

Tidal rhythms: crabs (*Uca minax*) – come out to feed when tide is low; return to burrows when tide is high so don't get stranded above high tide line: bivalves open when tide is high, close when low.

Lunar rhythms: related to tidal rhythms: Grunion spawn during the spring tides; many insects coordinate eclosion, mating and egg-laying with lunar cycle.

Circadian Rhythms: daily cycle = 24 hrs. **Diurnal**= peak activity during day; **nocturnal** – night; crepuscular= dusk/dawn

Note that *daily rhythms can vary w/ time of year*: temperate zone birds = crepuscular in summer => diurnal in winter (avoid being active when it is really cold); may also vary with age (ie, young animals may be crepuscular whereas adults are diurnal).

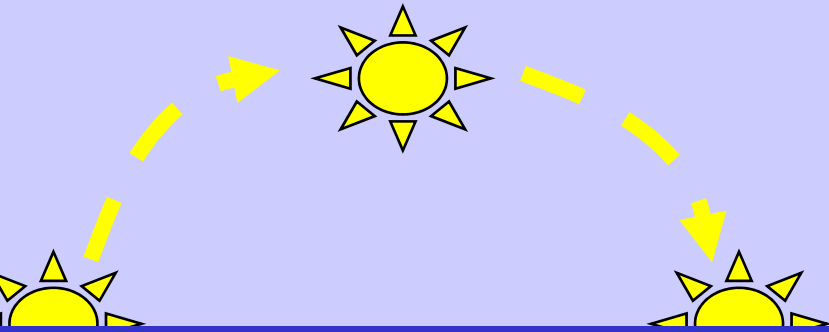
Circannual rhythms: period = 1 yr.

Hibernation – reduced metabolic activity

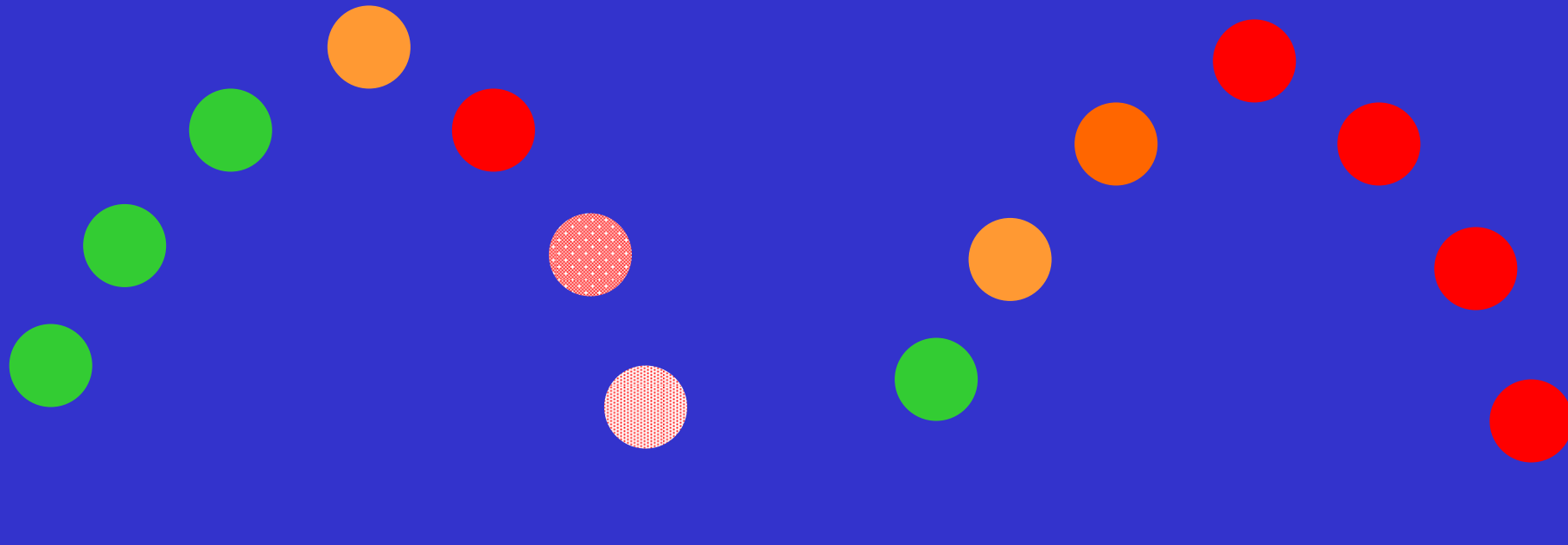
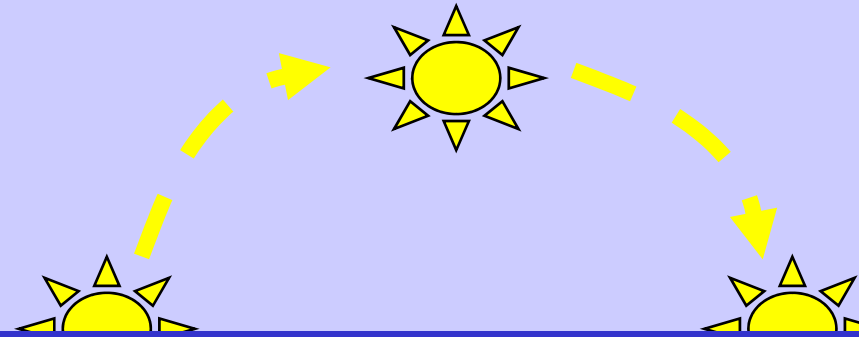
Migration

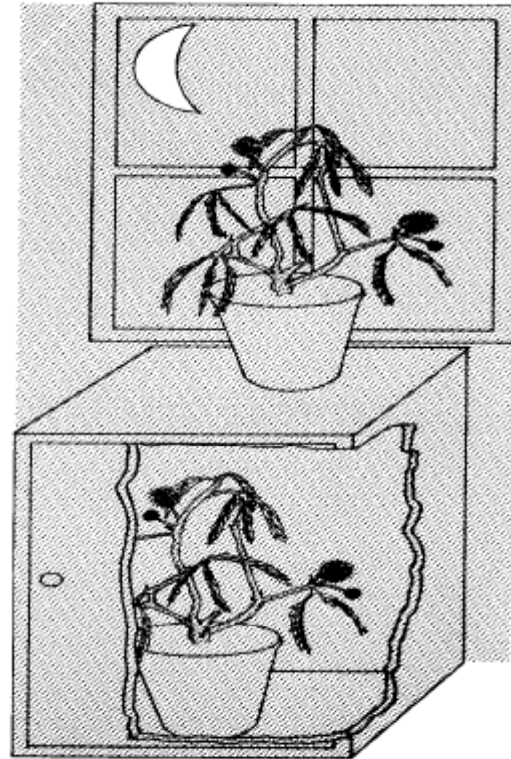
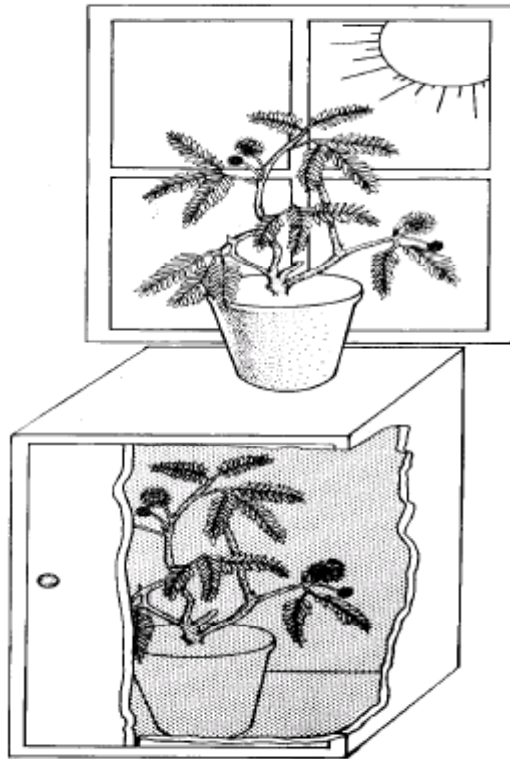
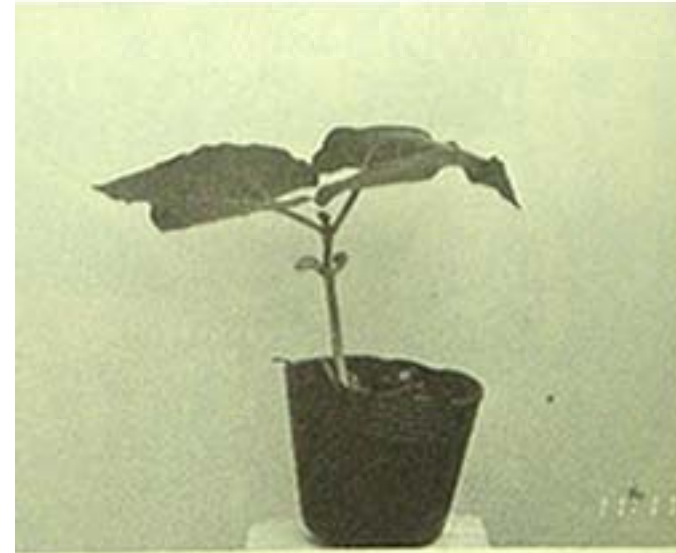
Diapause- period of dormancy (eg, many insects lay eggs that are dormant through the winter).

Organismi reattivi



Organismi predittivi





Jacques Ortous de Mairan

Activity



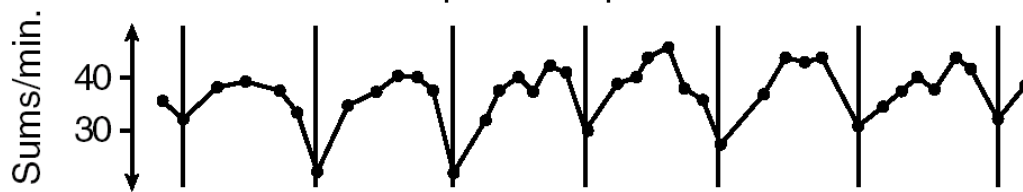
Rectal temperature



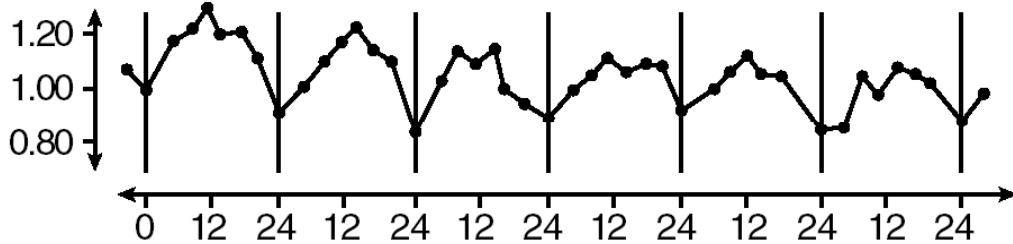
Potassium excretion



Computation speed



Time estimation



Time of day (hrs)

I ritmi sono:

Ubiquitari

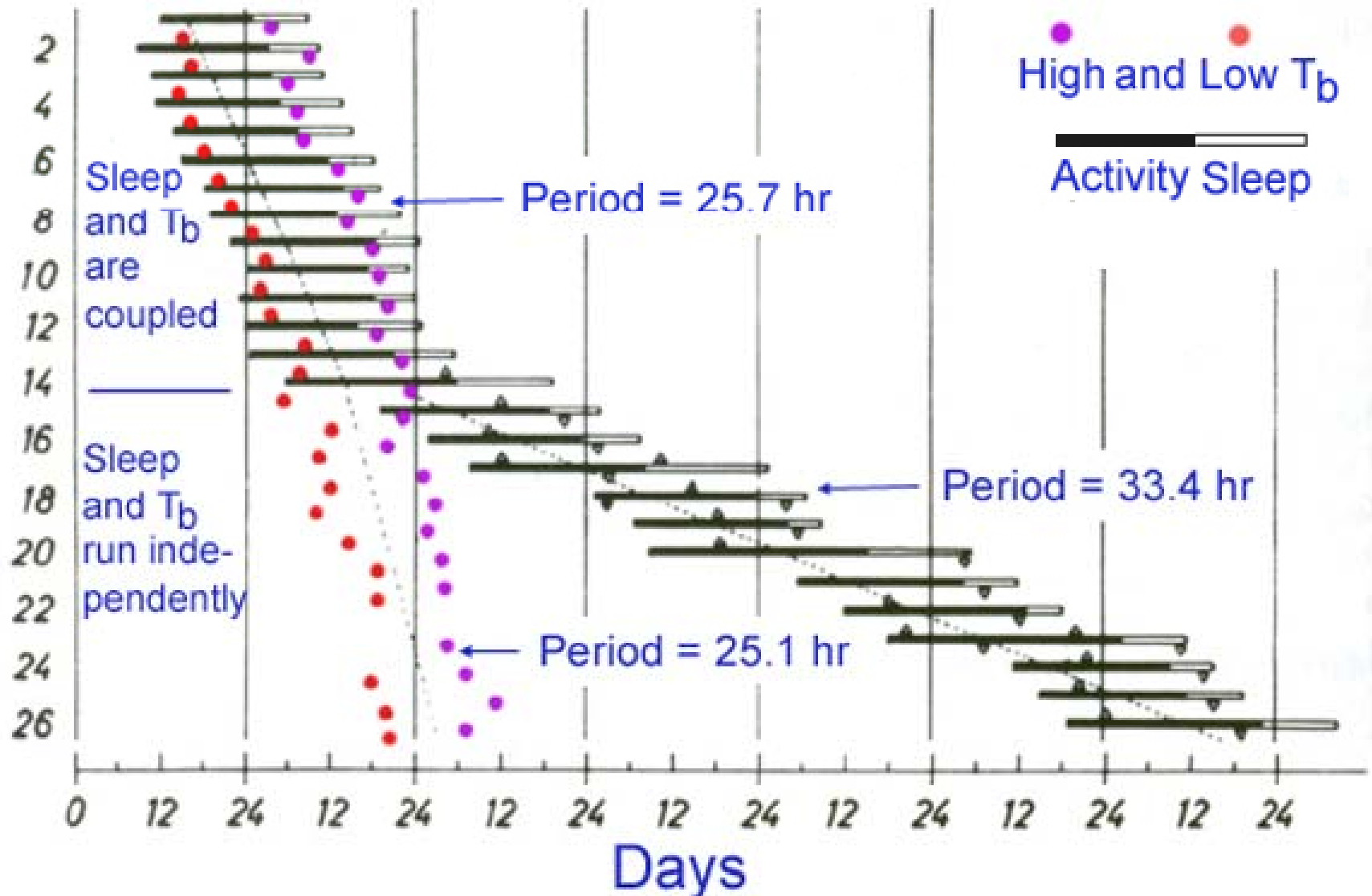
Generati intrinsecamente

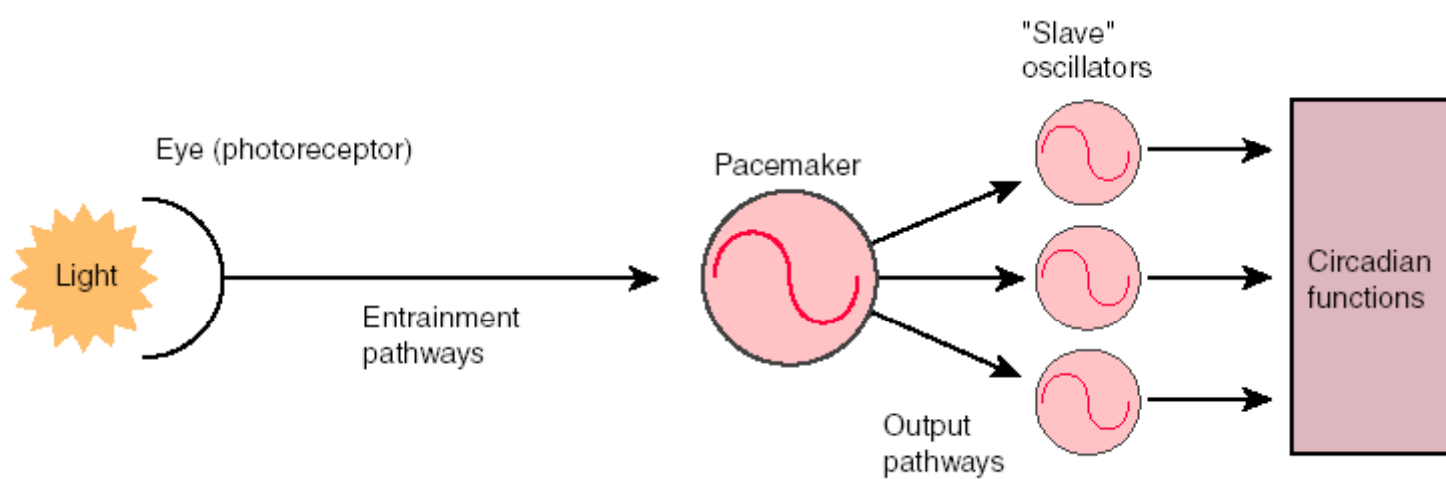
**Autonomi dagli stimoli
esterni**

Ritmatori (pacemaker)

Sincronizzatori (zeitgeber)

Free-running Sleep and Temperature (T_b) Rhythms





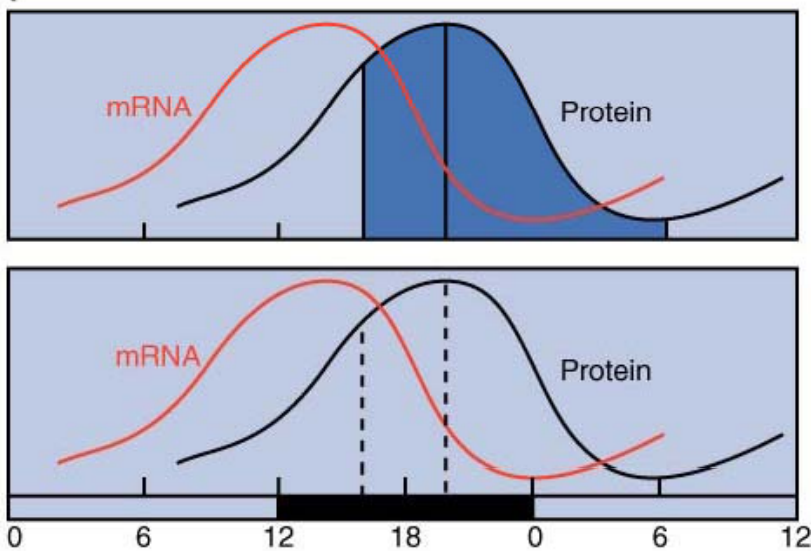
Copyright © 2002, Elsevier Science (USA). All rights reserved.

Proprietà di un ritmatore circadiano

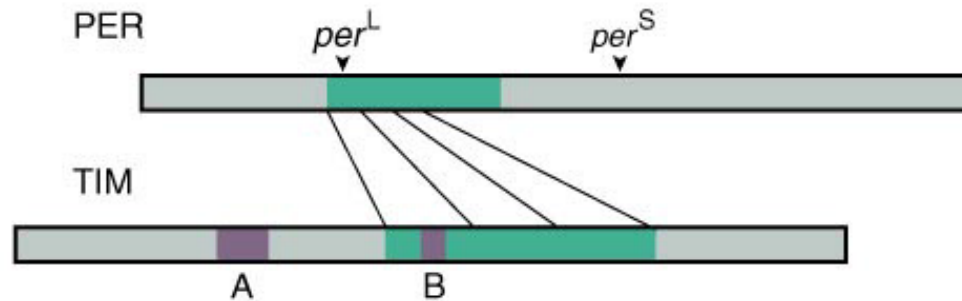
- sintonizzato con il ciclo luce/buio con un periodo di 24 ore
- fase stabile rispetto al ciclo luce-buio
- persistente anche in assenza del ciclo luce-buio esterno
- ciclo non-dipendente dalla temperatura
- ereditario e regolato da geni specifici

Componenti di un ritmatore circadiano

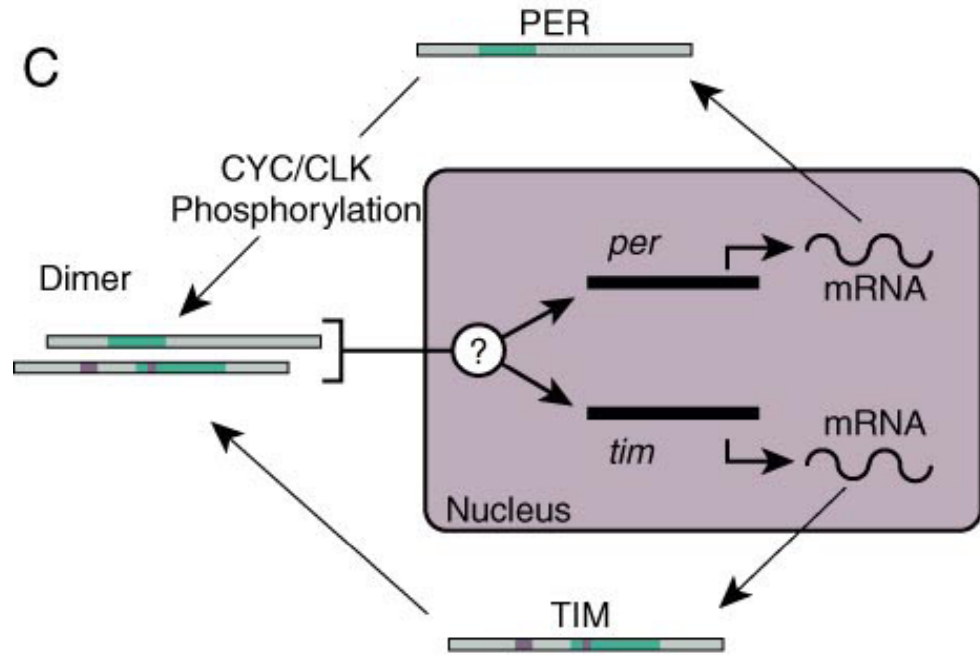
- Fotorecettore
- Pacemaker (ritmatore): **ZEITGEBER**
- Strutture con funzione circadiana



B



C



Copyright © 2002, Elsevier Science (USA). All rights reserved.

Geni circadiani

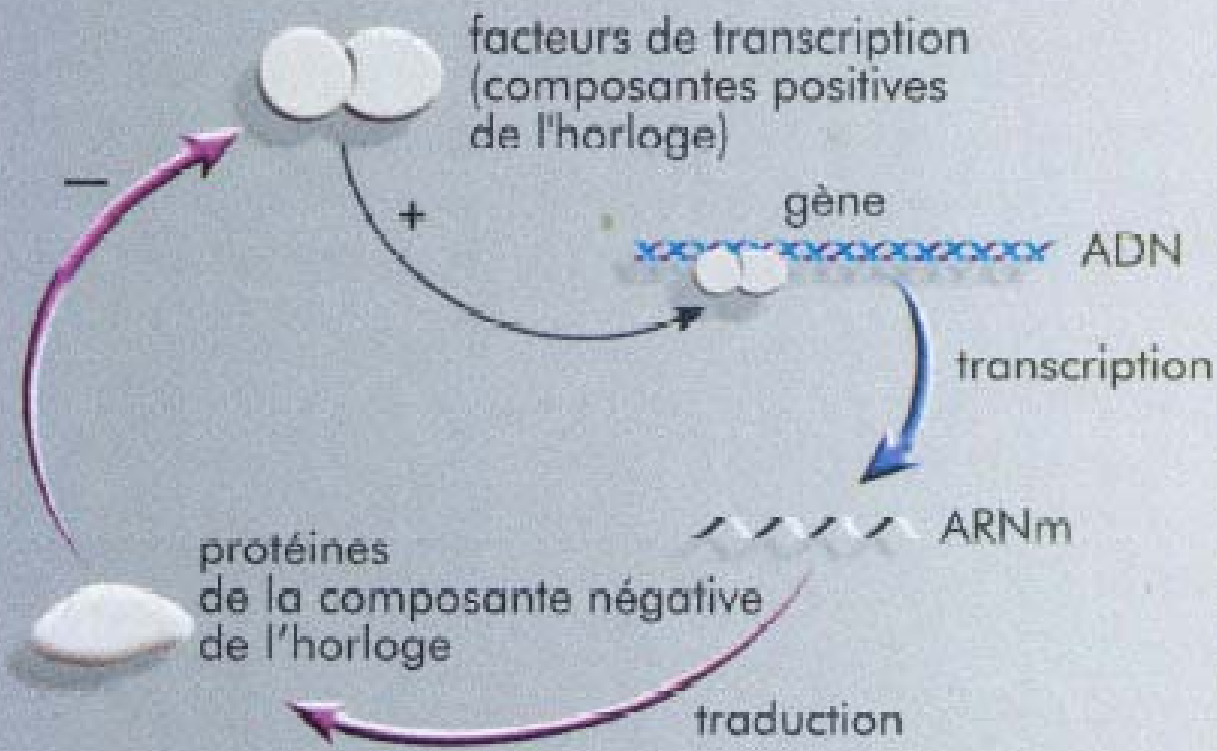
- Produzione ciclica (24h)
- In fase con cicli L/B
- Perdita del ritmo biochimico induce perdita di quello funzionale o comportamentale
- Mutazioni dei geni devono modificare le proprietà del ritmatore e/o abolire il ritmo funzionale

I meccanismi genici fondamentali sono conservati nell'evoluzione

champignon
neurospora
drosophile
mammifères



WC-1 et WC-2
CLOCK et CYCLE
CLOCK et BMAL 1



FRQ
PER et TIM
PER 1, 2, 3 et CRY 1, 2

2 tipi di ritmo

giorno

notte

Animali diurni

Animali notturni

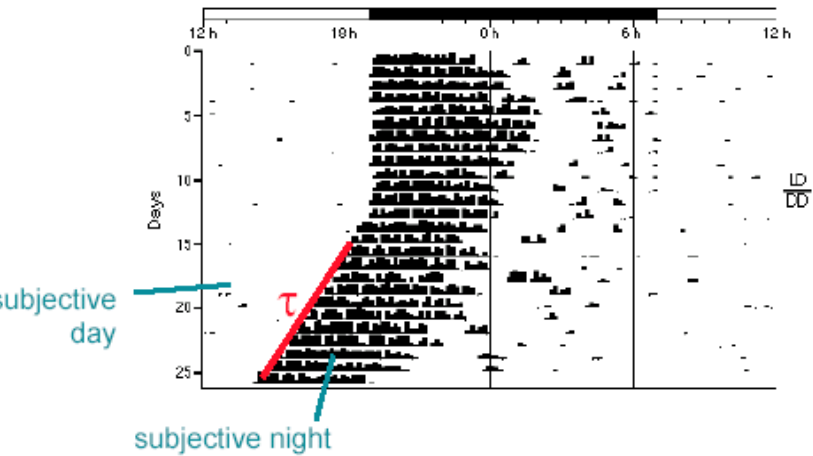
Senso primario: visione

Senso primario: udito-olfatto

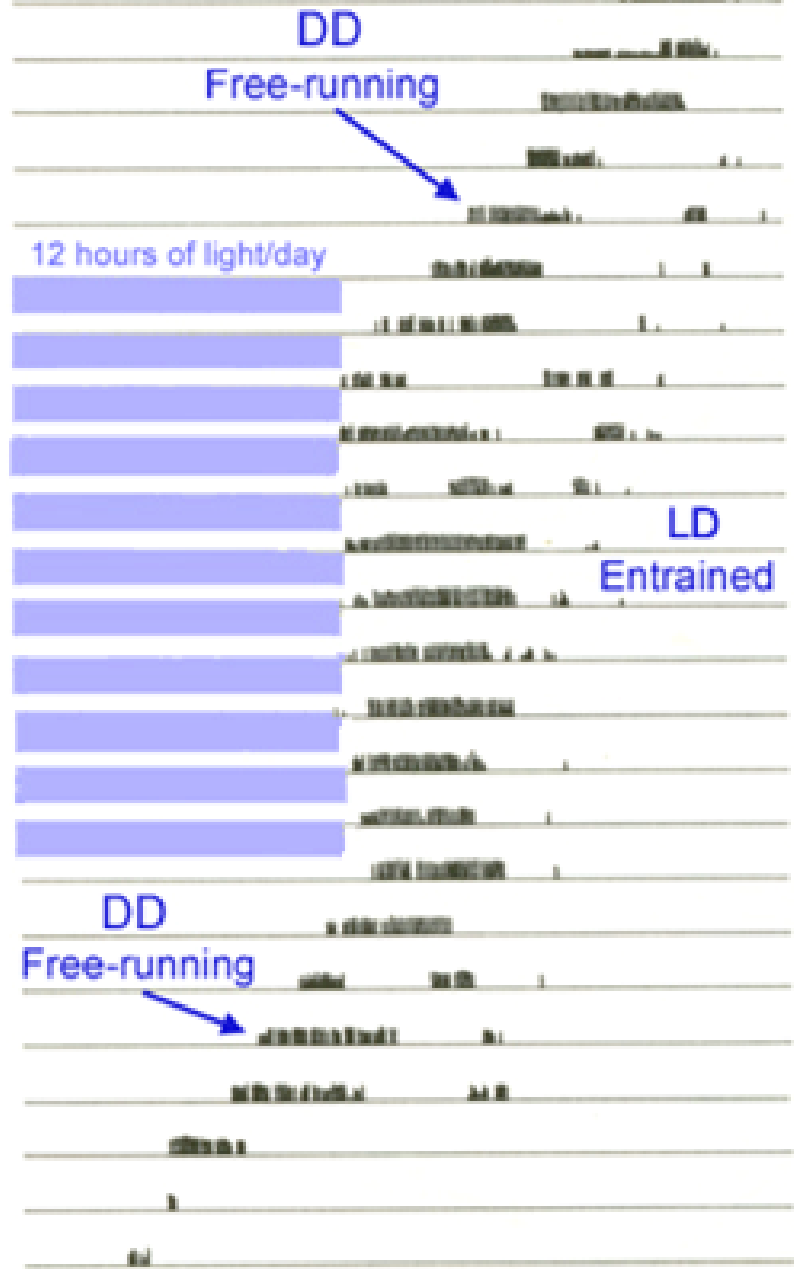
**Attivi durante il giorno
A riposo durante la notte**

**Attivi durante la notte
A riposo durante il giorno**

**Ricerca del cibo
Accoppiamento riproduzione
Fuga dai predatori**

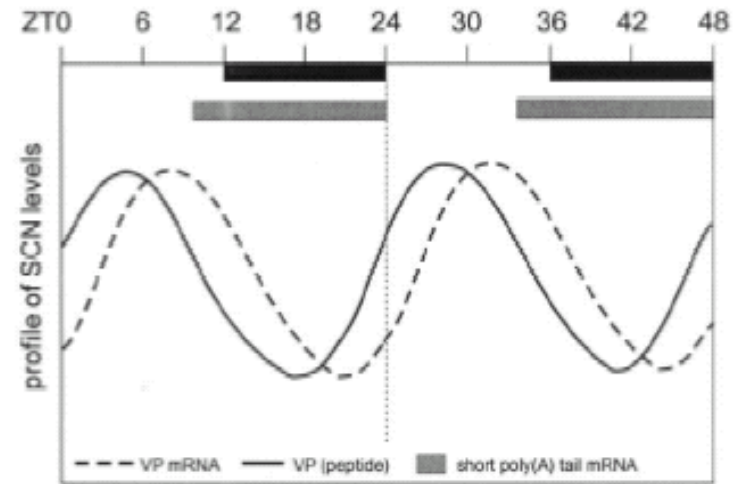


An actogram
(activity rhythm of a mouse in a cage with a wheel)



Il nucleo soprachiasmatico (SCN) come pacemaker

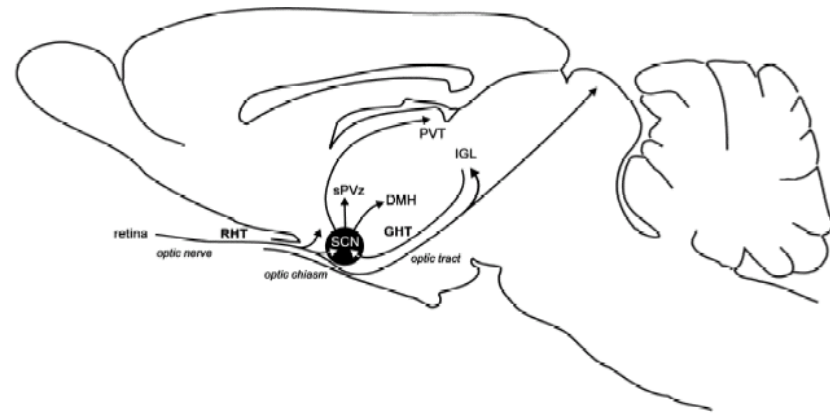
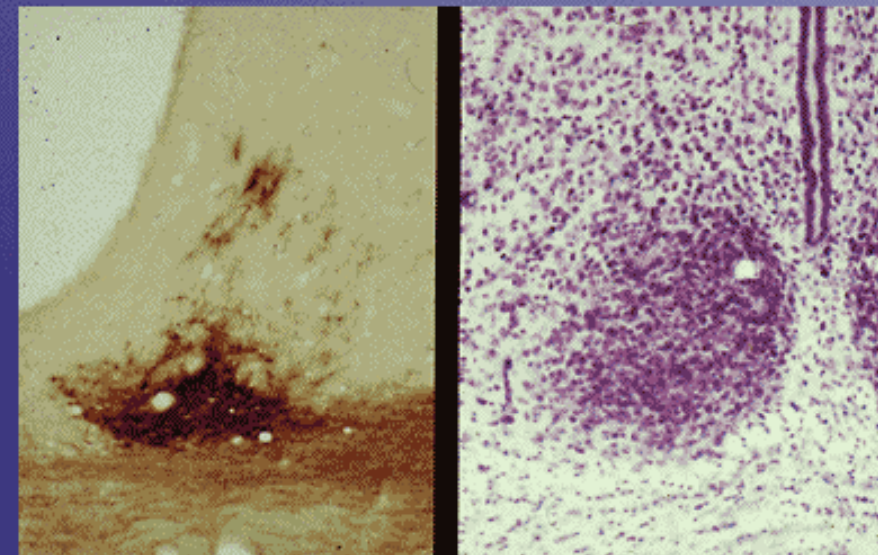
- È il sito di terminazione di RHT (input visivo)
- Lesione di SCN abolisce il ritmo circadiano, ma non altera le funzioni ritmiche
- L'isolamento di SCN (es DD o lesione di RHT) non altera la capacità di SCN di generare il ritmo in maniera intrinseca
- Dopo lesione di SCN il ritmo può essere ripristinato da un trapianto di SCN embrionale (che impone un ritmo tipico del donatore non del ricevente)

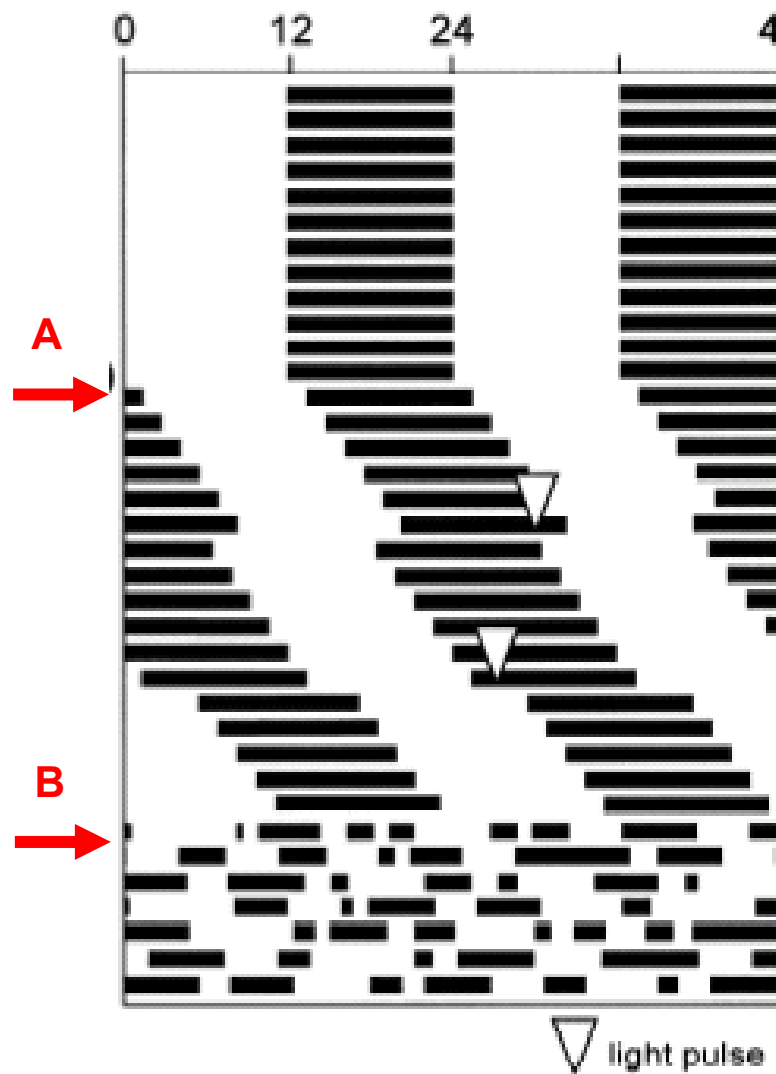
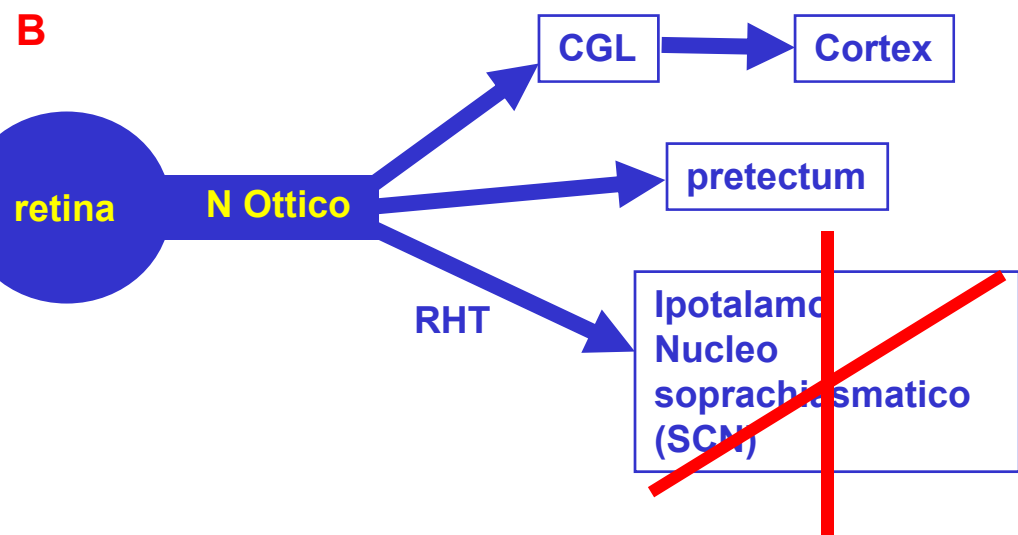
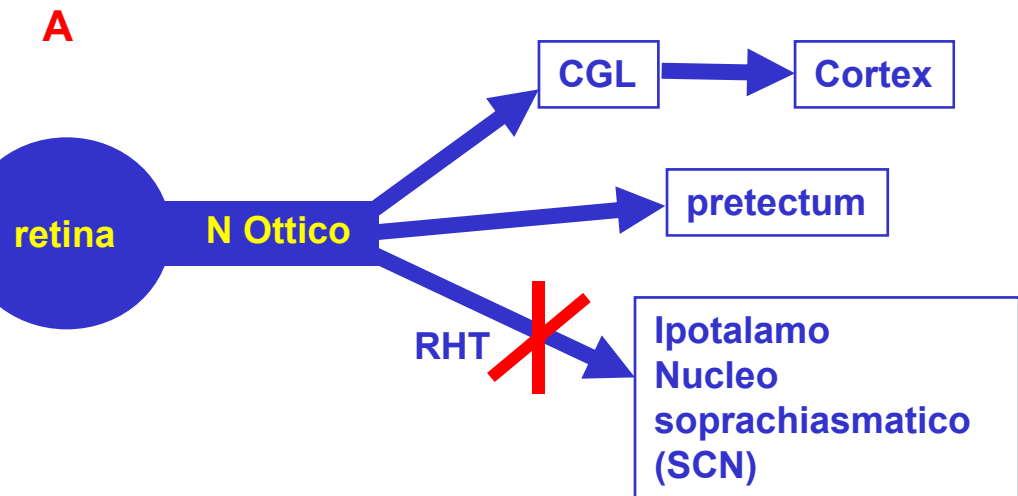


RETINOHYPOTHALAMIC (RHT) TRACT

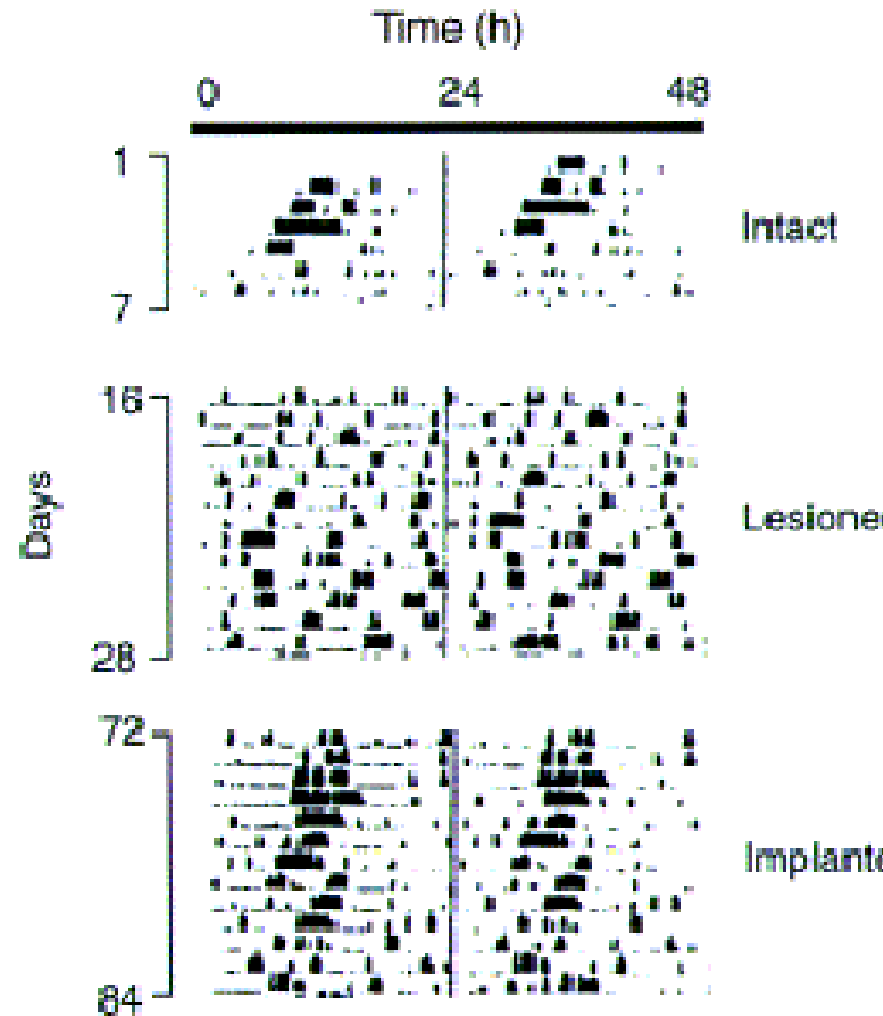
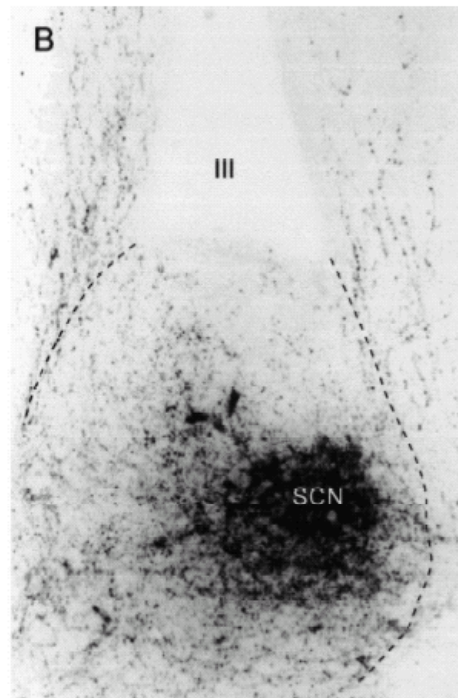
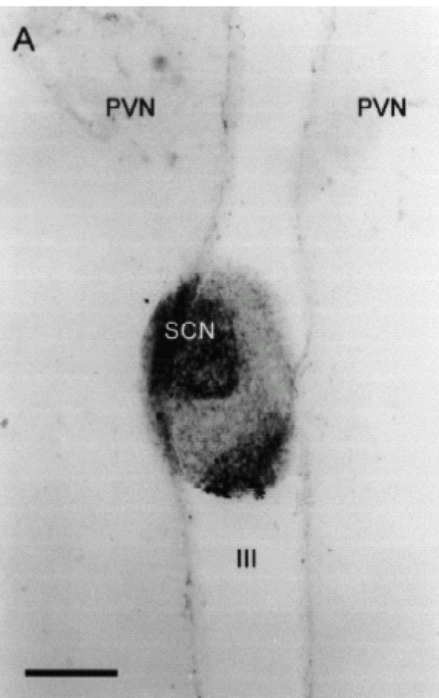
RHT

SCN (Nissl)

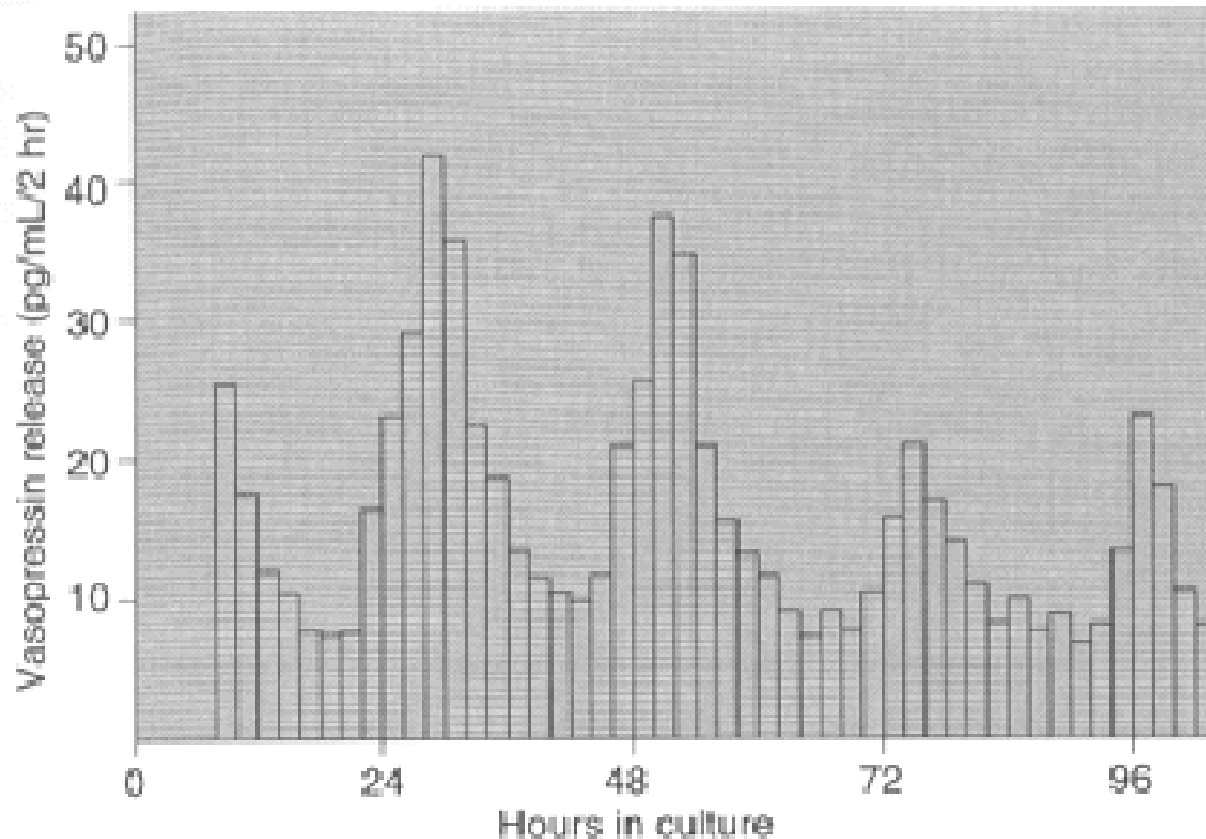




Il trapianto di SCN embrionale in un animale leso ristabilisce il ritmo circadiano



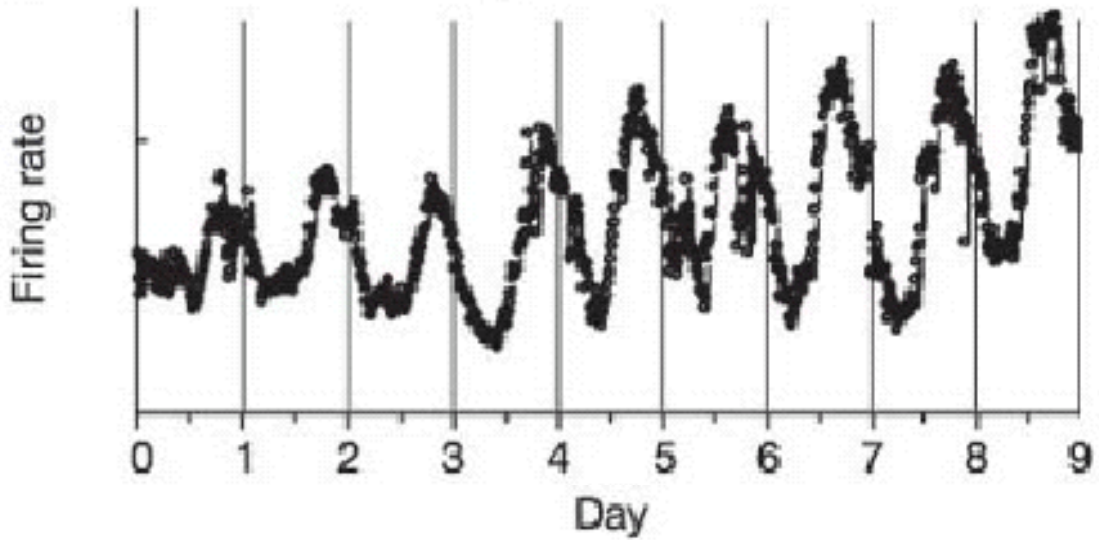
Proprietà intrinseche dei neuroni SCN



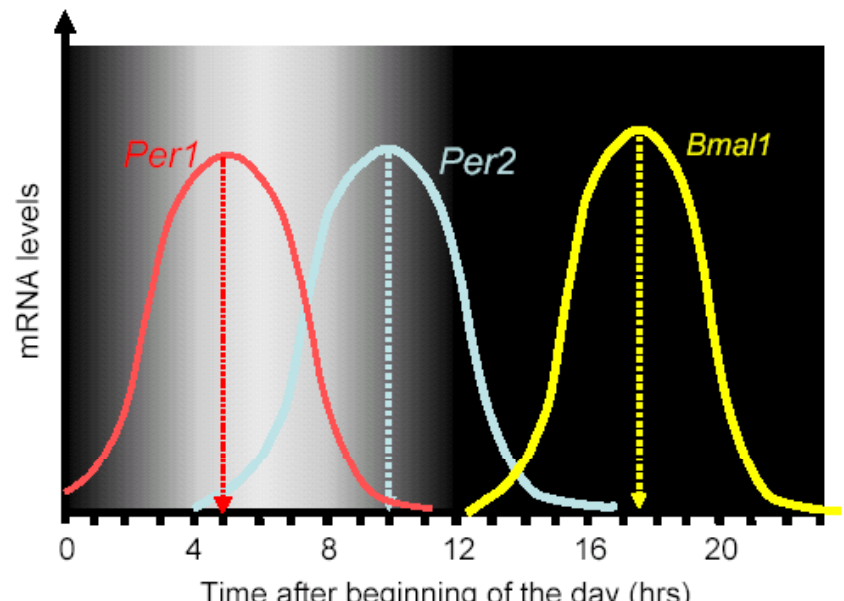
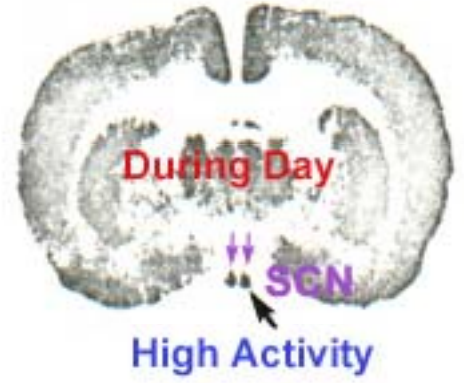
**Circadian rhythm of vasopressin release from SCN
Is maintained in SCN kept alive in tissue culture.**

Oscillazioni circadiane dell'attività elettrica e dell'espressione genica nei neuroni di SCN

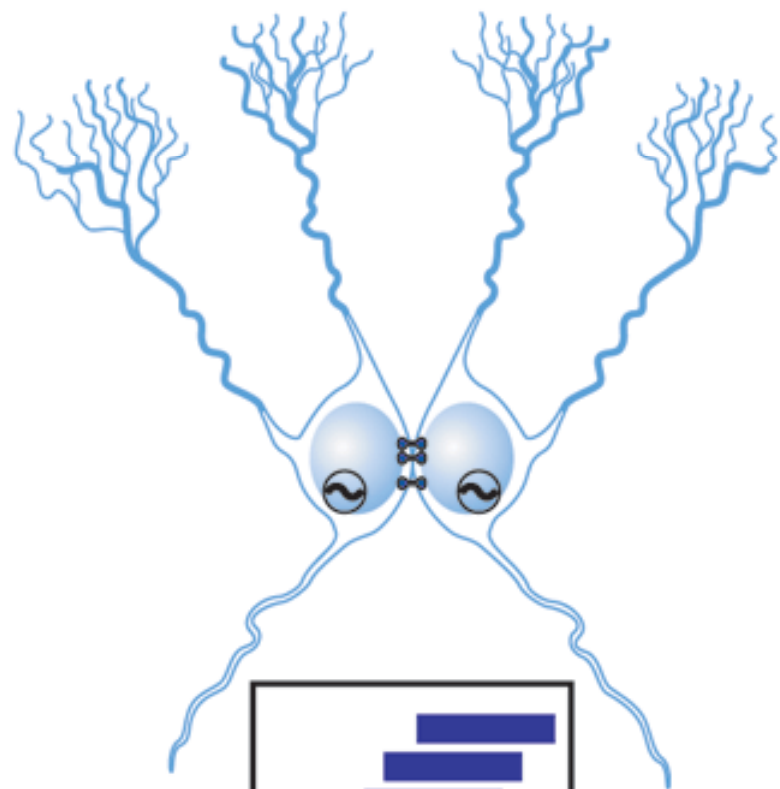
Single SCN neuron



Autoradiographs of the brain (dark areas are radioactive)

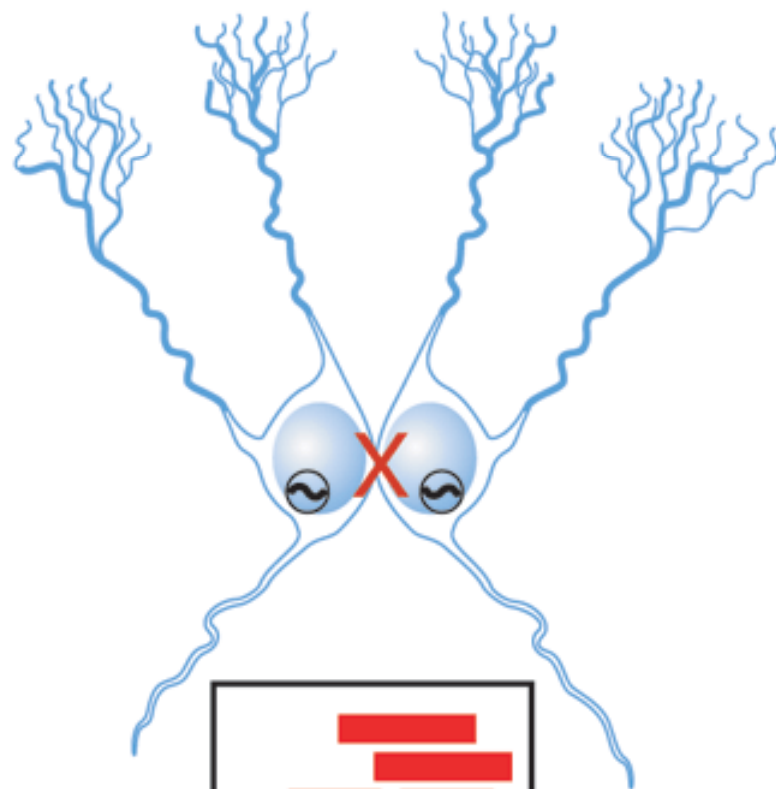


WT

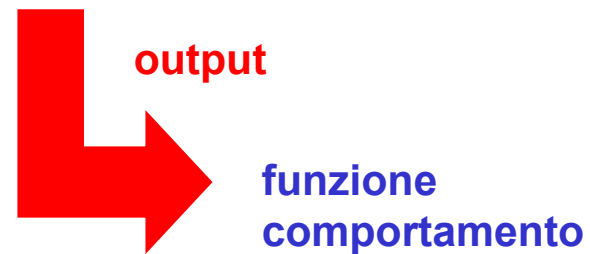
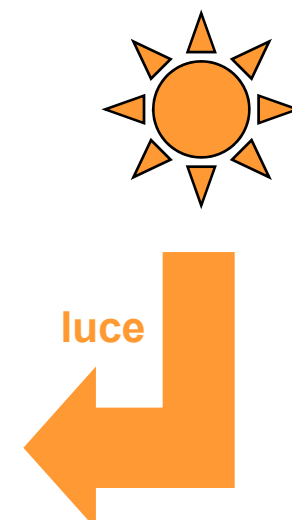
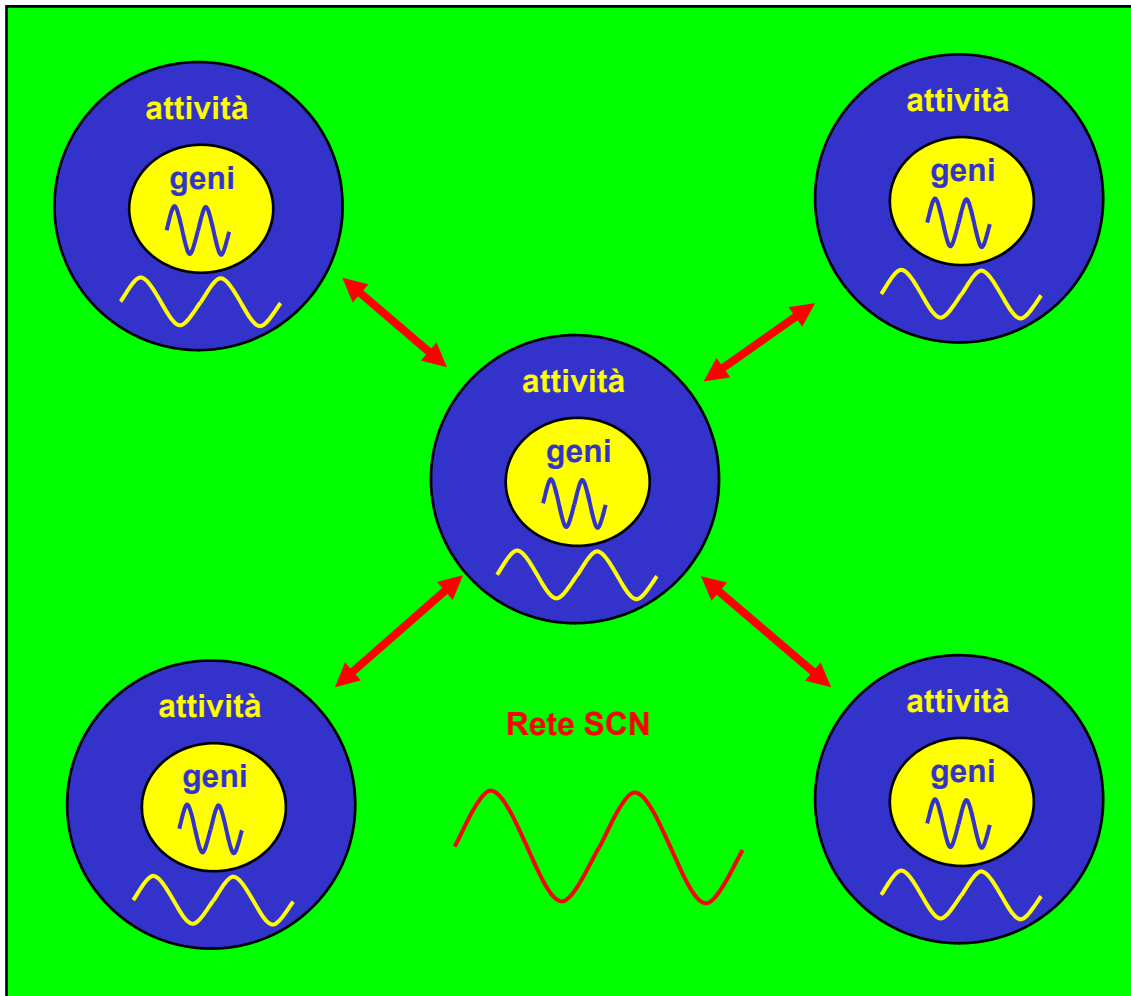


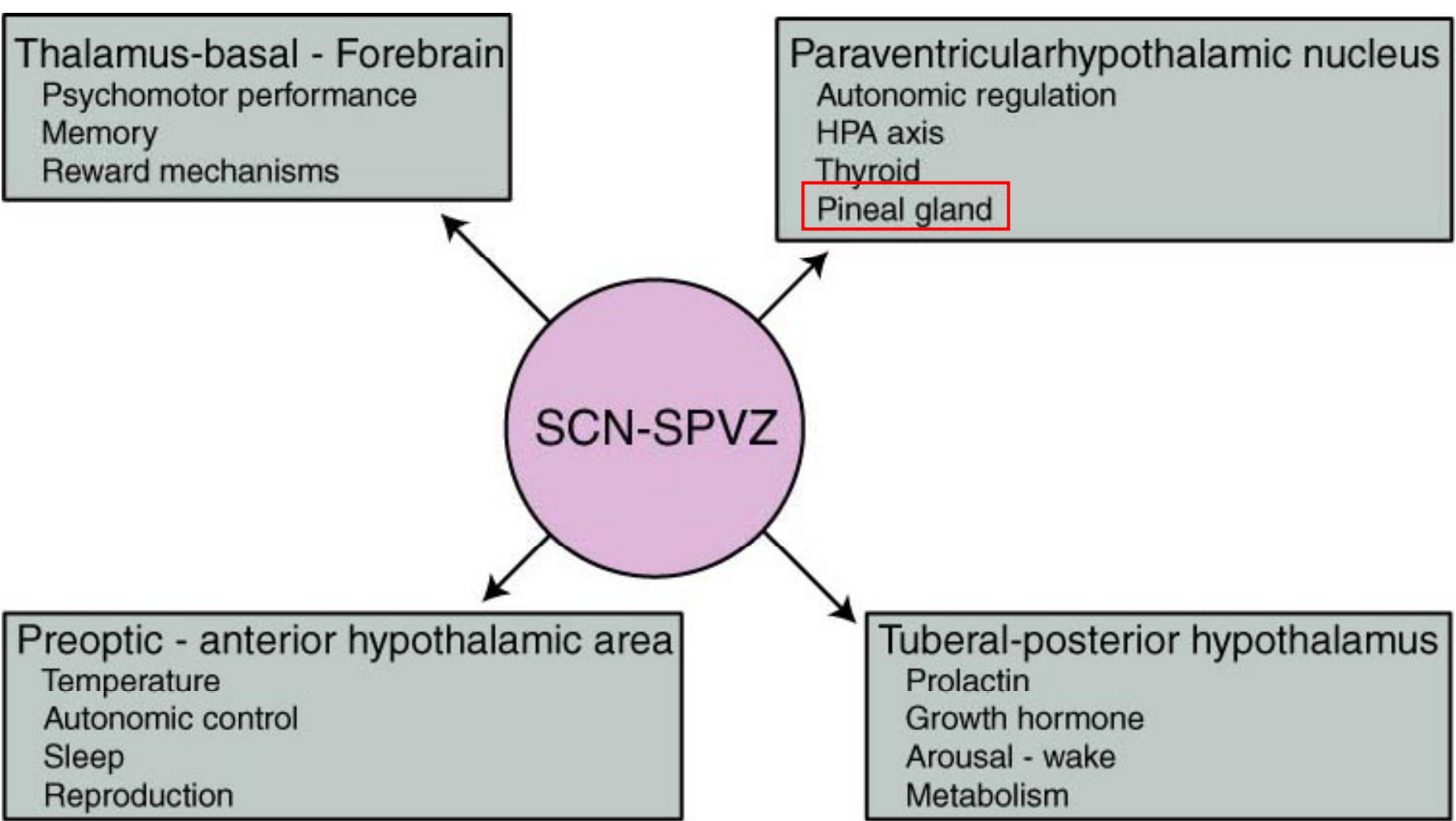
0 12 24
Time (h)

Cx36^{-/-}

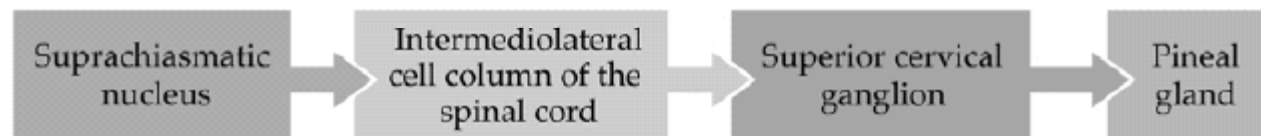


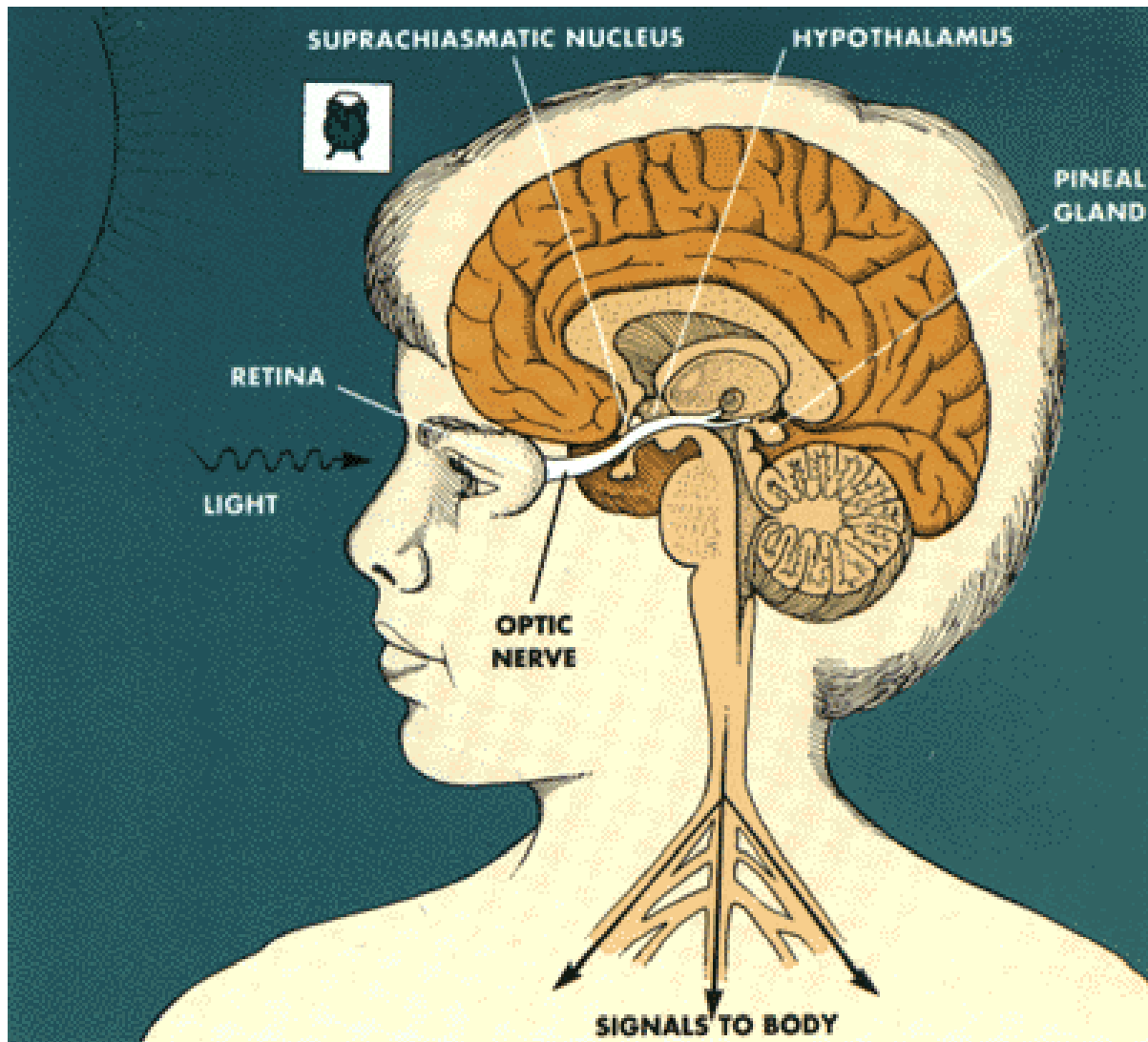
0 12 24
Time (h)



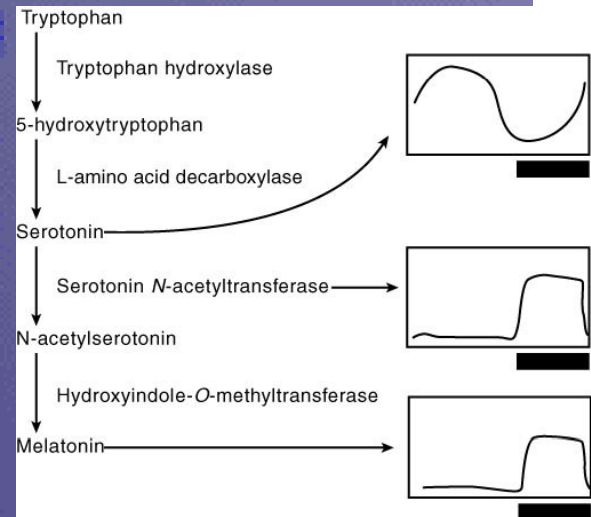
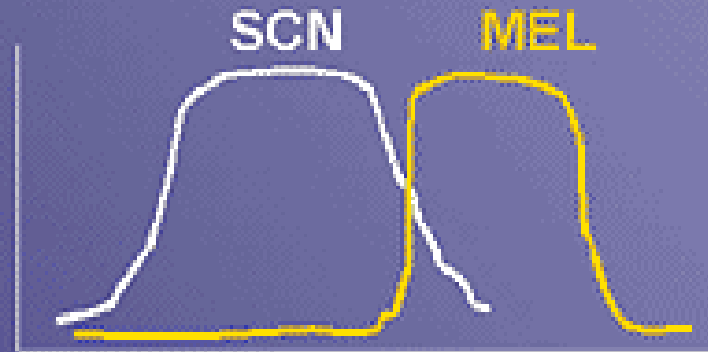
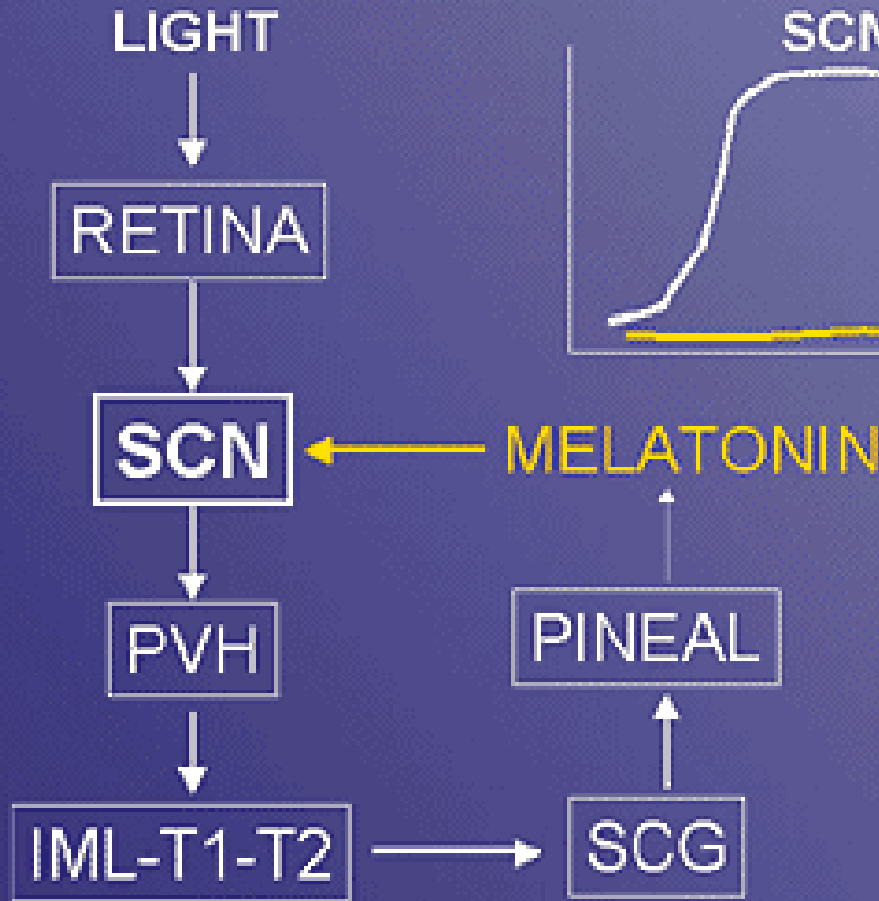


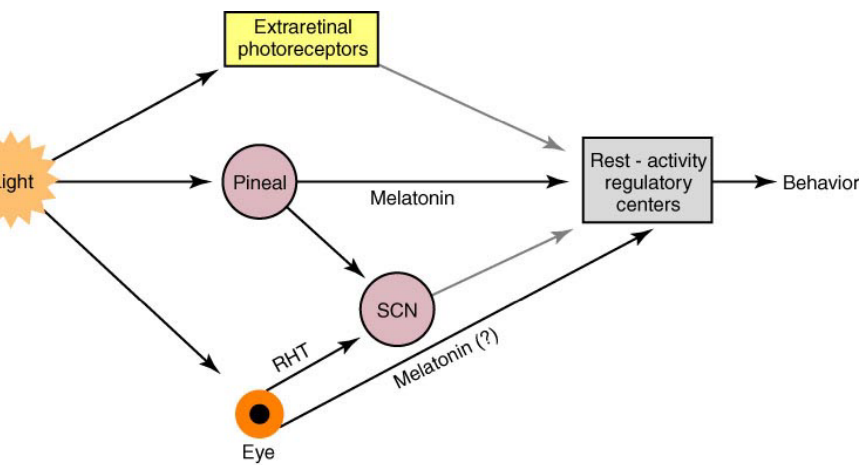
Copyright © 2002, Elsevier Science (USA). All rights reserved.



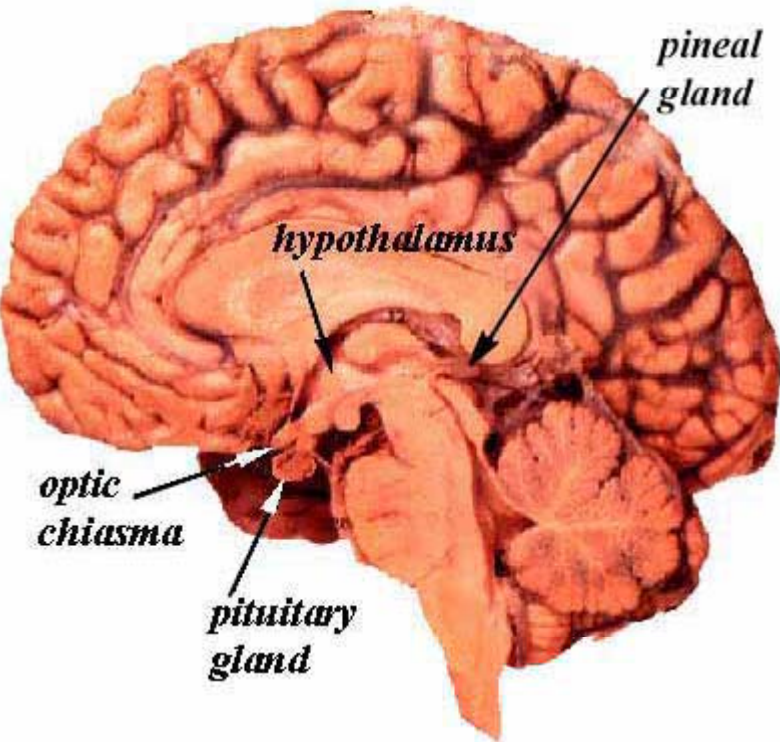


CIRCADIAN CONTROL OF MELATONIN PRODUCTION

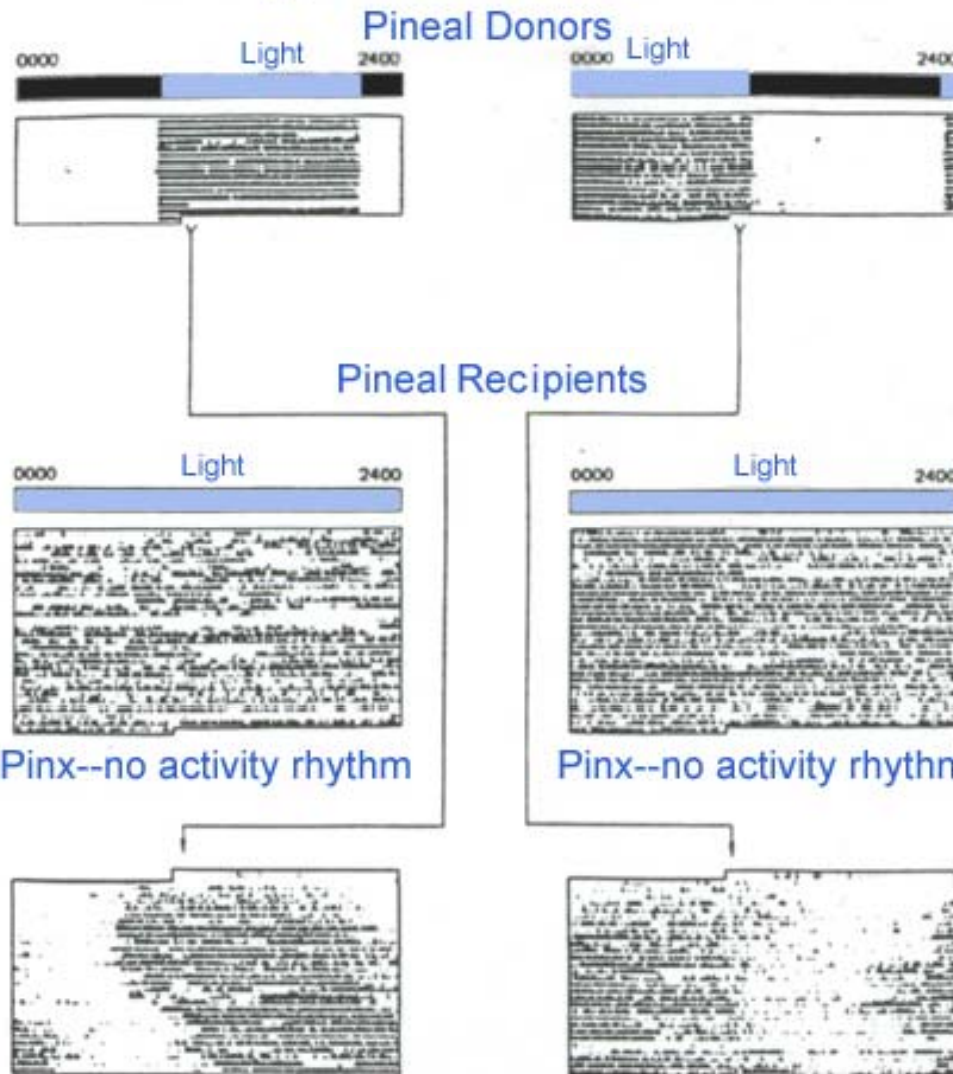




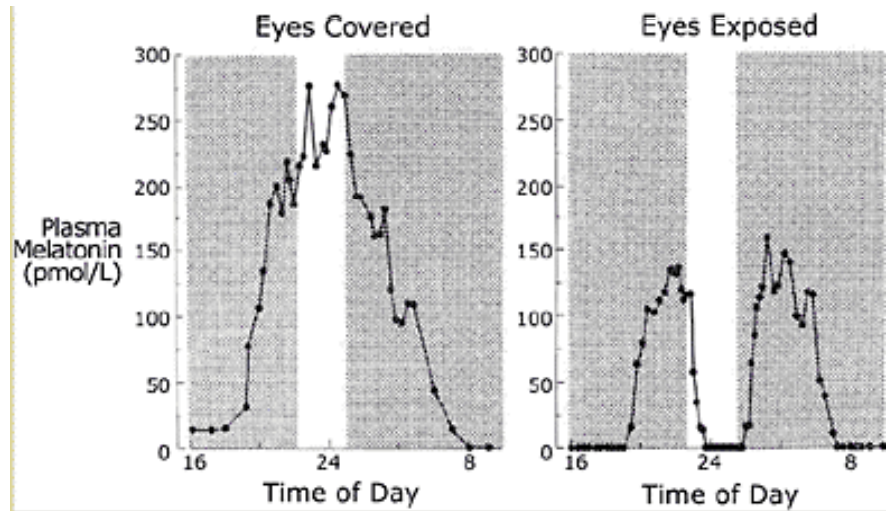
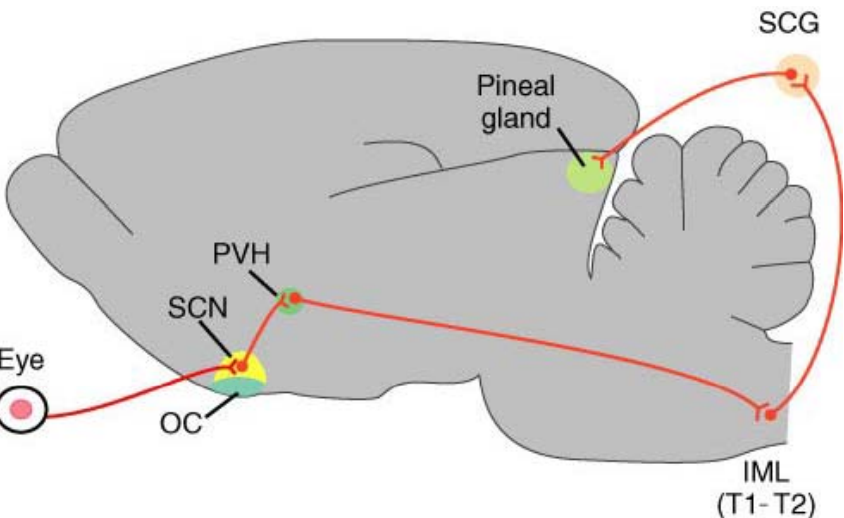
Copyright © 2002, Elsevier Science (USA). All rights reserved.



Pineal gland is a clock in birds



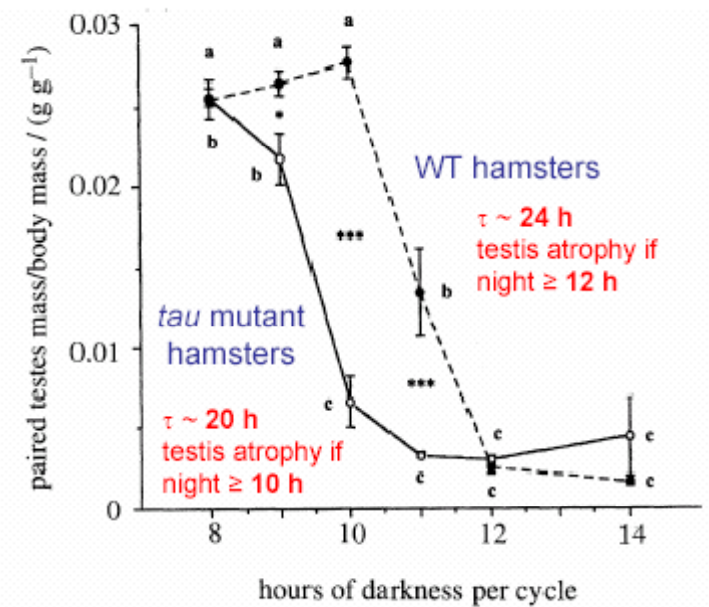
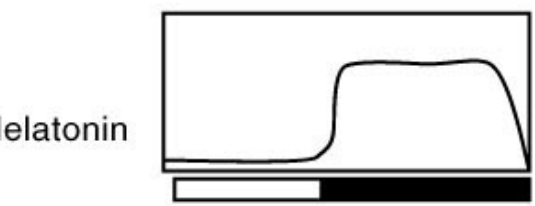
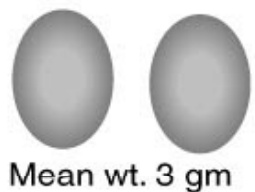
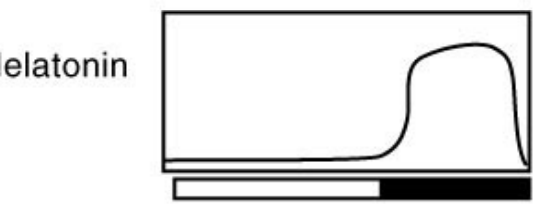
Ghiandola pineale ed il controllo della riproduzione in animali long day (hamster) o short-day (pecora) breeders



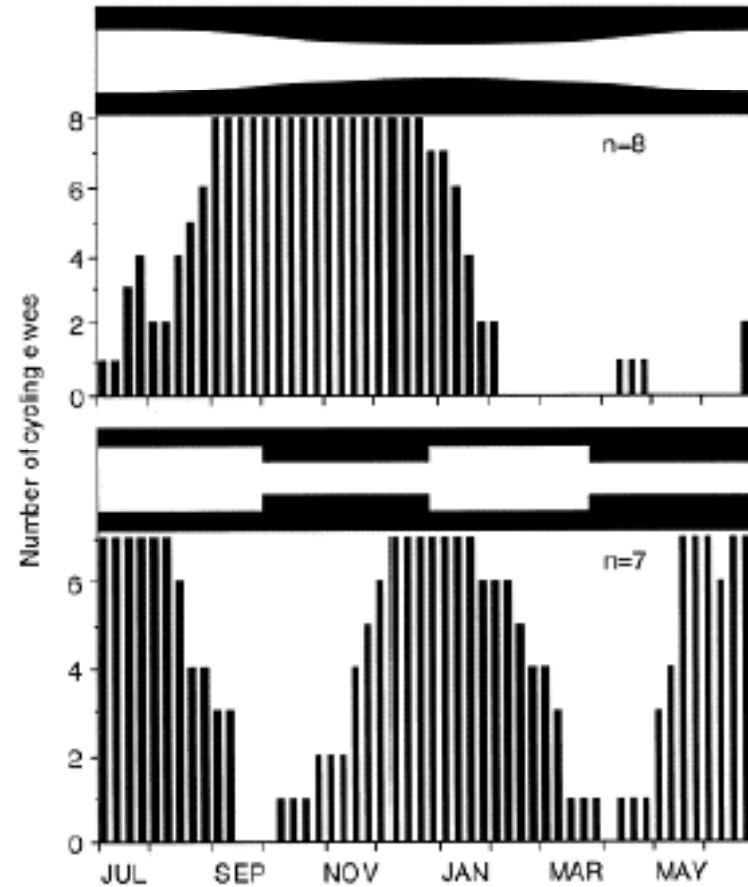
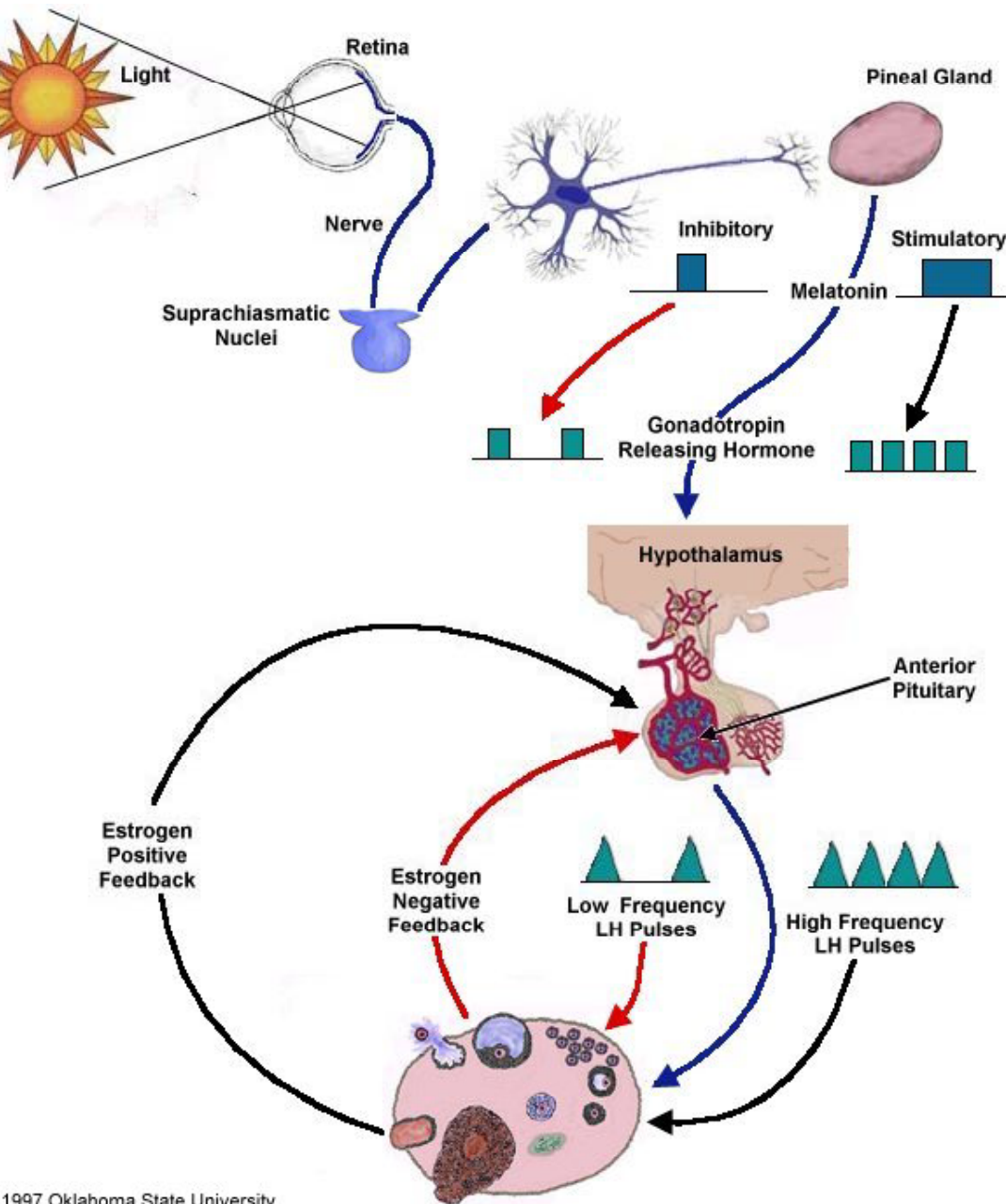
Copyright © 2002, Elsevier Science (USA). All rights reserved.

Melatonin rhythm

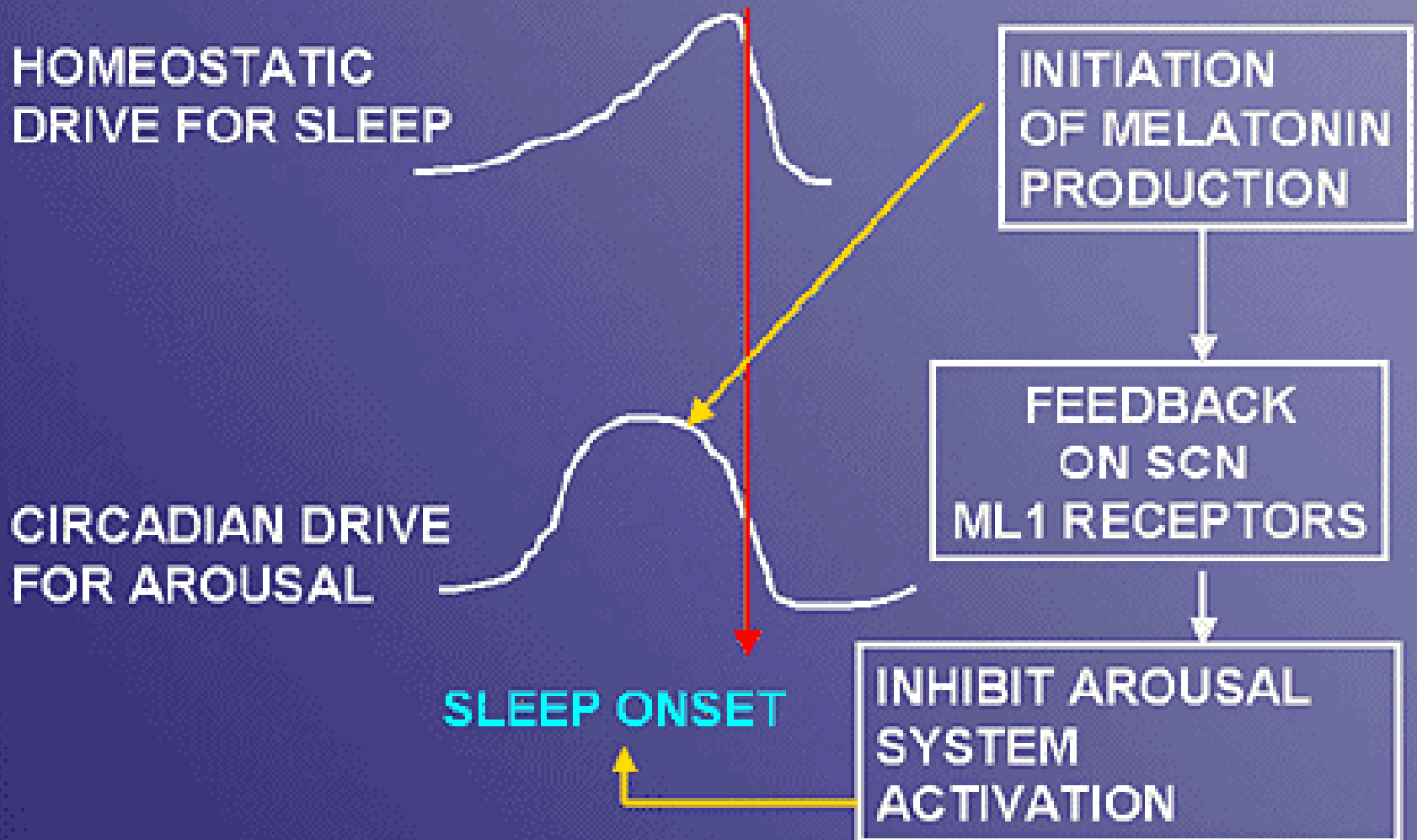
Testicular size



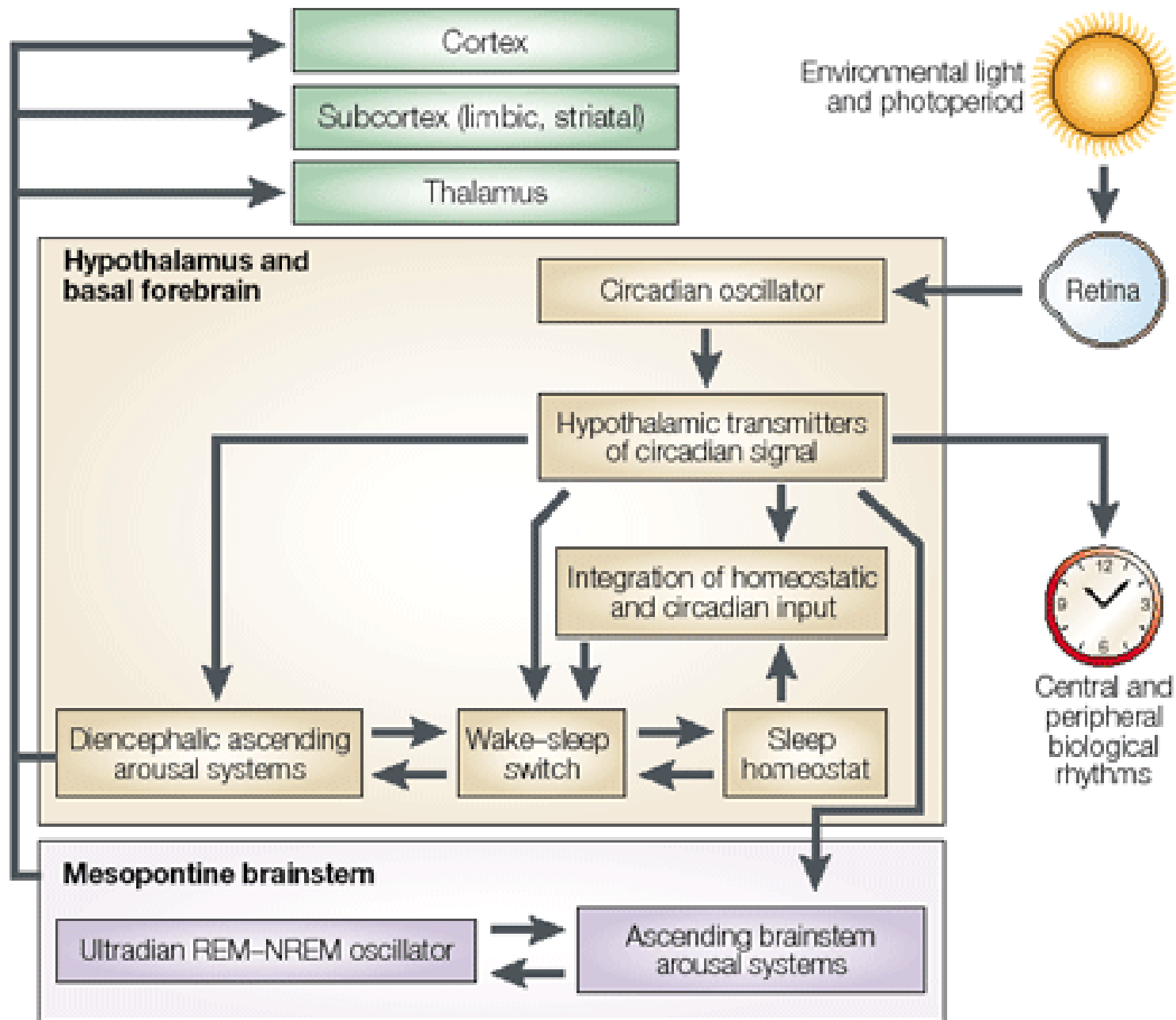
Regolazione circannuale della riproduzione nelle pecore

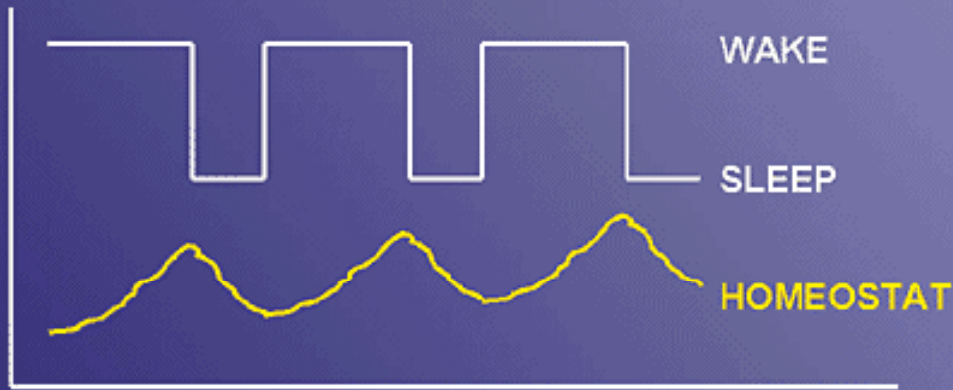


CIRCADIAN MAINTENANCE OF WAKING AND THE SLEEP-WAKE TRANSITION



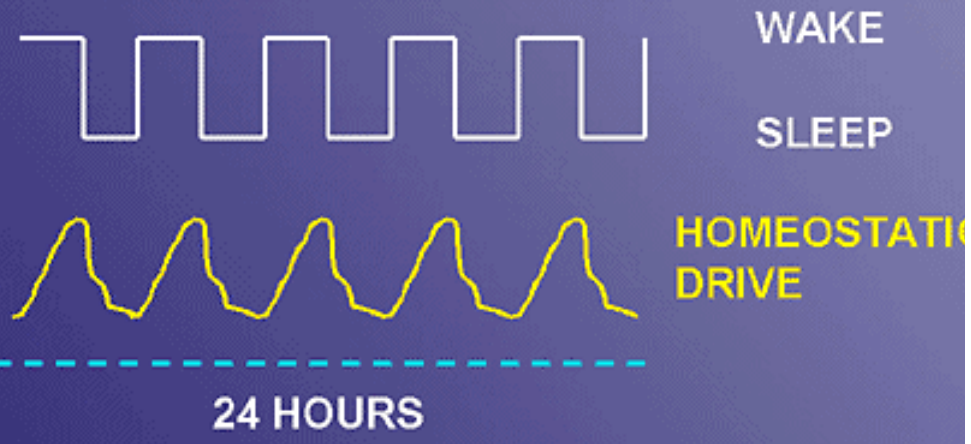
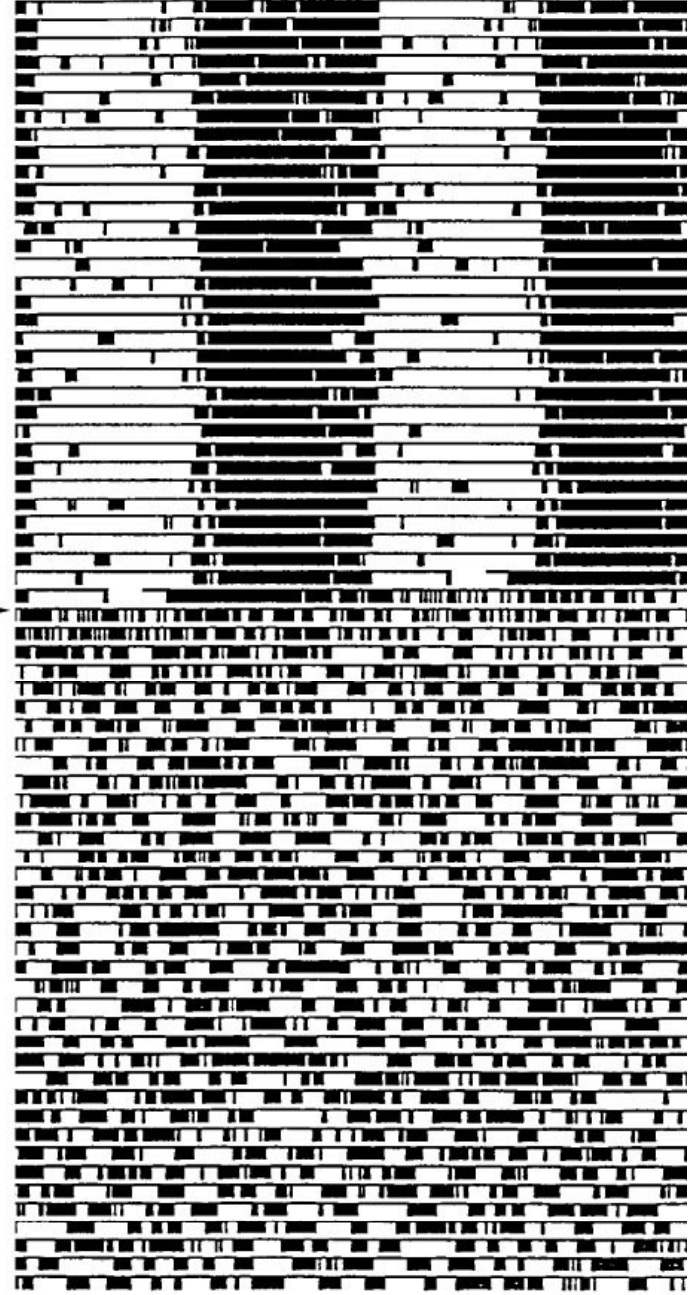
Sleep-wake control systems





sonno 8 ore; veglia 16 ore

Lesione SCN →



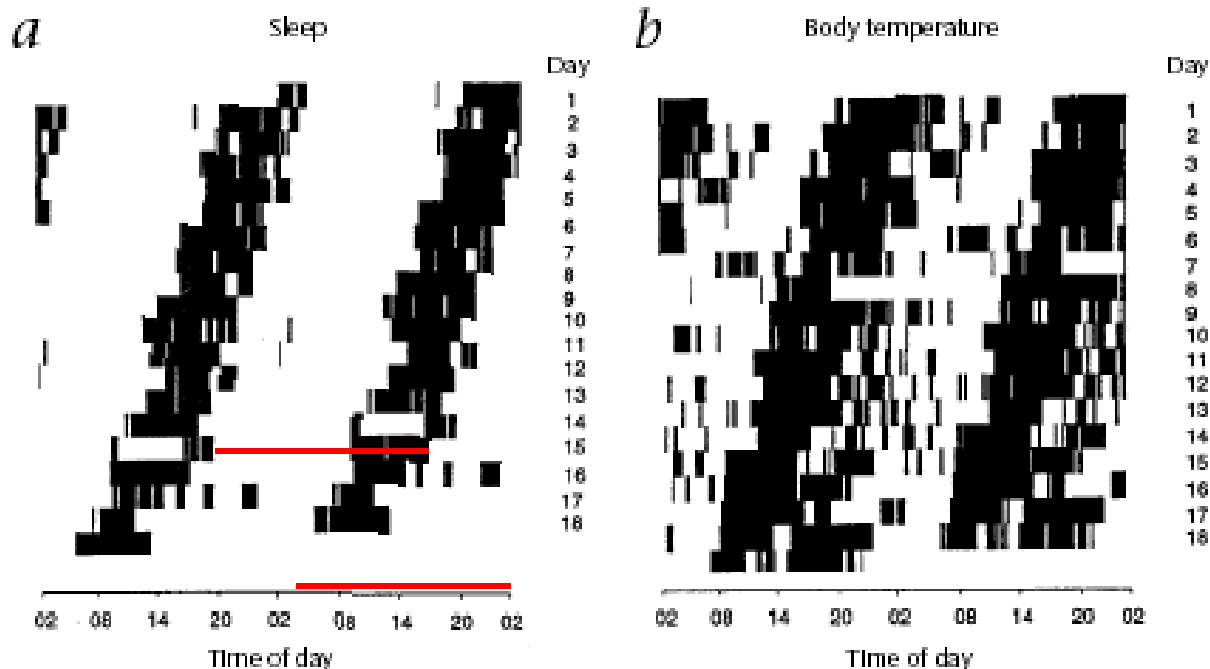
sonno 12 ore; veglia 12 ore

FASPS

(Familial advanced sleep phase syndrome)

| | Control (<i>n</i> = 6) Mean ± s.d. | FASPS(<i>n</i> = 6) Mean ± s.d. | Difference (hours:minutes) | <i>P</i> value |
|---------------------------|---|-------------------------------------|-------------------------------|----------------|
| Sleep Onset | 23:10 ± 0:40 | 19:25 ± 1:44 | 3:45 | < 0.0005 |
| Sleep Offset ^a | 07:44 ± 1:13 | 04:18 ± 2:00 | 3:26 | < 0.0005 |
| 1st Slow Wave Sleep | 23:55 ± 1:17 | 20:14 ± 2:35 | 3:41 | 0.002 |
| 1st REM ^a | 00:55 ± 1:29 | 21:16 ± 2:25 | 3:39 | < 0.0005 |
| DLMO | 21:21 ± 0:28 | 17:31 ± 1:49 | 3:50 | < 0.0005 |
| Temp Nadir ^b | 03:35 ± 1:33 | 23:22 ± 2:55 | 4:13 | 0.002 |

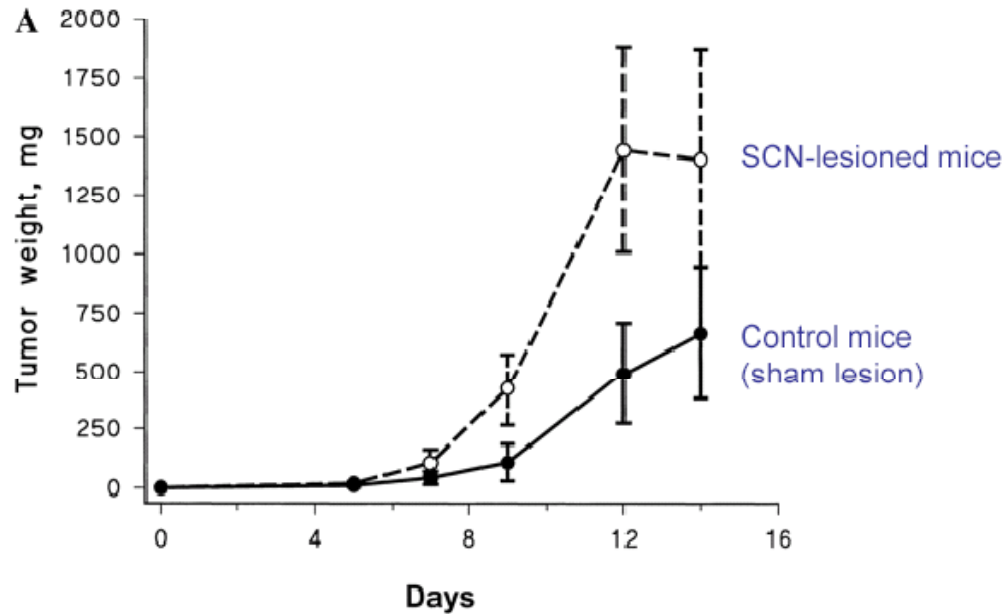
^a*n* = 5 for FASPS only. ^b*n* = 5 for control and FASPS. Data include both nights of study. REM, rapid eye movement; DLMO, dim-light melatonin onset; Temp, temperature.



Malattia ereditaria con disturbo del ritmo circadiano dovuto ad una riduzione del periodo endogeno

Other human circadian rhythm disorders

- Delayed Sleep Phase Syndrome
- SAD (Seasonal Affective Disorder)
- Non-24h sleep-wake syndrome
- Health problems of shift workers
- Jet lag
- Cancer?



Accelerated tumor growth in SCN-lesioned mice
(Filipski et al., 2002)

Table 1. Neoplastic Growth Phenotypes of *mPer2tm* Mice

| Phenotypes | <i>mPer2tm</i> Mice (18 months old) (n = 20) | Wild-Type Mice (18 months old) (n = 20) | <i>mPer2tm</i> Mice 16 months after IR (n = 14 ^a) | Wild-Type Mice 16 months after IR (n = 20) | p value |
|--------------------------------|---|---|--|--|---------|
| Salivary gland hyperplasia | 20 (50%) ^b | 0 | 14 (100%) | 1 (5%) | <0.0001 |
| Teratoma in male mice | 10 (100%) | 0 | 9 (100%) | 0 | |
| Hair graying 6 months after IR | | | 14 (100%) | 0 | |
| Lymphoma | 3 (15%) | 0 | 10 (71%) | 1 (5%) | <0.0001 |
| Angiosarcoma | 0 | 0 | 0 | 2 (10%) | |

^aSix irradiated *mPer2tm* mice were lost at 9 months after irradiation during the summer flooding in Houston in 2001.

^b50% of *mPer2tm* mice showed enlarged salivary glands by physical examination. At autopsy, all the *mPer2tm* mice older than 8 month of age were found to have salivary gland hyperplasia.

Spontaneous development of cancers in *Per2* knock-out mice
(Fu et al., 2002)

