Table 1.1. *A list of the main biological rhythms, classified according to increasing period. Rhythms marked by an asterisk occur at the cellular level (sometimes they may also arise from interactions between cells, e.g. in neural networks)*

Rhythm	Period
Neural rhythms*	0.01 to 10 s (and more?)
Cardiac rhythm*	1 s
Calcium oscillations*	1 s to several minutes
Biochemical oscillations*	1 min to 20 min
Mitotic cycle*	10 min to 24 h (or more)
Hormonal rhythms*	10 min to several hours (also 24 h)
Circadian rhythms*	24 h
Ovarian cycle	28 days (human)
Annual rhythms	1 year
Epidemiology and ecological oscillations	years

REPROD. CICADAS 13 or 17 ys (SPECIES-SPECIFIC)

LINKED OR NOT TO ENVIRONMENTAL CYCLES

BIOLOGICAL RHYTHMS

Fundamental features.

A) ENDOGENOUS (persist in the absence of the environmental cyclic variable)

B) INDEPENDENT OF TEMPERATURE (within limits)

C) THE ENVIRONMENTAL CYCLE (typically the photoperiod) REGULATE THE ENDOGENOUS RHYTHM, to obtain synchrony (possible conditional arrhythmia in case of large variations of the external relevant parameters, such as T, O_2, etc.)

ULTRADIAN (cycle period < 24 h)

Cell cycle (depending on species), pulsatile hormone release, brain waves, cardiac and respiratory cycles, etc.

Possible regulation by environmental factors (e.g. circatidal).

CIRCADIAN (cycle period ~ 24 h)

Sleep-waking cycle, body temperature, etc.

INFRADIAN (cycle period > 24 h)

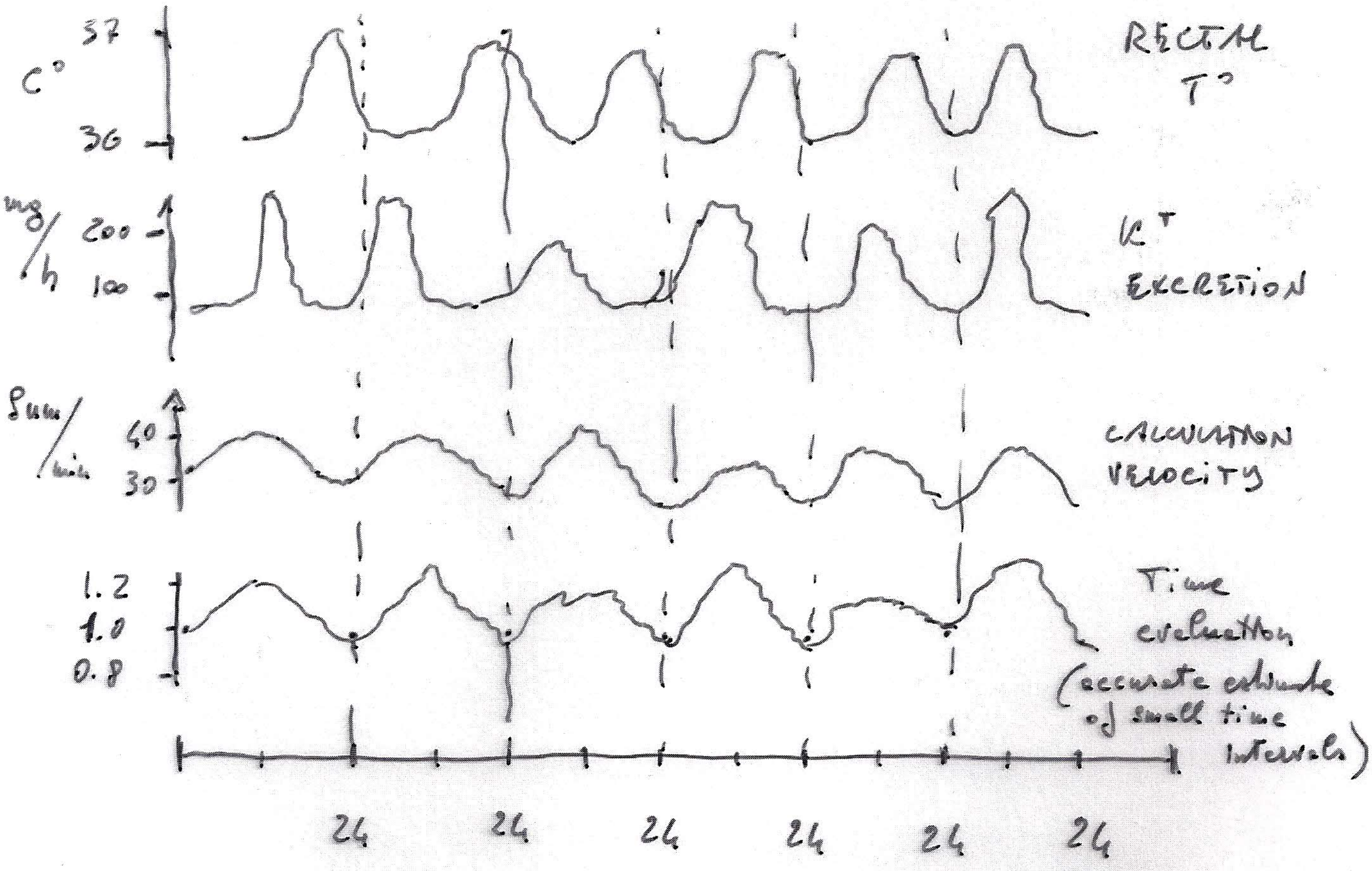
CIRCALUNAR (moon cycle, e.g. reproductive cycles)

CIRCANNUAL (season-dependent cycles, e.g. hibernation, migration, certain reproductive cycles)

SLOWER PERIODS (years)

SOME CIRCADIAN RHYTHMS IN HUMANS:

BOTH PHYSIOLOGICAL and COGNITIVE



THE ENDOGENOUS RHYTHM IS STUDIED IN COMPLETE ISOLATION FROM POSSIBLE PERTURBING FACTORS:

from SOCIAL INTERACTION
to MAGNETIC FIELDS (even the Earth's one)
A WEAK $\vec{B}$ CAN SYNCHRONIZE THE ACTIVITY RHYTHM (in absence of EARTH'S $\vec{B}$), BUT NOT THE OTHERS

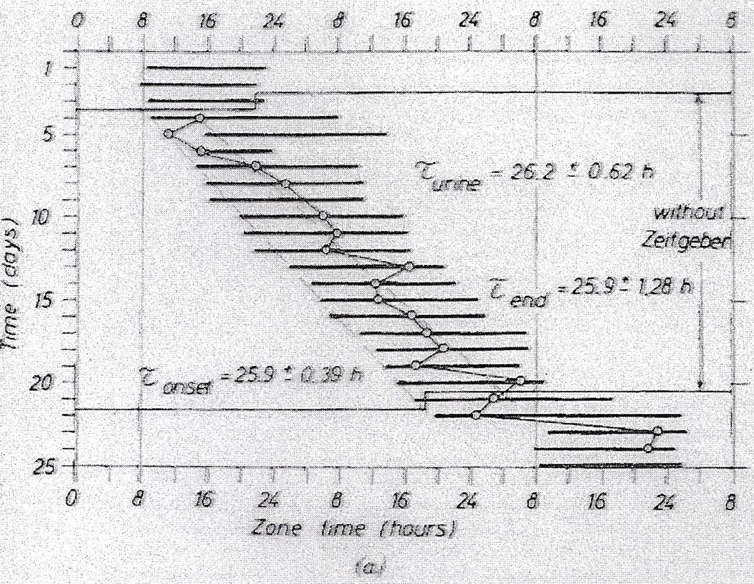


Figure 2a. Circadian rhythm of activity and urine excretion in a human subject kept for 3 days under normal living conditions, then for 18 days in isolation, and finally again under normal conditions. *Black bars*, times of being awake; *circles*, maxima of urine excretion; τ, mean values of period for onset and end of activity and for urine maxima (12).

From: LADD PROSSER (Ed.)
COMPARATIVE ANIMAL PHYSIOLOGY
4th Ed. 1991

- Multiple non identical rhythms (e.g. T° and sleep-wake)
- Can be desinchronized
- SIMILAR EXPERIMENTS ON SEASONAL RHYTHMS

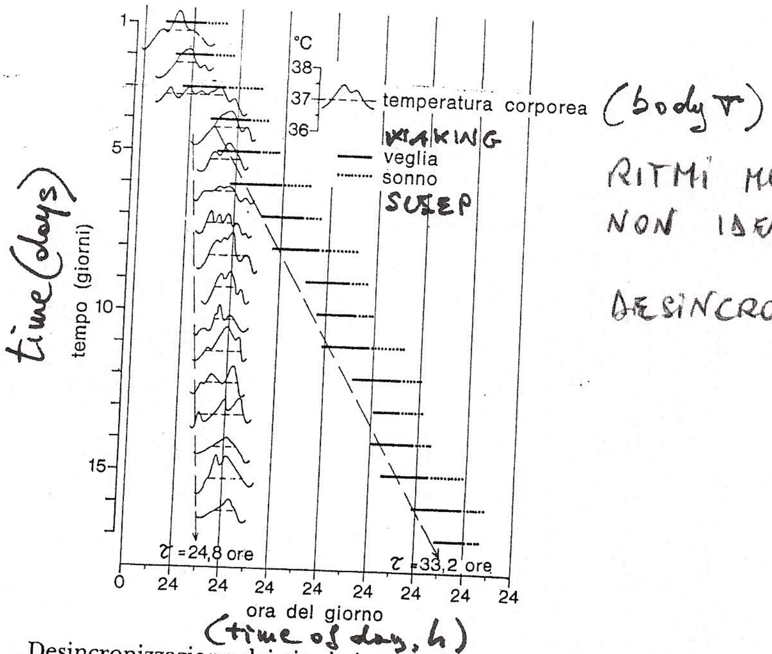


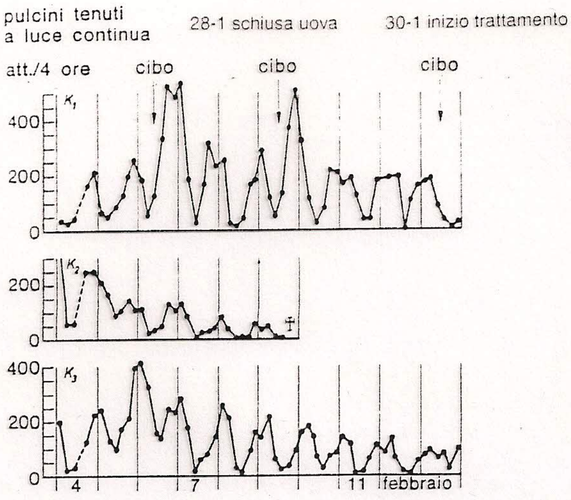
Fig. 17.8. Desincronizzazione dei ritmi circadiani in una persona isolata e priva di orologio. Linee orizzontali continue e linee punteggiate: rispettivamente periodo di veglia e di sonno. La linea tratteggiata rappresenta la temperatura corporea di 37 °C. Da J. Aschoff (1966).

RITMI MULTYPLI NON IDENTICI

DESINCRONIZZ.

EXAMPLE OF DESYNCHRONIZATION OF DIFFERENT RHYTHMS

Test on an isolated person, with no clock.



RITMO INNATO

Fig. 17.5. Periodicità dell'attività di tre pulcini tenuti a luce continua. Da J. Aschoff e J. Meyer-Lohmann (1954).

COMPONENTE GENETICA - MUTANTI IN *Drosophila*

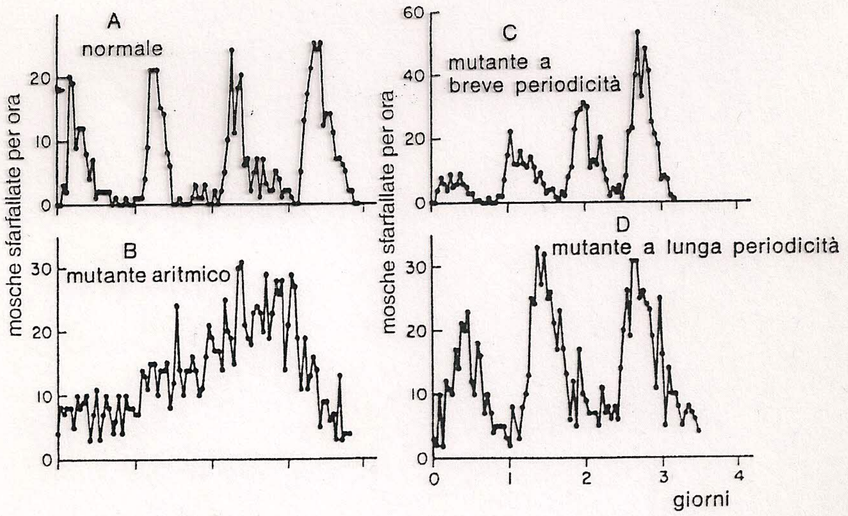


Fig. 17.6. Ritmo di sfarfallamento in condizioni di oscurità continua in una popolazione « normale » di *Drosophila* e nei suoi mutanti. Le popolazioni erano state precedentemente esposte a un'alternanza periodica di dodici ore di luce e dodici ore di oscurità. Da R.J. Konopka e S. Benzer (1971).

BIOLOGICAL RHYTHMS

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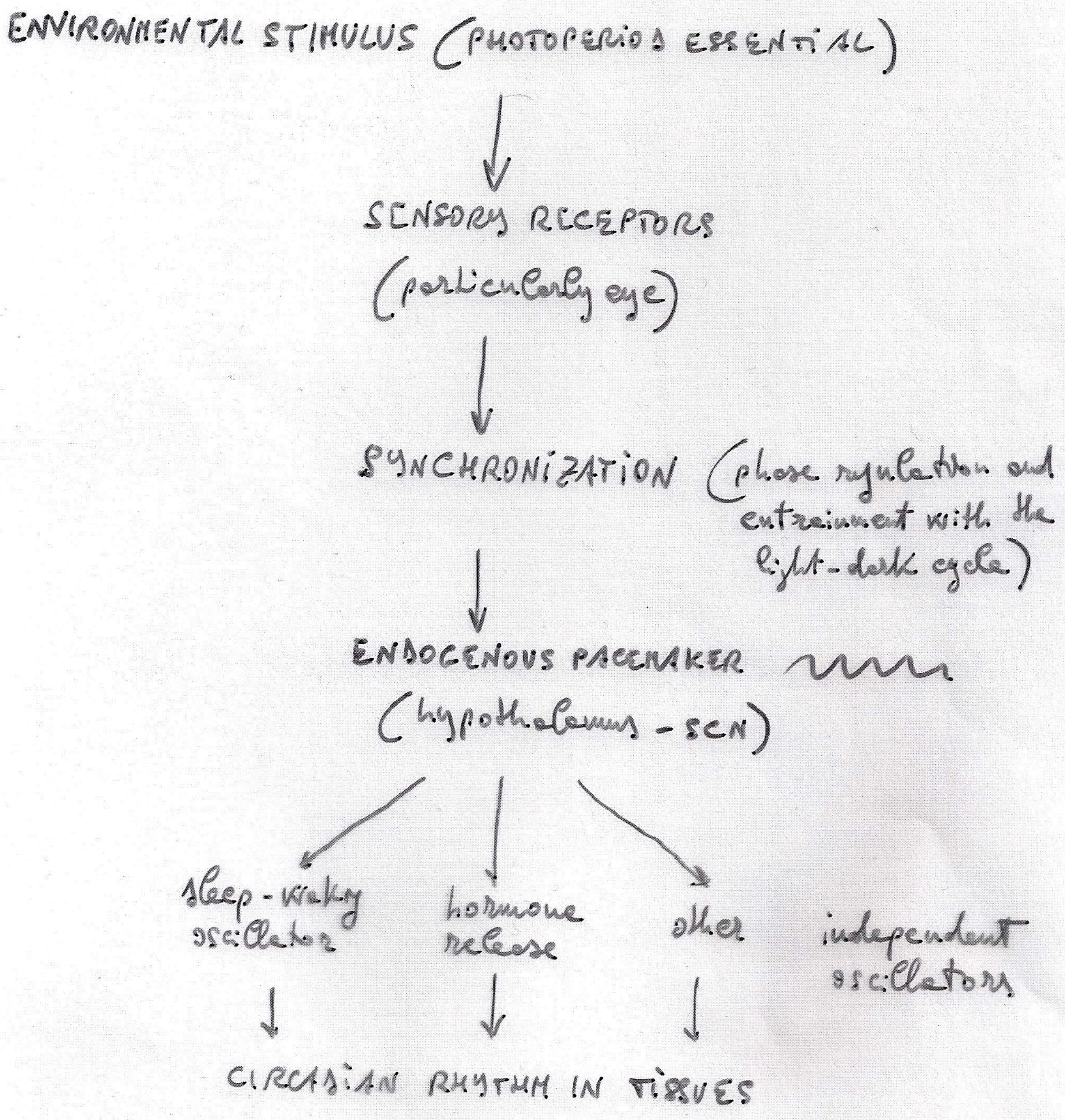


COMPENSATION OF TEMPERATURE

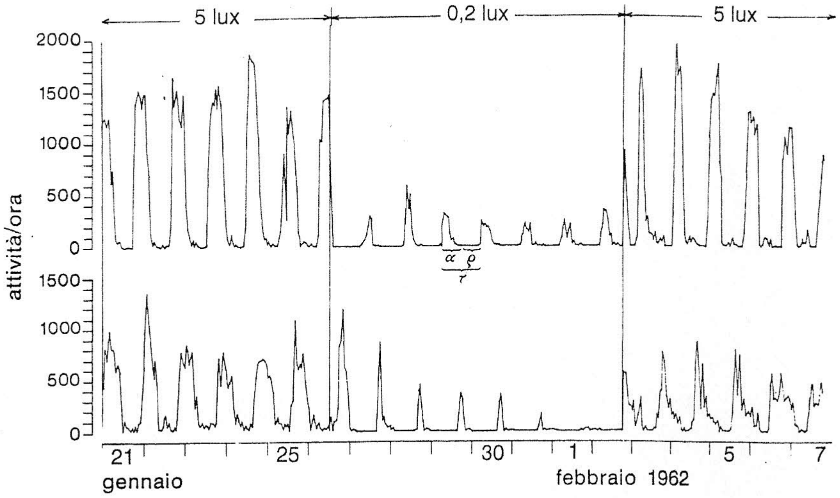


Fig. 17.3. Periodicità delle attività di due fringuelli (*Fringilla coelebs*) tenuti in condizioni costanti a luce continua di 5. 0,2 e 5 lux. La lunghezza del periodo (attività α + riposo ϱ) è indicata con τ Da J. Aschoff e R. Wever (1962 *a*).

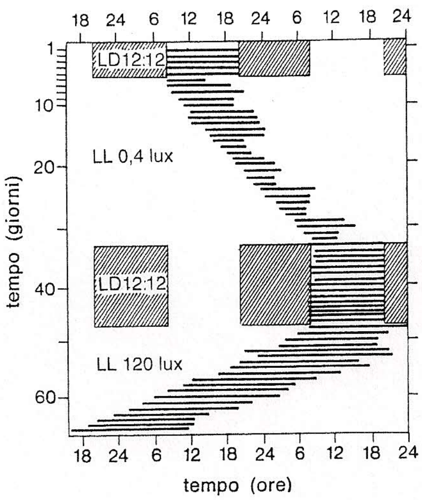
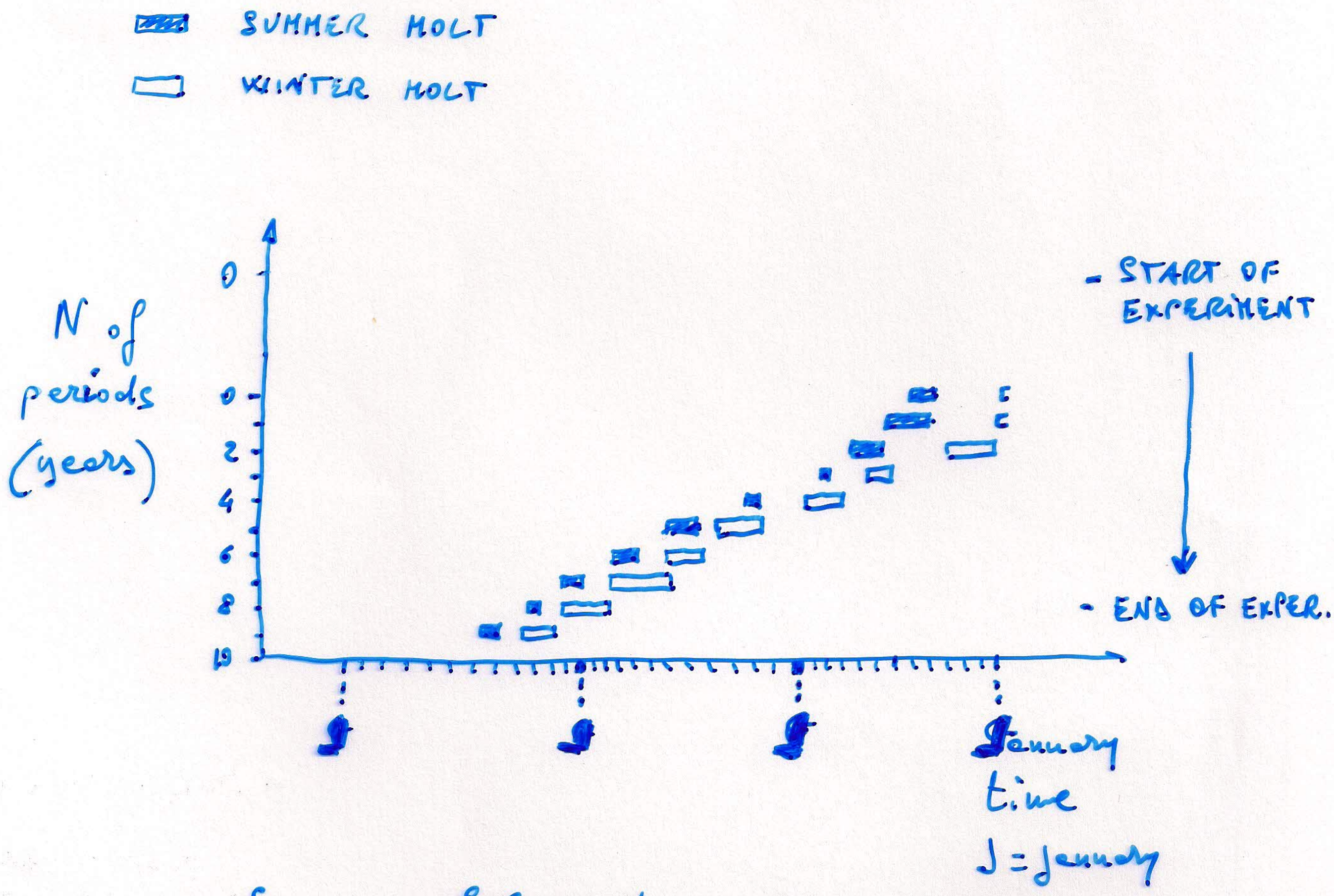


Fig. 17.4. Periodicità dell'attività di un fringuello in condizioni di luce continua (LL) di diverse intensità, e durante un alternarsi periodico di dodici ore di luce e dodici ore di oscurità (LD). Da J. Aschoff (1965).

A CIRCANNUAL RHYTHM IN BIRDS



Species: Sylvia atracapilla
period = 9.4 months

Other similar cycles:

tendency to migrate (disquietude/restlessness)
" to hybernate
sexual maturation dependent on season
etc ...

ZEITGEBER = photoperiod
(less critical than in the case of circadian rhythms)

IDENTIFICATION AND ROLE OF SUPRACHIASMATIC NUCLEUS (SCN)

Two symmetric nuclei in frontal hypothalamus (about 20000 neurons); analogous structures in birds and reptiles.

Identified by:

a) Lesion: total ablation abolishes the cycles of locomotion, liquid assumption, estrogens, etc.

b) Synchrony with environmental rhythms depends on the **optic pathway**, which must not be interrupted before the SCN.

c) Retino-hypothalamic tract: distinct from the visual projections; identified by injecting AA* in eyes and tracing radioactivity up to the SCN.

SUPRACHIASMATIC NUCLEUS
NUCLEO SOPRACHIASMATICO (SCN)

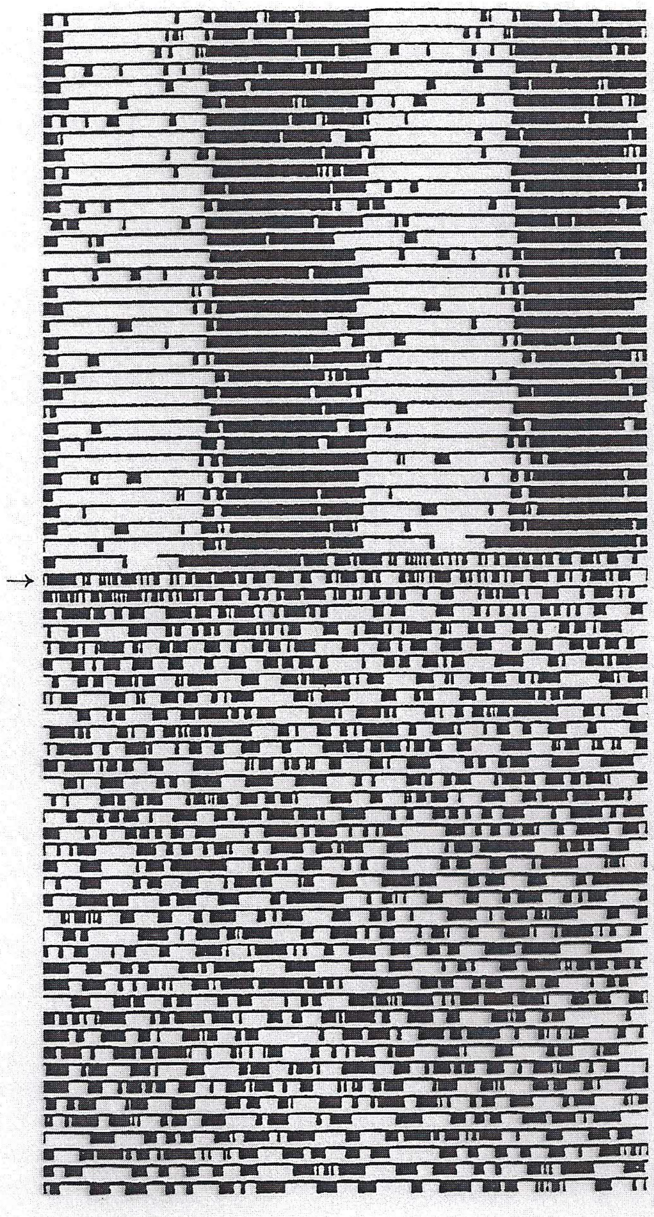


FIGURA 45.3 L'ablazione del SCN provoca una perdita della funzione circadiana. Qui è mostrata una registrazione dell'attività di un ratto albino, mantenuto in un ciclo luce/buio. Dal margine superiore fino alla freccia, l'animale esibisce un ritmo normale di attività, indicato dalle zone scure. La registrazione è ripetuta due volte, cioè ciascuna linea di 48 ore rappresenta 2 giorni consecutivi per facilitare la lettura della registrazione. A livello della freccia è stata effettuata una lesione bilaterale del SCN. Da questo momento, l'attività è distribuita casualmente, indicando che l'organizzazione circadiana riposo/attività è andata persa.

ABLAZIONE
TRAPIANTO

(ABLATION
↓
TRANSPLANTATION)

DOES THE SCN LINK EXTERNAL SIGNALS TO HORMONE RELEASE OSCILLATIONS?

OR IS IT JUST A RELAY?

- **Ablation and transplantation** of fetal SCNs in rodents.

- **Isolation of SCN *in vivo***.

Measuring rhythmic firing activity, higher during the day, even after isolation (fiber cutting). In these conditions, in the nearby hypothalamic nuclei, rhythms increases at night as is not controlled anymore by SCN).

- **Rhythms observed also *in vitro*** (neuronal cultures from SCN).

- **Rhythmic metabolic activity in SCN** but scarcely in the rest of the brain (measured with 2-deoxyglucose*).

IT WOULD STILL BE POSSIBLE THAT THE SCN IS PART OF A COMPLEX CIRCUIT AND INTERACTS WITH SOME OTHER CRITICAL REGION.

A) **Genetic evidence:** normal hamsters have an activity rhythm of about 24 h, with a **range** of 23 to 24.5 h.

Such range was hypothesized to have a genetical basis.

Isolation of hamsters with a cycle of 22 h (probably Tτ)

↓

CROSSES

↓

TT	Tτ	ττ	
24h	22h	20h	of average rhythm

Transplantation of SCN ττ into ablated WT → rhythm of 20 h

" " of SCN TT into ablated ττ → rhythm of 24 h

B) Cells dissociated from the SCN and cultured on a multielectrode matrix.

Cells oscillate with an overall rhythm of 24.35 h.

Single neurons display firing frequencies between 0.3 and 10 Hz.

HOW CAN A SINGLE MASTER BIOLOGICAL CLOCK COORDINATE FUNCTIONS CHARACTERIZED BY DIFFERENT RHYTHMS?

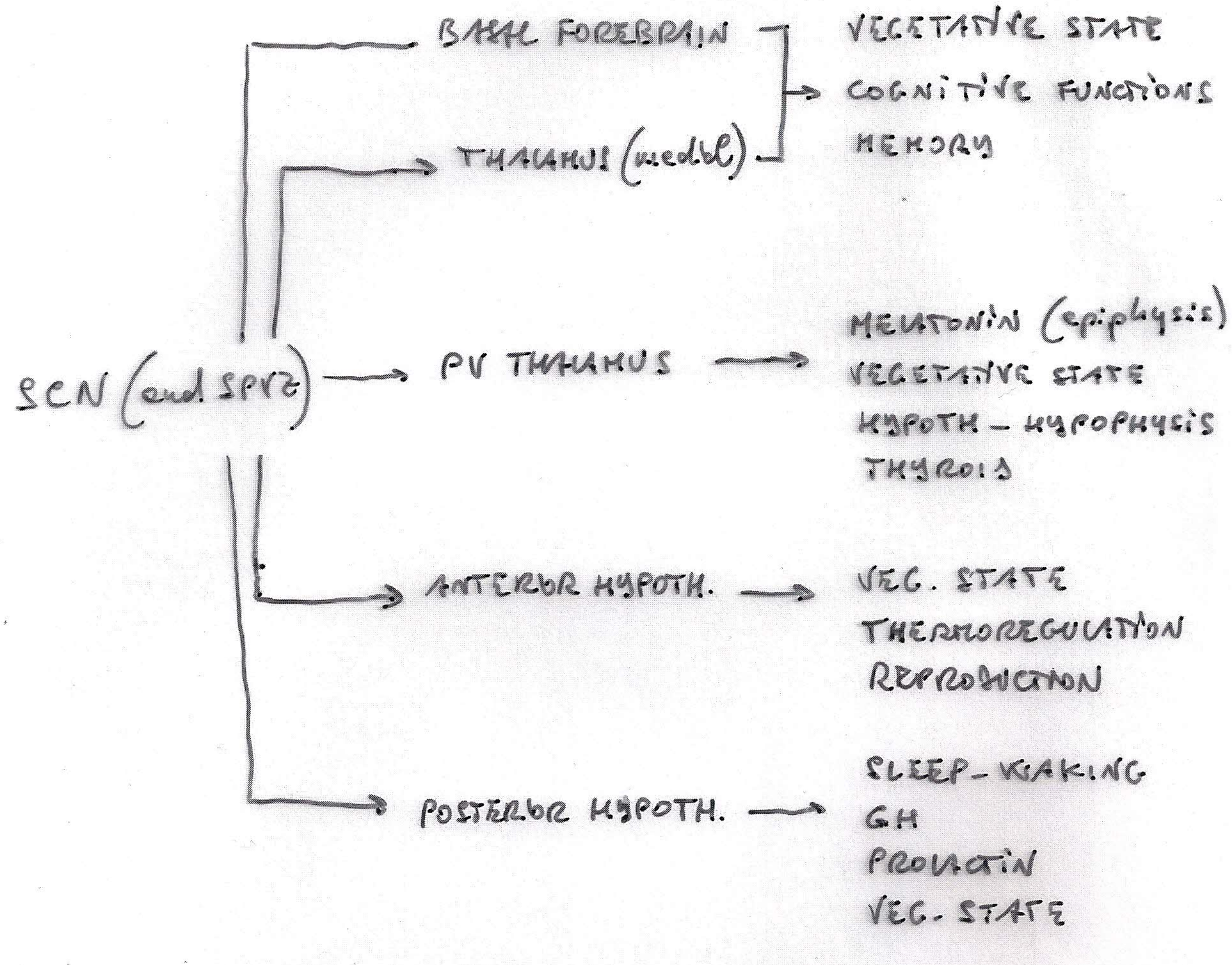
(e.g., sleep-waking and alimentary cycles)

1) **Many projections**, especially to:
   - Hypothalamic nuclei
   - Thalamus
   - Mesencephalon

2) A **transplanted SCN** is not controlled by light, and the function recovery is too quick for efficacious connections to re-form.
   Even transplantation in cerebral ventricles is efficacious.

3) **If a transplant is wrapped in a porous tissue:**
   - fibers cannot traverse the capsule
   - there must be diffusible factors

By considering also the previous experiments with local registrations, one deduces that there is a concourse of humoral factors and neuronal signaling through firing.


SCN (and SPVZ)
BASAL FOREBRAIN
THALAMUS (medial)
VEGETATIVE STATE
COGNITIVE FUNCTIONS
MEMORY
PV THALAMUS
MELATONIN (epiphysis)
VEGETATIVE STATE
HYPOTH – HYPOPHYSIS
THYROID
ANTERIOR HYPOTH.
VEG. STATE
THERMOREGULATION
REPRODUCTION
POSTERIOR HYPOTH.
SLEEP-WAKING
GH
PROLACTIN
VEG. STATE

ARE THERE MULTIPLE CLOCKS?

INSECTS: multiple clocks have been demonstrated.

For instance, circadian rhythms of gene expression in different body parts, even Malpighi tubules.

There are local photoreceptors, connection to the brain is not necessary (experiments of fusion of luciferase with PER).

MAMMALS: independent clocks in different tissues (or in long-term cell cultures).

For instance, the liver can respond to food.

Even with a destroyed SCN, rhythms remain (e.g., to anticipate parturition). In case of necessity, it can be useful to ignore the innate program.

But the SCN regulates the overall rhythm (it is the only region that works in transplant).

PHOTOPERIODIC CONTROL.

It is the most reliable, but not the only circadian regulator.

Very useful to increase activity at the right time, anticipating the events. Also affects blood pressure, attention tasks, mood, etc.

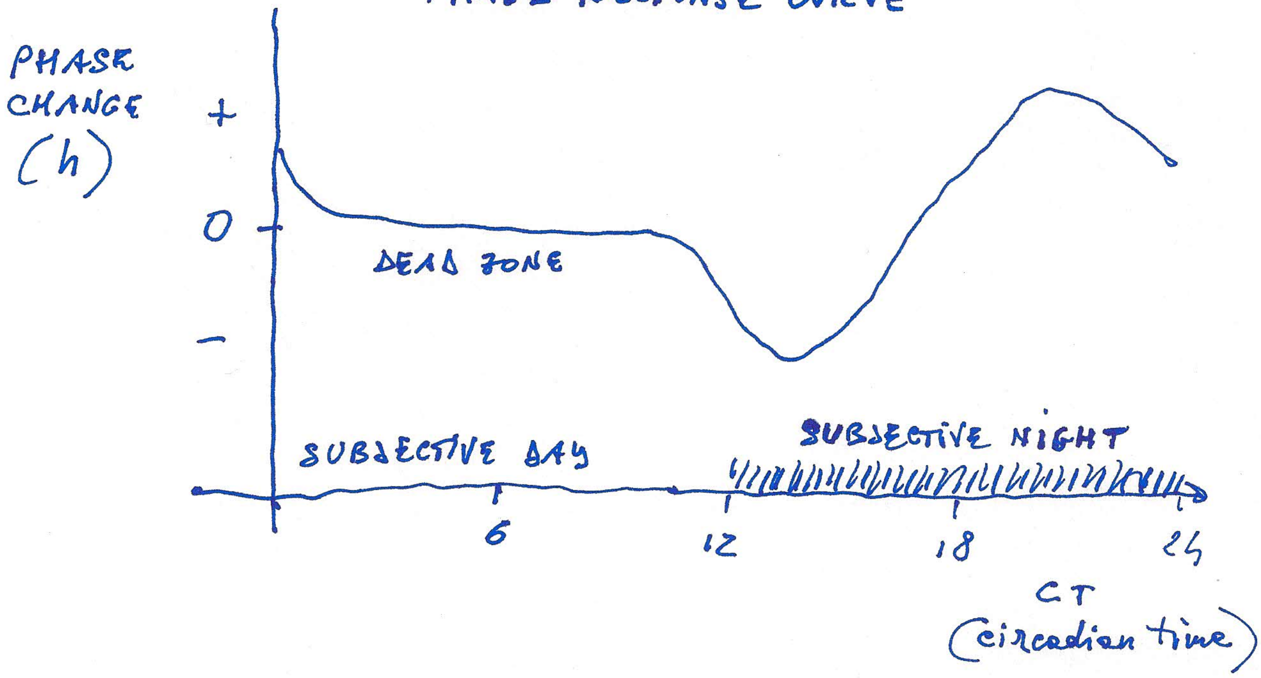
Effect of phasic light (e.g., flash) in constant darkness:

- -little effect on the subjective day
- -delay of rhythm if applied in the 1st half of the subjective night.
- -anticipation of rhythm (the day after) if applied in the 2nd half of the subjective night.

This is the general scheme. The details vary in different species.

EFFECT OF A LIGHT IMPULSE AT DIFFERENT CIRCADIAN TIMES, IN MAMMALS KEPT IN THE DARK

PHASE-RESPONSE CURVE



+ = PHASE ANTICIPATION

− = " DELAY

The extent of the response depends a lot on the intensity and time extension of the STIMULUS.