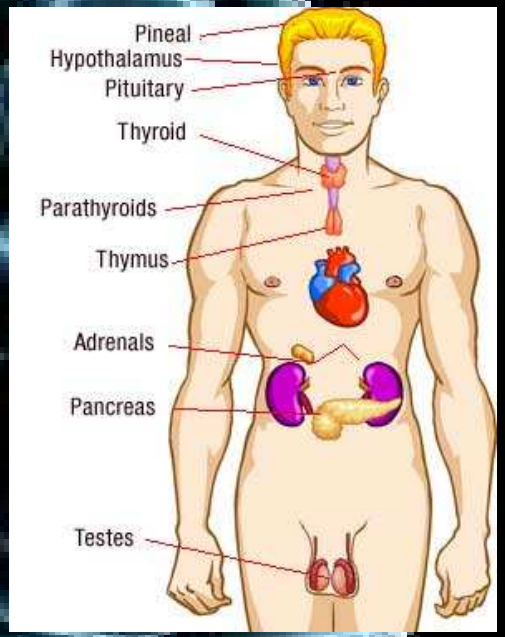
Chronobiologie

et



Hormones…

Chronobiologie ???

Plan du cours :

I. La chronobiologie

II. Les hormones

III. Les relations hormones et rythmes : 4 exemples

IV. Les conséquences : vieillissement & troubles métaboliques

I. La chronobiologie

1. Constats-définitions

2. Les rythmes biologiques

3. La régulation des rythmes

I.1. Constats-définitions

- Récits du sommeil d'une femelle orang-outang :

Ce récit étonnant (extrait des "Expériences hors du temps" de M. Siffre) montre la stabilité du rythme veille-sommeil d'une femelle orang-outang, capturée à Java en 1896 et qui fait le voyage vers Hambourg en bateau à voile :

"Au début la guenon, qui habitait sur le pont, se réveillait au lever du soleil, à 6 heures, et se couchait à 18 heures environ. Au cours de ce voyage vers l'ouest, elle gardait une durée de sommeil de 12 heures, avec un décalage de phase sur le temps local. Si bien qu'au Cap de Bonne-Espérance, elle se réveillait à 2 heures du matin et se couchait à 14 heures l'après-midi...

I.1. Constats-définitions

- Récits du sommeil d'une femelle orang-outang :

"La guenon continuait à vivre, à se lever et à se coucher comme si elle était encore à l'heure solaire de Java. Malheureusement, ces précieuses observations ont été interrompues par la mort prématurée de l'orang-outang, qui avait vidé une bouteille de rhum !"

De Java au Cap de Bonne Espérance, il y a six fuseaux horaires. En 3 ou 4 semaines de traversée, l'organisme de la guenon avait compensé 2 des 6 heures de décalage horaire. Elle vivait en fonction de son horloge interne, résistante aux rythmes du soleil, encore réglée sur l'heure de l'île de Java.

I.1. Constats-définitions

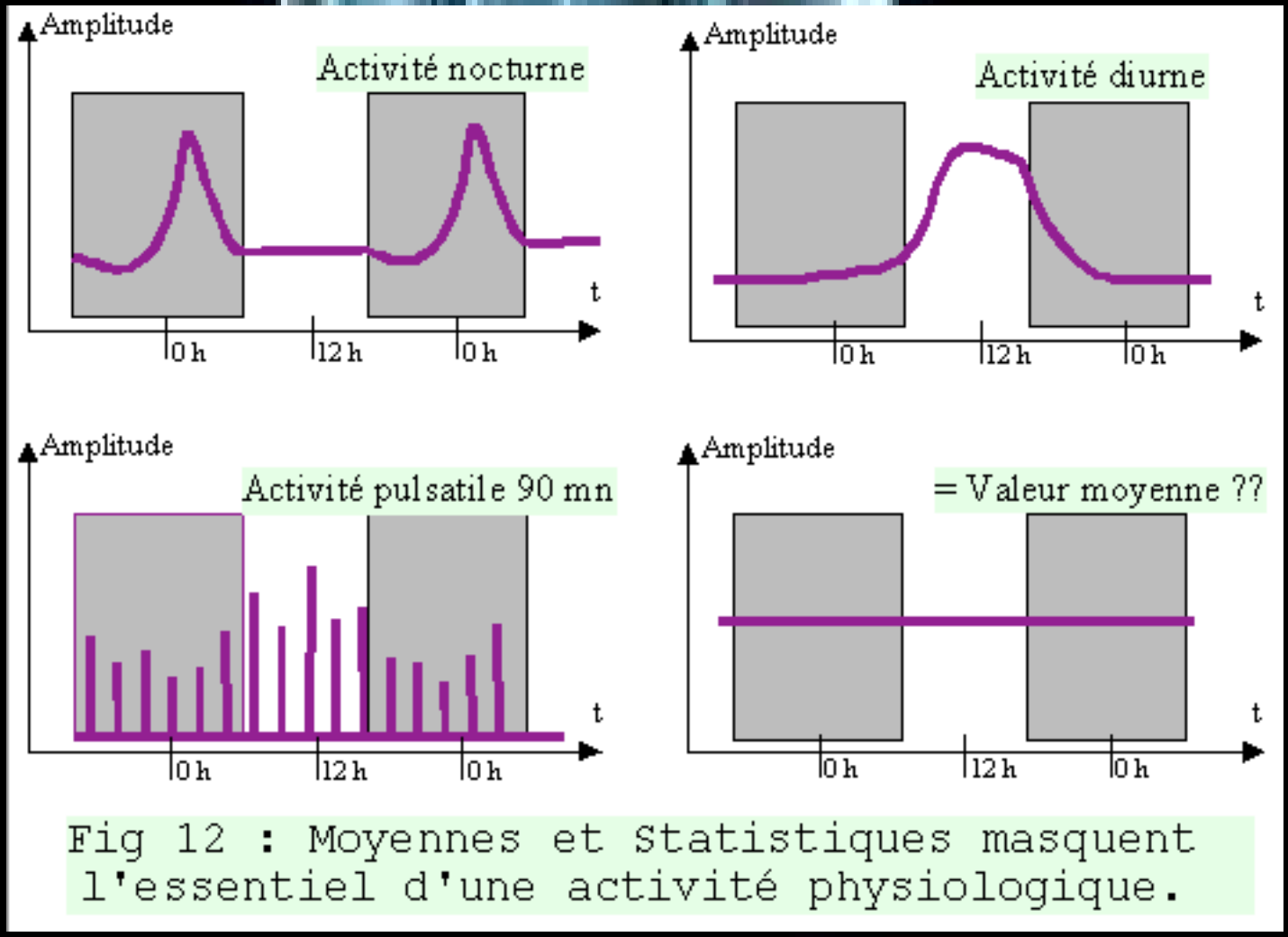


Fig 12 : Moyennes et Statistiques masquent l'essentiel d'une activité physiologique.

I.1. Constats-définitions

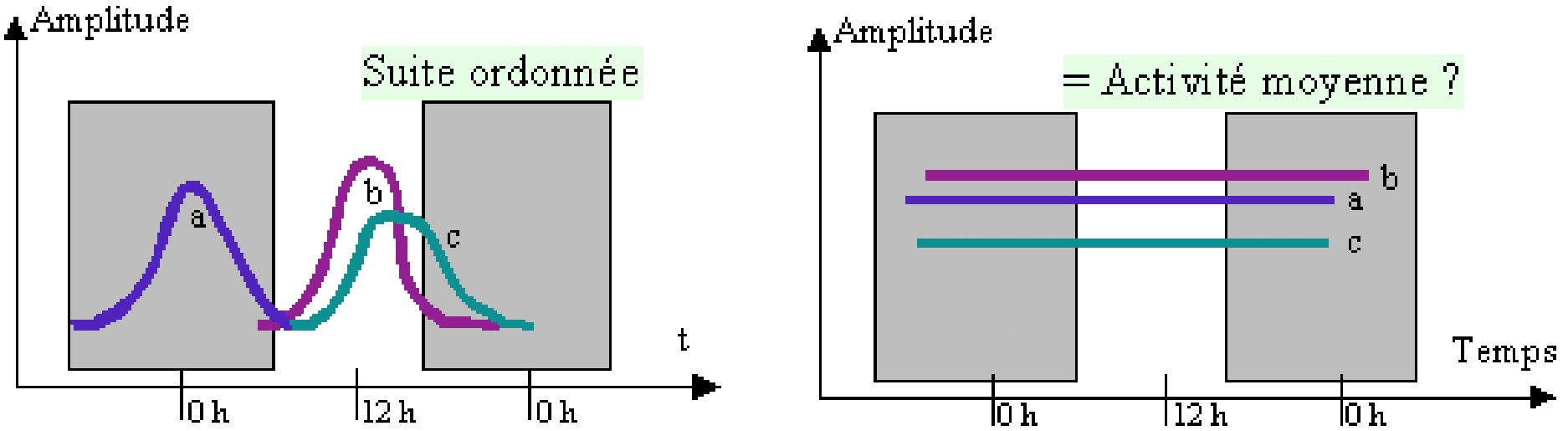
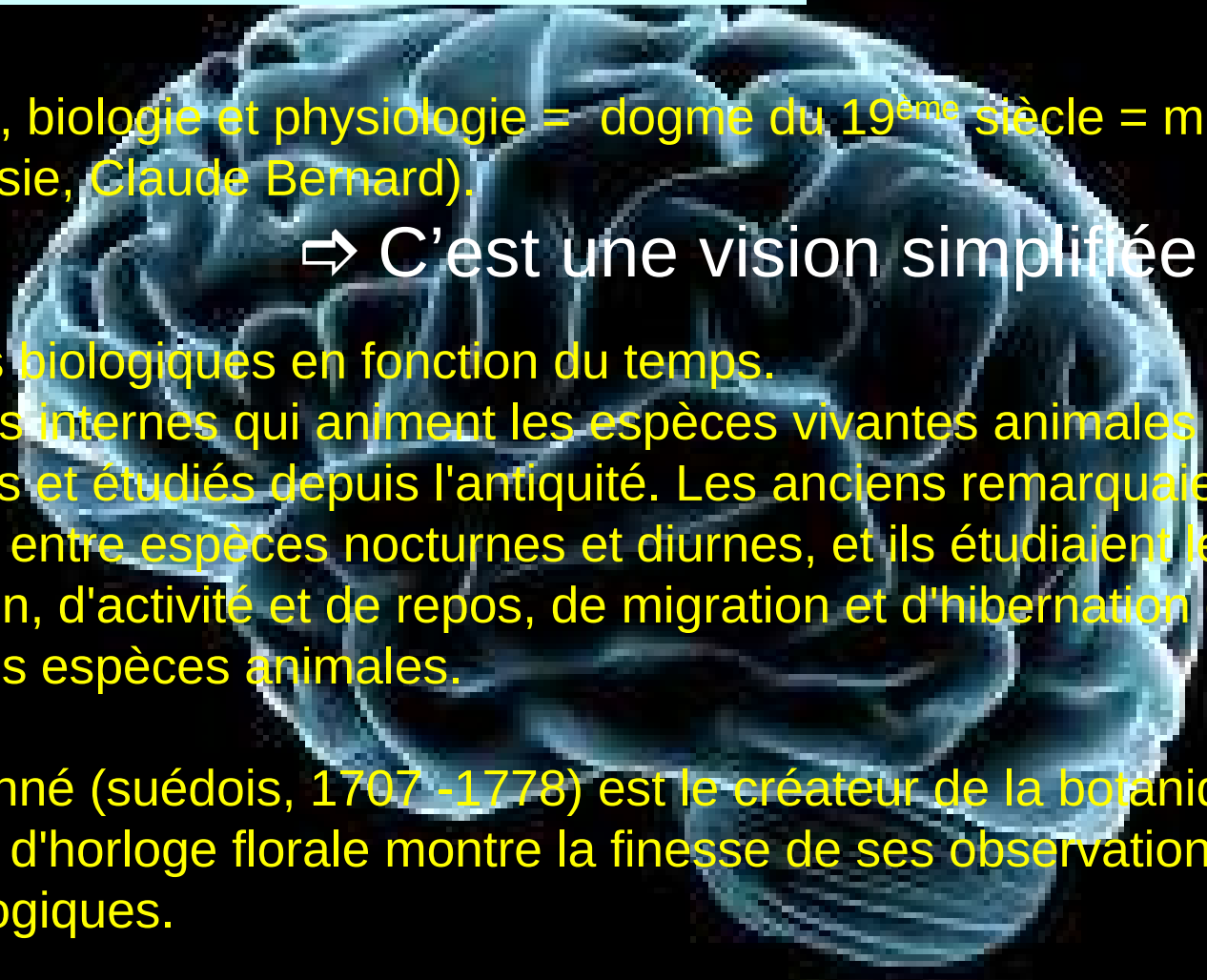


Fig 12 : L'ordre chronologique, aspect essentiel des activités physiologiques.

I.1. Constats-définitions



- Médecine, biologie et physiologie = dogme du 19ème siècle = milieu intérieur (Homéostasie, Claude Bernard).

⇨ C'est une vision simplifiée

- Variations biologiques en fonction du temps.

Les rythmes internes qui animent les espèces vivantes animales et végétales sont connus et étudiés depuis l'antiquité. Les anciens remarquaient les différences entre espèces nocturnes et diurnes, et ils étudiaient les cycles de reproduction, d'activité et de repos, de migration et d'hibernation de nombreuses espèces animales.

Carl von Linné (suédois, 1707 -1778) est le créateur de la botanique moderne et son idée d'horloge florale montre la finesse de ses observations chronobiologiques.

I.1. Constats-définitions

☞ Chronos = Le temps

→ Chronobiologie = Études des rythmes biologiques

- 1ers laboratoires : dans les années 1920.
- 1ère société de chronobiologie : 1937 en Suède.
- Expériences « libre cours »

I.1. Constats-définitions

☞ Expériences hors du temps de Michel Siffre

- L'Expérience du 18 juillet au 14 septembre 1962

  - Siffre à 23 ans et reste dans une grotte par 130 m de fond pendant 2 mois avec des conditions matérielles et sanitaires terribles.

  - Bilan = évaluation de 25 jours de retard sur 58 au total.

D'après Crabbé, 2000, http://www.membres.lycos.fr/jmcmed/rythmes/

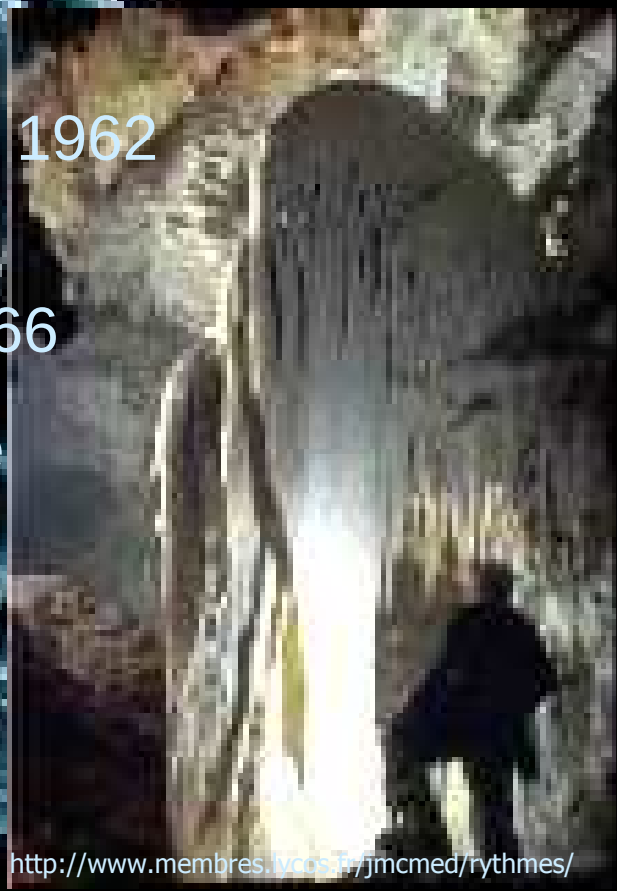
I.1. Constats-définitions

☞ Expériences hors du temps de Michel Siffre

- L'Expérience du 18 juillet au 14 septembre 1962

- L'Expérience du 1 juin au 30 novembre 1966

  - Expérience de 6 mois avec étude de différents paramètres biologiques (EEG, ECG, Performances psychomotrices, T°, Pouls, Notion subjective du temps).



D'après Crabbé, 2000, http://www.membres.lycos.fr/jmcmed/rythmes/

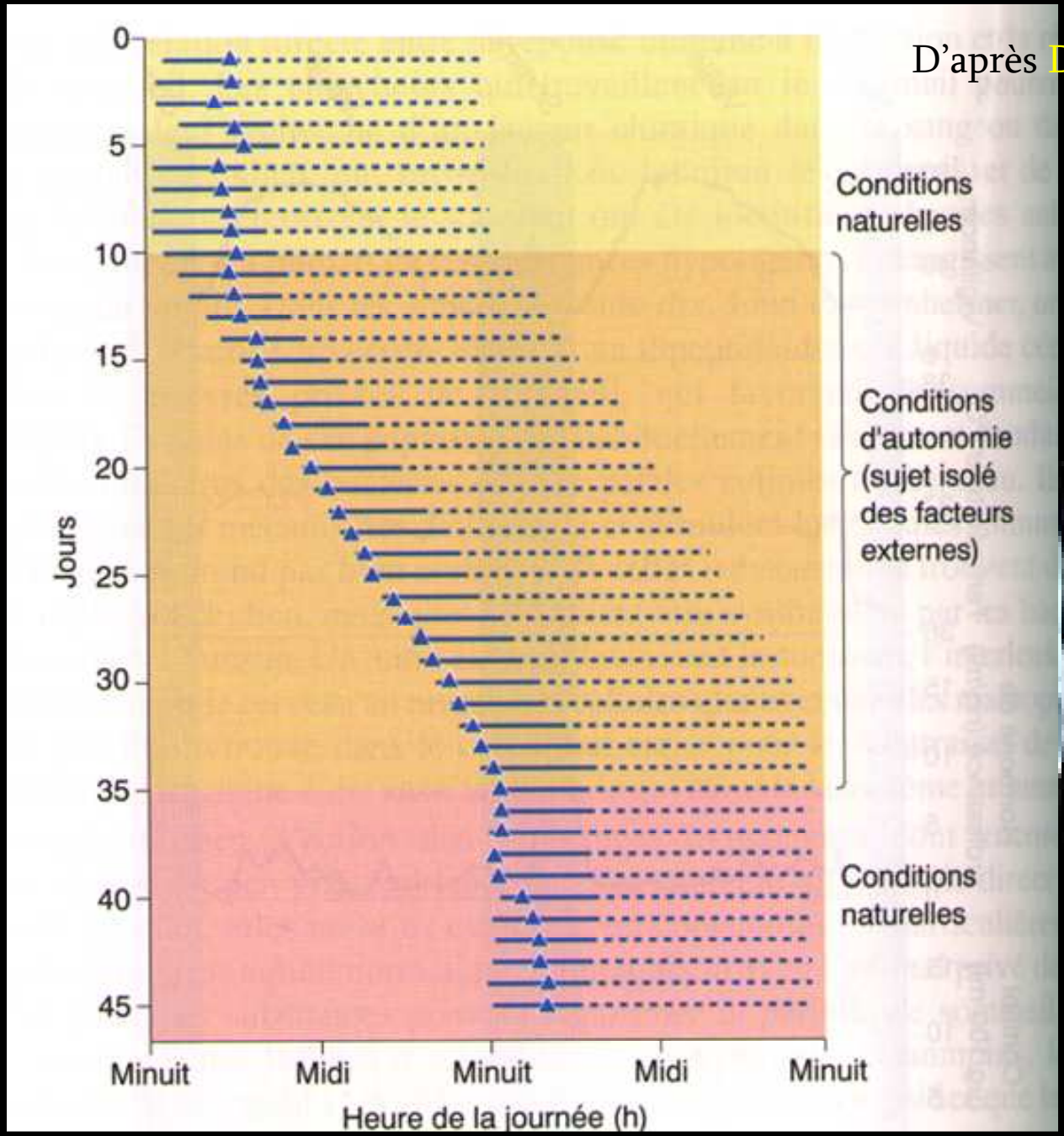
I.1. Constats-définitions

☞ Expériences hors du temps de Michel Siffre

- L'Expérience du 18 juillet au 14 septembre 1962
- L'Expérience du 1 juin au 30 novembre 1966
- L'Expérience de 205 jours en 1972 au Texas

D'après Crabbé, 2000, http://www.membres.lycos.fr/jmcmed/rythmes/

D'après Dément, 1976



I.1. Constats-définitions

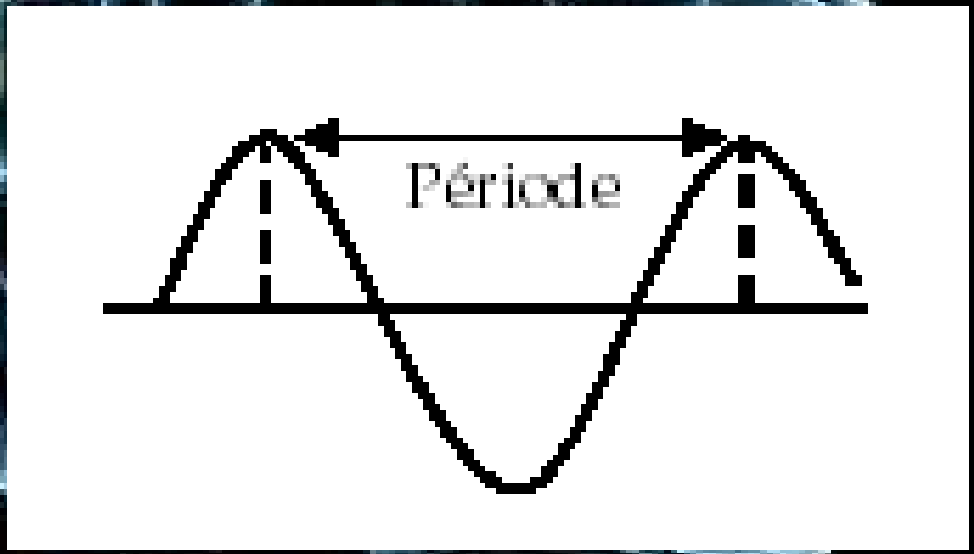
☞ Définition :

• Rythme biologique : Variation régulière et involontaire d'une fonction physiologique, d'un métabolisme d'une activité cellulaire ou tissulaire ou d'une fonction neurophysiologique.

I.2. Les rythmes biologiques

- Caractéristiques : 4 paramètres

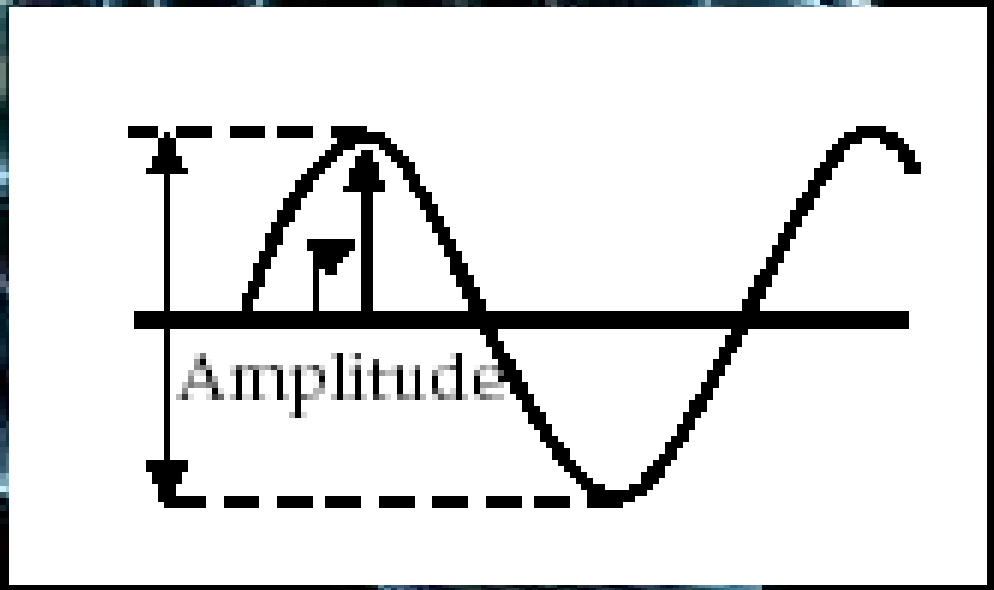
  - Période



I.2. Les rythmes biologiques

☞ Caractéristiques : 4 paramètres

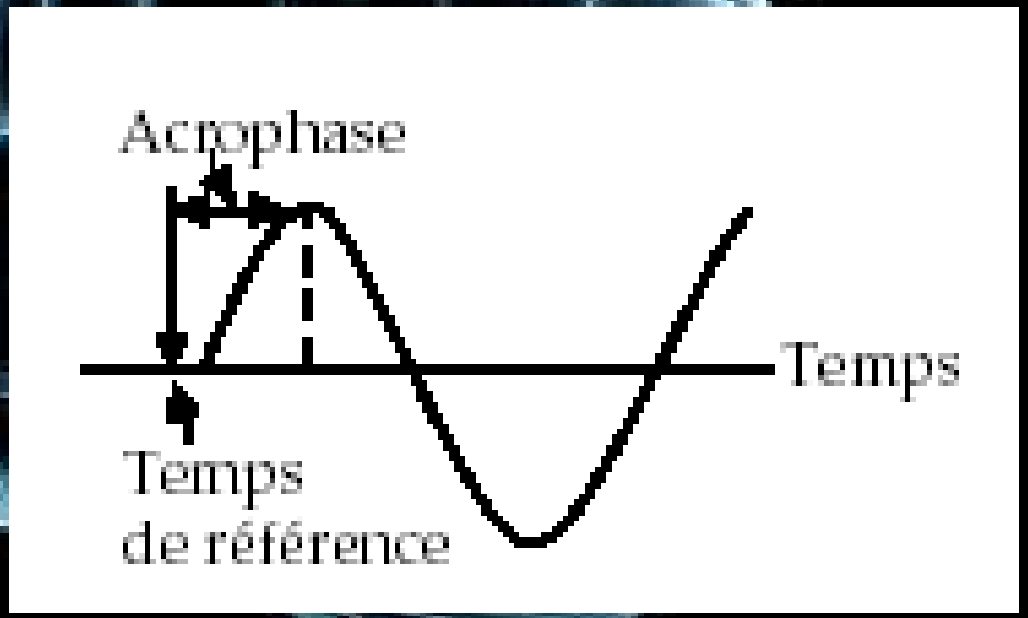
- Amplitude



I.2. Les rythmes biologiques

☞ Caractéristiques : 4 paramètres

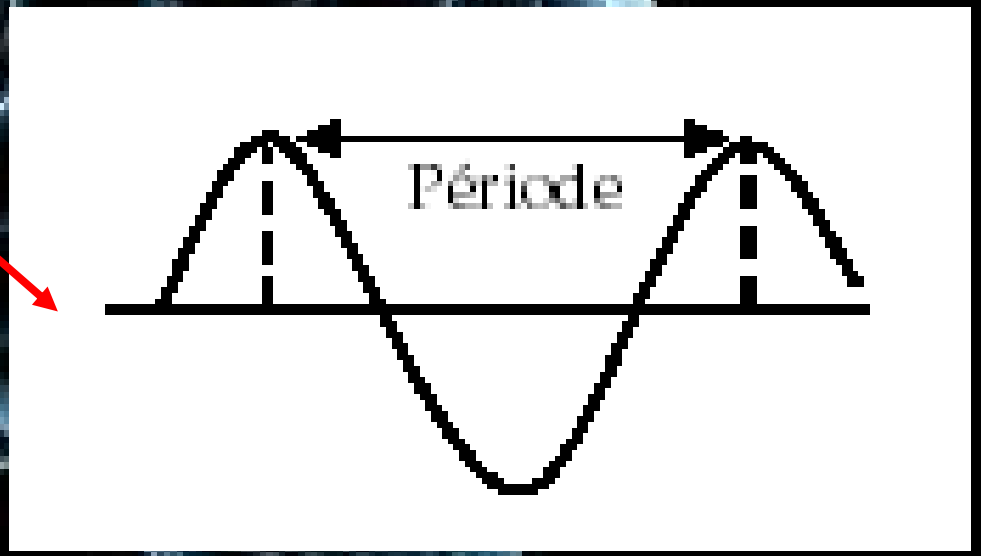
- Acrophase (Bathyphase)



I.2. Les rythmes biologiques

☞ Caractéristiques : 4 paramètres

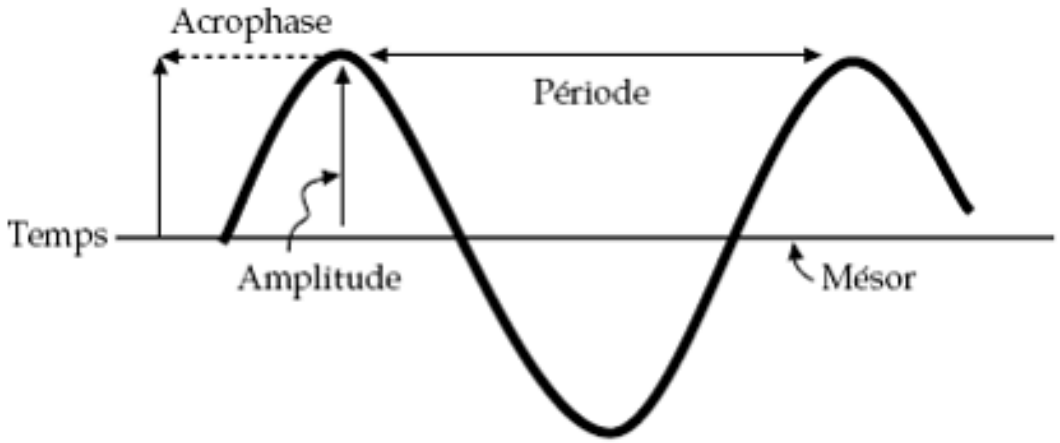
- Niveau Moyen



I.2. Les rythmes biologiques

☞ Caractéristiques : 4 paramètres

- Période
- Amplitude
- Acrophase (Bathyphase)
- Niveau Moyen



Paramètres caractéristiques d'une fonction rythmique (d'après Touitou et Haus, 1994)

I.2. Les rythmes biologiques

Figure 1 Child on a swing, a metaphor of the oscillations and required internal and external drives.

I.2. Les rythmes biologiques

☞ Les différents rythmes biologiques :
selon le niveau biologique

- Cellules : Rythme de division des cellules hépatiques

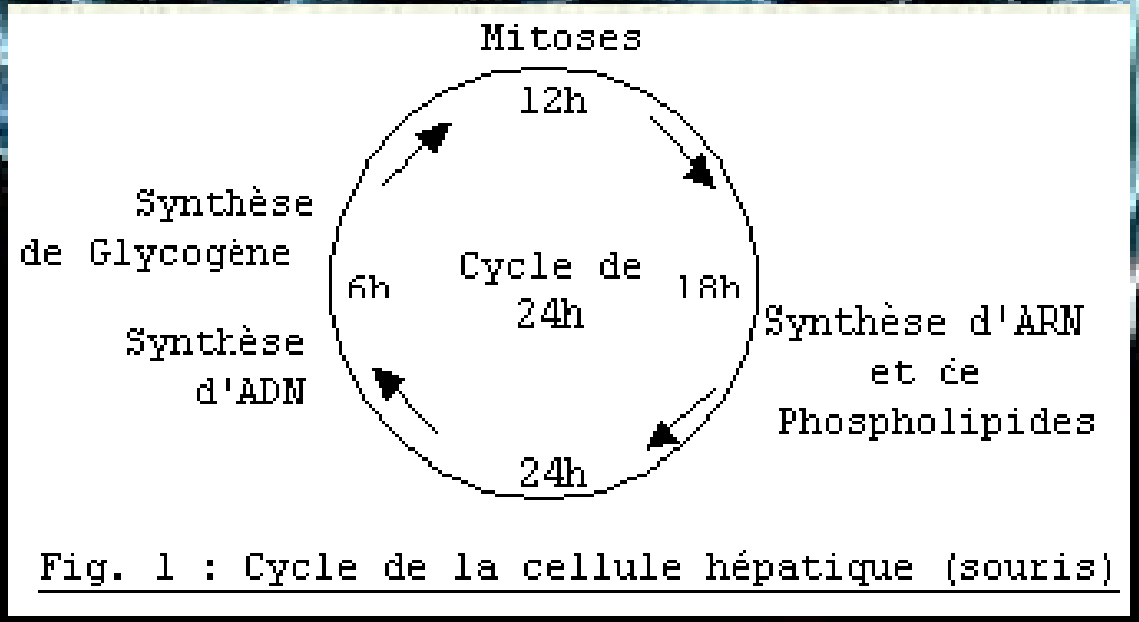


Fig. 1 : Cycle de la cellule hépatique (souris)

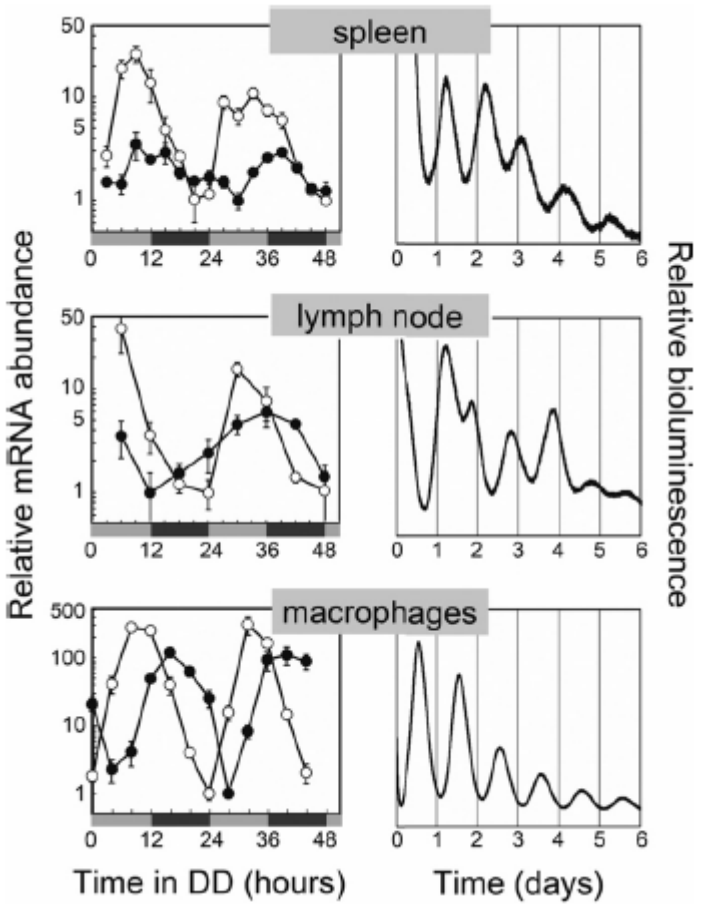


Fig. 1. Fully competent circadian clocks in tissues and cells of the immune system. (*Left*) Circadian clock genes *Per2* (filled circles) and *Rev-Erbα* (open circles) are rhythmically expressed in murine spleen cells, lymph nodes, and peritoneal macrophages. Tissues and cells were harvested at regular intervals over the course of the first 2 days after transfer of the mice from a LD cycle to DD. Gray and black bars refer to the previous light and dark periods, respectively. CT 0 corresponds to the time in DD when the light would have turned on in the prior LD cycle. Transcript levels were analyzed by using quantitative RT-PCR. Displayed are the means ± SEM. (spleen: $n = 3–6$; lymph nodes: $n = 3–4$ except for $n = 2$ at CT 6/day 2; macrophages: $n = 3–4$) normalized to nonoscillating *Gapdh* expression levels. (*Right*) Autonomous clock gene oscillation in in vitro conditions. A small piece of spleen, superficial inguinal lymph nodes as well as peritoneal macrophages from PER2::LUC knockin mice (20) were cultured in medium containing luciferin. Circadian bioluminescence was continuously recorded for ≈1 week by using photomultiplier tubes. Representative time series for at least three independent experiments are shown.

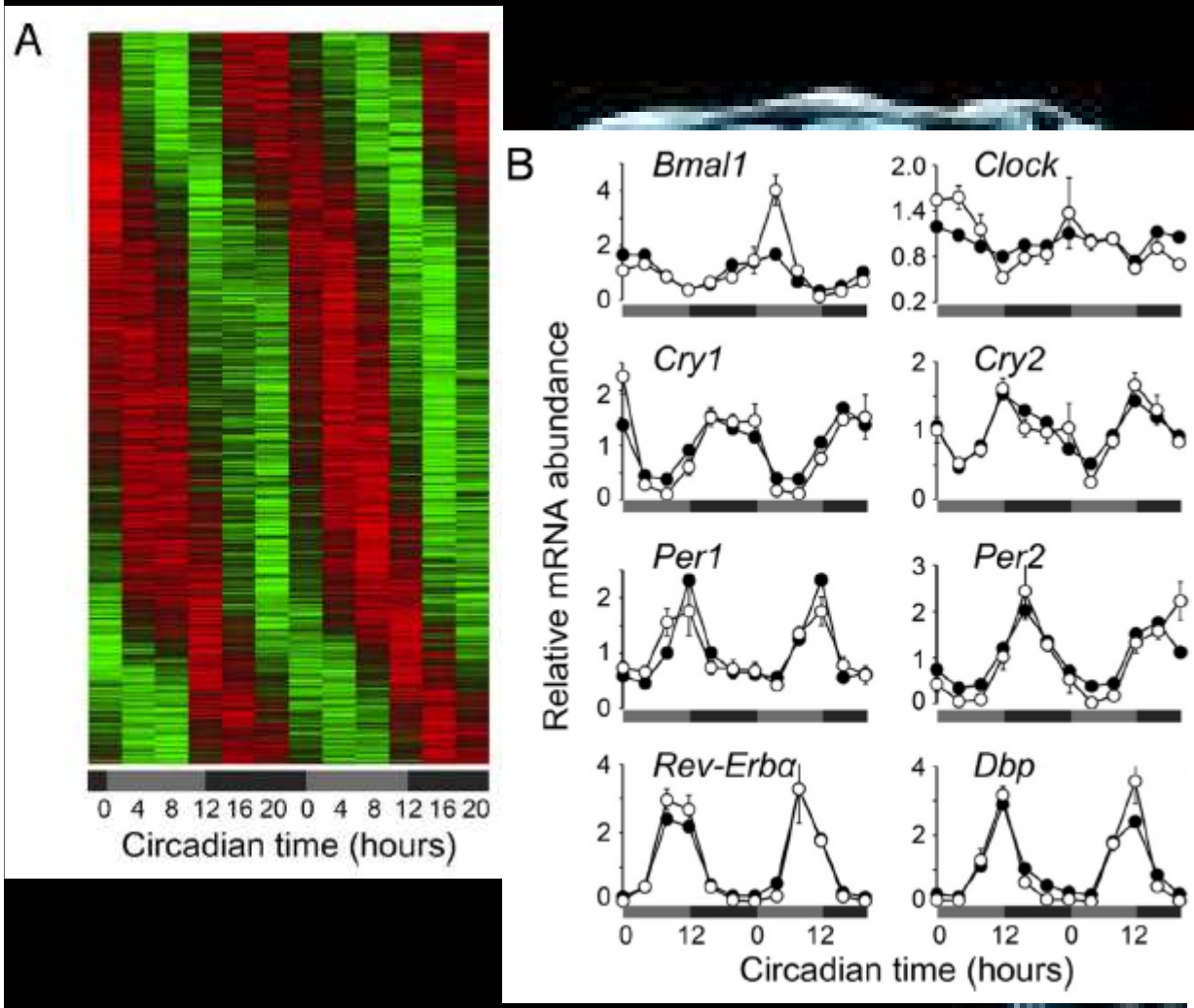
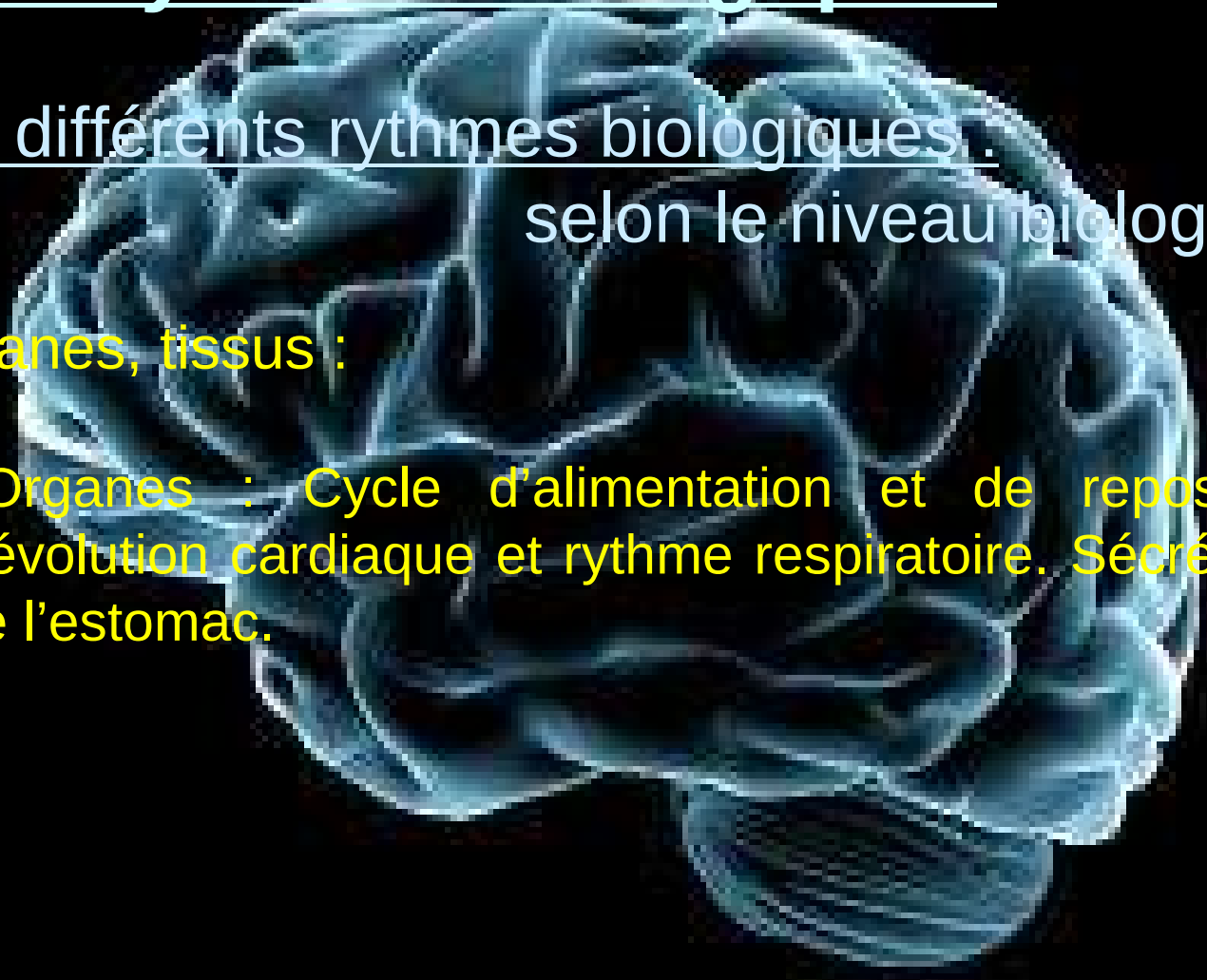


Fig. 4. Eight percent of all transcripts in macrophages are expressed with a circadian rhythm. (*A*) Phase-sorted heat map of genes transcribed in a circadian manner in peritoneal macrophages. Cells harvested via peritoneal lavage from four C57BL/6 mice every 4 h were magnetically purified for CD11b surface expression (see Fig. S5). Three individual RNA samples of each time were pooled and subjected to global gene transcription measurement by using Affymetrix chips. The analysis on circadian rhythmicity was done with CircWaveBatch. Lfdrs were determined and cut-off value was arbitrarily set to 0.1 as a measure for rhythmic versus nonrhythmic transcripts (see Fig. S7). Genes expressed in a circadian manner were plotted phase-sorted in a heat-map style (colors indicate min–max normalized relative expression: green, minimum expression; red, maximum expression). (*B*) Canonical clock gene expression in peritoneal macrophages. Individual datasets from *A* were plotted (filled circles) together with data obtained by a quantitative RT-PCR assay of the same samples (open circles, means ± SEM, $n = 4$, except for times CT 24 and 28, $n = 3$). Statistical analysis for qPCR data and chip data were performed with CircWave and CircWaveBatch, respectively (microarray: $P \leq 0.0001$: *Bmal1*, *Cry1*, *Per2*; $P \leq 0.01$: *Rev-Erbα*, *Dbp*, *Cry2*; $P \leq 0.05$: *Per1* and *Clock*; qPCR: $P \leq 0.0001$: *Bmal1*, *Cry1*, *Per1/2*, *Clock*, *Rev-Erbα*, *Dbp*; $P \leq 0.001$: *Cry2*).

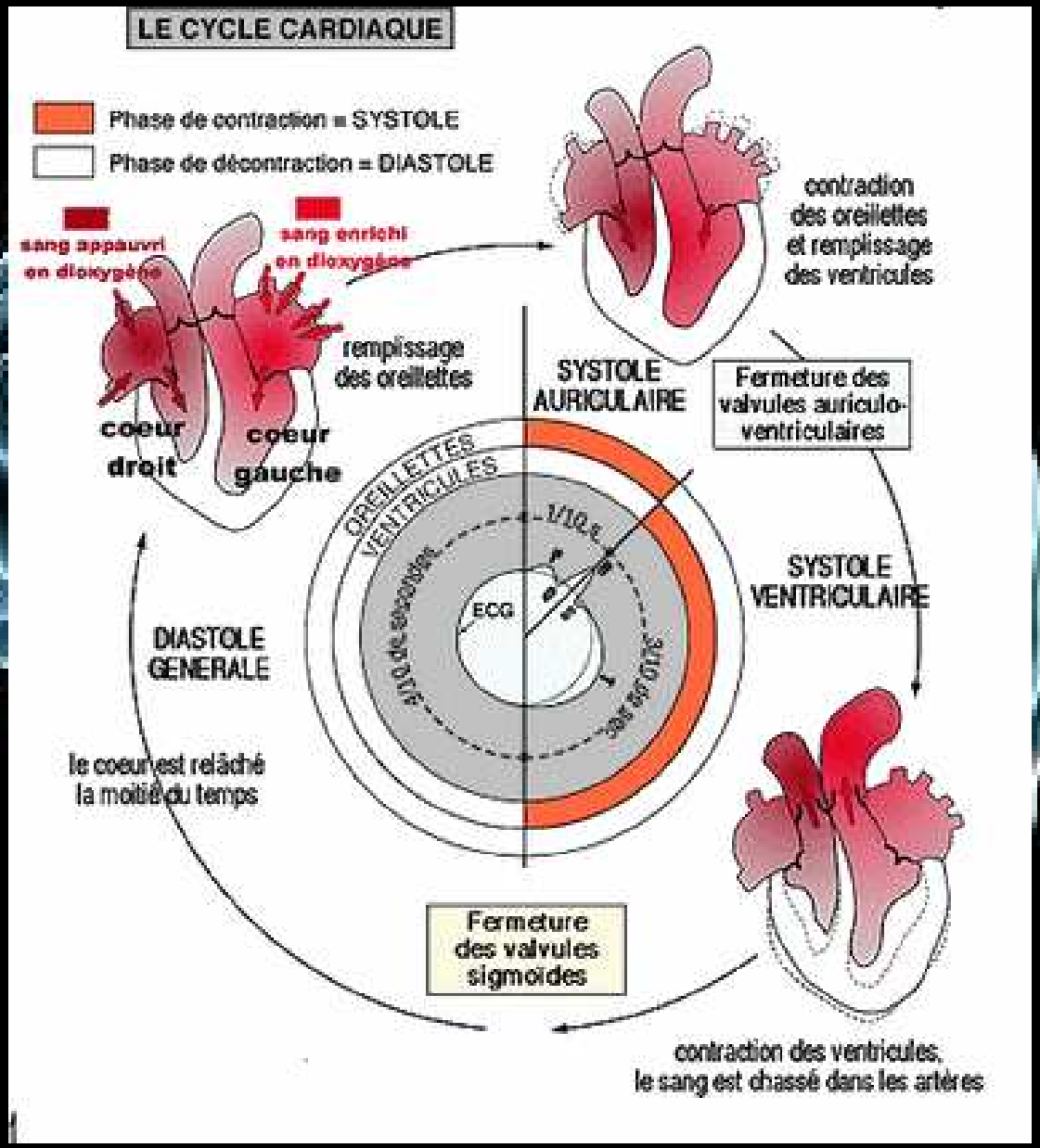
I.2. Les rythmes biologiques



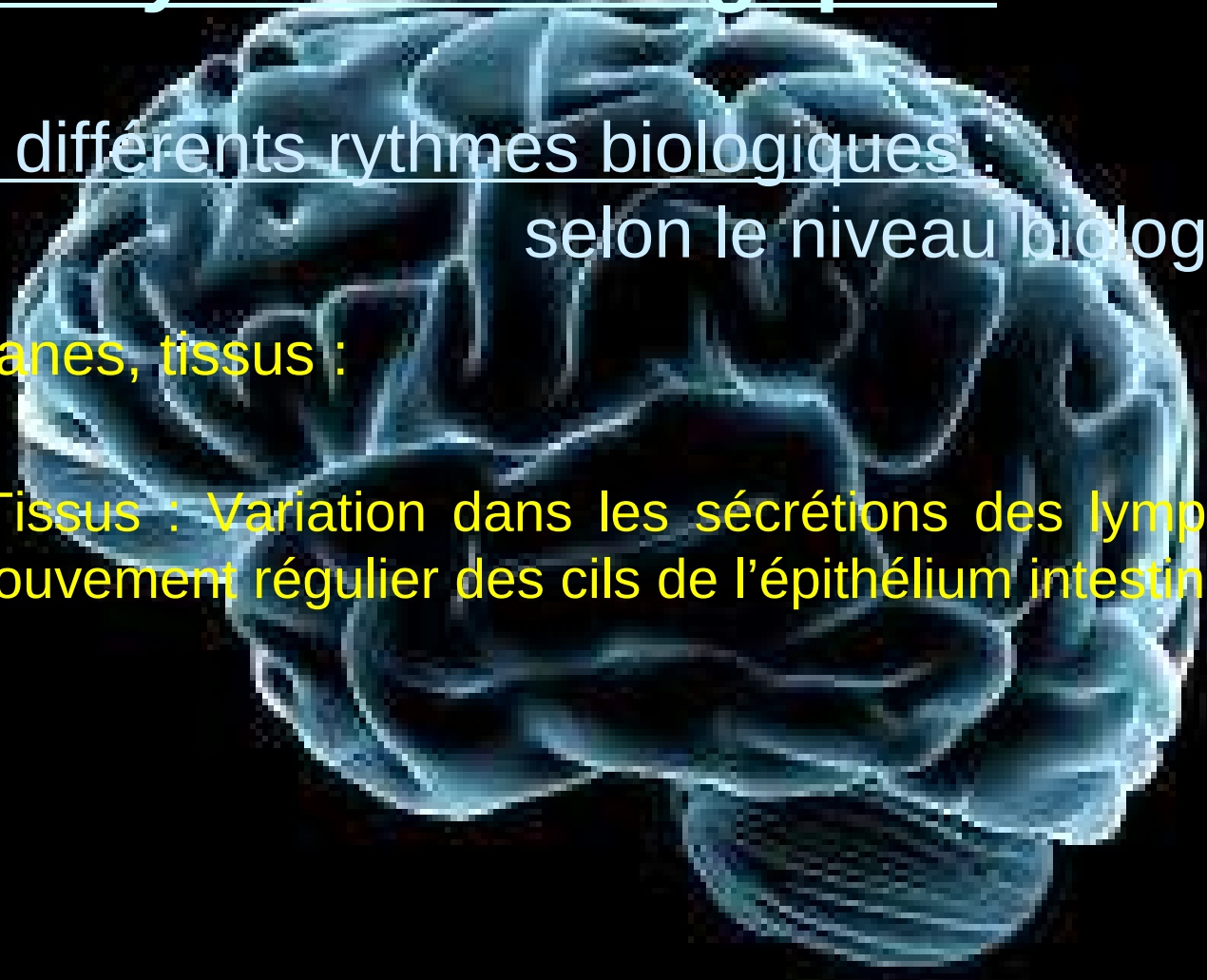
☞ Les différents rythmes biologiques :
selon le niveau biologique

- Organes, tissus :

- Organes : Cycle d'alimentation et de repos digestif. Révolution cardiaque et rythme respiratoire. Sécrétion acide de l'estomac.


LE CYCLE CARDIAQUE
Phase de contraction = SYSTOLE
Phase de décontraction = DIASTOLE
sang appauvri en dioxygène
sang enrichi en dioxygène
contraction des oreillettes et remplissage des ventricules
remplissage des oreillettes
SYSTOLE AURICULAIRE
Fermeture des valvules auriculo-ventriculaires
coeur droit
coeur gauche
OREILLETTES
VENTRICULES
1/10 s
0,4 s de repos
0,3 s de sys
ECG
SYSTOLE VENTRICULAIRE
DIASTOLE GENERALE
le coeur est relâché la moitié du temps
Fermeture des valvules sigmoïdes
contraction des ventricules, le sang est chassé dans les artères

I.2. Les rythmes biologiques



☞ Les différents rythmes biologiques :
selon le niveau biologique

- Organes, tissus :

  - Tissus : Variation dans les sécrétions des lymphocytes. Mouvement régulier des cils de l'épithélium intestinale.

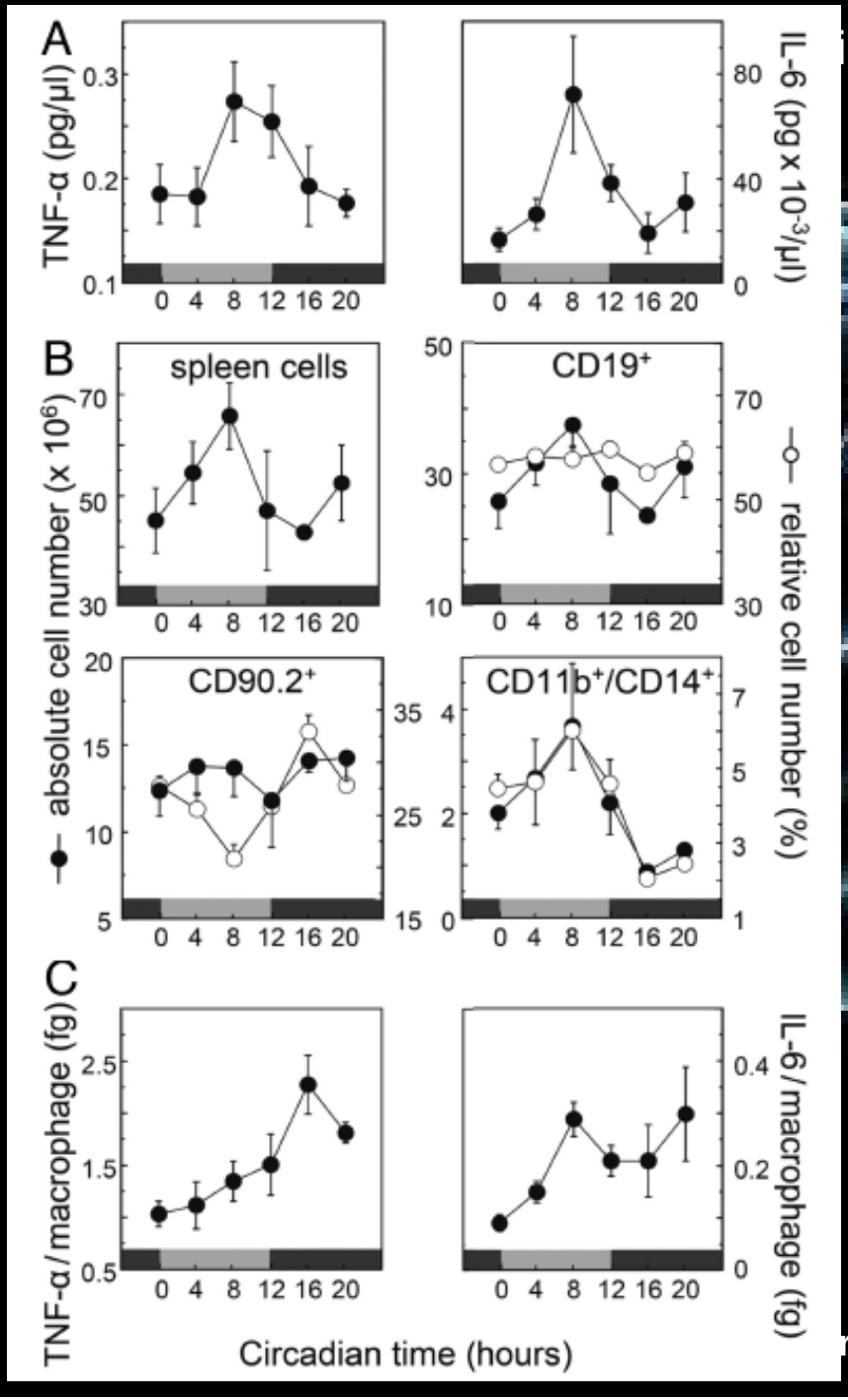
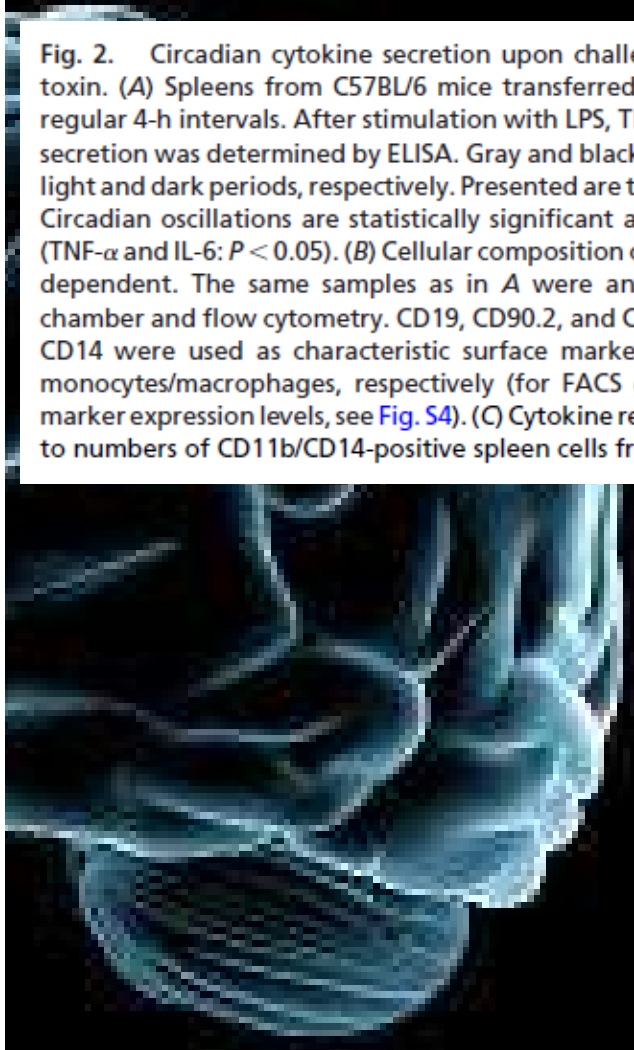
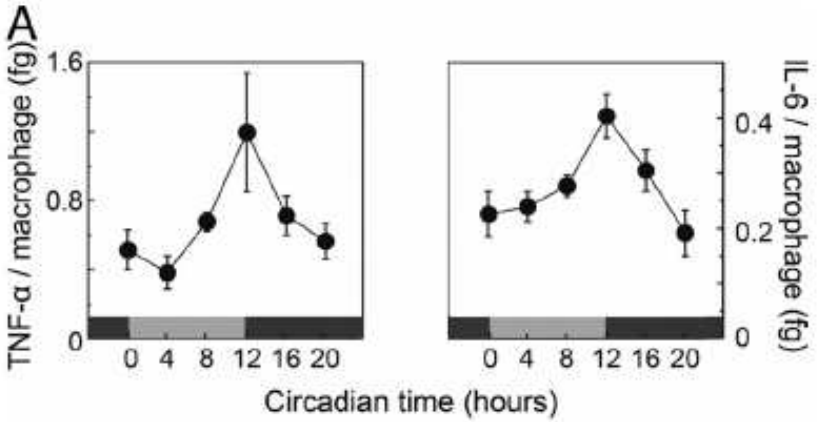


Fig. 2. Circadian cytokine secretion upon challenge with bacterial endotoxin. (*A*) Spleens from C57BL/6 mice transferred in DD were harvested at regular 4-h intervals. After stimulation with LPS, TNF-α (*Left*) and IL-6 (*Right*) secretion was determined by ELISA. Gray and black bars refer to the previous light and dark periods, respectively. Presented are the means ± SEM ($n = 4–5$). Circadian oscillations are statistically significant as analyzed with CircWave (TNF-α and IL-6: $P < 0.05$). (*B*) Cellular composition of the spleen is time-of-day dependent. The same samples as in *A* were analyzed with cell-counting chamber and flow cytometry. CD19, CD90.2, and CD11b in combination with CD14 were used as characteristic surface markers of B cells, T cells, and monocytes/macrophages, respectively (for FACS gate settings and surface marker expression levels, see Fig. S4). (*C*) Cytokine response as in *A* with respect to numbers of CD11b/CD14-positive spleen cells from *B* lower right.





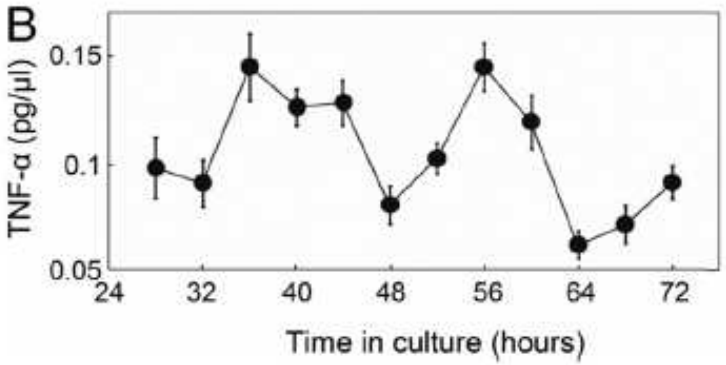


Fig. 3. A macrophage intrinsic clockwork regulates circadian TNF-α and IL-6 secretion upon LPS stimulation. (*A*) Circadian modulation of LPS-induced cytokine response is independent of systemic cortisol. Spleens from adrenalectomized C57BL/6 mice were harvested and analyzed as described in Fig. 2. TNF-α and IL-6 cytokine secretion per macrophage was determined via ELISA by taking the absolute number of monocytes/macrophages of the spleen into account (see also Figs. S2 and S4*A* and *Materials and Methods*). Circadian oscillations are statistically significant as analyzed with CircWave ($P < 0.001$ and $P < 0.05$ for TNF-α and IL-6, respectively). (*B*) TNF-α response upon LPS stimulation is regulated by a cell-intrinsic, local clock. Spleen cells from 20 C57BL/6 mice were harvested, pooled, and plated for tissue culture. Individual wells were stimulated for 4 h with LPS at indicated times, and supernatants were collected thereafter. TNF-α levels in supernatant were determined by ELISA and tested for statistical significance with CircWave (presented are means ± SEM, $n = 15$, $P < 0.0001$).

I.2. Les rythmes biologiques

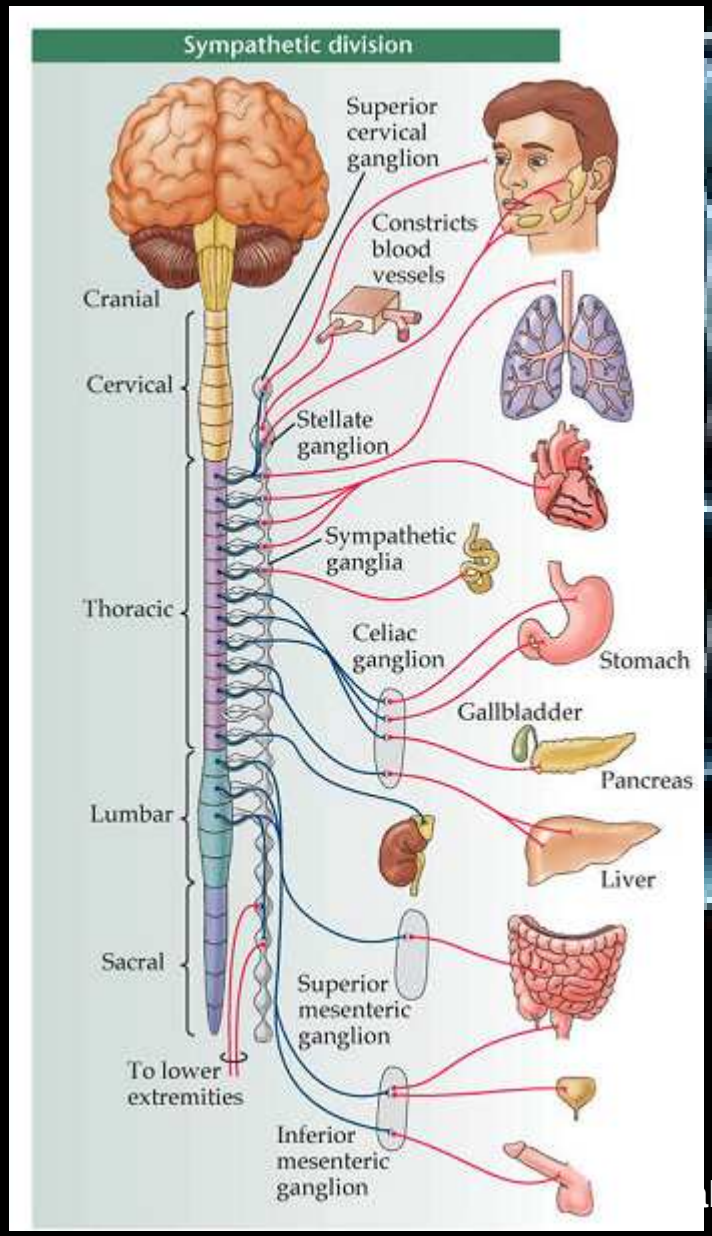
☞ Les différents rythmes biologiques :
selon le niveau biologique

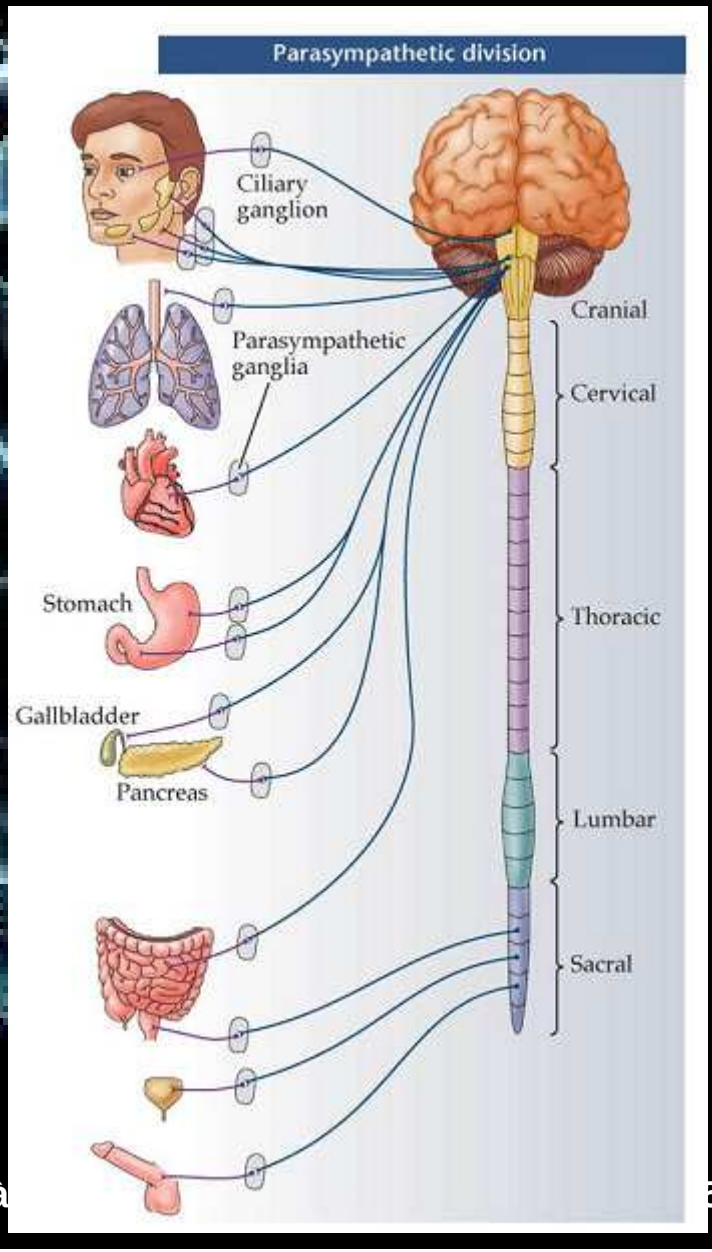
- Système :

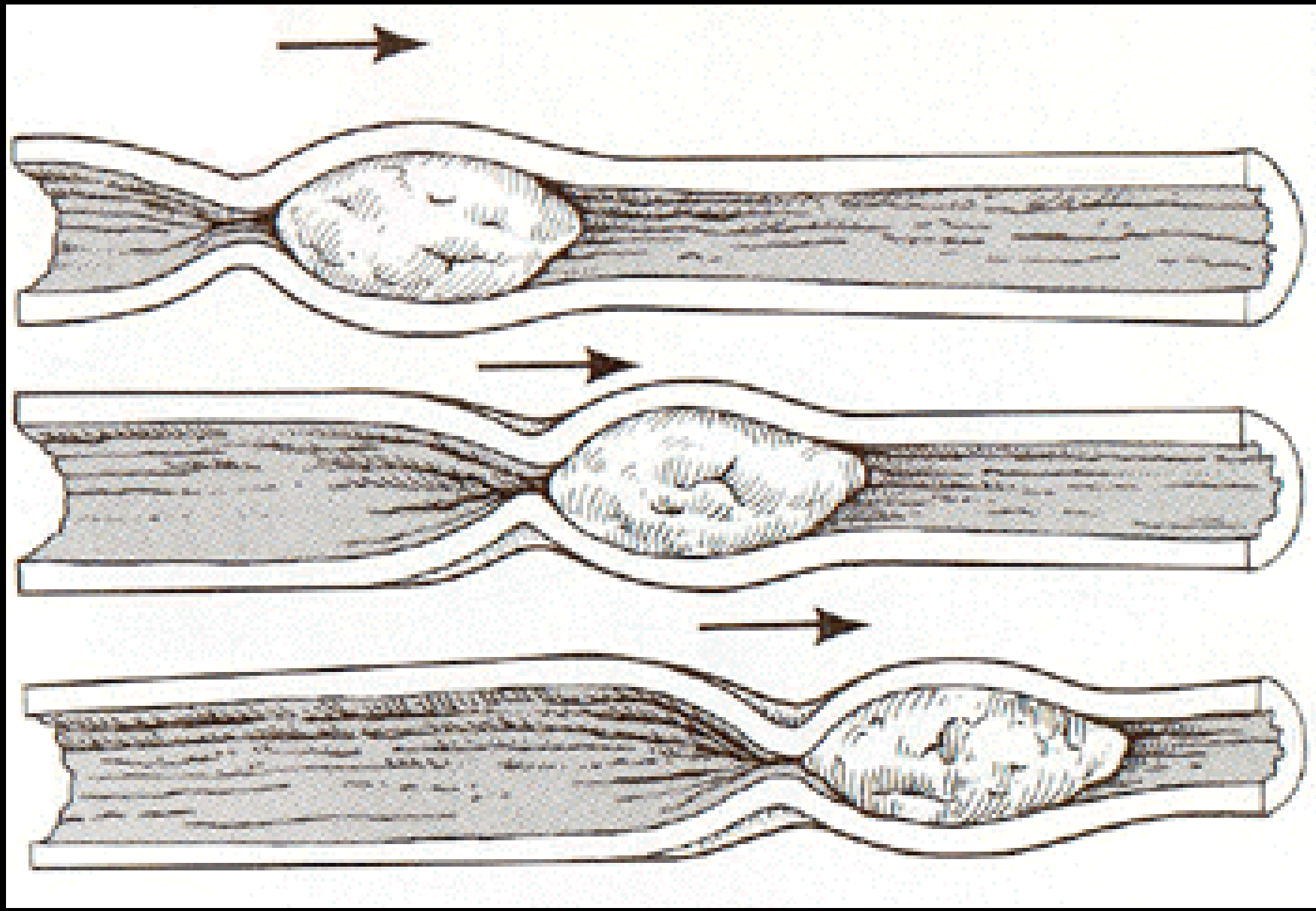
  - SNV : Péristaltisme intestinal.

Sympathique

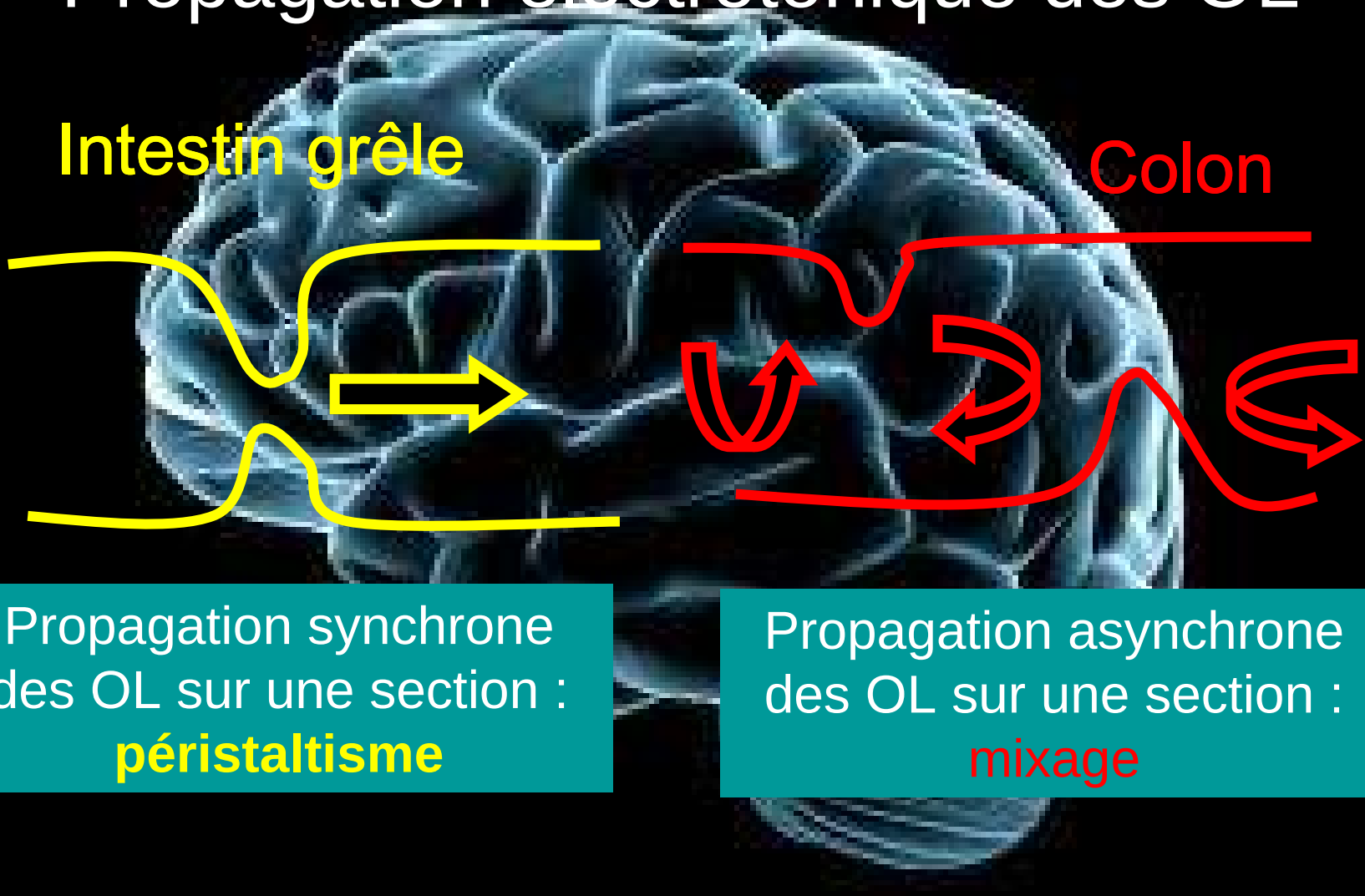
Parasympathique







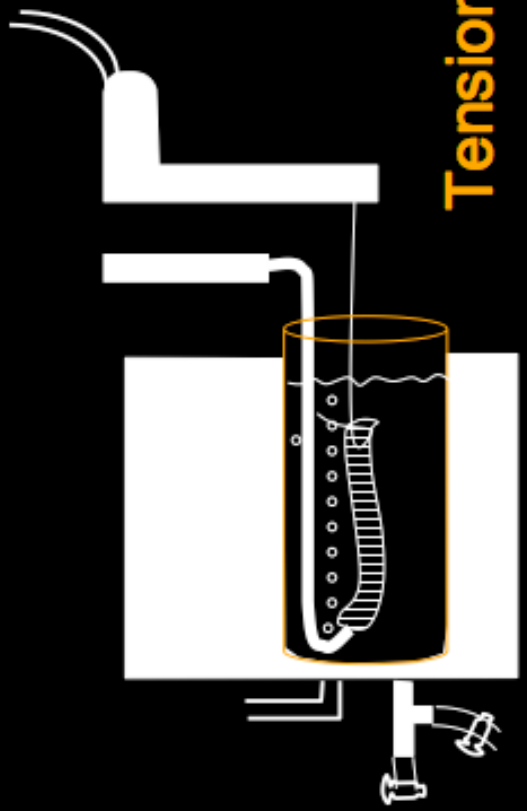
Propagation électrotonique des OL



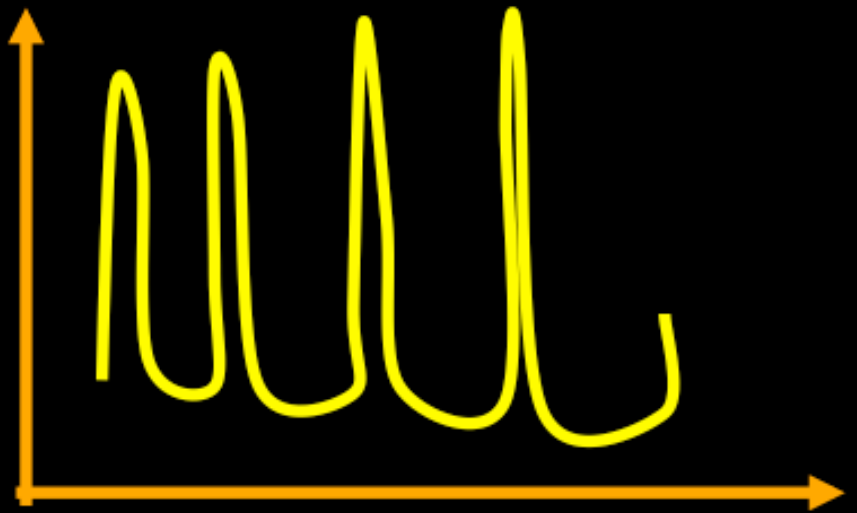
Propagation synchrone des OL sur une section : **péristaltisme**

Propagation asynchrone des OL sur une section : mixage

Automatisme: mise en évidence in vitro



Fragment isolé d'intestin



Contractions spontanées

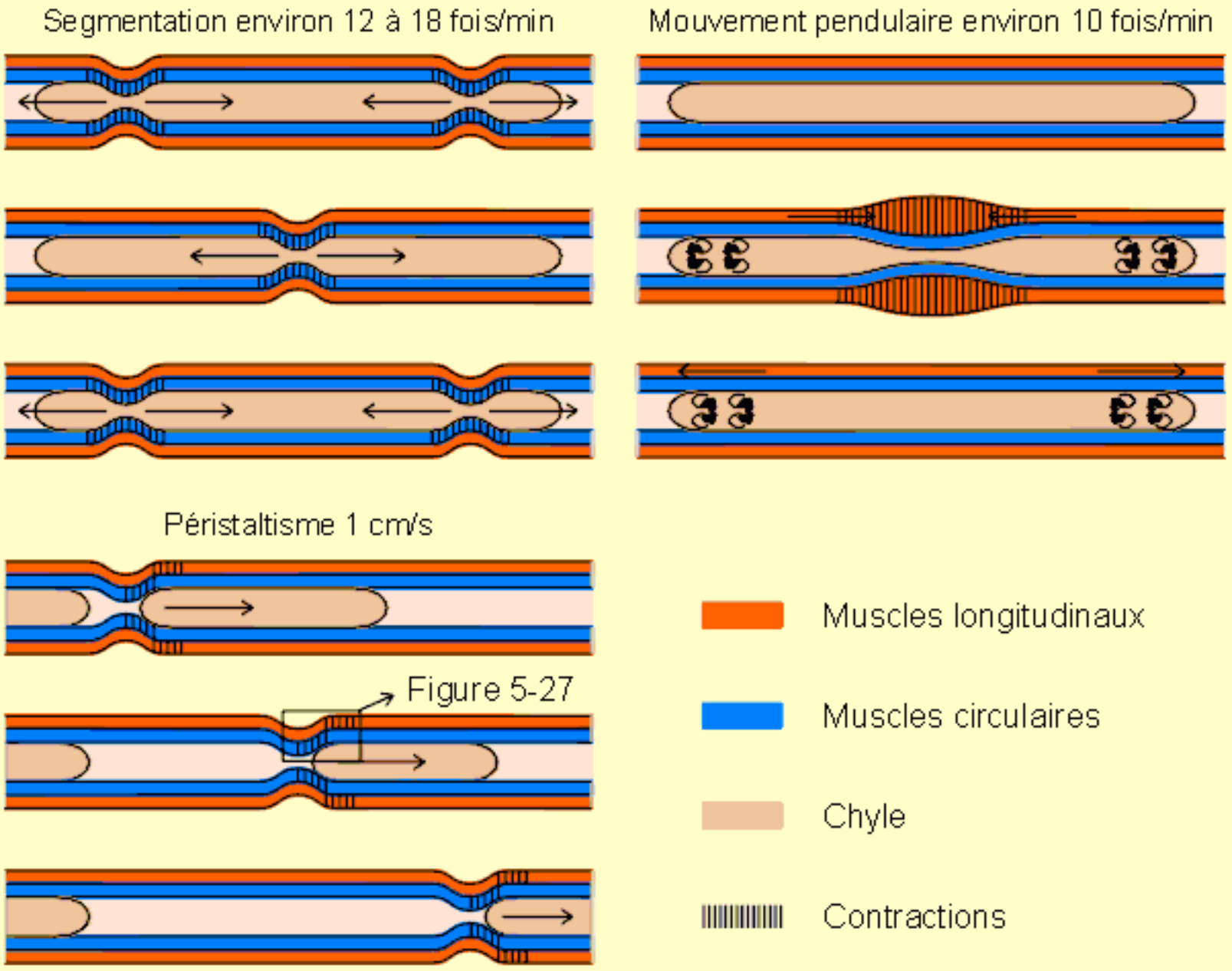
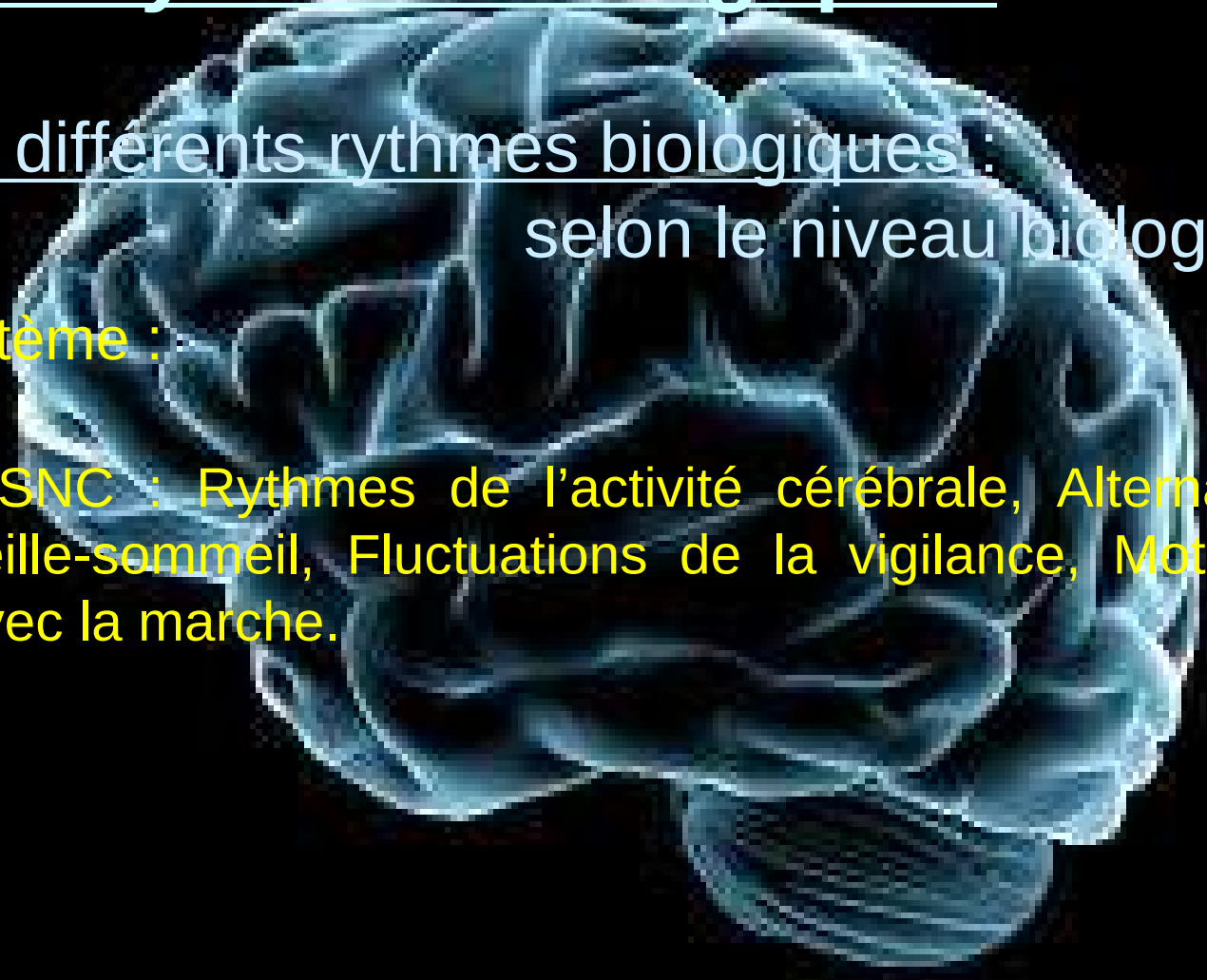


Figure 5-26: Les mouvements de l'intestin grêle chez l'homme.

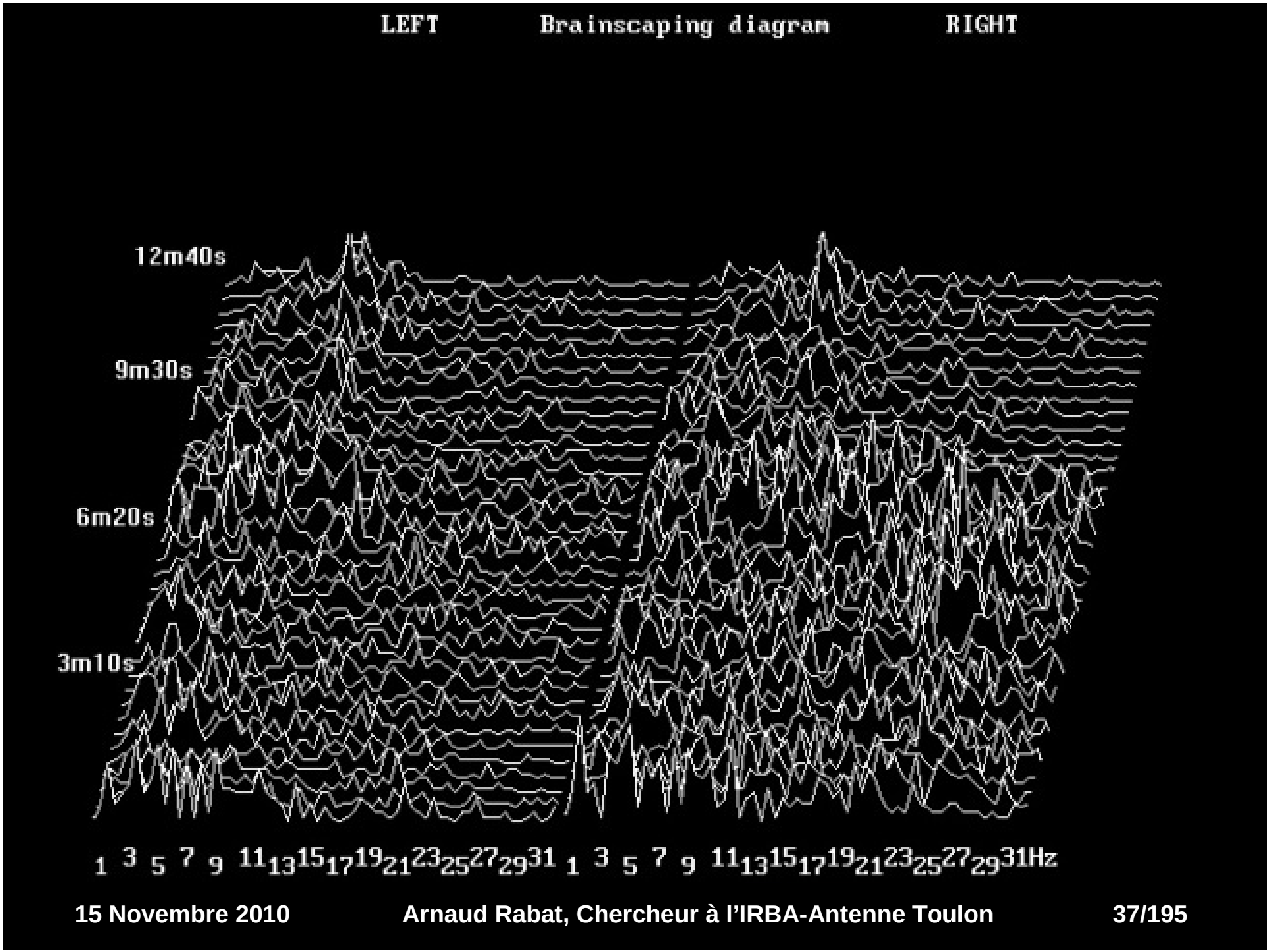
I.2. Les rythmes biologiques

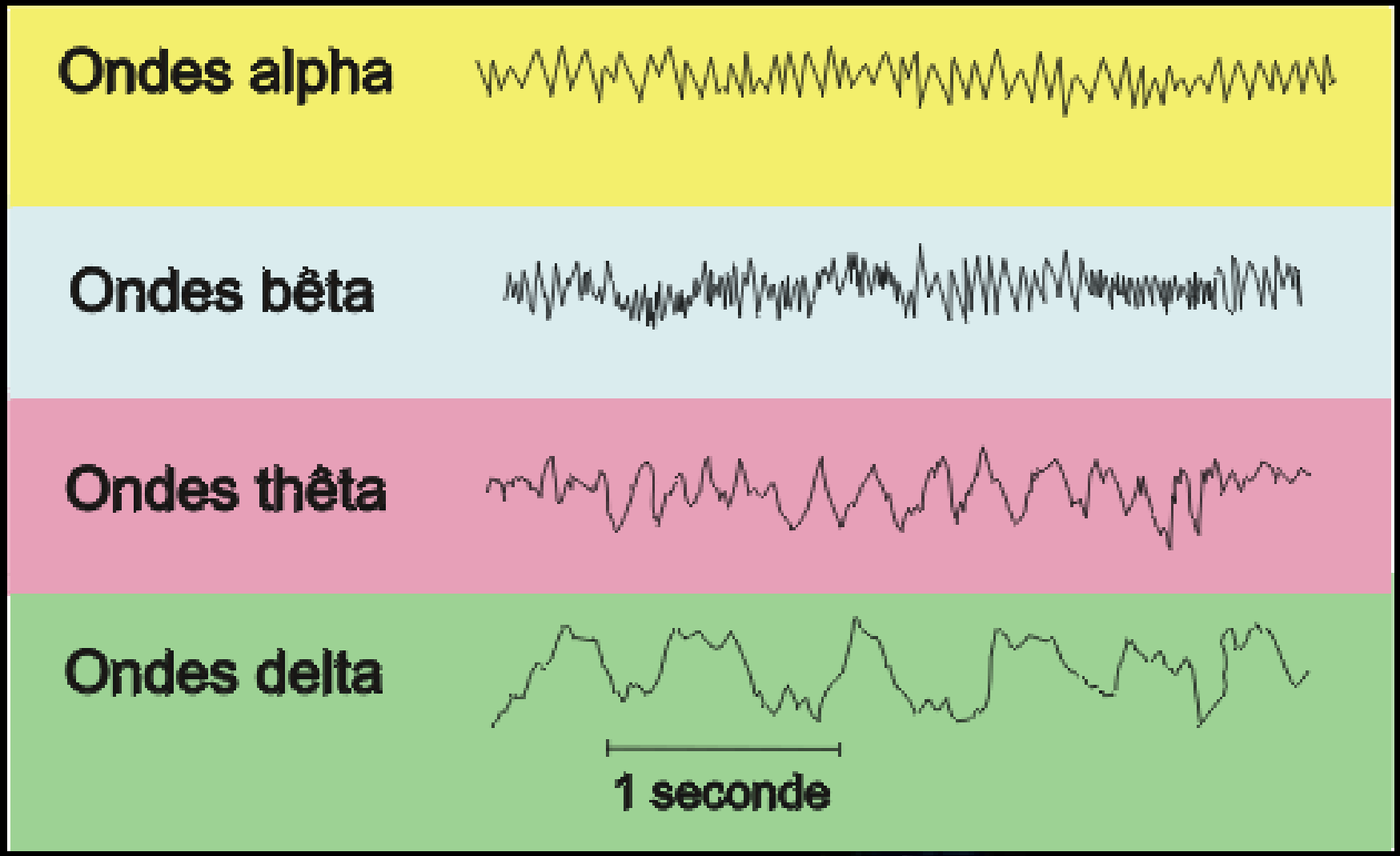


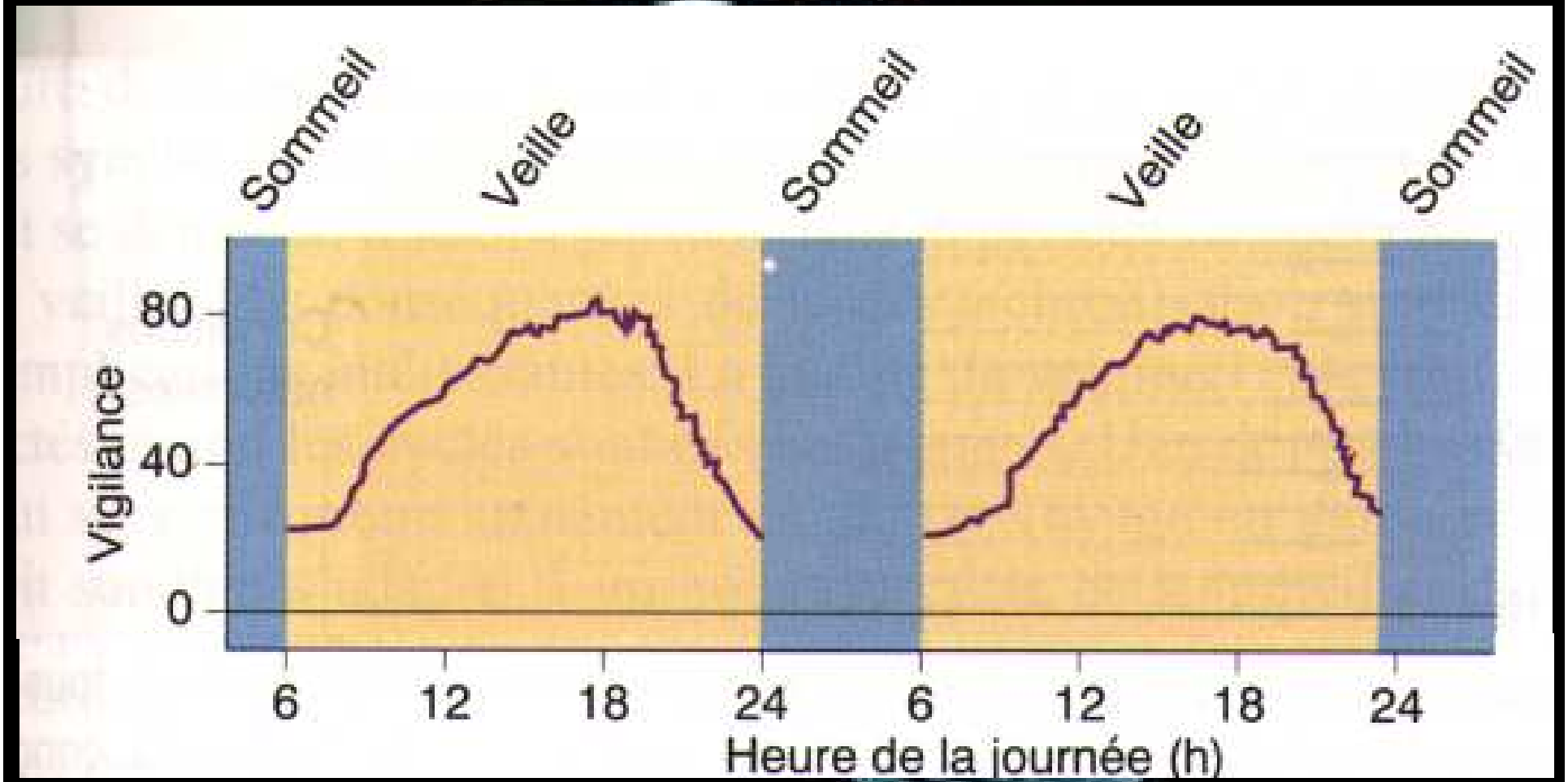
☞ Les différents rythmes biologiques :
selon le niveau biologique

- Système :

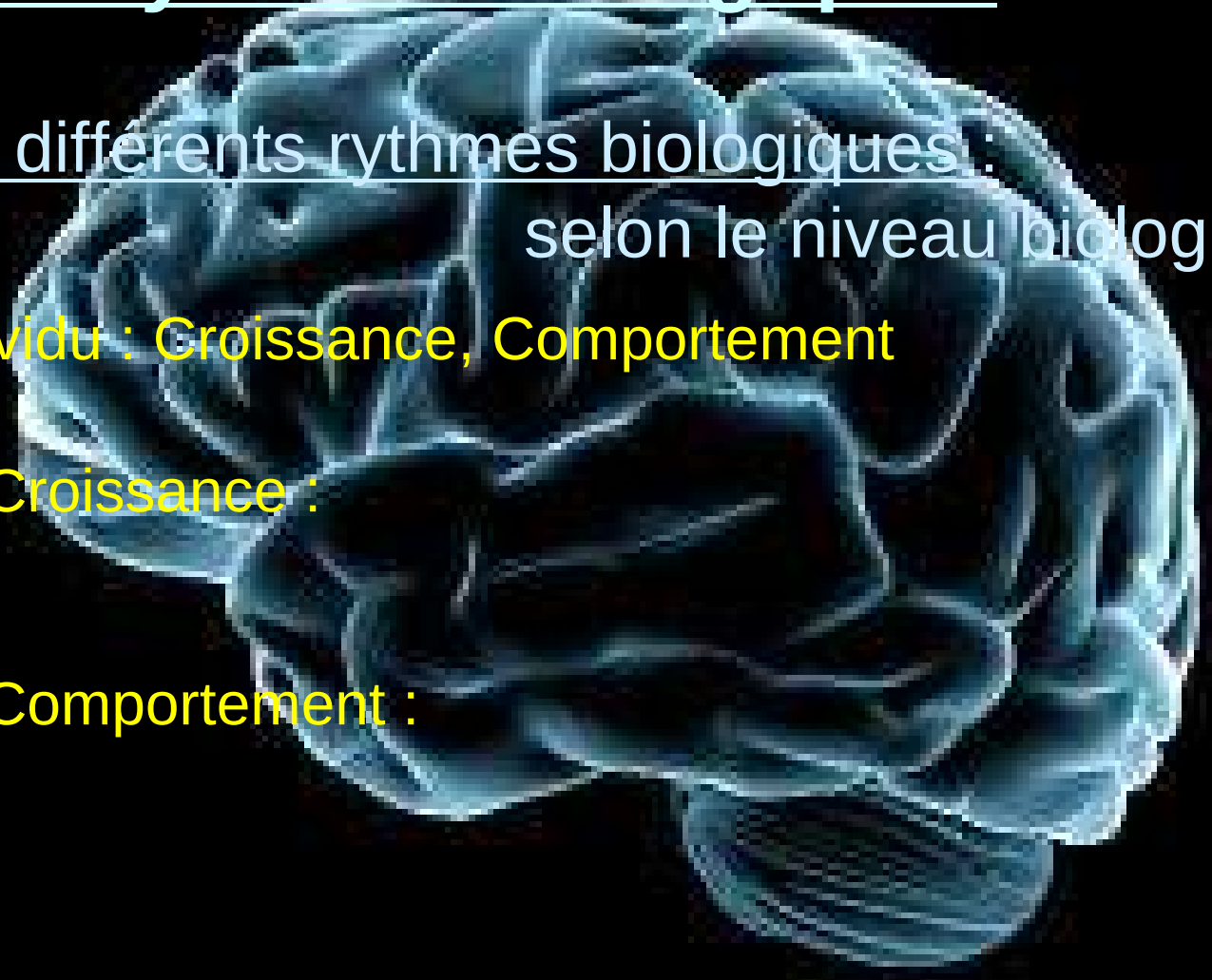
  - SNC : Rythmes de l'activité cérébrale, Alternance veille-sommeil, Fluctuations de la vigilance, Motricité avec la marche.


LEFT
Brainscaping diagram
RIGHT
12m40s
9m30s
6m20s
3m10s
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 Hz


Ondes alpha
Ondes bêta
Ondes thêta
Ondes delta
1 seconde


Sommeil
Veille
Sommeil
Veille
Sommeil
Vigilance
80
40
0
6
12
18
24
6
12
18
24
Heure de la journée (h)

I.2. Les rythmes biologiques



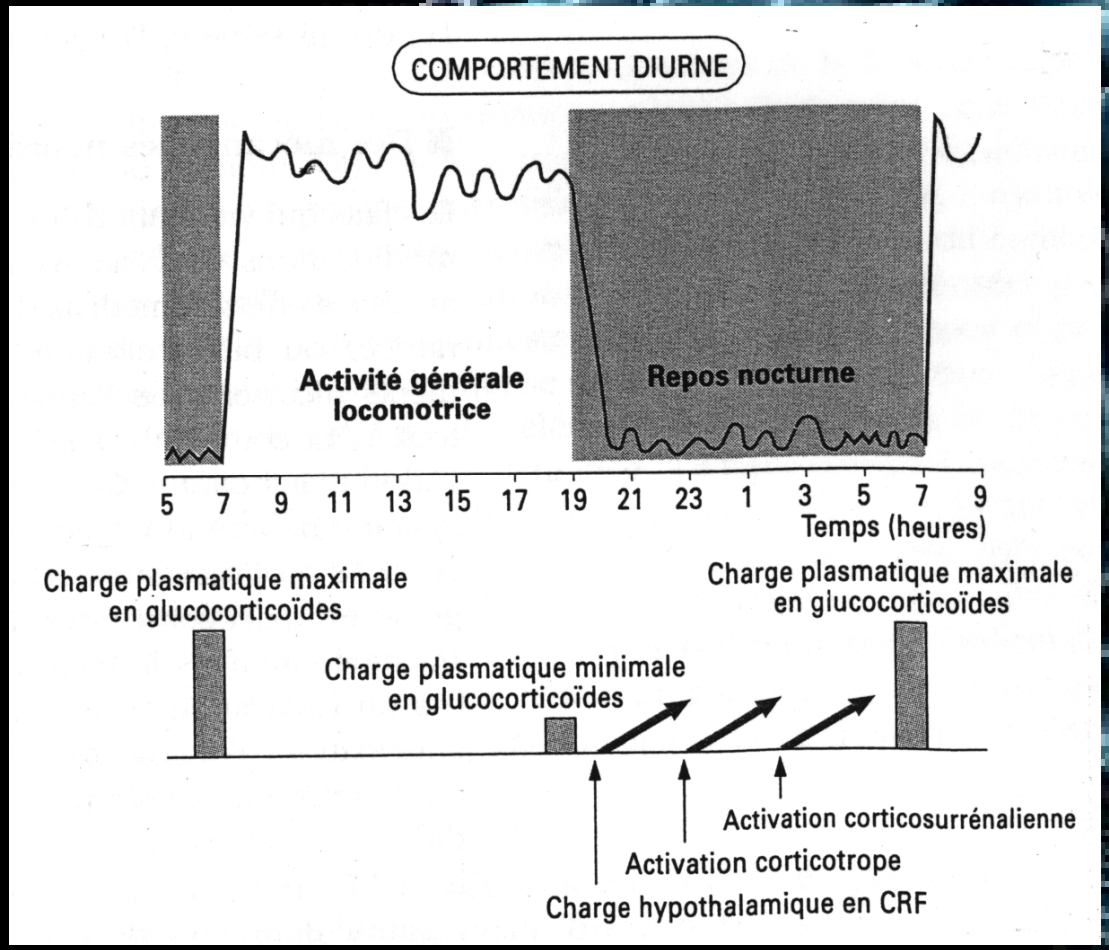
☞ Les différents rythmes biologiques :
selon le niveau biologique

- Individu : Croissance, Comportement

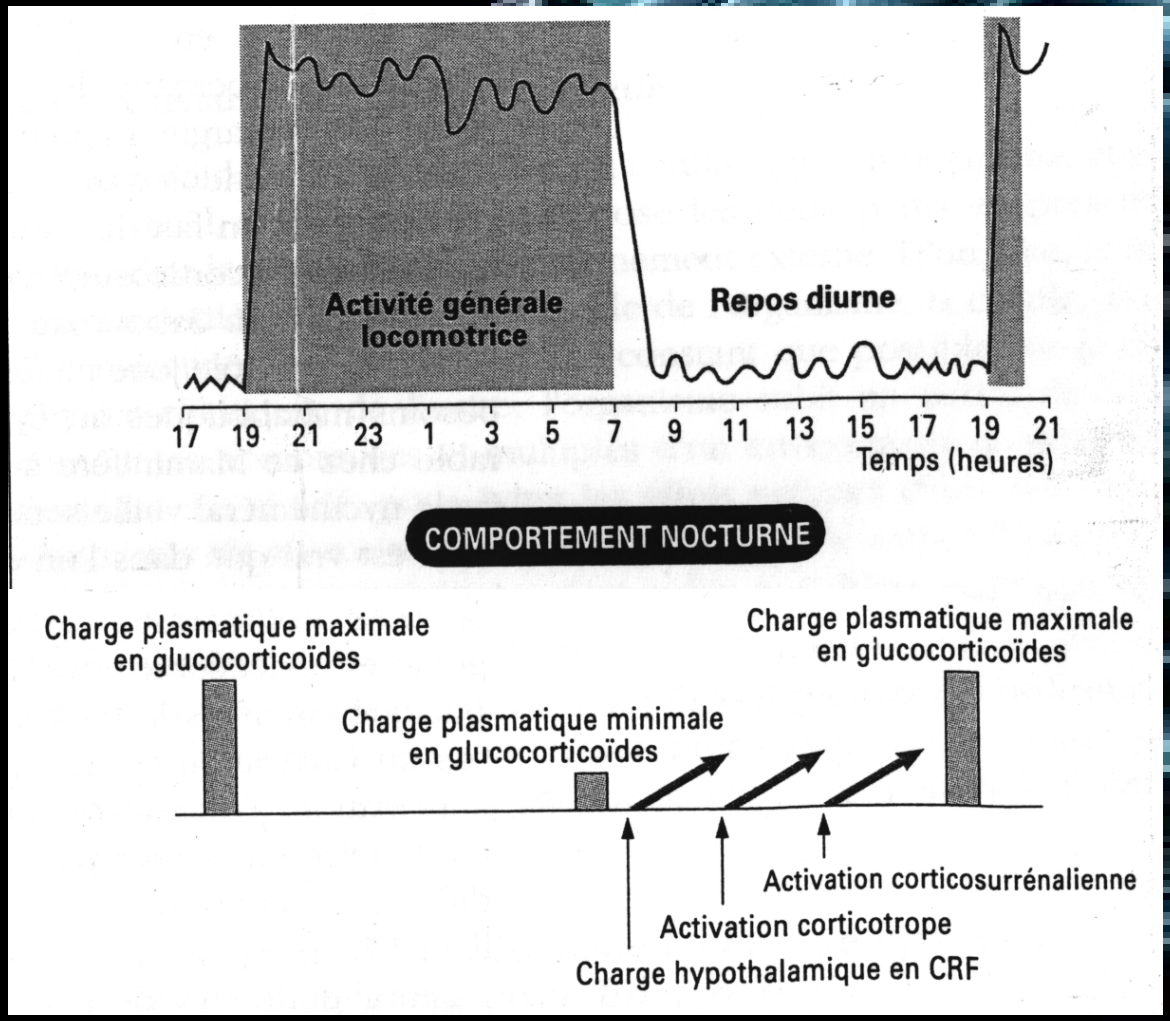
  - Croissance :

  - Comportement :

I.2. Les rythmes biologiques



I.2. Les rythmes biologiques



I.2. Les rythmes biologiques

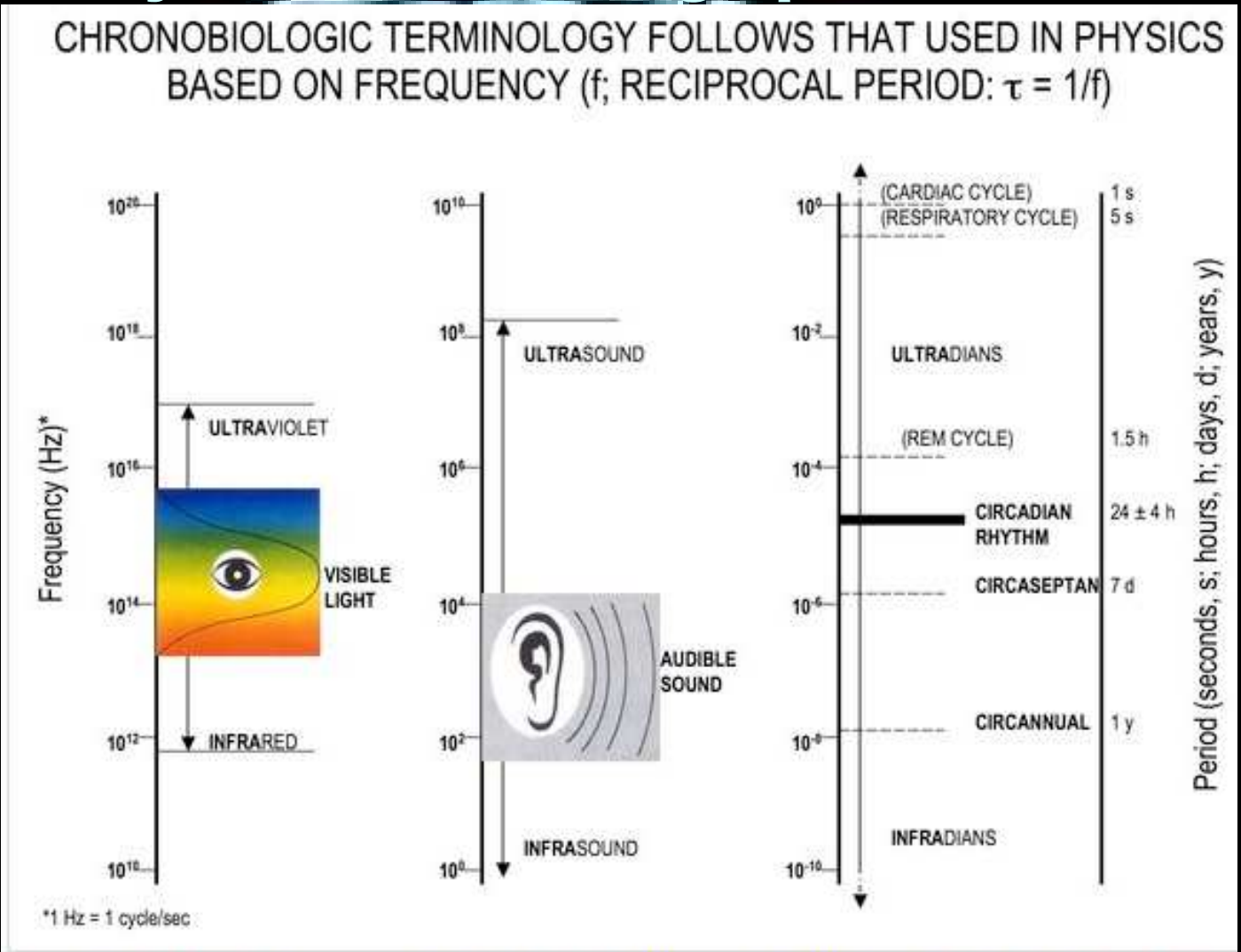


Figure 1: Terminology follows usage in physics. The broader division of biosphere spectra into 3 domains uses the circadian range of 1 cycle in 20–28 hours as a reference for frequencies (not periods!) higher (ultra) or lower (infra) than circadian, in keeping with precedents of nomenclature in physics. © Halberg.

I.2. Les rythmes biologiques

☞ Les différents rythmes biologiques : selon la période

CLASSIFICATION DES RYTHMES BIOLOGIQUES

- Rythmes de haute fréquence $\tau < 30$ min
  (cardiaques, respiratoires, électroencéphalographiques,……)

-Rythmes de moyenne fréquence 30 min $< \tau <$ 2,5 jours
  - ultradiens 30 min $< \tau <$ 20 heures
  - circadiens 20 heures $< \tau <$ 28 heures (conditions de free-running)
  - infradiens 28 heures $< \tau <$ 2,5 jours

- Rythmes de basse fréquence $\tau >$ 2,5 jours
  -circaseptidiens $\tau \approx$ 7 jours
  -circatrigintidiens $\tau \approx$ 30 jours
  -circanniens $\tau \approx$ 1 an

* nycthéméral (conditions de synchronisation)
* saisonnier

I.2.1. Les rythmes circanniens

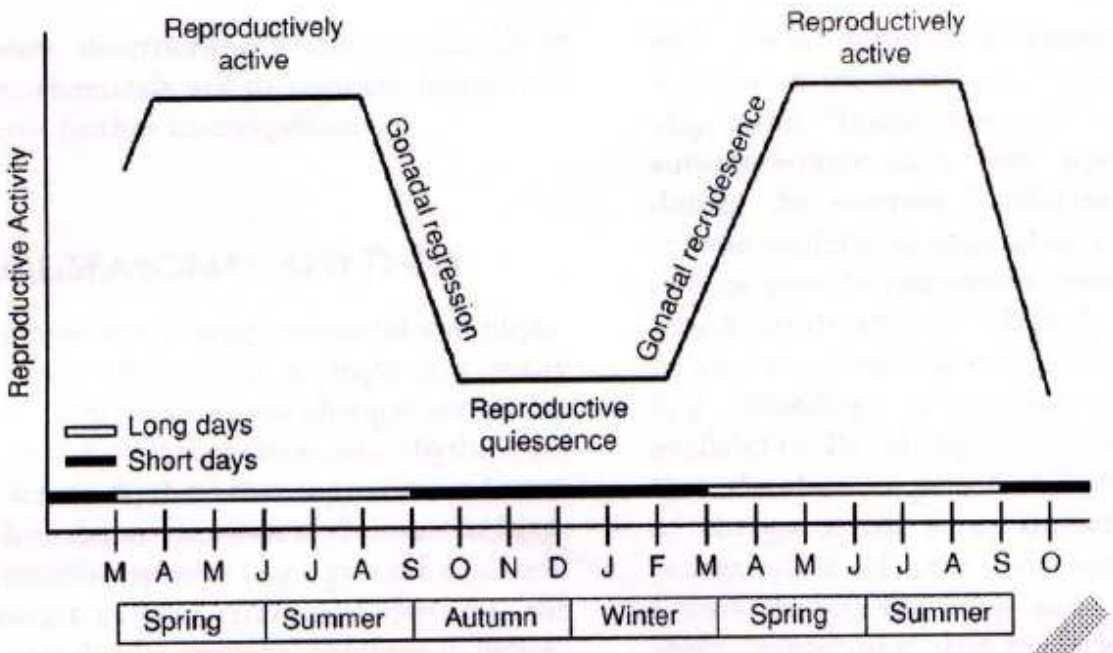


Figure 3 Typical pattern of seasonal/photoperiodic changes in reproductive physiology in a long-day breeding rodent. Reproductive activity is maximal during the long days of summer, but reproductive regression occurs as the days get shorter during the autumn. The reproductive system maintains a period of quiescence (inactivity) during the short days of winter. As the day length increases during the spring, reproductive activation (recrudescence) occurs anew.

I.2.1. Les rythmes circanniens

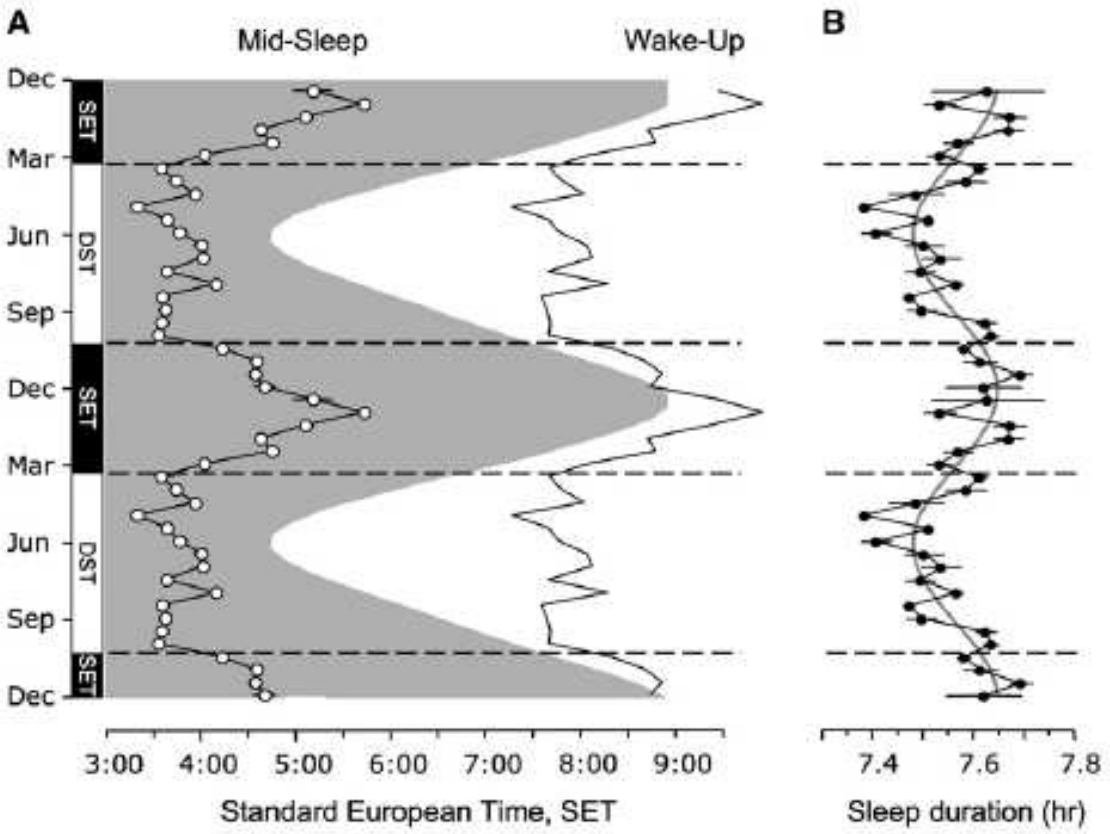
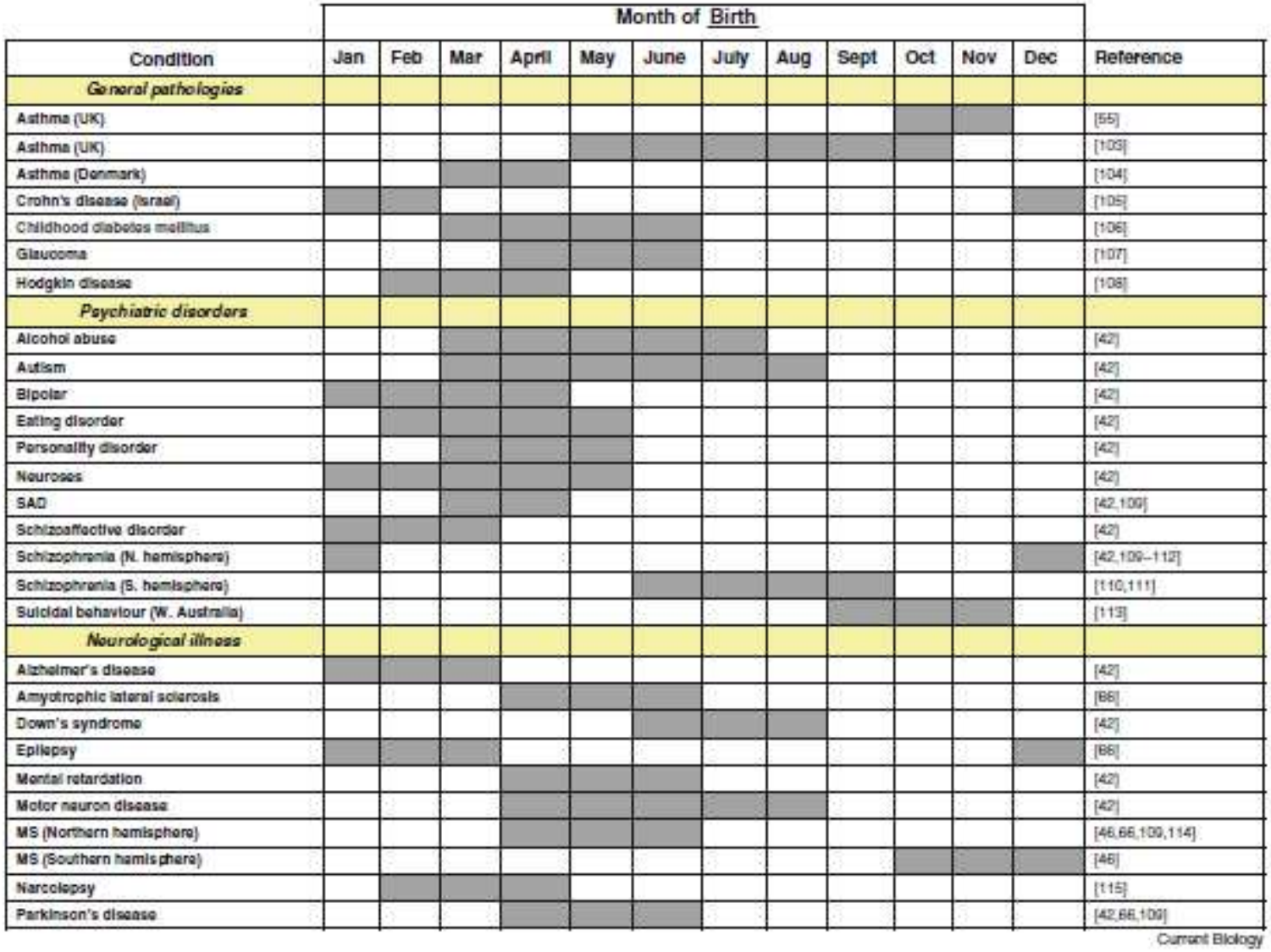


Figure 1. Seasonality in Sleep Timing Taken from the MCTQ Database

Annual time courses are double plotted (the same data are shown sequentially to more easily visualize systematic trends) ($n \approx 55{,}000$). (A) Half-monthly averages of midsleep times on free days [1], MSF (open circles ± SEM), and of wake-up times (line). DST periods are indicated by the open boxes and their transitions by dashed horizontal lines; dawn times are shown as a gray to white border. Whereas sleep times track dawn under standard time, midsleep is scattered around 3:30 (wake-up times around 7:40) under DST. Age and sex ratio were not significantly different in the 24 averages and showed no interactions.

(B) Seasonal changes in sleep duration (filled circles; averaged over both free and work days ± SEM) result in about 20 min more sleep in winter than in summer (cosine fit: $r = 0.75$; $p < 0.0001$).



	Month of Birth												
Condition	Jan	Feb	Mar	April	May	June	July	Aug	Sept	Oct	Nov	Dec	Reference
General pathologies													
Asthma (UK)													[55]
Asthma (UK)													[103]
Asthma (Denmark)													[104]
Crohn's disease (Israel)													[105]
Childhood diabetes mellitus													[106]
Glaucoma													[107]
Hodgkin disease													[108]
Psychiatric disorders													
Alcohol abuse													[42]
Autism													[42]
Bipolar													[42]
Eating disorder													[42]
Personality disorder													[42]
Neuroses													[42]
SAD													[42,109]
Schizoaffective disorder													[42]
Schizophrenia (N. hemisphere)													[42,109–112]
Schizophrenia (S. hemisphere)													[110,111]
Suicidal behaviour (W. Australia)													[113]
Neurological illness													
Alzheimer's disease													[42]
Amyotrophic lateral sclerosis													[66]
Down's syndrome													[42]
Epilepsy													[66]
Mental retardation													[42]
Motor neuron disease													[42]
MS (Northern hemisphere)													[46,66,109,114]
MS (Southern hemisphere)													[46]
Narcolepsy													[115]
Parkinson's disease													[42,66,109]

Current Biology

Figure 4. Summary of pathologies/conditions in humans that have been reliably associated with the season of birth.

Gray shading indicates the peak month of birth for the different conditions. Unless otherwise stated the results presented are from populations in the Northern hemisphere. This figure is based upon two excellent reviews of the literature [42,66] and additional papers. It is important to stress that although the percentage differences of a gradient are relatively small, they are statistically significant and do not occur by random chance. For example, in the Northern hemisphere, significantly fewer (8.5%) people with MS were born in November and significantly more (9.1%) were born in May. In the Southern hemisphere, the situation is reversed and November is the peak month and May the lowest. Likewise, multiple studies have shown there is an ~10% greater chance of developing schizophrenia if born in the winter/spring and a corresponding drop of approximately 10% if born in summer/autumn. This is also true for the Southern hemisphere [42].

RYTHMES CIRCANNUELS chez l'homme

- Variations saisonnières de la sécrétion de mélatonine (avance de phase l'hiver/été), du cortisol (diminution sécrétion pendant automne et hiver et ré-augmentation dès février)
- Augmentation fatigue et tristesse durant automne et hiver.
- Variation de l'attention, de la sociabilité et de la croissance corporelle.
- Mort subite, AVC : rythme circannuel

I.2. Les rythmes biologiques

☞ Les différents rythmes biologiques : selon la période

CLASSIFICATION DES RYTHMES BIOLOGIQUES

- Rythmes de haute fréquence $\tau < 30$ min
  (cardiaques, respiratoires, électroencéphalographiques,……)

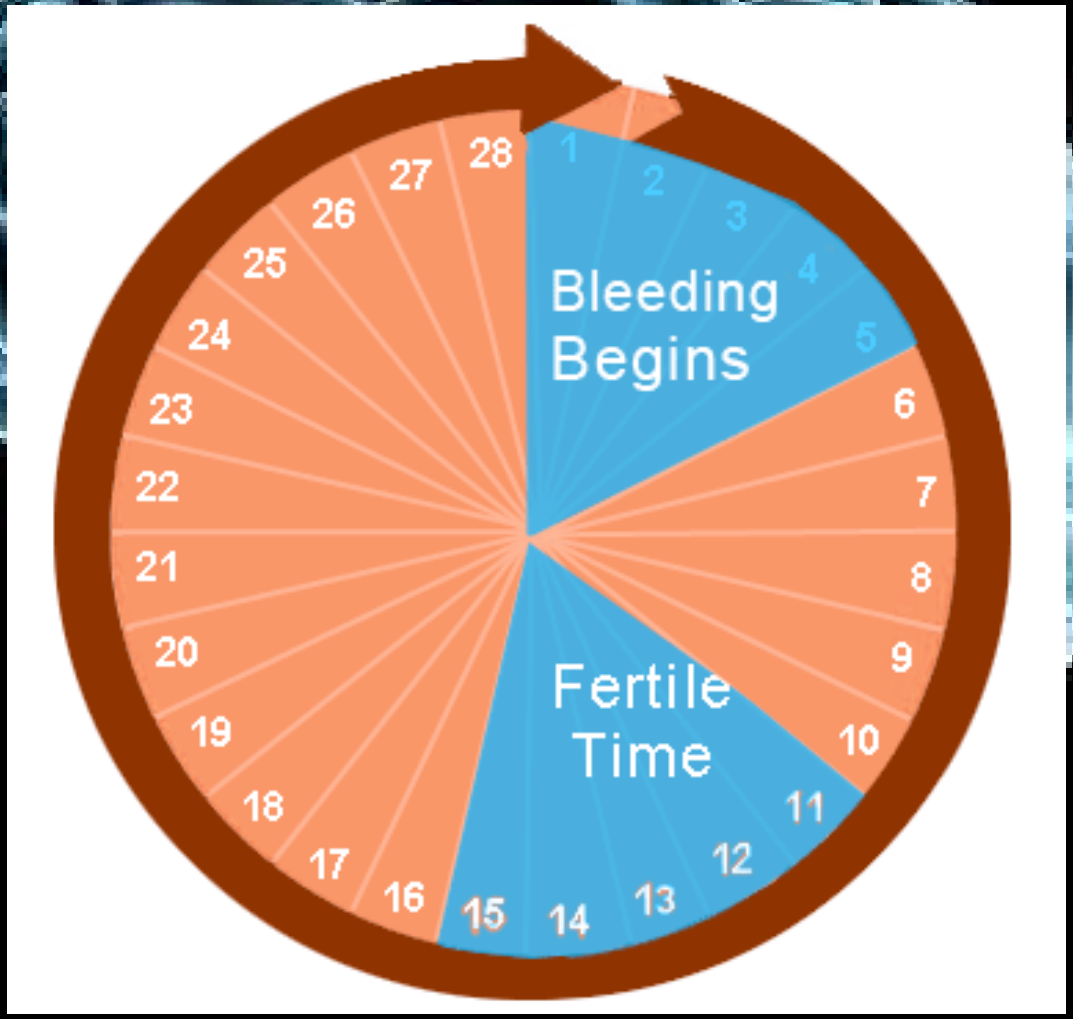
-Rythmes de moyenne fréquence 30 min $< \tau <$ 2,5 jours
  - ultradiens 30 min $< \tau <$ 20 heures
  - circadiens 20 heures $< \tau <$ 28 heures (conditions de free-running)
  - infradiens 28 heures $< \tau <$ 2,5 jours

- Rythmes de basse fréquence $\tau >$ 2,5 jours
  -circaseptidiens $\tau \approx$ 7 jours
  -circatrigintidiens $\tau \approx$ 30 jours
  -circannien$\tau \approx$ 1 an

* nycthéméral (conditions de synchronisation)
* saisonnier

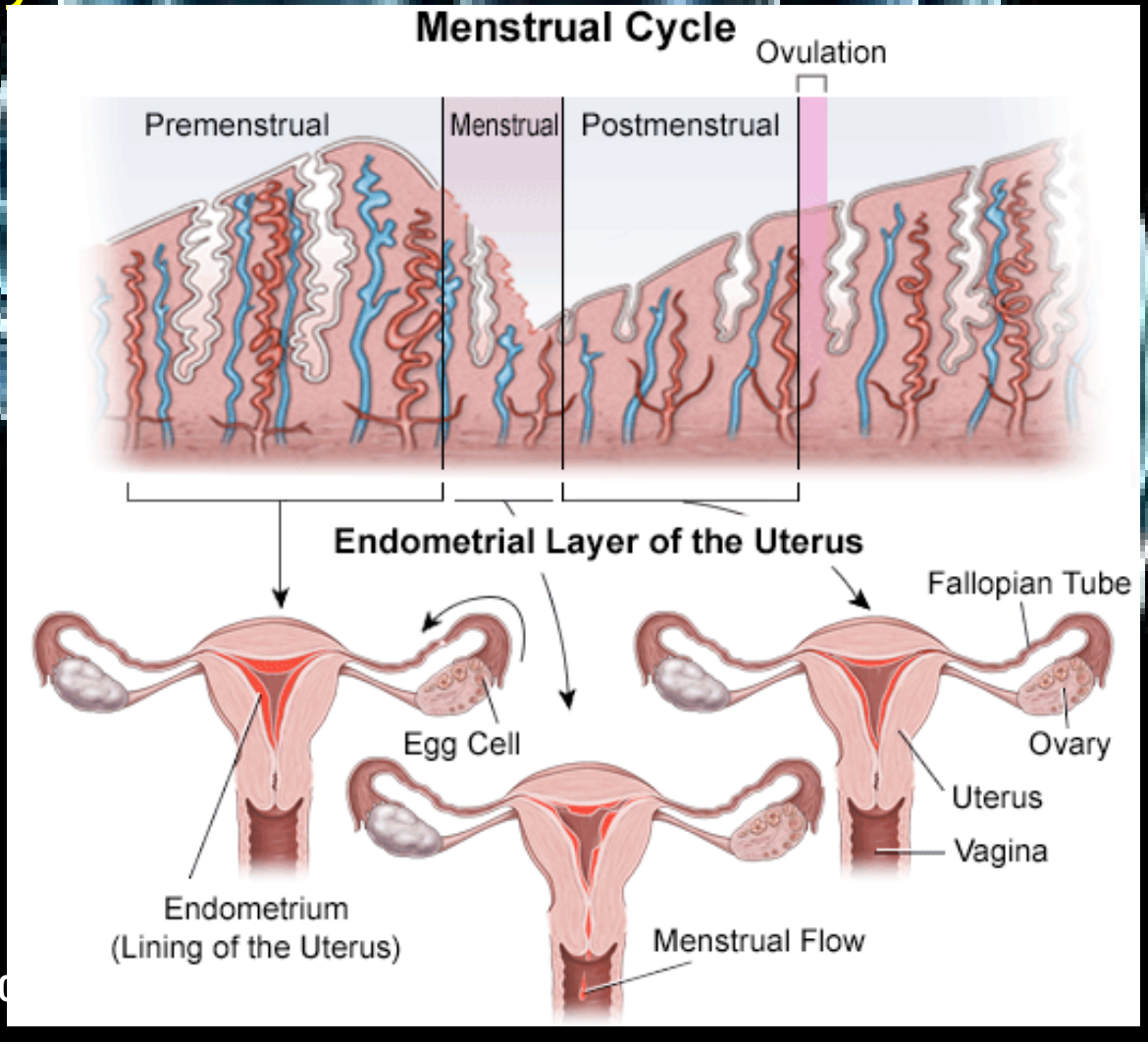
I.2.2. Les rythmes circatrigintidiens

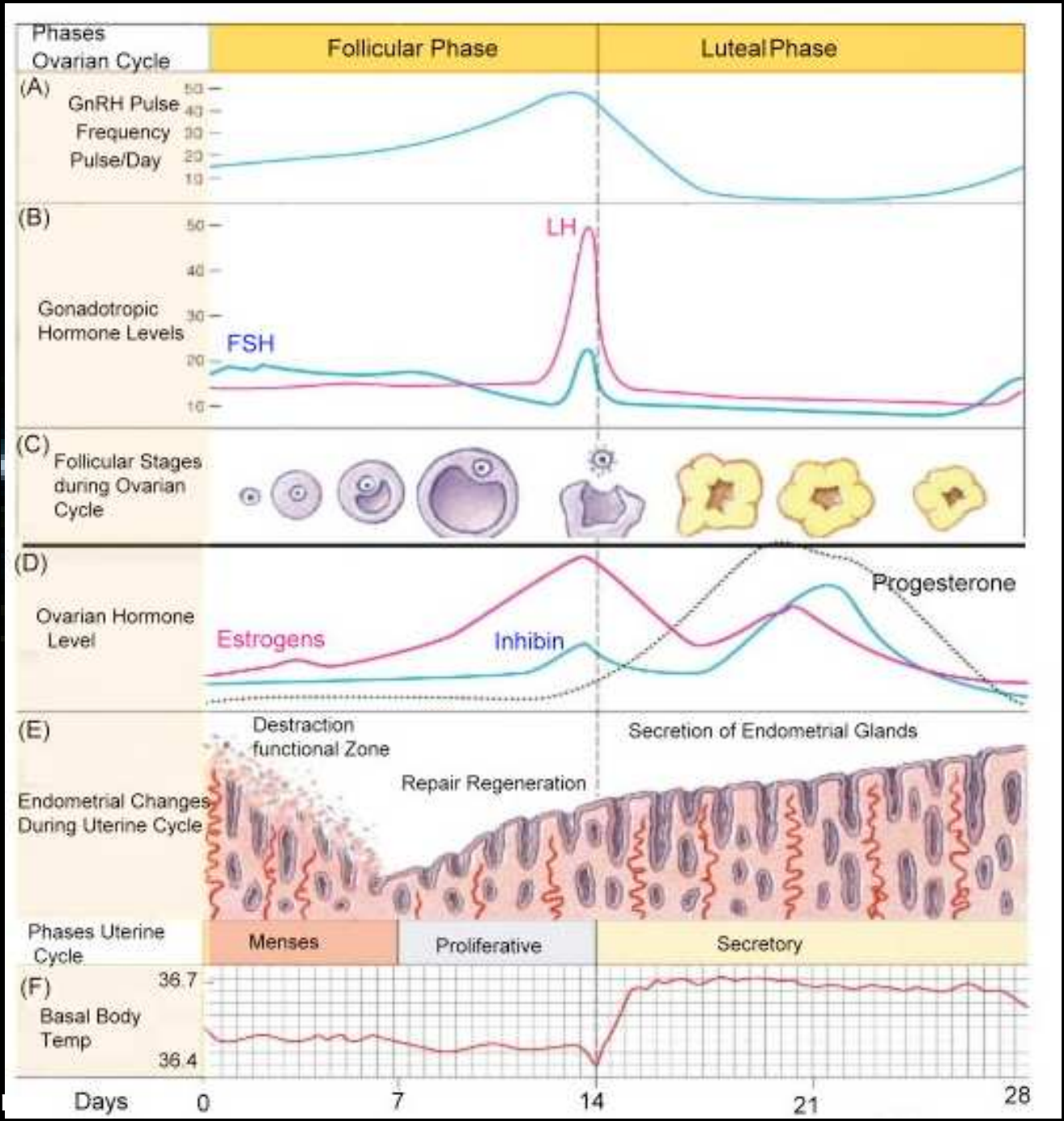
- Le cycle menstruel chez la femme :



I.2.2. Les rythmes circatrigintidiens

- Le cycle menstruel chez la femme :




Phases
Ovarian Cycle
Follicular Phase
Luteal Phase
(A)
GnRH Pulse
Frequency
Pulse/Day
50
40
30
20
10
(B)
Gonadotropic
Hormone Levels
LH
FSH
50
40
30
20
10
(C)
Follicular Stages
during Ovarian
Cycle
(D)
Ovarian Hormone
Level
Estrogens
Inhibin
Progesterone
(E)
Endometrial Changes
During Uterine Cycle
Destraction
functional Zone
Repair Regeneration
Secretion of Endometrial Glands
Phases Uterine
Cycle
Menses
Proliferative
Secretory
(F)
Basal Body
Temp
36.7
36.4
Days
0
7
14
21
28

I.2. Les rythmes biologiques

☞ Les différents rythmes biologiques : selon la période

CLASSIFICATION DES RYTHMES BIOLOGIQUES

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  -circanniens $\tau \approx$ 1 an

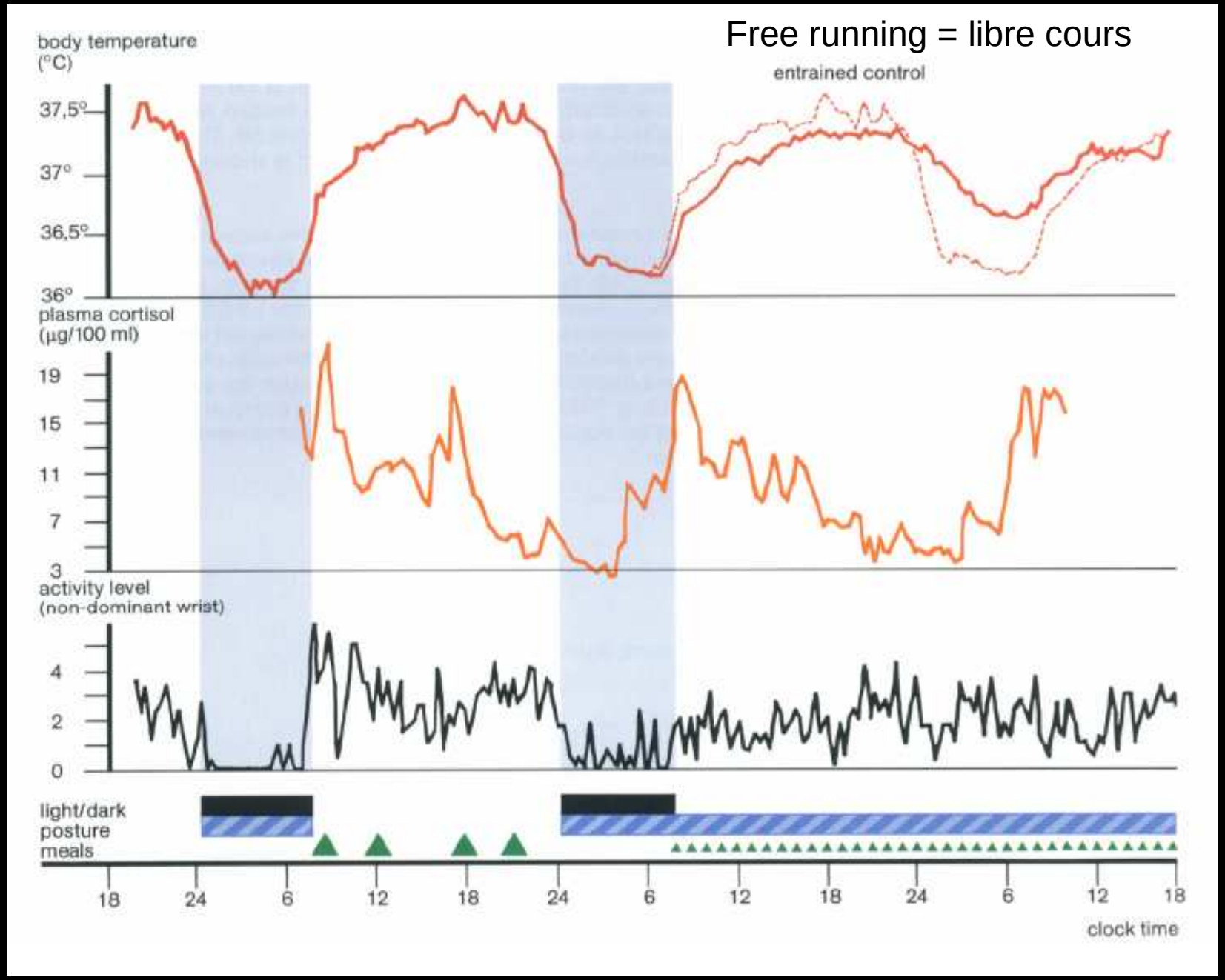
* nycthéméral (conditions de synchronisation)
* saisonnier

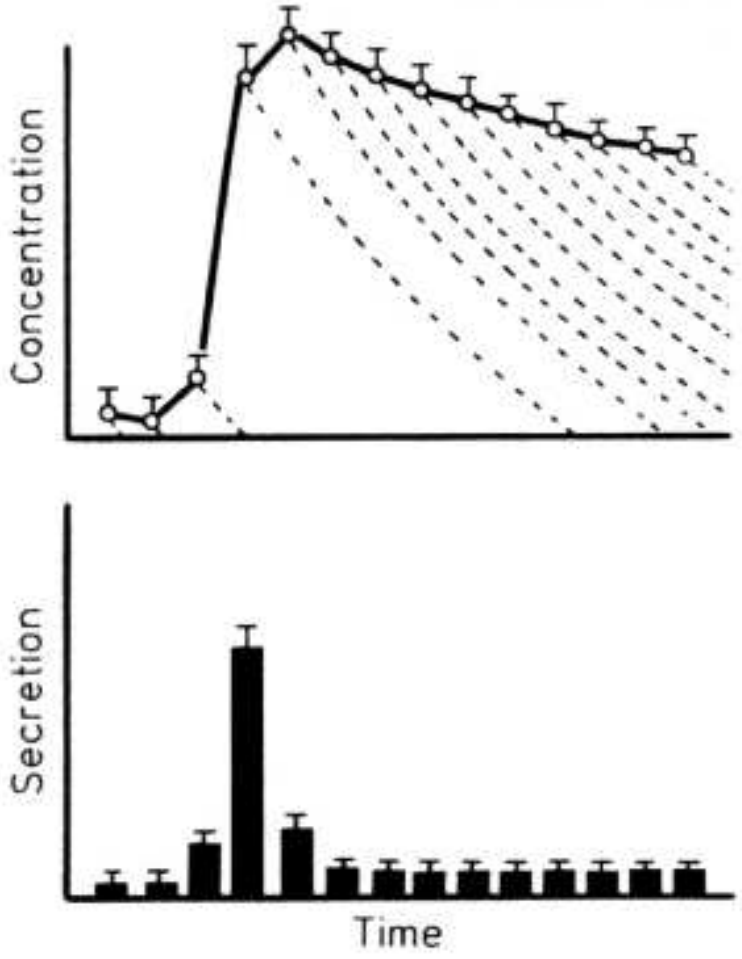
I.2.3. Les rythmes circadiens

- Principes d'analyses :

Chambre expérimentale individuelle

Chronobiologie & Hormones


Free running = libre cours
body temperature
(°C)
entrained control
37,5°
37°
36,5°
36°
plasma cortisol
(µg/100 ml)
19
15
11
7
3
activity level
(non-dominant wrist)
4
2
0
light/dark
posture
meals
18
24
6
12
18
24
6
12
18
24
6
12
18
clock time

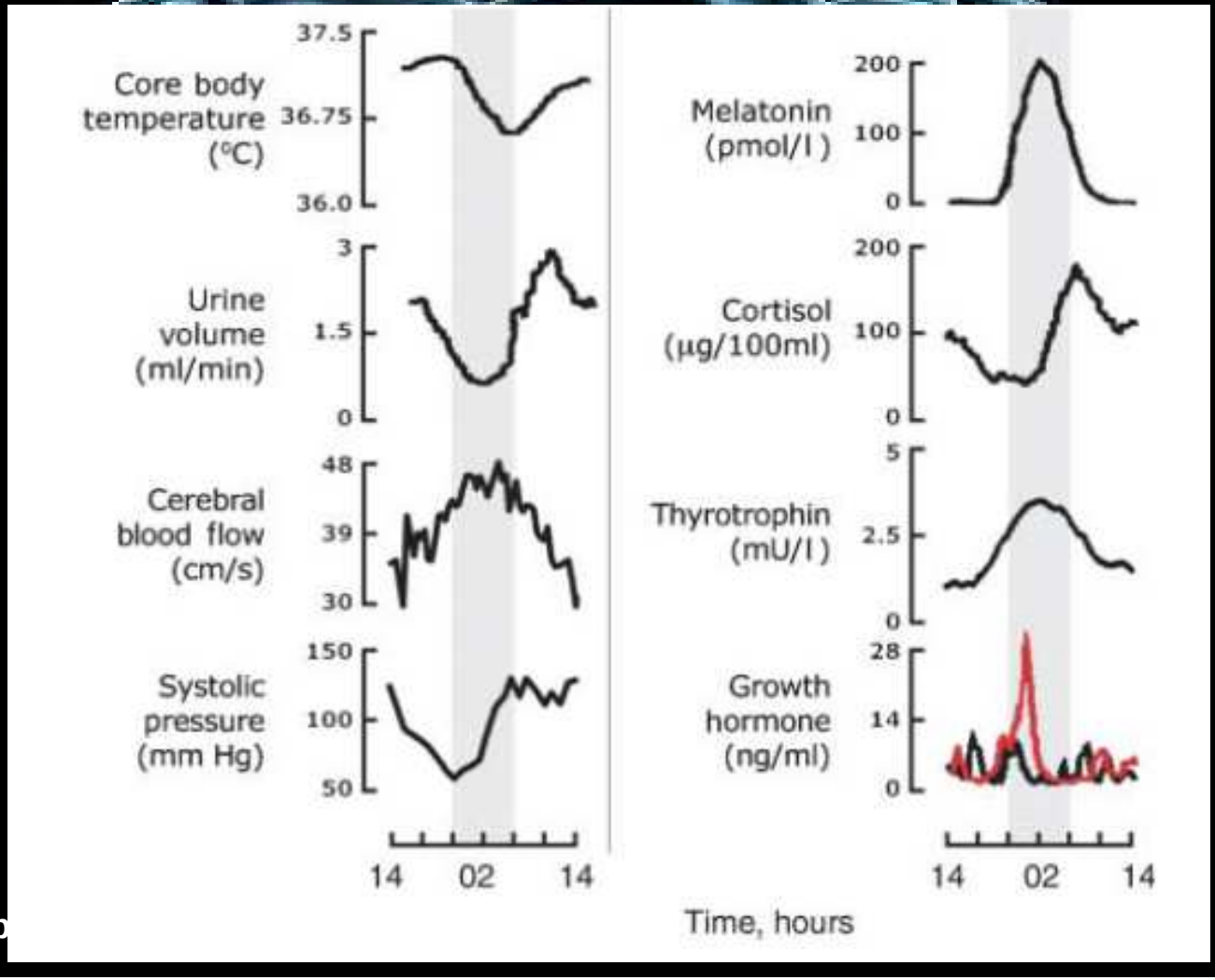


Kinetic parameters taken into account

- distribution type (mono, bi, … multi-compartmental)
- distribution volume
- half-life (elimination)

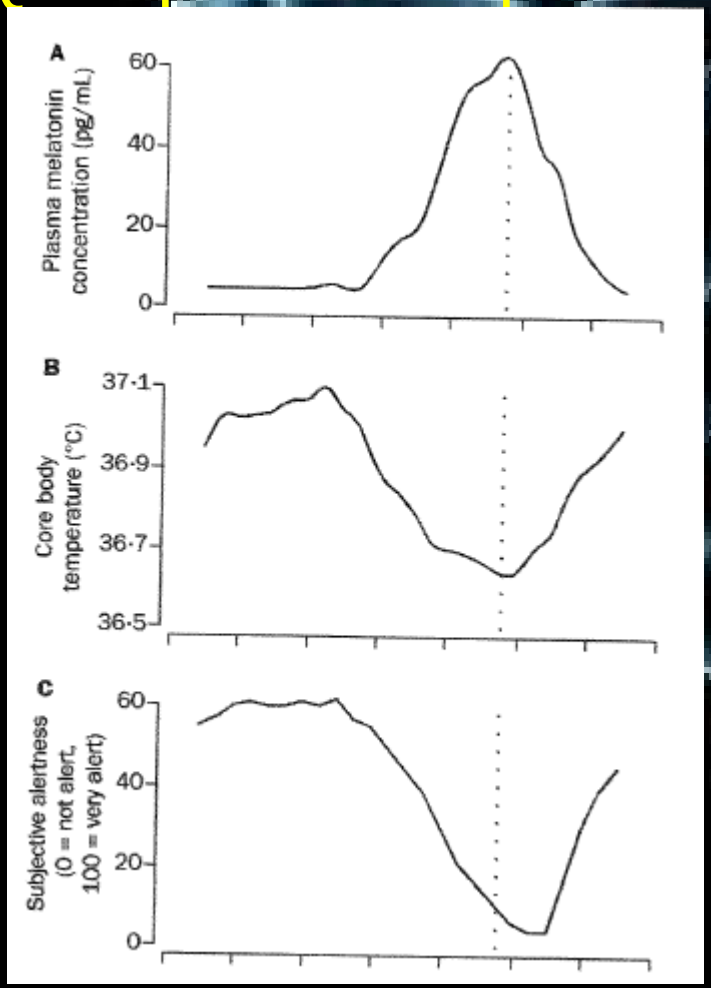
I.2.3. Les rythmes circadiens

- Quelques exemples :



I.2.3. Les rythmes circadiens

- Quelques exemples :



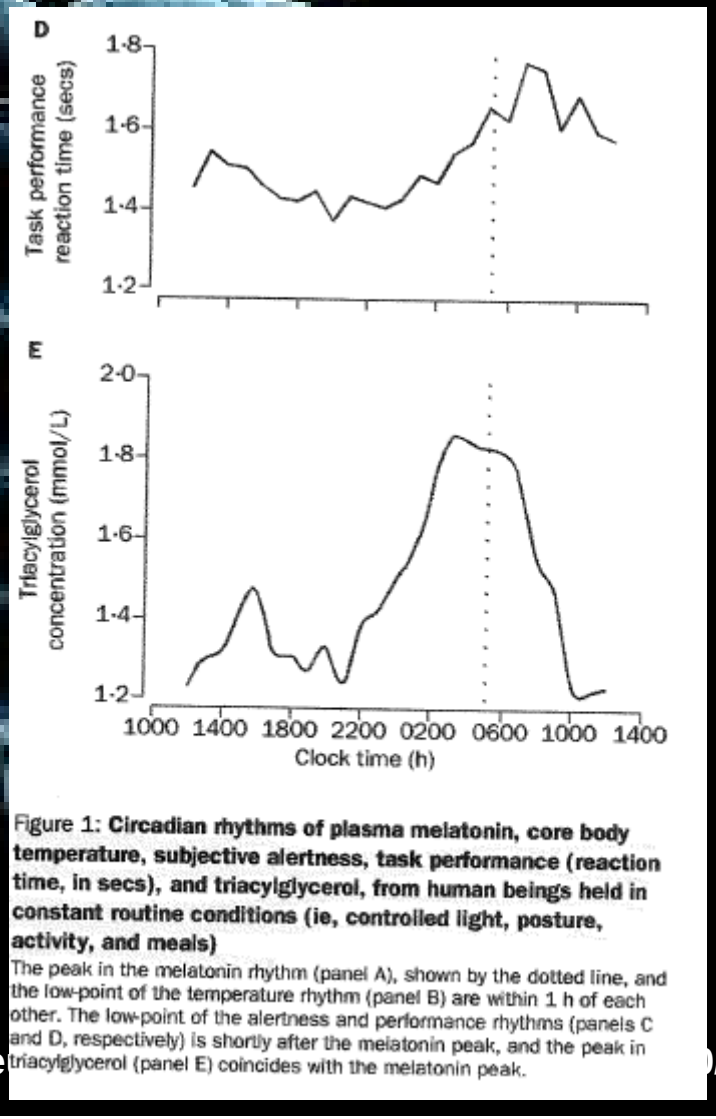
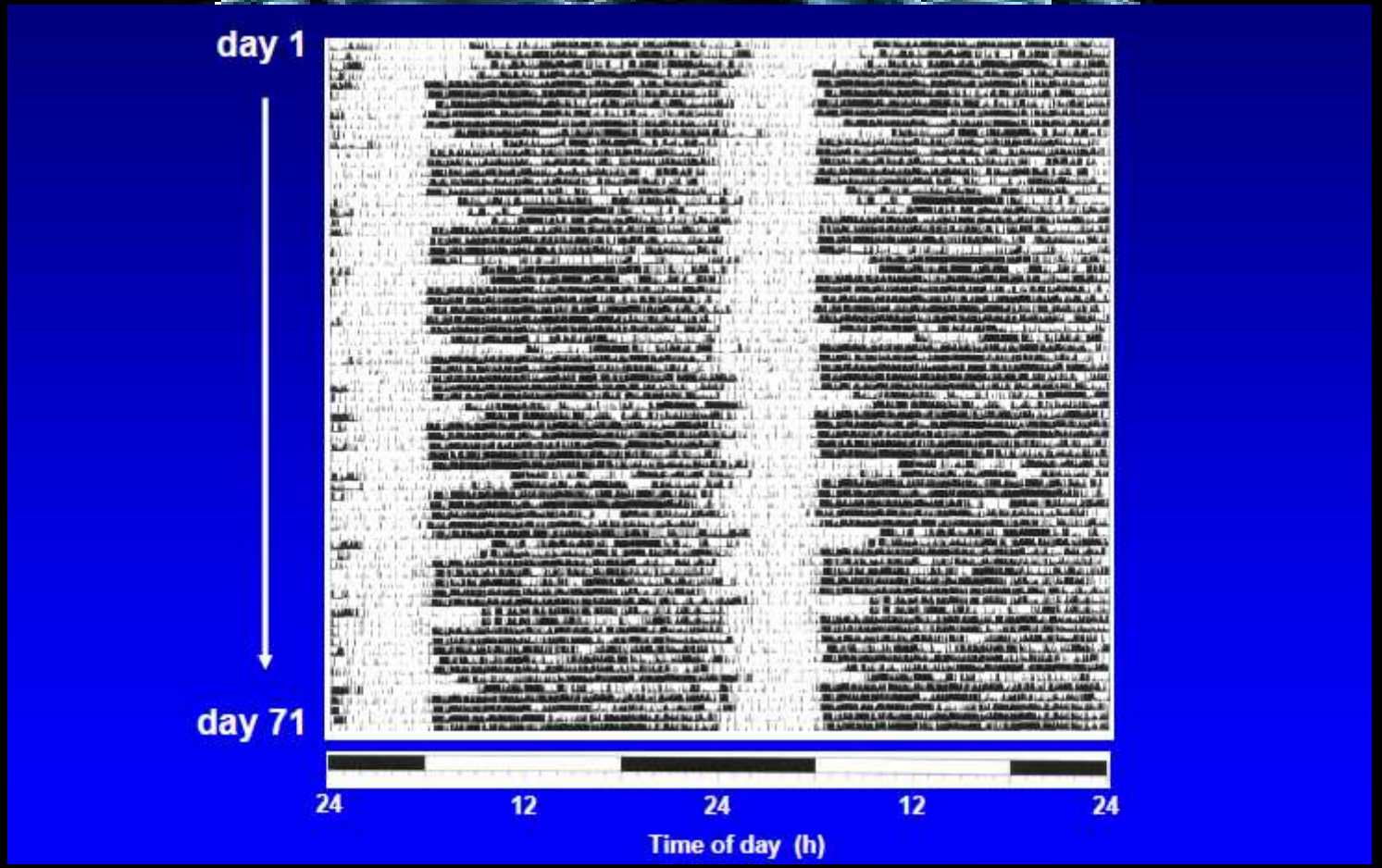


Figure 1: **Circadian rhythms of plasma melatonin, core body temperature, subjective alertness, task performance (reaction time, in secs), and triacylglycerol, from human beings held in constant routine conditions (ie, controlled light, posture, activity, and meals)**

The peak in the melatonin rhythm (panel A), shown by the dotted line, and the low-point of the temperature rhythm (panel B) are within 1 h of each other. The low-point of the alertness and performance rhythms (panels C and D, respectively) is shortly after the melatonin peak, and the peak in triacylglycerol (panel E) coincides with the melatonin peak.

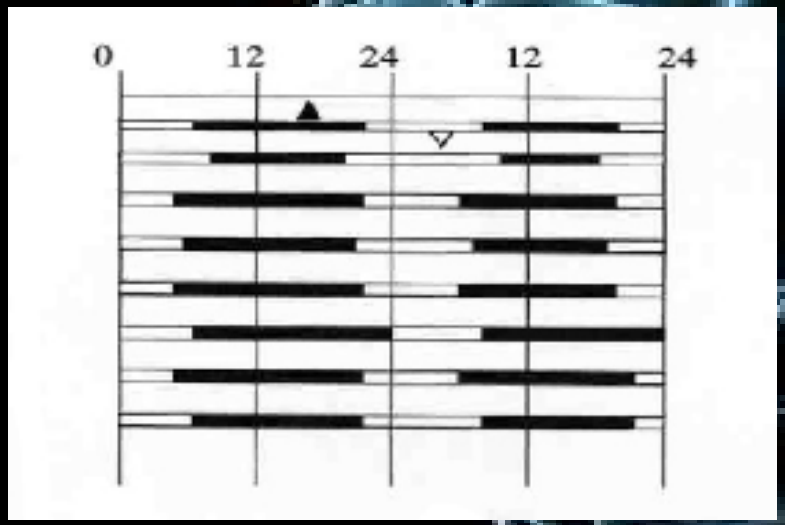
I.2.3. Les rythmes circadiens

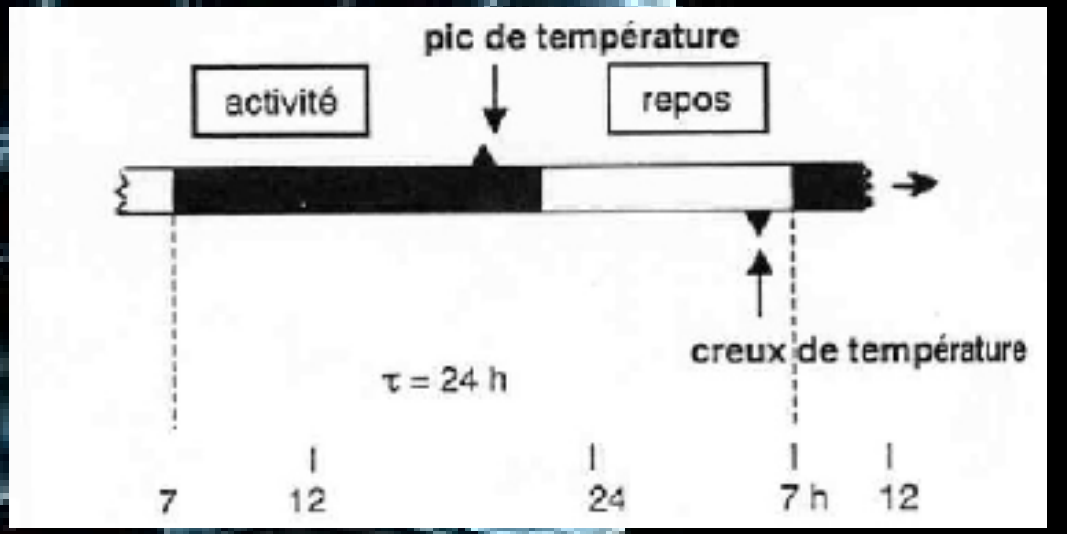
- Rythme activité/repos

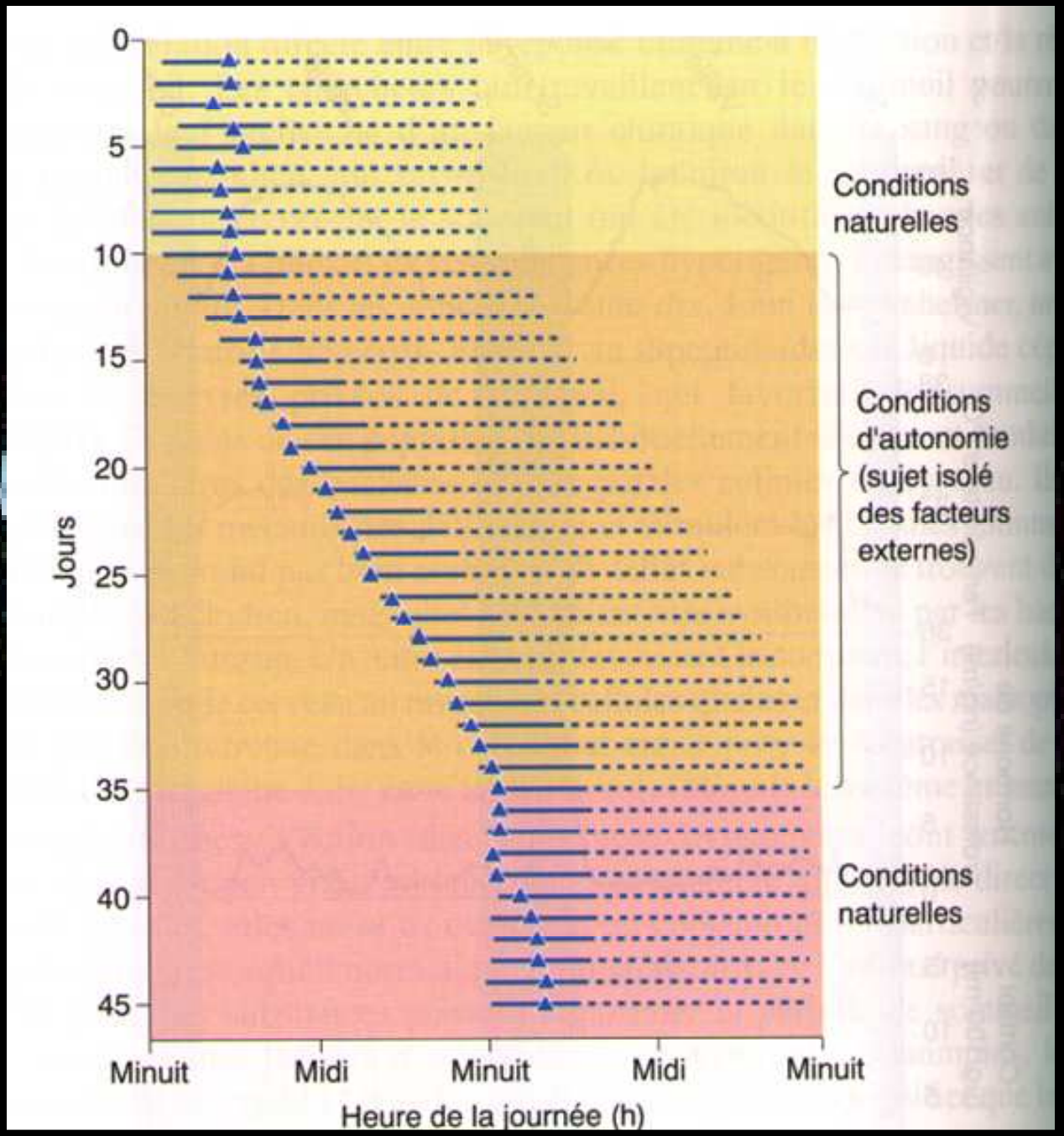


I.2.3. Les rythmes circadiens

- Rythme activité/repos

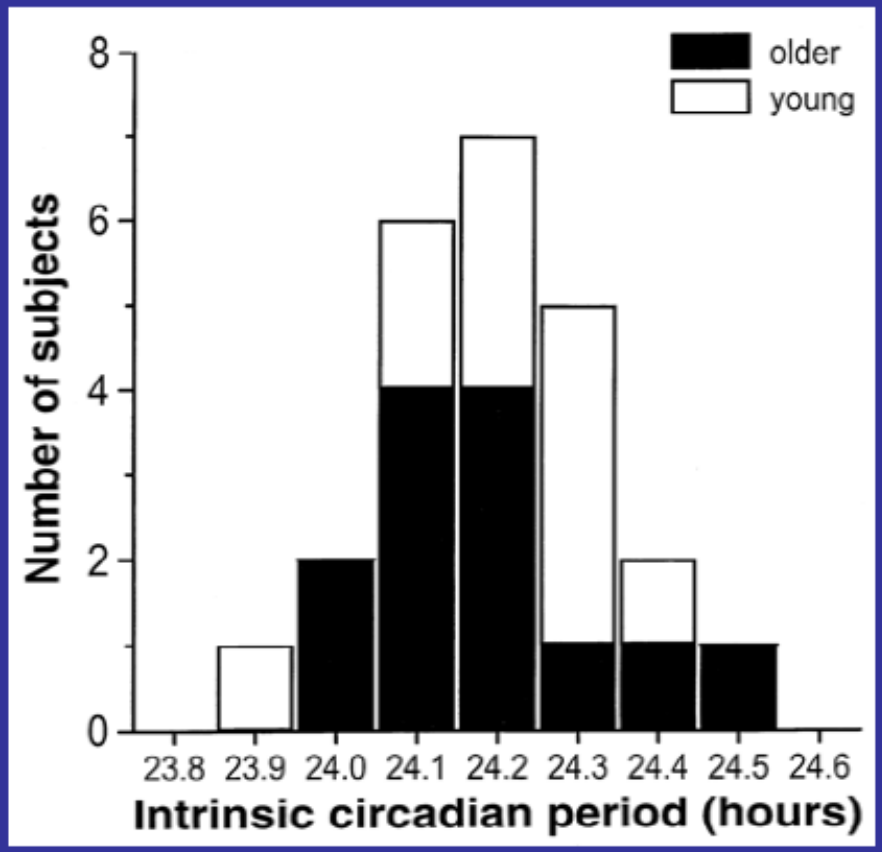





0
5
10
15
20
25
30
35
40
45
Jours
Conditions naturelles
Conditions d'autonomie (sujet isolé des facteurs externes)
Conditions naturelles
Minuit
Midi
Minuit
Midi
Minuit
Heure de la journée (h)

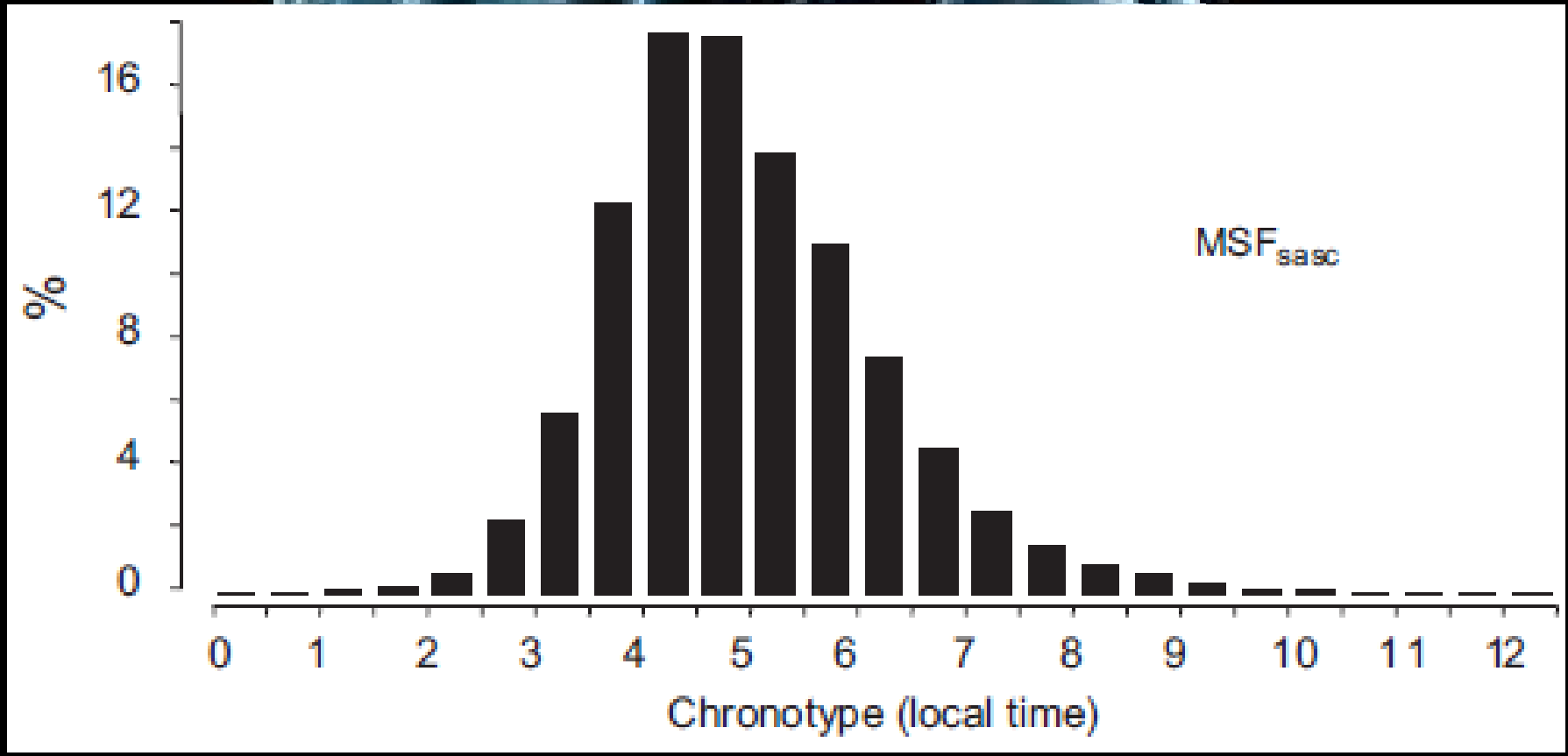
I.2.3. Les rythmes circadiens

Distribution de la période circadienne chez l'homme en condition de free-running(Czeisler et al, 1999)



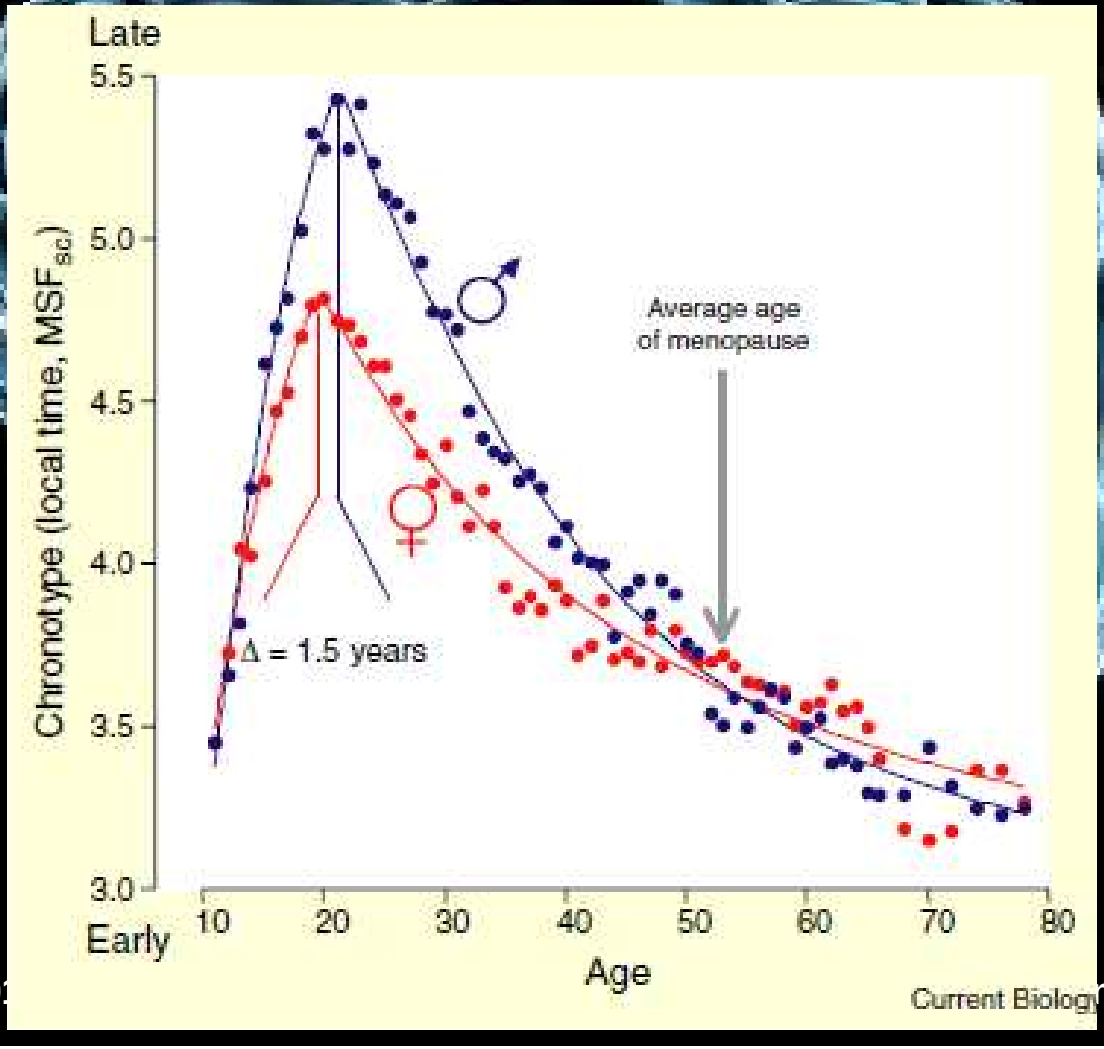
I.2.3. Les rythmes circadiens

- Rythme activité/repos



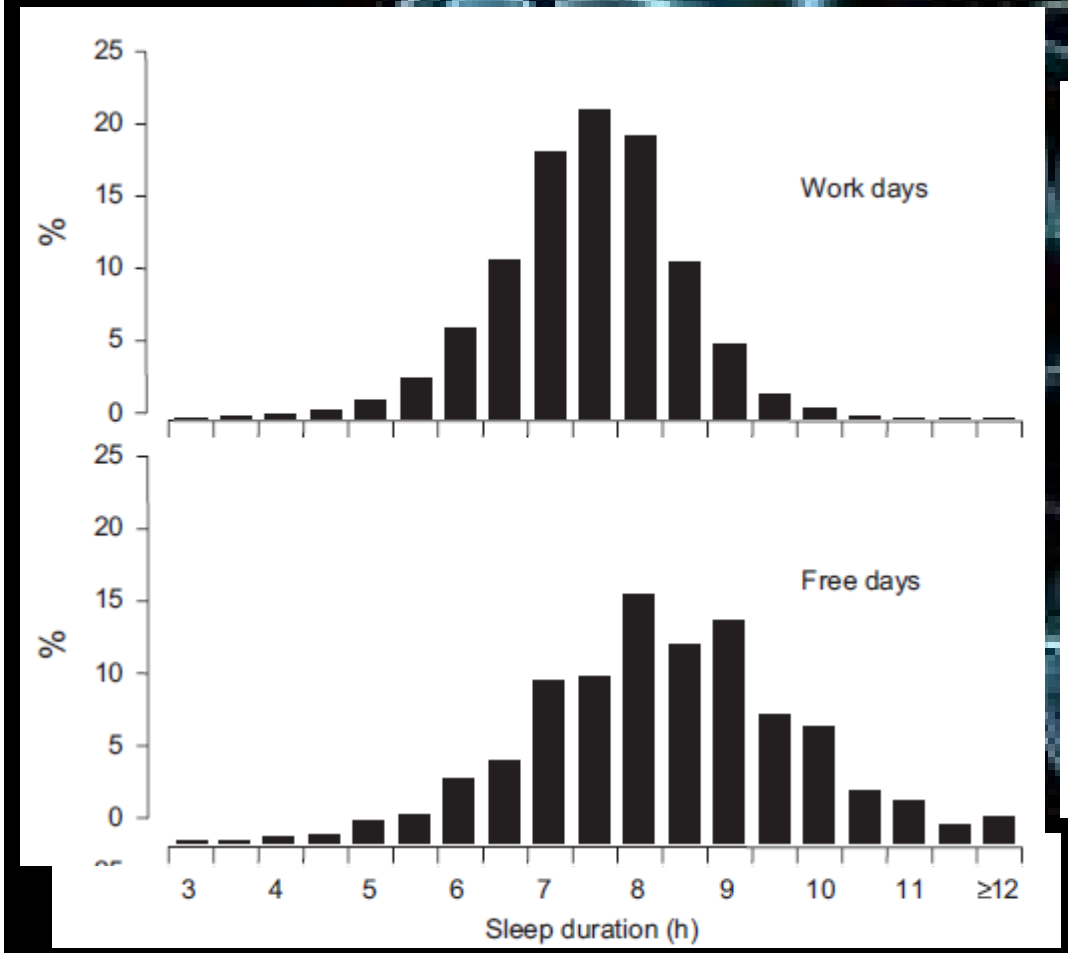
I.2.3. Les rythmes circadiens

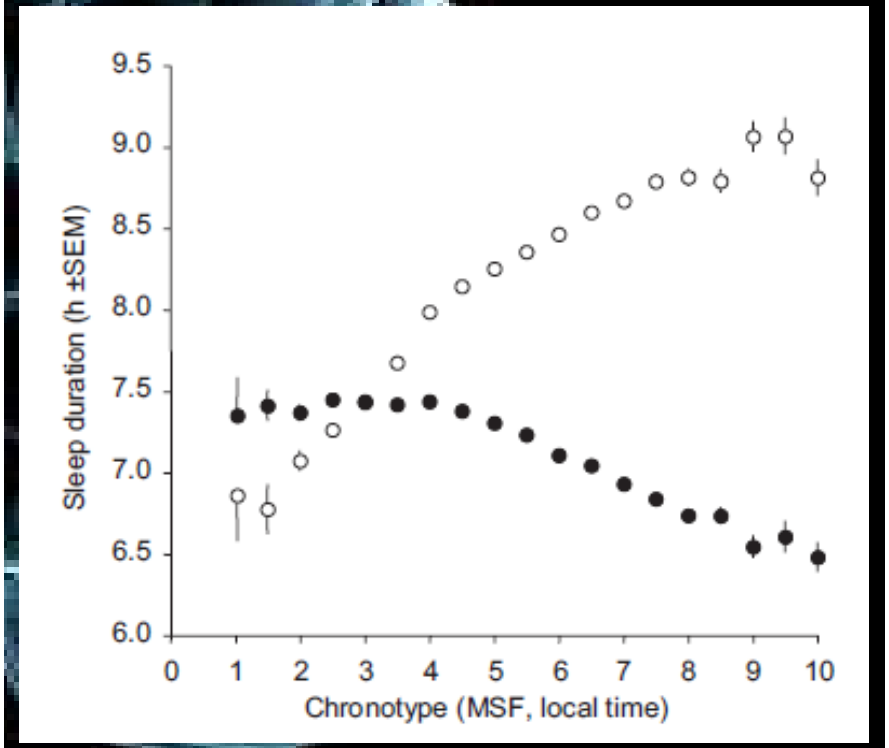
- Rythme activité/repos



I.2.3. Les rythmes circadiens

- Rythme activité/repos



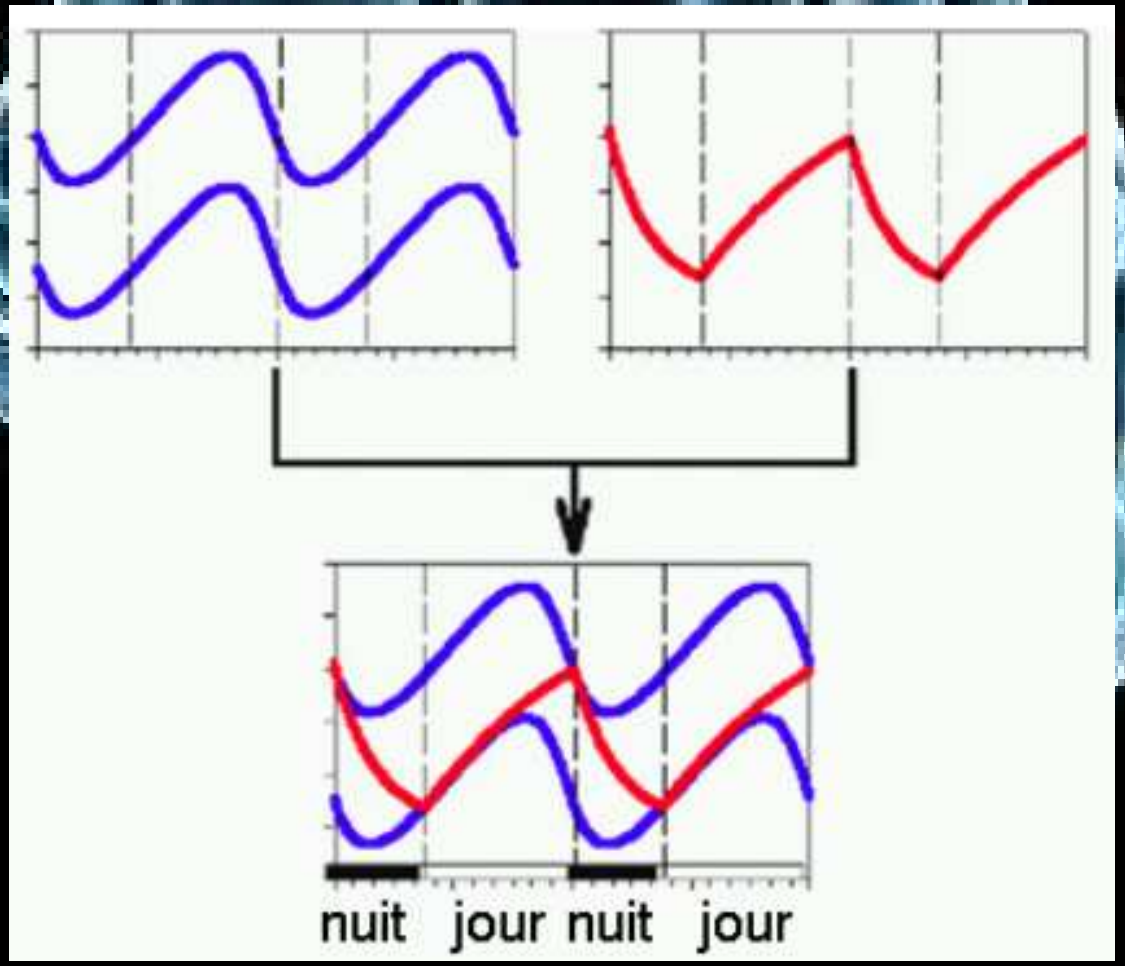


I.2.3. Les rythmes circadiens

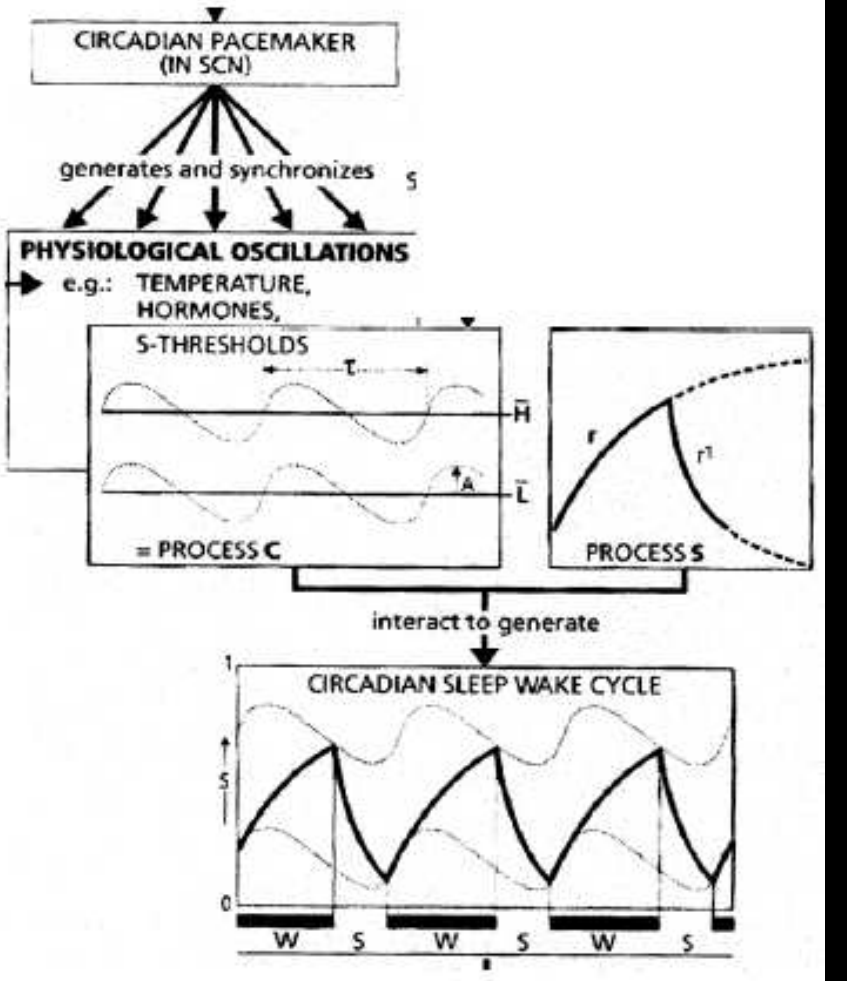
- Rythme T°

I.2.3. Les rythmes circadiens

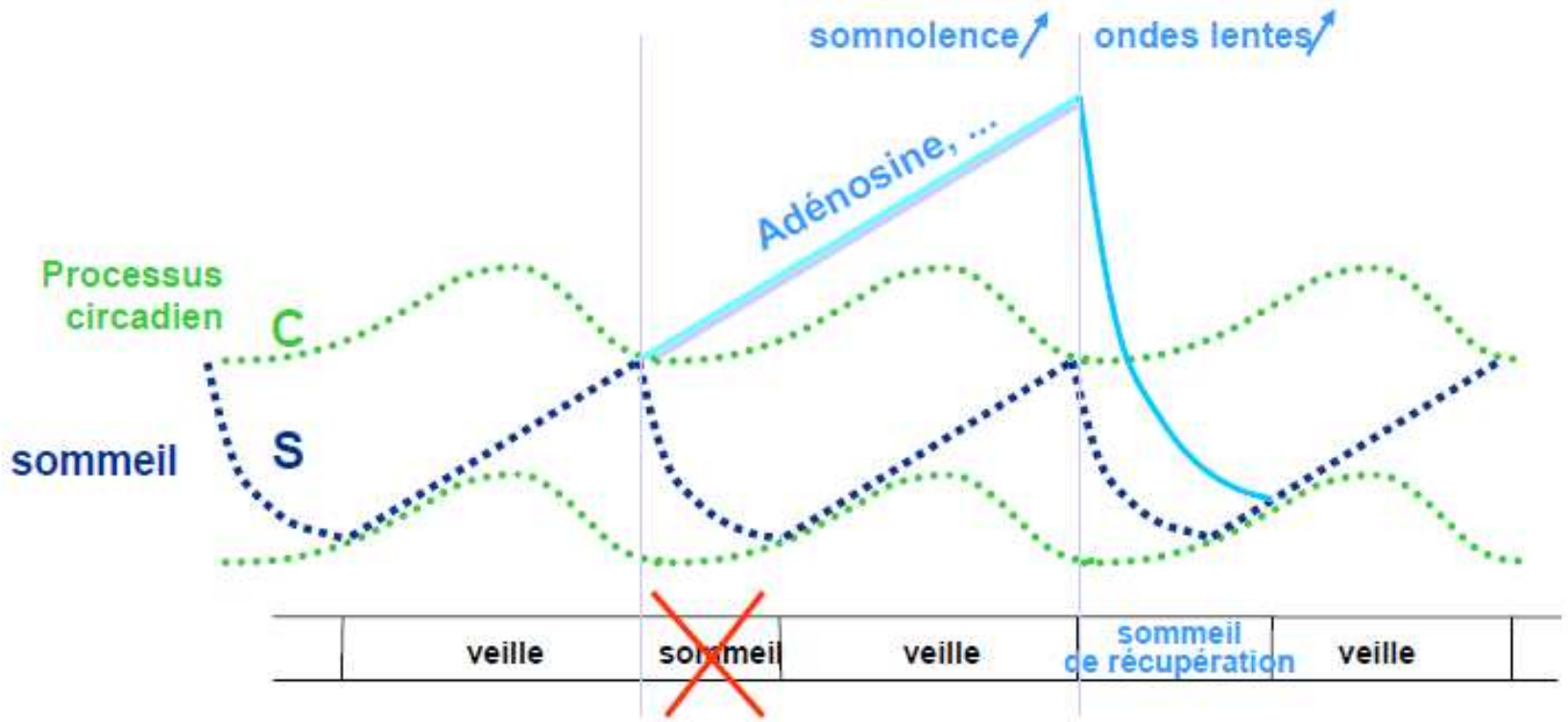
- Le rythme veille-sommeil



- Trois conditions sont requises pour cette action concertée:
  - **Un système homeostasique fonctionnel** (quantification des ondes lentes)
  - **Un système circadien fonctionnel**, incluant des synchroniseurs actifs (rythmes température/mélatonine en phase avec le cycle lumière-obscurité)
  - **Une relation de phase normale** entre l'horaire choisit des épisodes veille- sommeil (homeostasie) et la phase du système circadien

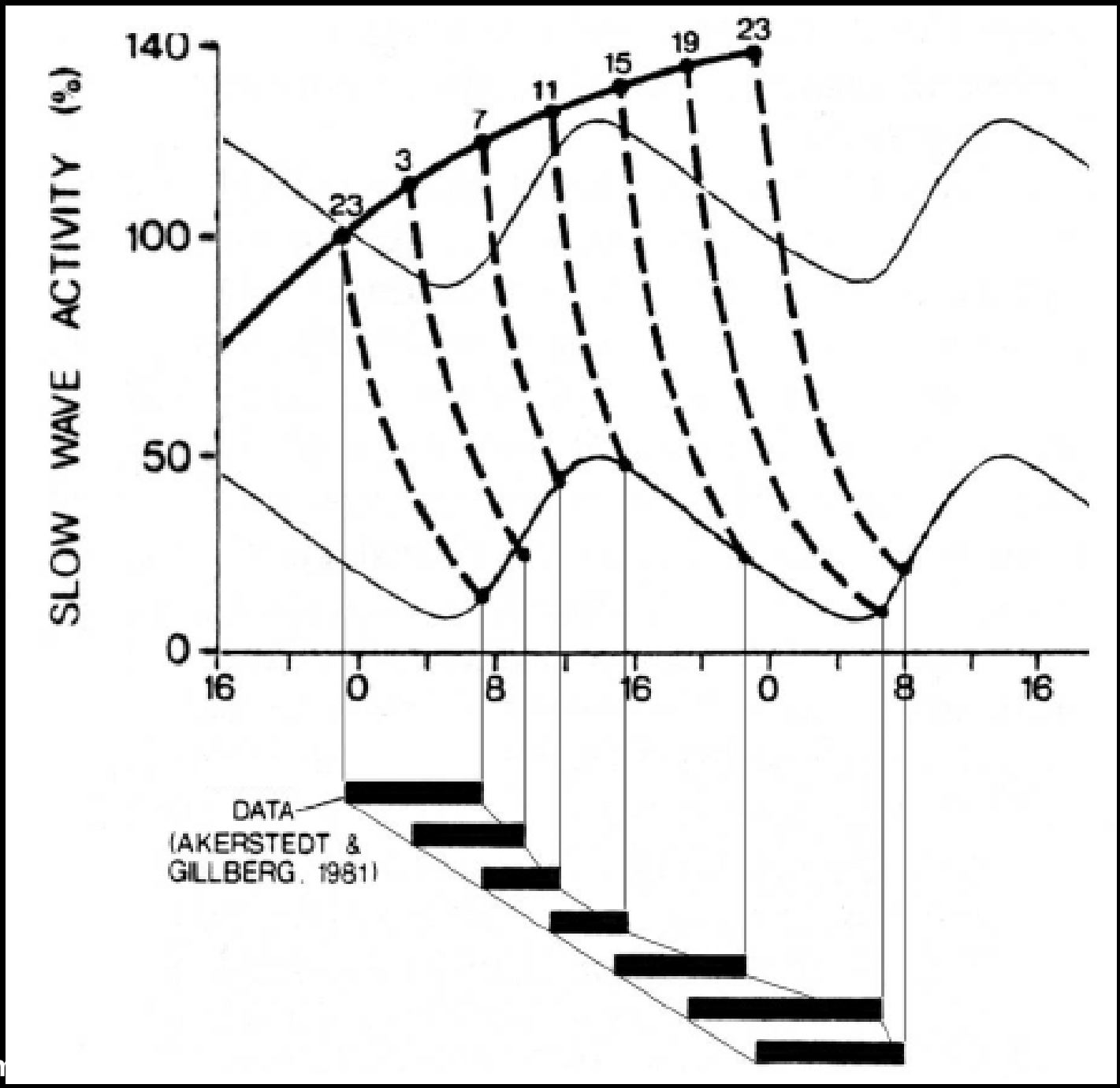


L'adénosine serait mise en jeu essentiellement lors de l 'éveil prolongé

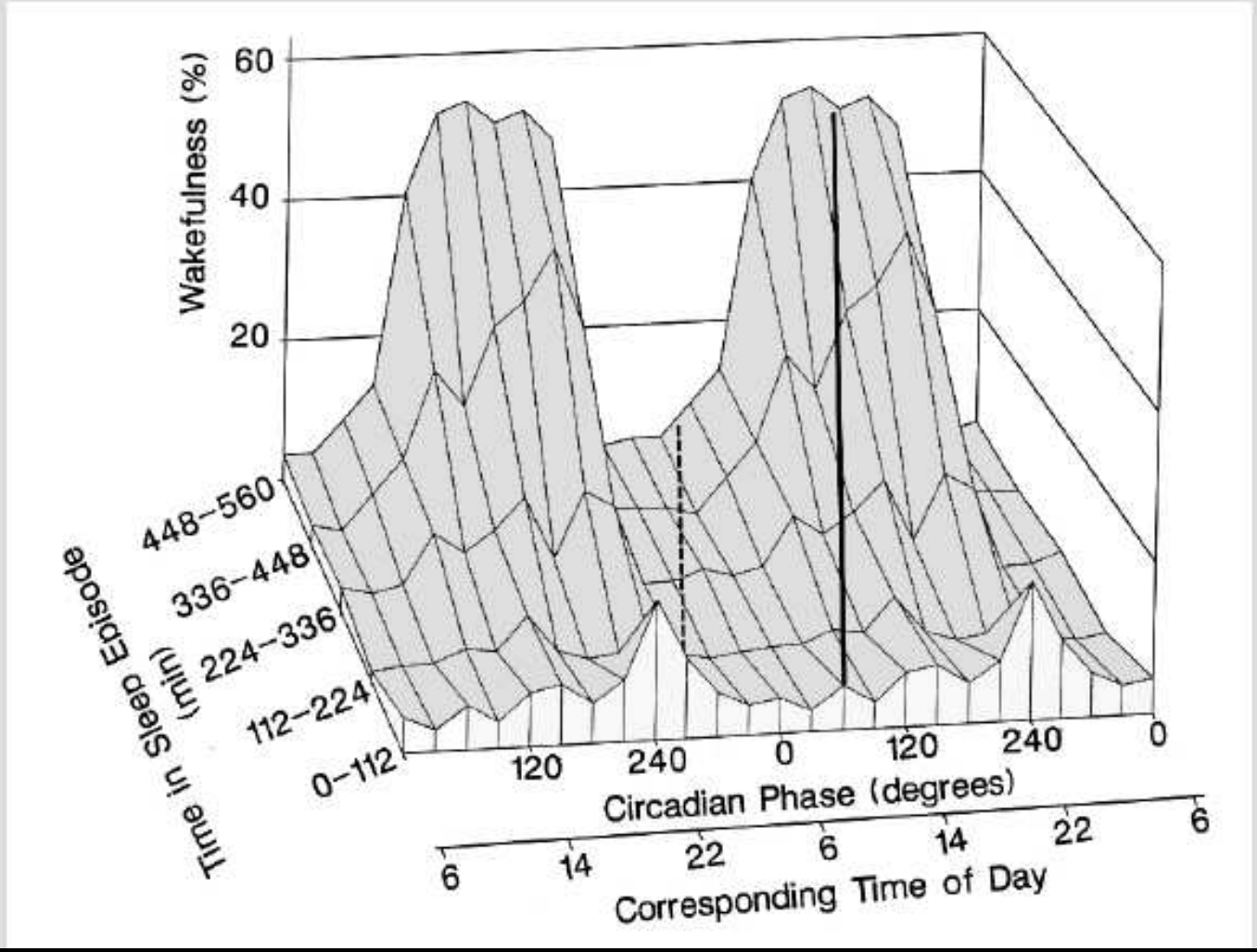


La somnolence apparaissant au cours de la privation de sommeil, et le rebond de sommeil lent consécutif seraient sous le contrôle de l'adénosine.

d'après Borbély 1982


SLOW WAVE ACTIVITY (%)
140
100
50
0
23
3
7
11
15
19
23
16
0
8
16
0
8
16
DATA
(AKERSTEDT &
GILLBERG, 1981)

"There is only a narrow range of sleep-onset times that allow for consolidated sleep throughout the sleep episode"



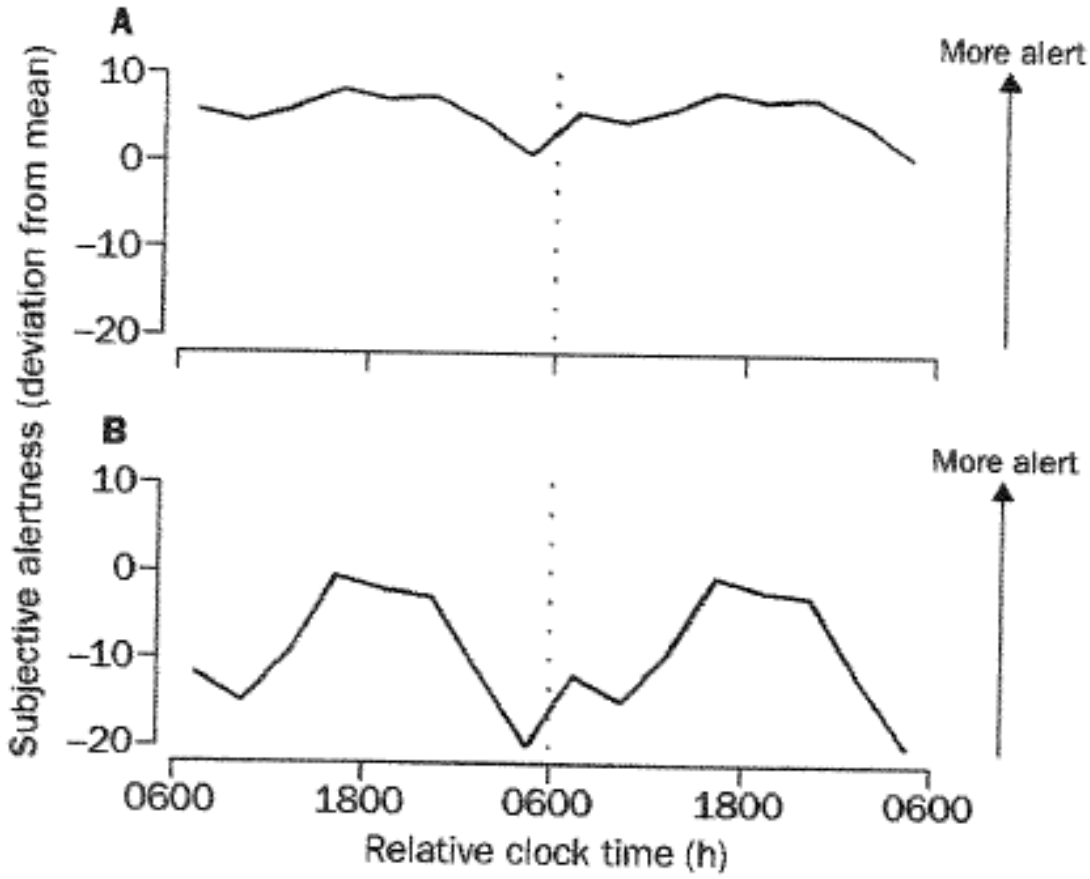
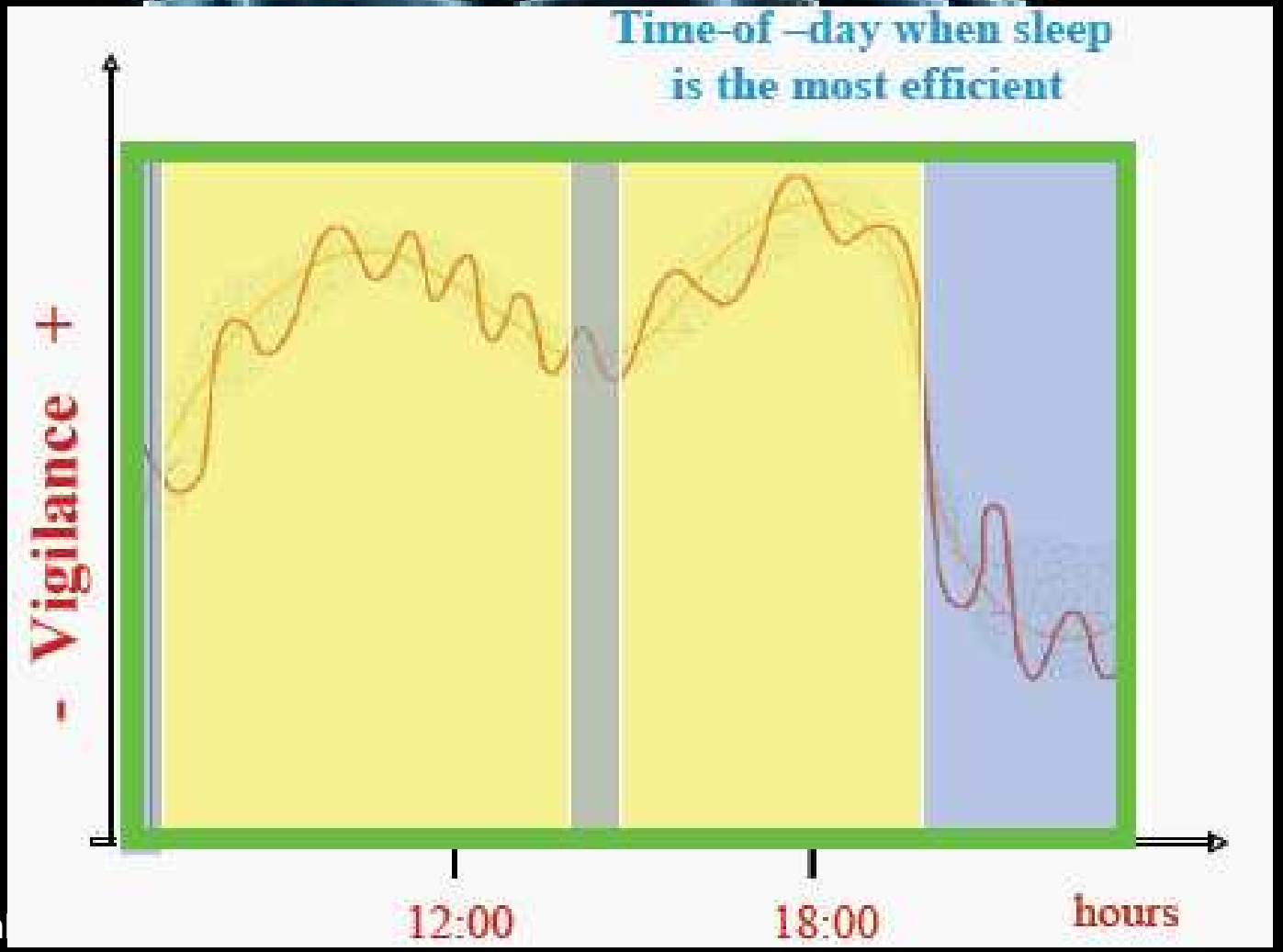


Figure 5: **Double plot (48 h) of the interactive effects of sleep debt and biological clock time on subjective alertness ratings.** Alertness was assessed at various times of the day. For each assessment, sleep debt (the duration of wakefulness preceding the assessment) was either less than 3 h (panel A) or between 16 and 19 h (panel B). The dotted vertical line at 0600 h is the time of core body temperature minimum in these participants. In both A and B, minimum alertness is just before 0600 h. However, in B, the average level of alertness is substantially lower, and the rhythm amplitude is greater. Clearly, with increasing sleep debt the circadian influence is more pronounced. Redrawn from Dijk[43] with permission.

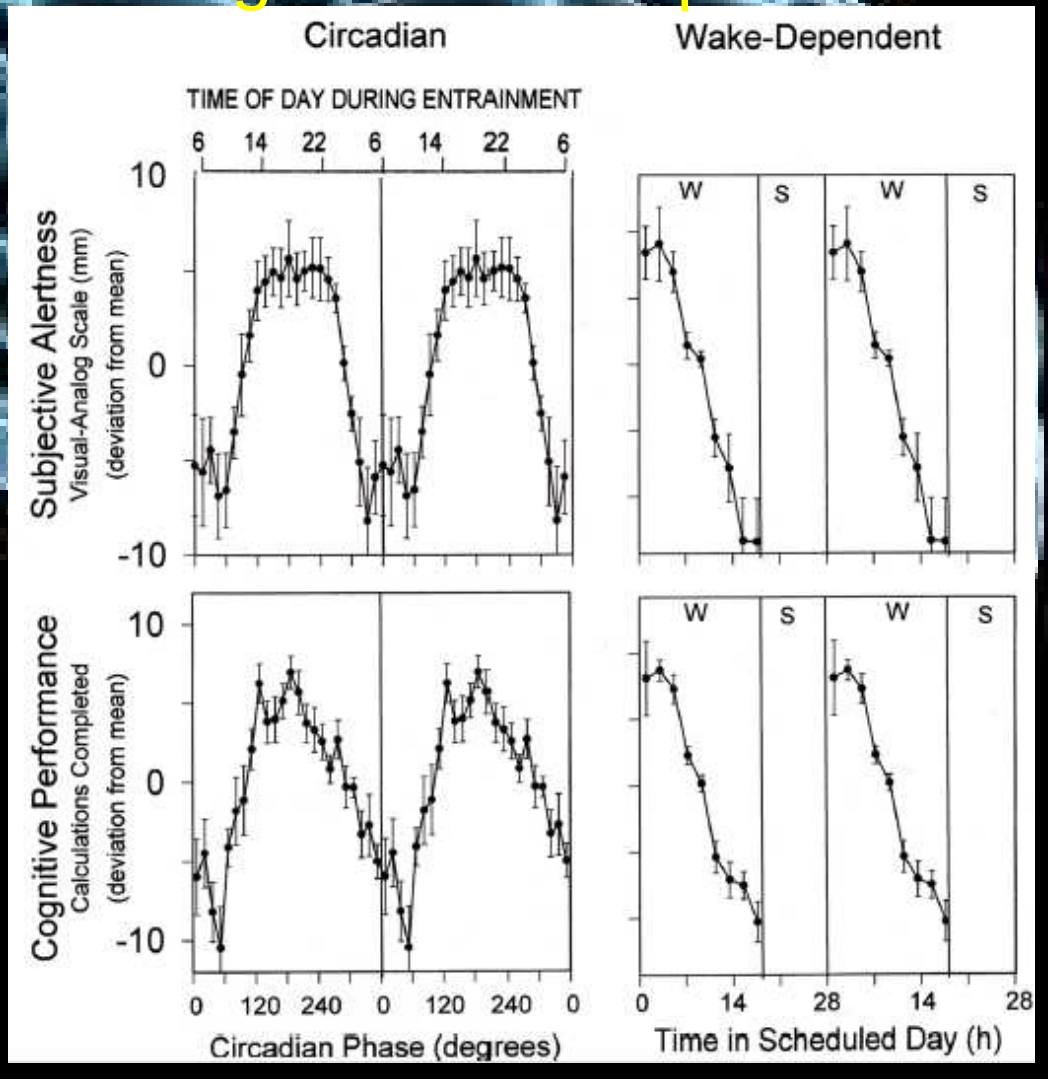
I.2.3. Les rythmes circadiens

- Le rythme de vigilance et de performance



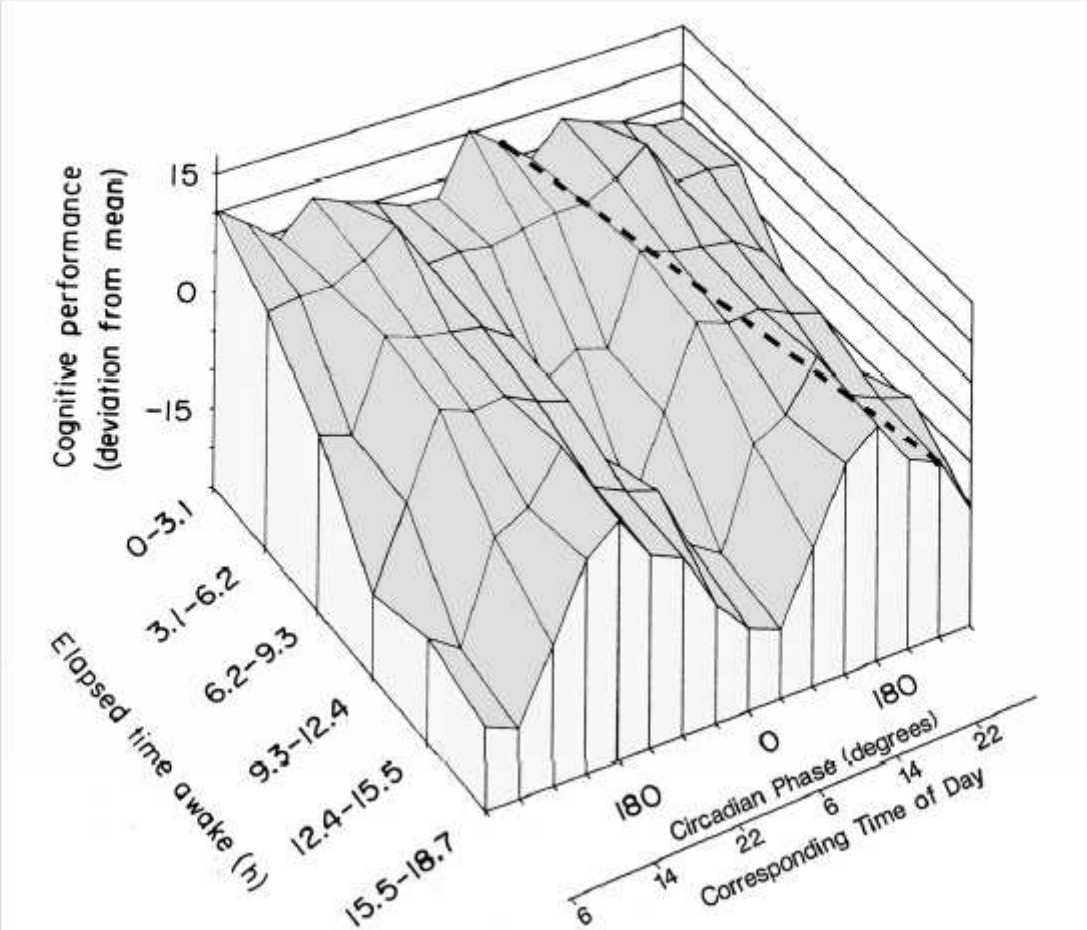
I.2.3. Les rythmes circadiens

- Le rythme de vigilance et de performance

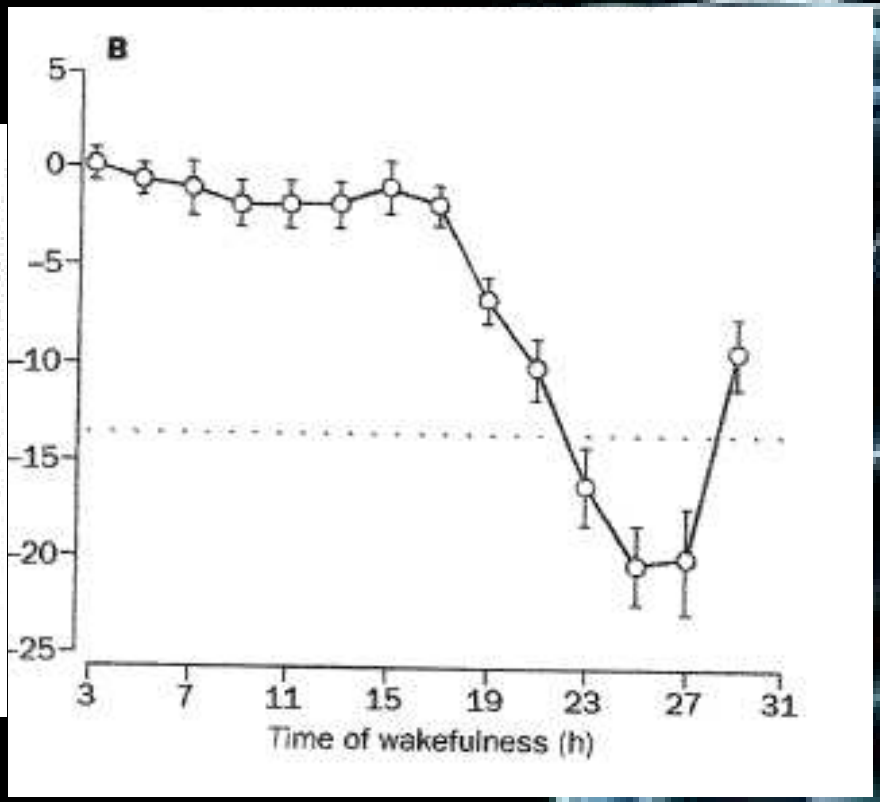


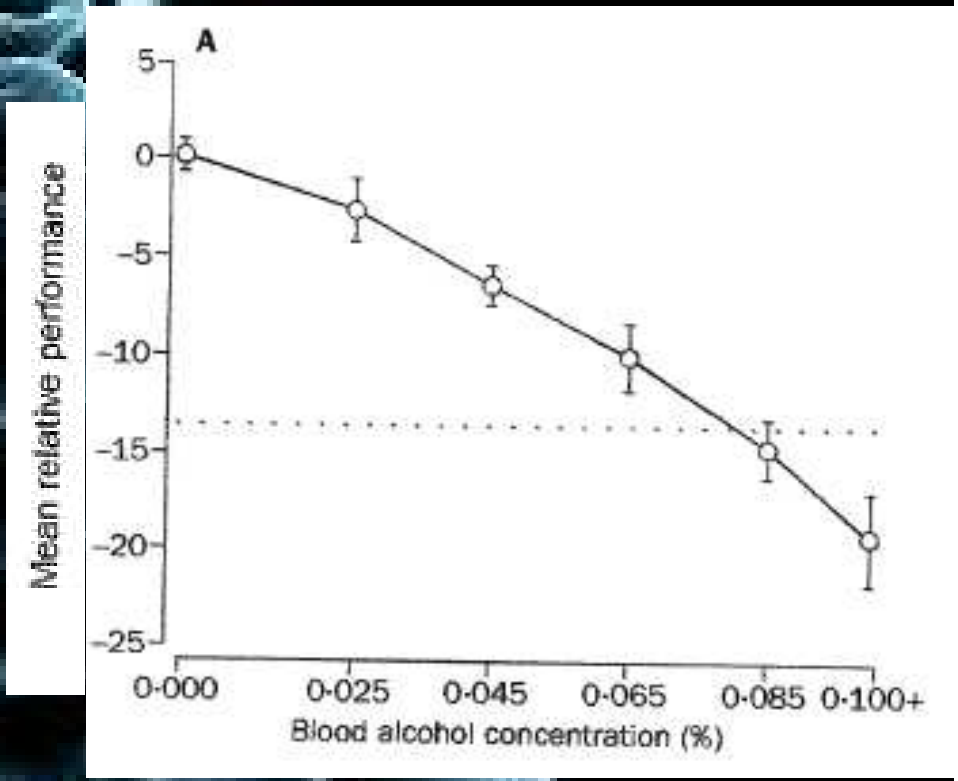
I.2.3. Les rythmes circadiens

There is only a narrow range of wake-up times that allow for a sustained high level of performance throughout the day



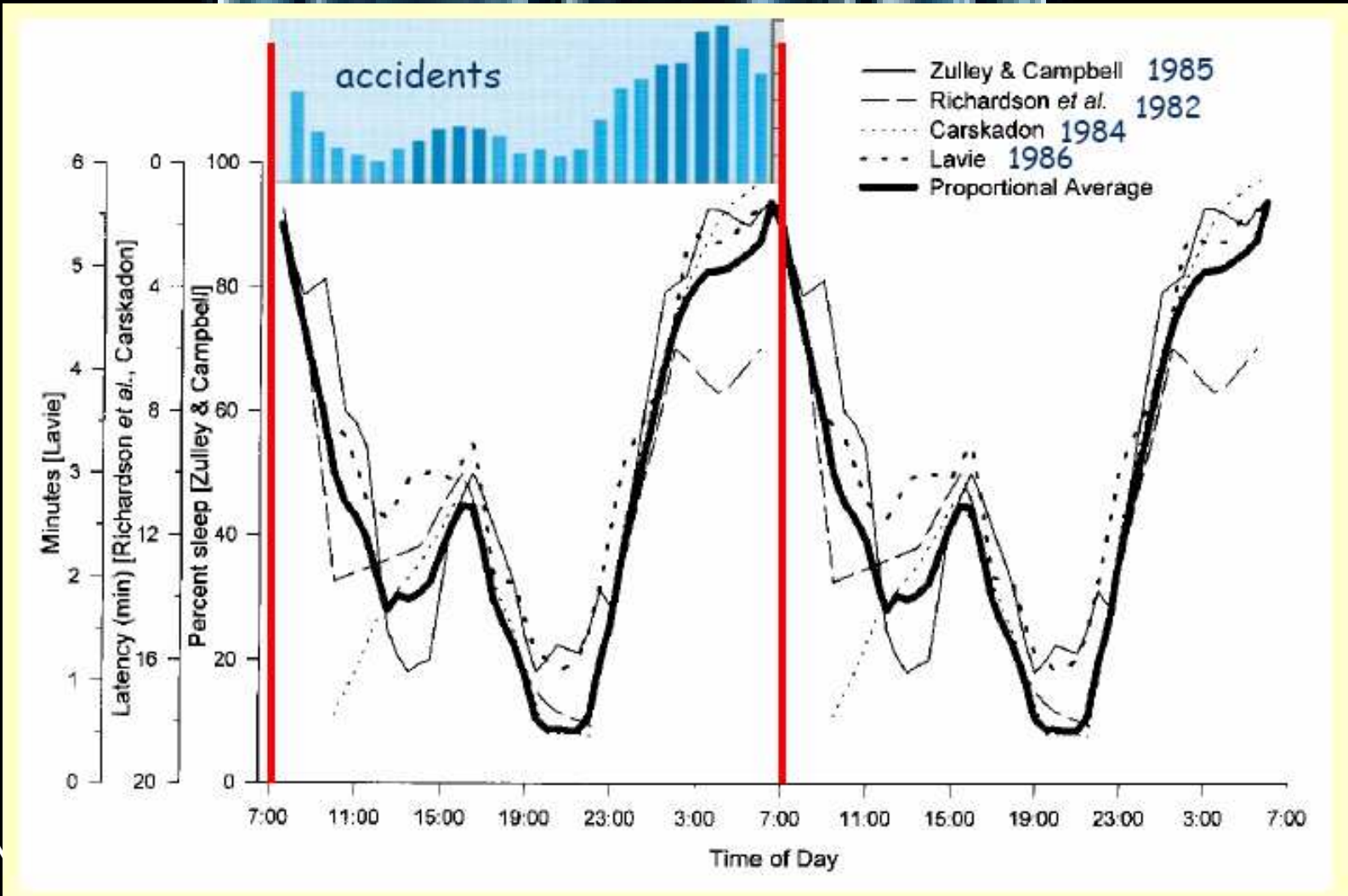
Chronobiologie & Hormones





I.2.3. Les rythmes circadiens

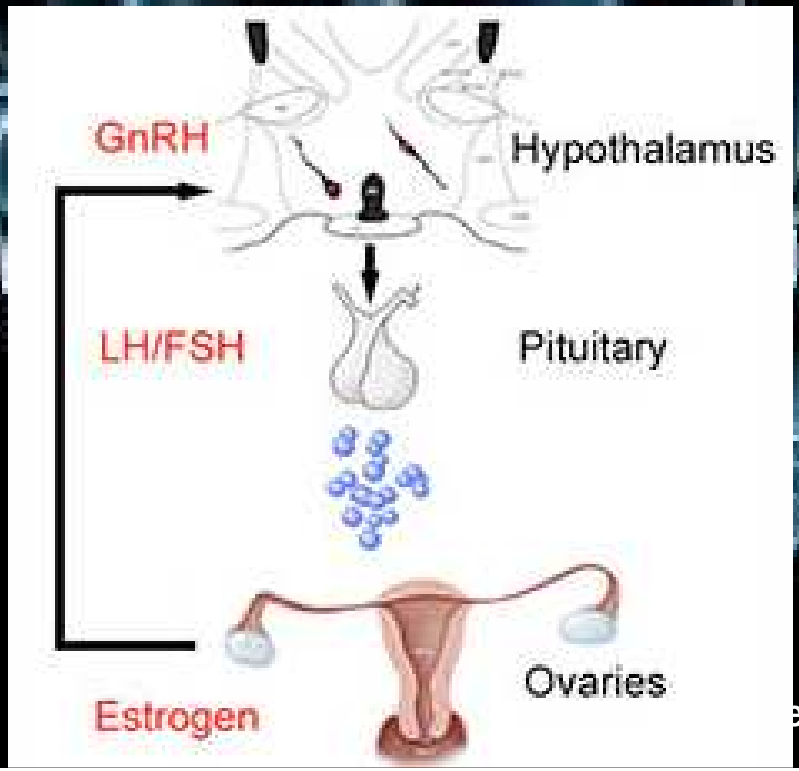
- Le rythme de vigilance et de performance

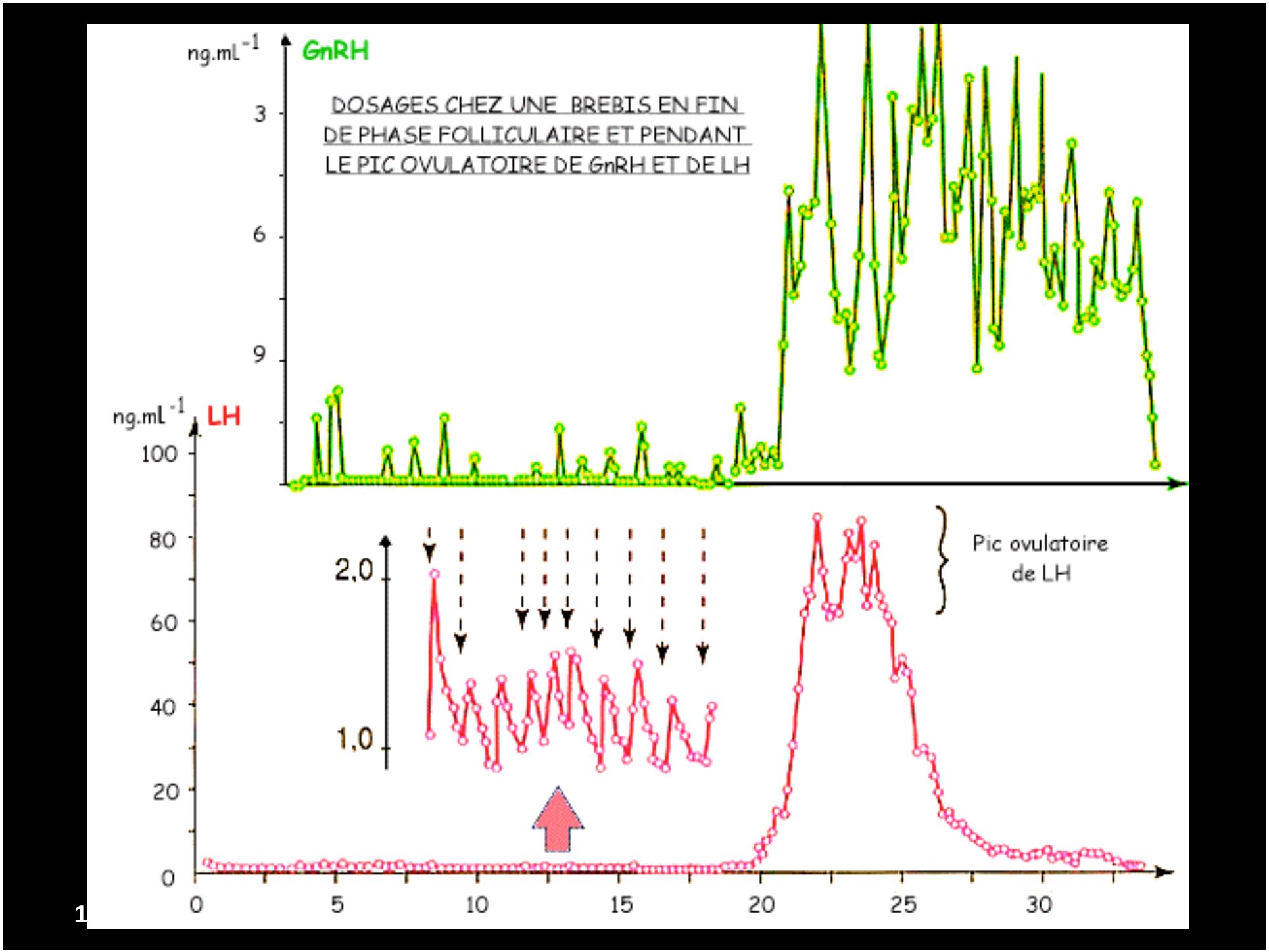


I.2.4. Les rythmes ultradiens

- Rythme ultradien : la GnRH

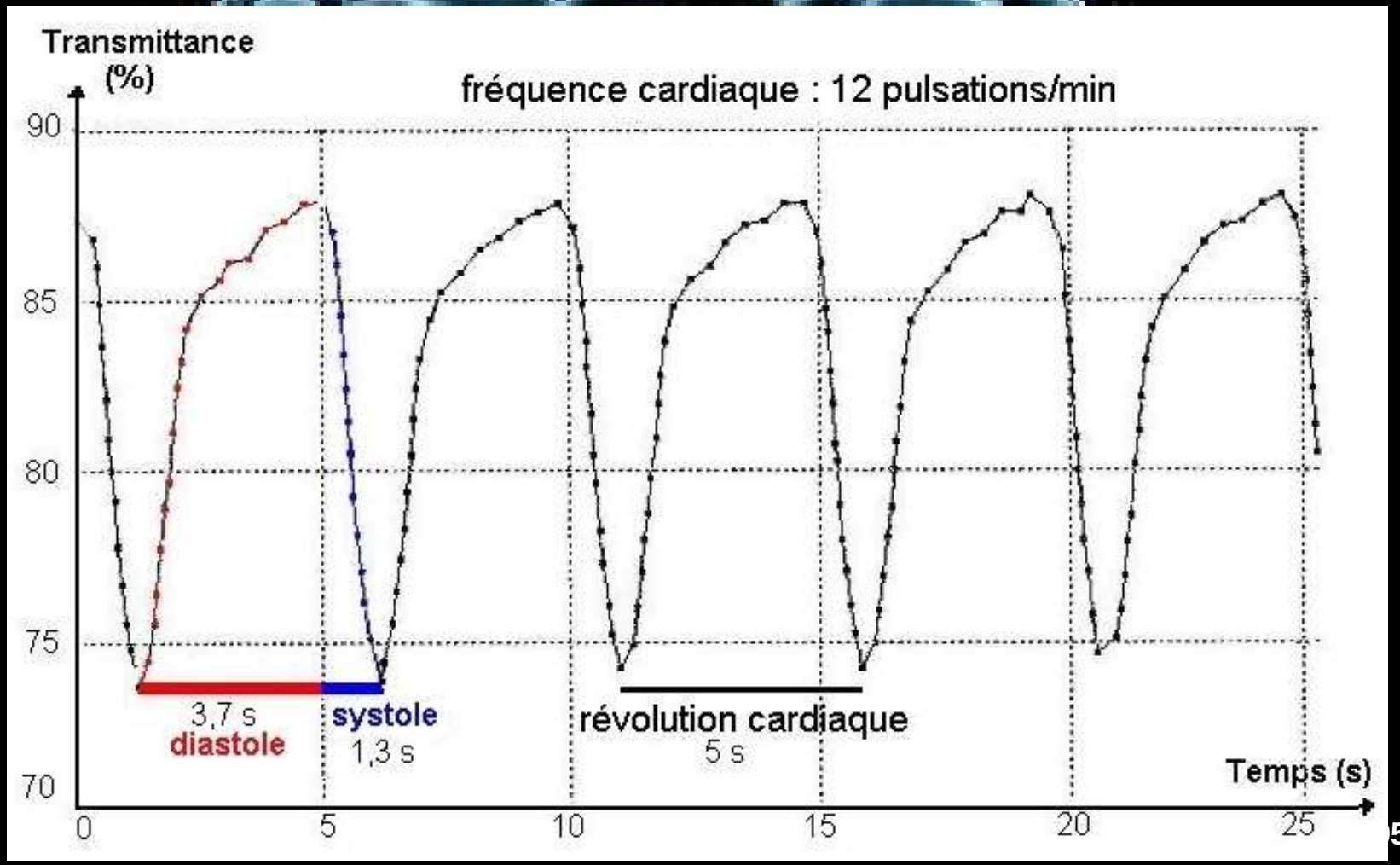
La GnRH contrôle la libération de FSH et LH. (Elle agit donc sur leurs propres cycles de rétrocontrôle pour influer sur leurs concentrations). FSH et LH jouent un rôle majeur dans la libération d'hormones sexuelles dans le sang. C'est en fonction de cette concentration en hormones sexuelles qu'est libérée la GnRH.




ng.mL-1
GnRH
DOSAGES CHEZ UNE BREBIS EN FIN DE PHASE FOLLICULAIRE ET PENDANT LE PIC OVULATOIRE DE GnRH ET DE LH
3
6
9
ng.mL-1
LH
100
80
60
40
20
0
2,0
1,0
Pic ovulatoire de LH
0
5
10
15
20
25
30

I.2.4. Les rythmes ultradiens

- Rythme ultradien : la révolution cardiaque



I.2.4. Les rythmes ultradiens

- Rythme ultradien : le sommeil paradoxal

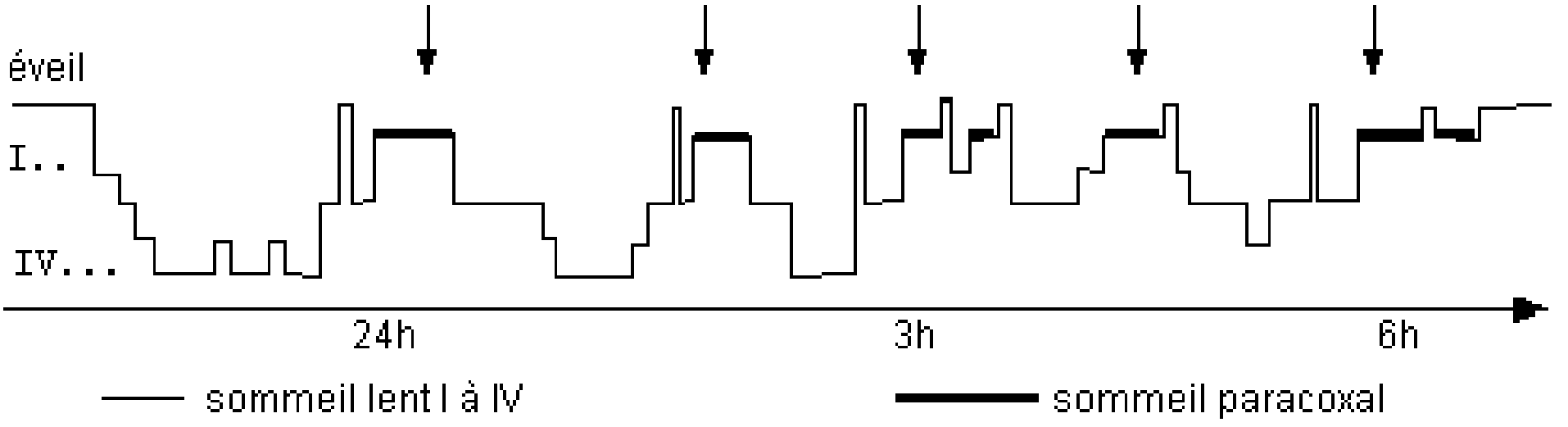
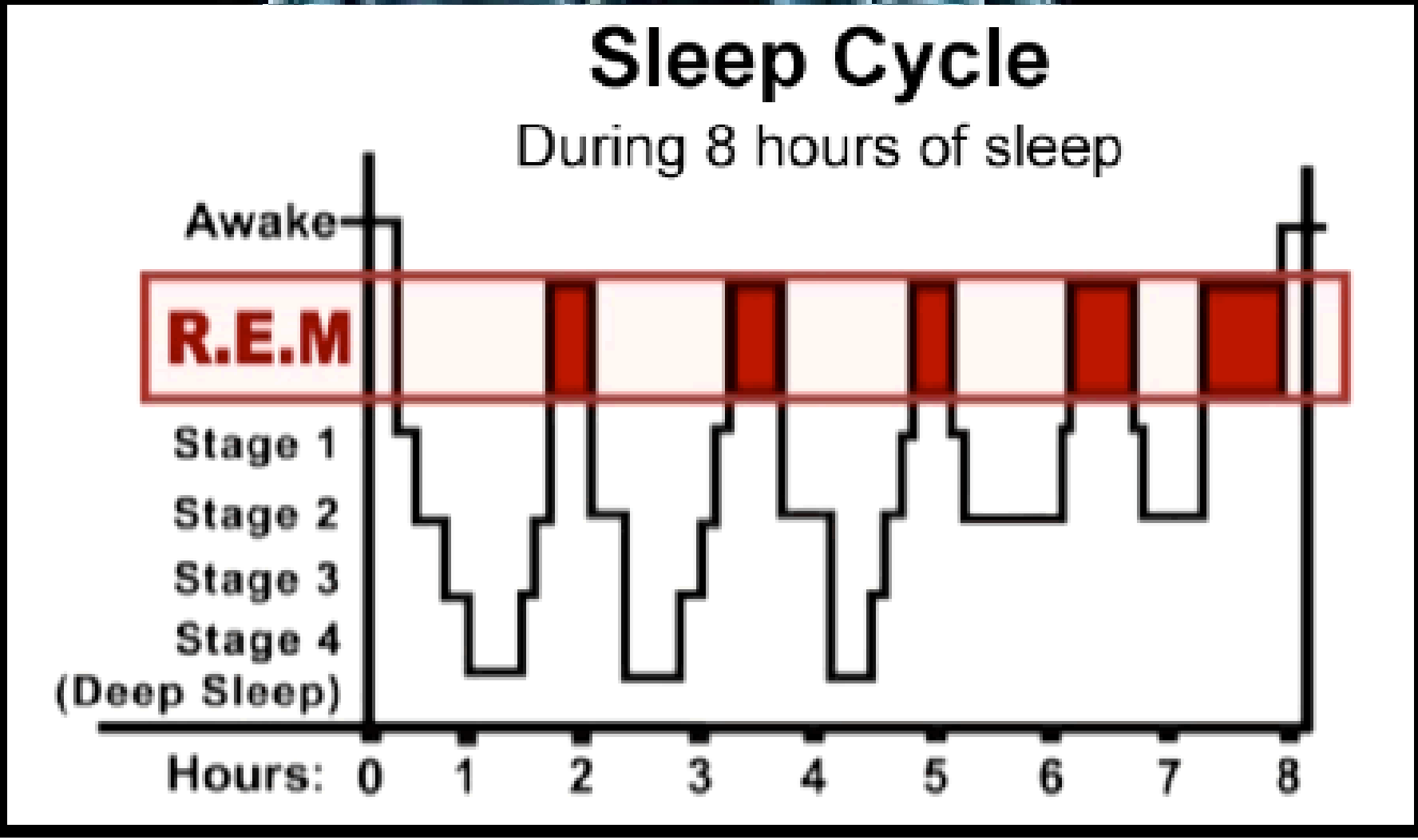


Fig 4 : Rythme de 90 mn du sommeil paradoxal et du rêve

I.2.4. Les rythmes ultradiens

- Rythme ultradien : le sommeil paradoxal

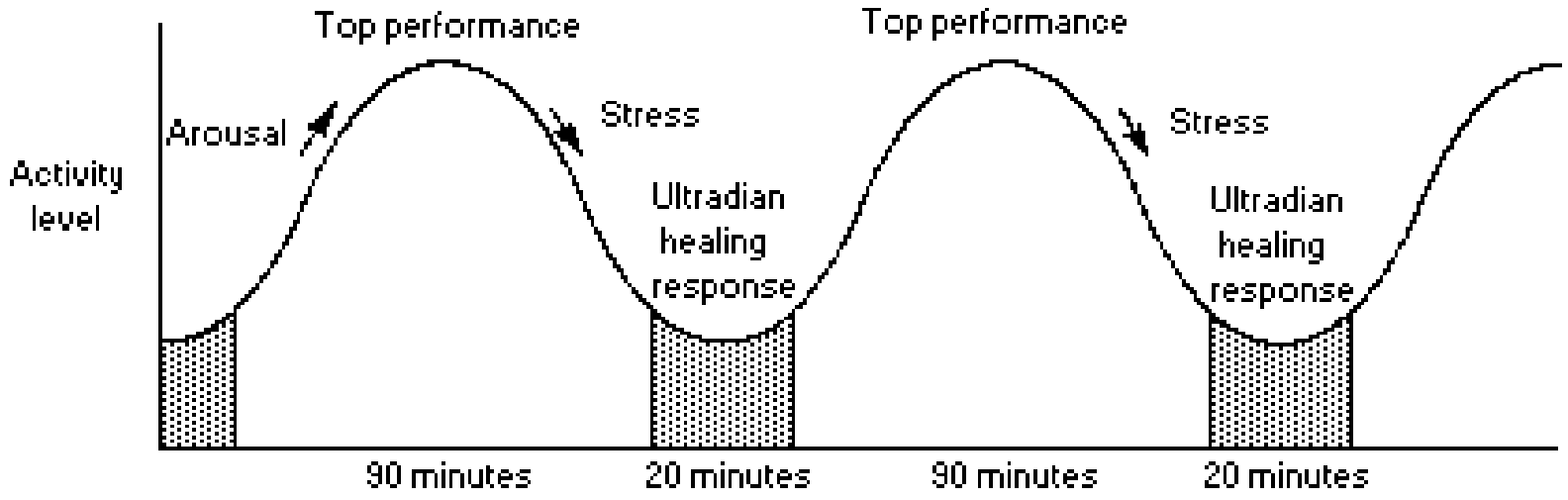


I.2.4. Les rythmes ultradiens

- Rythme ultradien : la performance cognitive

FIGURE 2

THE ULTRADIAN PERFORMANCE RHYTHM



Adapted from: Rossi, EL: The 20 Minute Break. Tarcher-Putnam, New York, 1991, p. 12.

I. La chronobiologie

1. Constats-définitions

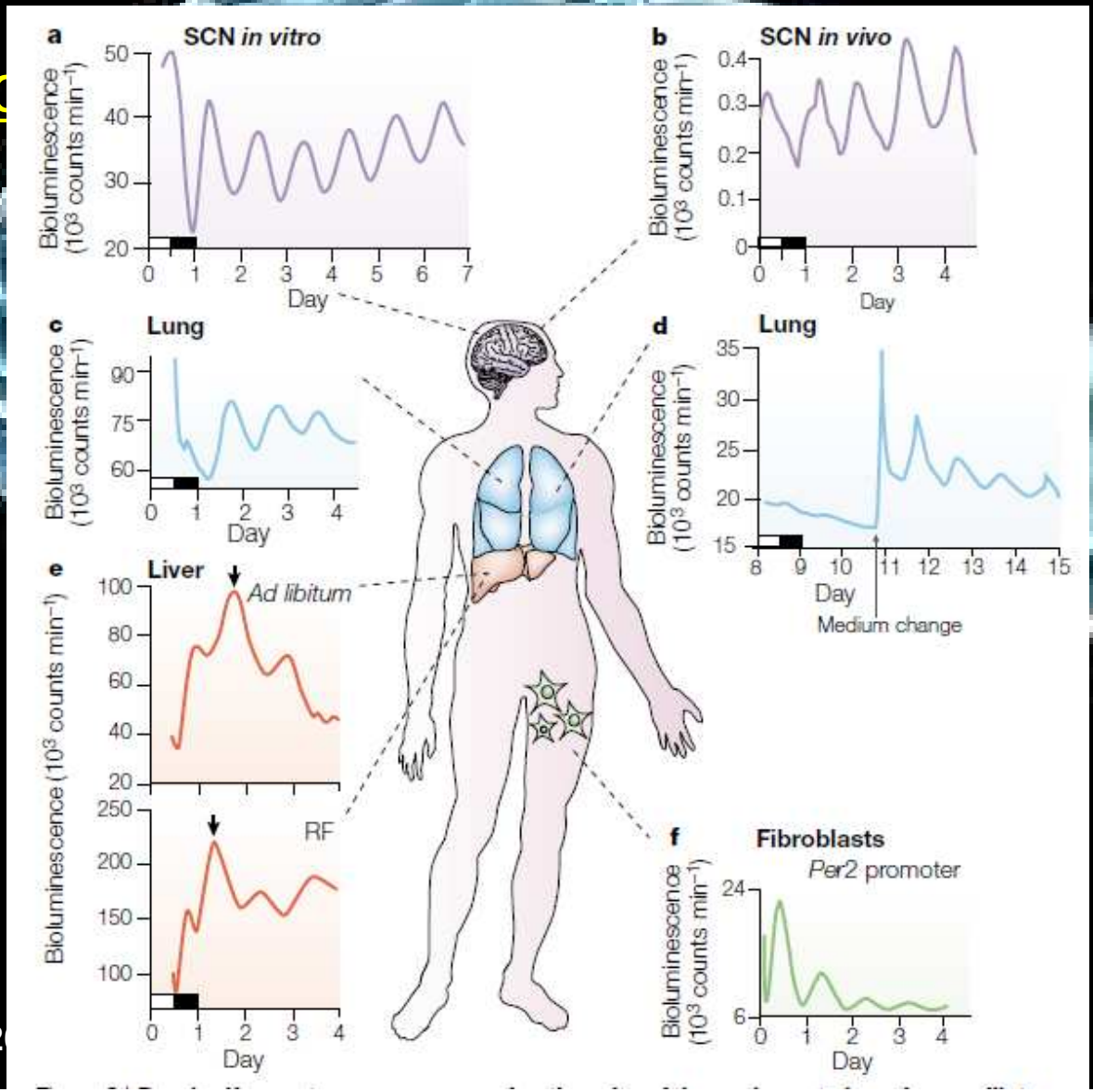
2. Les rythmes biologiques

3. La régulation des rythmes

Hastings et coll., 2003

I.3. La régulation des rythmes

☞ Les ho



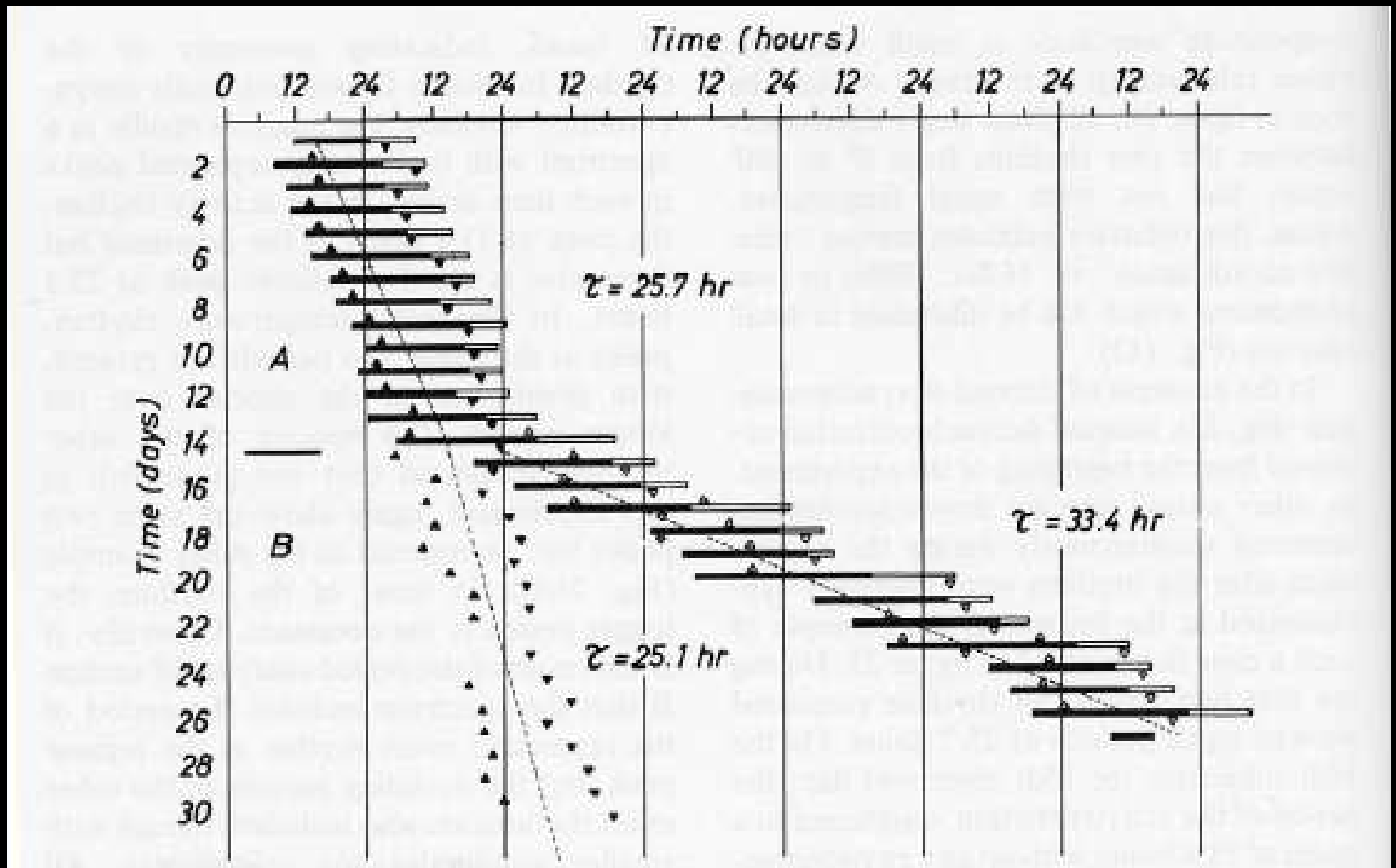
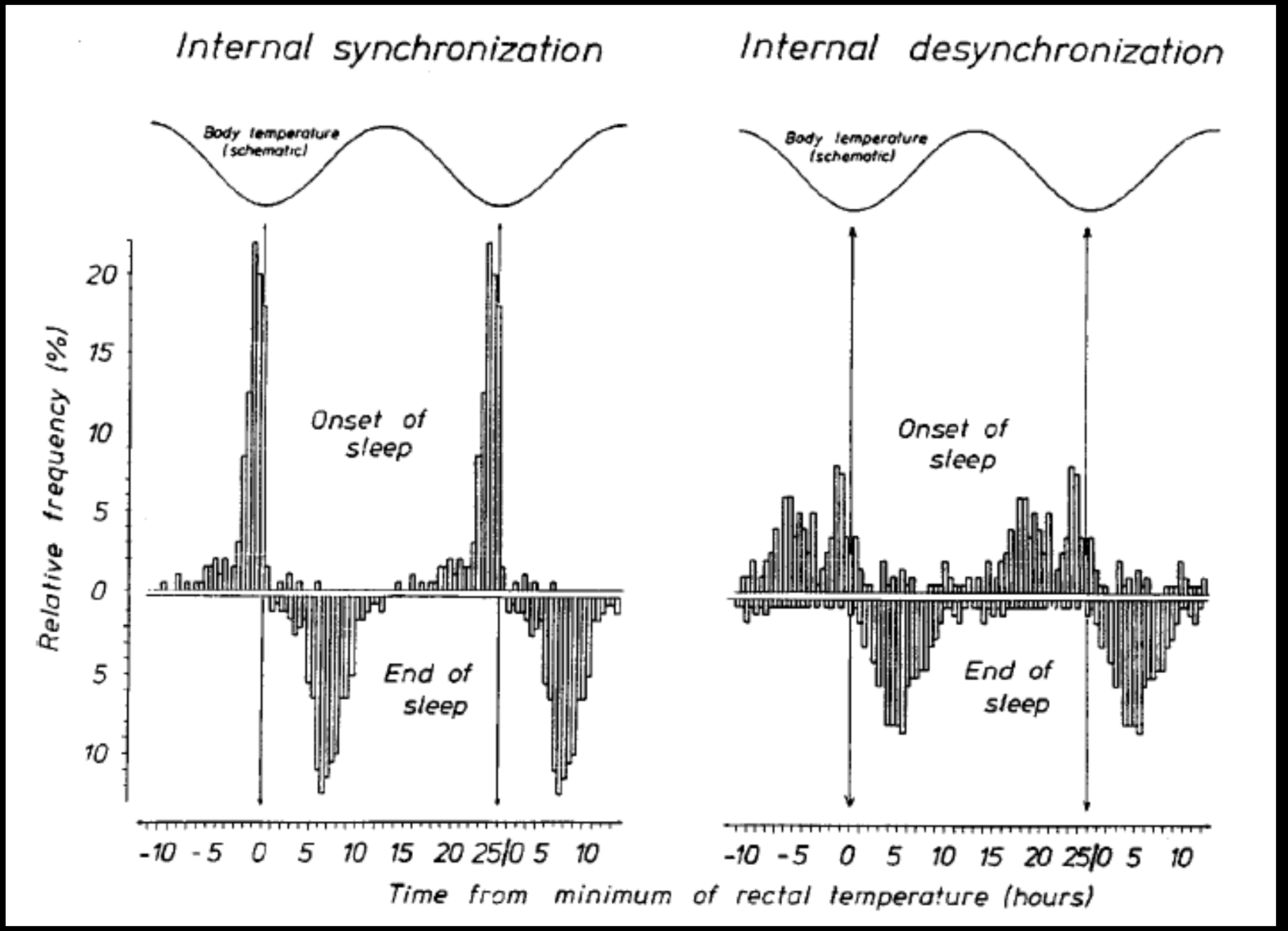
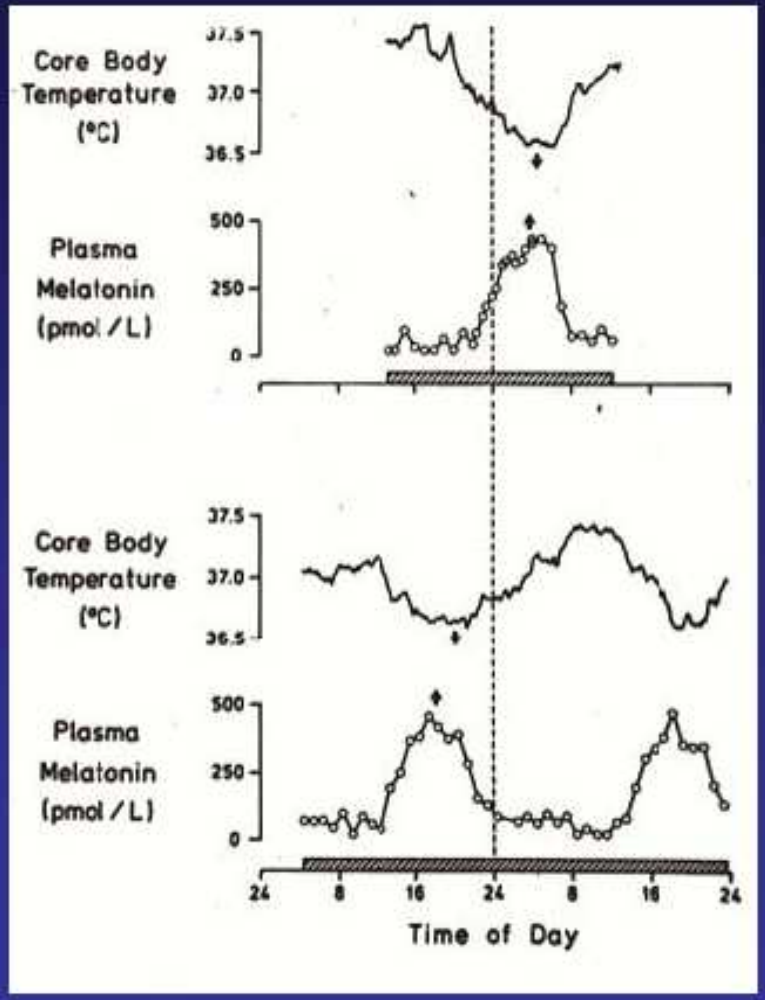


Figure 27. Autonomous rhythm of a subject (E.v.S., ♀ 24 y) living under constant conditions without time cues. The experiment is divided arbitrarily into two sections (A and B), for further analyses. *I*. Temporal courses of the rhythms of activity and rectal temperative, presented successively one period beneath the other. Indications are the same as in figure 16/I. White triangles are temporally correct redrawings of corresponding black triangles.

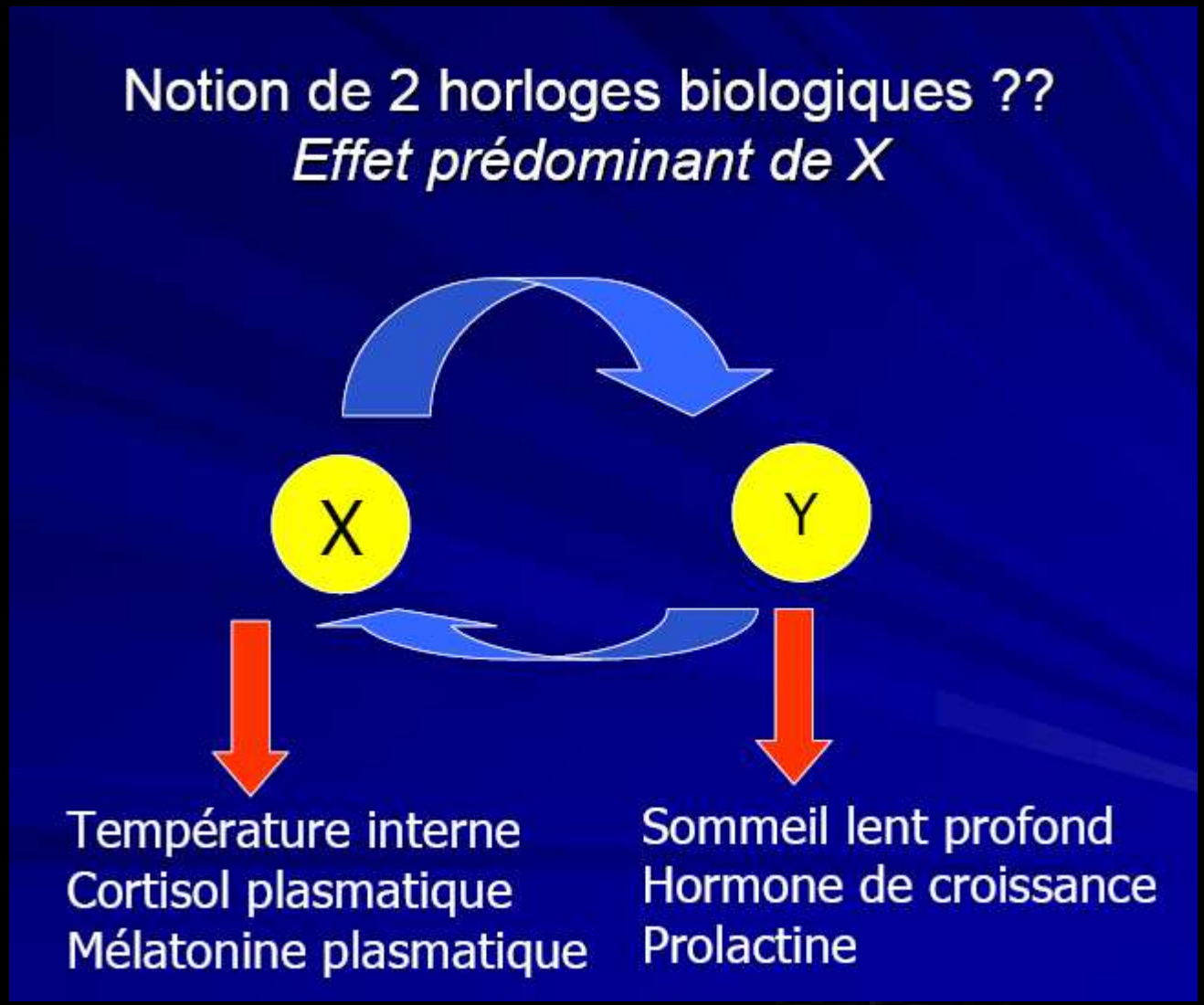

Internal synchronization
Internal desynchronization
Body temperature (schematic)
Body temperature (schematic)
Relative frequency (%)
20
15
10
5
0
5
10
Onset of sleep
End of sleep
Onset of sleep
End of sleep
-10 -5 0 5 10 15 20 25/0 5 10
-10 -5 0 5 10 15 20 25/0 5 10
Time from minimum of rectal temperature (hours)

Body temperature and plasma melatonin relationship



From Shanahan and Czeisler, JCEM, 1991, 73, N°2

Chronobiologie & Hormones


Notion de 2 horloges biologiques ??
Effet prédominant de X
X
Y
Température interne
Cortisol plasmatique
Mélatonine plasmatique
Sommeil lent profond
Hormone de croissance
Prolactine

I.3. La régulation des rythmes

- L'horloge centrale ?

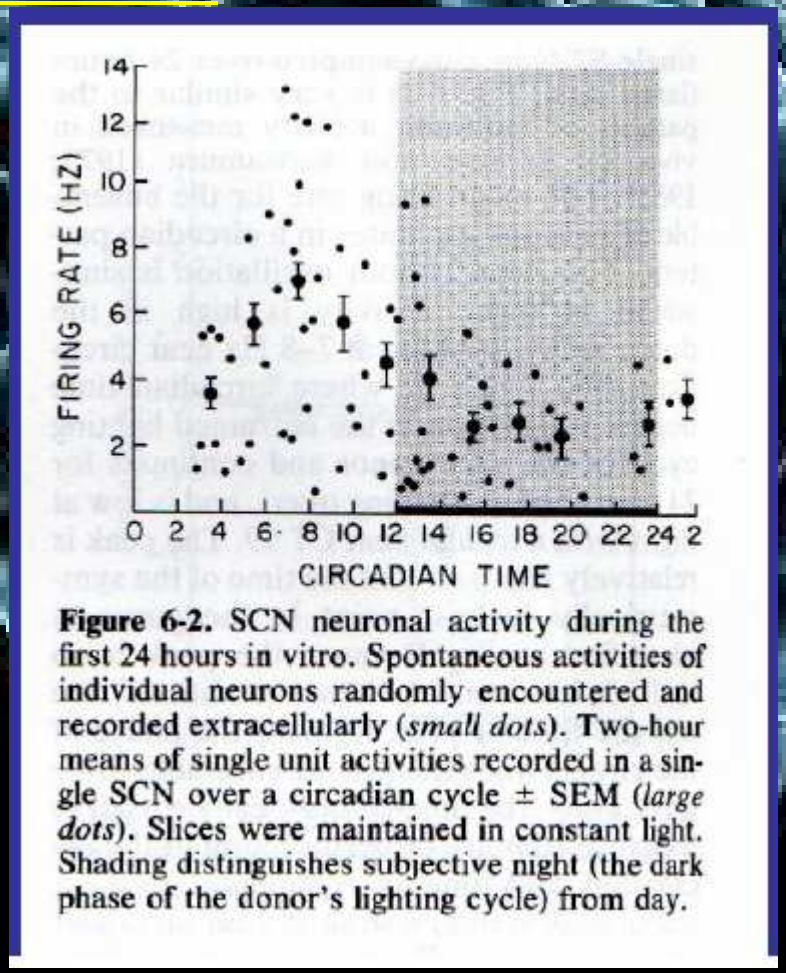
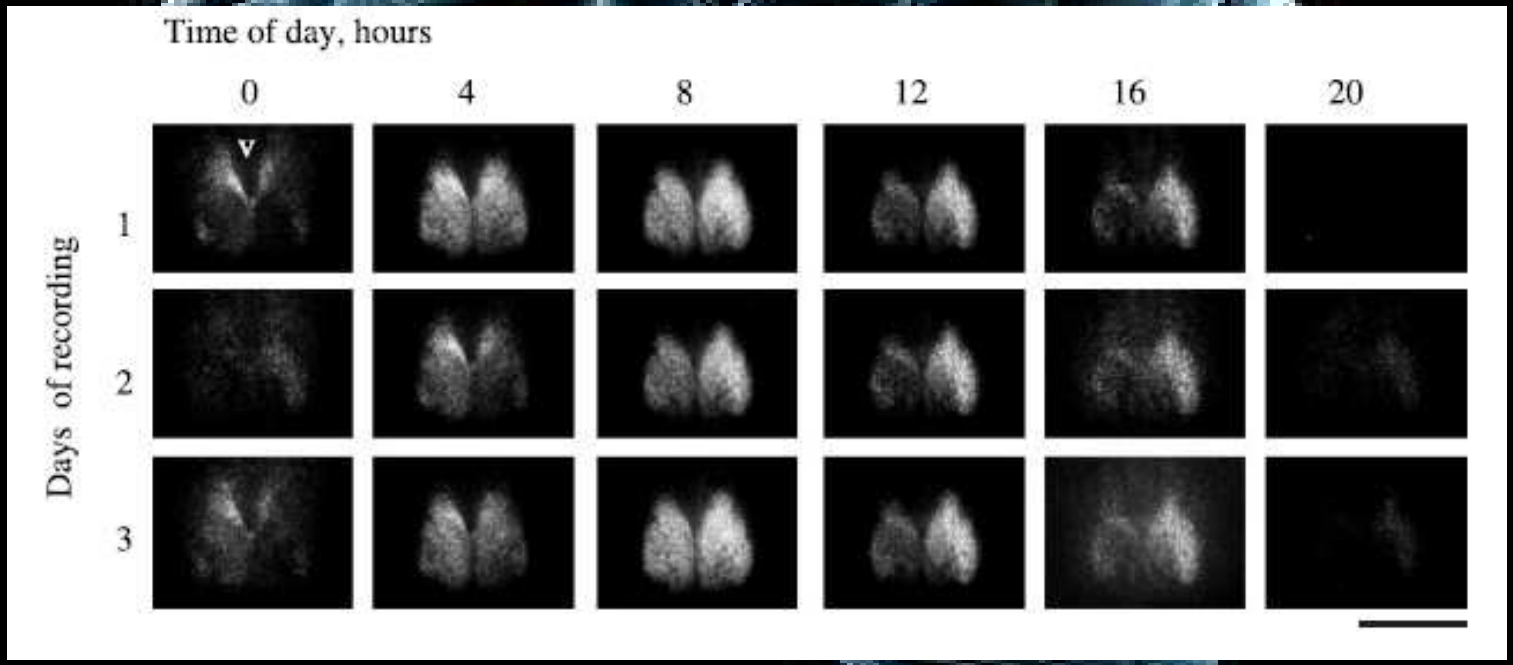


Figure 6-2. SCN neuronal activity during the first 24 hours in vitro. Spontaneous activities of individual neurons randomly encountered and recorded extracellularly (*small dots*). Two-hour means of single unit activities recorded in a single SCN over a circadian cycle ± SEM (*large dots*). Slices were maintained in constant light. Shading distinguishes subjective night (the dark phase of the donor's lighting cycle) from day.

Gilette 1986

I.3. La régulation des rythmes

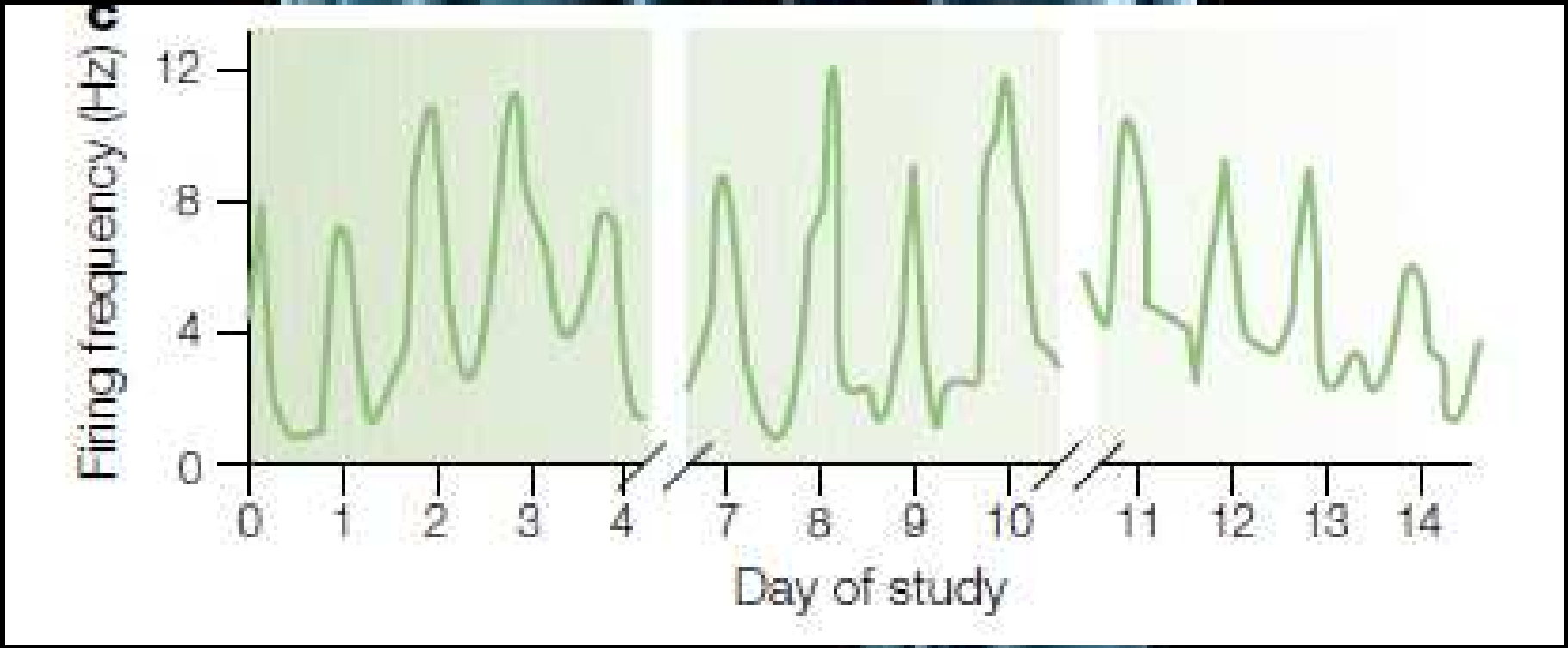
☞ L'horloge centrale ?



Hastings et coll., 2007

I.3. La régulation des rythmes

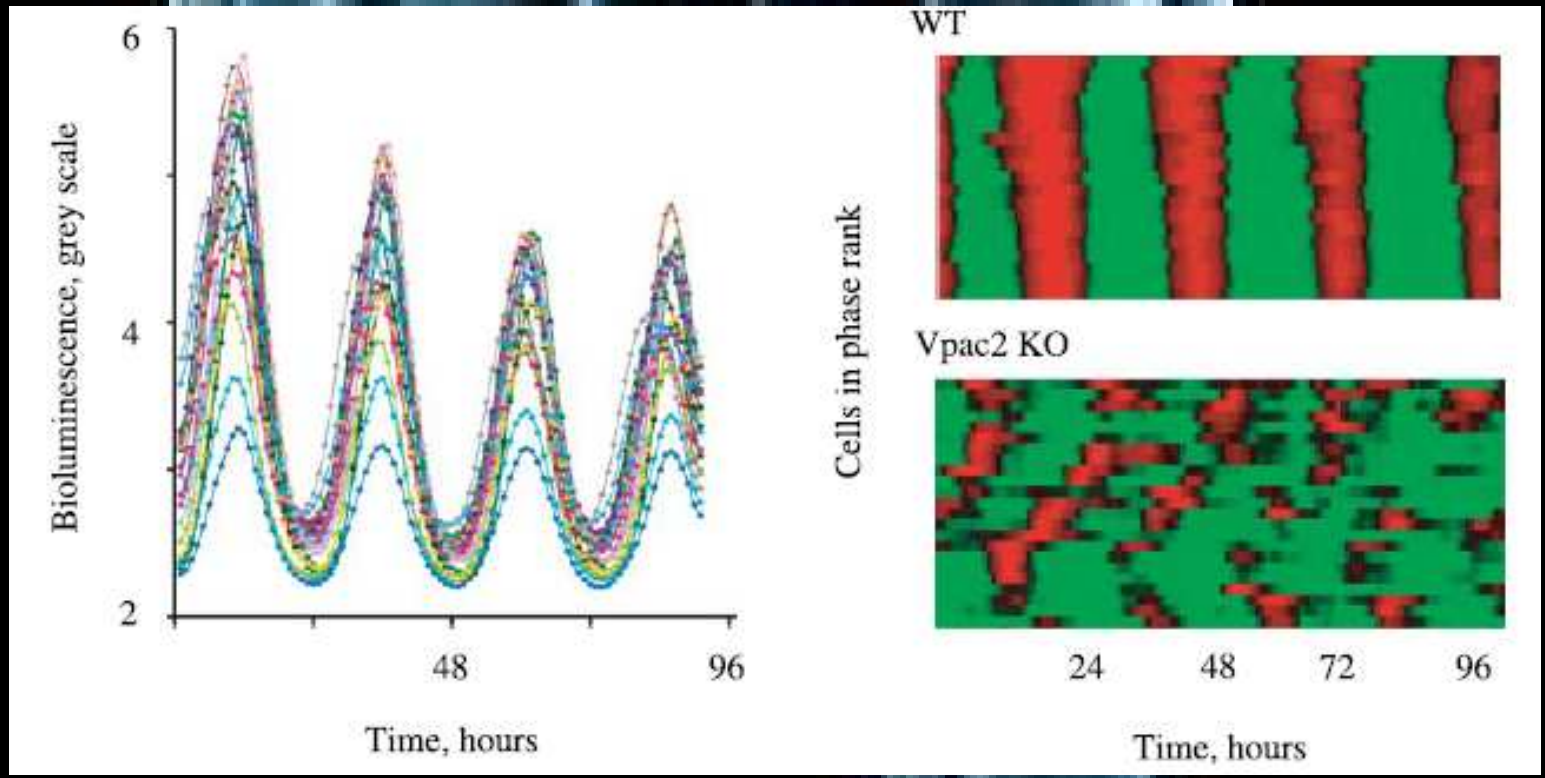
☞ L'horloge centrale ?



Hastings et coll., 2003

I.3. La régulation des rythmes

☞ L'horloge centrale ?



Hastings et coll., 2007

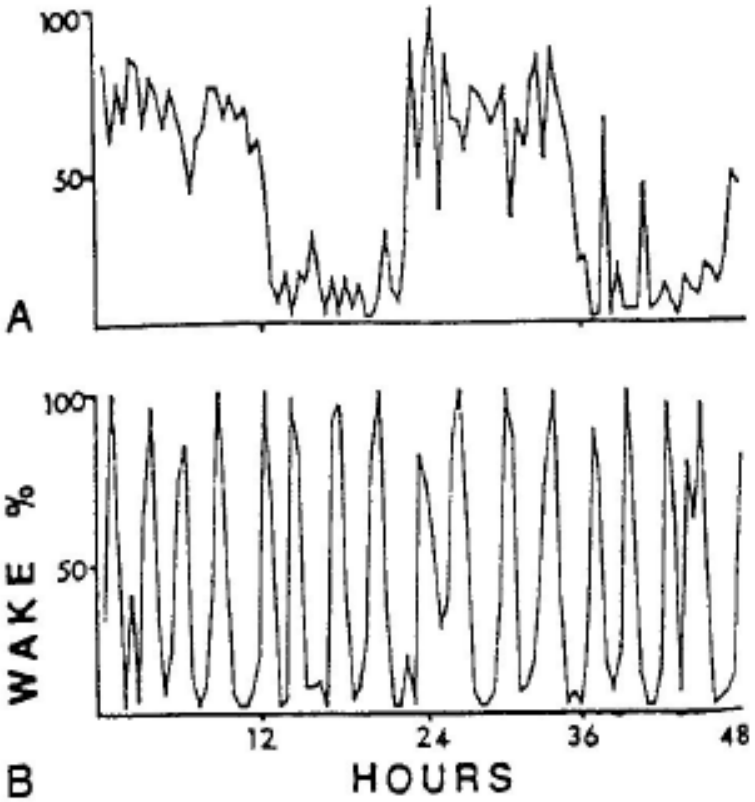
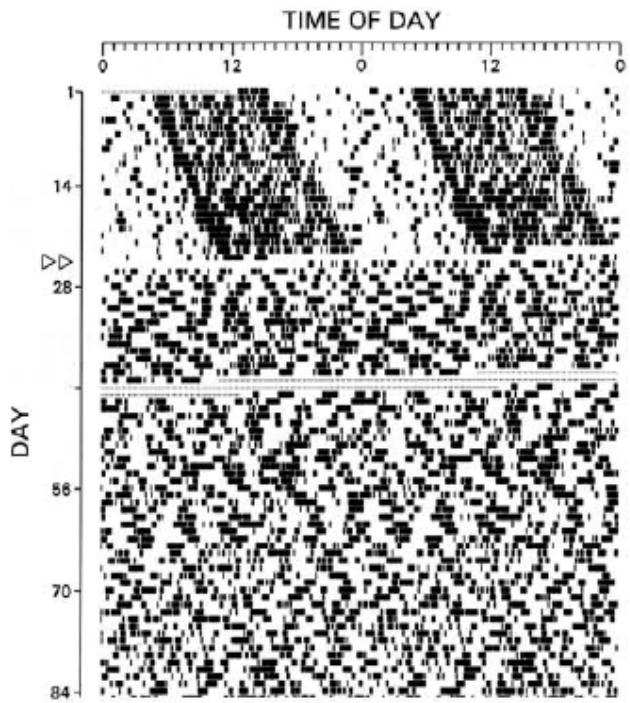
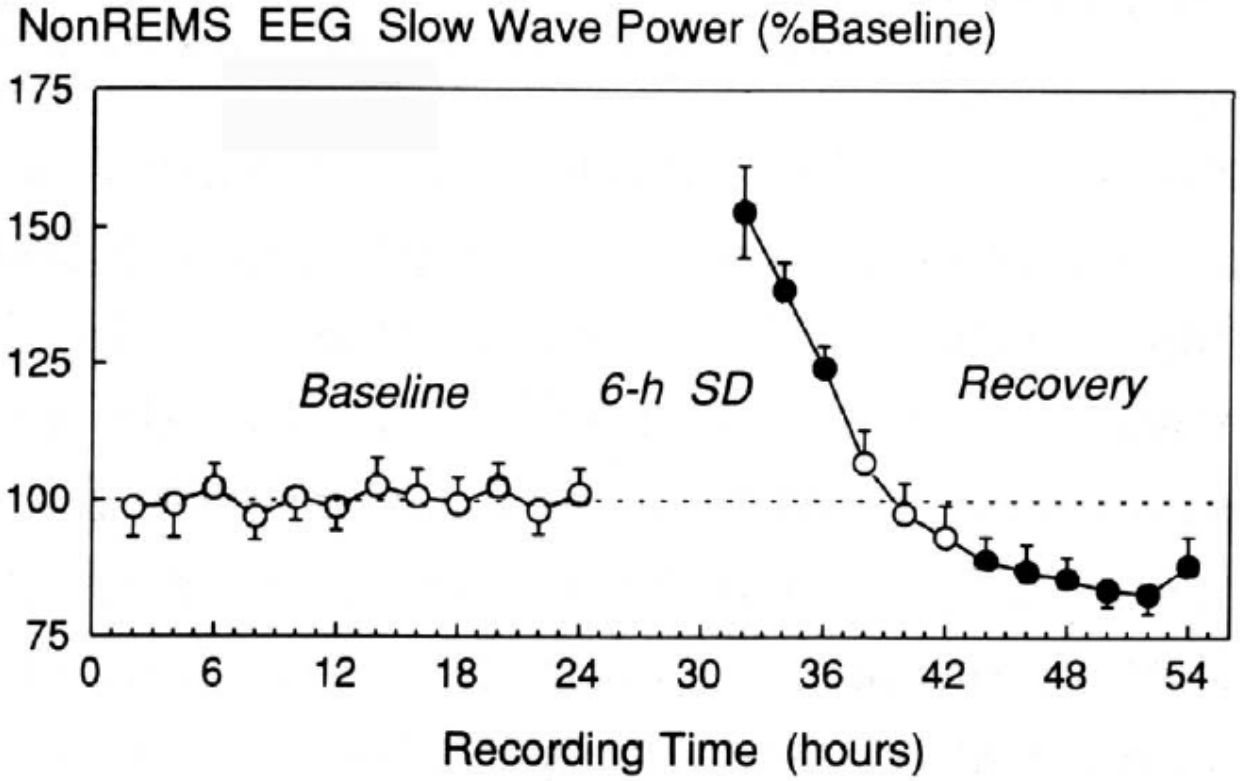


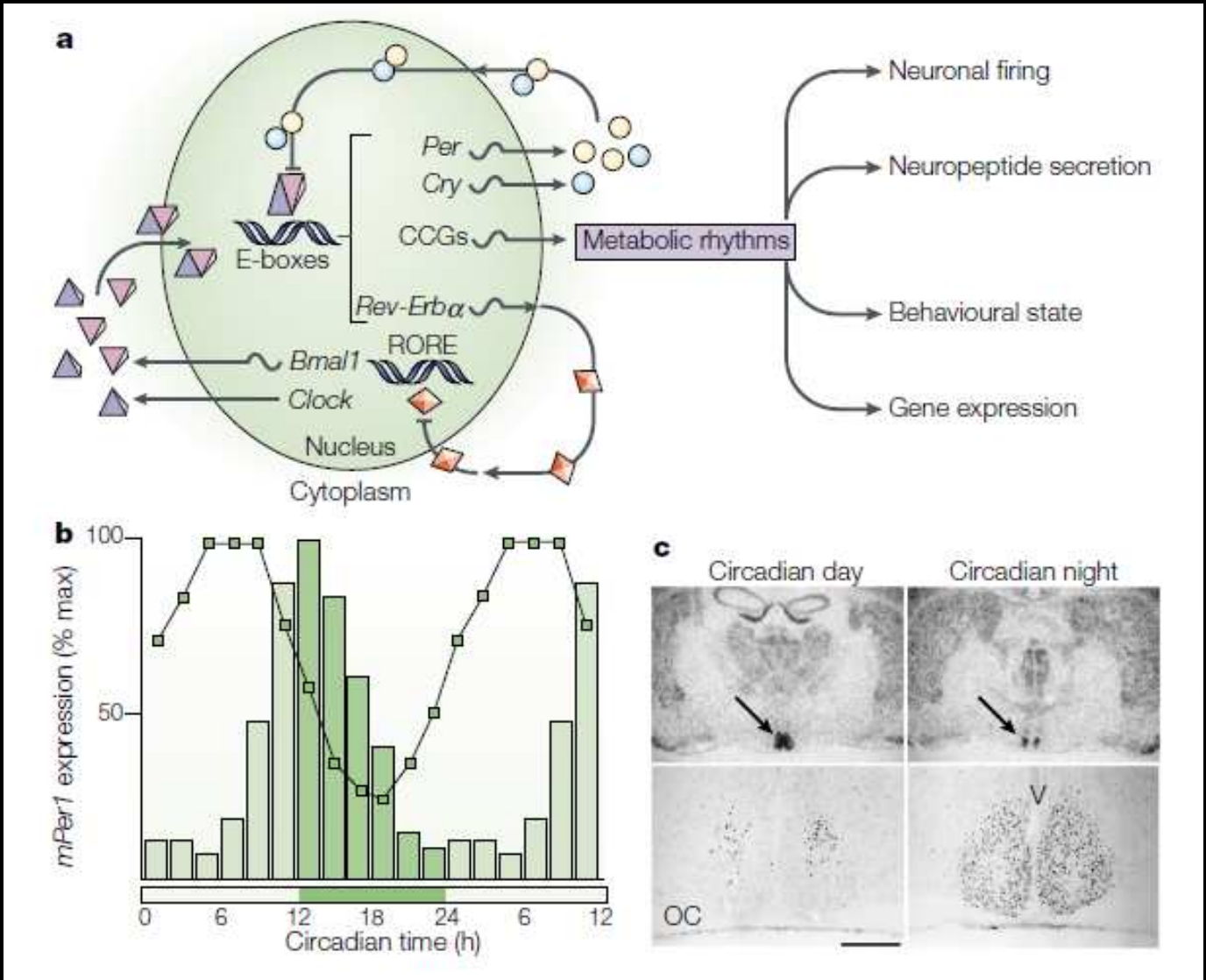
Figure 26–1. Percentage of polygraphically recorded wake time in each 30-min bin over 48 consecutive hours in two adult male rats recorded in constant dim light. *A* is from an intact control rat and illustrates a typical 24-h circadian rhythm of sleep-wake time. *B* is from a rat with complete ablation of the SCN. The 24-h rhythm of sleep-wake time was completely lost. This particular rat shows prominent ultradian rhythms in the 3- to 4-h range. SCN, suprachiasmatic nuclei. (Modified. Republished with permission of the American Sleep Disorders Association, 6301 Bandel Road, Suite 101, Rochester, MN 55901. Figure, R.E. Mistlberger, B.M. Bergmann, A. Rechtschaffen, Sleep, 1987, vol 10. Reproduced by permission of the publisher via Copyright Clearance Center Inc.)

Sleep homeostasis in suprachiasmatic nuclei-lesioned rats: effects of sleep deprivation and triazolam administration

Lorenz Trachsel, Dale M. Edgar, Wesley F. Seidel, H. Craig Heller and William C. Dement



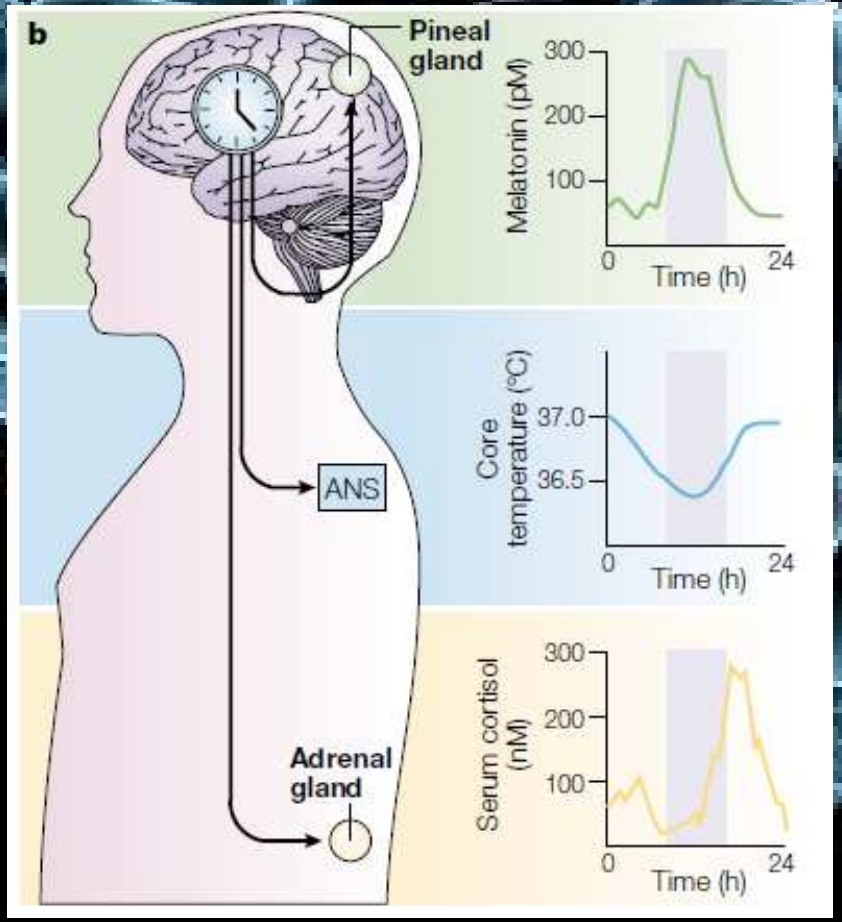




Hastings et coll., 2003

I.3. La régulation des rythmes

☞ La synchronisation des horloges :



Hastings et coll., 2003

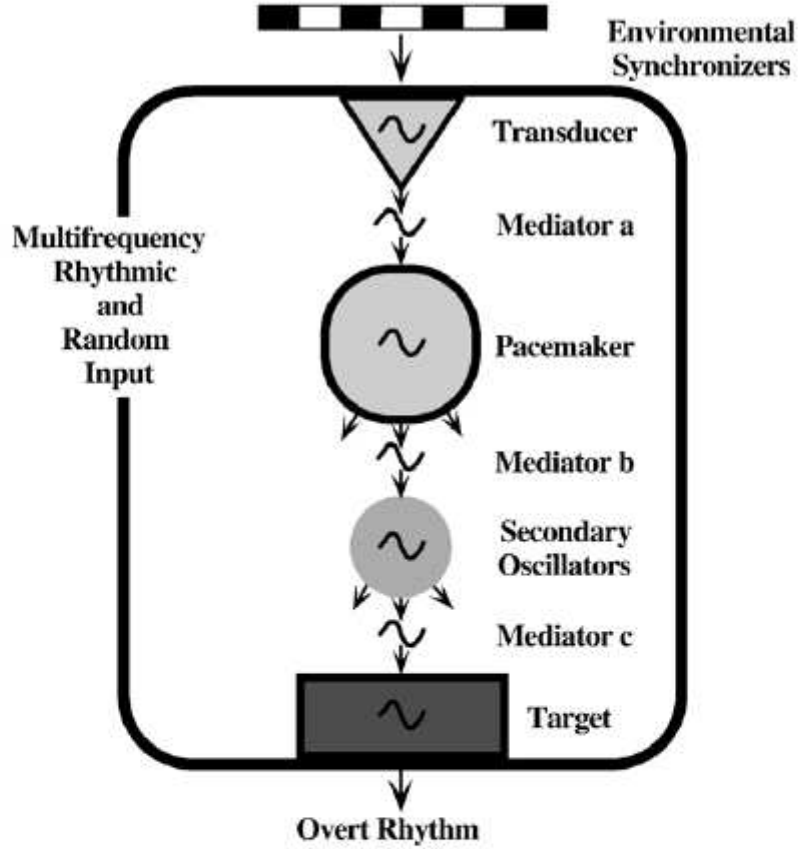
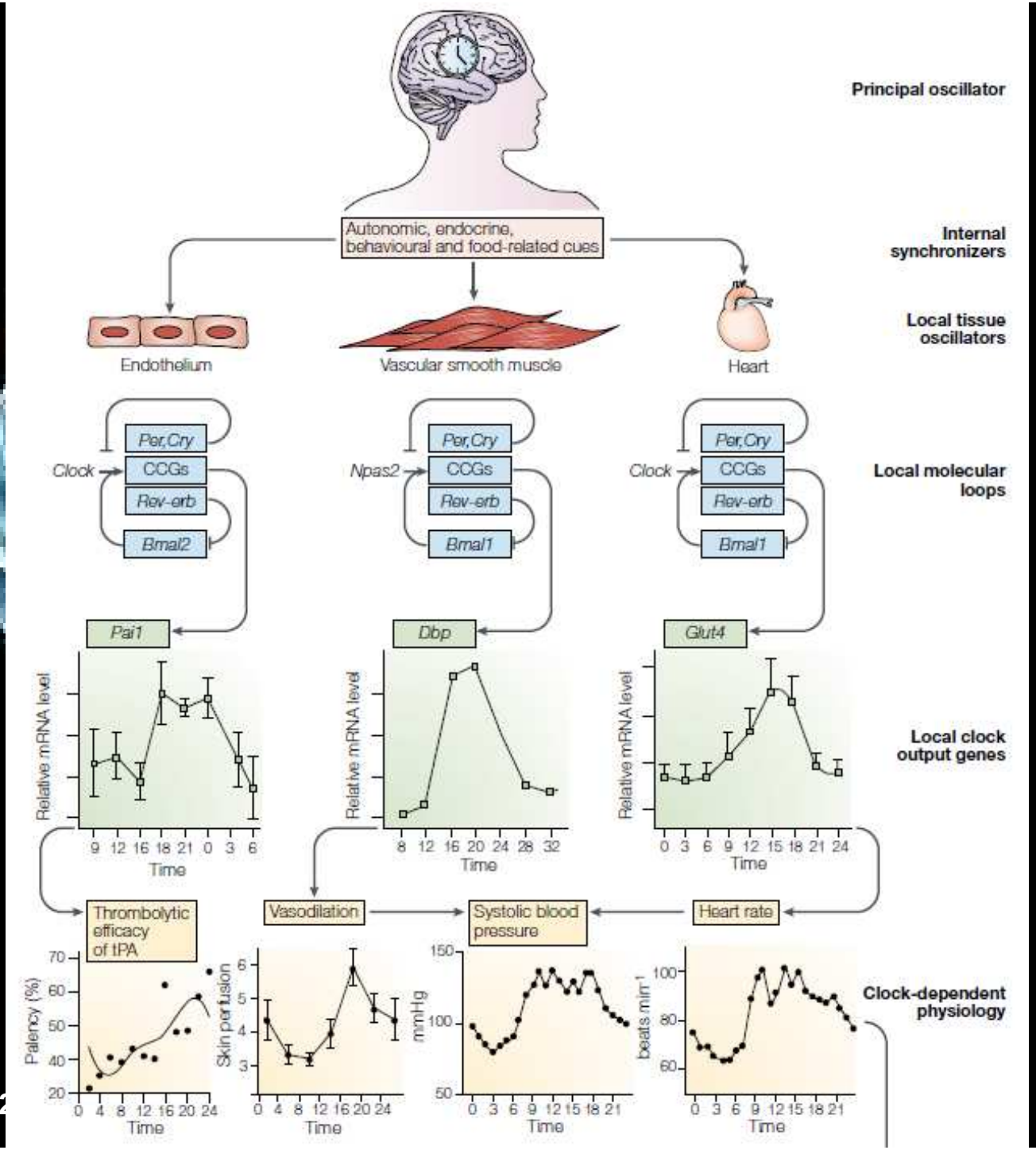
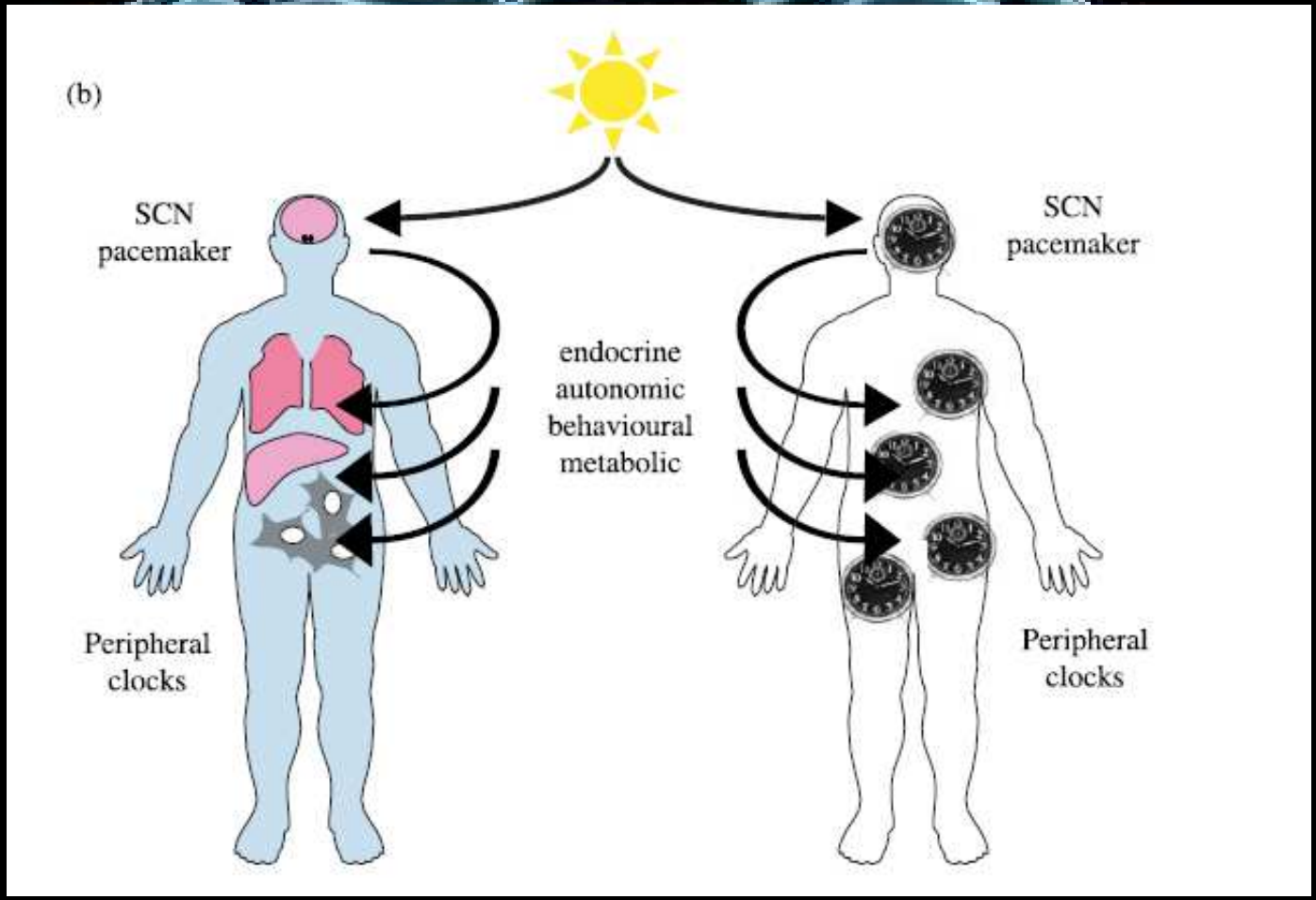


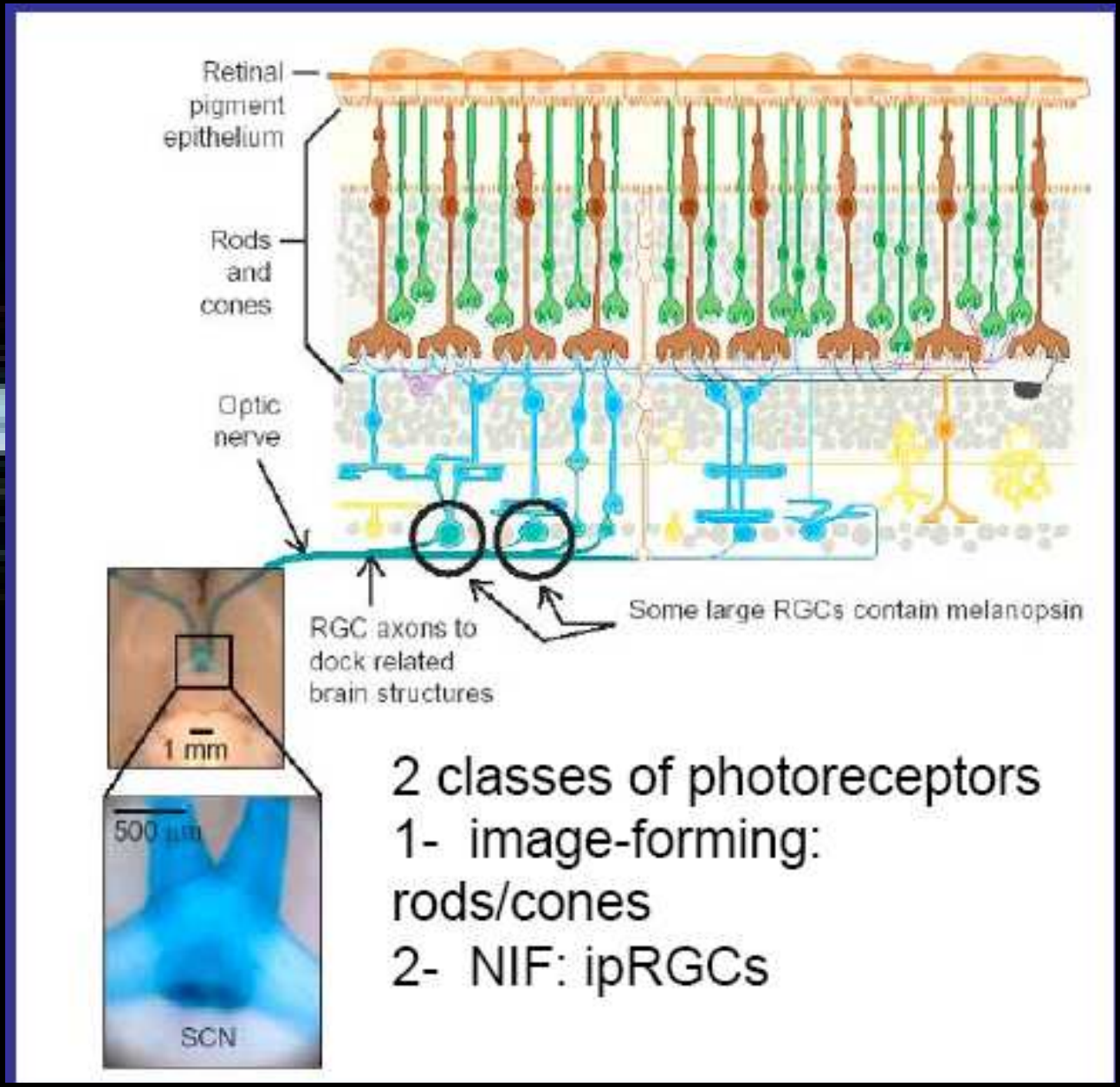
Fig. 1. Simplified diagram of circadian timing mechanism: self-sustained genetically determined circadian oscillations characterize the circadian pacemaker (i.e., the suprachiasmatic nuclei) but may also be found in transducers (i.e., the retina), secondary oscillations (e.g., pituitary and/or adrenal) and in target tissues (e.g., mesenchymal tissues, lymphocytes). The environmental circadian synchronizer acting upon the transducer provides time information which may be modified by multifrequency rhythmic interactions. Random or non-random environmental input may lead to alterations and/or masking of the rhythms measured (e.g., rhythms in plasma cortisol or in cell division). Figure adapted from Haus and Touitou [8].


Principal oscillator
Autonomic, endocrine, behavioural and food-related cues
Internal synchronizers
Endothelium
Vascular smooth muscle
Heart
Local tissue oscillators
Per,Cry
Clock
CCGs
Rev-erb
Bmal2
Npas2
Bmal1
Local molecular loops
Pai1
Dbp
Glut4
Relative mRNA level
Time
Local clock output genes
Thrombolytic efficacy of tPA
Vasodilation
Systolic blood pressure
Heart rate
Patency (%)
Skin perfusion
mmHg
beats min-1
Clock-dependent physiology

I.3. La régulation des rythmes

☞ La synchronisation des horloges :




Retinal pigment epithelium
Rods and cones
Optic nerve
RGC axons to dock related brain structures
Some large RGCs contain melanopsin
1 mm
500 µm
SCN
2 classes of photoreceptors
1- image-forming: rods/cones
2- NIF: ipRGCs

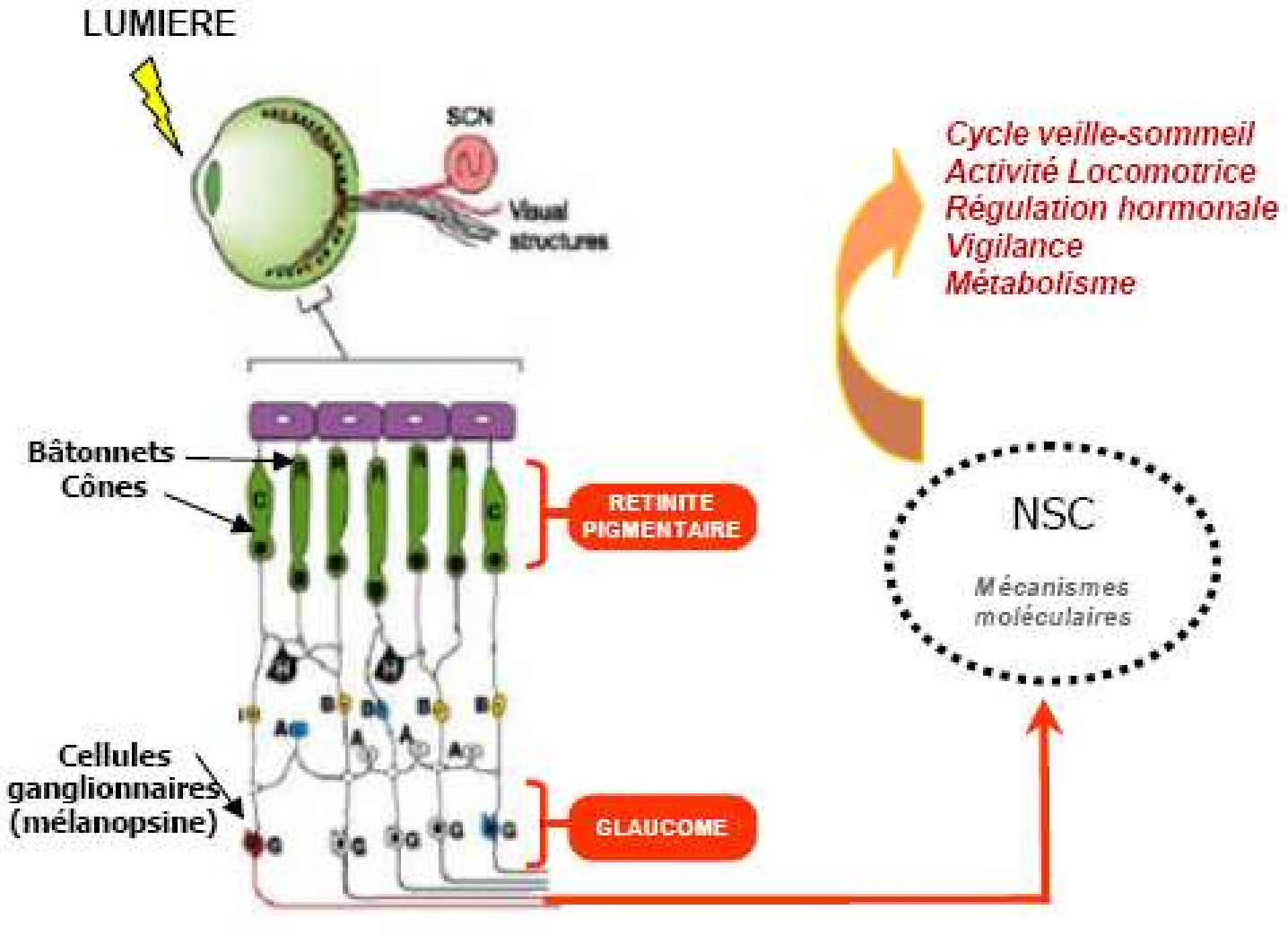
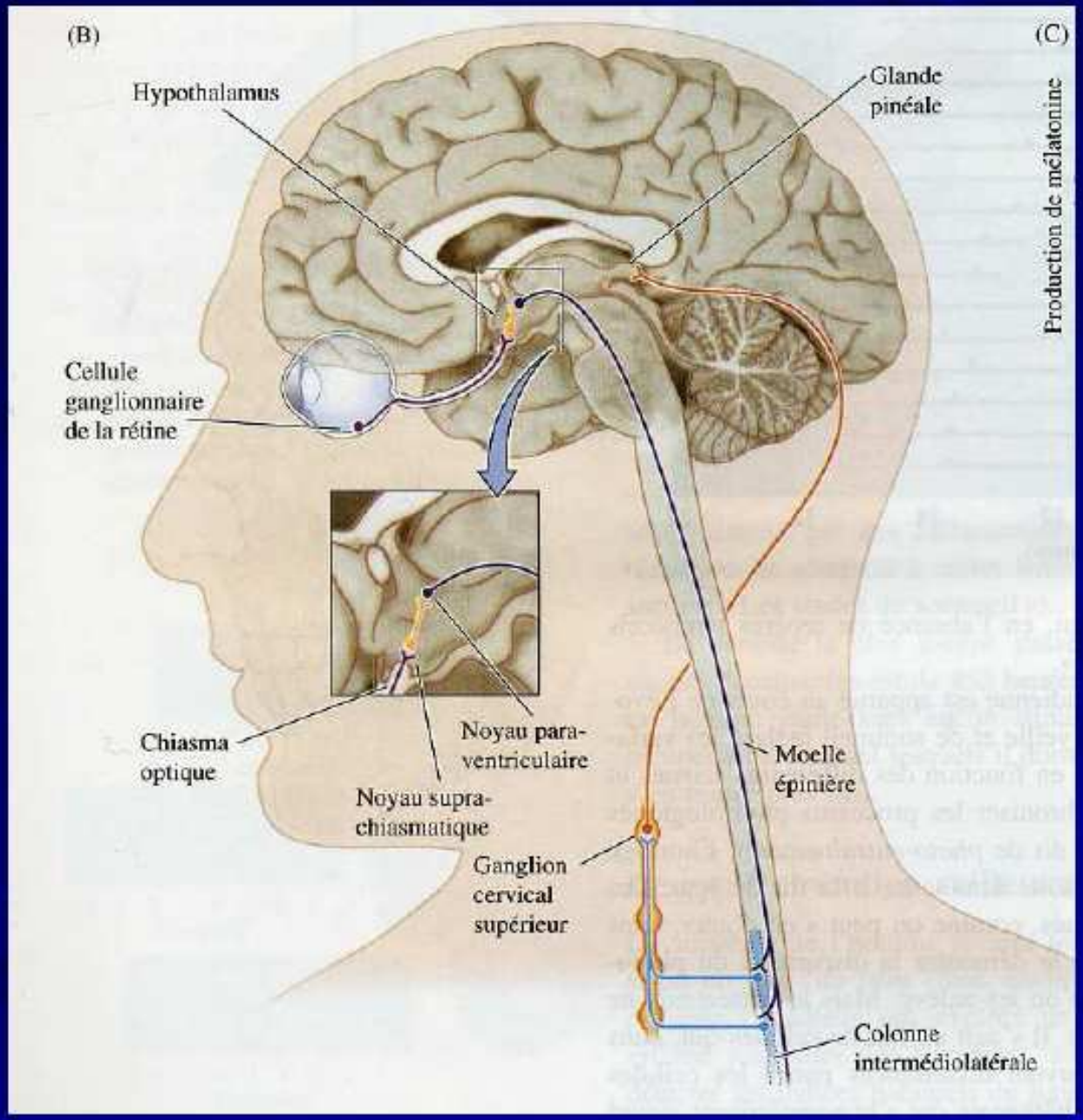


Fig.1: Représentation schématique du système circadien. L'information photique est transmise de la rétine au noyau suprachiasmatique (SNC). Notez que les pathologies dégénératives rétiniennes (glaucome, rétinite pigmentaire) affectent des systèmes photorécepteurs différents.

Chronobiologie & Hormones



Rétine

↓

NSC

↓

NPV

↓

GG CERVICAL SUP

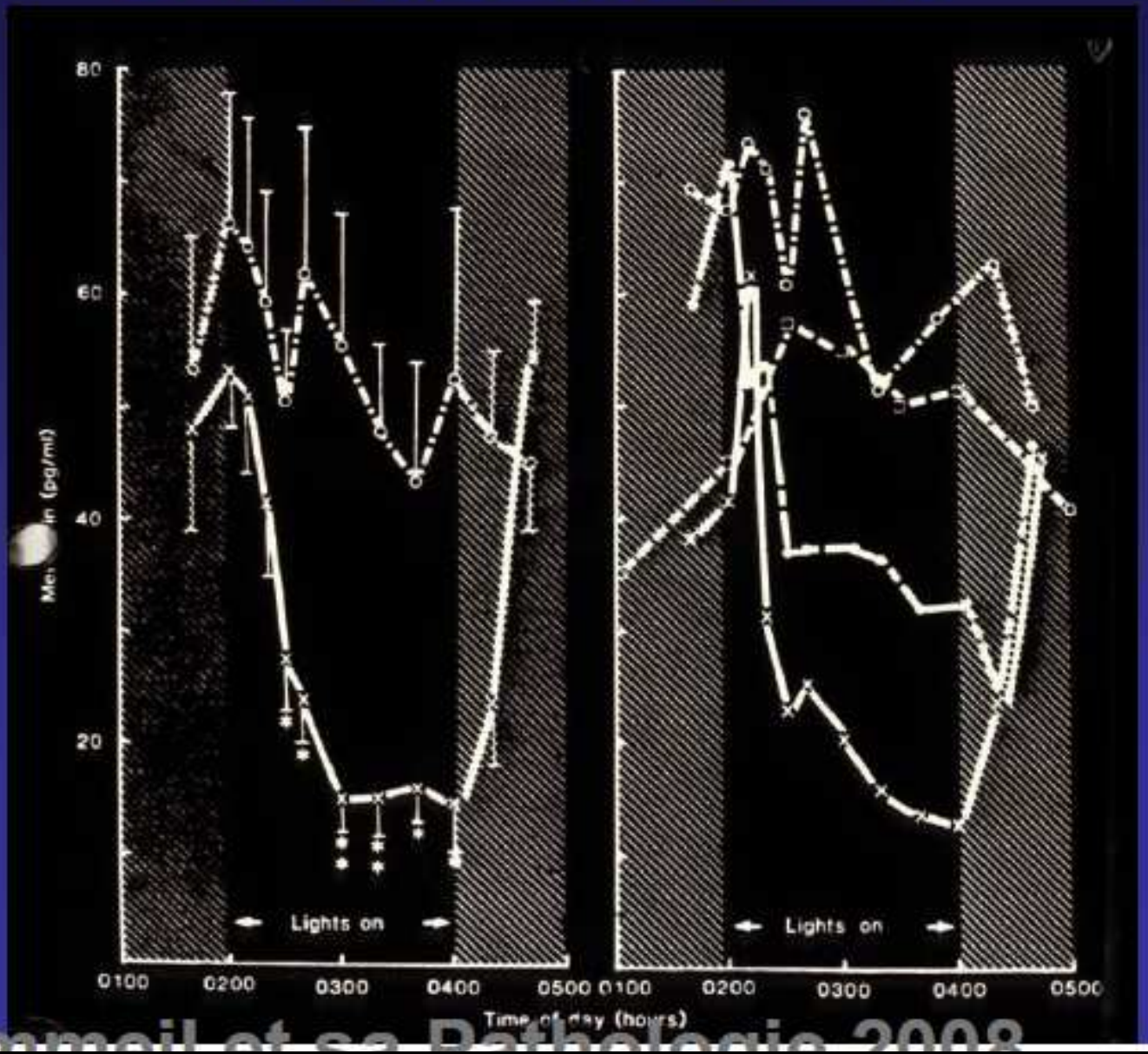
↓

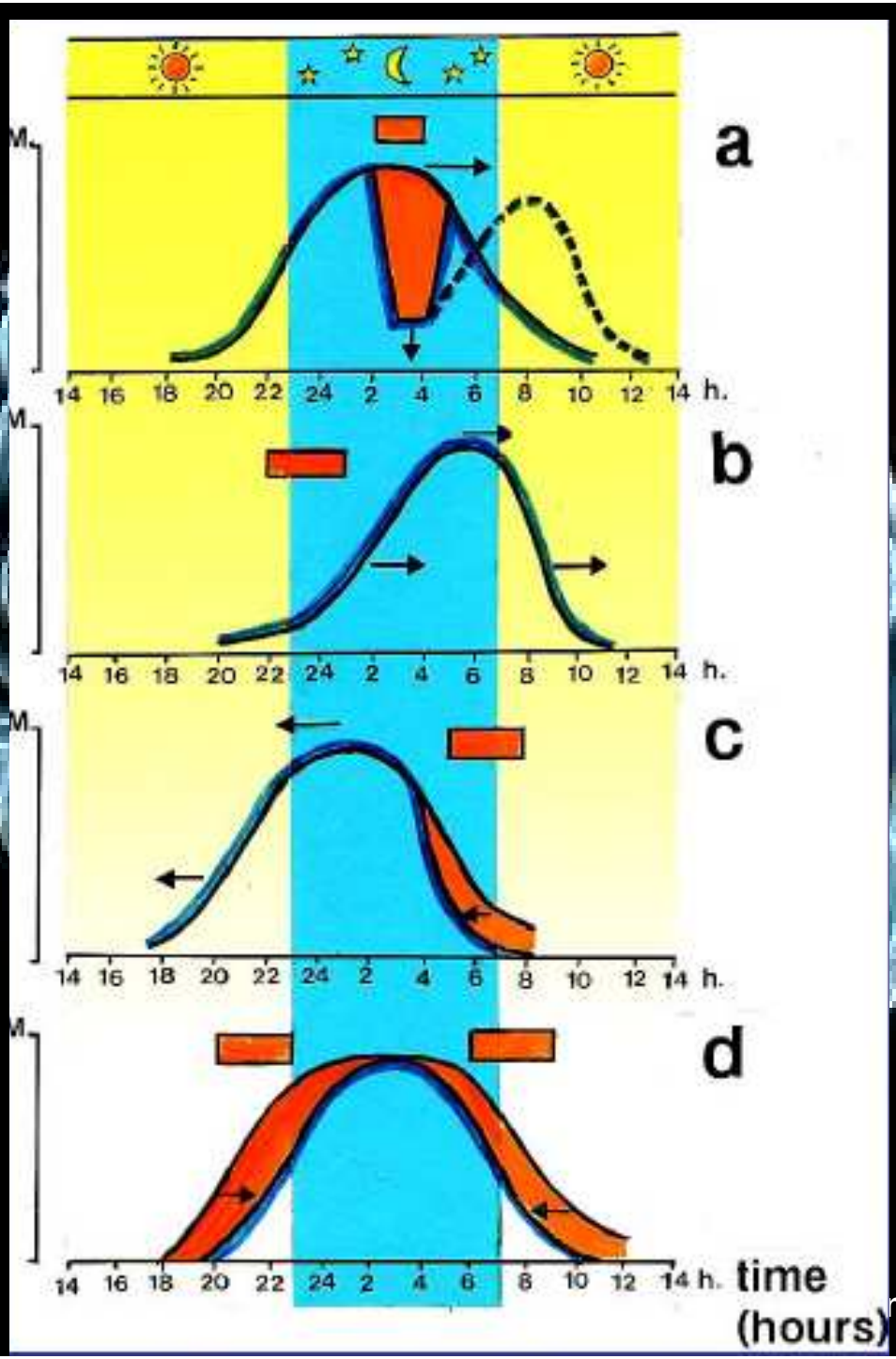
EPIPHYSE

↓

MELATONINE

Light suppresses melatonin secretion in humans
Lewy et al science 1980: 210 1267-1269




a
b
c
d
14 16 18 20 22 24 2 4 6 8 10 12 14 h.
time
(hours)

A human phase-response curve to light
Minors et al Neuroscience letters 1991 133 36-40

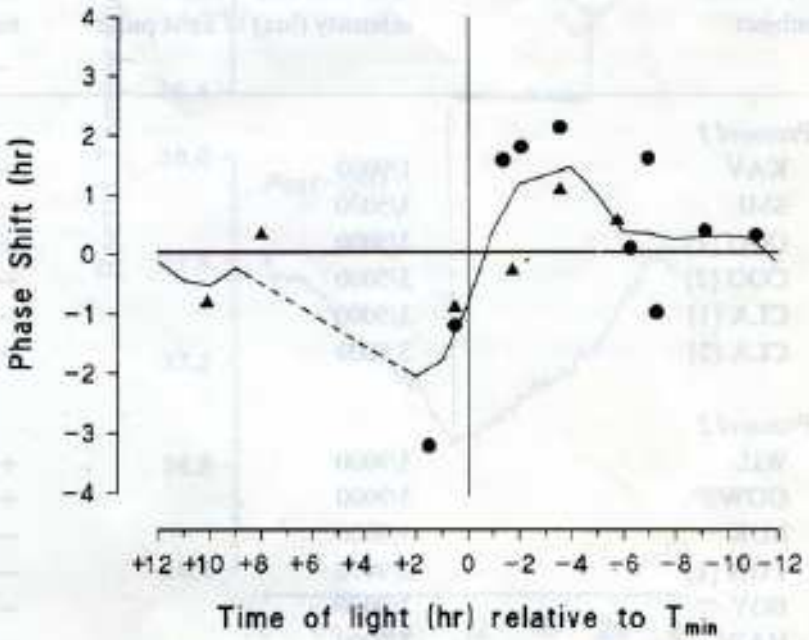


Fig. 2. Phase–response curve to single light pulses. Mean phase shifts, derived from the average of the two methods of estimation, are plotted as a function of time of the mid-point of the light pulse relative to the time of rectal temperature minimum. The mid-point of the light pulse is expressed as hours before (+), or after (−), the time of rectal temperature minimum. Negative phase shifts indicate phase delays. ▲: phase shifts derived from Protocol 1 experiments; ●: phase shifts derived from Protocol 2 experiments. The fitted curve is an hourly estimate of the phase shift using a weighted mean calculated from all values within the range of ±2 h. No estimate was made if less than two values were within this range (period of dashed line). Different weightings, with respect to overall bright and dim light exposure to estimate

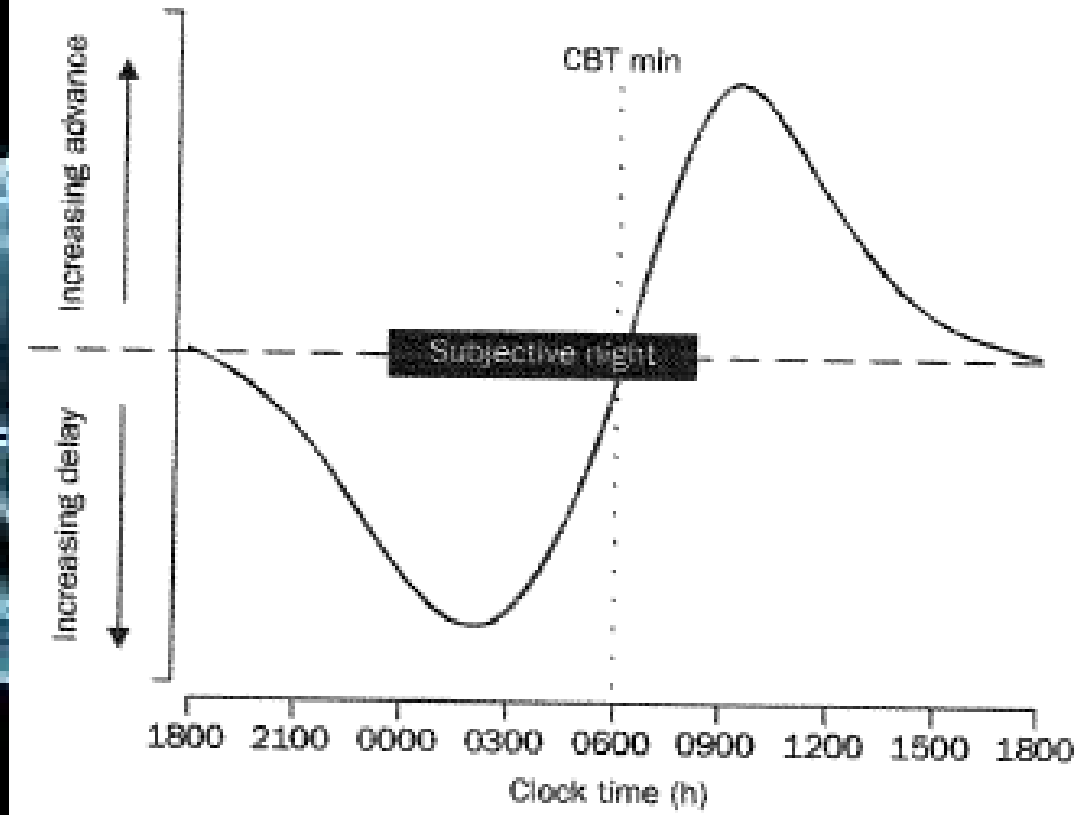


Figure 2: **Phase response curve (PRC) of a human being, in response to light**

Subjective night (ie, night-time according to the biological clock) is indicated by a black horizontal bar. Maximum phase shifts are within 4–5 h of the time of core body temperature (CBT) minimum. The precise shape and amplitude of PRCs for human beings depends on the strength (ie, intensity and duration) of the light stimulus.[18]

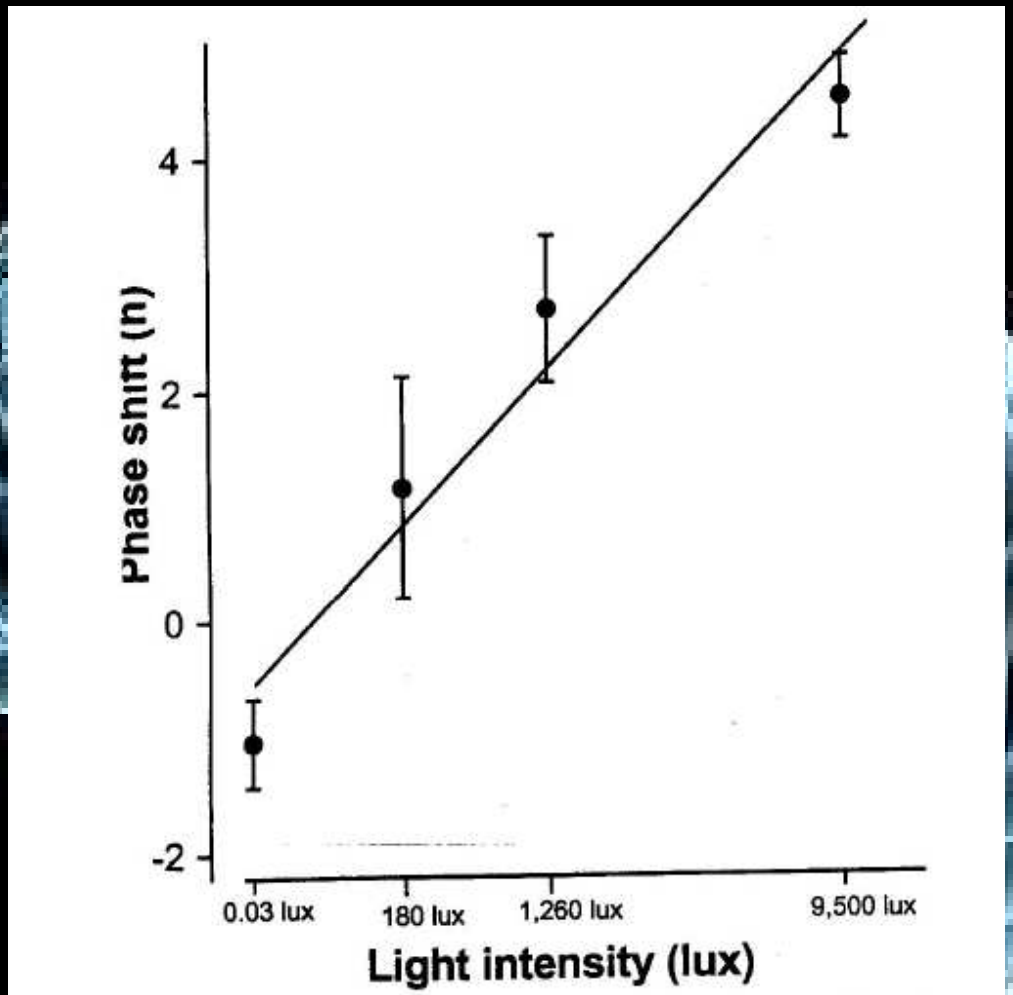
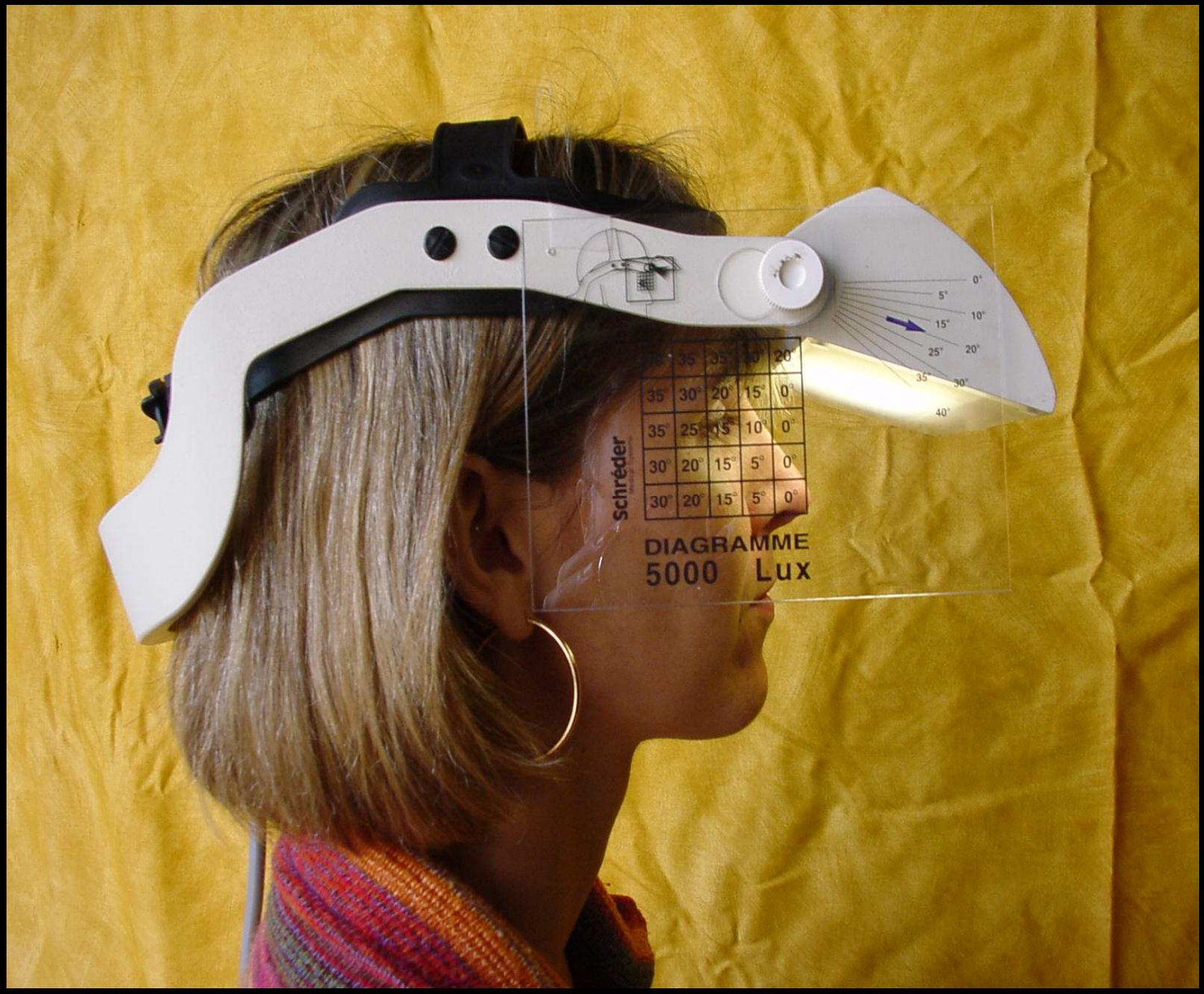
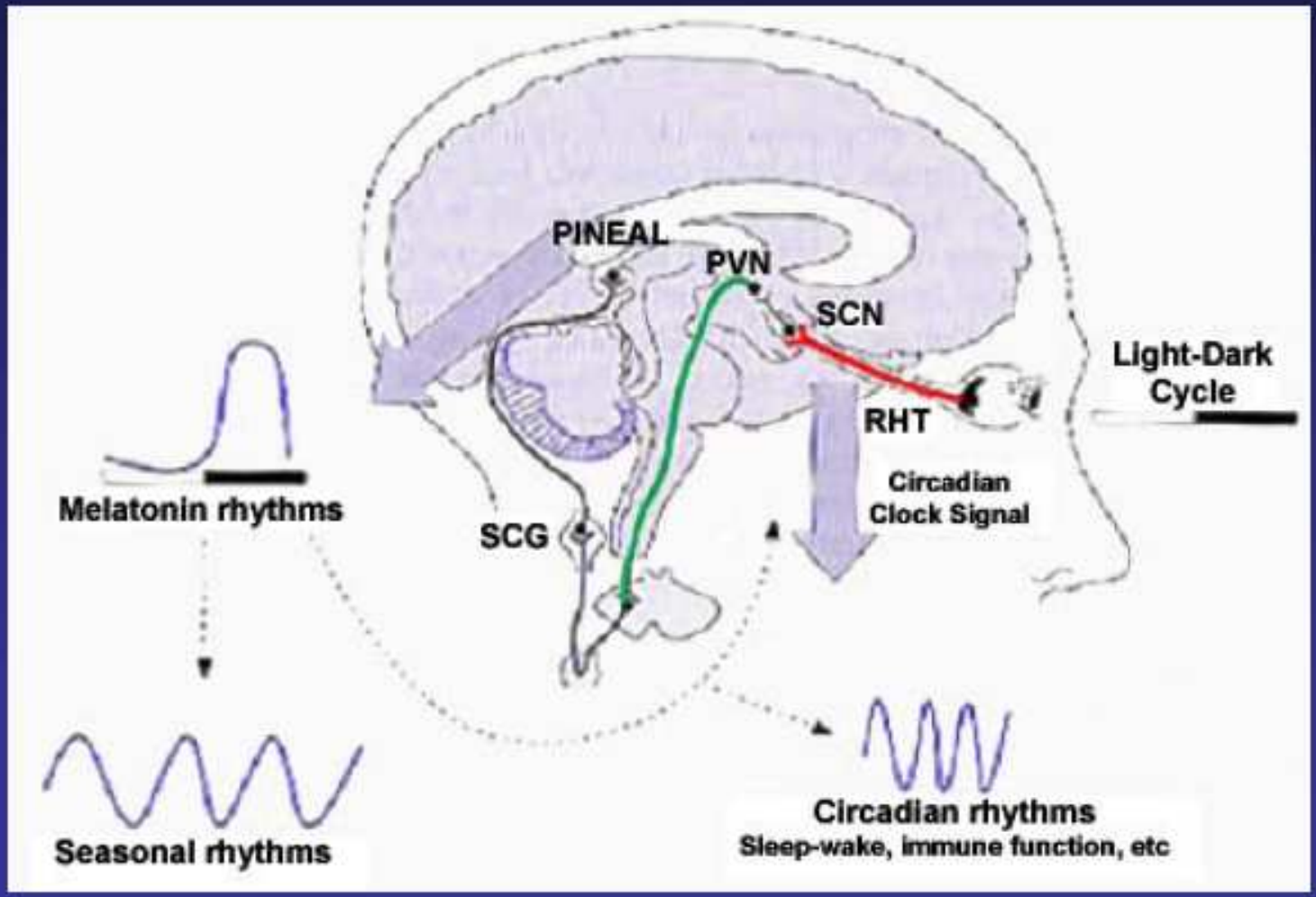


Figure 28–6. Dose-response curve of the phase-shifting effect of three consecutive daily cycles of a 5-h retinal light exposure. The ordinate represents the phase shift observed between the first and second constant routines in each group of subjects. The abscissa represents the light intensity (lux) plotted on a cube root scale. By convention, positive phase shifts represent phase advances, and negative phase shifts represent phase delays. Group averages

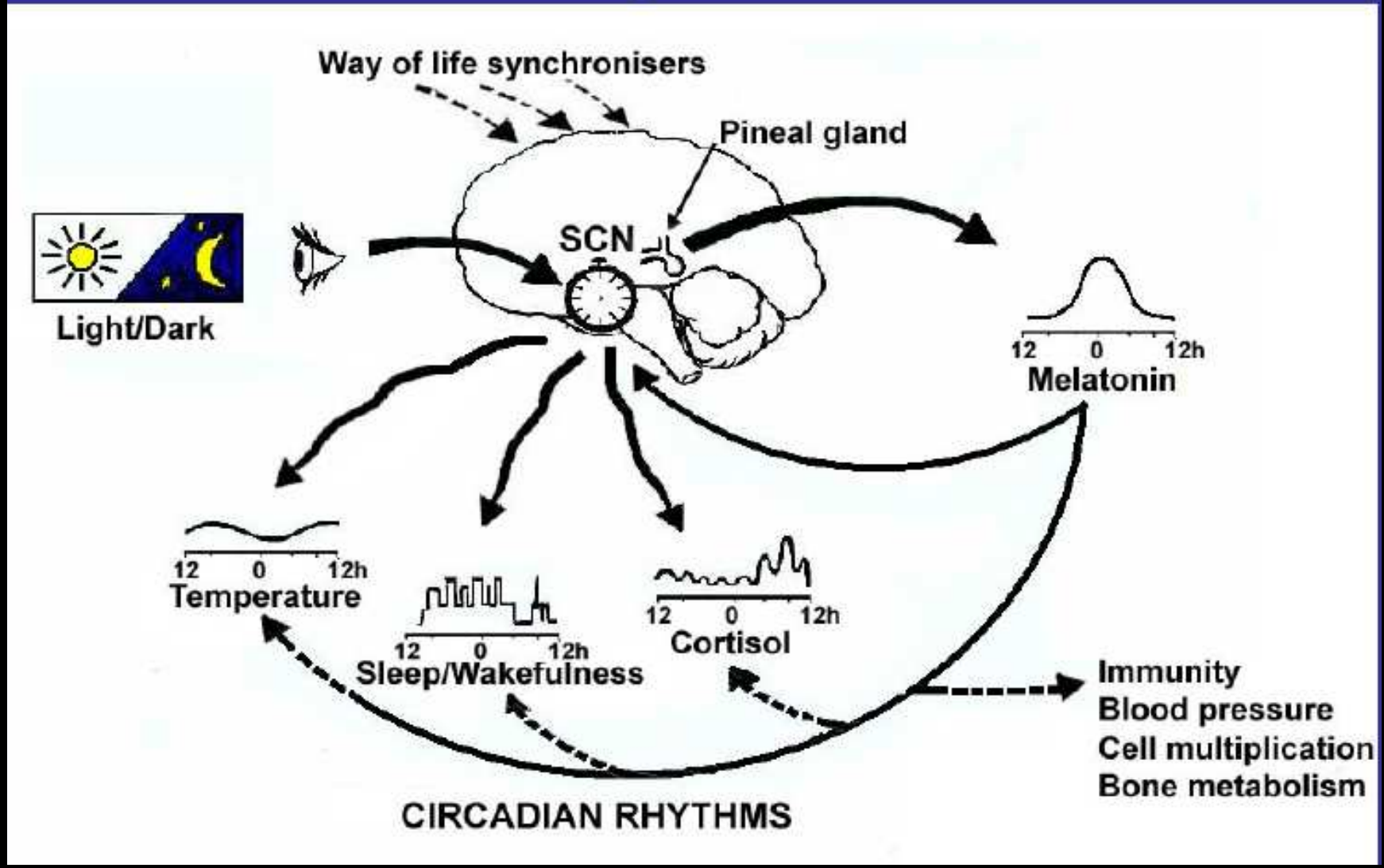

Schréder
DIAGRAMME
5000 Lux

Control of melatonin secretion

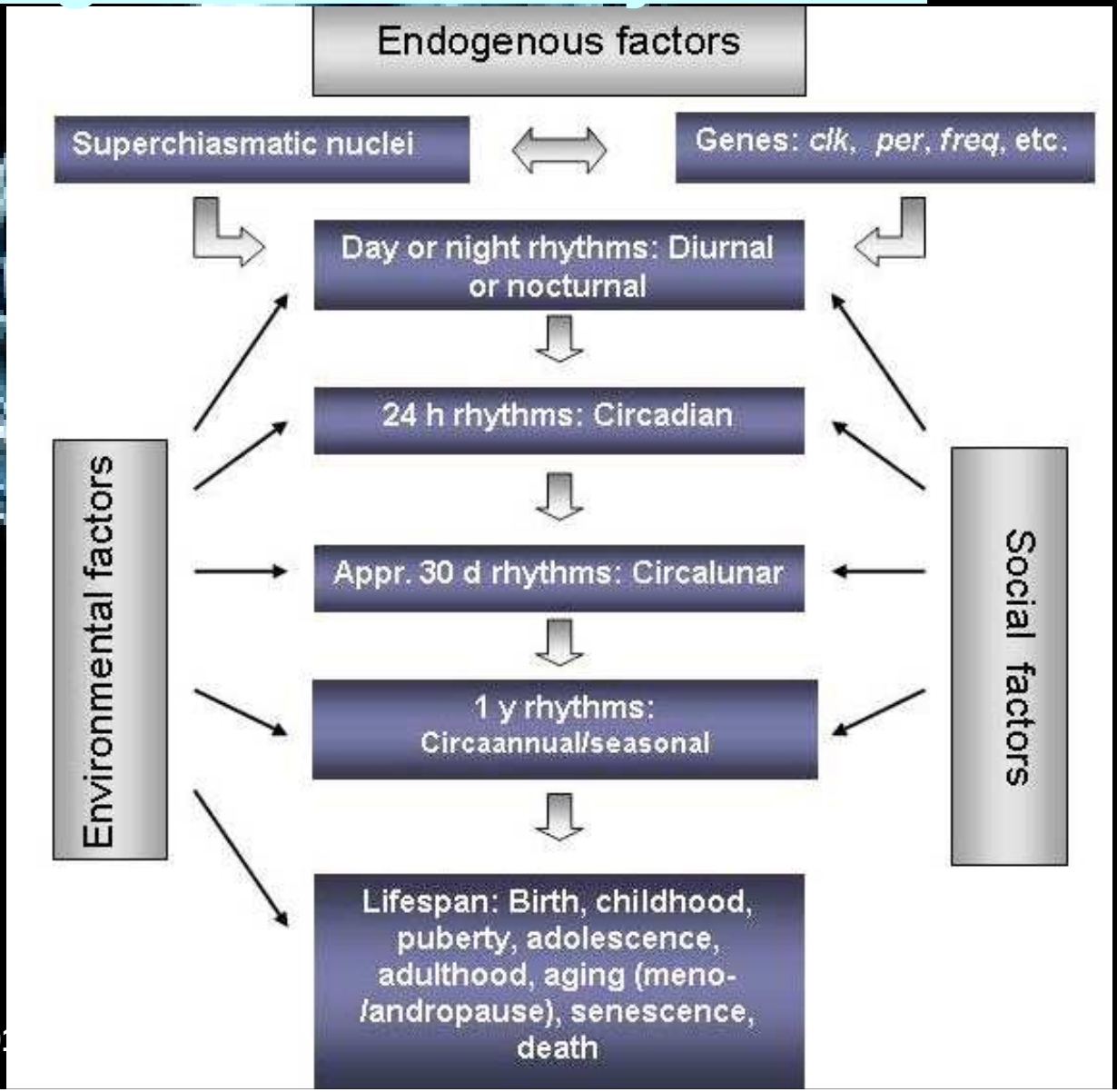
From Cardinali D , Pevet P ,Sleep Medecine Reviews, 1998, 2, 175-190



The circadian system in humans



I.3. La régulation des rythmes



I.3. La régulation des rythmes

PROPRIETES DES RYTHMES BIOLOGIQUES

1) les rythmes persistent dans des conditions constantes

= origine endogène - preuve génétique

contrôle par une horloge (rythmes circadiens)

2) les rythmes sont entraînables

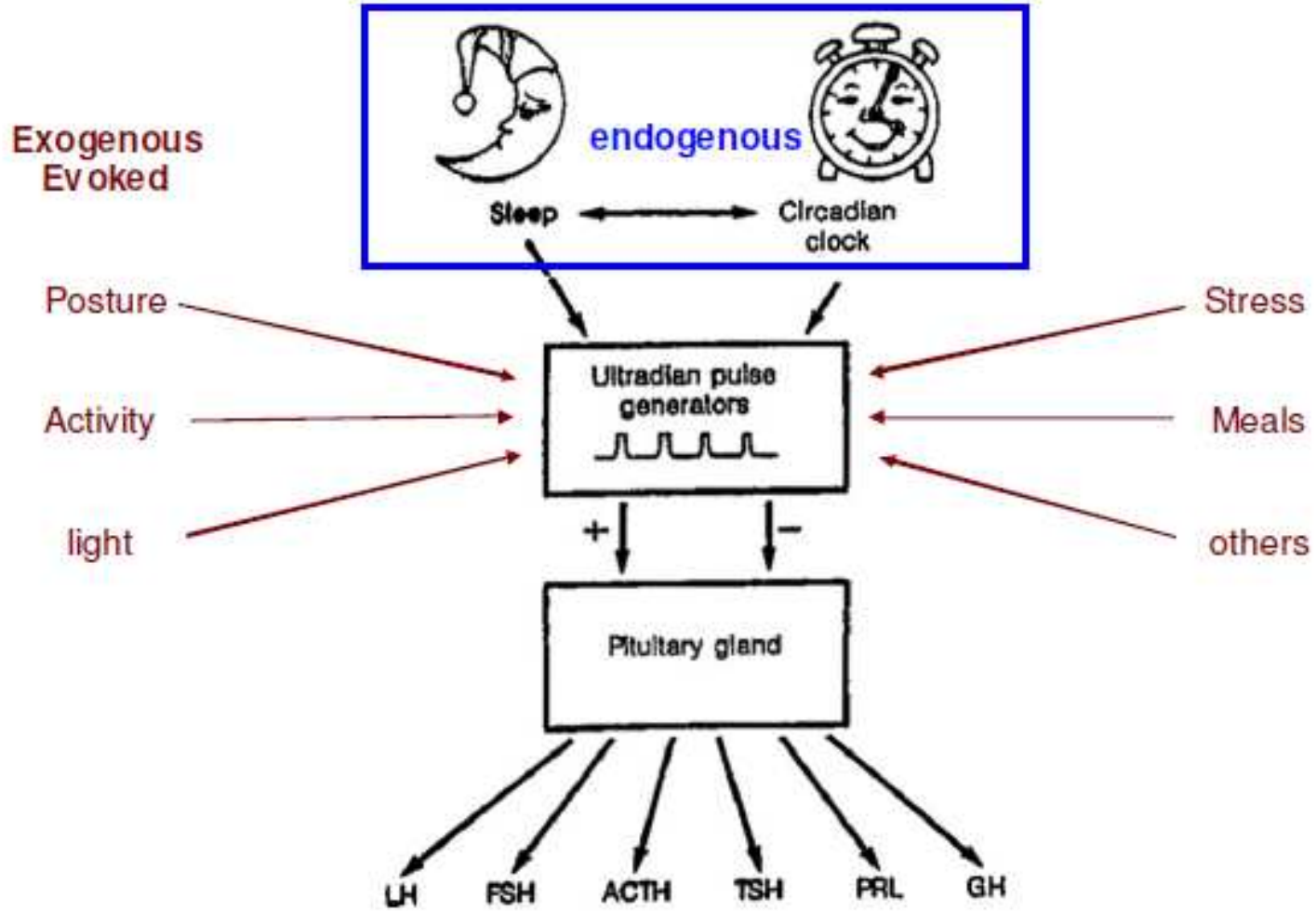
sous l'effet des synchroniseurs (alternance lumière-obscurité)

facilite l'adaptation à l'environnement

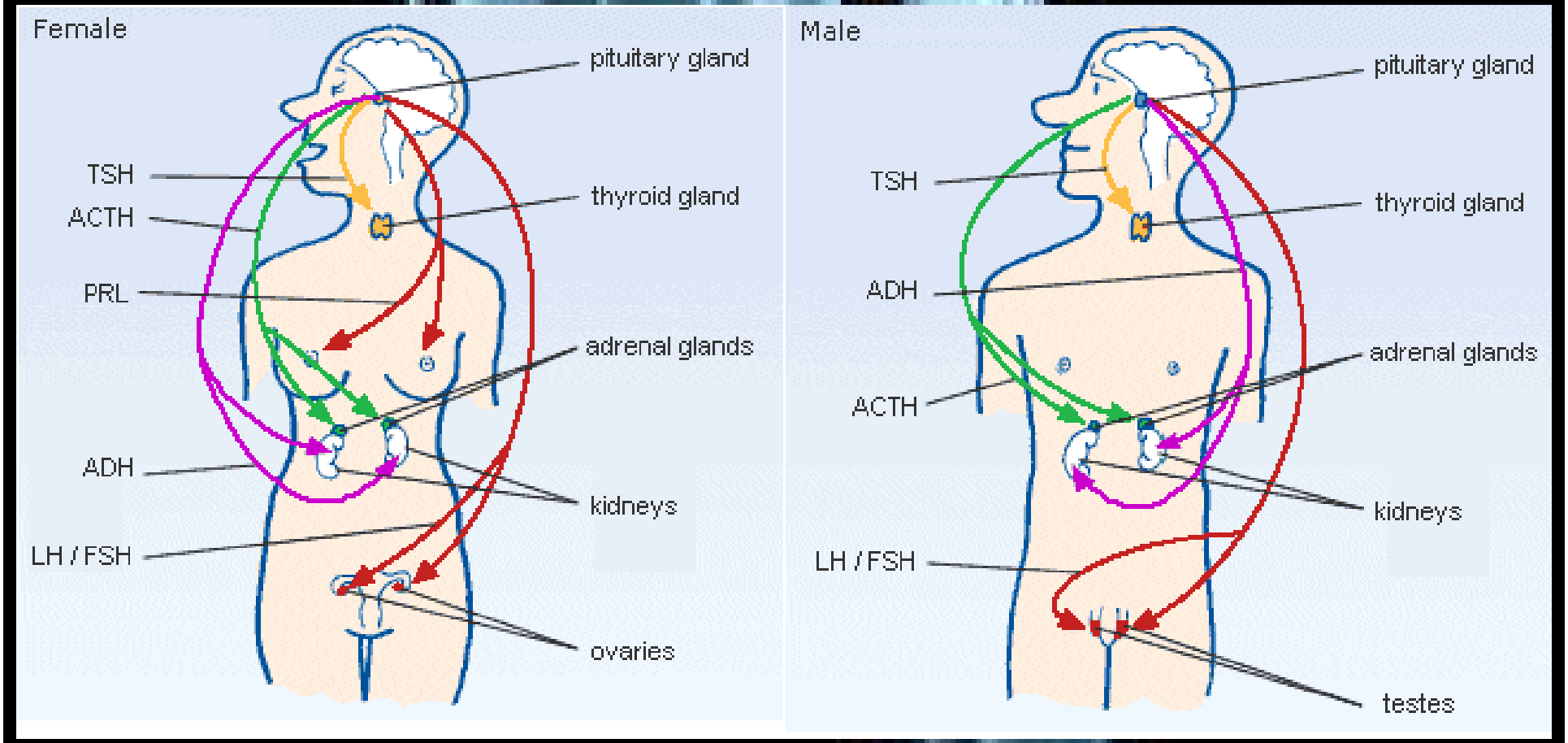
3) les rythmes sont organisés les uns par rapport aux autres

cohérence physiologique

synchronisation interne = relation de phase


Exogenous
Evoked
endogenous
Sleep
Circadian clock
Posture
Activity
light
Stress
Meals
others
Ultradian pulse generators
+
−
Pituitary gland
LH
FSH
ACTH
TSH
PRL
GH

II. Les hormones

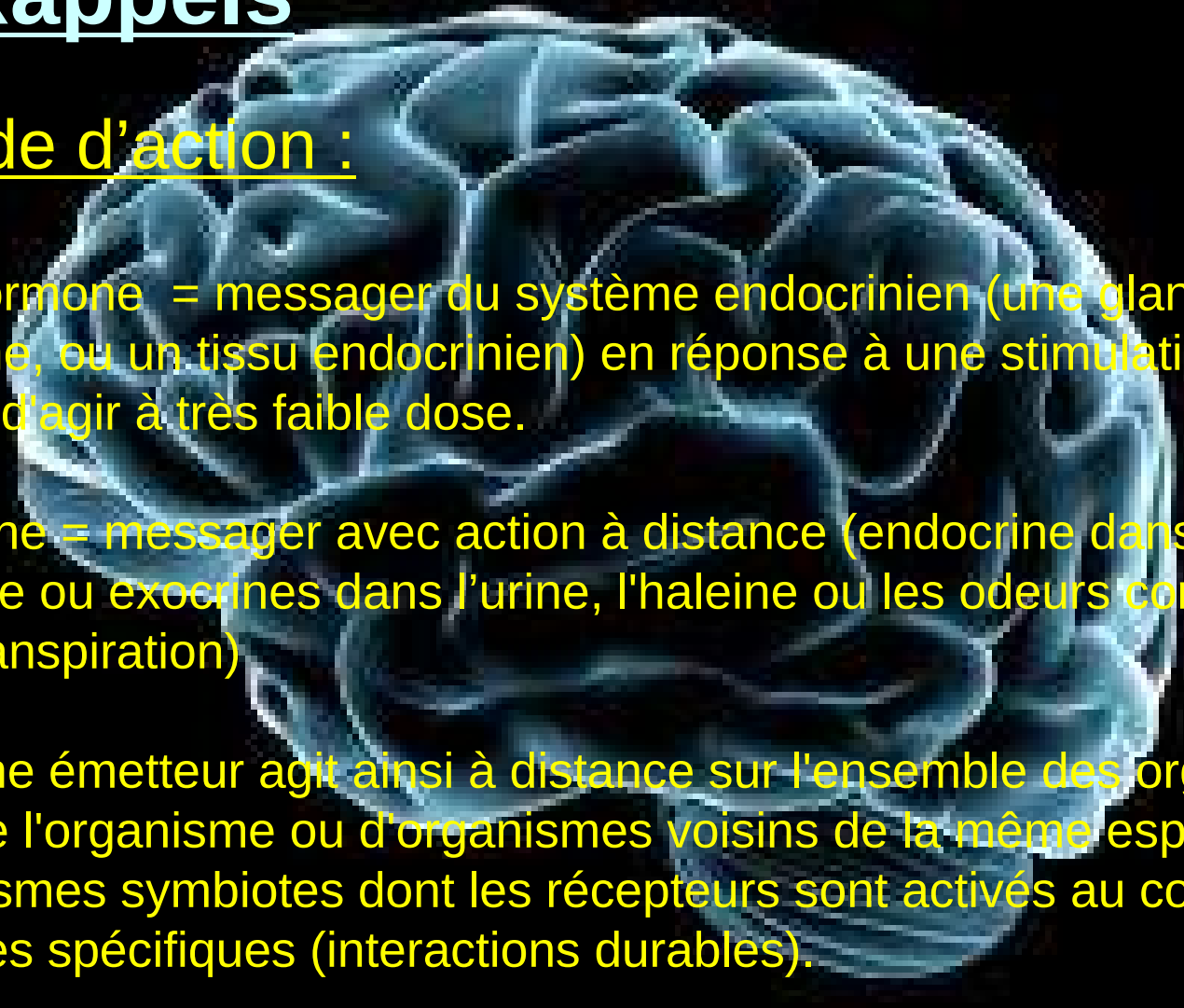


II. Les hormones

1. Rappels

2. Les hormones rythmées

II.1. Rappels



☞ Mode d'action :

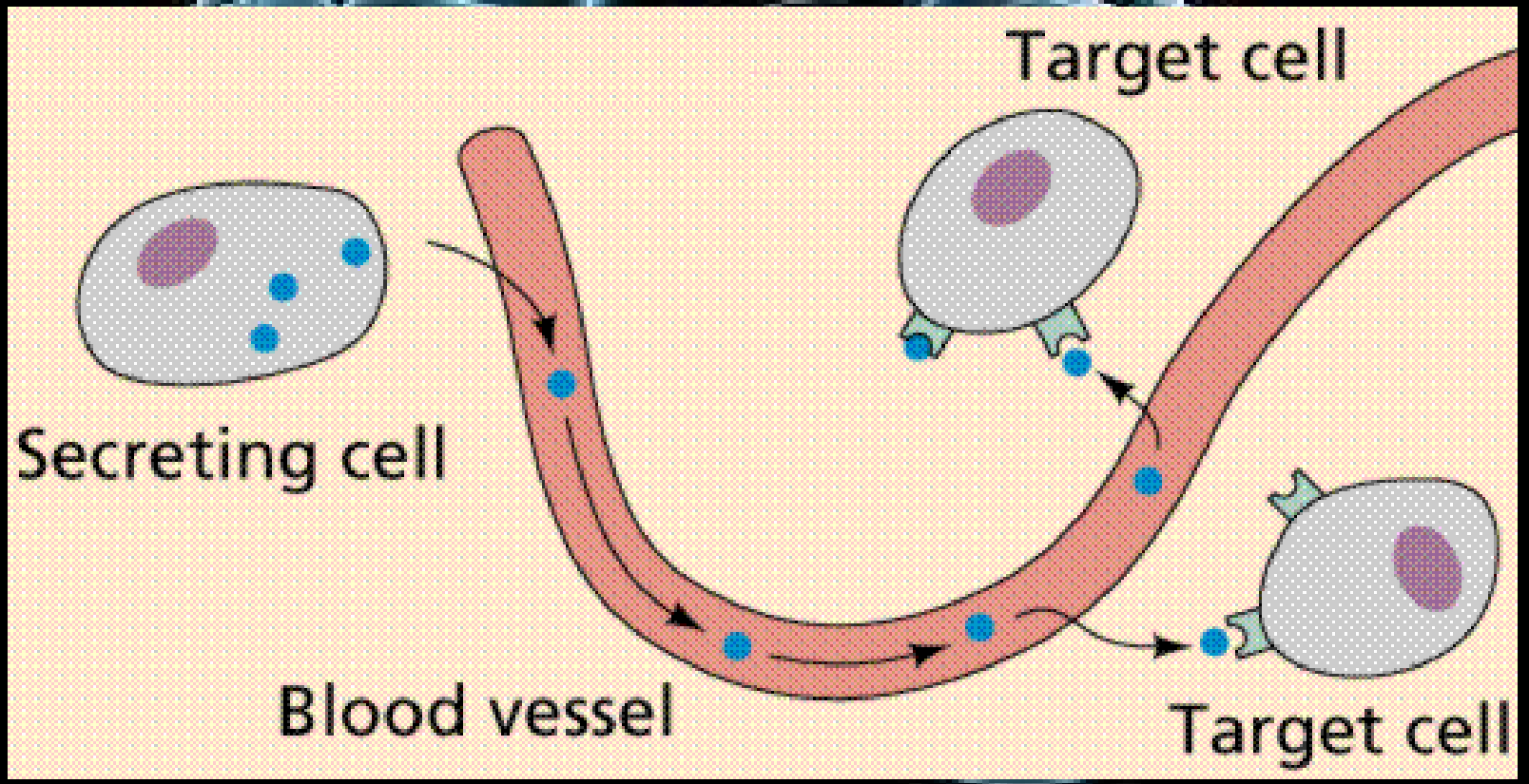
- Une hormone = messager du système endocrinien (une glande endocrine, ou un tissu endocrinien) en réponse à une stimulation, et capable d'agir à très faible dose.

- Hormone = messager avec action à distance (endocrine dans le sang ou la lymphe ou exocrines dans l'urine, l'haleine ou les odeurs corporelles par la transpiration)

- L'organe émetteur agit ainsi à distance sur l'ensemble des organes cibles de l'organisme ou d'organismes voisins de la même espèce, voire d'organismes symbiotes dont les récepteurs sont activés au contact des hormones spécifiques (interactions durables).

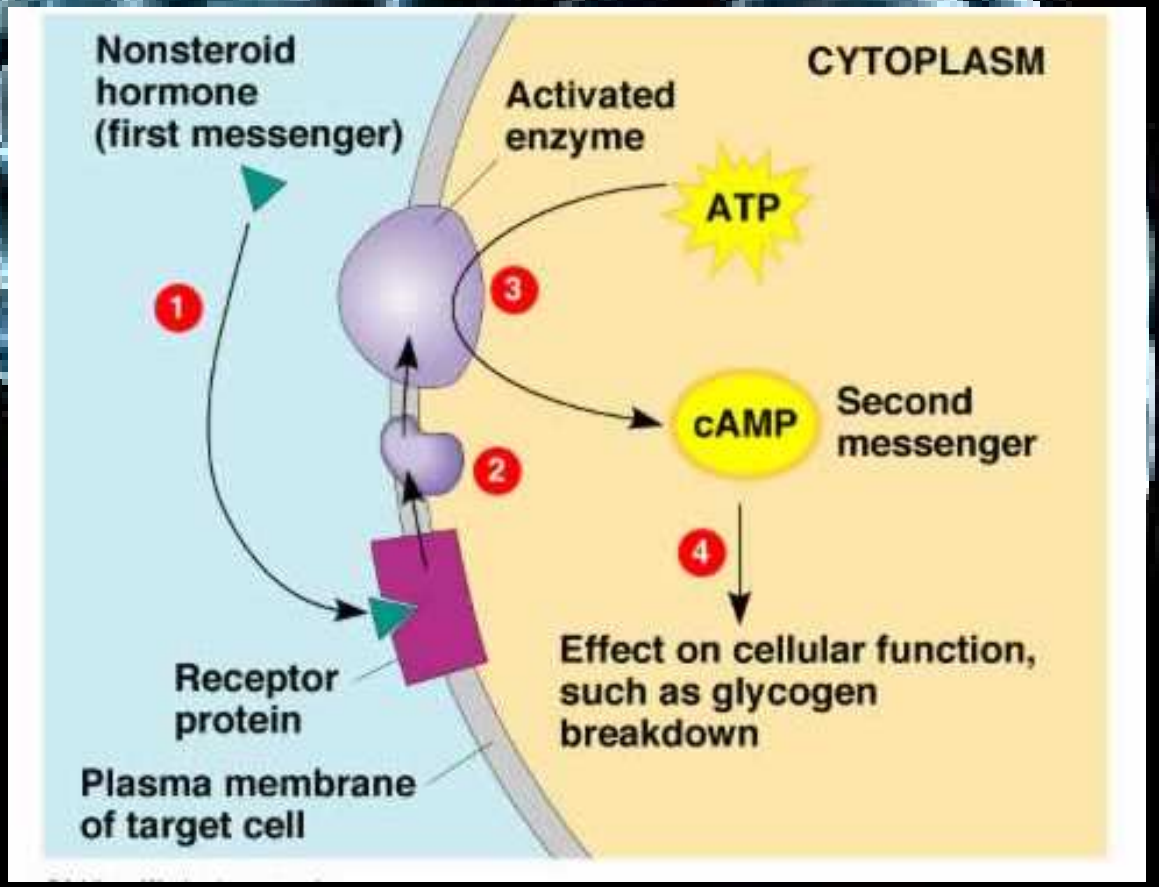
II.1. Rappels

☞ Mode d'action :



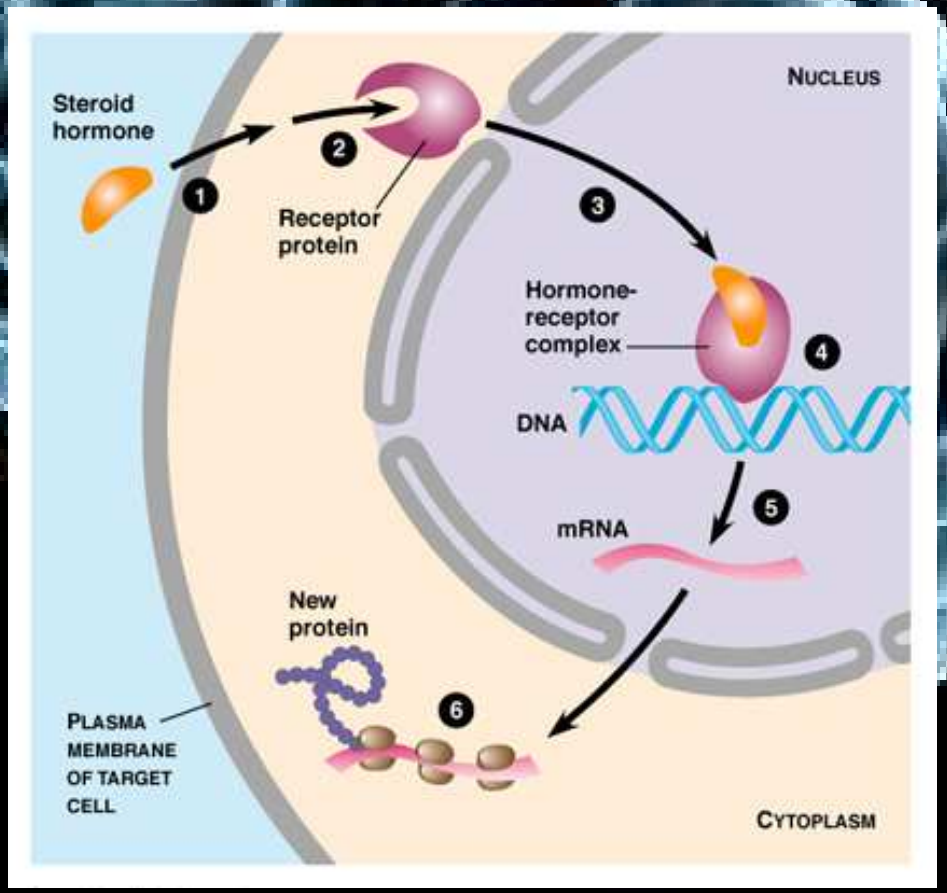
II.1. Rappels

☞ Mode d'action :

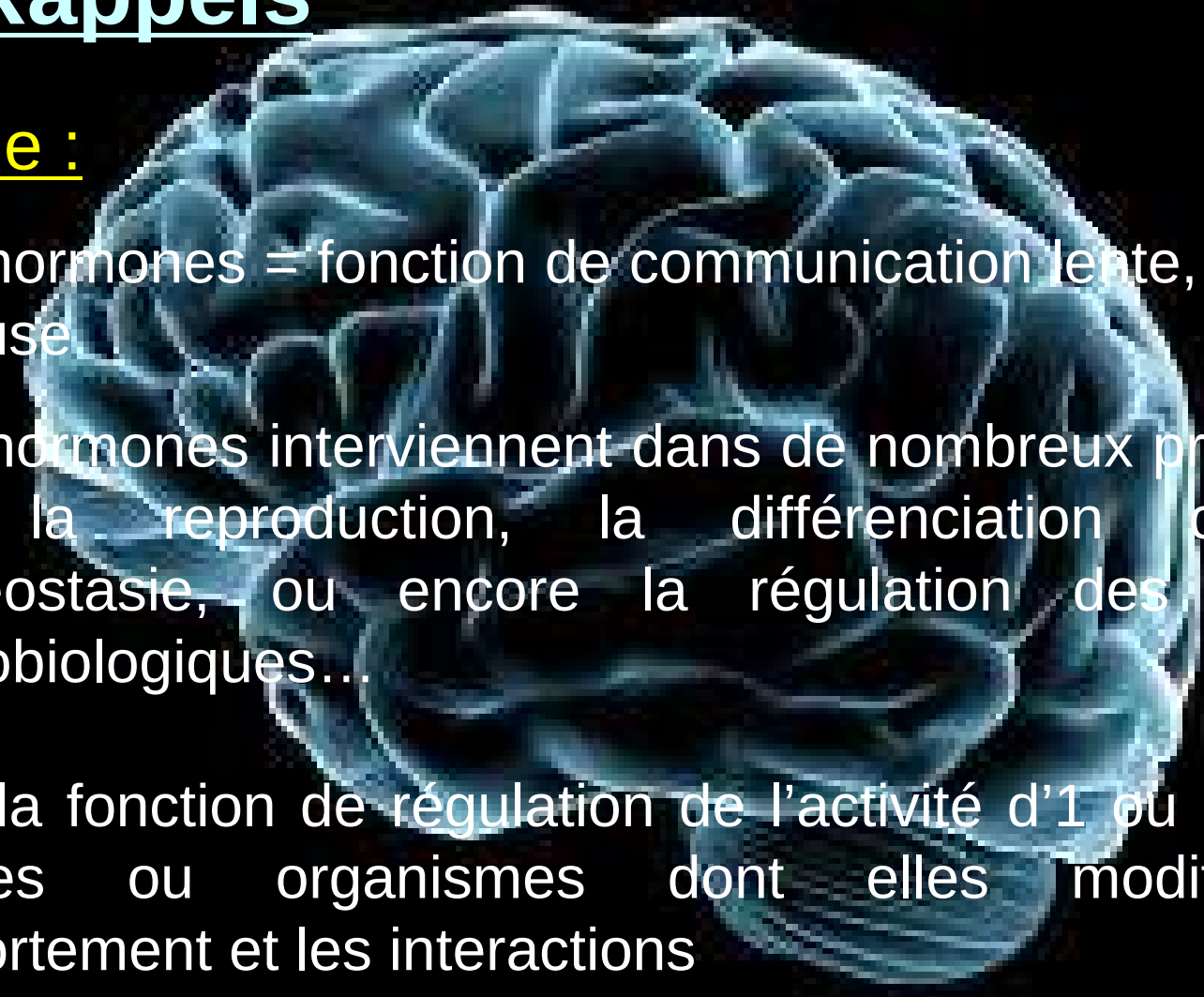


II.1. Rappels

☞ Mode d'action :



II.1. Rappels



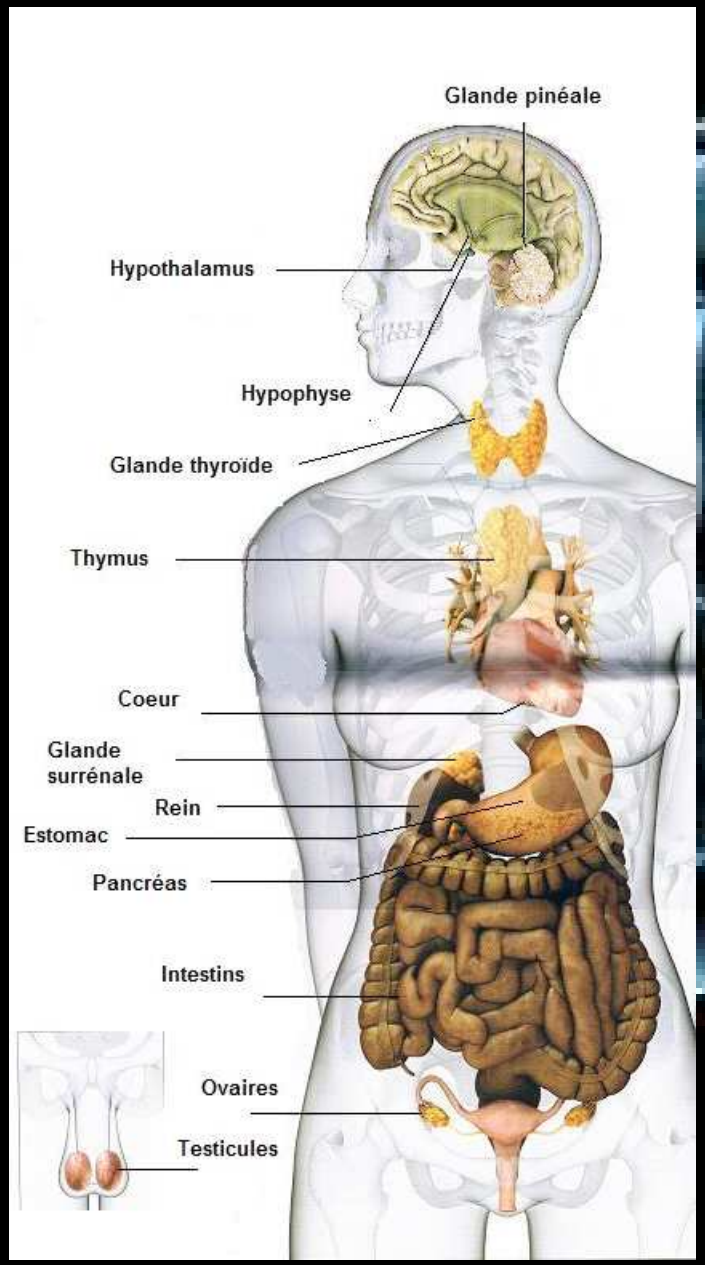
☞ Rôle :

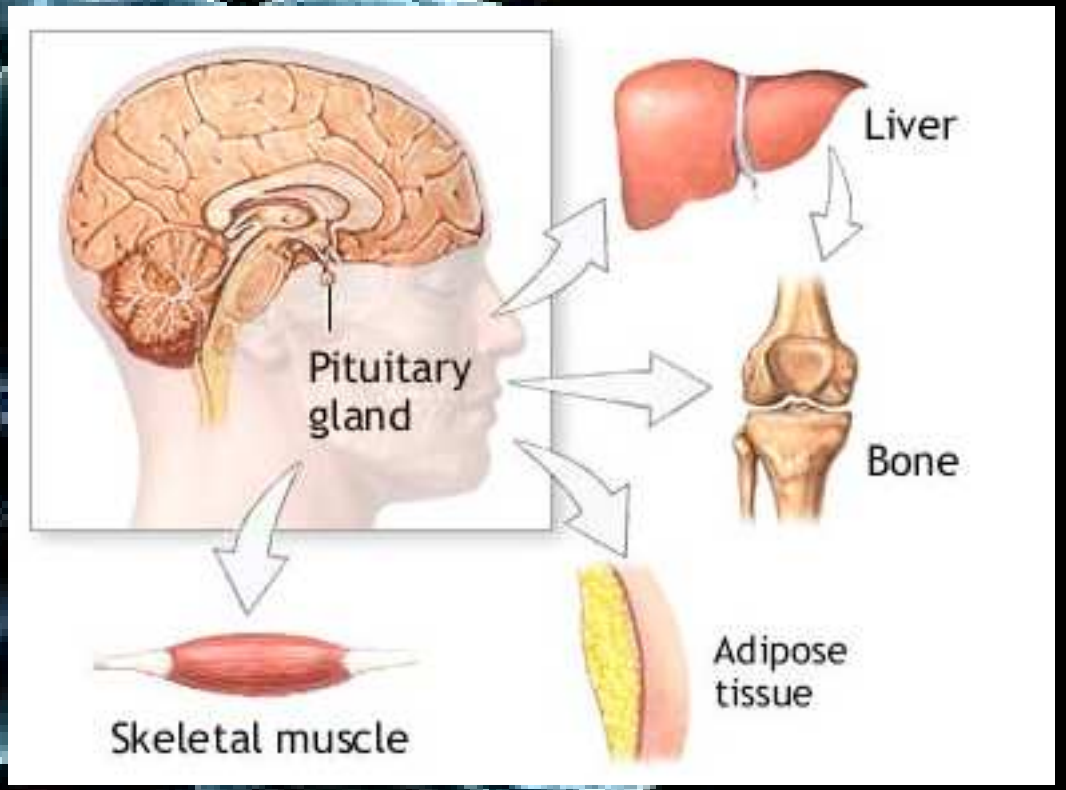
- Les hormones = fonction de communication lente, continue et diffuse.

- Les hormones interviennent dans de nombreux processus, dont la reproduction, la différenciation cellulaire, l'homéostasie, ou encore la régulation des rythmes chronobiologiques…

- Elle la fonction de régulation de l'activité d'1 ou plusieurs organes ou organismes dont elles modifient le comportement et les interactions

Chronobiologie & Hormones



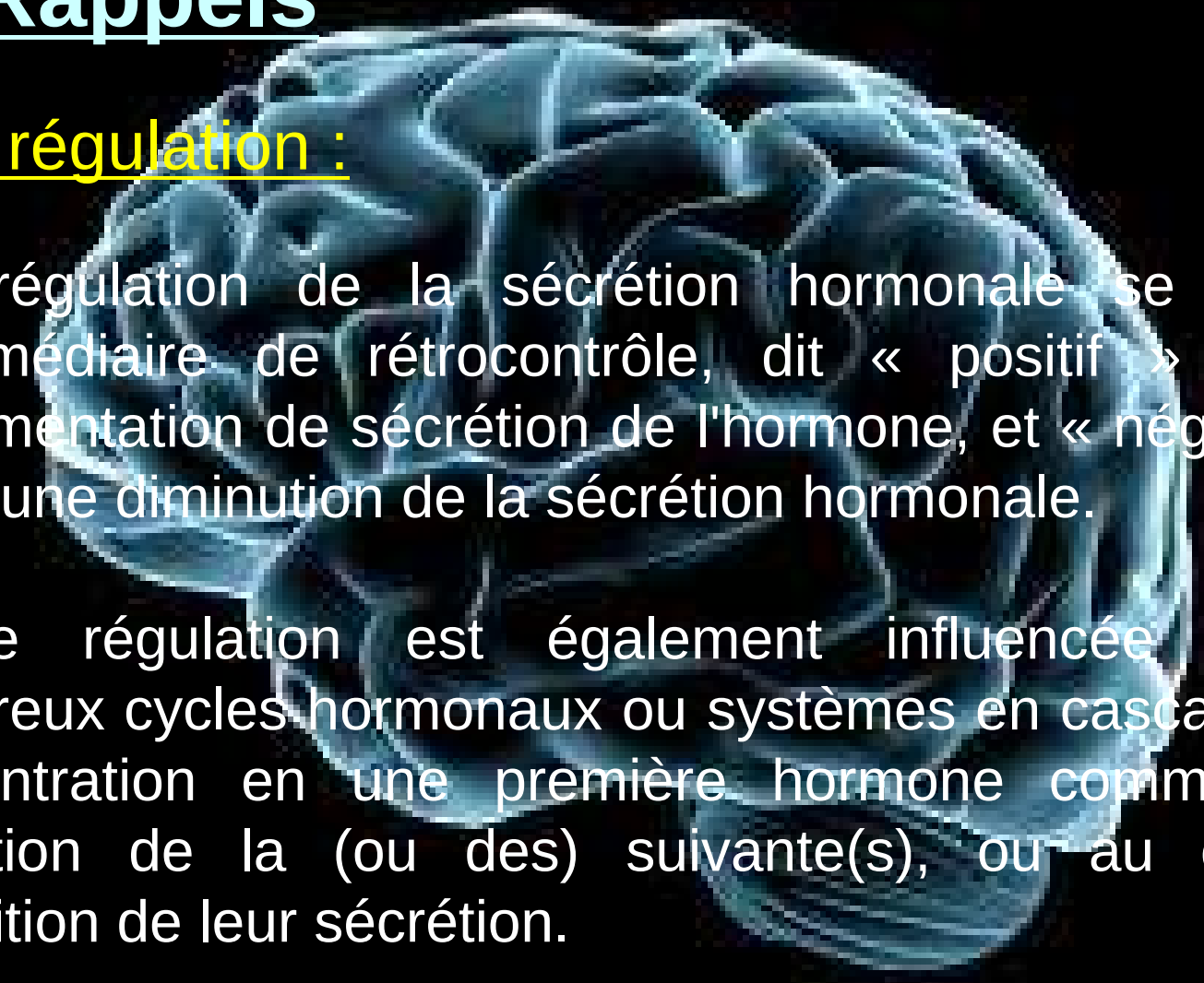


II.1. Rappels

☞ Rôle :

Nom	Cible	Action hormonale	Effets physiologique
GnRH (gonadolibérine)	Adénohypophyse	Libération des Gonadotrophines (FSH et LH)	Taux d'hormone sexuelle, gamétogénèse, ...
CRH	Adénohypophyse	Libération d'hormone corticotrope (ACTH)	Effets des glucocorticoïdes et des androgènes, ...
TRH (TSH releasing hormone)	Adénohypophyse	Libérations de TSH	Agit sur la libération des hormones thyroïdiennes (T3 et T4)
Dopamine	Adénohypophyse	inhibe la prolactine, ...	Stimulation de la circulation sanguine, Effet de *récompense* (ex:nicotine et cocaïne agissent par la dopamine), ...
Orexine			Appetit, éveil, ...
vasopressine	canaux collecteurs rénaux	augmentation de l'expression des aquaporines à la surface des cellules	augmentation de la réabsorption de l'eau dans les reins, augmentation de la volémie et de la pression sanguine ...
ocytocine	cellules musculaires lisses	augmentation de la contraction des cellules musculaires lisses	ejection du lait de la glande mammaire, contractions utérines lors de l'accouchement ...

II.1. Rappels



☞ La régulation :

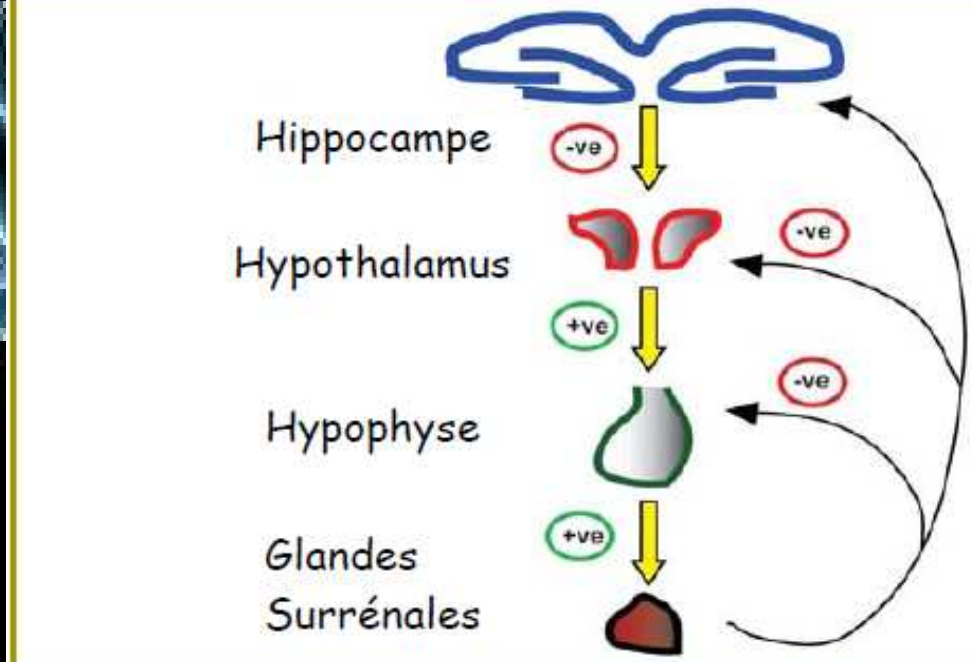
- La régulation de la sécrétion hormonale se fait par l'intermédiaire de rétrocontrôle, dit « positif » en cas d'augmentation de sécrétion de l'hormone, et « négatif » s'il induit une diminution de la sécrétion hormonale.

- Cette régulation est également influencée par de nombreux cycles hormonaux ou systèmes en cascade où la concentration en une première hormone commande la libération de la (ou des) suivante(s), ou au contraire l'inhibition de leur sécrétion.

II.1. Rappels

☞ La régulation :

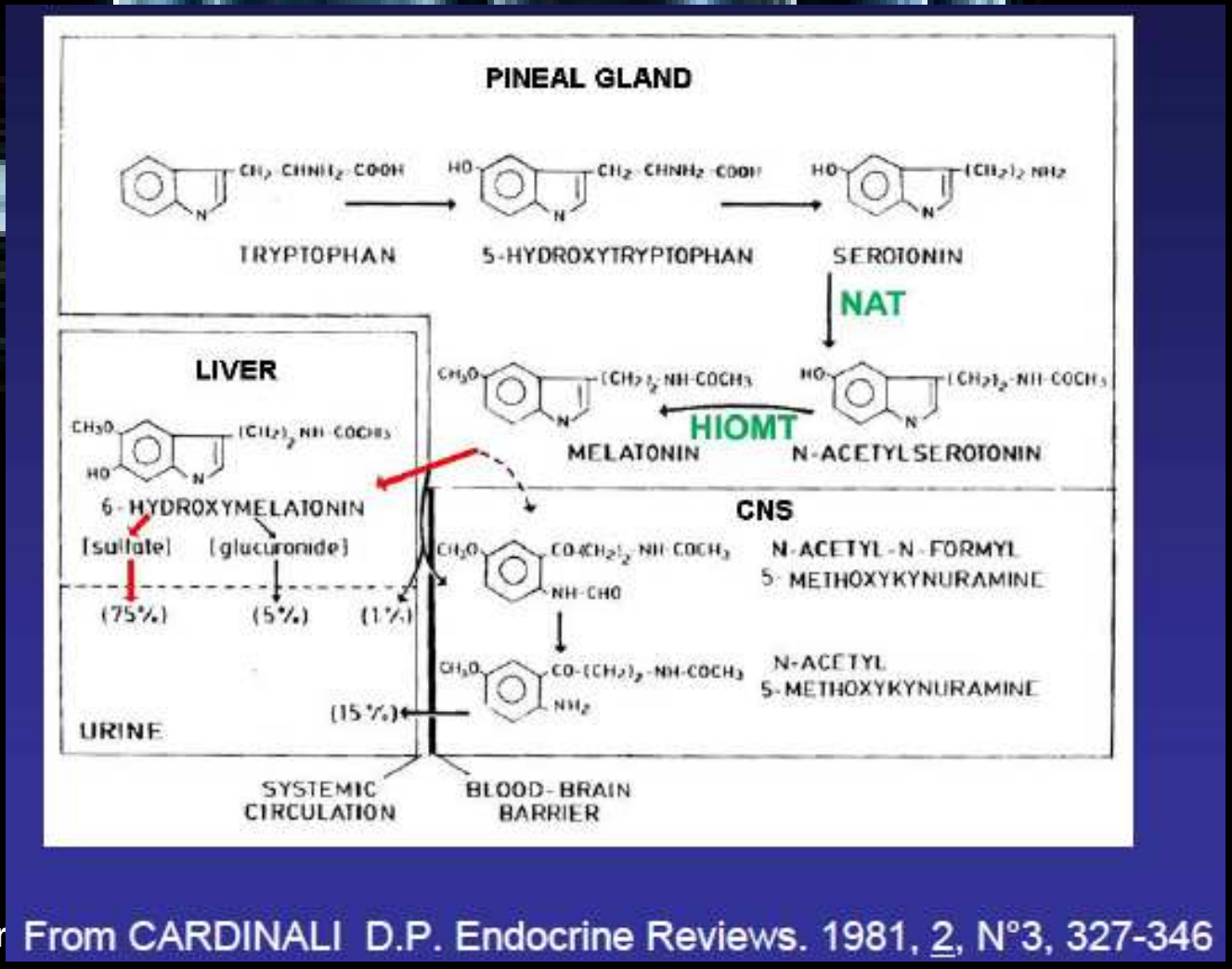
L'axe hypothalamique-hypophysaire-surrénale



L'axe HPA (venant de l'anglais Hypothalamic-Pituitary-Adrenal axis). L'hypothalamus au centre contrôle la relâche des hormones de la glande hypophysaire qui agit sur les glandes surrénales. Le feedback négatif des hormones ainsi relâchées est transmis aux différents niveaux de l'axe.

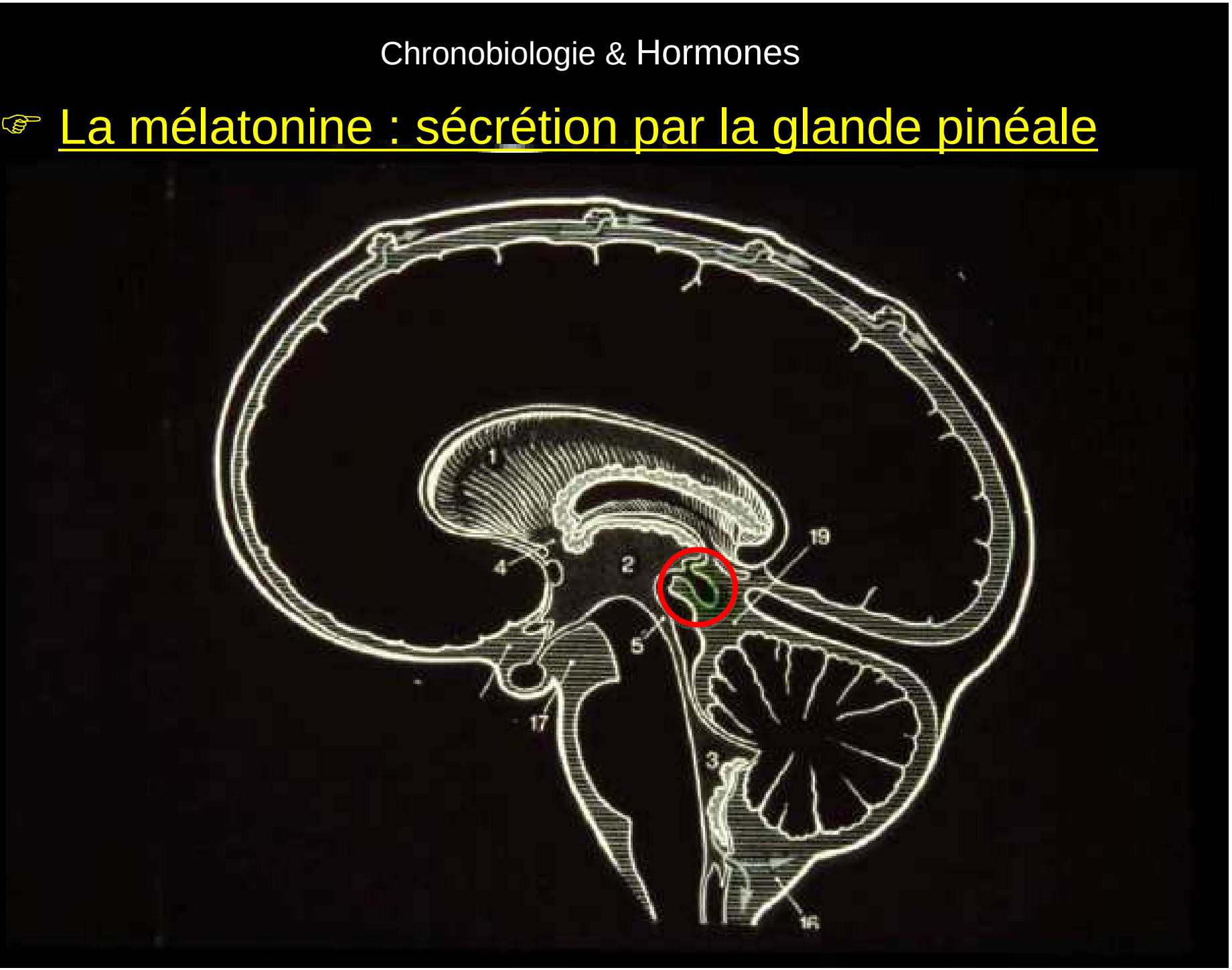
II.2. Les hormones rythmées

☞ La mélatonine : sa synthèse

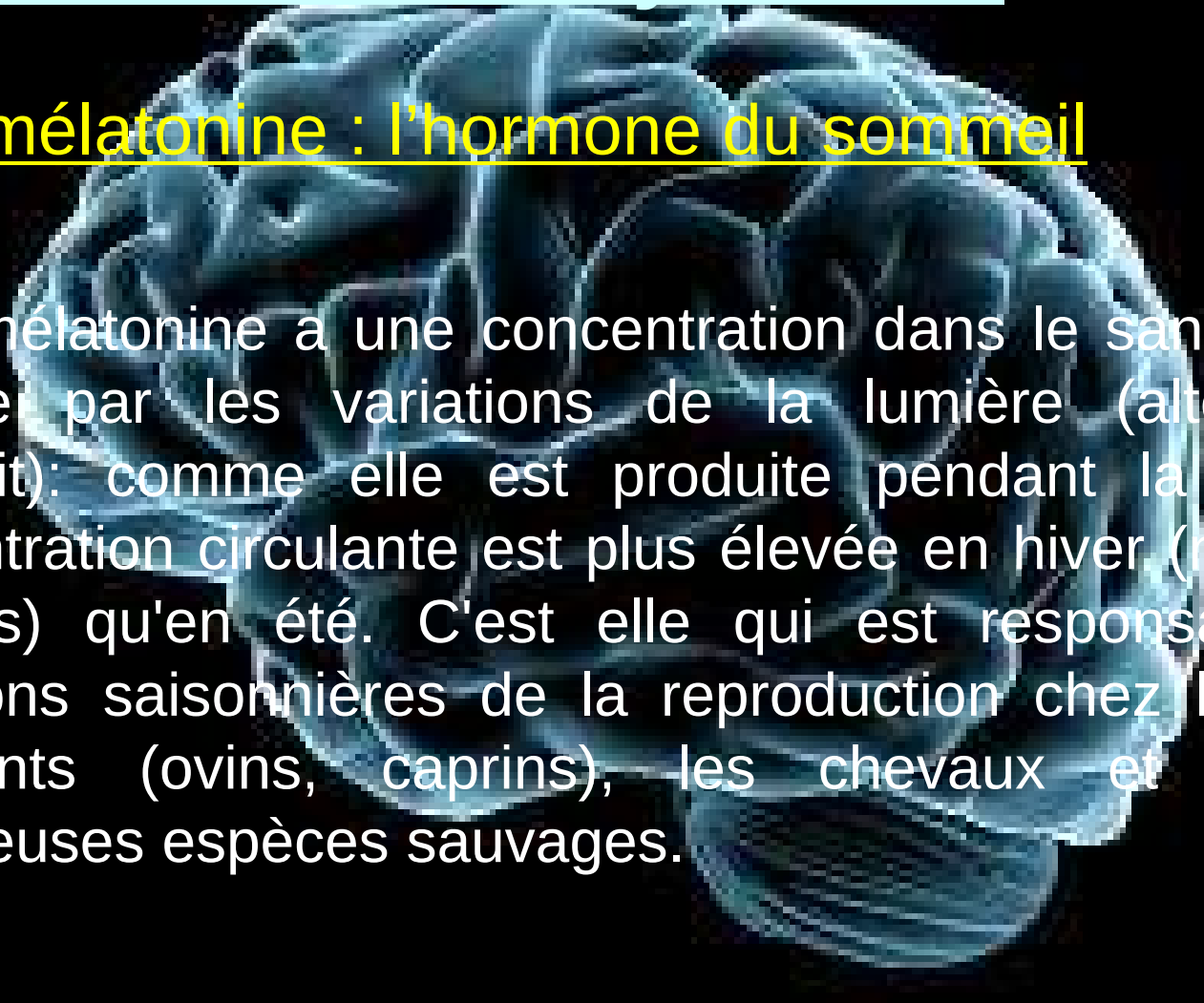


From CARDINALI D.P. Endocrine Reviews. 1981, 2, N°3, 327-346

☞ La mélatonine : sécrétion par la glande pinéale



II.2. Les hormones rythmées



☞ La mélatonine : l'hormone du sommeil

La mélatonine a une concentration dans le sang qui est régulée par les variations de la lumière (alternances jour/nuit): comme elle est produite pendant la nuit, sa concentration circulante est plus élevée en hiver (nuits plus longues) qu'en été. C'est elle qui est responsable des variations saisonnières de la reproduction chez les petits ruminants (ovins, caprins), les chevaux et de très nombreuses espèces sauvages.

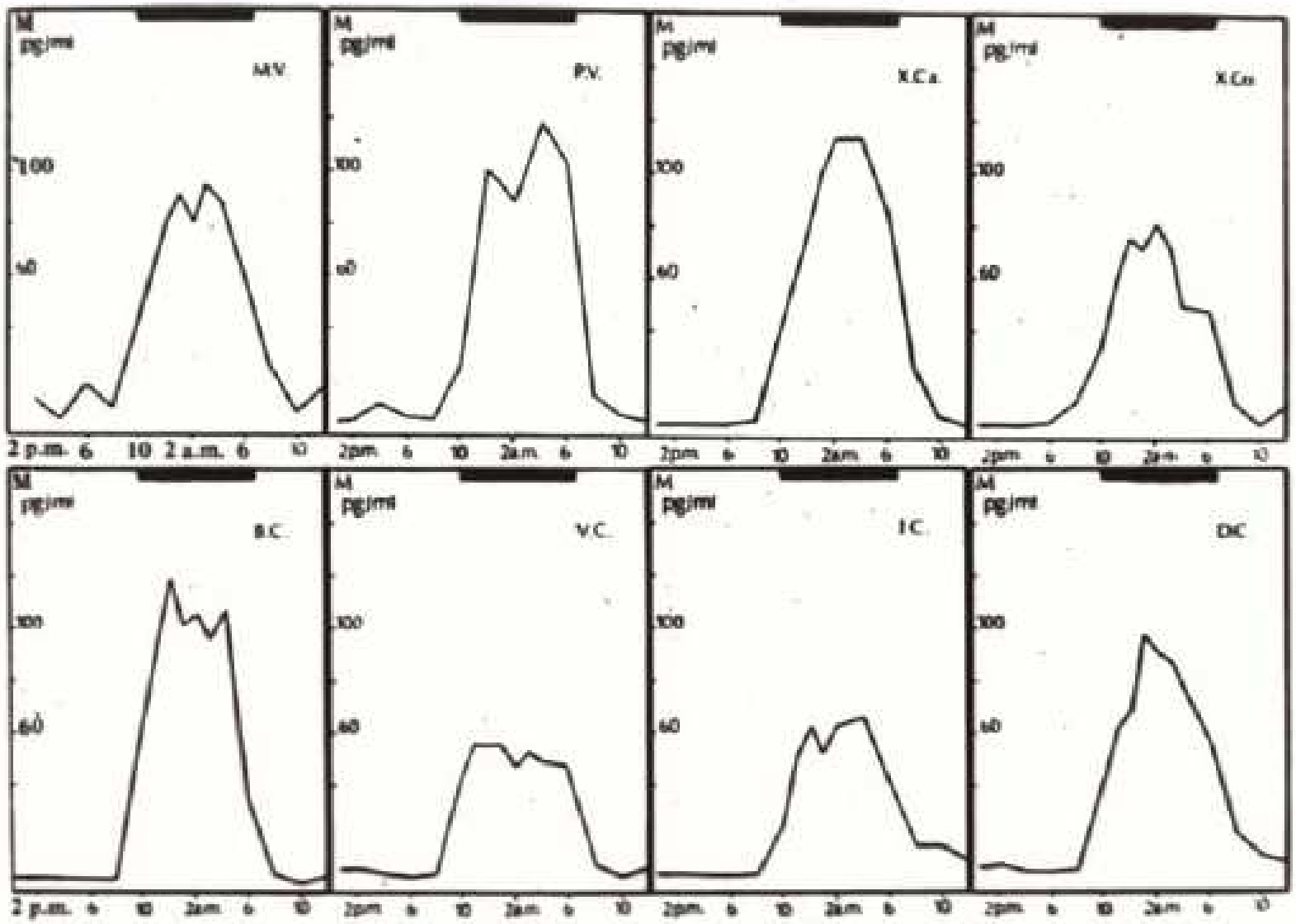
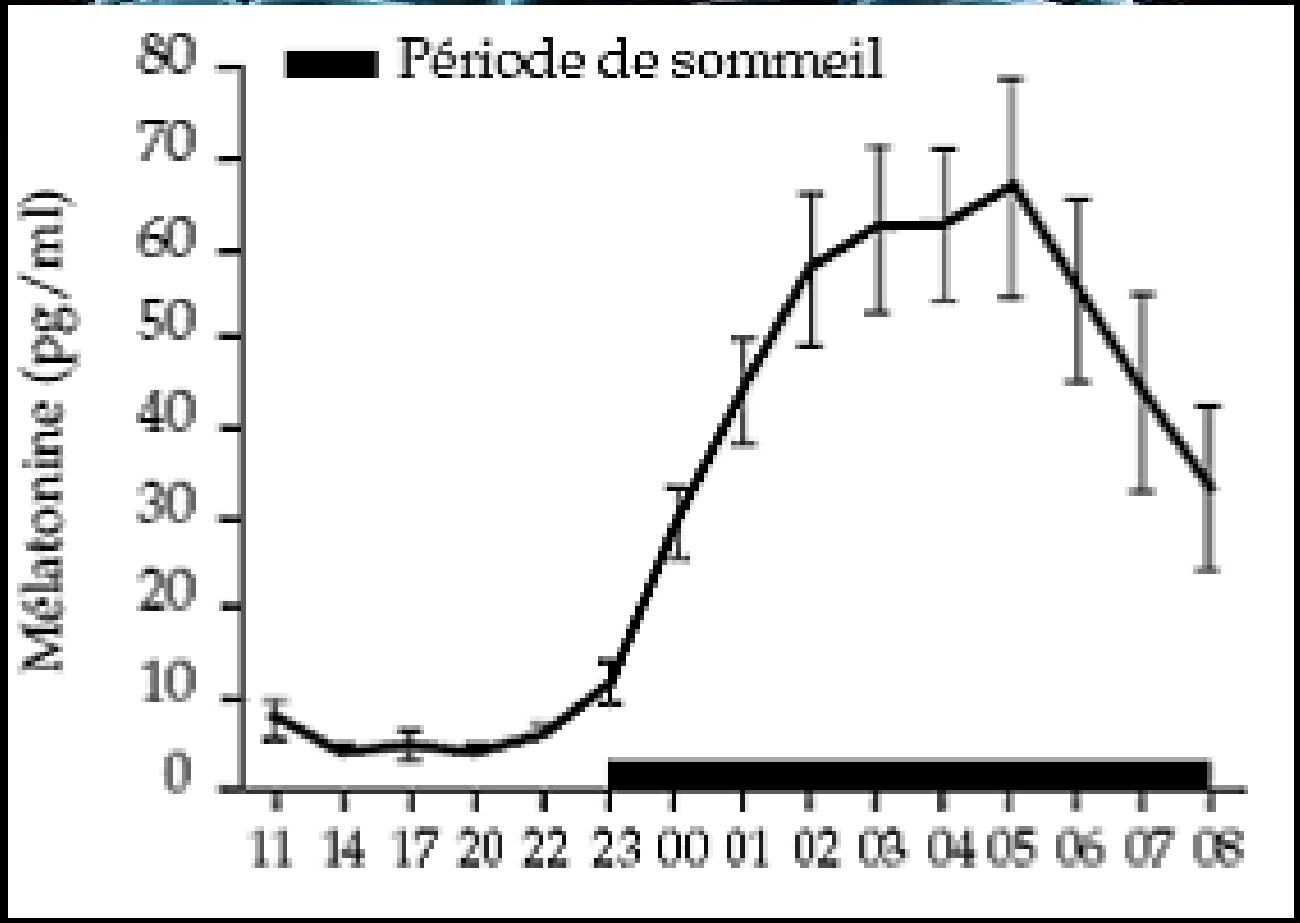


Fig. 1. Individual 24-hr profiles of plasma melatonin in control subjects.

From B. CLAUSTRAT et al, Biol. Psychiat. 1984, 19 (1215-1228)

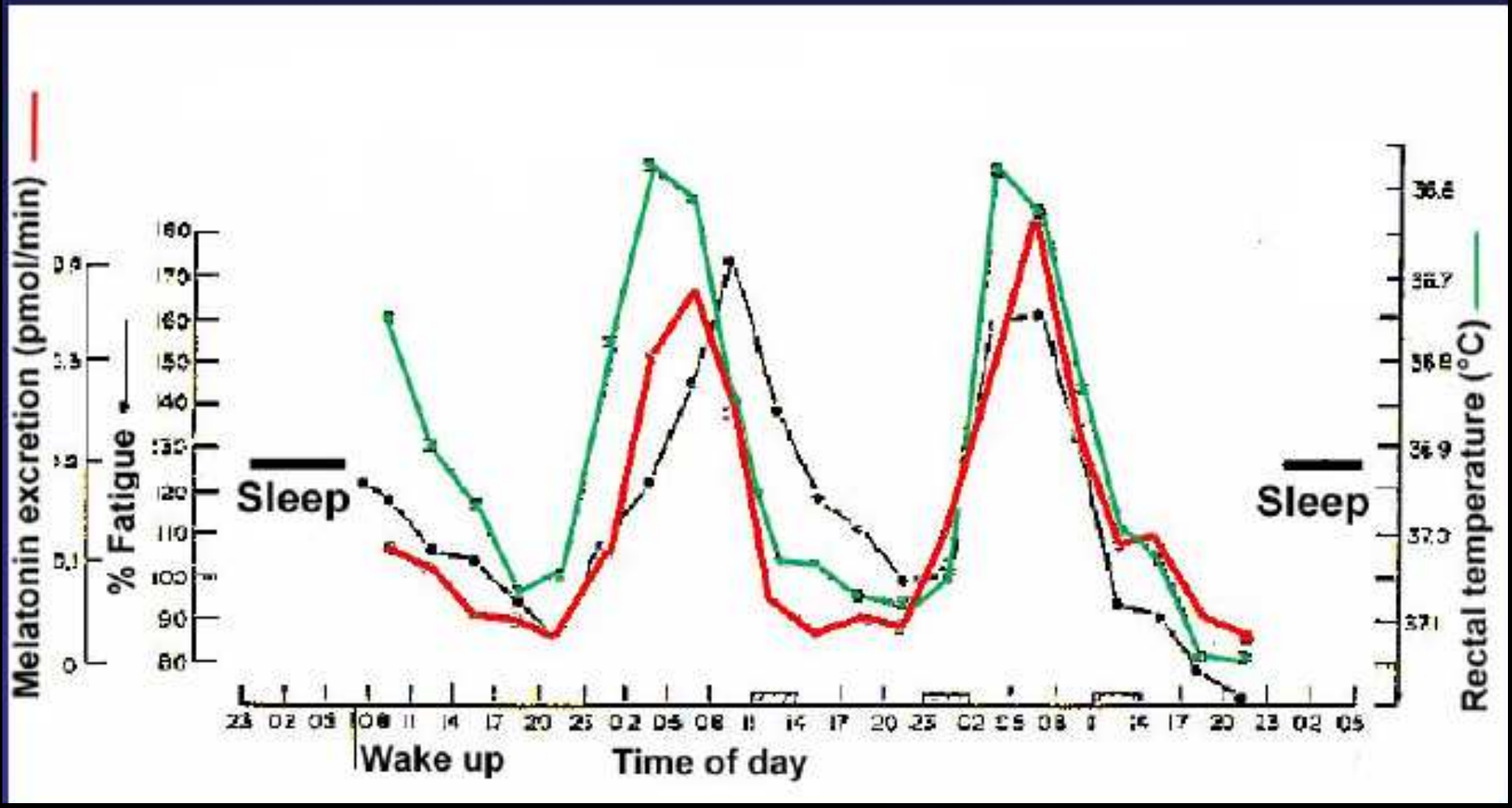
II.2. Les hormones rythmées

☞ La mélatonine : l'hormone du sommeil

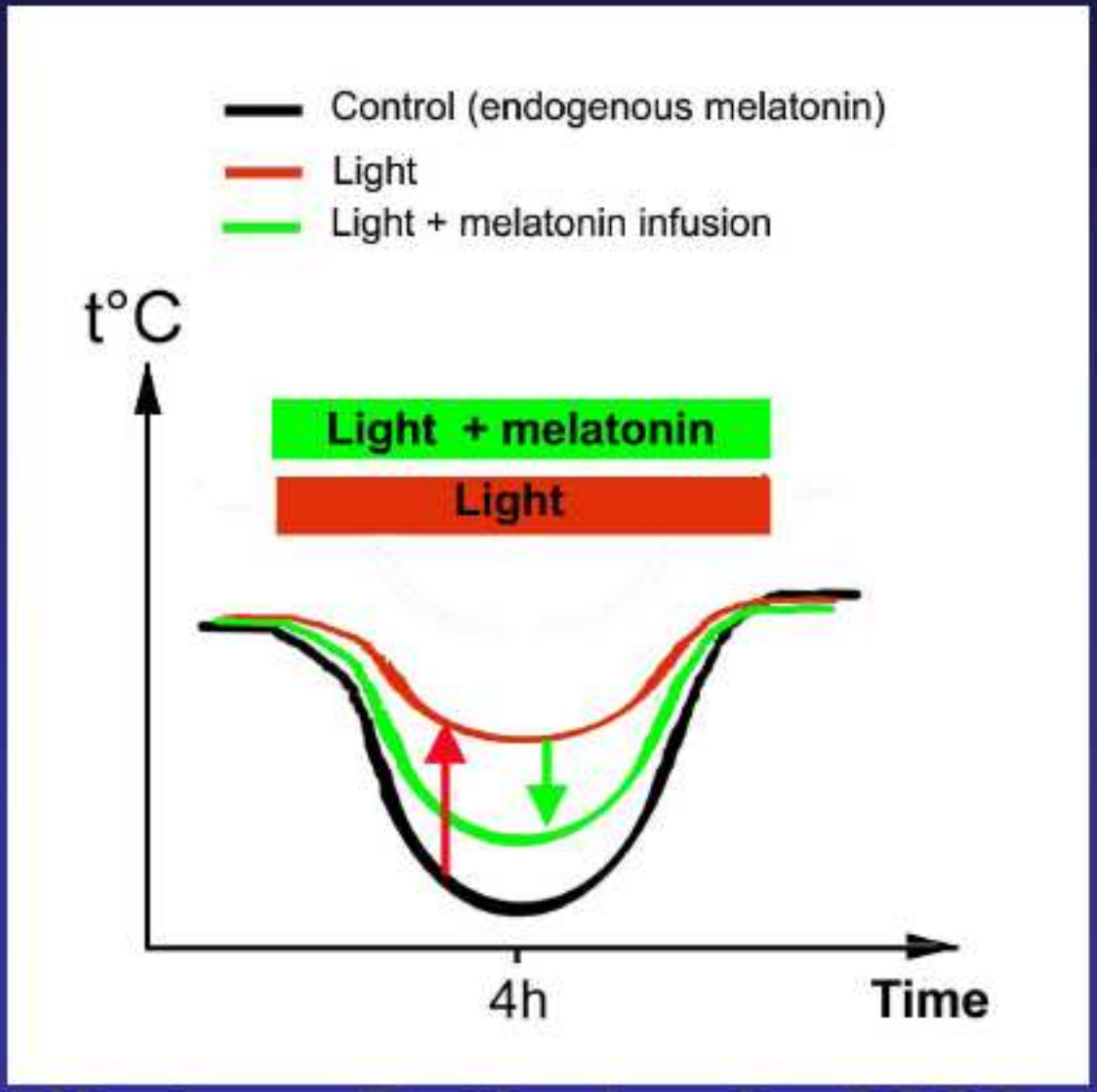


Melatonin excretion, body temperature and self-rated fatigue during 64 hours of sleep deprivation

from Akerstedt et al, Psychoneuroendocrinology, 1978, 4, 219-225

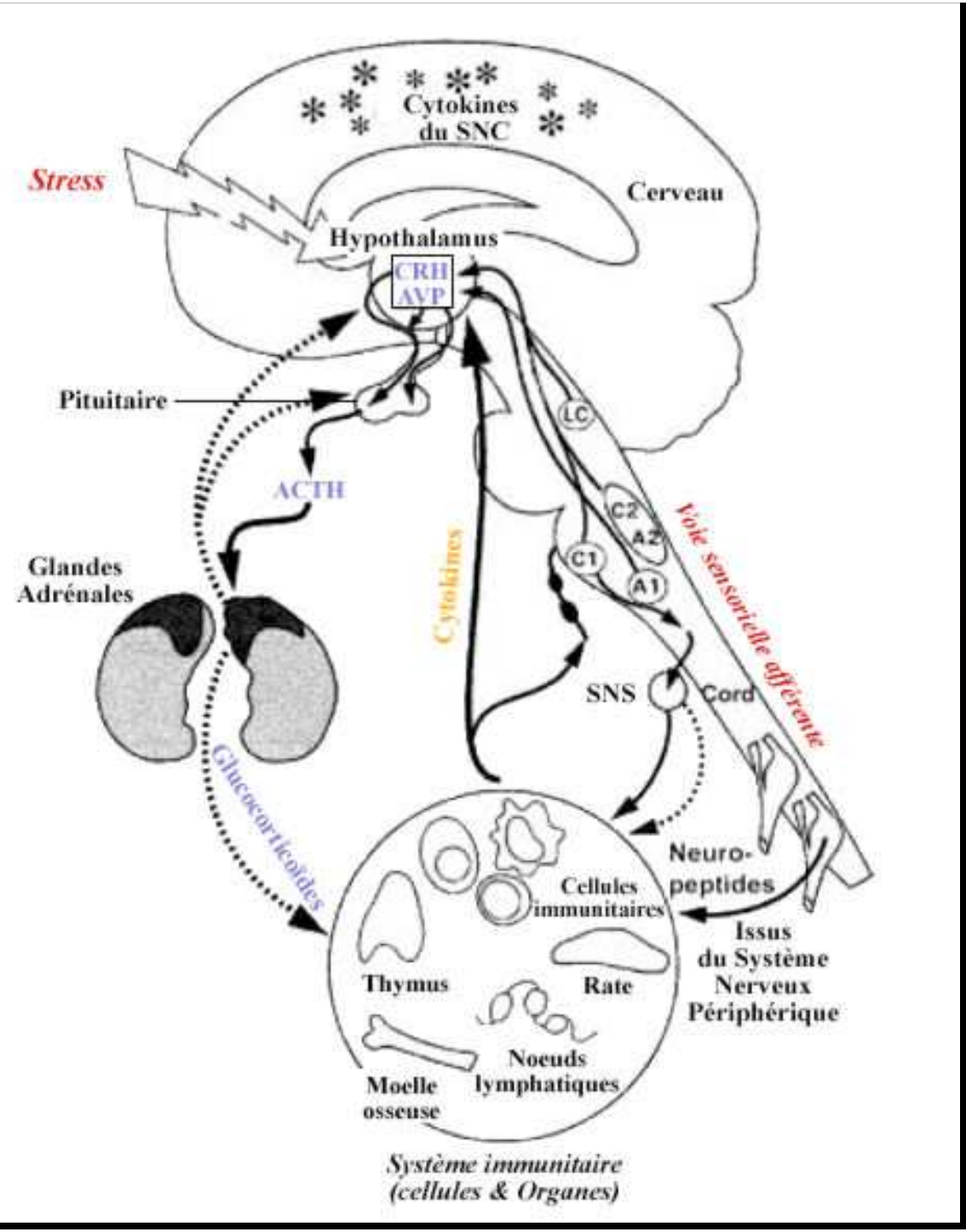


Effect of light or light + melatonin on temperature rhythm



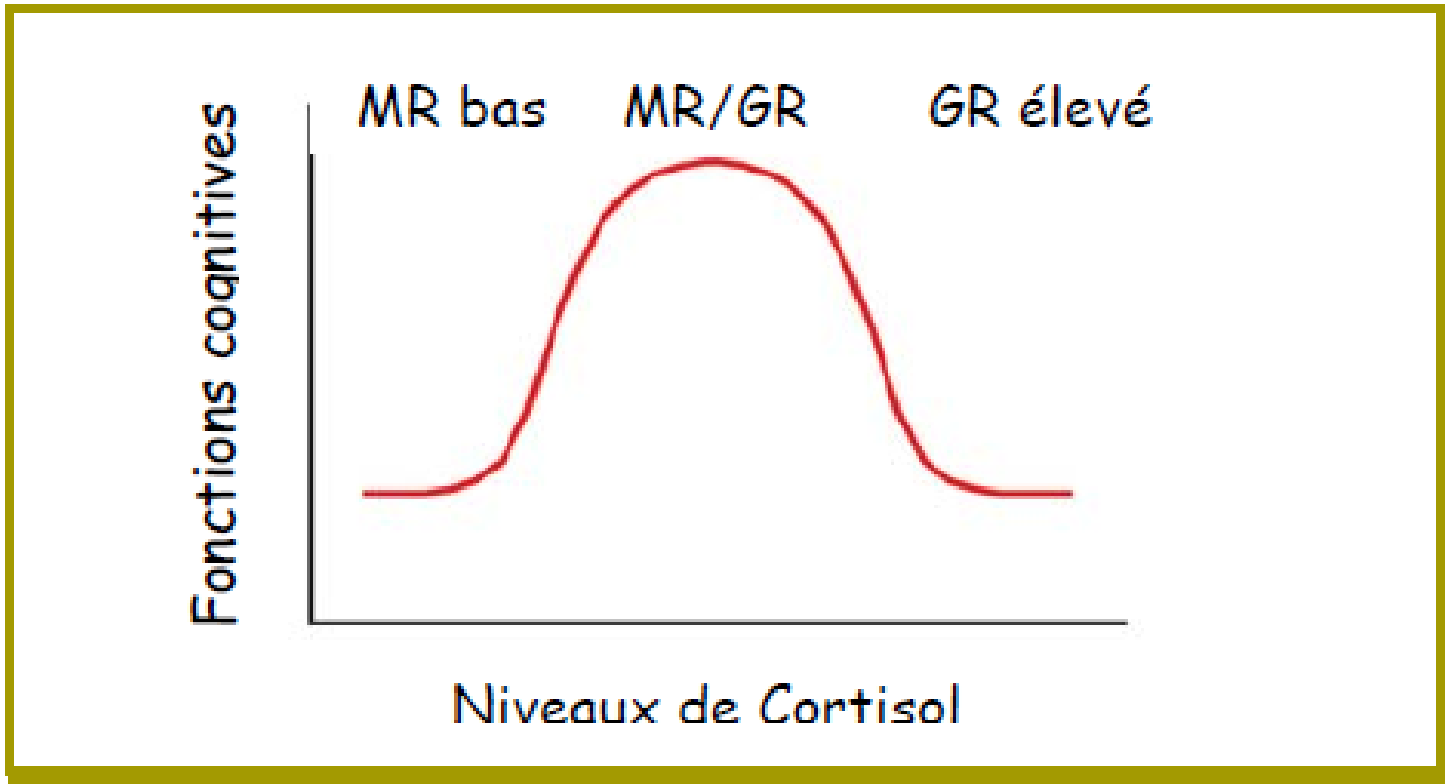
II.2. Les hormones rythmées

☞ Les hormones du stress : les axes du stress


Cytokines du SNC
Stress
Cerveau
Hypothalamus
CRH
AVP
Pituitaire
ACTH
Glandes Adrénales
Cytokines
LC
C2
A2
C1
A1
Voie sensorielle afférente
SNS
Cord
Glucocorticoïdes
Neuro-peptides
Cellules immunitaires
Issus du Système Nerveux Périphérique
Thymus
Rate
Noeuds lymphatiques
Moelle osseuse
Système immunitaire (cellules & Organes)

II.2. Les hormones rythmées

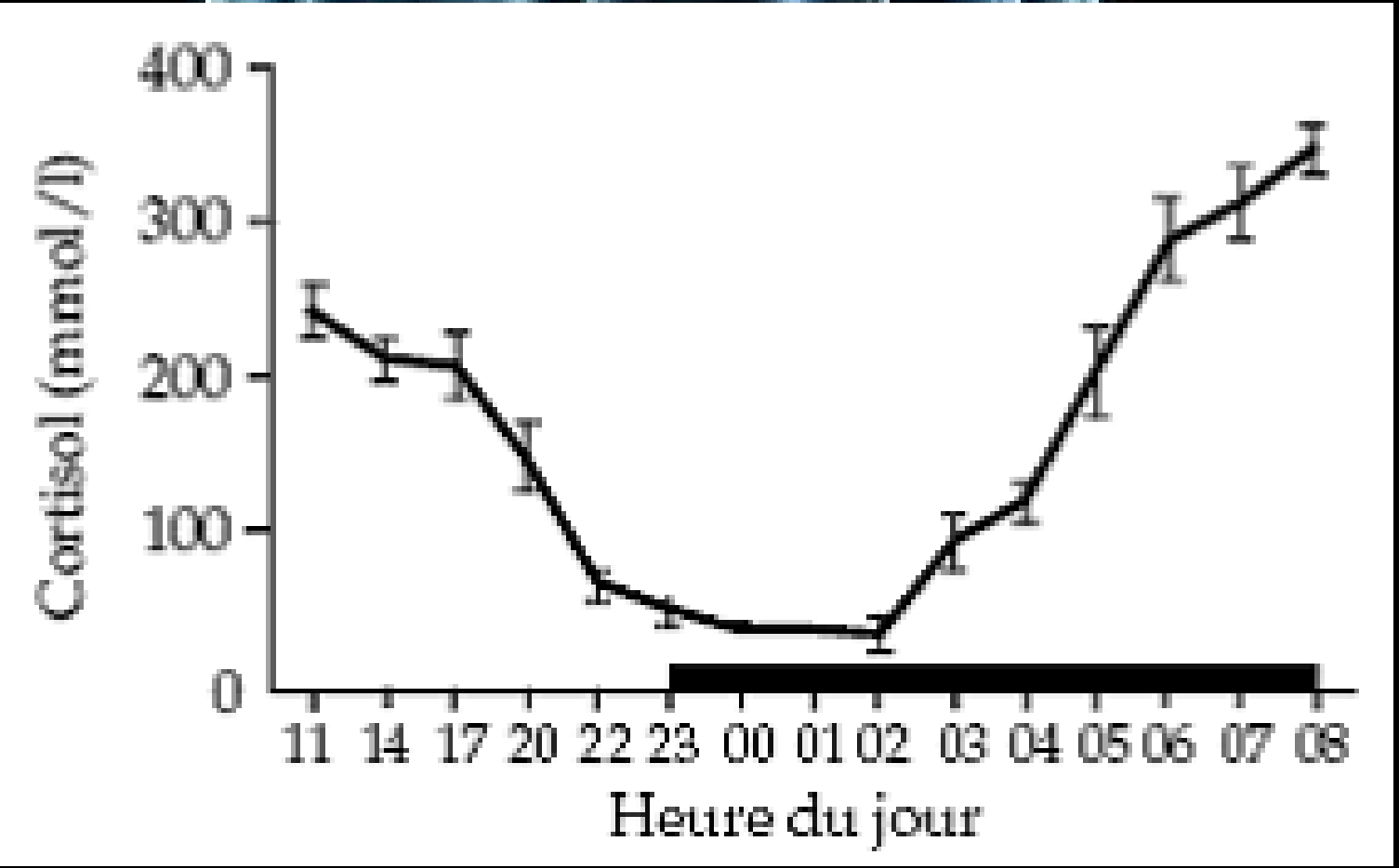
☞ Les hormones du stress : le cortisol



La courbe en forme de cloche du stress. Un peu de stress peut rendre les choses meilleures, mais trop de stress les rend pires.

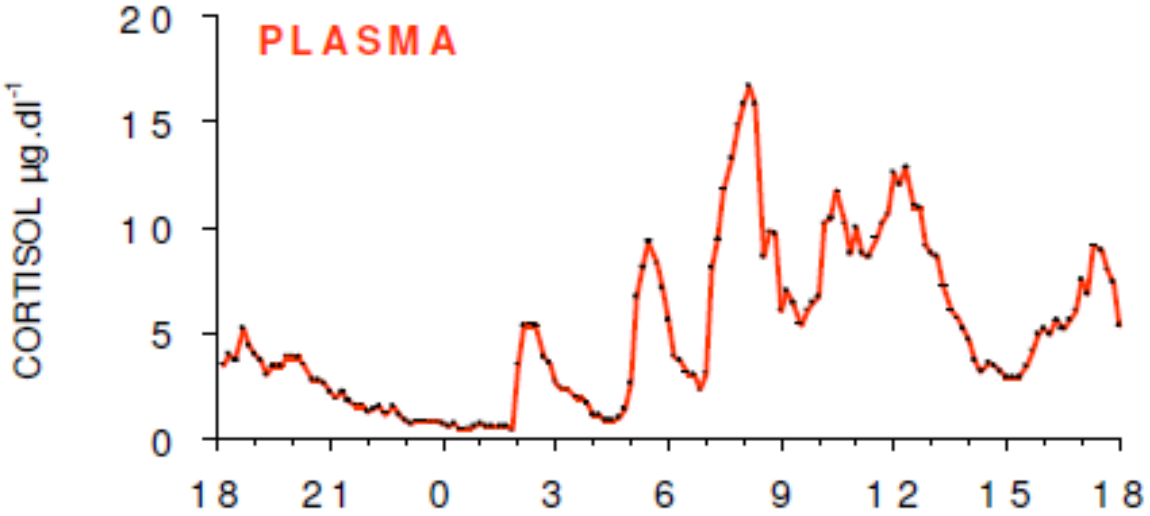
II.2. Les hormones rythmées

☞ Les hormones du stress : le cortisol



II.2. Les hormones rythmées

☞ Les hormones du stress : le cortisol

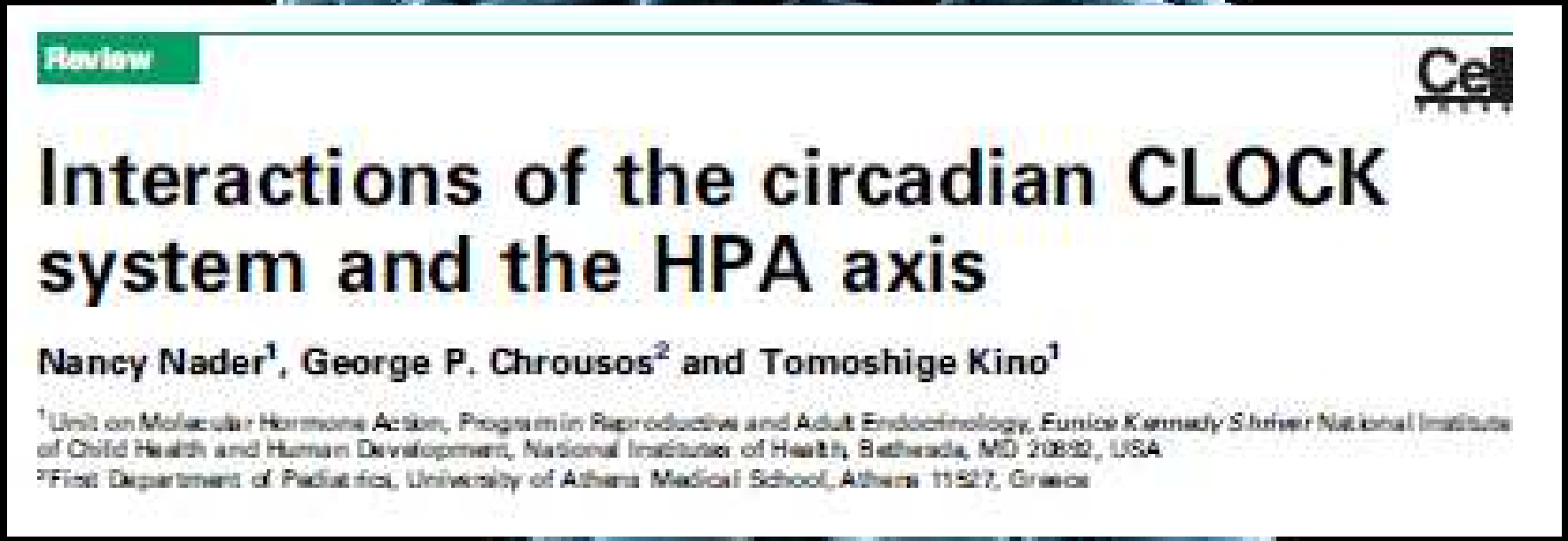


24-hour rhythm in plasma concentrations of cortisol

...

II.2. Les hormones rythmées

☞ Les hormones du stress : le cortisol



II.2. Les hormones rythmées

☞ Les hormones du stress : le cortisol

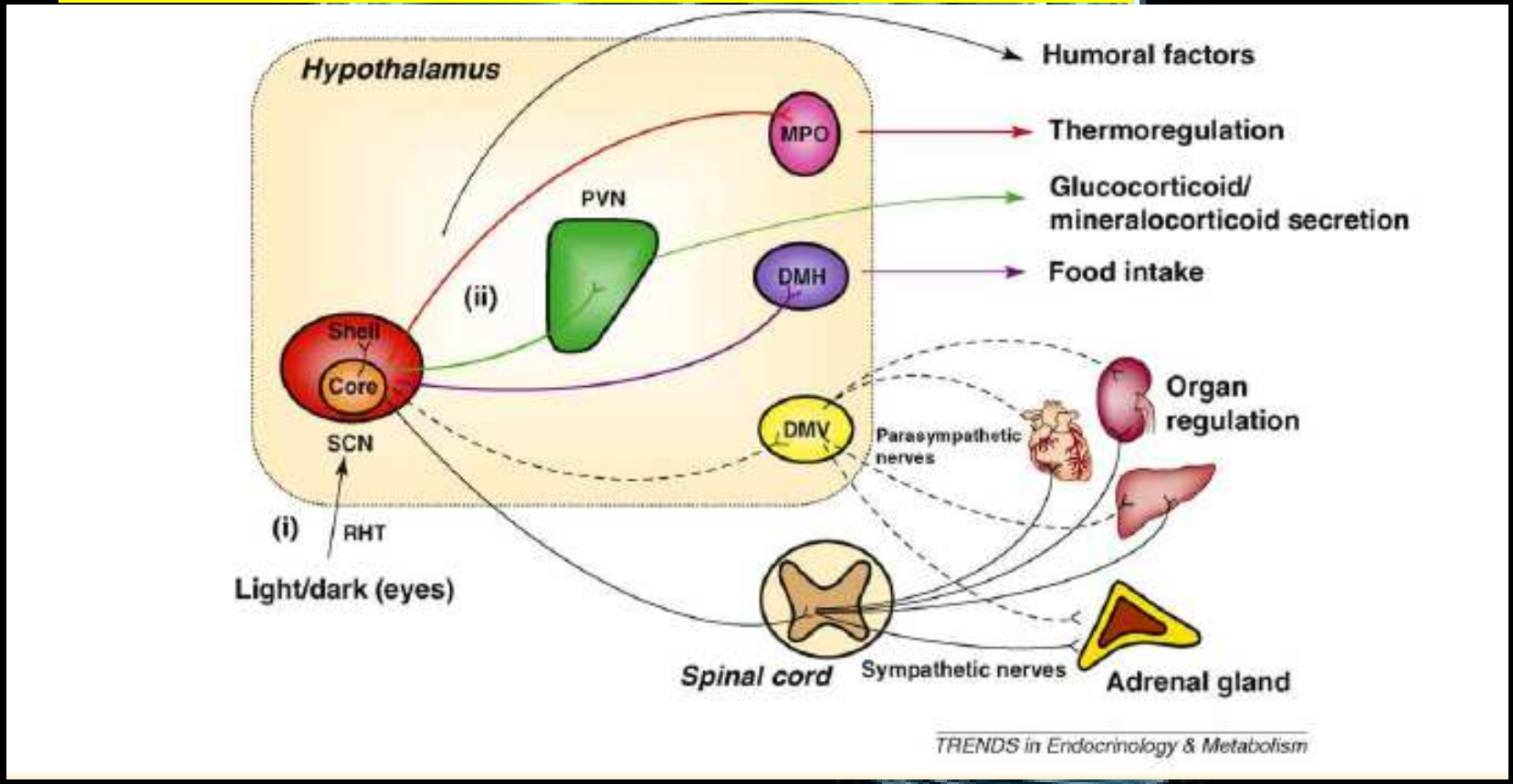


Figure I. Central CLOCK synchronizes the peripheral CLOCKs and regulates peripheral organ activities via neural and humoral interactions. **(i)** The central master CLOCK located in the SCN (core) obtains light/dark information from the retina through the retinohypothalamic track (RHT) and adjusts to synchronize its circadian rhythm, whereas **(ii)** it indirectly projects several efferent neurons to transmit timing information to other parts of the brain and distant organs their peripheral CLOCKs and influence their activities, such as secretion of pituitary hormones and melatonin, food intake, sleep and body temperature. The central master CLOCK employs the autonomic nervous system and humoral mediators for organ regulation. For simplicity, detailed anatomical structures for the sympathetic and parasympathetic nervous systems, such as nuclei located in the brain stem including the solitary nucleus and the ambiguous nucleus and the sympathetic and parasympathetic ganglia, are omitted. DMH: dorsomedial nucleus of hypothalamus, DMV: dorsal motor nucleus of vagus, MPO: medial preoptic region, PVN: paraventricular nucleus, SCN: suprachiasmatic nucleus.

II.2. Les hormones rythmées

☞ Les hormones du stress : le cortisol

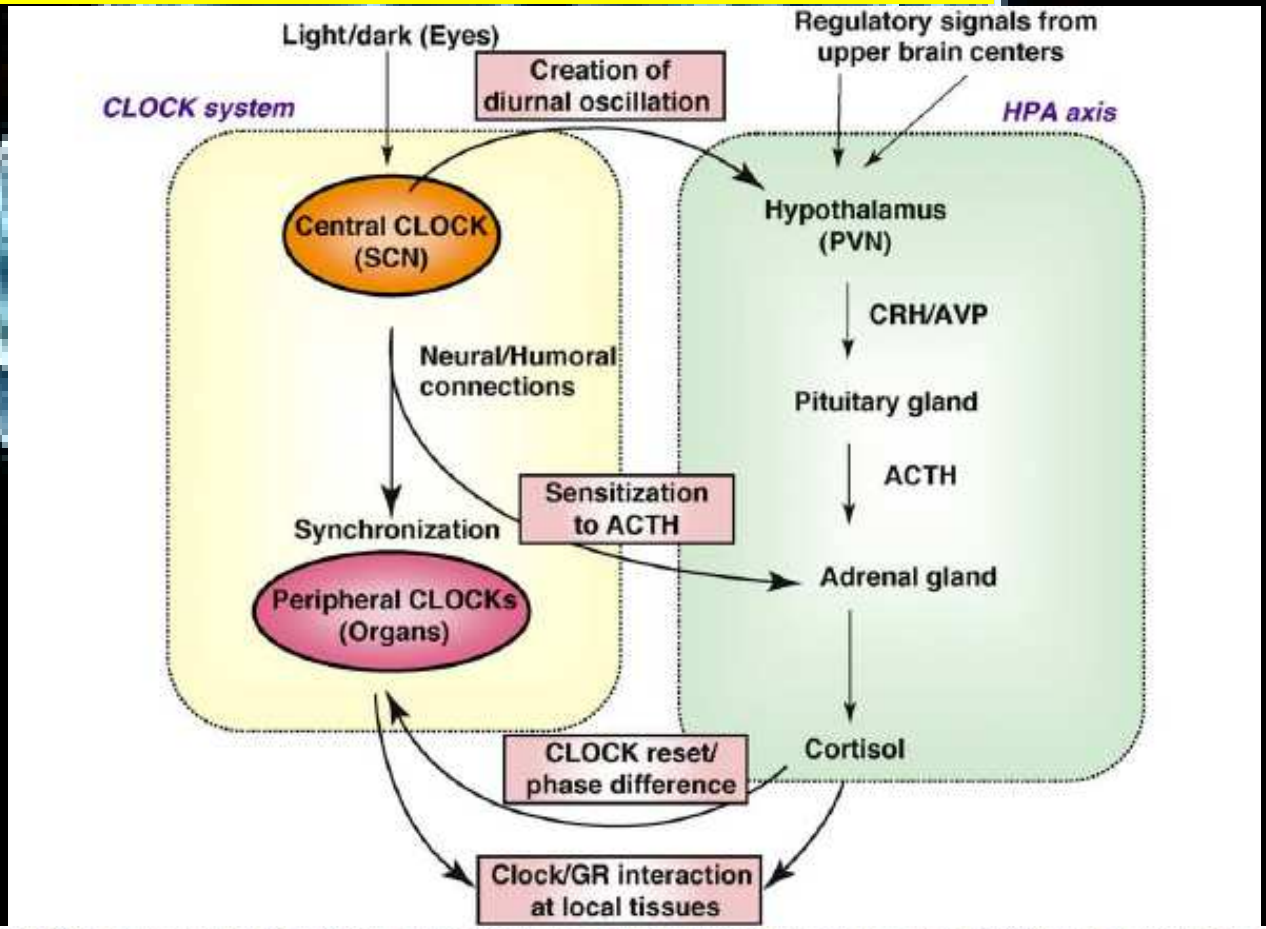
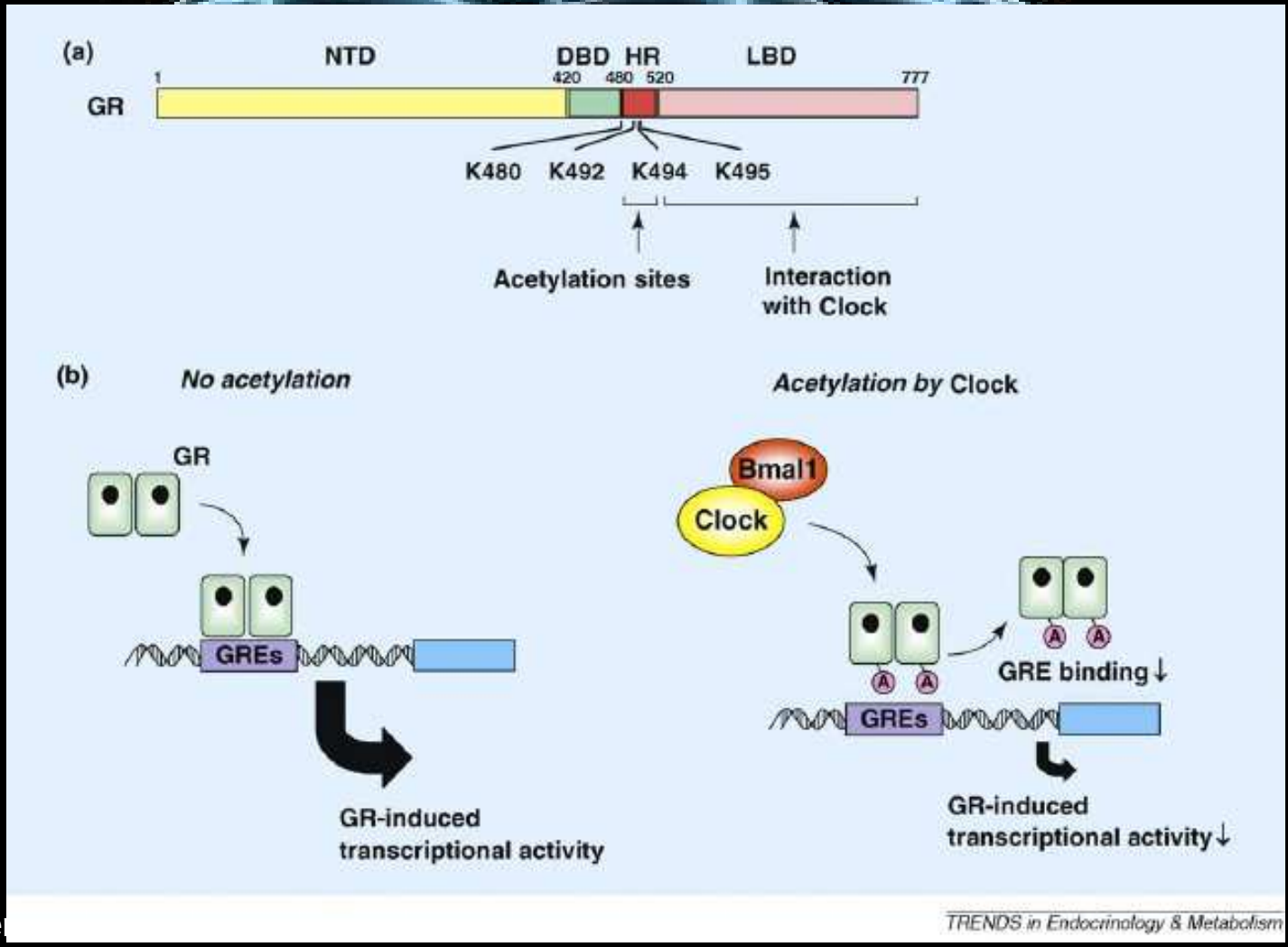


Figure 2. The circadian CLOCK system and the HPA axis influence the activity of one another at multiple levels. The central CLOCK under the regulation of the light input controls the HPA axis and produces regular diurnal secretion of glucocorticoid hormones from the adrenal glands, whereas the peripheral CLOCKs, which are located in the adrenal glands and other components of the HPA axis and are regulated by the central CLOCK through the sympathetic nervous system, also contribute to the rhythmic glucocorticoid secretion from these organs. Secreted glucocorticoids in turn reset and phase-shift the circadian rhythm of the peripheral CLOCKs by stimulating the expression of several CLOCK-related genes; this is particularly important for temporal adjustment of activity of the body against stress. The peripheral CLOCKs also regulate the glucocorticoid effect in local tissues through interaction between Clock/Bmal1 and the GR, providing a local counter regulatory feedback loop to the effect of central

II.2. Les hormones rythmées

☞ Les hormones du stress : le cortisol



II.2. Les hormones rythmées

☞ Les hormones de la satiété / de la faim :

- La leptine

- La ghréline

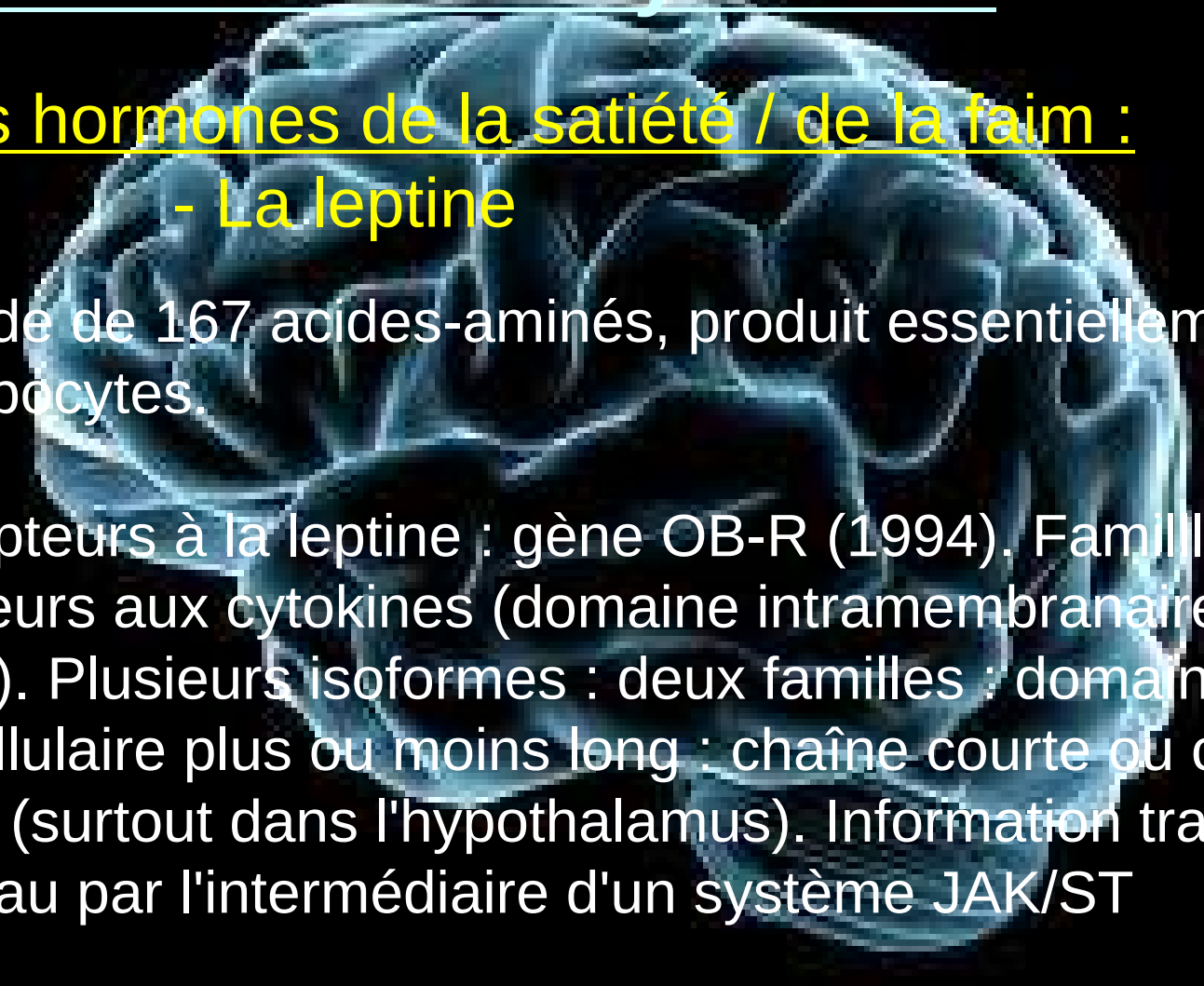
II.2. Les hormones rythmées

☞ Les hormones de la satiété / de la faim : - La leptine

On sait depuis longtemps que l'hypothalamus, petite zone à la base du cerveau, joue un rôle essentiel dans la régulation des prises alimentaires. Il y coexiste un centre de la satiété et un centre de la faim. On sait depuis encore plus longtemps que l'hérédité et la génétique jouent un rôle décisif dans bon nombre d'obésités (mais pas dans toutes). Mais ce qu'on ne savait pas, c'est comment relier les deux ordres de phénomènes.

À la fin de 1994, des chercheurs américains et français mettent en évidence chez certaines souris obèses, la relation entre un gène, appelé (ob), et l'adiposité desdites souris. Le gène (ob) code une protéine, la leptine. Cette protéine est libérée par les adipocytes adultes et sert de signal au cerveau en lui indiquant les dimensions des réserves de tissu adipeux.

II.2. Les hormones rythmées



☞ Les hormones de la satiété / de la faim :
- La leptine

• Peptide de 167 acides-aminés, produit essentiellement par les adipocytes.

• Récepteurs à la leptine : gène OB-R (1994). Famille des récepteurs aux cytokines (domaine intramembranaire unique). Plusieurs isoformes : deux familles : domaine intracellulaire plus ou moins long : chaîne courte ou chaîne longue (surtout dans l'hypothalamus). Information transmise au noyau par l'intermédiaire d'un système JAK/ST

II.2. Les hormones rythmées

☞ Les hormones de la satiété / de la faim :

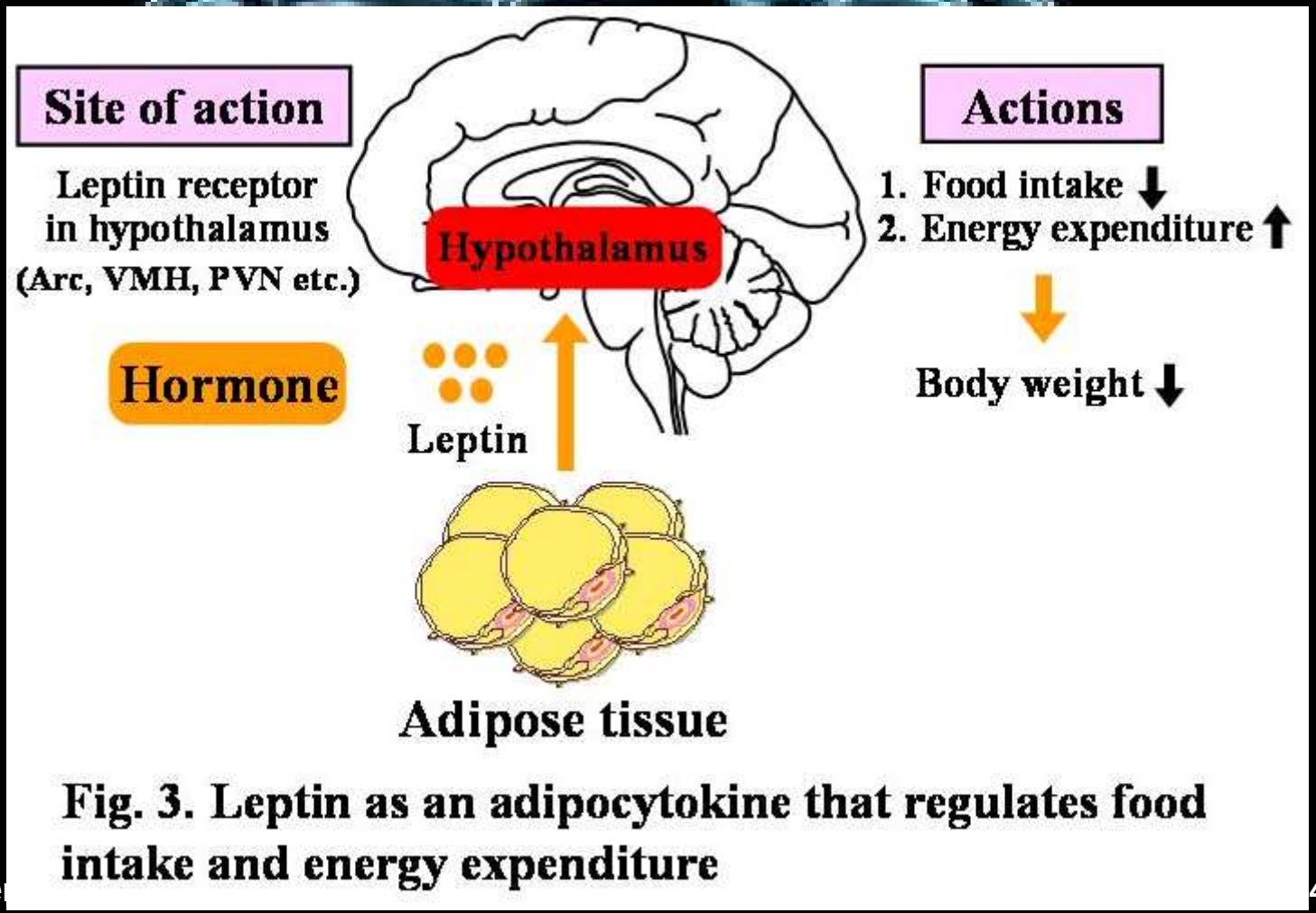
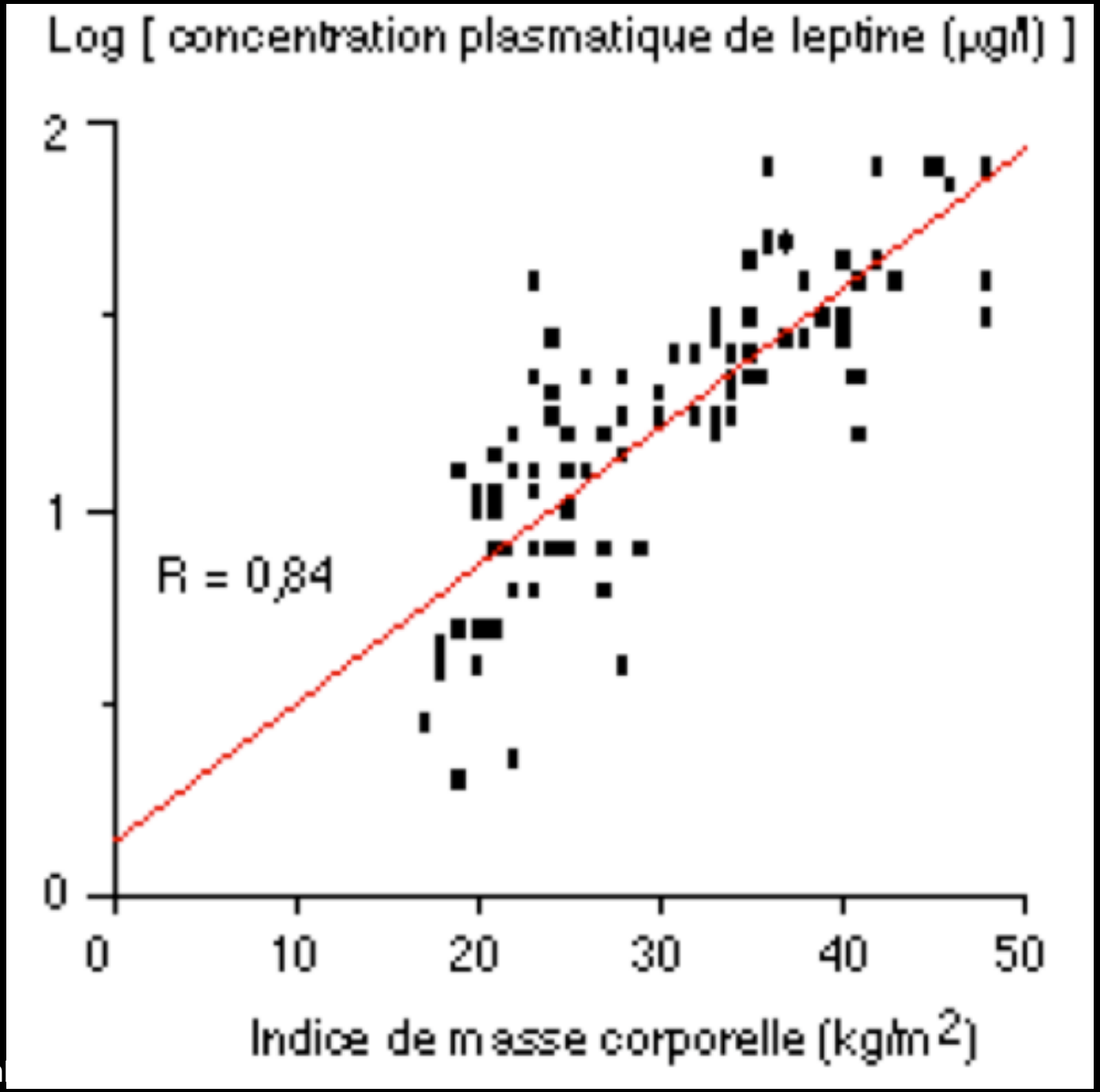
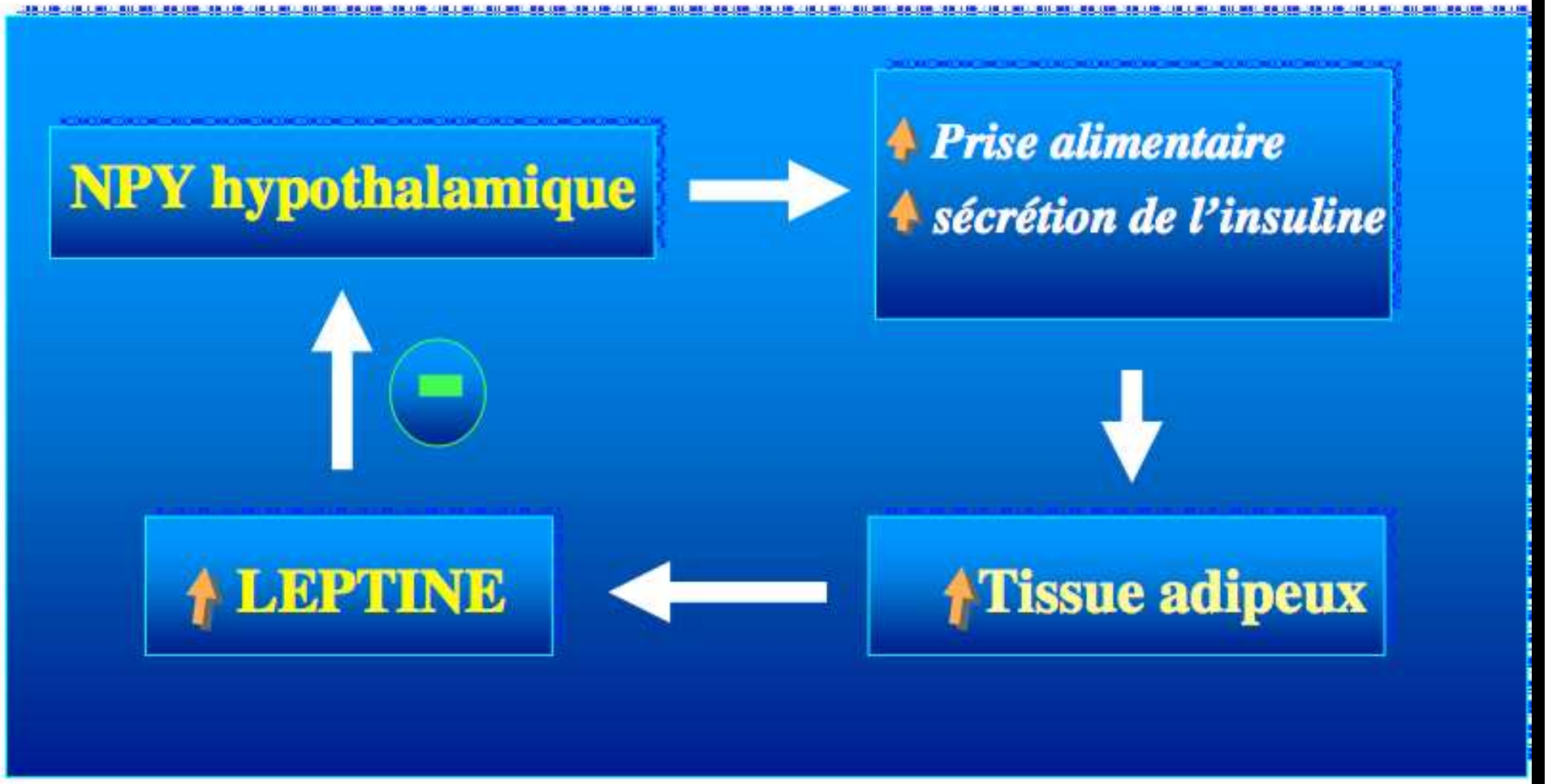
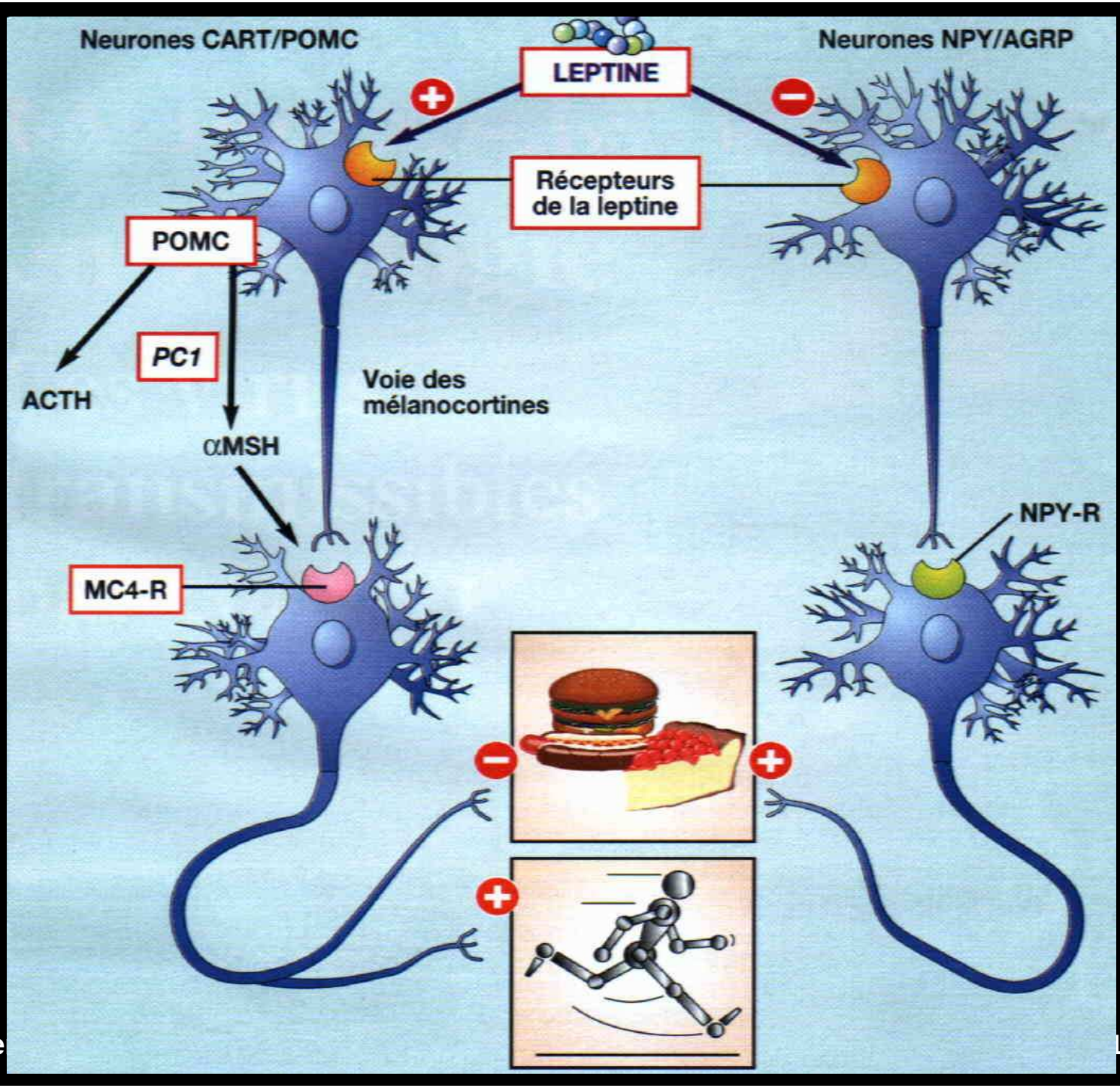


Fig. 3. Leptin as an adipocytokine that regulates food intake and energy expenditure


Log [concentration plasmatique de leptine (µg/l)]
2
1
0
R = 0,84
0
10
20
30
40
50
Indice de masse corporelle (kg/m 2)

INTERACTION LEPTIN - NPY




Neurones CART/POMC
LEPTINE
Neurones NPY/AGRP
Récepteurs de la leptine
POMC
PC1
ACTH
αMSH
Voie des mélanocortines
MC4-R
NPY-R

II.2. Les hormones rythmées

☞ Les hormones de la satiété / de la faim :
- La ghréline

• Peptide orexigène qui agit sur des neurones à neuropeptide Y

• Ligand endogène du growth hormone secretagogue receptor (GHS-R) (estomac). Il provoque la libération GH après administration IV.
immunoréactivité ghréline dans le noyau arqué hypothal.
ghréline chronique SNC augmente la prise alimentaire et poids (+expression du neuropeptide Y et de l'AGRP) effet orexigène indépendant GH, insuline, glucose, leptine

(***Diabetes* 2001 ; 50 : 2438-2443, Jun Kamegai)**

Prise alimentaire diminue le taux de ghréline

Faim stimule la libération de ghréline (estomac)

Ghréline entre dans le cerveau

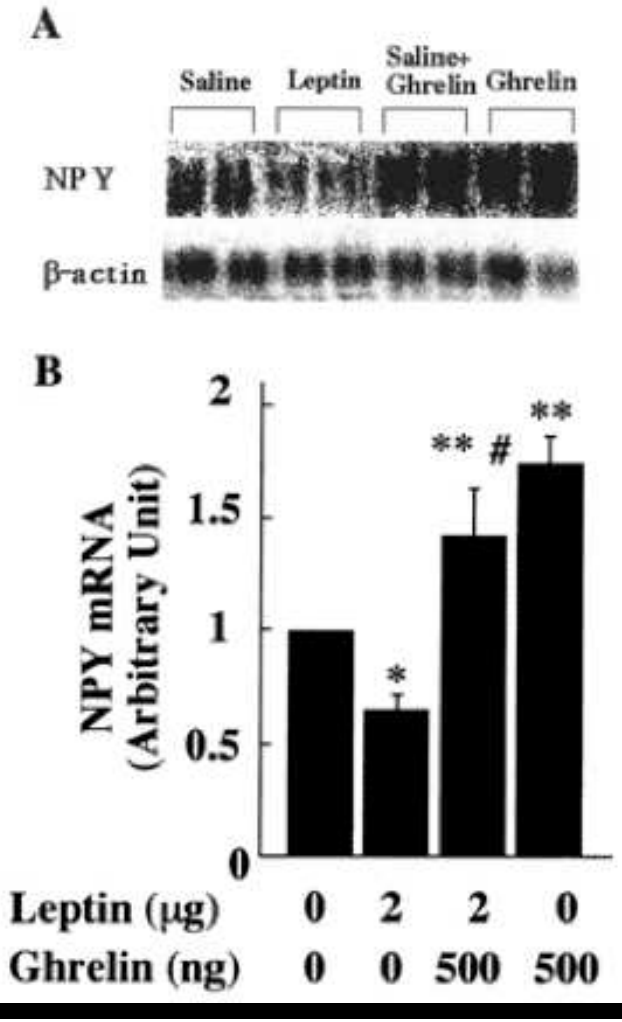
Ghréline augmente l'appétit

Effet à court terme

II.2. Les hormones rythmées

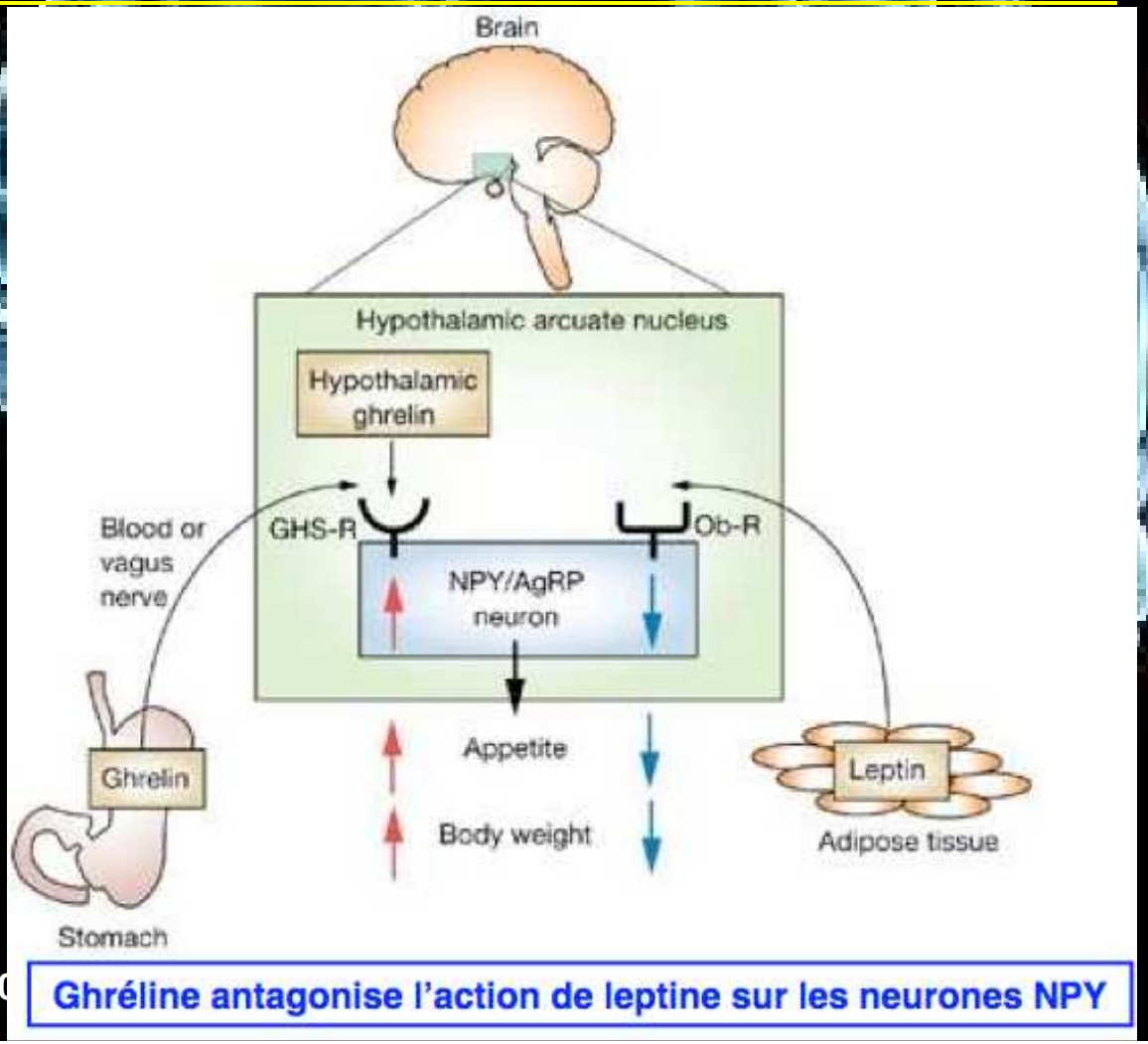
☞ Les hormones de la satiété / de la faim :

Ghréline antagonise l'action de leptine sur les neurones NPY

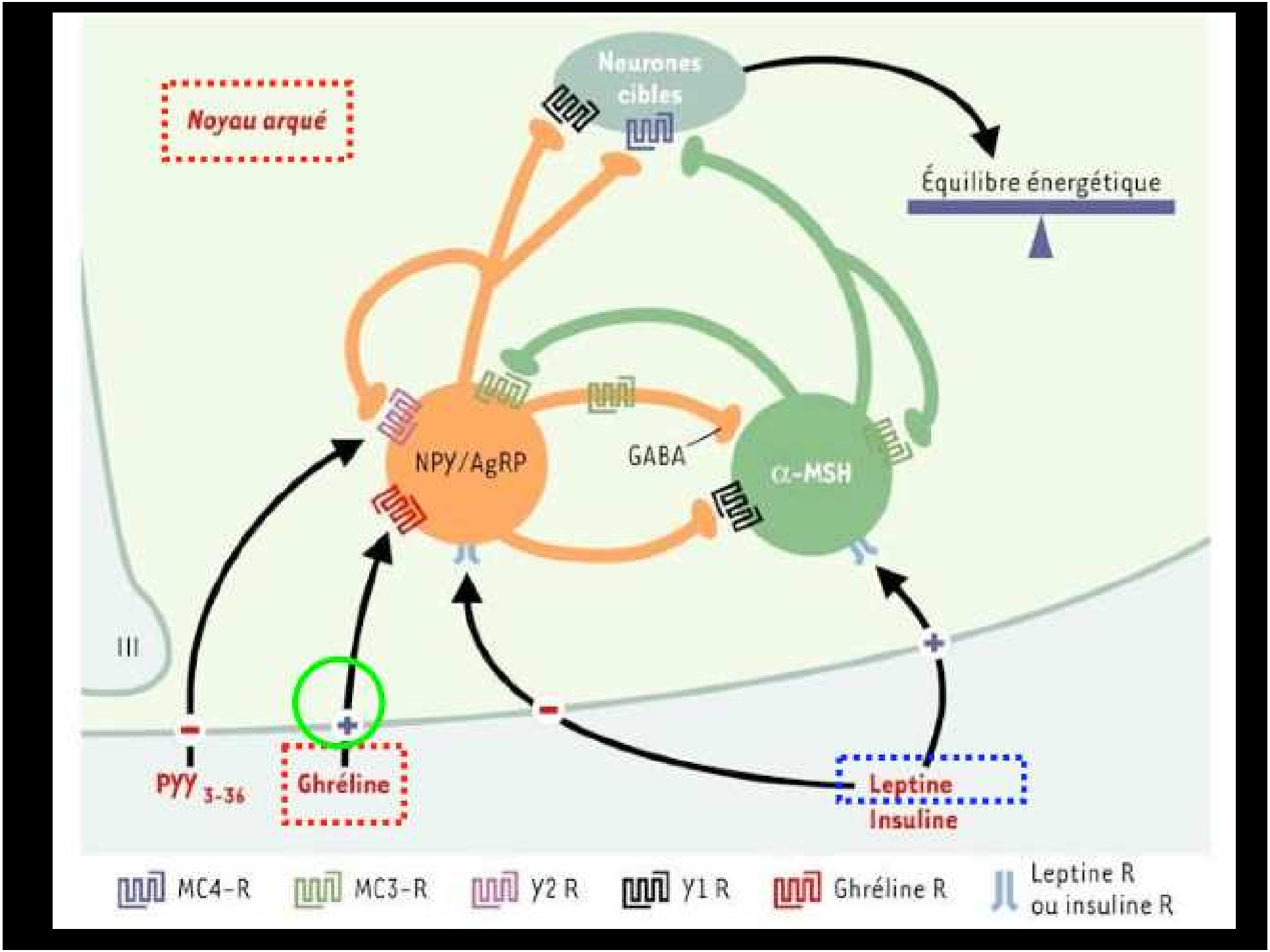


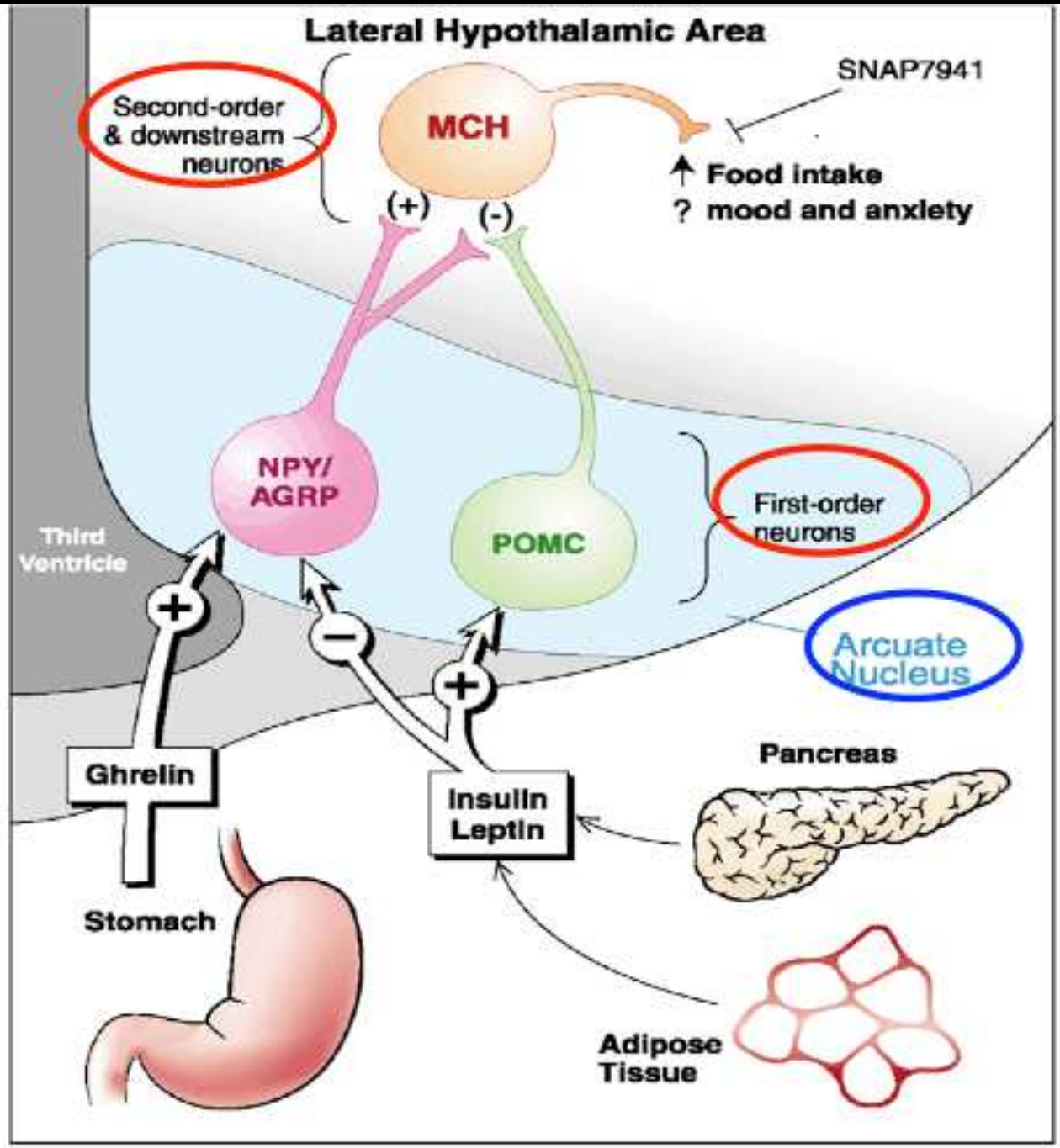
II.2. Les hormones rythmées

☞ Les hormones de la satiété / de la faim :



Ghréline antagonise l'action de leptine sur les neurones NPY

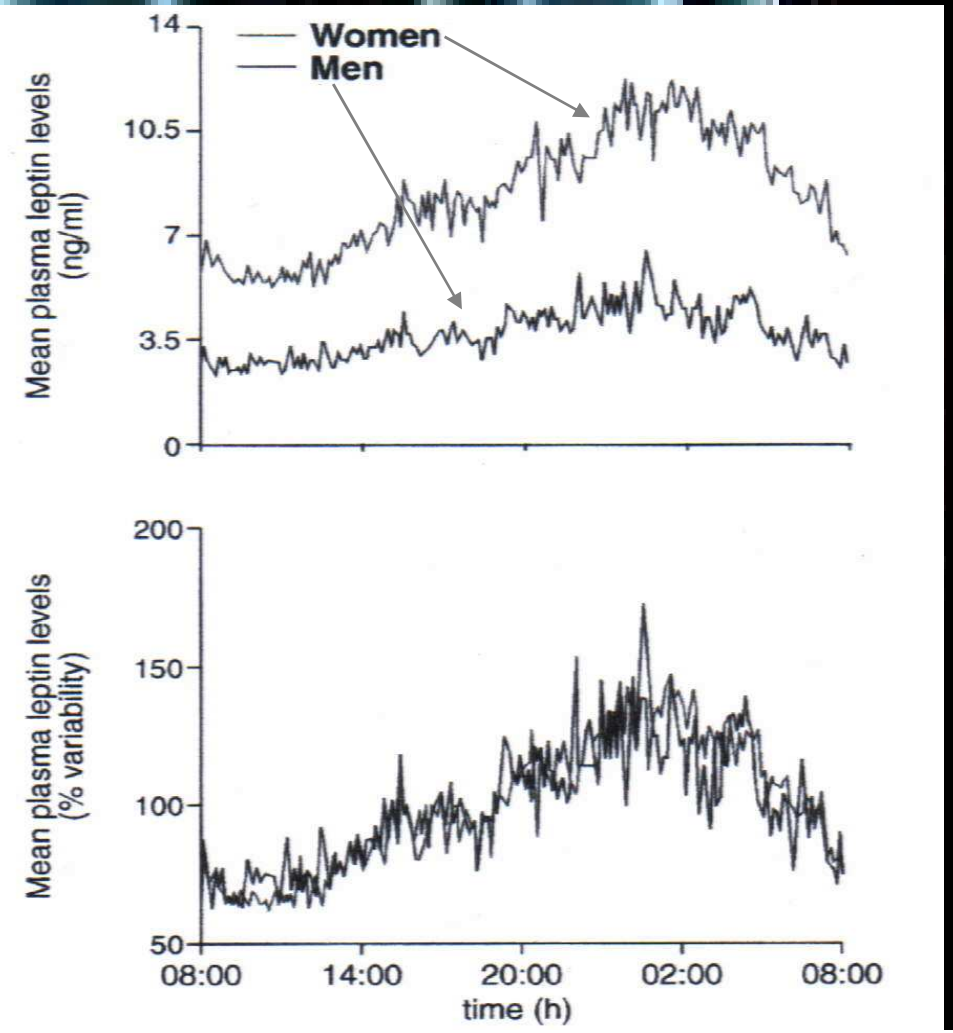

Noyau arqué
Neurones cibles
Équilibre énergétique
NPY/AgRP
GABA
α-MSH
III
PYY 3-36
Ghréline
Leptine
Insuline
MC4-R
MC3-R
Y2 R
Y1 R
Ghréline R
Leptine R
ou insuline R


Lateral Hypothalamic Area
SNAP7941
Second-order & downstream neurons
MCH
↑ Food intake
? mood and anxiety
(+)
(-)
NPY/ AGRP
POMC
First-order neurons
Third Ventricle
Arcuate Nucleus
Ghrelin
Insulin Leptin
Pancreas
Stomach
Adipose Tissue

II.2. Les hormones rythmées

☞ Les hormones de la satiété / de la faim :

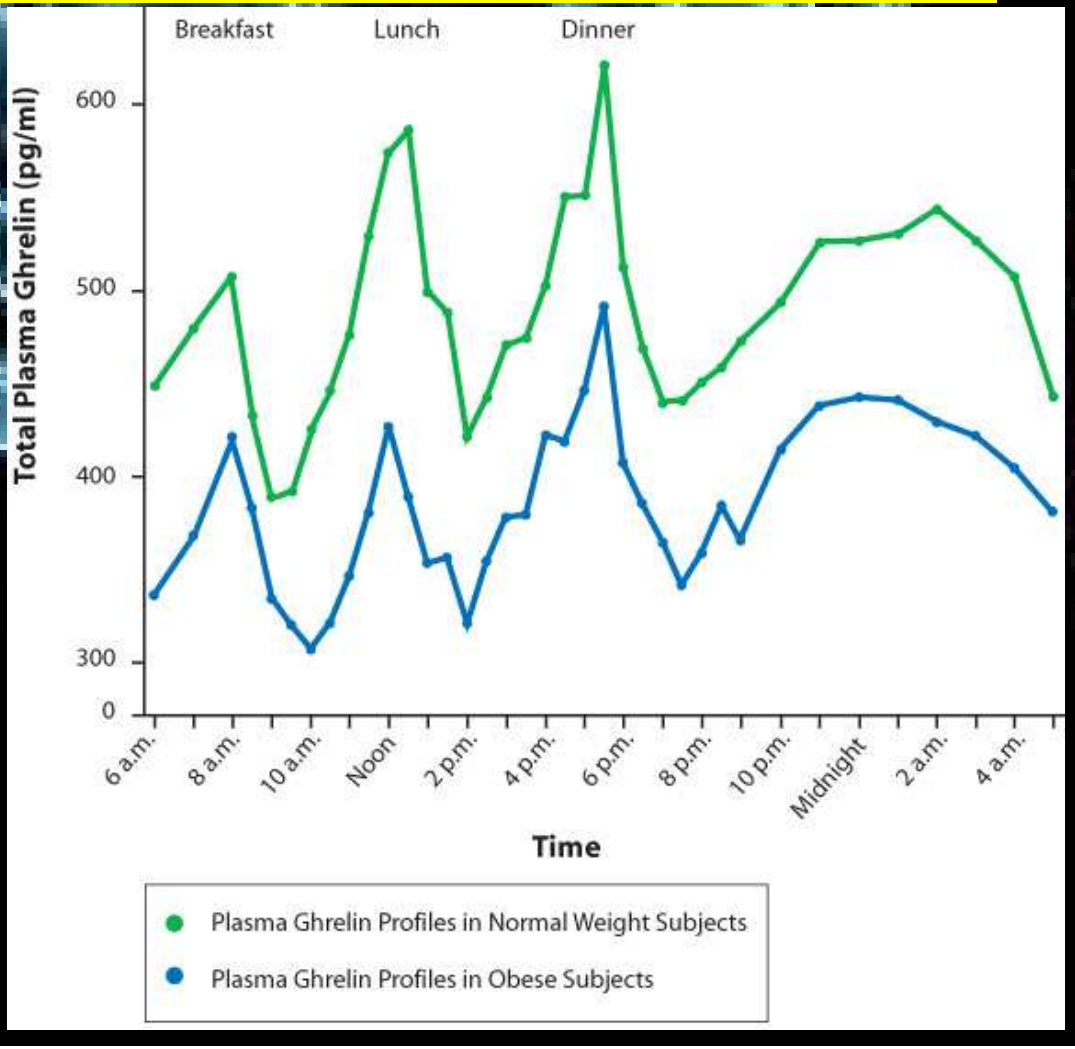
Leptinémie des 24h chez homme et femme



II.2. Les hormones rythmées

☞ Les hormones de la satiété / de la faim :

Ghrélinémie de 24 H



II.2. Les hormones rythmées

☞ L'hormone de croissance :

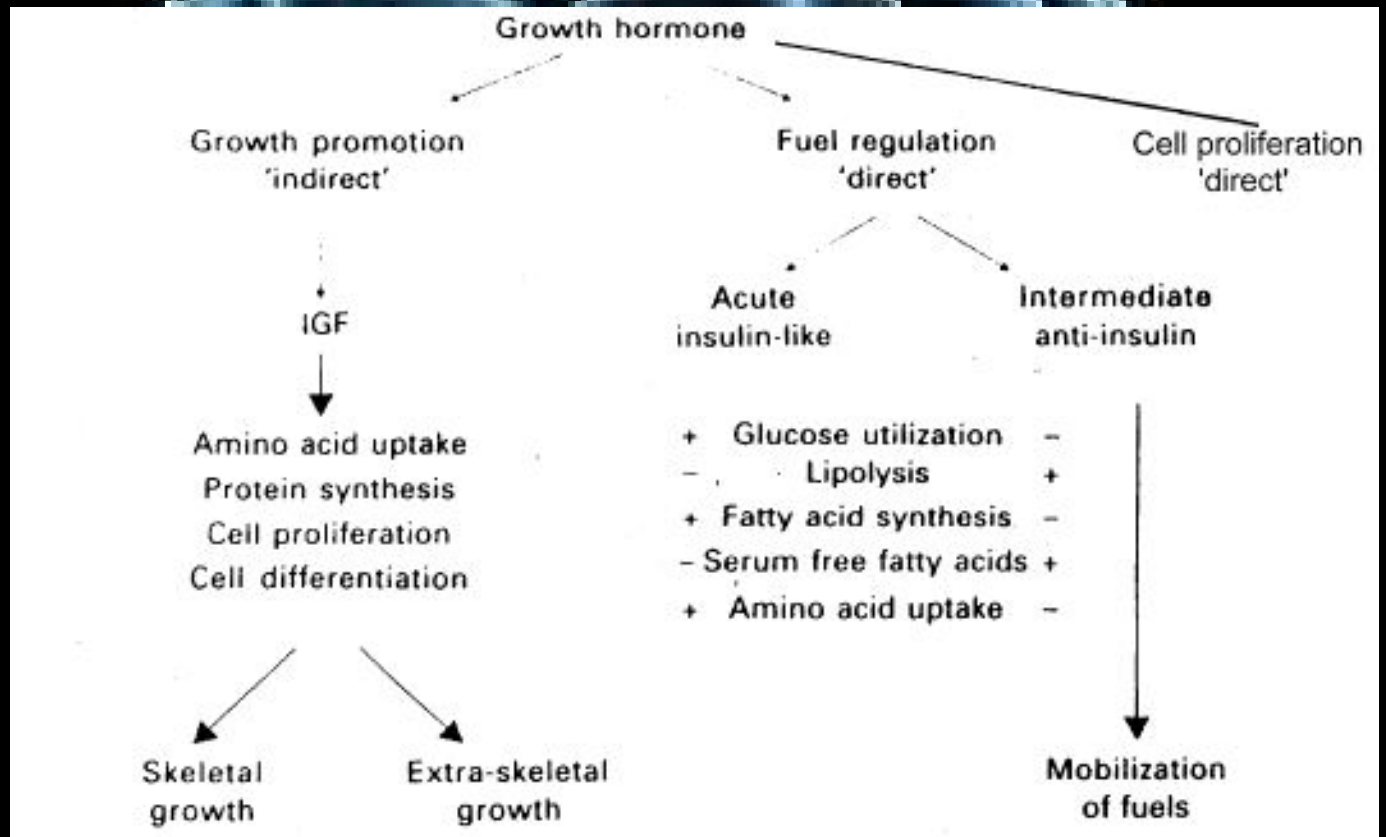
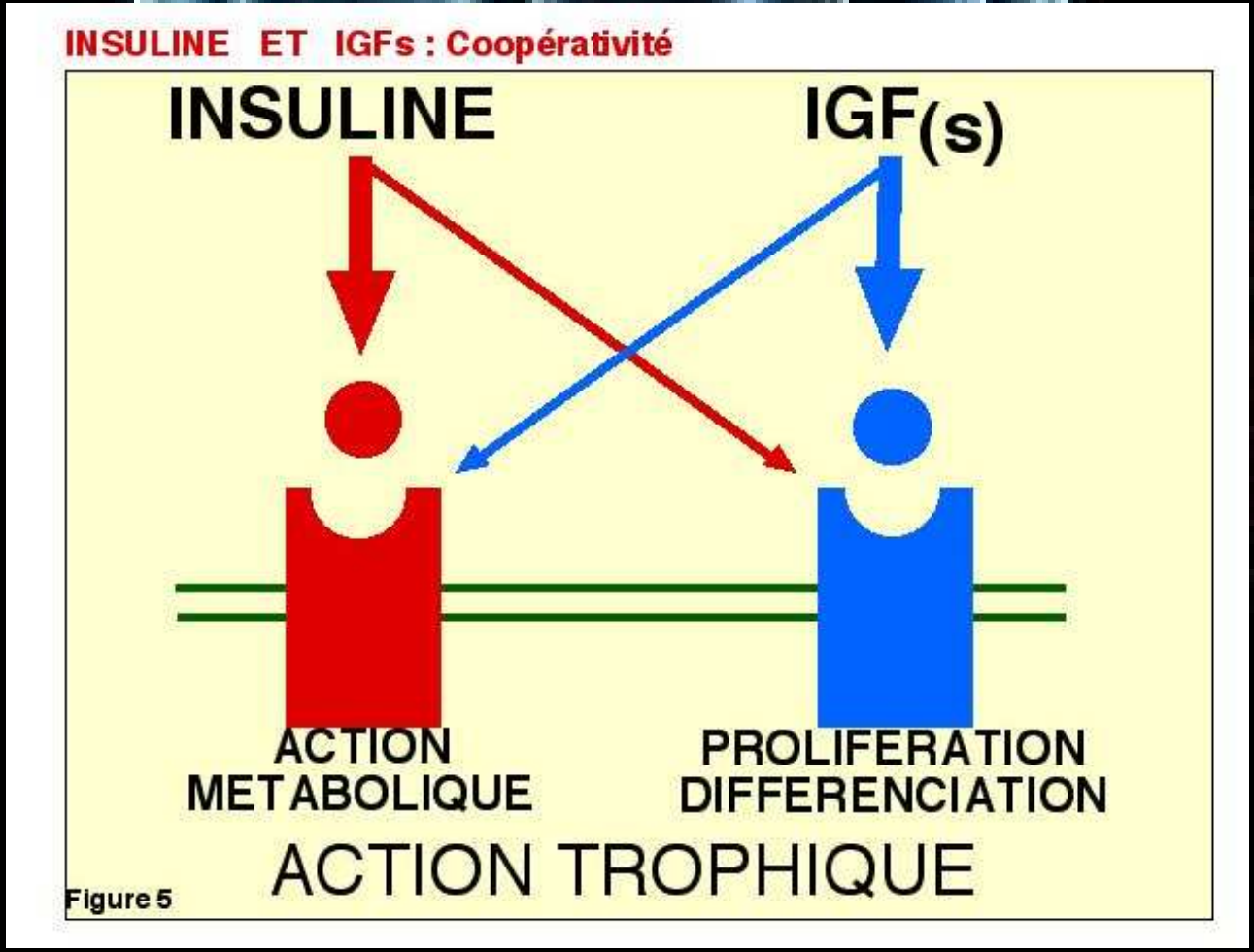


Fig. 1. Actions of growth hormone (GH). The growth-promoting effects are mediated predominantly through local tissue generation of insulin-like growth factor (IGF-1). Acute insulin-like effects have been demonstrated within 2 h of GH administration, before tissues become refractory to further GH exposure. The major impact of GH on fat and carbohydrate metabolism is, however, to antagonize the actions of insulin.

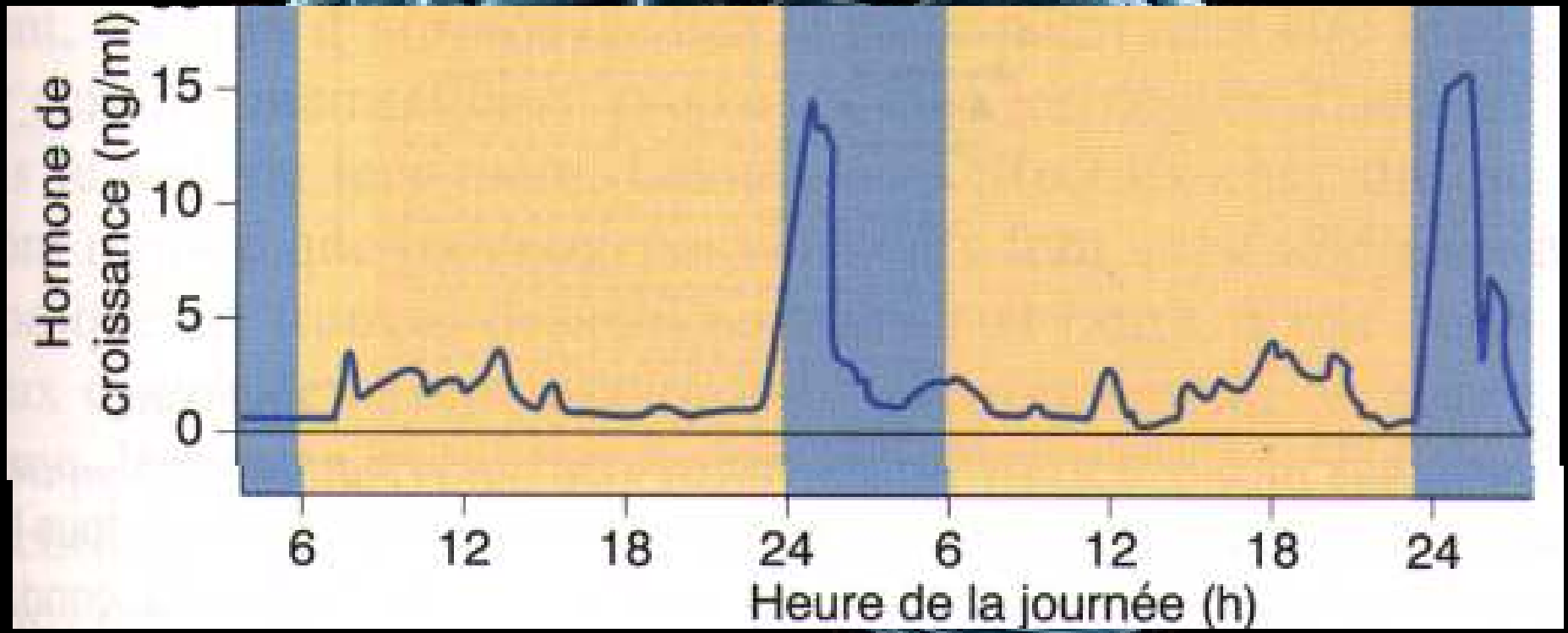
II.2. Les hormones rythmées

☞ L'hormone de croissance :



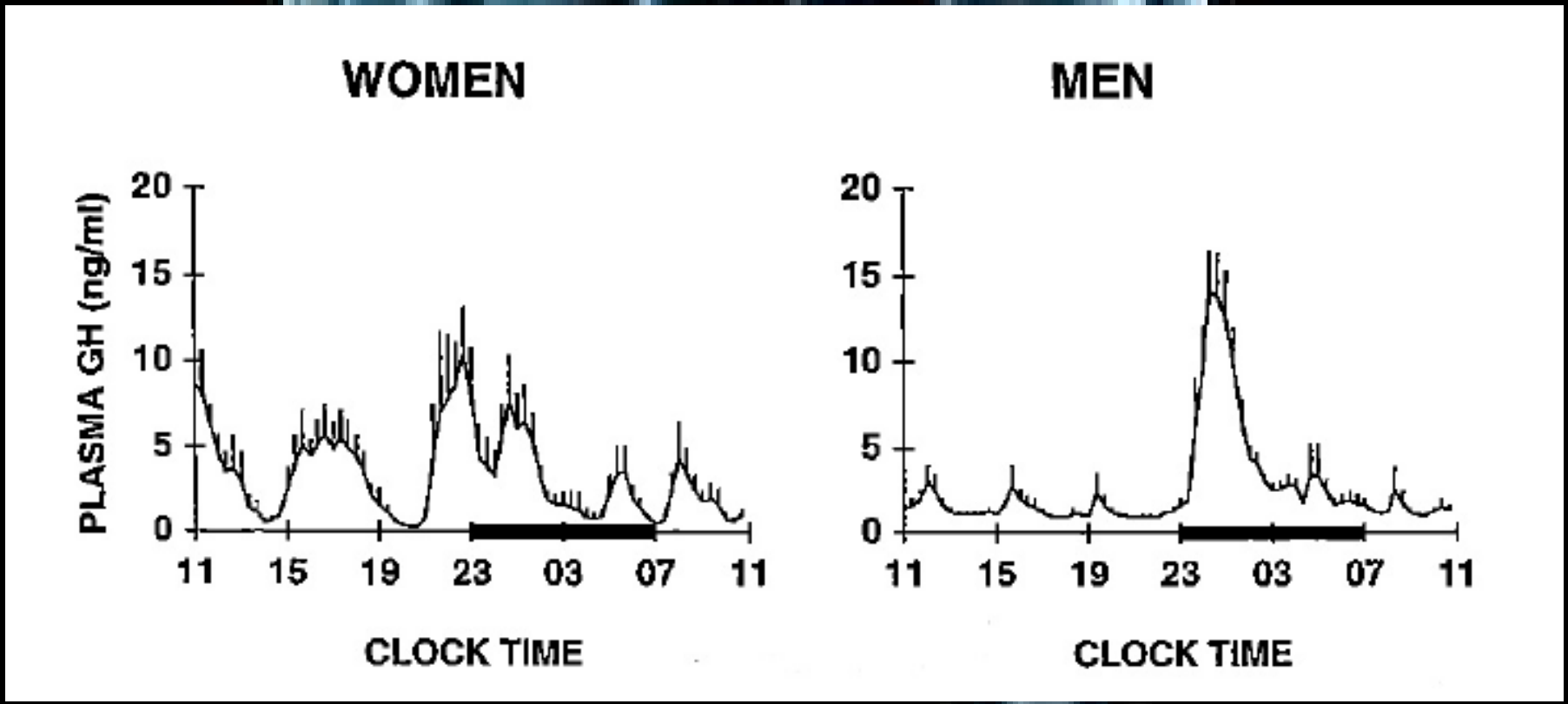
II.2. Les hormones rythmées

☞ L'hormone de croissance :



II.2. Les hormones rythmées

☞ L'hormone de croissance :

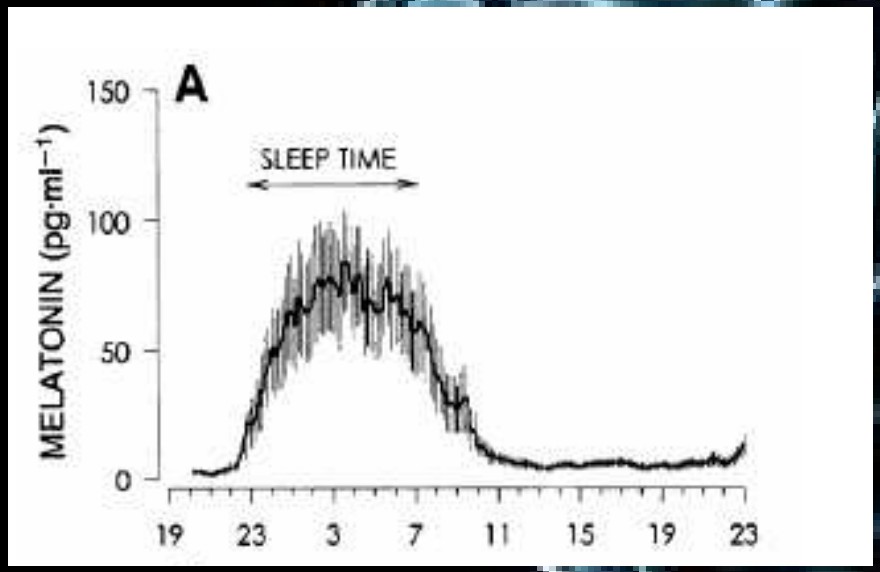


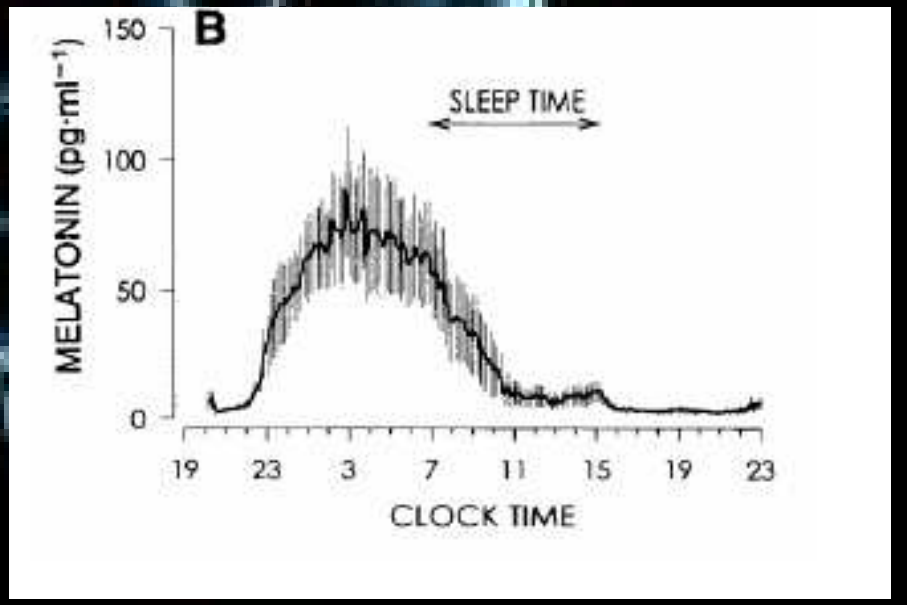
III. Les relations hormones et rythmes

Rythmes circadiens *versus* Rythmes nycthéméraux ?

III. Les relations hormones et rythmes

☞ La mélatonine :





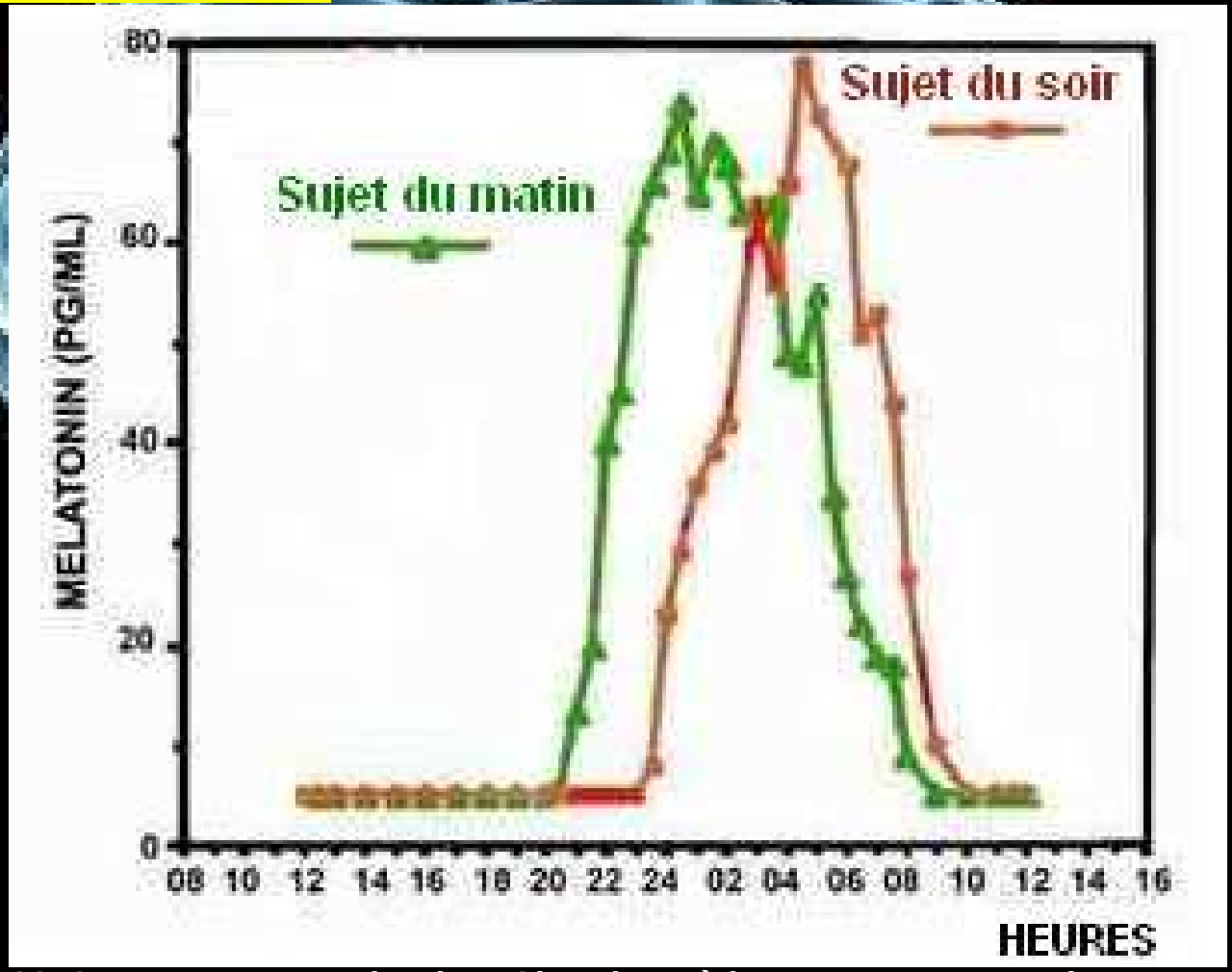
Pas d'influence du sommeil

=

rythme circadien pur (C+)

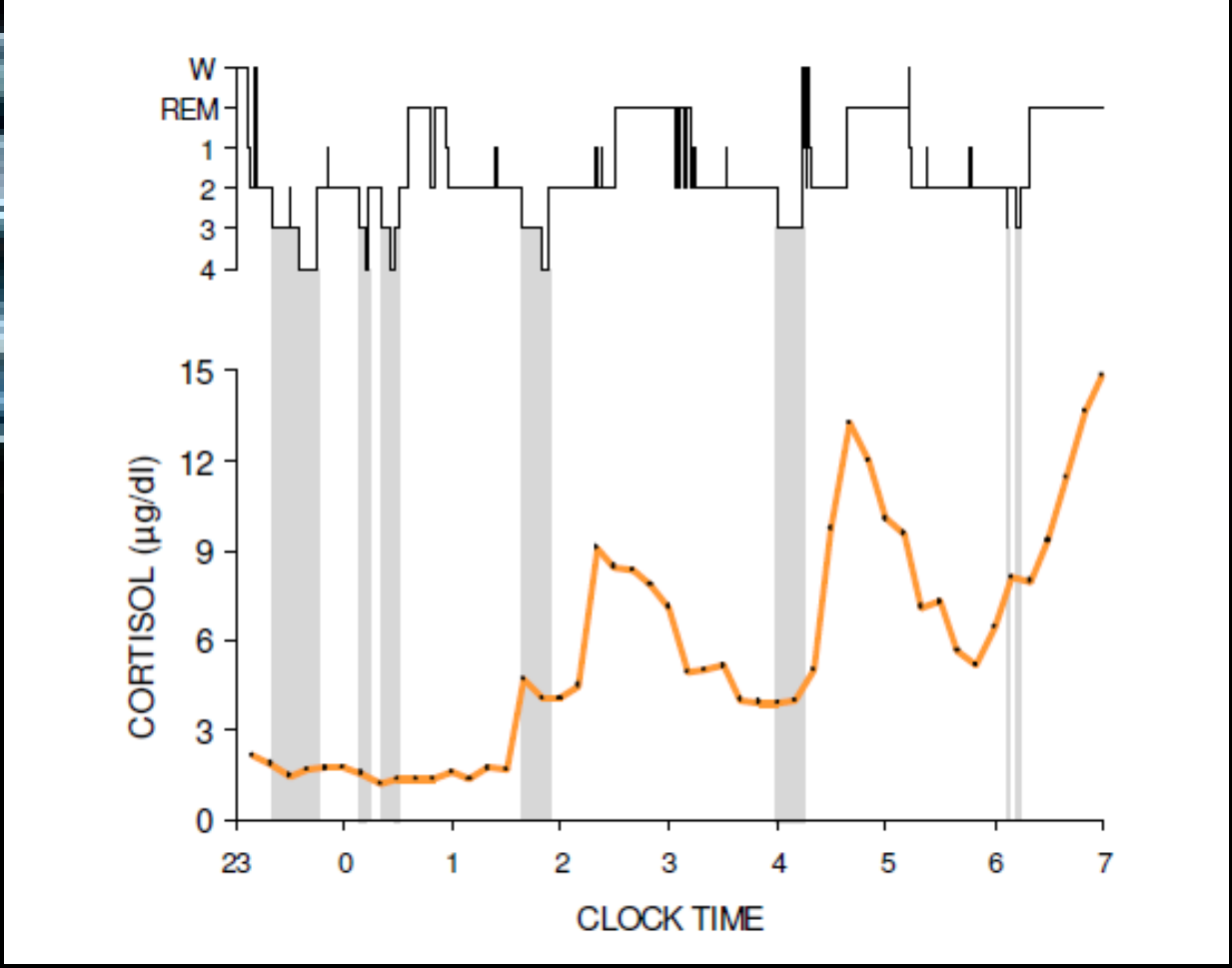
III. Les relations hormones et rythmes

☞ La mélatonine :



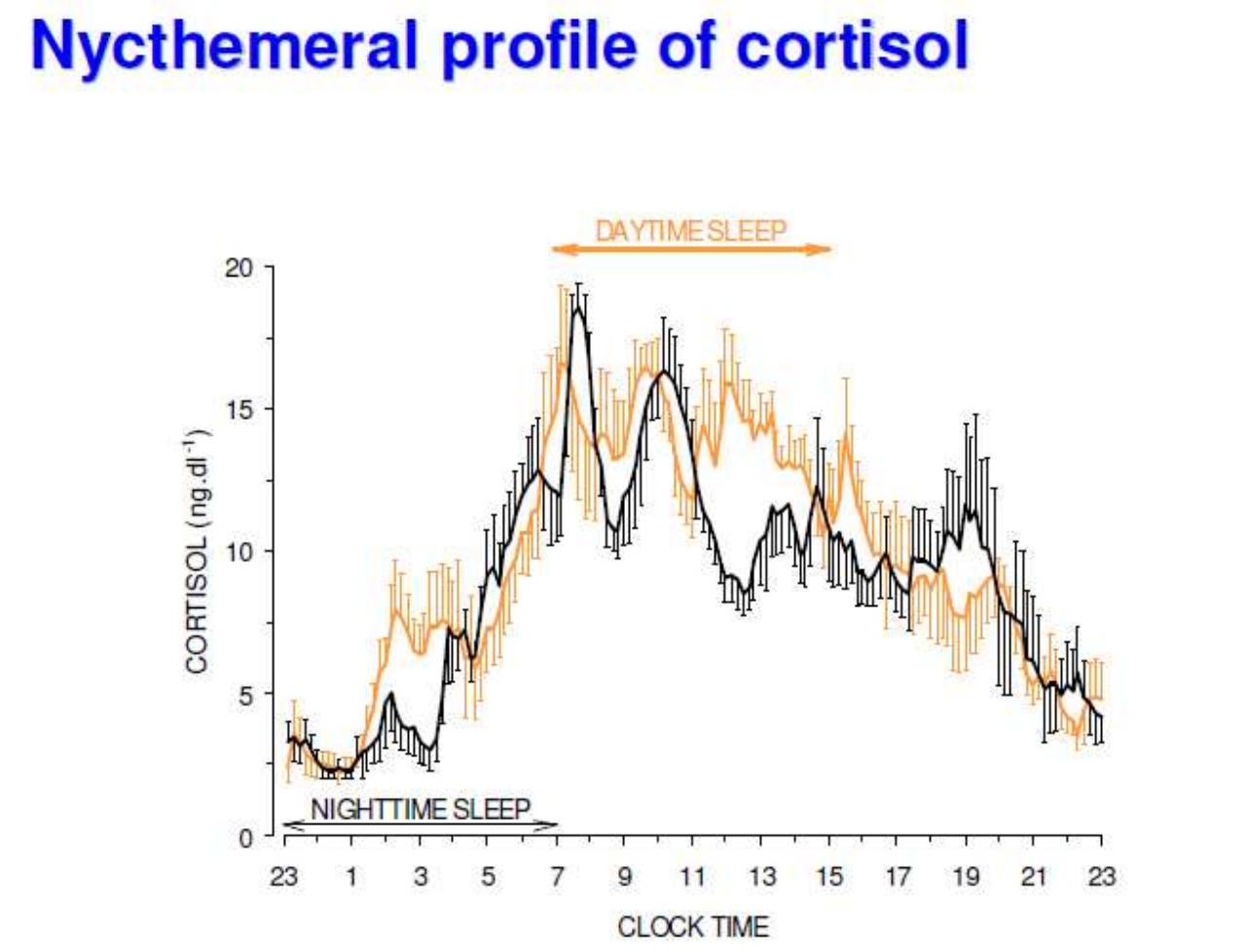
III. Les relations hormones et rythmes

☞ Le cortisol :



III. Les relations hormones et rythmes

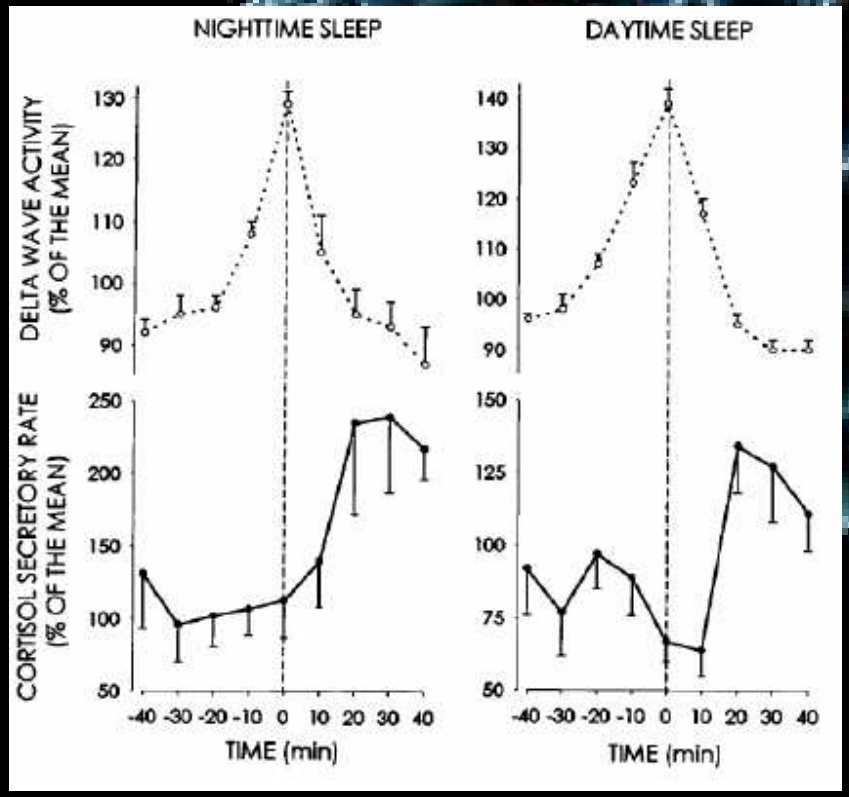
☞ Le cortisol :

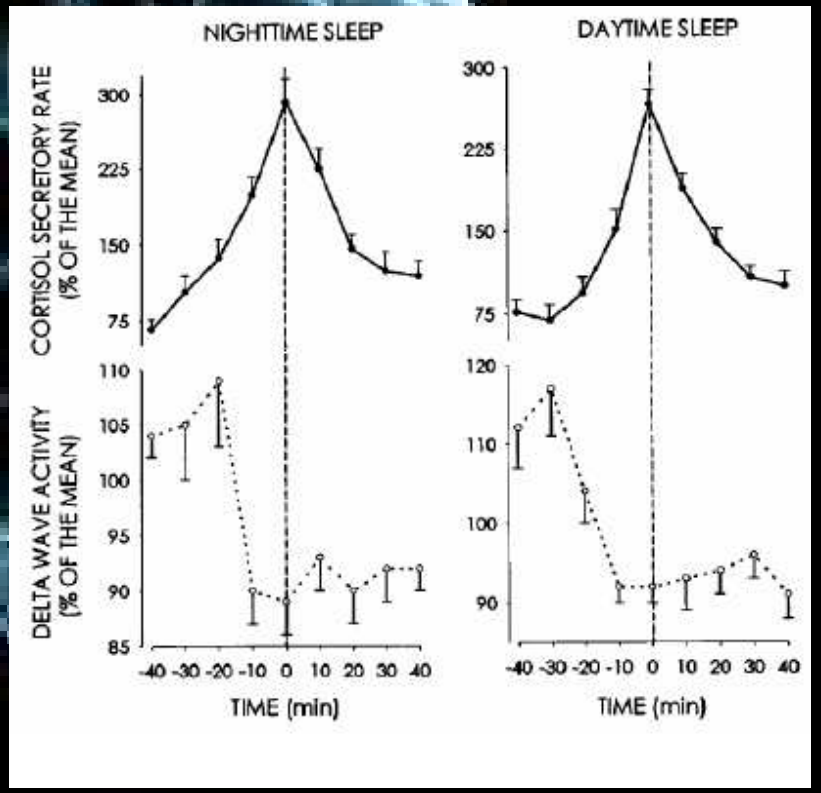


III. Les relations hormones et rythmes

☞ Le cortisol :

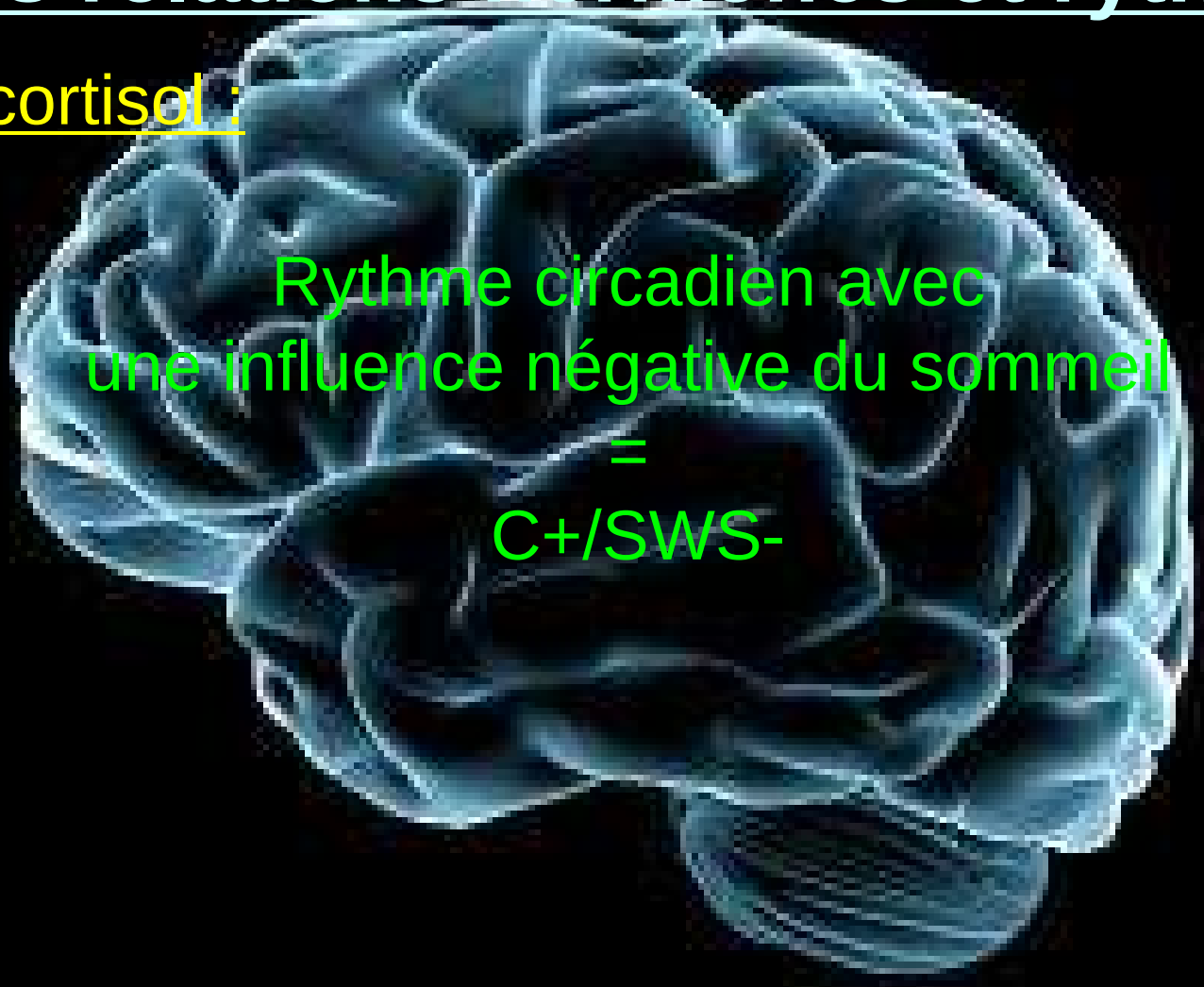
- Sécrétion de cortisol et sommeil lent profond :





III. Les relations hormones et rythmes

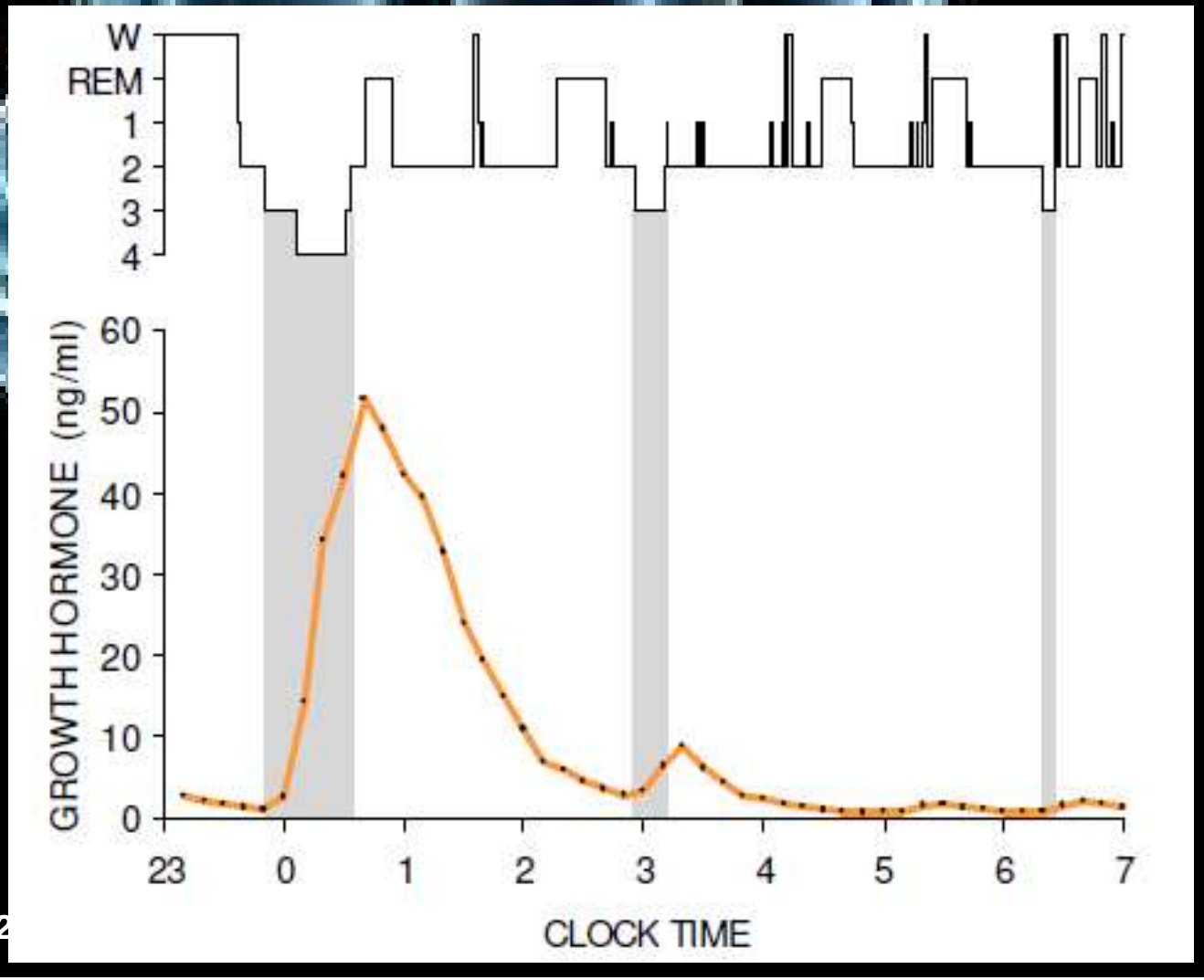
☞ Le cortisol :



Rythme circadien avec
une influence négative du sommeil
=
C+/SWS-

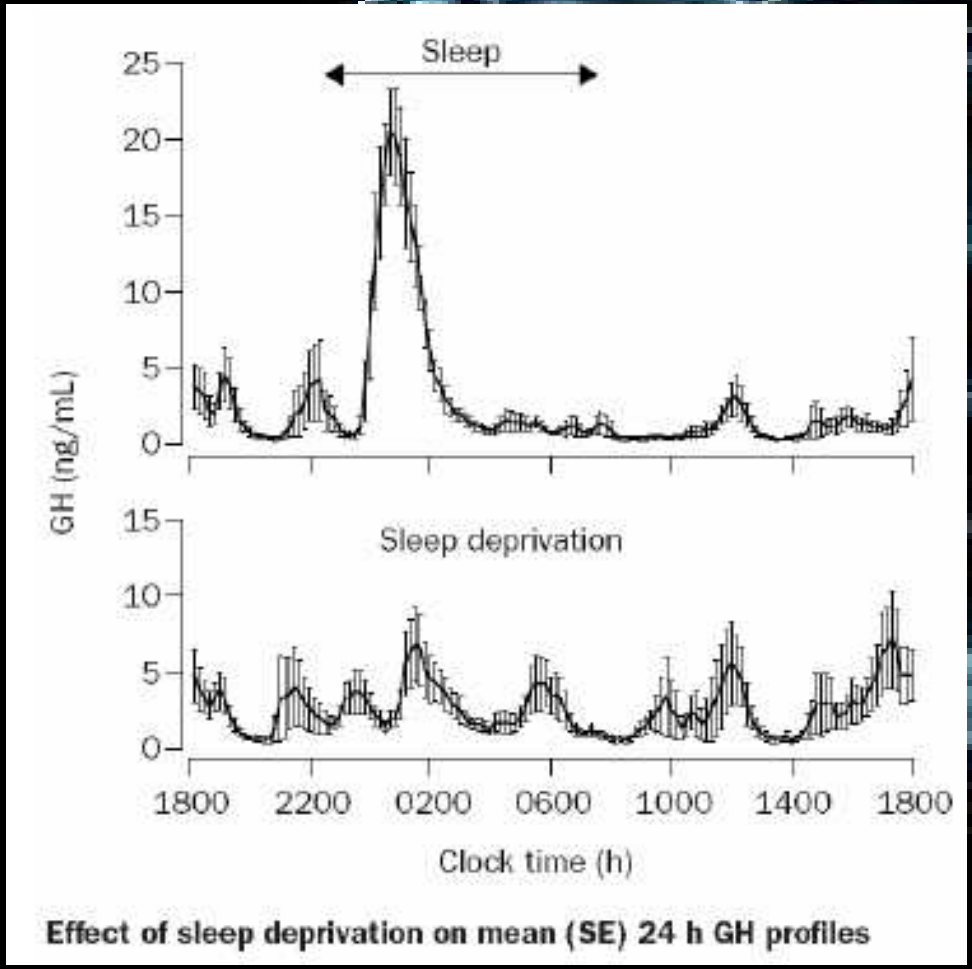
III. Les relations hormones et rythmes

☞ La GH : - Sécrétion de GH et sommeil

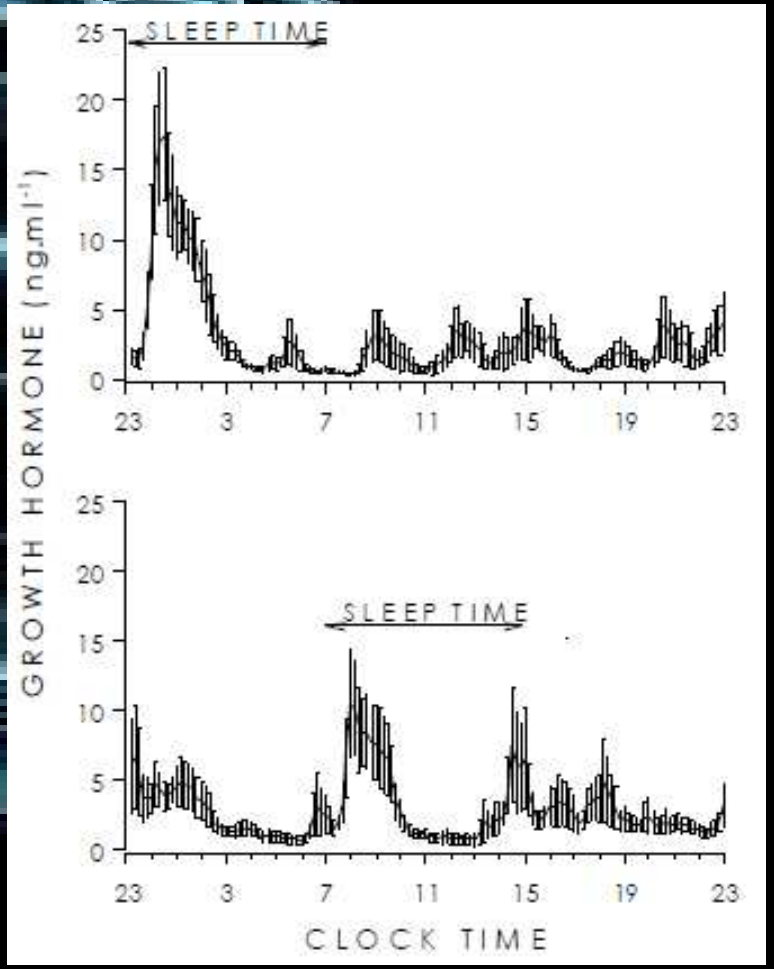


III. Les relations hormones et rythmes

☞ La GH : - Sécrétion de GH et sommeil

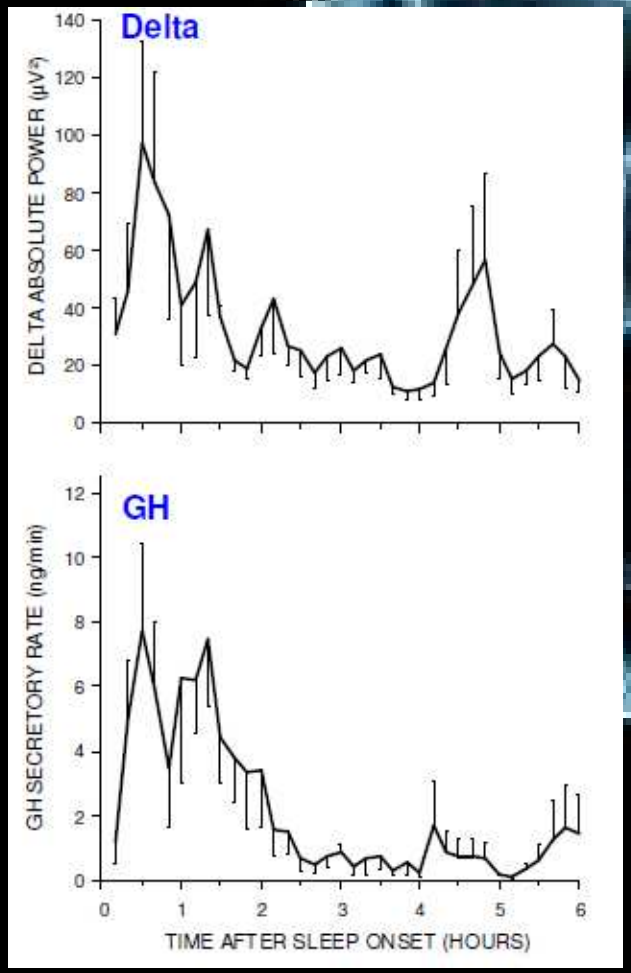


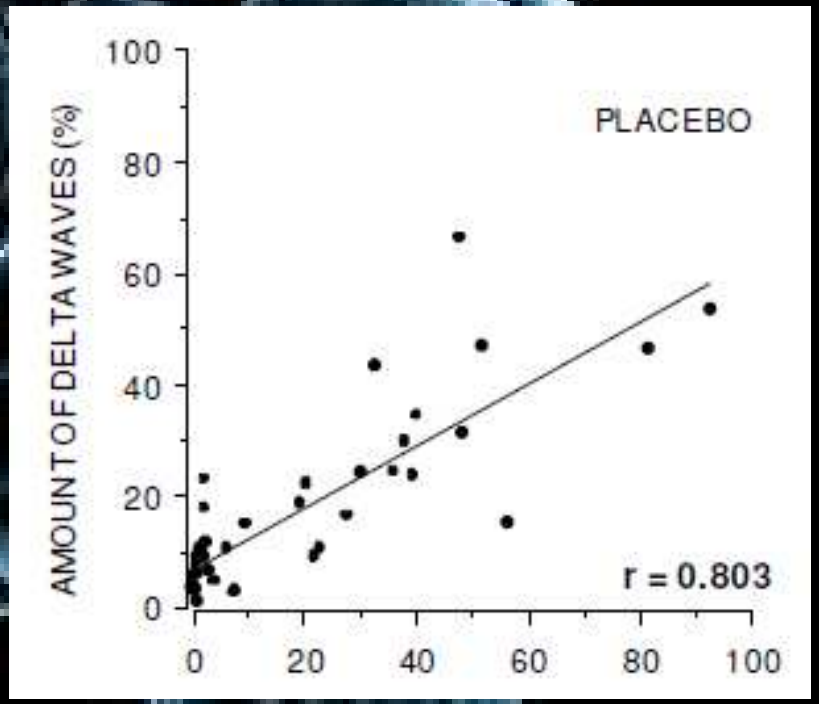
Effect of sleep deprivation on mean (SE) 24 h GH profiles



III. Les relations hormones et rythmes

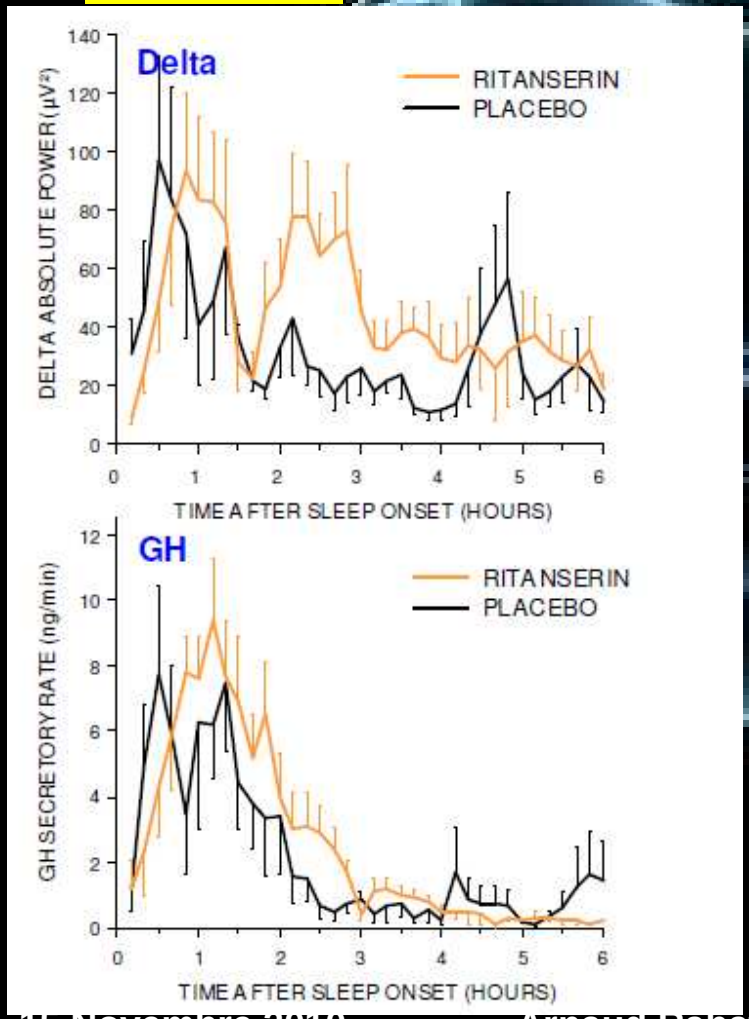
☞ La GH : - Sécrétion de GH et sommeil





III. Les relations hormones et rythmes

☞ La GH : - Sécrétion de GH et sommeil



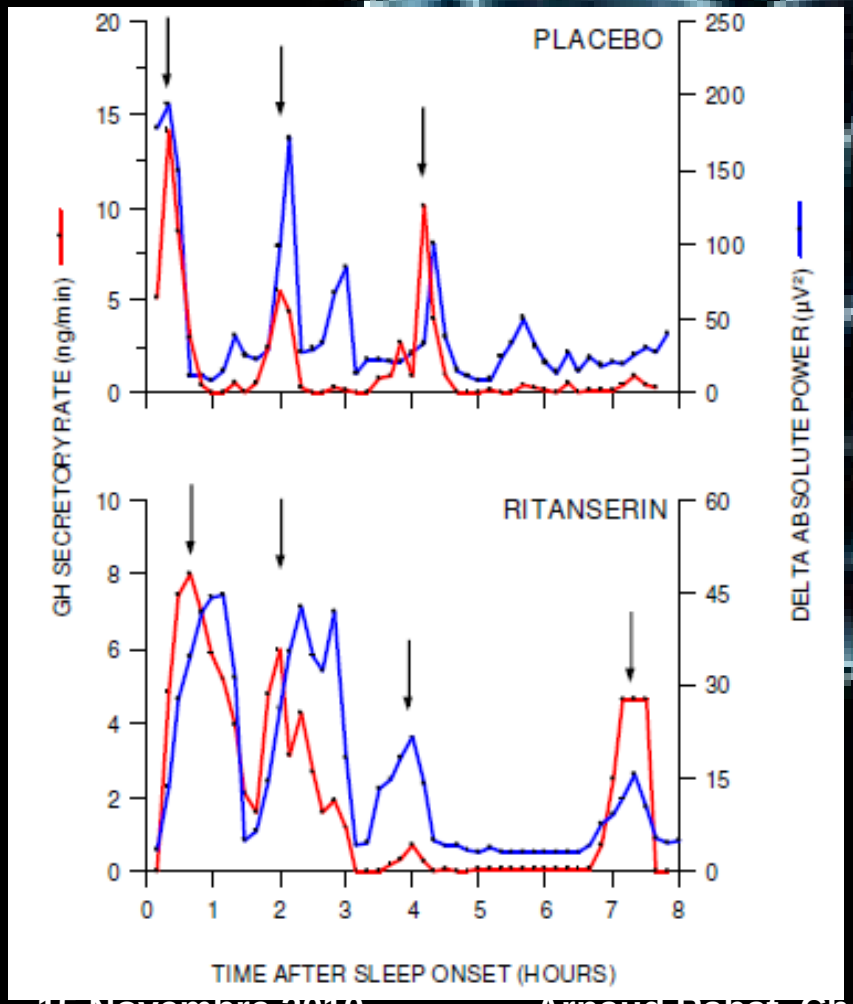
Ritanserin was know to increase SWS

Results:
For the first 3-hours :
- delta wave activity: + 24 %
- GH secretion: + 29 %

=> Causal link?

III. Les relations hormones et rythmes

☞ La GH : - Sécrétion de GH et sommeil

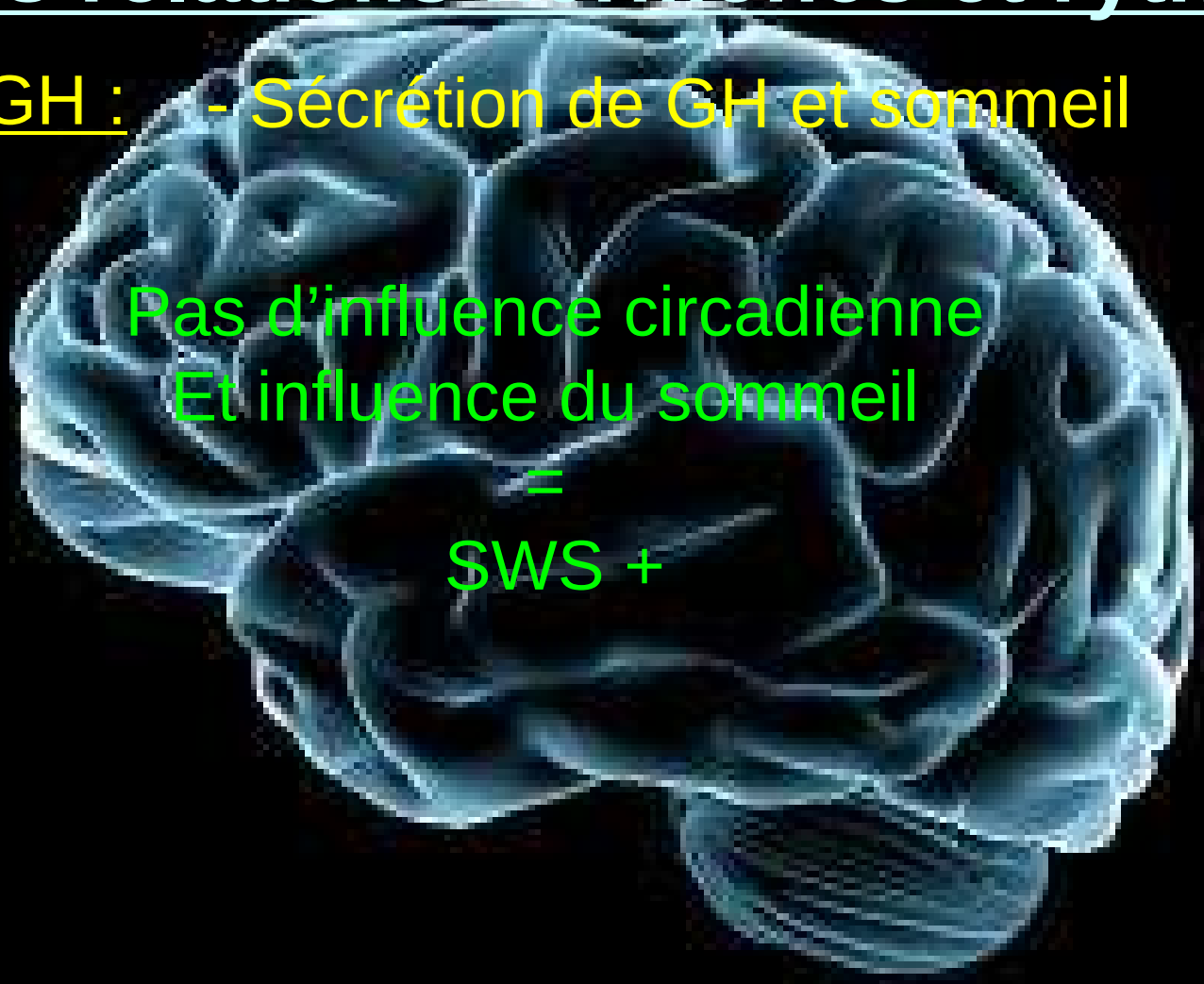


- **coïncidence** between GH pulses and delta peaks

- **concomitant** variations of GH secretion and delta wave activity

III. Les relations hormones et rythmes

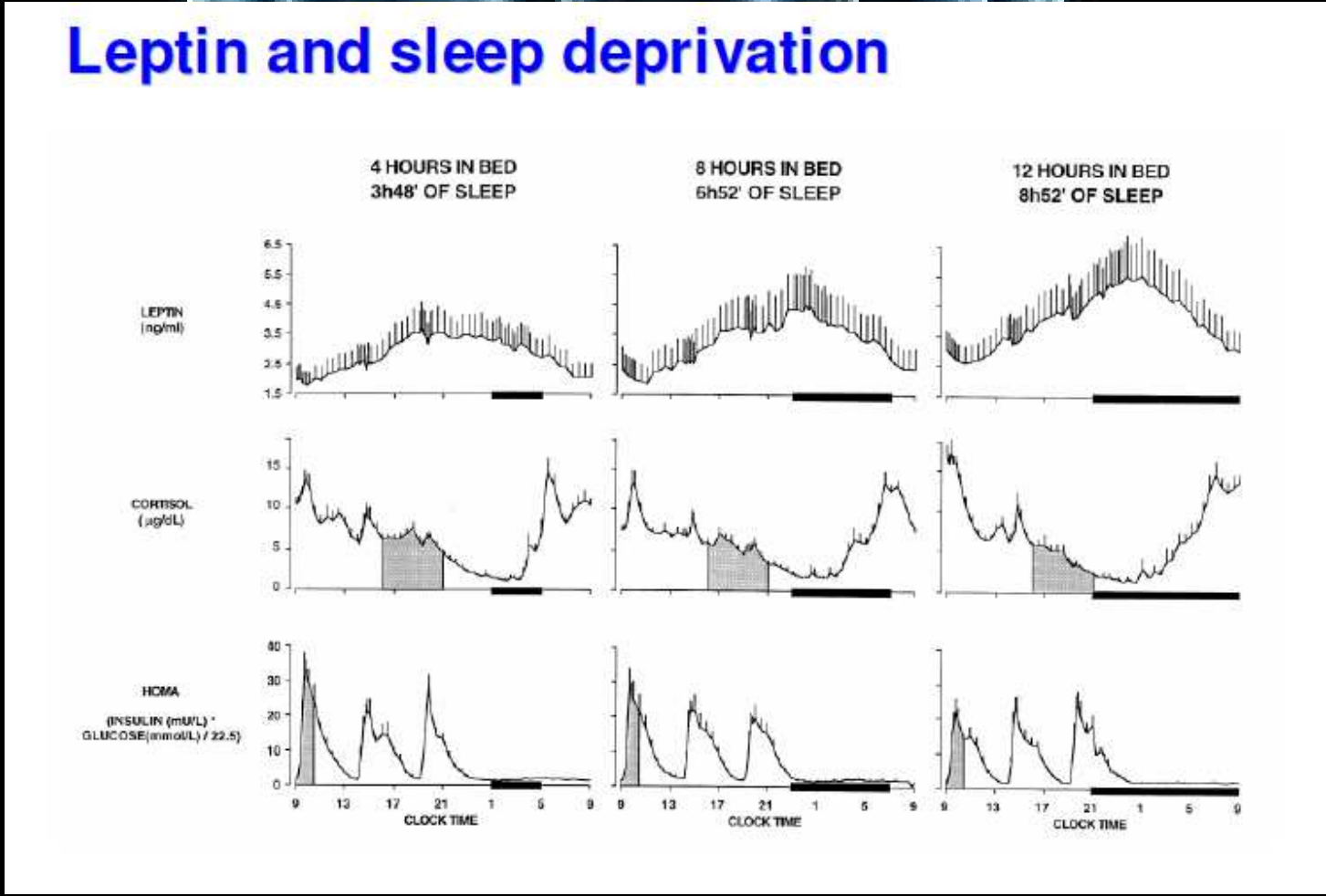
☞ La GH : - Sécrétion de GH et sommeil



Pas d'influence circadienne
Et influence du sommeil
=
SWS +

III. Les relations hormones et rythmes

☞ La leptine, la ghréline :



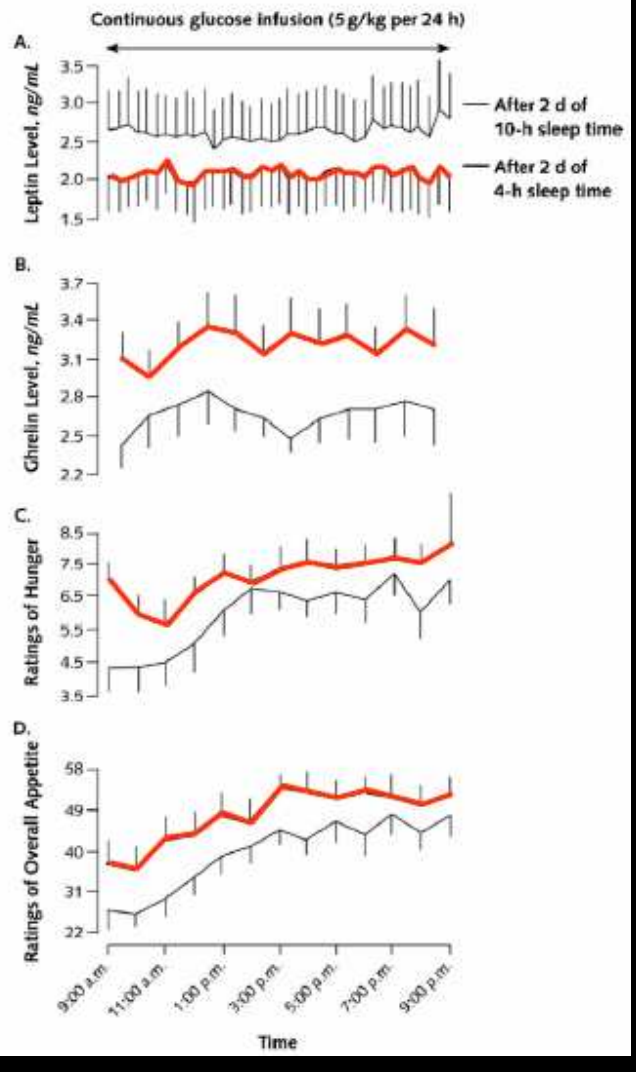
III. Les relations hormones et rythmes

☞ La leptine, la ghréline :

Effects of sleep debt on the satiety axis

Leptin: anorexigenic
Ghrelin: orexigenic

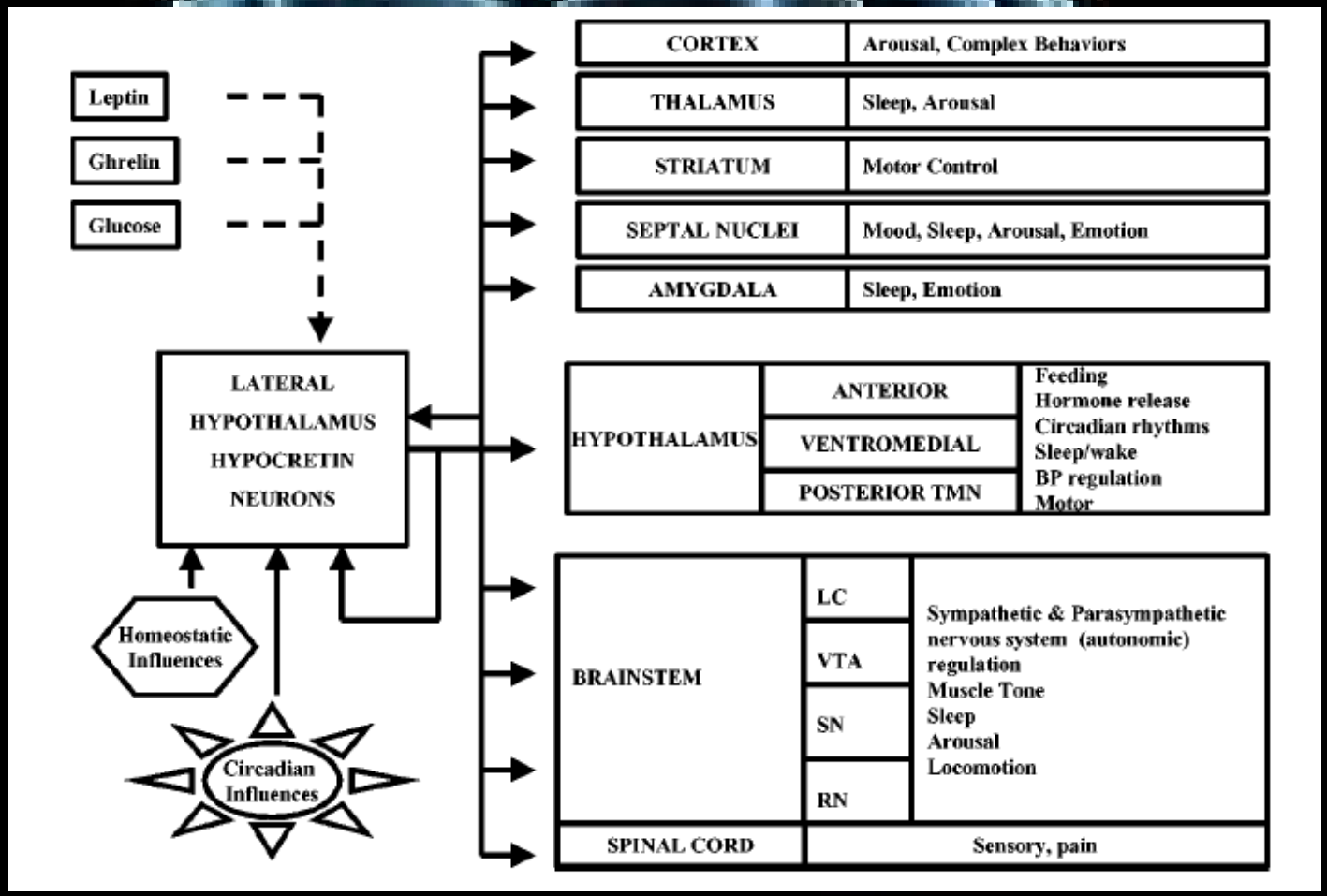
Sleep debt associated with increase in Ghrelin, decrease in leptin, increase in hunger and appetite



Spiegel et al. Ann Intern Med 2004

III. Les relations hormones et rythmes

☞ La leptine, la ghréline :



III. Les relations hormones et rythmes

☞ Bilan :

Deux grandes catégories d'hormones ont été initialement décrites (Pincus 1966):

- Hormones "**associées au sommeil**" sans influence du système circadien:
GH, PRL

-Hormones "**circadiennes**" sans influence du sommeil:
cortisol, mélatonine

Les résultats récents (études mieux contrôlées et techniques + sensibles) suggèrent que les 2 systèmes (circadiens et sommeil) exercent des influences sur la plupart des hormones

III. Les relations hormones et rythmes

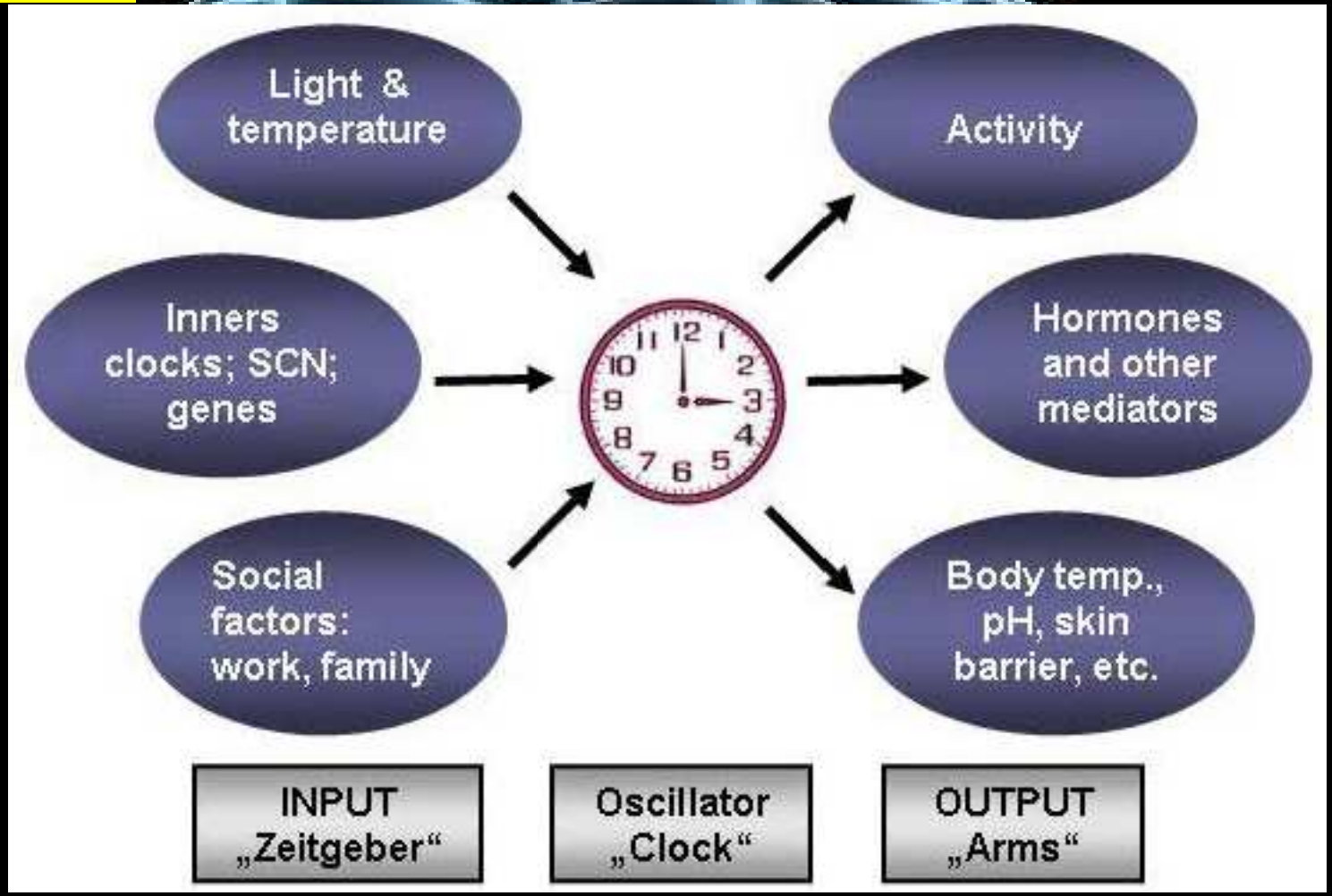
☞ Bilan :

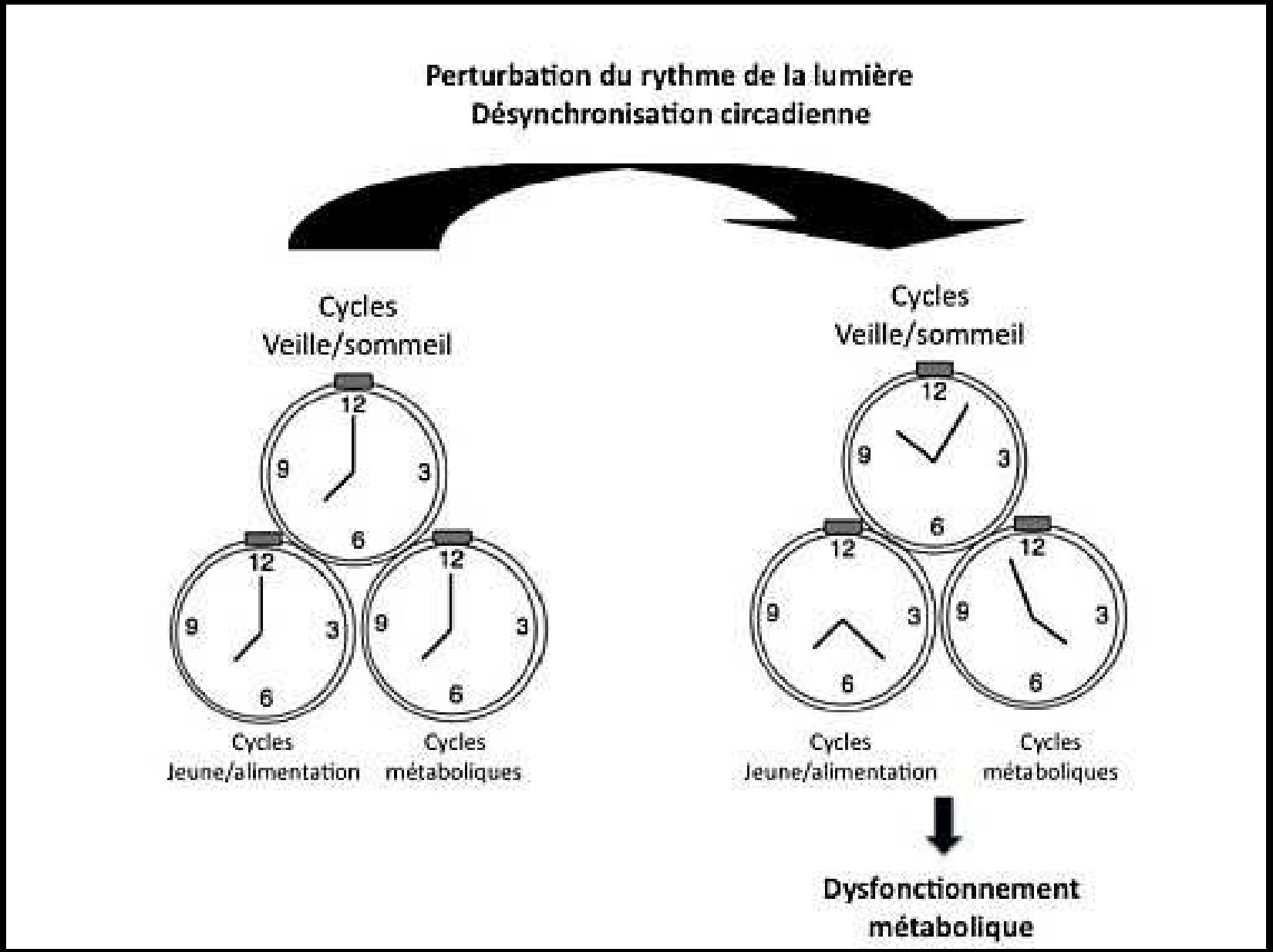
Les relations entre les secrétions hormonales et le sommeil peuvent être de type positif ou négatif et être complexes:
GH (SWS+), TSH (C+, S/SWS-), cortisol (C+, inter delta-), …

Il existe des interactions réciproques entre hormones et sommeil => pathologie ou action sur l'un des systèmes peut avoir un impact sur l'autre (sommeil, hormones, circadien)

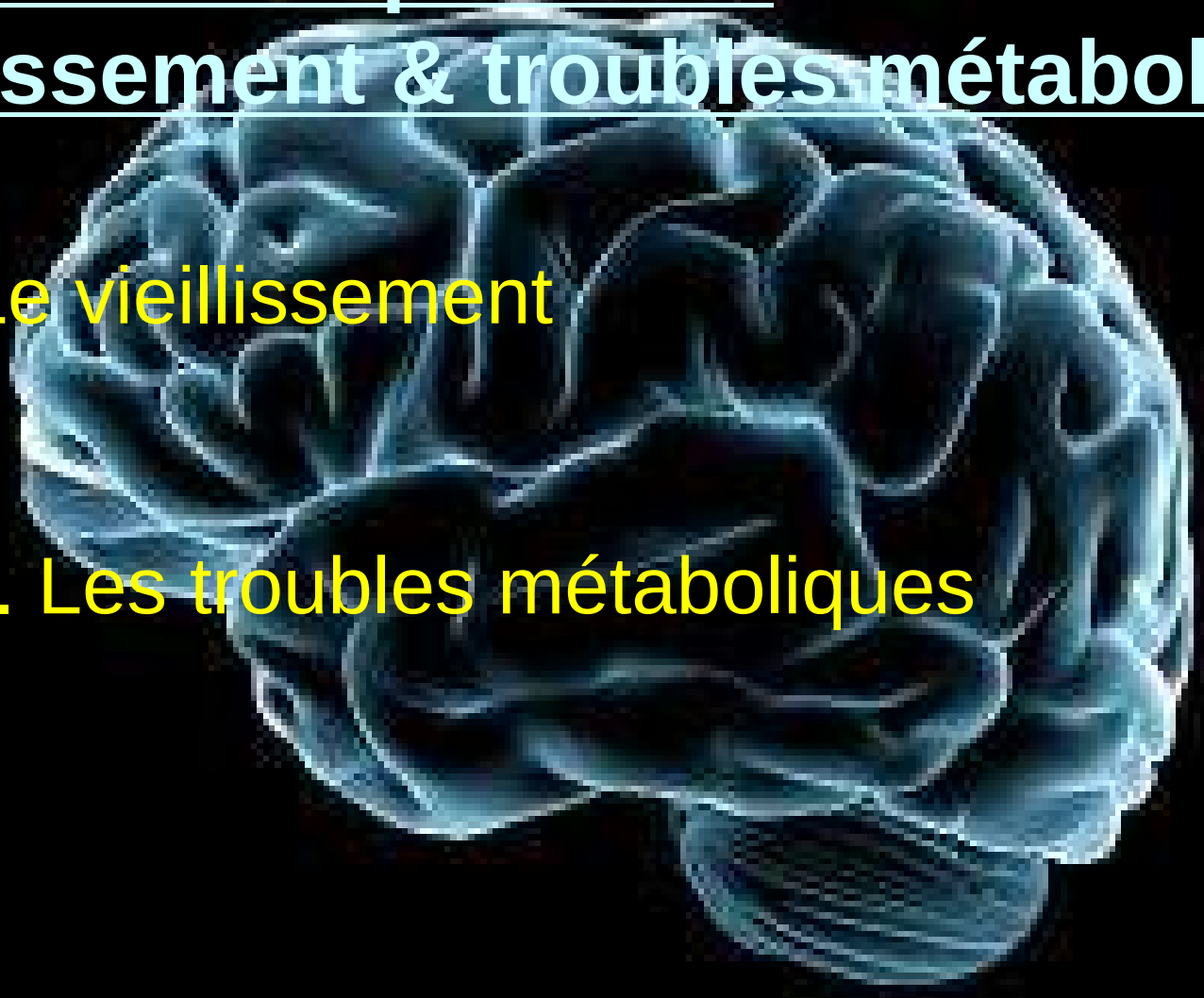
III. Les relations hormones et rythmes

☞ Bilan :




Perturbation du rythme de la lumière
Désynchronisation circadienne
Cycles
Veille/sommeil
Cycles
Jeune/alimentation
Cycles
métaboliques
Cycles
Veille/sommeil
Cycles
Jeune/alimentation
Cycles
métaboliques
Dysfonctionnement
métabolique

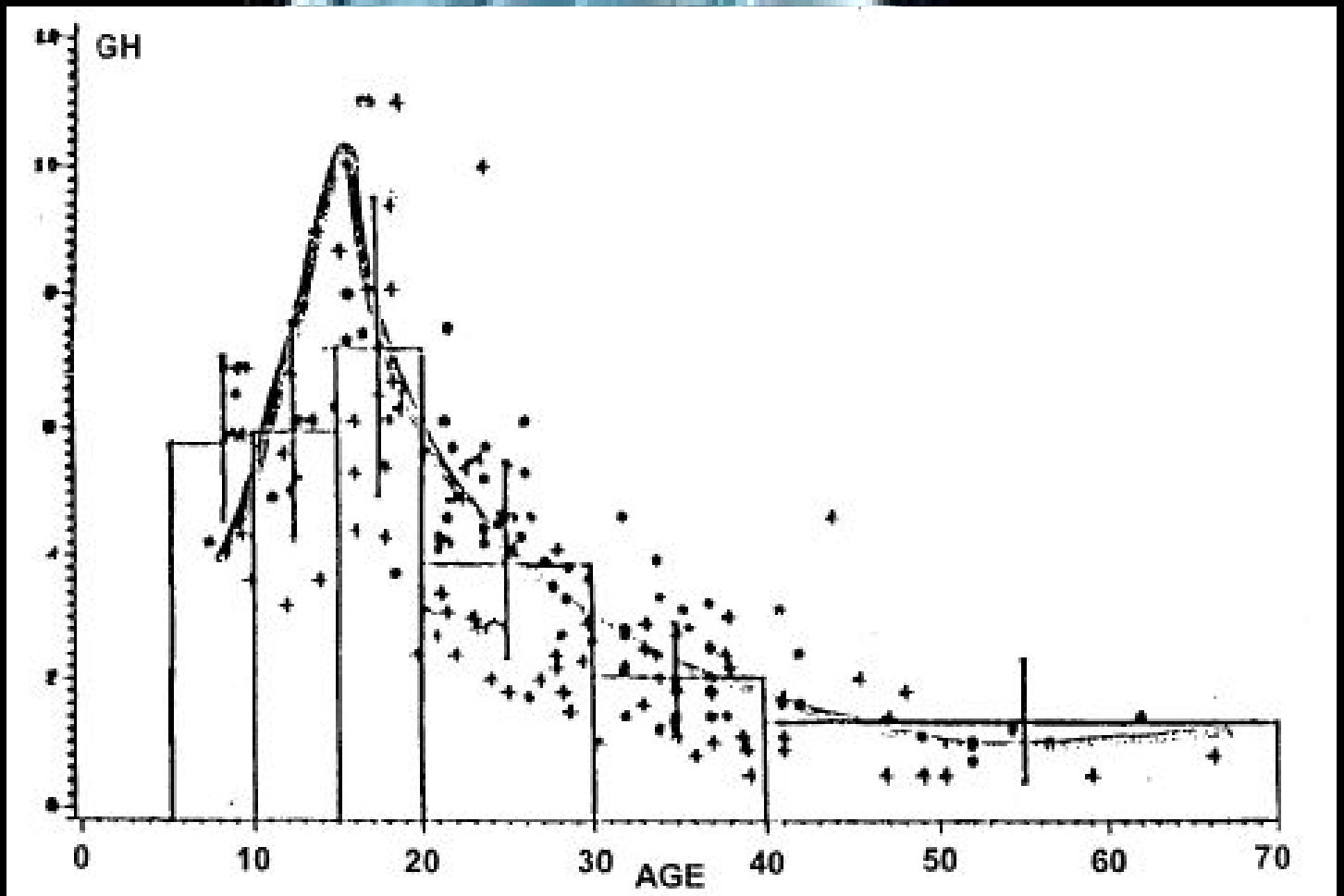
IV. Les conséquences : vieillissement & troubles métaboliques



1. Le vieillissement

2. Les troubles métaboliques

IV.1. Le vieillissement



The relationship between GH and age of 89 male (*)

IV.1. Le vieillissement

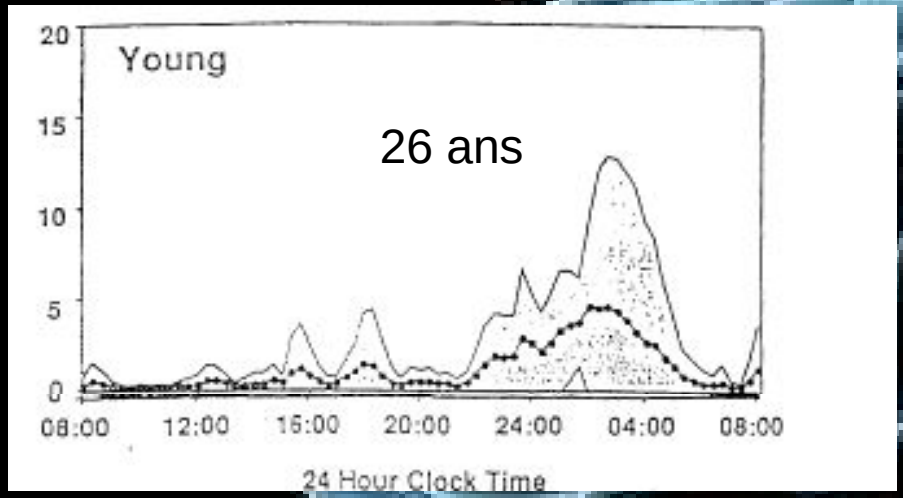
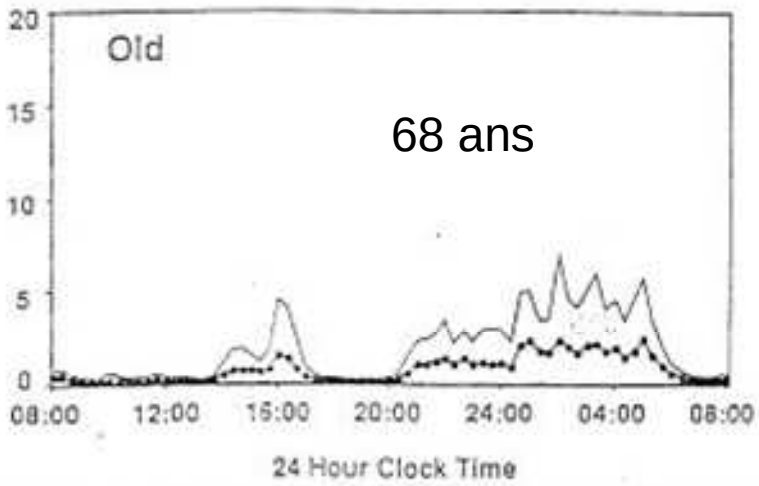


FIG. 2. Mean (± 1 SD) 24 h GH release in nine young (mean age 26 ± 4 yr) and 10 old (68 ± 6 yr) men sampled at 20 min intervals, demonstrating the normal diurnal pattern of GH secretion and the reduced nocturnal peak amplitude in the older men (117).



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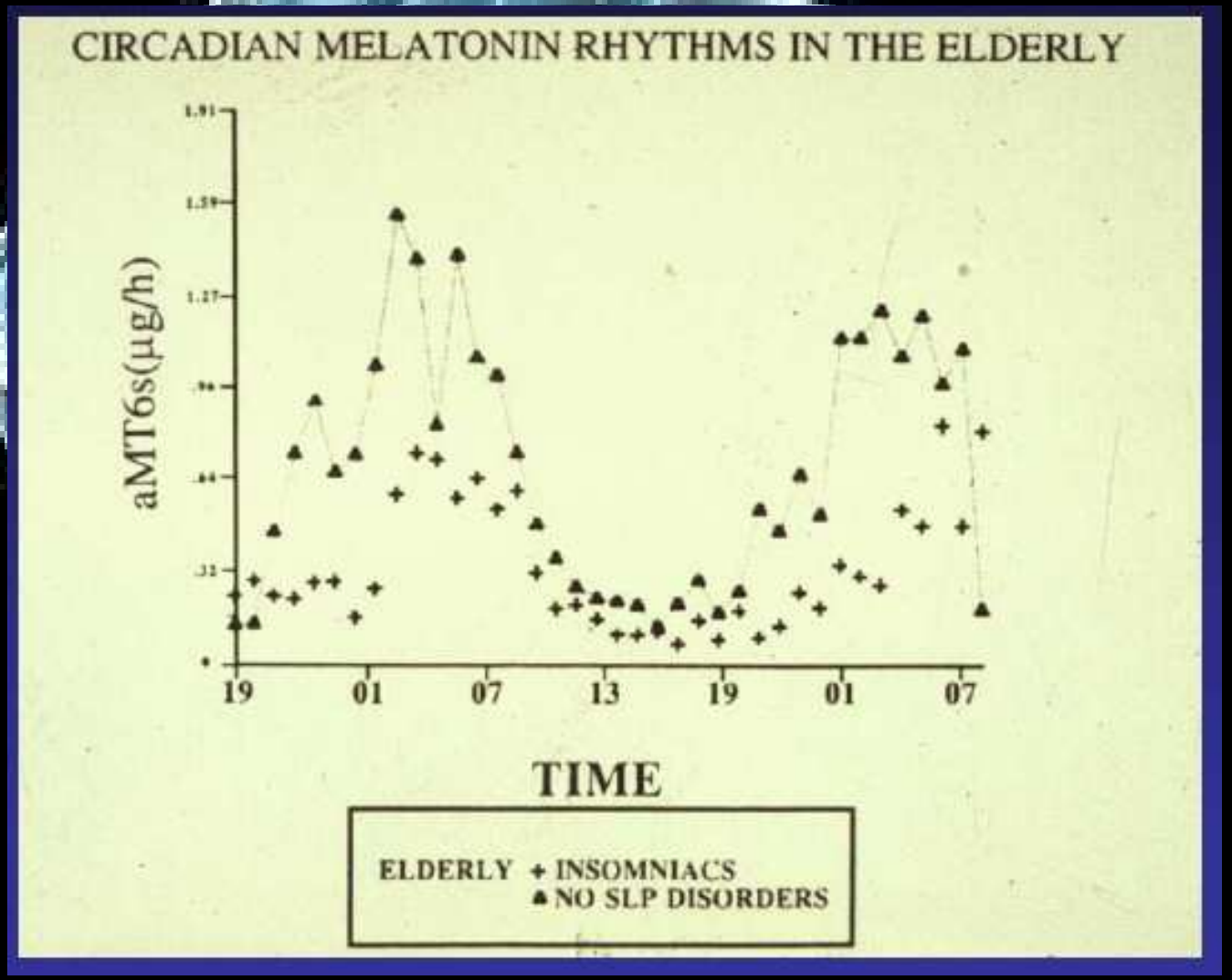
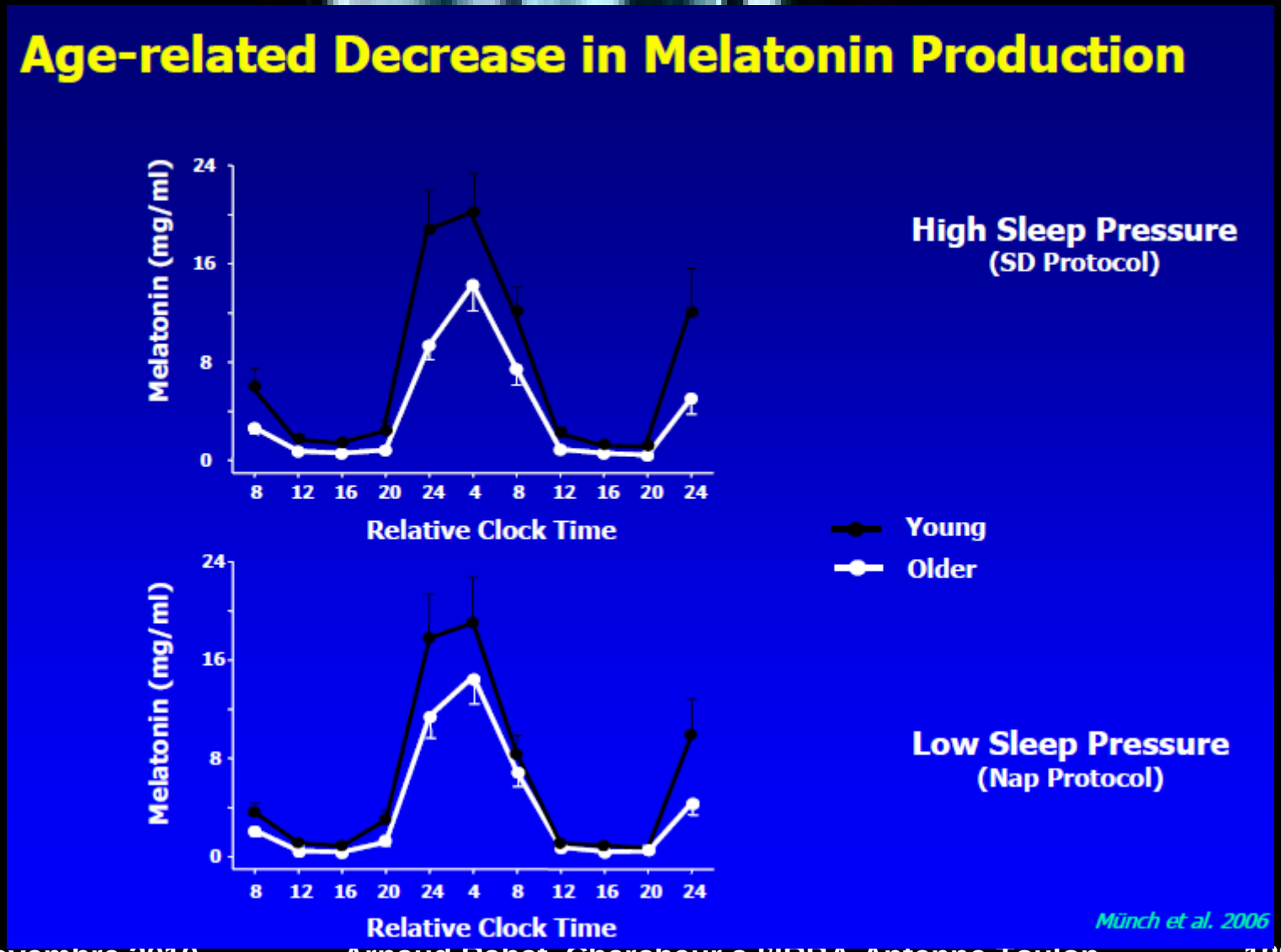
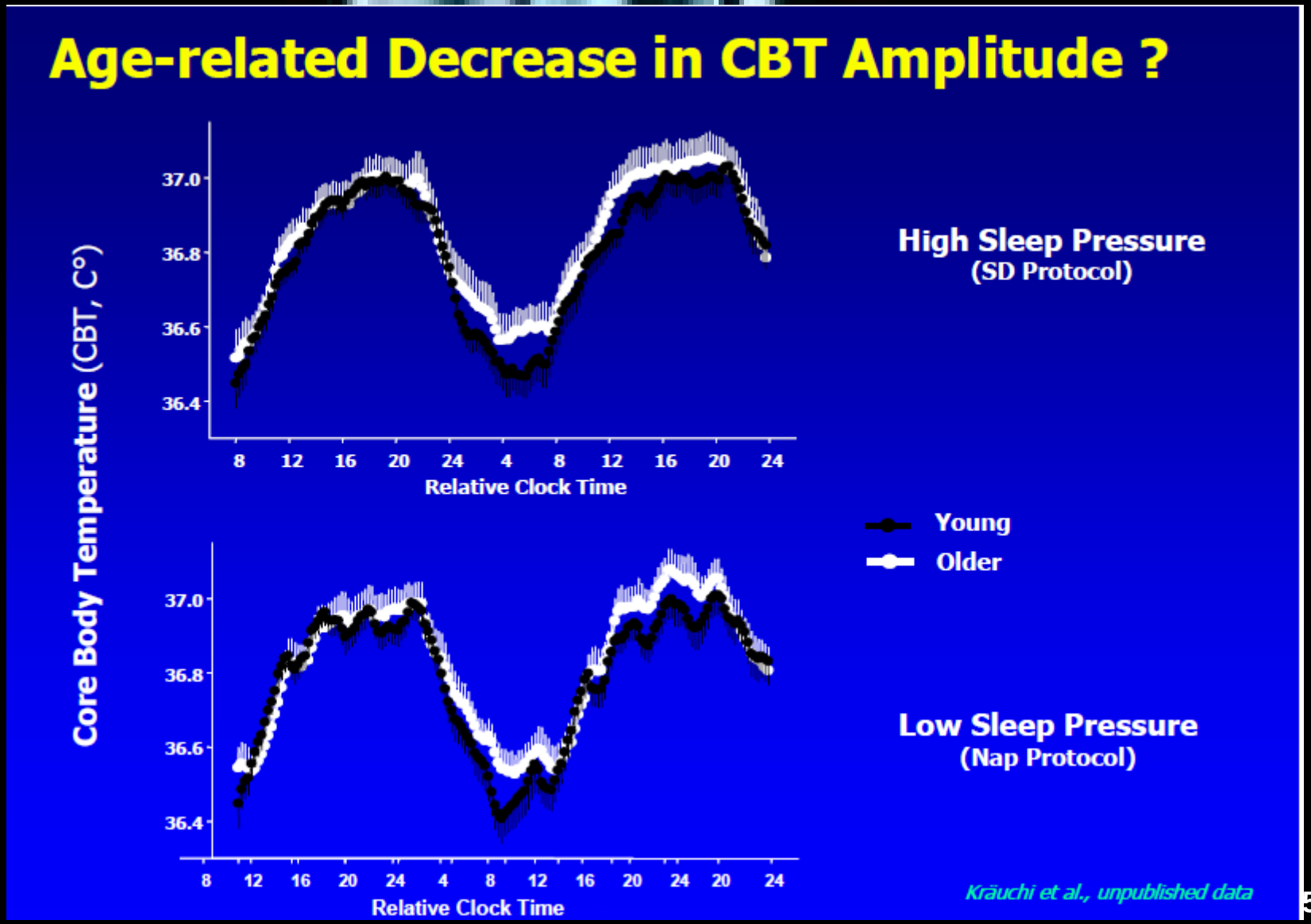
IV.1. Le vieillissement



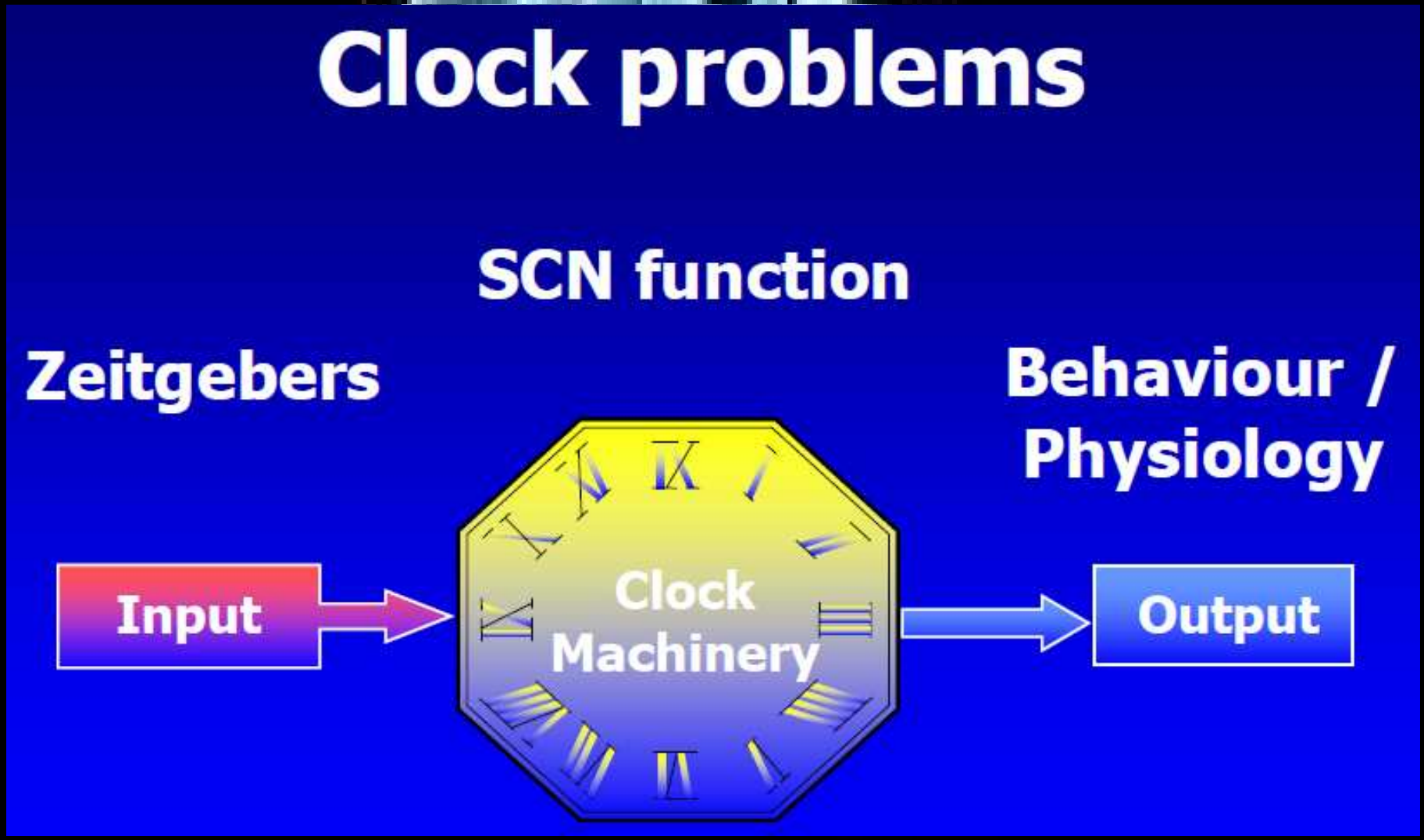
IV.1. Le vieillissement



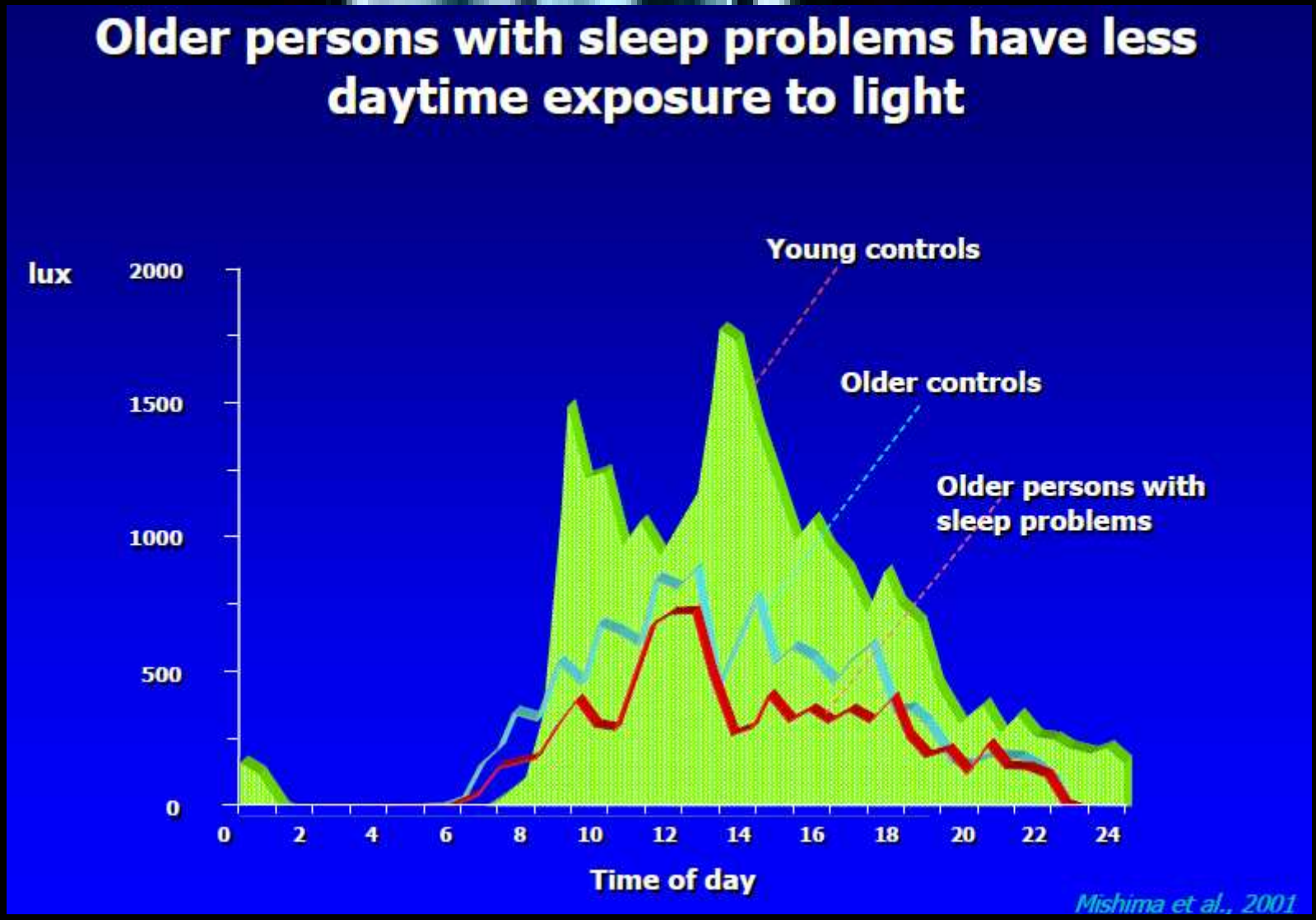
IV.1. Le vieillissement



IV.1. Le vieillissement



IV.1. Le vieillissement



IV.1. Le vieillissement

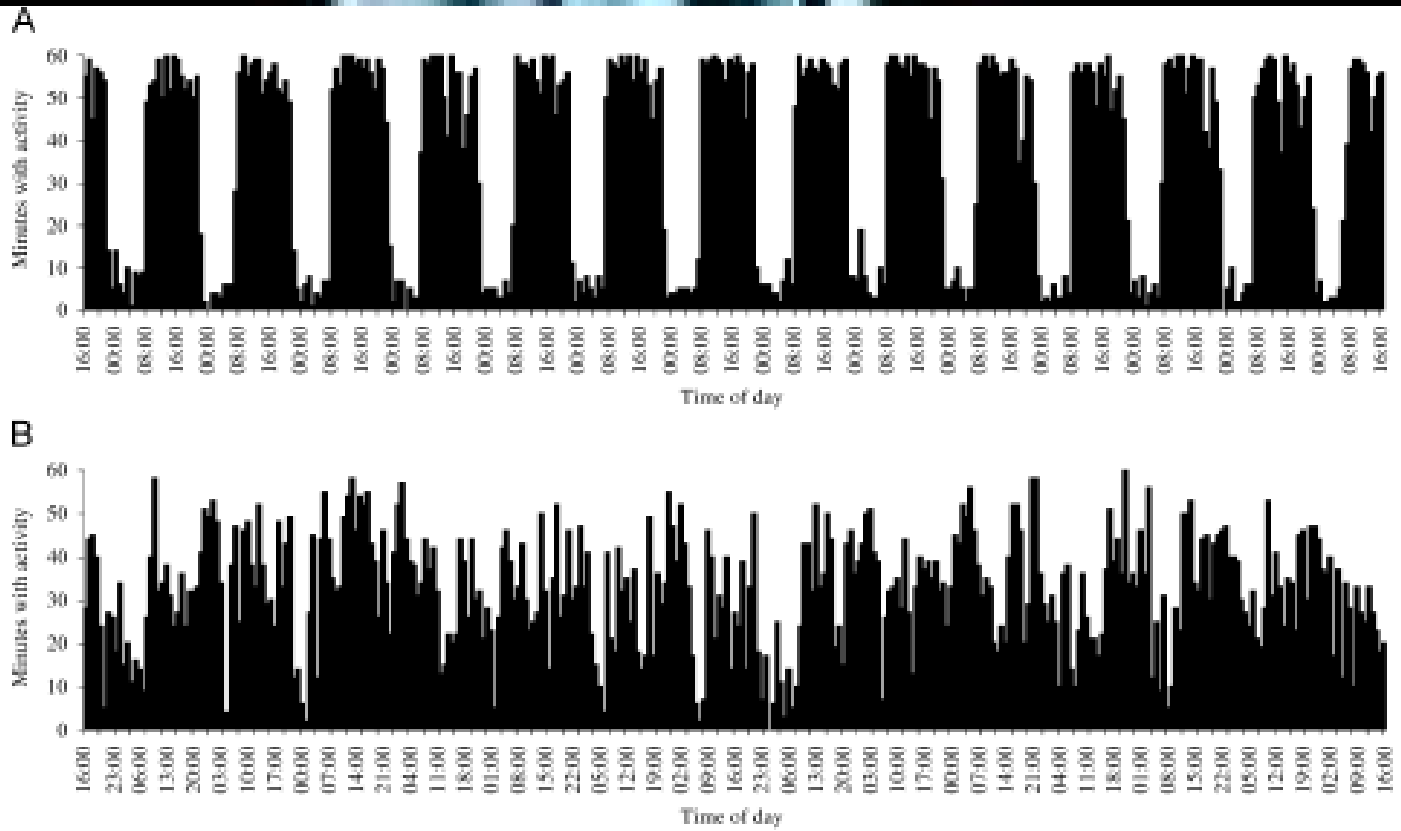


Figure 3 Examples of 14-day activity profiles of two demented elderly subjects. Bins represent the number of minutes with activity for each individual hour. The upper panel shows a subject with a very well-maintained rest–activity rhythm. Note especially the interdaily stability: the 14 individuals daytime profile much resemble each other. The lower panel shows a subject with a virtually complete loss of 24-h rhythmicity. Daily profiles do not resemble each other (Interdaily Stability parameter = 0.10) and the 'spiky' alteration of hours of much activity and little activity represent a strong fragmentation, also known as intradaily variability. Of note, the degree of such fragmentation of the activity pattern shows moderate correlations ($r = 0.25–0.35$) with several parameters of functional, emotional and social well-being (from Carvalho-Bos et al.[68] with permission).

IV.1. Le vieillissement

Annals of Internal Medicine | REVIEW

Systematic Review: The Safety and Efficacy of Growth Hormone in the Healthy Elderly

Hau Liu, MD, MBA, MPH; Dena M. Bravata, MD, MS; Ingram Olkin, PhD; Smita Nayak, MD; Brian Roberts, MD; Alan M. Garber, MD, PhD; and Andrew R. Hoffman, MD

Background: Human growth hormone (GH) is widely used as an antiaging therapy, although its use for this purpose has not been approved by the U.S. Food and Drug Administration and its distribution as an antiaging agent is illegal in the United States.

Purpose: To evaluate the safety and efficacy of GH therapy in the healthy elderly.

Data Sources: The authors searched MEDLINE and EMBASE databases for English-language studies published through 21 November 2005 by using such terms as *growth hormone* and *aging*.

Study Selection: The authors included randomized, controlled trials that compared GH therapy with no GH therapy or GH and lifestyle interventions (exercise with or without diet) with lifestyle interventions alone. Included trials provided GH for 2 weeks or more to community-dwelling participants with a mean age of 50 years or more and a body mass index of 35 kg/m^2 or less. The authors excluded studies that evaluated GH as treatment for a specific illness.

Data Extraction: Two authors independently reviewed articles and abstracted data.

Data Synthesis: 31 articles describing 18 unique study populations met the inclusion criteria. A total of 220 participants who received GH (107 person-years) completed their respective studies. Study participants were elderly (mean age, 69 years [SD, 6]) and overweight (mean body mass index, 28 kg/m^2 [SD, 2]). Initial daily GH dose (mean, 14 μg per kg of body weight [SD, 7]) and treatment duration (mean, 27 weeks [SD, 16]) varied. In participants treated with GH compared with those not treated with GH, overall fat mass decreased (change in fat mass, −2.1 kg [95% CI, −2.8 to −1.35] and overall lean body mass increased (change in lean body mass, 2.1 kg [CI, 1.3 to 2.9]) ($P < 0.001$), and their weight did not change significantly (change in weight, 0.1 kg [CI, −0.7 to 0.8]; $P = 0.87$). Total cholesterol levels decreased (change in cholesterol, −0.29 mmol/L [−11.21 mg/dL]; $P = 0.006$), although not significantly after adjustment for body composition changes. Other outcomes, including bone density and other serum lipid levels, did not change. Persons treated with GH were significantly more likely to experience soft tissue edema, arthralgias, carpal tunnel syndrome, and gynecomastia and were somewhat more likely to experience the onset of diabetes mellitus and impaired fasting glucose.

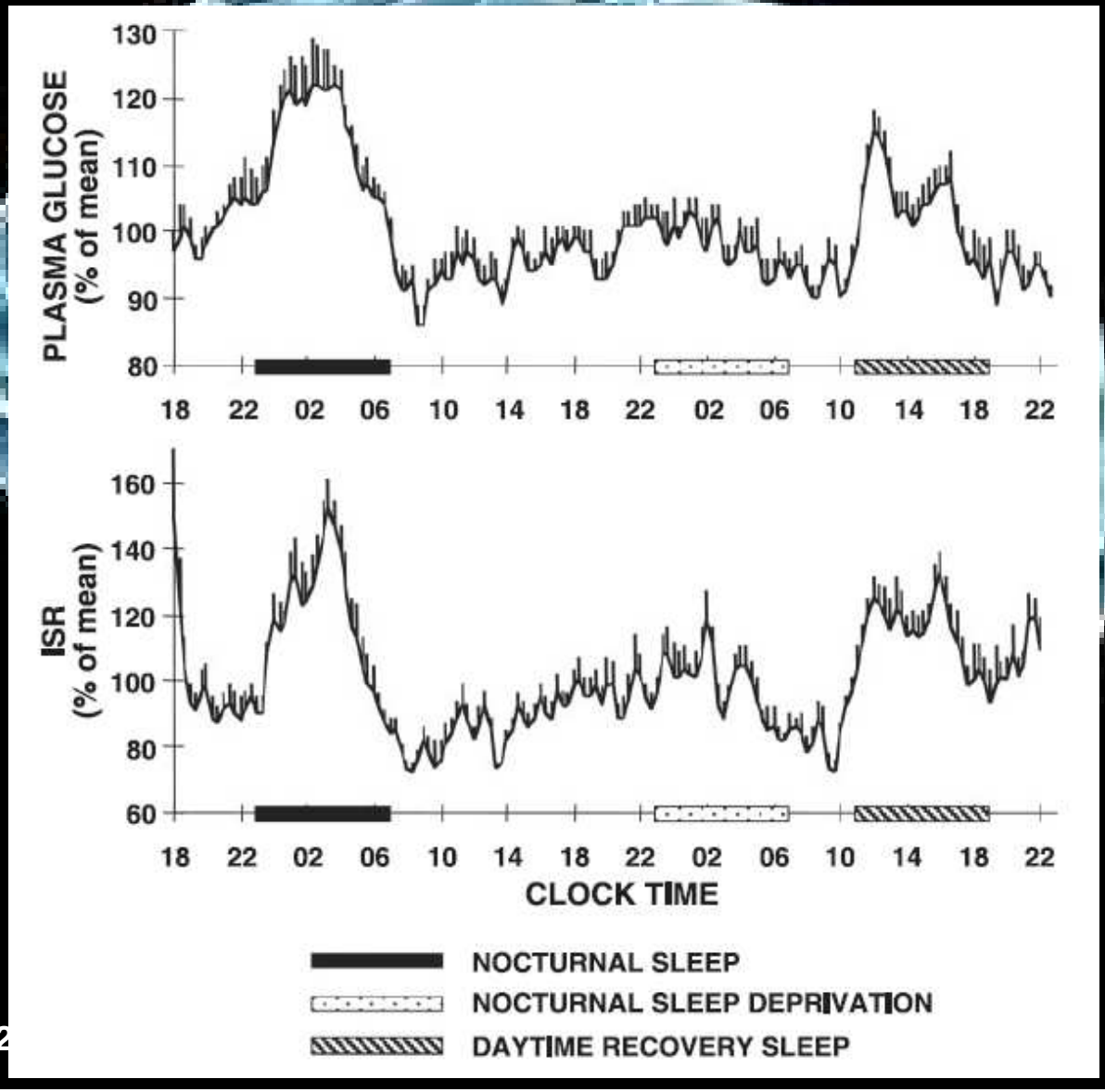
Limitations: Some important outcomes were infrequently or heterogeneously measured and could not be synthesized. Most included studies had small sample sizes.

Conclusions: The literature published on randomized, controlled trials evaluating GH therapy in the healthy elderly is limited but suggests that it is associated with small changes in body composition and increased rates of adverse events. On the basis of this evidence, GH cannot be recommended as an antiaging therapy.

Ann Intern Med. 2007;146:104-115. www.annals.org

For author affiliations, see end of text.

IV.2. Les troubles du métabolisme



Spiegel et coll., 2005

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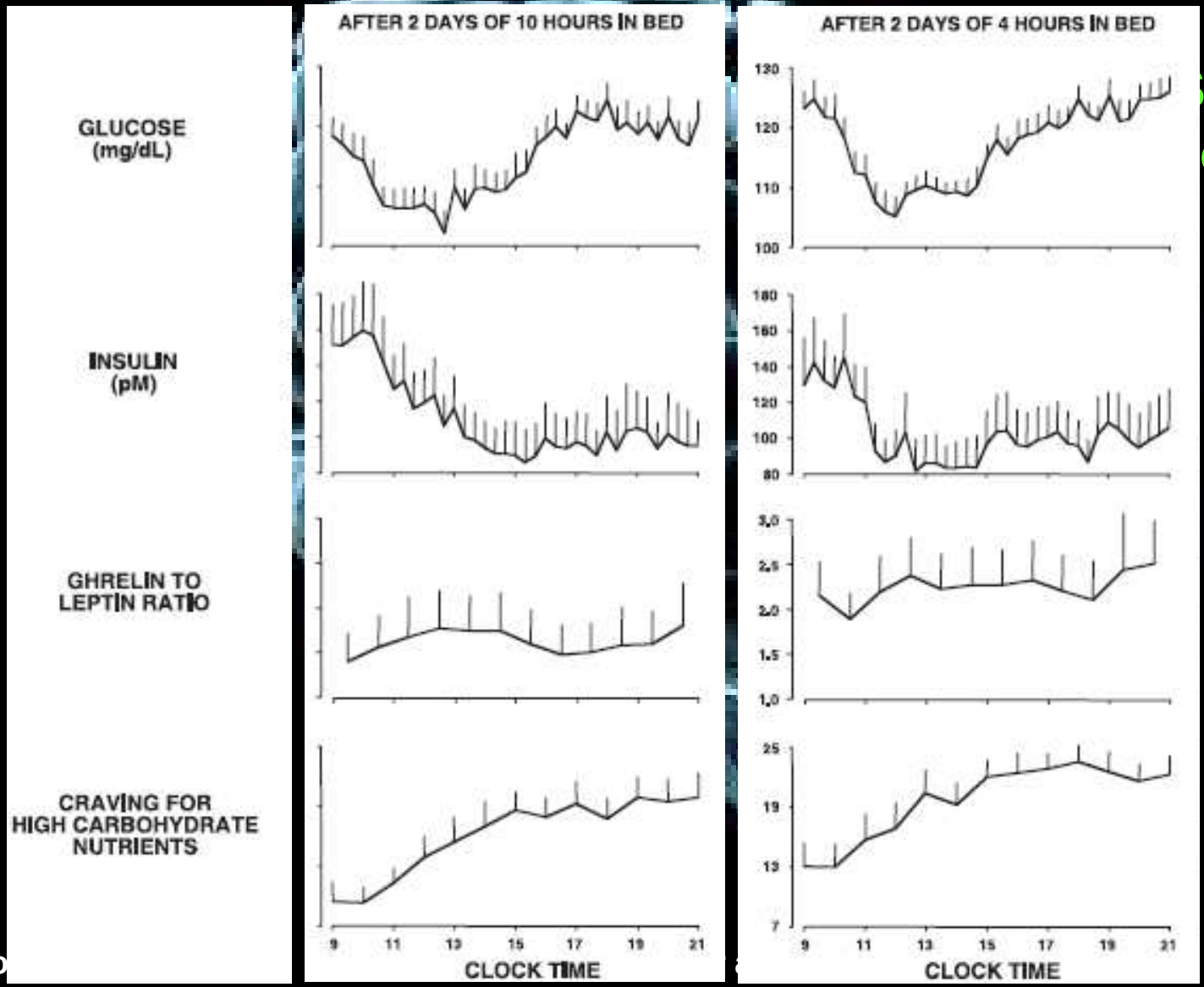

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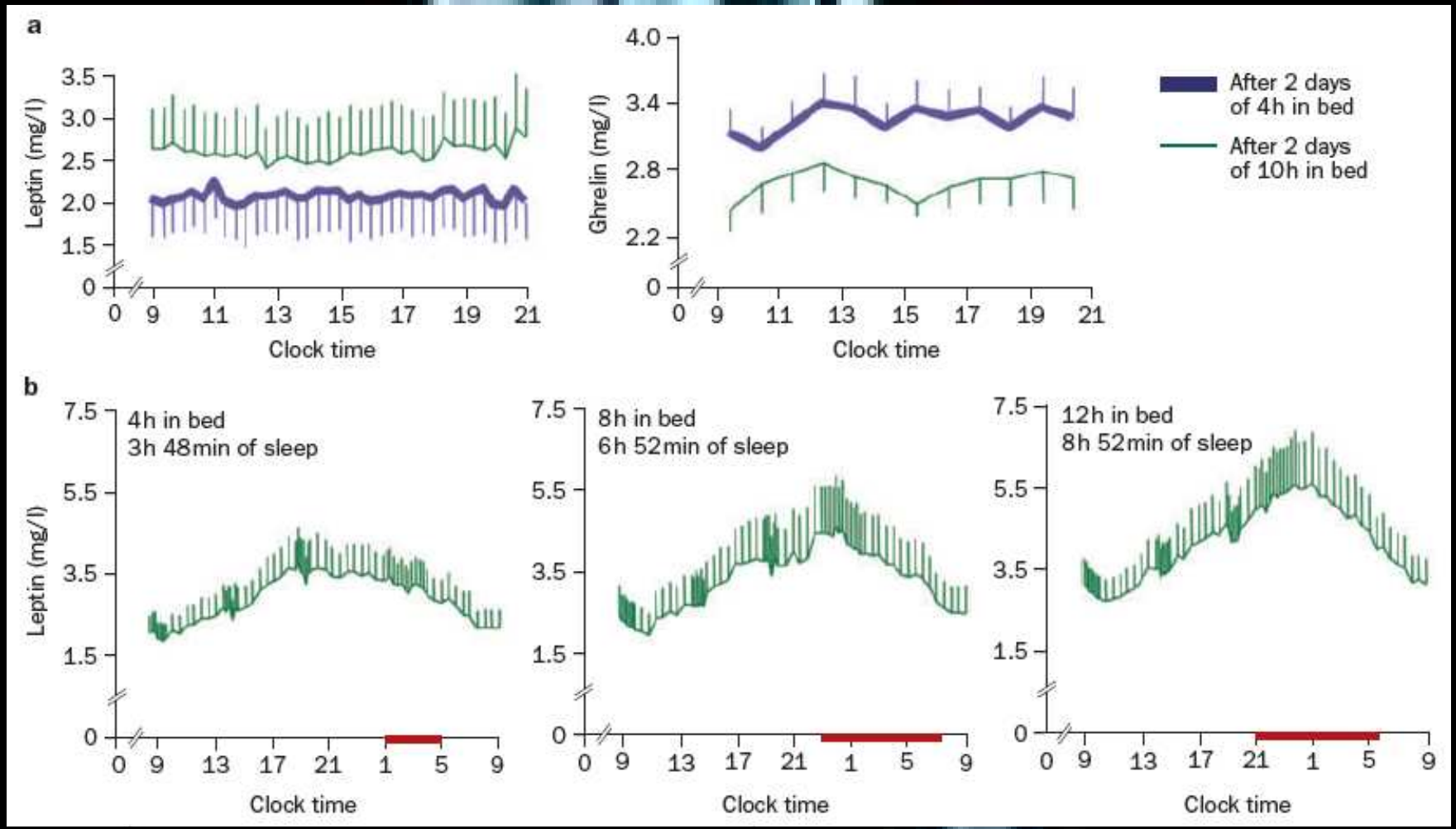

Spiegel et coll., 2009

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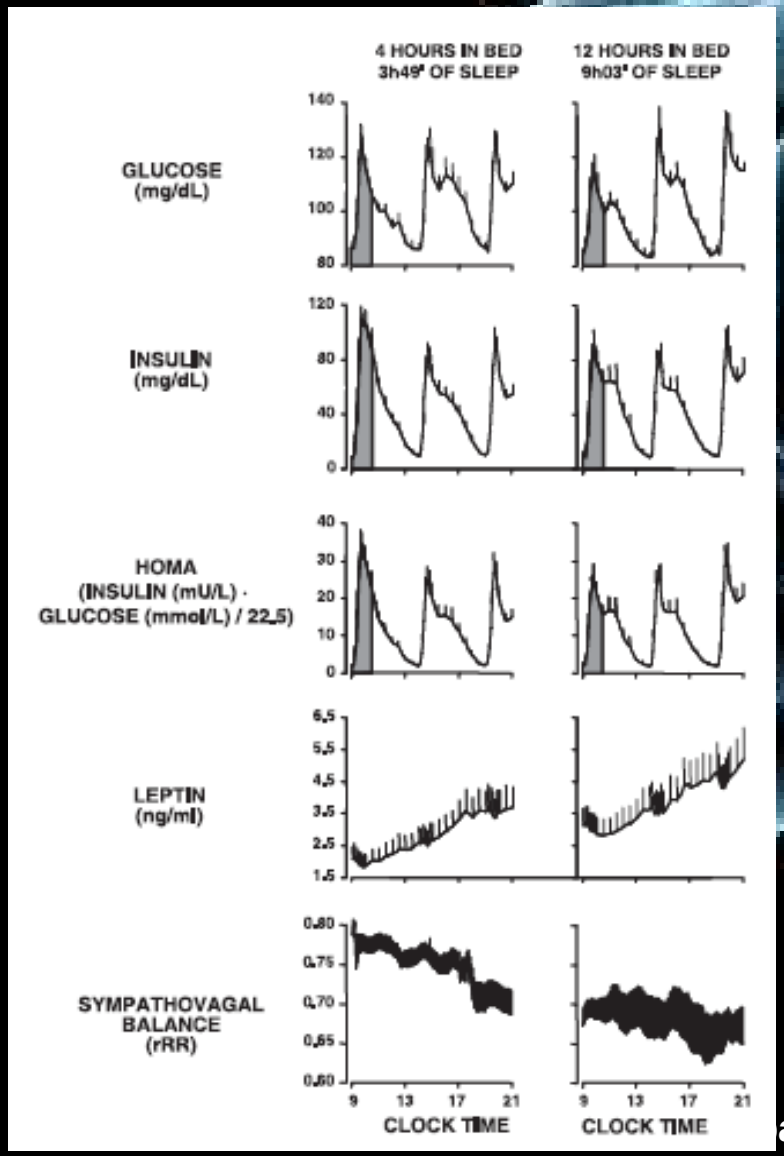
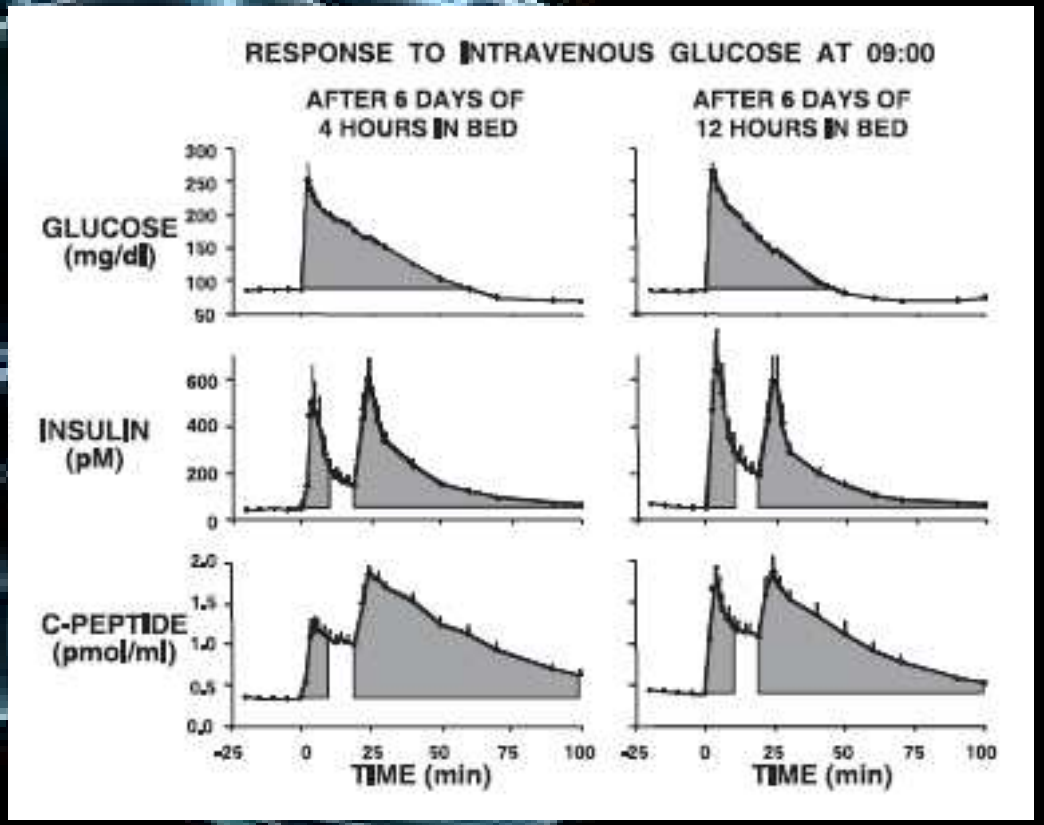
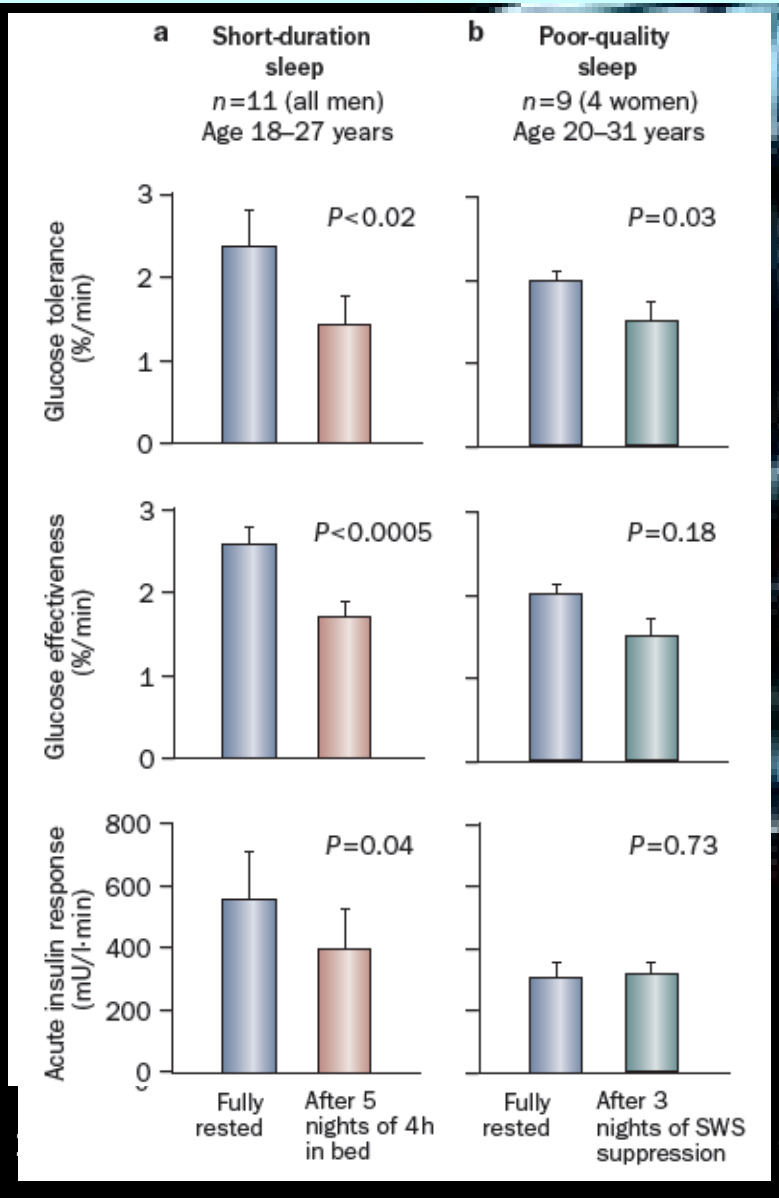
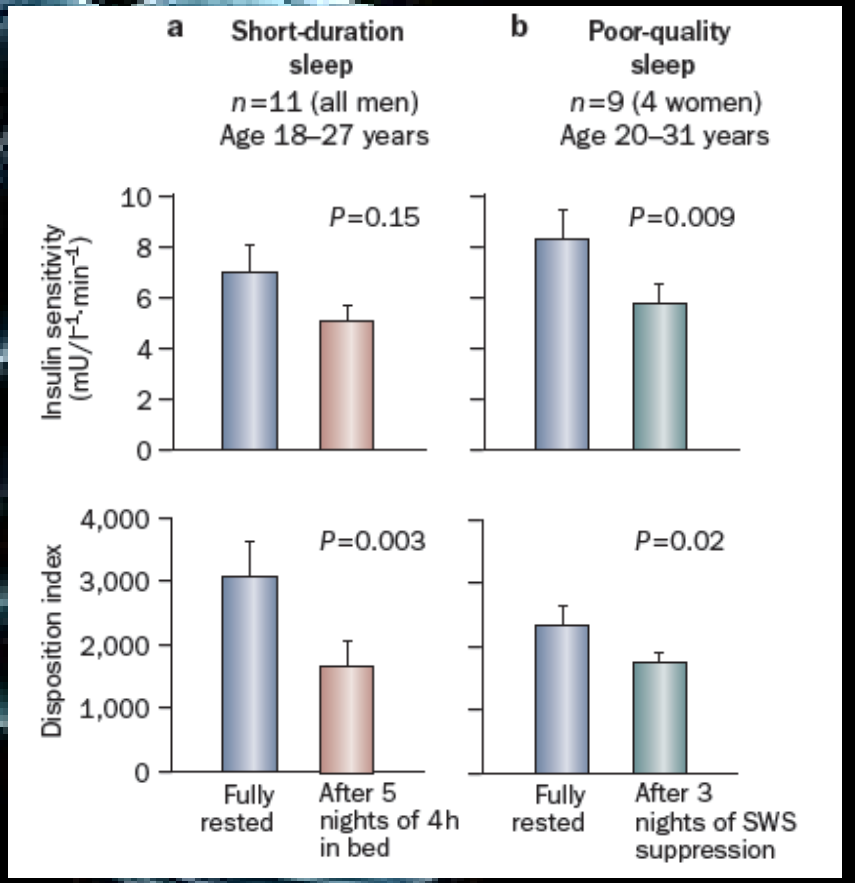




Spiegel et coll., 2005

IV.2. Les troubles du métabolisme





Spiegel et coll., 2009

IV.2. Les troubles du métabolisme

Table 1. *Impact of sleep restriction on leptin and ghrelin levels*

	Laboratory Study	Epidemiological Study
	Spiegel et al. (77) Within-subject comparison 2 days of 4-h bedtimes vs. 2 days of 10-h bedtimes $n=12$ age: 22±2 yr 100% men	Taheri et al. (79) Across-subject comparison Usual sleep time of 5 h vs. 8 h $n=1,024$ age: 53±8 yr 54% men
Change in leptin (satiety hormone)	−18%*	−16%†
Change in ghrelin (appetite hormone)	+28%*	+15%†

Spiegel et coll., 2005

IV.2. Les troubles du métabolisme

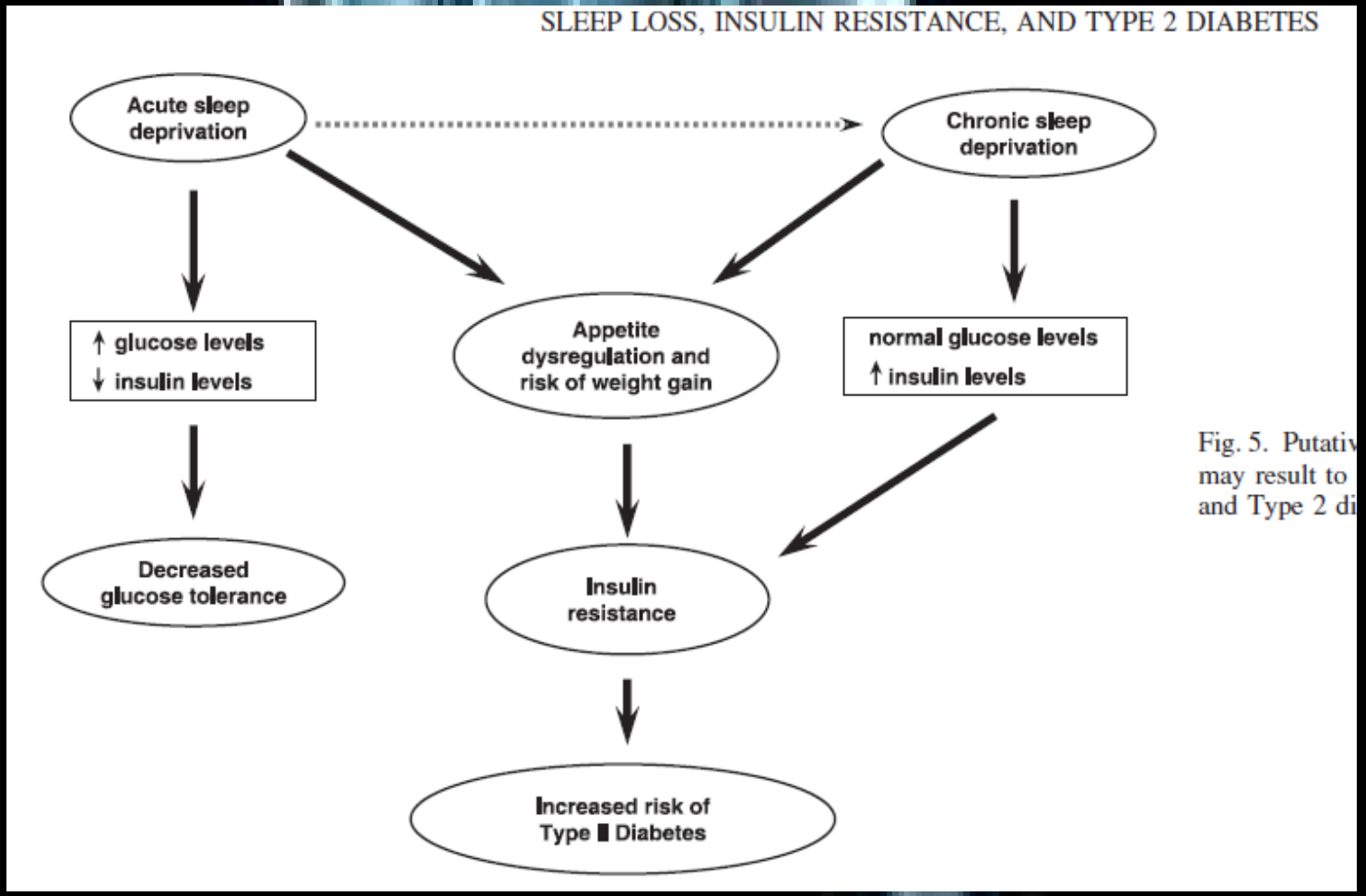


Fig. 5. Putativ
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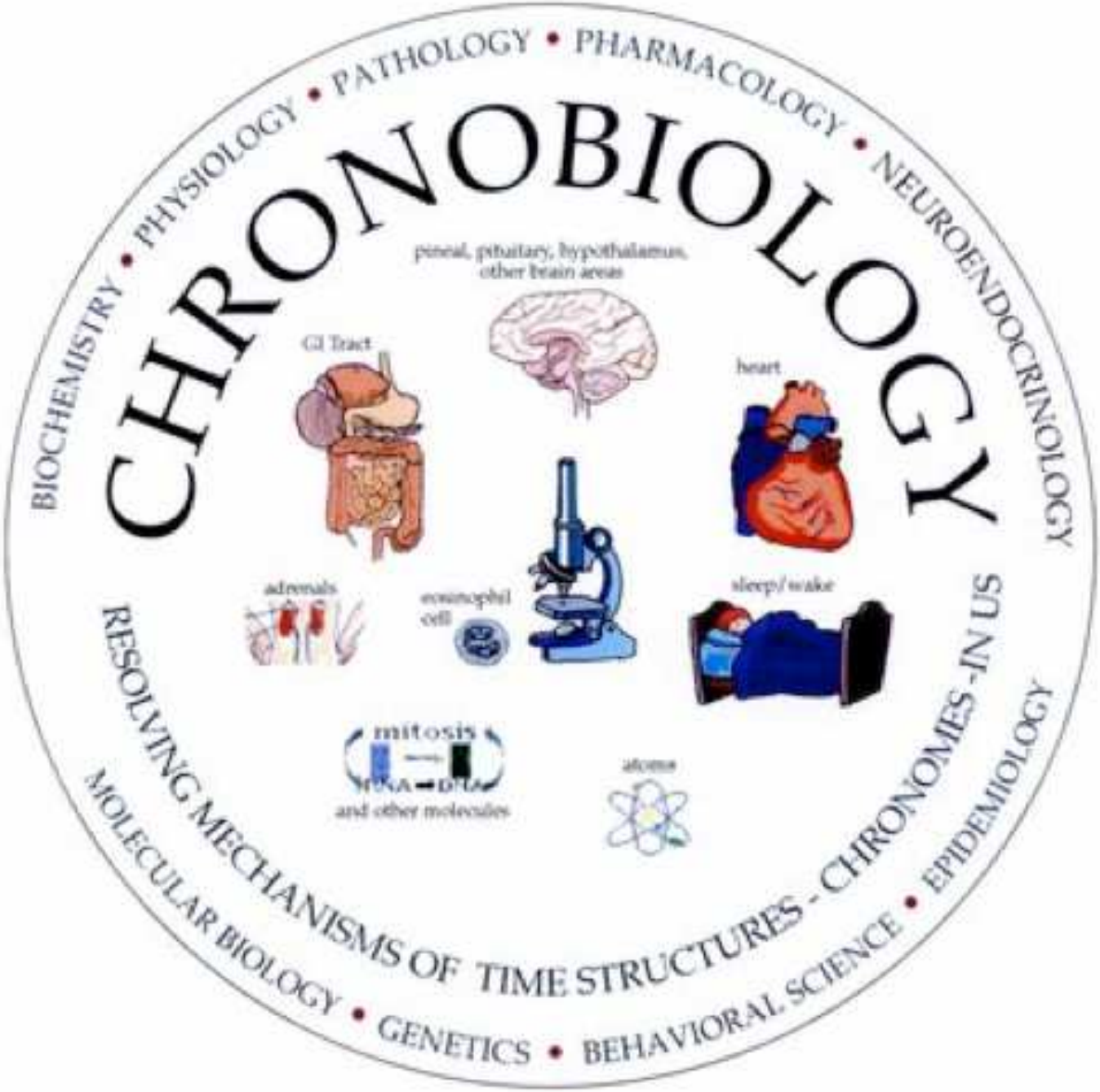
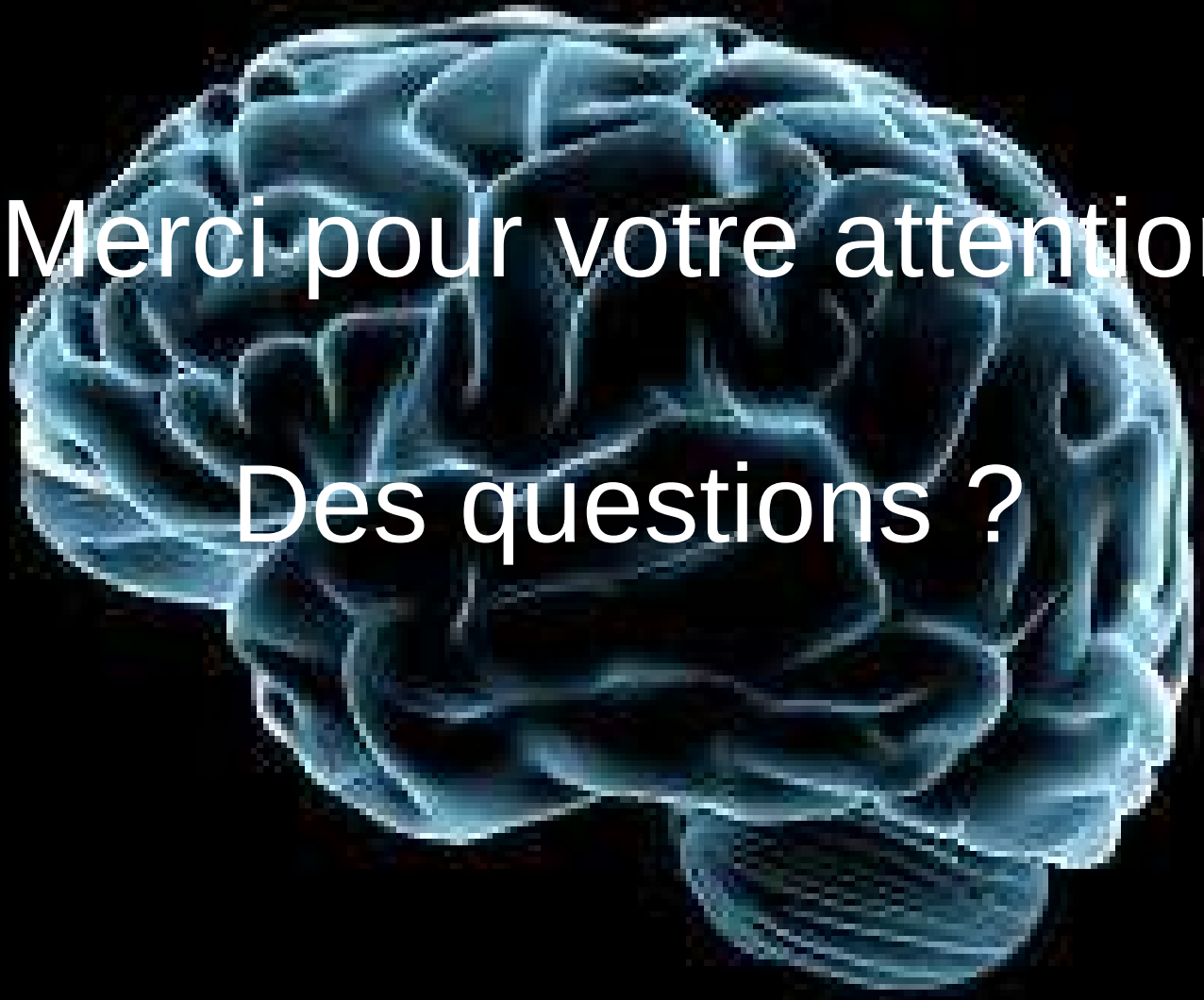
Spiegel et coll., 2005


CHRONOBIOLOGY
BIOCHEMISTRY • PHYSIOLOGY • PATHOLOGY • PHARMACOLOGY • NEUROENDOCRINOLOGY
RESOLVING MECHANISMS OF TIME STRUCTURES - CHRONOMES - IN US
MOLECULAR BIOLOGY • GENETICS • BEHAVIORAL SCIENCE • EPIDEMIOLOGY
pineal, pituitary, hypothalamus, other brain areas
GI Tract
heart
adrenals
eosinophil cell
sleep/wake
mitosis
and other molecules
atoms



Merci pour votre attention

Des questions ?