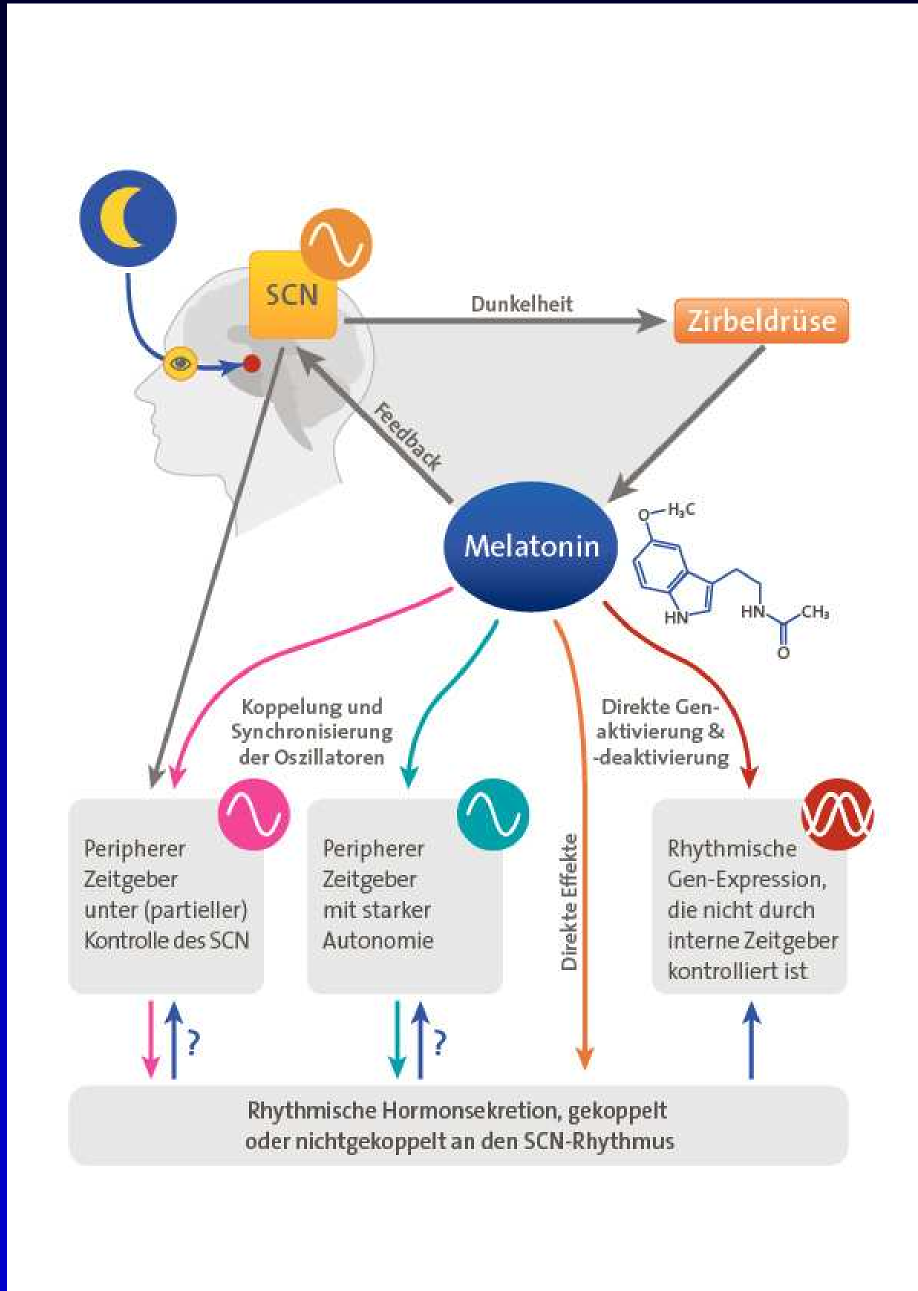
Biorhythmen – Möglichkeiten der Therapieoptimierung

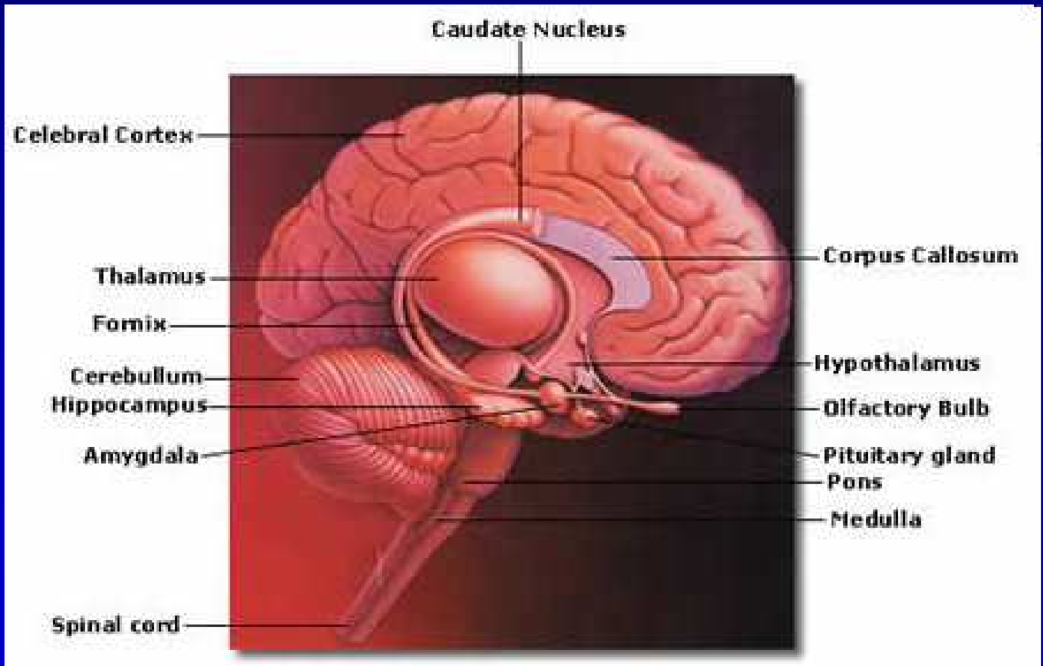
Dr. Jan-Dirk Fauteck
ea3m GmbH & Co. KG
Kalletal


SCN
Dunkelheit
Zirbeldrüse
Feedback
Melatonin
Koppelung und Synchronisierung der Oszillatoren
Direkte Gen-aktivierung & -deaktivierung
Direkte Effekte
Peripherer Zeitgeber unter (partieller) Kontrolle des SCN
Peripherer Zeitgeber mit starker Autonomie
Rhythmische Gen-Expression, die nicht durch interne Zeitgeber kontrolliert ist
Rhythmische Hormonsekretion, gekoppelt oder nichtgekoppelt an den SCN-Rhythmus

Aktivatoren (Transkriptionsinduktoren)

Clock (Circadian Locomotor output cycles kaput)

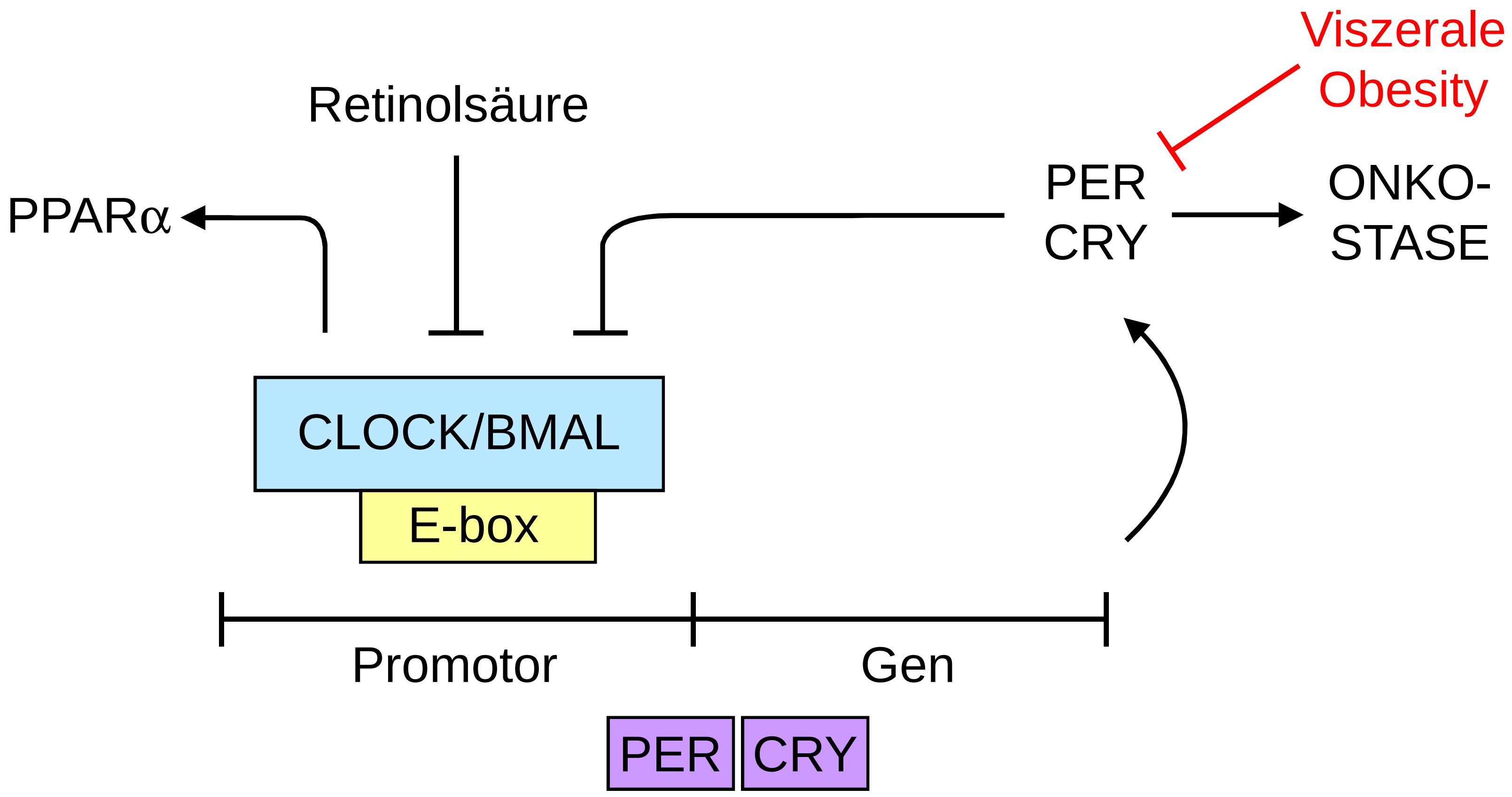
BMAL 1 (Brain muscle arnt like proteine 1)



Repressoren

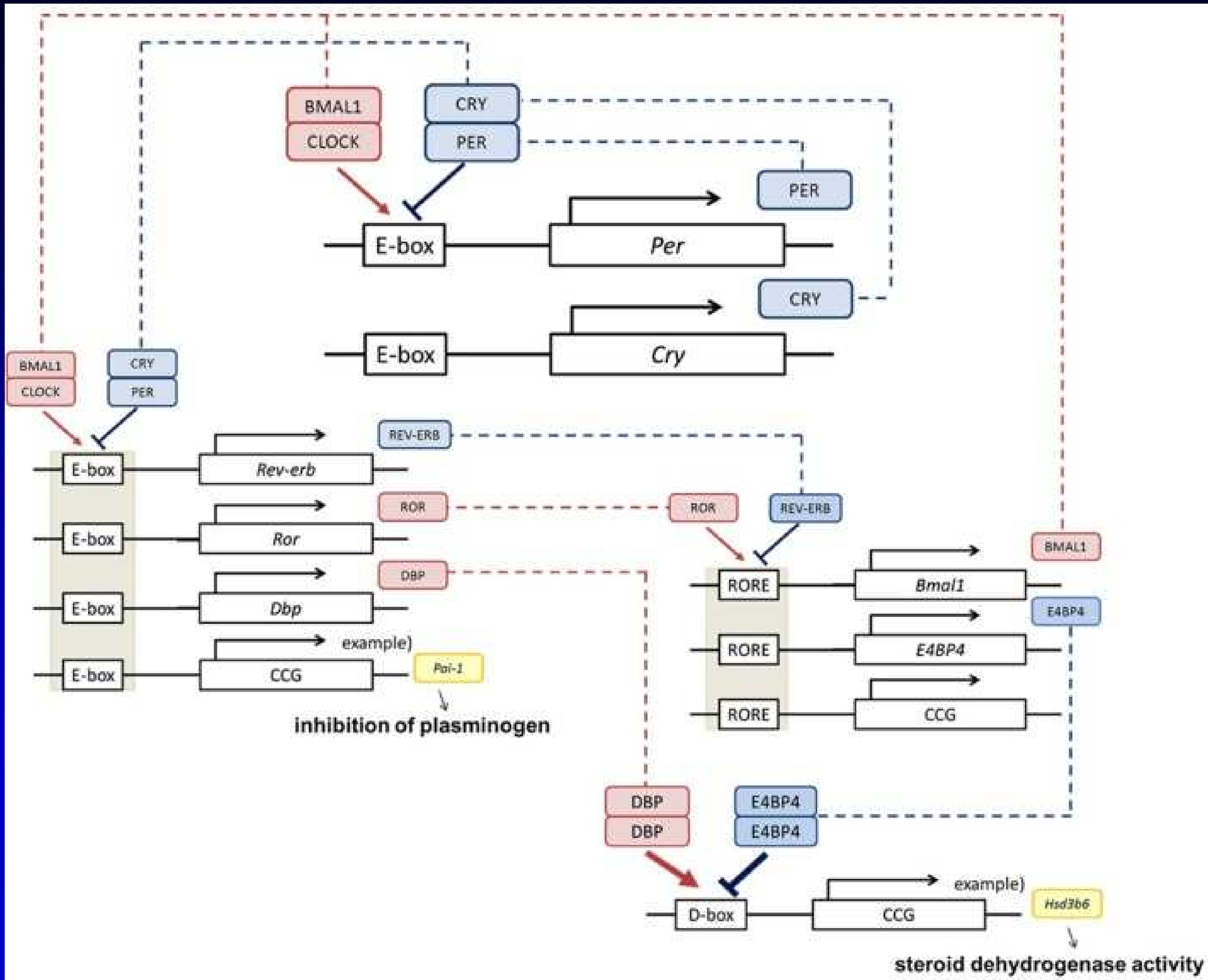
PER (Period)

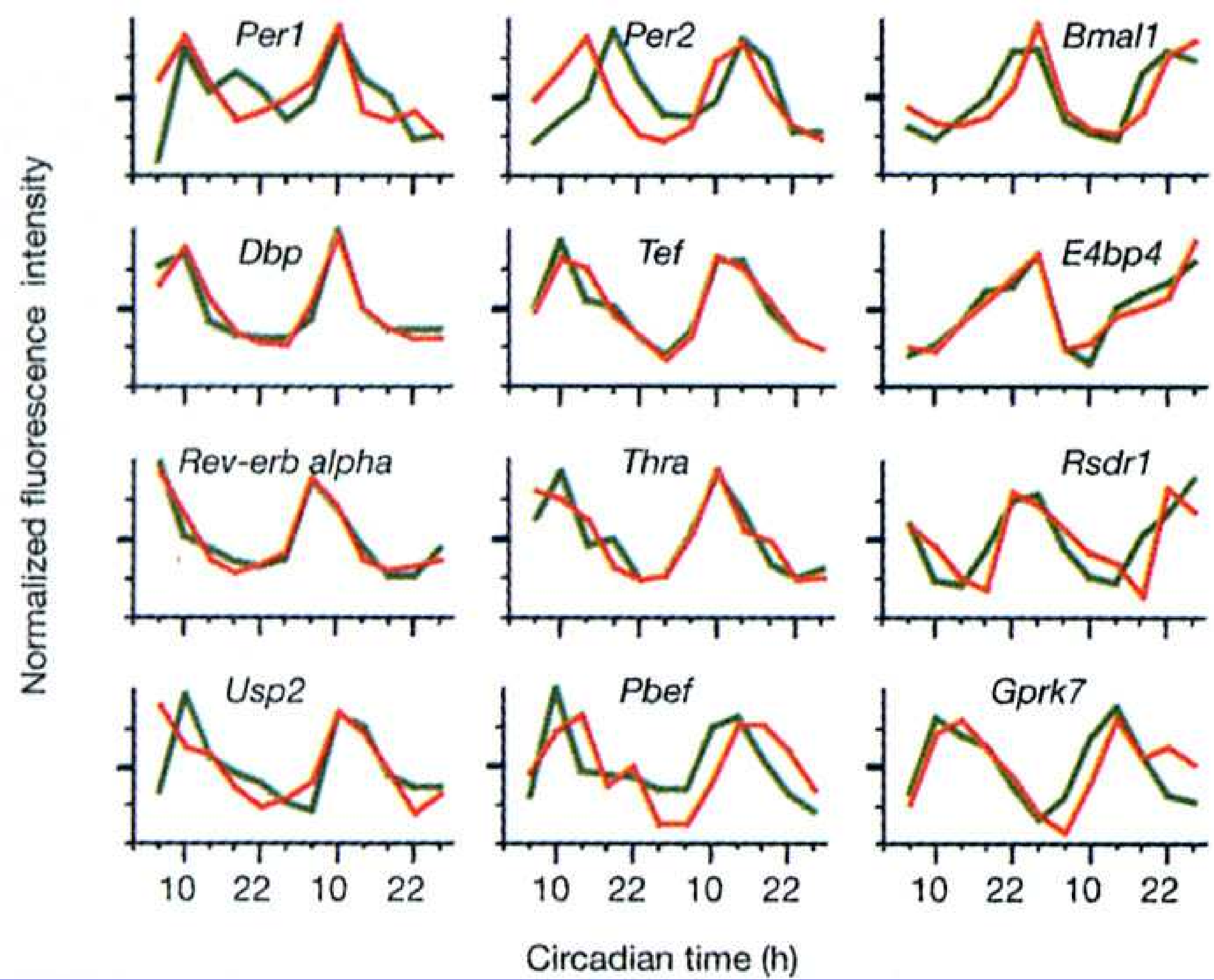
CRY (Cryptochrome)


Viszerale
Obesity
Retinolsäure
PPARα
PER
CRY
ONKO-
STASE
CLOCK/BMAL
E-box
Promotor
Gen
PER
CRY

Clock genes and physiological function.

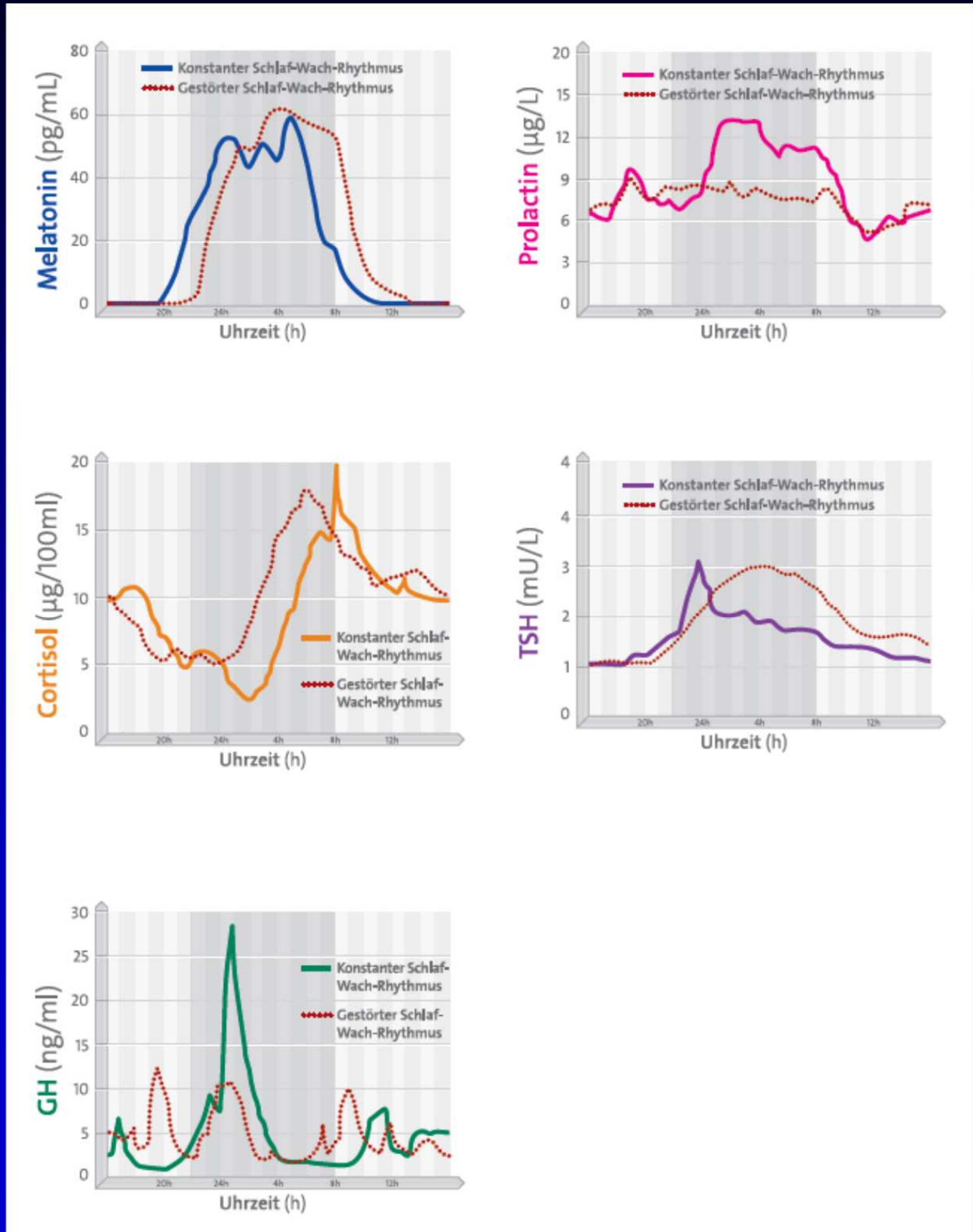
The core clock is composed by the *Per*, *Cry*, *Bmal1*, and *Clock* clock genes (Okamura et al., 2010; Takeda and Maemura, 2011). BMAL1 and CLOCK activate transcriptional levels through E-boxes, and CRY and PER suppress this activity. *Cis* elements such as RORE and D-box can be regulated by ROR, REV-ERB, DBP, and E4BP4, and multilayered rigid circadian rhythms are ticked down. **This negative feedback loop produces the rhythm of transcription**. These regulations are transmitted via transcriptional fluctuations of clock controlled genes (ccg) such as *plasminogen activator inhibitor-1* (*Pai-1*) (Maemura et al., 2000; Haus, 2007), *type VI 3 beta-hydroxyl-steroid dehydrogenase* (*Hsd3b6*) (Bass, 2012).


BMAL1
CLOCK
CRY
PER
E-box
Per
PER
CRY
E-box
Cry
BMAL1
CLOCK
CRY
PER
E-box
Rev-erb
REV-ERB
E-box
Ror
ROR
E-box
Dbp
DBP
E-box
CCG
example)
Pai-1
inhibition of plasminogen
ROR
REV-ERB
RORE
Bmal1
BMAL1
RORE
E4BP4
E4BP4
RORE
CCG
DBP
DBP
E4BP4
E4BP4
D-box
CCG
example)
Hsd3b6
steroid dehydrogenase activity


Per1
Per2
Bmal1
Dbp
Tef
E4bp4
Rev-erb alpha
Thra
Rsdr1
Usp2
Pbef
Gprk7
Normalized fluorescence intensity
10 22 10 22
10 22 10 22
10 22 10 22
Circadian time (h)

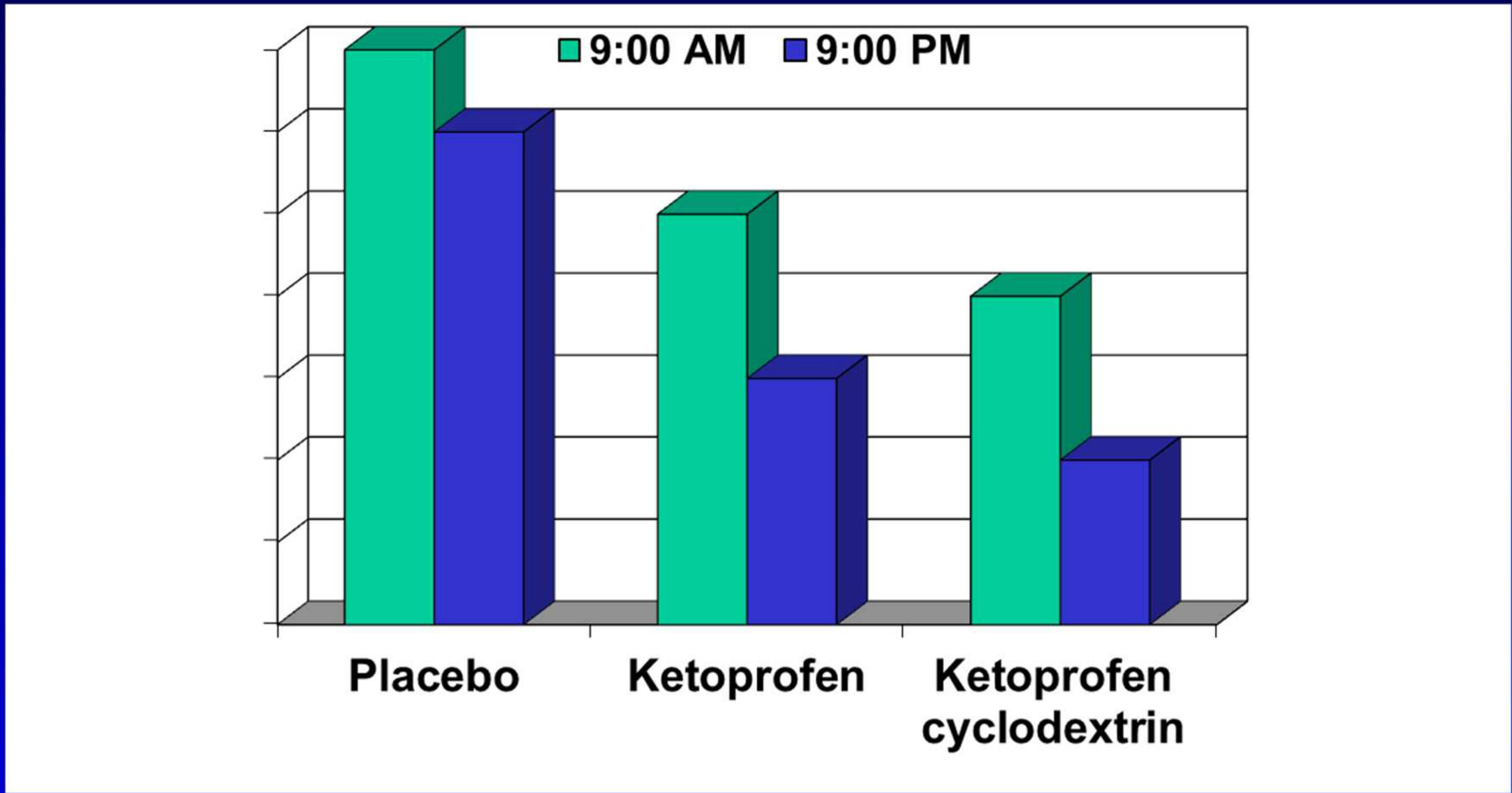
J Biol Rhythms. 2013 Apr;
Sex difference in daily rhythms of clock gene expression in the aged human cerebral cortex.
Lim AS, Myers AJ, Yu L, Buchman AS, Duffy JF, De Jager PL, Bennett DA.

……. **The expression levels of 3 clock genes-PER2, PER3, and ARNTL1-were quantified in samples of dorsolateral prefrontal cortex from 490 deceased individuals in 2 cohort studies of older individuals**, the Religious Orders Study and the Rush Memory and Aging Project, using mRNA microarray data. Clock gene expression at death was parameterized as a function of time of death using cosine curves and was examined for sex differences in the phase of these curves. **Significant daily variation was seen in the expression of PER2 (p = 0.004), PER3 (p = 0.003), and ARNTL1 (p = 0.0005).** PER2/3 expression peaked at 10:38 (95% confidence interval [CI], 09:20-11:56) and 10:44 (95% CI, 09:29-11:59), respectively, and ARNTL1 expression peaked in antiphase to this at 21:23 (95% CI, 20:16-22:30). **The timing of the expression of all 3 genes was significantly earlier in women than in men** (PER2 6.8 h, p = 0.002; PER3 5.5 h, p = 0.001; ARNTL1 4.7 h, p = 0.007). Daily rhythms of clock gene expression are present in human cerebral cortex and can be inferred from postmortem samples. **Moreover, these rhythms are relatively delayed in men compared with women.**


Melatonin (pg/mL)
Konstanter Schlaf-Wach-Rhythmus
Gestörter Schlaf-Wach-Rhythmus
Uhrzeit (h)
Prolactin (µg/L)
Konstanter Schlaf-Wach-Rhythmus
Gestörter Schlaf-Wach-Rhythmus
Uhrzeit (h)
Cortisol (µg/100ml)
Konstanter Schlaf-Wach-Rhythmus
Gestörter Schlaf-Wach-Rhythmus
Uhrzeit (h)
TSH (mU/L)
Konstanter Schlaf-Wach-Rhythmus
Gestörter Schlaf-Wach-Rhythmus
Uhrzeit (h)
GH (ng/ml)
Konstanter Schlaf-Wach-Rhythmus
Gestörter Schlaf-Wach-Rhythmus
Uhrzeit (h)

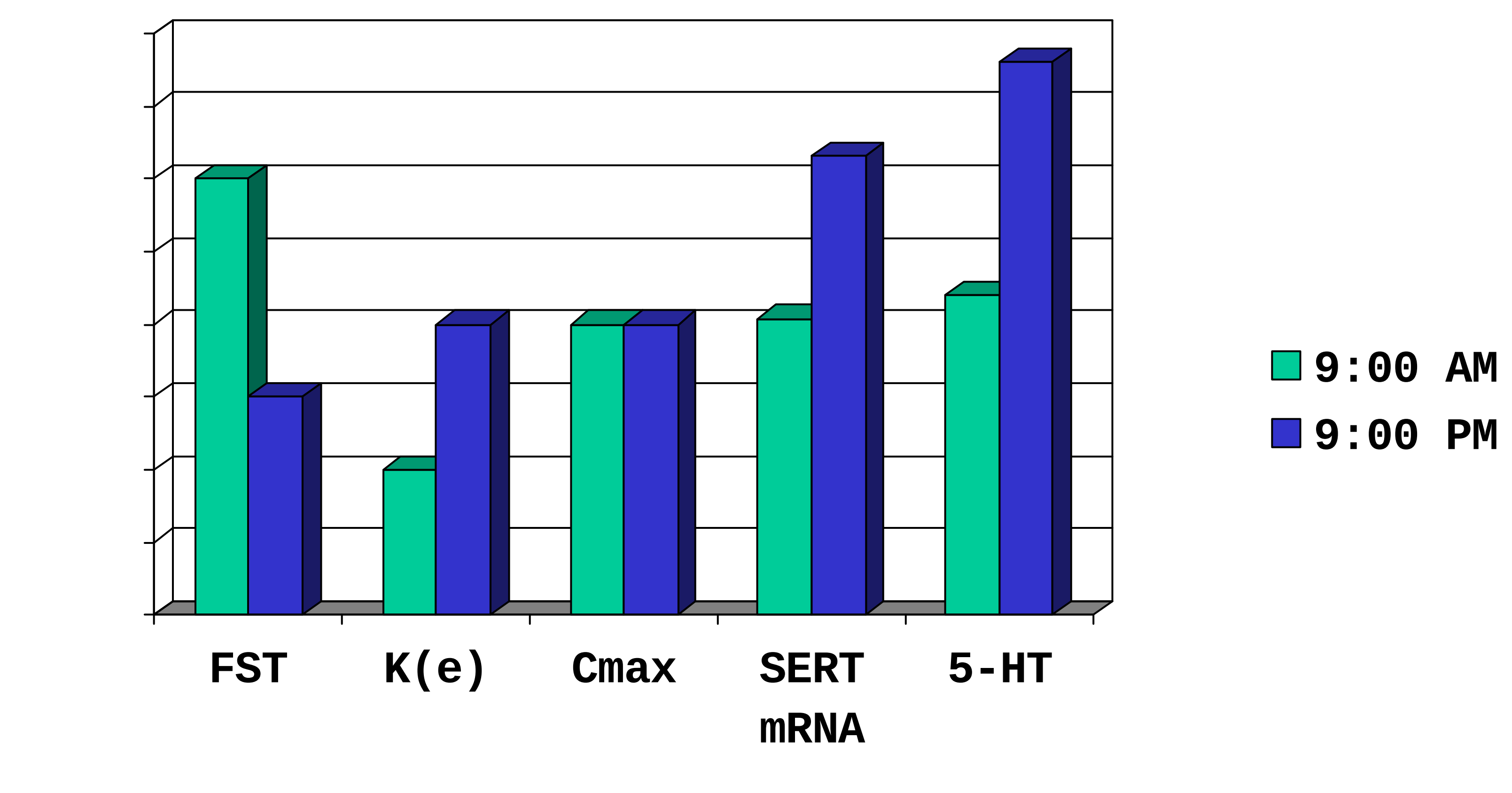
Chronopharmacalogy of established medication (literature research)

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



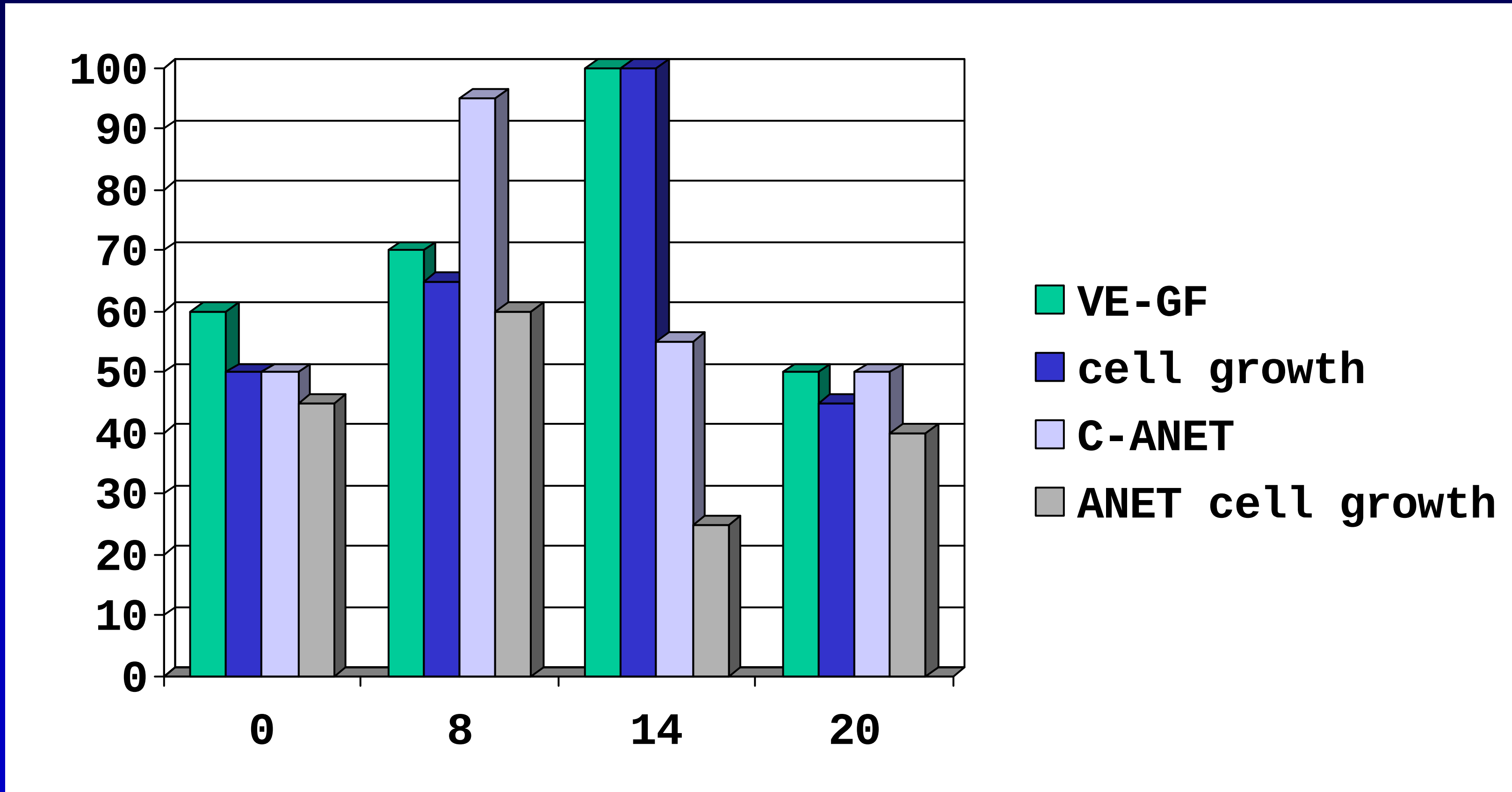
Solankar AK et al.,
Chronobiological and chronopharmacological studies of ketoprofen and its solid dispersion form using adjuvant arthritis model in rats.
Indian J Exp Biol 2005 Jan;43(1):46-52

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



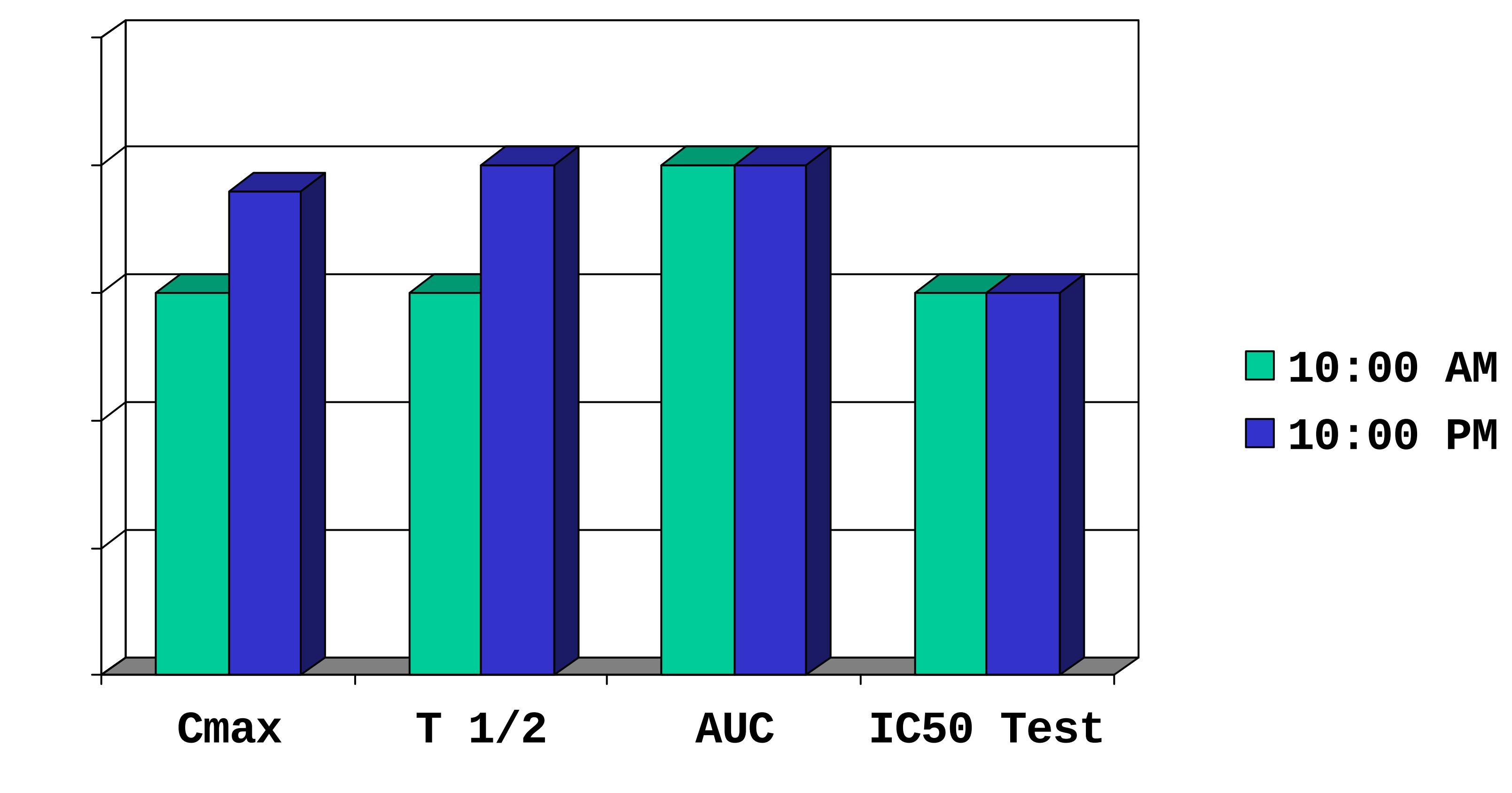
Ushijima K et al.
Chronopharmacological study of antidepressants in forced swimming test of mice.
J Pharmacol Exp Ther 2005 Nov; 315(2):764-70

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



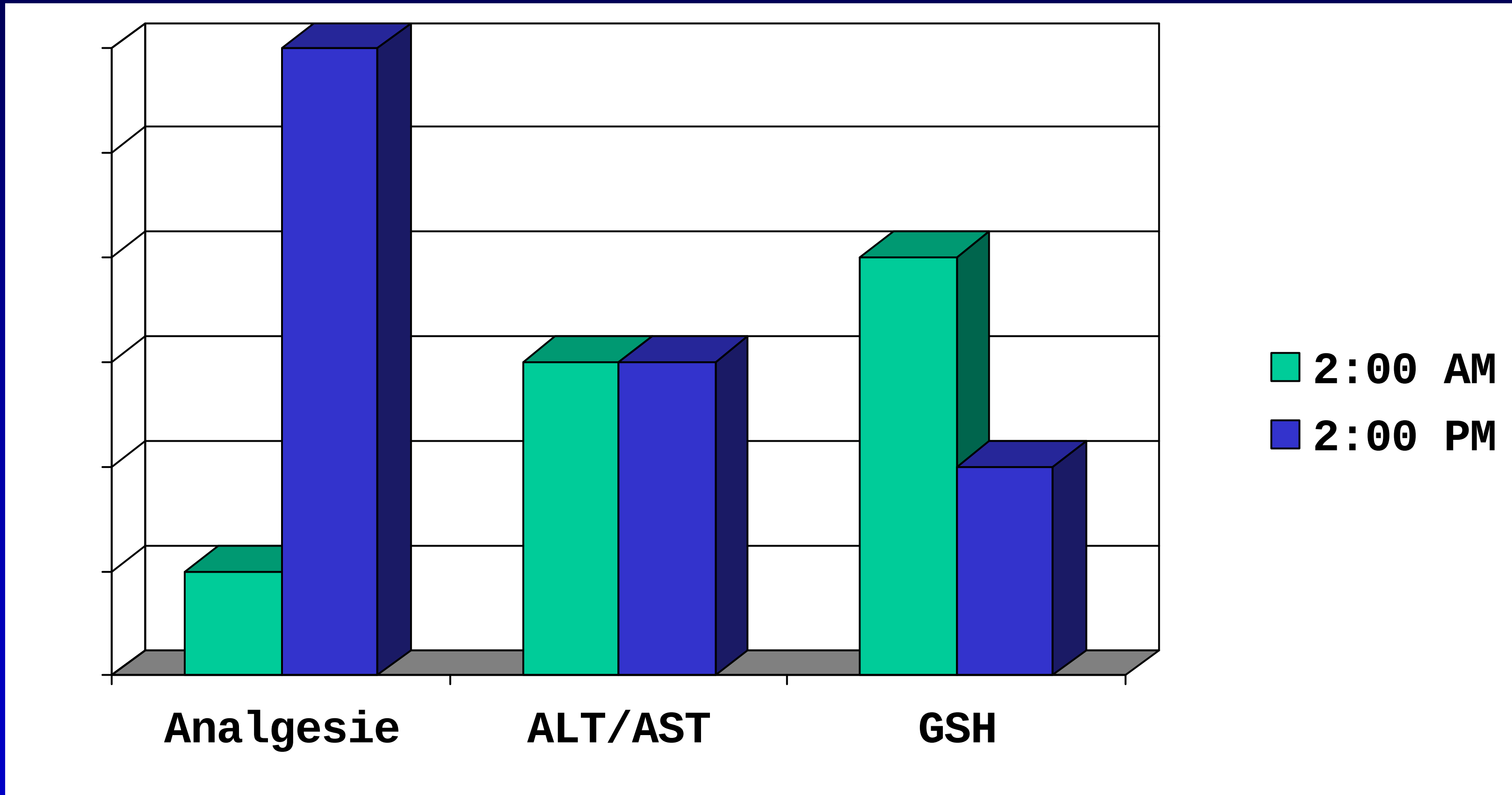
Shimizu K et al.
Chronopharmacologic cancer treatment with an angiogenic vessel-targeted liposomal drug.
Biol Pharm Bull 2008 Jan;31(1):95-8;

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



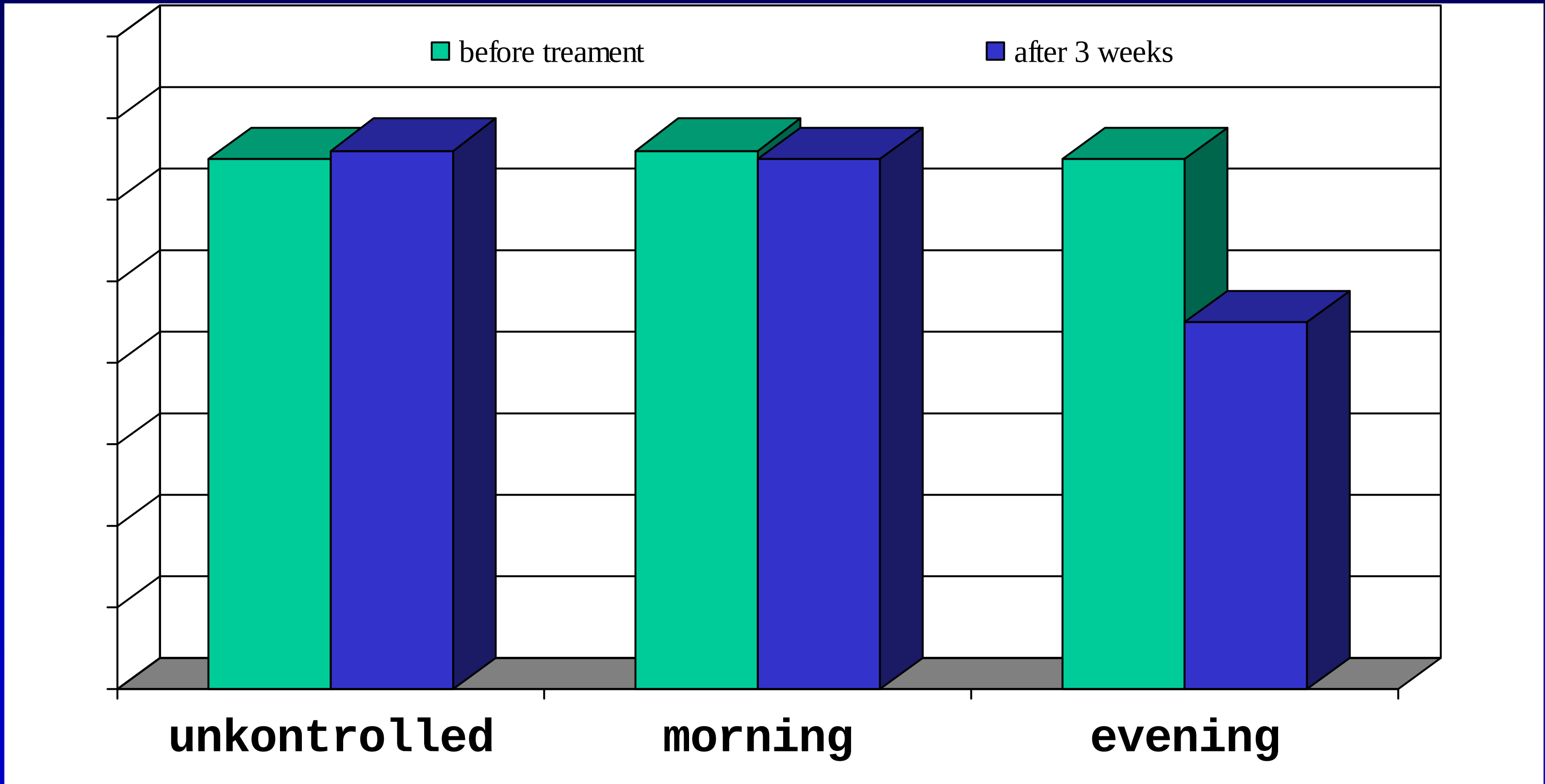
Prados AP et al.,
Chronopharmacological study of cephalexin in dogs.
Chronobiol Int 2007;24(1):161-70

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



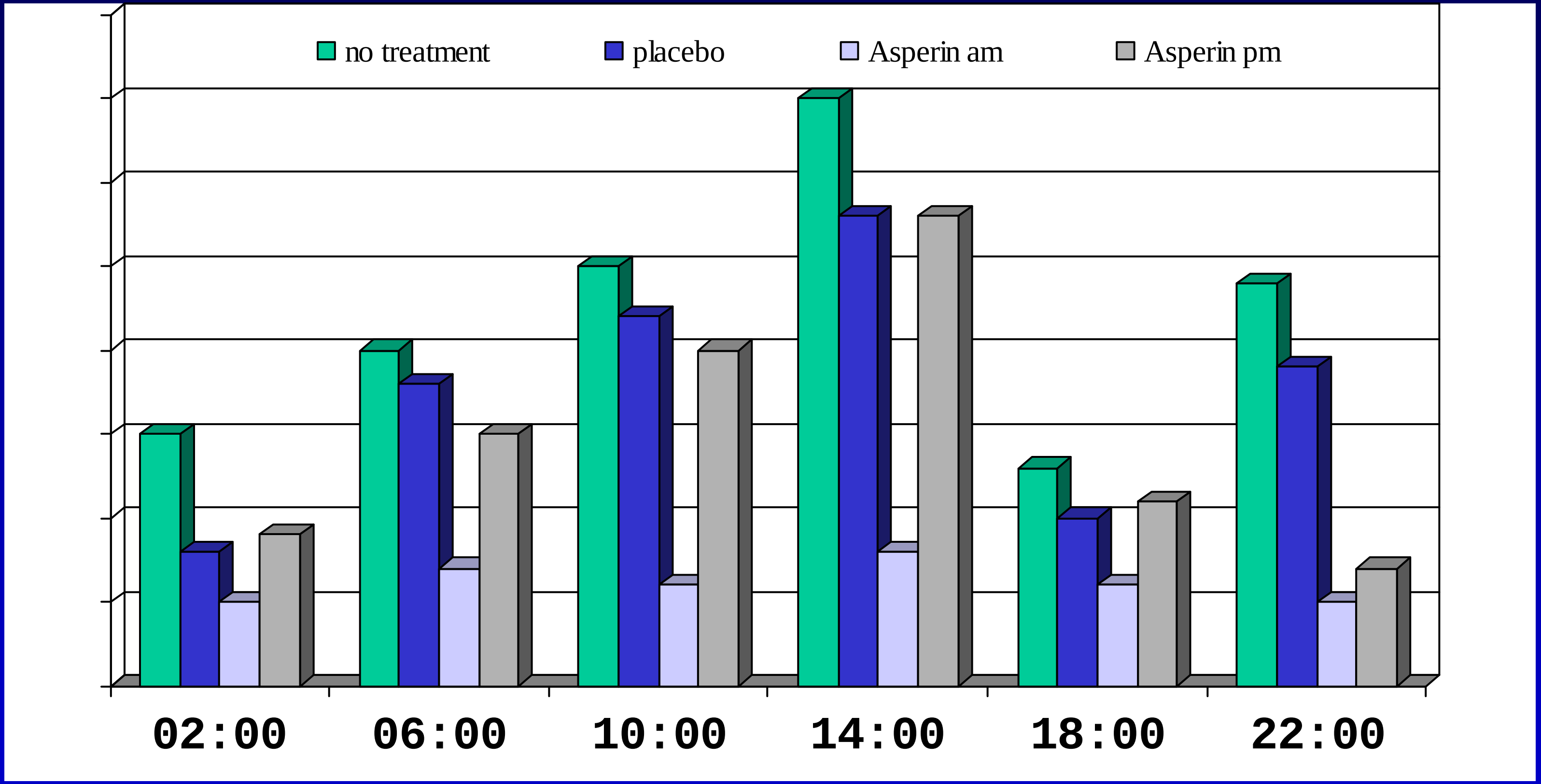
Cui Y et al.,
Chronopharmacology of morphine in mice.
Chronobiol Int 2005;22(3):515-22

Effect of Asperin 100 on blood pressure in dependency of application time in hypertensive patients

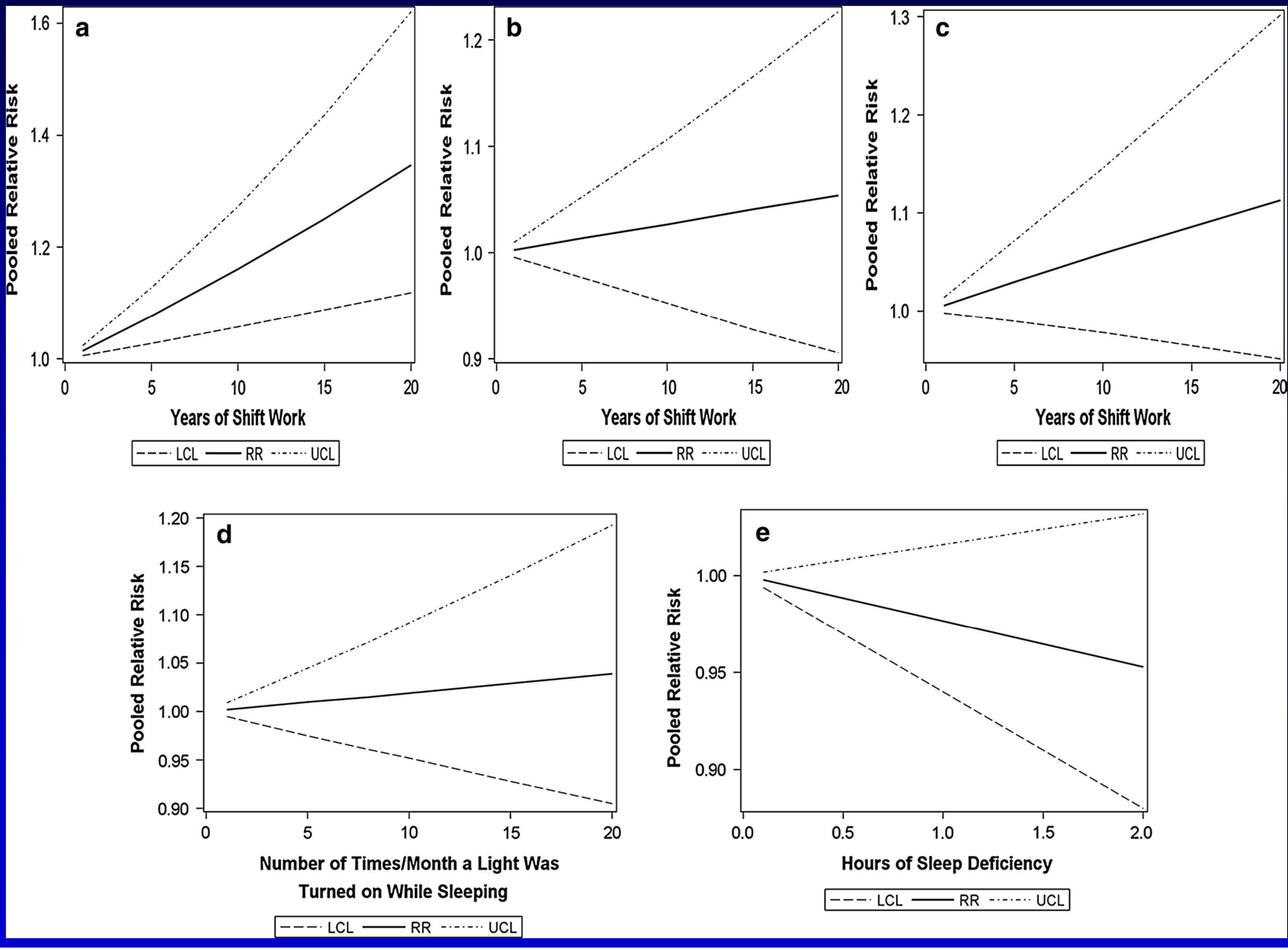


Hermida RC et al.,
Administration time-dependent effects of aspirin on blood pressure in untreated hypertensive patients.
Hypertension 2003 Jun;41(6):1259-67

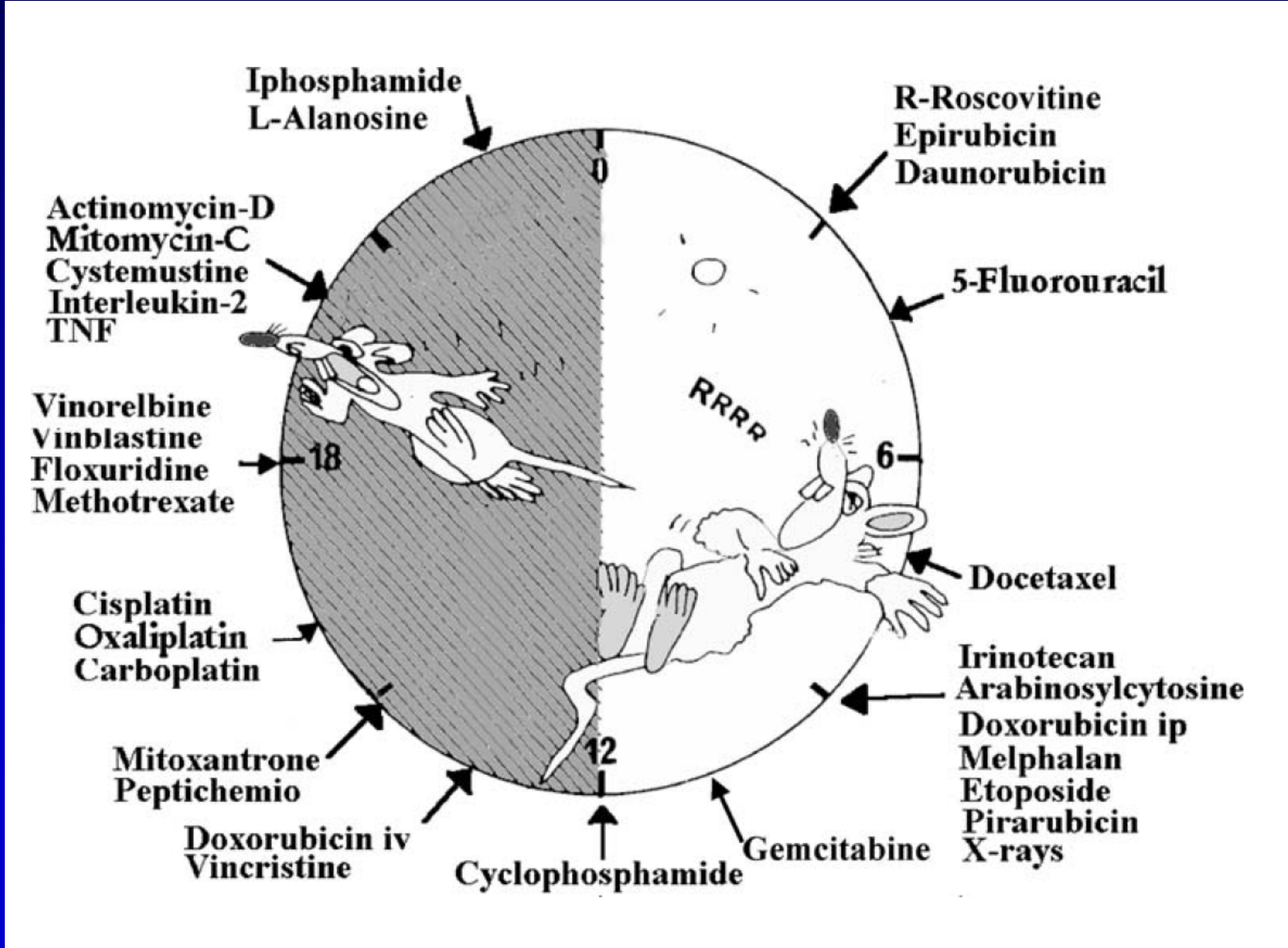
Effect of Asperin 100 on heart attack in dependency of application time in hypertensive patients



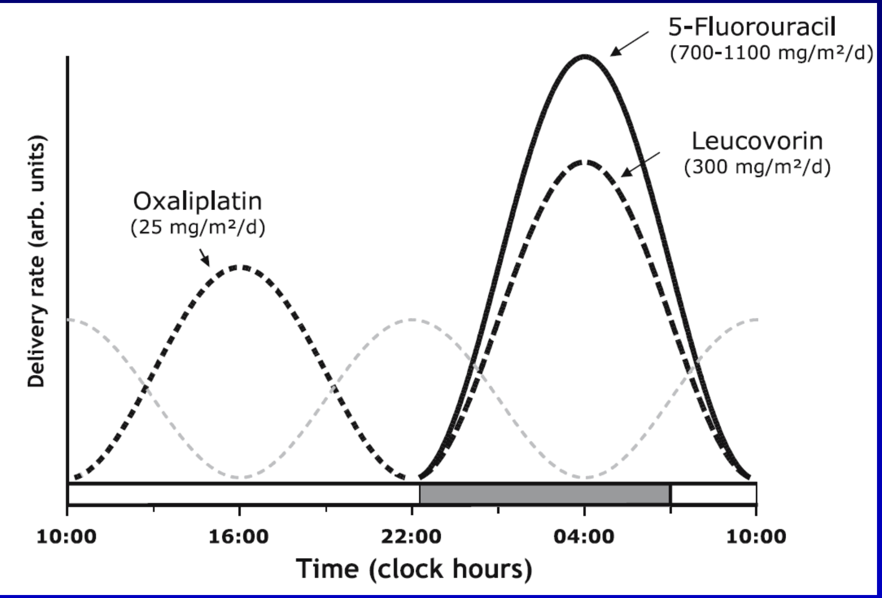
Circadian disruption exposure and breast cancer
(He C. et al., Int. Arch. Occup Environ Health, 2014)

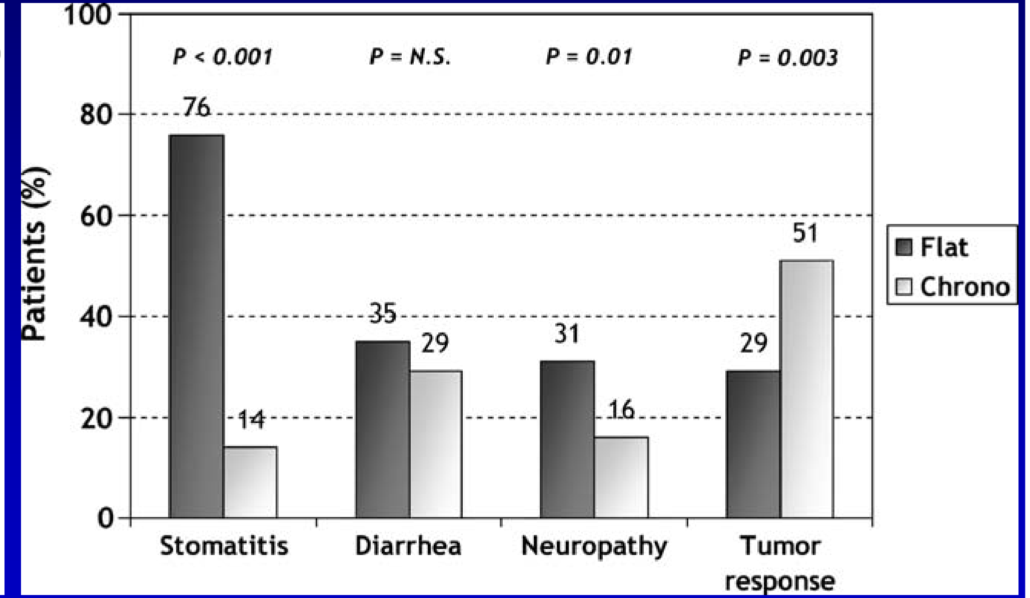


Chronotherapeutics: the relevance of timing in cancer therapy
(Lévi F. Cancer Causes Control, 2006)



Efficacy and tolerability of chronotherapy vs. normal therapy
(Lévi F. Cancer Causes Control, 2006)



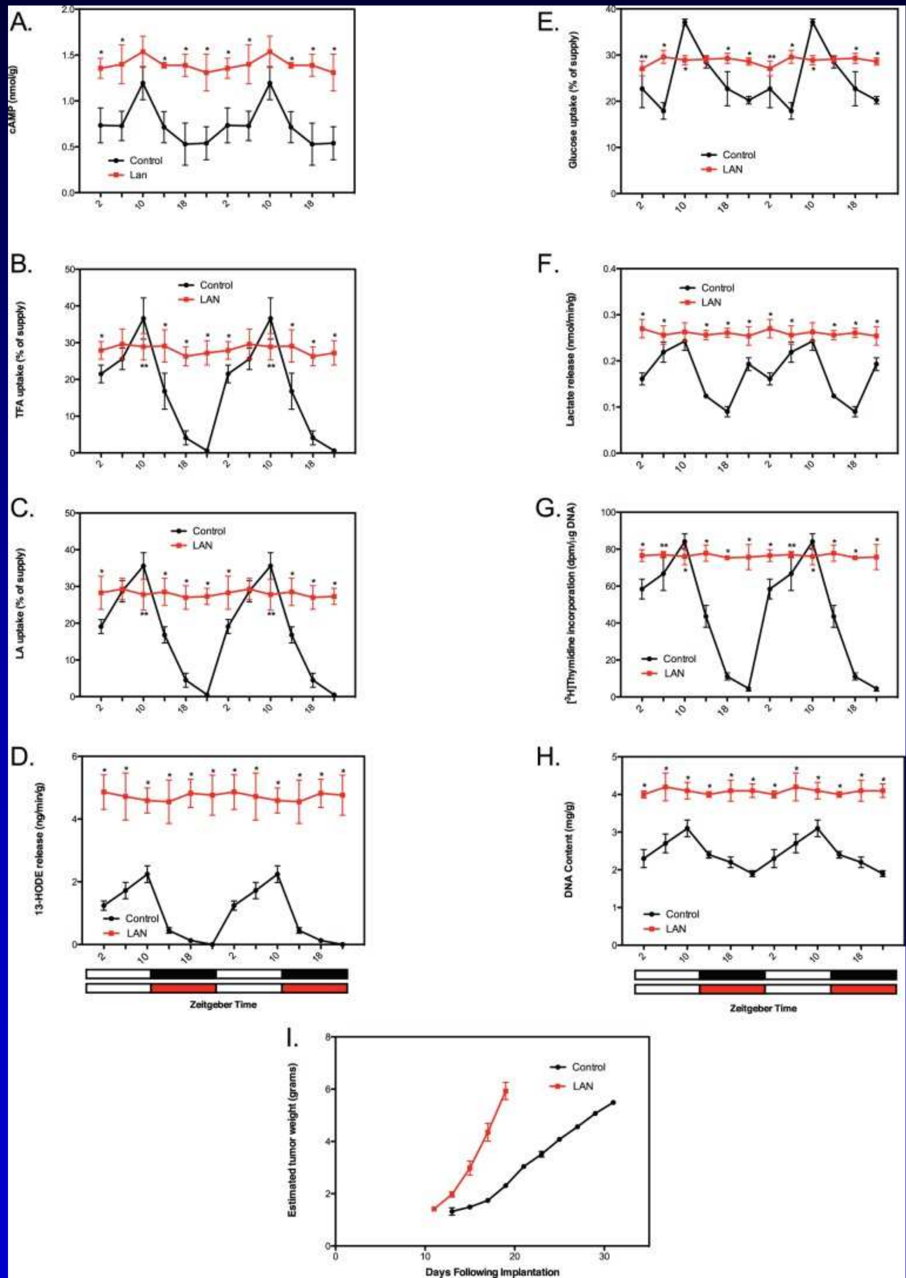


Circadian oscillations and their LAN-induced disruption in tumor cAMP signaling, fatty acid uptake and metabolism, the Warburg effect and proliferative activity and their impact on tumor growth.

PLoS One. 2014 Aug

Light exposure at night disrupts host/cancer circadian regulatory dynamics: impact on the Warburg effect, lipid signaling and tumor growth prevention.

Blask DE[1], Dauchy RT[1], Dauchy EM[1], Mao L[2], Hill SM[2], Greene MW[3], Belancio VP[2], Sauer LA[4], Davidson L[3].



Expert Opin Investig Drugs. 2012

Melatonin uses in oncology: breast cancer prevention and reduction of the side effects of chemotherapy and radiation.

Sanchez-Barcelo EJ[1], Mediavilla MD, Alonso-Gonzalez C, Reiter RJ.

INTRODUCTION:
The possible oncostatic properties of melatonin on different types of neoplasias have been studied especially in hormone-dependent adenocarcinomas. Despite the promising results of these experimental investigations, the use of melatonin in breast cancer treatment in humans is still uncommon.

AREAS COVERED:
This article reviews the usefulness of this indoleamine for specific aspects of breast cancer management, particularly in reference to melatonin's antiestrogenic and antioxidant properties: i) treatments oriented to breast cancer prevention, especially when the risk factors are obesity, steroid hormone treatment or chronodisruption by exposure to light at night (LAN); ii) treatment of the side effects associated with chemo- or radiotherapy.

EXPERT OPINION:
The clinical utility of **melatonin depends on the appropriate identification of its actions**. Because of **its SERM (selective estrogen receptor modulators) and SEEM (selective estrogen enzyme modulators**) properties, and its virtual absence of contraindications, melatonin could be an excellent adjuvant with the drugs currently used for breast cancer prevention (antiestrogens and antiaromatases). **The antioxidant actions also make melatonin a suitable treatment to reduce oxidative stress associated with chemotherapy**, especially with anthracyclines, and radiotherapy.

additional Information:

www.chronobiology.com

or

www.ea3m.org

Thanks for your attention!

Any questions:
0172 5323277

Fauteck@ea3m.org
www.ea3m.org

ea3m European Academy of Preventive and Anti-Aging Medicine