

**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.

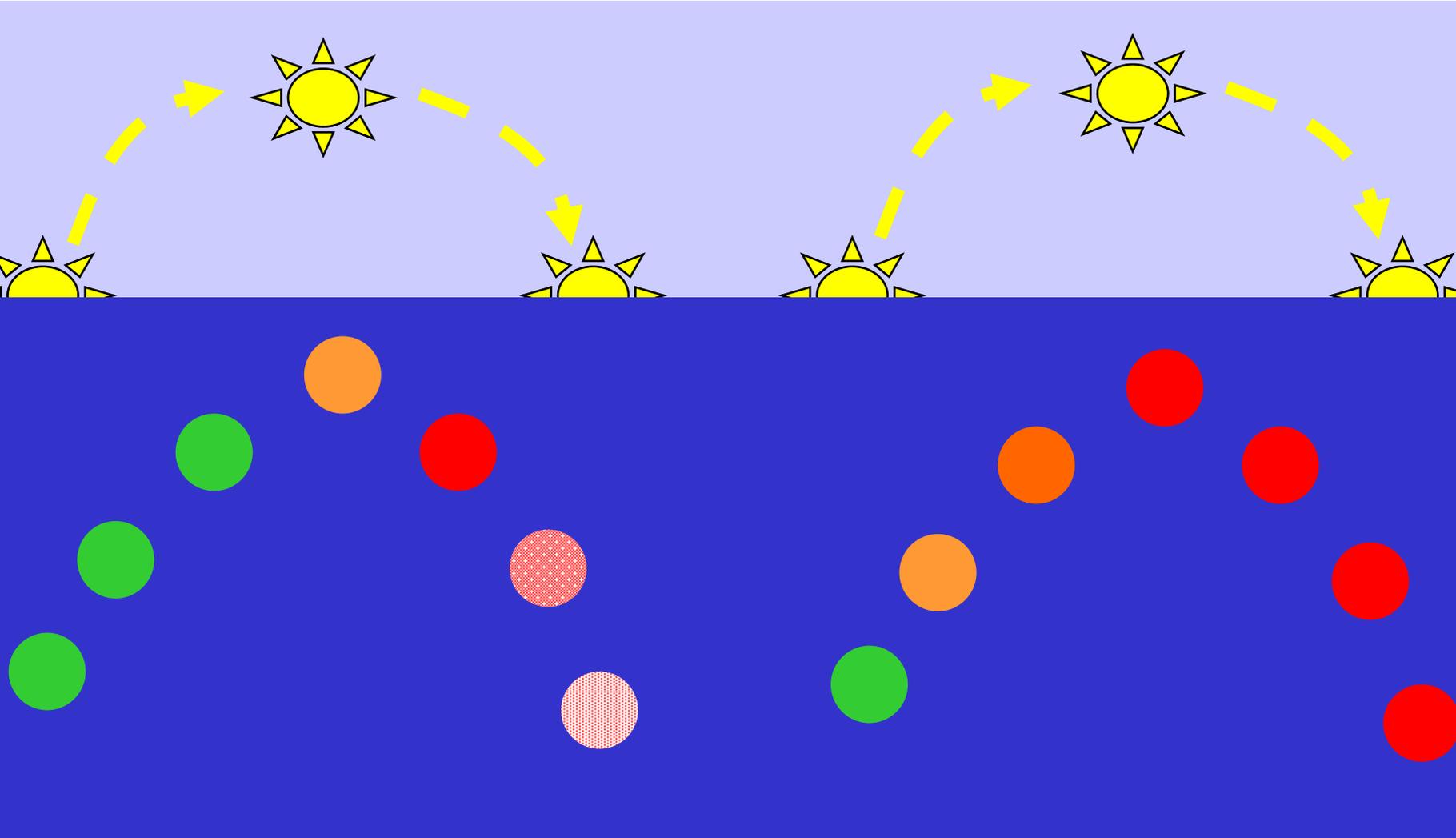
Hibernation – reduced metabolic activity

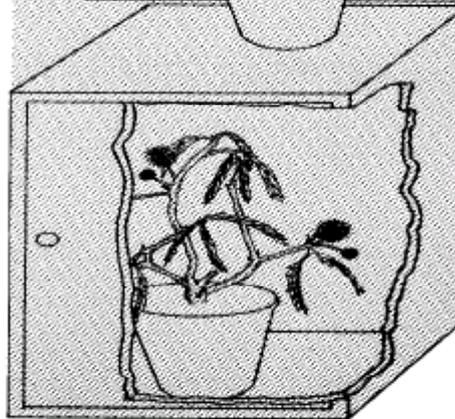
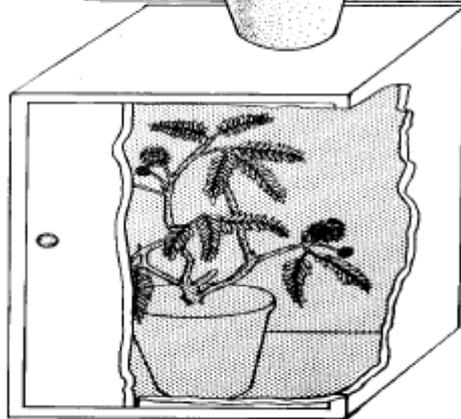
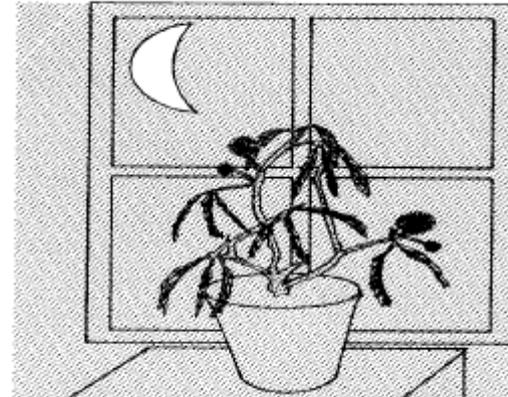
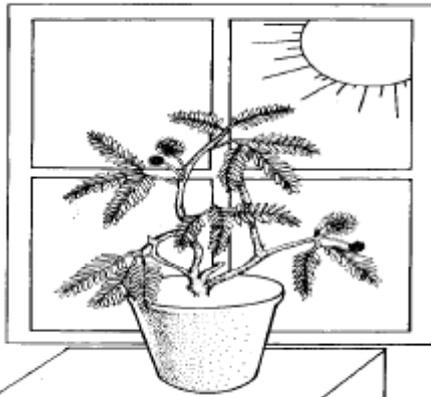
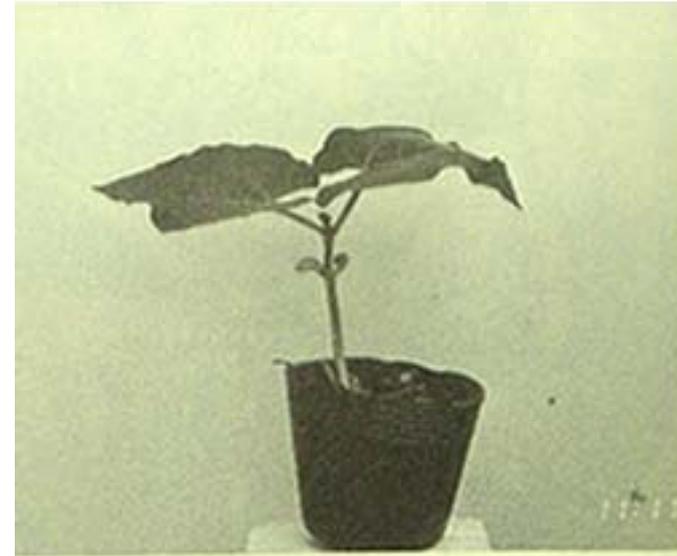
Migration

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

**Organismi reattivi**

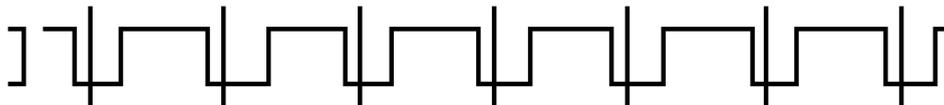
**Organismi predittivi**



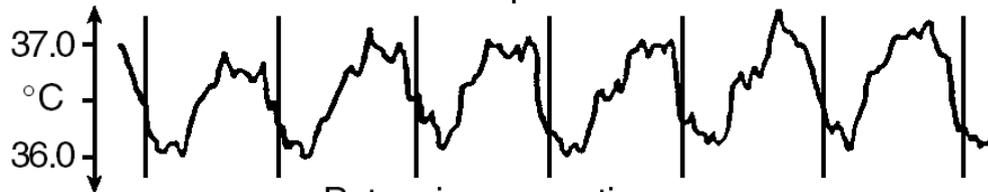


*Jacques Ortous de Mairan*

# Activity



# Rectal temperature



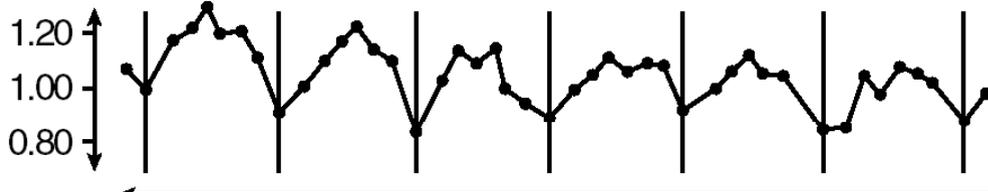
# Potassium excretion



# Computation speed



# Time estimation



0 12 24 12 24 12 24 12 24 12 24 12 24

Time of day (hrs)

**I ritmi sono:**

**Ubiquitari**

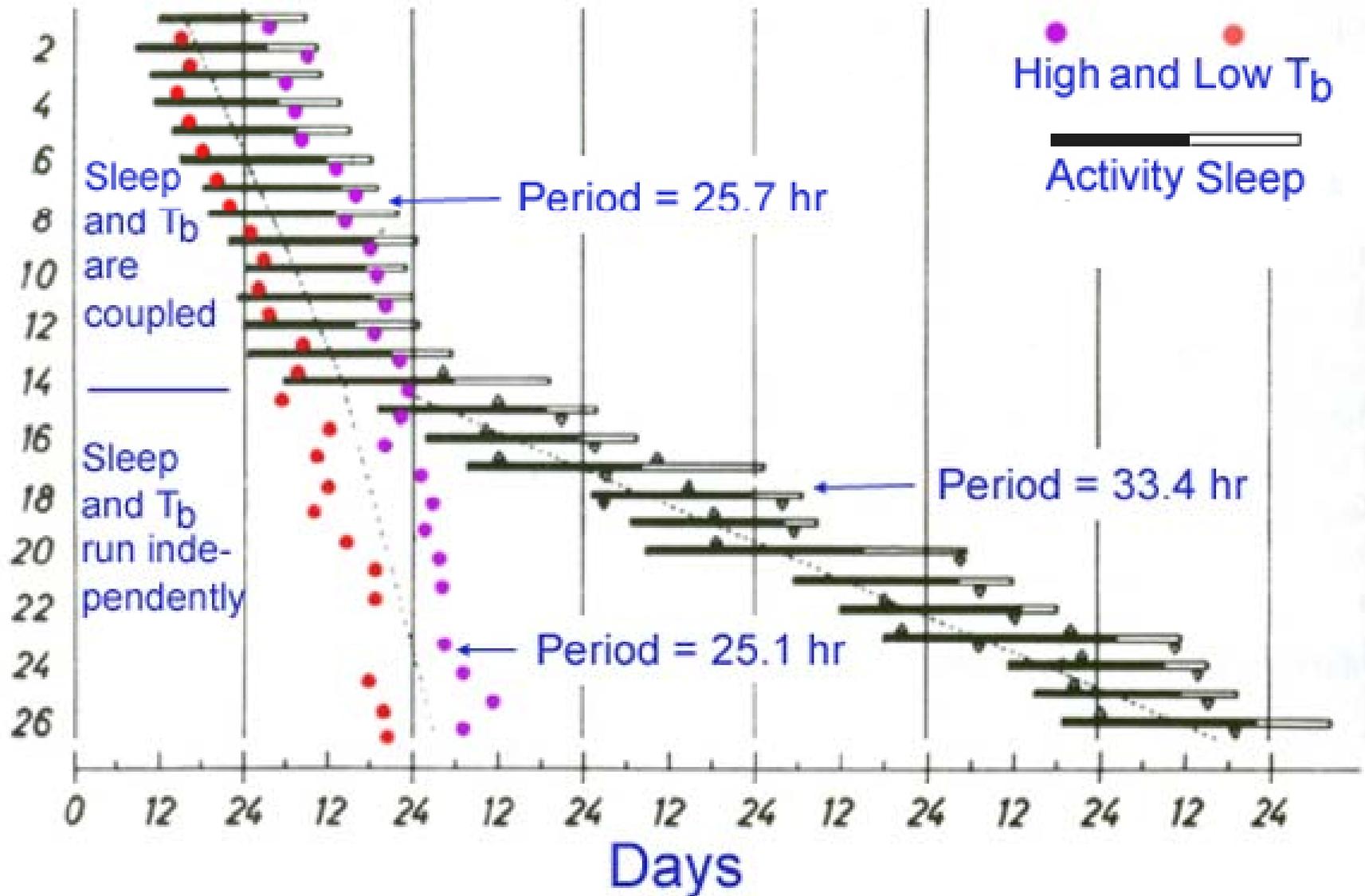
**Generati intrinsecamente**

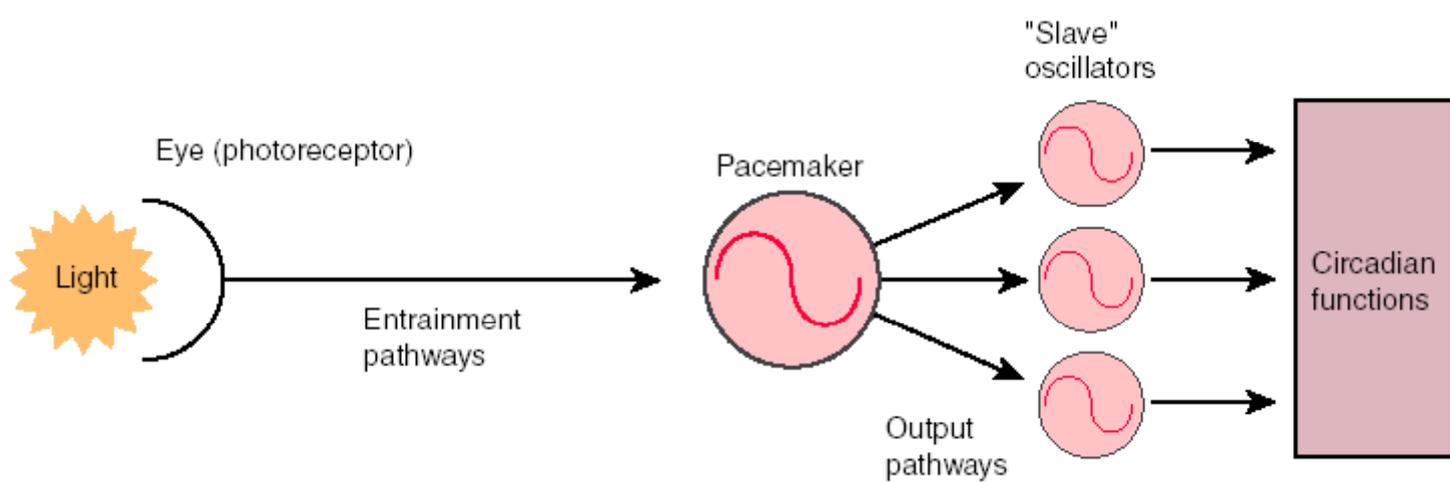
**Autonomi dagli stimoli  
esterni**

**Ritmatori (pacemaker)**

**Sincronizzatori (zeitgeber)**

# Free-running Sleep and Temperature ( $T_b$ ) Rhythms





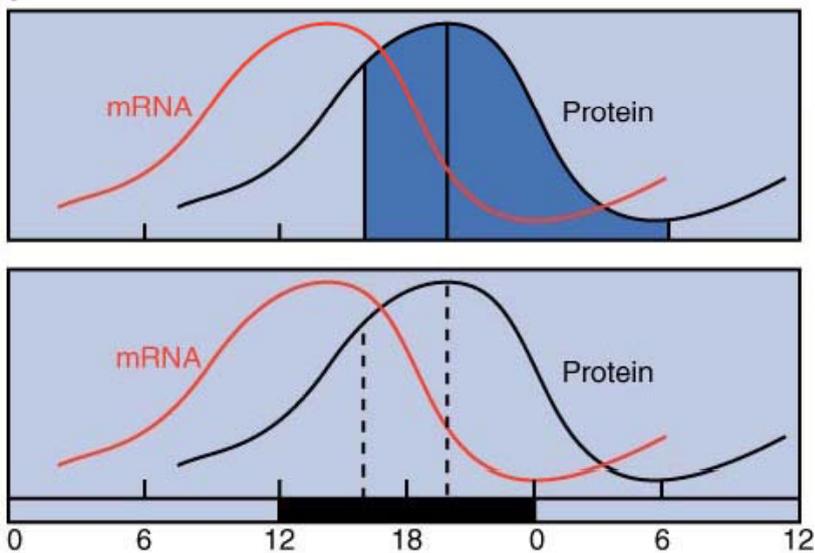
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## Proprietà di un ritmatore circadiano

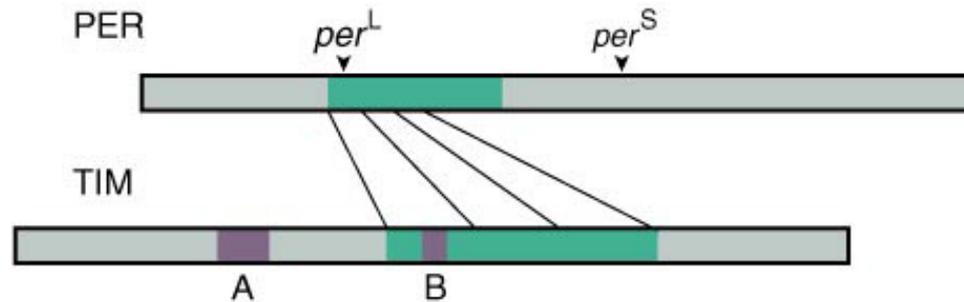
- sintonizzato con il ciclo luce/buio con un periodo di 24 ore
- fase stabile rispetto al ciclo luce-buio
- persistente anche in assenza del ciclo luce-buio esterno
- ciclo non-dipendente dalla temperatura
- ereditario e regolato da geni specifici

## Componenti di un ritmatore circadiano

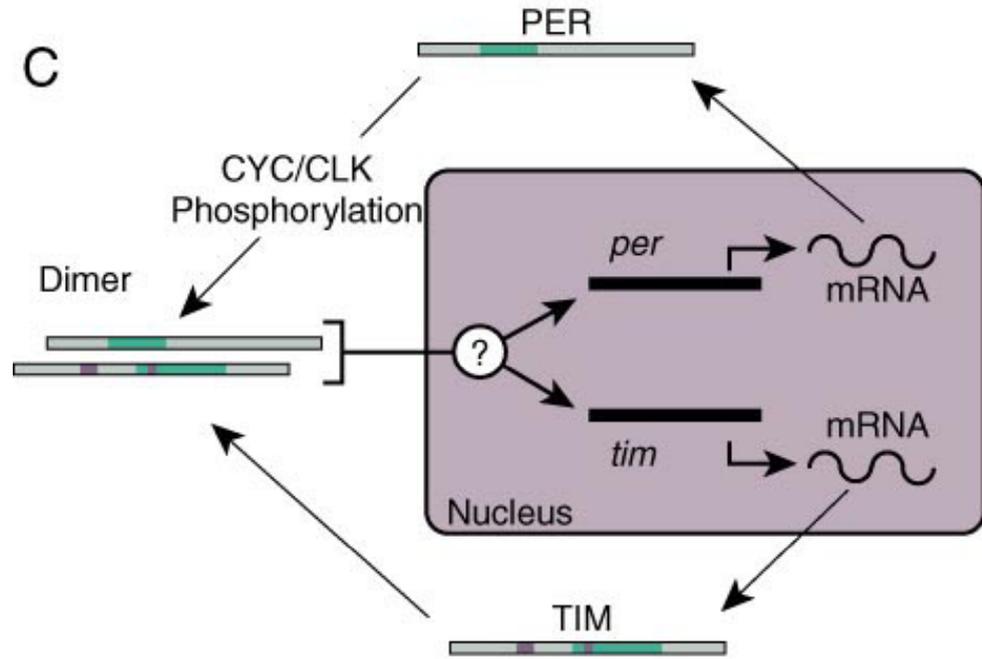
- Fotorecettore
- Pacemaker (ritmatore): **ZEITGEBER**
- Strutture con funzione circadiana



B



C



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**Geni circadiani**

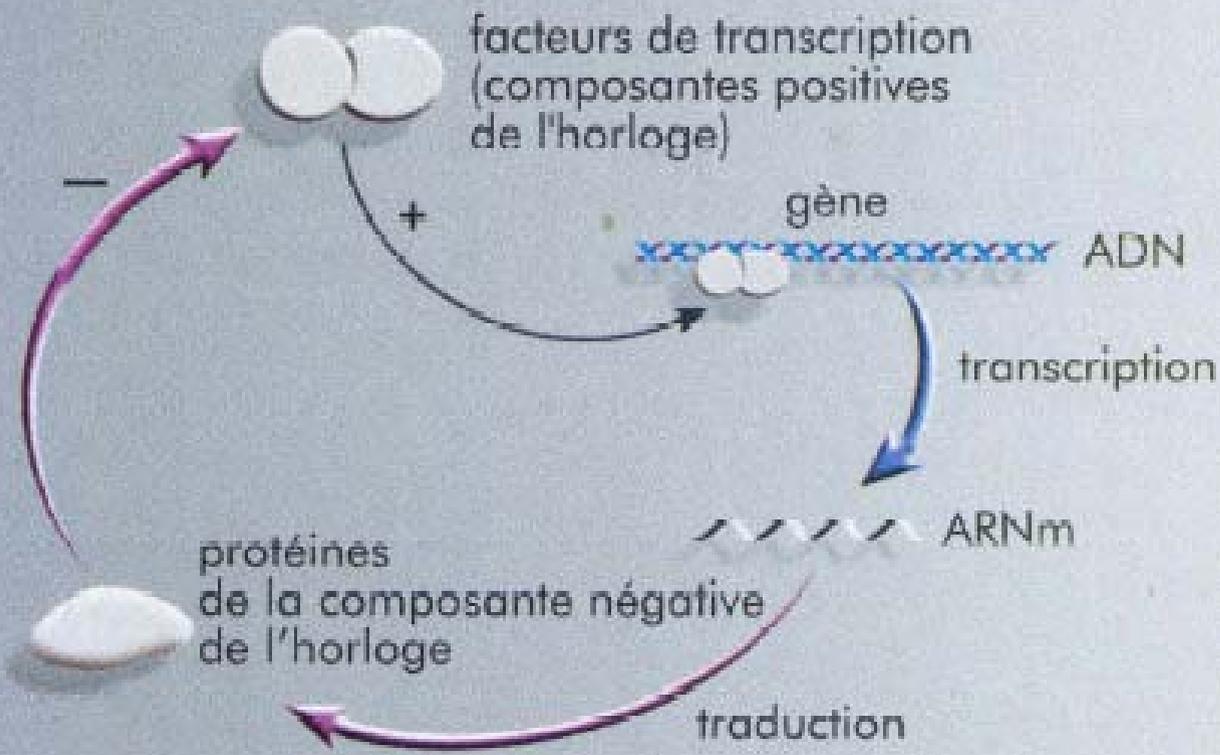
- Produzione ciclica (24h)
- In fase con cicli L/B
- Perdita del ritmo biochimico induce perdita di quello funzionale o comportamentale
- Mutazioni dei geni devono modificare le proprietà del ritmatore e/o abolire il ritmo funzionale

**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**

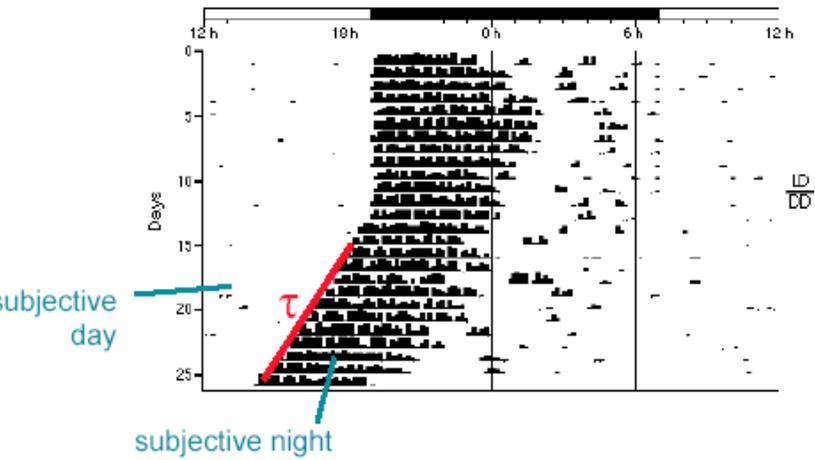
**Senso primario: visione**

**Senso primario: udito-olfatto**

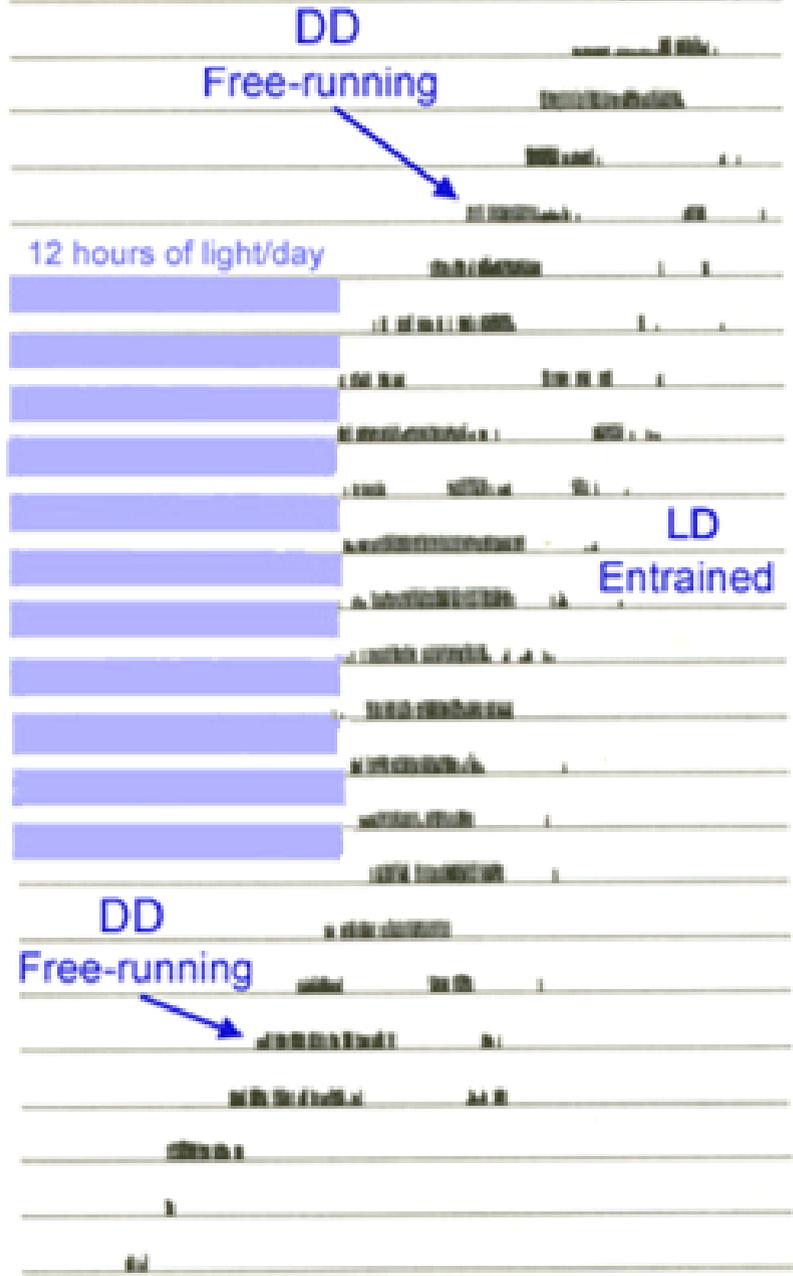
**Attivi durante il giorno  
A riposo durante la notte**

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

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

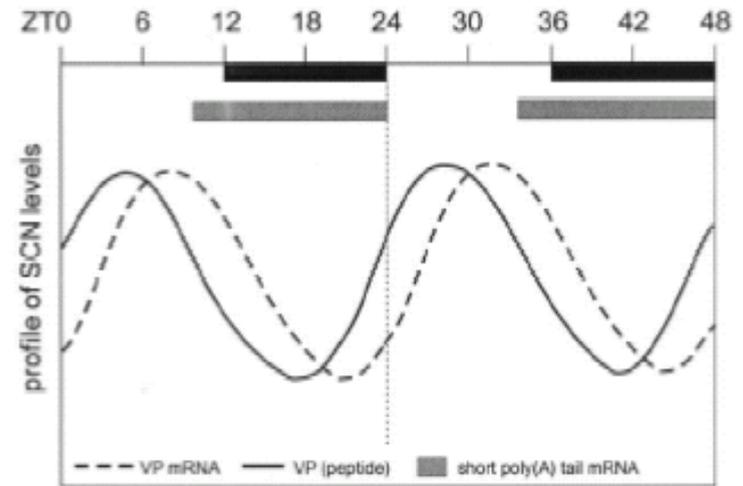


An actogram  
(activity rhythm of a mouse in a cage with a wheel)



# Il nucleo soprachiasmatico (SCN) come pacemaker

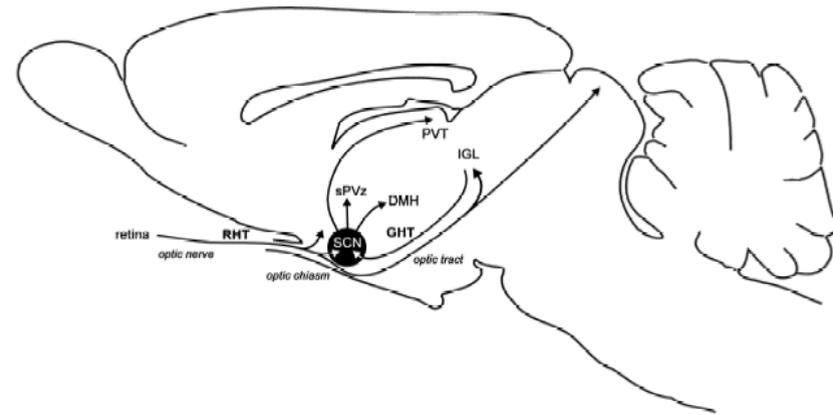
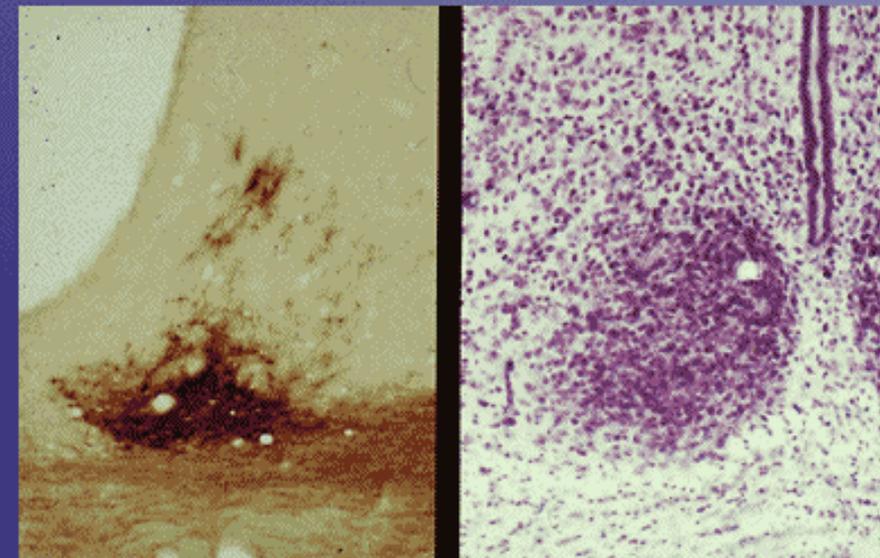
- È il sito di terminazione di RHT (input visivo)
- Lesione di SCN abolisce il ritmo circadiano, ma non altera le funzioni ritmiche
- L'isolamento di SCN (es DD o lesione di RHT) non altera la capacità di SCN di generare il ritmo in maniera intrinseca
- Dopo lesione di SCN il ritmo può essere ripristinato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

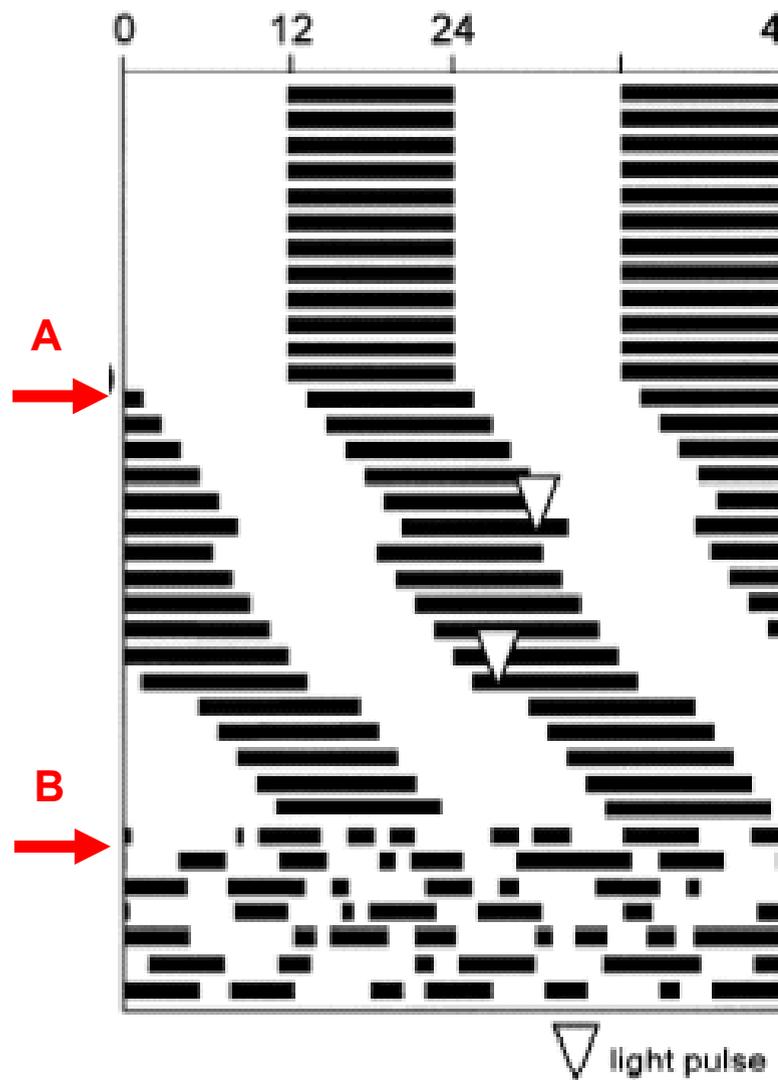
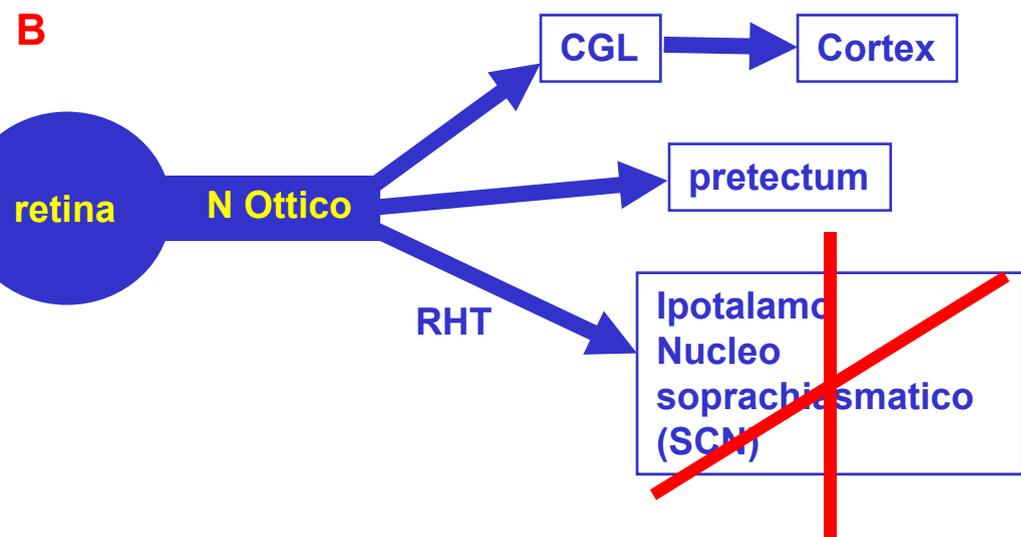
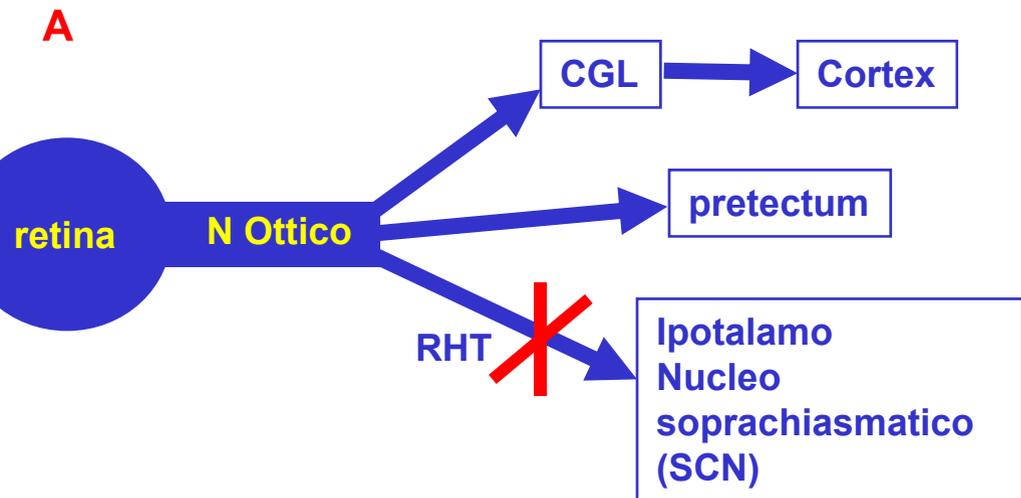


## RETINOHYPOTHALAMIC (RHT) TRACT

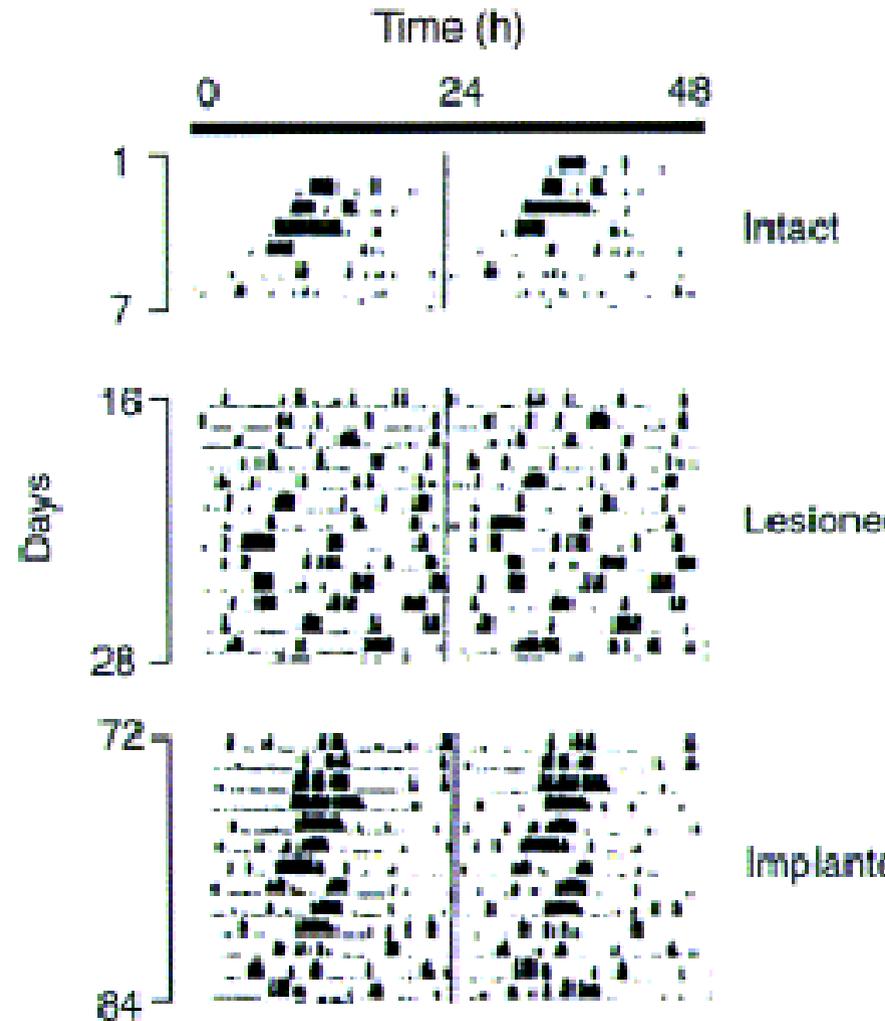
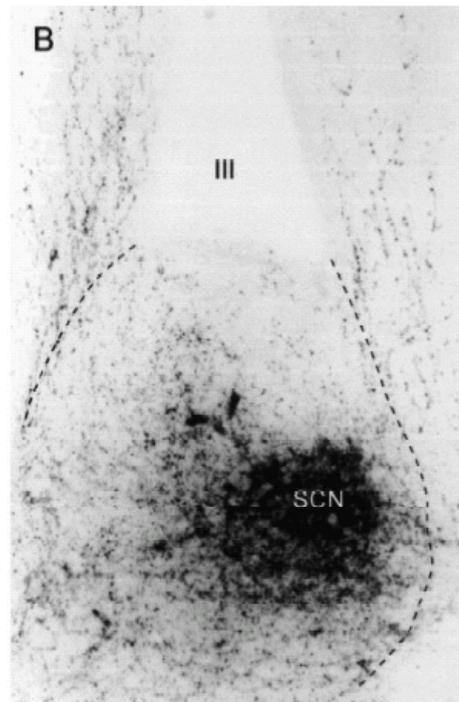
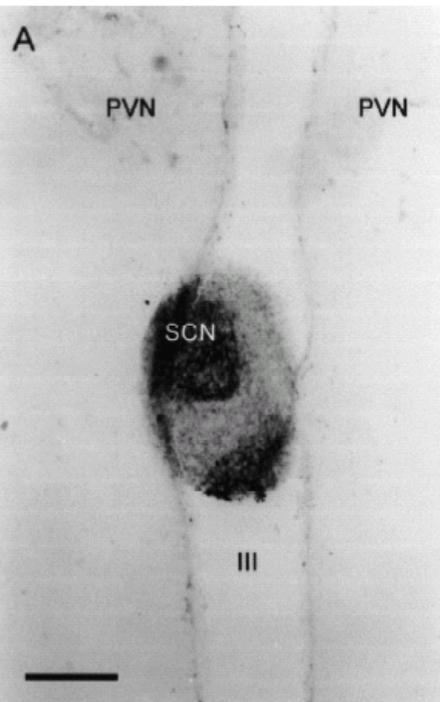
RHT

SCN (Nissl)

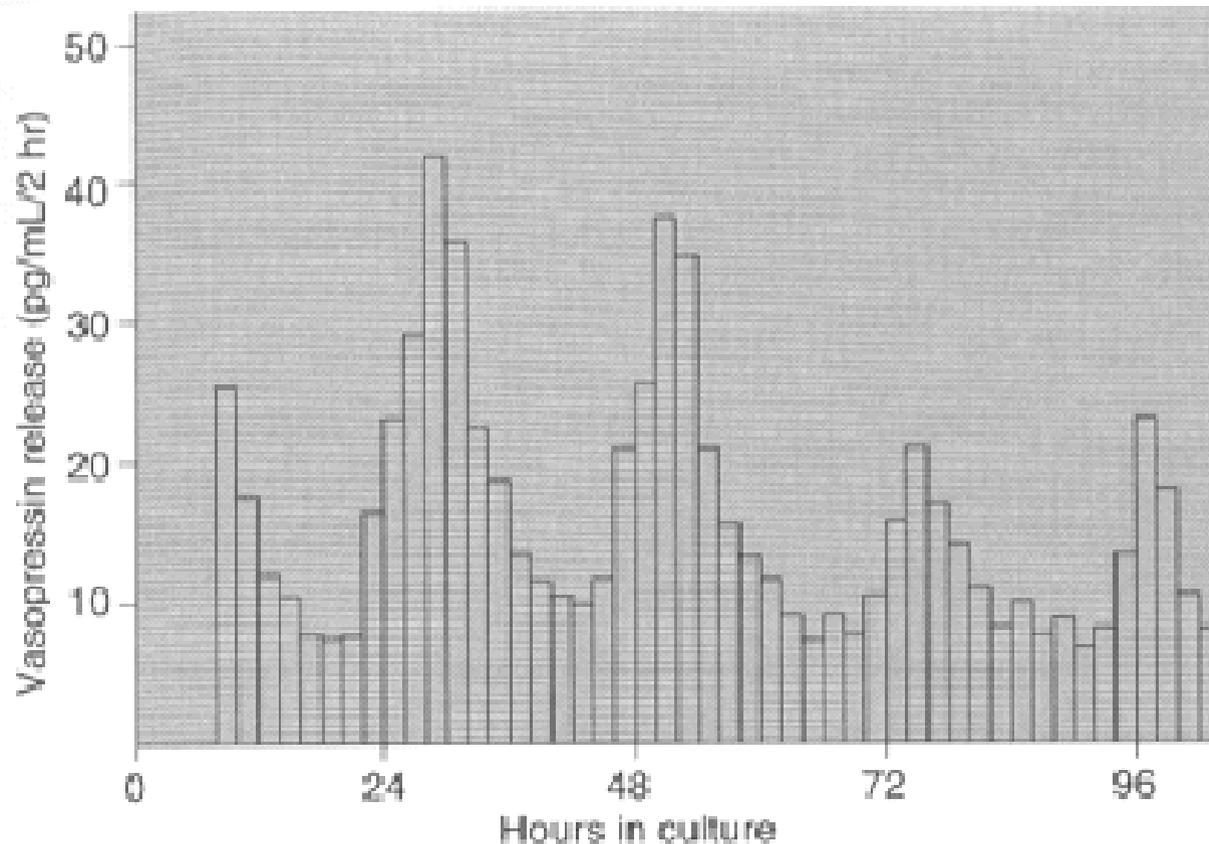




# Il trapianto di SCN embrionale in un animale leso ristabilisce il ritmo circadiano



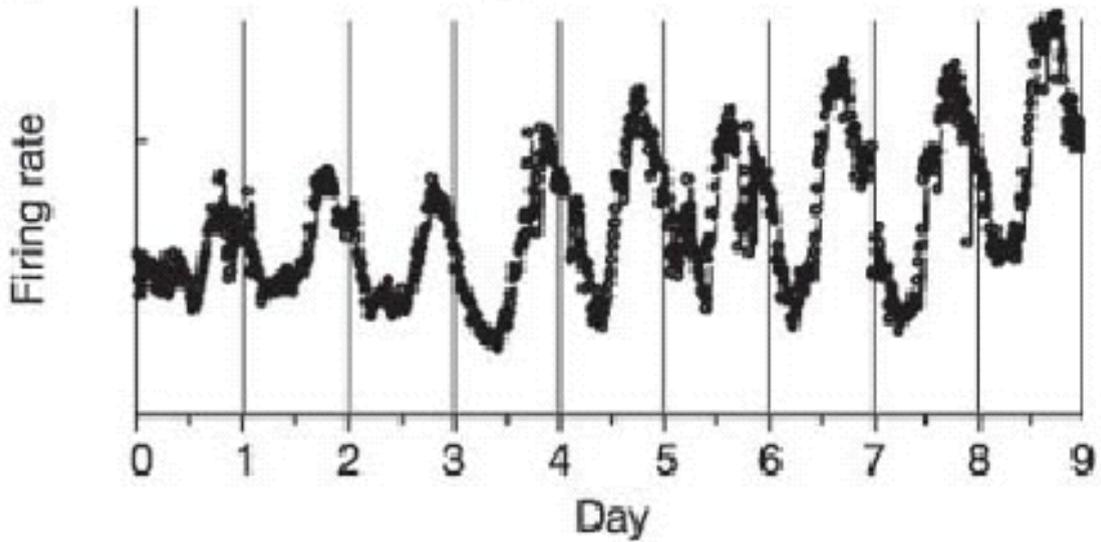
## Proprietà intrinseche dei neuroni SCN



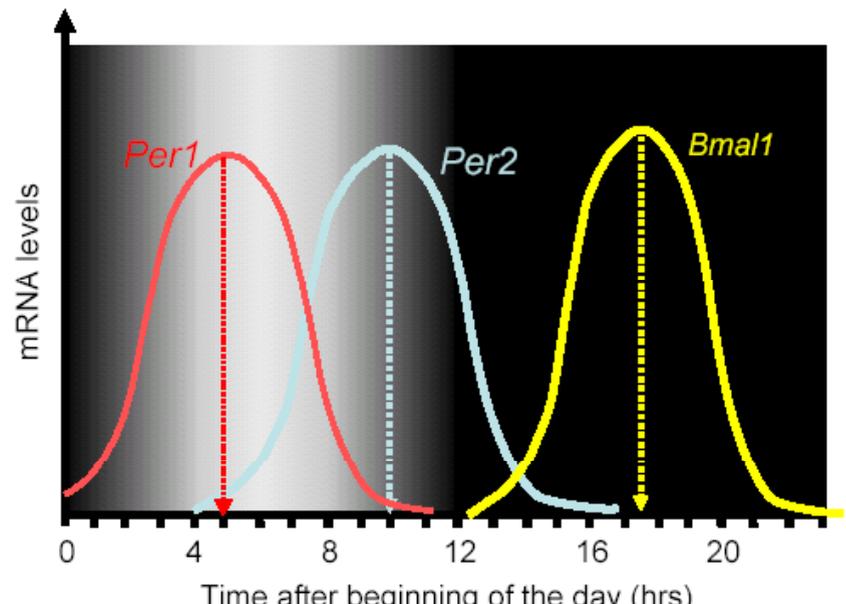
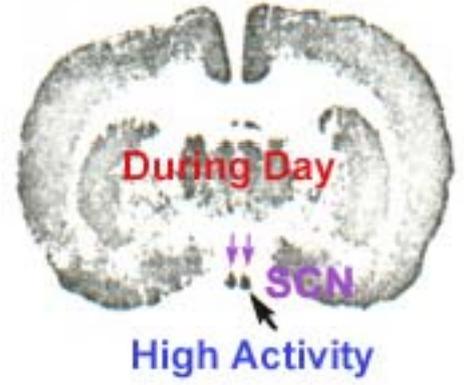
**Circadian rhythm of vasopressin release from SCN  
Is maintained in SCN kept alive in tissue culture.**

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

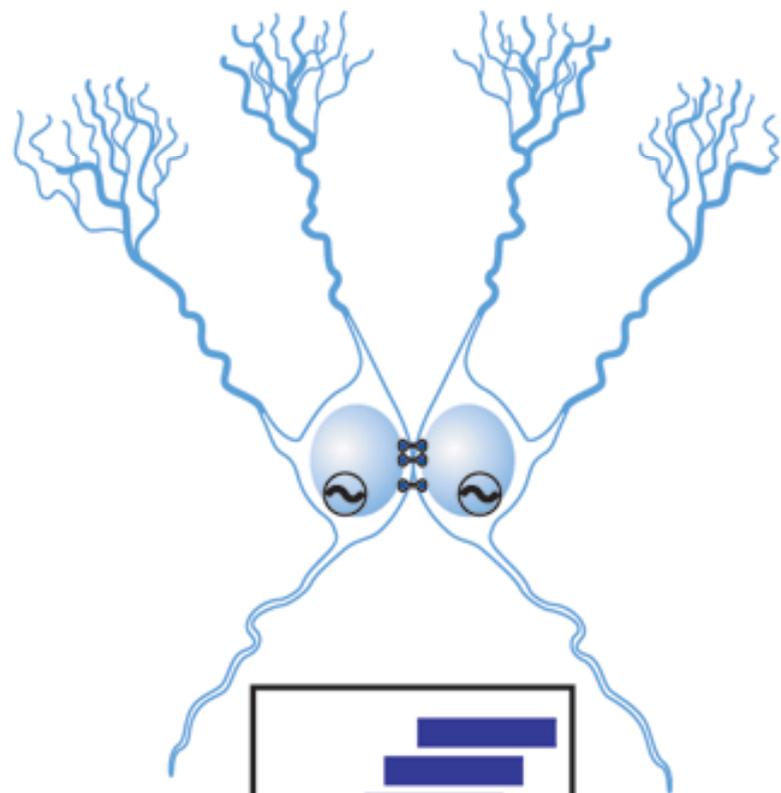
Single SCN neuron



Autoradiographs of the brain (dark areas are radioactive)

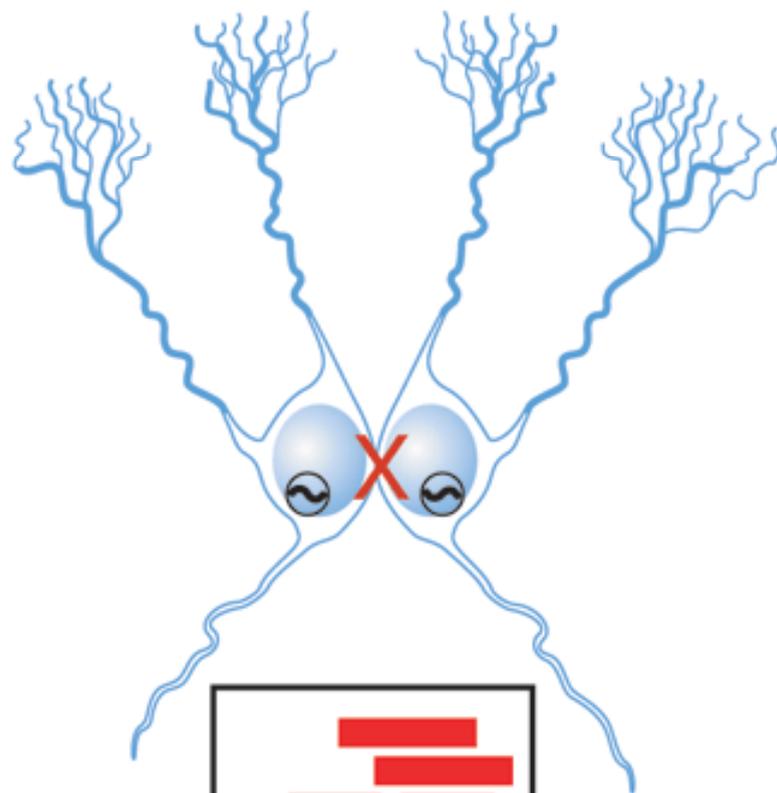


WT

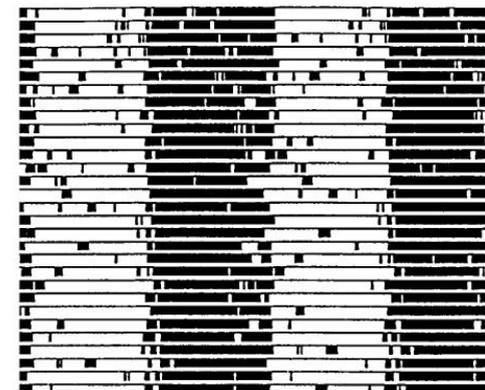
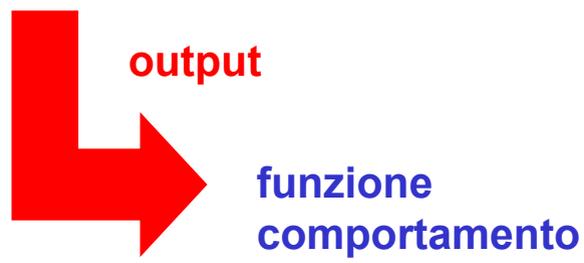
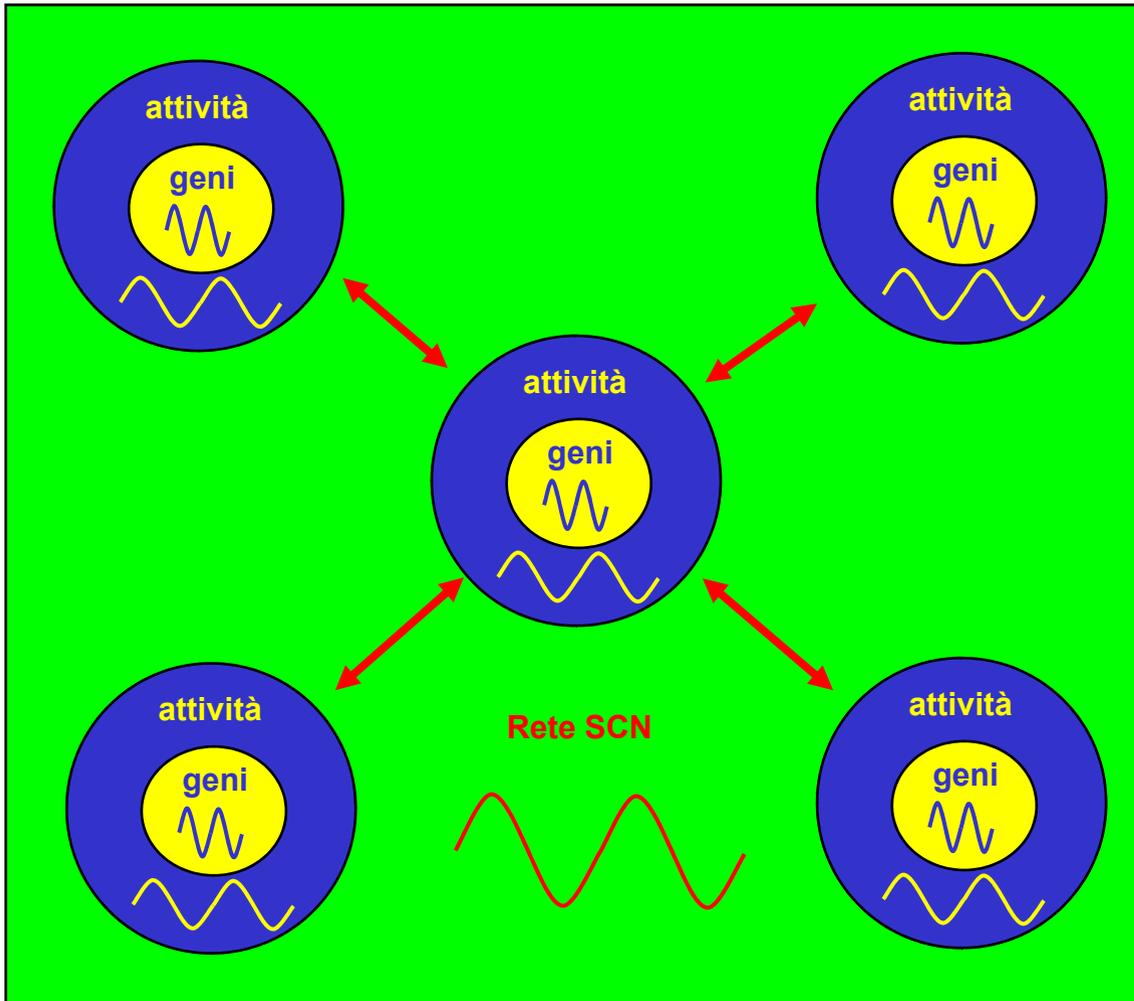


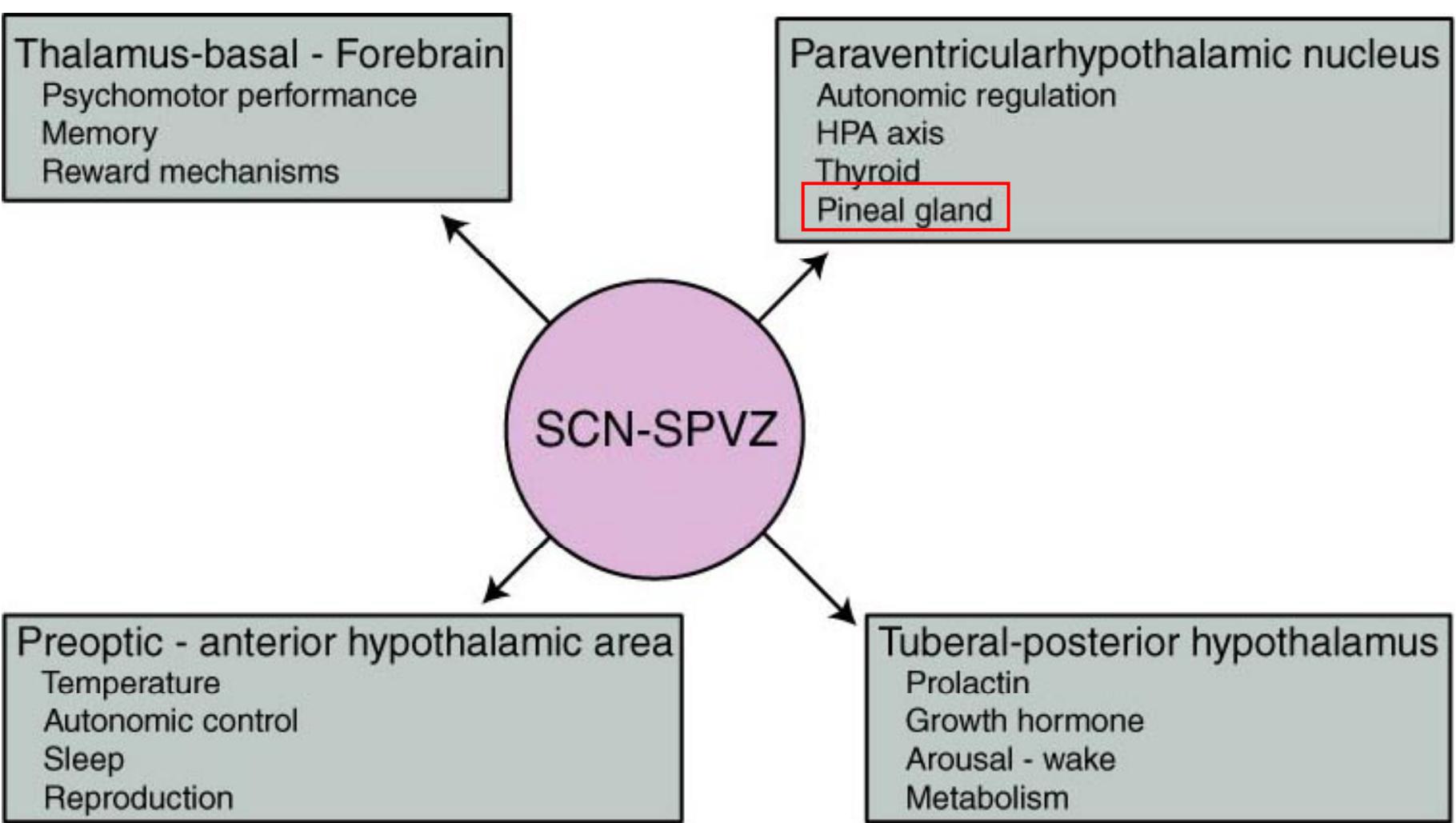
0 12 24  
Time (h)

*Cx36*<sup>-/-</sup>

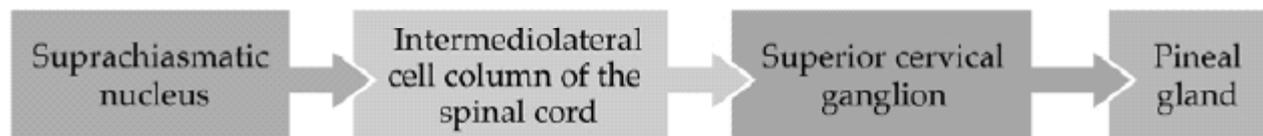


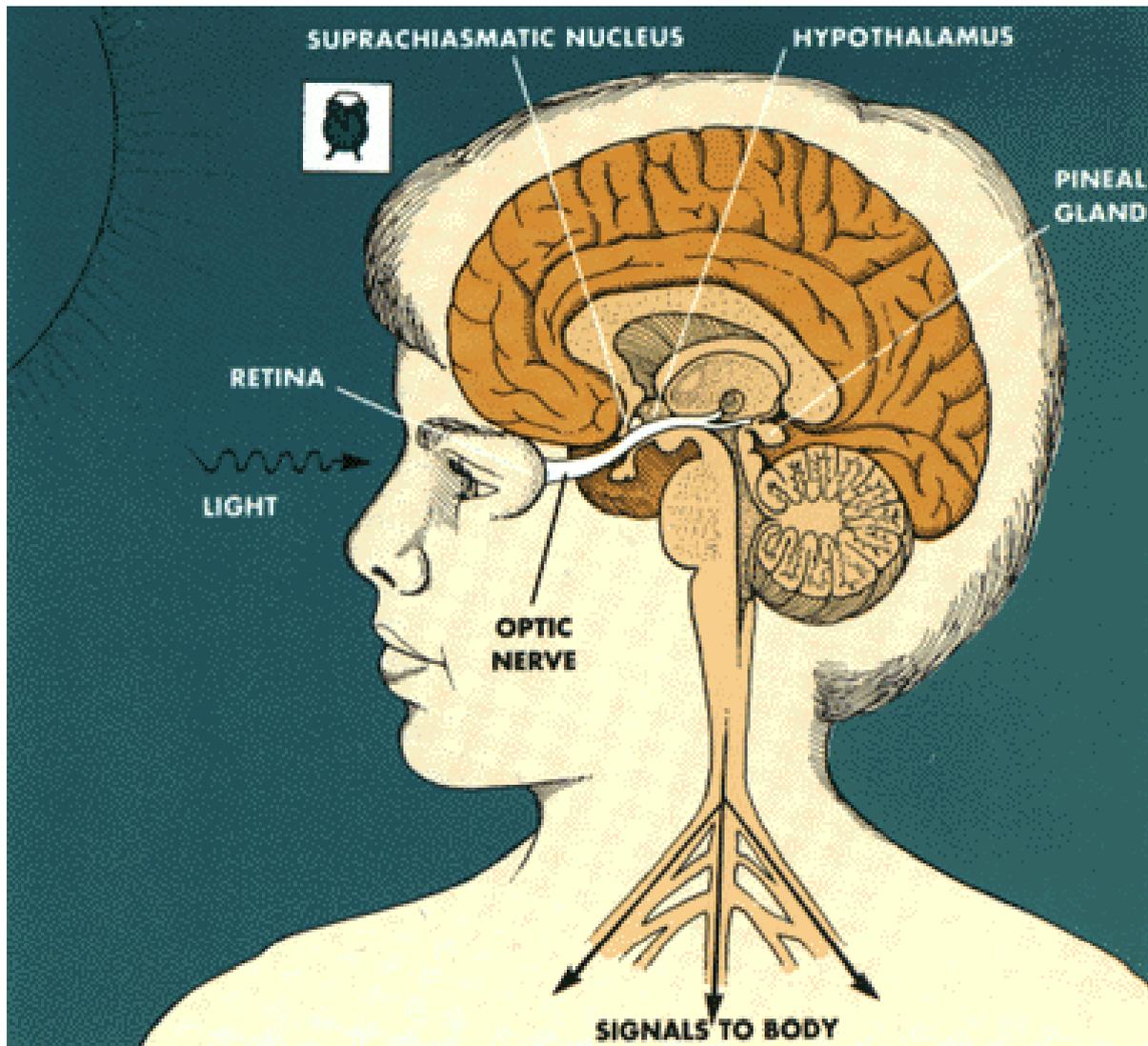
0 12 24  
Time (h)



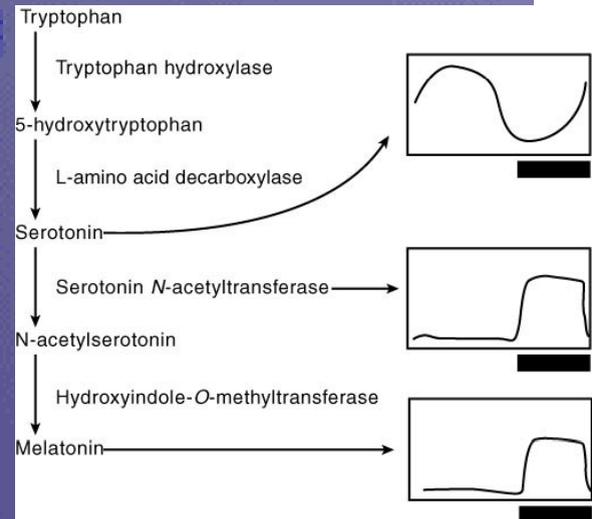
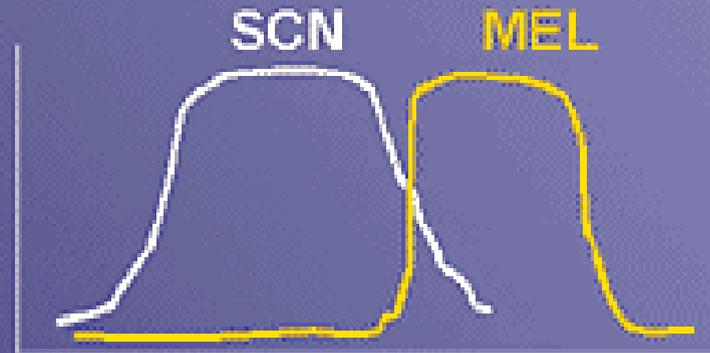
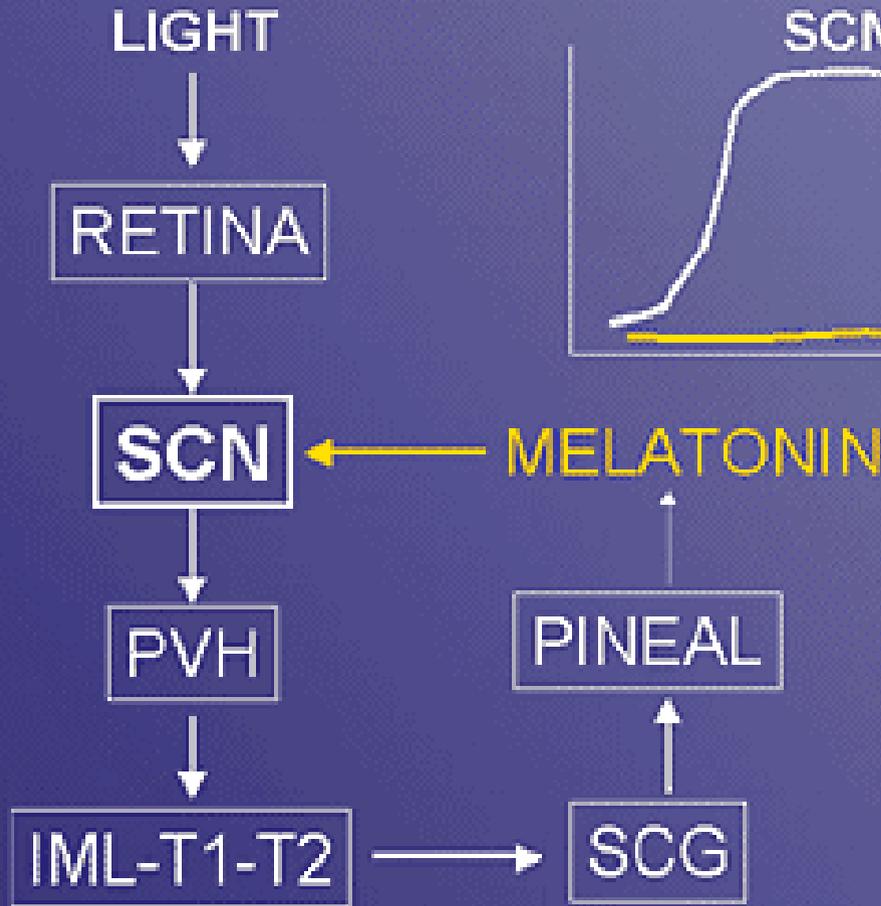


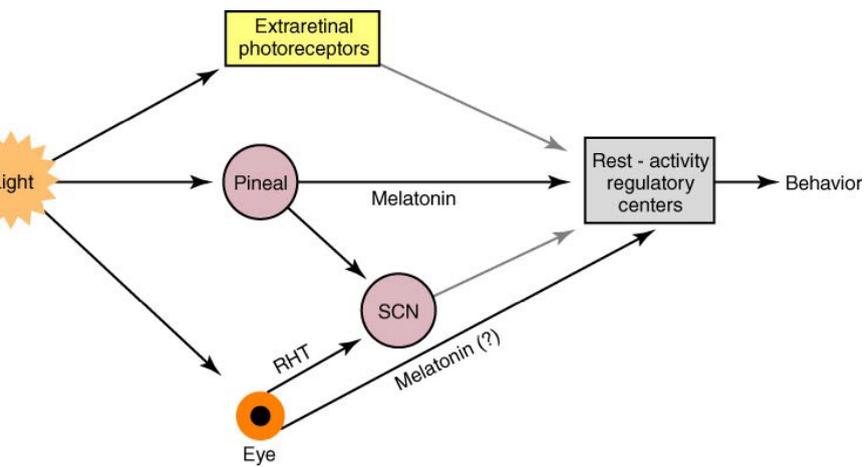
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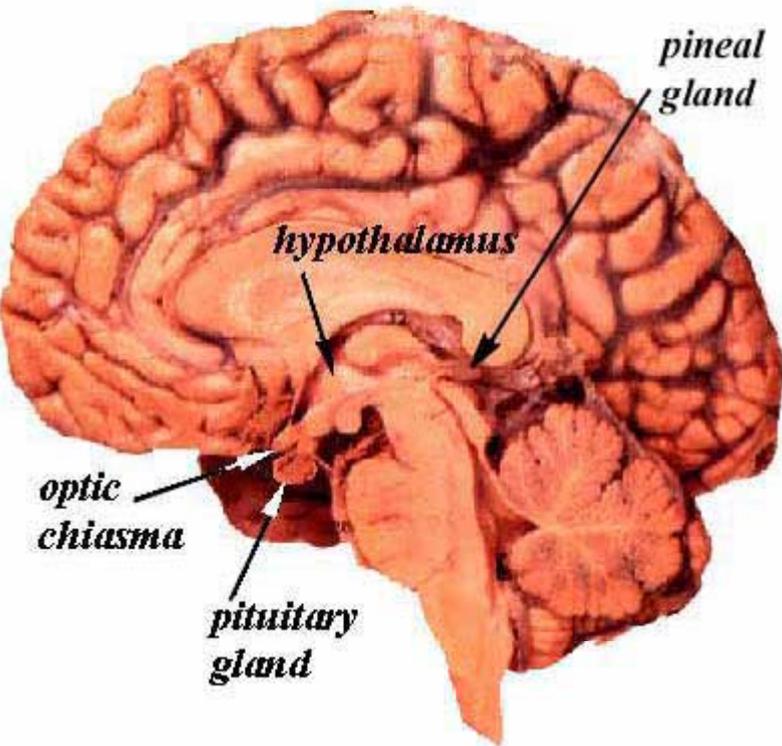


# CIRCADIAN CONTROL OF MELATONIN PRODUCTION

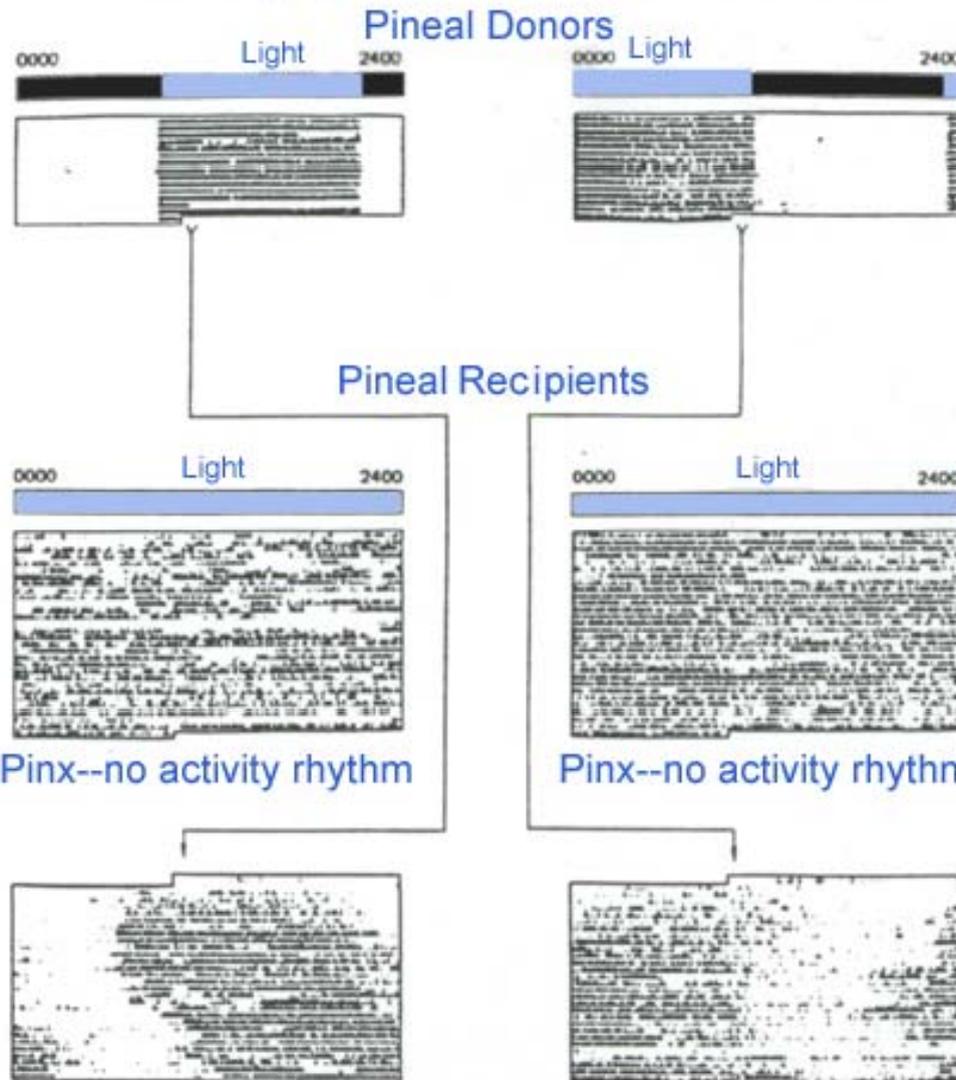




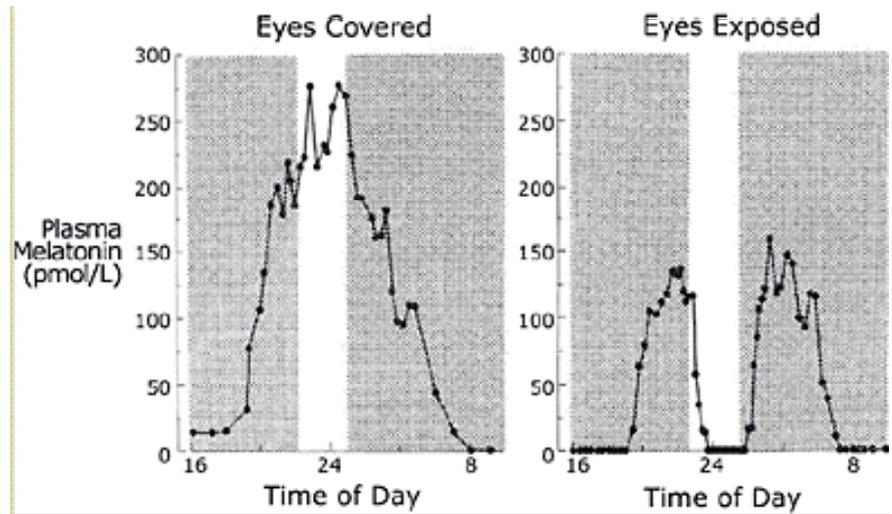
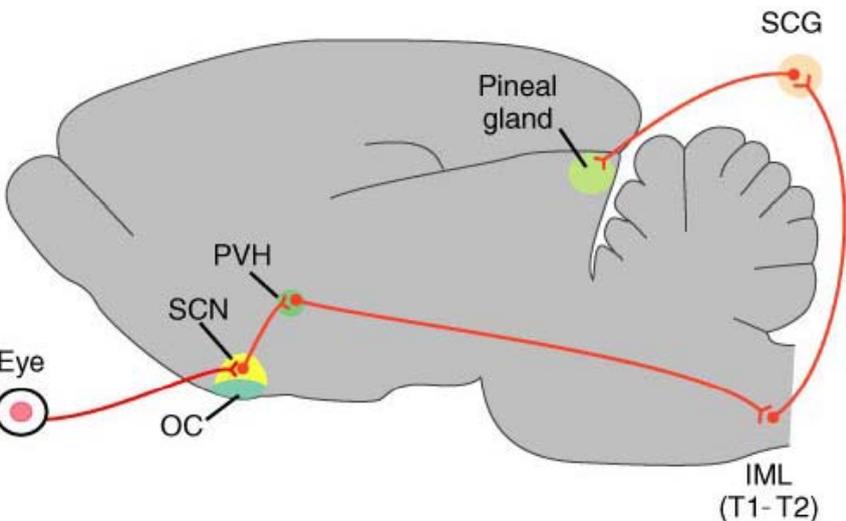
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## Pineal gland is a clock in birds



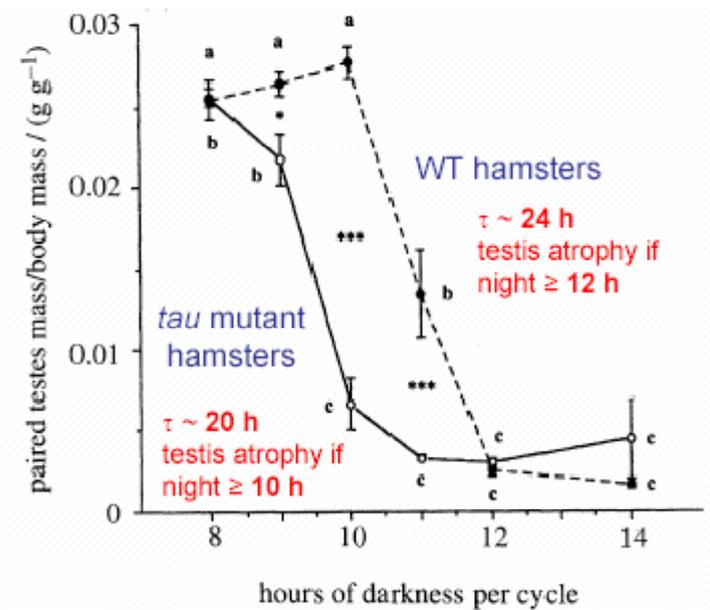
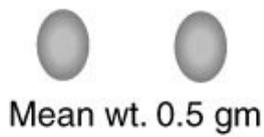
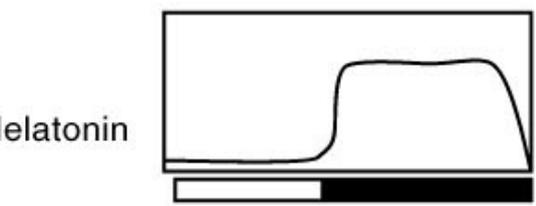
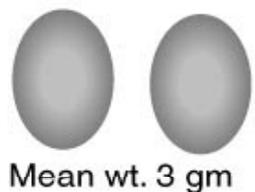
# Ghiandola pineale ed il controllo della riproduzione in animali long day (hamster) o short-day (pecora) breeders



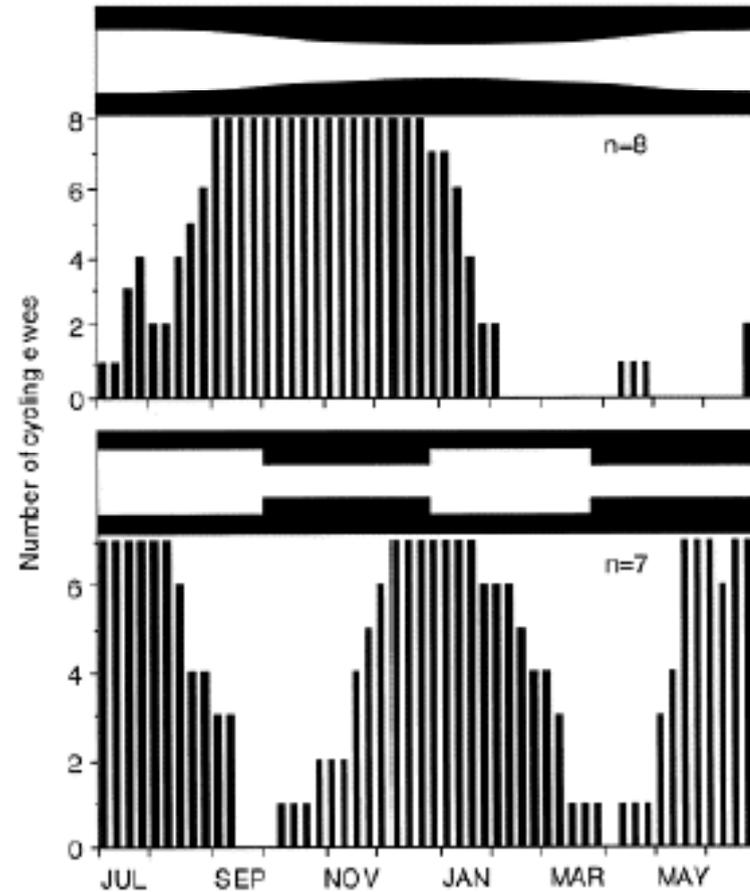
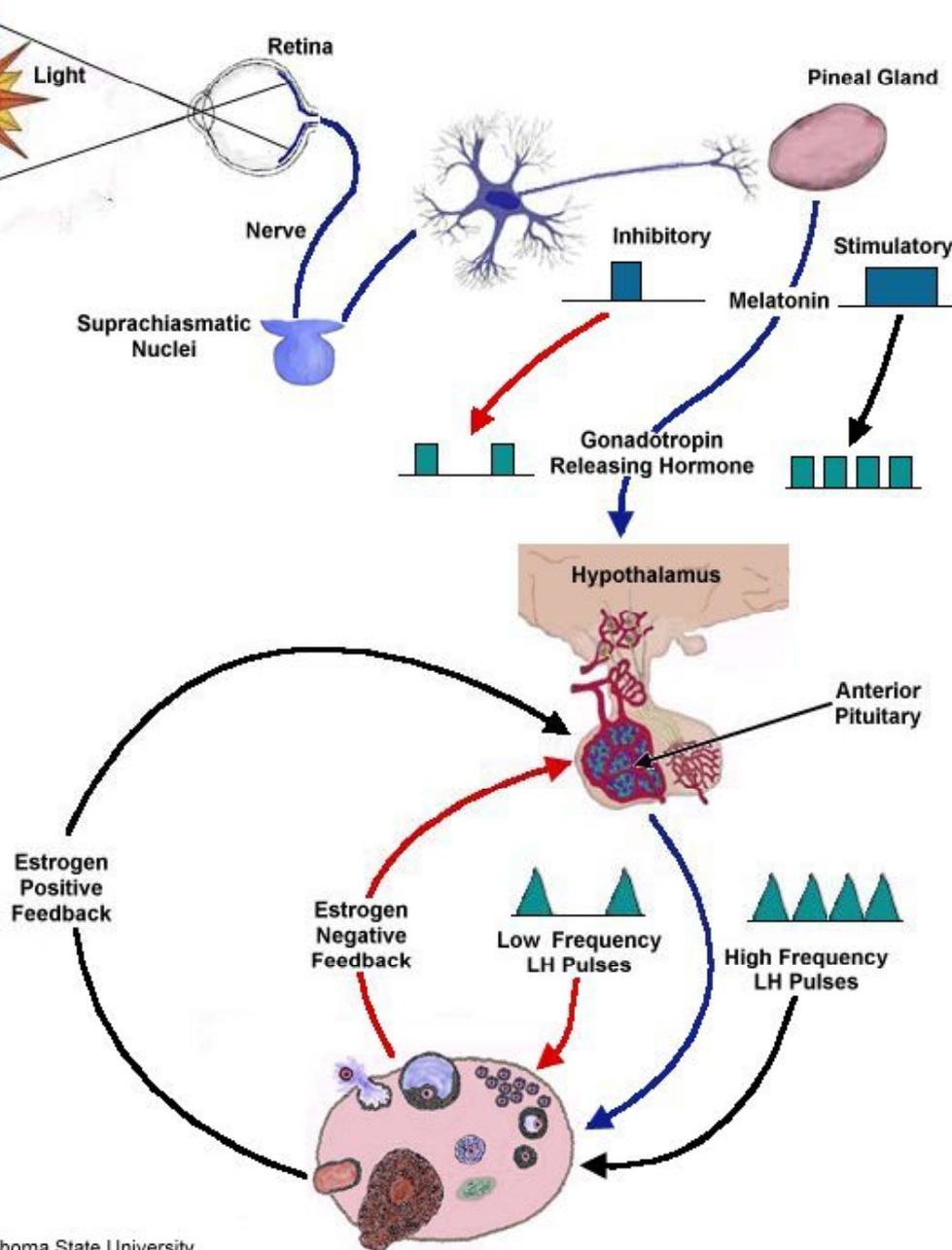
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Melatonin rhythm

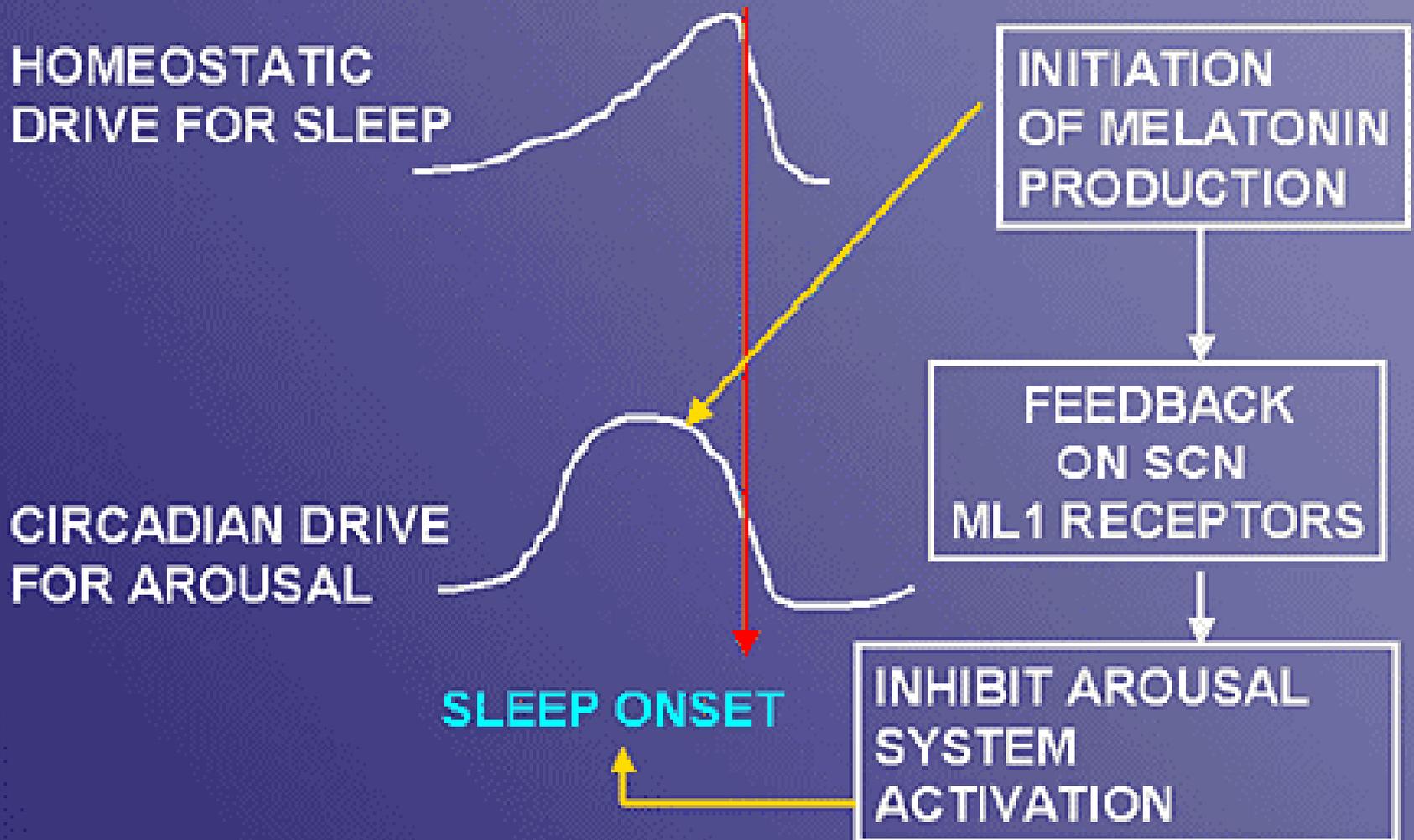
Testicular size



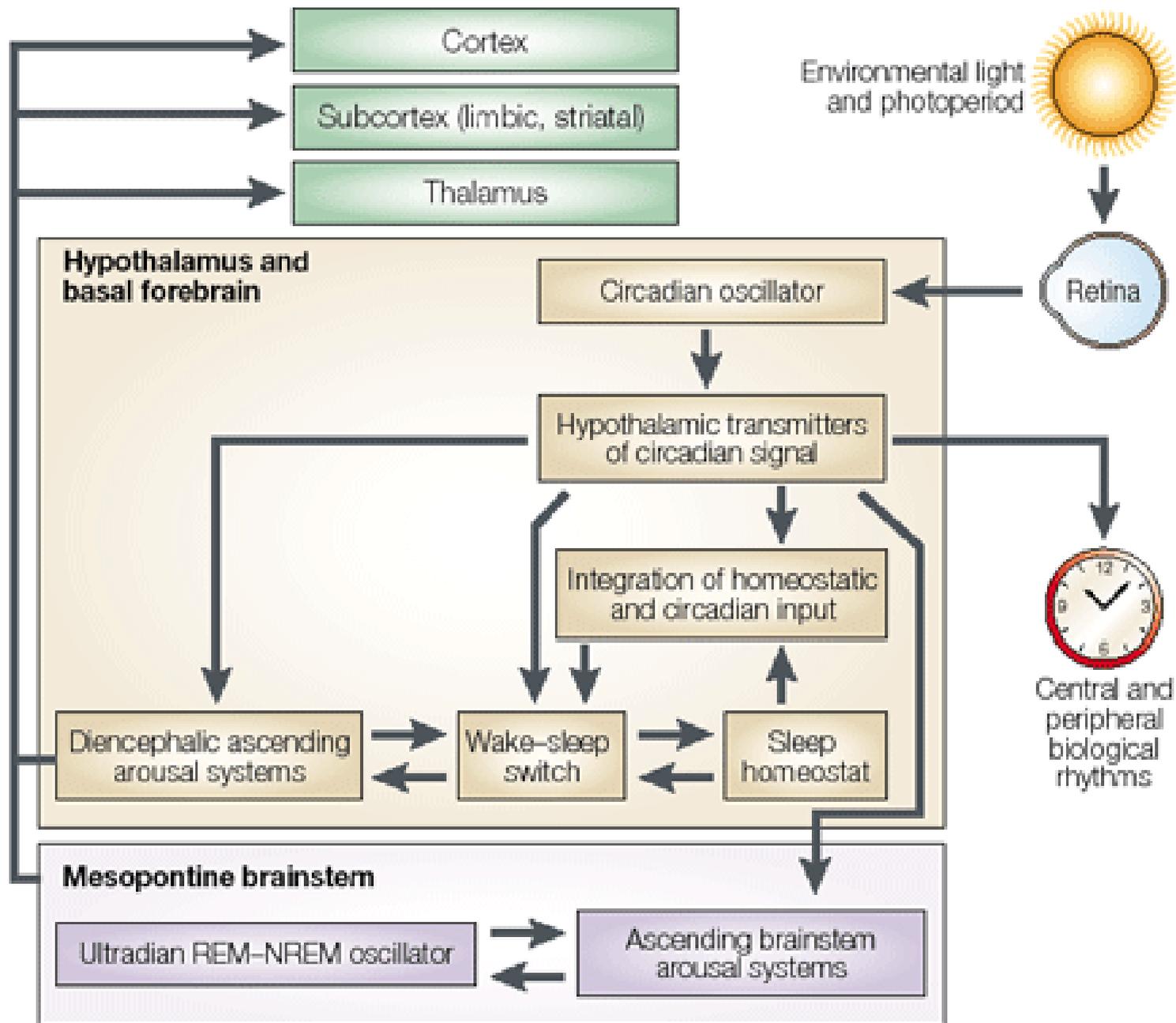
# Regolazione circannuale della riproduzione nelle pecore

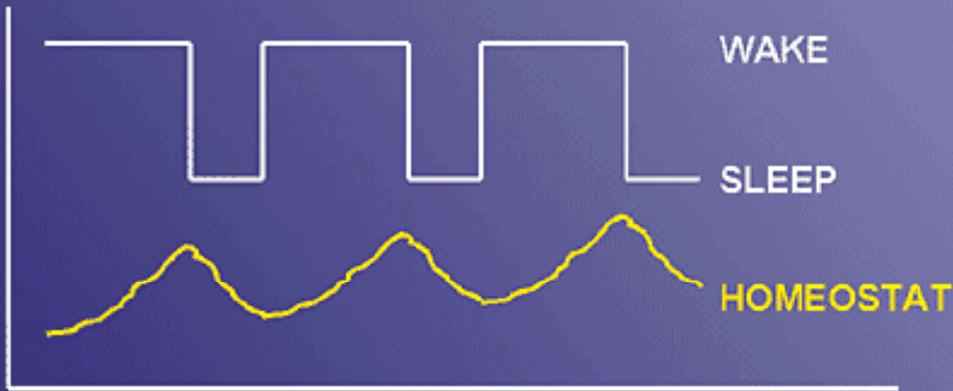


# CIRCADIAN MAINTENANCE OF WAKING AND THE SLEEP-WAKE TRANSITION



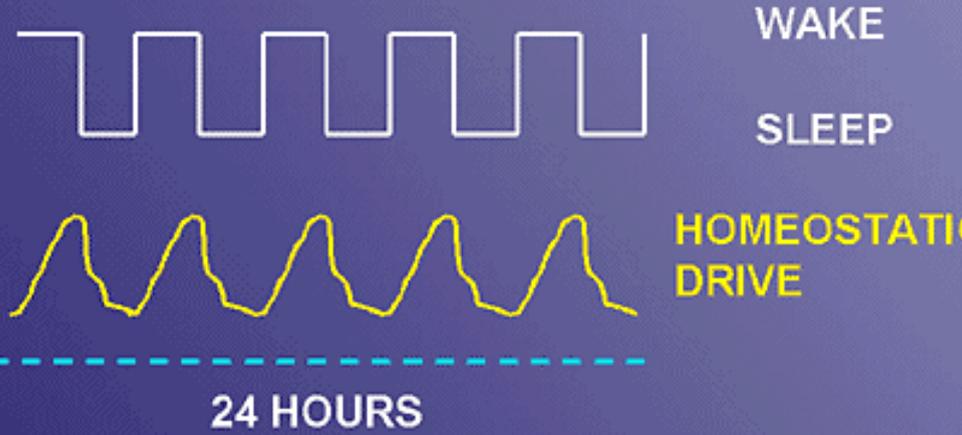
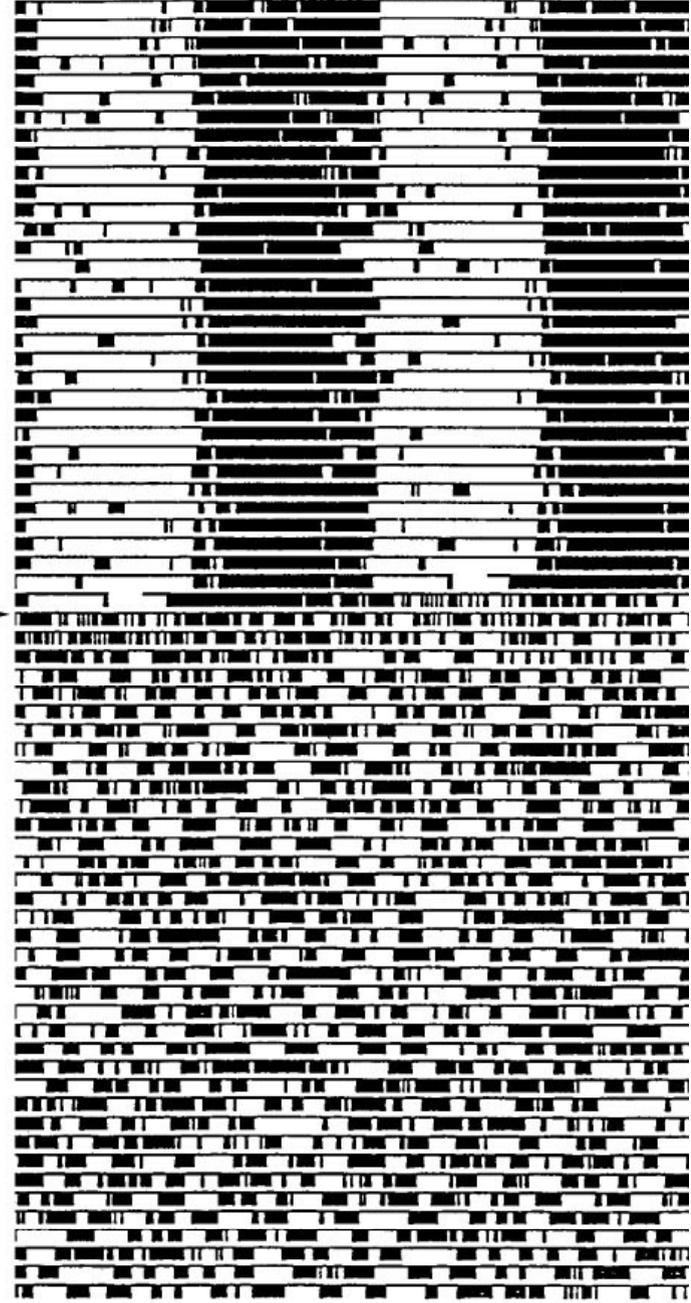
# Sleep-wake control systems





**sonno 8 ore; veglia 16 ore**

Lesione SCN →



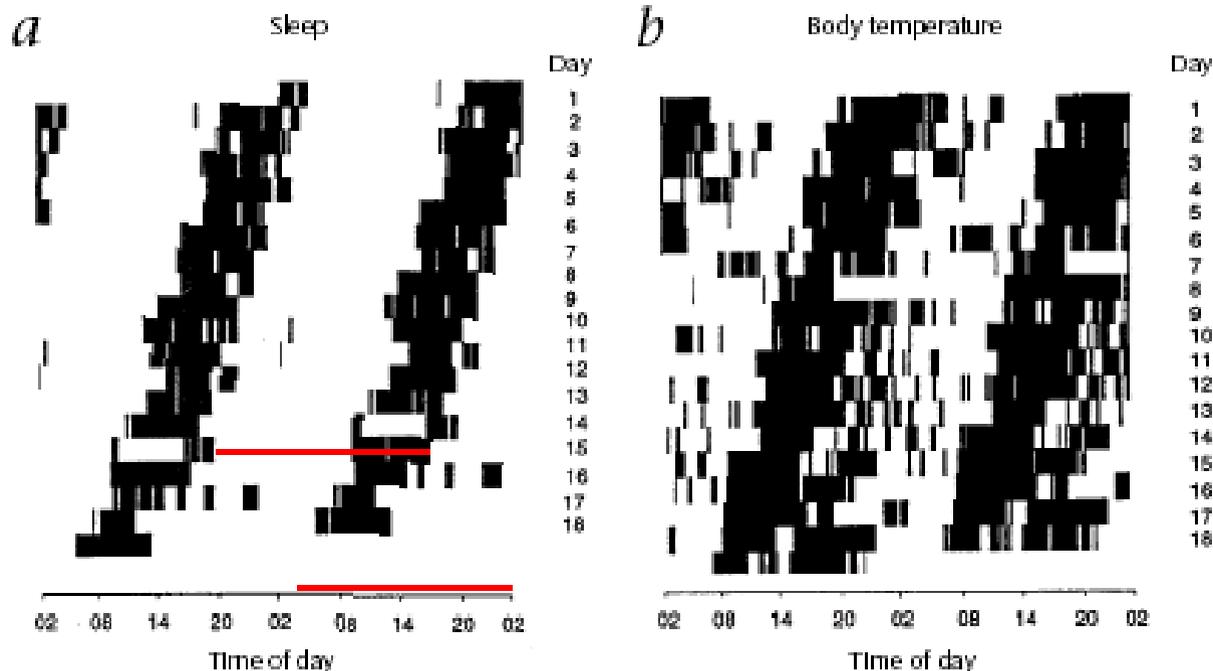
**sonno 12 ore; veglia 12 ore**

# 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 <sup>a</sup>	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 <sup>a</sup>	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 <sup>b</sup>	03:35 ± 1:33	23:22 ± 2:55	4:13	0.002

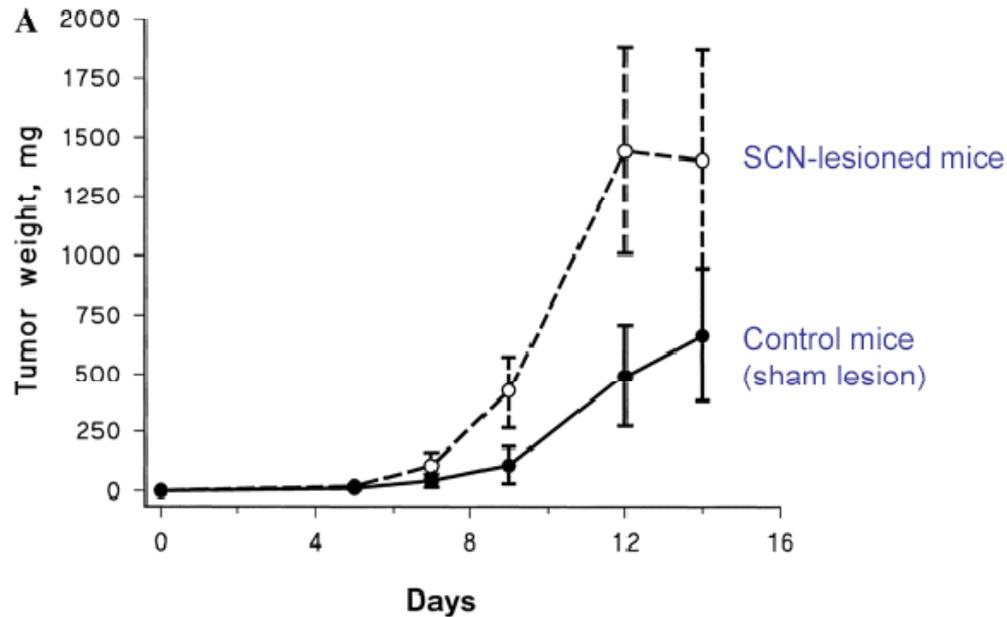
<sup>a</sup>*n* = 5 for FASPS only. <sup>b</sup>*n* = 5 for control and FASPS. Data include both nights of study. REM, rapid eye movement; DLMO, dim-light melatonin onset; Temp, temperature.



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 *mPer2<sup>tm</sup>* Mice

Phenotypes	<i>mPer2<sup>tm</sup></i> Mice (18 months old) (n = 20)	Wild-Type Mice (18 months old) (n = 20)	<i>mPer2<sup>tm</sup></i> Mice 16 months after IR (n = 14 <sup>a</sup> )	Wild-Type Mice 16 months after IR (n = 20)	p value
Salivary gland hyperplasia	20 (50%) <sup>b</sup>	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%)	

<sup>a</sup>Six irradiated *mPer2<sup>tm</sup>* mice were lost at 9 months after irradiation during the summer flooding in Houston in 2001.

<sup>b</sup>50% of *mPer2<sup>tm</sup>* mice showed enlarged salivary glands by physical examination. At autopsy, all the *mPer2<sup>tm</sup>* 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)

