IL SIGNIFICATO DEL RITMO CIRCADIANO DEL CORTISOLO:

FISIOLOGIA E PATOLOGIA

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Conditions with altered HPA axis activity

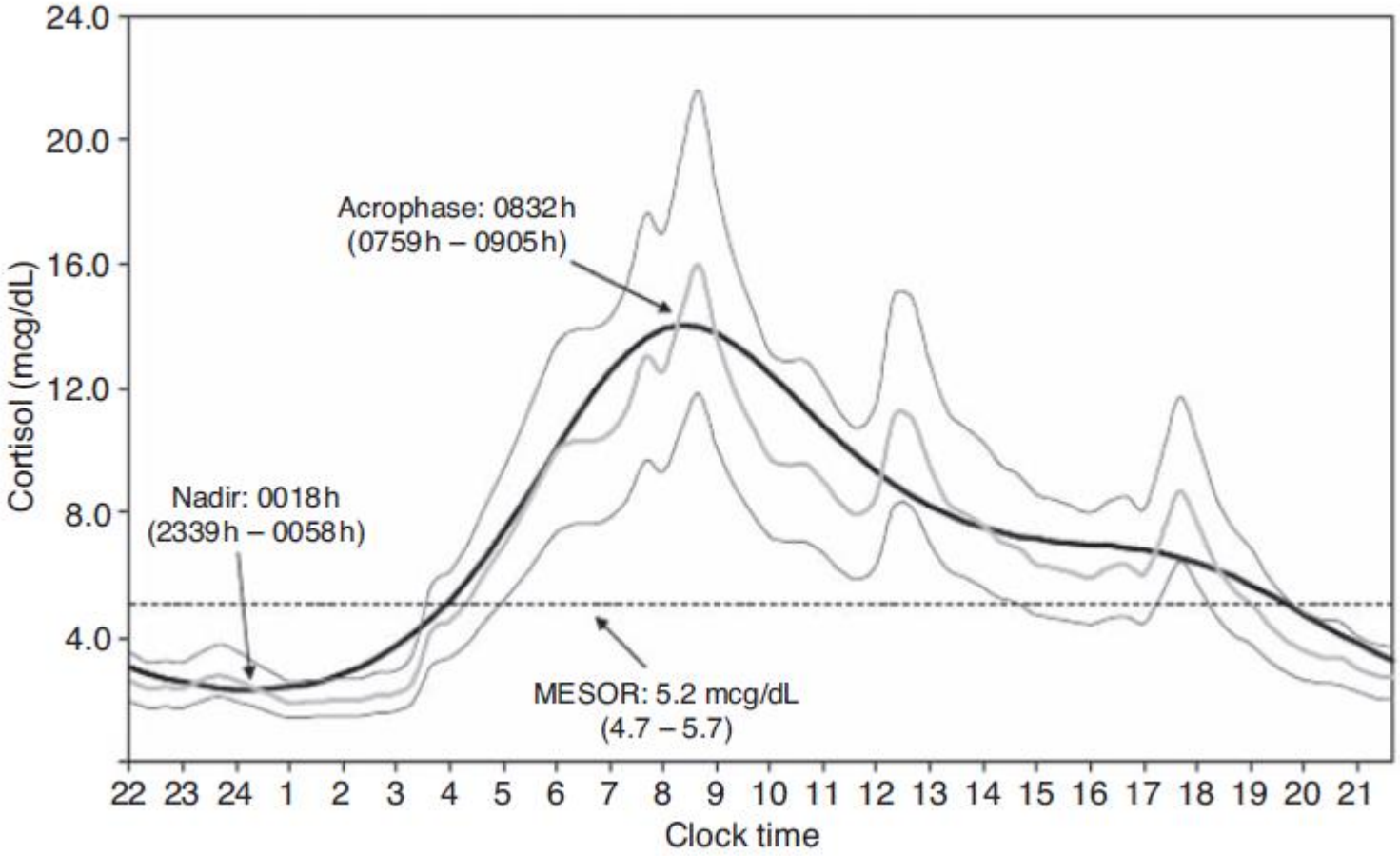
Although the precise significance of the daily GC rhythm is not yet well established, a growing body of evidence does point to its clinical importance.

Alterations in its rhythmicity are frequently found in many human diseases

Increased activity of the HPA axis	Decreased activity of HPA axis
■ Cushing syndrome	■ Adrenal insufficiency
■ Chronic stress	■ Atypical/ seasonal depression
■ Melancholic depression	■ Chronic fatigue syndrome
■ Anorexia nervosa	■ Fibromyalgia
■ Obsessive–compulsive disorder	■ Premenstrual tension syndrome
■ Panic disorder	■ Climacteric depression
■ Excessive exercise (obligate athleticism)	■ Nicotine withdrawal
■ Chronic, active alcoholism	■ Following cessation of glucocorticoid therapy
■ Alcohol and narcotic withdrawal	■ Following Cushing syndrome cure
■ Diabetes mellitus	■ Following chronic stress
■ Central obesity (metabolic syndrome)	■ Postpartum period
■ Post-traumatic stress disorder in children	■ Adult post-traumatic stress disorder
■ Hyperthyroidism	■ Hypothyroidism
■ Pregnancy	■ Rheumatoid arthritis
	■ Asthma, eczema

Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol 2009;5:374–381

Circadian rhythm of cortisol

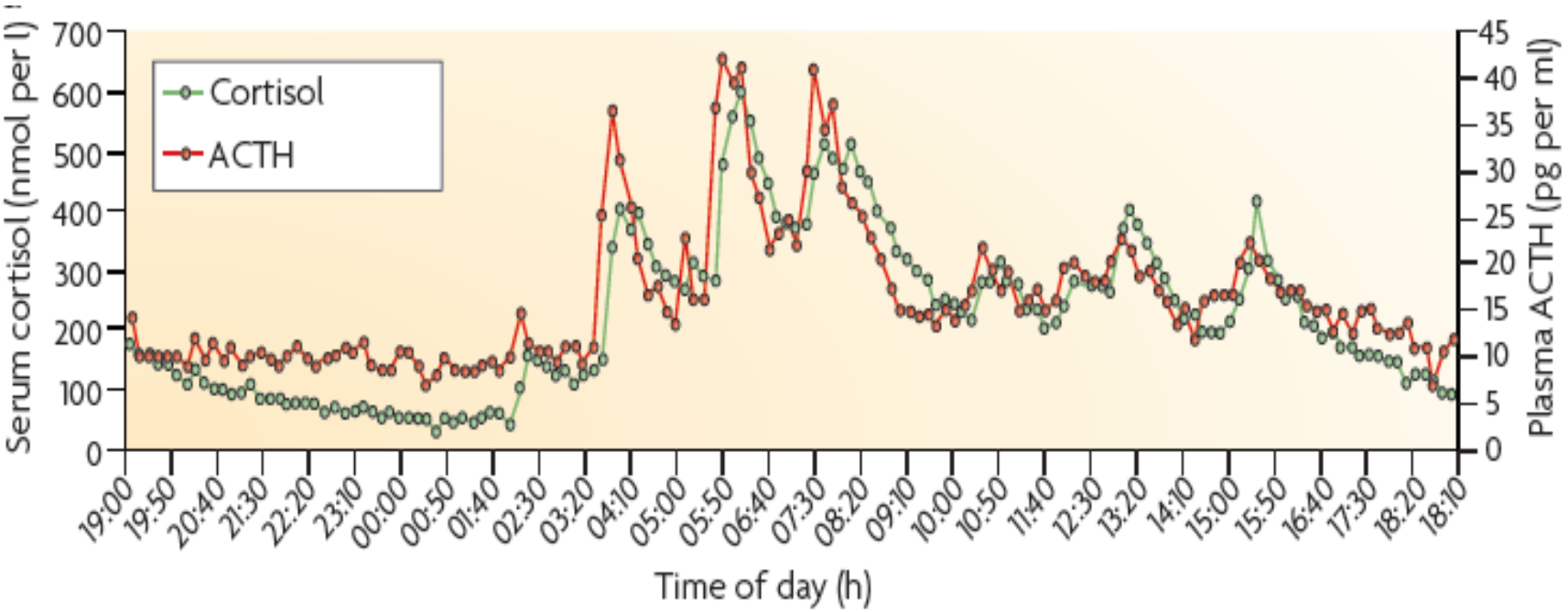


Circadian rhythm of cortisol in 33 individuals with 20-minute cortisol profiling

Chan S & De Bono M. Replication of cortisol circadian rhythm: new advances in hydrocortisone replacement therapyTher Adv Endocrinol Metab(2010) 1(3)

Circadian rhythm of cortisol

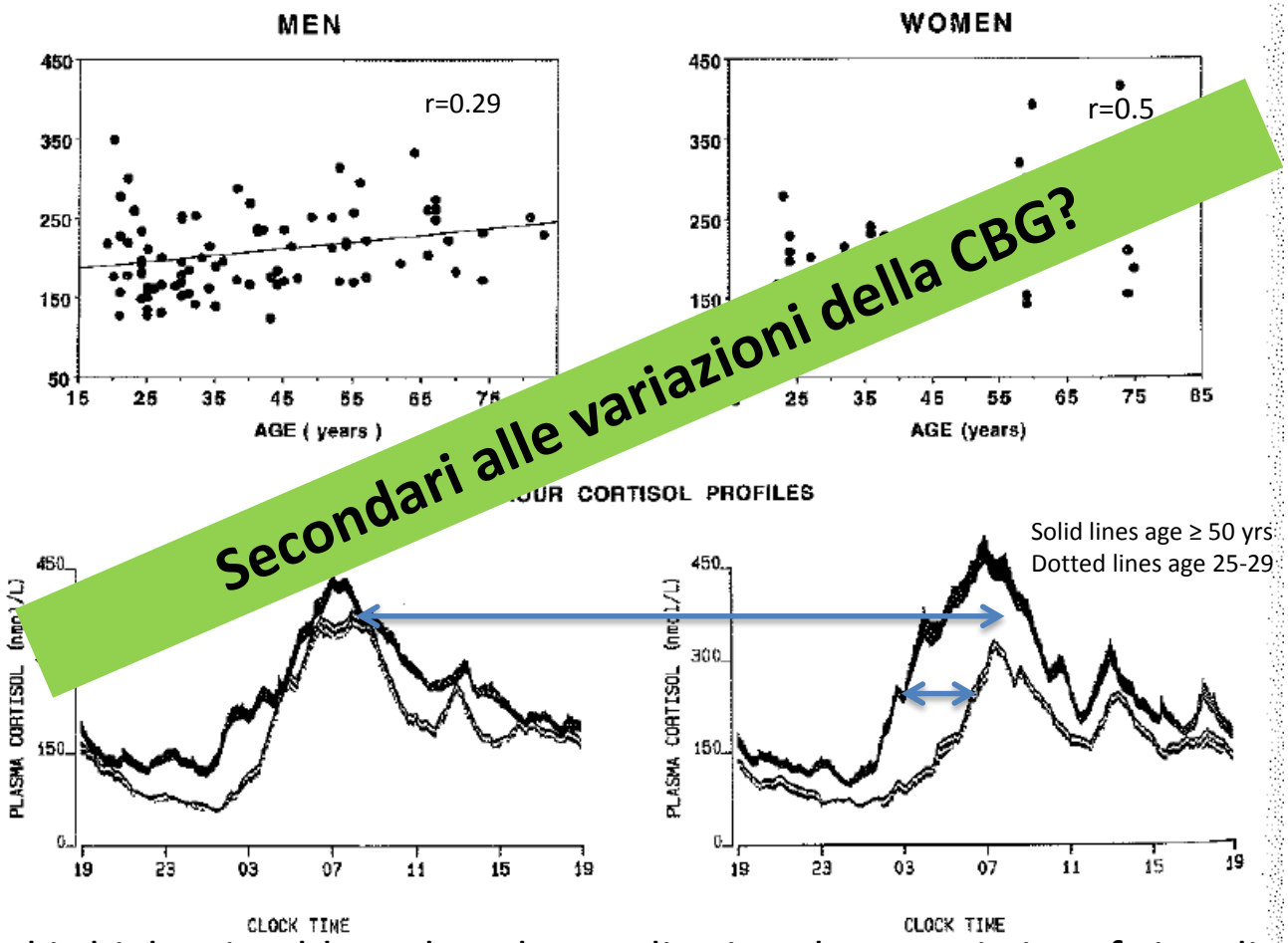
The circadian rhythm tracks an underlying ultradian activity of the HPA axis.



The apparent peak and trough of circadian activity actually reflects changes in the amplitude of the pulses, with the largest pulses coinciding with the awakening response and the onset of circadian activity daytime in humans (nighttime in nocturnal animals such as rodents)

Lightman SL et al The crucial role of pulsatile activity of the HPA axis for continuous dynamic equilibration. Nat Rev Neurosci. 2010 Oct;11(10):710-8

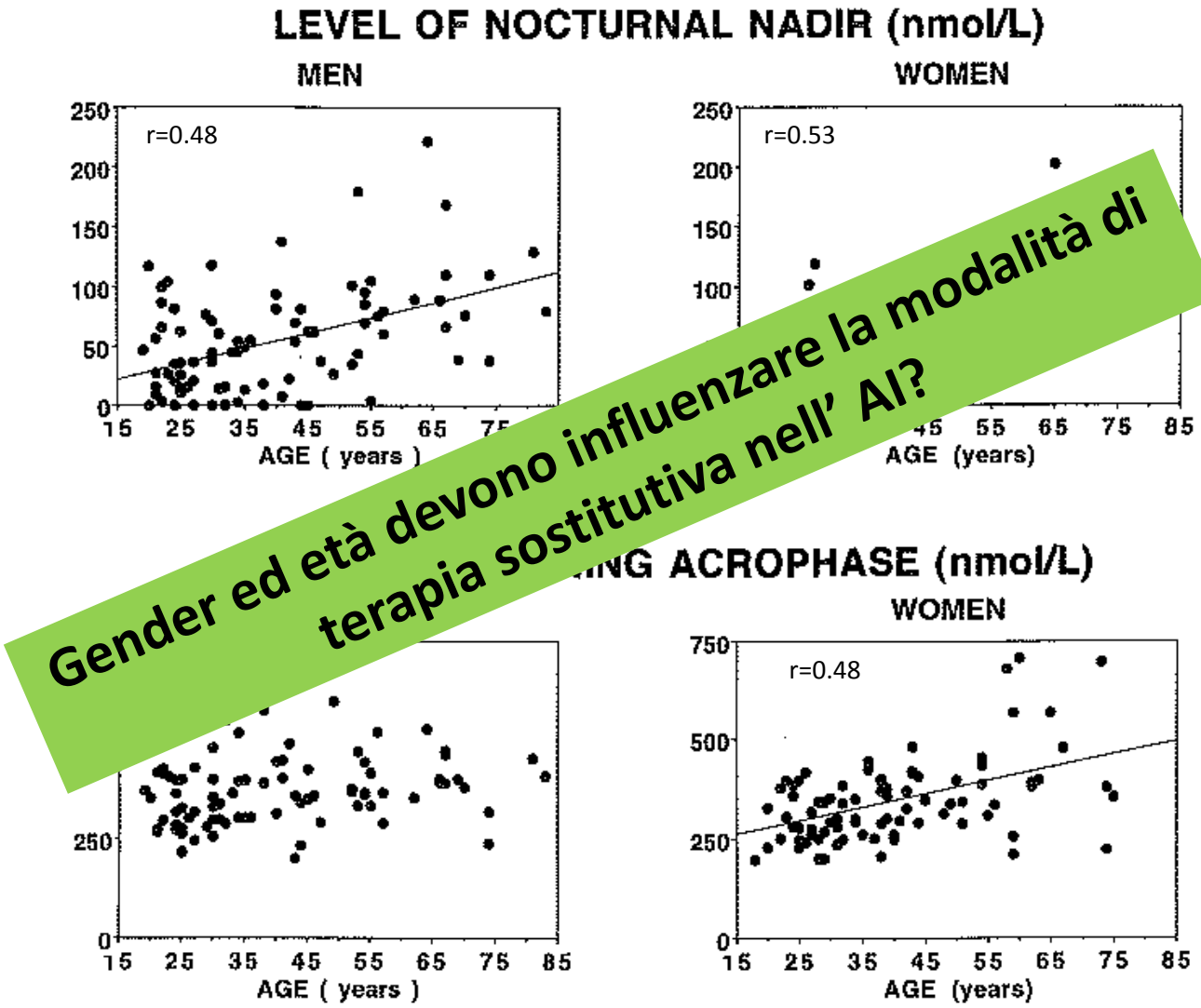
Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol



Cortisol level is higher in old age but the qualitative characteristics of circadian wave shape is preserved. In young women the quiescent period is longer and the level of morning acrophase is lower than in men

E Van Cauter, R Leproult, D J Kupfer Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. USA. Journal of Clinical Endocrinology &Metabolism. 08/1996; 81(7):2468-73.

Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol

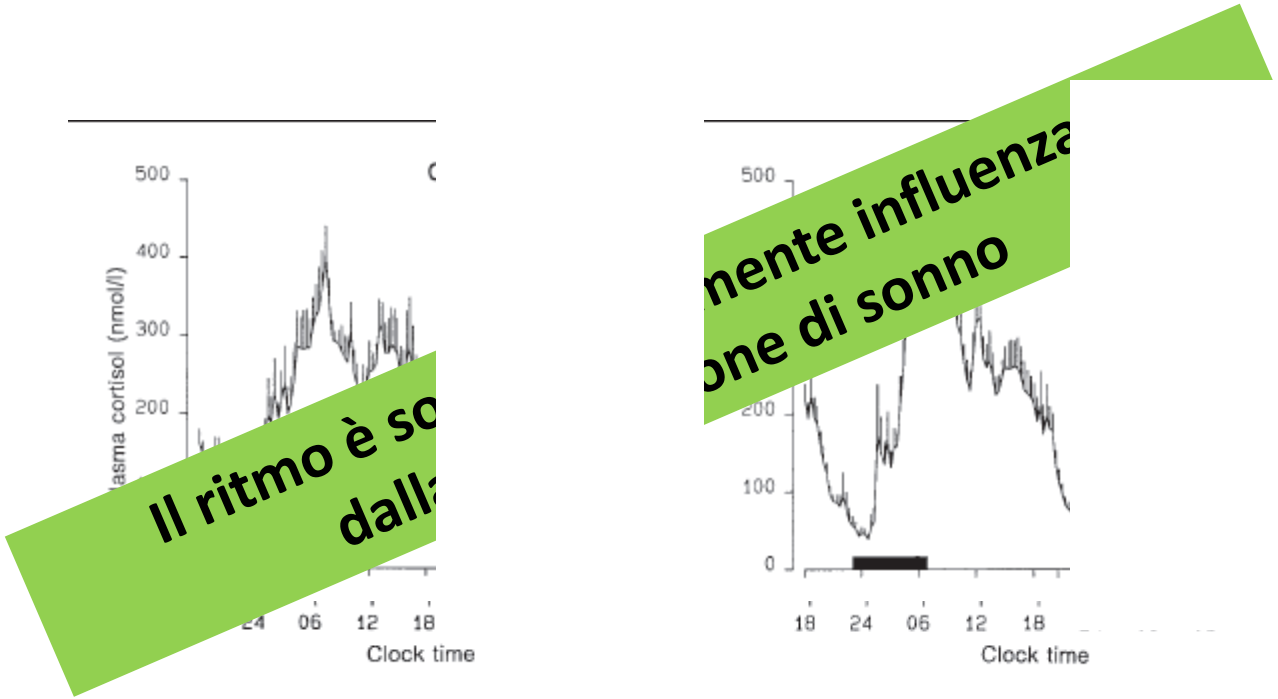


Gender ed età devono influenzare la modalità di terapia sostitutiva nell' AI?

E Van Cauter, R Leproult, D J Kupfer Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. USA. Journal of Clinical Endocrinology &Metabolism. 08/1996; 81(7):2468-73.

Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol

With aging, there is a progressive delay of the onset of the evening quiescent period and an advance of the onset of the circadian morning elevation.



Mean (B SEM) profiles of plasma cortisol in 8 young men (aged 25 ±4 years) and 8 older men (65 ± 5 years) studied during a 53-hour period including an 8-hour period of nocturnal sleep, a 28-hour period of continuous wakefulness and an 8-hour period of daytime recovery sleep. The blacks bars represent the sleep periods. The shaded bars represent the nocturnal periods of sleep deprivation

Van cauter E. Horm Res 1998;49:147–152. Alterations of Circadian.Rhythmicity and Sleep in Aging: Endocrine Consequences

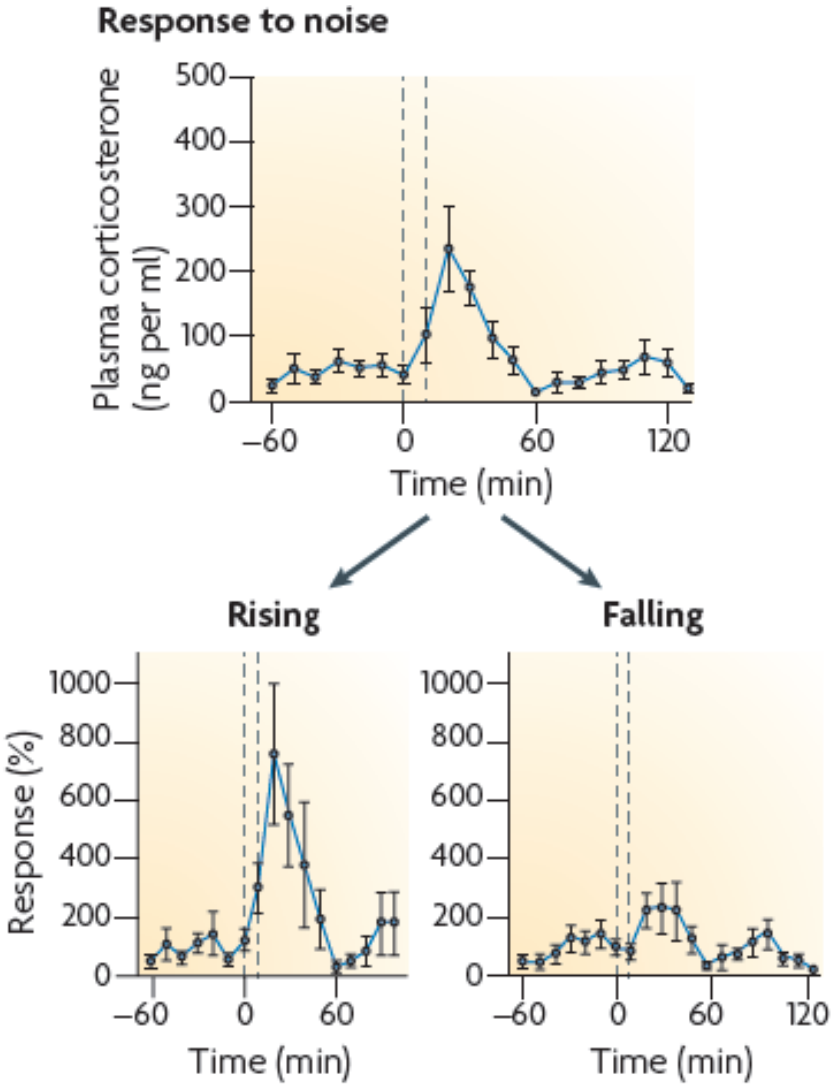
Circadian rhythm of cortisol

Nei roditori il rilascio di corticosterone e la sintesi di CRH delle femmine è superiore ai maschi. La gonadectomia annulla questa differenza.

Treatment group	AVP mRNA (% ± SEM of sham male controls)	CRH mRNA (% ± SEM of sham male controls)	POMC mRNA (% ± SEM of sham male controls)	GR mRNA controls) (% ± SEM of sham male controls)
Sham male	100 (4.9)	100 (7.4)	100 (4.6)	100 (4.4)
Castrated male	166 (7.1)**†††‡‡	186.1 (5.4)*†††‡‡	160 (3.9)**†††‡‡	77 (6.1)†
Sham female	130 (6.1)†‡‡	150.6 (5.9)†††‡‡	135.7 (4)†††‡‡	68 (12.4)*‡
Ovariectomized female	97 (2.4)	94.8 (7.0)	98.6 (3.7)	90 (2.)

J. V. Seale et al. Gonadectomy Reverses The Sexually Diergic Patterns Of Circadian and Stress-Induced Hypothalamic-Pituitary-Adrenal Axis Activity In Male and Female Rats Journal of Neuroendocrinology, 2004, Vol. 16, 516–524

Influence of circadian rhythm of cortisol on acute response to stress

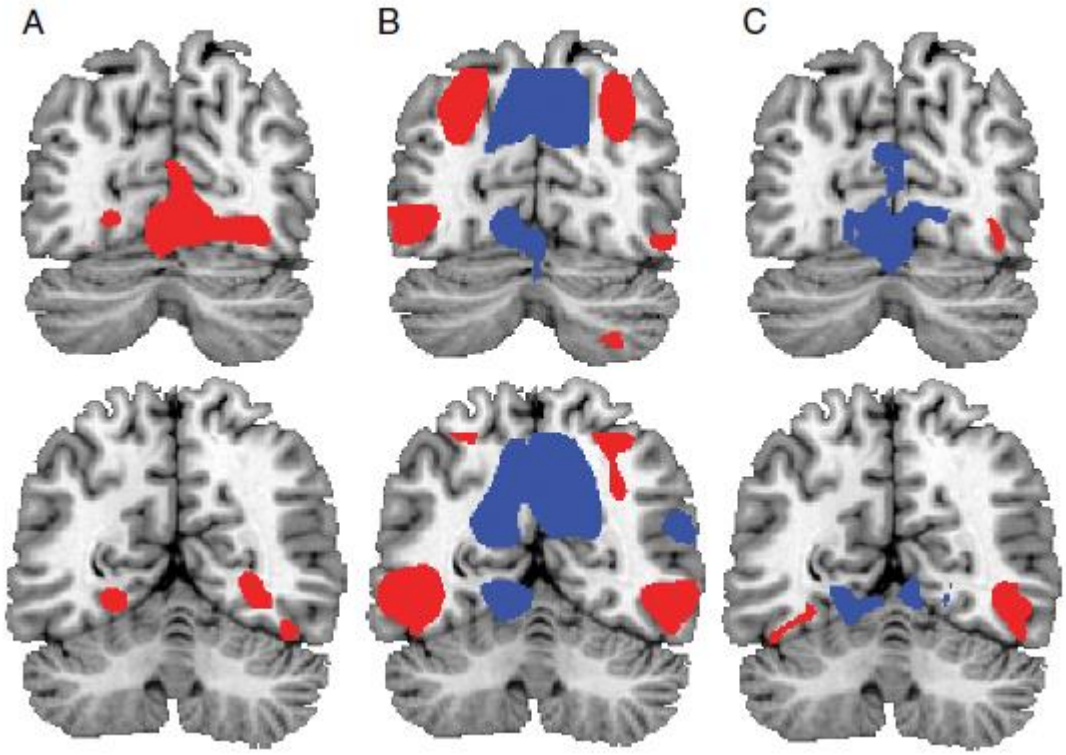


A stress coincident with the rising (secretory) phase

A stress coincident with the falling phase

Windle, R. J., Wood, S. A., Shanks, N., Lightman, S. L.& Ingram, C. D. Ultradian rhythm of basal corticosterone release in the female rat: dynamicinteraction with the response to acute stress. *Endocrinology 139, 443–450 (1998).*

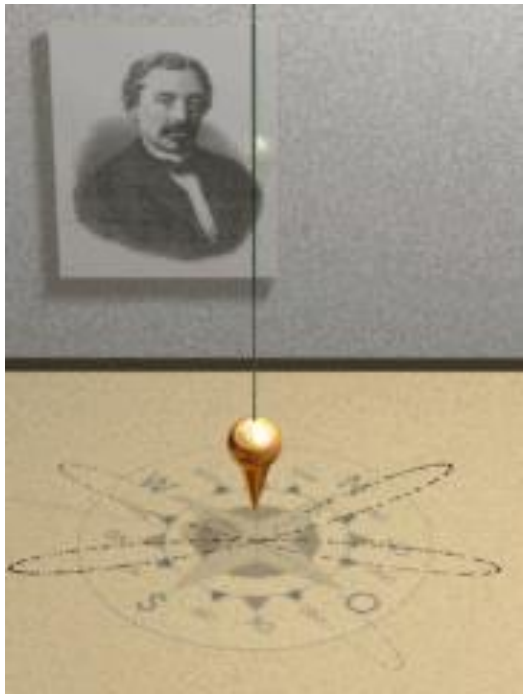
GC fluctuations postively and negatively affect memory



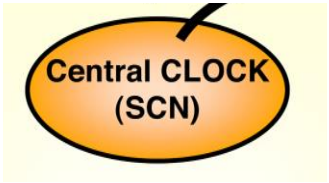
The mammalian circadian clockwork

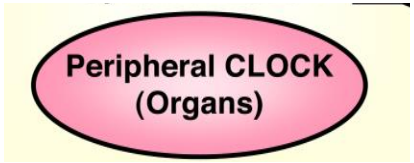
Most organisms have evolved circadian clocks to optimally adjust their behavior and physiology to such recurring changes.

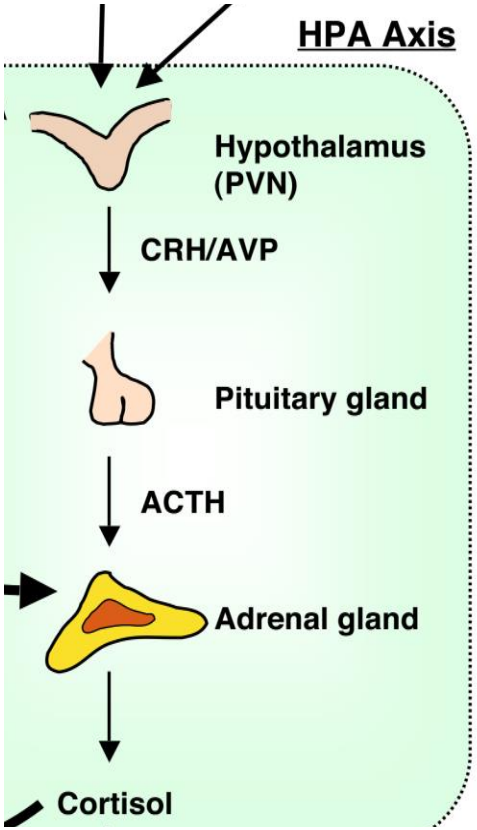
- Autonomous and self-sustainable circadian oscillator
- "Zeitgebers"
- Output rhythm



Interactions of the Circadian CLOCK System and the HPA Axis

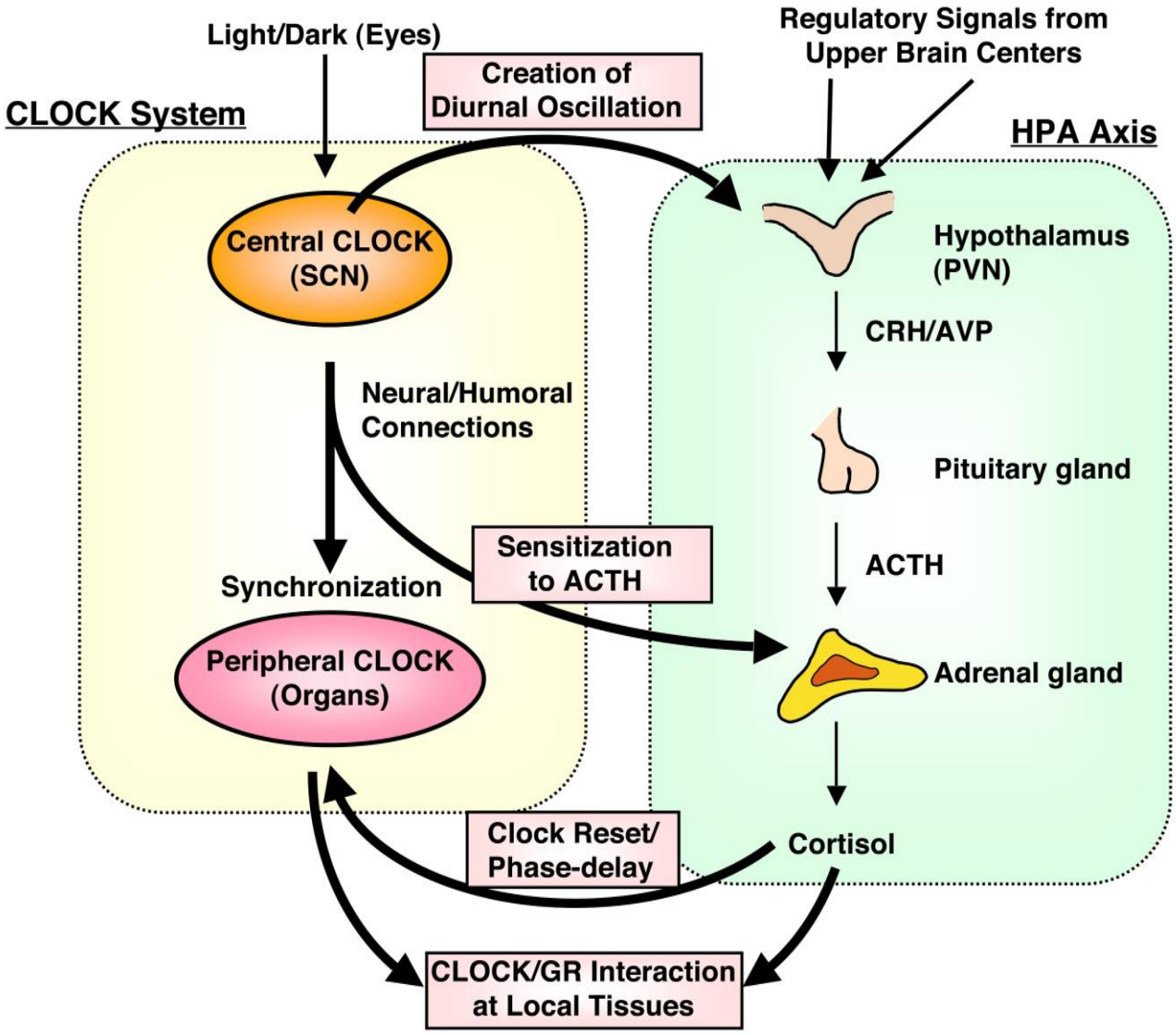






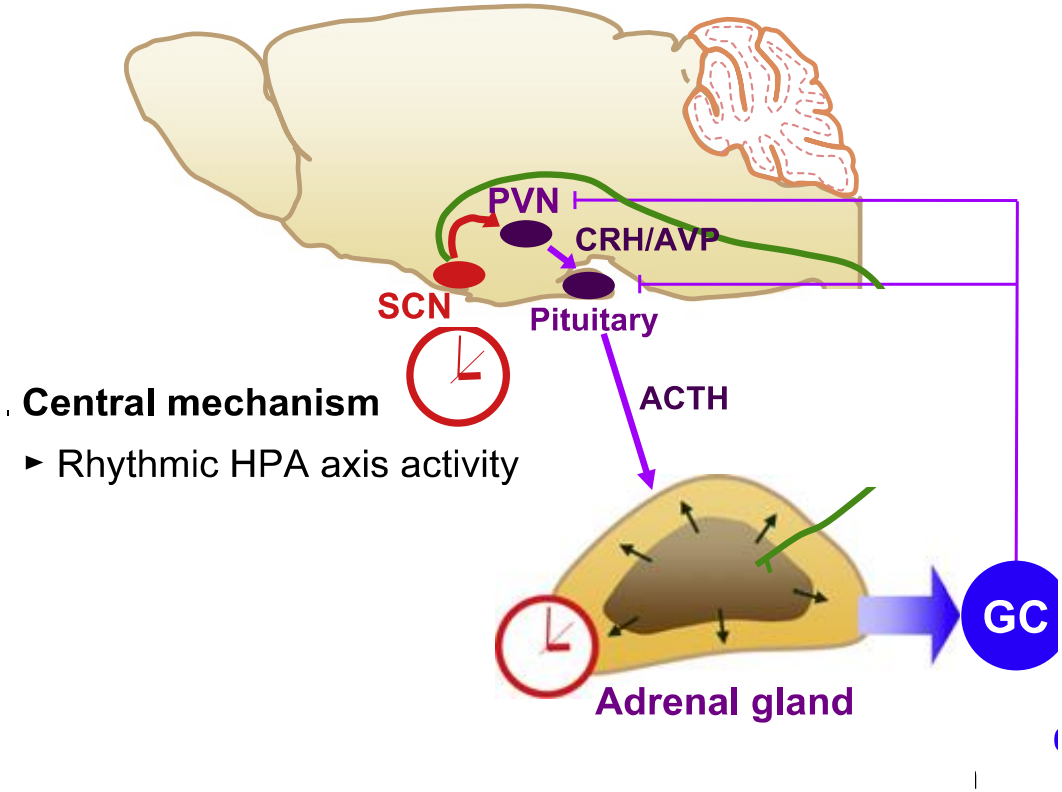
Nancy Nader et al Trends Endocrinol Metab. 2010 May ; 21(5): 277–286.

Interactions of the Circadian CLOCK System and the HPA Axis



Nancy Nader et al Trends Endocrinol Metab. 2010 May ; 21(5): 277–286.

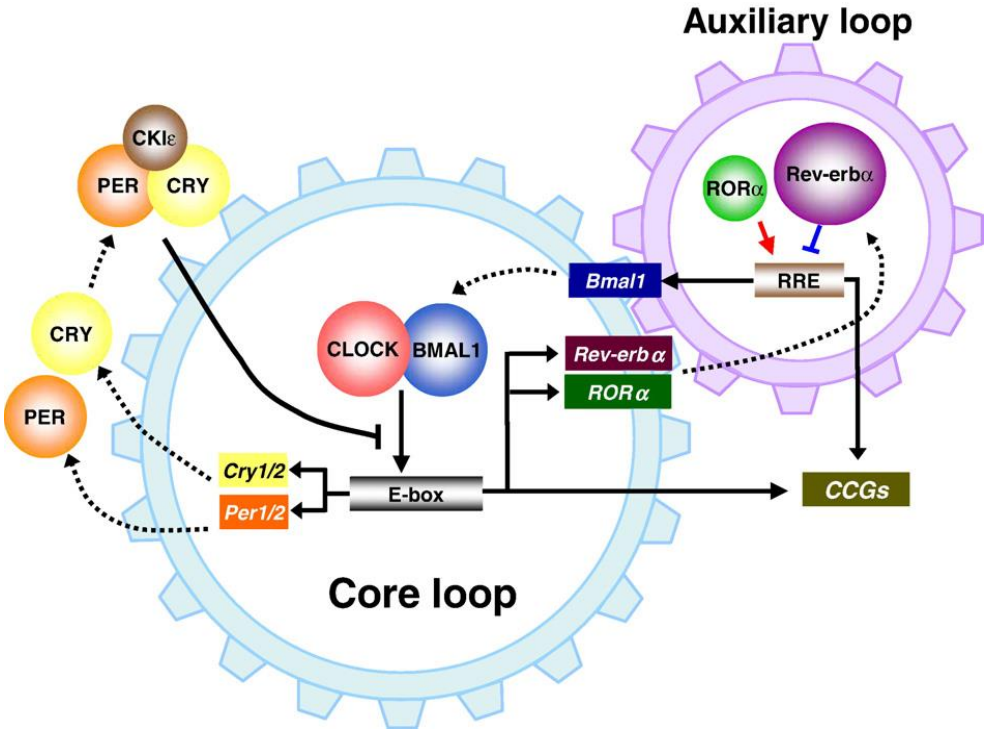
Multiple mechanisms underlying the circadian regulation of glucocorticoid biosynthesis and secretion

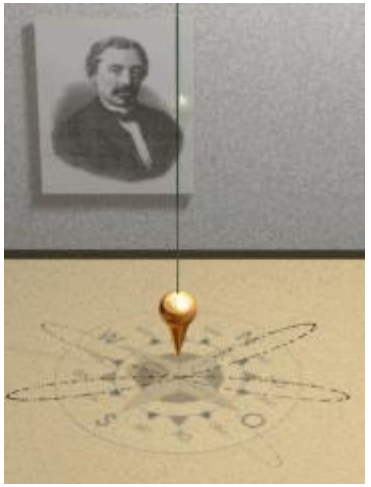


1. The driving role of the SCN via the neuroendocrine ACTH axis
2. The independent autonomic nervous system
3. The intrinsic mechanisms involving the adrenal local clockwork
4. The terminal effects on peripheral clocks

Molecular circadian clockwork

Principal or core feedback loop CLOCK and BMAL1, form heterodimers to activate the transcription of their target genes containing E-box element



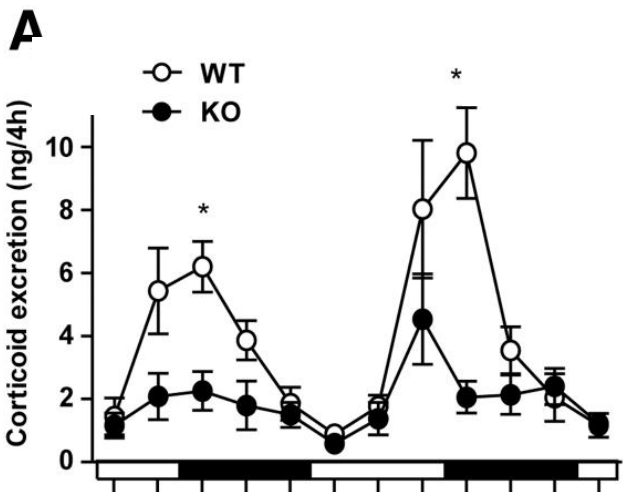


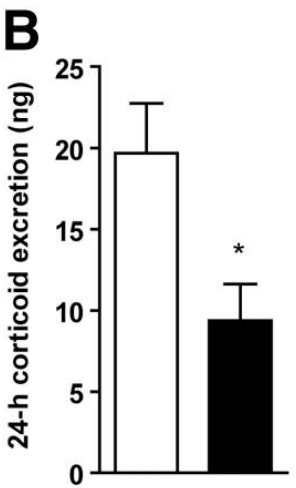
These target genes include their negative regulators the Periods (PERs: PER1, PER2 and PER3) and the Cryptochromes (CRYs: CRY1 and CRY2).
The concentration of BMAL1 is adjusted by an auxiliary or stabilizing feedback loop formed by the clock-controlled nuclear receptors REVERBα

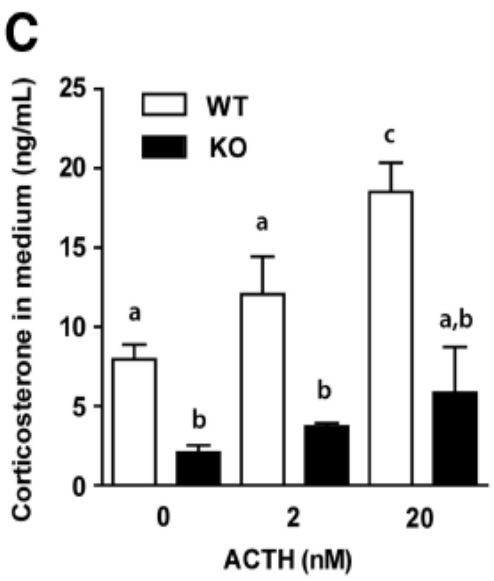
Gi Hoon Son, Sooyoung Chung, Kyungjin Kim The adrenal peripheral clock: Glucocorticoid and the circadian timing system Frontiers in Neuroendocrinology 32 (2011) 451–465

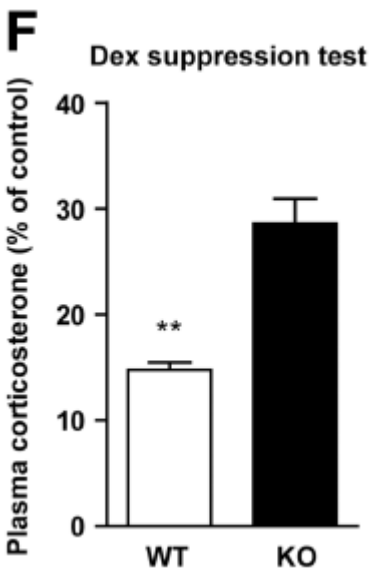
Clock genes influence GC rhythm and release

BMAL1 (arntl -/-) ko mice

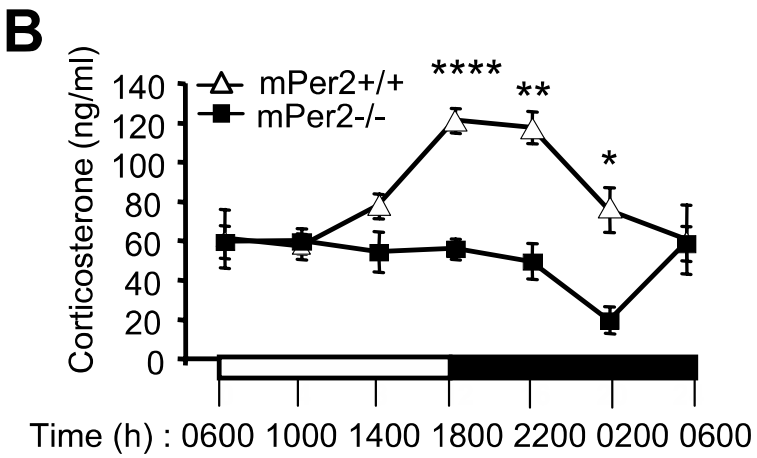








Per ko mice

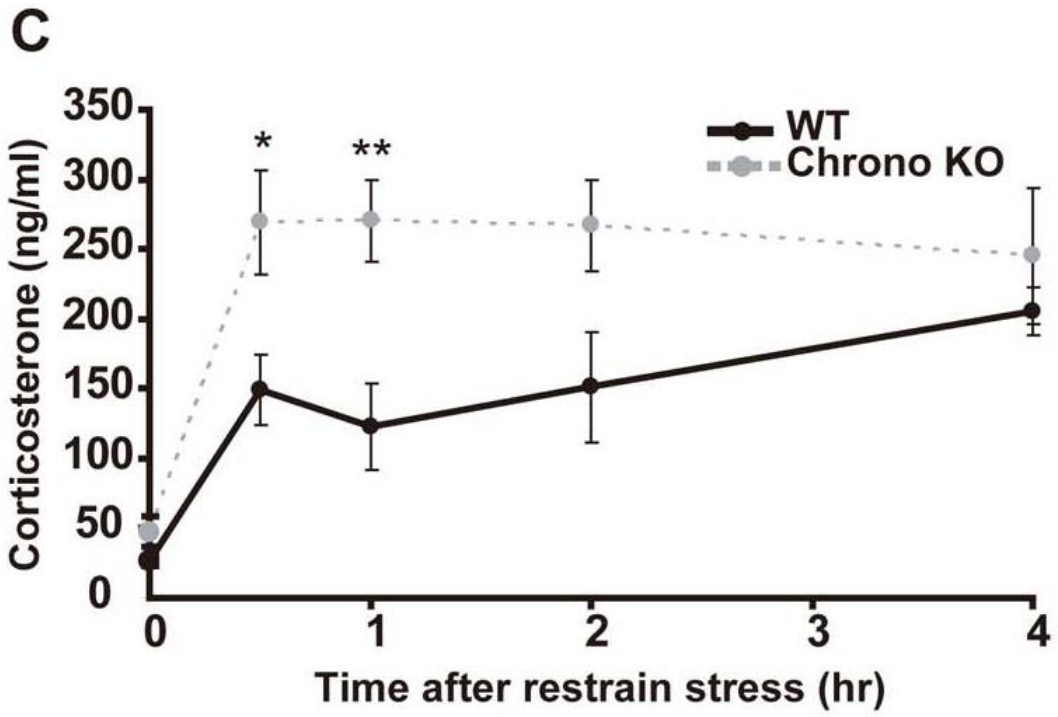


Alexei Leliavski, Anton Shostak, Jana Husse, and Henrik Oster Impaired Glucocorticoid Production and Response to Stress in Arntl-Deficient Male Mice Endocrinology 155: 133–142, 2014

Shutong Yang et al The Role of mPer2 Clock Gene in Glucocorticoid and Feeding Rhythms Endocrinology 150: 2153–2160, 2009

Recent development in Molecular circadian clockwork

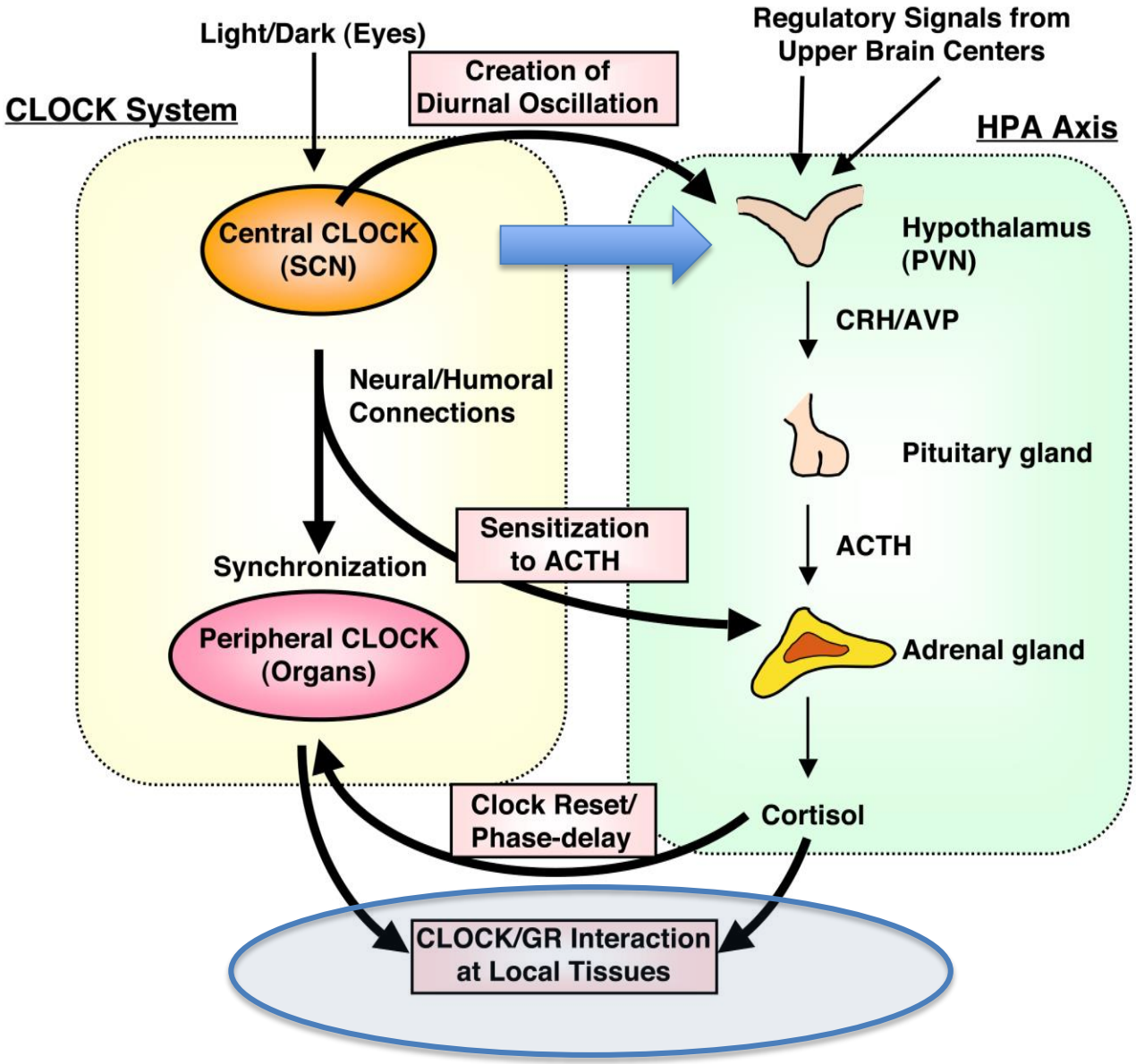
A Novel Protein, CHRONO, Functions as a Core Component of the Mammalian Circadian Clock



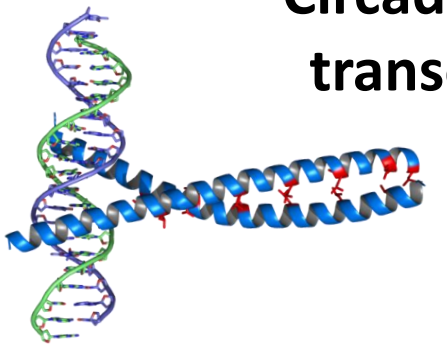
Serum corticosterone levels in vivo were also robustly increased in Chrono KO when compared with WT mice after 0.5 h and 1 h of restraint stress

Goriki A et al A novel protein, CHRONO, functions as a core component of the mammalian circadian clock. PLoS Biol. 2014 Apr 15;12(4):e1001839.

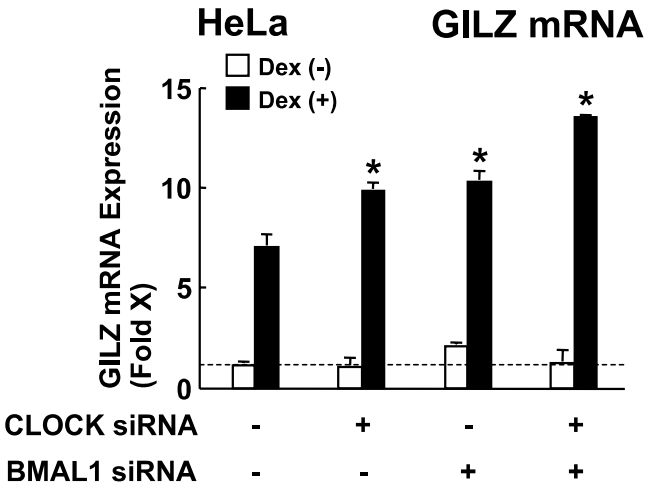
Interactions of the Circadian CLOCK System and the HPA Axis

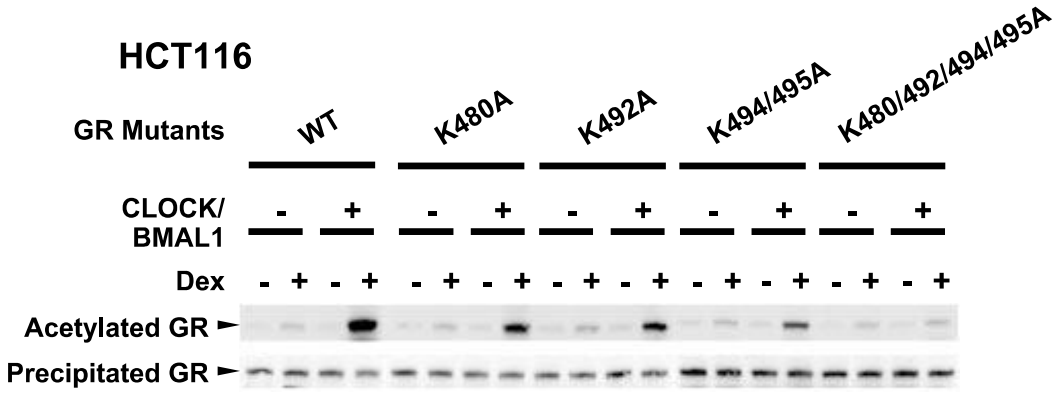


Nancy Nader et al Trends Endocrinol Metab. 2010 May ; 21(5): 277–286.



Circadian rhythm transcription factor CLOCK regulates the transcriptional activity of the glucocorticoid receptor by acetylating its hinge region lysine cluster

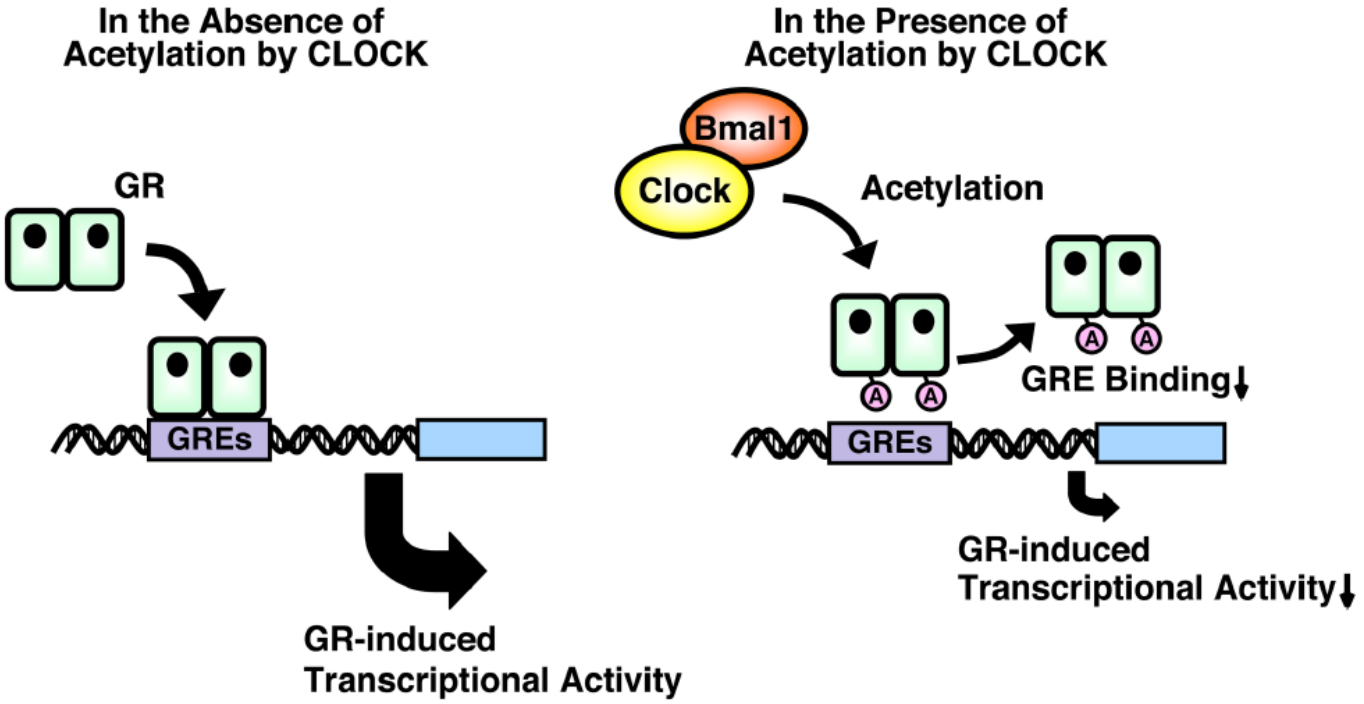




Nader, N., Chrousos, G. P., Kino, T. Circadian rhythm transcription factor CLOCK regulates the transcriptional activity of the glucocorticoid receptor by acetylating its hinge region lysine cluster: potential physiological implications. FASEB J. 23, 1572–1583 (2009)

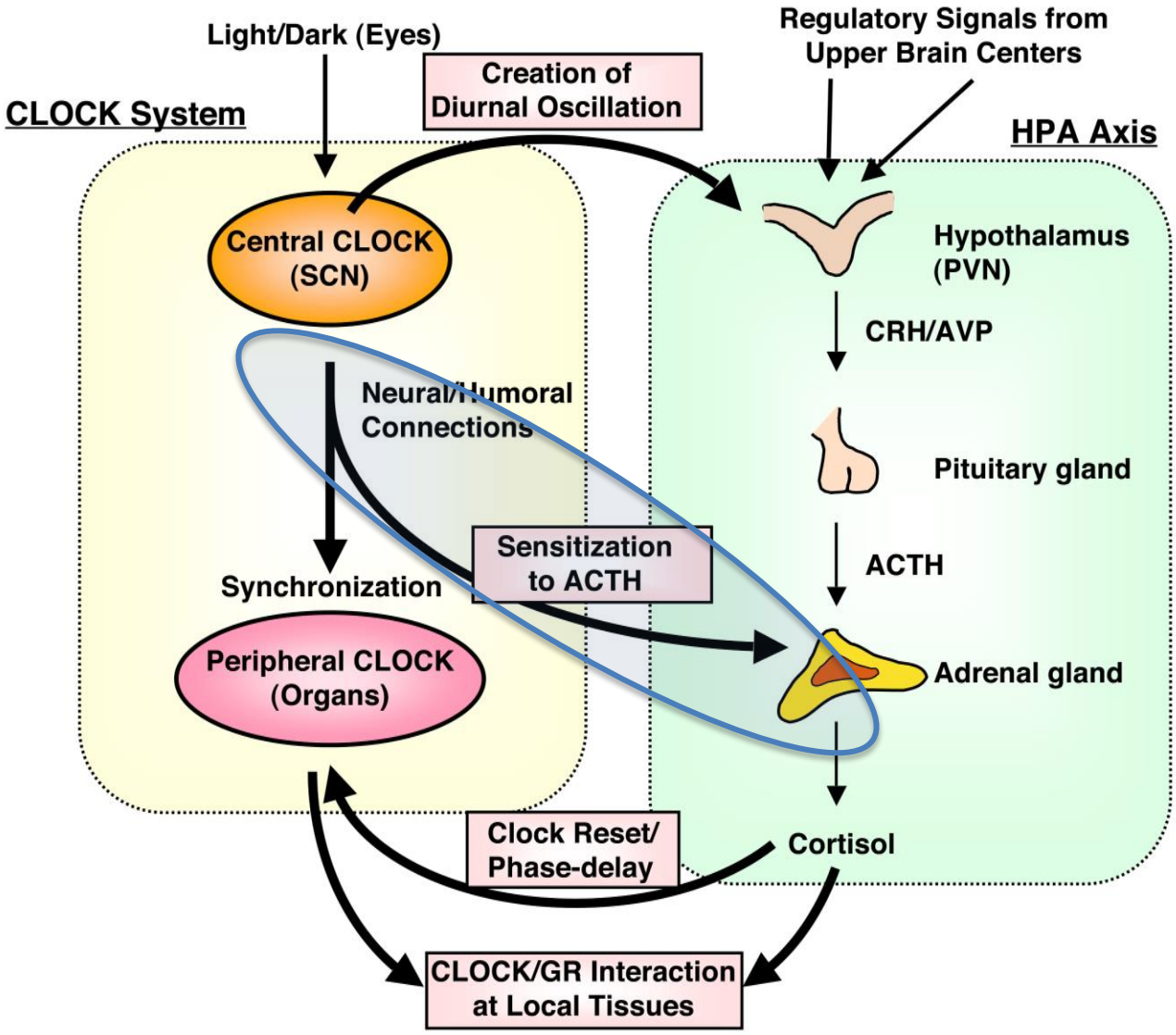
The clockwork influence responsiveness to GC

Clock/Bmal1 physically interact with the ligand-binding domain of the GR through a region enclosed in the C-terminal part of the Clock protein, and suppressed GR-induced transcriptional activity



Nancy Nader et al Trends Endocrinol Metab. 2010 May ; 21(5): 277–286.

Interactions of the Circadian CLOCK System and the HPA Axis



Nancy Nader et al Trends Endocrinol Metab. 2010 May ; 21(5): 277–286.

The mammalian circadian clockwork

The driving role of the Suprachiasmatic nucleus

The oscillatory patterns of GC in the periphery have been primarily attributed to the SCN control of the HPA neuroendocrine Axis.

Lesione del SCN elimina il ritmo di ACTH e corticosterone, aumentando la secrezione di corticosterone

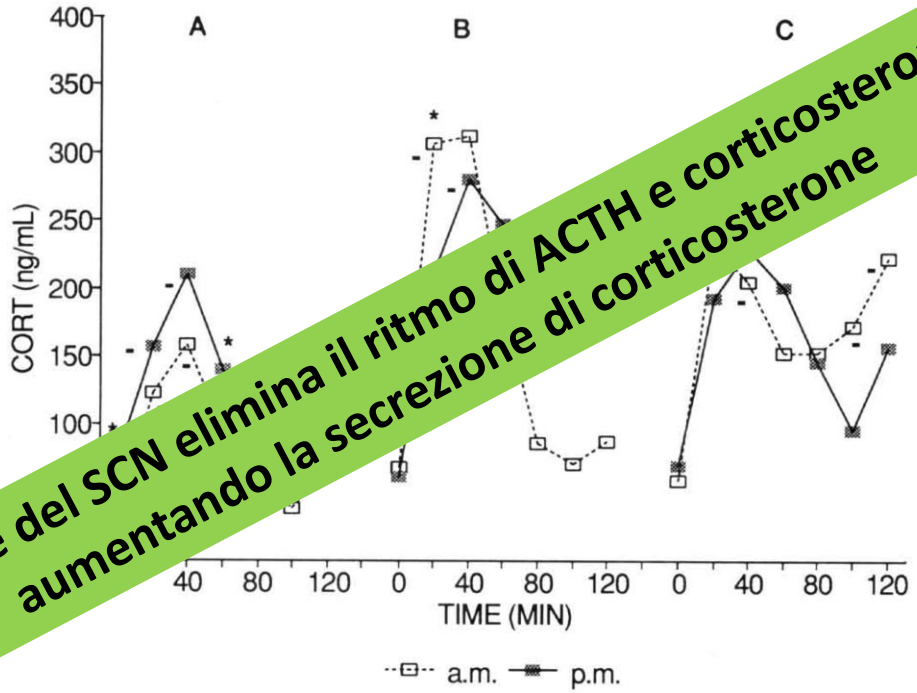


Fig. 3. Basal *time 0* and novelty-induced plasma corticosterone (Cort) levels comparing morning and evening values for intact (*A*), SCN-lesioned (*B*), and partial SCN-lesioned groups (*C*) separately. * $P < 0.05$ compared with morning values. ▬ $P < 0.05$ compared with *time 0* of same group. Animals were moved to a new cage at *time 0*.

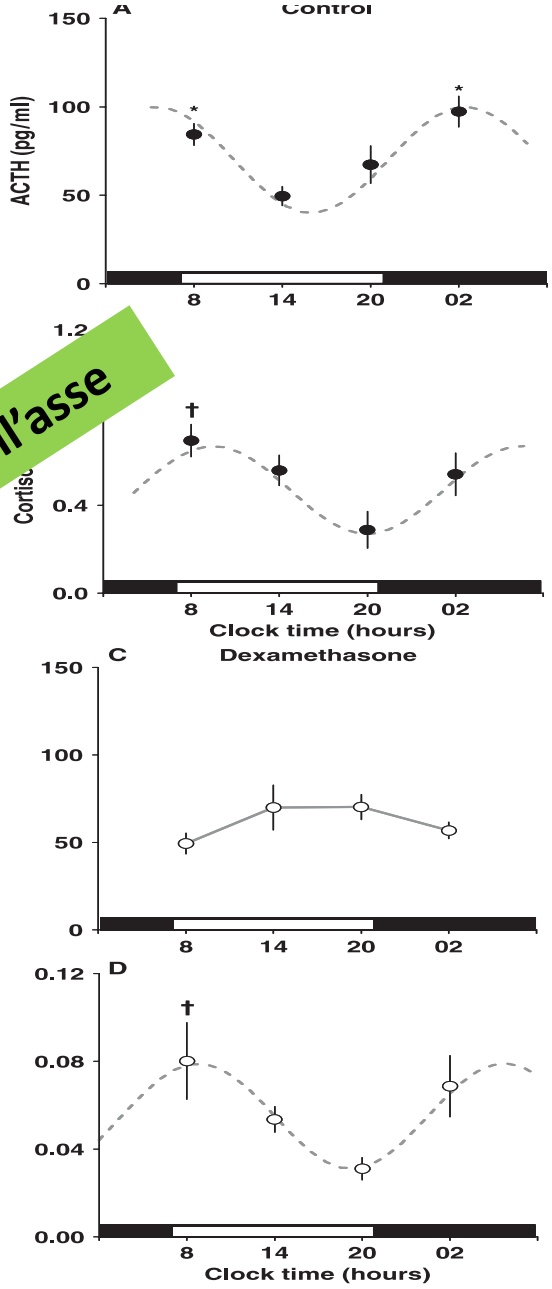
R.M. Buijs, A. Kalsbeek, T.P. van der Woude, J.J. van Heerikhuize, S. Shinn, Suprachiasmatic nucleus lesion increases corticosterone secretion, Am. J.Physiol. 264 (1993) R1186–R1192

Circadian regulation of GC biosynthesis and secretion

GC rhythm does not simply depend on the rhythmic release of ACTH.

The plasma GC rhythm persists in: monkeys administered dexamethasone to suppress endogenous CRH/ACTH secretion

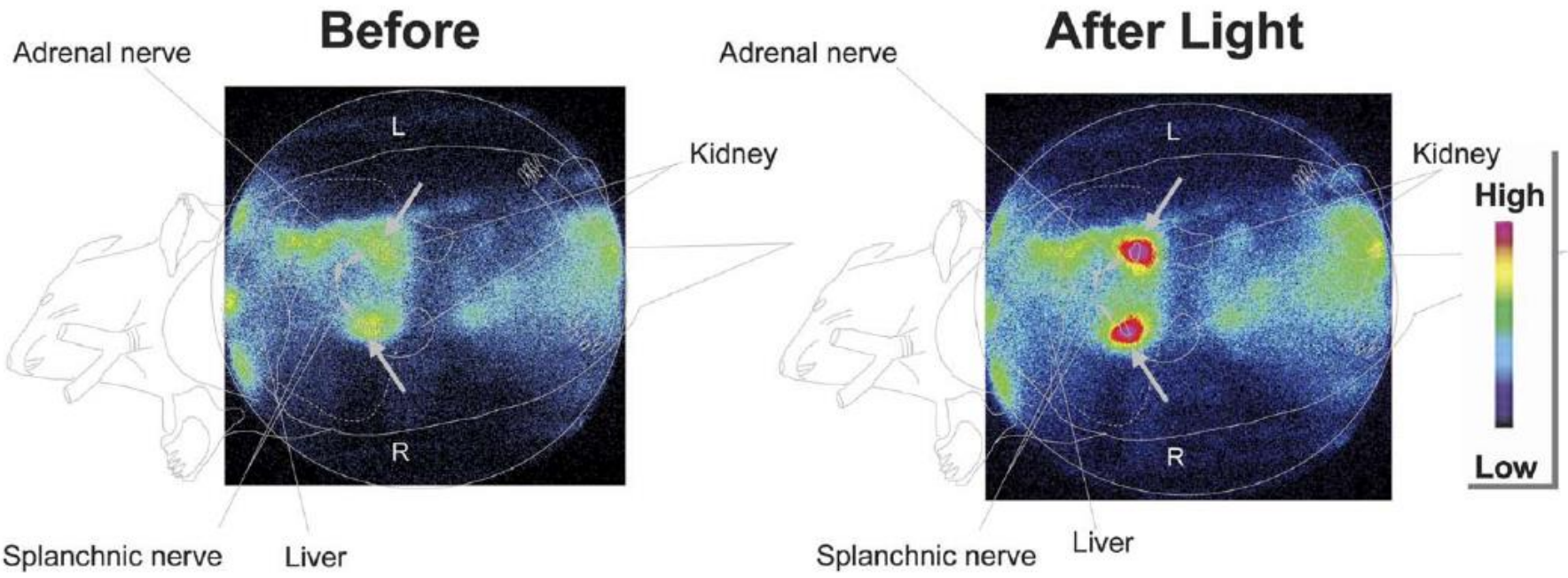
Ritmo dei GC persiste anche dopo soppressione dell'asse



C. Torres-Farfan, F.J. Valenzuela, R. Ebensperger, N. Mendez, C. Campino, H.G. Richter, G.J. Valenzuela, M. Seron-Ferre, Circadian cortisol secretion and circadian adrenal responses to ACTH are maintained in dexamethasone suppressed capuchin monkeys (Cebus apella), Am. J. Primatol. 70 (2008) 93– 100.

HOW?

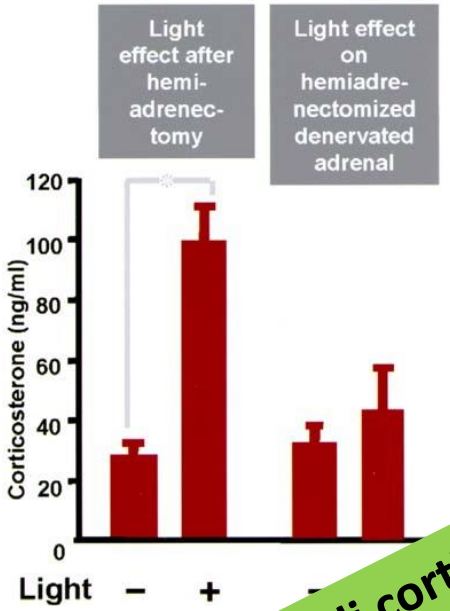
Light activates the adrenal gland



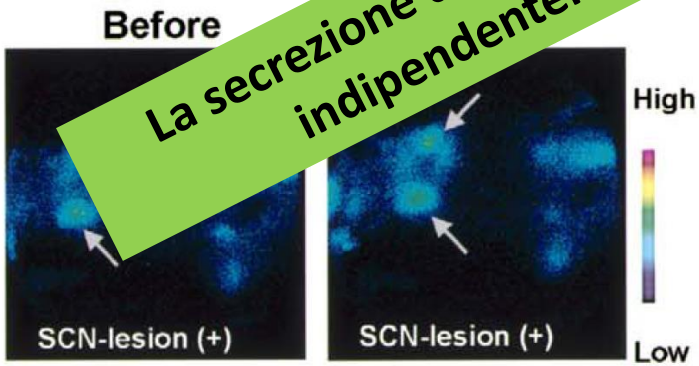
Per1-luc luminescence in visceral organs

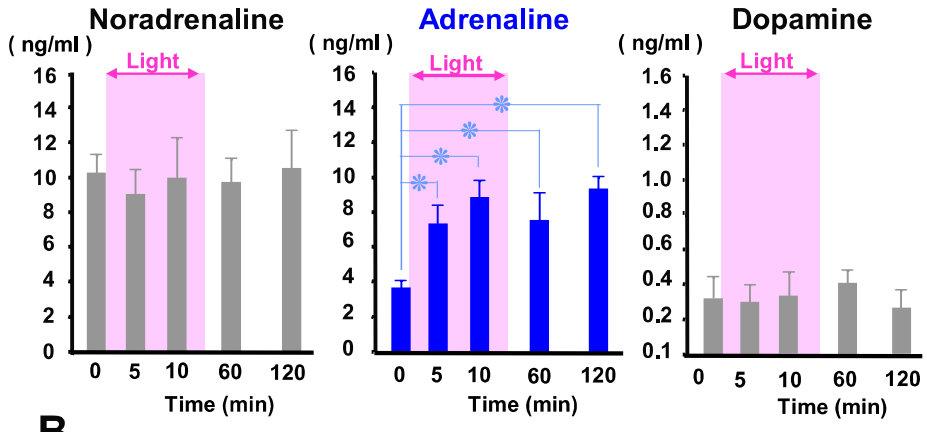
A. Ishida, T. Mutoh, T. Ueyama, H. Bando, S. Masubuchi, D. Nakahara, G. Tsujimoto, H. Okamura, Light activates the adrenal gland: timing of gene expression and glucocorticoid release, Cell Metab. 2 (2005) 297–307.

Light activates the adrenal gland through SCN activation and splanchnic innervation of the gland



La secrezione di corticosterone aumenta 60-120' dopo lo stimolo luminoso indipendentemente dall'ACTH ed è dipendente dall'adrenalina



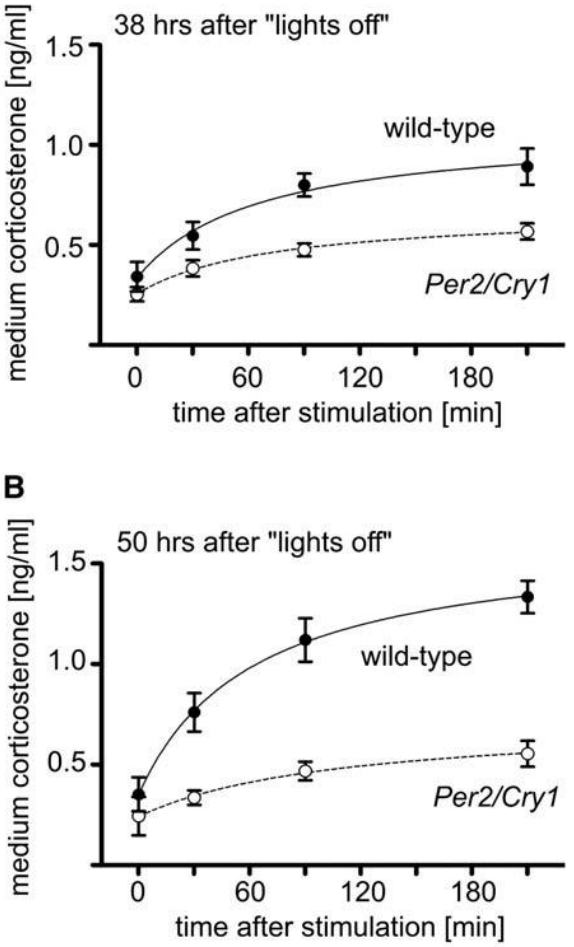


A. Ishida, T. Mutoh, T. Ueyama, H. Bando, S. Masubuchi, D. Nakahara, G. Tsujimoto, H. Okamura, Light activates the adrenal gland: timing of gene expression and glucocorticoid release, Cell Metab. 2 (2005) 297–307.

Adrenal intrinsic mechanisms: the involvement of adrenal oscillator

"Gating mechanism": the local clock machinery in the adrenal gland contributes to the diurnal rhythm of GC by controlling the daily variation in the adrenal sensitivity to ACTH.

I geni clock regolano La sensibilità del surrene all'ACTH

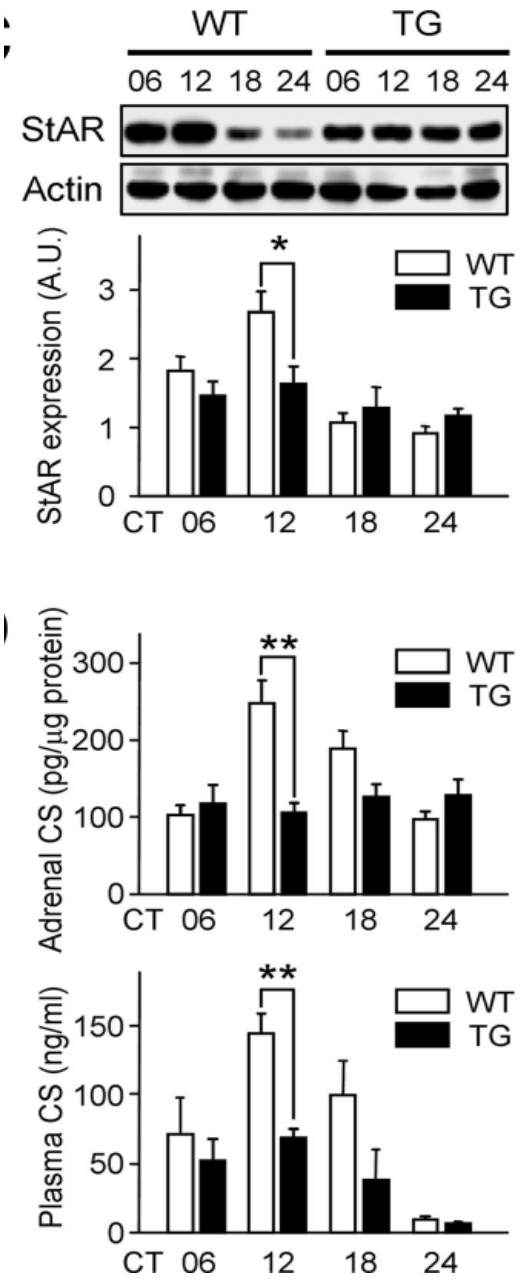


H. Oster, S. Damerow, S. Kiessling, V. Jakubcakova, D. Abraham, J. Tian, M.W. Hoffmann, G. Eichele, The circadian rhythm of glucocorticoids is regulated by a gating mechanism residing in the adrenal cortical clock, Cell Metab. 4 (2006) 163–173.

Adrenal intrinsic mechanisms: the involvement of adrenal oscillator

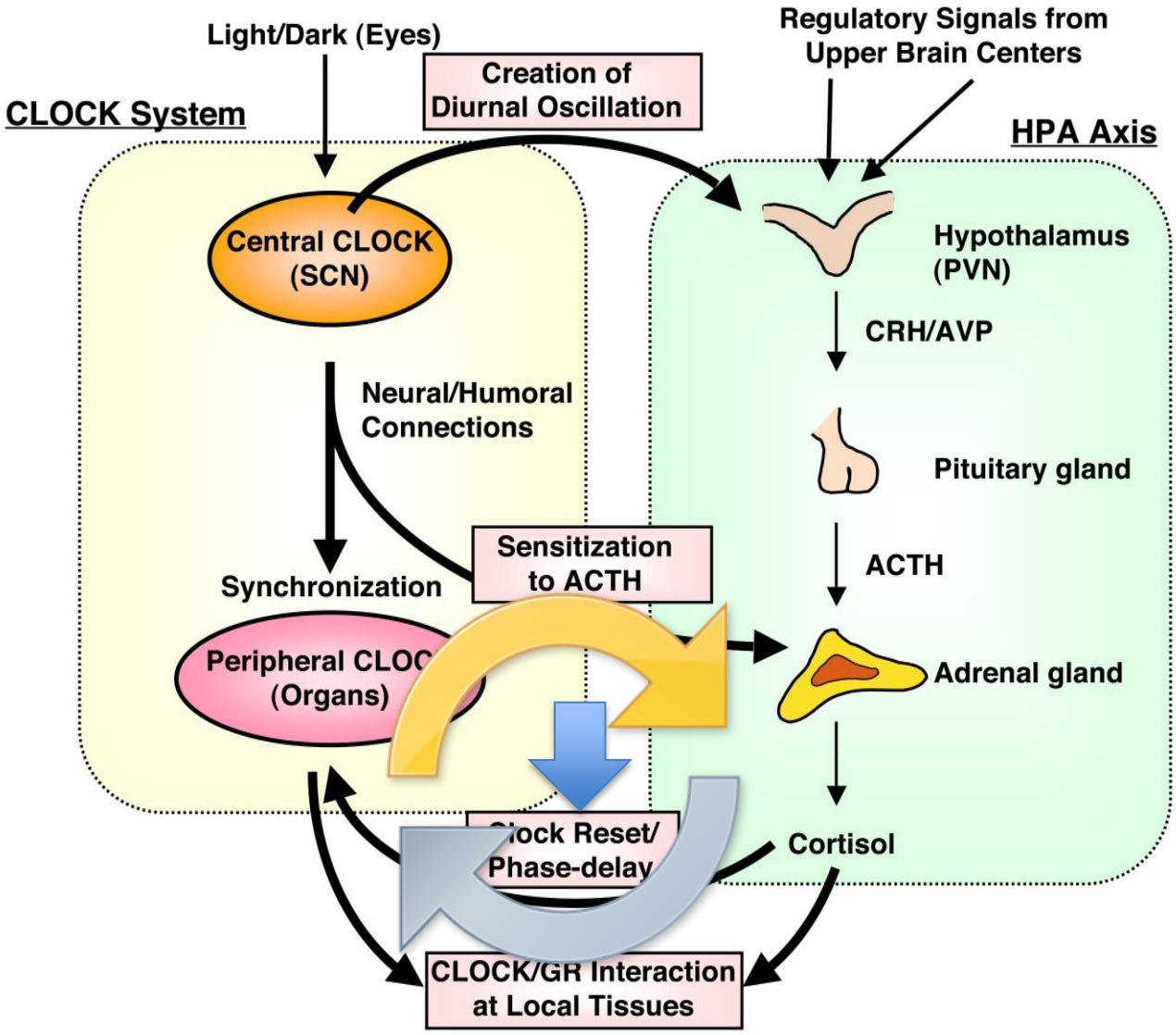
Geni clock controllano la produzione dei glucocorticoidi modulando l'espressione StAR

Examination of mice with adrenal-specific knockdown of the canonical clock protein BMAL1 reveals that the adrenal clock machinery is required for circadian GC production



Son GH et al Proc Natl Acad Sci U S A. 2008 Dec 30;105(52):20970-5 Adrenal peripheral clock controls the autonomous circadian rhythm of glucocorticoid by causing rhythmic steroid production

Interactions of the Circadian CLOCK System and the HPA Axis



Nancy Nader et al Trends Endocrinol Metab. 2010 May ; 21(5): 277–286.

Adrenal intrinsic mechanisms: the involvement of adrenal oscillator

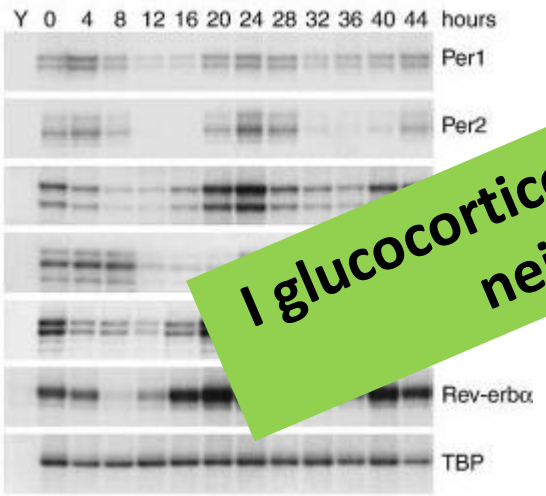
An acute administration of GC can induce phase synchronization in a wide range of peripheral clocks both in vivo and in vitro

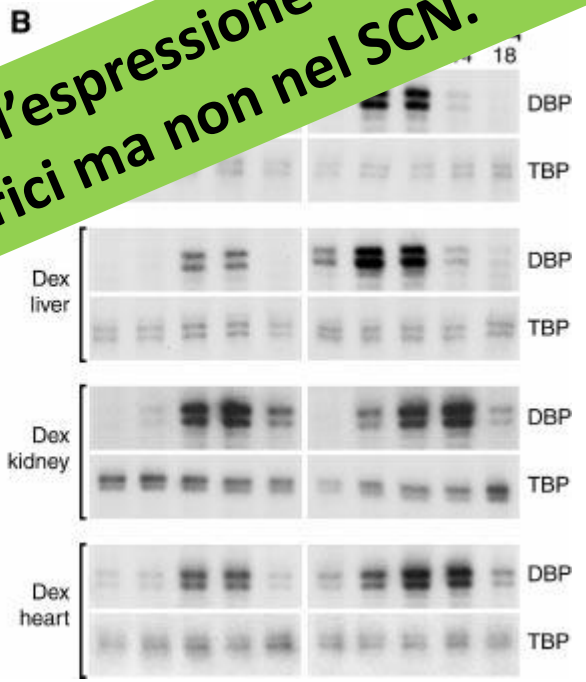
Resetting of Circadian Time in Peripheral Tissues by Glucocorticoid Signaling
Aurélio Balsalobre *et al.*
Science **289**, 2344 (2000);
DOI: 10.1126/science.289.5488.2344

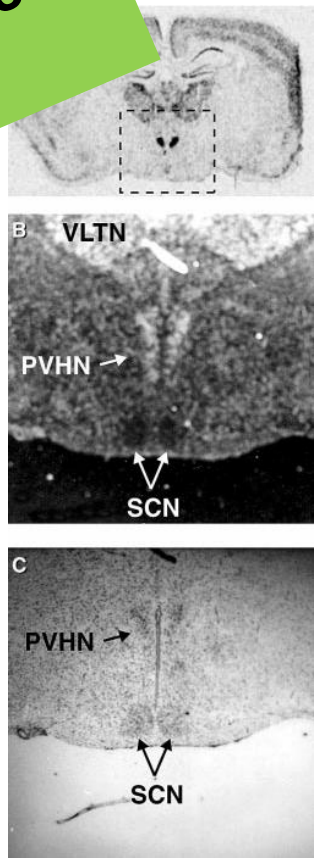
Dexamethasone induces circadian gene expression in rat-1 fibroblasts grown in tissueculture.

The GR is required for dexamethasone i… and *DBP* expression and phase …

I glucocorticoidi inducono l'espressione dei geni clock nei tessuti periferici ma non nel SCN.



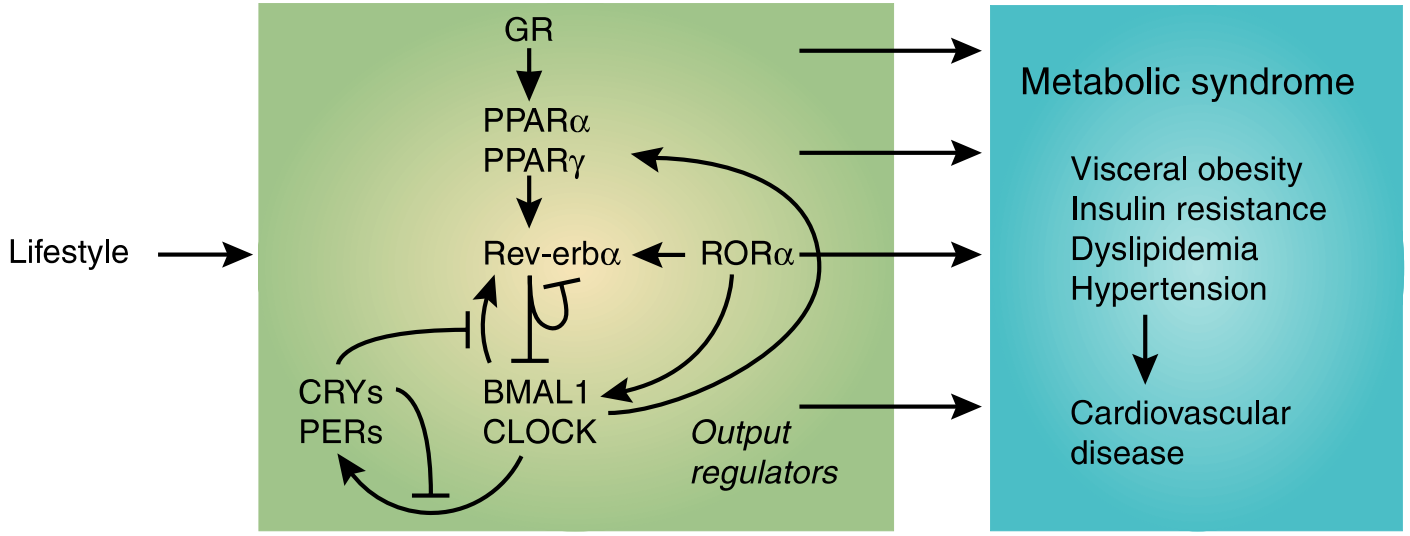




GR^AlfpCre mice with a liver-specific disruption of the GR gene

Clock genes are implicated in the human metabolic syndrome

When the Clock stops ticking, metabolic syndrome explodes



Staels B. When the Clock stops ticking, metabolic syndrome explodes. Nat Med 2006;12:54–55.

Metabolic Disturbances Associated with Loss of Circadian Rhythm or Glucocorticoid Excess

Signs and symptoms	Loss of circadian rhythm	Glucocorticoid excess
Glucose metabolism		
Elevation of plasma glucose	++	++
Peripheral insulin resistance	++	++
Fat metabolism		
Elevation of circulating triglycerides	++	+
Elevation of circulating cholesterol	+	+
Fatty liver	+	+
Central obesity	++	++
Protein turnover	Biosynthesis ↓?	Catabolism ↑
Appetite	↑	↑
Hypertension	+	+

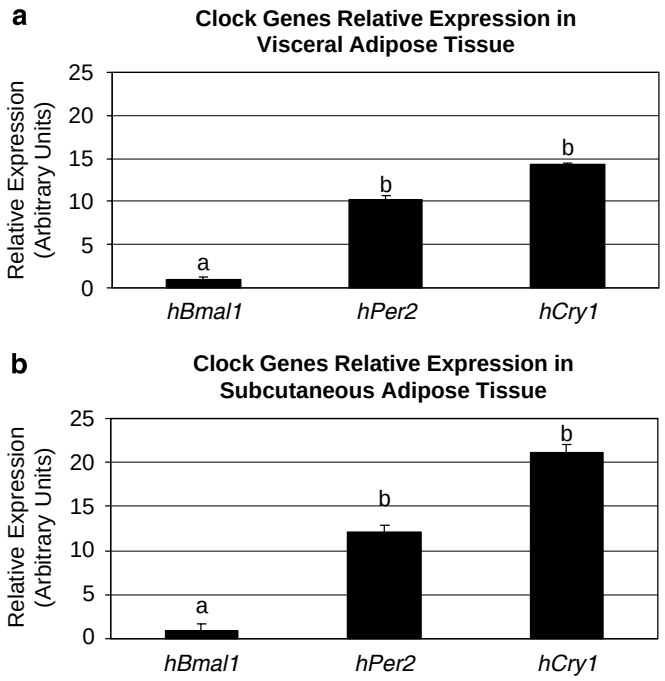
Nancy Nader et al Trends Endocrinol Metab. 2010 May ; 21(5): 277–286.

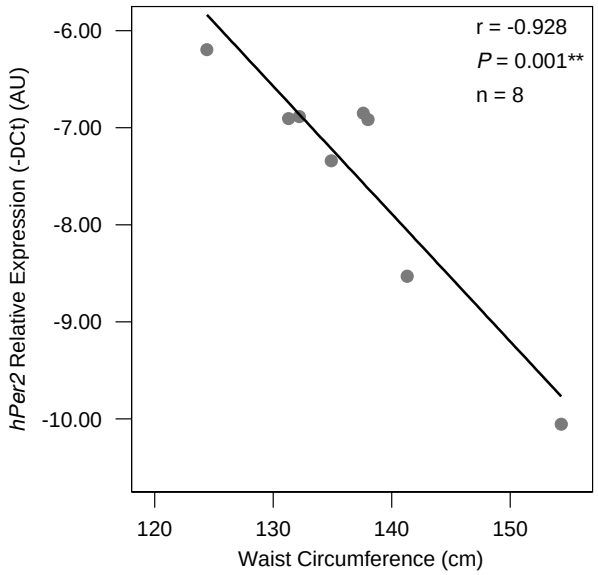
Symptoms of circadian clock mutant animals and human glucocorticoid dysregulation

Target system	Circadian rhythm abnormalities (Mutations in core clock genes)	Glucocorticoid dysregulation [31,36,84]	
		Excess	Deficiency
Central nervous system			
Sleep disturbance	– Increased but fragmented sleep (*Bmal1*$^{-/-}$ mice) [112] – Reduced total sleep (*Clock*/*Clock* mice) [149]	– Insomnia – Sleep fragmentation	– Hypersomnia – Fatigue
Mood regulation	– Bipolar-like and increased cocaine rewards (*Clock*/*Clock* mice) [134,142,170]	– Anxiety/depression	– Anxiety/depression
Cognition/memory	– Impaired hippocampal long-term potentiation and memory (Per2^{brdm1} mice*) [207]	– Cognitive defect	– Cognitive defect
Metabolism			
Body weight	– Obesity (*Clock*/*Clock* and *Bmal1*$^{-/-}$ mice) [110,132,202]	– Central obesity	– Weight loss
Glucose metabolism	– Hyperglycemia (*Clock*/*Clock* and *Bmal1*$^{-/-}$ mice) [110,132,202] – Hypoinsulinemia (*Clock*/*Clock* and *Bmal1*$^{-/-}$ mice) [110,132,202] – Glucose intolerance (*Clock*/*Clock* and *Bmal1*$^{-/-}$ mice) [110,132,202]	– Hyperglycemia – Glucose intolerance	– Hypoglycemia – Resistance to diabetes mellitus
Lipid metabolism	– Elevated triglycerides and cholesterol in circulation (*Clock*/*Clock* mice) [202] – Hepatic steatosis (*Clock*/*Clock* mice) [202]	– Hyperlipidemia – Accumulation of visceral fat	– Hypolipidemia
Cardiovascular activity			
Blood pressure	– Hypertension-associated SNP in spontaneously hypertensive rat (SHR): impaired Bmal1 promoter activity [211]	– Hypertension	– Hypotension
Immune/inflammation			
Immune/inflammation	– Impaired proinflammatory cytokines such as IFN-γ and IL-1β in response to endotoxic challenge (Per2^{brdm1} mice) [124]	– Immune suppression – Anti-inflammation	– Increased inflammation – Autoimmunity
Tumor development	– Increased tumorigenesis (Per2^{brdm1} mice) [69,210]	– Vulnerable to tumorigenesis	

Gi Hoon Son, Sooyoung Chung, Kyungjin Kim The adrenal peripheral clock: Glucocorticoid and the circadian timing system Frontiers in Neuroendocrinology 32 (2011) 451–465

Clock genes are implicated in the human metabolic syndrome



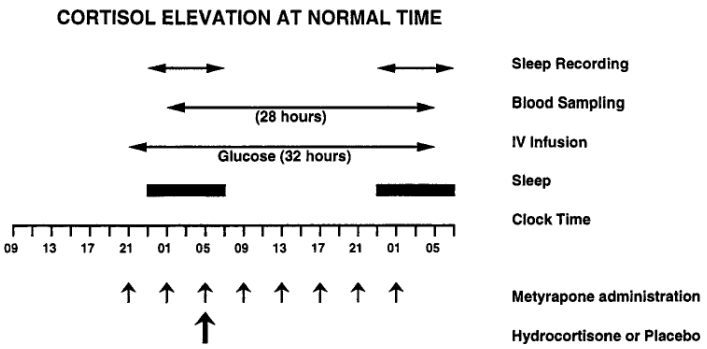


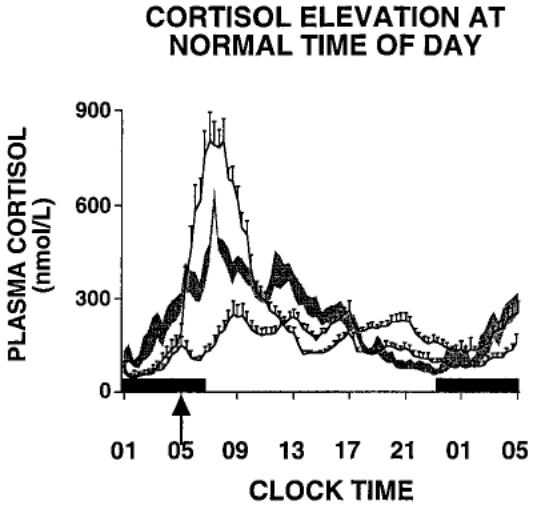
Differences in clock genes expression in both visceral and subcutaneous adipose tissue. Relative expression of clock genes (hBmal1, hPer2 y mCry1) in visceral (a) and subcutaneous (b) adipose tissue.

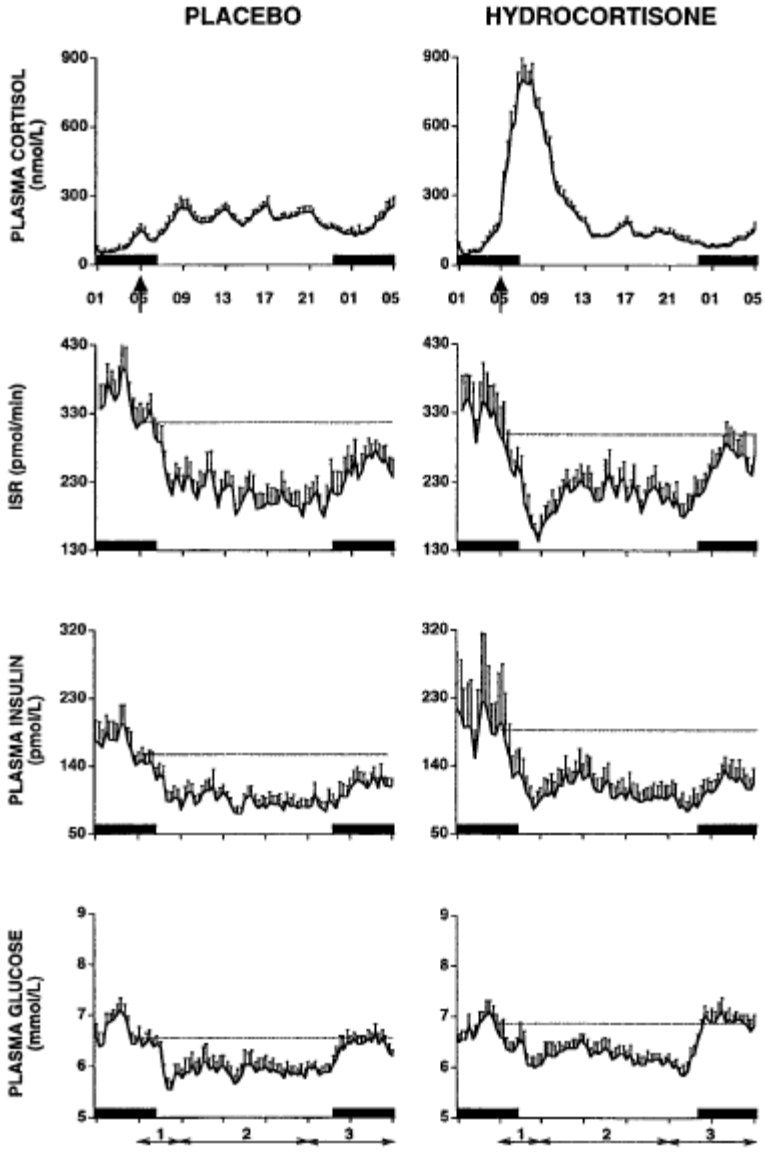
Differente espressione dei geni clock in grasso viscerale e nel sottocutaneo

Gomez-Abellan P, et al. Clock genes are implicated in the human metabolic syndrome. Int J Obes (Lond) 2008;32:121–128.

Metabolic Effects of Short-Term Elevations of Plasma Cortisol

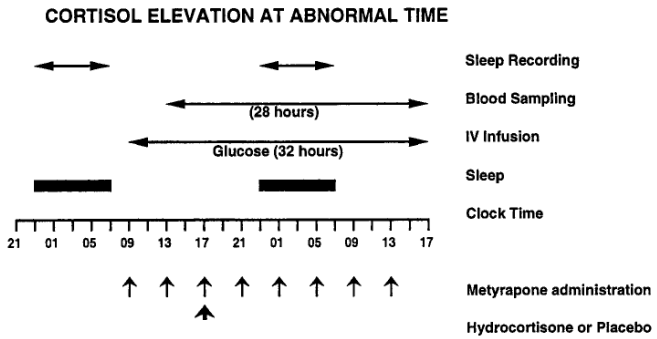


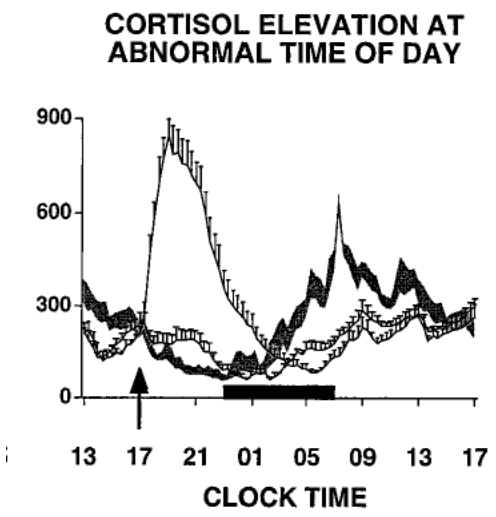


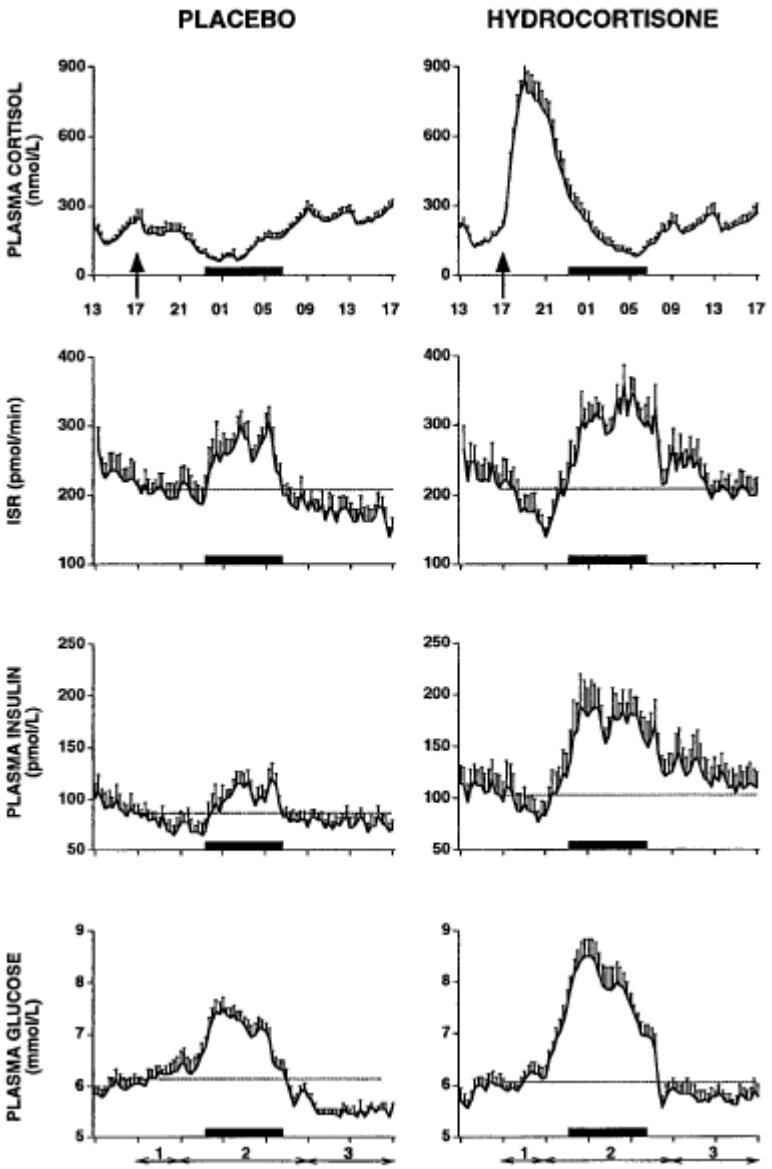


LAURENCE PLAT, RACHEL LEPROULT, MIREILLE L'HERMITE-BALERIAUX,FRANDOISE FERY, JEAN MOCKEL, KENNETH S. POLONSKY, AND EVE VAN CAUTER Metabolic Effects of Short-Term Elevations of Plasma Cortisol Are More Pronounced in the Evening Than in the Morning* *J Clin Endocrinol Metab 84: 3082–3092, 1999*

Metabolic Effects of Short-Term Elevations of Plasma Cortisol







Oral HC 50 mg given at 17.00 h gives more pronounced increase in insulin secretion

LAURENCE PLAT, RACHEL LEPROULT, MIREILLE L'HERMITE-BALERIAUX,FRANDOISE FERY, JEAN MOCKEL, KENNETH S. POLONSKY, AND EVE VAN CAUTER Metabolic Effects of Short-Term Elevations of Plasma Cortisol Are More Pronounced in the Evening Than in the Morning* *J Clin Endocrinol Metab 84: 3082–3092, 1999*

Clinical consequences of environmentally disrupted GC rhythm

Rotating shift workers show a higher risk of obesity, hypertension, high triglycerides, insulin resistance.

Extended night-time shift work is associated with increased incidence of breast cancer and colorectal cancer

A working population of 27 485 people from the Västerbotten intervention program (VIP)

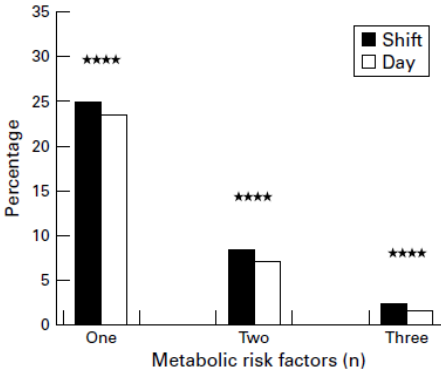


*Figure 1 Age adjusted prevalence of number of metabolic risk factors (obesity, hypertension, and high triglycerides) among shift working and day working women. ****p<0.0001.*

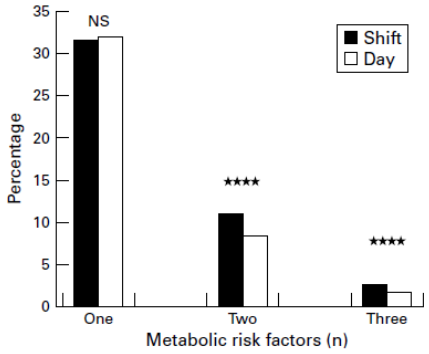


*Figure 2 Age adjusted prevalence of number of metabolic risk factors (obesity, hypertension, and high triglycerides) among shift working and day working men. ****p<0.0001.*

Table 2. Adjusted relative risk (RR) and 95% confidence intervals (CIs) of colon and rectal cancers associated with night-shift work among 78 586 women in the Nurses' Health Study with prospective follow-up from 1988 through 1998 with 602 cases of colorectal cancer

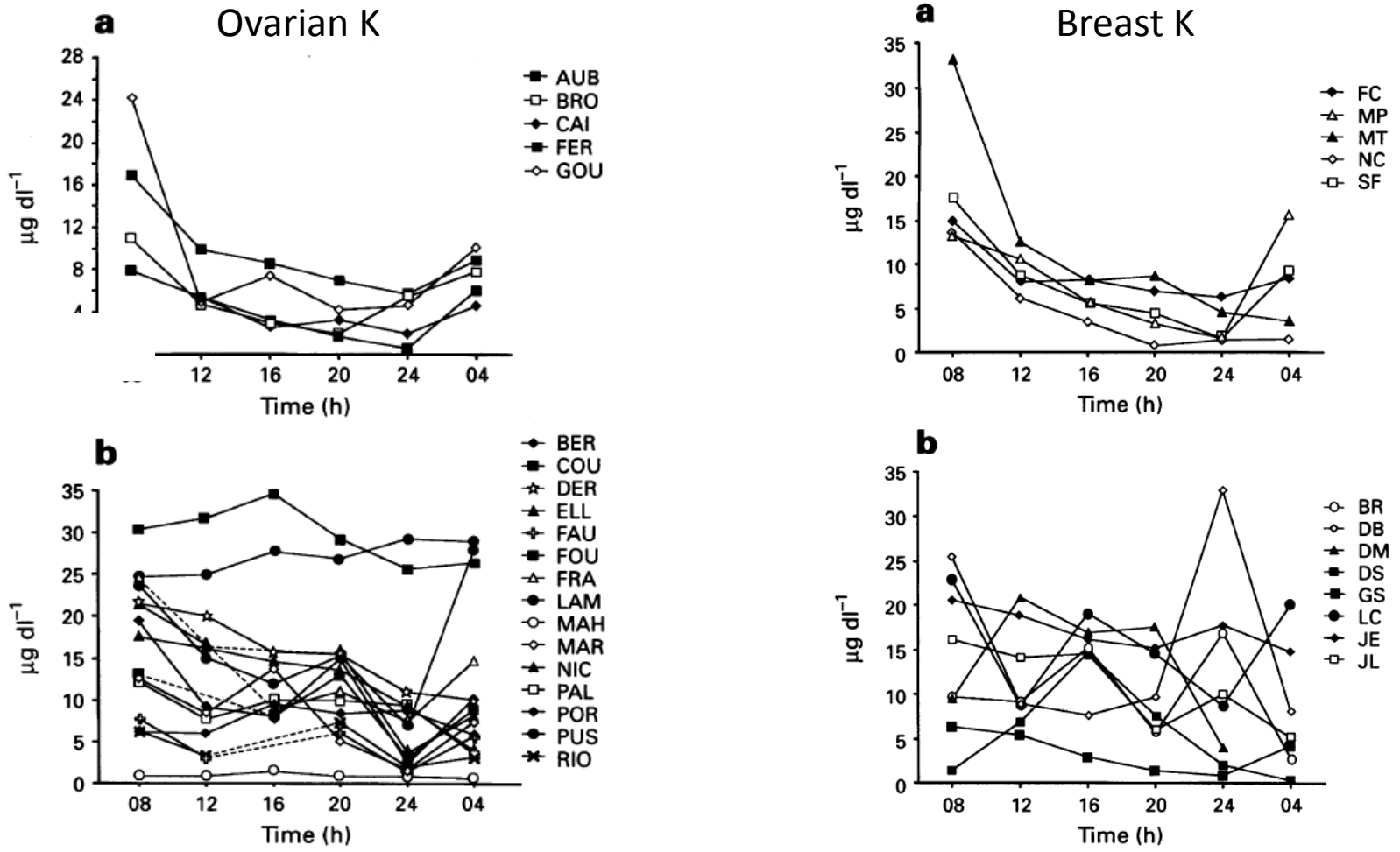
Cancer site and years on rotating night shift	No. of cases	Age-adjusted RR (95% CI)	Multivariate RR* (95% CI)
Colon and rectum combined†			
Never	229	1.0 (referent)	1.0 (referent)
1–14	303	1.00 (0.84 to 1.18)	1.00 (0.84 to 1.19)
⩾15	70	1.44 (1.10 to 1.89)	1.35 (1.03 to 1.77)
P_{trend}‡		.01	.04
Right colon			
Never	73	1.0 (referent)	1.0 (referent)
1–14	93	0.95 (0.70 to 1.30)	0.97 (0.71 to 1.32)
⩾15	23	1.47 (0.91 to 2.37)	1.41 (0.88 to 2.27)
P_{trend}‡		.38	.31
Left colon			
Never	64	1.0 (referent)	1.0 (referent)
1–14	76	0.90 (0.64 to 1.25)	0.89 (0.63 to 1.24)
⩾15	18	1.27 (0.75 to 2.14)	1.22 (0.72 to 2.09)
P_{trend}‡		.50	.44
Combined colon			
Never	137	1.0 (referent)	1.0 (referent)
1–14	169	0.93 (0.74 to 1.16)	0.93 (0.74 to 1.17)
⩾15	41	1.37 (0.97 to 1.95)	1.32 (0.93 to 1.87)
P_{trend}‡		.26	.20
Rectum			
Never	41	1.0 (referent)	1.0 (referent)
1–14	48	0.87 (0.57 to 1.33)	0.86 (0.56 to 1.30)
⩾15	14	1.54 (0.75 to 3.16)	1.51 (0.82 to 2.81)
P_{trend}‡		.15	.15

Karlsson B, Knutsson A, Lindahl B 2001 Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,485 people. Occup Environ Med 58:747–752

Schernhammer ES et al Night-shift work and risk of colorectal cancer in the nurses' health study. J Natl Cancer Inst. 2003 Jun 4;95(11):825-8.

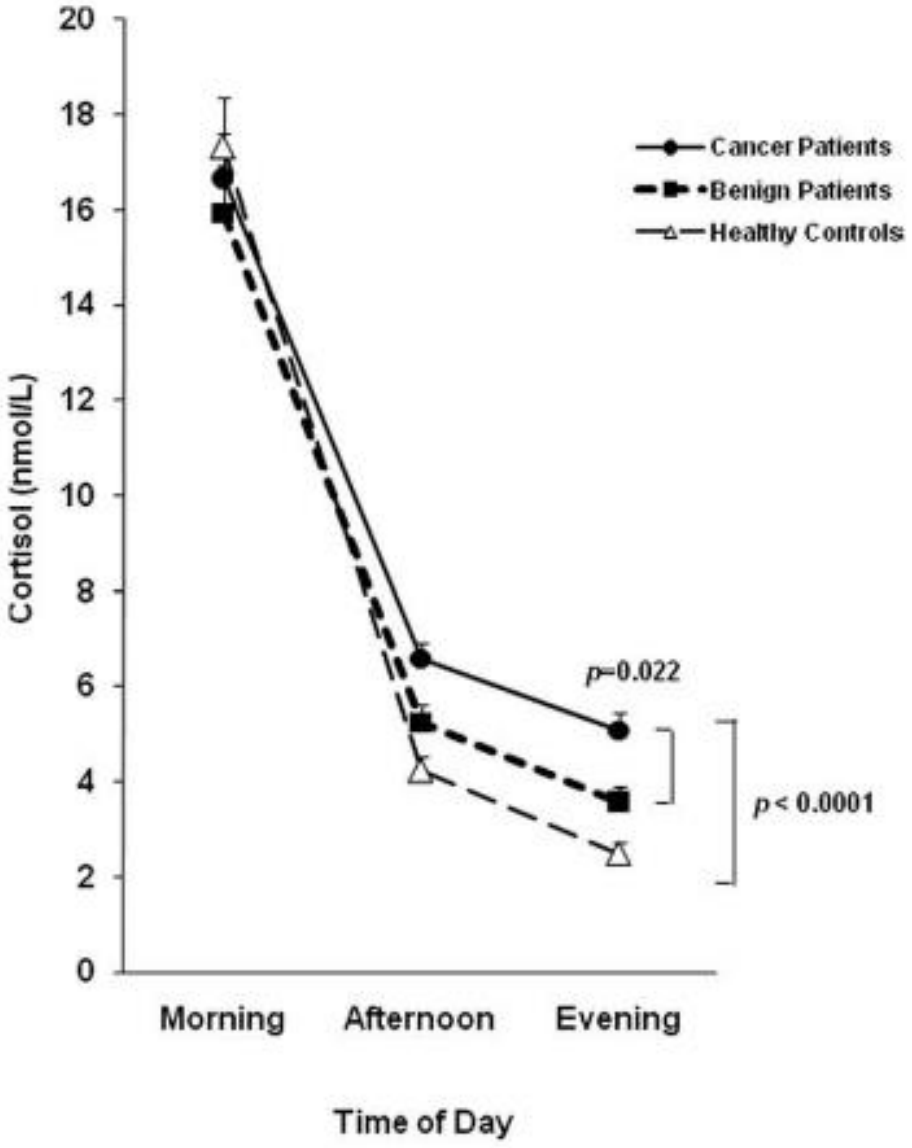
Role of circadian disruption in cancer development

Cortisol circadian frequency has been found to be disrupted in breast and ovarian cancer patients : 22 out of 33 cancer patients have deeply altered serum cortisol circadianprofiles.



Touitou Y, Bogdan A, Lévi F, Benavides M, Auzéby A. Disruption of the circadian patterns of serum cortisol in breast and ovarian cancer patients: relationships with tumour marker antigens Br J Cancer. 1996 Oct;74(8):1248-52.

Role of circadian disruption in cancer development



Nocturnal cortisol and cortisol variability show significant dysregulation in ovarian cancer and this dysregulation is associated

With greater functional dysability, fatigue and depression

Weinrib A, Cancer 2010 116:4410-9

Effects of circadian gene disruption on the immune system

Similar interactions between the CLOCK system and the HPA axis are also observed in the regulation of immune function.

In humans and rodents, the CLOCK system produces a circadian fluctuation of several cytokines, including interferon (IFN) γ, interleukin-1 (IL-1)β, IL-6, and TNFα in T- and B-lymphocytes and natural killer cells

Several GREs elements

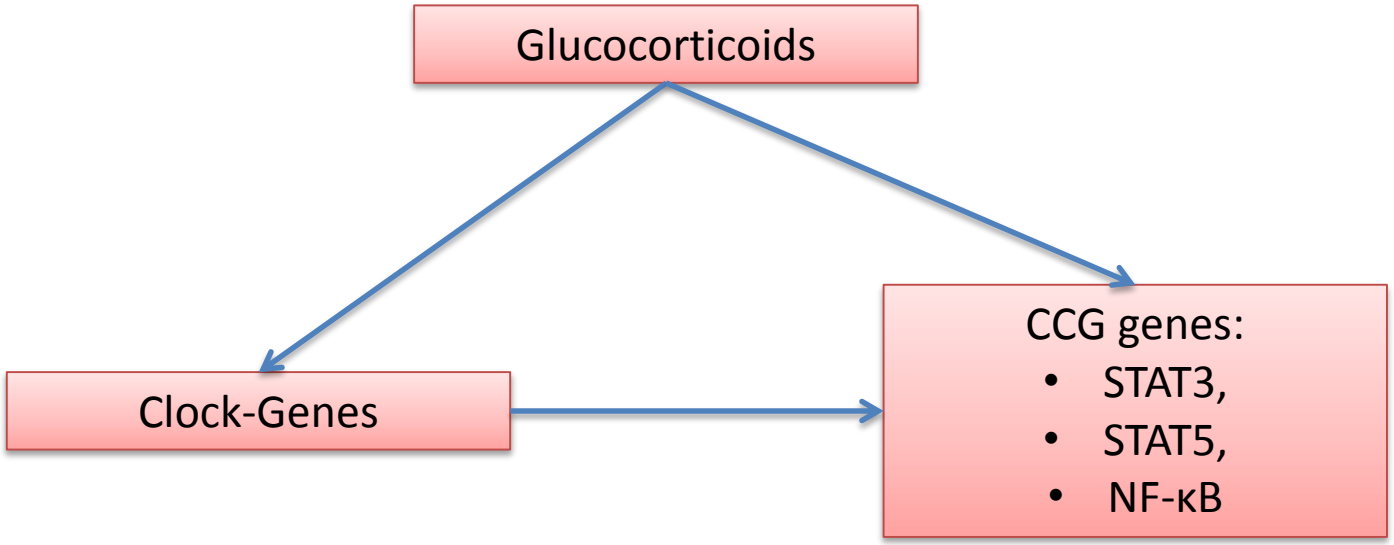
Gene	Manipulation	Effect
Per2	Mutation	Loss of daily rhythm of IFN-γ [111]
Per2	Mutation	Resistance to LPS-induced endotoxic shock [112]
Per2	Knockdown by RNAi	Decrease in granzyme B and perforin levels [74]
Bmal1	Deletion	Impaired B cell development [113]
Clock	Mutation	Suppression of daily rhythms in circulating leukocytes [114]
Clock	Mutation	Reduced expression levels of multiple immune-related genes [115]

Arjona A, Sarkar DK. Are circadian rhythms the code of hypothalamic-immune communication? Insights from natural killer cells. Neurochem Res 2008;33:708–718.

Effects of circadian gene disruption on the immune system

Since glucocorticoids interact with clock genes and regulate their expression, they indirectly modulate clock mediated pathways and CCG.

This results in far-reaching effects, as glucocorticoids influence circadian cytokine production, leukocyte distribution, proliferation, and apoptosis.



Arjona A, Sarkar DK. Are circadian rhythms the code of hypothalamic-immune communication? Insights from natural killer cells. Neurochem Res 2008;33:708–718.

Conditions with altered HPA axis activity

Although the precise significance of the daily GC rhythm is not yet well established, a growing body of evidence does point to its clinical importance.

Alterations in its rhythmicity are frequently found in many human diseases

Increased activity of the HPA axis	Decreased activity of HPA axis
■ Cushing syndrome	■ Adrenal insufficiency
■ Chronic stress	■ Atypical/ seasonal depression
■ Melancholic depression	■ Chronic fatigue syndrome
■ Anorexia nervosa	■ Fibromyalgia
■ Obsessive–compulsive disorder	■ Premenstrual tension syndrome
■ Panic disorder	■ Climacteric depression
■ Excessive exercise (obligate athleticism)	■ Nicotine withdrawal
■ Chronic, active alcoholism	■ Following cessation of glucocorticoid therapy
■ Alcohol and narcotic withdrawal	■ Following Cushing syndrome cure
■ Diabetes mellitus	■ Following chronic stress
■ Central obesity (metabolic syndrome)	■ Postpartum period
■ Post-traumatic stress disorder in children	■ Adult post-traumatic stress disorder
■ Hyperthyroidism	■ Hypothyroidism
■ Pregnancy	■ Rheumatoid arthritis
	■ Asthma, eczema

Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol 2009;5:374–381

Mortality Risk in Patients with Addion's disease

Premature Mortality in Patients with Addison's Disease: A Population-Based Study

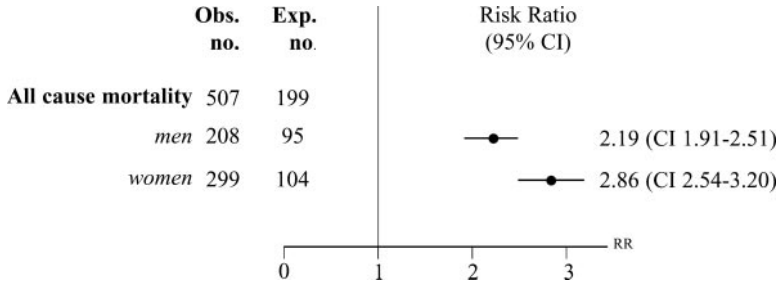
The Journal of Clinical Endocrinology & Metabolism 91(12):4849–4853

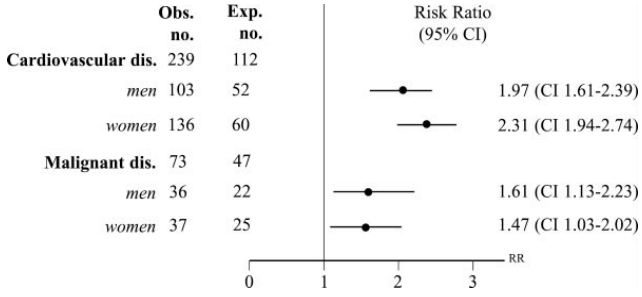
doi: 10.1210/jc.2006-0076

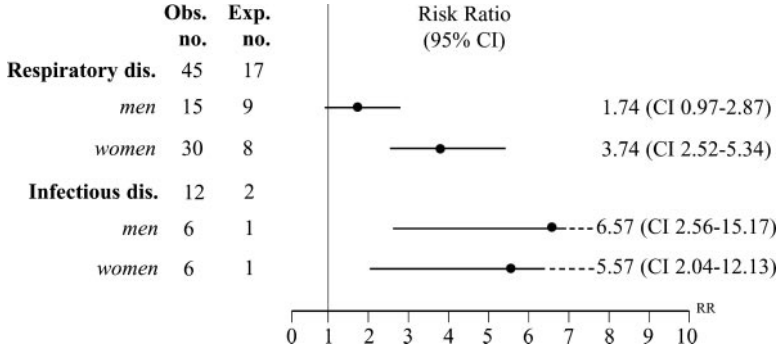
Ragnhildur Bergthorsdottir, Maria Leonsson-Zachrisson, Anders Odén, and Gudmundur Johannsson

Department of Endocrinology (R.B., M.L.-Z., G.J.), Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden; and Department of Mathematical Sciences (A.O.), Chalmers University of Technology, SE-412 96 Gothenburg, Sweden

Primary adrenal Insuficiency is associated with 2-3 fold increased mortality rate compared to the background population

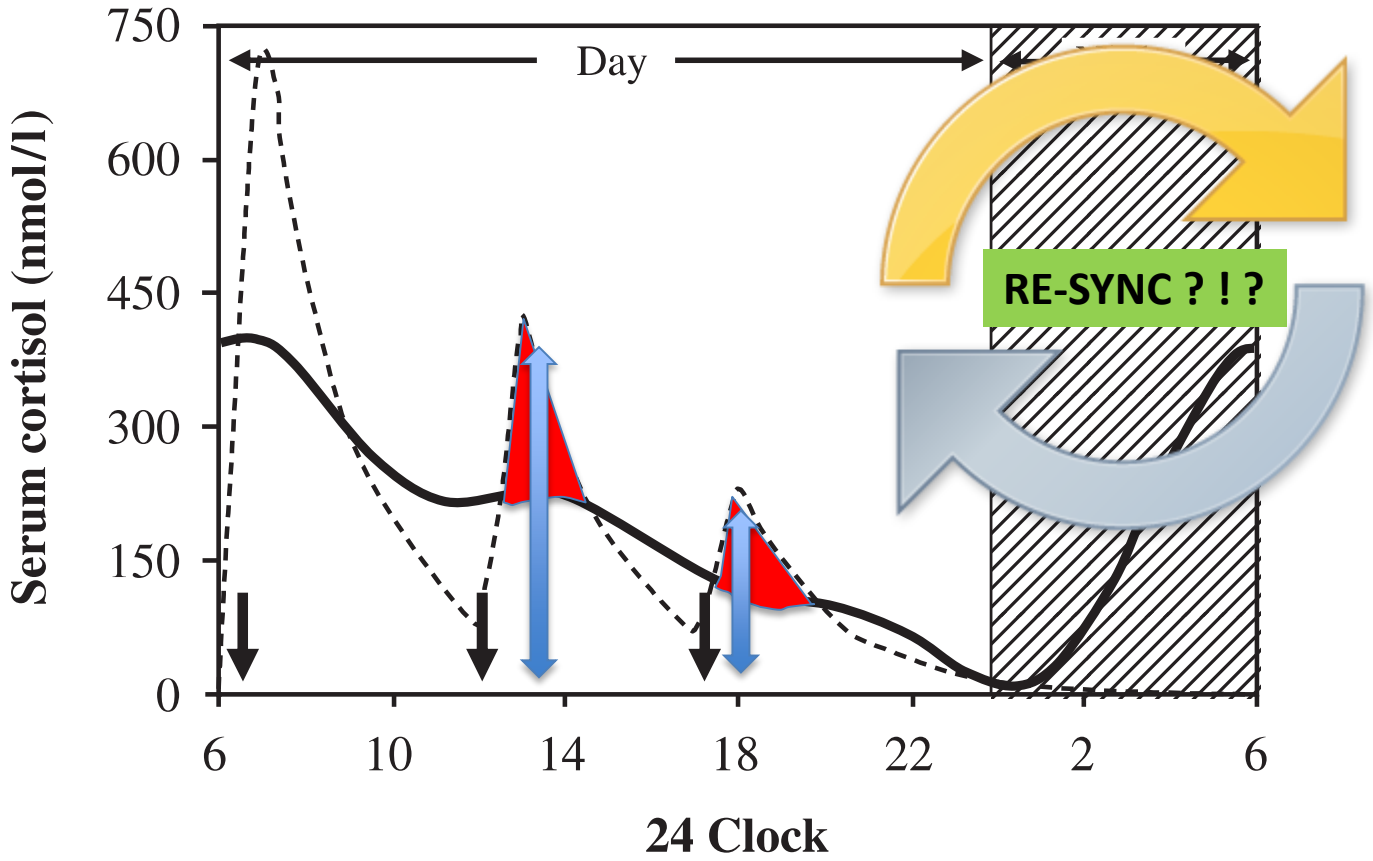






Non-physiological cotisol replacement in Adrenal Insufficiency

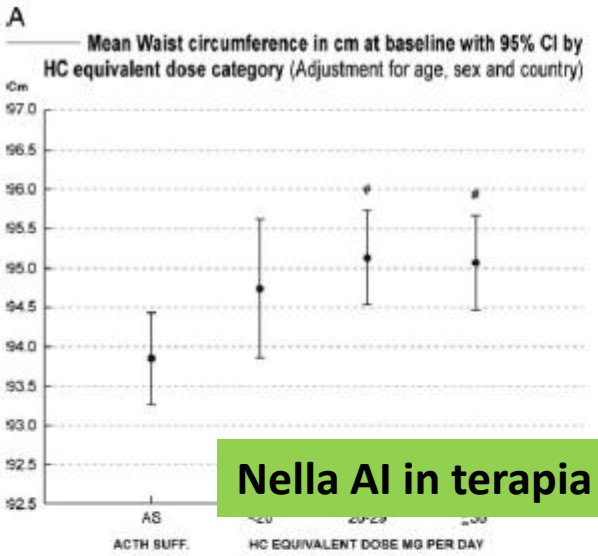
Conventional GC replacement therapy in patients with AI does not provide appropriate physiological replacement in terms of **precisely mimicking this rhythm**

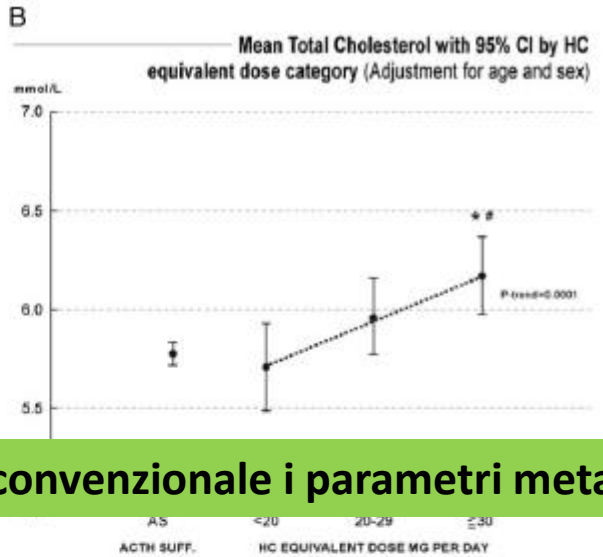


The non –physiological circadian profile rather than the dose could be the major explanation for worse outcome of AI

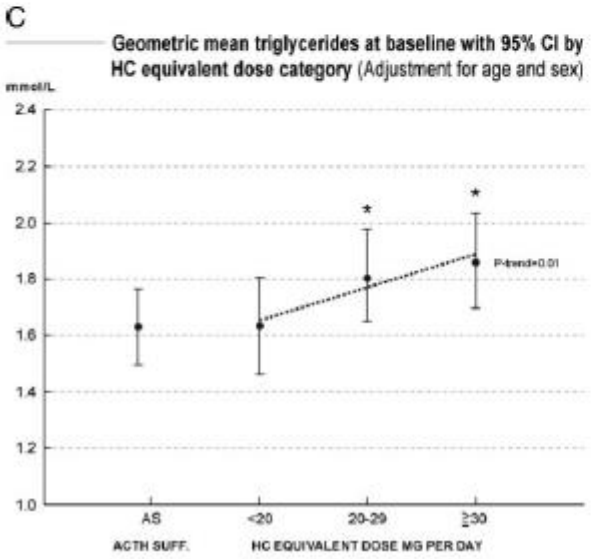
Peak M. Mah Clinical Endocrinology (2004) 61, 367–375

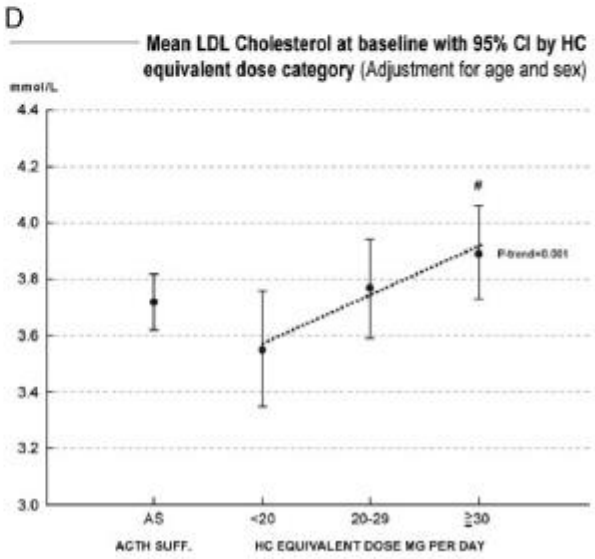
Metabolic consequences

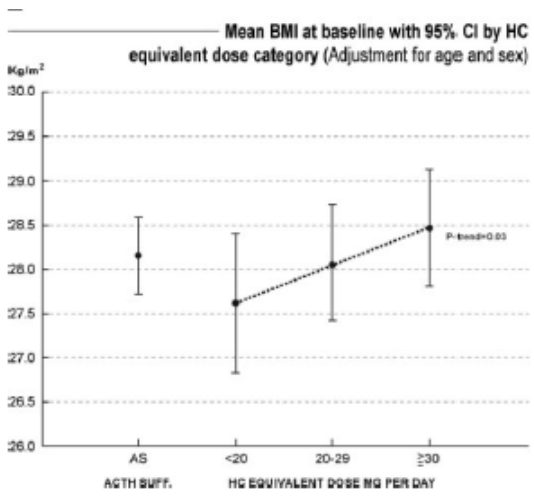




Nella AI in terapia convenzionale i parametri metabolici peggiorano







Helena Filipsson et al The Impact of Glucocorticoid Replacement Regimens on Metabolic Outcome and Comorbidity in Hypopituitary PatientsThe Journal of Clinical Endocrinology & Metabolism 91(10):3954–3961

Effects on bone metabolism

Bone loss secondary to suppression of osteoblastic function, evident by lower osteocalcin levels, may also occur with increasing HC doses.
Serum osteocalcin levels significantly decrease with an increase in HC doses

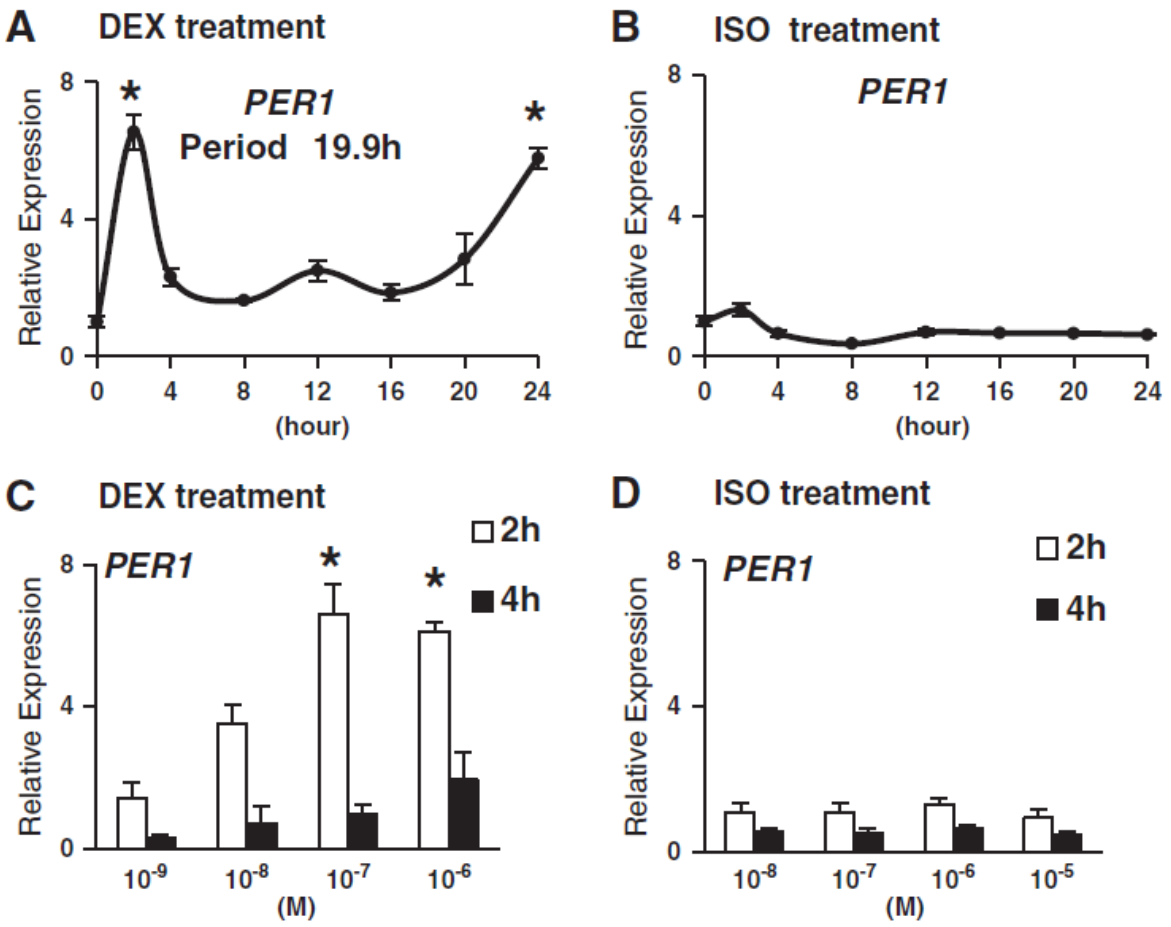
HC (mg/day)	AP (U/l)	BAP (μkat/l)	Osteocalcin (μg/l)	Crosslaps (pmol/l)	S-Calcium (mmol/l)	Pyr (nmol/mmol creatinine)	D-Pyr (nmol/mmol creatinine)	U-Calcium (mmol/24 h)
15	87·9 ± 6·9	0·21 ± 0·03	2·3 ± 0·49	1520 ± 331	2·3 ± 0·02	39·6 ± 5·5	5·4 ± 0·68	3·6 ± 0·72
20	87·3 ± 6·8	0·21 ± 0·03	2·1 ± 0·42	1680 ± 372	2·3 ± 0·02	36·5 ± 5·5	5·3 ± 0·85	3·3 ± 0·54
30	86·0 ± 5·8	0·21 ± 0·03	1·8 ± 0·38	1483 ± 263	2·3 ± 0·02	35·8 ± 3·9	5·1 ± 0·50	3·4 ± 0·46
Normal	55·0–170	0·19–0·73	1·8–6·6	302–7579	2·1–2·6	12·8–37·0	2·3–9·5	< 6·2

HC, hydrocortisone; AP, alkaline phosphatase; BAP bone specific alkaline phosphatase; Pyr, urinary pyridinoline; D-Pyr, urinary deoxypyridinoline; S-Calcium, serum calcium; U-Calcium, urinary calcium.

Maria Wichers et al .The influence of hydrocortisone substitution on the quality of life and parameters of bone metabolism in patients with secondary hypocortisolism Clinical Endocrinology (1999) 50, 759–765

Glucocorticoids mediate circadian timing in peripheral osteoclasts resulting in the circadian expression rhythm of osteoclast-related genes

DEX



Glucocorticoids are one of the most important factors in the transmission of circadian timing from the SCN to peripheral osteoclasts, and that the osteoclast peripheral clock may regulate the circadian rhythm of bone resorption by regulating CTSK and NFATc1 expression.

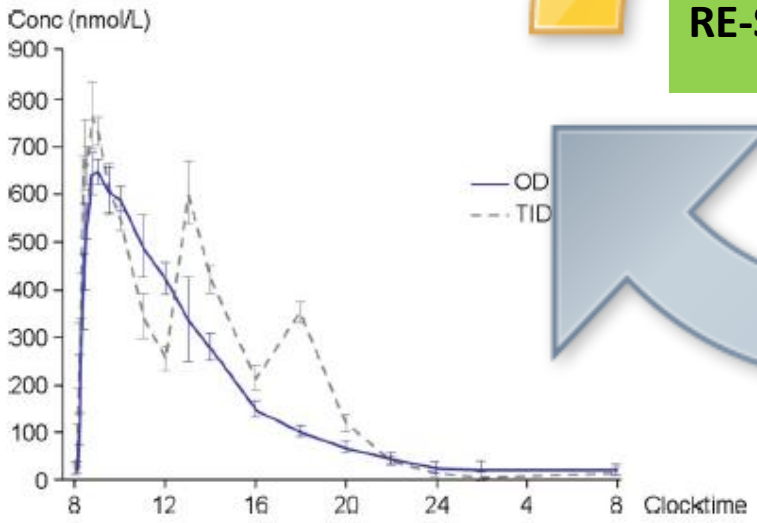
Fujihara Y, Kondo H, Noguchi T, Togari A. Bone. 2014 Apr;61:1-9

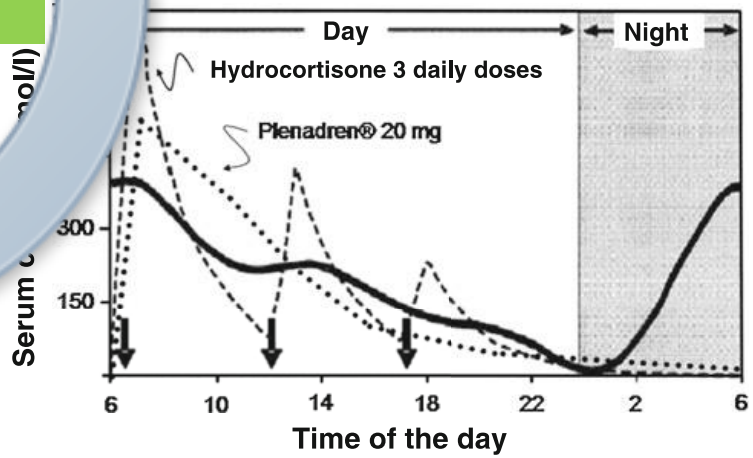
Modified-release hydrocortisone tablet to provide circadian profile

A comparison between

- Once Daily (OD) oral modified-release HC tablet (Plenadren)
- Th… …nvent…nal hydrocortisone (HC) tablets …ved by a 6-… …ension on OD

RE-SYNC ? ! ?





G. Johannsson et al Improved Cortisol Exposure-Time Profile and Outcome in Patients with Adrenal Insufficiency: A Prospective Randomized Trial of a Novel Hydrocortisone Dual-Release Formulation J Clin Endocrinol Metab 97: 473–481, 2012

Grazie per l’attenzione !

In particolare a **Chiara Graziadio**, **Daniela Fiore** e **Mary Venneri**
per gli studi su immunità GC e ritmo circadiano