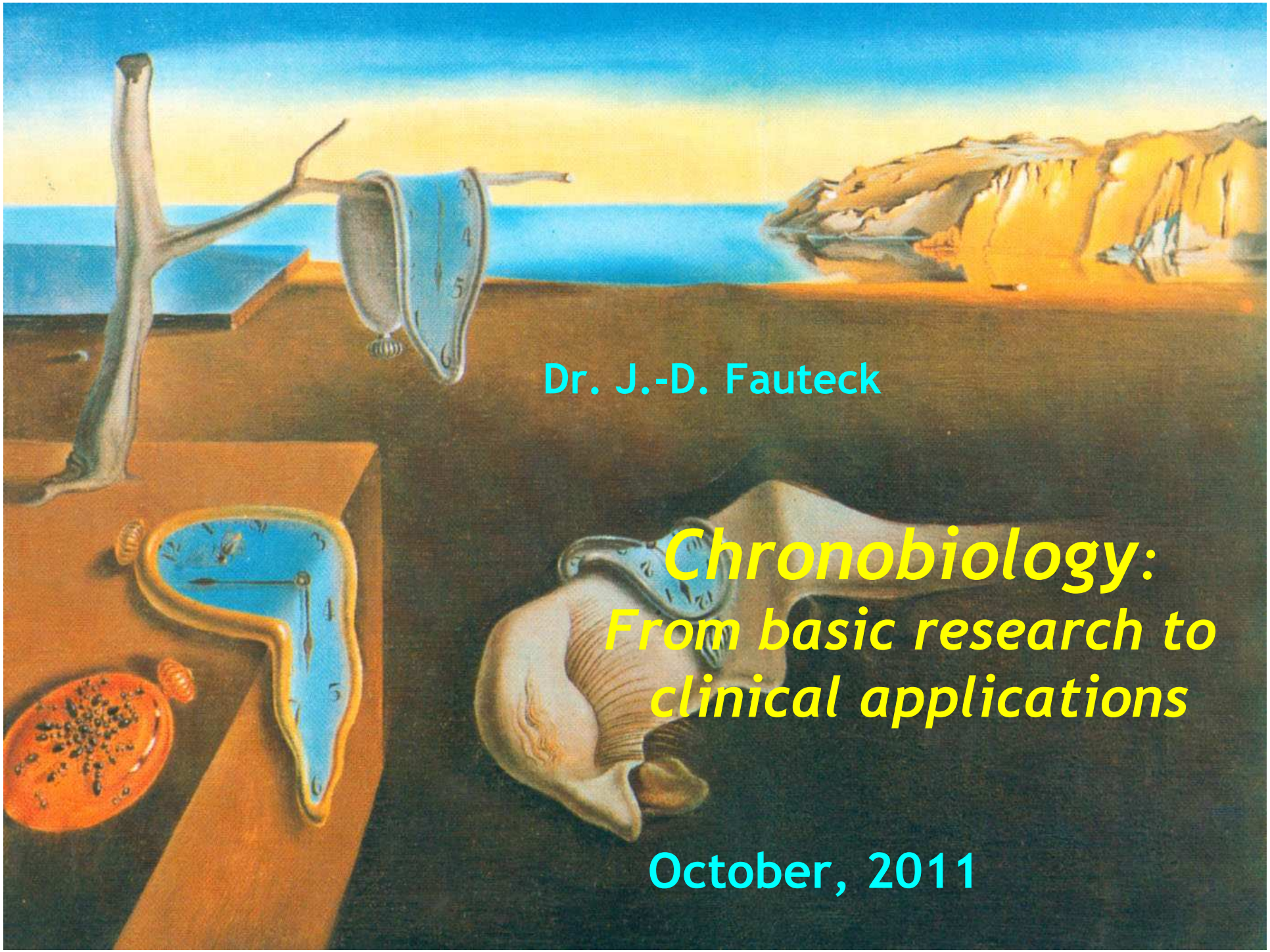
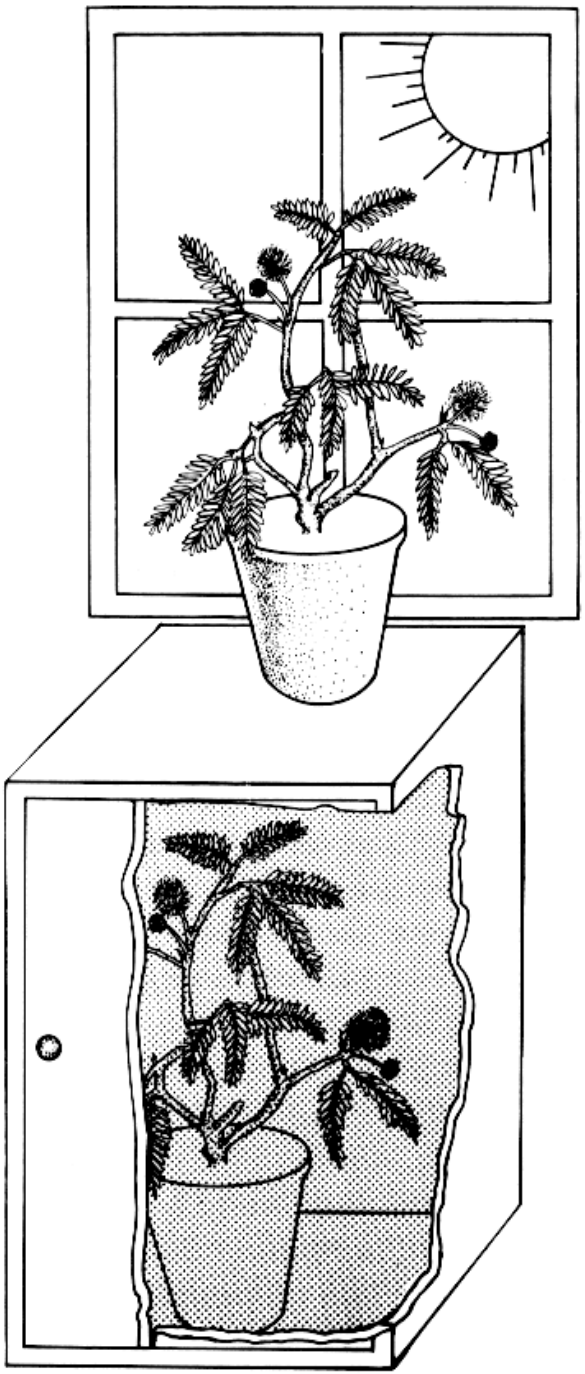
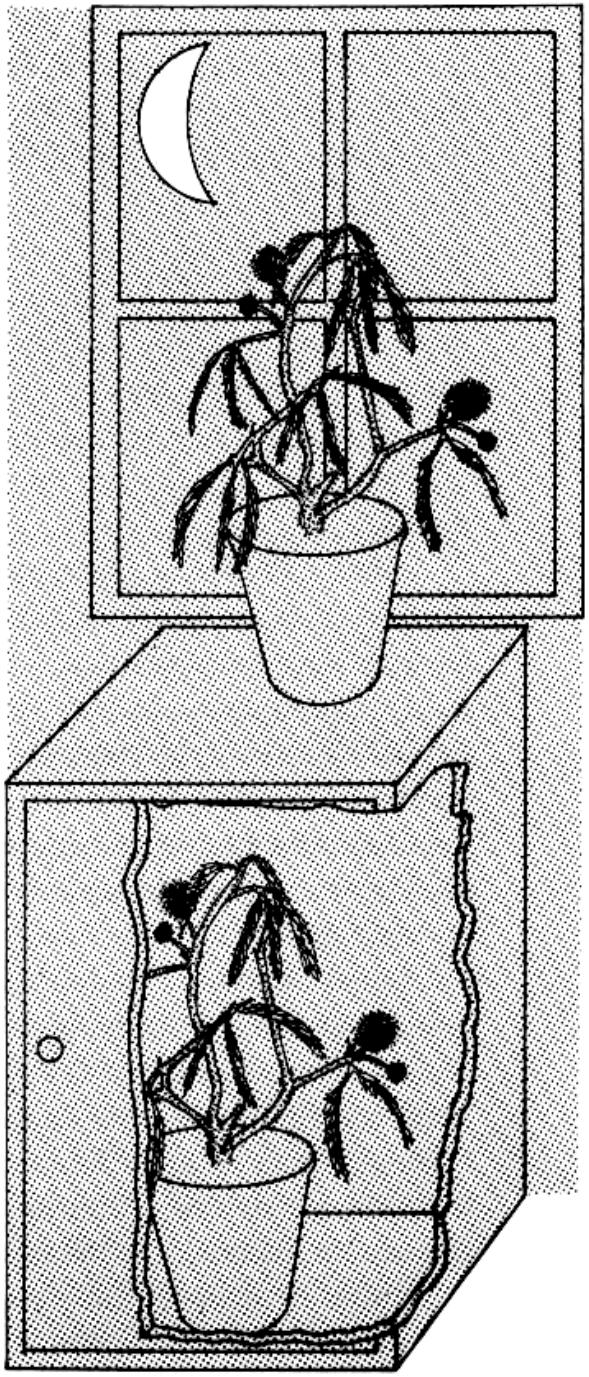

Dr. J.-D. Fauteck
Chronobiology:
From basic research to clinical applications
October, 2011



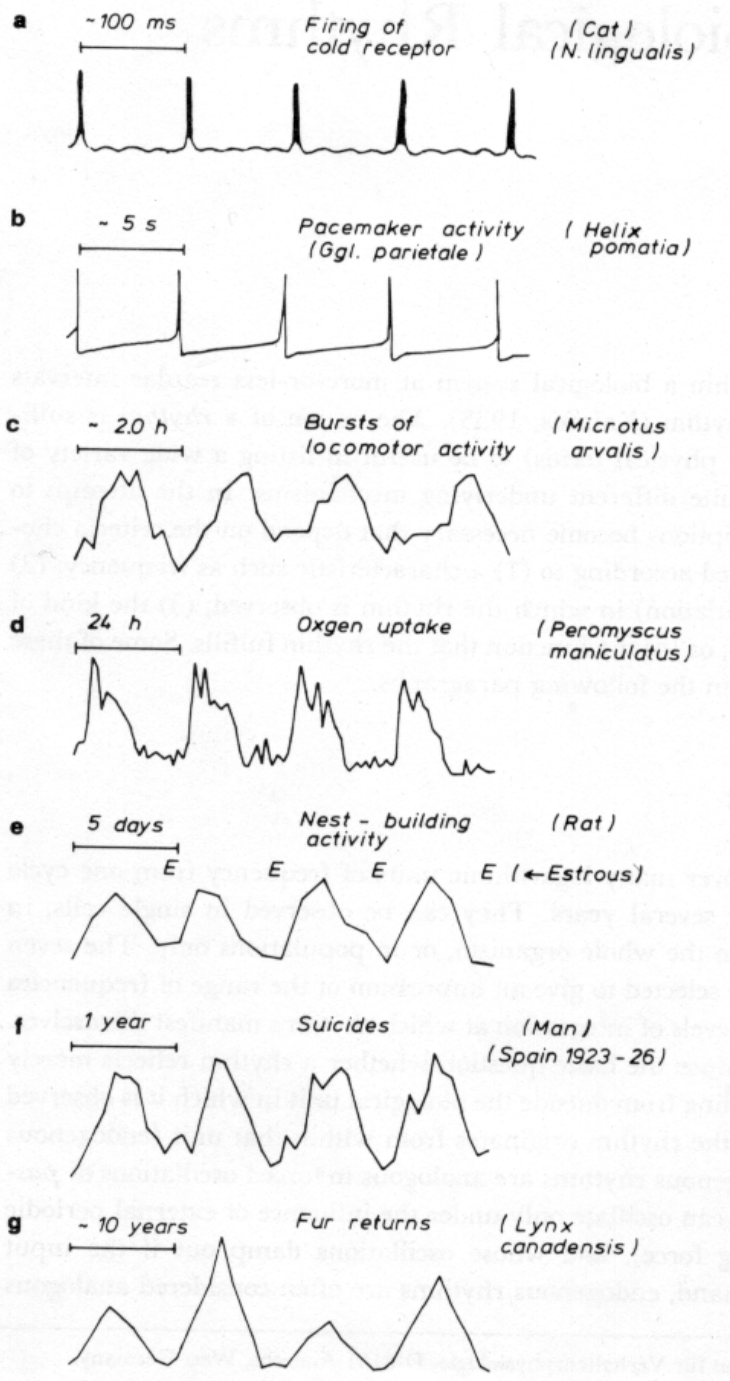


First evidence of an Endogenous, Circadian Rhythm

J.J. de Mairen' 1729
Conducted the first such 'temporal isolation' experiment, using the prayer plant.

Biological rhythms

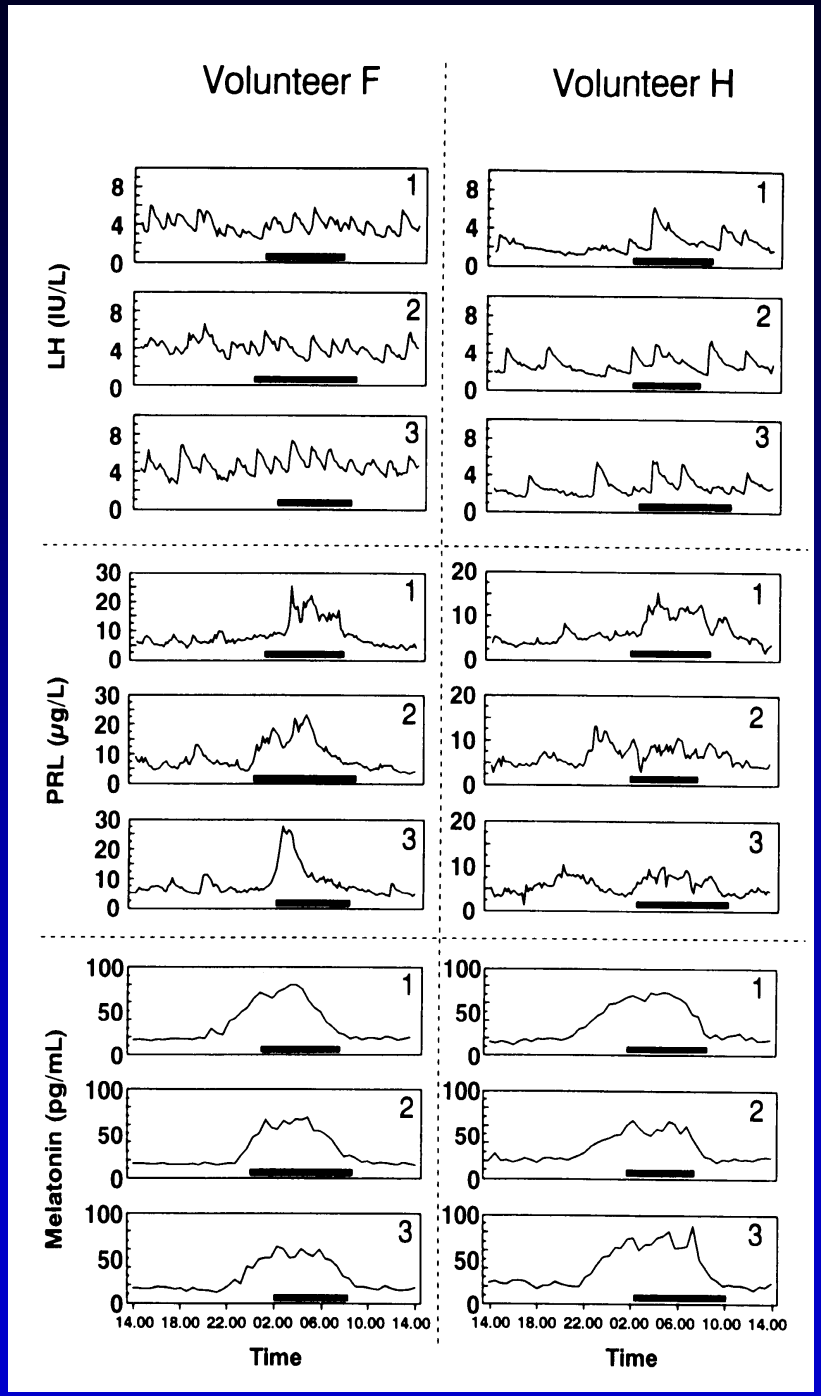
- Each repeating biological process automatically creates a biological rhythm by itself



e.g. endocrine rhythm:
LH, PRL, Melatonin

physiologically important

but individually



Lerchl et al., 1995

Which parameter is constant during 24 h?

- Temperature
- BP, HF
- Blood concentration, cell number
- Vigilance
- Body weight, body height
- Size of shoe
- etc ....

Classification of Biorhythm

- Ultradian (<< 24h)
- **Diurnal (24 h)**
- Infradian (>>24 h)
- **Annual (1 year)**

The four „Circa“-Rhythm

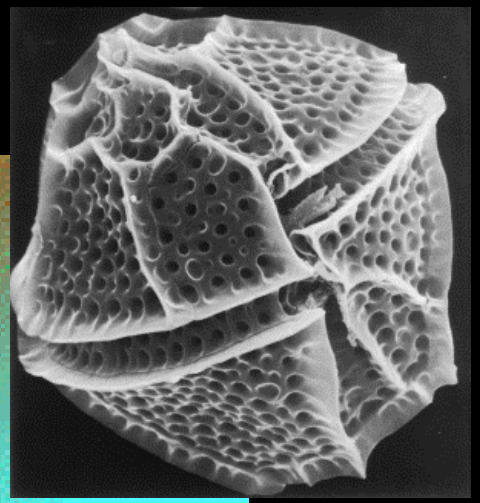
- **Circadian ~24 h**
- Circatidal ~12.5 h
- Circalunar ~30 days
- **Circannual ~one year**

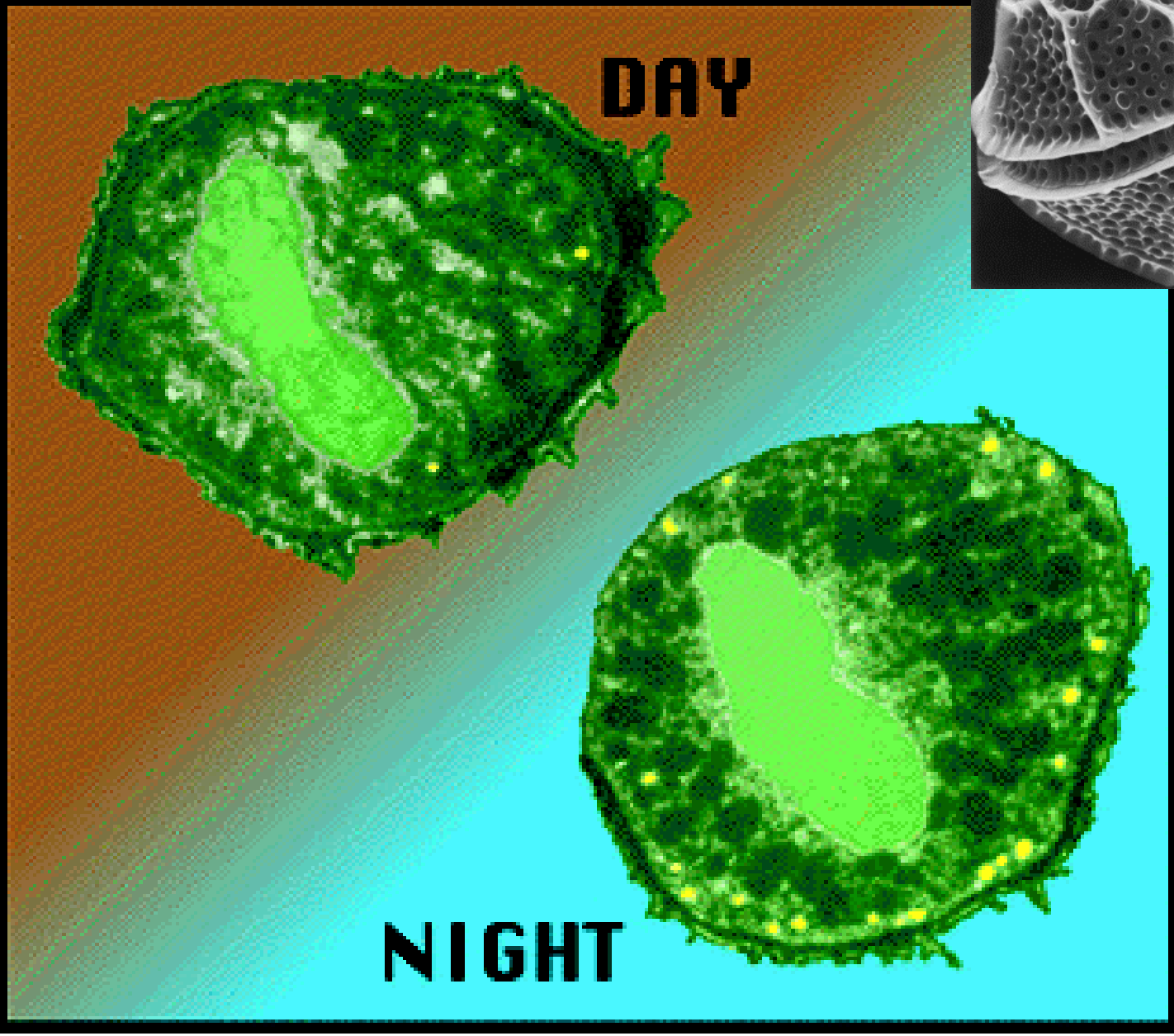
Note: The heading could be:
Is there any constancy within our life?

Biorhythm – where they are coming from?

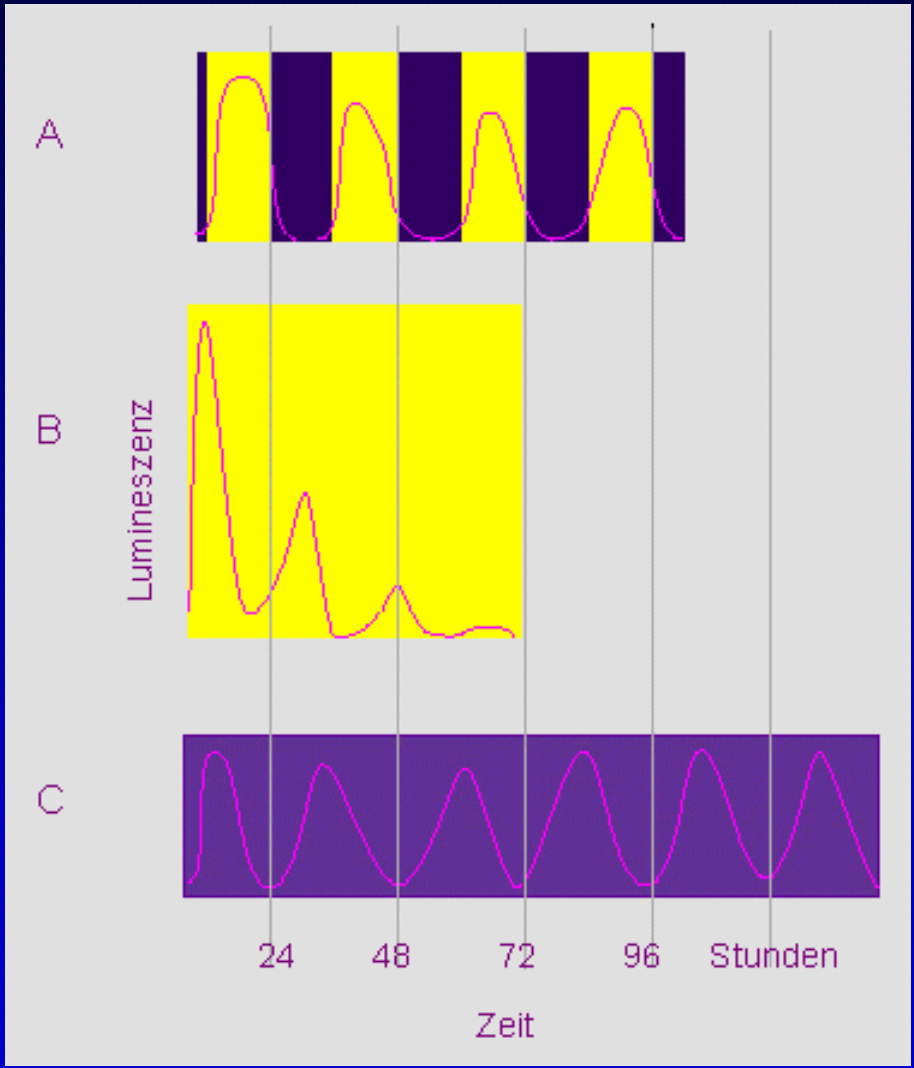
- Multi-celluar eukaryotic organism - yes
  - (z. B. Drosophila, Maus, Human)
- Single-cellular eukaryotic organism - yes
  - (z. B. Green algea (Chlamydomonas))
- Prokaryotic organism - yes
  - (z.B. blue-green Algea (Cyanobakteria)
- **Note:**
  - Circadiane clocks are age-old systems of the evolution and probably of the same age of life itself. Disruptions within this system might be followed by severe consequences for life.

Gonyaulax polyedra





Gonyaulax polyedra



12/12 L/D

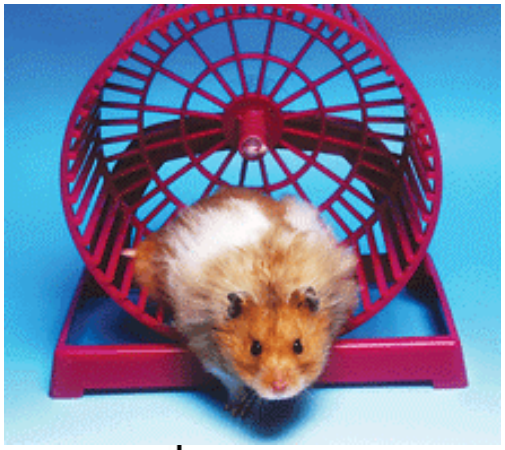
24/0 L/D

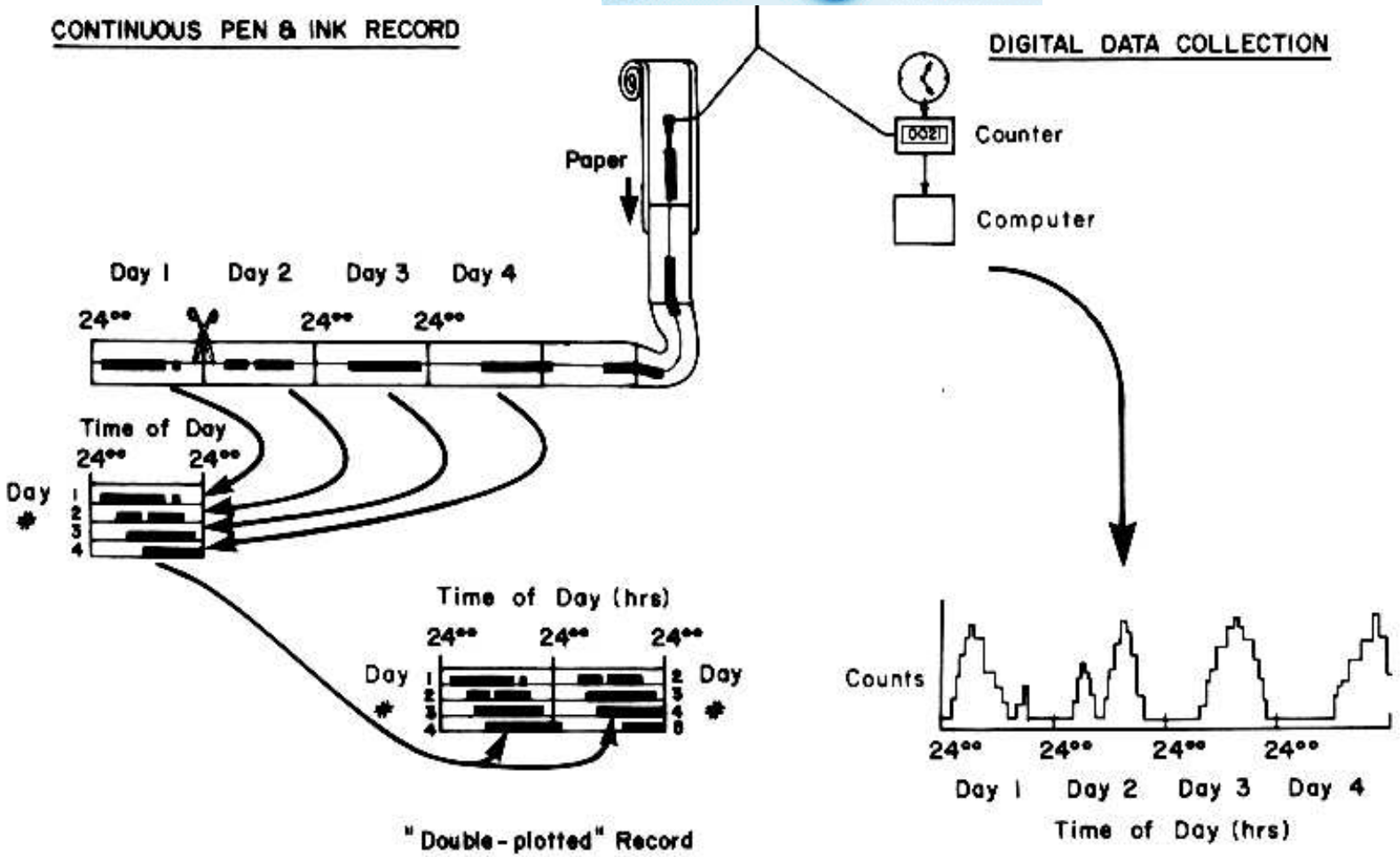
0/24 L/D

Prof. Dr. med. Jürgen Aschoff

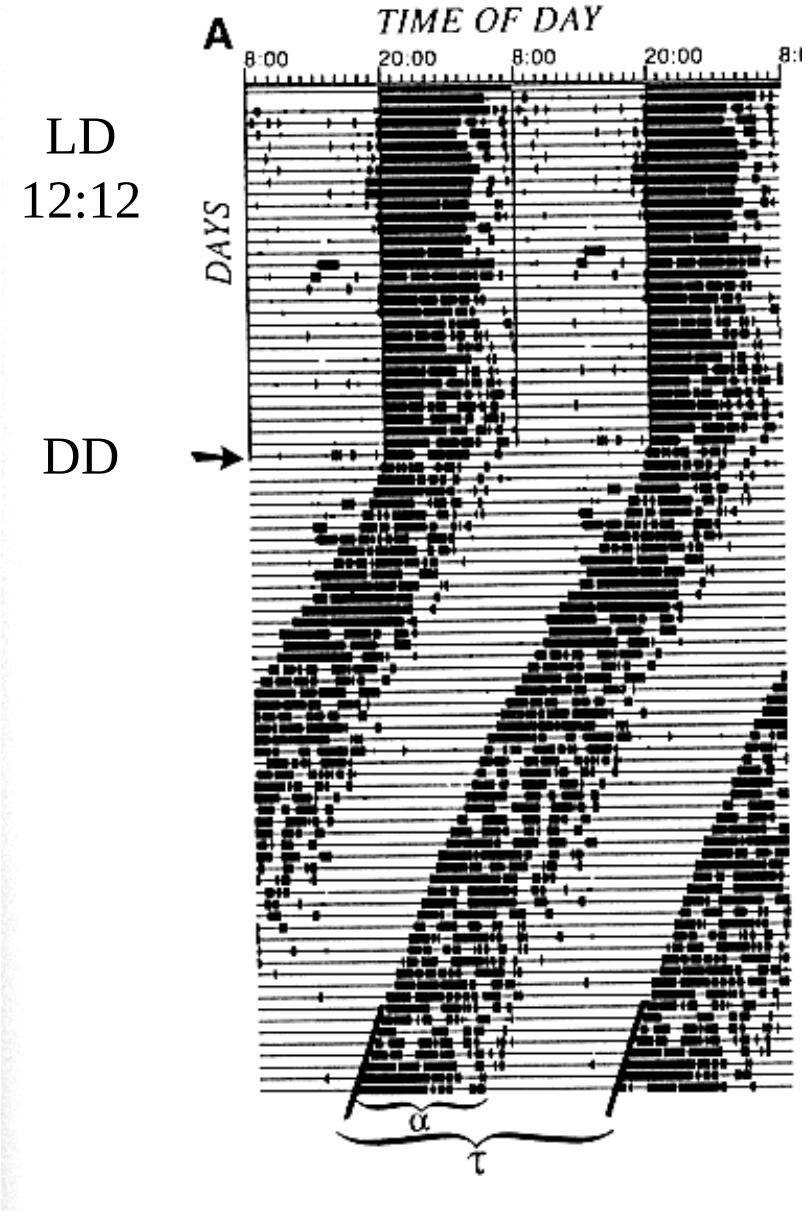
1913 - 1998

Registration of rhythm in rodents





Free-running rhytm (e.g. blind person!)



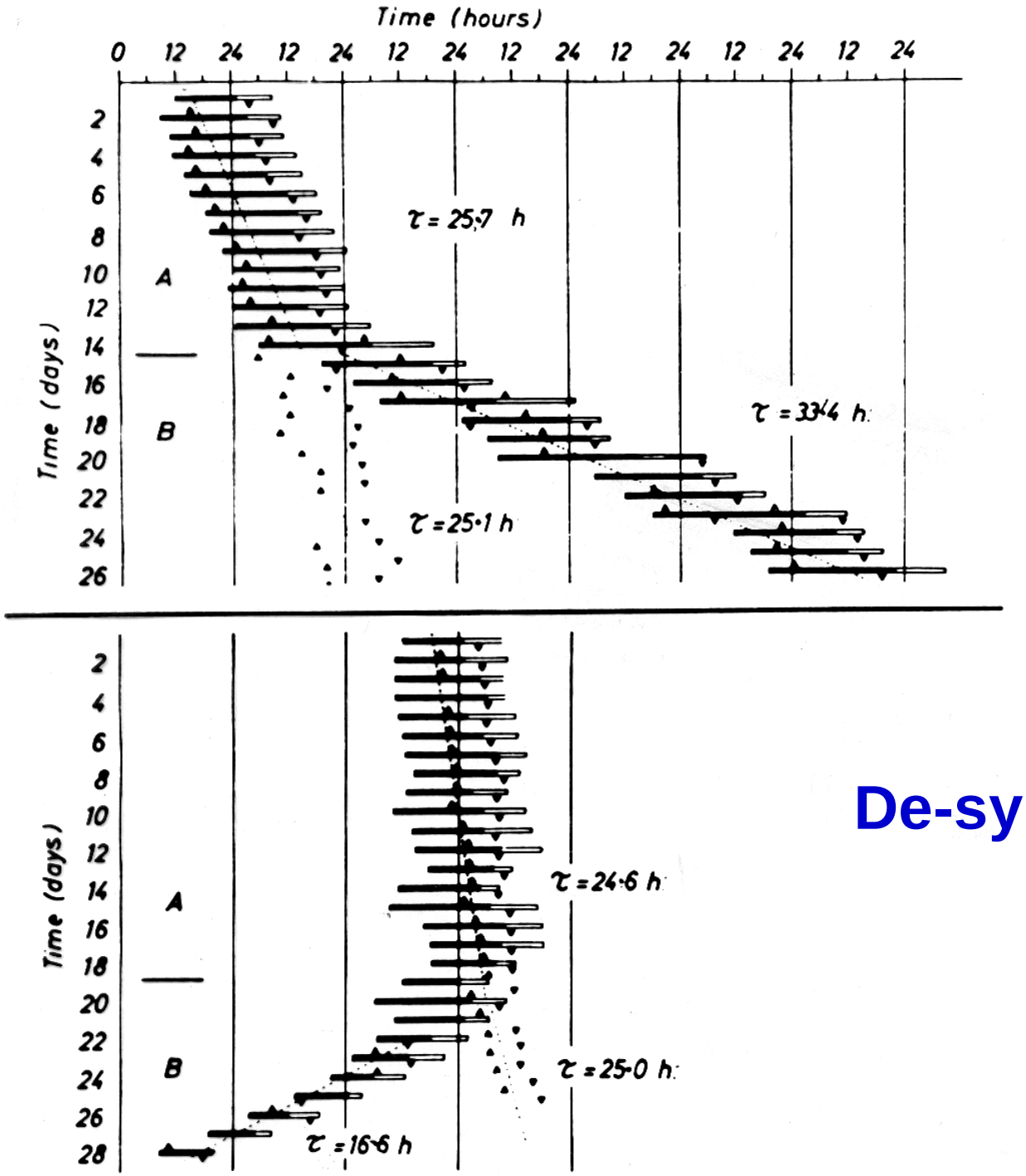
<u>Parameter:</u>

Periode (tau, ‘τ’)

Phase (phi, ‘ϕ’)

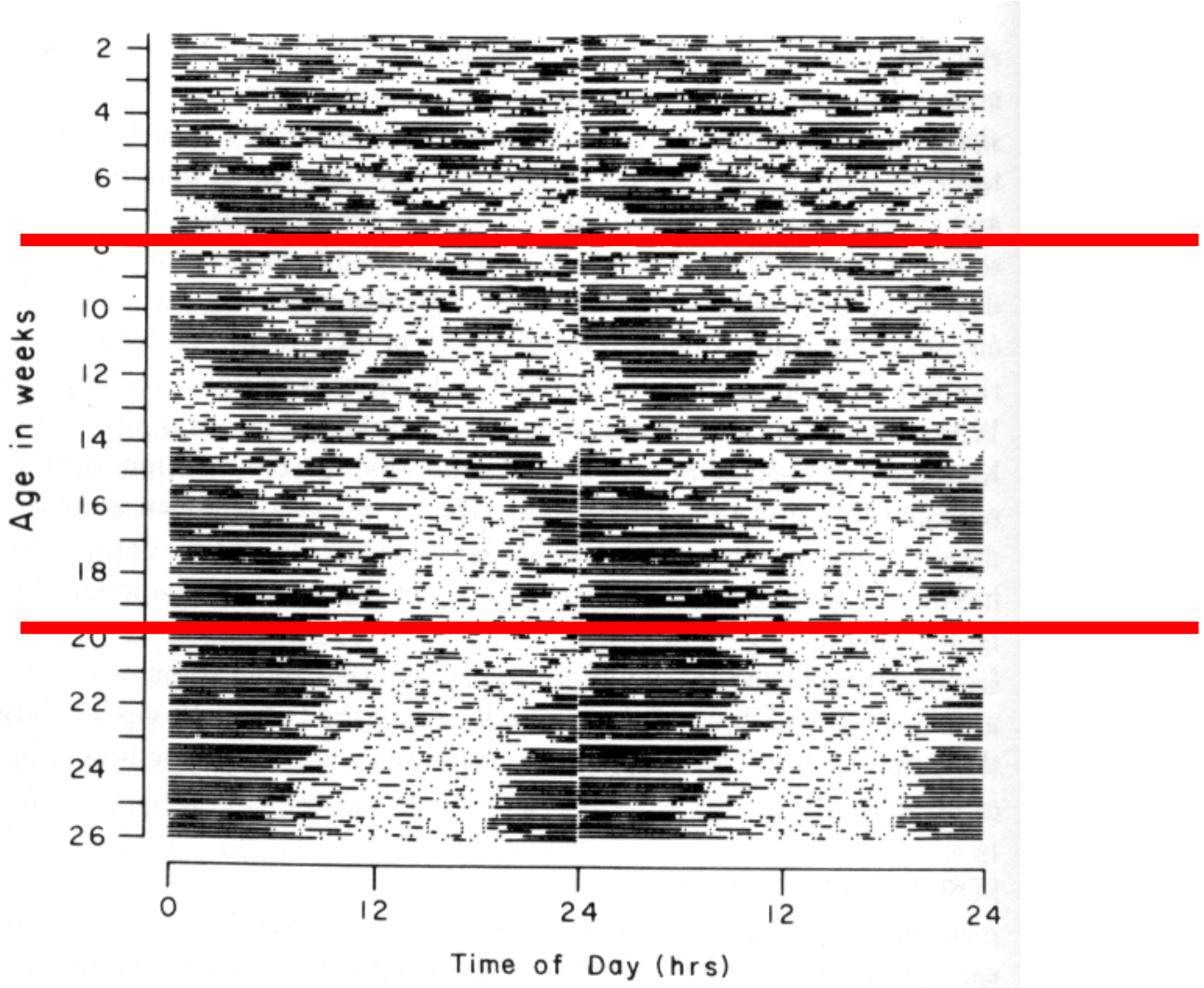
Subjektiver Tag (‘α’)

Subjektive Nacht (‘ρ’)

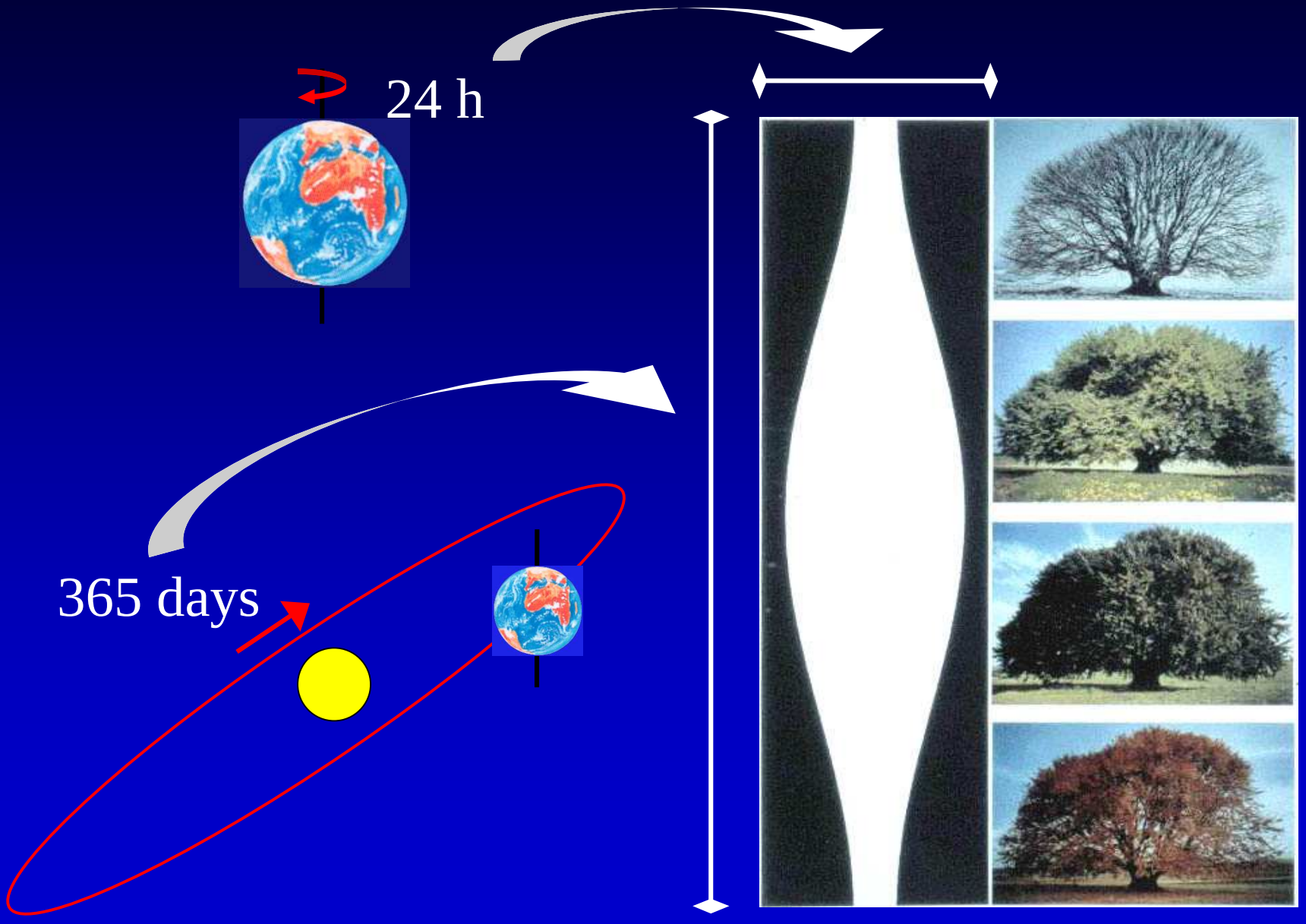


Internal De-synchronisation

Ontogeny of rhythm
(human: sleep/wake pattern)



Astronomic „Zeitgeber”



Synchronisation of rhythm

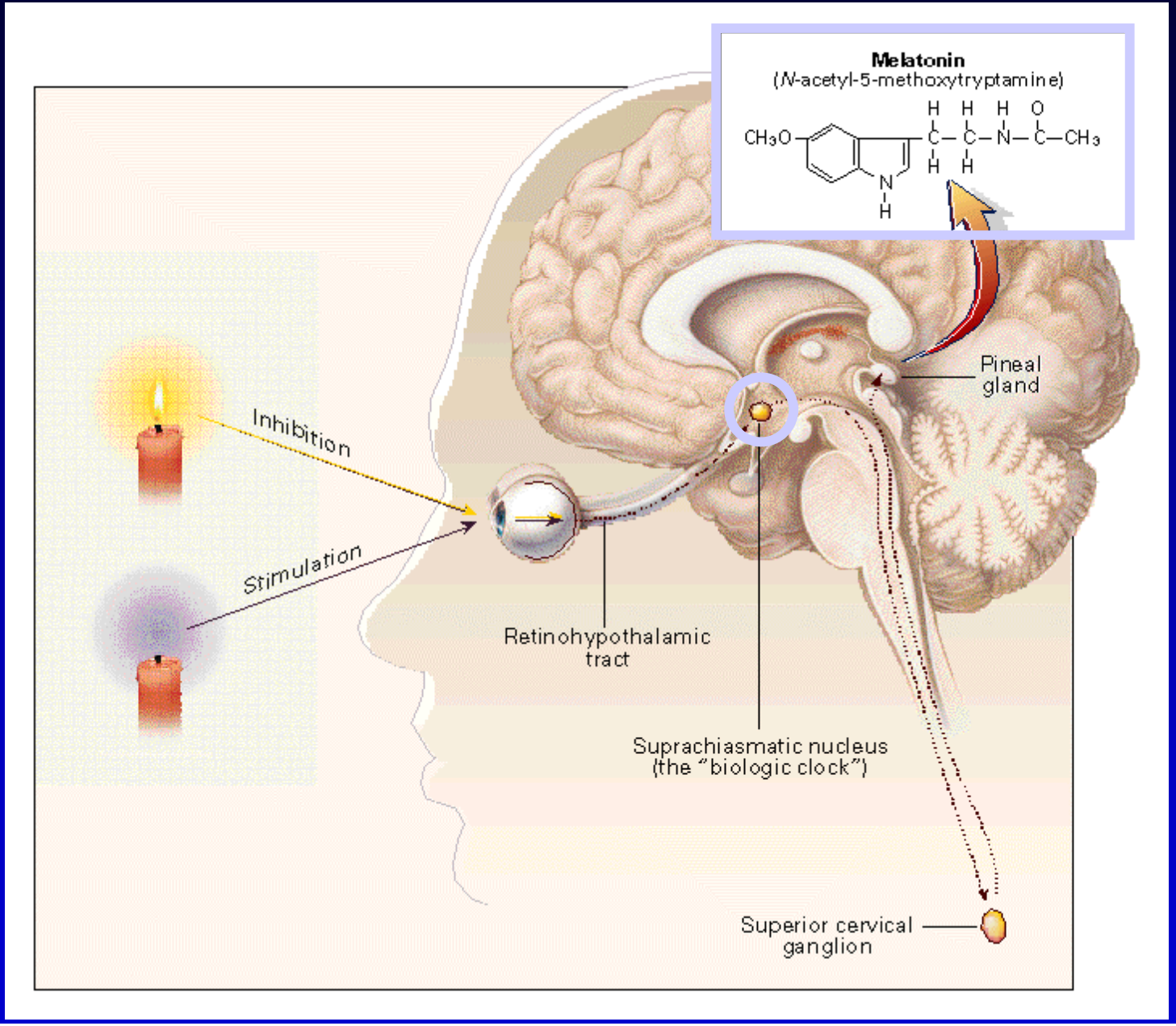
Central pace maker
(Master Clock)

Rhythmical Input

Rhythmical Output

("Zeitgeber")

Light and the „Internal clock“

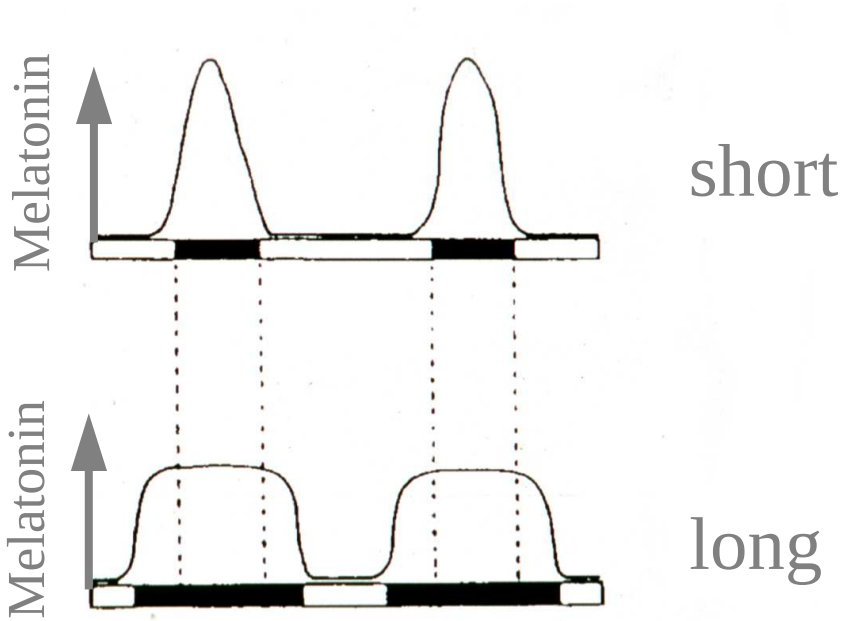


The duration of Melatonin secretion depends on **daytime and season**

Synthesis duration

Summer:
long days
short nights

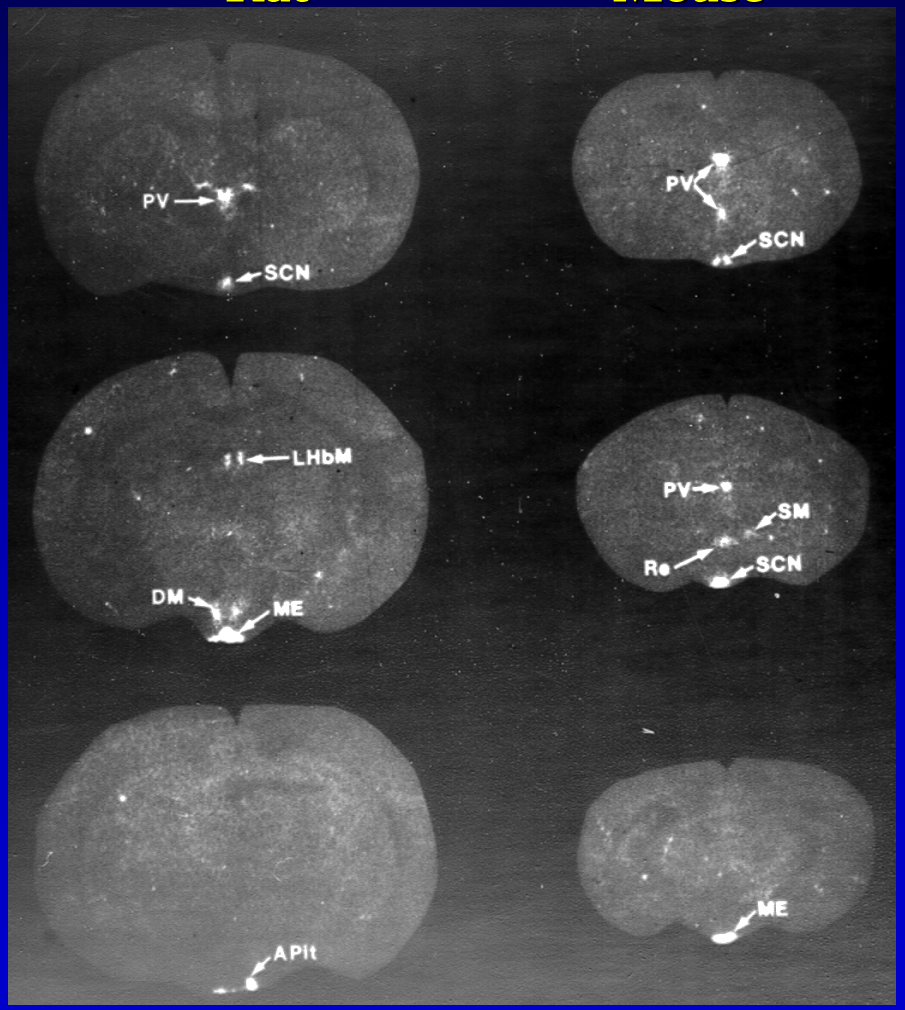
Winter:
short days
long nights



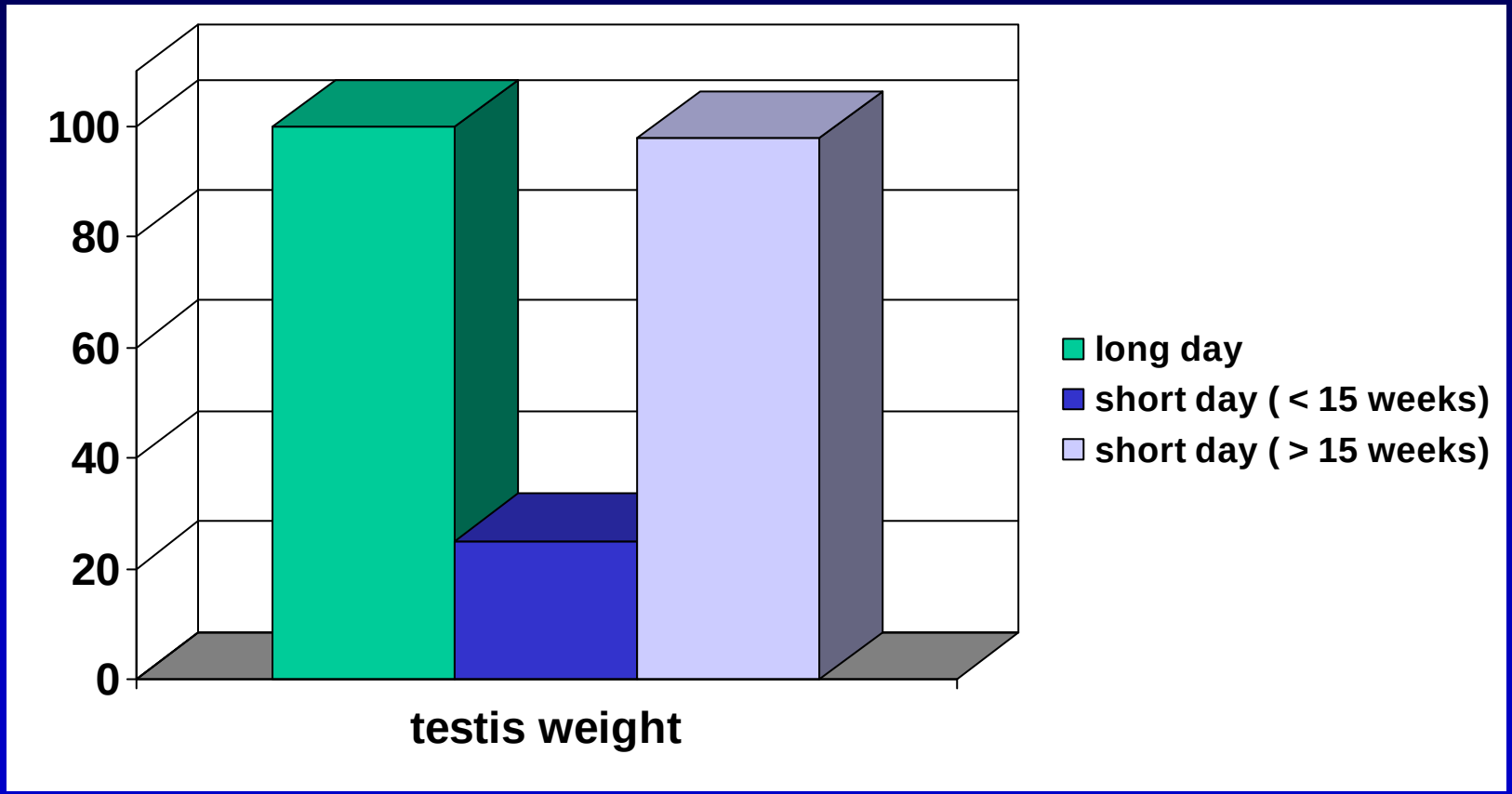
Arendt, 1995

Melatonin receptor in CNS of rodents (Reppert et at.)

Rat **Mouse**



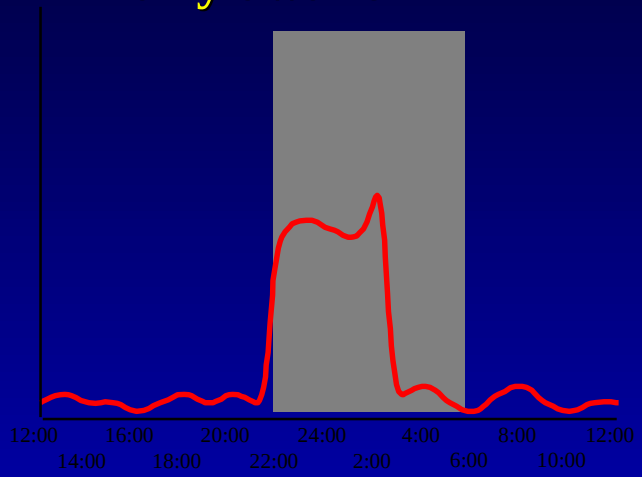
Melatonin and reproduction (hamster)



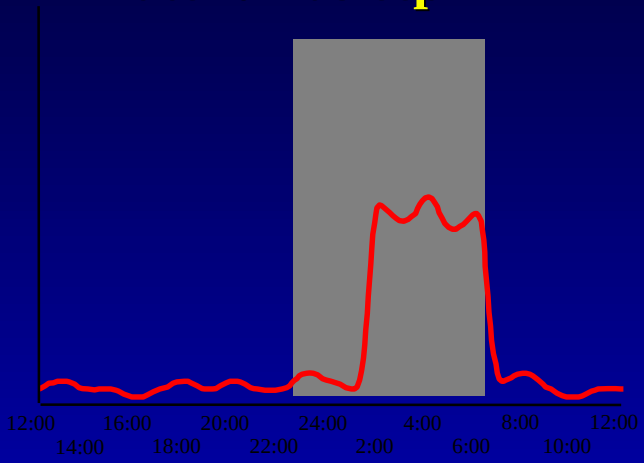
Melatonin deficits within humans

Melatonin deficits in correlation to sleep diseases

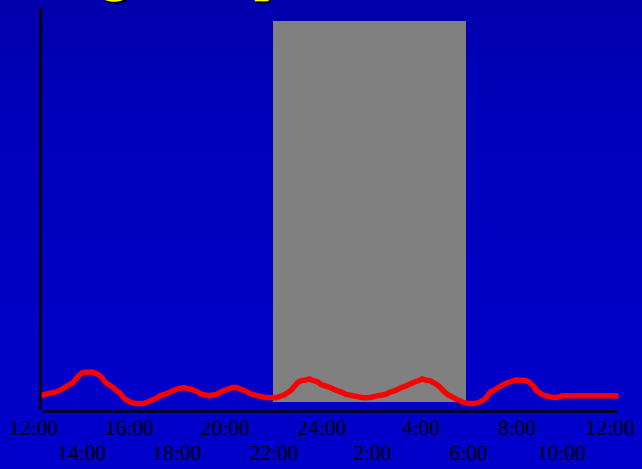
Early awake



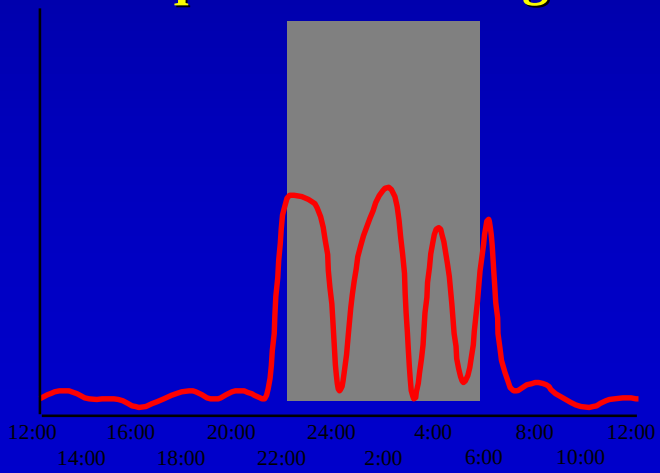
Late full asleep



High sleep disorders

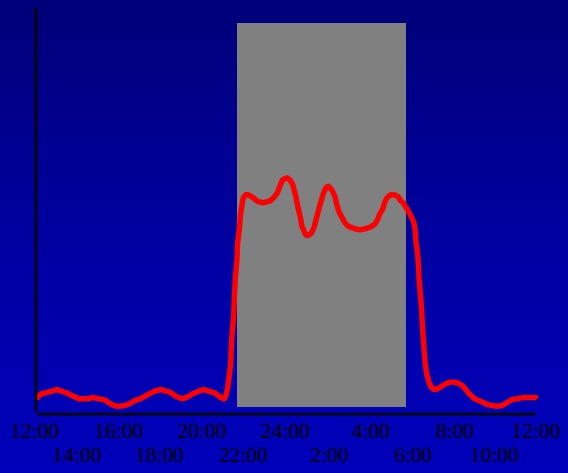


Frequent awakenings

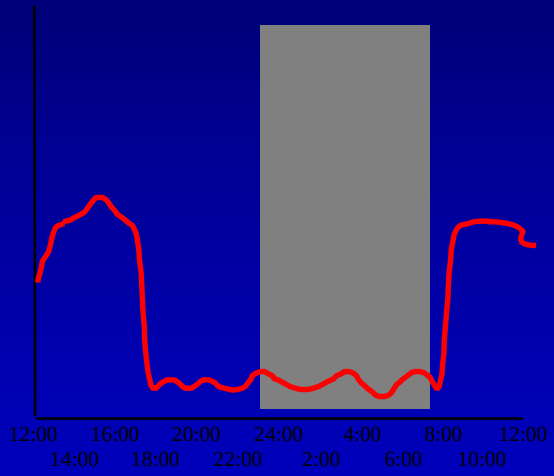


Melatonin rhythm disorders

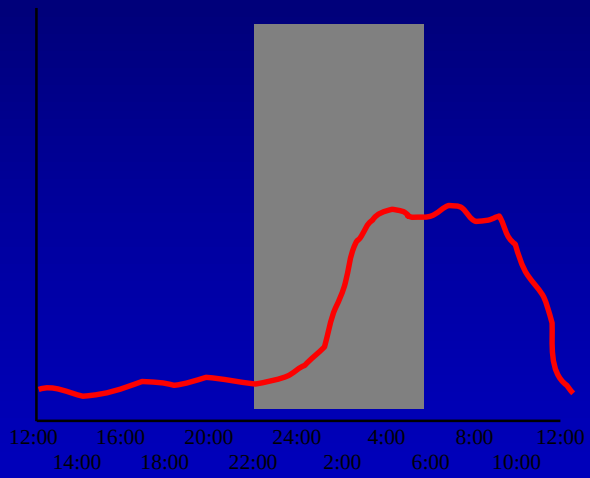
Normal Rhythm



Free Rhythm (blind persons; jet lag)



Delayed Rhythm (DSOS; Winter depression)



Chronoceuticals
vs.
Hormone replacement

Crucial considerations within Chronopharmacology:

1. Drugs with specific kinetiks
2. Drugs given at specific time points
3. Drug interaction when given in combination
4. Drugs given for different time periods
5. Drugs interacting the internal clock

Drug delivery systems (solid oral forms):

1.) fast release form
- fasting-postprandial status
- acid resistant
- bioavailability of the active ingredient
- induction of metabolism
- gen polymorphism

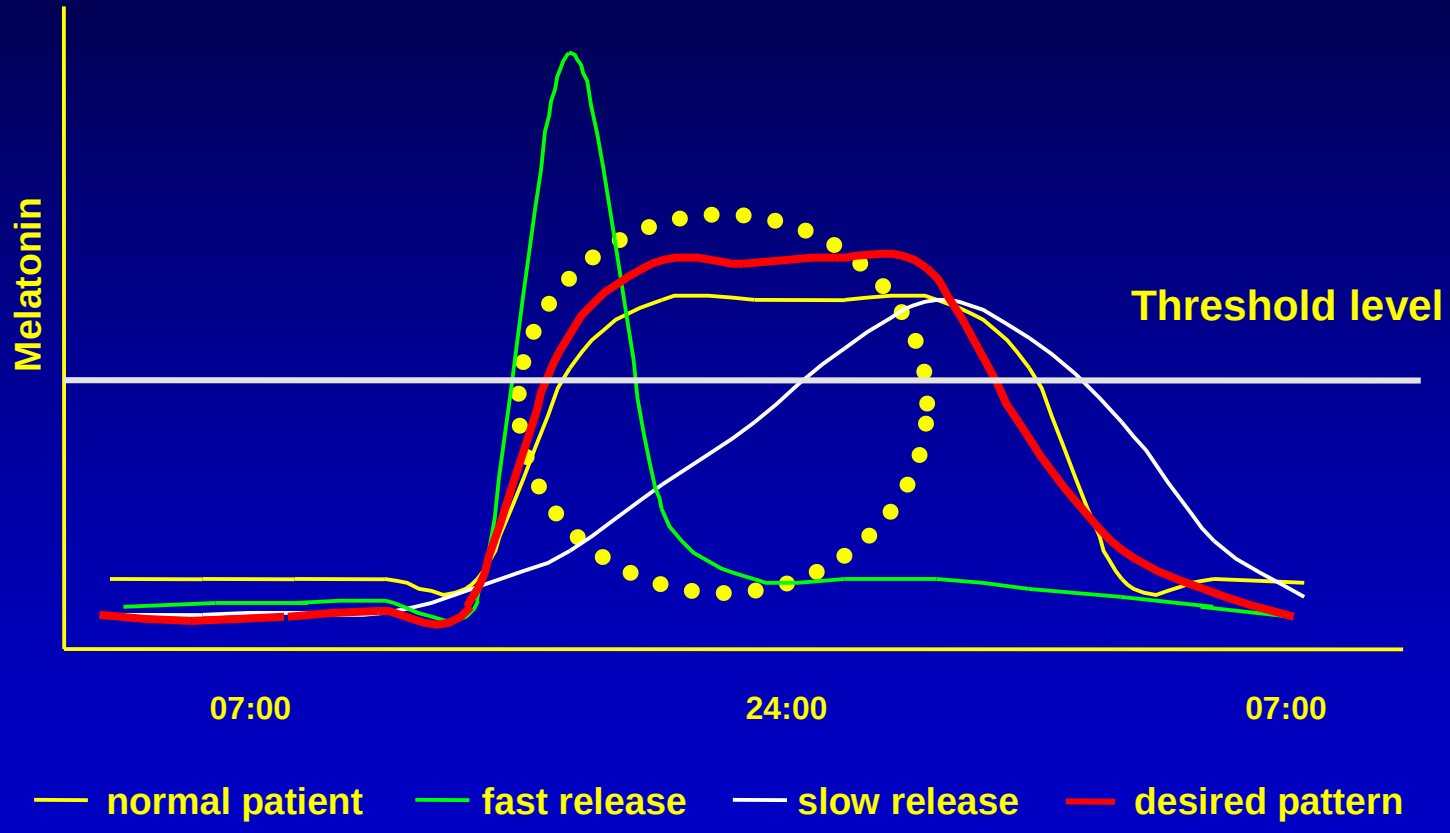
2.) slow release form
- delayed release
- timed release
- pulsatile release

Slow release preparations:

Melatonin:

Pharmacological analysis of different galenic preparations sold over the counter

THEORETICAL TREATMENT

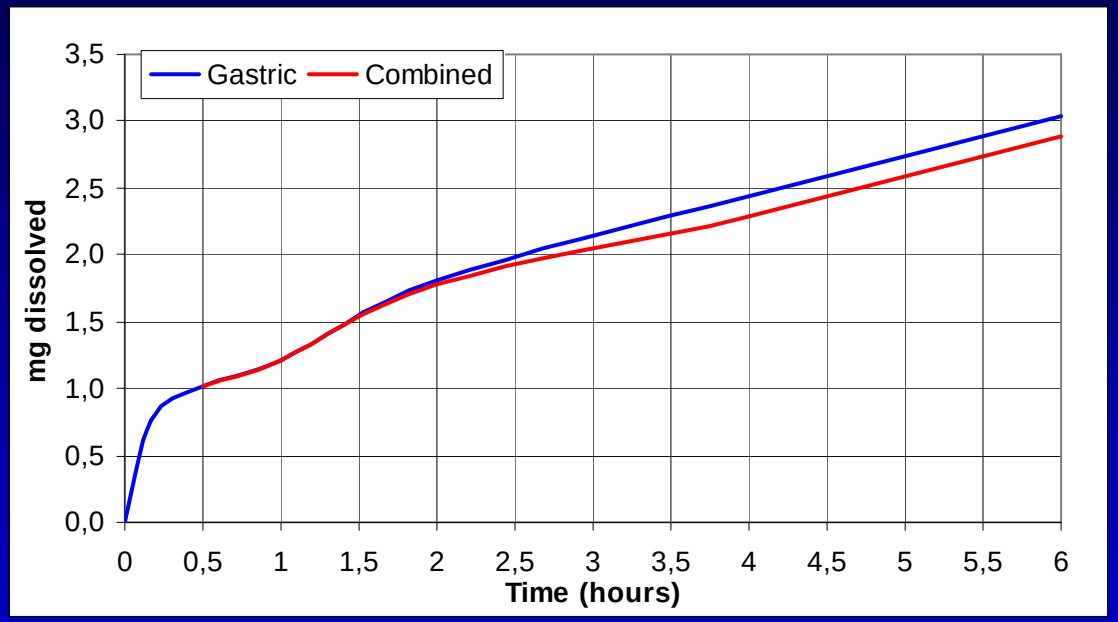


Commune characteristics of all formulations:

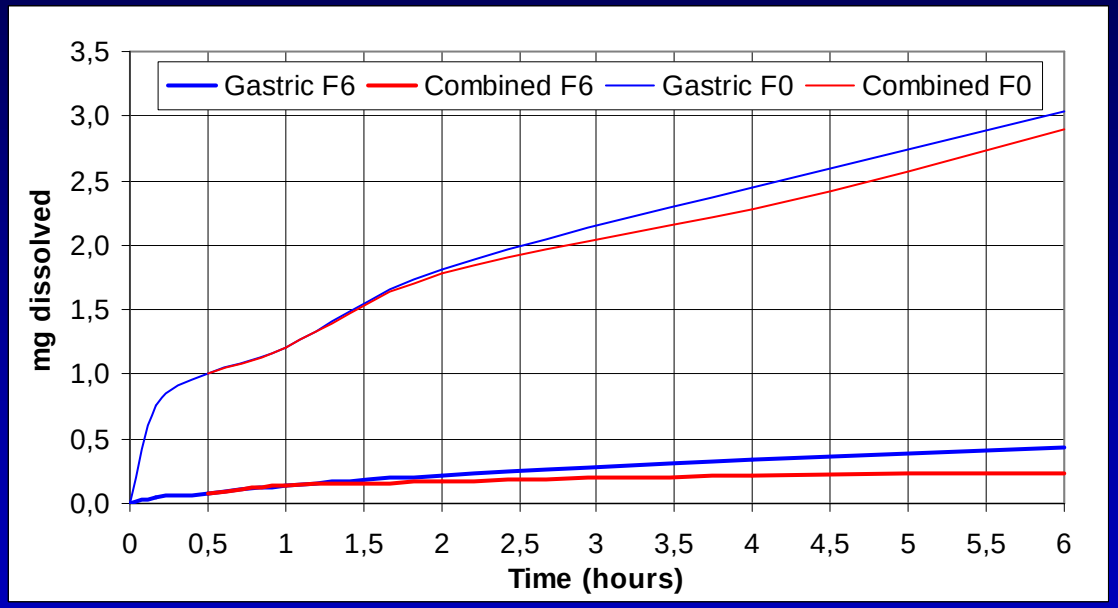
Oral preparations
2-3 mg Melatonin as active ingrediant
EC10 as retard additive
Indication:

- late sleep onset
- early awakening
- frequent awakening

“*CHRONOBIOTIC*” MELATONIN (F0).



"*CHRONOBIOTIC*" MELATONIN (F0) vs "*SUSTAINED RELEASE*"(F6).



Conclusion:

Slow dose not mean always slow!!!

It depends often on additives, which might influence the disolution and therefore the bioavailibility of active ingrediants.

Note:
OTC are frequently different concerning their additives and therefore not equally potent.

Melatonin as „Zeitgeber“ within the endocrine system

Hormonal rhythm in blind people without treatment

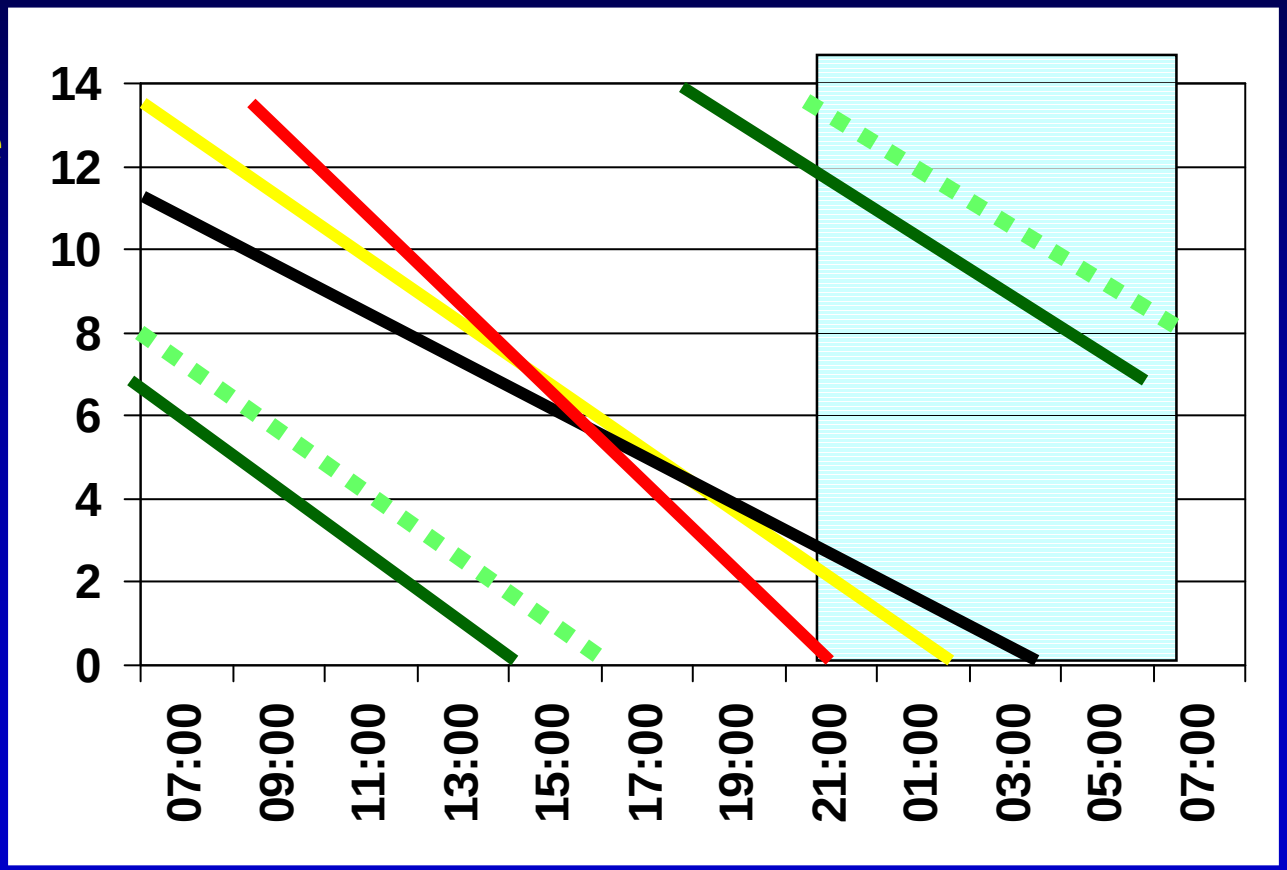
Testosterone

DHEA

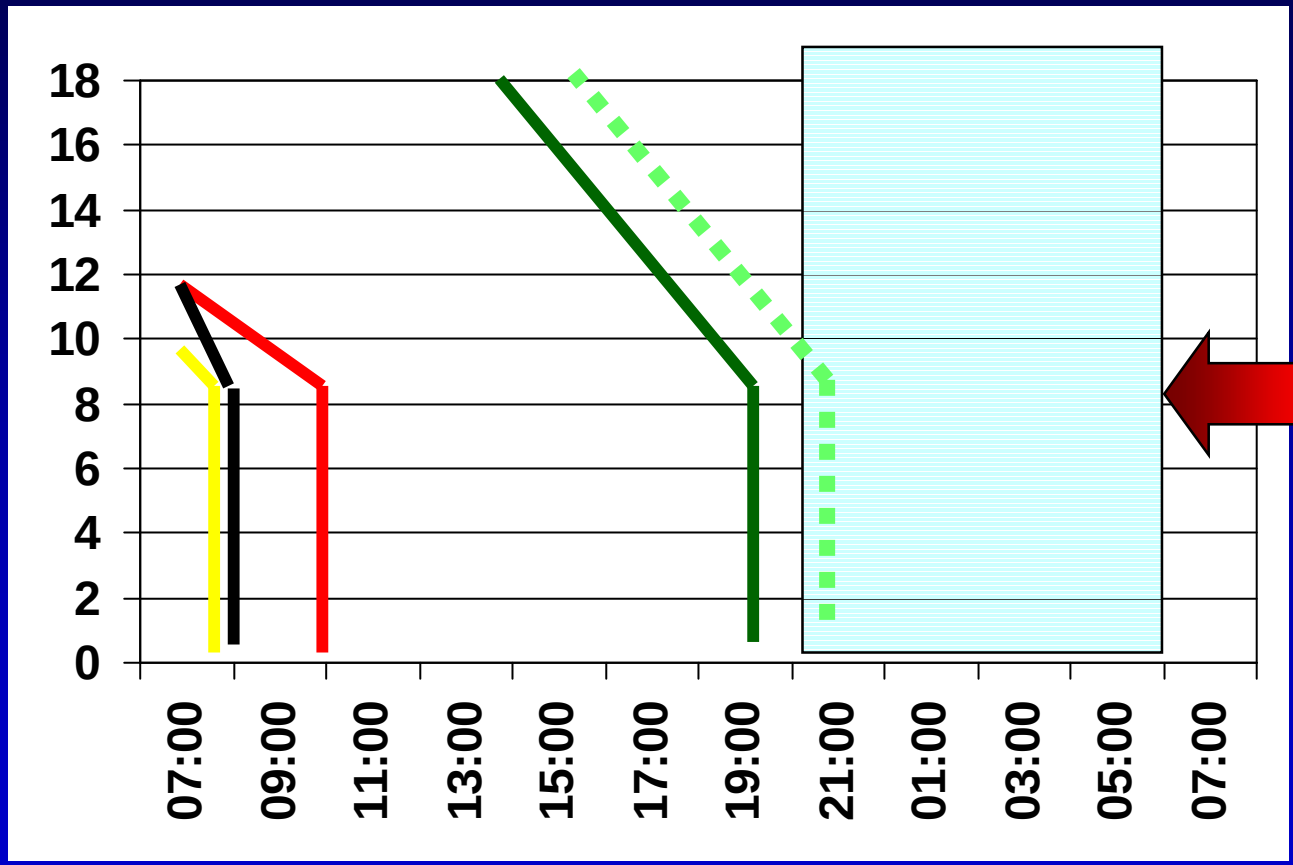
Cortison

GnRH

Melatonin

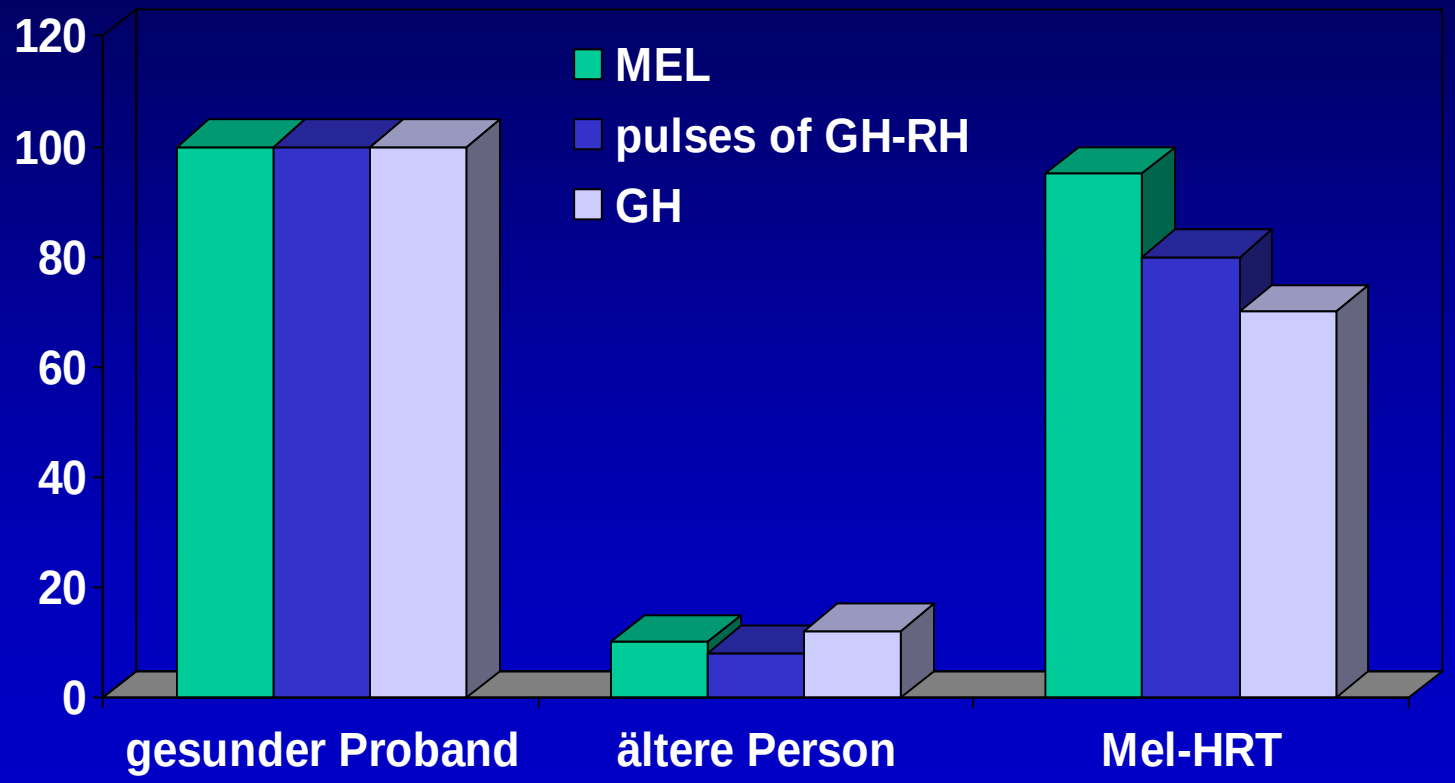


Hormonal rhythm in blind people after treatment



Melatonin‘s effects on other systems: e.g. GH

Melatonin's effects on GH/GH-RH release in elderly people (Lewy et al. 2005)



- Is there any correlation between circadian rhythms and alimentation?

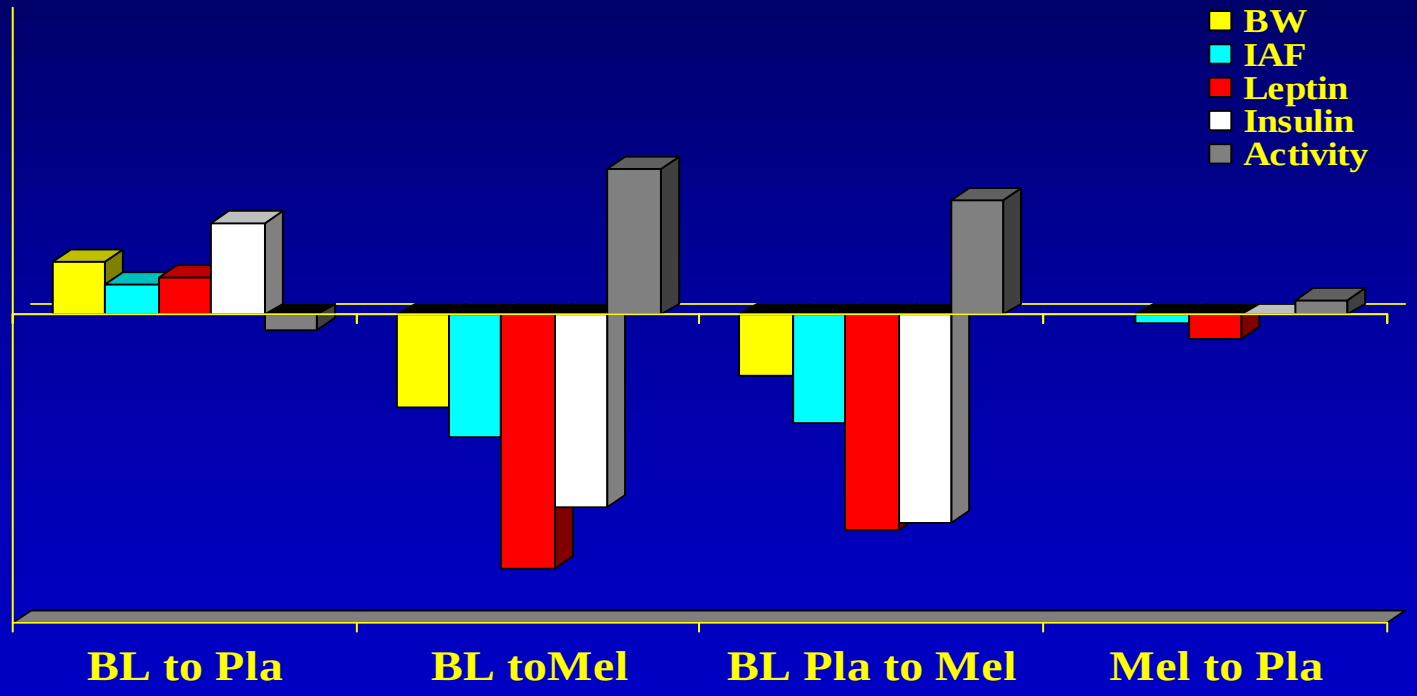
Insulin and circadian rhythm

Fat burning strategy: with 3 meals per day the insulin levels are stable and fat will be consumed

Fat pitfall: with 5 ore more meals per day the insulin levels are fluctulating often and fat will be stored

BW, intraadominal Fat, Leptin- and Insulin- serum levels after 3-week therapy with Melatonin in rats in cross-over

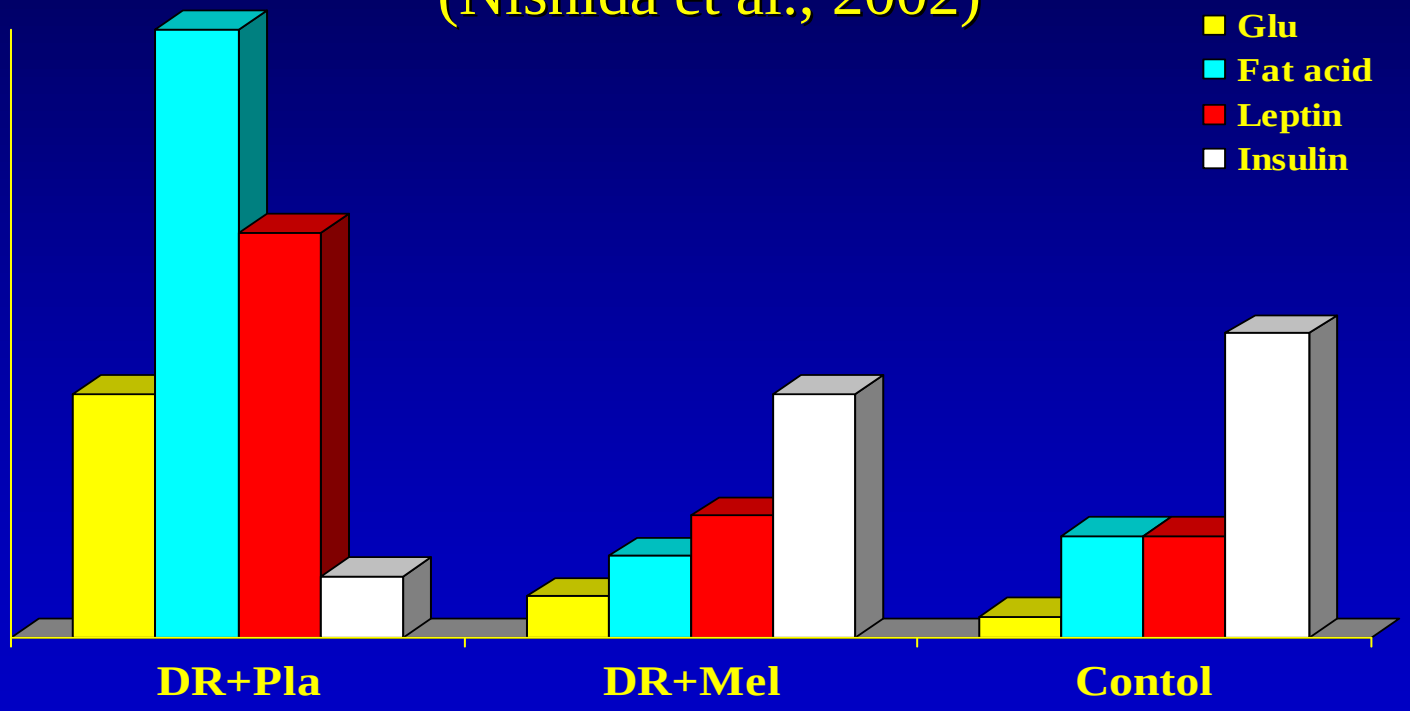
(Alter: middle-aged) (Wolden-Hanson et al.; 2000)



Note: Melatonin significantly influence the metabolism specially in aged rats

Glucose- ,Fat, Leptin- and Insulin- serum levels after 35-week therapy with Melatonin or Placebo in diabetic cats compared to normal rats

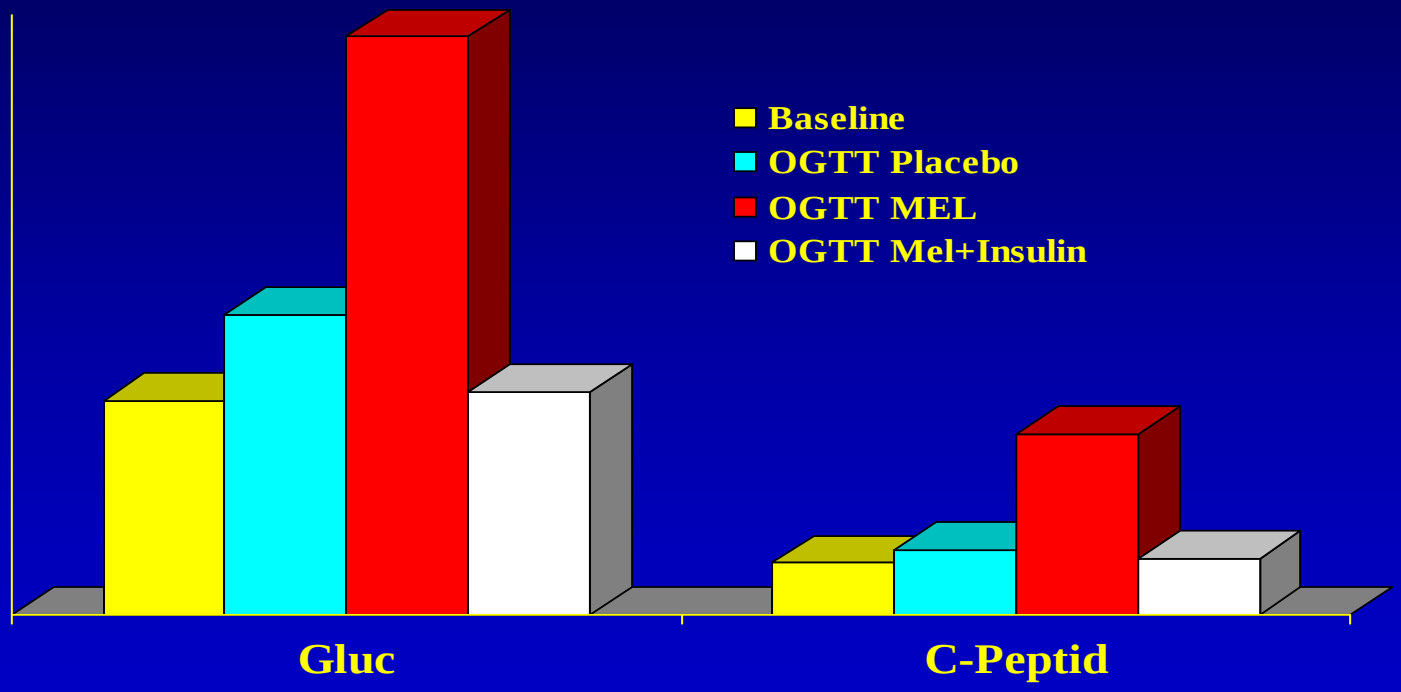
(Nishida et al.; 2002)



Note: Melatonin normalize the Methabolismus in aged diabetic rats

In-Vivo data concerning the relationship Melatonin – Insulin within humans

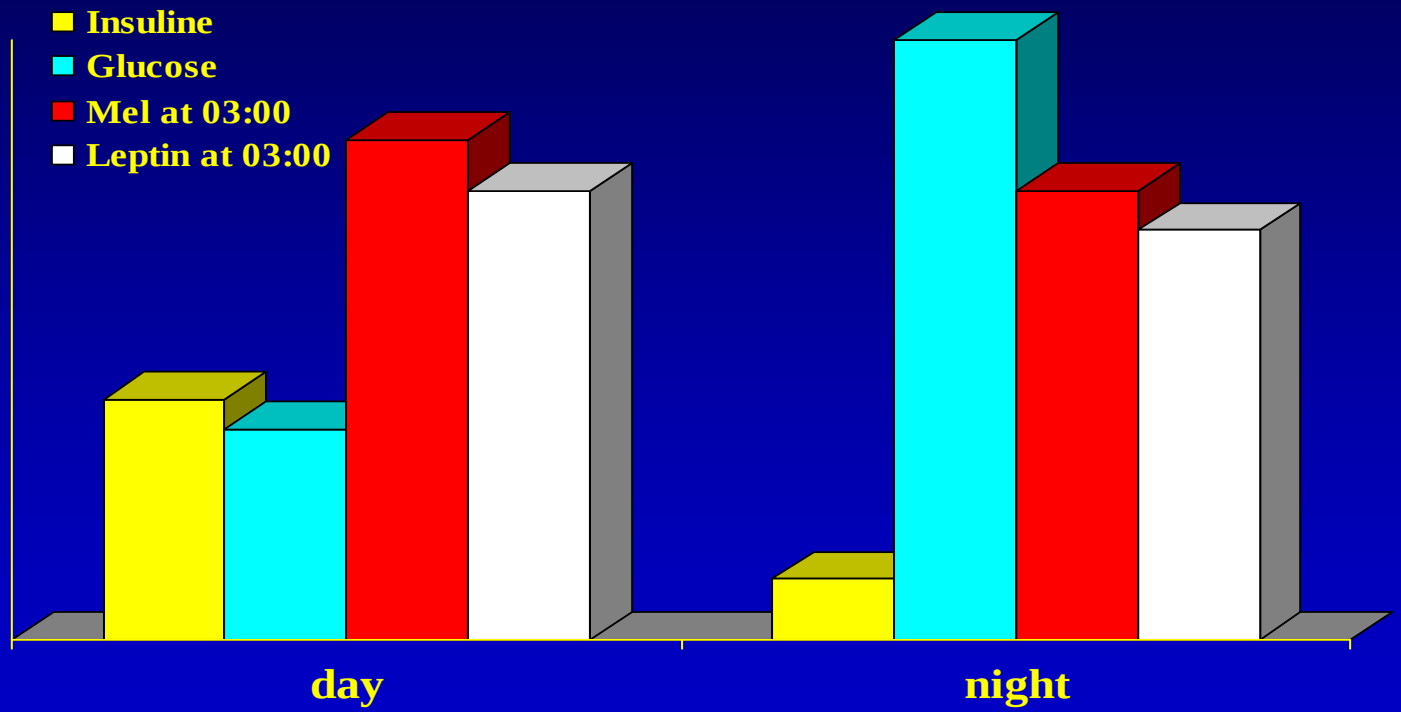
morning oral Glucose Toleranz Test if concurrently Placebo or Melatonin is given (Cagnacci et al. 2001)



Note: Melatonin rduces the oGTT and Insulin effect if given in the morning

Glucose and Insulin serum levels by s.c. „day-“ or „night-“ eaters

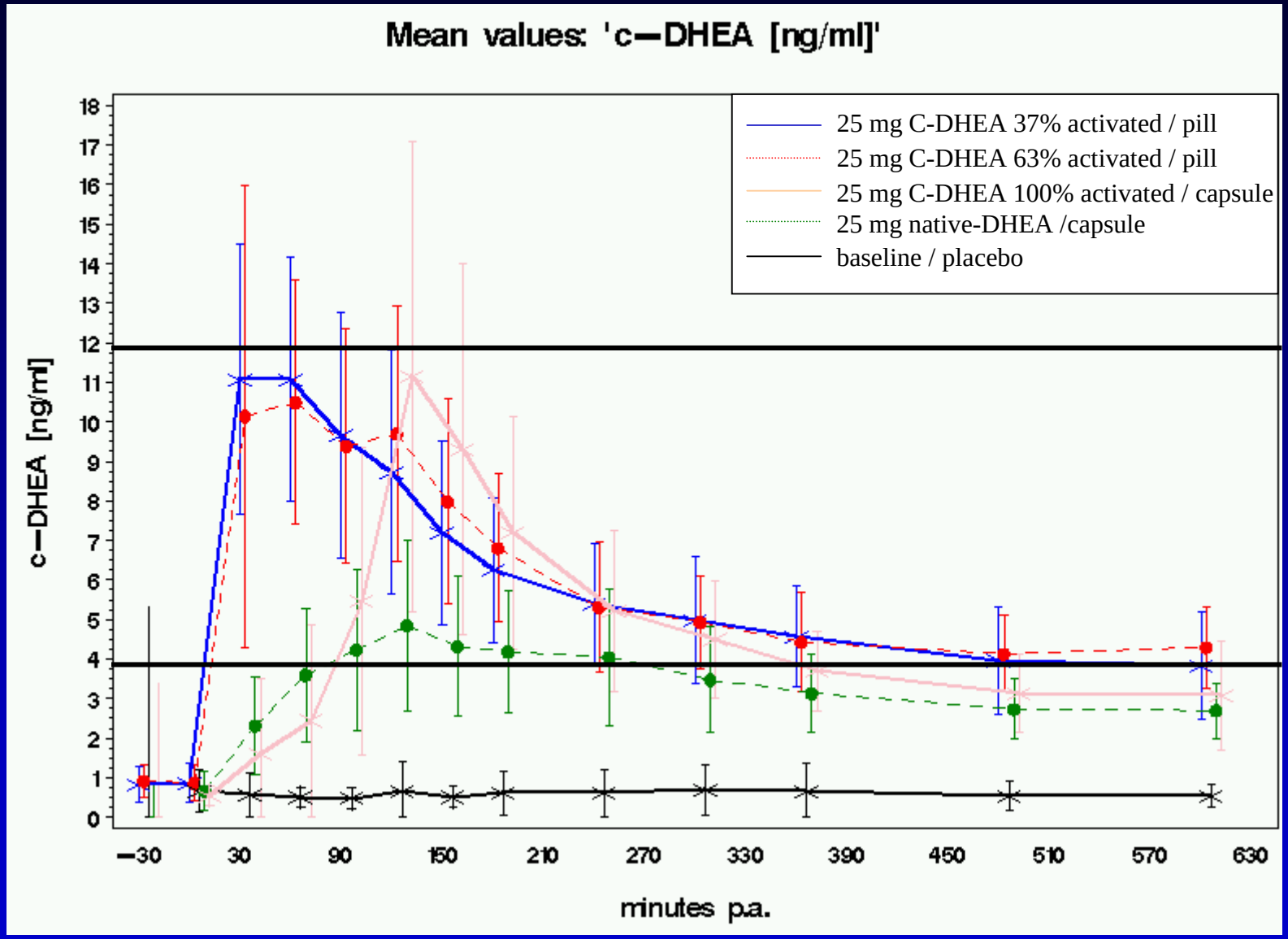
(sleep: 0:30 - 08:30)(Qin et al. 2003)

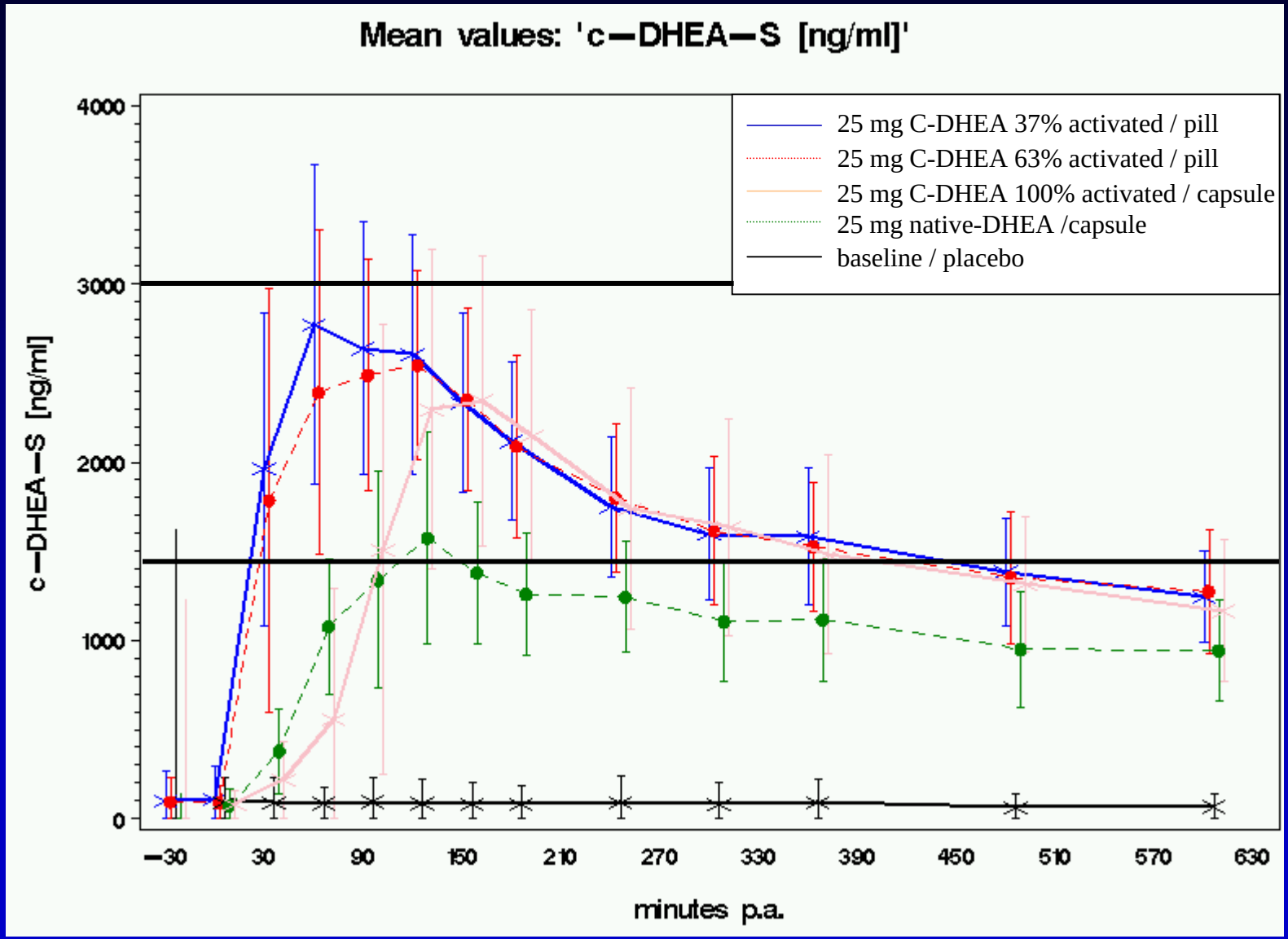


Note: night time Melatonin reduce the Insulin effect and enhaince therefor Glucose levels during night: Fat pitfall !!!

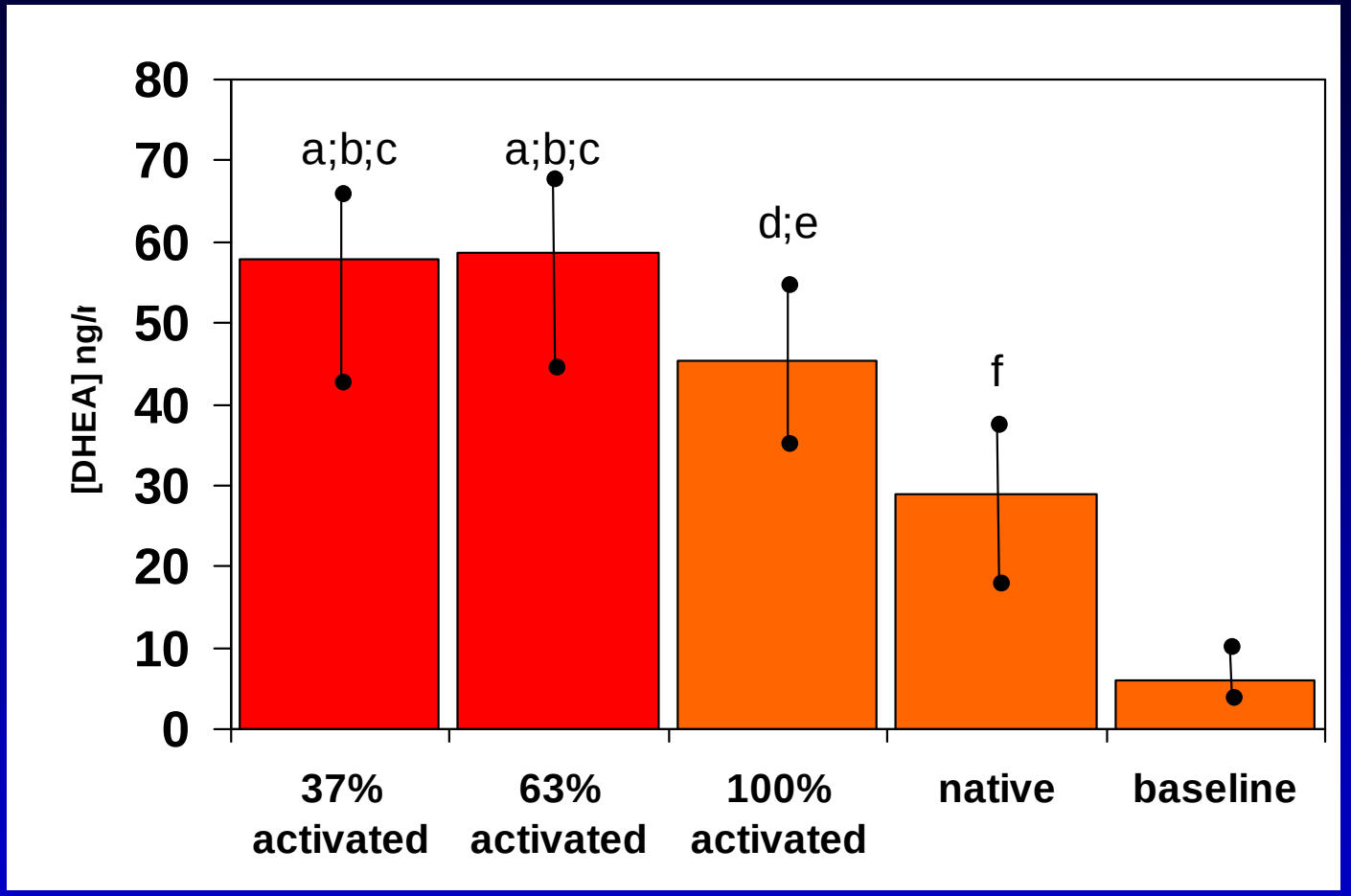
chronobiological HRT:
Different preparations of DHEA:

DHEA-native (fast release)
DHEA (clathrate fast release)


Mean values: 'c—DHEA [ng/ml]'
25 mg C-DHEA 37% activated / pill
25 mg C-DHEA 63% activated / pill
25 mg C-DHEA 100% activated / capsule
25 mg native-DHEA /capsule
baseline / placebo
c—DHEA [ng/ml]
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
—30
30
90
150
210
270
330
390
450
510
570
630
minutes p.a.


Mean values: 'c—DHEA—S [ng/ml]'
25 mg C-DHEA 37% activated / pill
25 mg C-DHEA 63% activated / pill
25 mg C-DHEA 100% activated / capsule
25 mg native-DHEA /capsule
baseline / placebo
c—DHEA—S [ng/ml]
4000
3000
2000
1000
0
—30
30
90
150
210
270
330
390
450
510
570
630
minutes p.a.

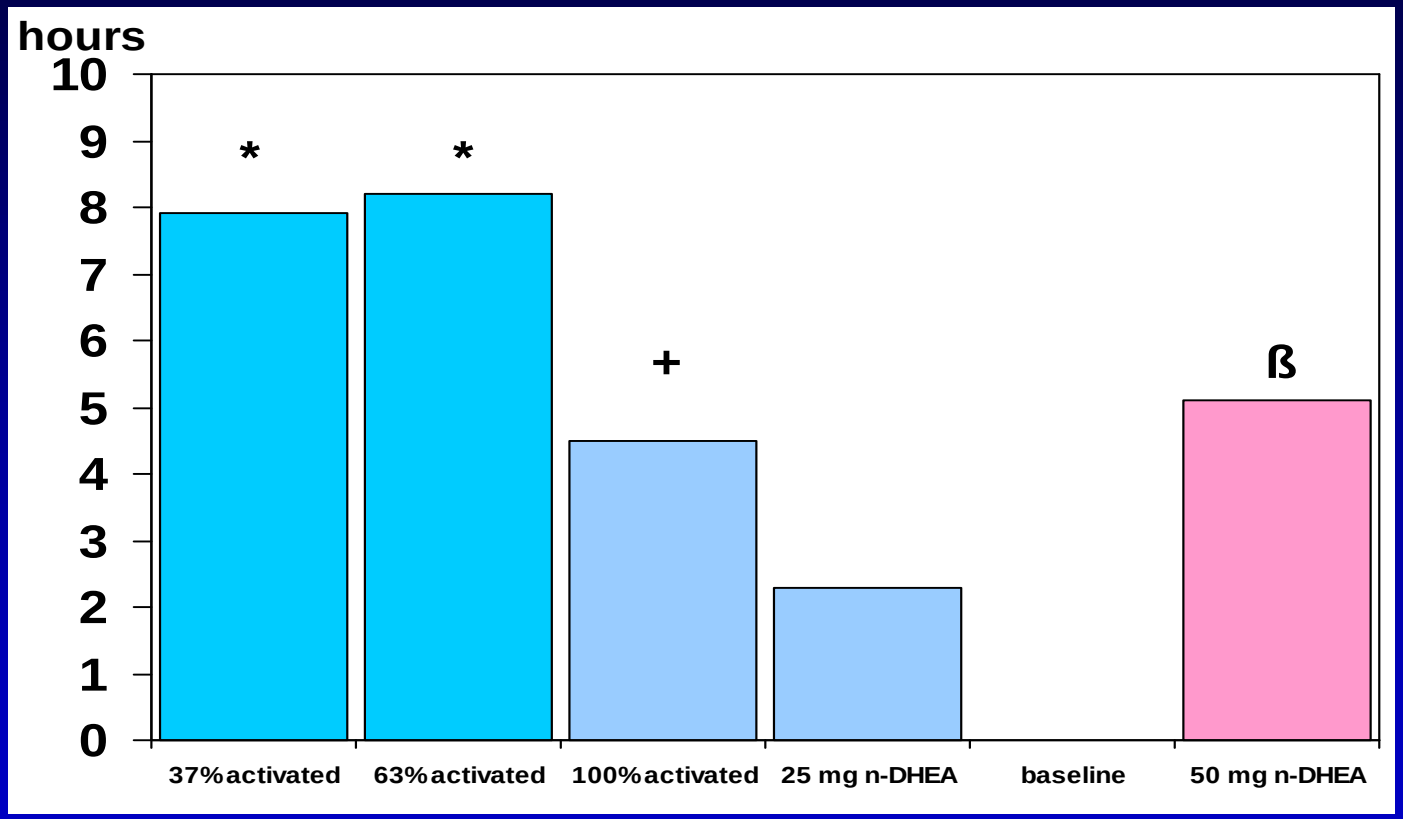
Mean $AUC_{(0-24)}$ after DHEA administration



a: c-pill *vs.* c-capsule	**p> 0.02**
b: c-pill *vs.* native capsule	**p> 0.001**
c: c-pill *vs.* baseline	**p> 0.0001**

d: c-capsule *vs.* native-capsule	**p> 0.05**
e: c-capsule *vs.* baseline	**p> 0.001**
f: c-native-capsule *vs.* baseline	**p> 0.001**

Mean time with DHEA serum levels over minimal normal concentration (> 3.9 ng/ml)



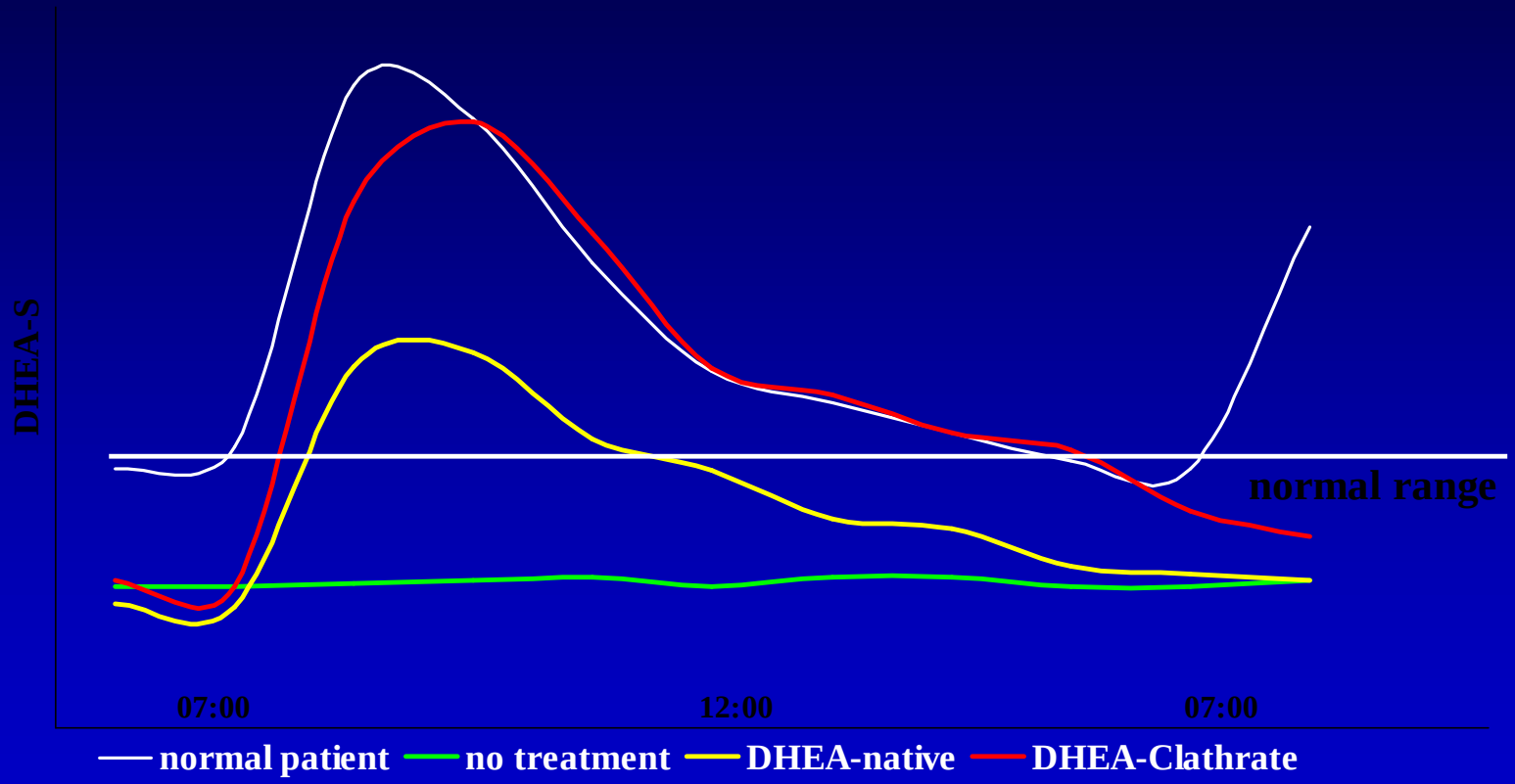
* = significant difference Clathrate-pills vs. native-capsules

+ = significant difference Clathrate capsules vs.: nativecapsiles

ß = obtained by an other study (Jenapharm kinetic –Study 100mg vs.50 mg)

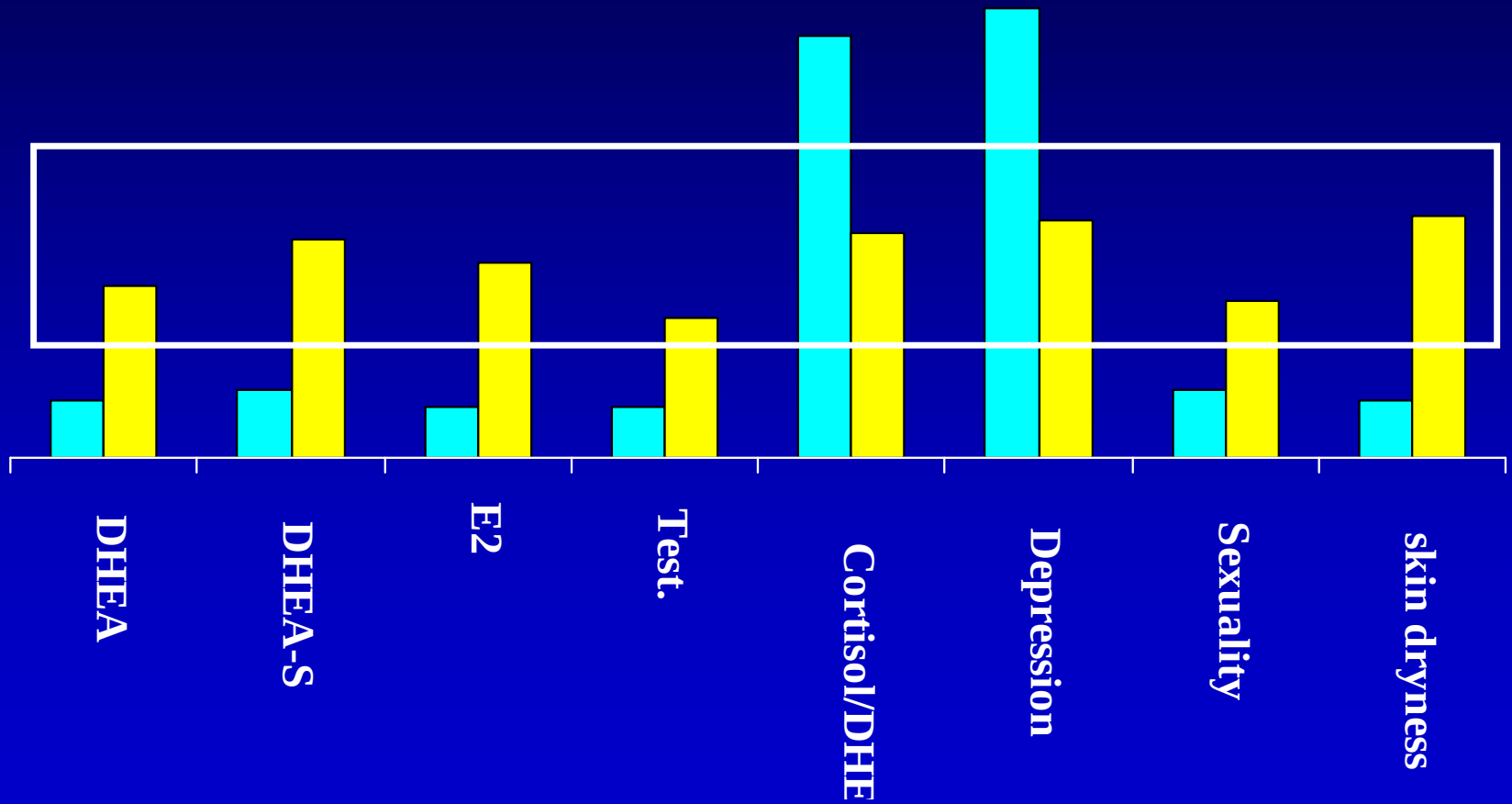
Product research: scientific background

DHEA



Clinical results

DHEA

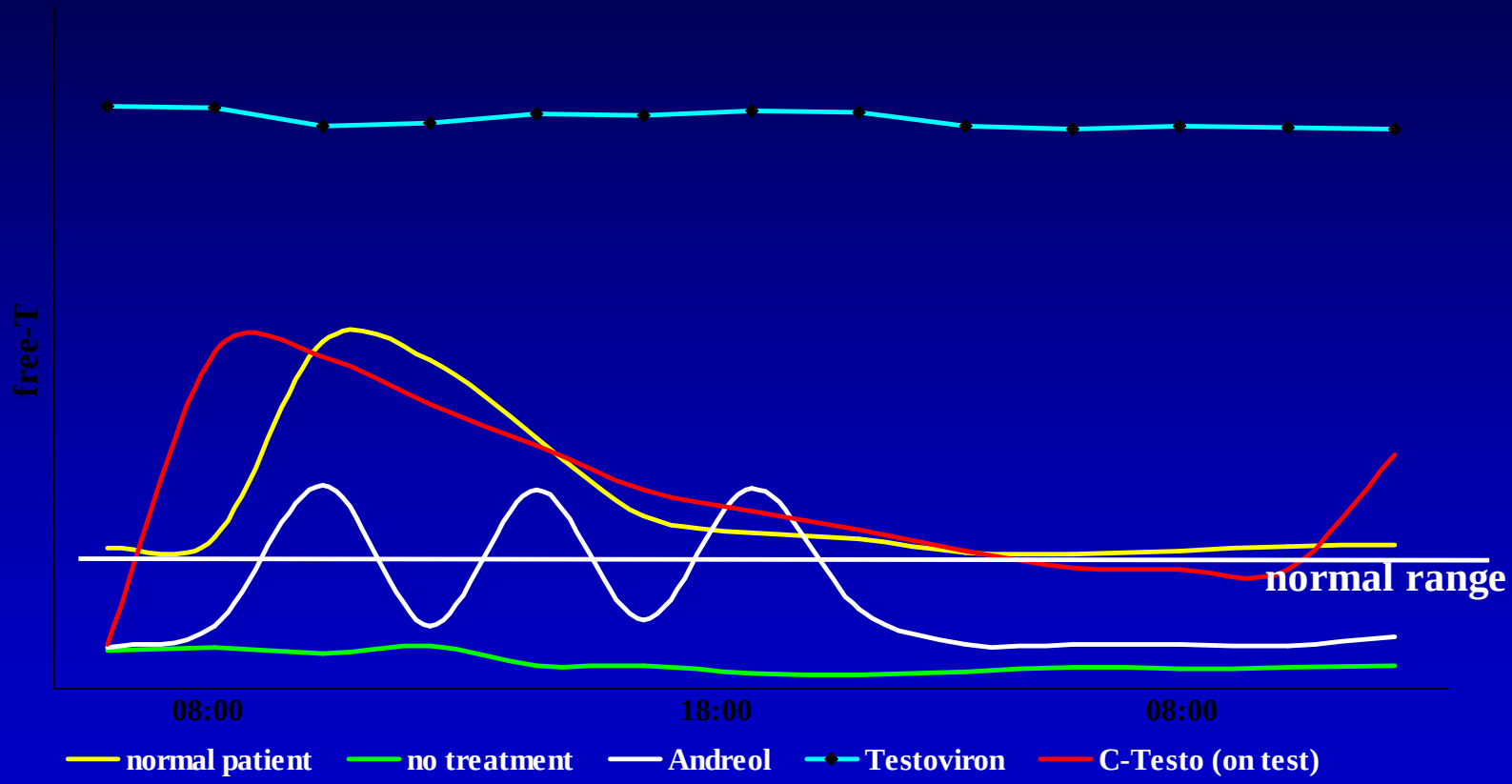


chronobiological HRT:
Different preparations of Testosterone:

Testosterone-oily preparation (fast release)
Testosterone (clathrate fast release)
Testosterone injectable

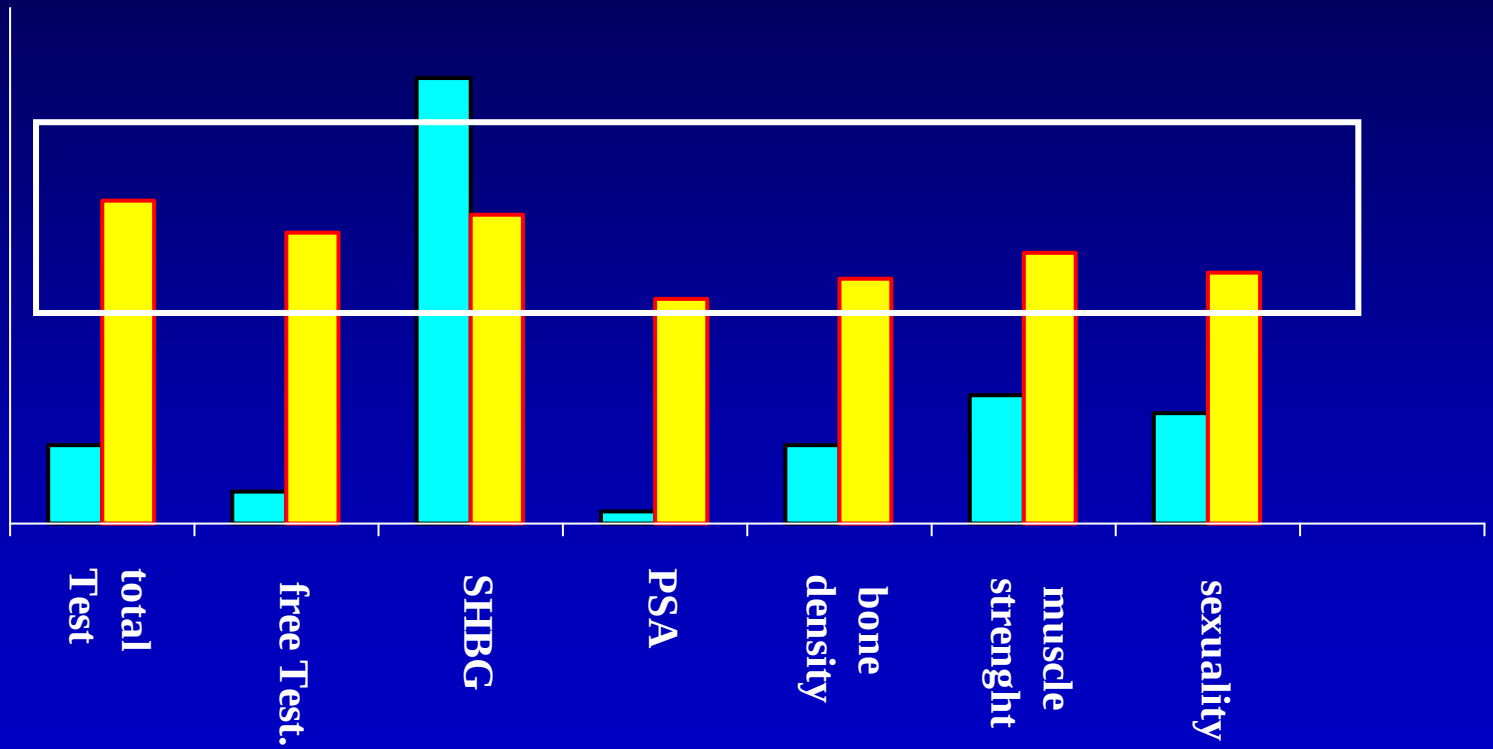
Product research: scientific background

Testosterone



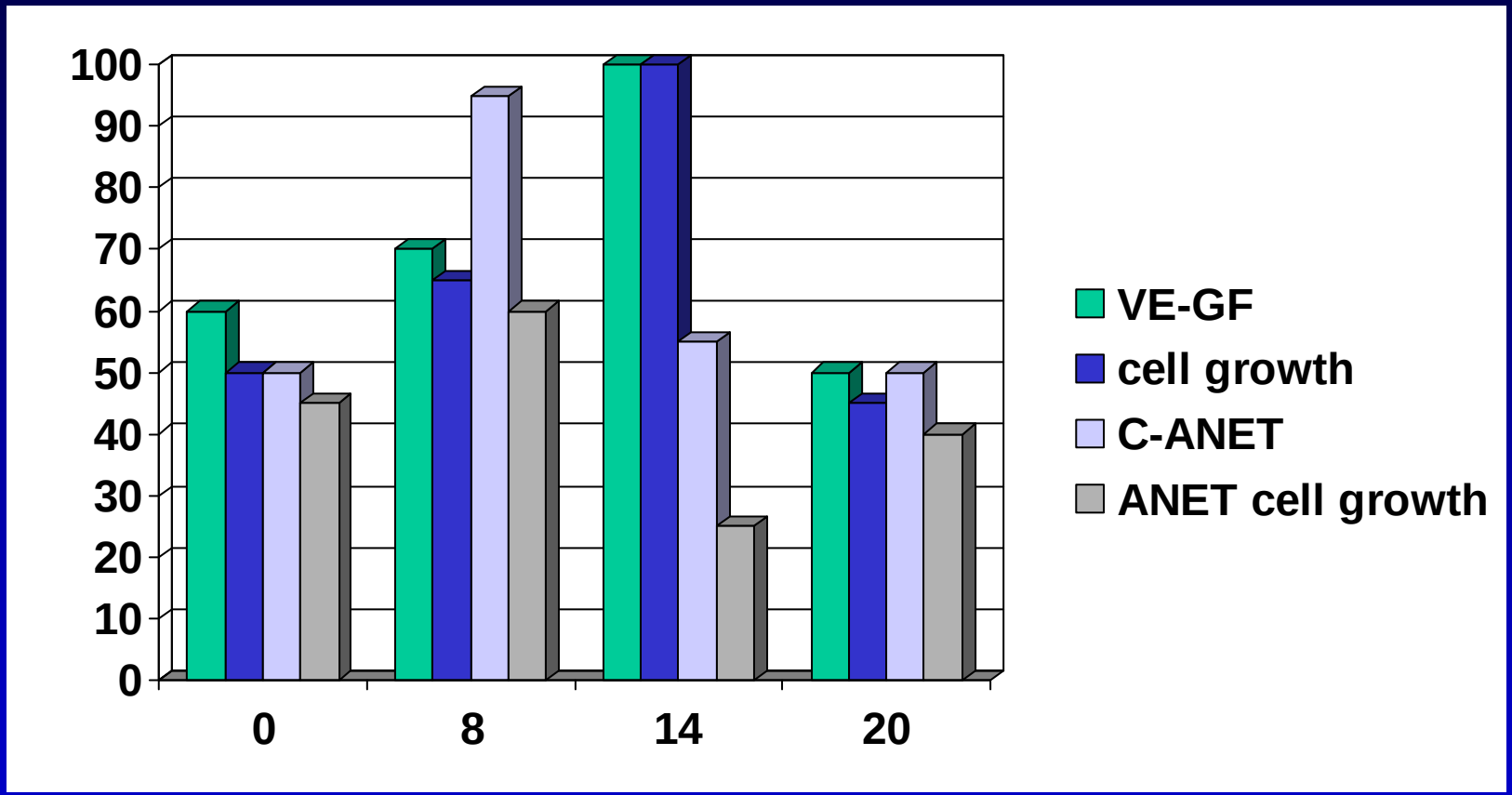
Clinical results

Testosterone



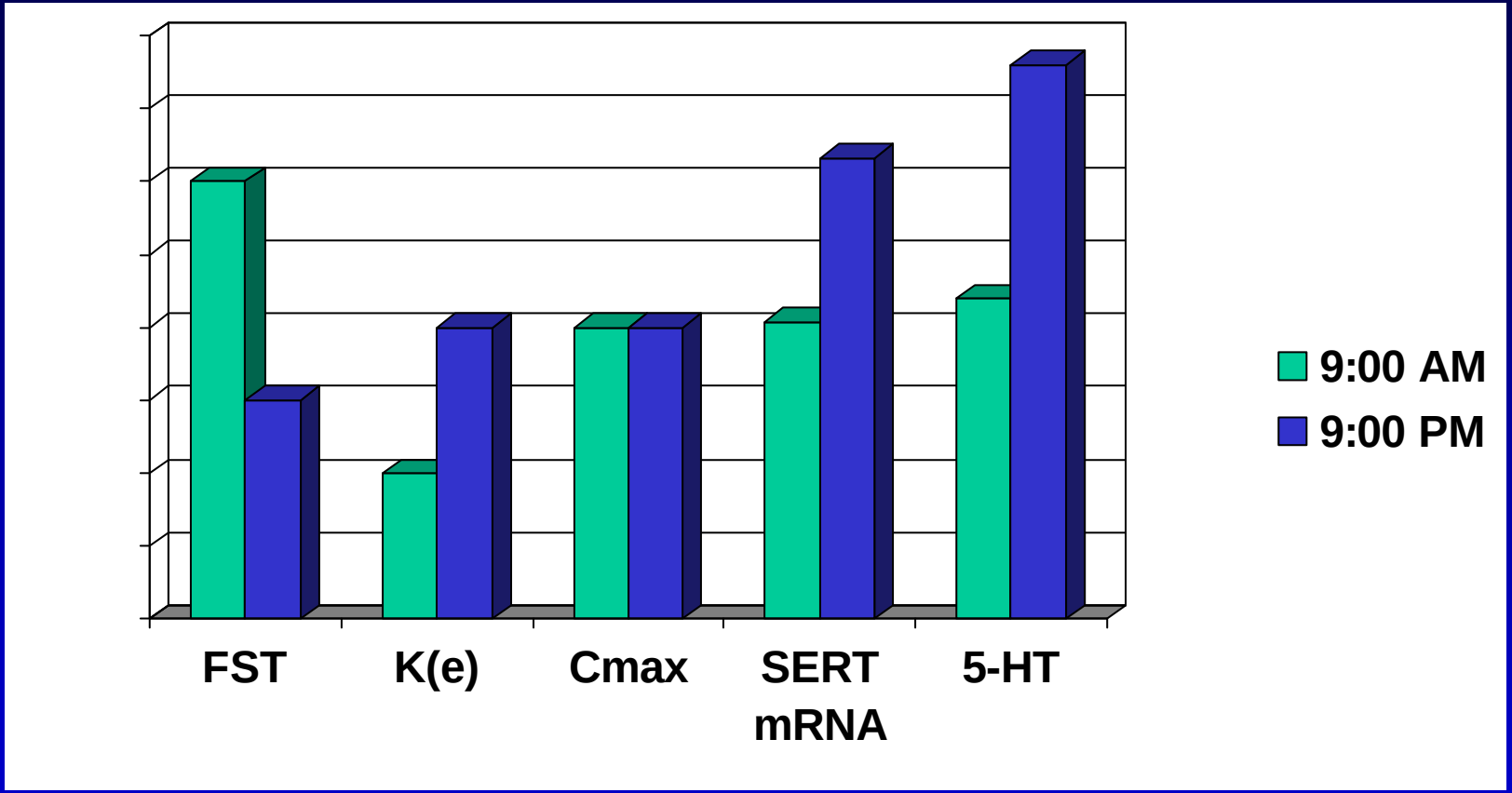
Chronopharmacalogy of established medication (literature research)

Effect of an anti-neo-vascular therapy in dependency of day-time (mice, 0 = light on)



Shimizu K et al.
Chronopharmacologic cancer treatment with an angiogenic vessel-targeted liposomal drug.
Biol Pharm Bull 2008 Jan;31(1):95-8;

Anti-depressive effect of Fluvoxamin (SSRI) measured by the forced-swimming test in dependency of application time



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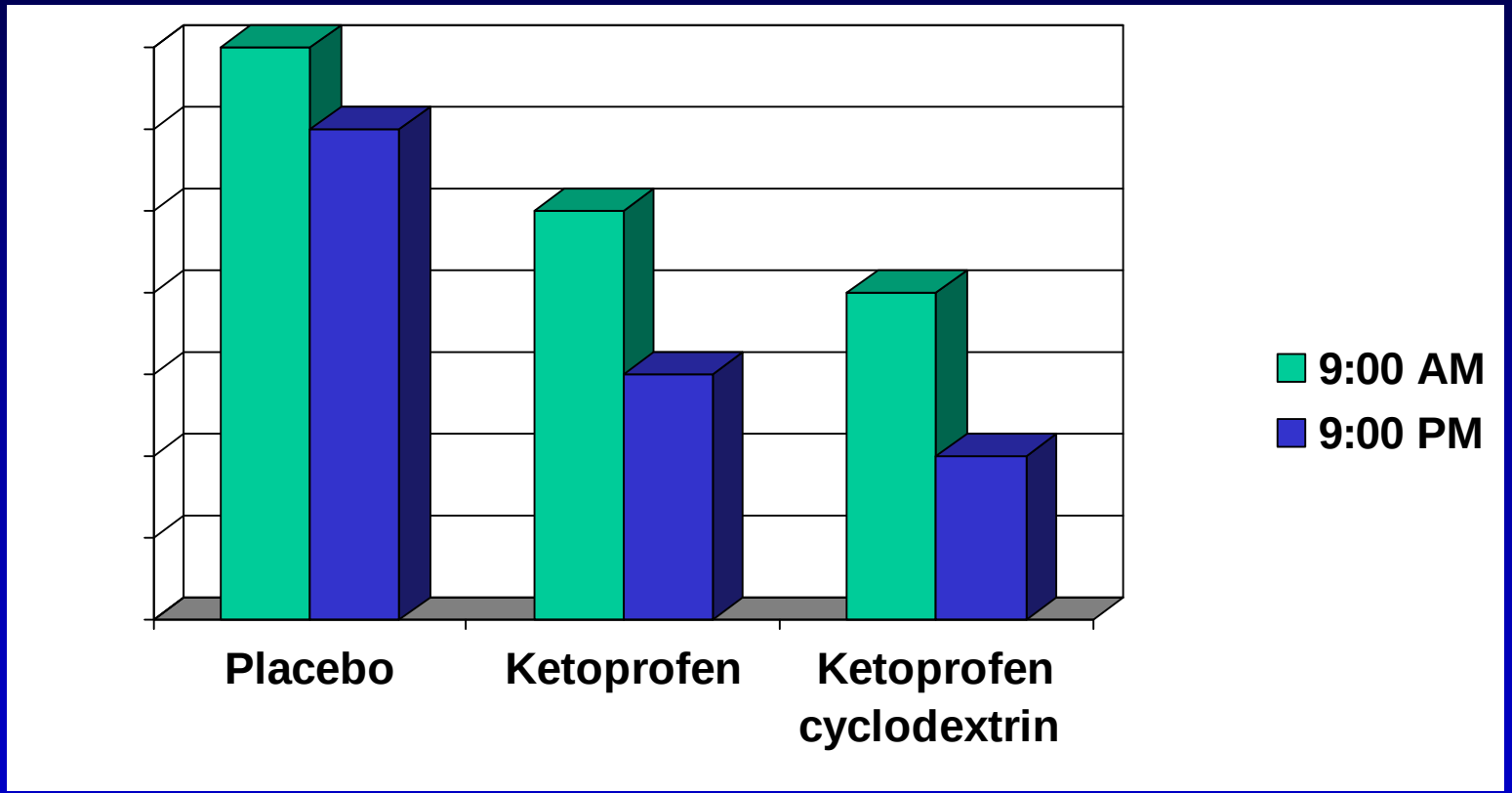
Anti-inflammatoric effect of Ketoprofen on induced Arthritis reumatoide in rats in dependency of application time



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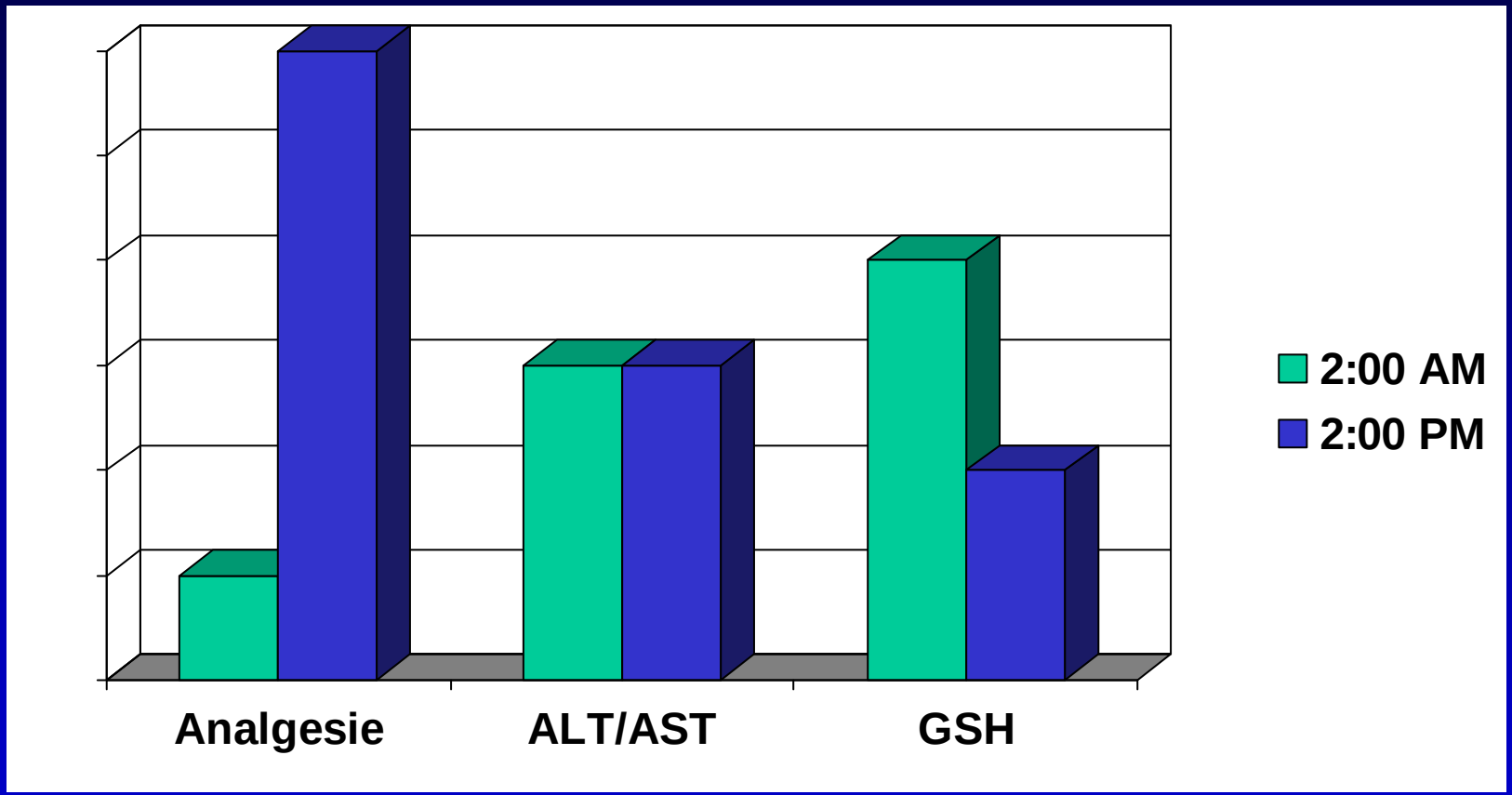
Effect of Morphine on pain and liver function in dependency of application time in mice



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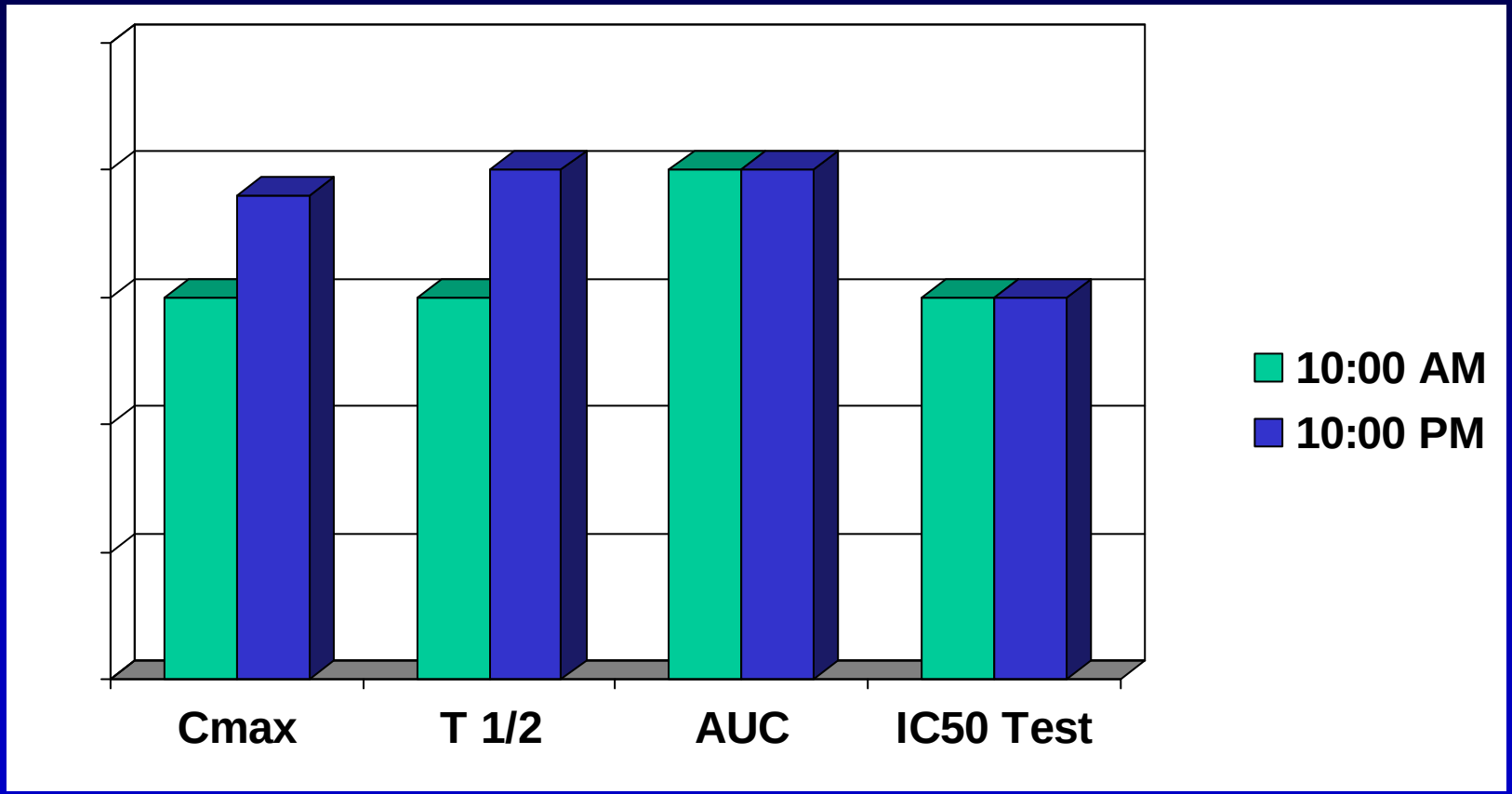
Chronobiol Int 2005;22(3):515-22

The blood concentration and the anti-bacterial effect of Cephalexin in dependency of application time in dogs



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Chronopharmacological study of cephalexin in dogs.
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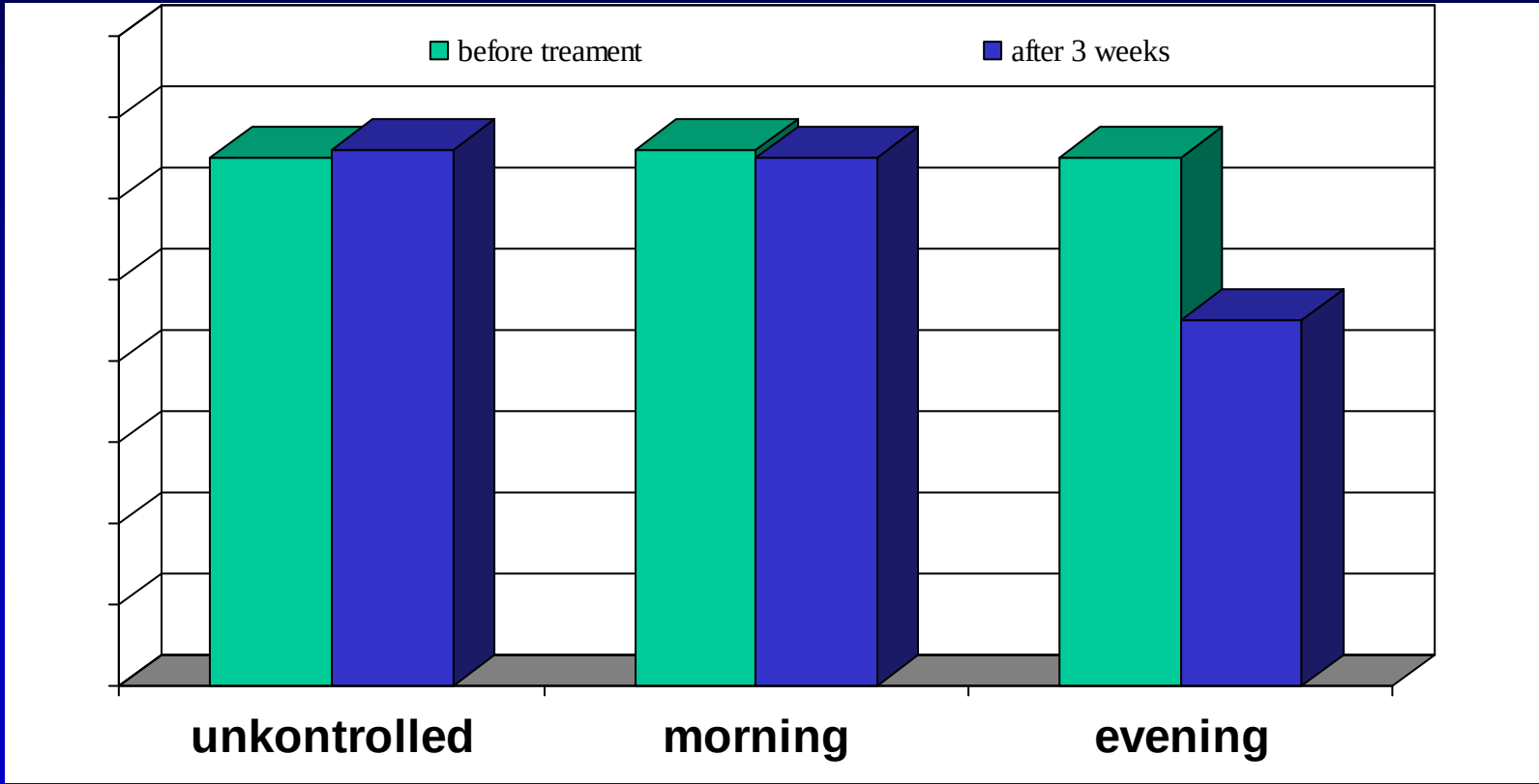
Effect of Asperin 100 on blood pressure in dependency of application time in hypertensive patients



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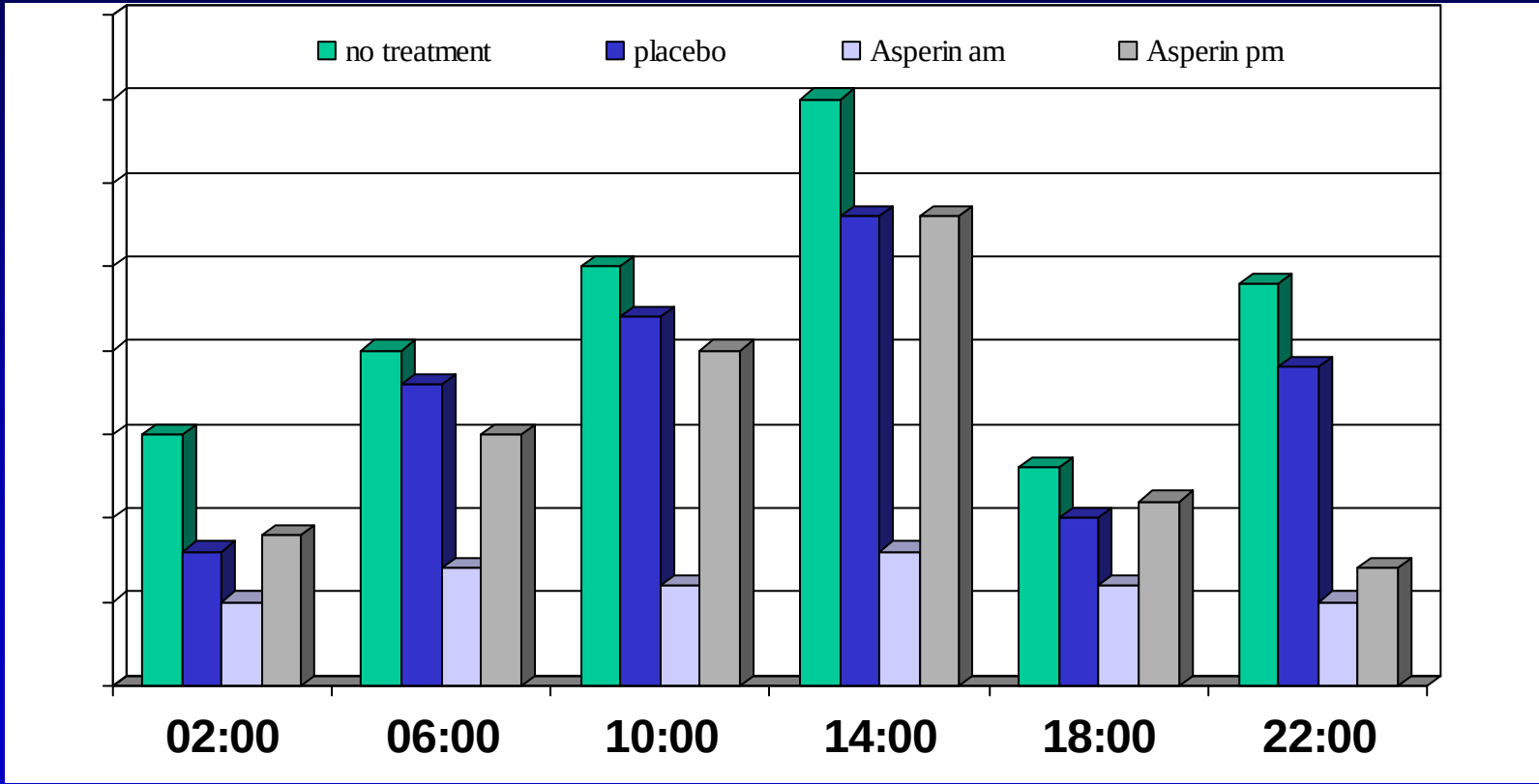
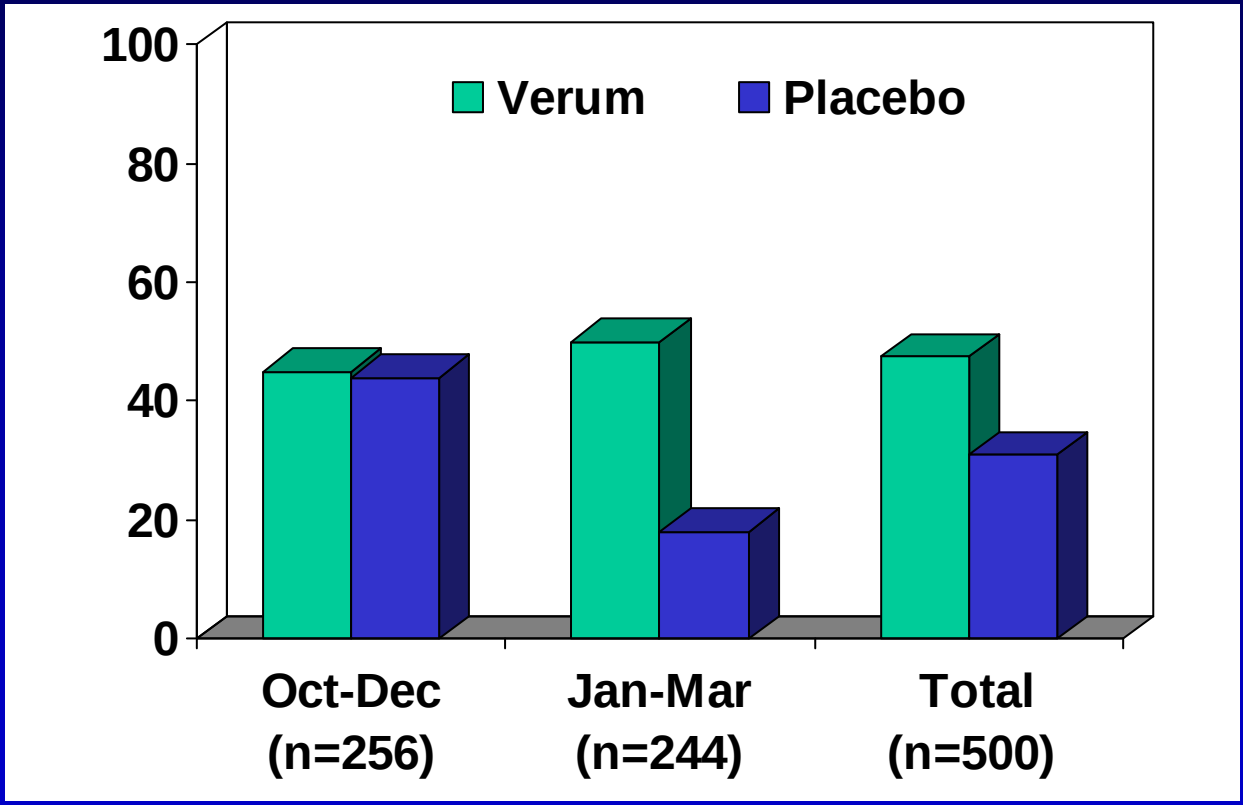
Effect of Asperin 100 on heart attack in dependency of application time in hypertensive patients



Effect of time on the out-come of clinical trials: Anti-itching effect of Anaesthesulf® in children suffering from chickenpox (Fauteck et al. 2005)




JAN-DIRK FAUTECK
IMRE KUSZTRICH
LEBEN MIT
DER INNEREN UHR
Wie die Chronobiologie unsere Gesundheit,
Wirtschaft und Gesellschaft beeinflusst
Econ

Thanks to all colleagues from:

University of Milan; Institute of Pharmacology

University of Münster, Institute of Anatomy

University of Münster; Institute of Physiology

University of Halle; Institute of Anatomy

University of Vienna; Institute of Psychiatry

Department of clinical research, Jenapharm

VITABASIX for their financial support

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