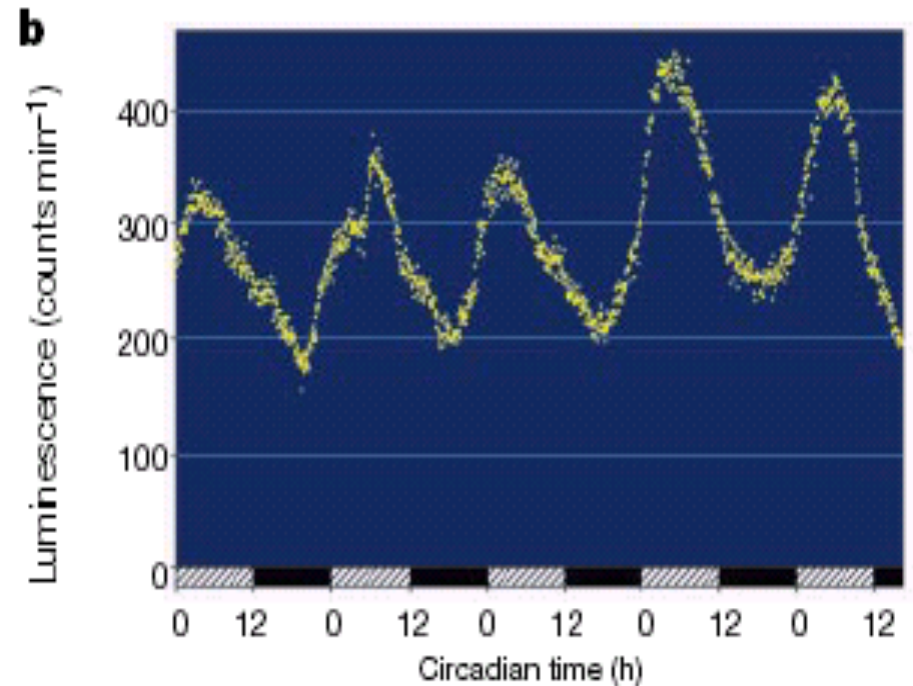
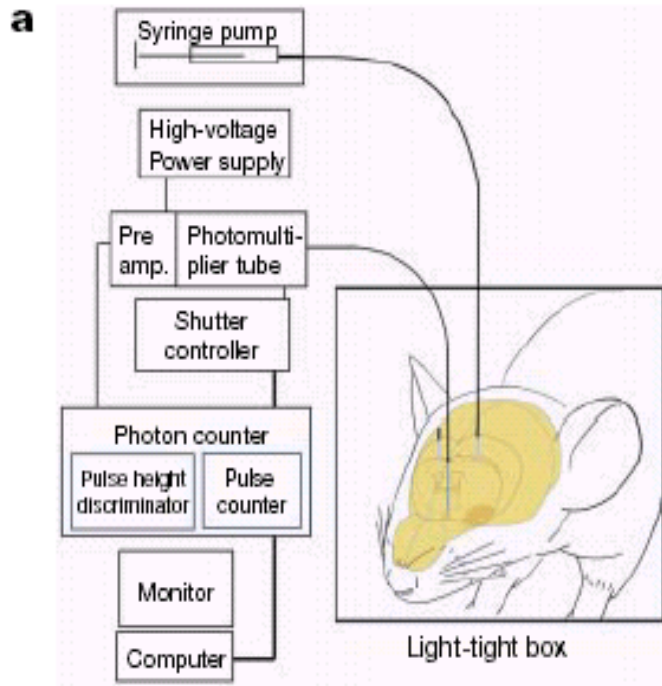
Oscilação circadiana da liberação de AVP de neurônios vasopressinérgicos localizados na porção dorso-medial do NSQ. Células isoladas de animais mantidos em 12:12 - medidas iniciadas logo após início da cultura

Expressão rítmica de mPer1 e mPer2



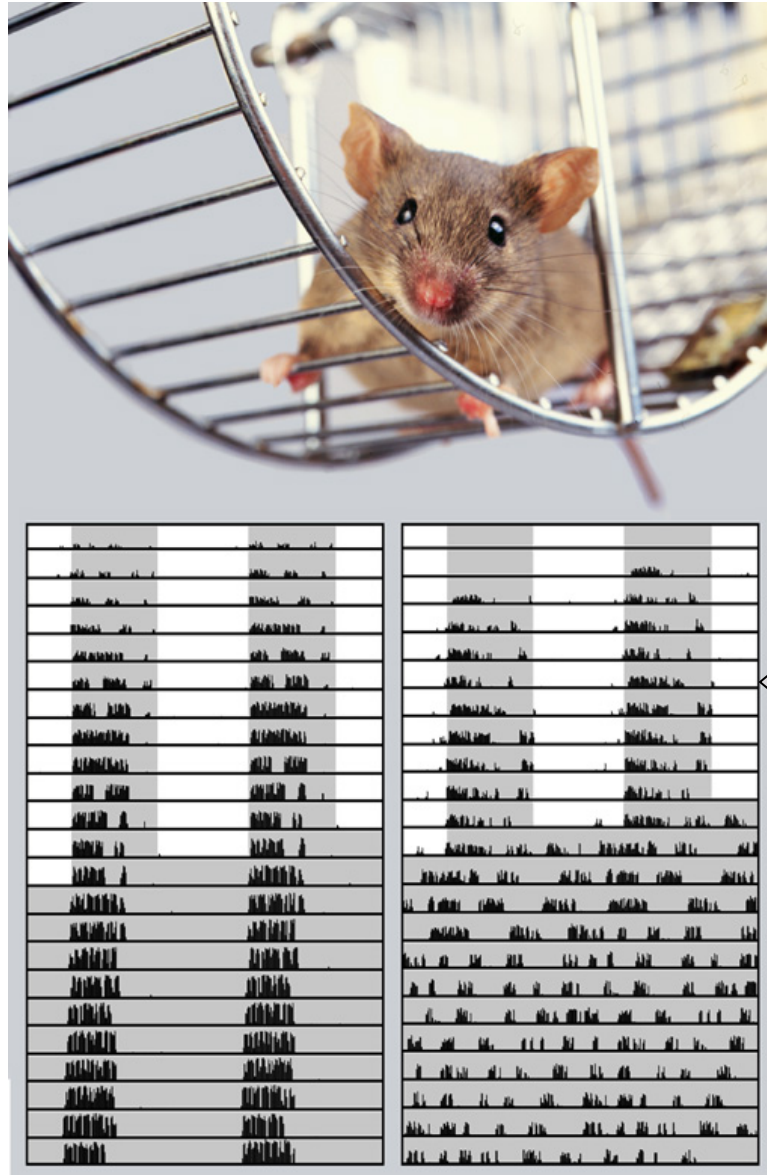
NSQ - Secção coronal

Expressão rítmica de mPer1 “in vivo”



transgênico que expressa mPer1-luc

Flutuação circadiana da bioluminescência
no NSQ



normal

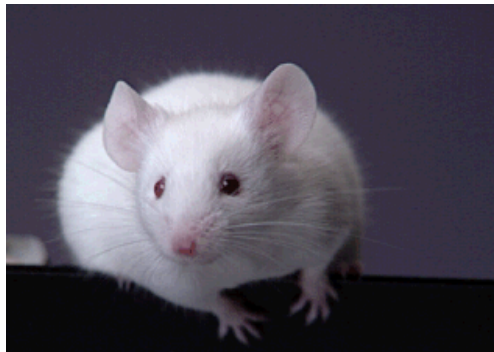
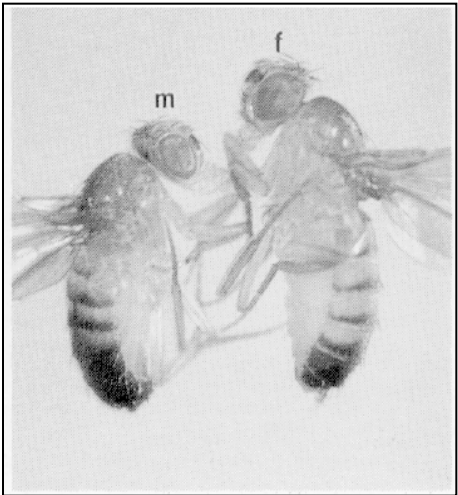
~~cry1 e cry2~~

Genes do Relógio Circadiano

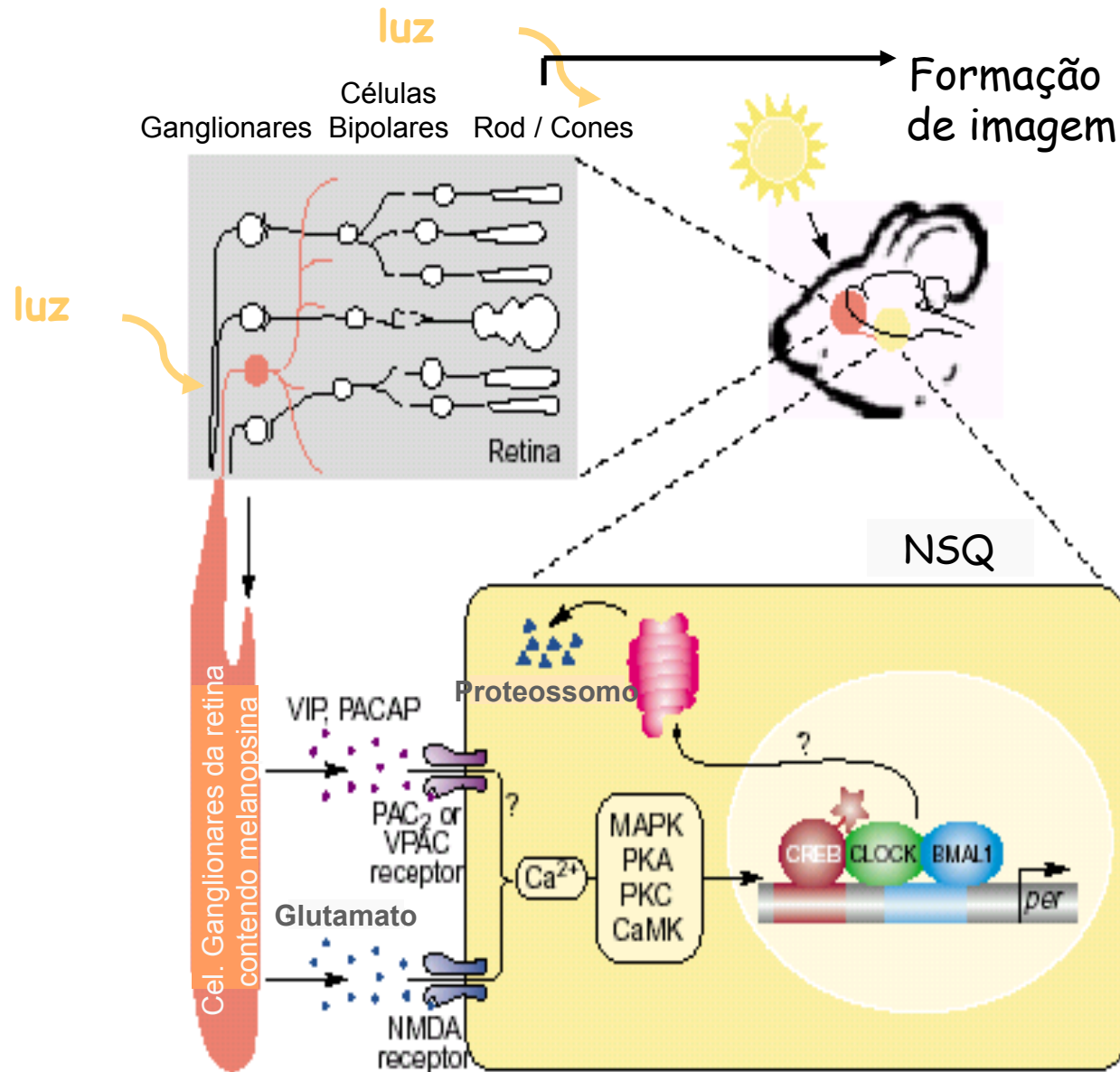
- Altamente conservados entre *Drosophila* e mamíferos
- Possuem uma alça de feedback autoregulatória com translocação de proteínas para o núcleo
- A proteína PER regula negativamente a transcrição de seu próprio RNAm
- As velocidades de transcrição e/ou degradação dos genes são sensíveis à luz

Interface entre o Ambiente e o Relógio - Fotorrecepção

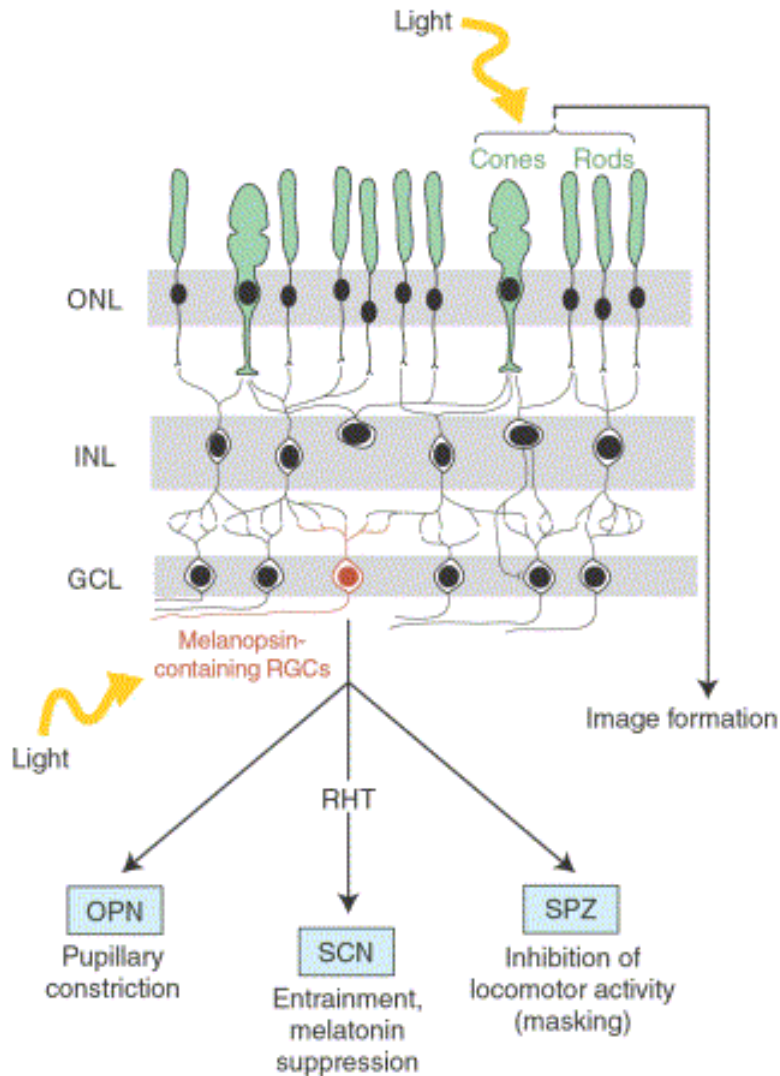
- Retina
- Pineal
- Regiões encefálicas profundas
- Órgão Frontal/Parietal (extracranianos)



Distintos fotorreceptores na retina de mamíferos



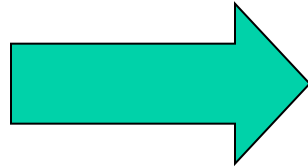
Distintos fotorreceptores na retina de mamíferos



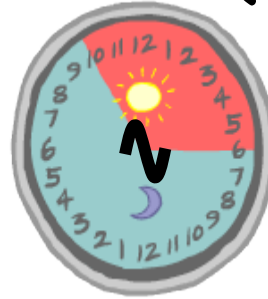
Current Opinion in Neurobiology

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

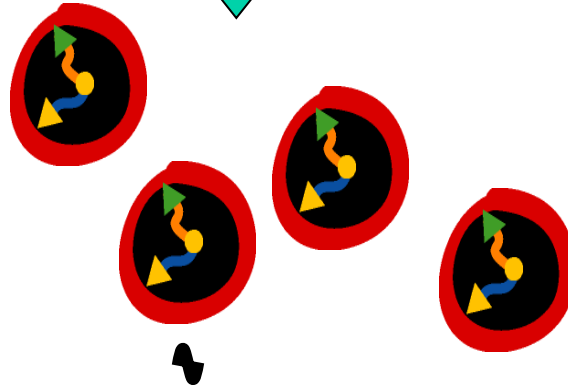
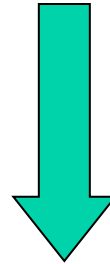


NSQ



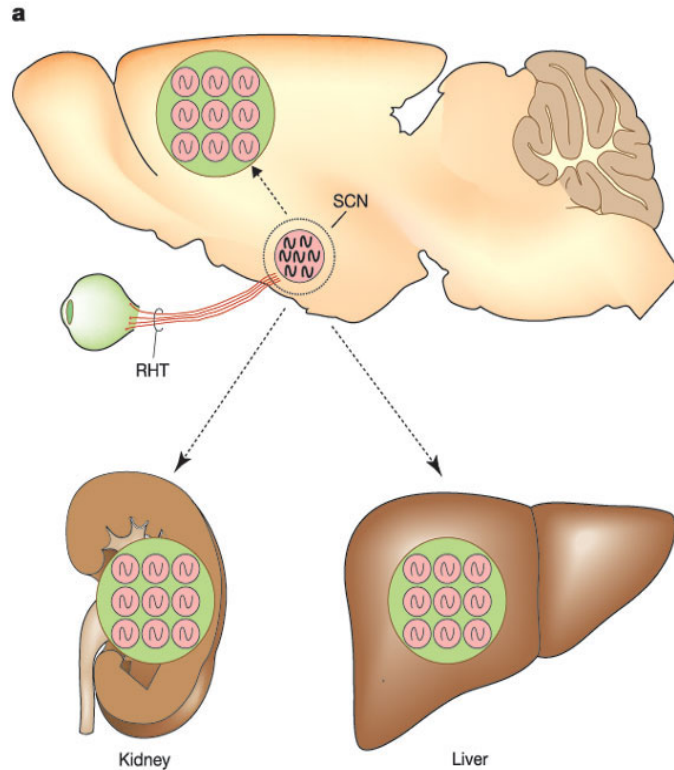
Neural

Humoral

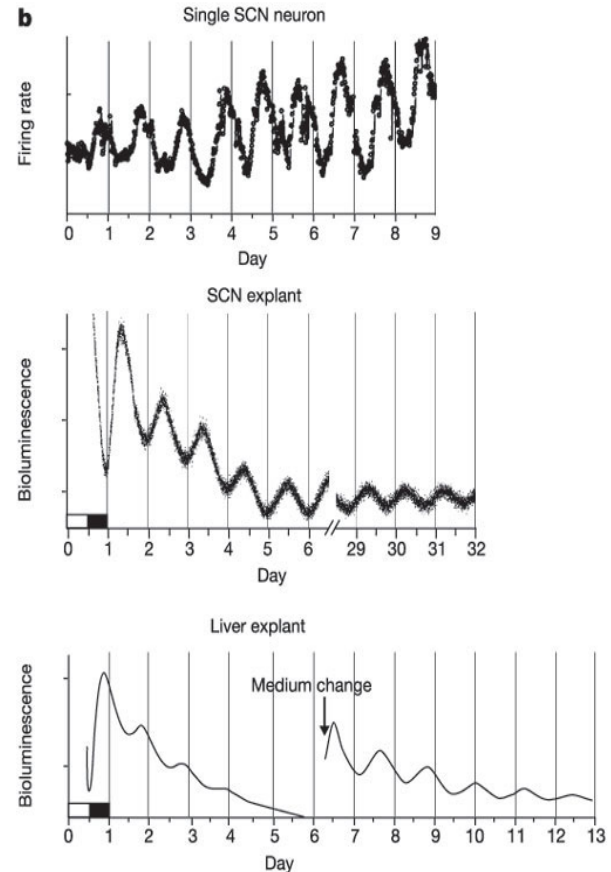


Distribuição hierárquica de relógios

Múltiplos osciladores circadianos hierárquicos

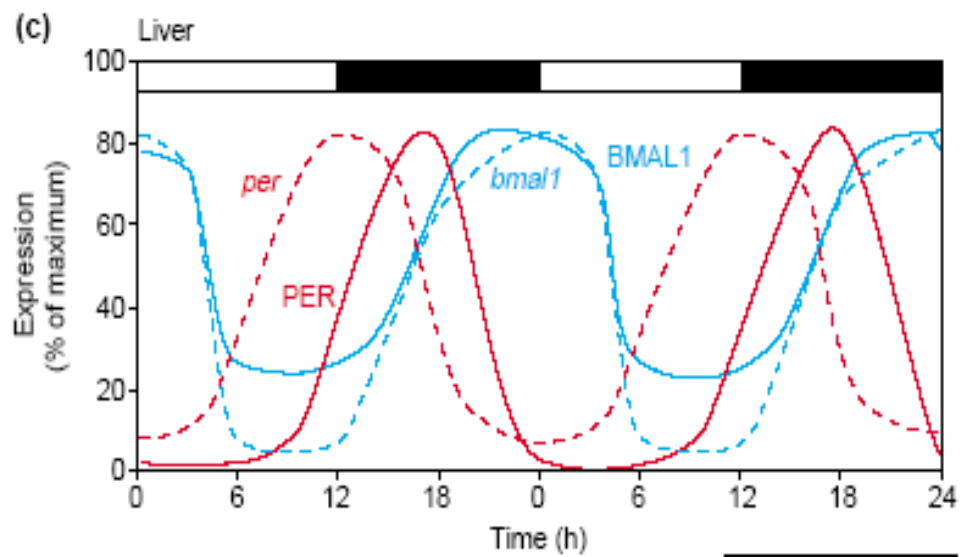
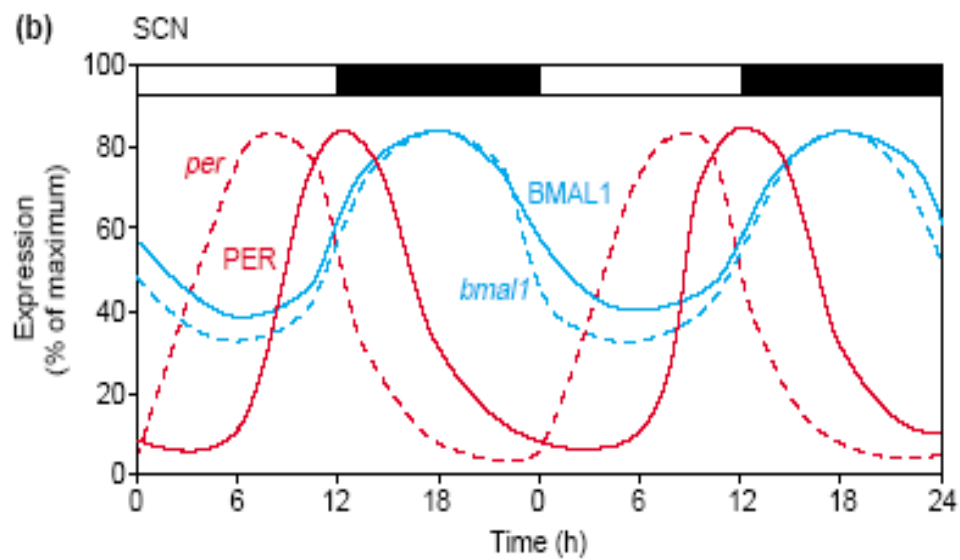


cada célula é o oscilador

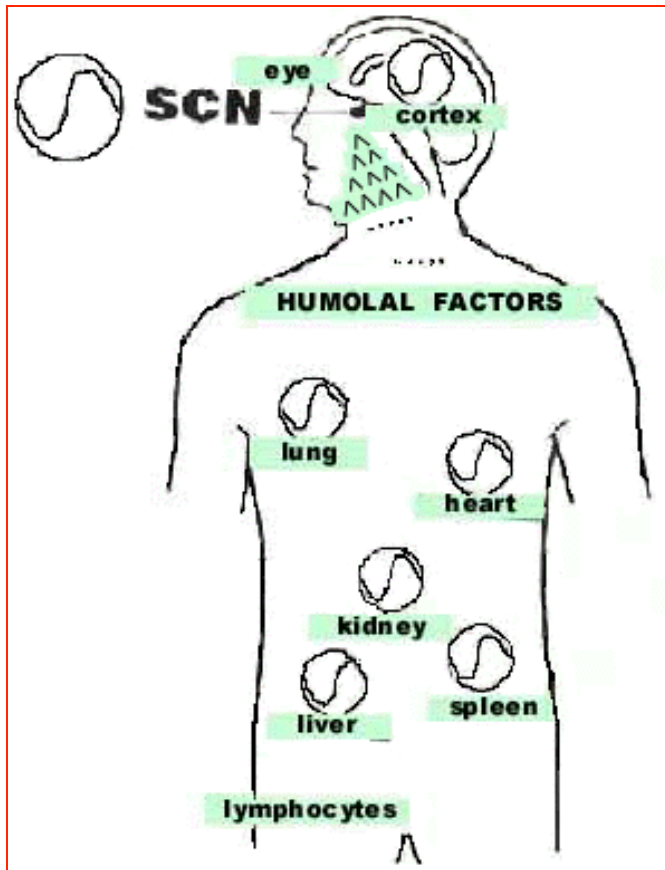


Componentes bioquímicos responsáveis pelos servo-osciladores e pelo oscilador principal são muito semelhantes

Reppert & Weaver, 2002



O SCN é responsável por vários ritmos fisiológicos



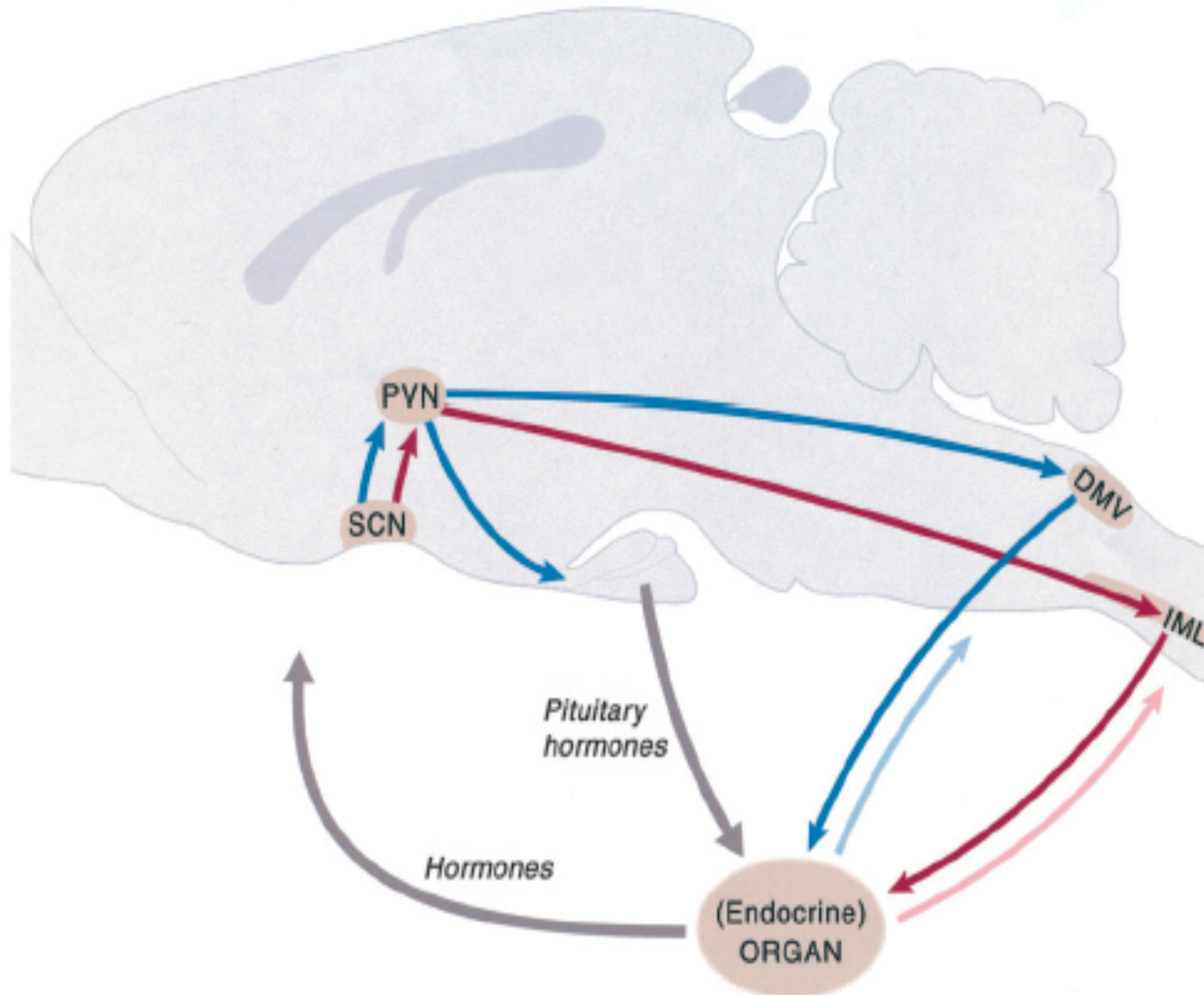
Lesão dos SCN afetam:

- 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

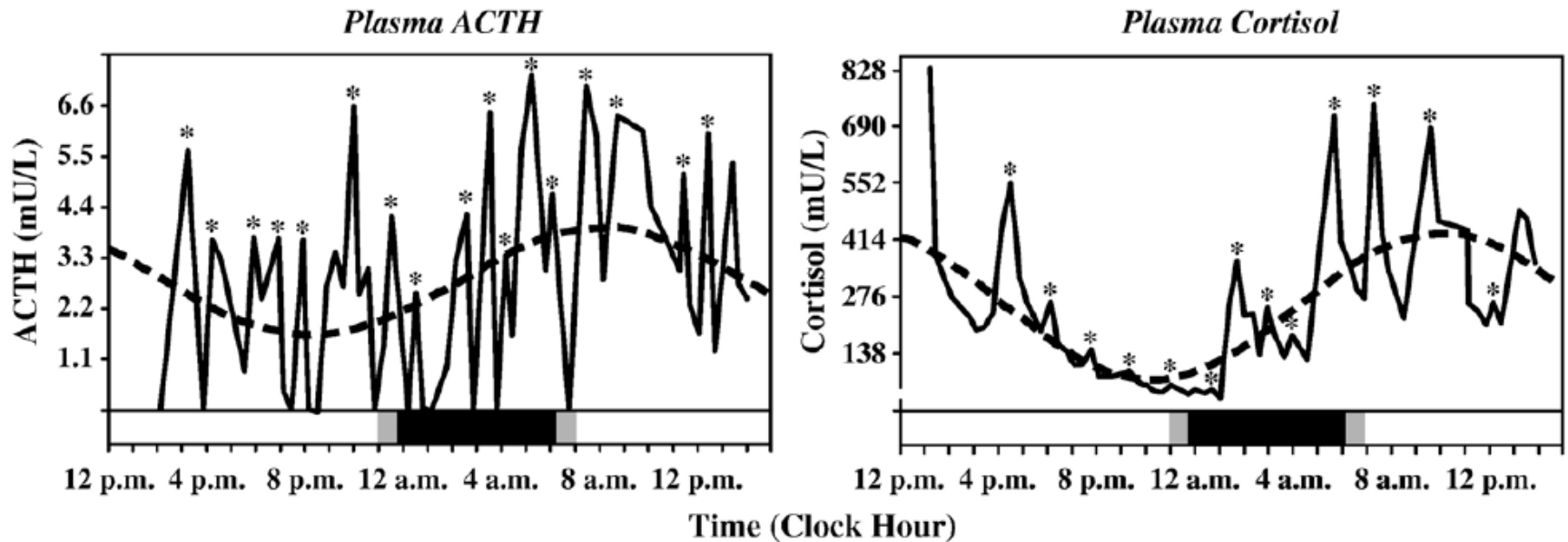
Comunicação circadiana para o organismo

Comunicação circadiana para o organismo



Neurônios neuroendócrinos - projeções parassimpáticas - projeções simpáticas

Variação circadiana e pulsátil de ACTH e cortisol

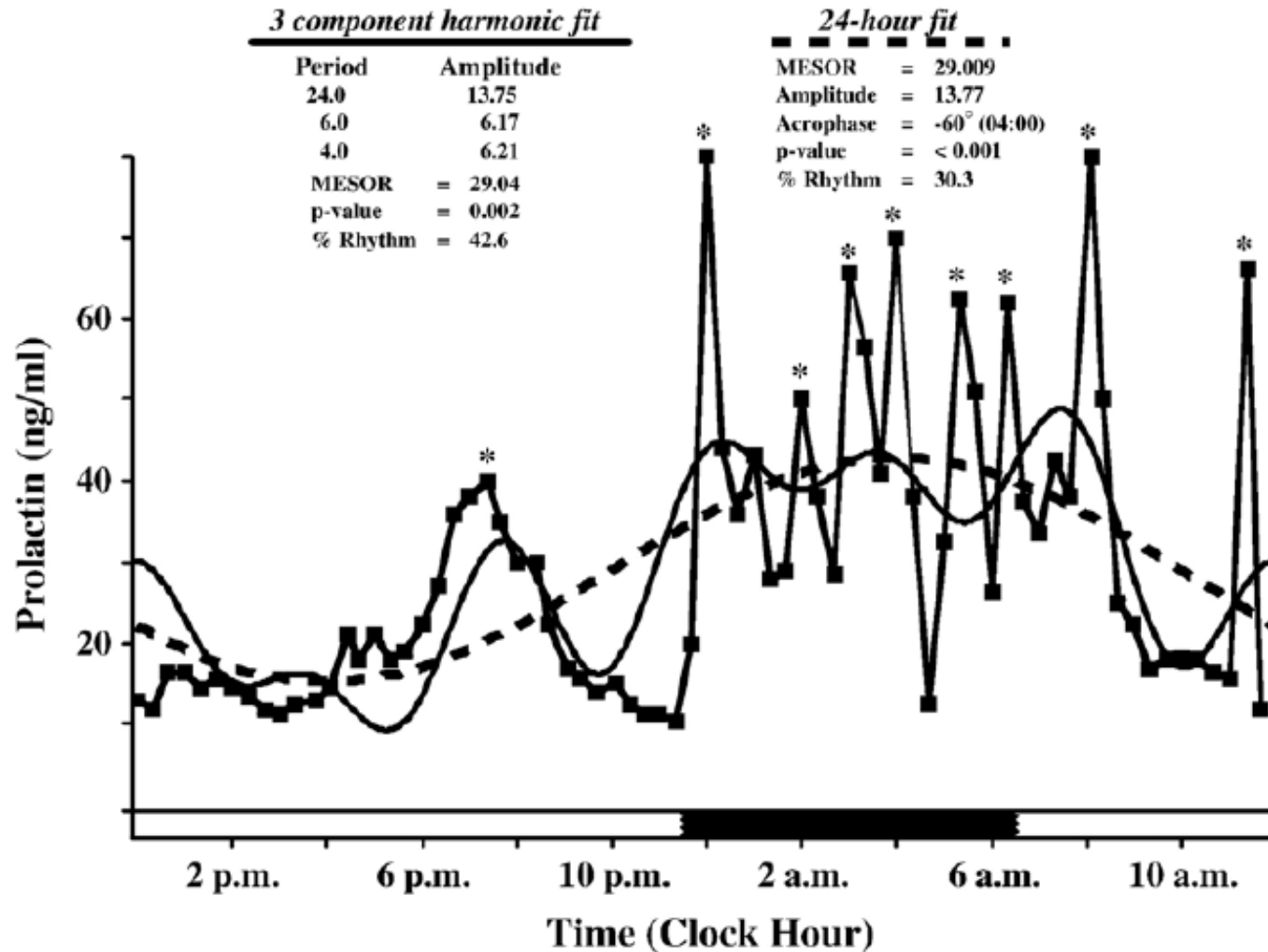


- ◆ Secreção pulsátil superimposta e modulada por um ritmo circadiano
- ◆ Aumento do pico no final da noite e começo da manhã



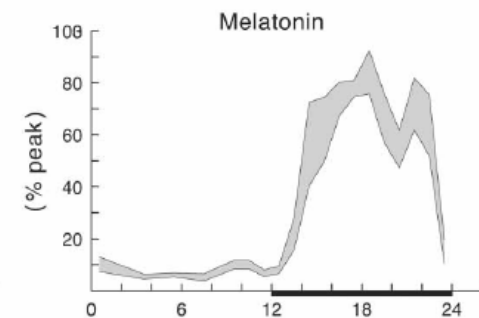
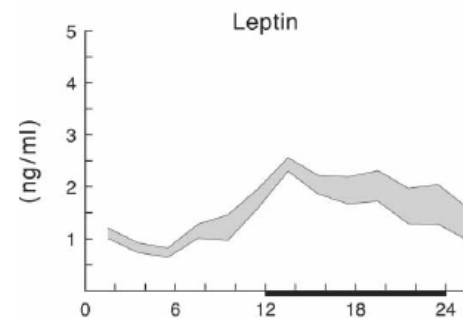
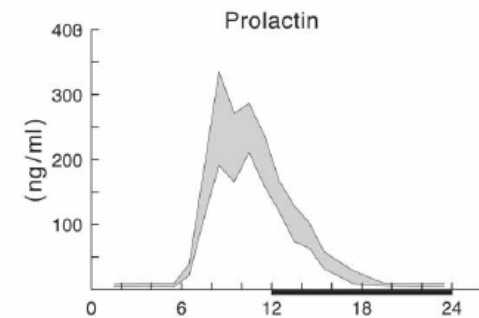
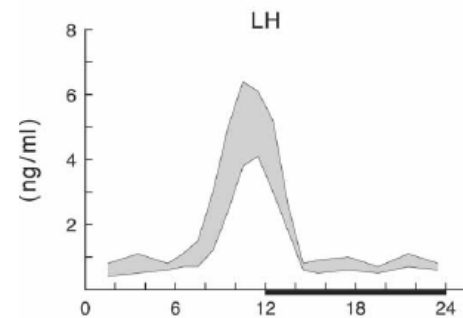
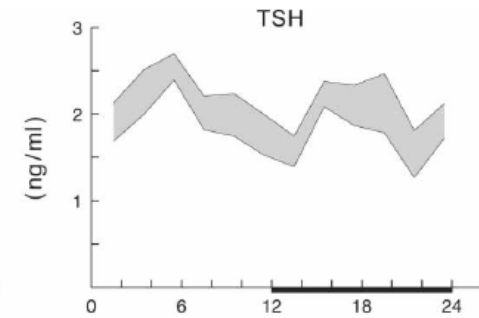
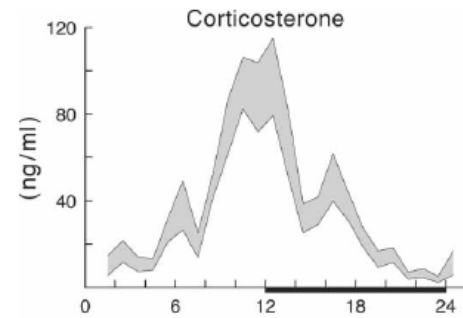
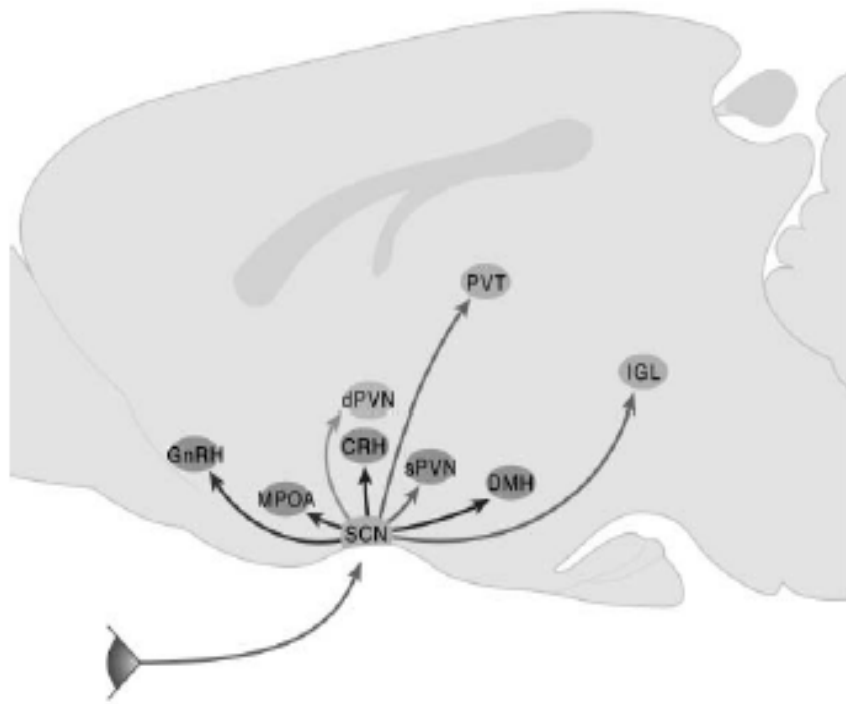
variação circadiana da concentração hormonal

Prolactina - variação ritmica e secreção pulsátil



Alvos do NSQ

Ritmos hormonais de mamíferos de habito noturno

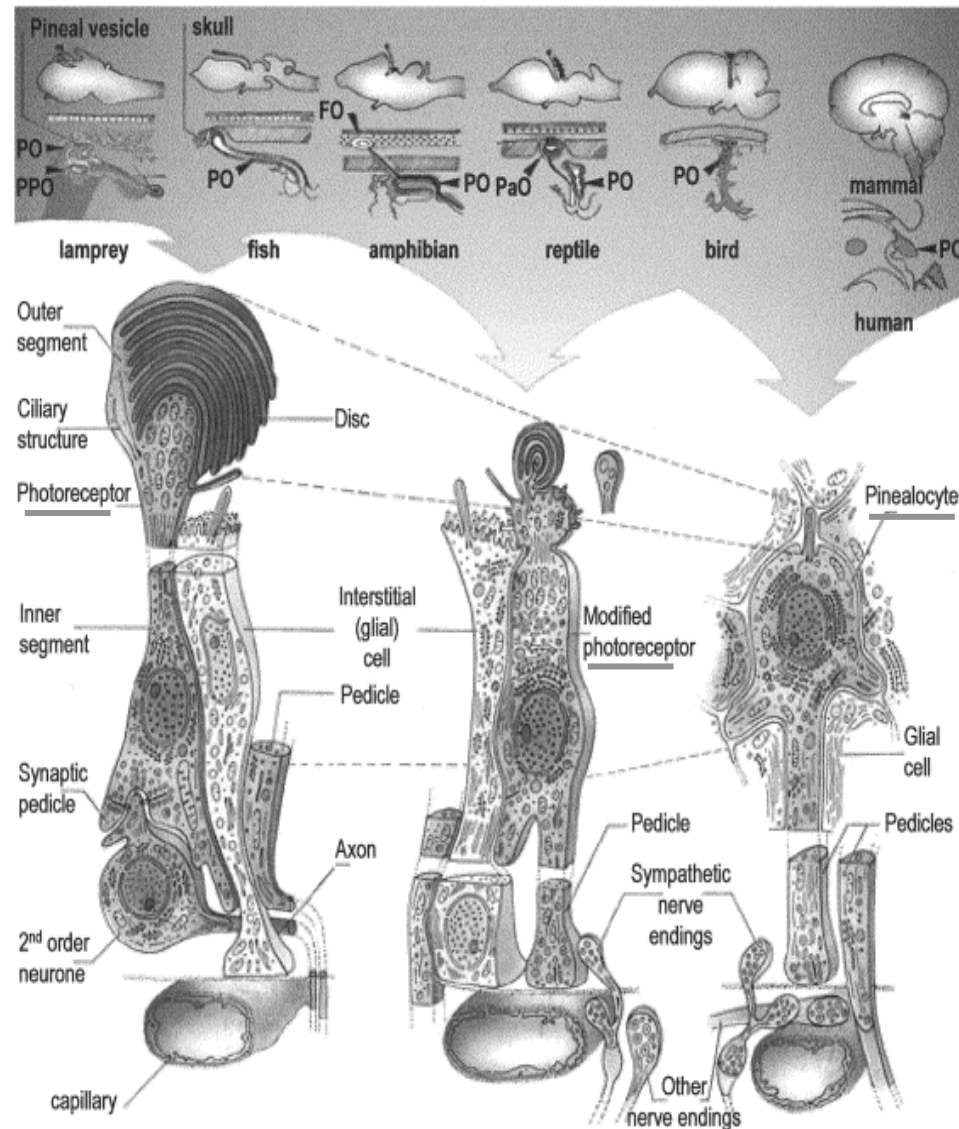


Morfologia Comparativa da Pineal

Órgão fotossensível

Transformação Funcional
Transformação Estrutural

Órgão neuroendócrino

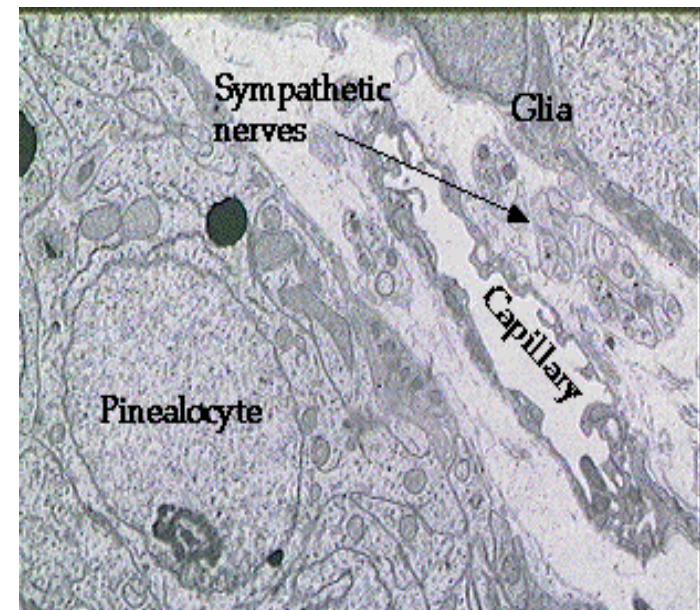
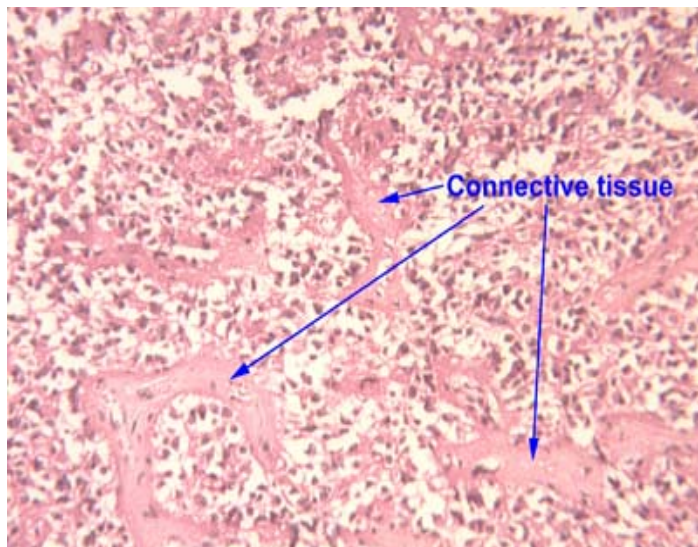
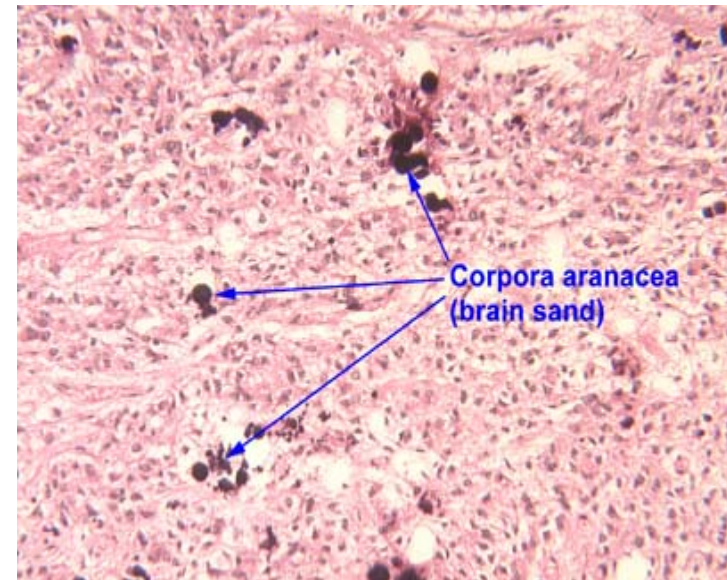
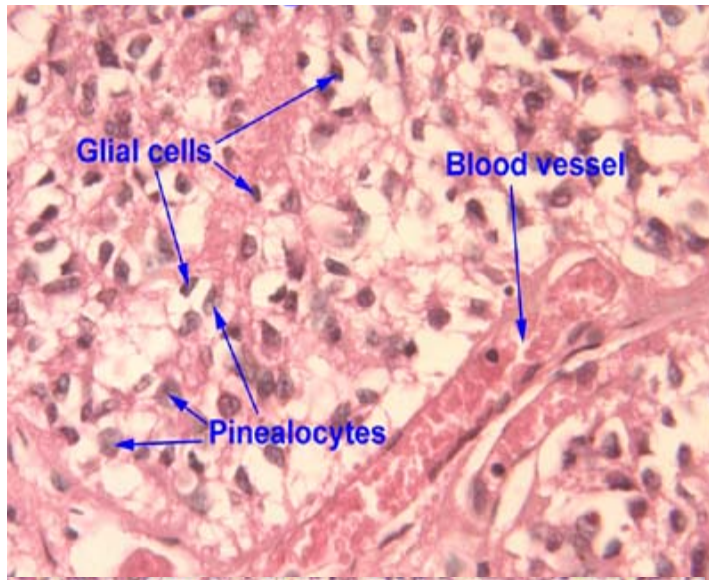


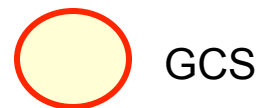
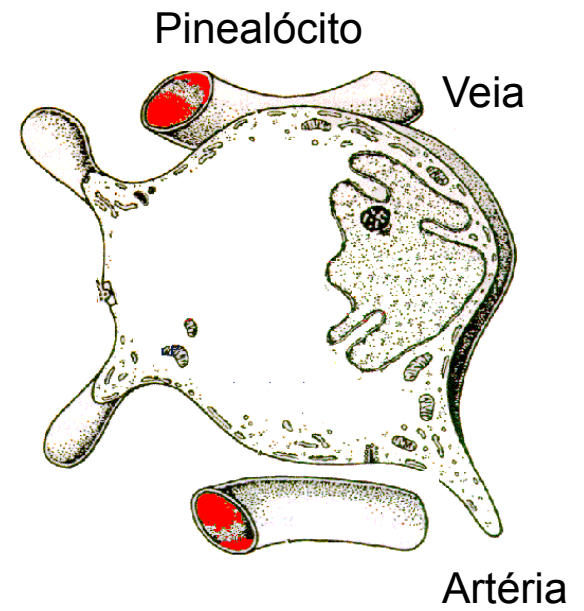
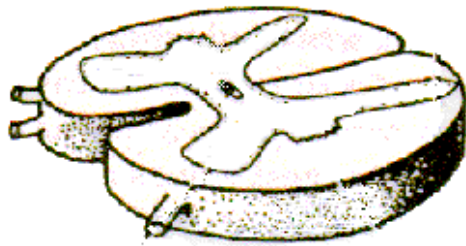
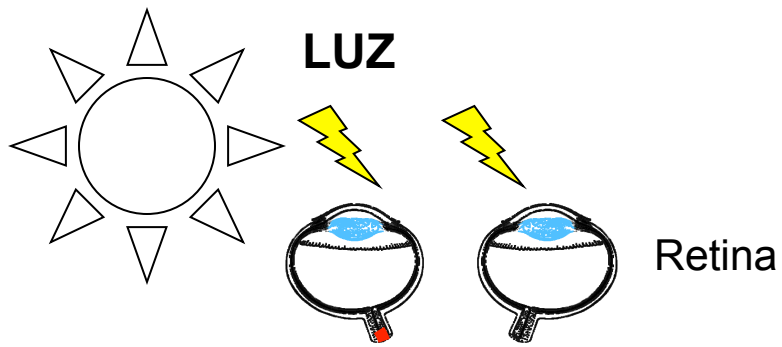
Diversidade Anatômica e Funcional da Pineal

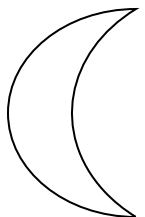
Reflexo das funções às quais está implicada:

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

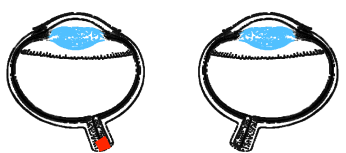
Glândula Pineal







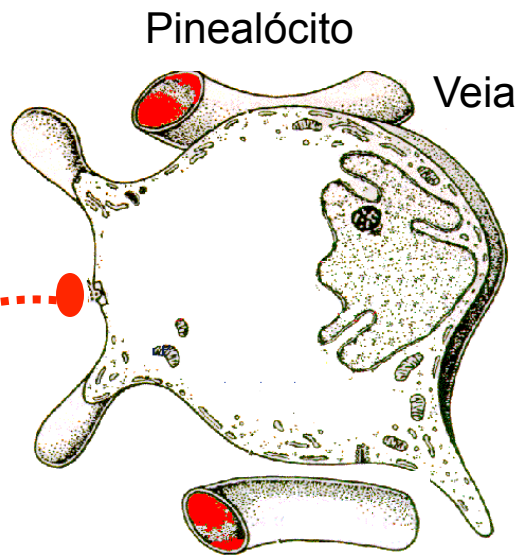
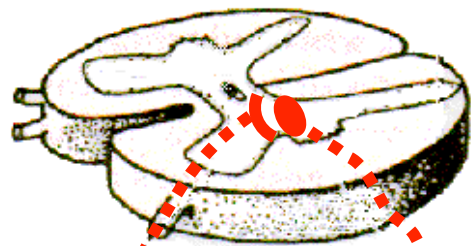
ESCURO



Retina



NSQ



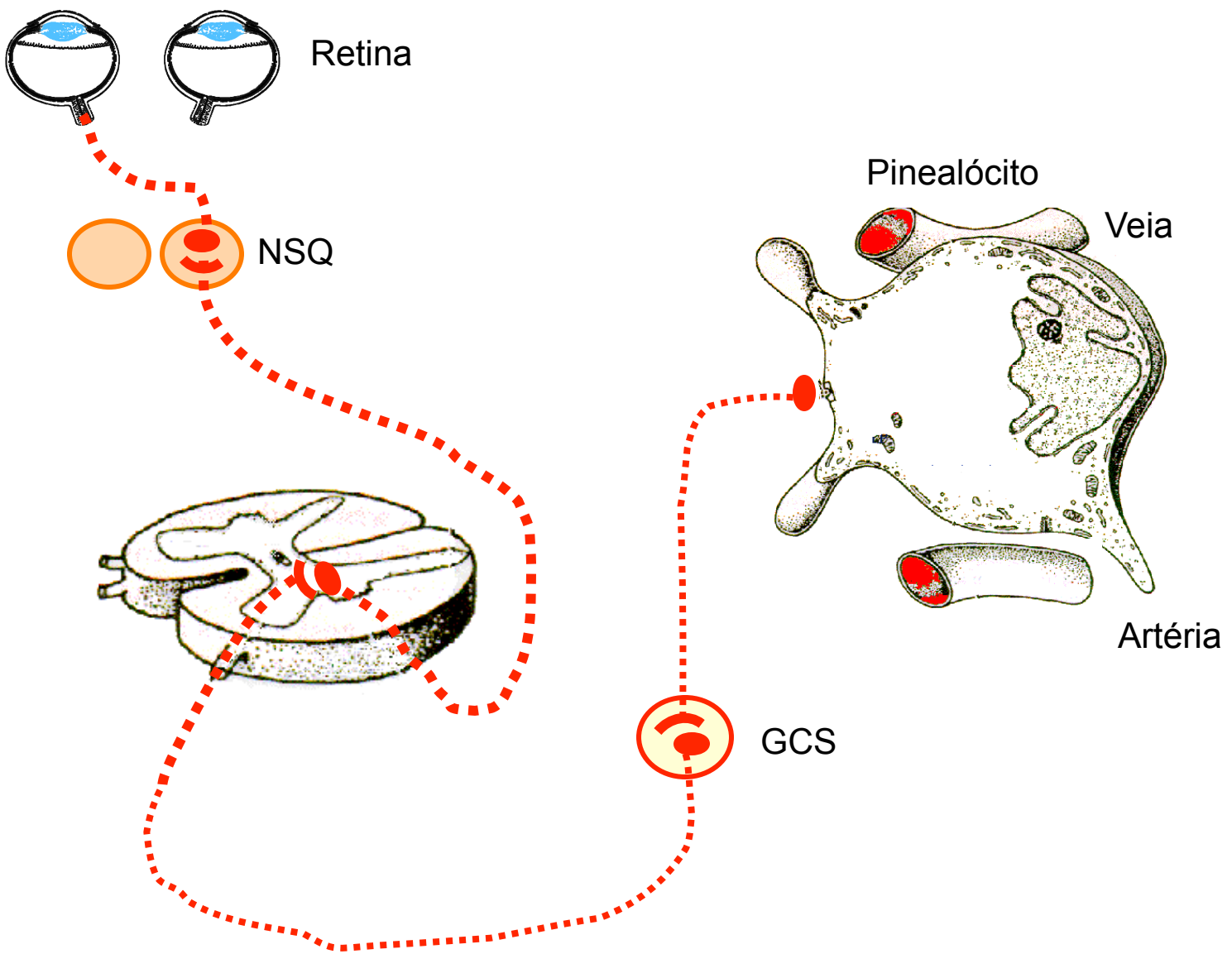
Pinealócito

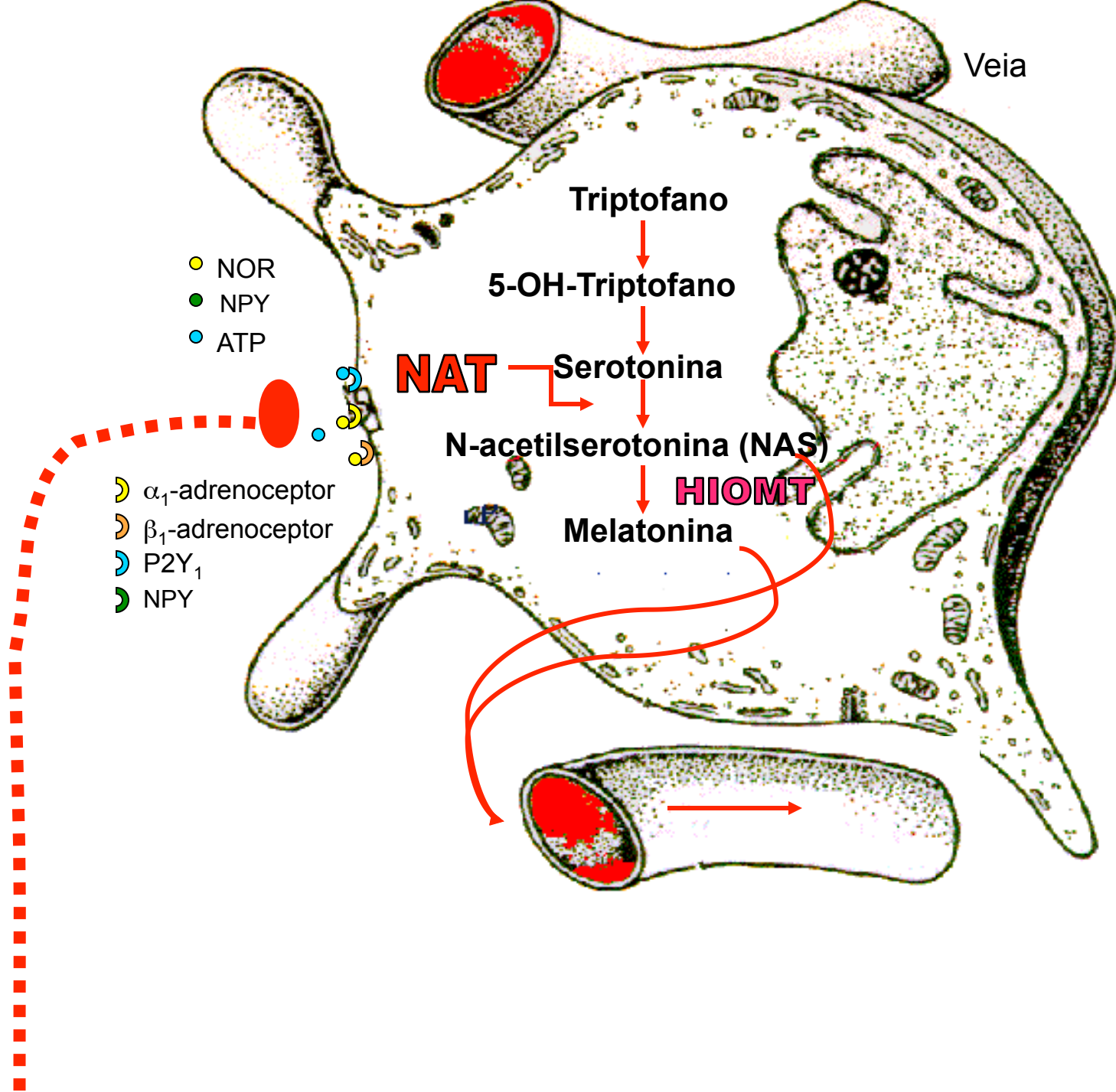
Veia

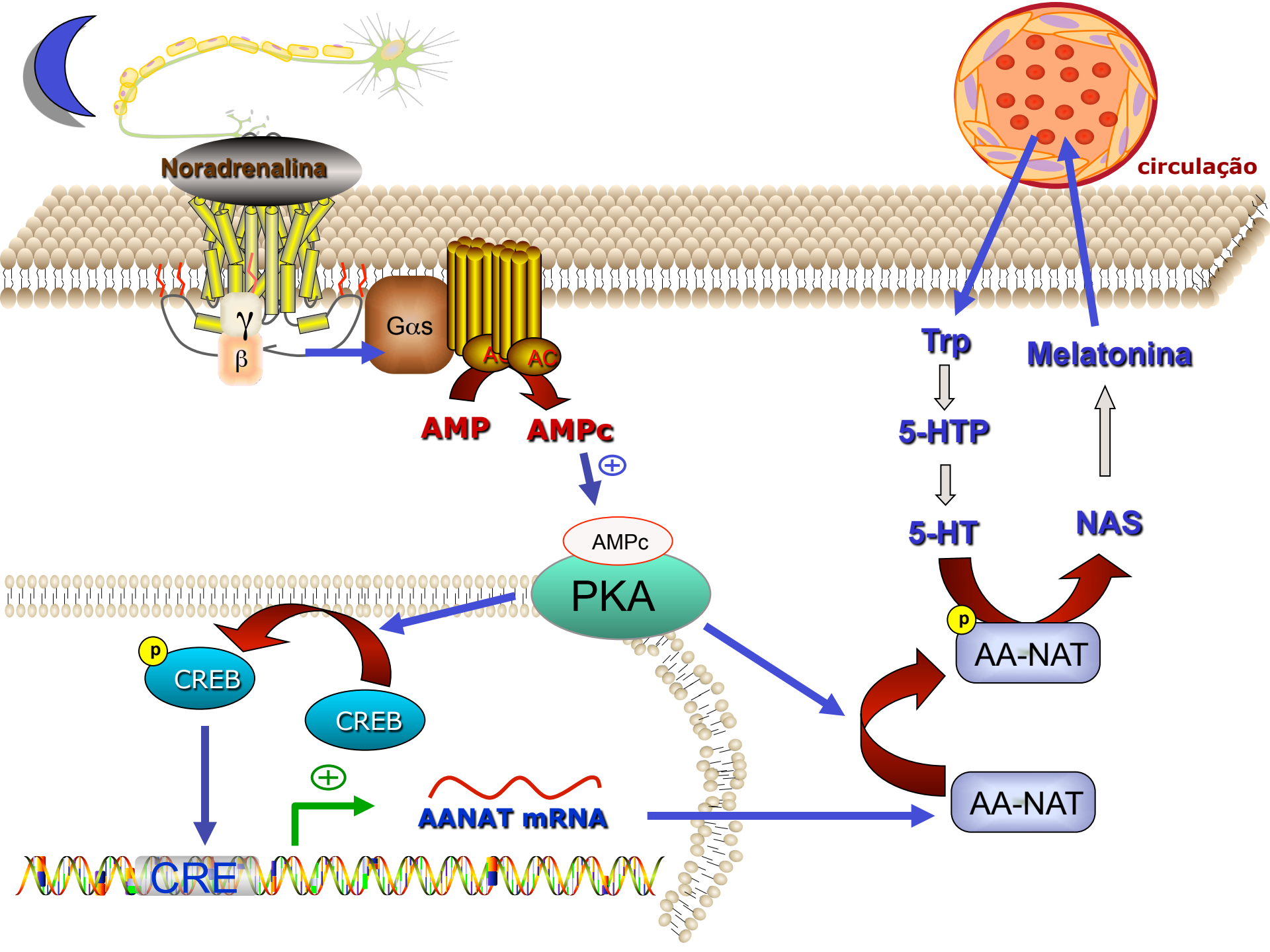
Artéria



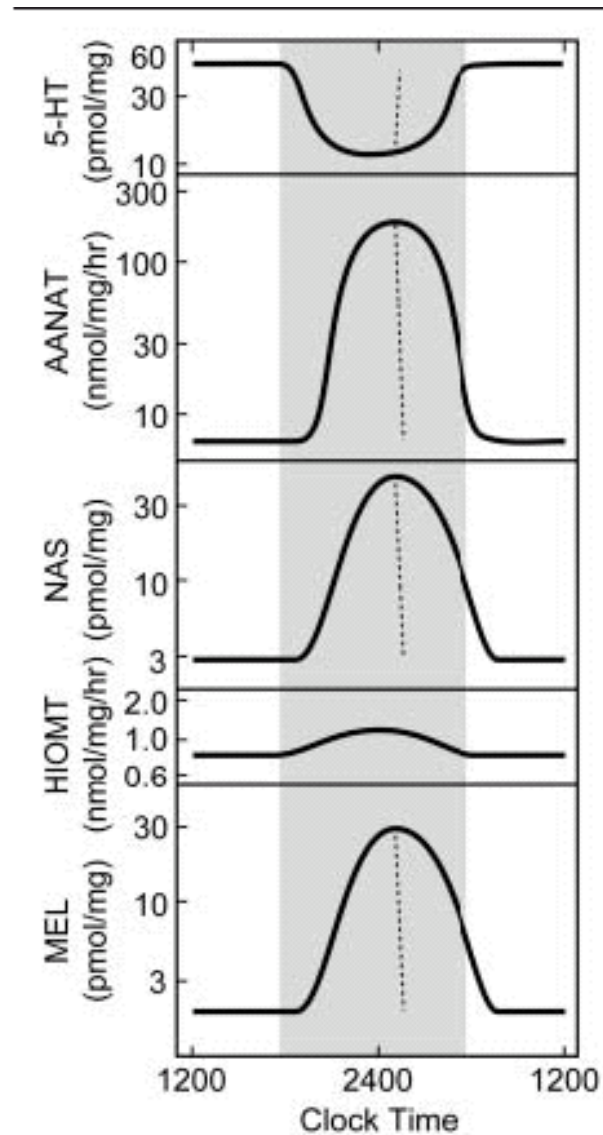
GCS



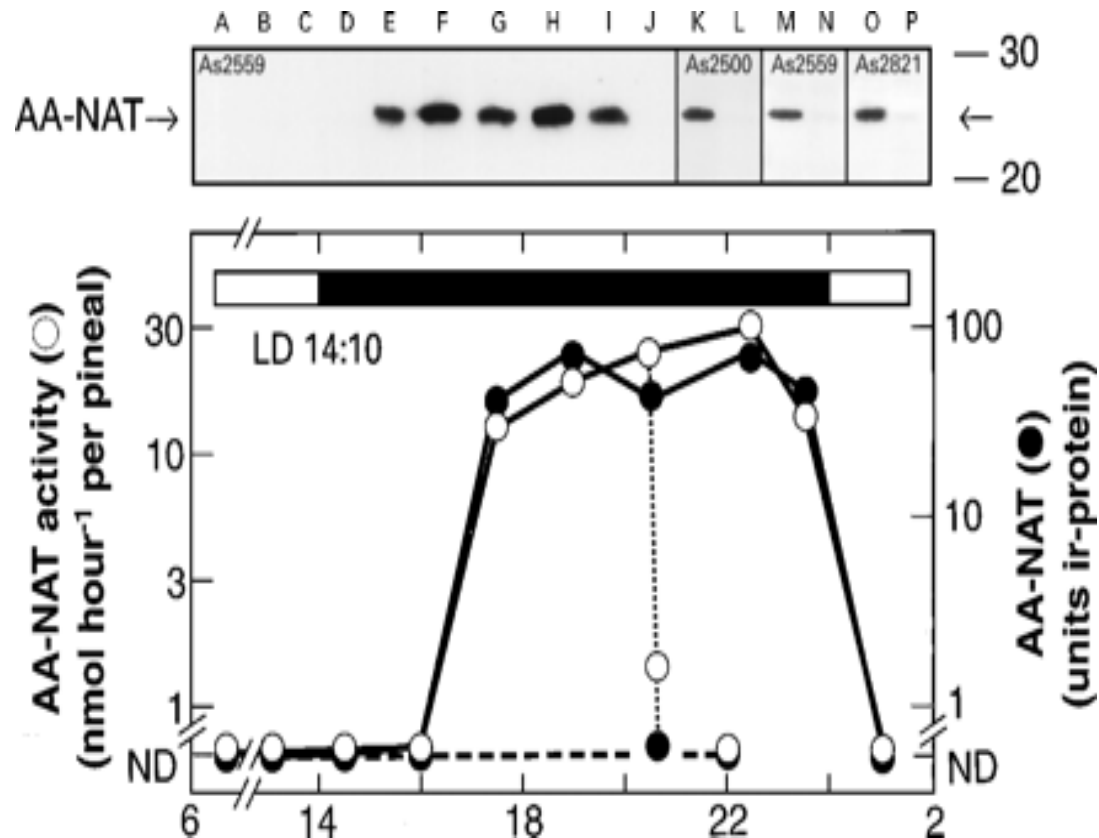




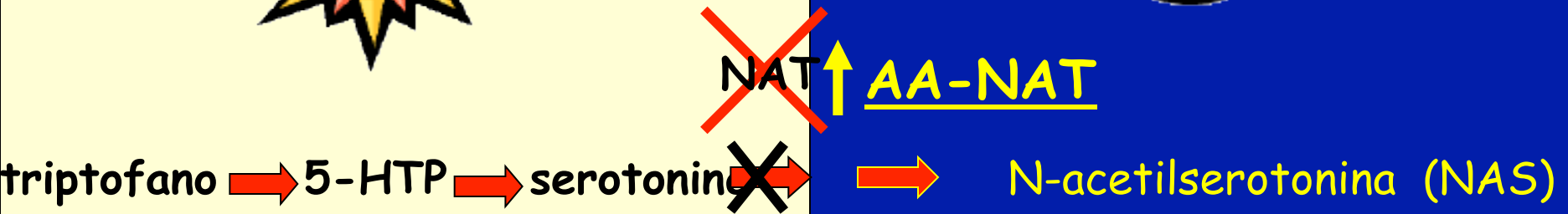
Ritmos no metabolismo da glândula pineal



AA-NAT na glândula pineal de ratos



Controle da produção de melatonina pela pineal



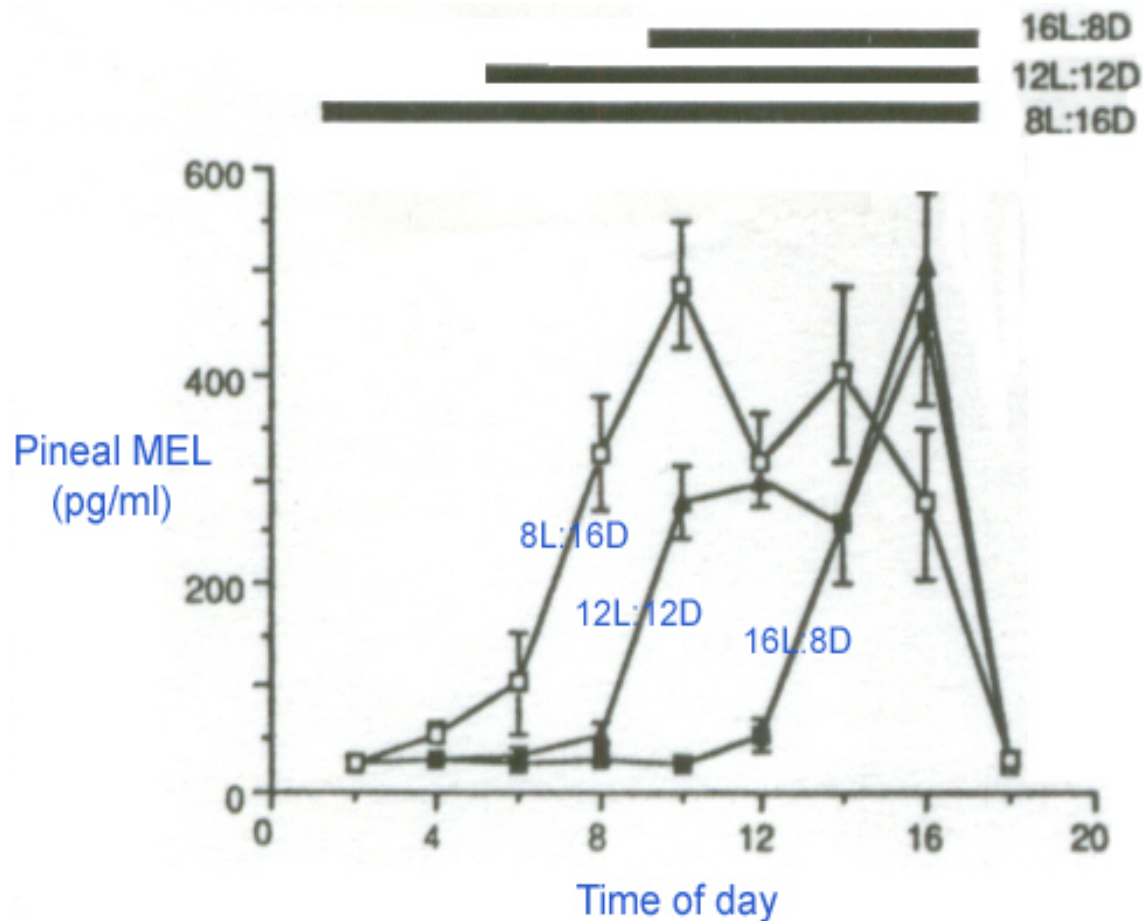
↓ HIOMT
Melatonina

Produção de melatonina inibida

NAS e Melatonina
produzidas e liberadas

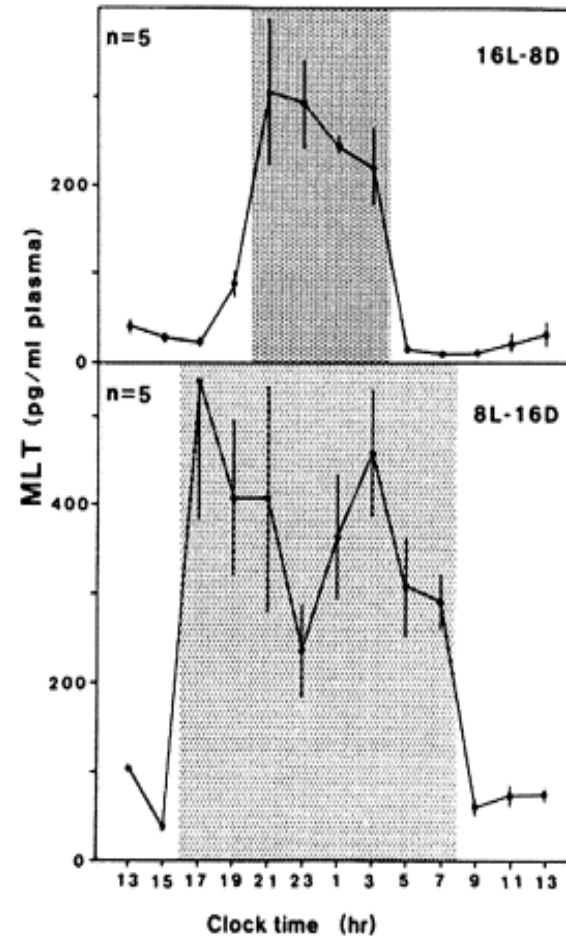


Melatonina - o hormônio marcador do escuro



Importância do Fotoperíodo

adaptação para as estações do ano





Verão

Dias longos, Noites curtas

↓ melatonina



Outono



Inverno

Dias curtos, Noites longas

↑ melatonina



Primavera

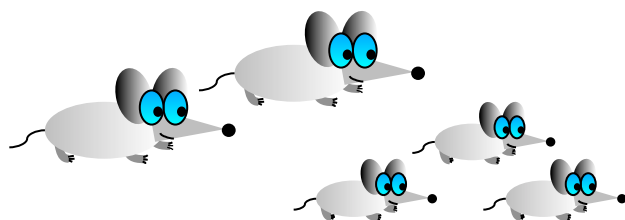




Verão

Dias longos, Noites curtas

↓ melatonina



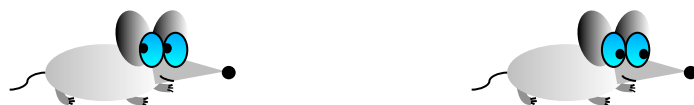
Outono



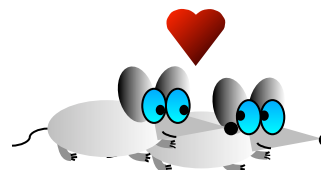
Inverno

Dias curtos, Noites longas

↑ melatonina



Primavera



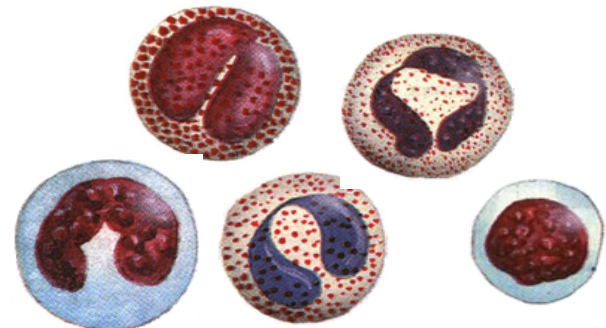
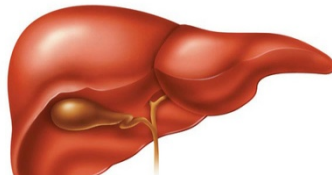
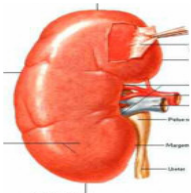
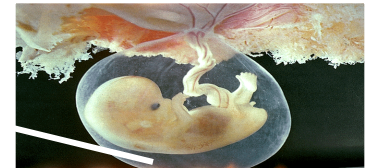
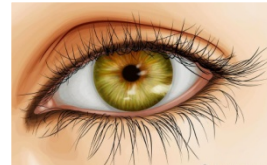
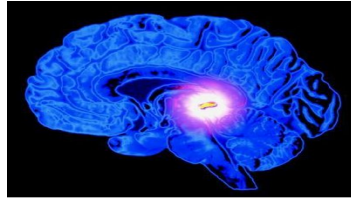
Melatonina - o Hormônio do escuro

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



Variação diária de respostas imunes

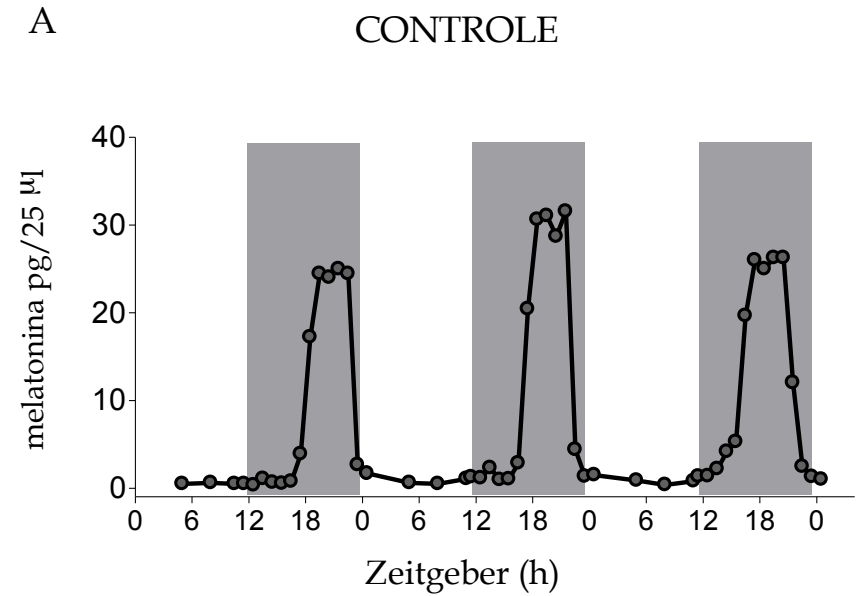
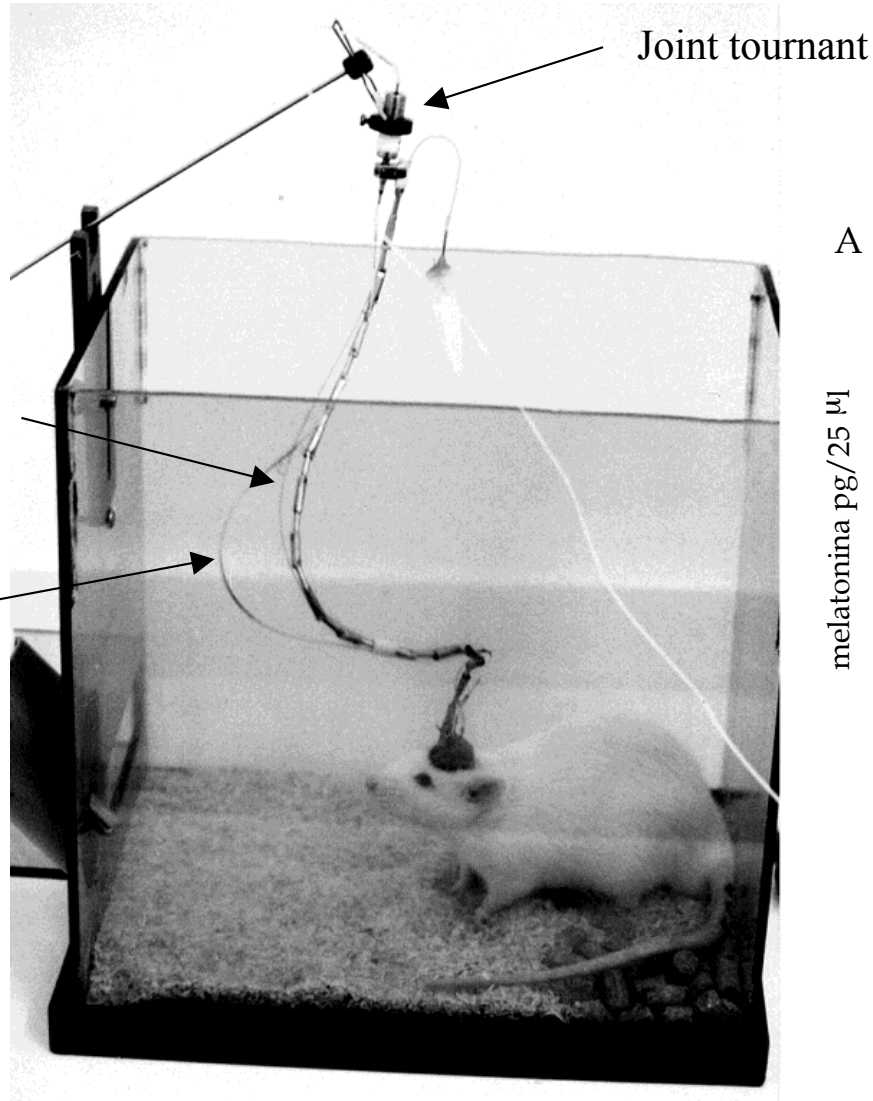
Locais de produção da melatonina



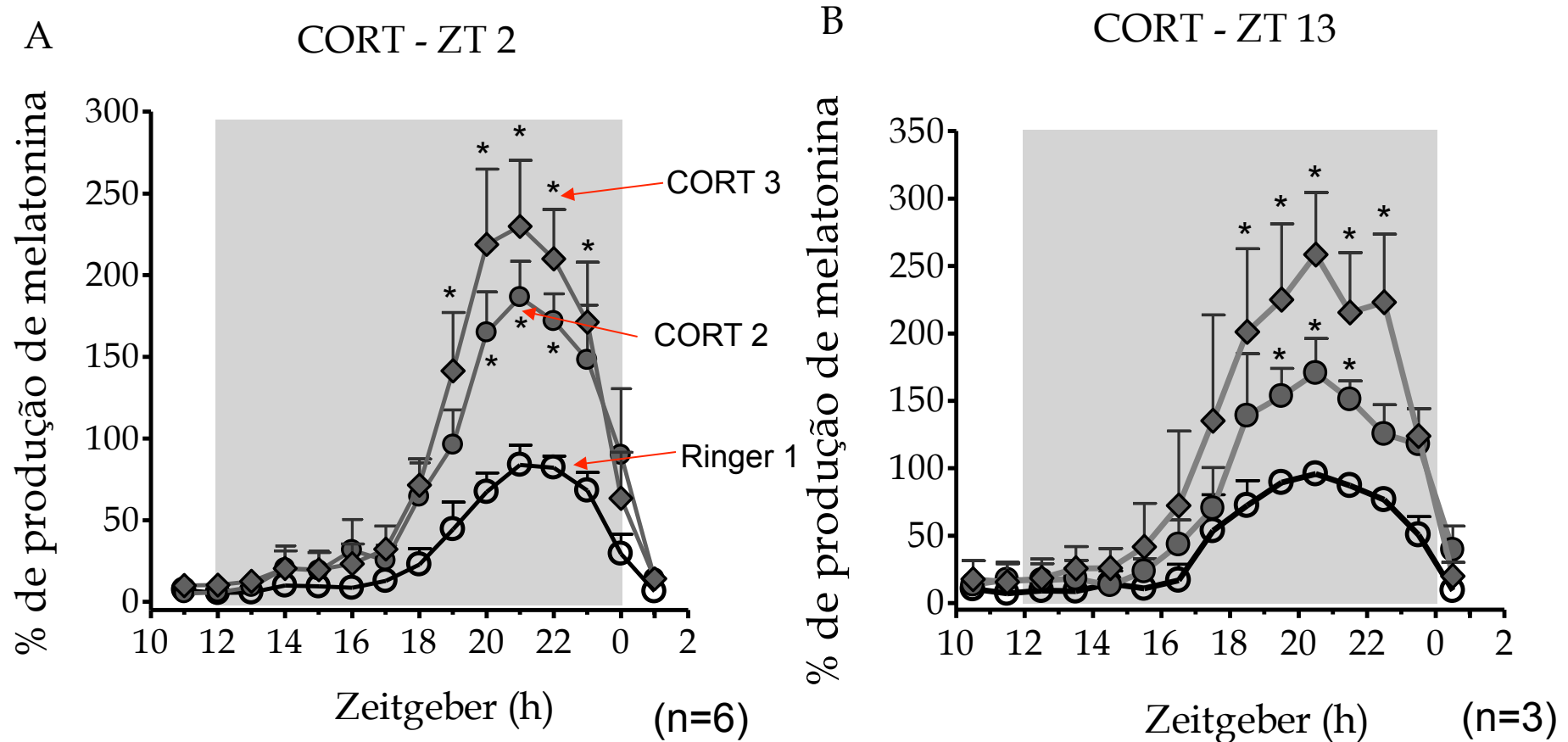
Exemplo:

**Interações imuno-neuroendócrinas
na glândula pineal**

Microdialyse Intrapineale

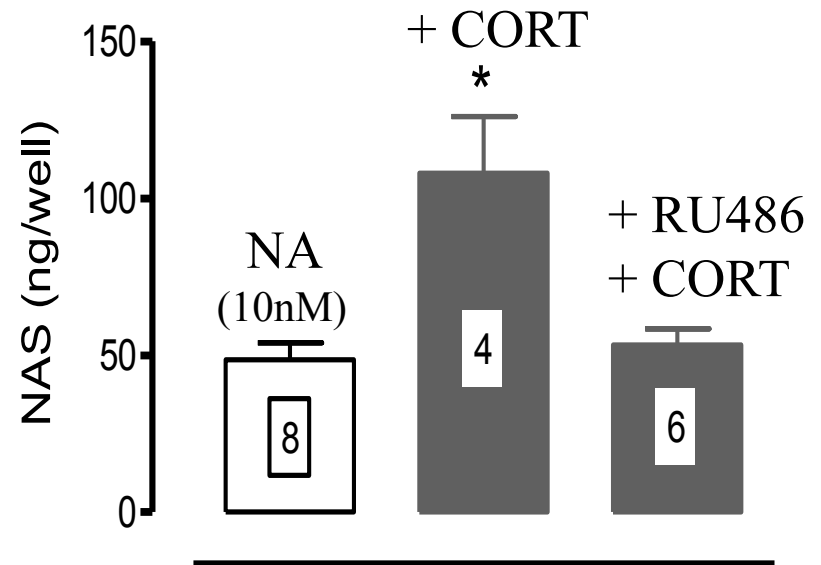
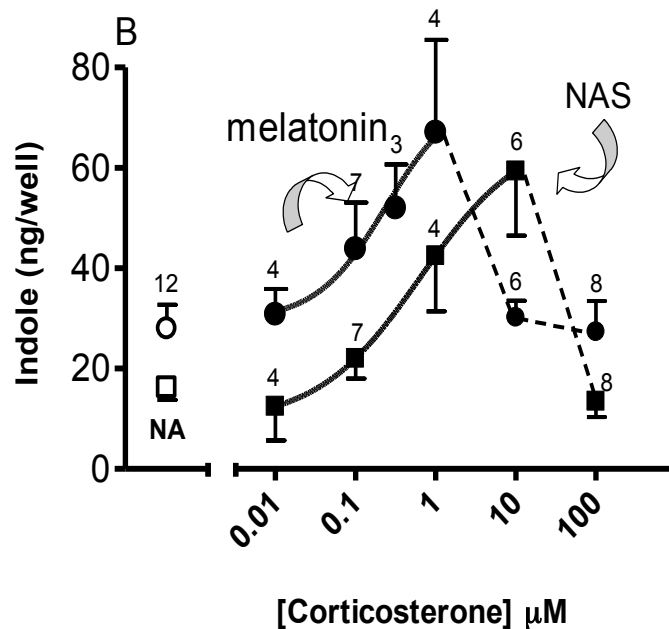


Corticosterona Aumenta a Produção de Melatonina *in vivo*

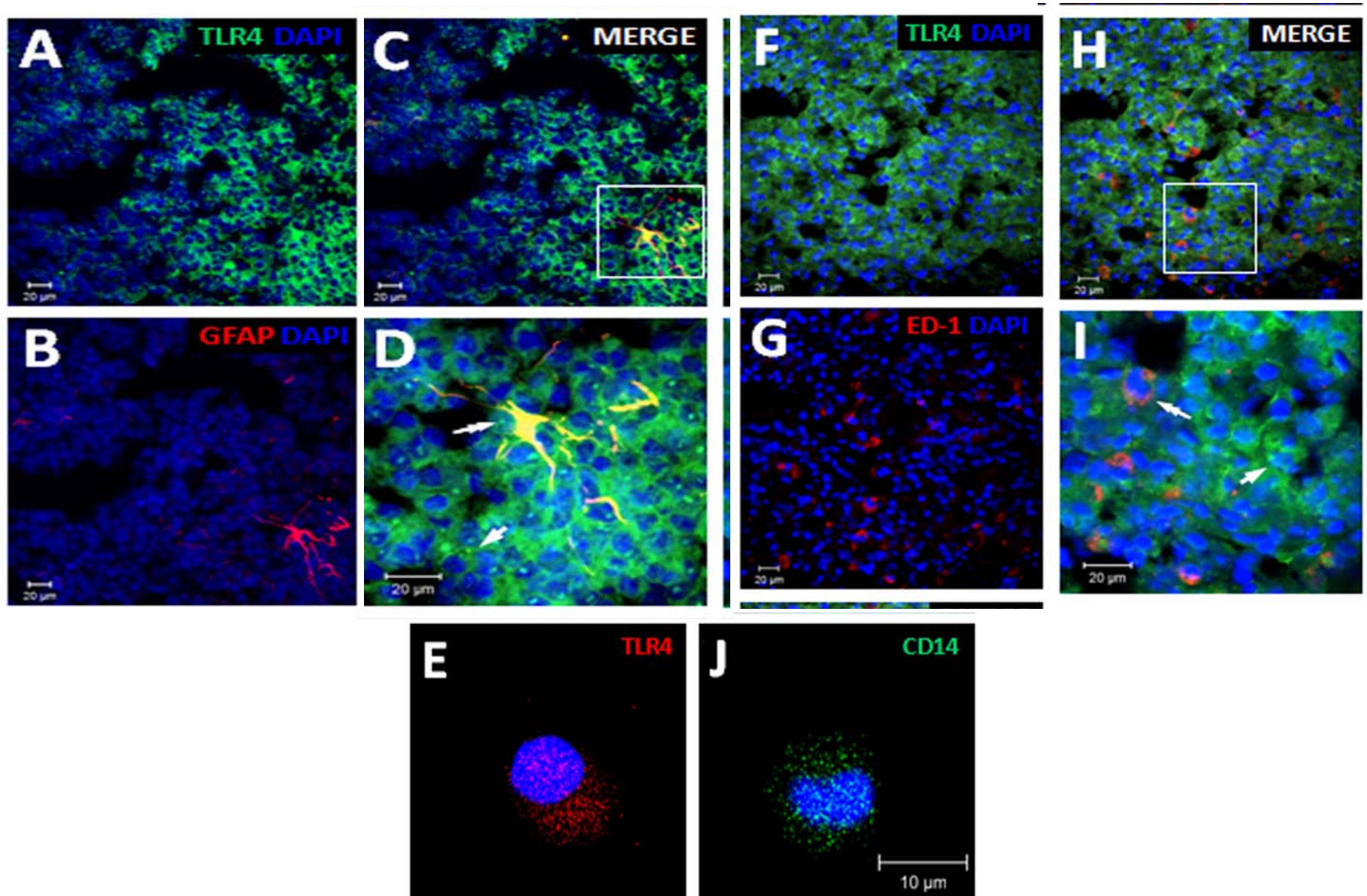


Corticosterone

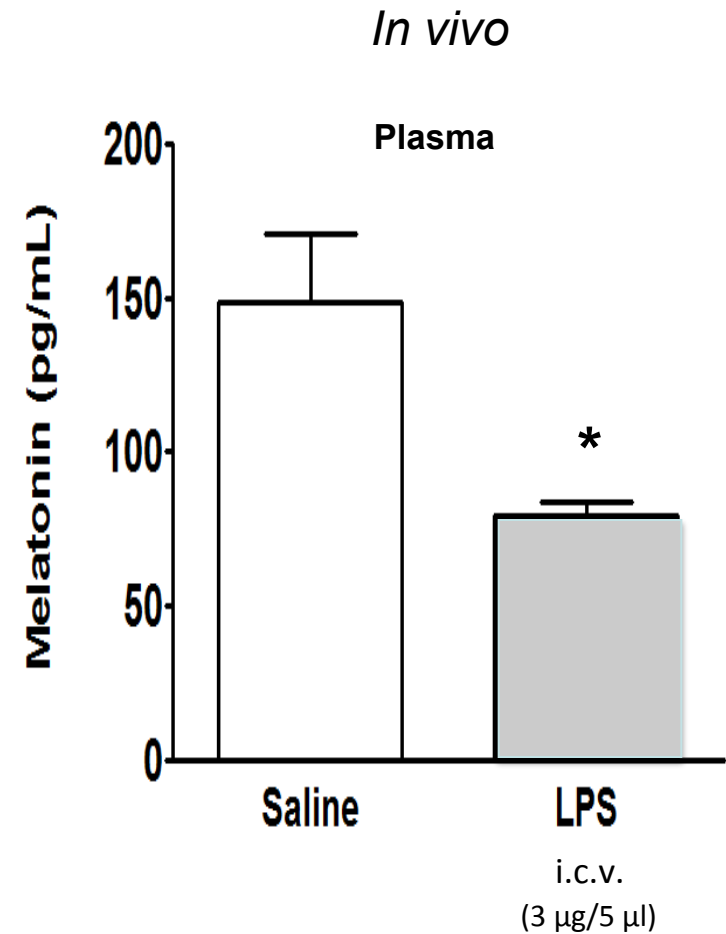
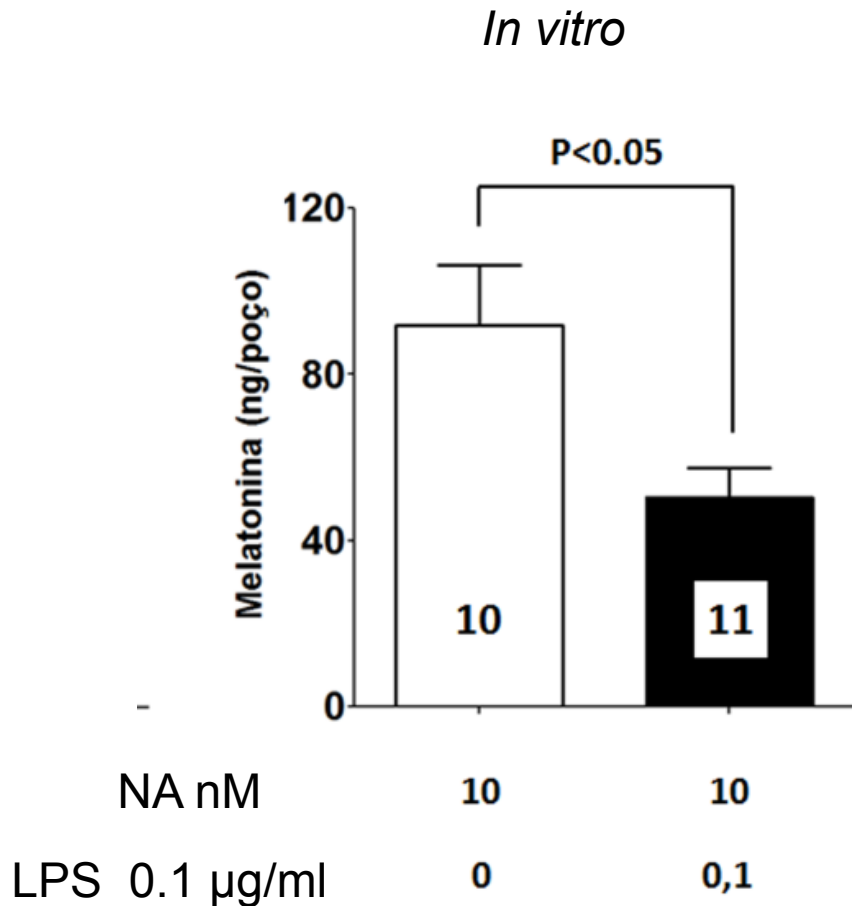
1. potentiates noradrenaline-induced melatonin synthesis
2. through an intracellular glucocorticoid receptor



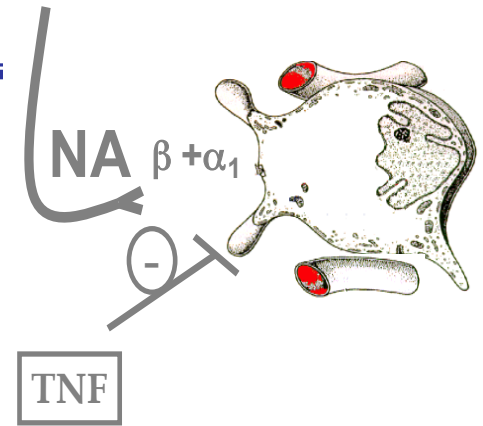
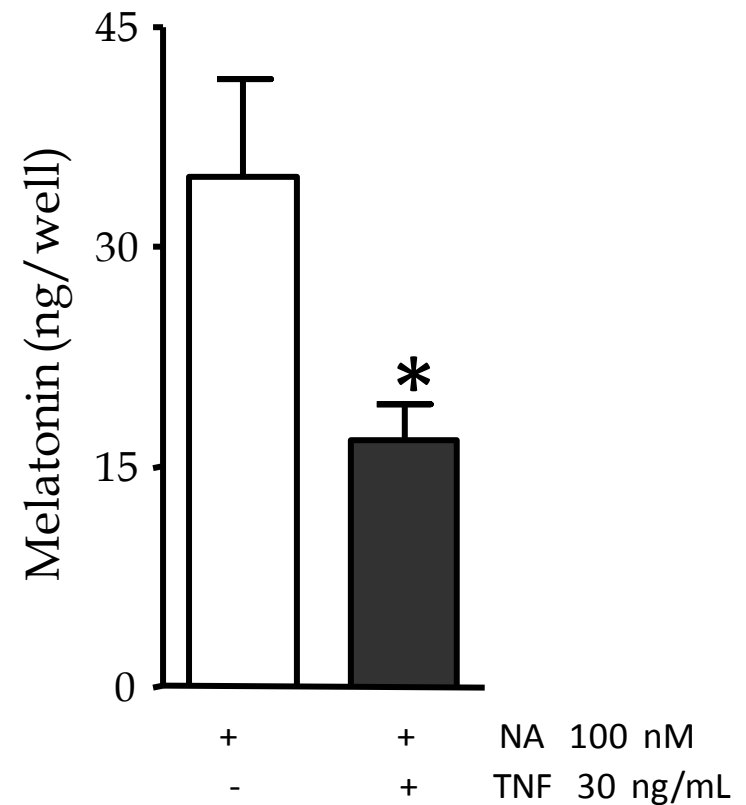
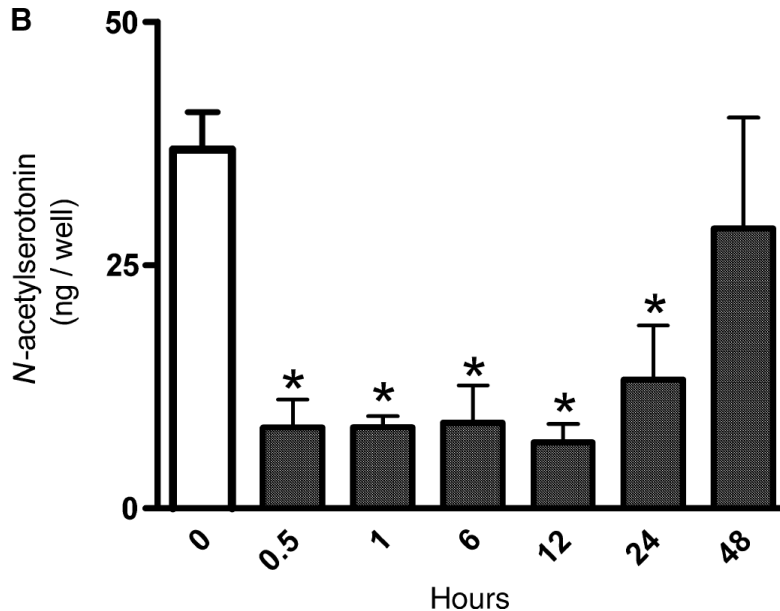
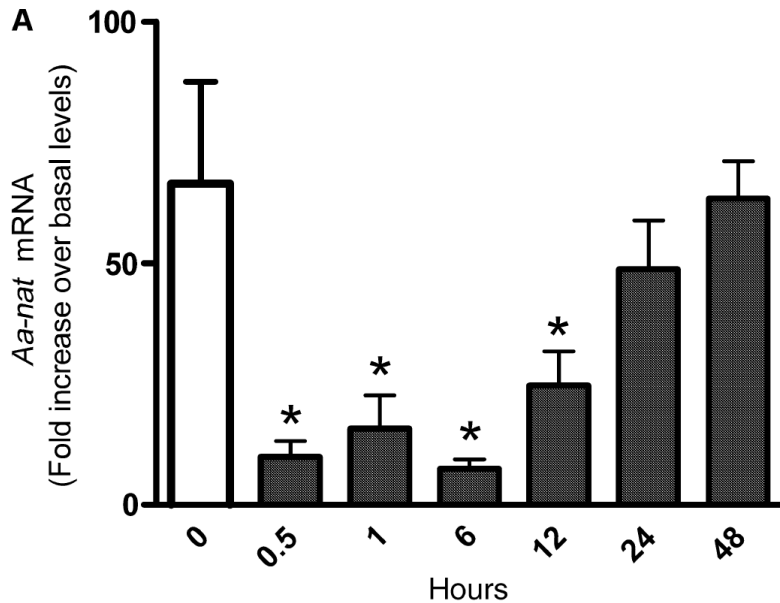
Cellular expression of TLR4 in the rat pineal gland.



LPS inhibits nocturnal pineal melatonin production

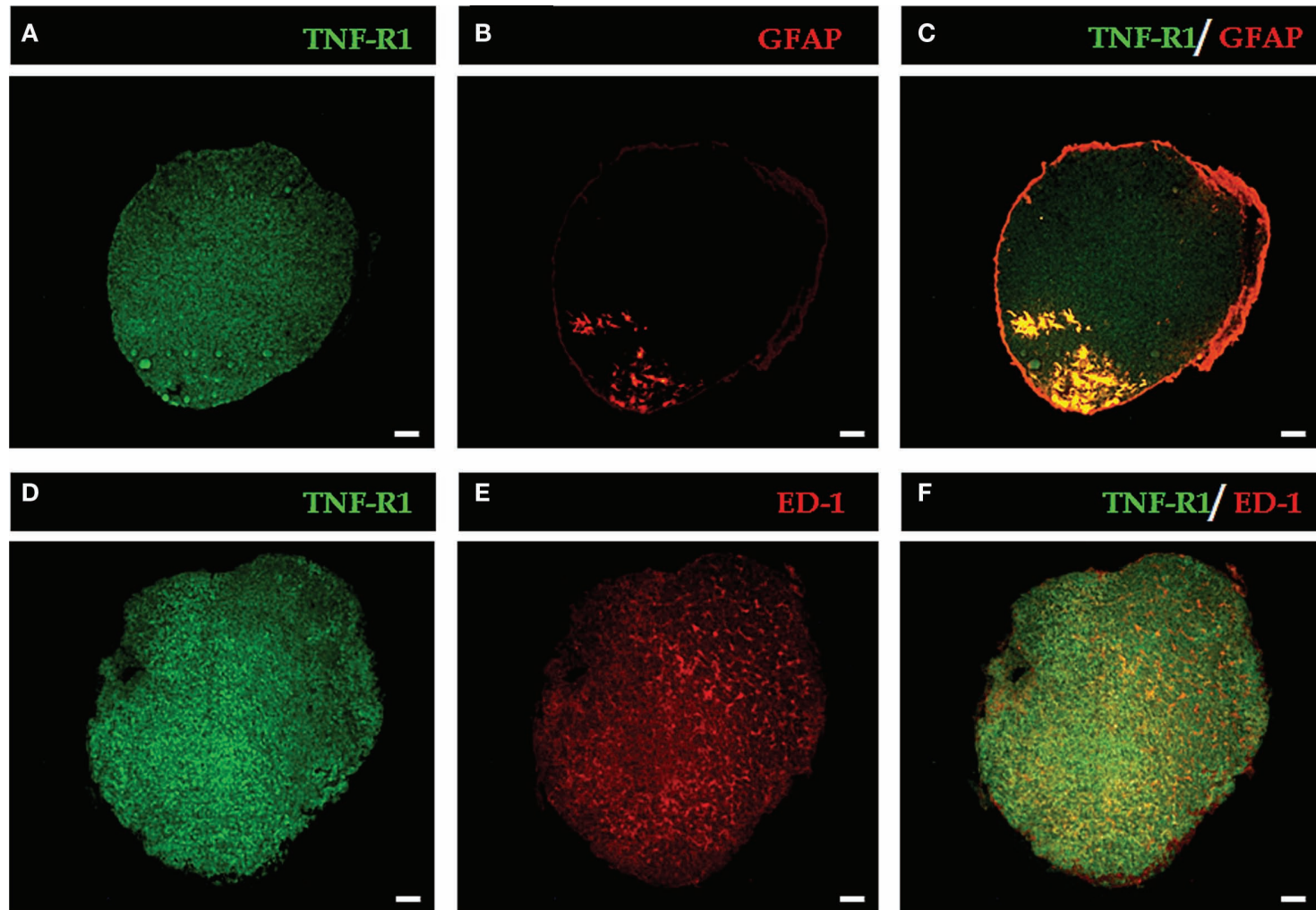


A citocina TNF atuando na pineal

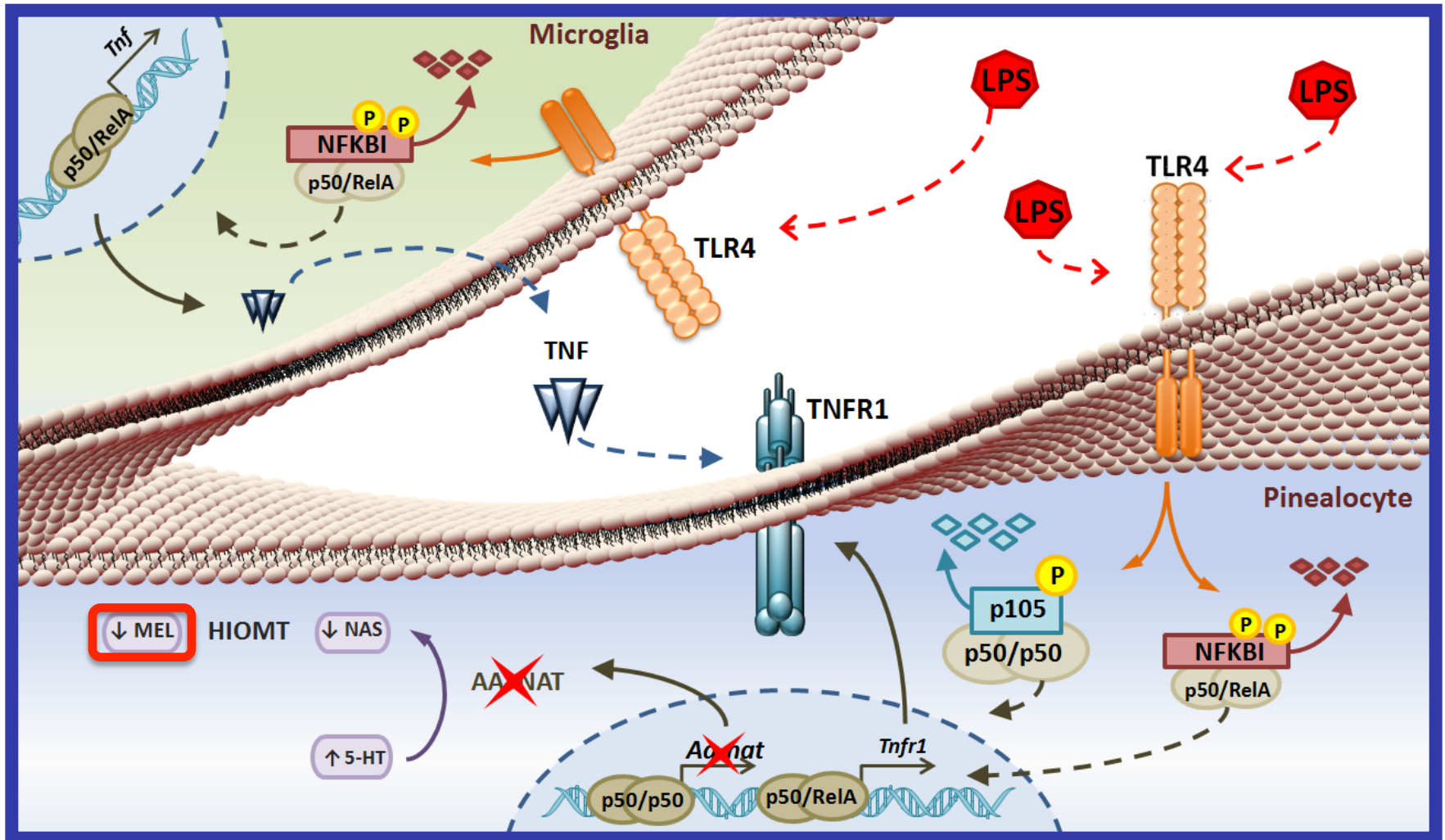


Fernandes *et al.*, 2006

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)

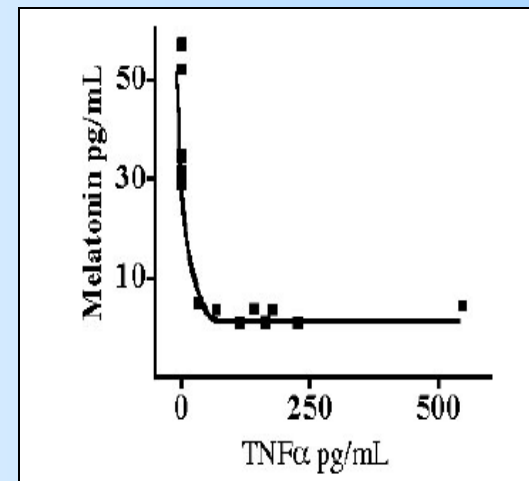
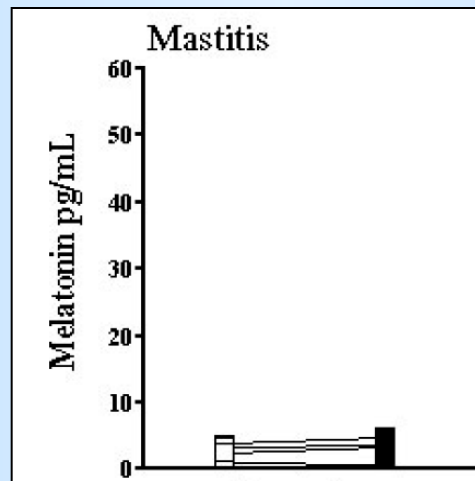
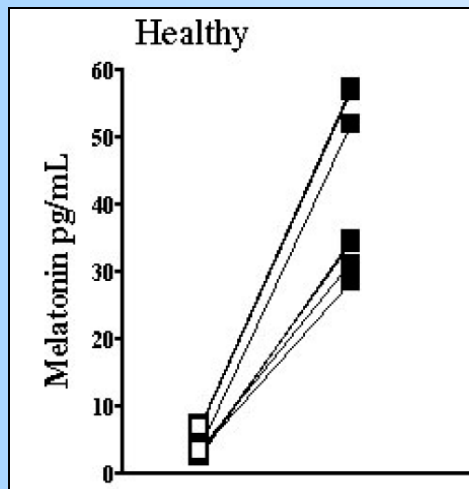
 - sepsis (Mundigler et al., 2002),

 - 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



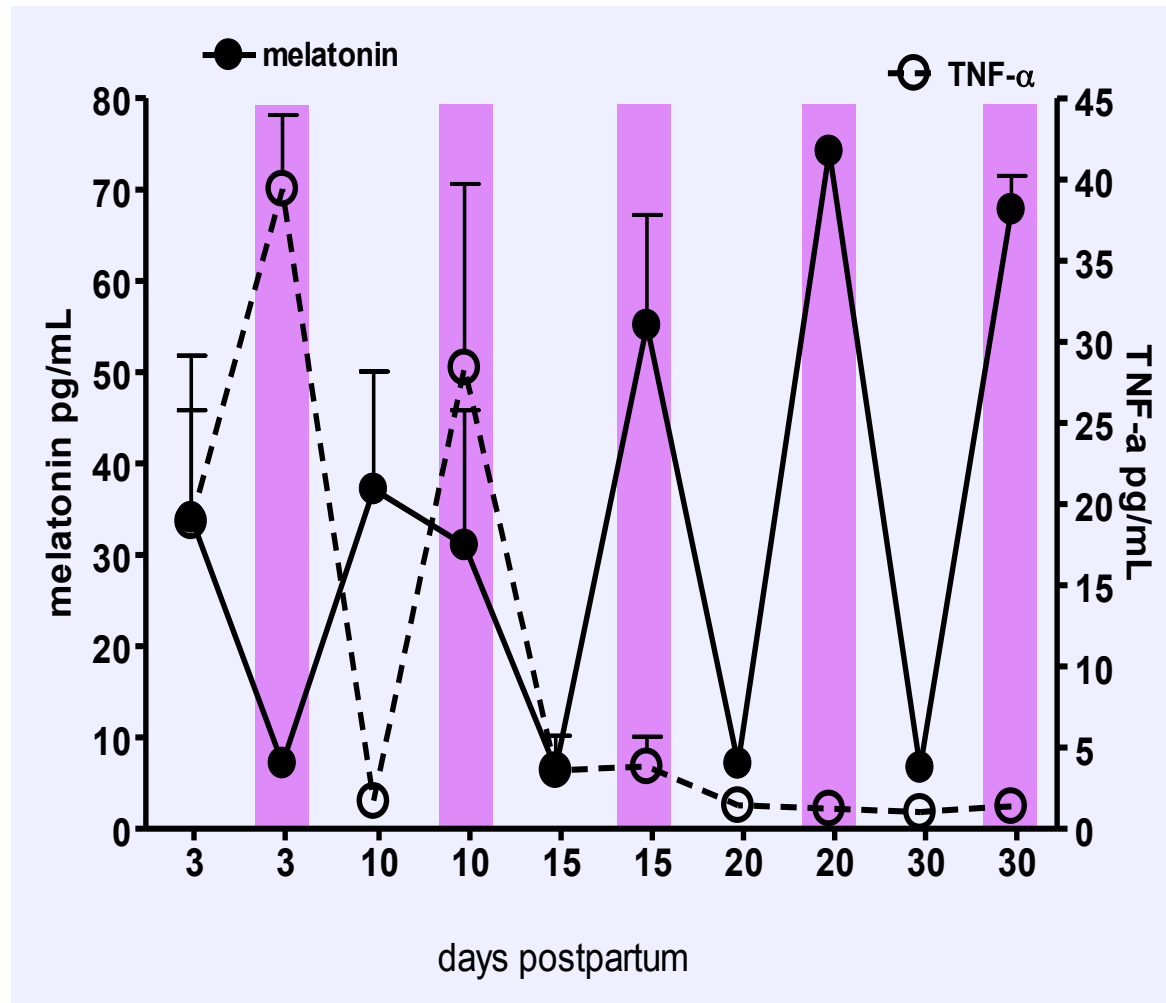
Pontes *et al.*, 2006

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



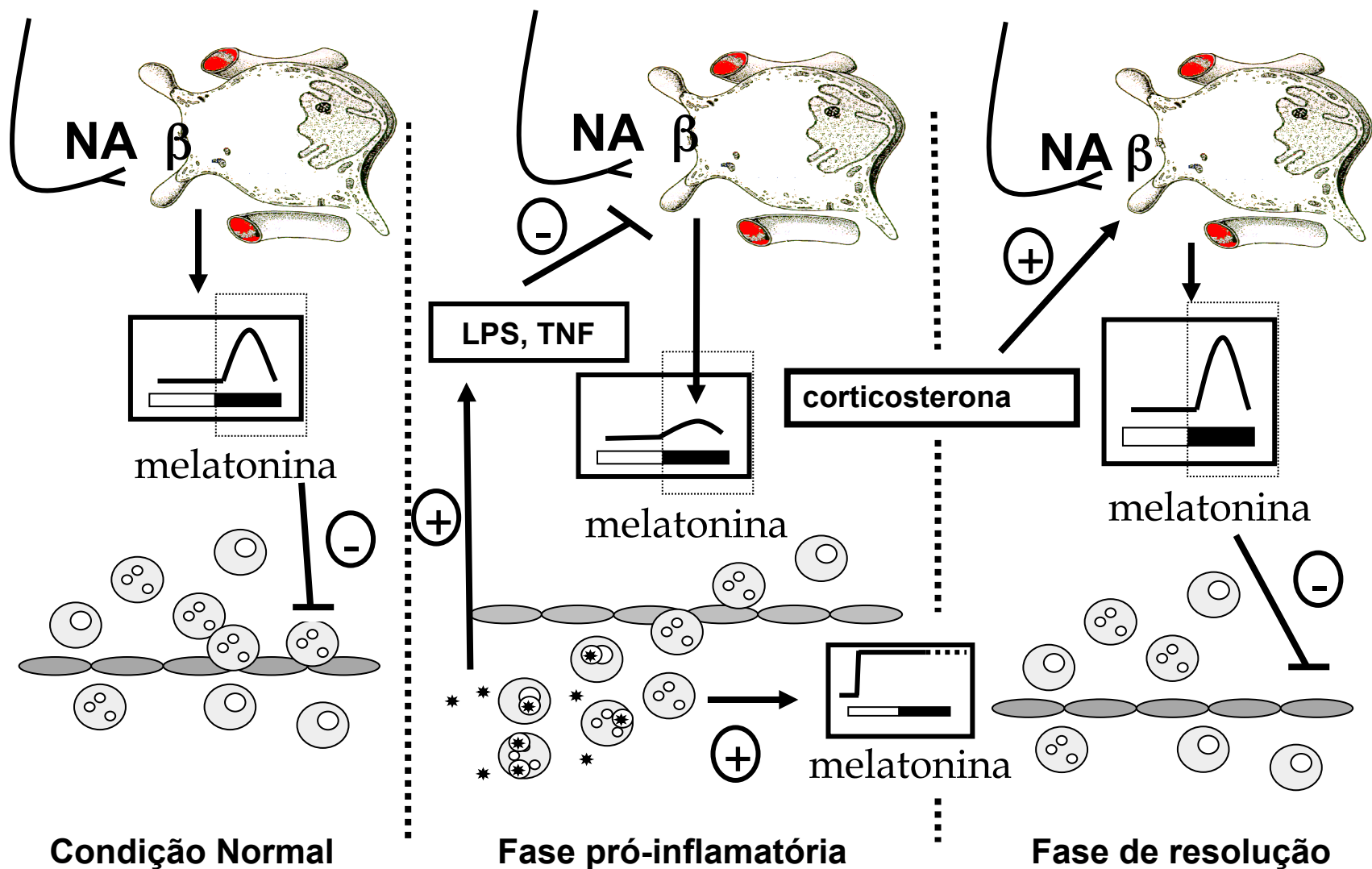
obtained after a great reduction in the levels of TNF- α .

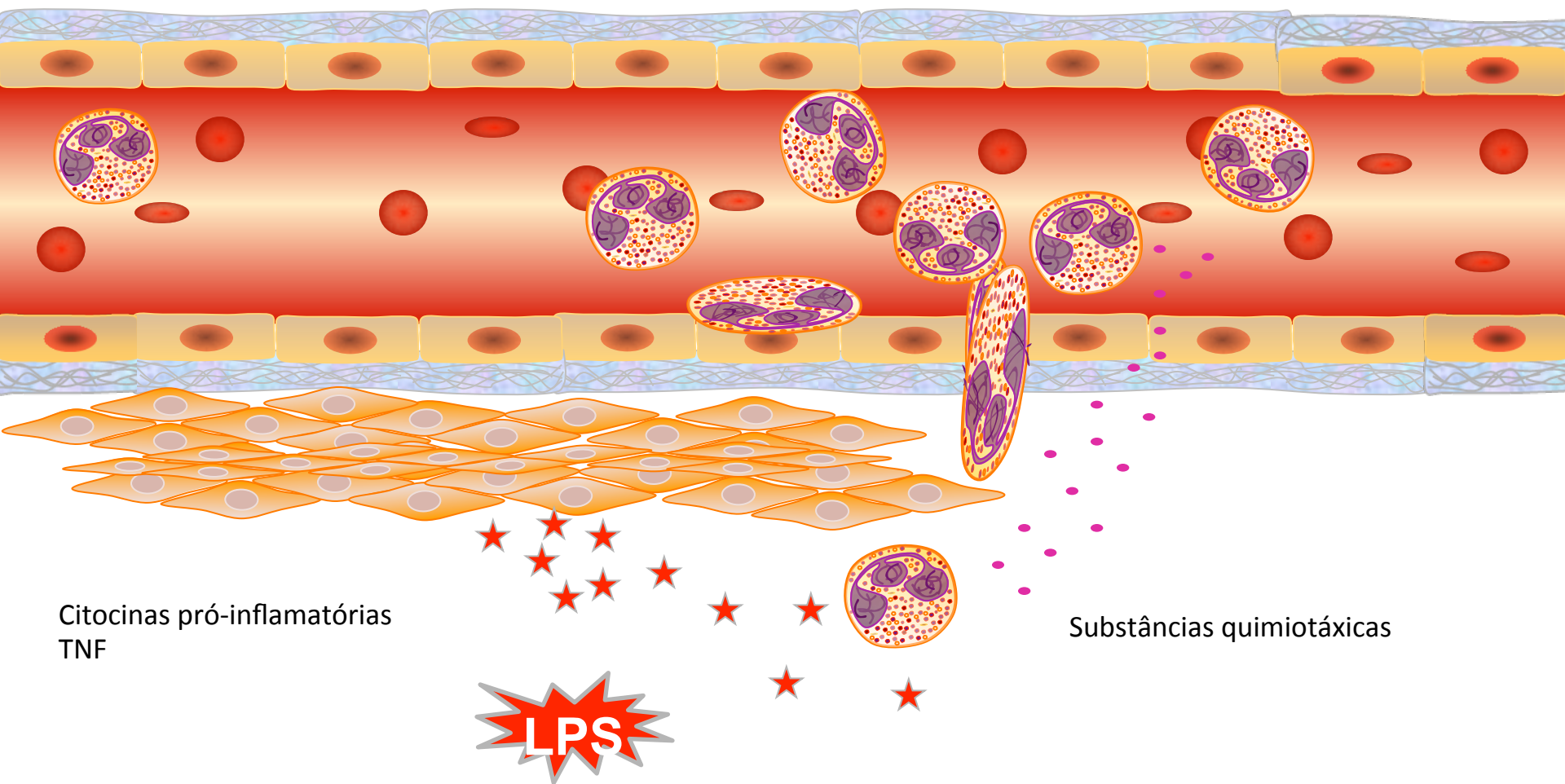
Supressão e/ou potenciação da síntese de melatonina

Quando ?

Por que ?

Eixo Imune-pineal





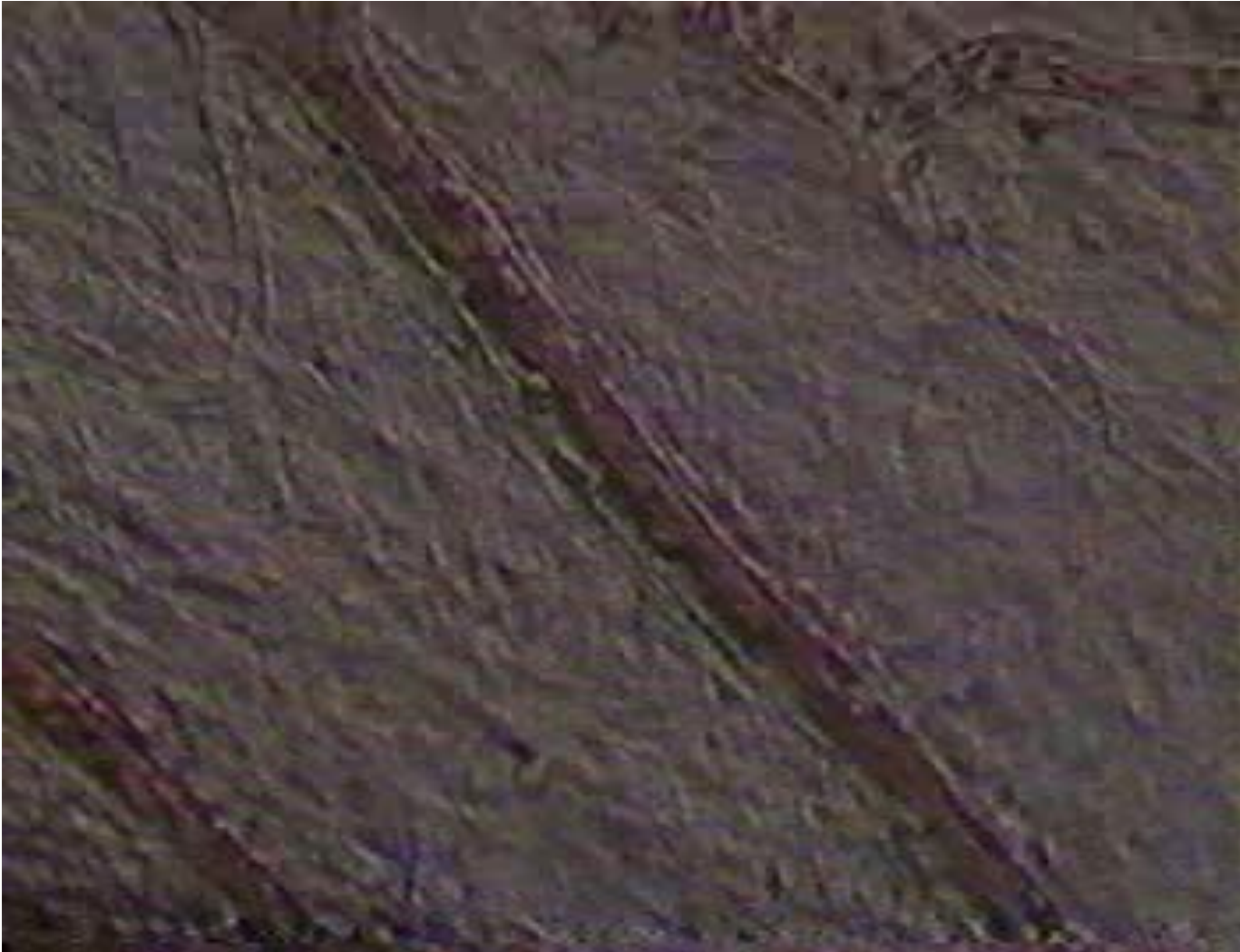
Citocinas pró-inflamatórias
TNF

Substâncias quimiotáticas

LPS

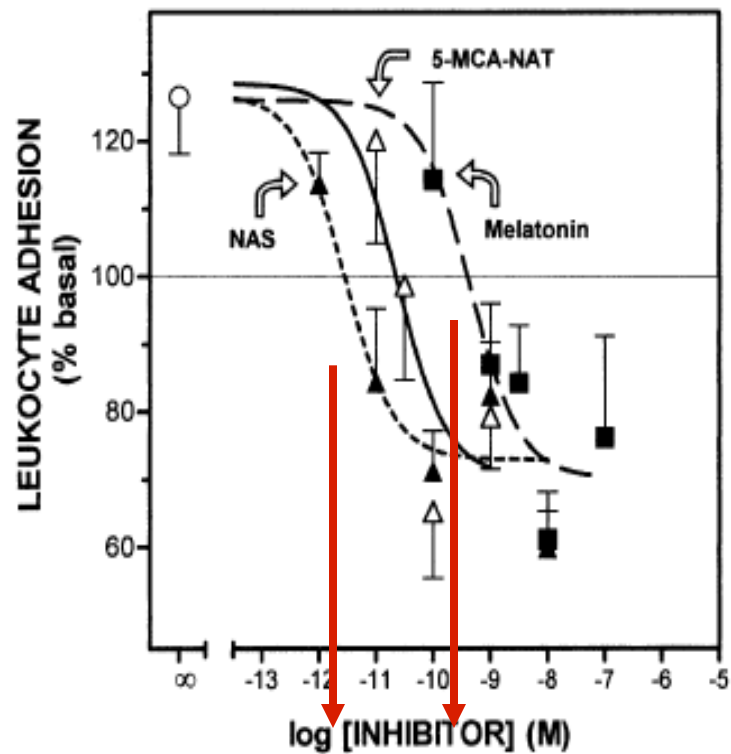
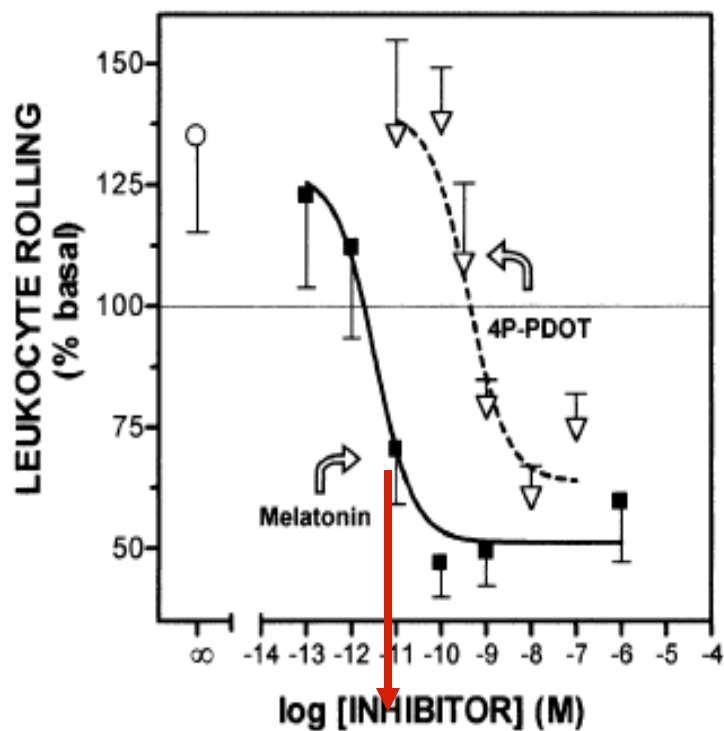
Processo Inflamatório

Melatonina atua no rolamento e adesão de leucócitos

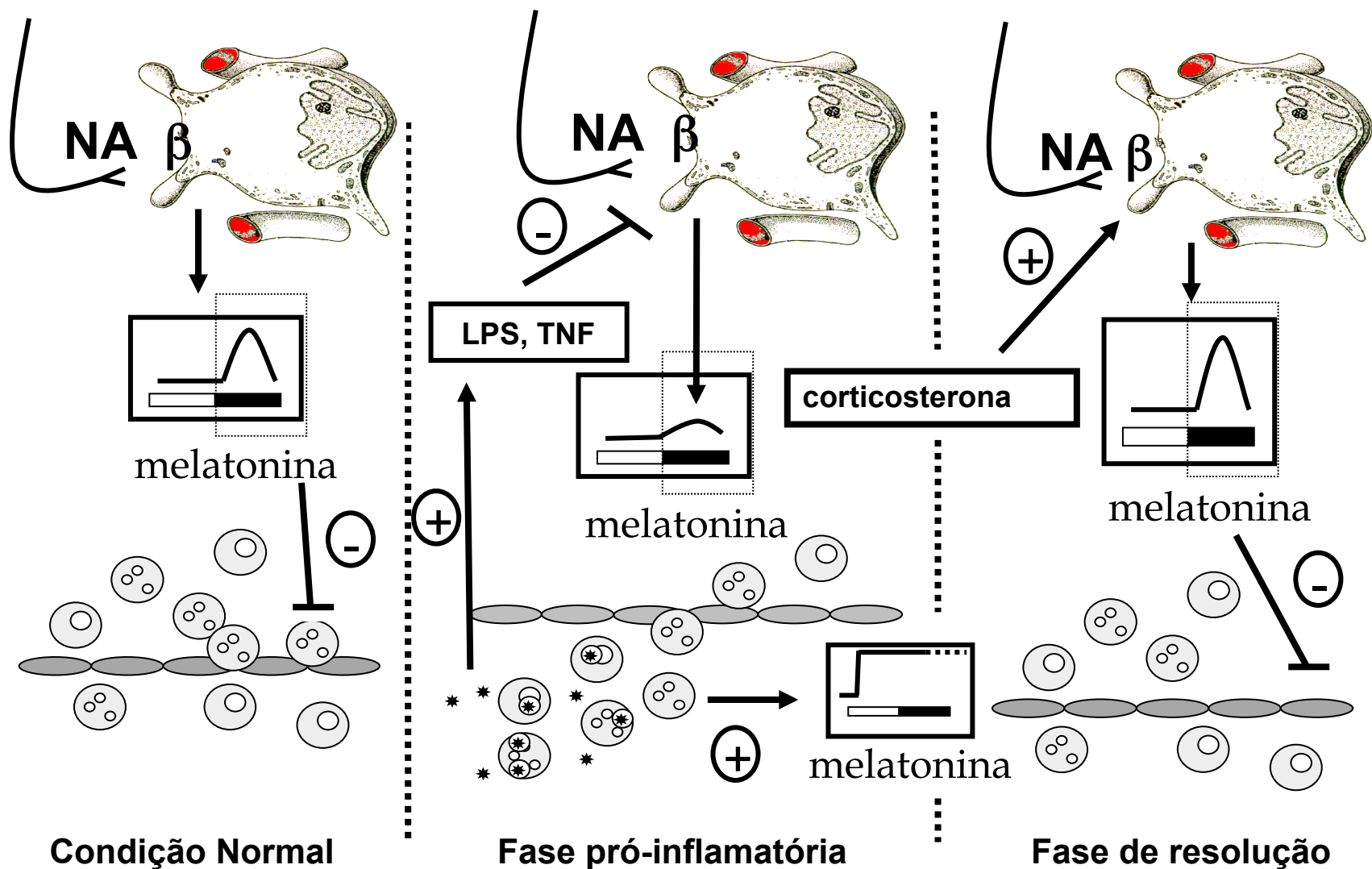


Melatonina e NAS

Inibição do rolamento e adesão de leucócitos



Eixo Imune-pineal



Leituras complementares

Markus RP, Mortani-Barbosa E., Ferreira ZS. **Ritmos biológicos: entendendo as horas, os dias e as estações do ano.**

Einstein, v. 1, p. 143-148, 2003.

disponível em <<http://www.einstein.br/biblioteca/artigos/143%20%20148.pdf>>, acesso em 10/05/2010.

Markus RP, Cecon E. **O tempo biológico e a defesa do organismo: uma conversa bidirecional entre a glândula pineal e o sistema imunológico.**

cienciaecultura.bvs.br/scielo.php?

[pid=S0009-67252013000100021...](http://cienciaecultura.bvs.br/scielo.php?pid=S0009-67252013000100021...)