BIF 214
Fisiologia Animal:
Mecanismos e Adaptação do Controle Interno, *Reprodução* e Defesa

Cronobiologia no sistema endócrino

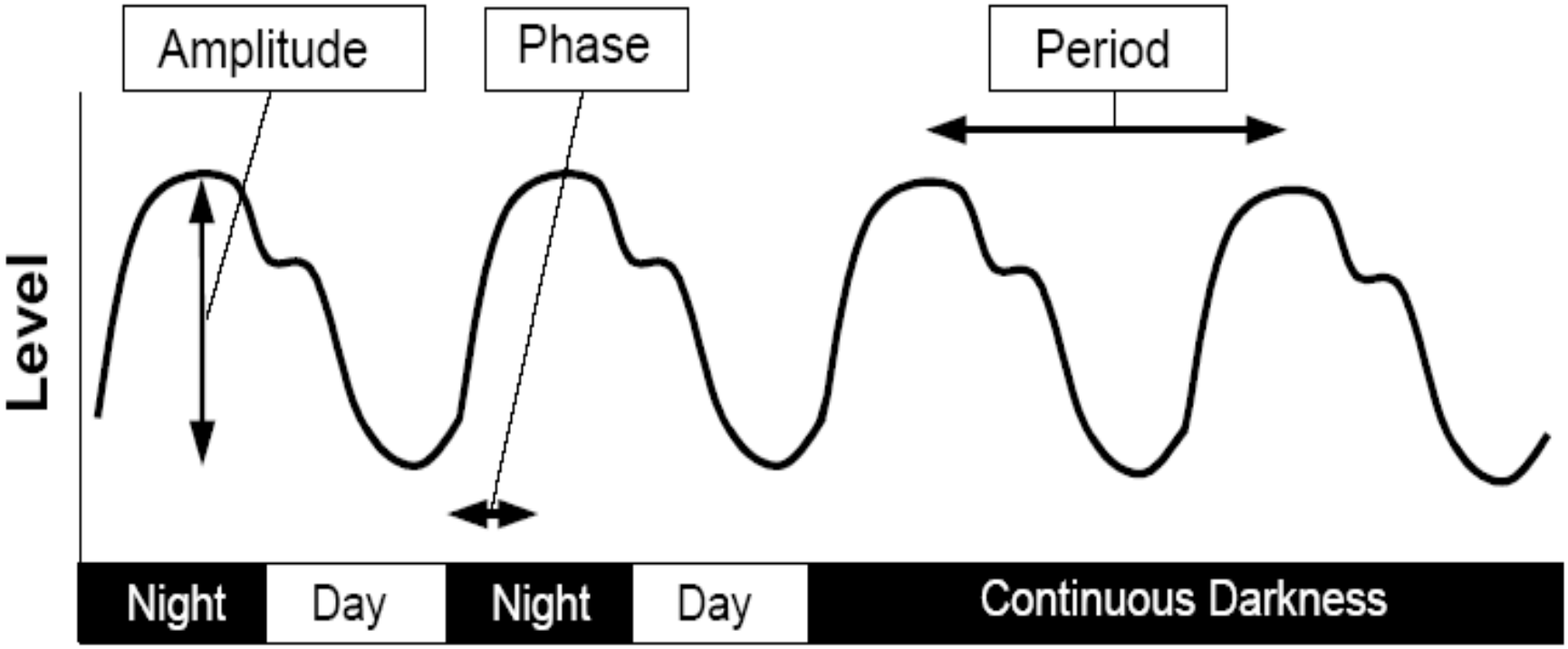
Cronobiologia

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

Ritmos Biológicos

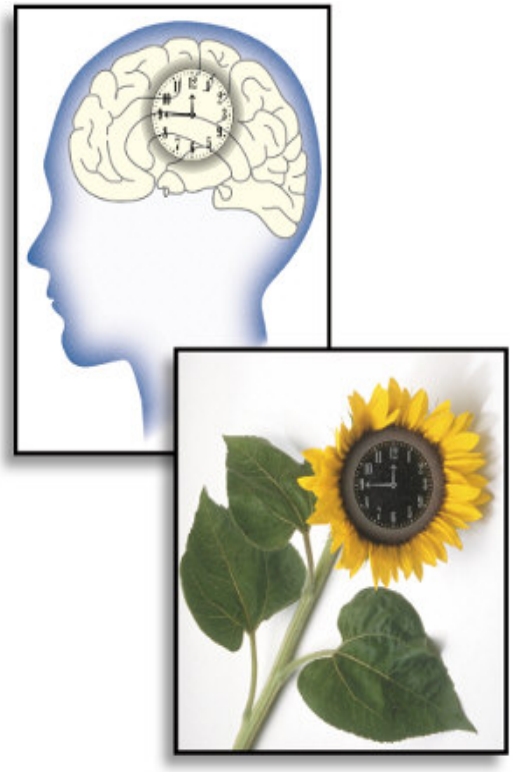
- **Circadianos** – períodos de ~ 24 h
  atividade locomotora
- **Infradianos** – baixa freqüência
  período > 28 h
- **Ultradianos** – batimentos rápidos
  período < 20 h
- **Circanual**

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

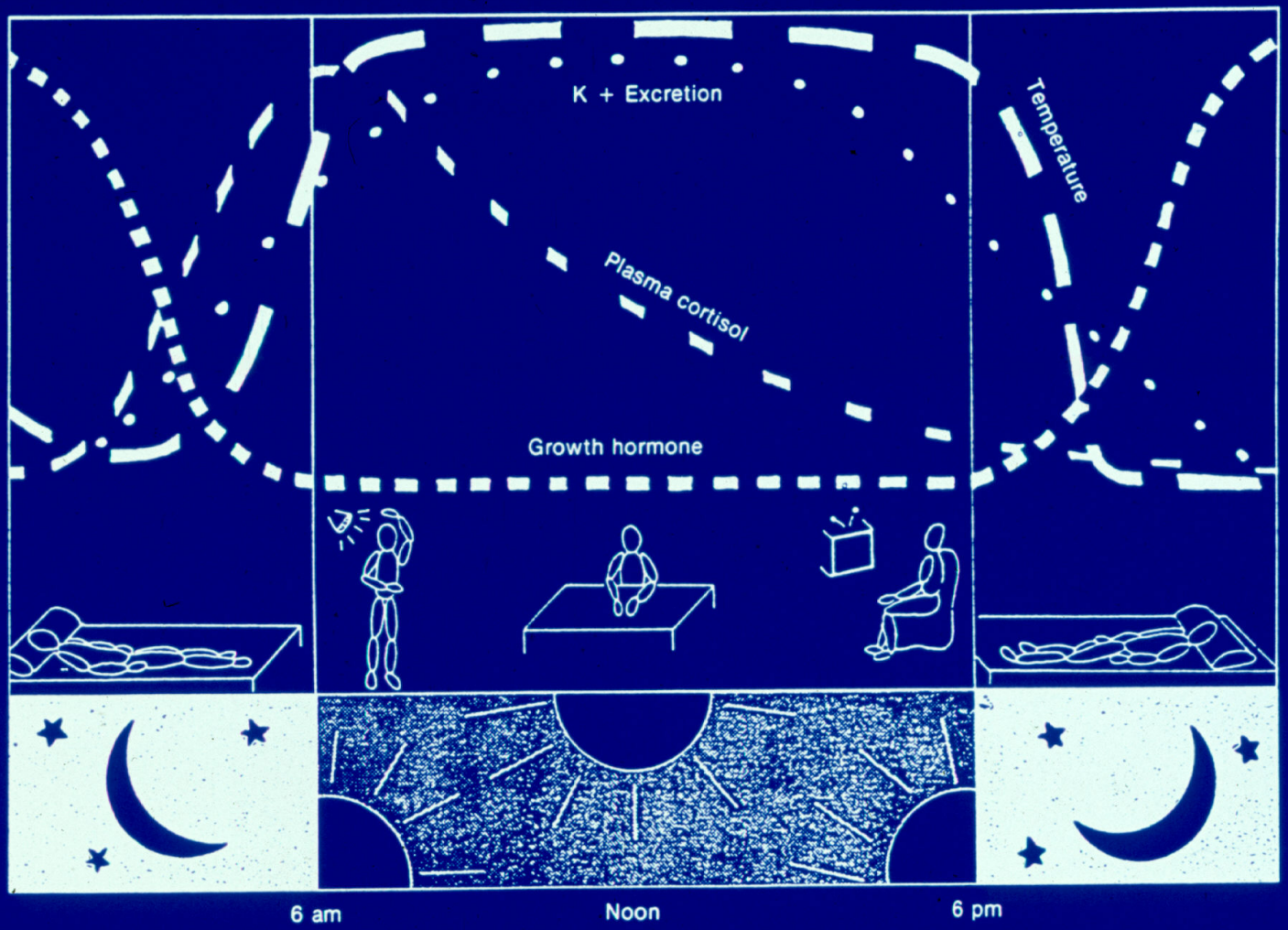
- preparação fisiológica do organismo para responder de forma adequada a eventos recorrentes.

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.

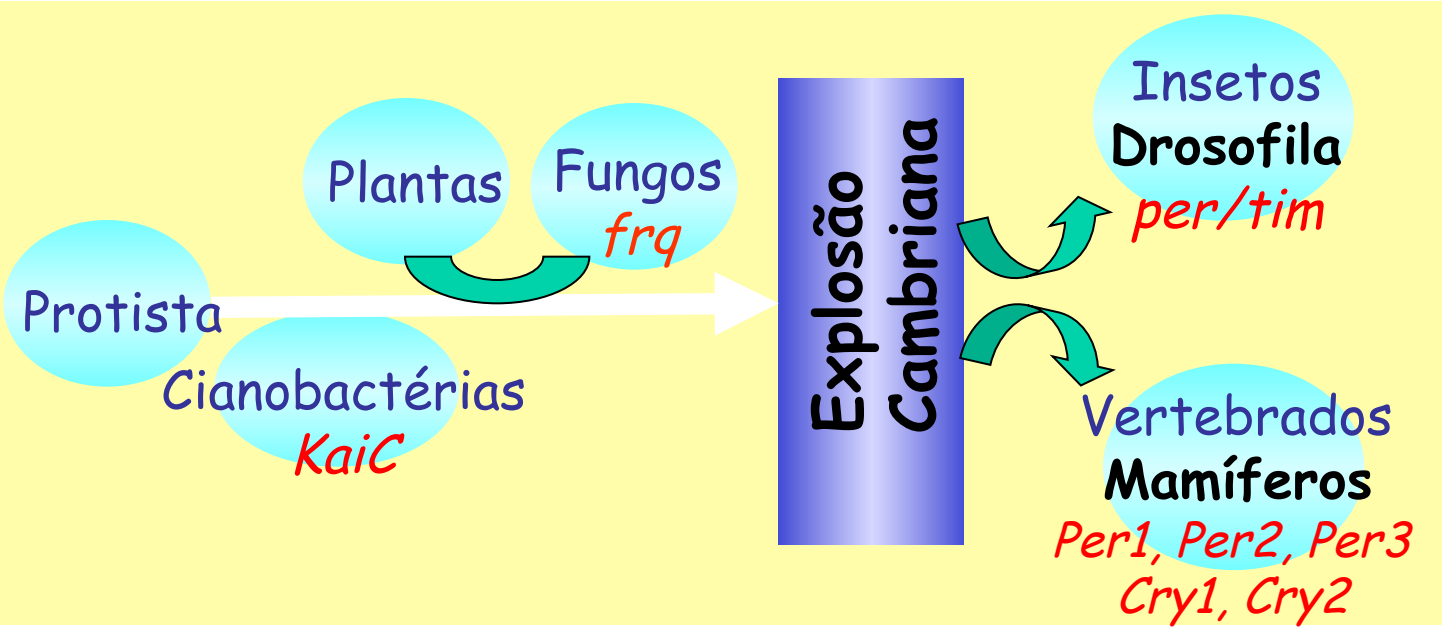
SOURCE: Adapted from G.S. Richardson and J.B. Martin, "Circadian Rhythms in Neuroendocrinology and Immunology: Influence of Aging," *Progress in NeuroEndocrinImmunology* 1:16-20, 1988.

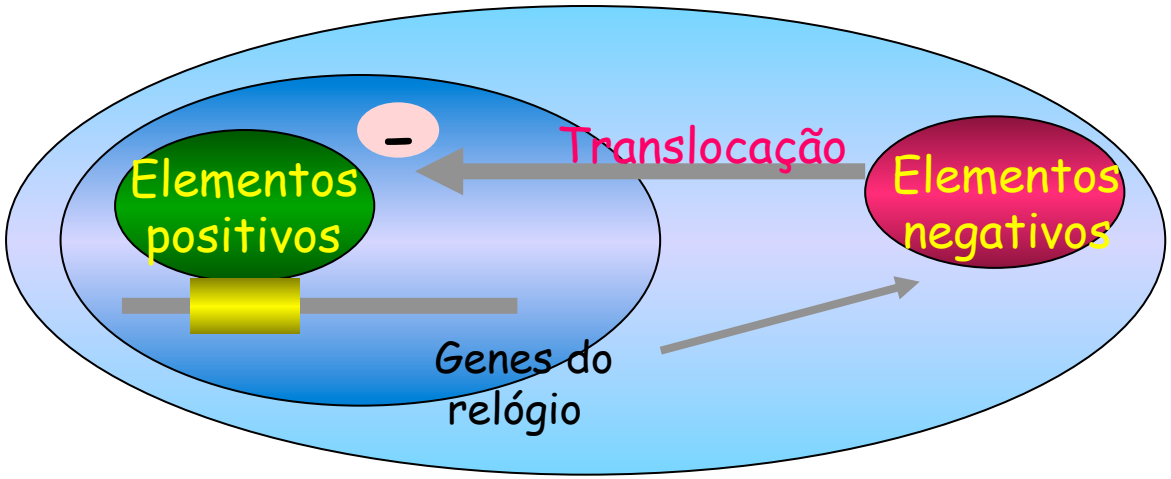
Significado adaptativo do relógio circadiano em cianobactérias

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

(Yan et al., 1998)

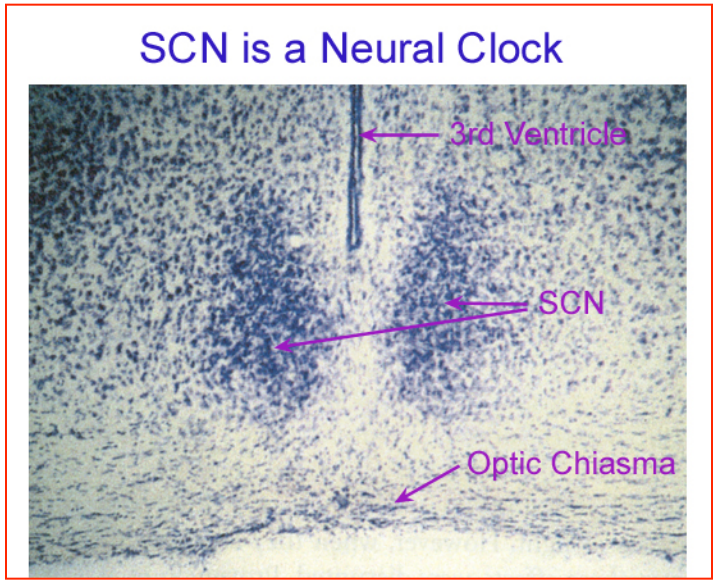
Ritmos Circadianos são gerados por genes do relógio

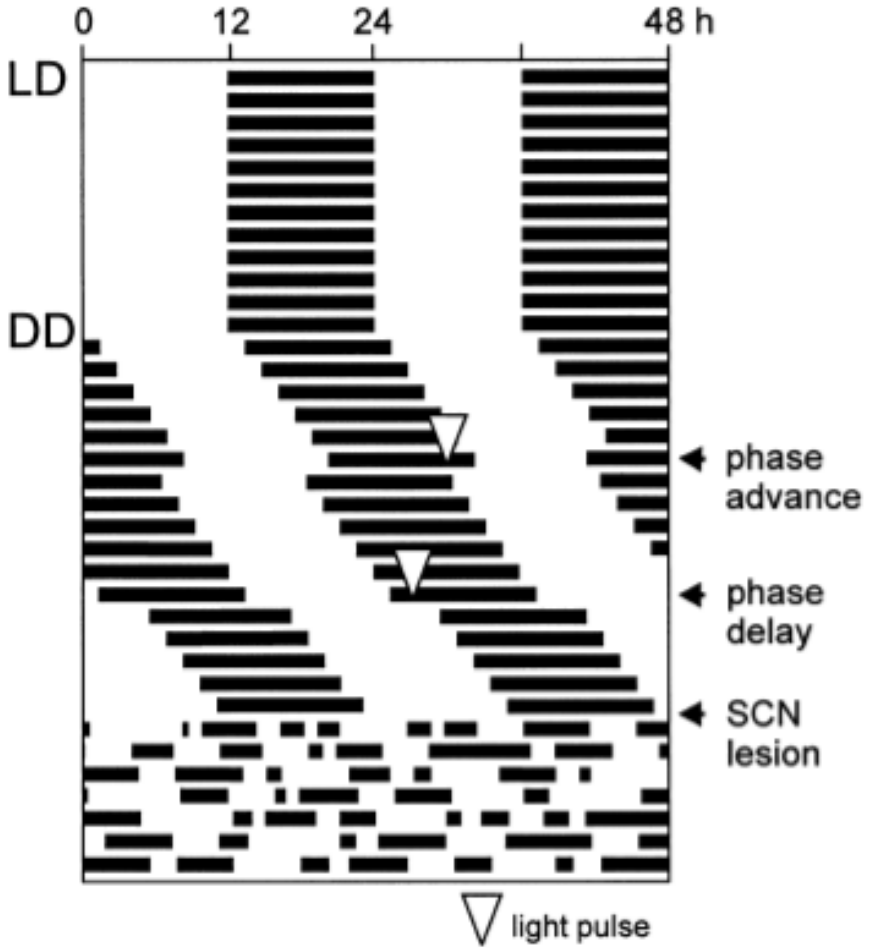




Okamura et al., 2002

Núcleos Supraquiasmáticos – Principal relógio em mamíferos





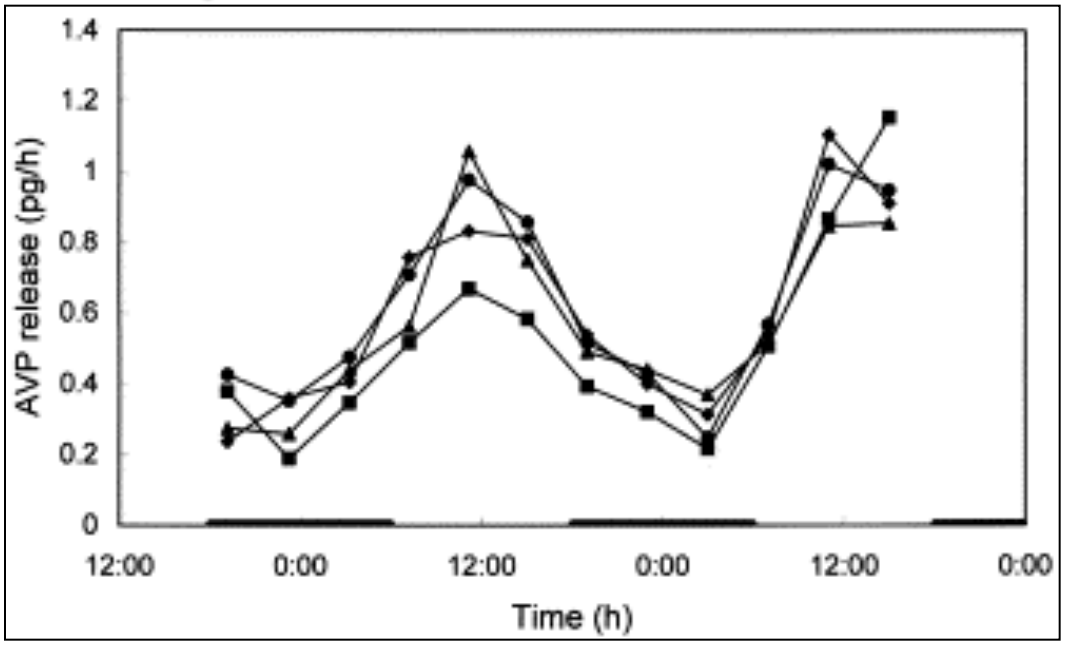
Características

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

Van Esseveldt et al., 2000

O relógio pode funcionar fora do organismo

NSQ "in vitro" também cicla

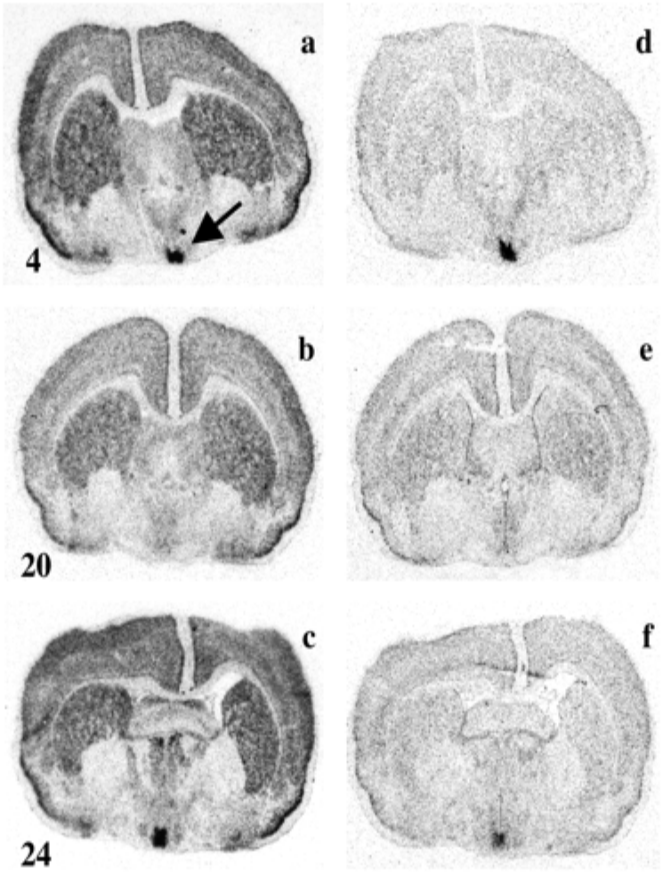


Oscilação circadiana da liberação de AVP de neurônios vasopressinérgicos localizados na porção dorso-medial do NSQ. Células isoladas de animais mantidos em 12:12 - medidas iniciadas logo após inicio da cultura

Watanabe et al., 2000

Expressão rítmica de mPer1 e mPer2

mPer1 →

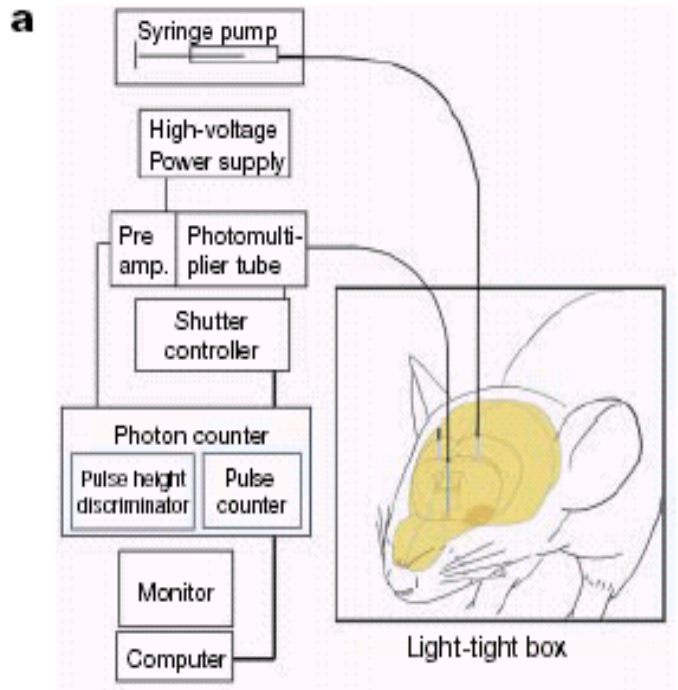


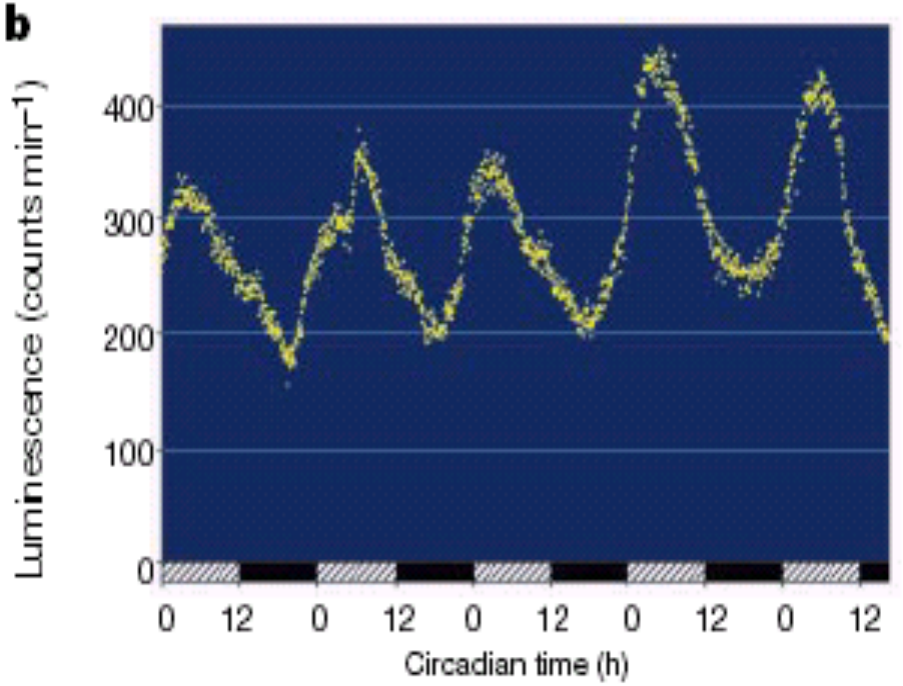
← mPer2

NSQ - Secção coronal

Mayewood E.S. et al., 2000

Expressão rítmica de mPer1 "in vivo"

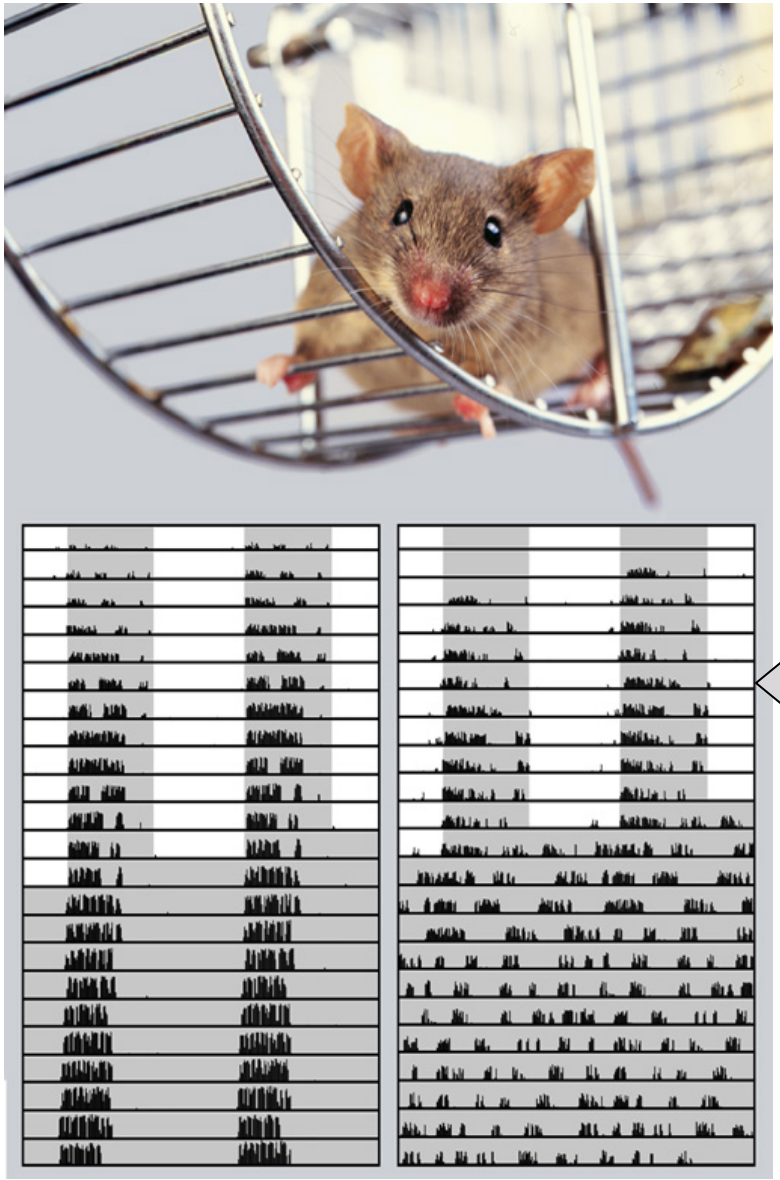




transgênico que expressa mPer1-luc

Flutuação circadiana da bioluminescência no NSQ

normal



cry1 e cry2

http://www.eur.nl/fgg/ch1/gen_research/clock.html

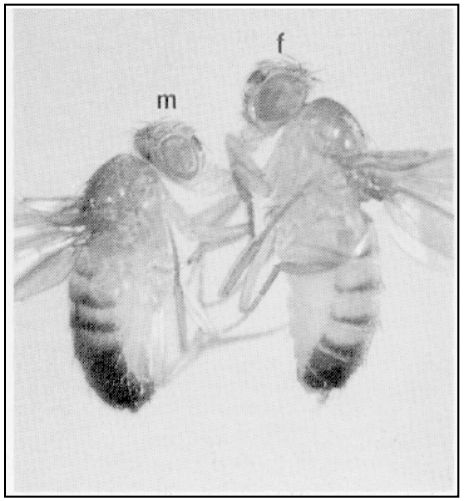
van der Horst et, 1999

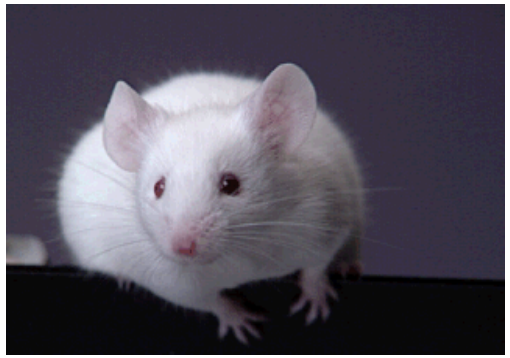
Genes do Relógio Circadiano

- Altamente conservados entre Drosofila 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

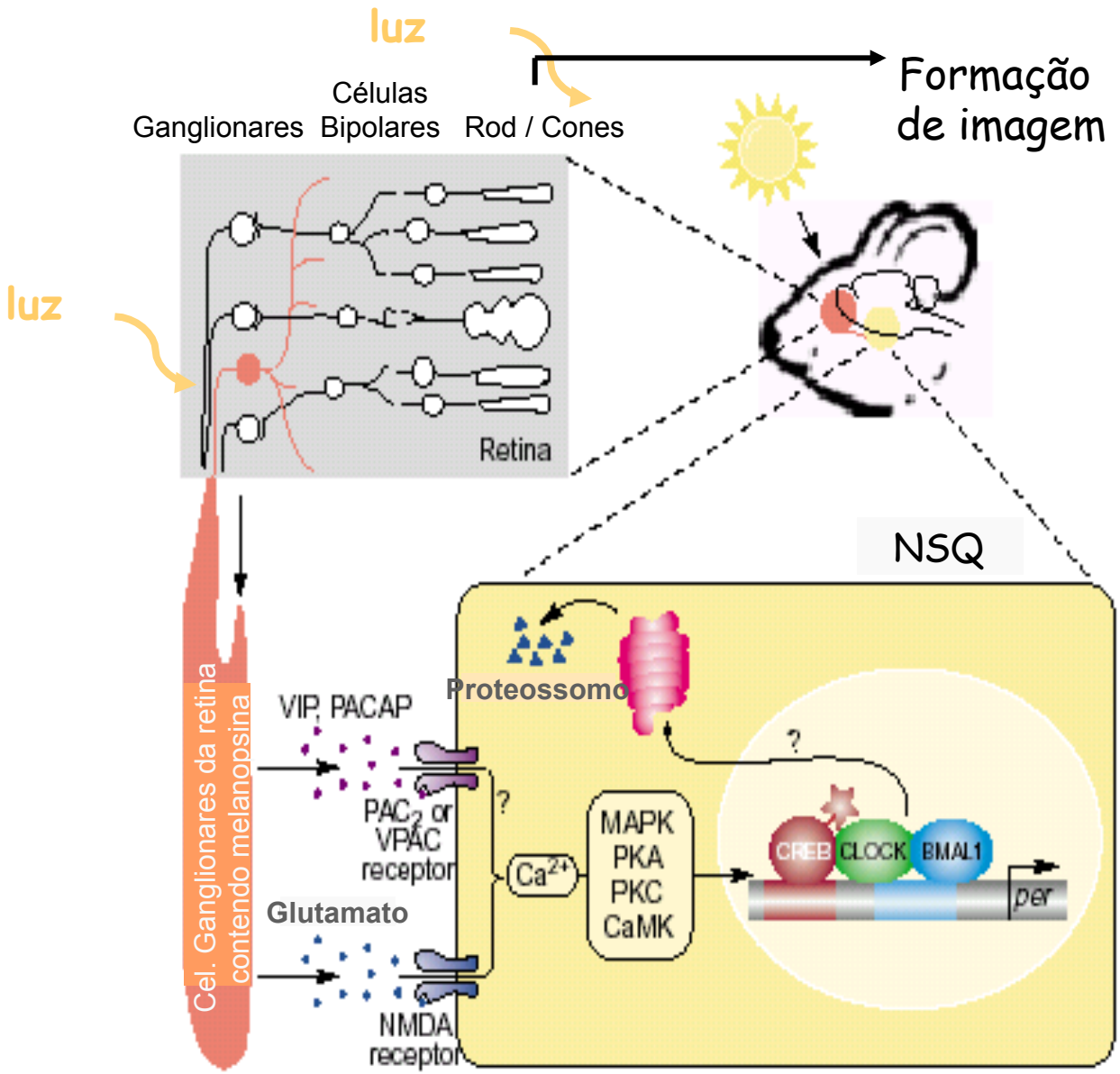
Interface entre o Ambiente e o Relógio - Fotorrecepção

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





Distintos fotorreceptores na retina de mamíferos



Morse e Sassoni-Corsi, 2002

Distintos fotorreceptores na retina de mamíferos

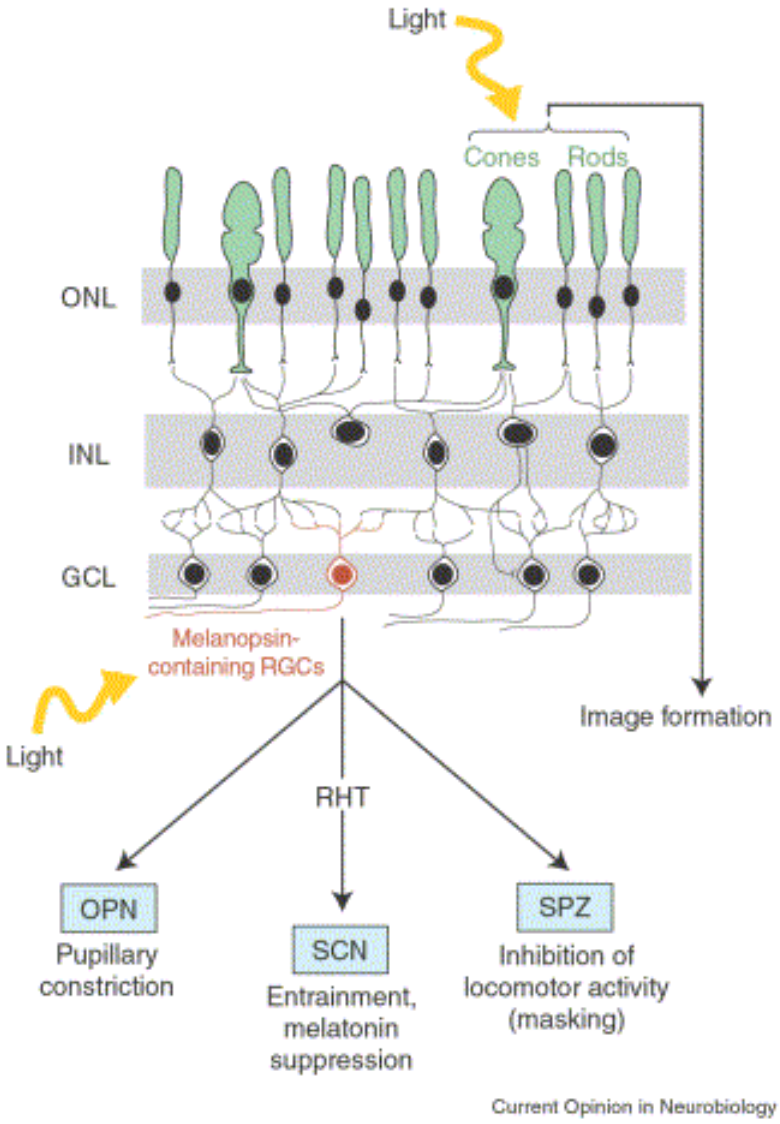
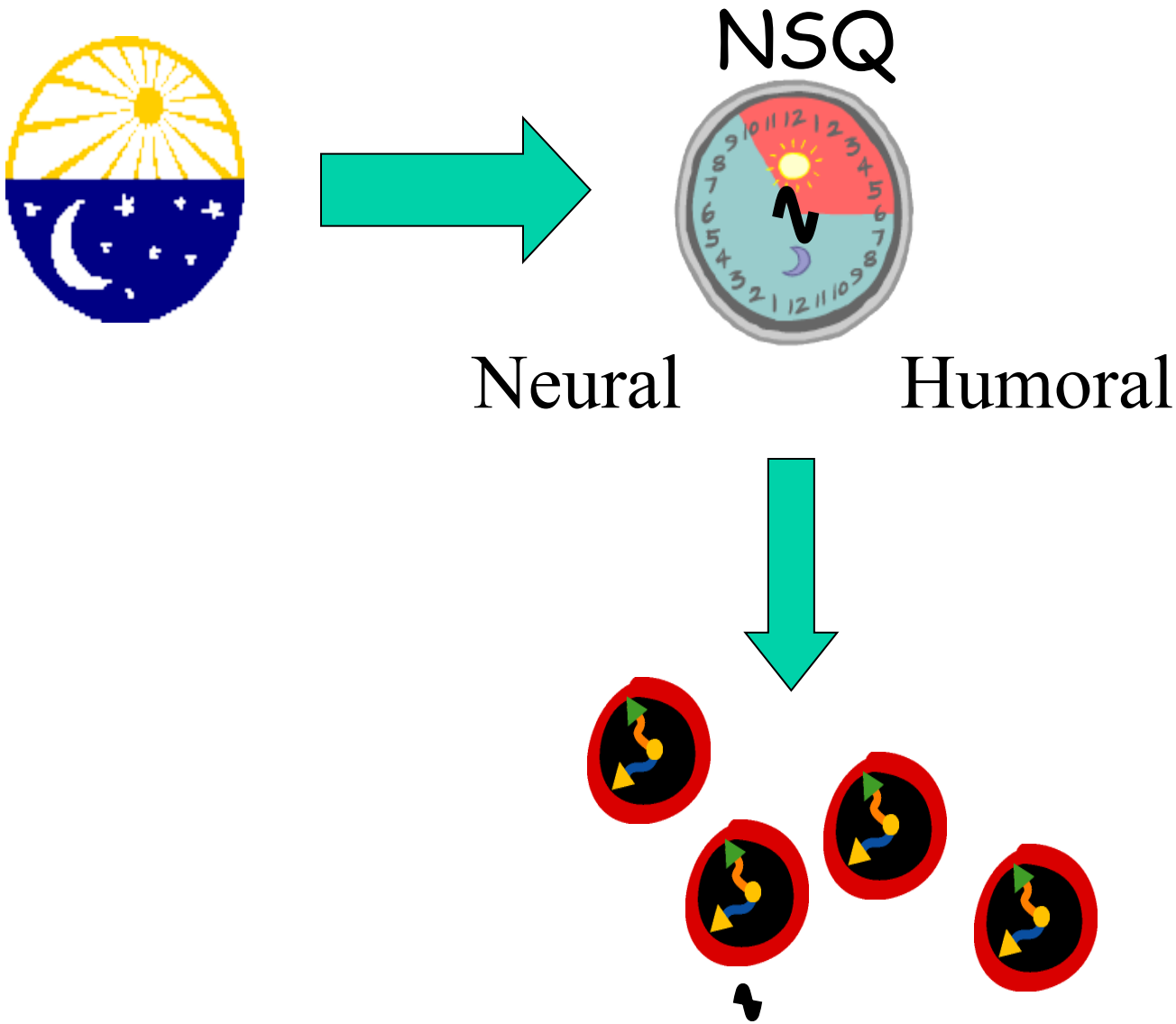


Fig. 2. Distinct photoreceptors in the mammalian retina for vision and non image-forming tasks. Cones and rods mediate light perception for image formation. Other light-regulated processes depend on different photoreceptors within the retina. These non image-forming processes are thought to involve a 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.

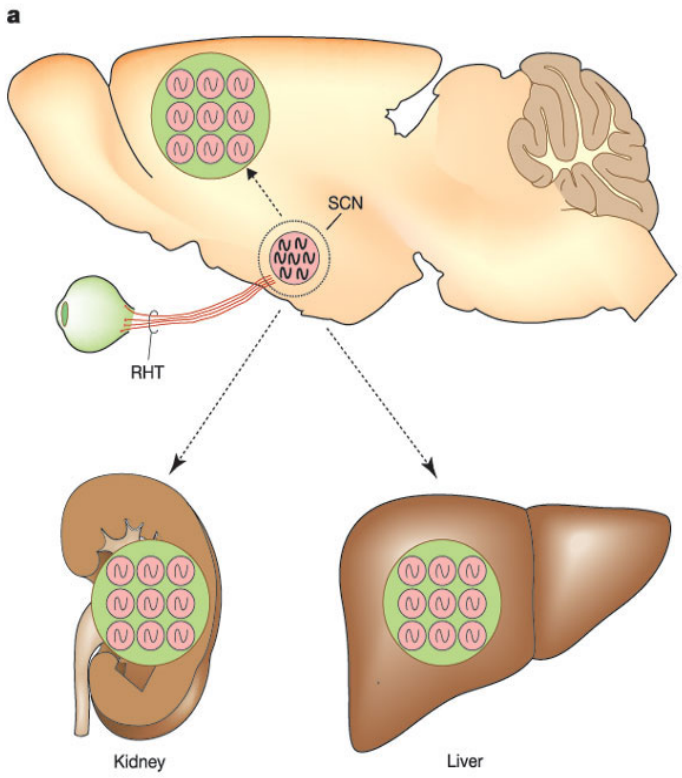
Cermakian N and Sassone-Corsi, P. 2001

Estrutura Molecular do Relógio – Presente em todos os tecidos

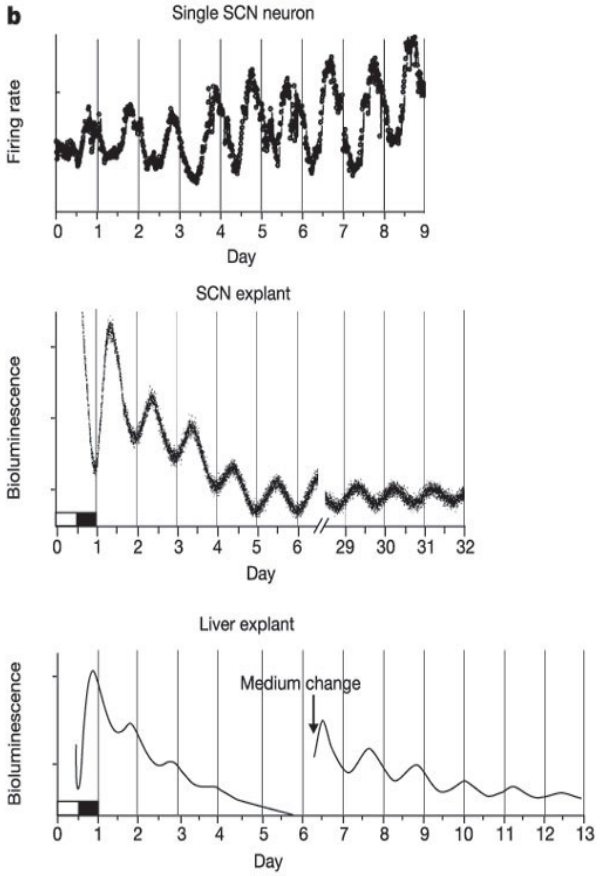


Distribuição hierárquica de relógios

Múltiplos osciladores circadianos hierárquicos

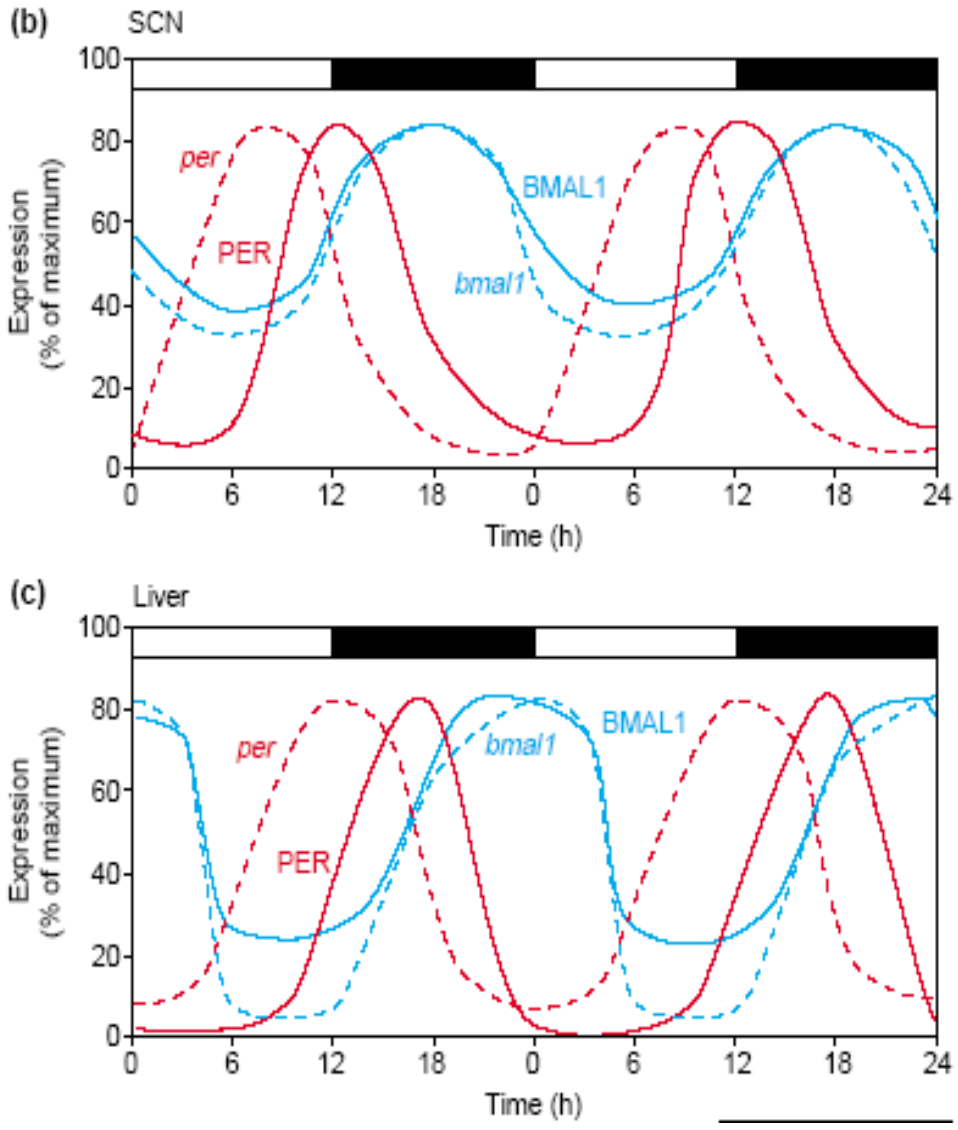


cada célula é o oscilador

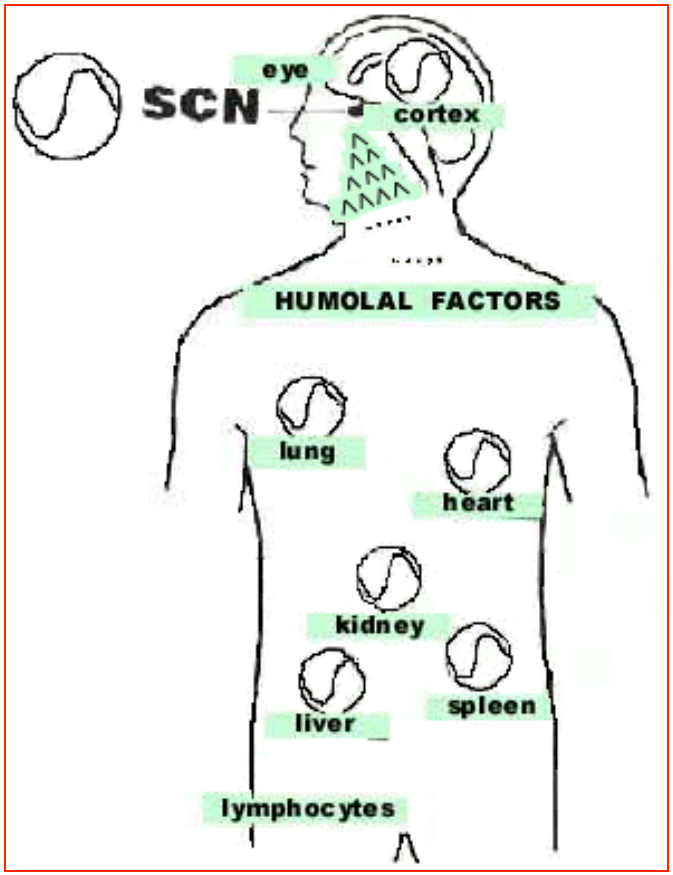


Componentes bioquímicos responsáveis pelos servo-osciladores e pelo oscilador principal são muito semelhantes

Reppert & Weaver, 2002


(b)
SCN
100
80
60
40
20
0
Expression
(% of maximum)
per
PER
BMAL1
bmal1
0
6
12
18
0
6
12
18
24
Time (h)
(c)
Liver
100
80
60
40
20
0
Expression
(% of maximum)
per
PER
bmal1
BMAL1
0
6
12
18
0
6
12
18
24
Time (h)

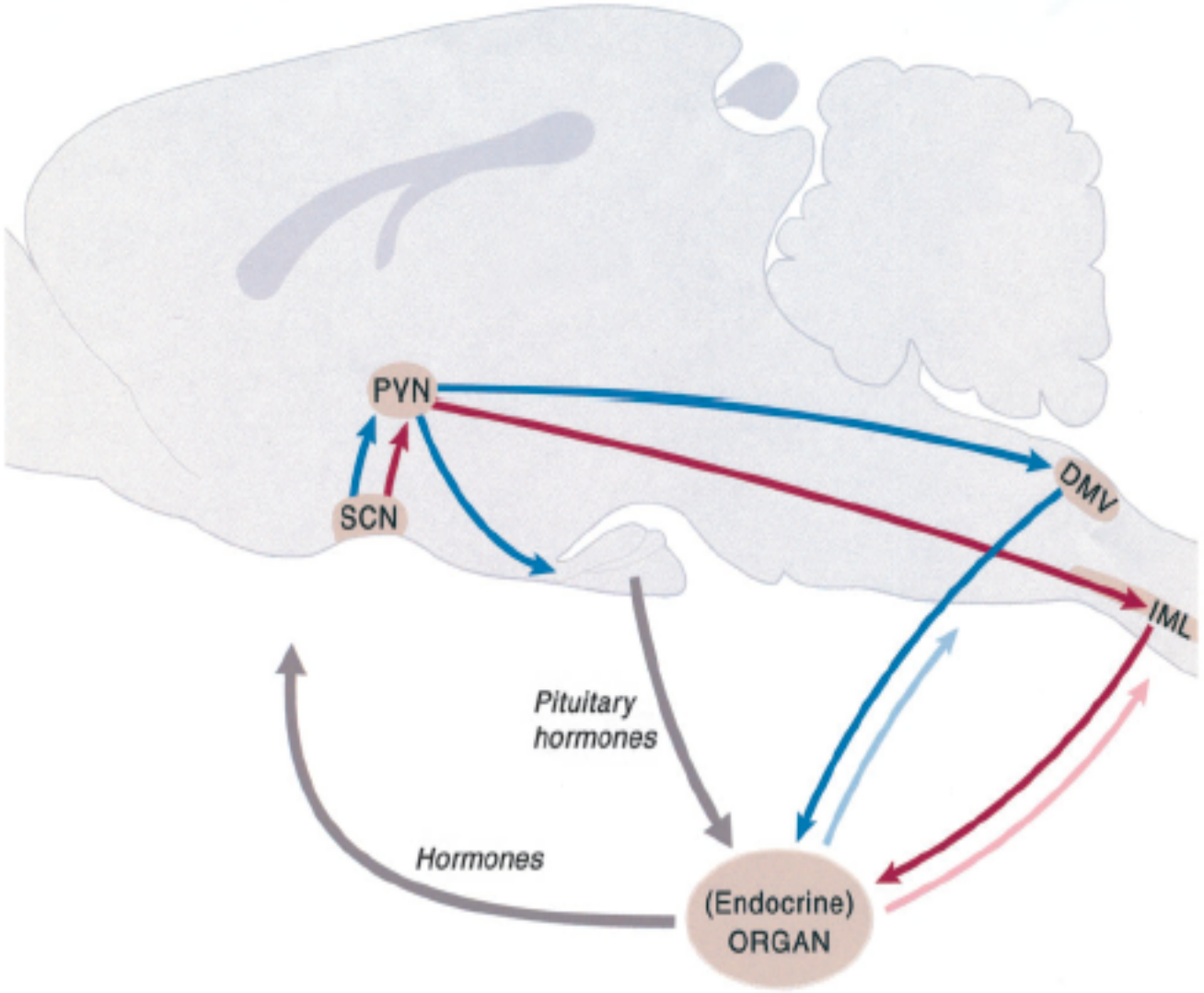
O SCN é responsável por vários ritmos fisiológicos



Lesão dos SCN afetam:

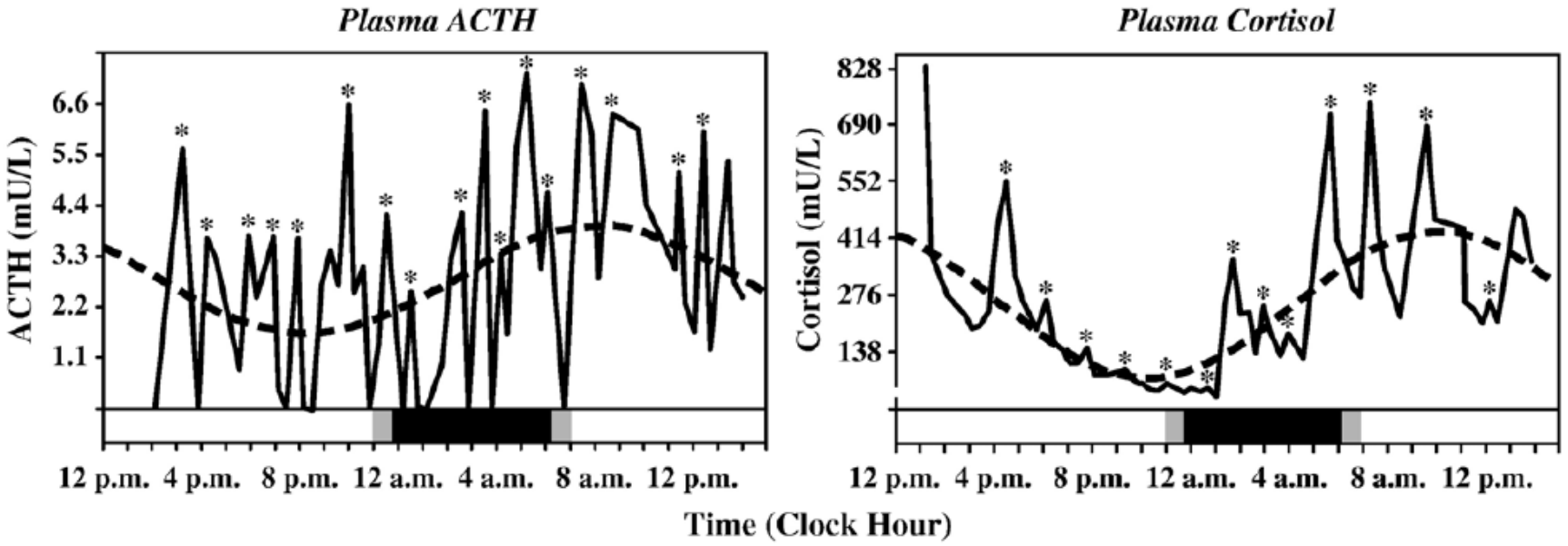
1 – locomoção (Rusak, 1977)
2 – ingesta (Boulos et al., 1980)
3 – comportamento sexual (Eskes et al., 1983, Sodersten et al., 1981)
4 – temperatura corporal (Eastman et al., 1983)
5 – ciclo sono-vigília (Eastman et al., 1983)
6 – produção hormonal - (corticosterona pela adrenal de ratos (Moore & Elchler,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

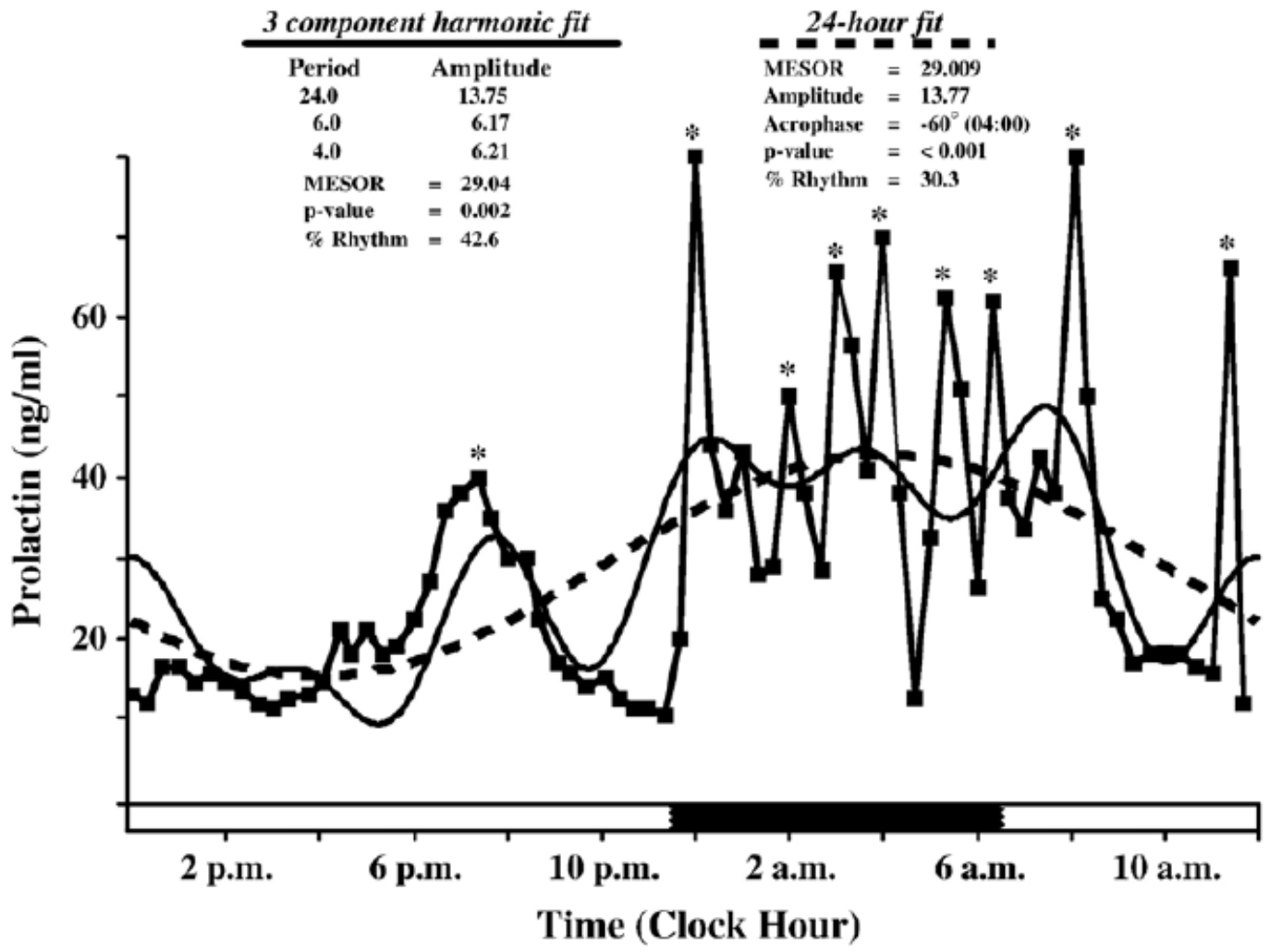


- Secreção pulsátil superimposta e modulada por um ritmo circadiano
- Aumento do pico no final da noite e começo da manhã l

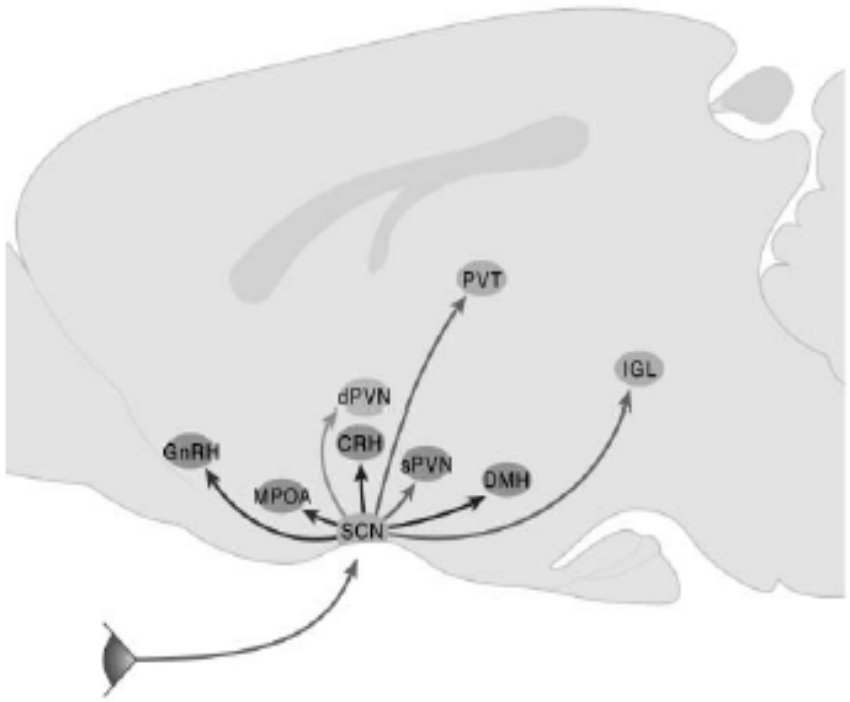
↓

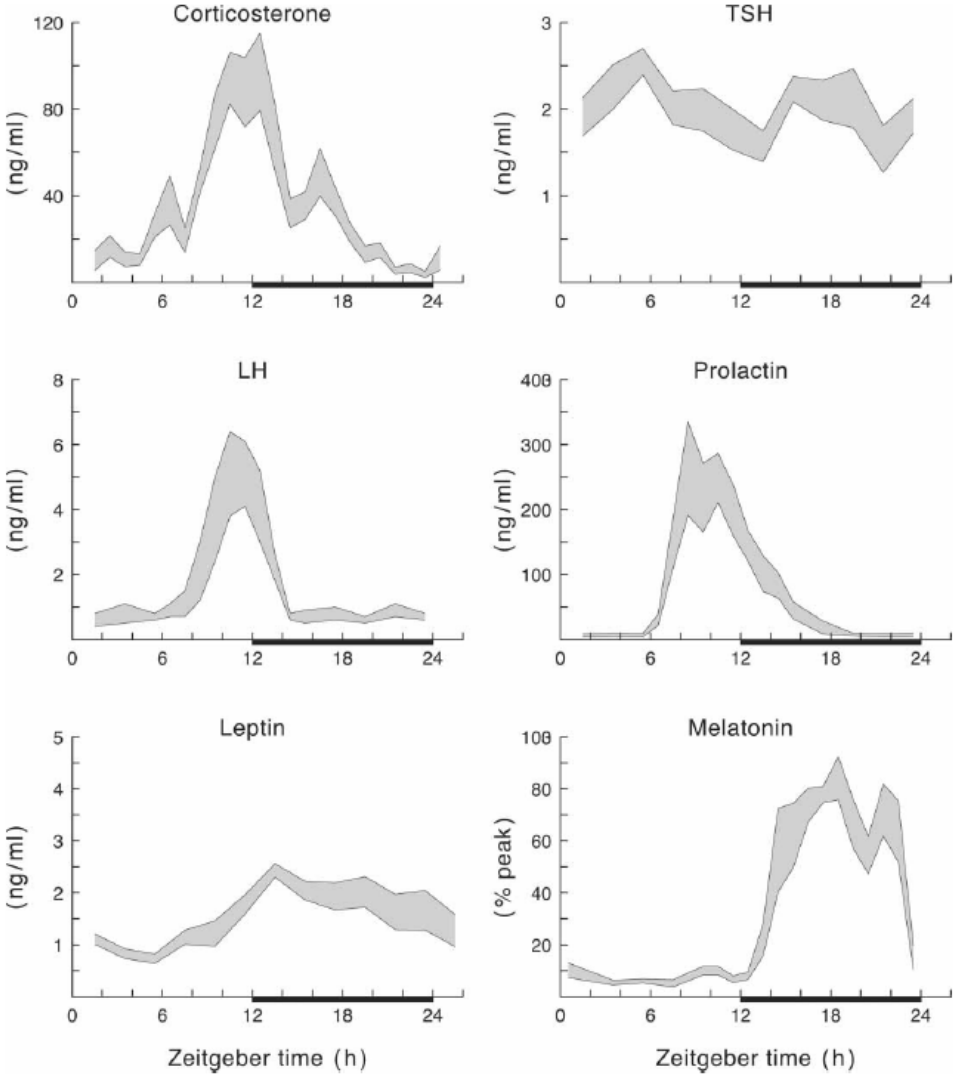
variação circadiana da concentração hormonal

Prolactina – variação ritmica e secreção pulsatil



Alvos do NSQ
Ritmos hormonais de mamiferos de habito noturno

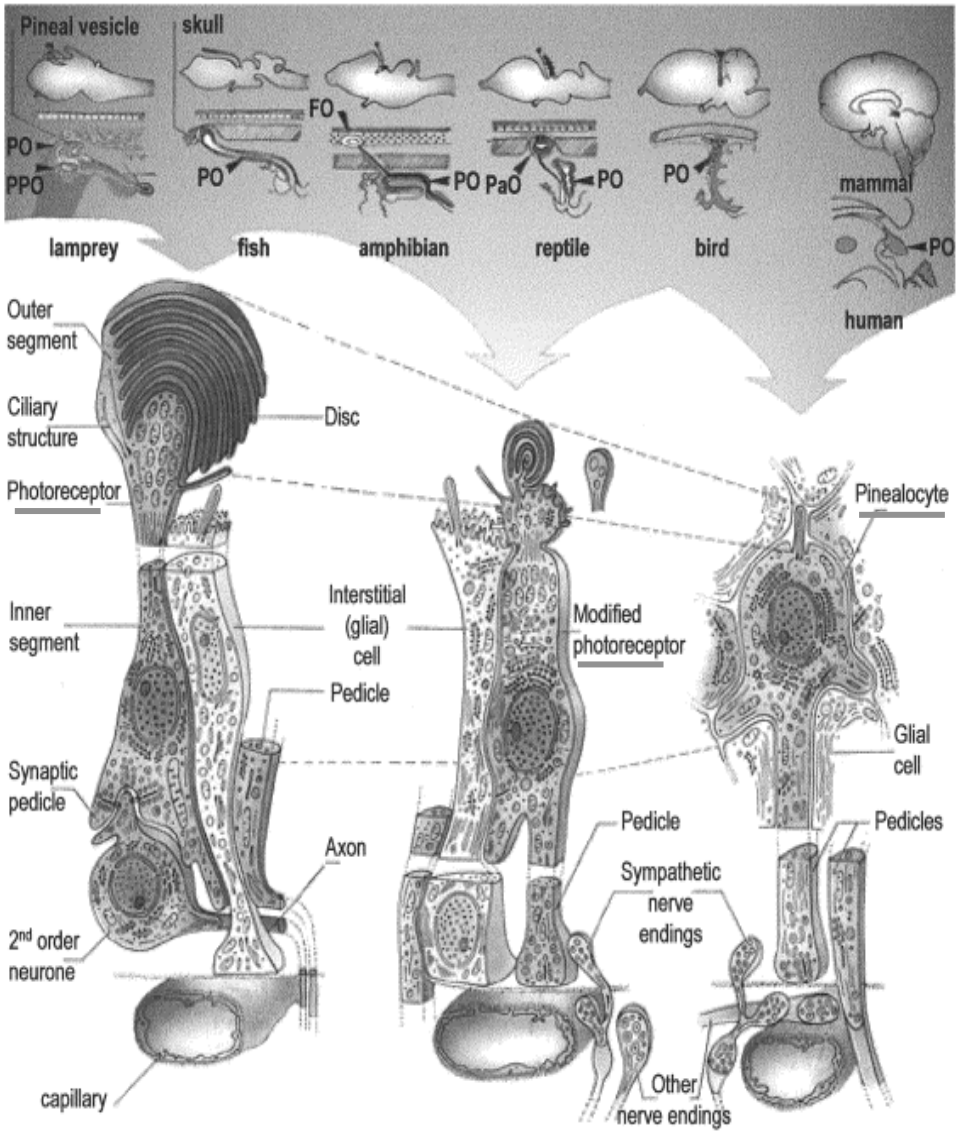




Kalsbeek et al., 2006

Morfologia Comparativa da Pineal

Órgão fotossensível → **Transformação Funcional** / **Transformação Estrutural** → **Órgão neuroendócrino**



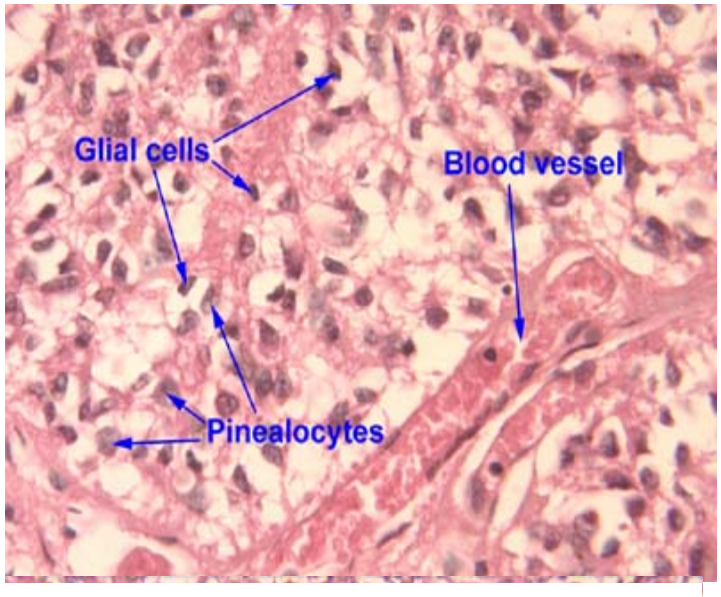
Fálcon, 1999

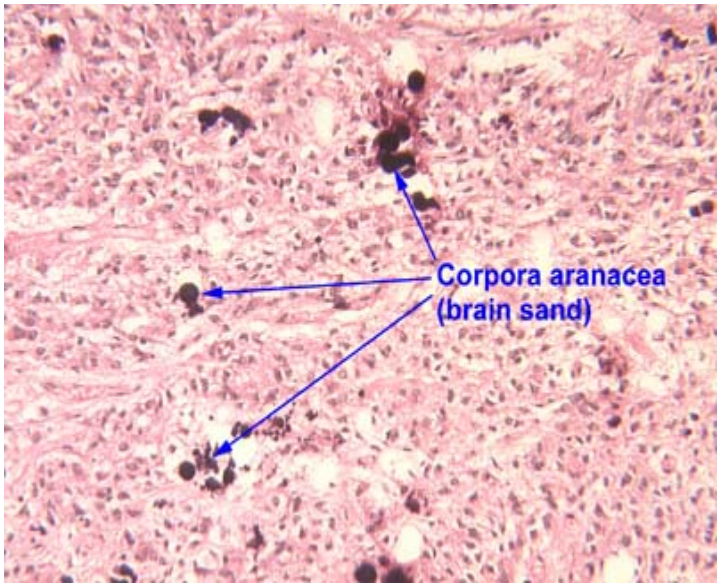
Diversidade Anatômica e Funcional da Pineal

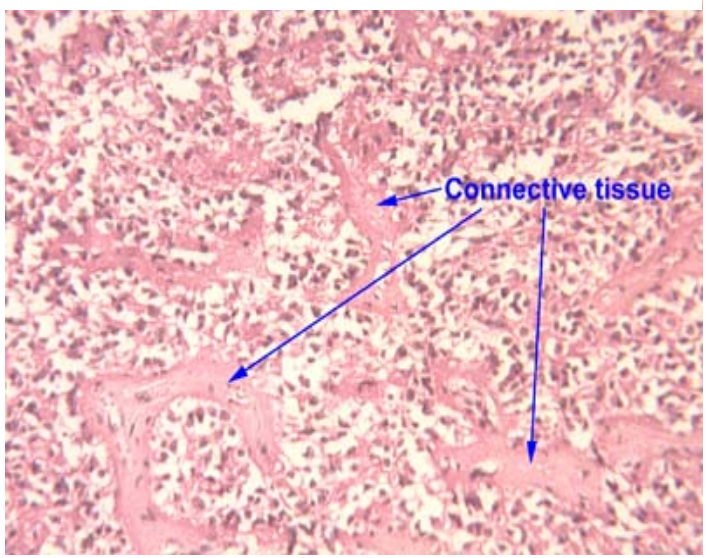
Reflexo das funções às quais está implicada:

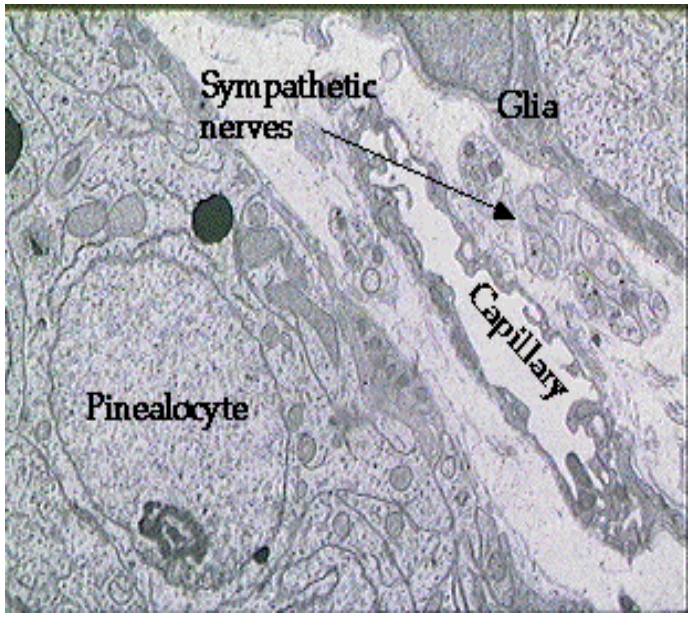
- Pigmentação da pele
- Fototaxia
- Orientação
- Locomoção
- Respostas metabólicas e termoregulatórias
- Outros eventos ritmicos

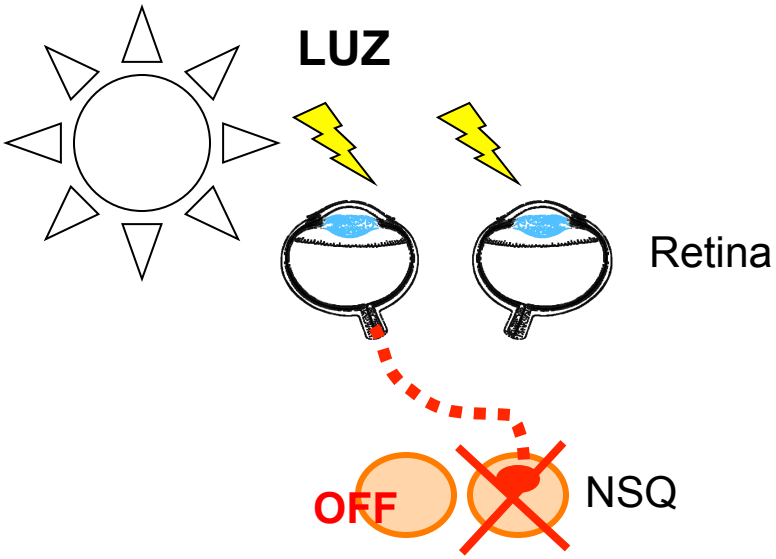
Glândula Pineal

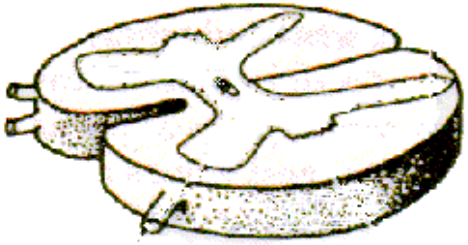


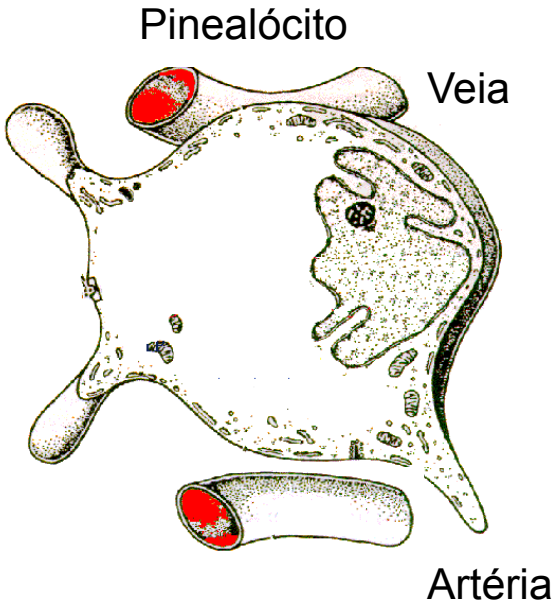




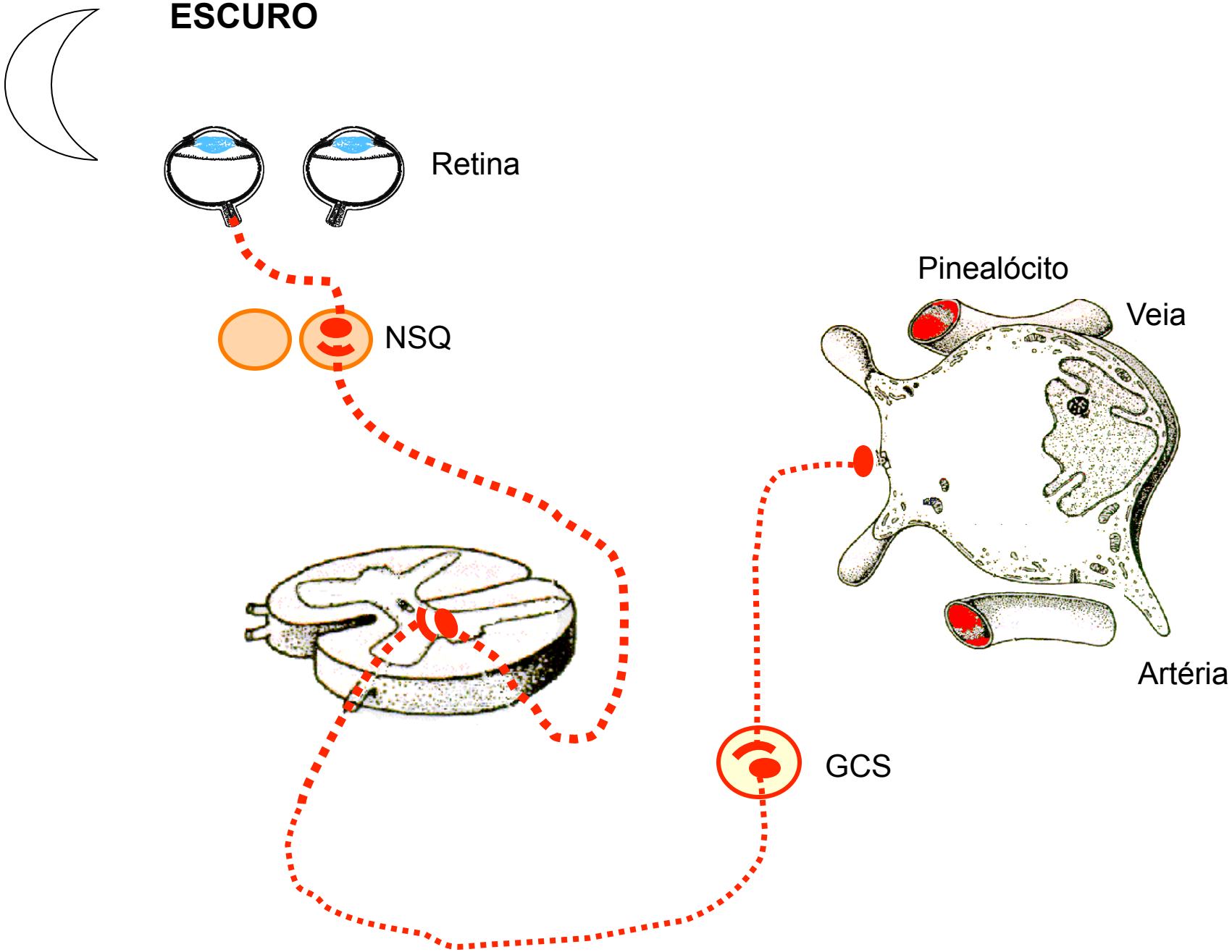


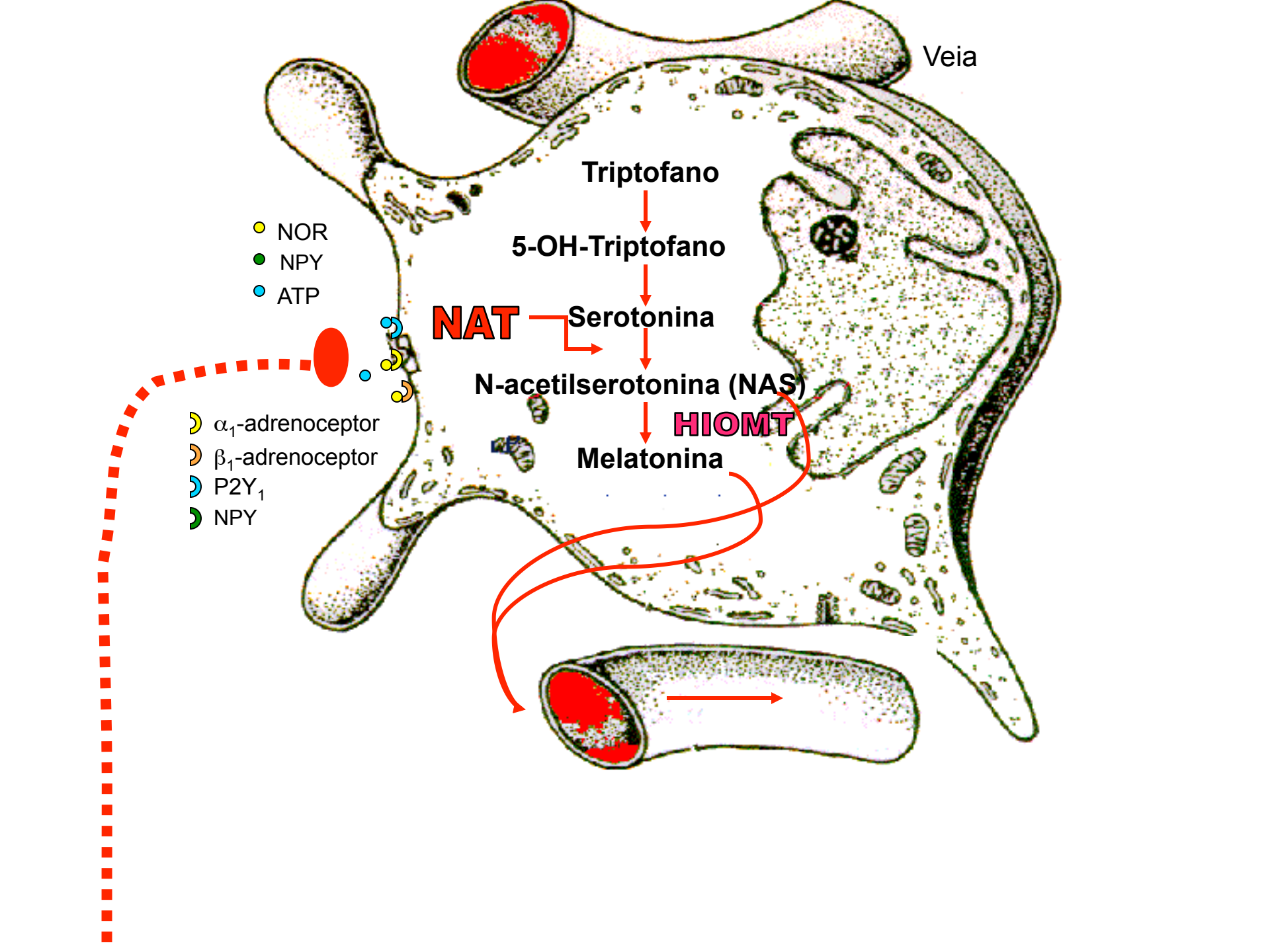


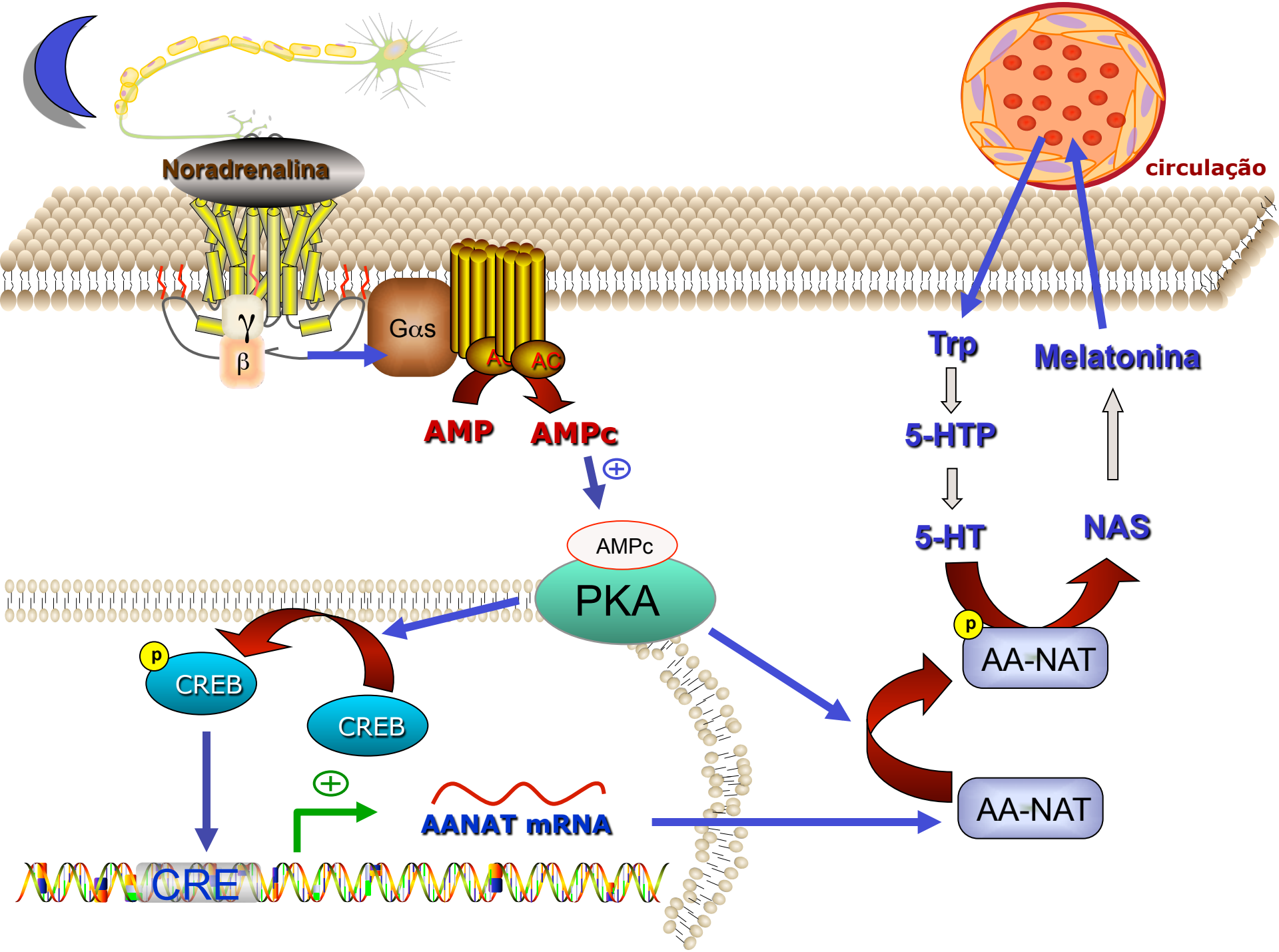




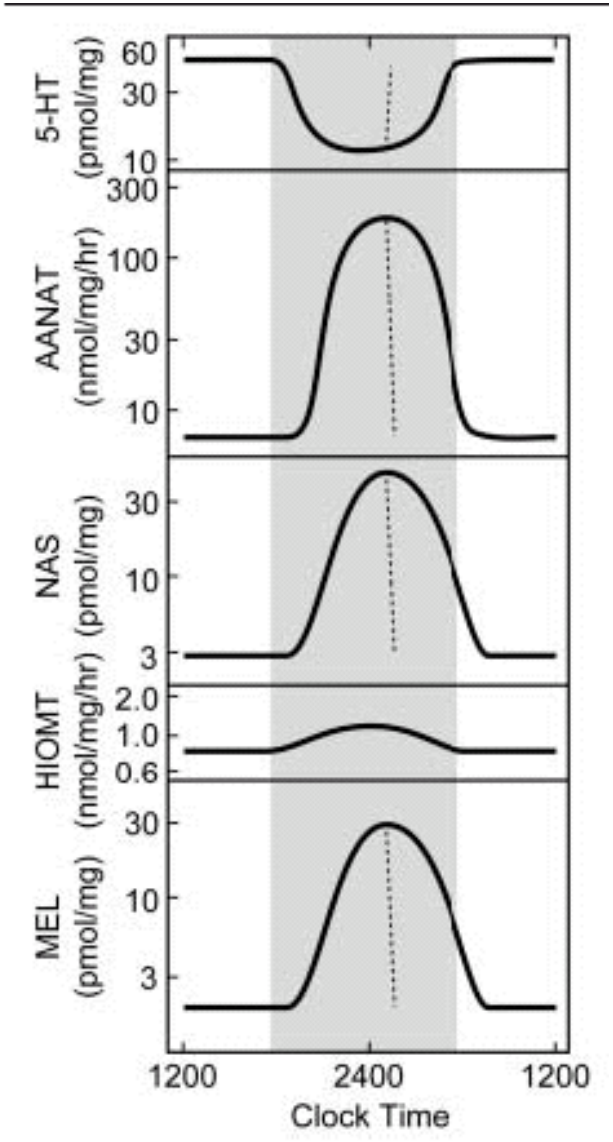
GCS


ESCURO
Retina
NSQ
Pinealócito
Veia
Artéria
GCS


Veia
Triptofano
5-OH-Triptofano
NAT
Serotonina
N-acetilserotonina (NAS)
HIOMT
Melatonina
NOR
NPY
ATP
α_1-adrenoceptor
β_1-adrenoceptor
P2Y$_1$
NPY

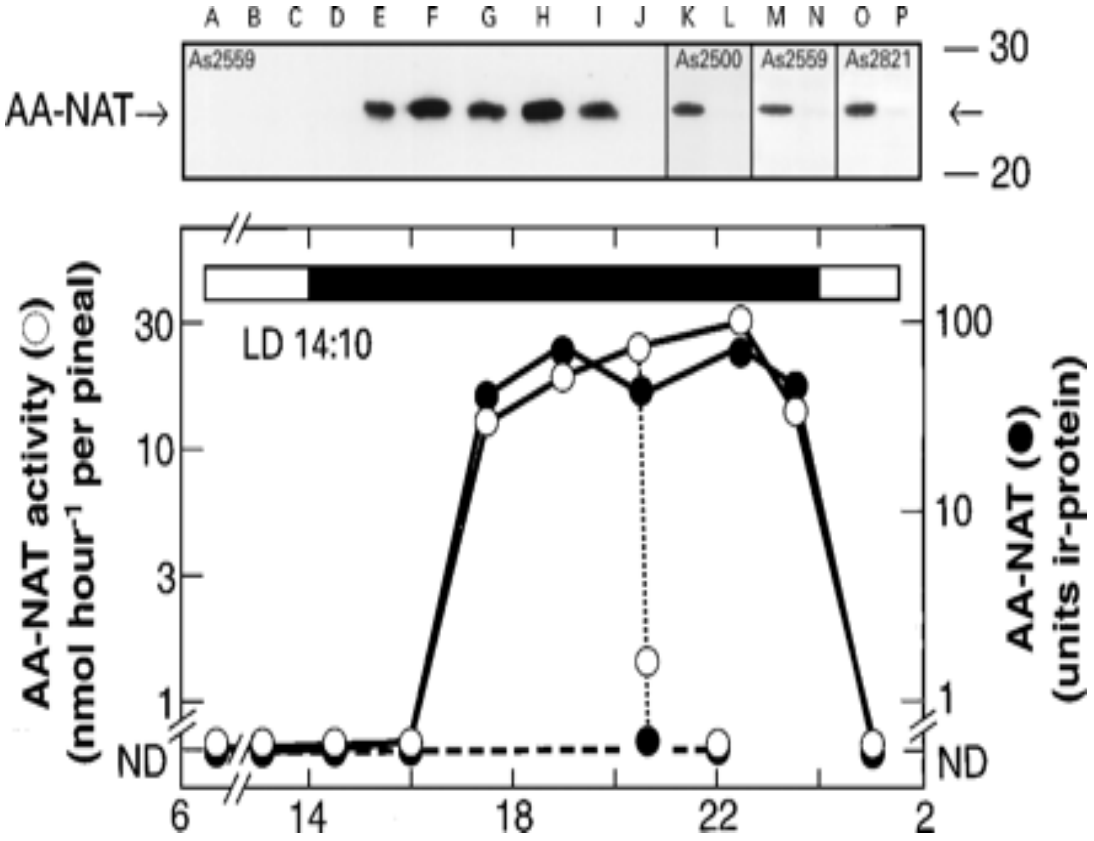

Noradrenalina
γ
β
Gαs
AC
AMP
AMPc
circulação
Trp
5-HTP
5-HT
Melatonina
NAS
AMPc
PKA
p
CREB
CREB
p
AA-NAT
AA-NAT
AANAT mRNA
CRE

Ritmos no metabolismo da glândula pineal



Klein, 2004

AA-NAT na glândula pineal de ratos



Gatel et al, 1998c

Controle da produção de melatonina pela pineal

triptofano → 5-HTP → serotonina

~~NAT~~ ↑ AA-NAT

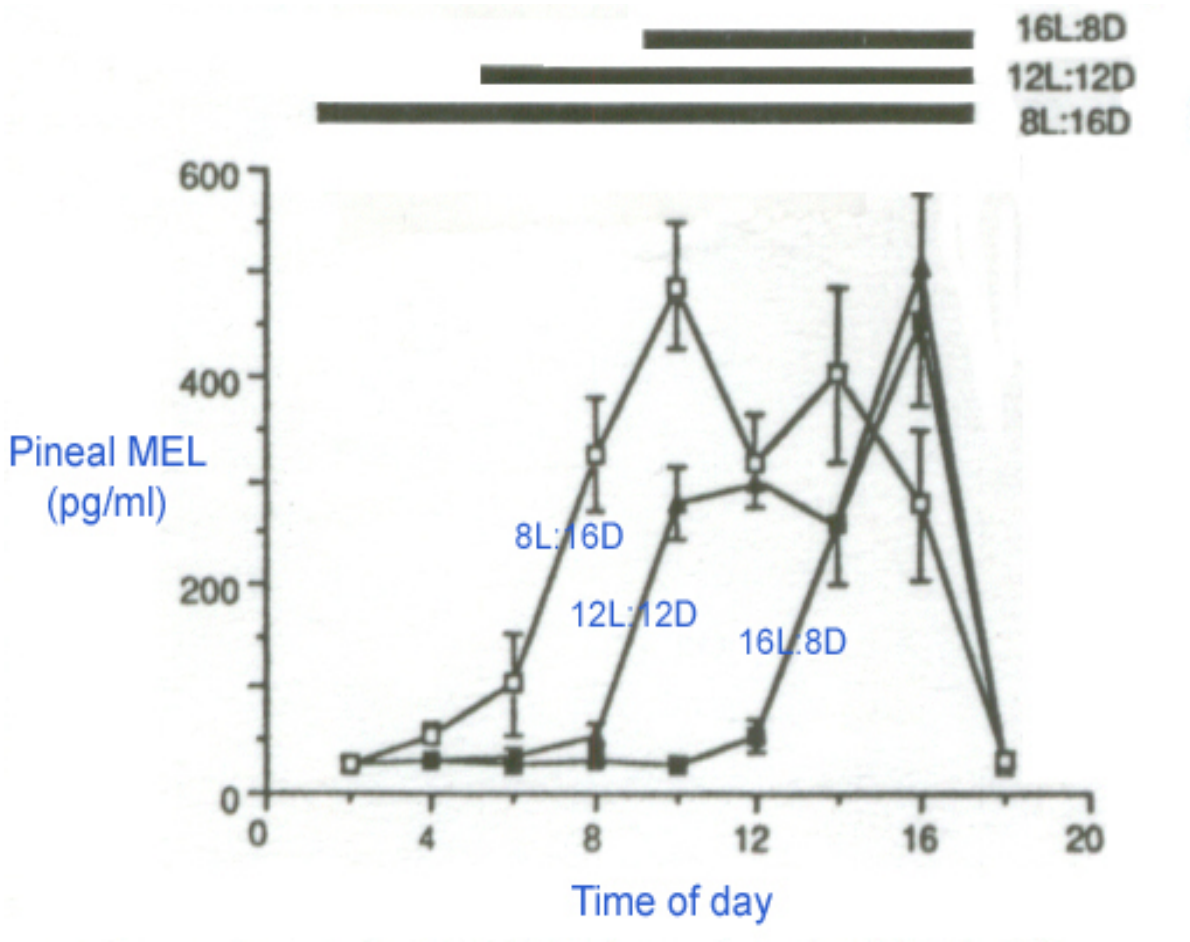
serotonina → N-acetilserotonina (NAS)

↓ HIOMT

Melatonina

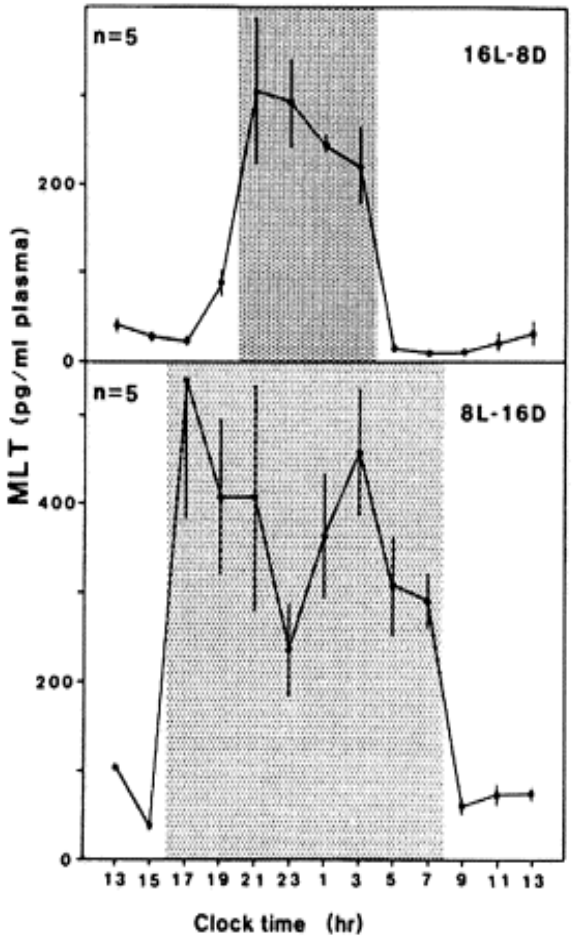
Produção de melatonina inibida

Melatonina – o hormônio marcador do escuro



Importância do Fotoperíodo

adaptação para as estações do ano



Falcon, 1999

Verão

Dias longos, Noites curtas

⇩ melatonina

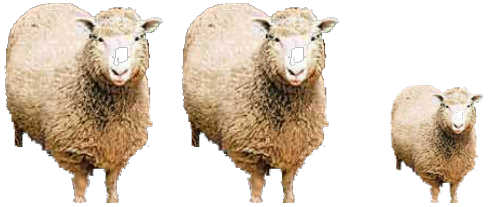
Outono

Inverno

Dias curtos, Noites longas

⇧ melatonina

Primavera

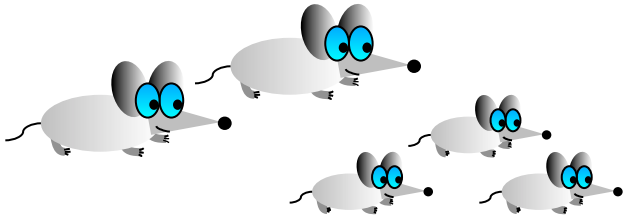


Barbosa. E., 2001

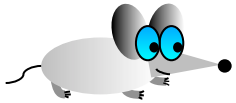
Verão

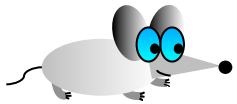
Dias longos, Noites curtas

⇩ melatonina



Outono

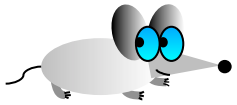


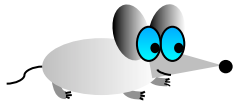


Inverno

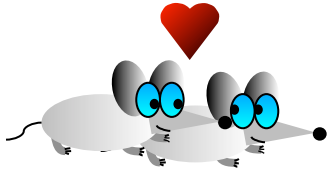
Dias curtos, Noites longas

⇧ melatonina





Primavera



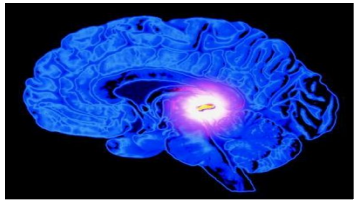
Barbosa. E., 2001

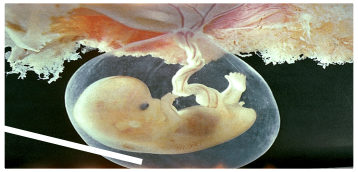
Melatonina - o Hormônio do escuro

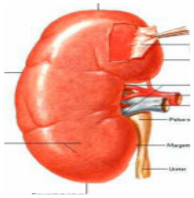
- *Transdutor endocrino da informação fotoperiódica*
- *Importante papel modulador na imunidade inata e adquirida*
  - *periférica*
  - *pineal*

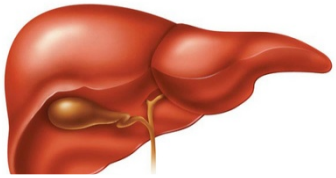
Variação diária de respostas imunes

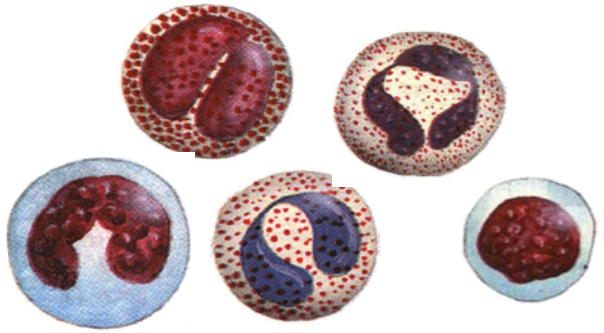
Locais de produção da melatonina







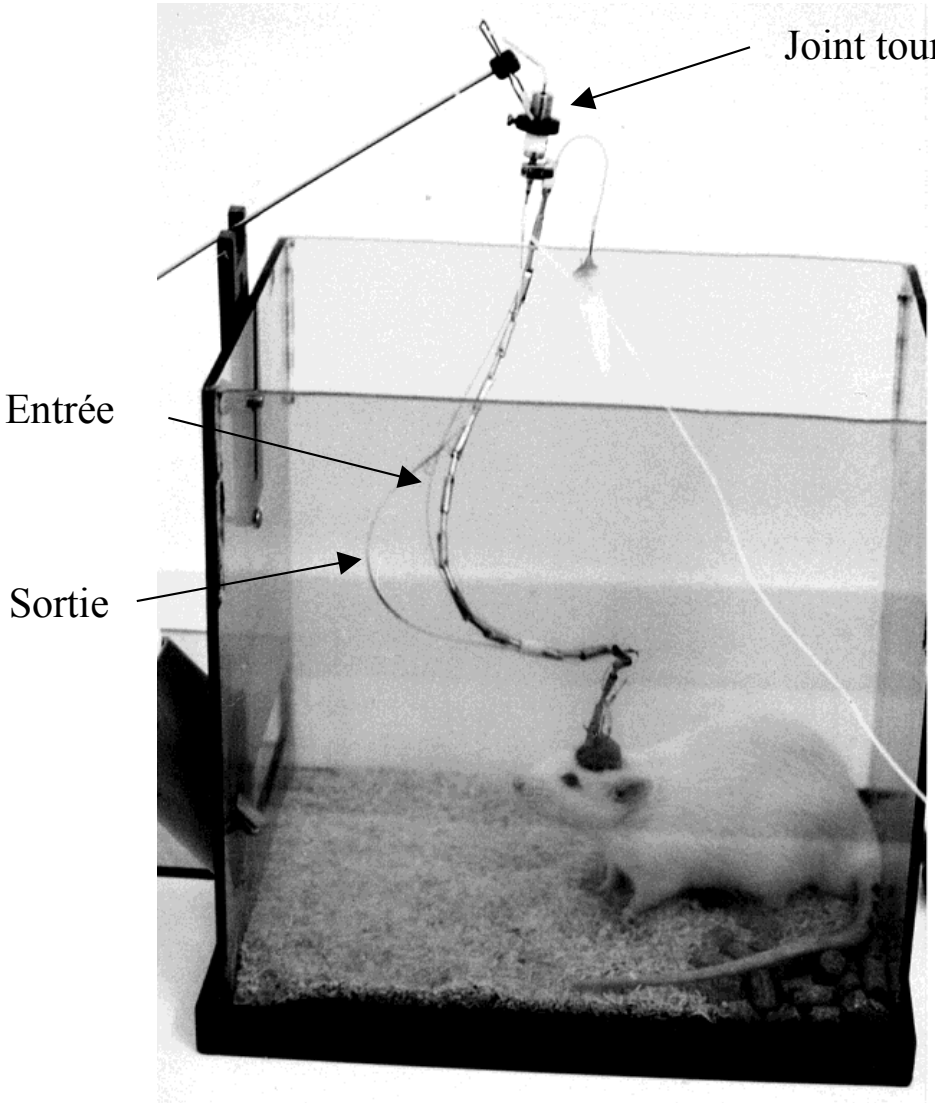


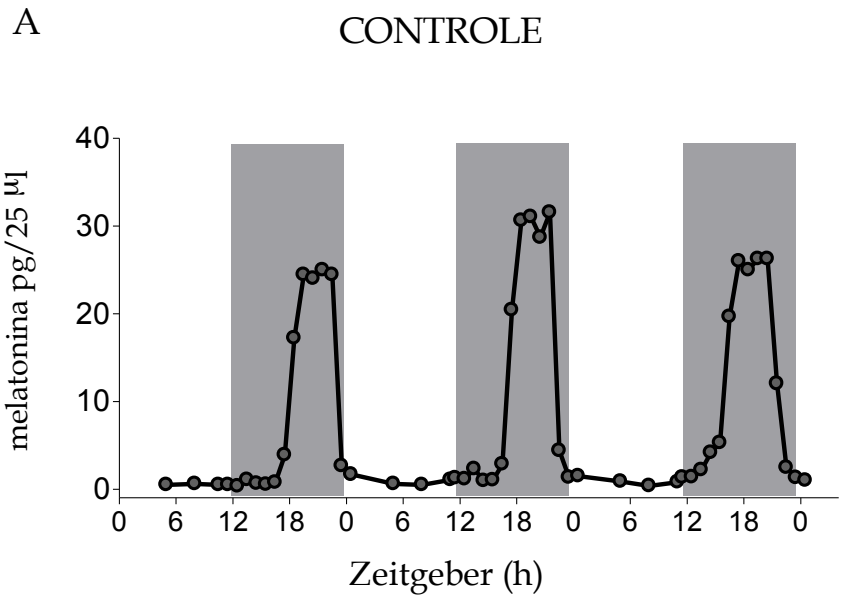


Exemplo:

Interações imuno-neuroendócrinas na glândula pineal

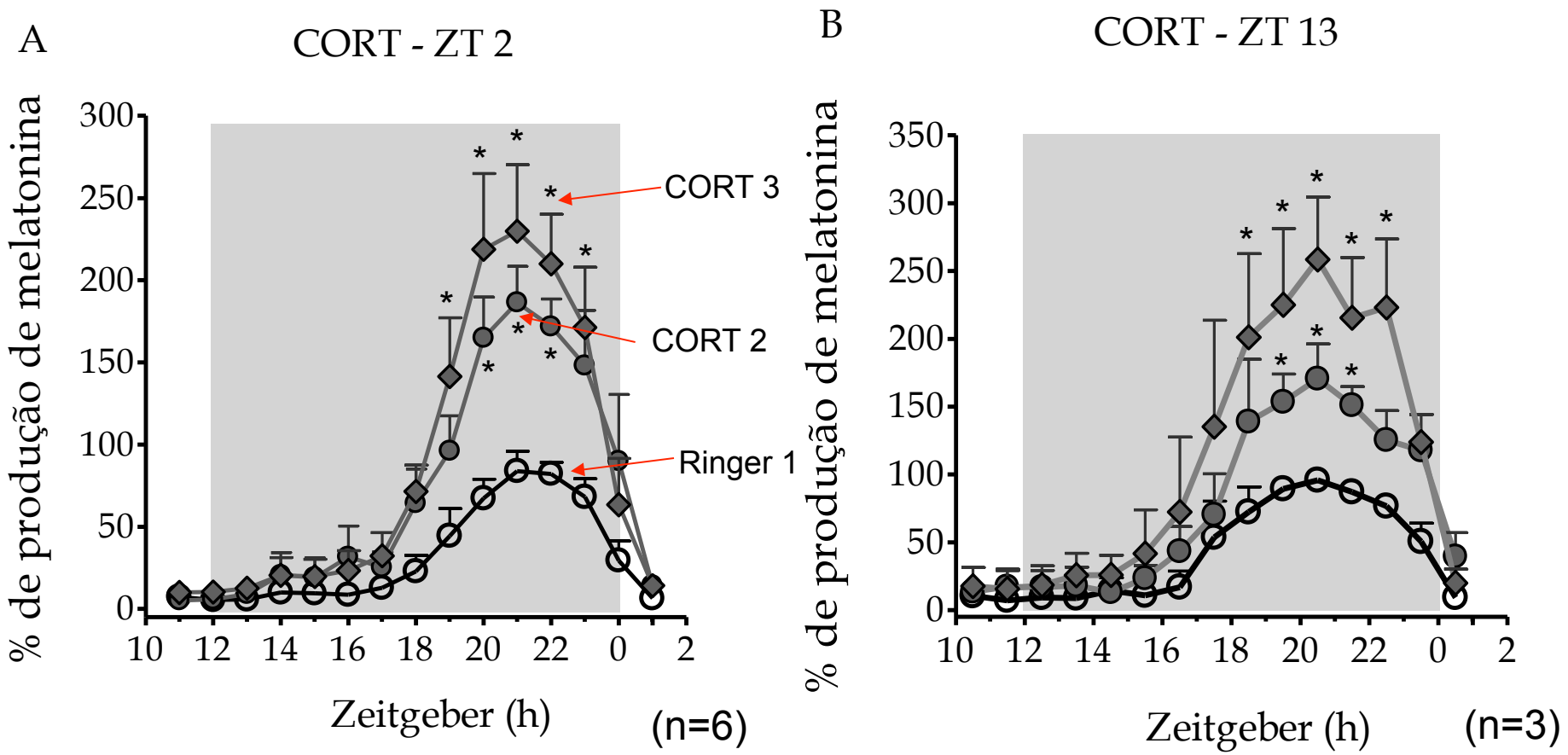
Microdiálise Intrapineal





Barassin et al., 1999

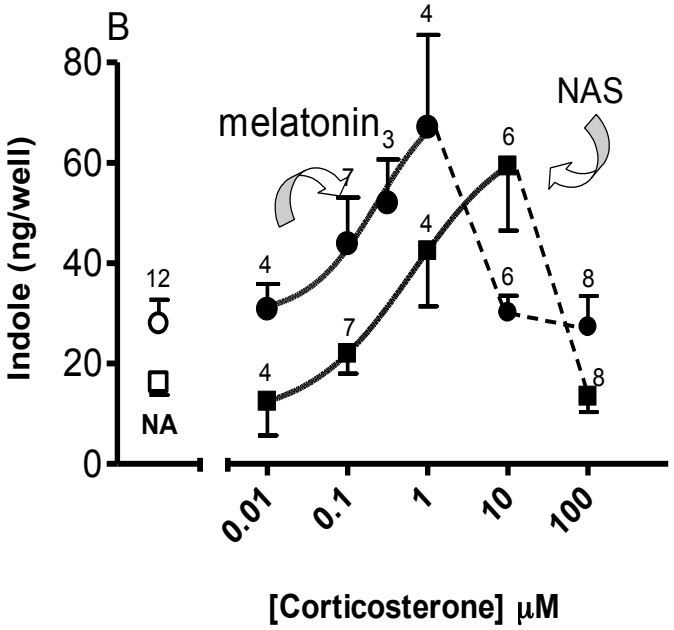
Corticosterona Aumenta a Produção de Melatonina *in vivo*

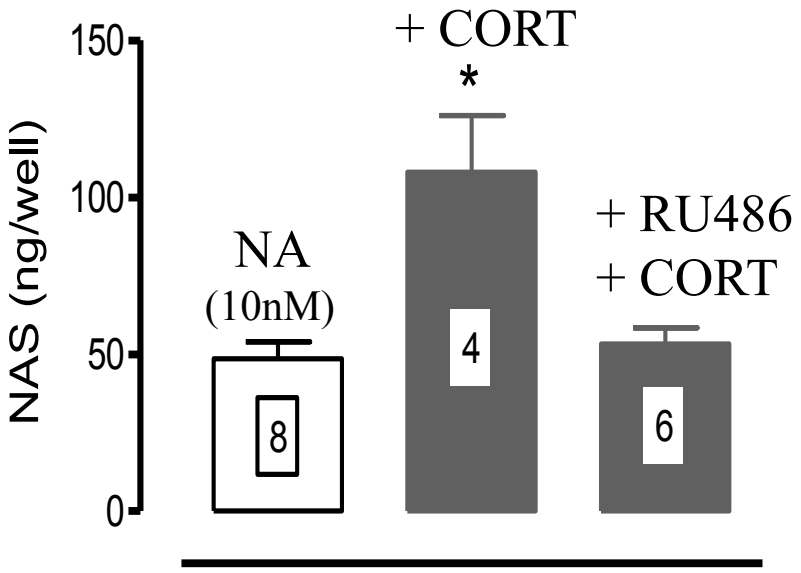


Fernandes et al., 2008, *no prelo*

Corticosterone

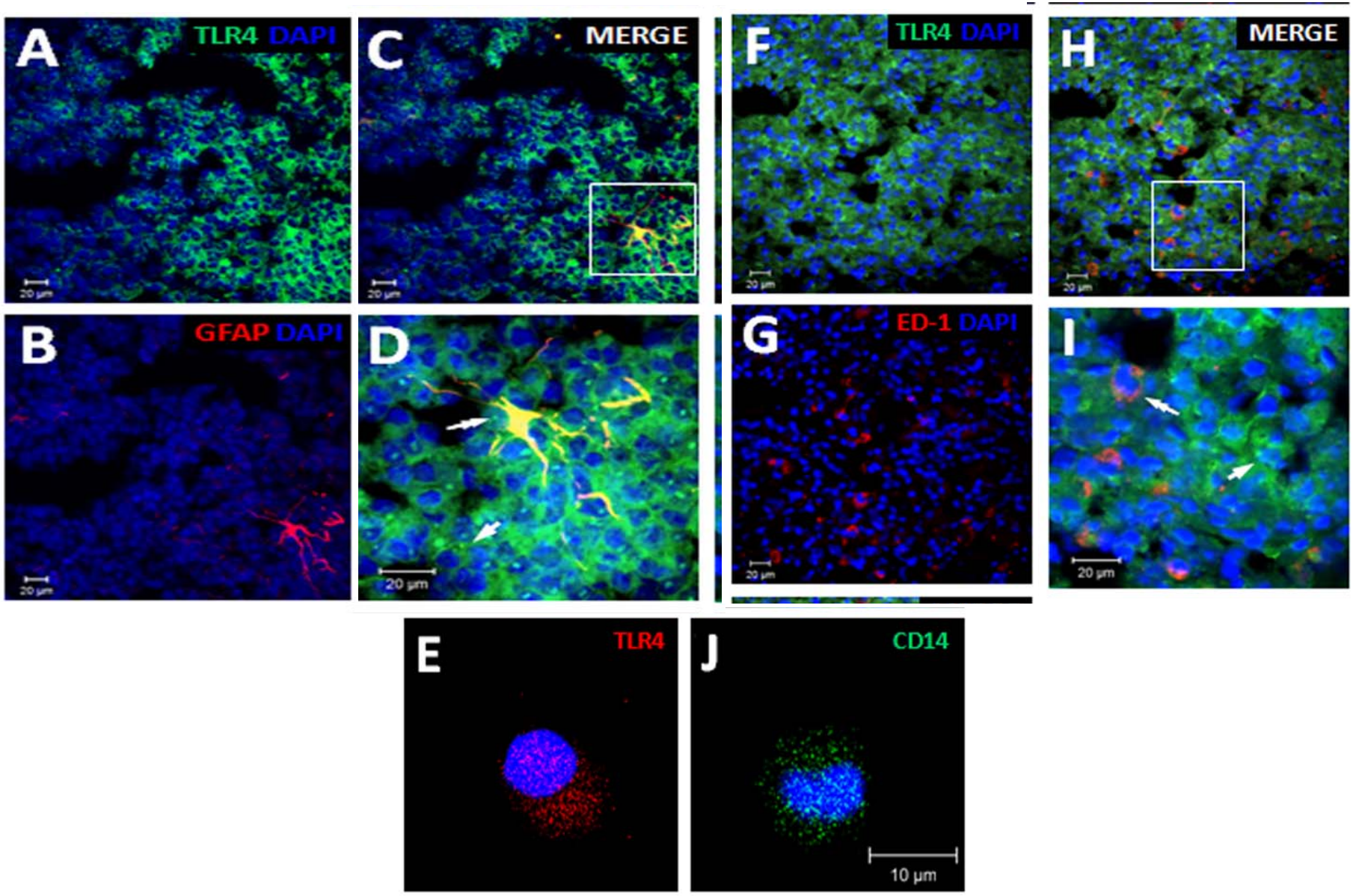
1. potentiates noradrenaline-induced melatonin synthesis
2. through an intracellular glucocorticoid receptor





Ferreira et al., 2005; J. Pineal Res. 38:182.

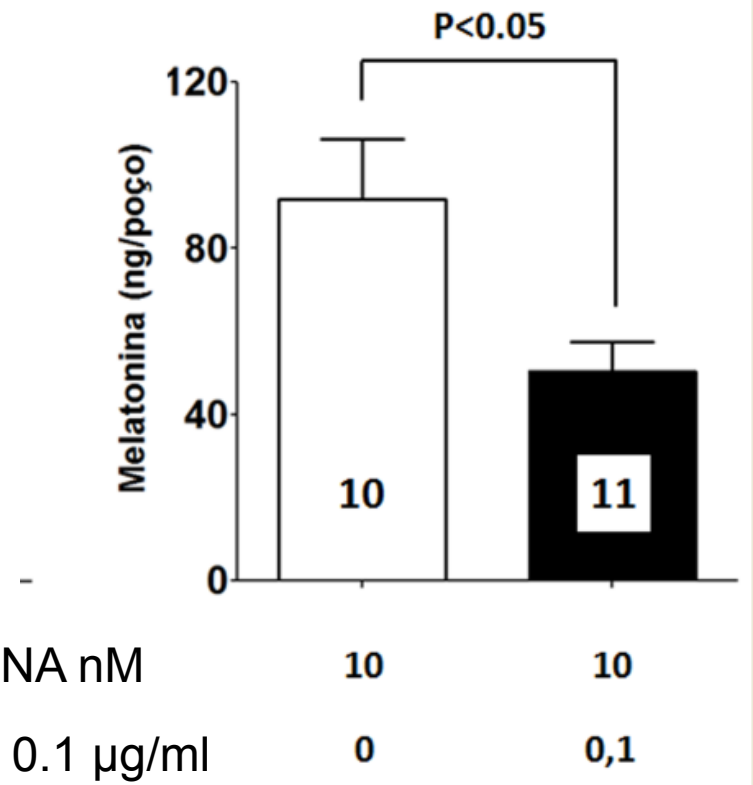
Cellular expression of TLR4 in the rat pineal gland.



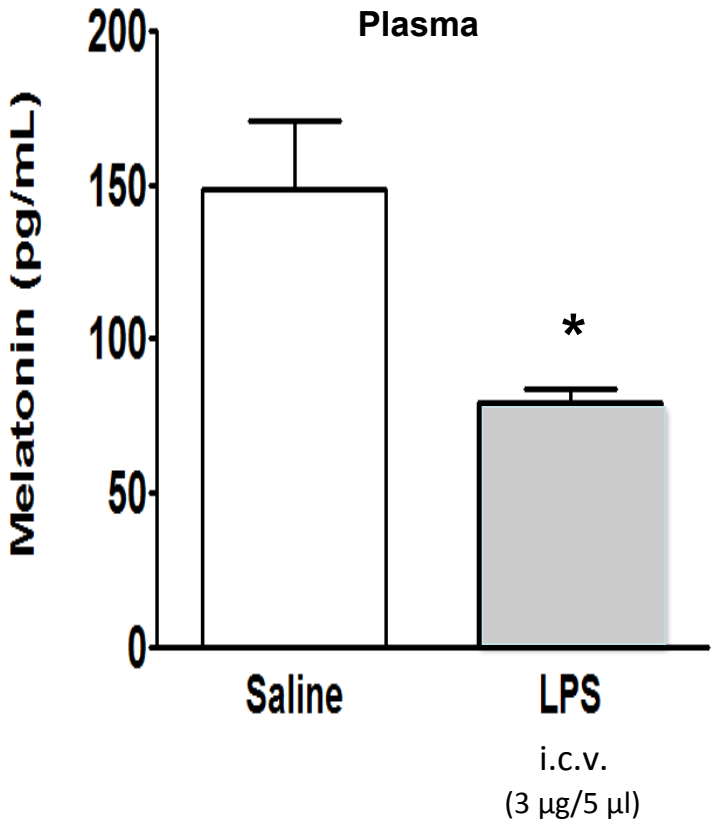
da Silveira Cruz Machado et al., 2010

LPS inhibits nocturnal pineal melatonin production

In vitro



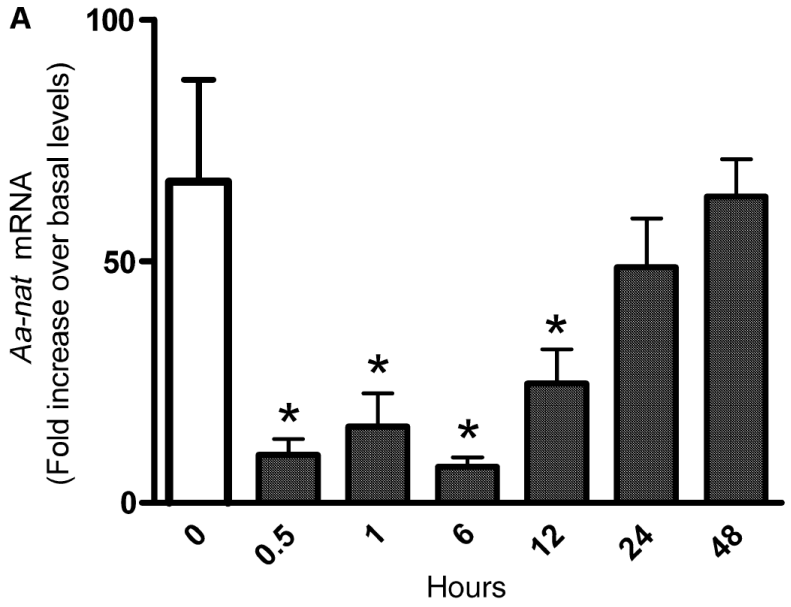
In vivo

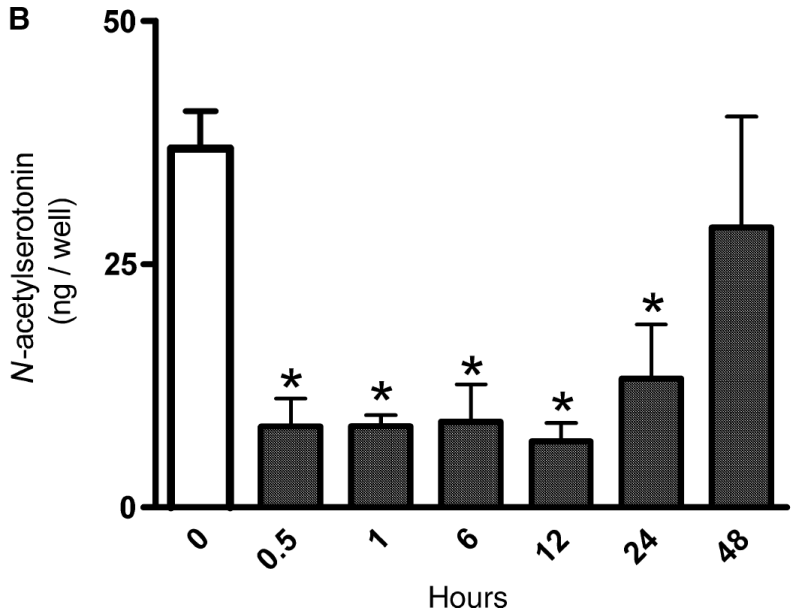


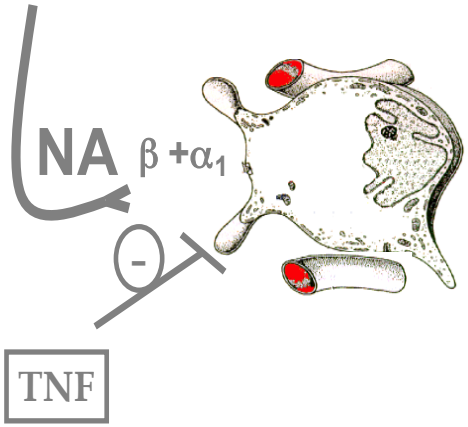
da Silveira Cruz –Machado et al., 2010

Pinato et al., 2015

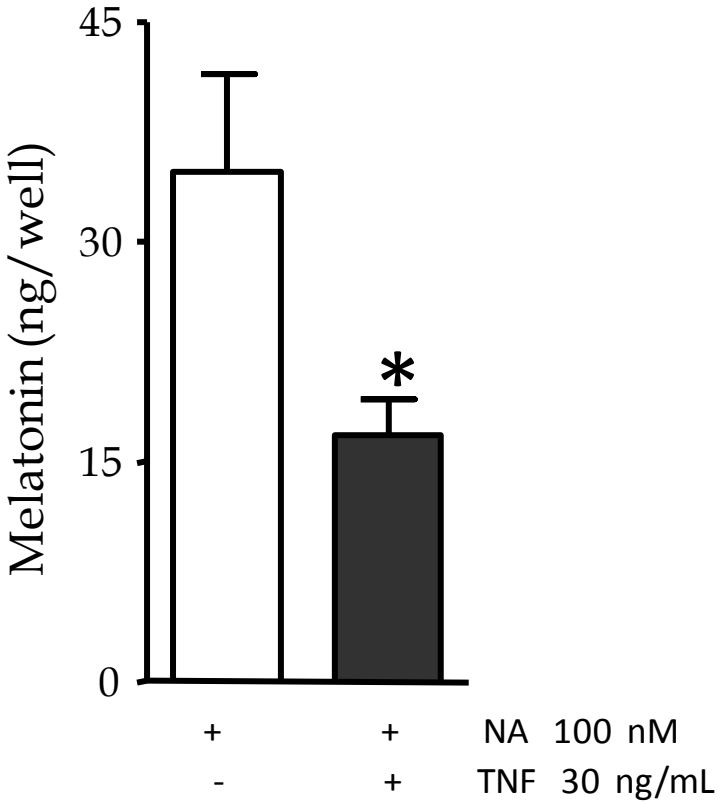
A citocina TNF atuando na pineal



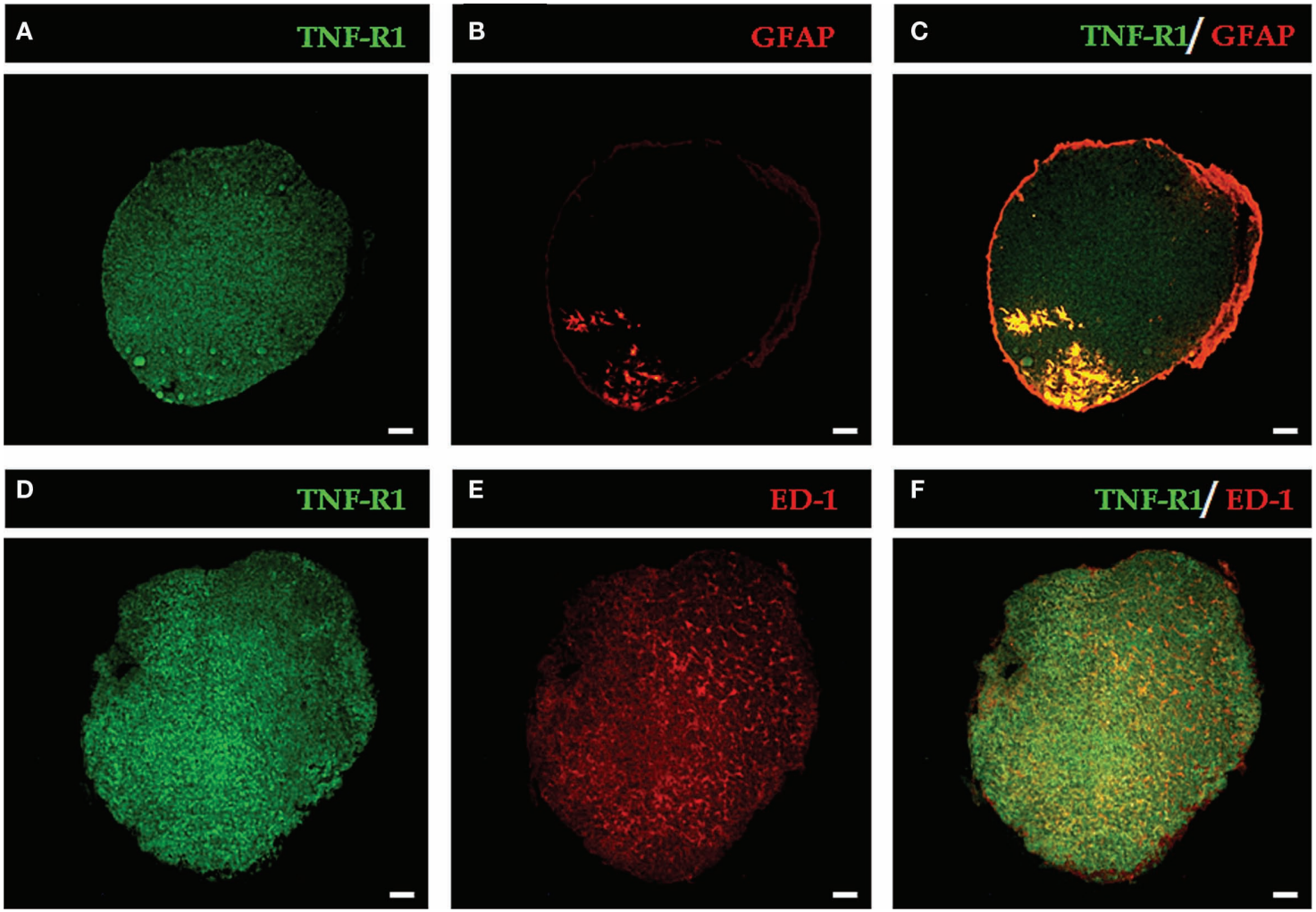




Fernandes *et al.*, 2006



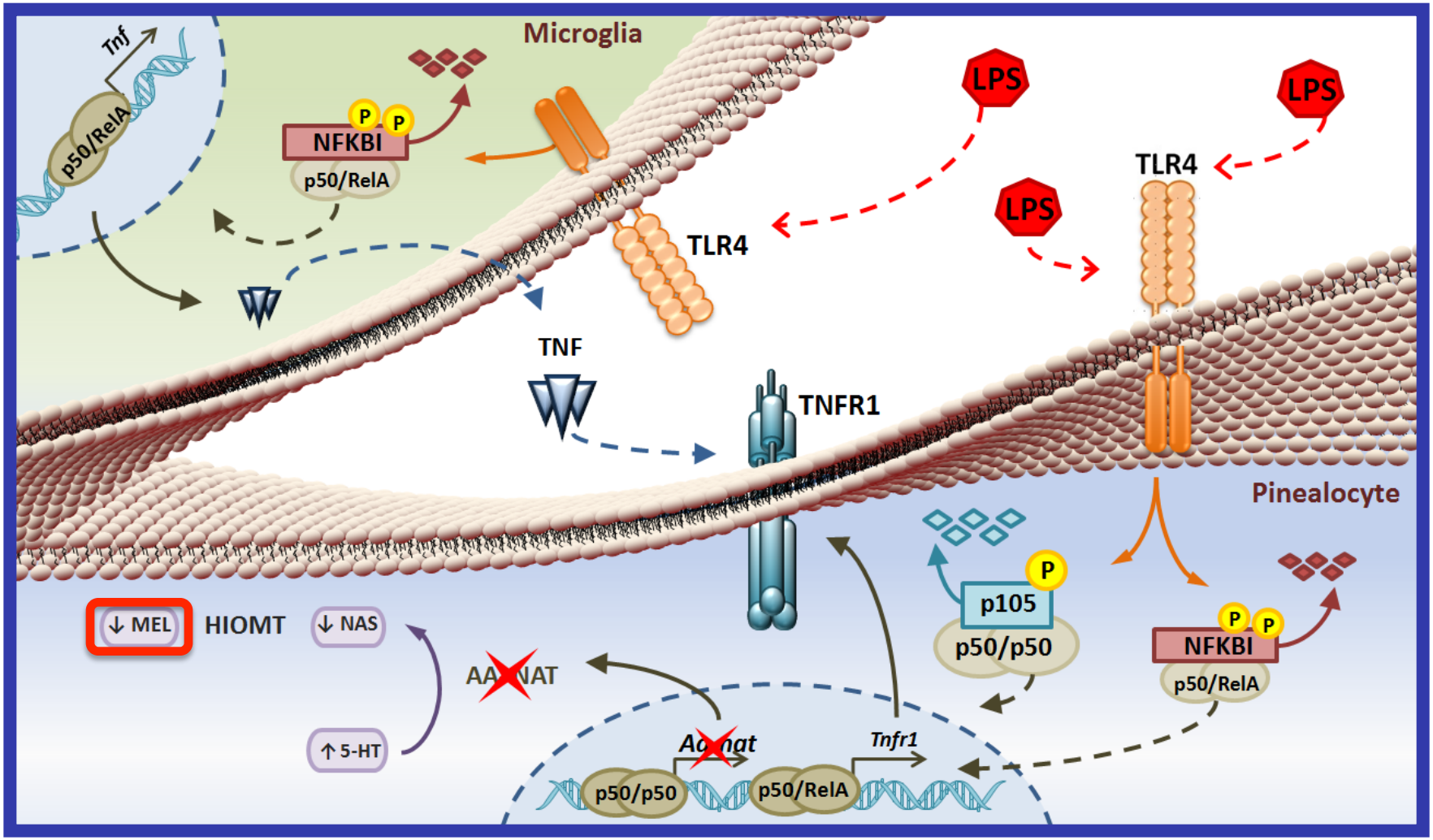
TNF-R1 DISTRIBUTION IN THE DIFFERENT CELL TYPES IN PINEAL PARENCHYMA



Carvalho-Souza et al., 2011

LPS effect on rat pineal gland:

TNF production



da Silveira Cruz Machado et al., 2012

TNF-R1 em pinealócitos

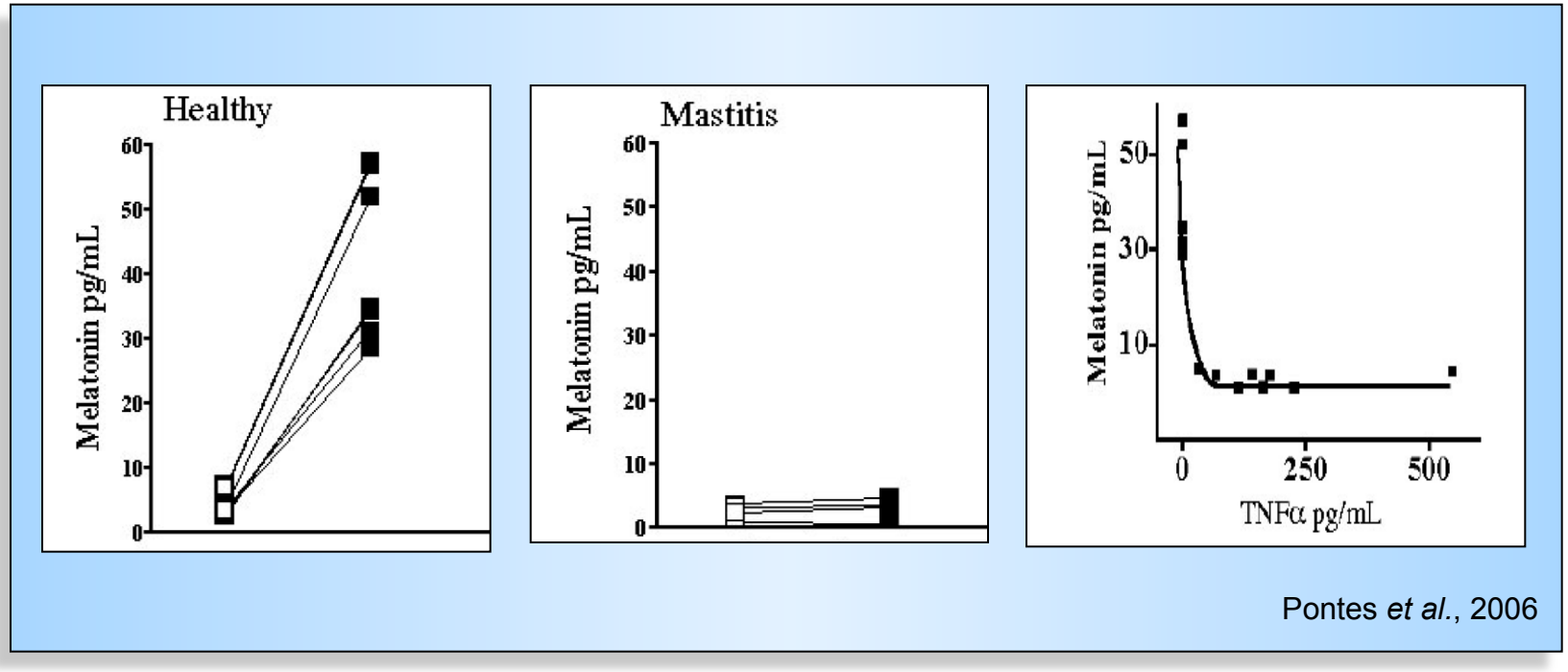
TNF afeta diretamente a produção de melatonina

- *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

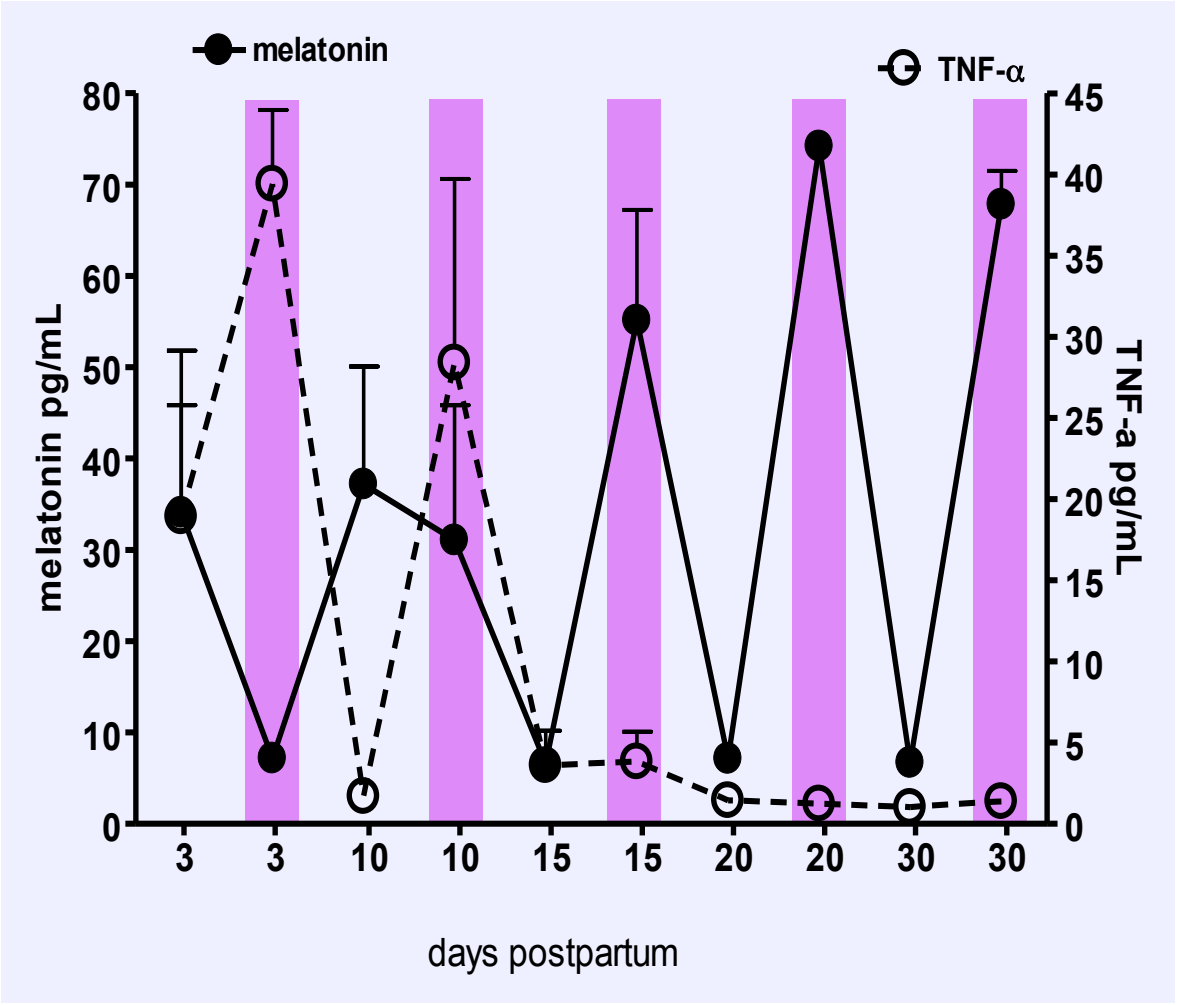


Pontes *et al.*, 2006

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.

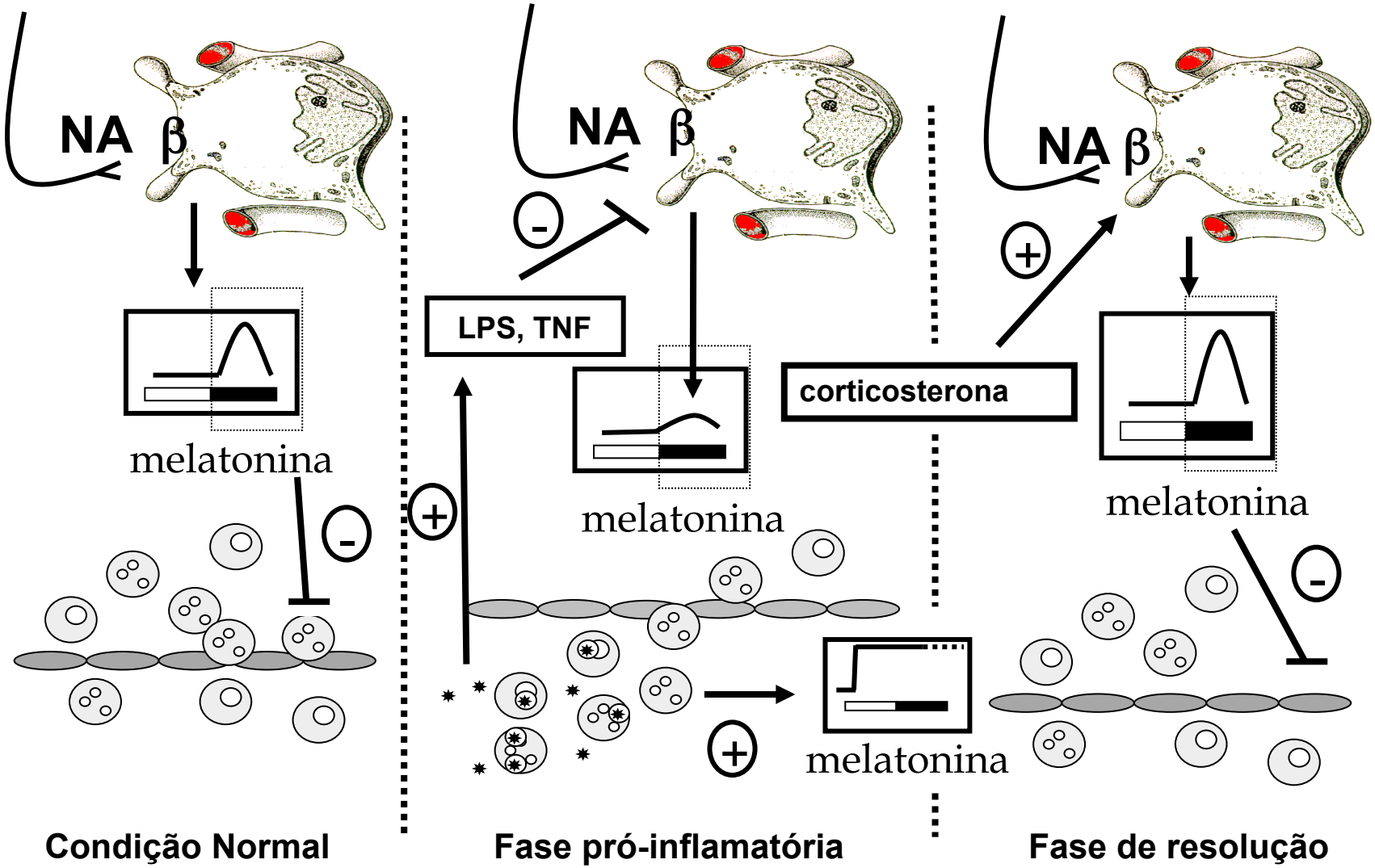
Pontes et al., 2006

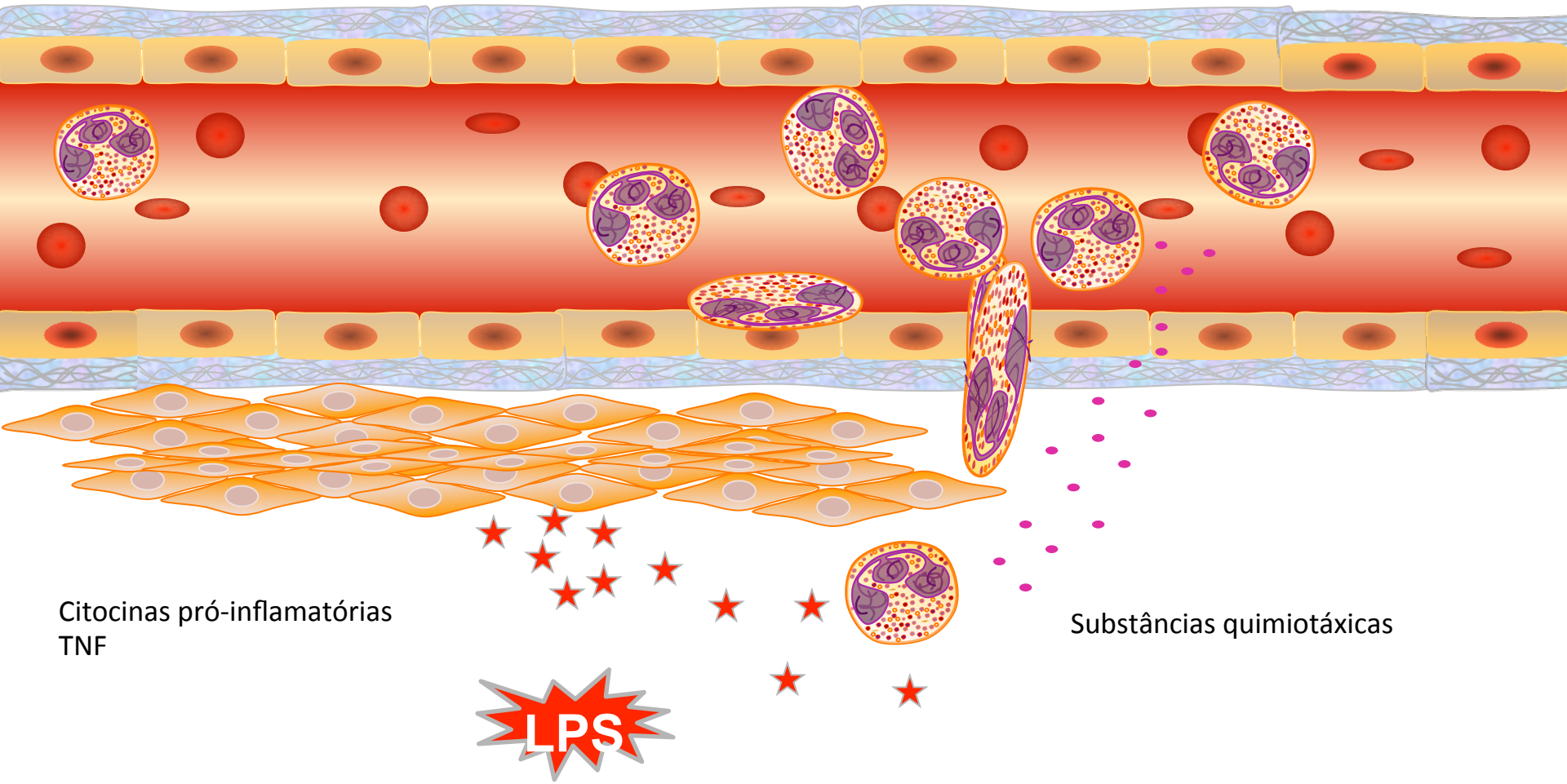
Supressão e/ou potenciação da síntese de melatonina

Quando ?

Por que ?

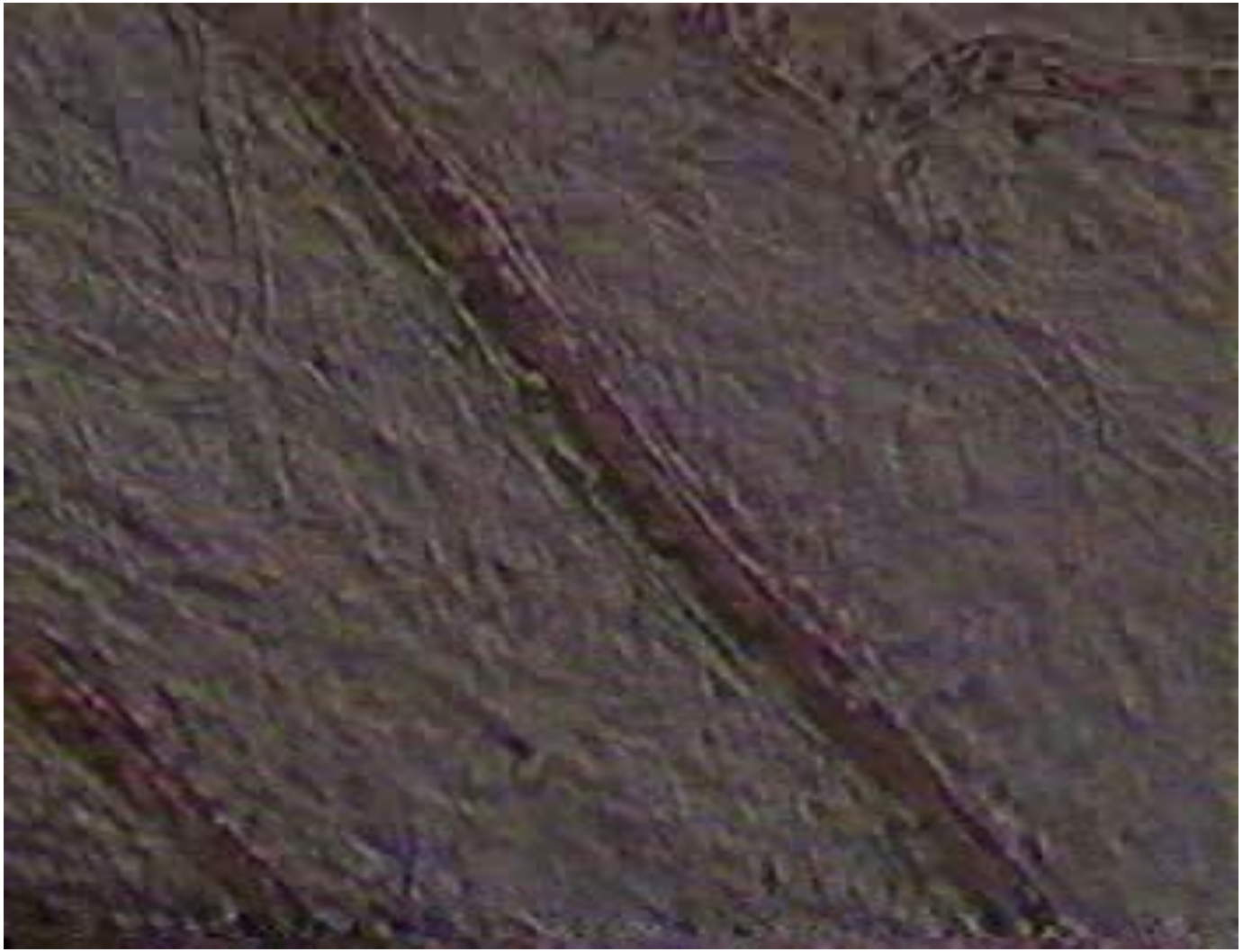
Eixo Imune-pineal





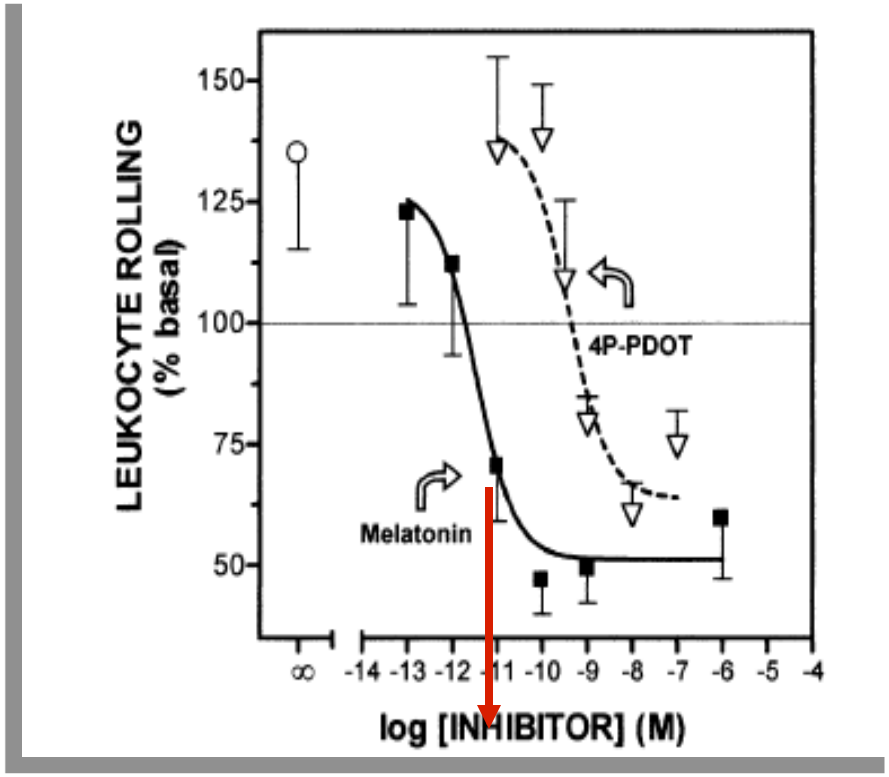
Processo Inflamatório

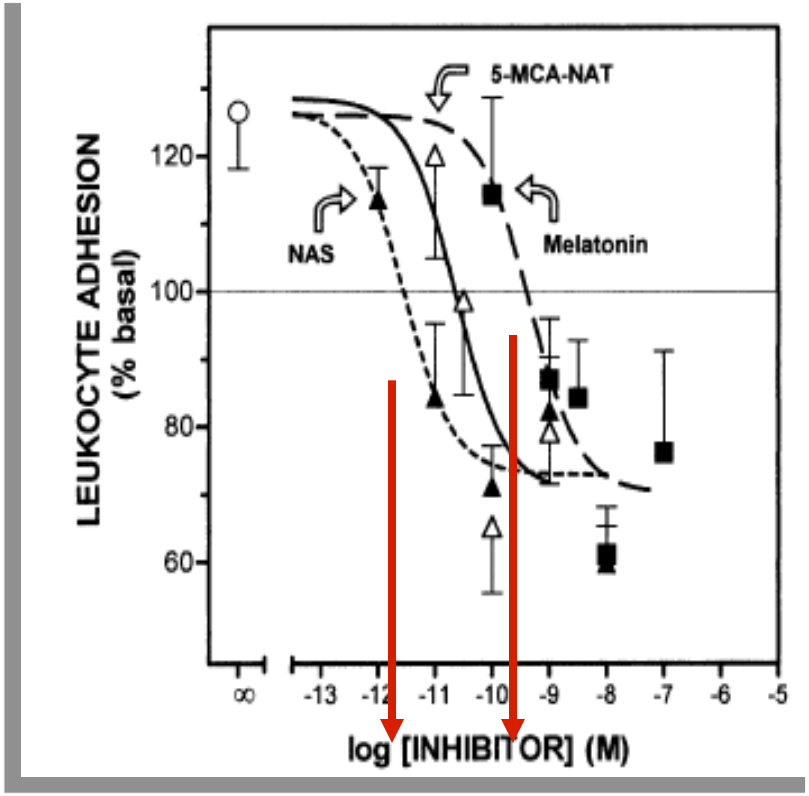
Melatonina atua no rolamento e adesão de leucócitos



Melatonina e NAS

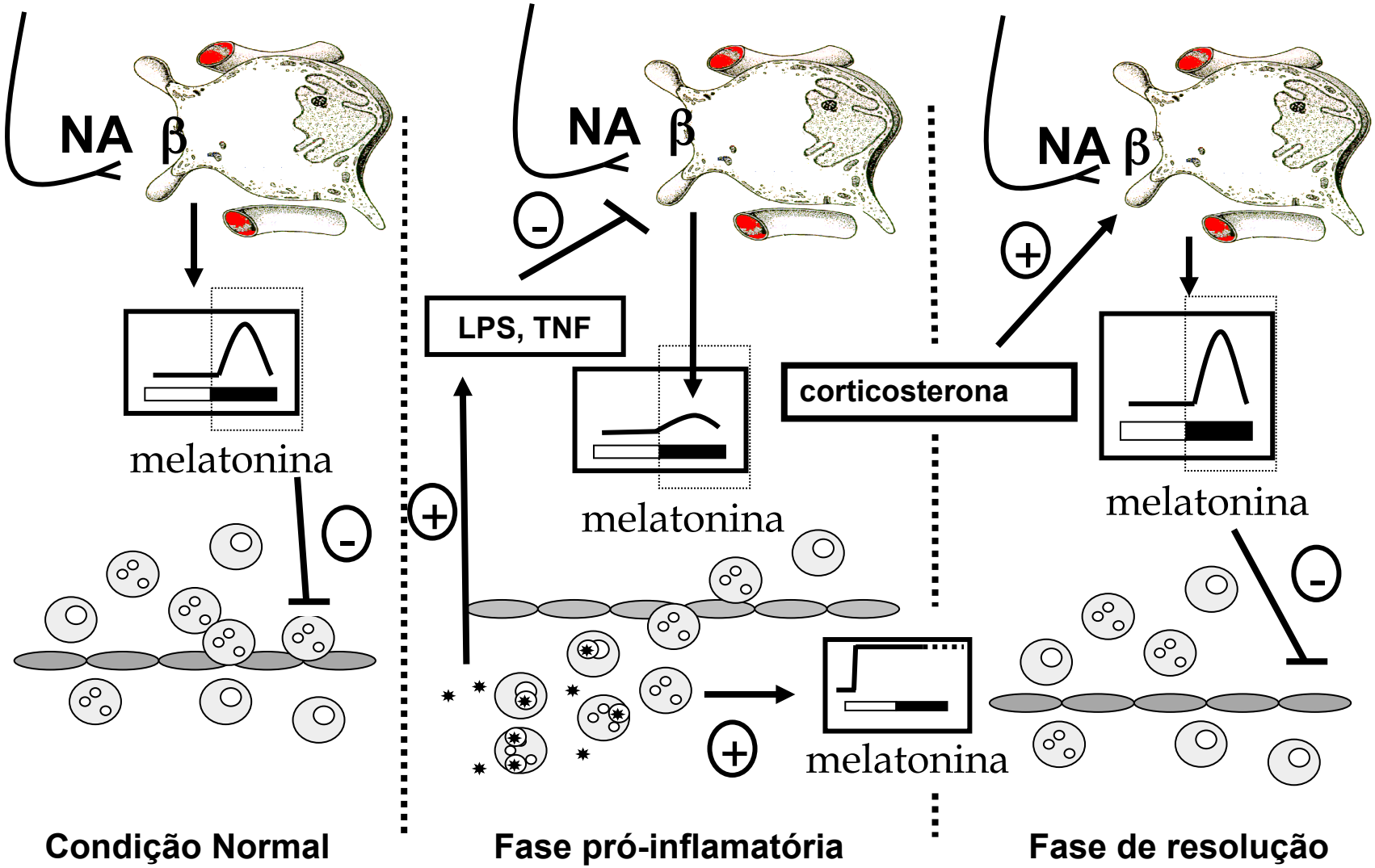
Inibiçao do rolamento e adesão de leucócitos





Lotufo et al., 2001; Eur. J. Pharmacol. 430: 351.

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...