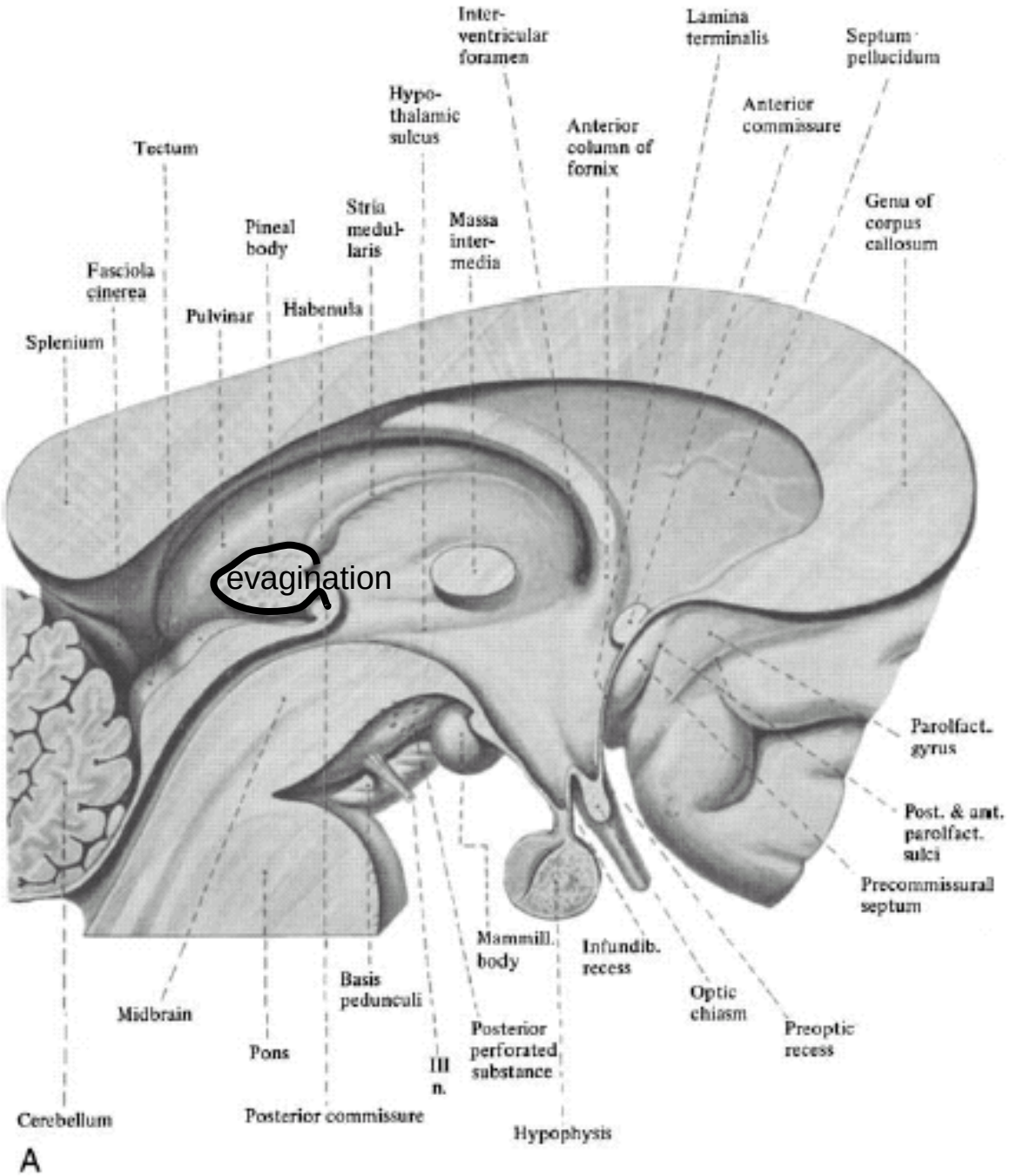
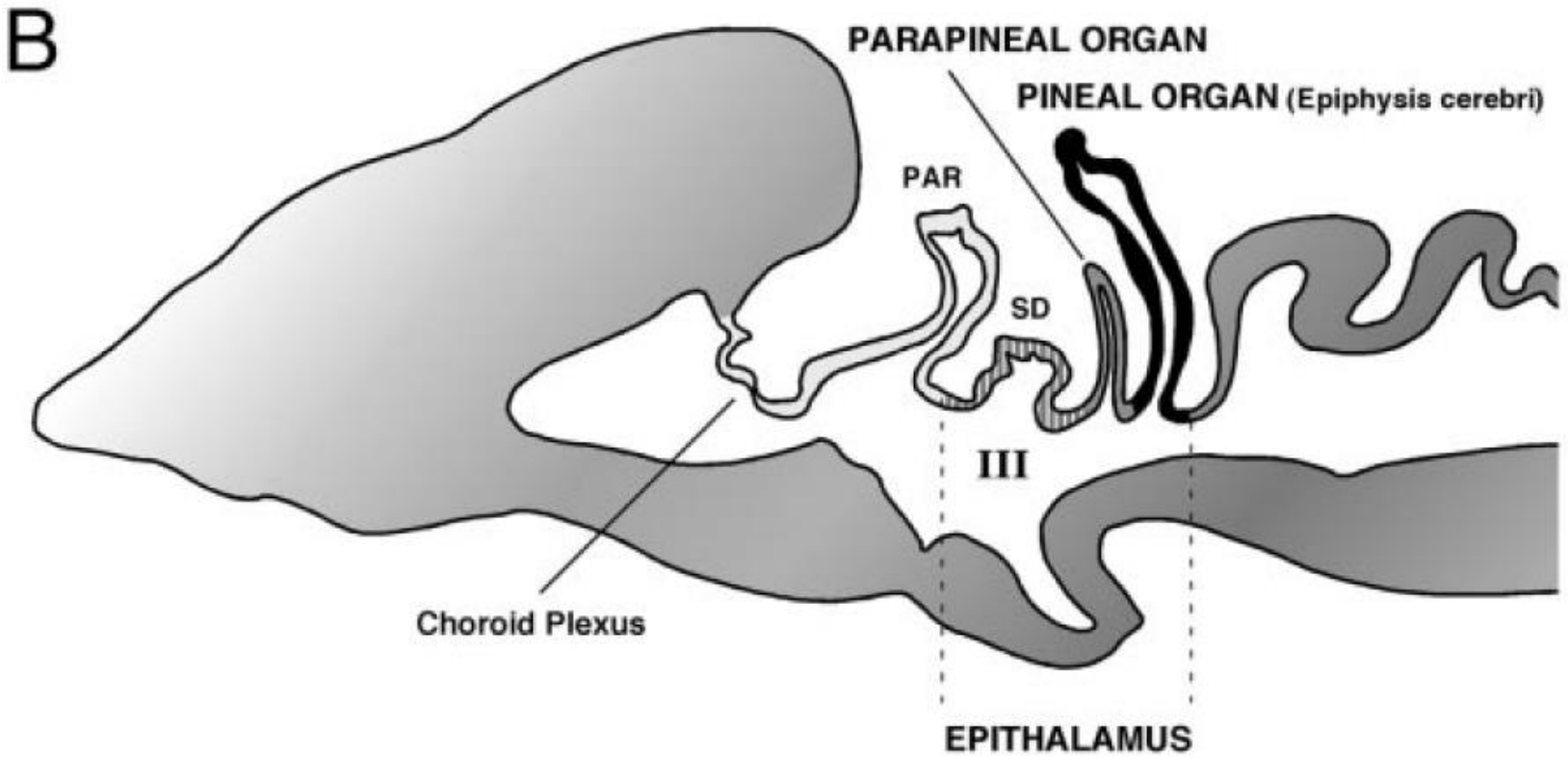

Inter-
ventricular
foramen
Lamina
terminalis
Septum
pellucidum
Hypo-
thalamic
sulcus
Anterior
commissure
Tectum
Anterior
column of
fornix
Gena of
corpus
callosum
Pineal
body
Stria
medul-
laris
Massa
inter-
media
Fasciola
cinerea
Pulvinar
Habenula
Splenium
evagination
Parolfact.
gyrus
Post. & ant.
parolfact.
sulci
Precommissural
septum
Mammill.
body
Infundib.
recess
Basis
pedunculi
Optic
chiasm
Midbrain
Posterior
perforated
substance
Preoptic
recess
Pons
III
n.
Cerebellum
Posterior commissure
Hypophysis

A

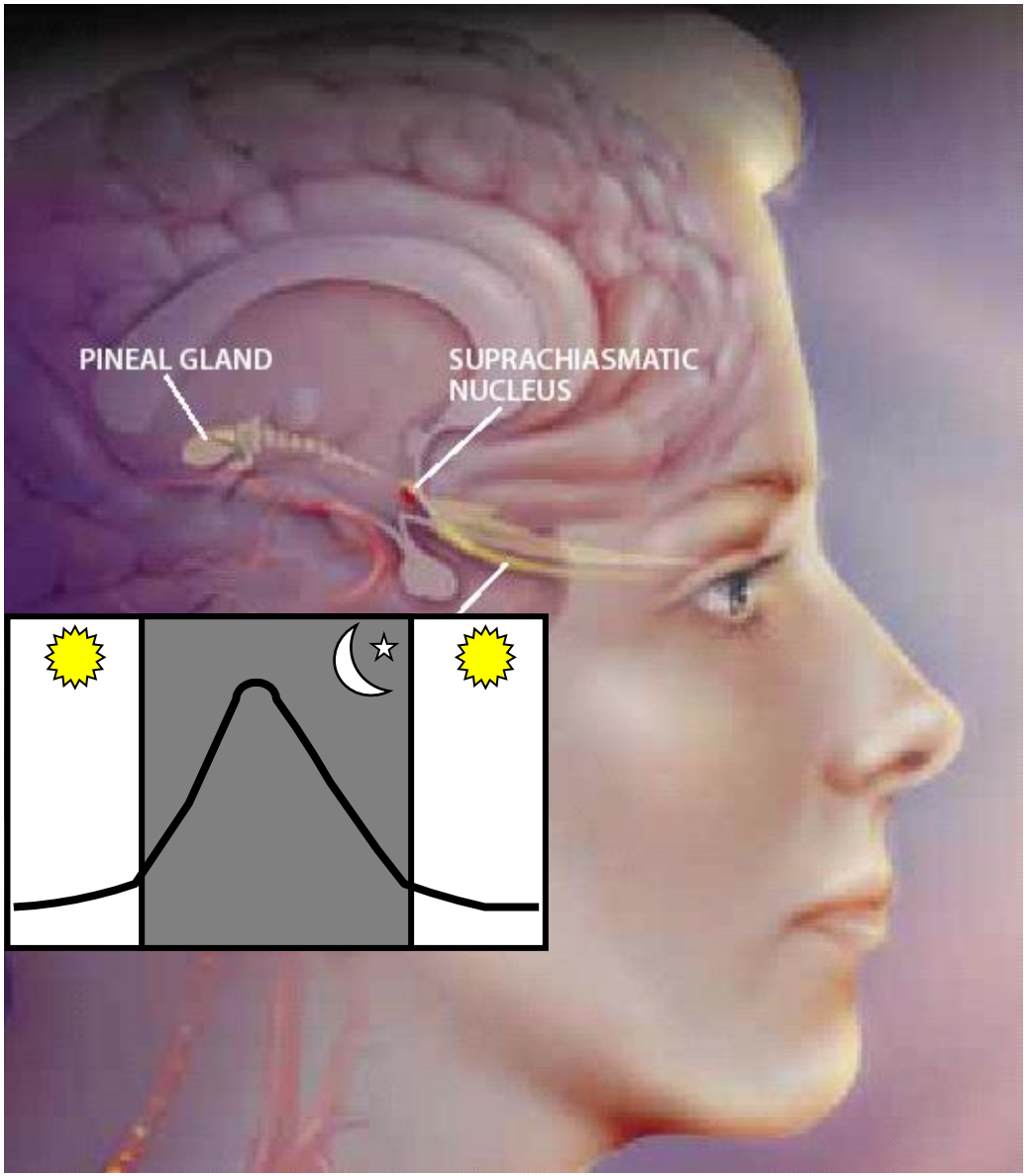


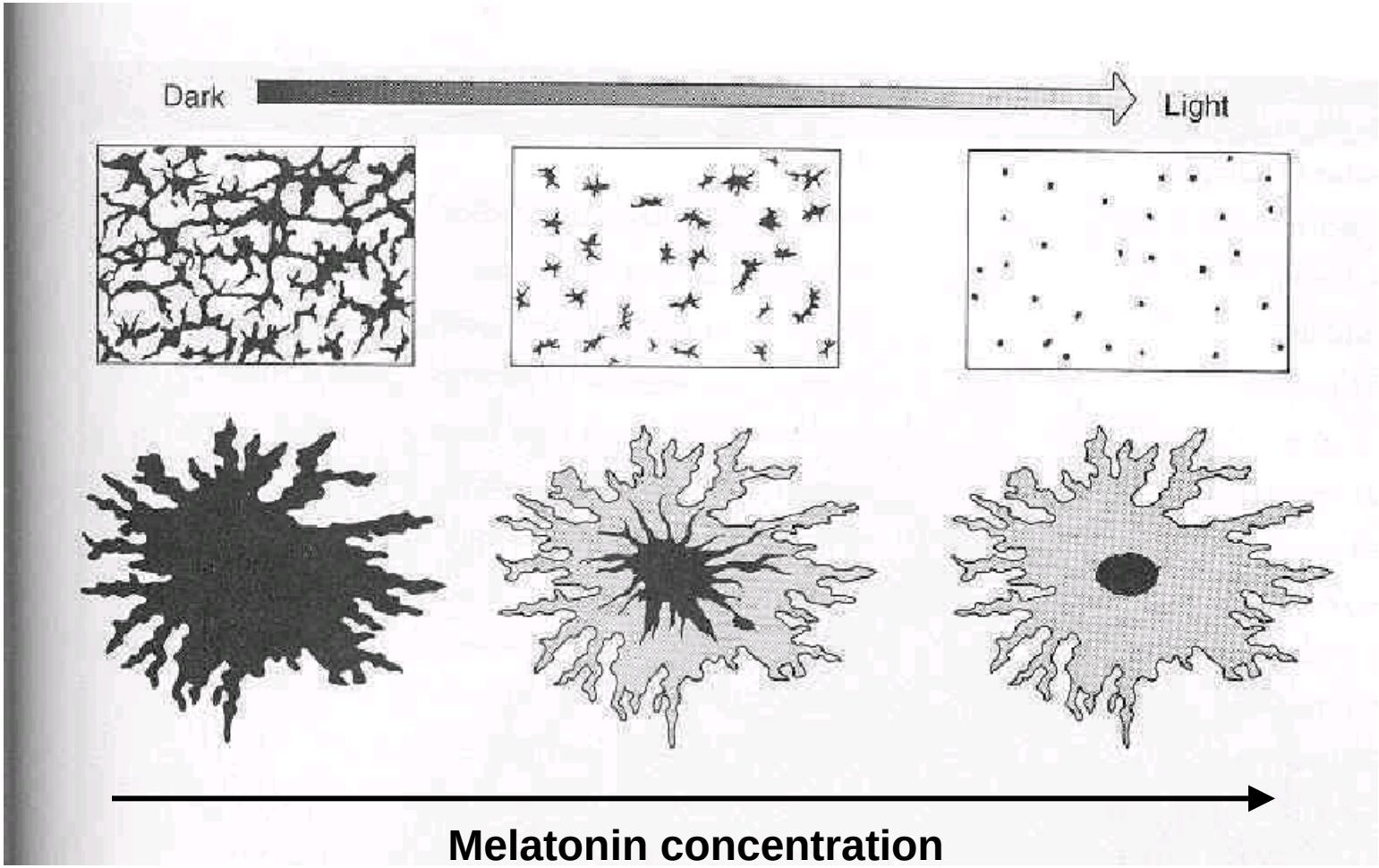
Evaginations

Concha and Wilson, 2001

Melatonin

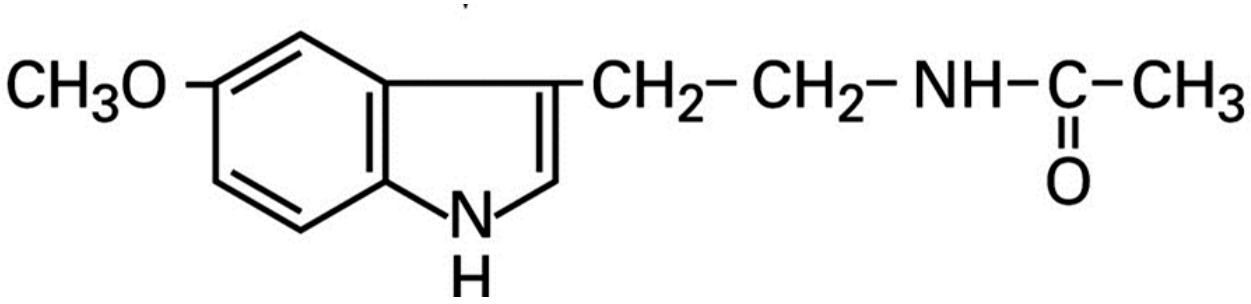
- Synthesis
- Regulation
- Roles
- Mammalian vs. non-mammalian



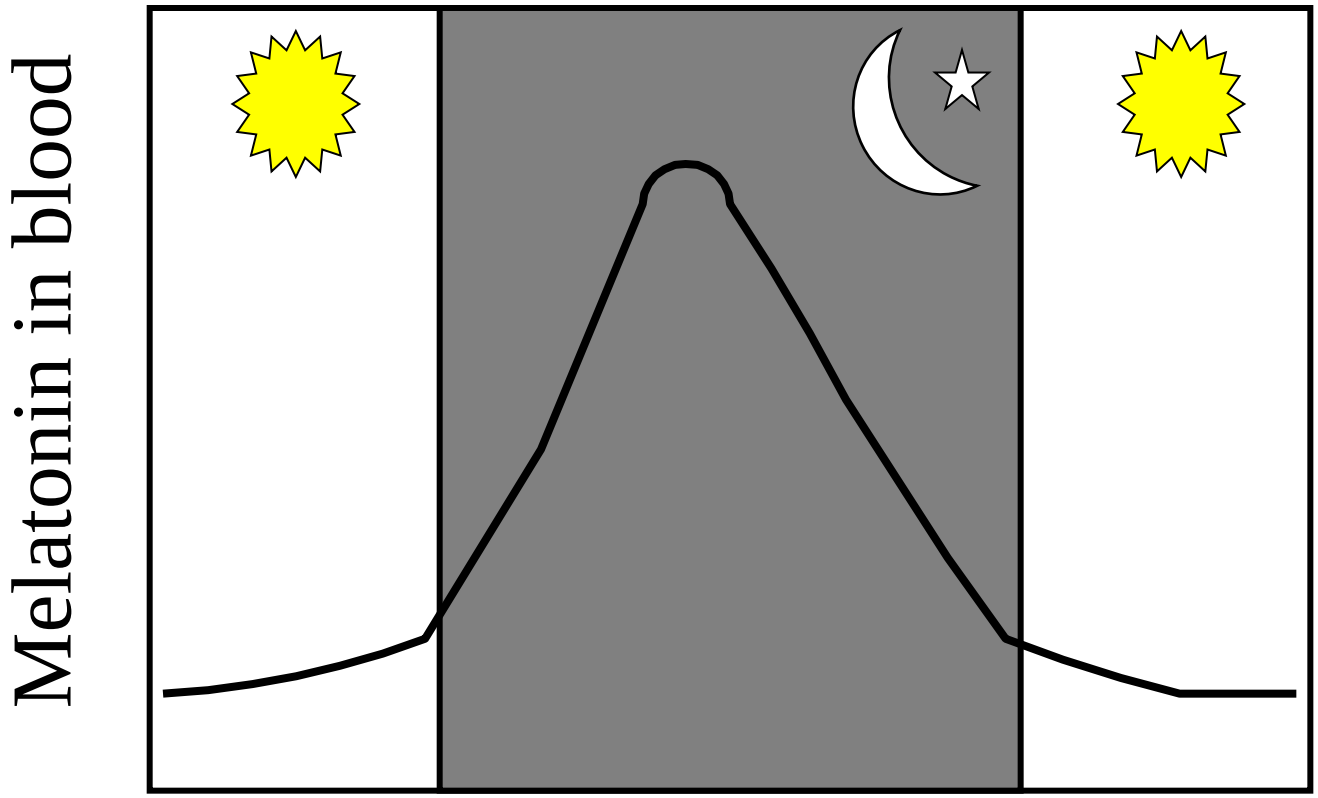


Lerner, 1958

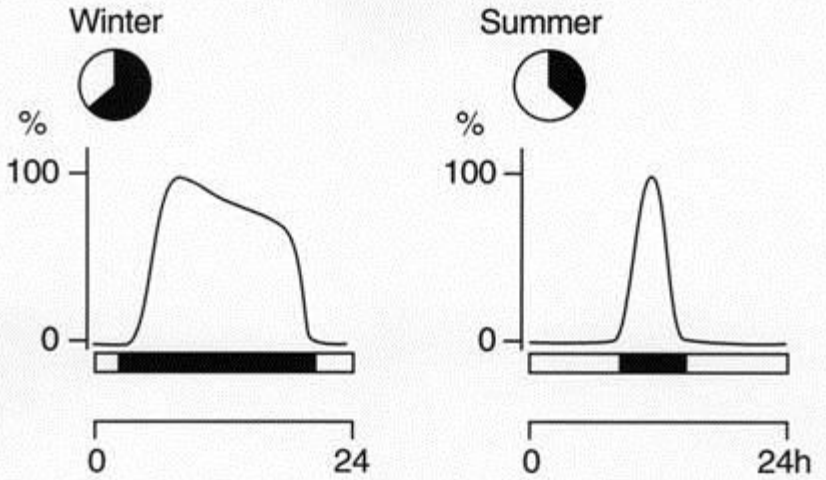
Melatonin

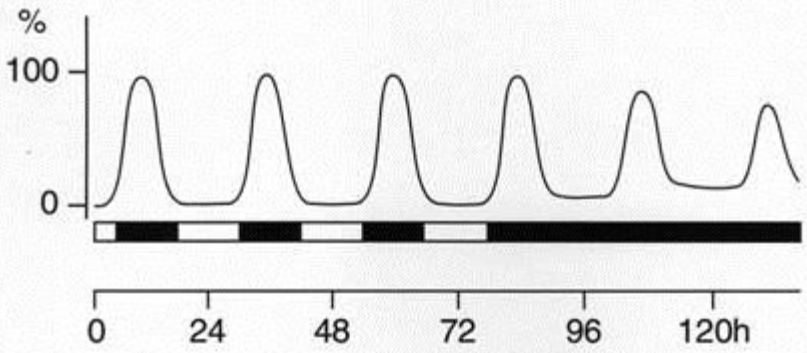


Daily rhythm of melatonin is common in all vertebrates



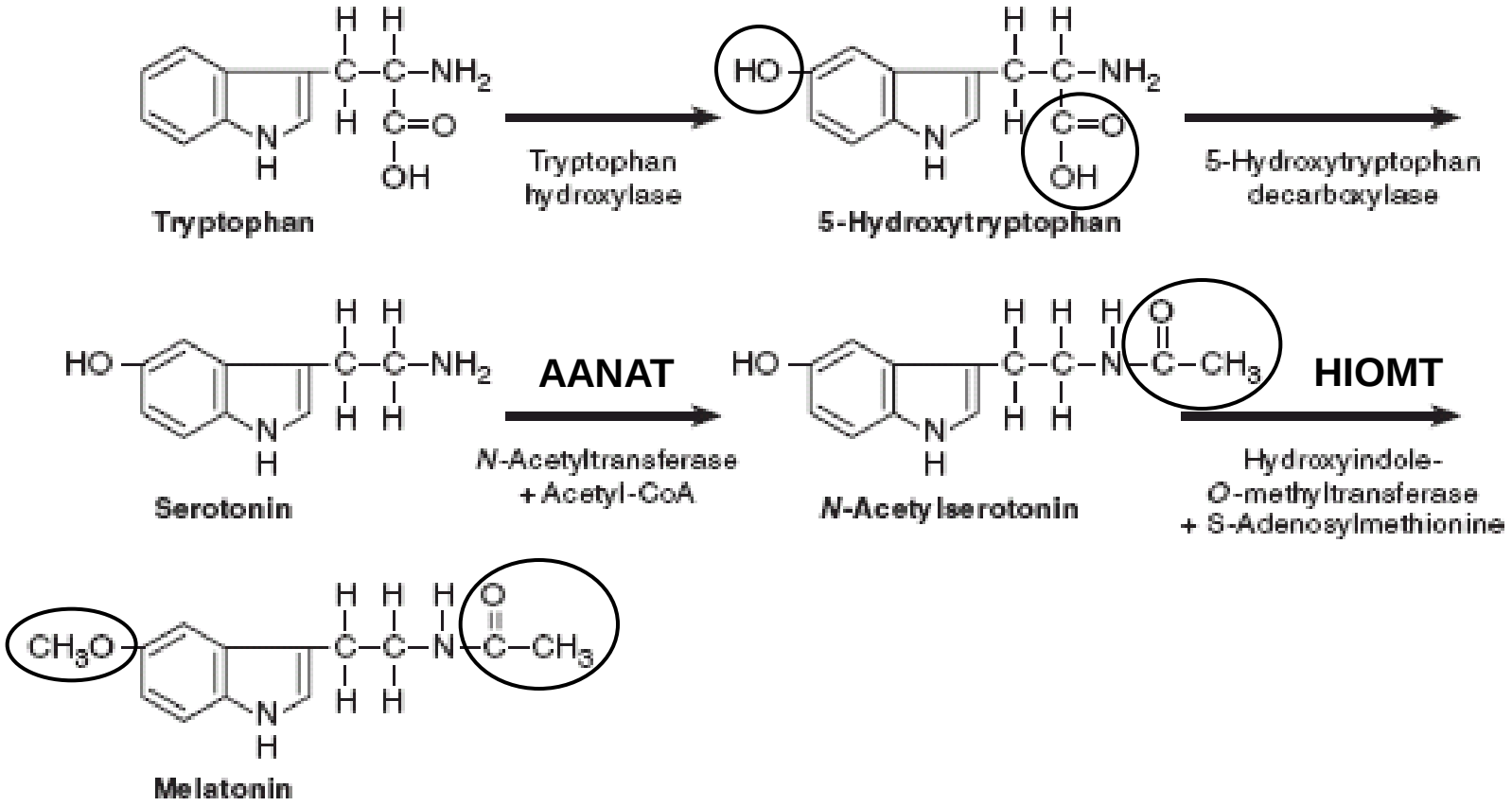
Characteristics of the Melatonin Rhythm



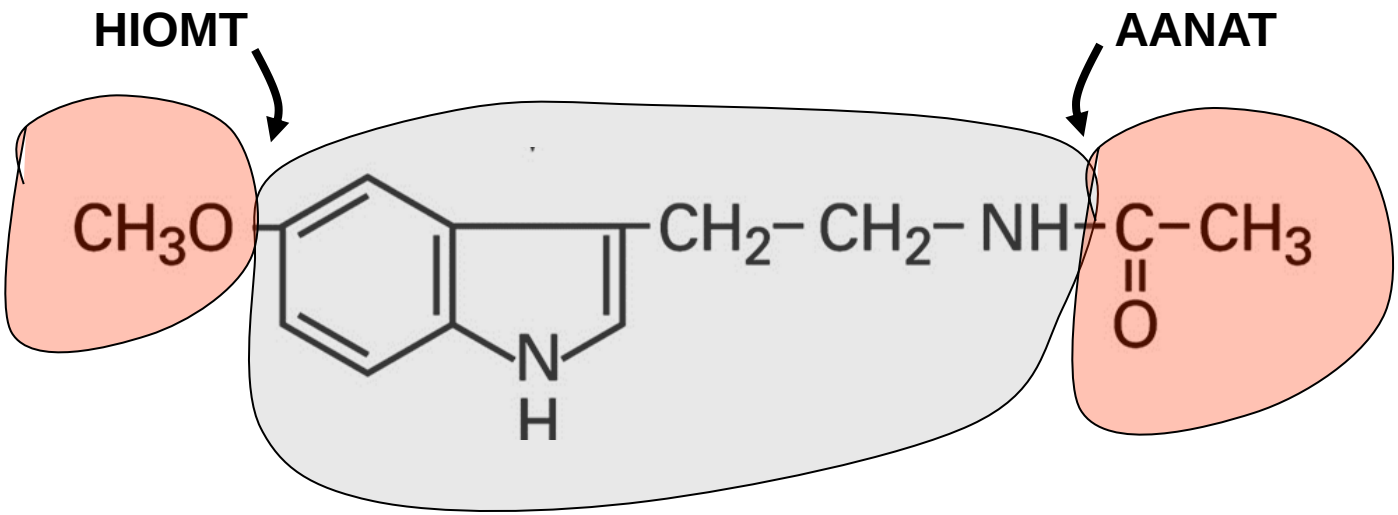


What do you think about this?

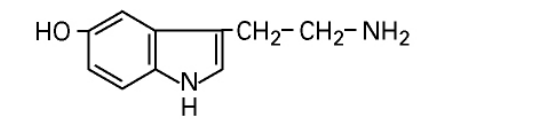
Rhythms are driven by an intrinsic clock


Tryptophan
Tryptophan hydroxylase
5-Hydroxytryptophan
5-Hydroxytryptophan decarboxylase
Serotonin
AANAT
N-Acetyltransferase + Acetyl-CoA
N-Acetylserotonin
HIOMT
Hydroxyindole-O-methyltransferase + S-Adenosylmethionine
Melatonin

Melatonin

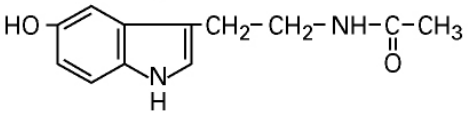


Daily rhythm in the serotonin → melatonin pathway



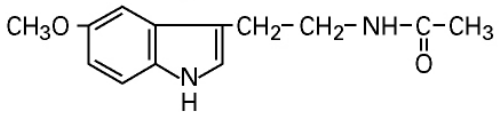
Serotonin
(5-Hydroxytryptamine)

Arylalkylamine
N-Acetyltransferase (AANAT)

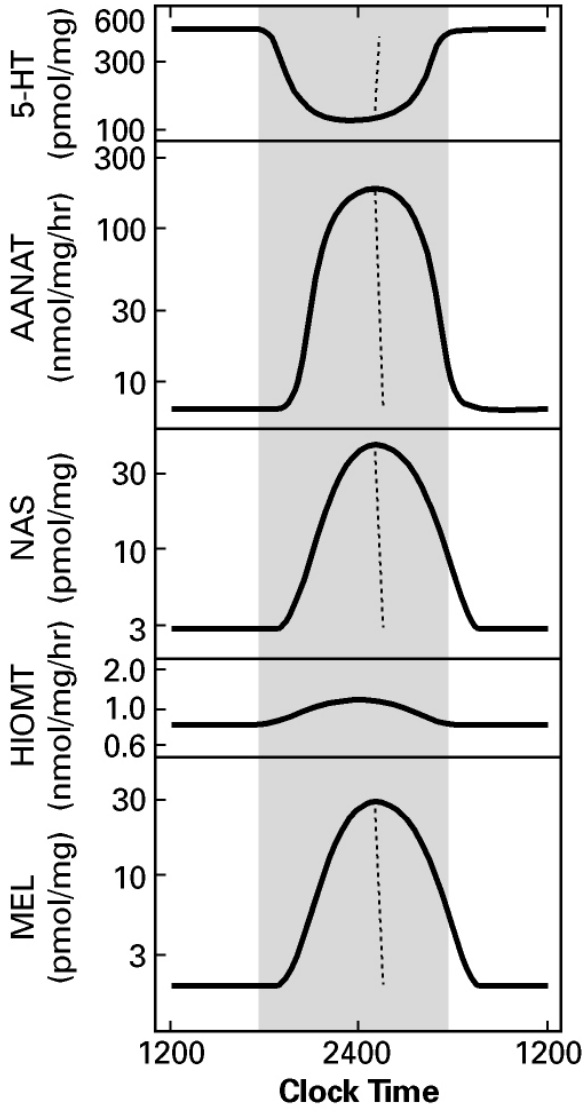


N-Acetylserotonin
(*N*-Acetyl 5-hydroxytryptamine)

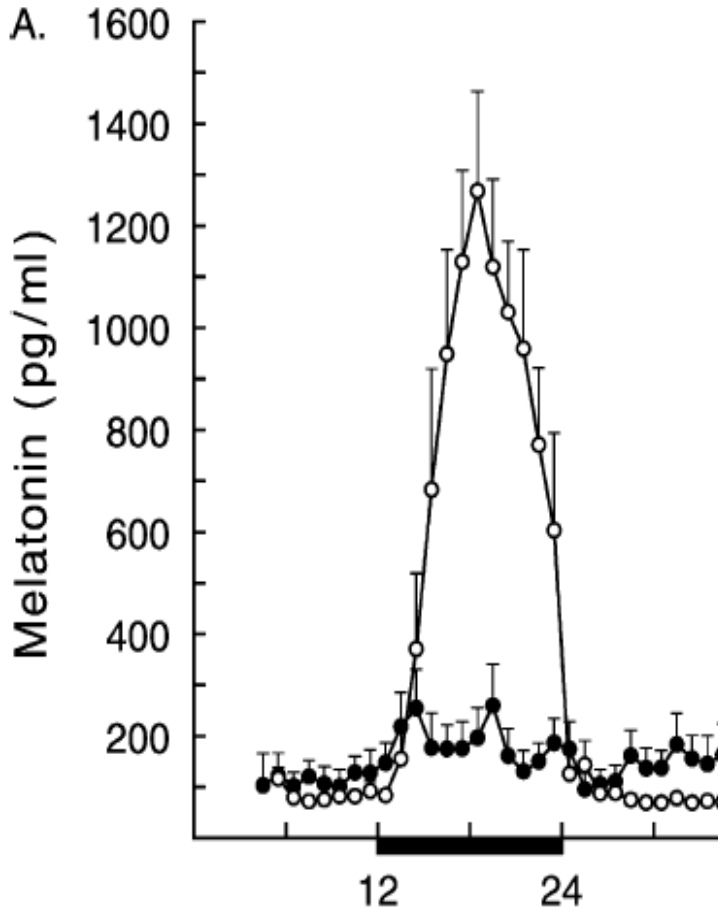
Hydroxyindole-*O*-
methyltransferase (HIOMT)



Melatonin
(*N*-Acetyl 5-methoxytryptamine)



Effect of SCN lesion on melatonin production



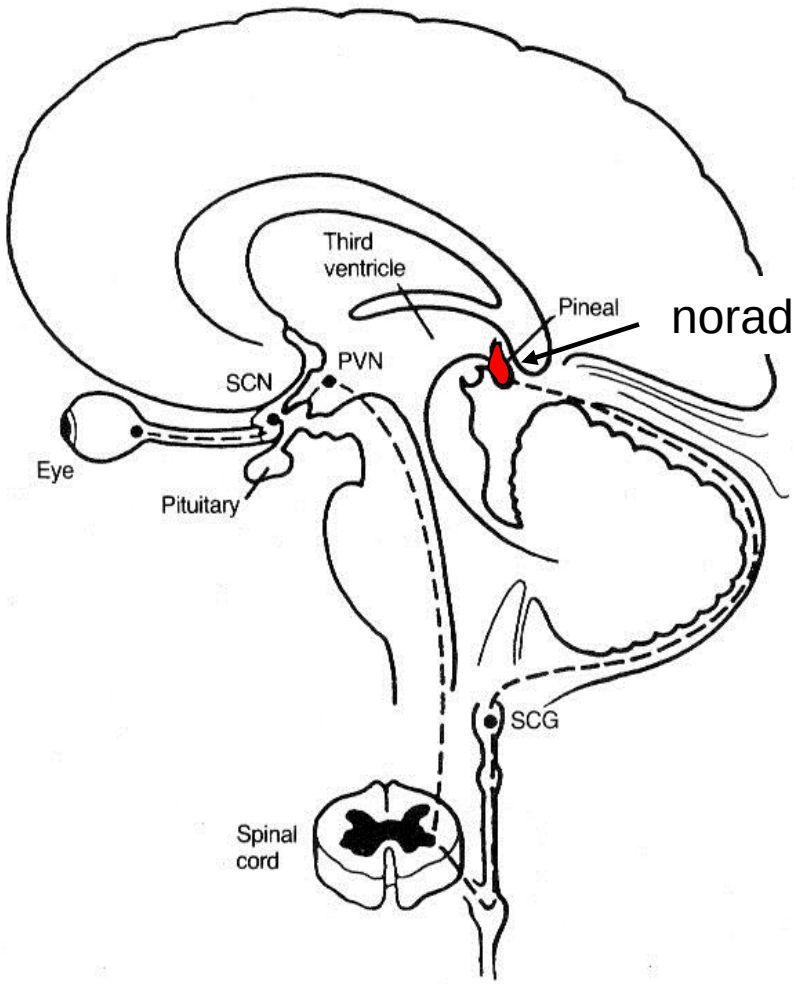
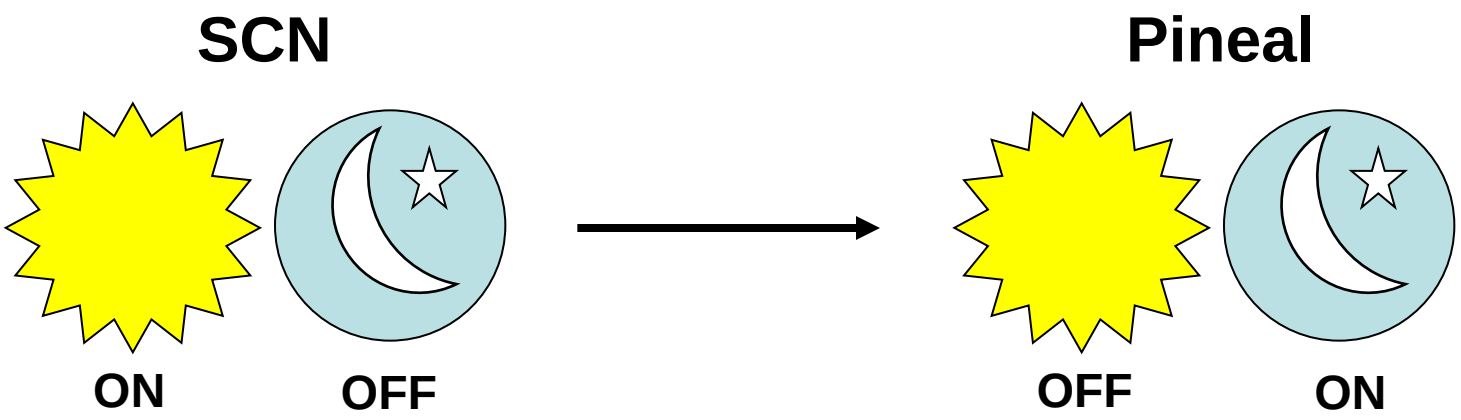
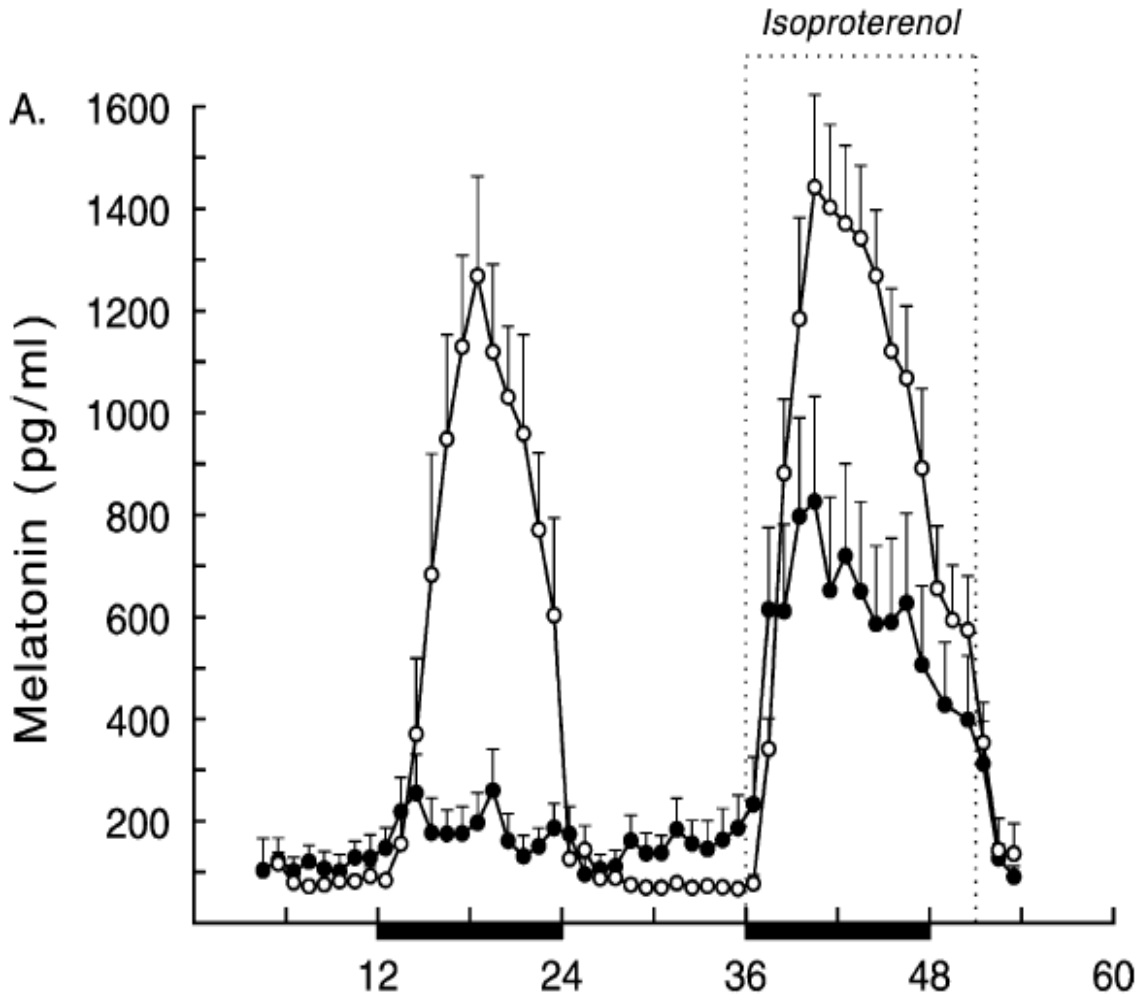


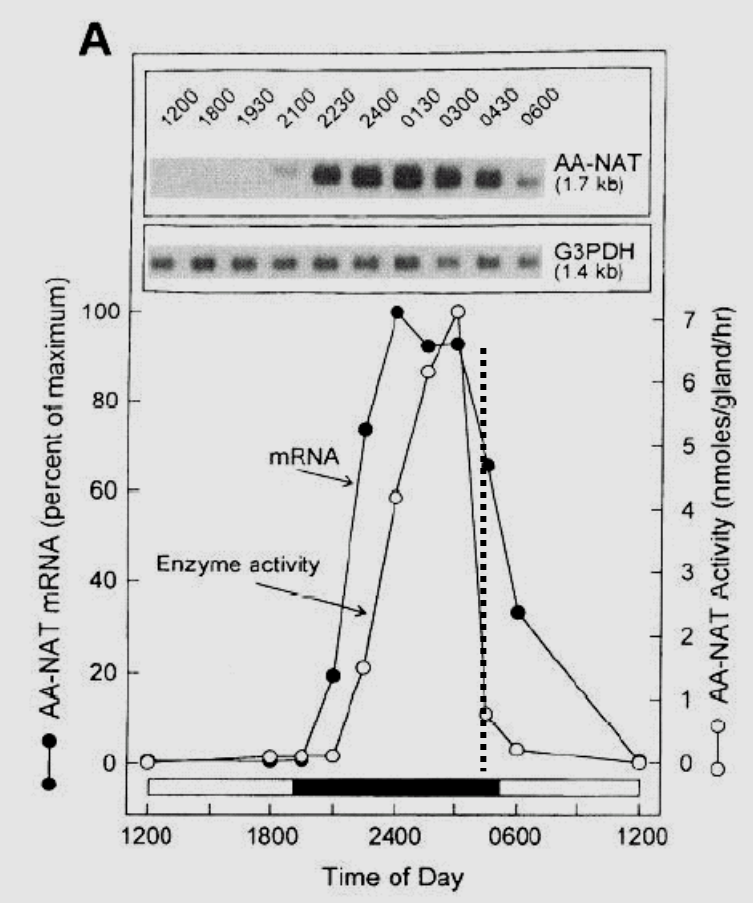
Fig. 7.9 Neural connections of the human pineal. SCN=suprachiasmatic nucleus, PVN=paraventricular nucleus, SCG=superior cervical ganglion. (Redrawn from Tamarkin, K., Baird, C.J. and Almeida, O.F.X. Melatonin: a coordinating signal for mammalian reproduction *Science*, **227**, 714–20, copyright 1985 by the AAAS.)

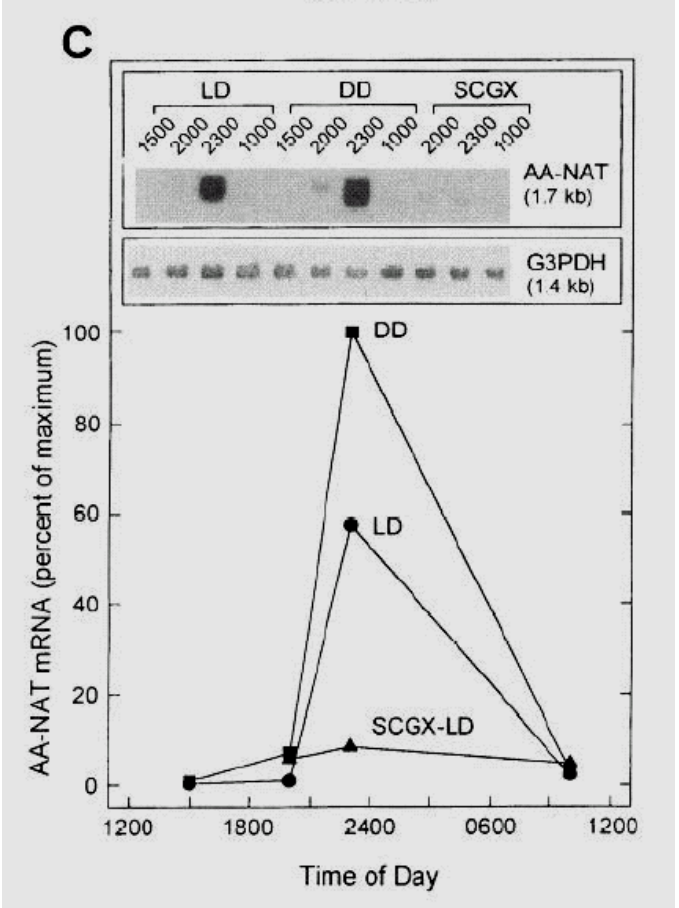

SCN
Pineal
ON
OFF
OFF
ON

Effect of SCN lesion on melatonin production



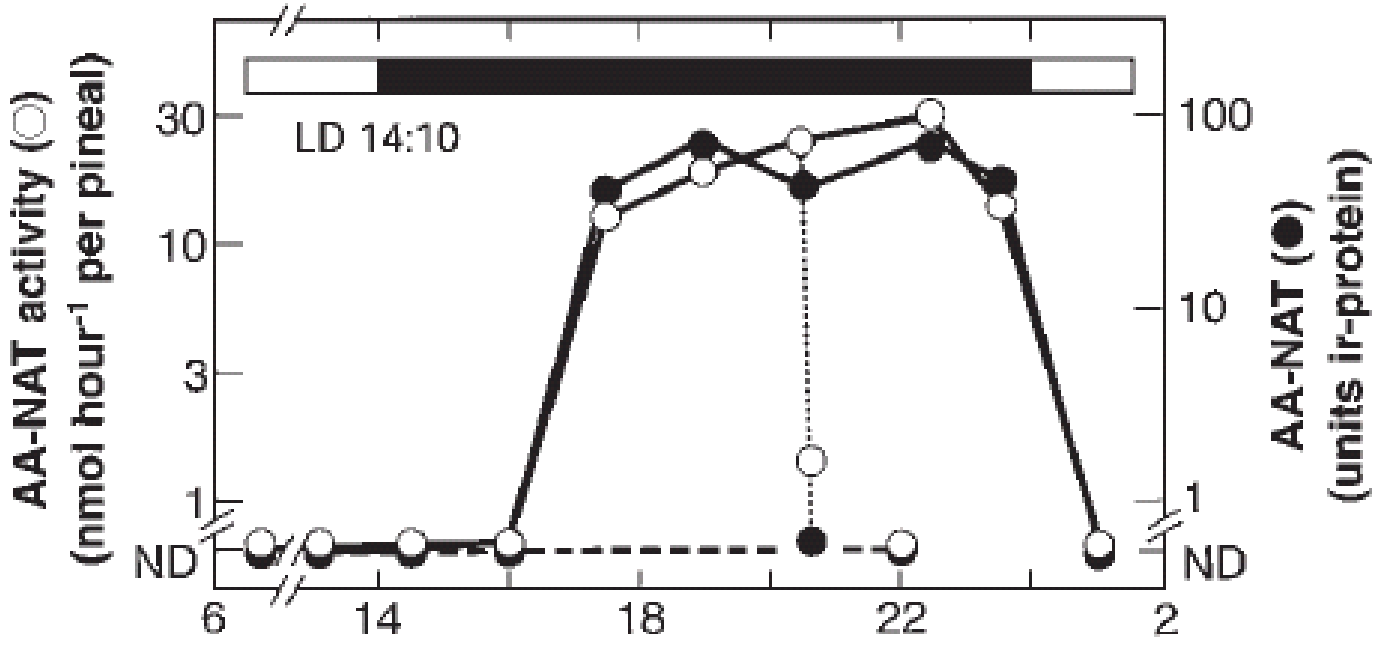
AANAT rhythms in the rat pineal gland

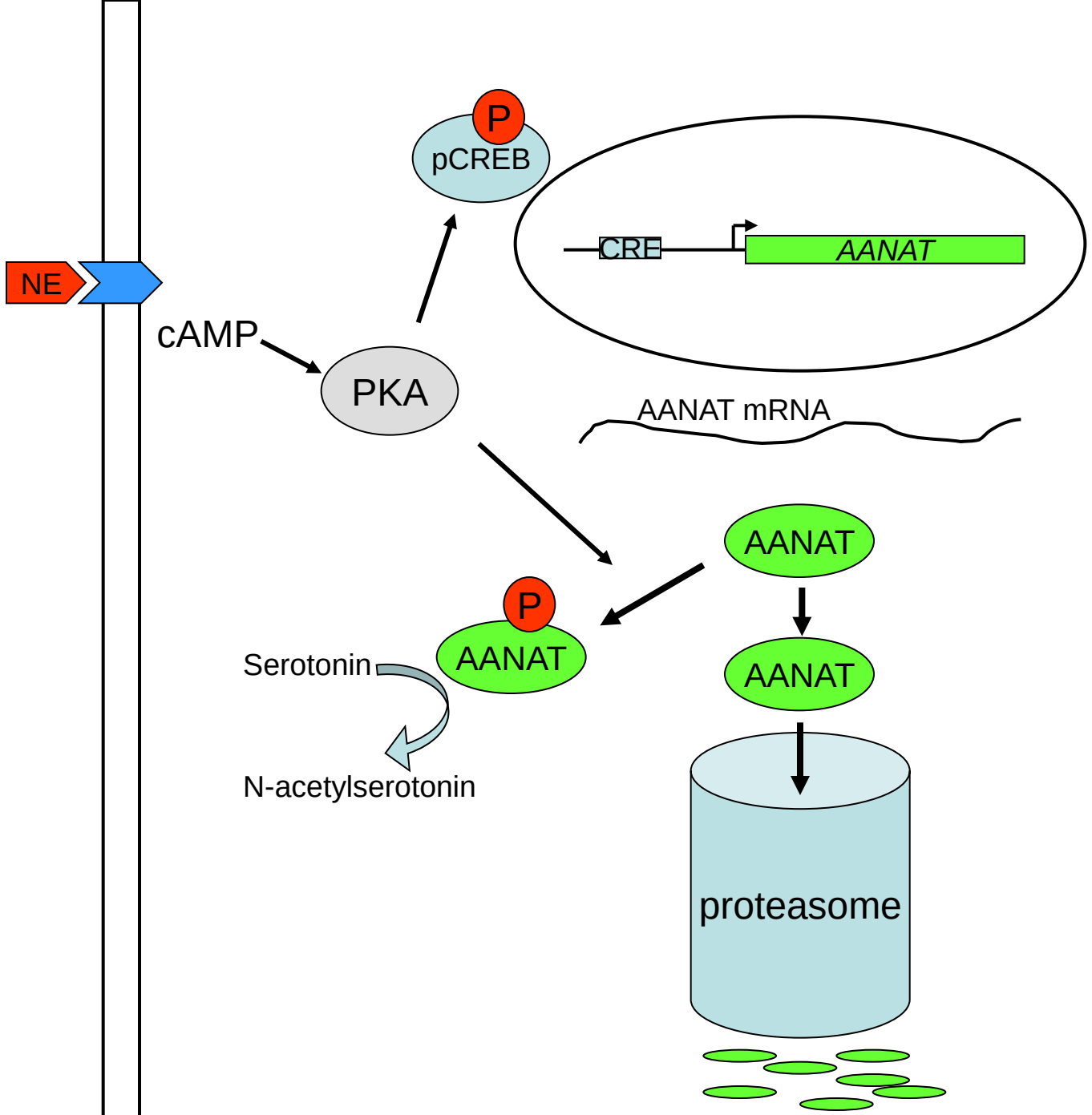




Roseboom et al., 1996

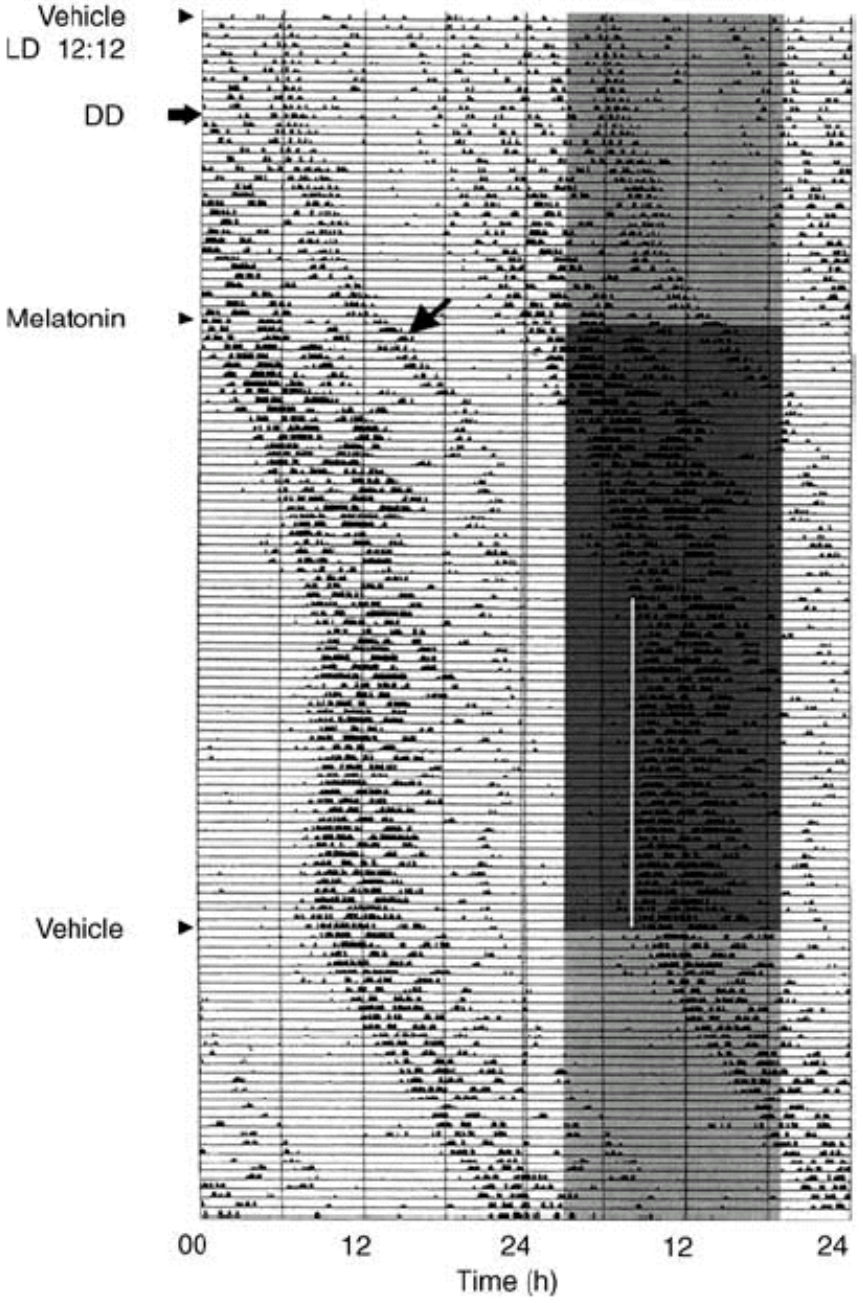
Effect of light of AANAT activity and protein levels



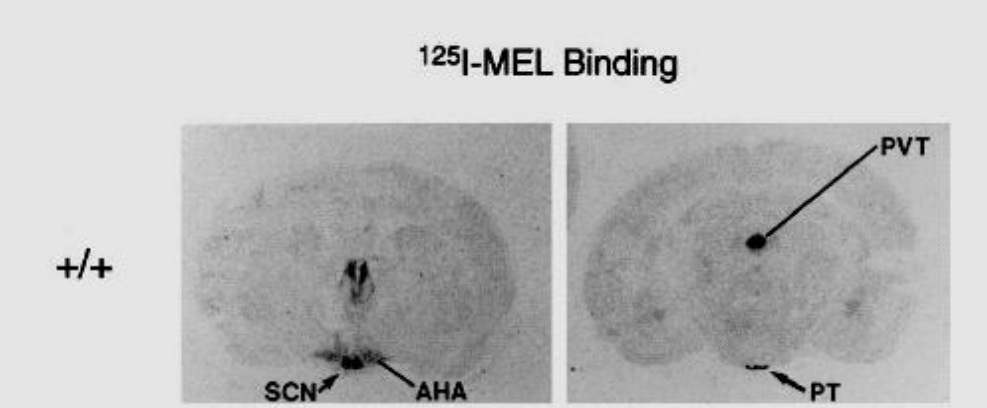

P
pCREB
CRE
AANAT
NE
cAMP
PKA
AANAT mRNA
AANAT
P
AANAT
AANAT
Serotonin
N-acetylserotonin
proteasome

The role of melatonin

- Affects other daily rhythms
- Affects annual/seasonal rhythms

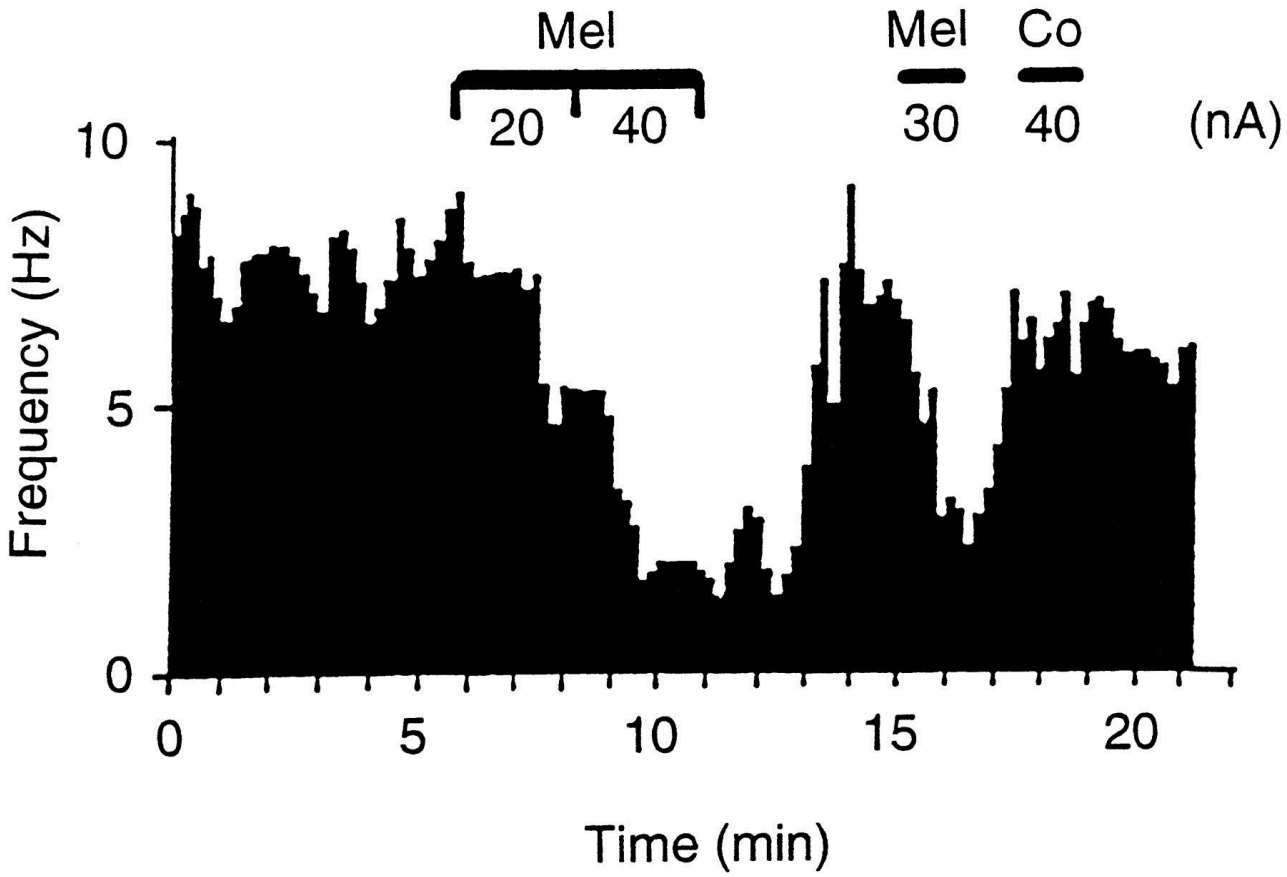

Vehicle
LD 12:12
DD
Melatonin
Vehicle
00
12
24
12
24
Time (h)

Melatonin binding sites in the mice brain



Liu et al., 1997

Effect of melatonin on SCN activity



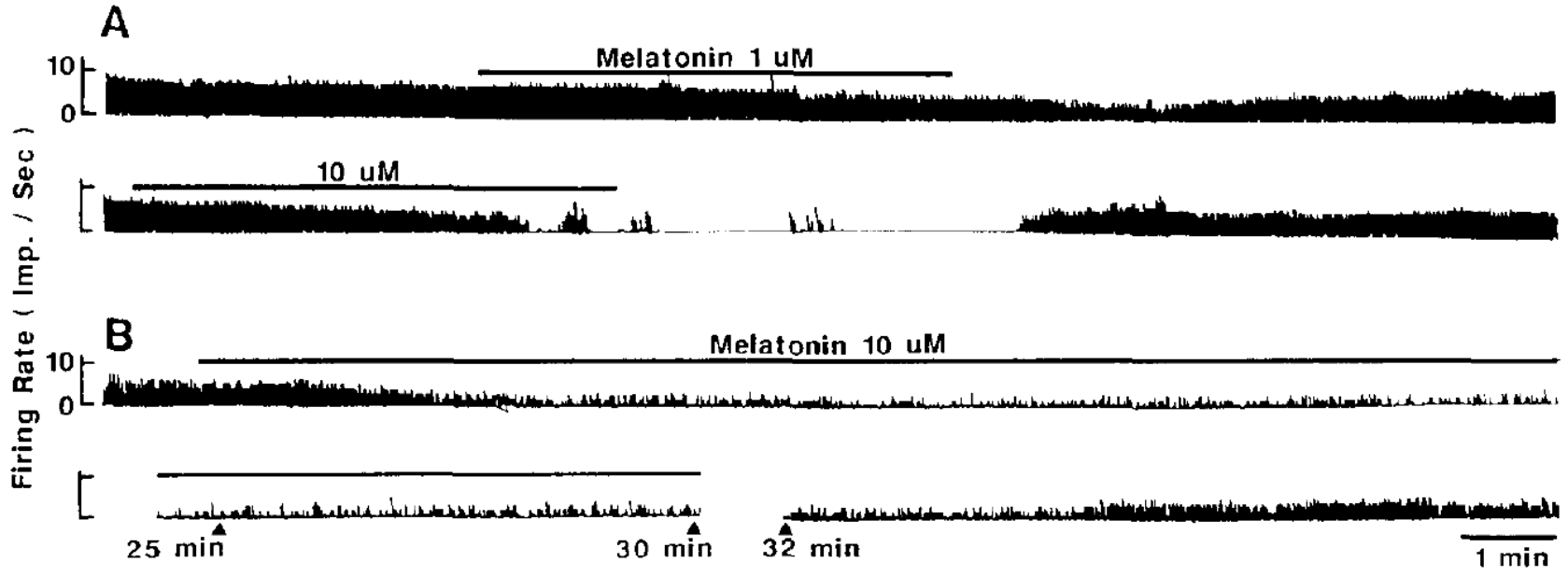
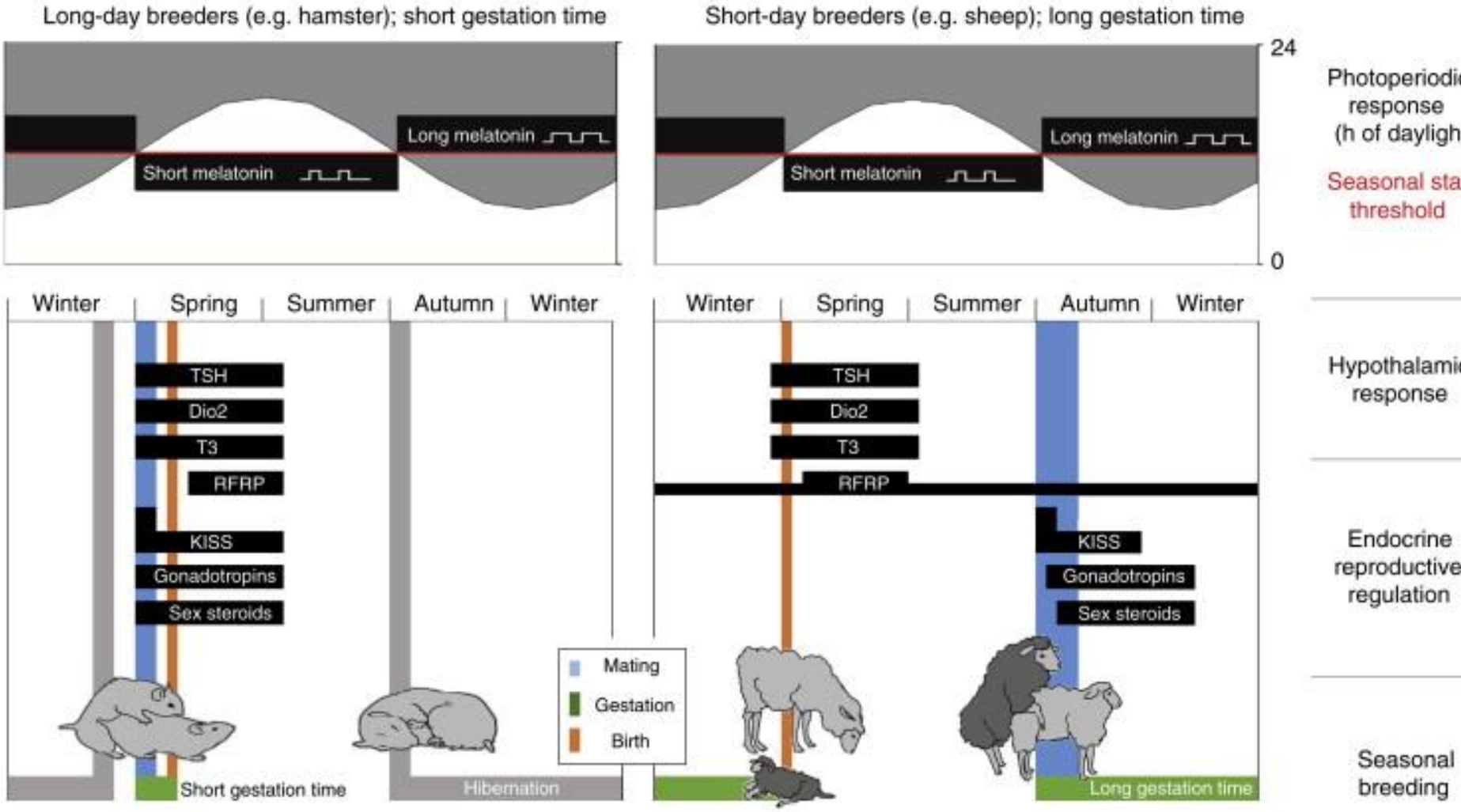


Fig. 1. Effect of melatonin on suprachiasmatic nucleus discharge during late subjective day, from CT09 to CT11 in vitro. A: short perfusion time (5 min). Infusion of melatonin produces a dose-dependent inhibitory response in SCN neurons. B: prolonged perfusion time (5–30 min). The inhibitory effect lasted throughout the melatonin application but firing rate recovered 5 min after melatonin washout.

Shibita et al., 1989



Current Biology

Removal of the pineal prevented winter testicular atrophy in humbsters

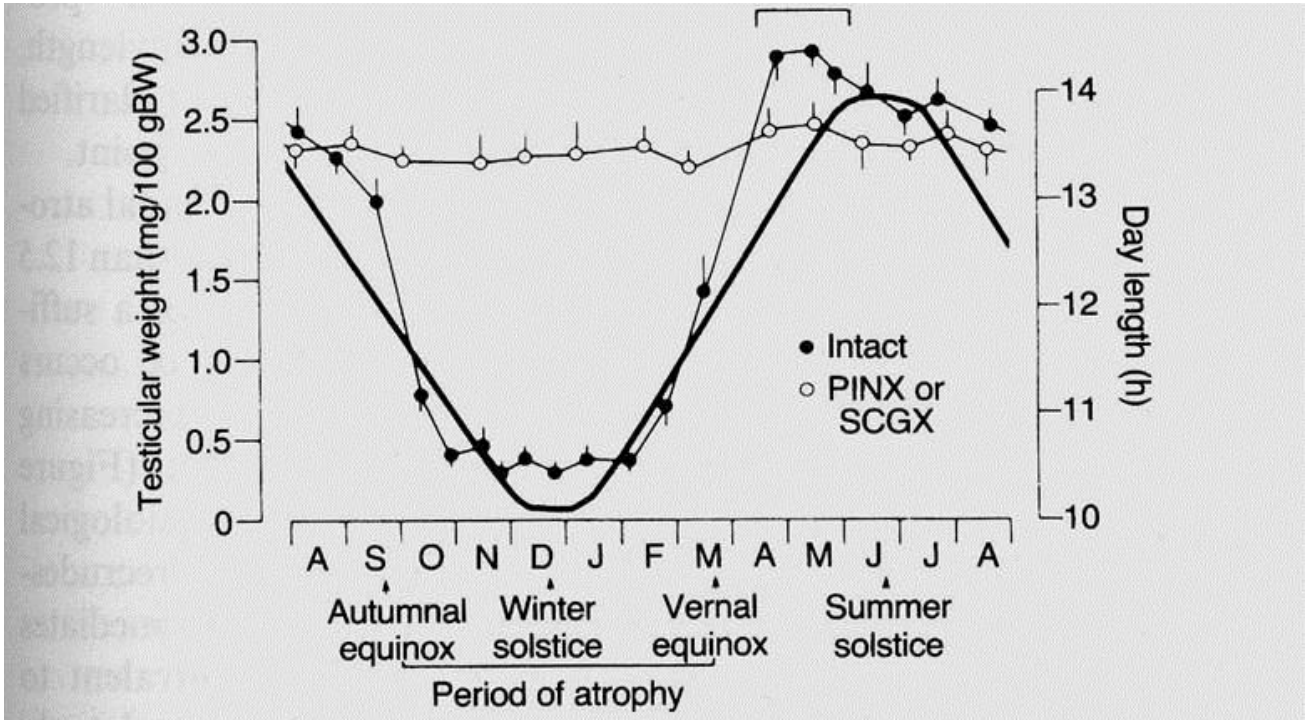
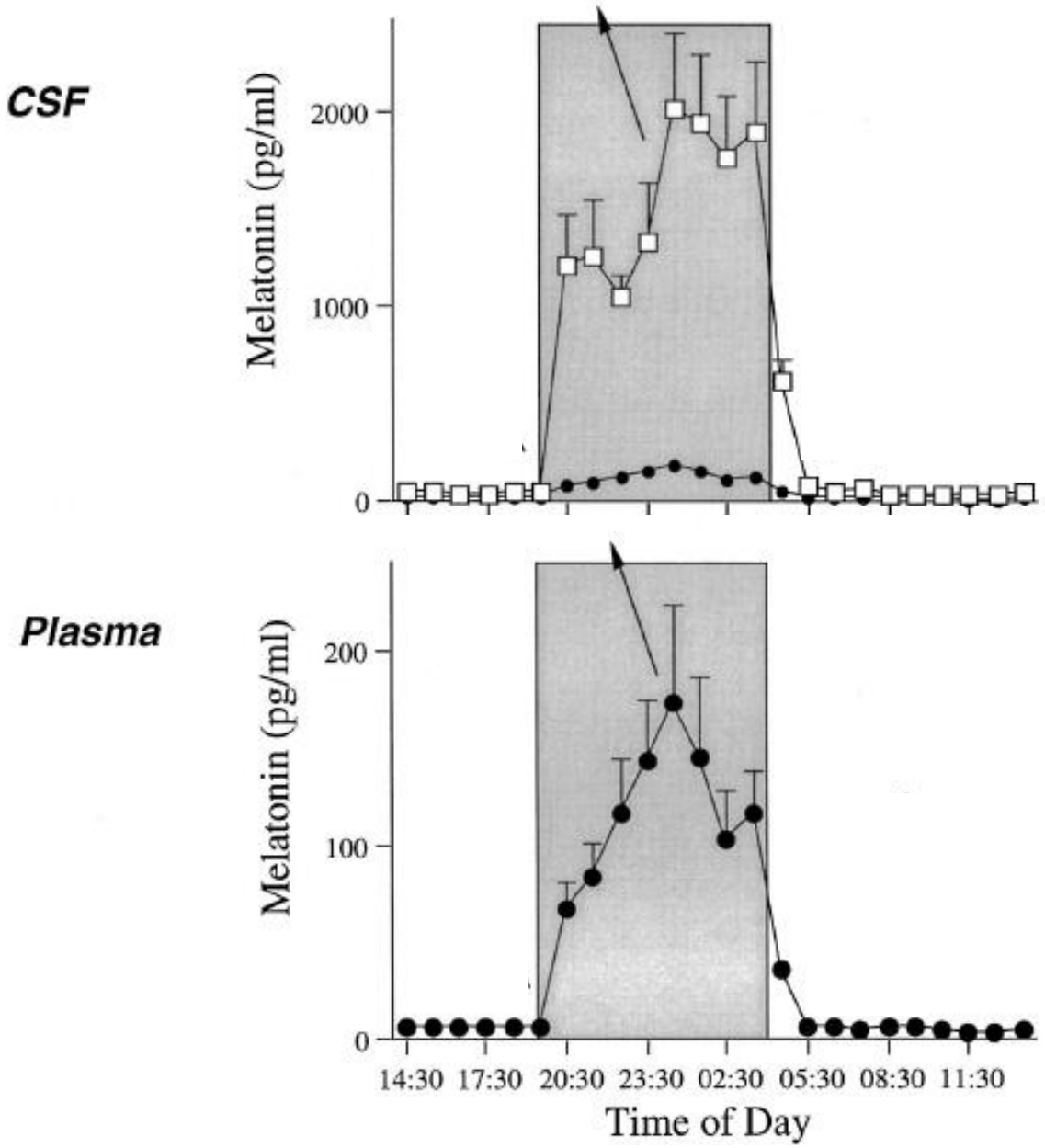


Fig. 5.8 Testicular weights in intact and pinealectomized (PINX) hamsters throughout the year when animals are kept under natural photoperiodic and temperature conditions. Either pinealectomy or superior cervical ganglionectomy (SCGX) completely prevents gonadal atrophy normally induced by short days. (Reproduced with permission from Reiter, R.J. The pineal and its hormones in the control of reproduction in mammals. *Endocr. Rev.* **1**, 109–31, 1980 © The Endocrine Society.)

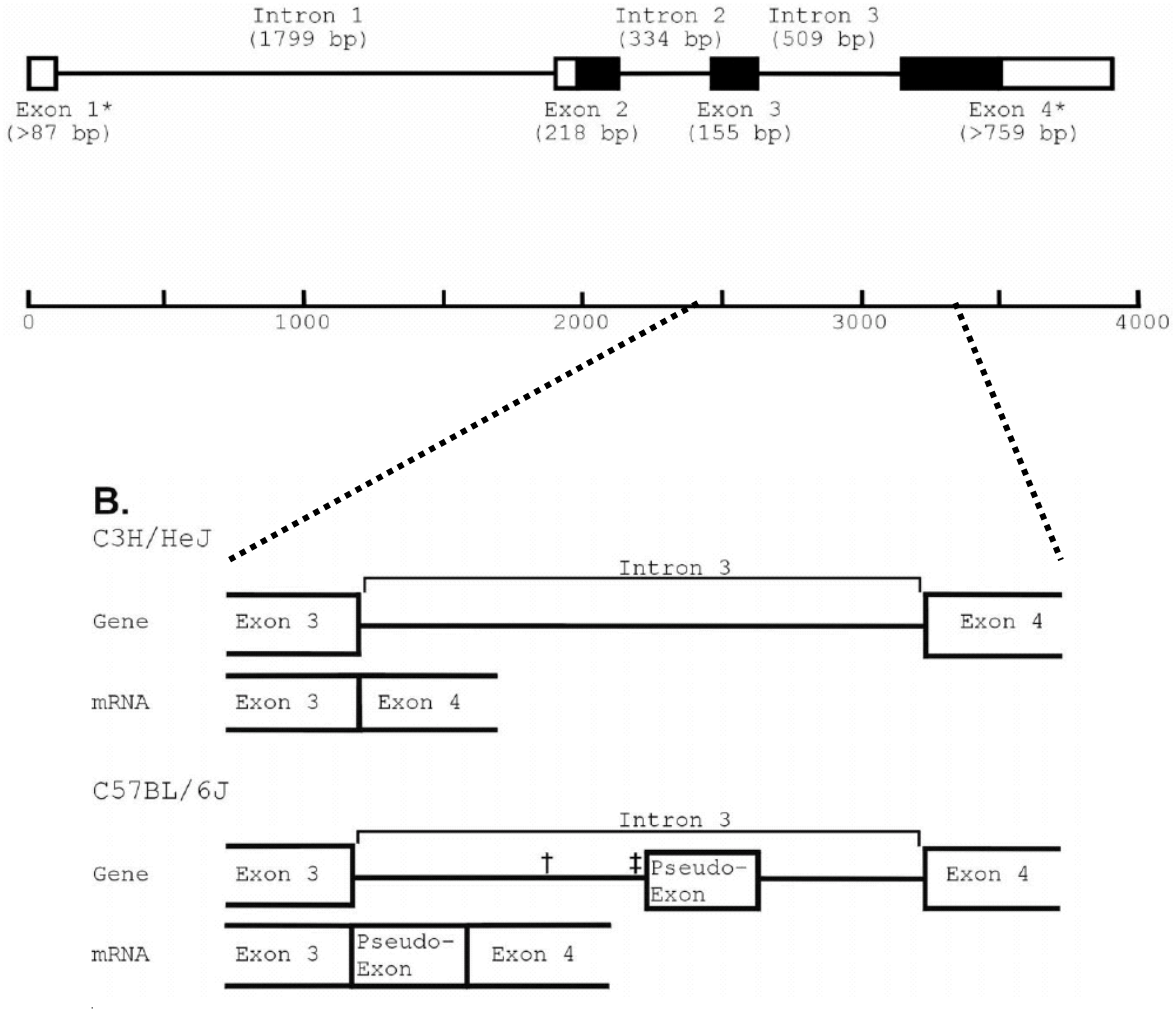
What can be the uses of melatonin?
Who may use melatonin?

- Shift workers
- Jet-lag
- Circadian related sleep disorders
- Blind people with unsynchronized clock
- Sleep (?)

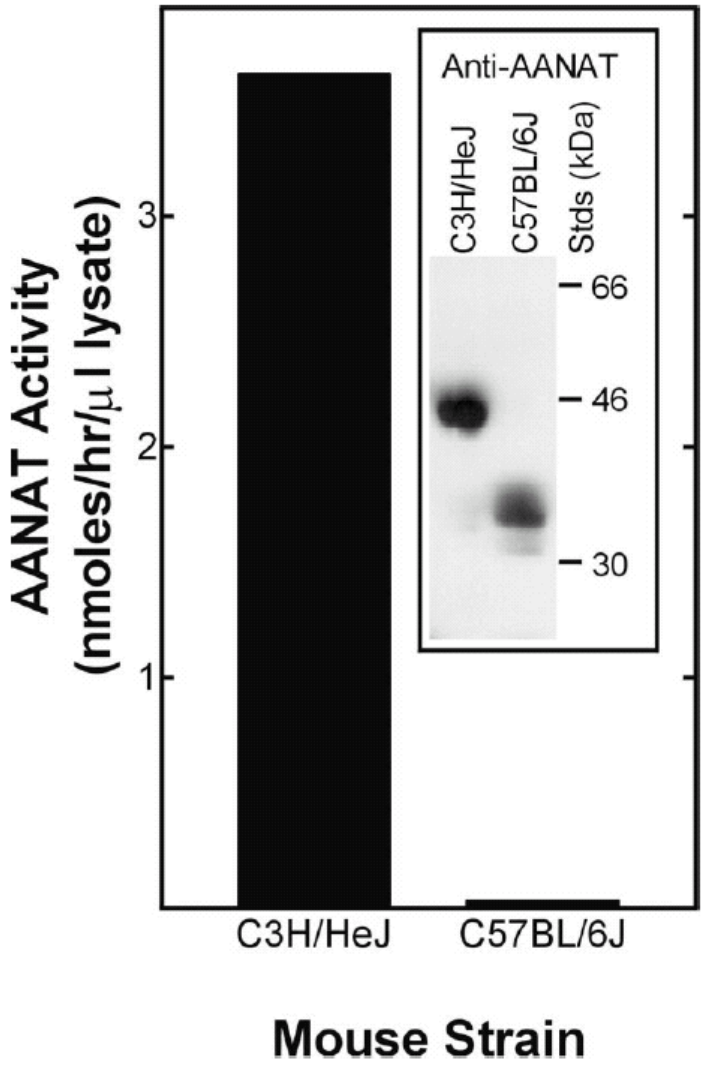
- Breading farmed animals


CSF
Melatonin (pg/ml)
2000
1000
0
Plasma
Melatonin (pg/ml)
200
100
0
14:30 17:30 20:30 23:30 02:30 05:30 08:30 11:30
Time of Day

spontanous melatonin KO in mice



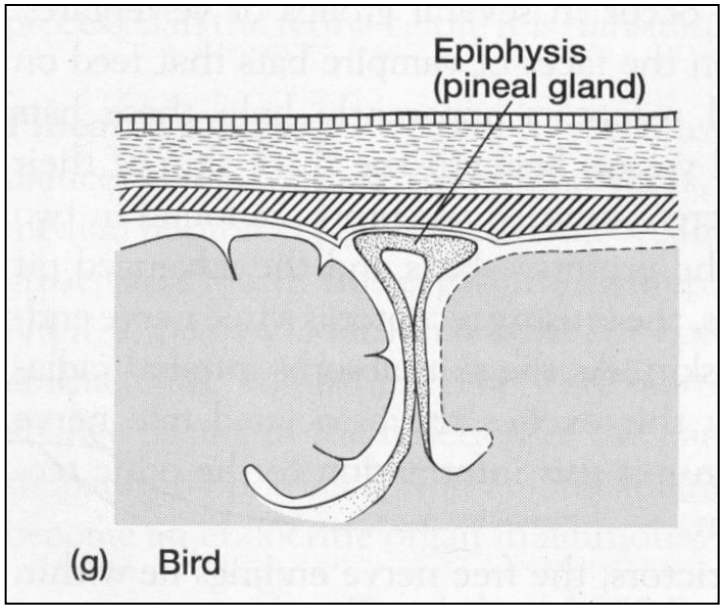
Roseboom et al., 1998

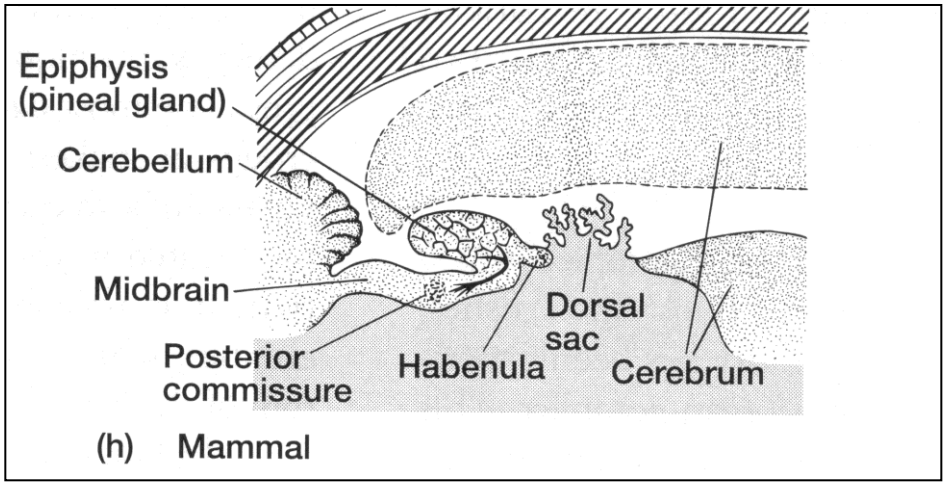


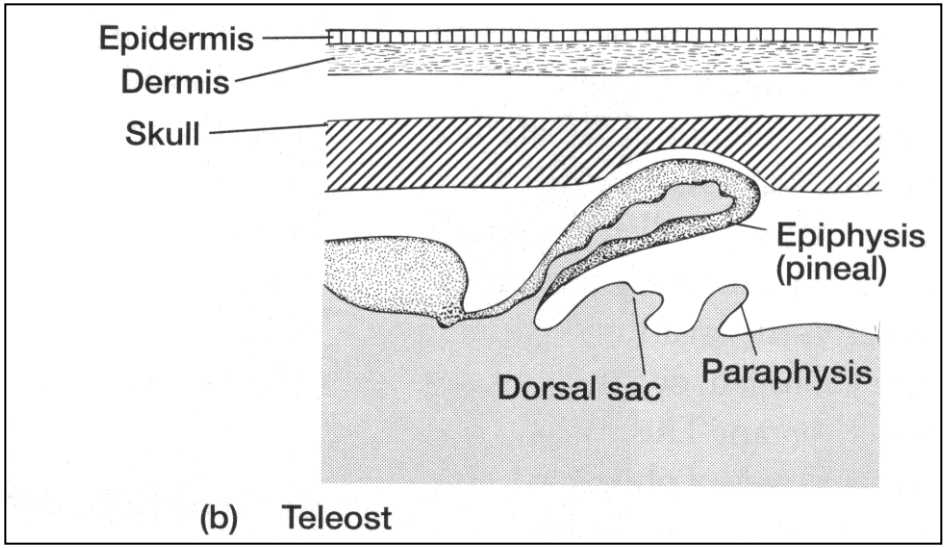
Why would such a mutation occur?

Non-mammalian vertebrates pineal gland

Location of the pineal gland

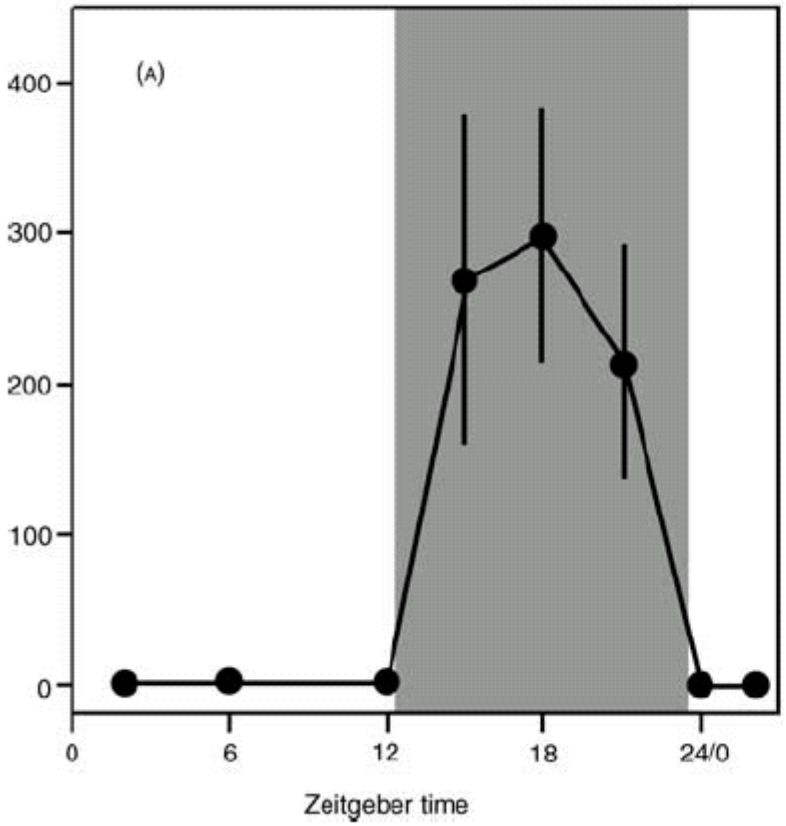




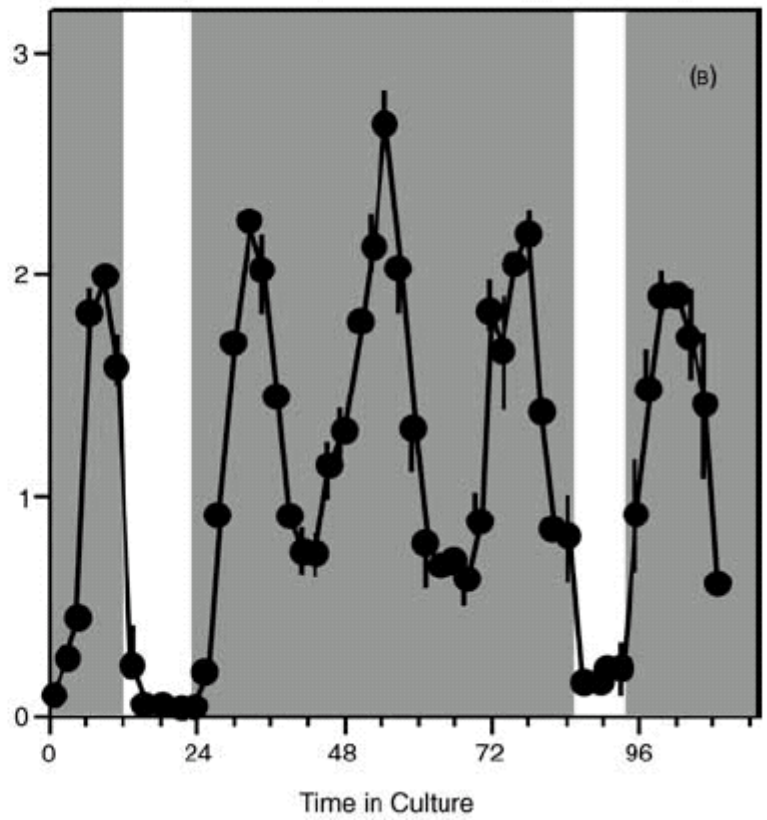


Rhythmic melatonin production in chicken

In vivo

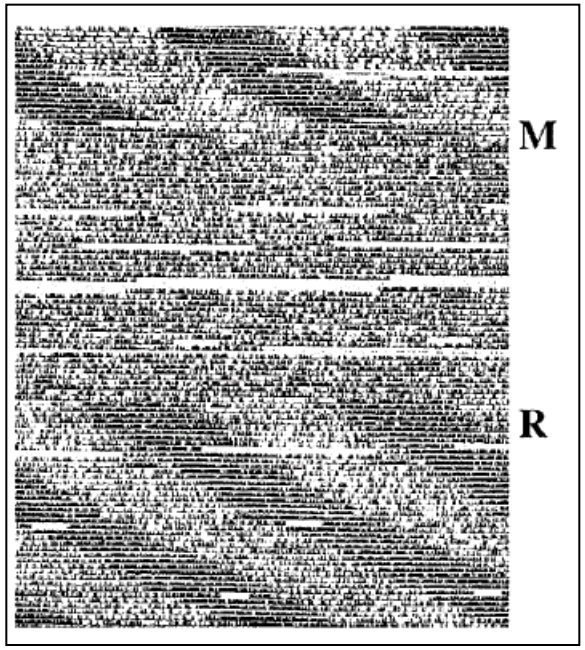


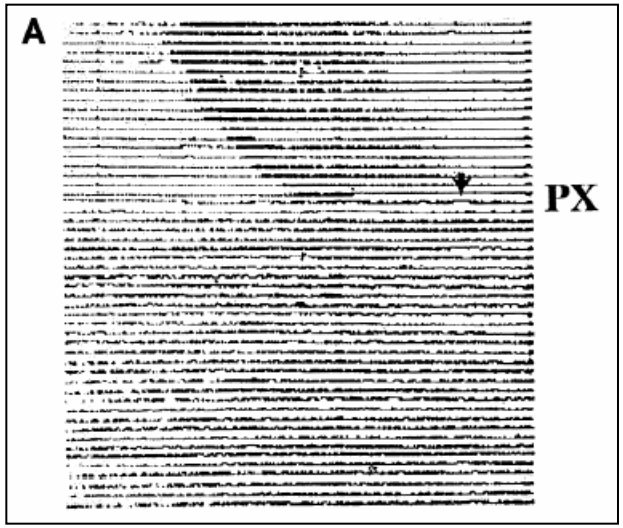
In vitro



The role of the sparrow pineal gland/melatonin in determining rhythmic locomotor activity

- Pinealectomy (right) or continuous melatonin (left) affected rhythmic locomotor activity





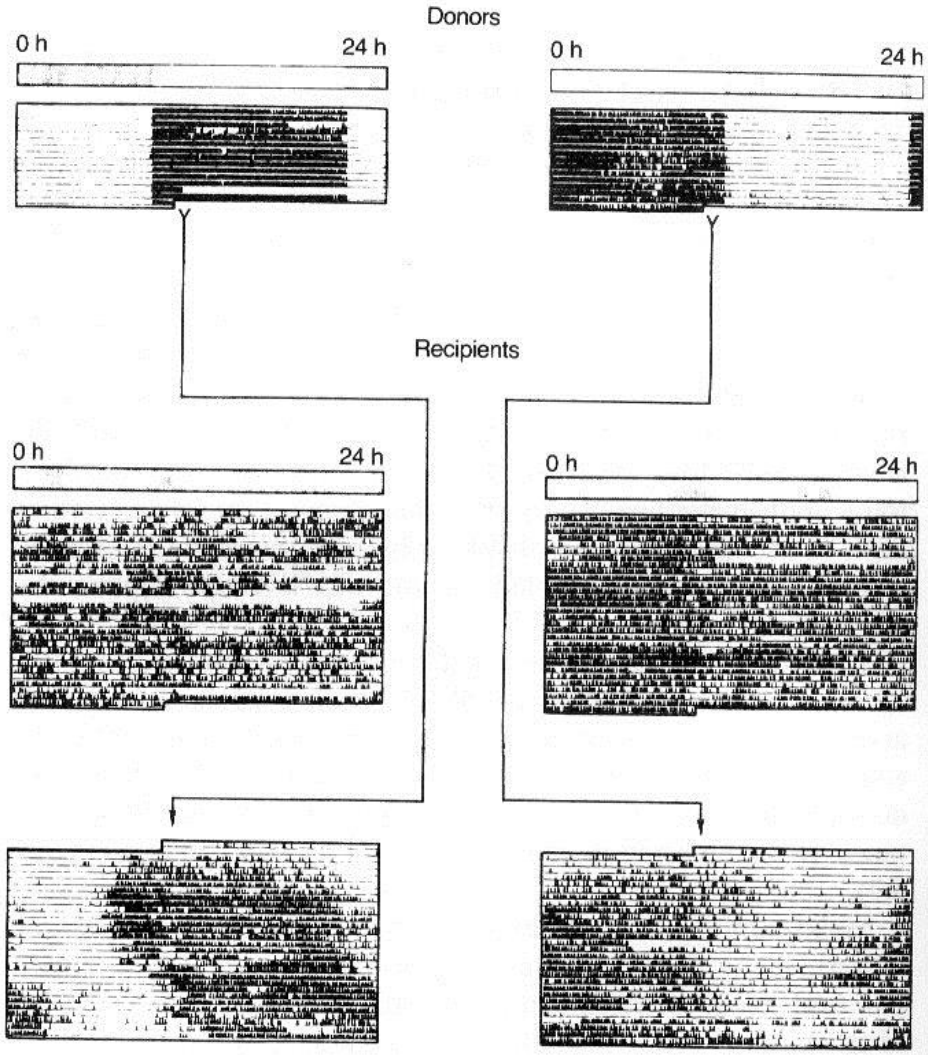
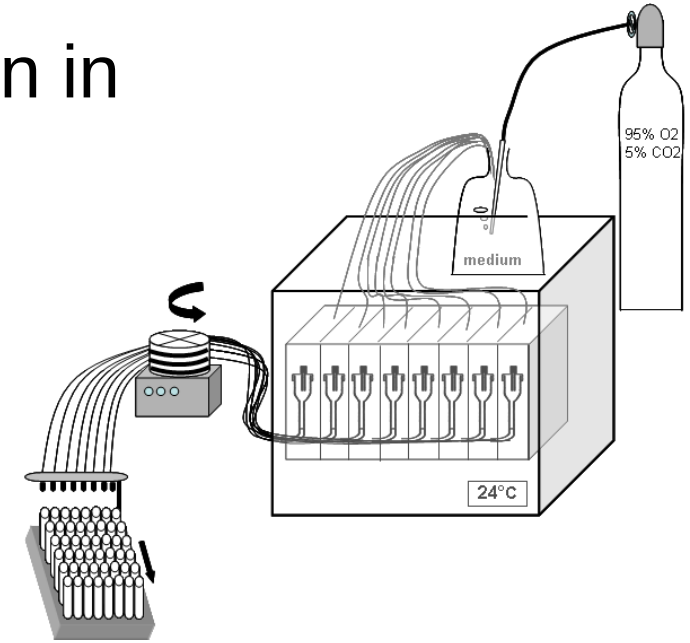
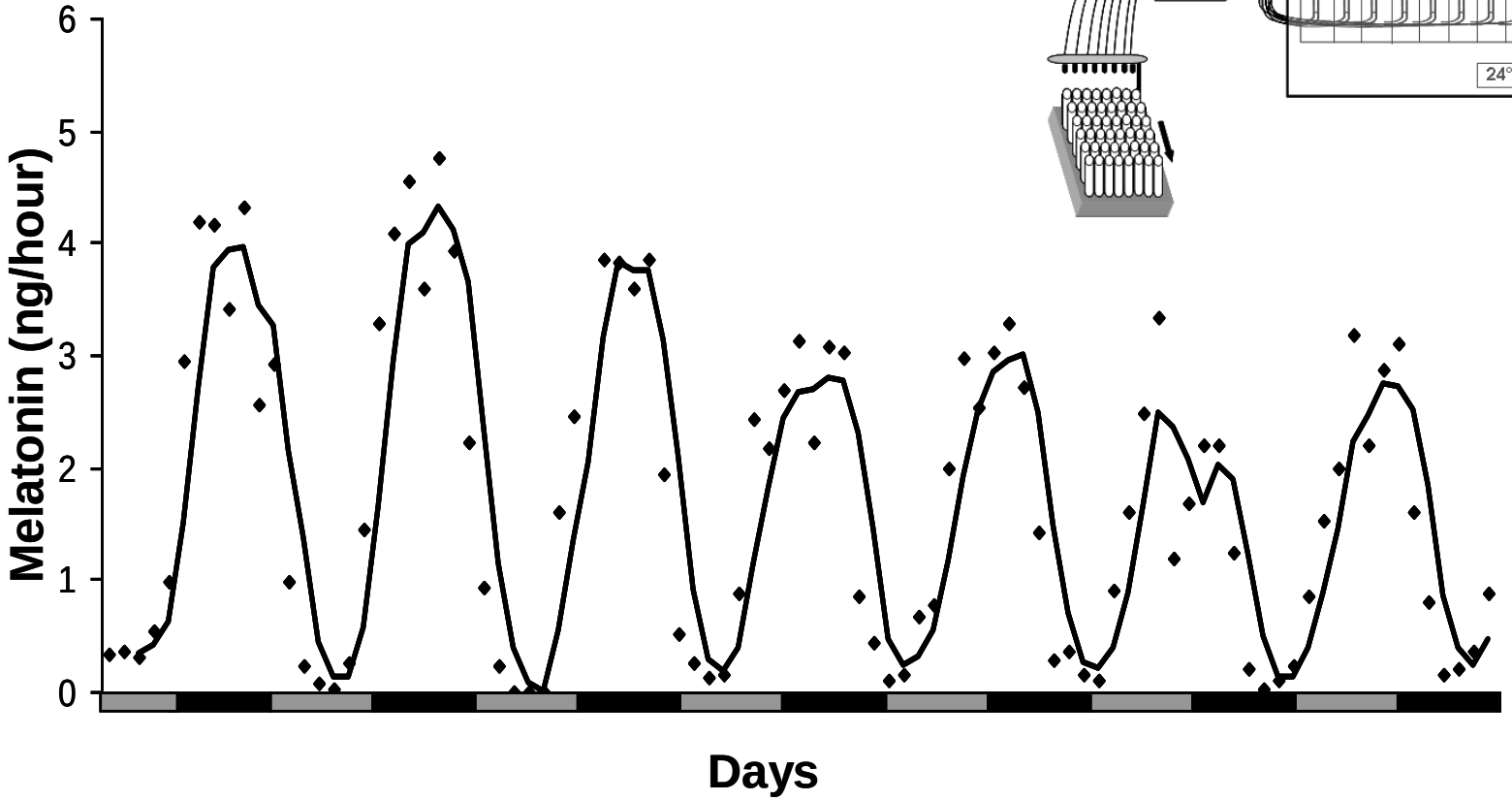


Fig. 6.2 The pineal in some birds can act as a master clock or circadian rhythm generator. Transplantation transfers the phase of the donor to pinealectomized sparrows, *Passer domesticus*, whose circadian rhythms of activity (and deep body temperature) are abolished by pinealectomy. Experimental design for transplantation of pineals from donors on different light schedules. The donors' light cycles and activity records are shown in the top panel. The pinealectomized hosts were kept in constant darkness. Their activity records before transplantation are shown in the middle panel and after transplantation in the bottom panel. (Reproduced with permission from Zimmerman, N.H. and Menaker, M.; published by the National Academy of Sciences, 1979).

- Pinealectomy led to loss of rhythm
- Pineal implantation conferred the rhythm of the donor

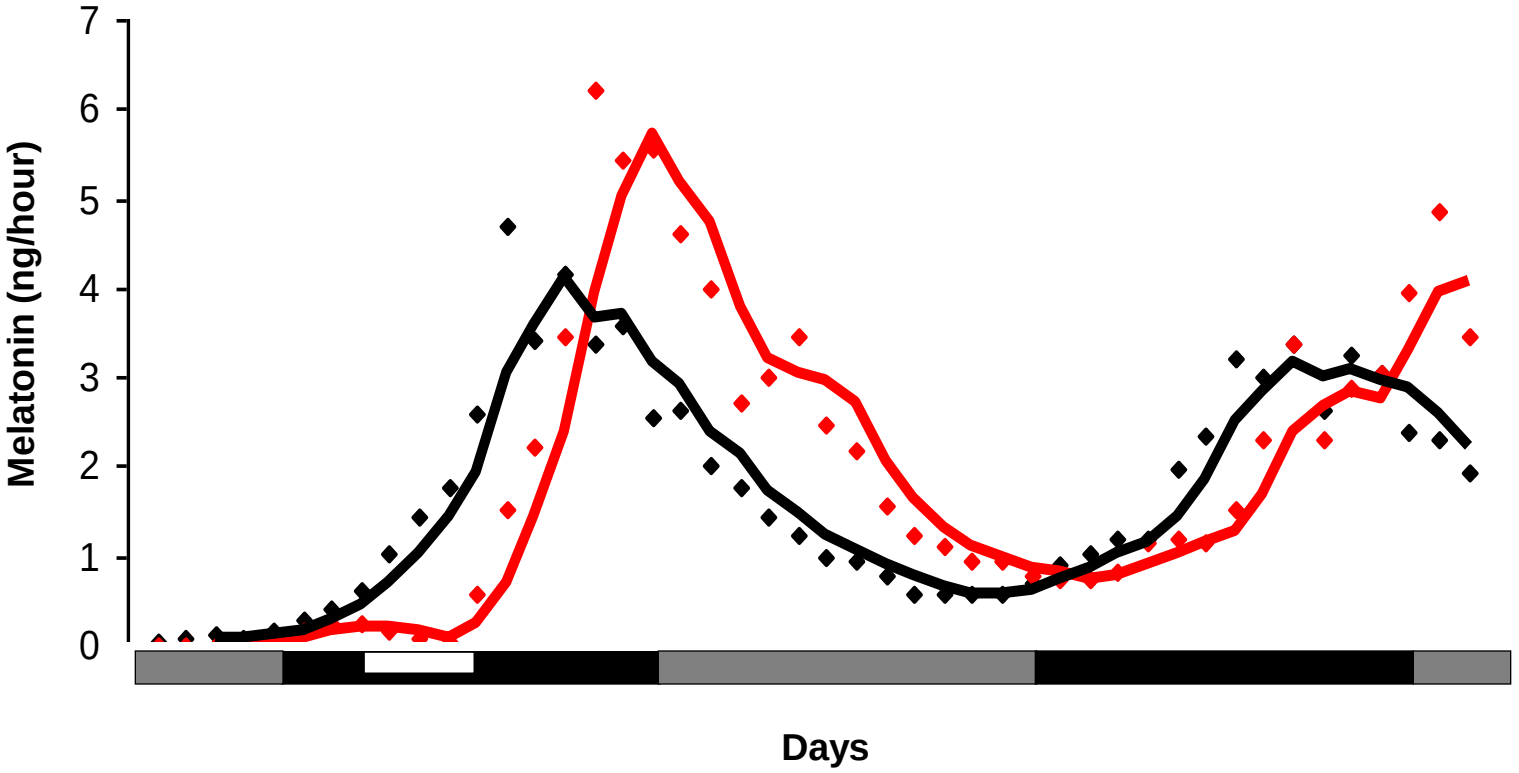
Rhythms of melatonin production in cultured zebrafish pineal glands





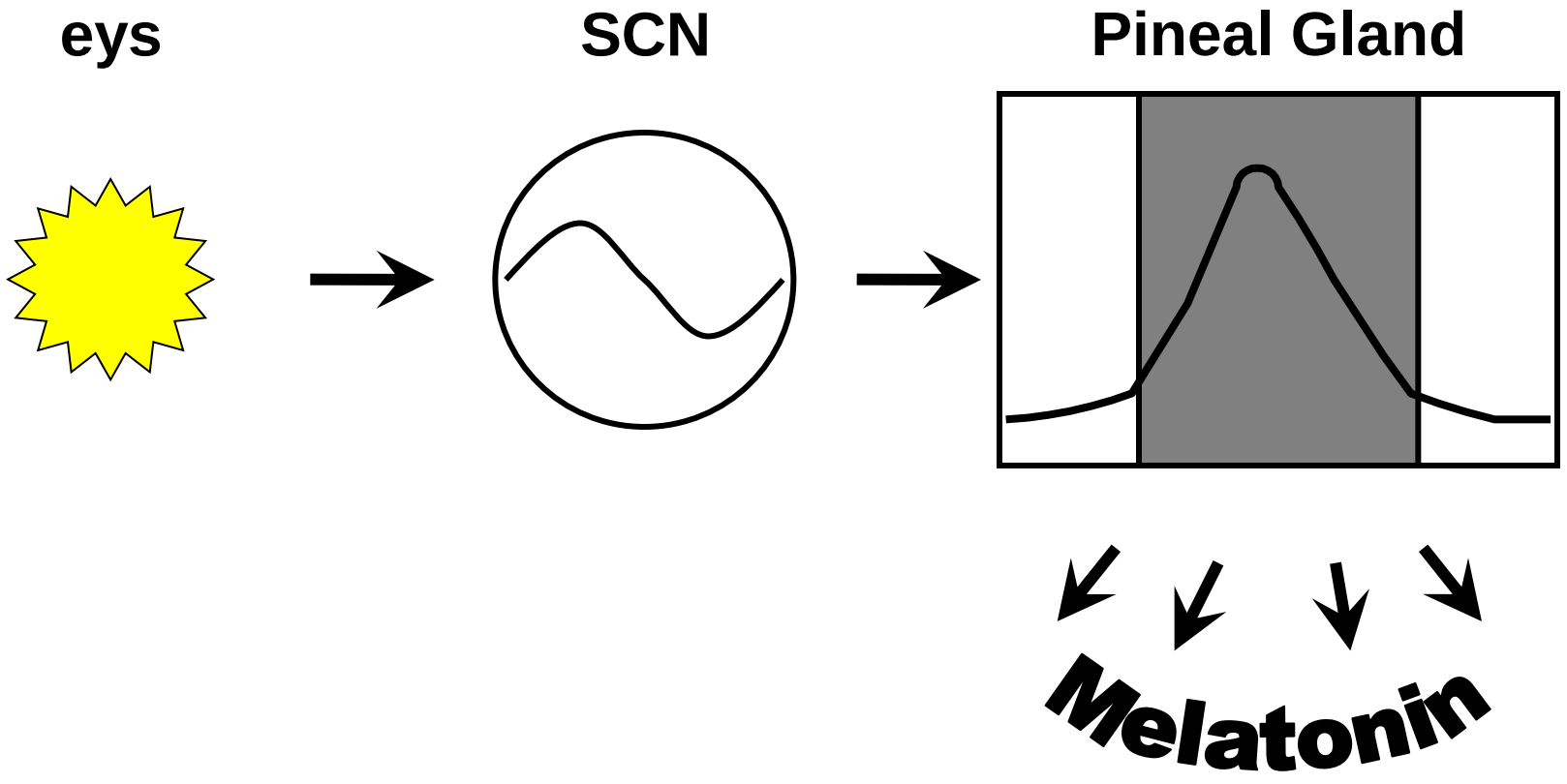
Adi Tovin

Rhythmic melatonin production is affected by light – photoreception.

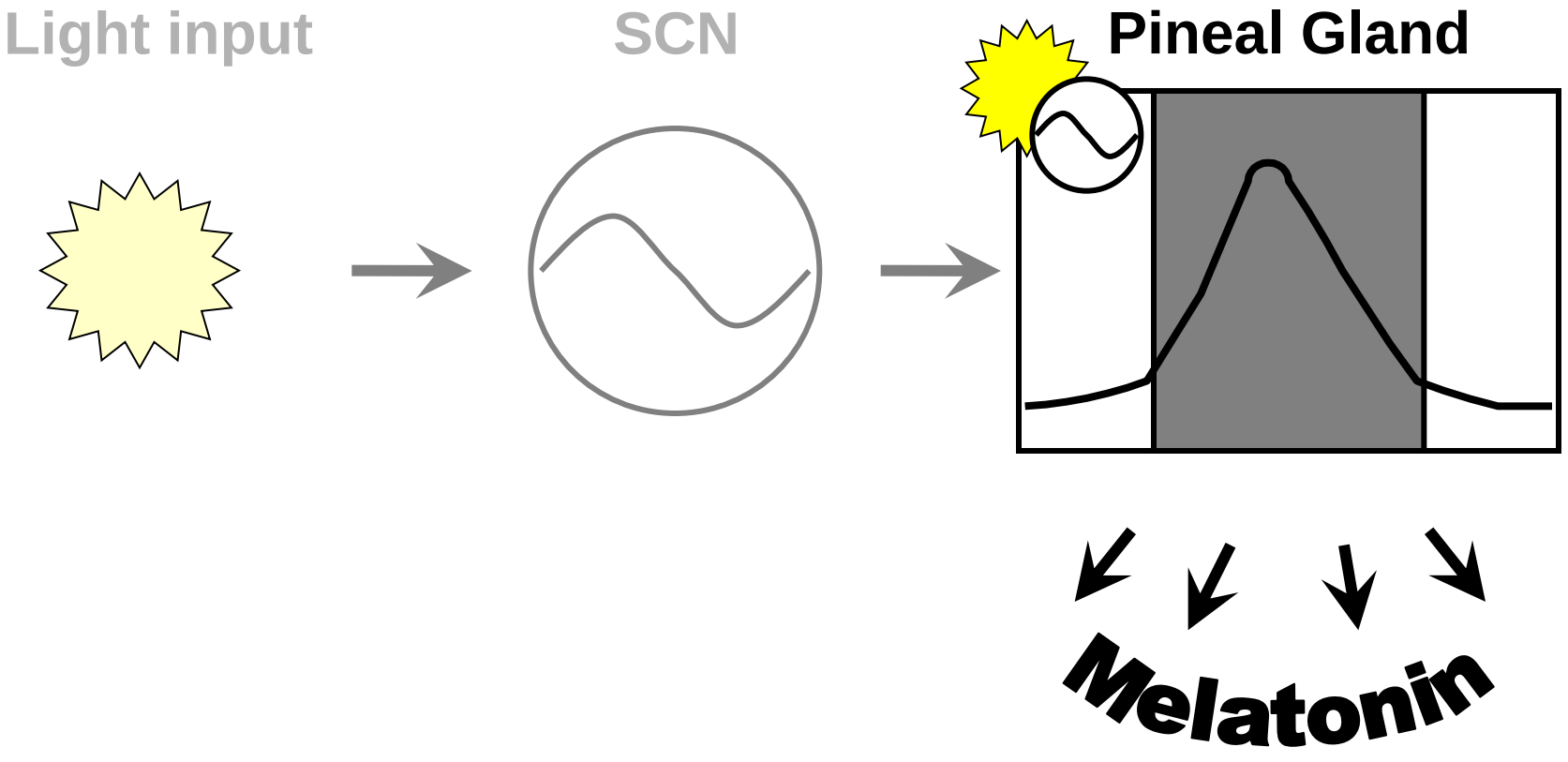


Adi Tovin and Limor Ziv

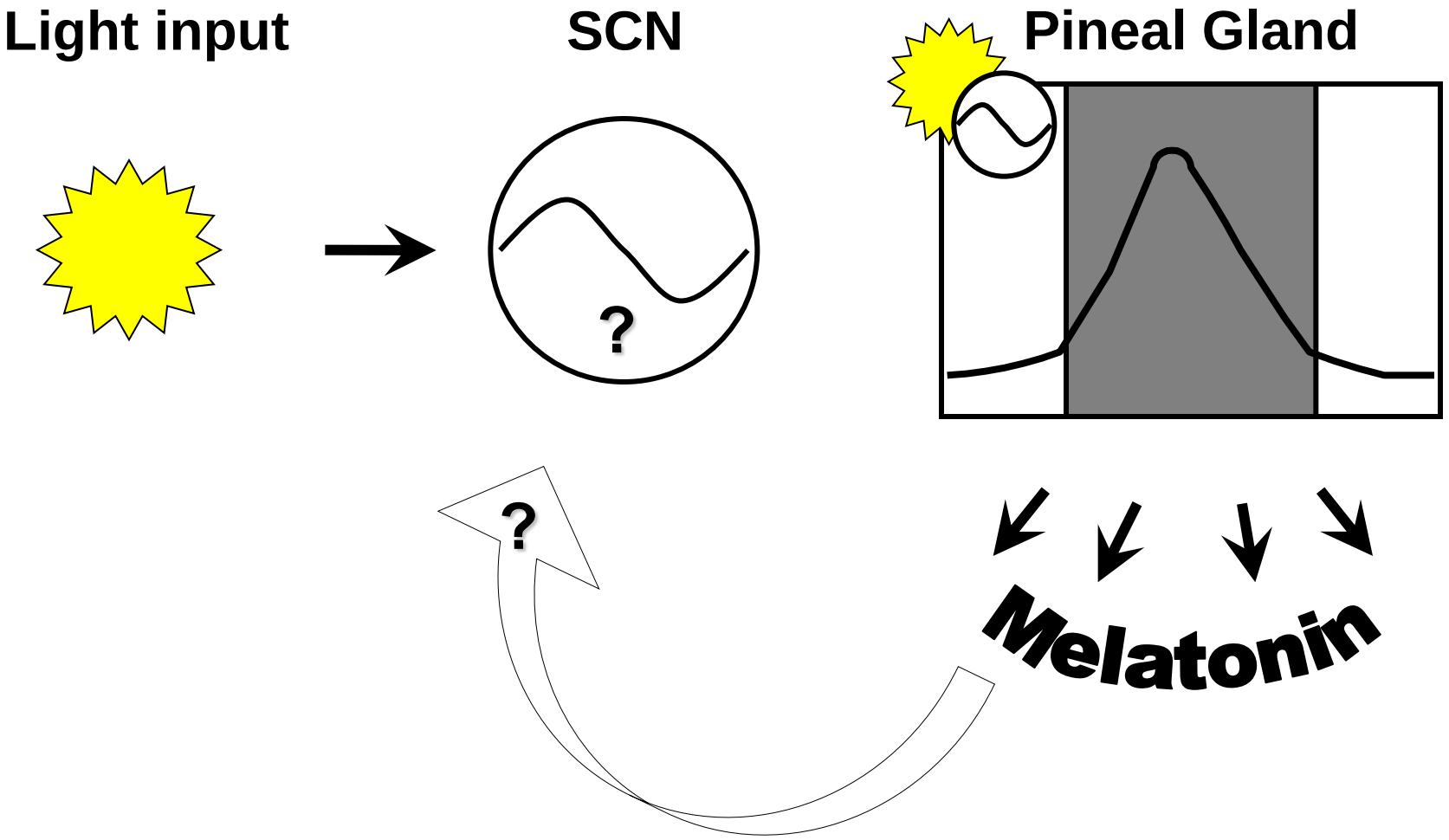
Regulation of the melatonin rhythm in mammals



Regulation of the melatonin rhythm in fish



Regulation of the melatonin rhythm in fish



The roles of non-mammalian pineal glands

- Affect daily rhythms and sleep
- Affect annual rhythms
- Pigmantation
- Thermoregulation
- Development

- Huge amount of species variation