PRIVACIÓN DE SUEÑO Y SÍNDROME METABÓLICO ¿UN VÍNCULO CAUSAL?

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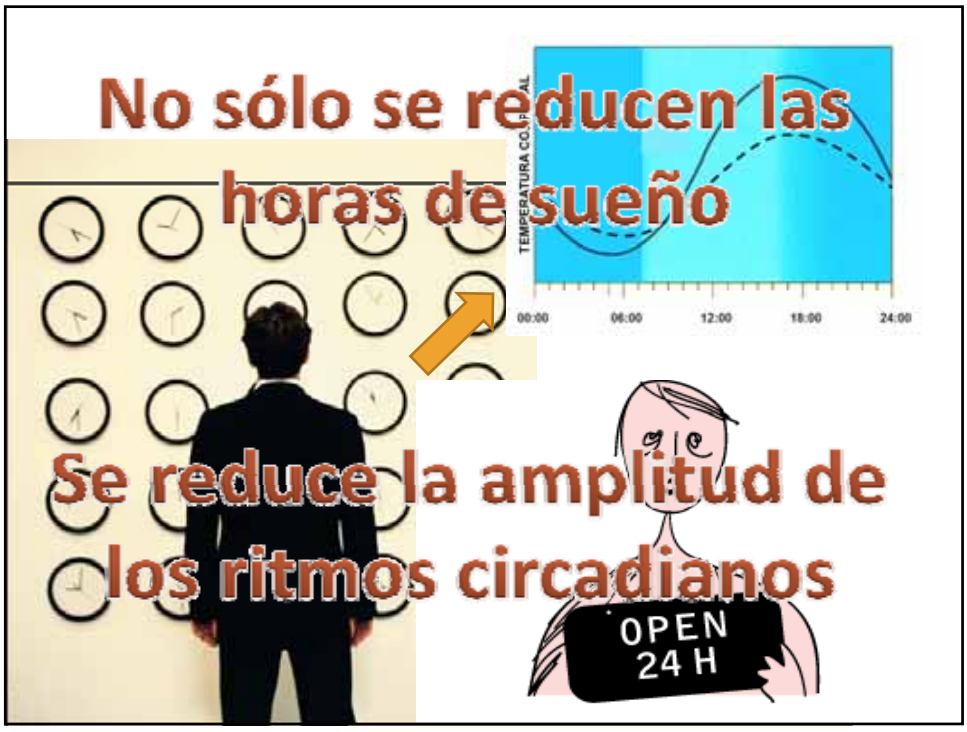
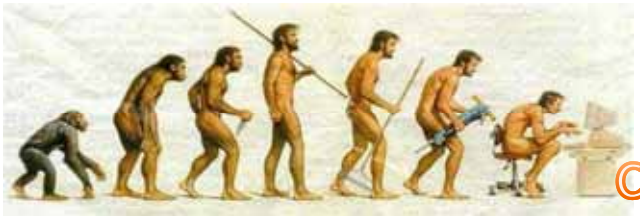
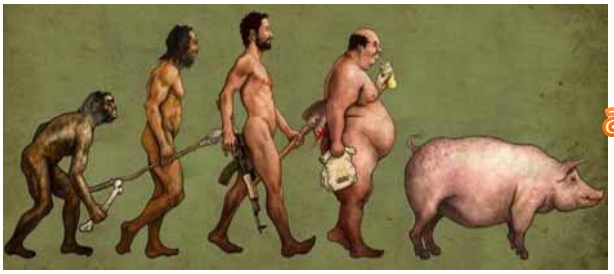
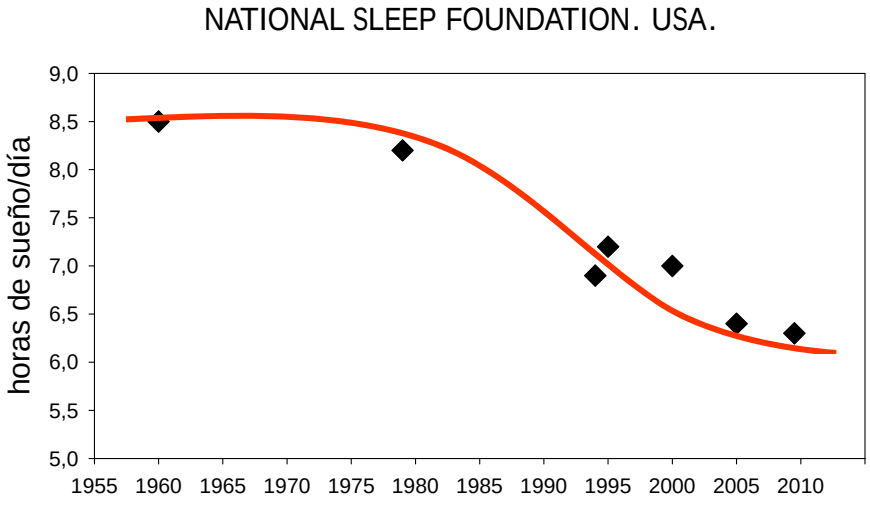
Cronodisrupción


No sólo se reducen las horas de sueño
TEMPERATURA CORPORAL
00:00
06:00
12:00
18:00
24:00
Se reduce la amplitud de los ritmos circadianos
OPEN 24 H

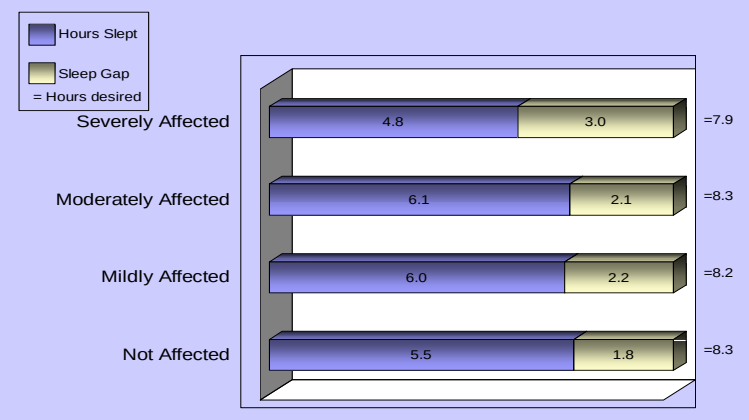




Carecemos de un diseño fisiológico adecuado para el mundo que hemos creado



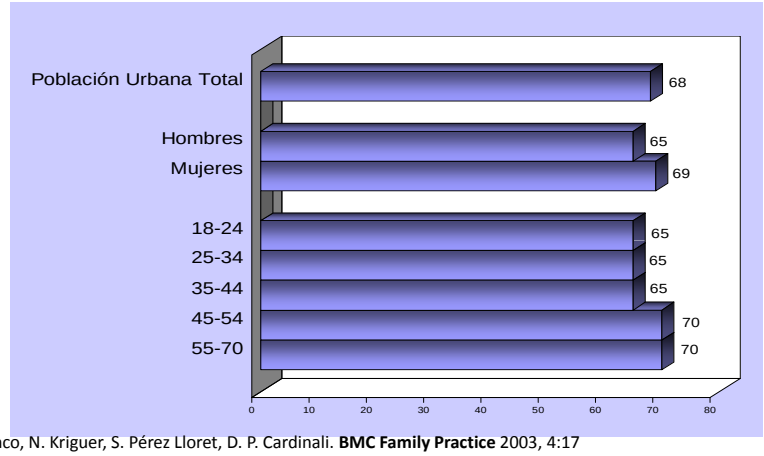
SOCIEDAD LATINOAMERICANA DE MEDICINA DEL SUEÑO. 2000



M. Blanco, N. Kriguer, S. Pérez Lloret, D. P. Cardinali. **BMC Family Pract** 2003, 4:177

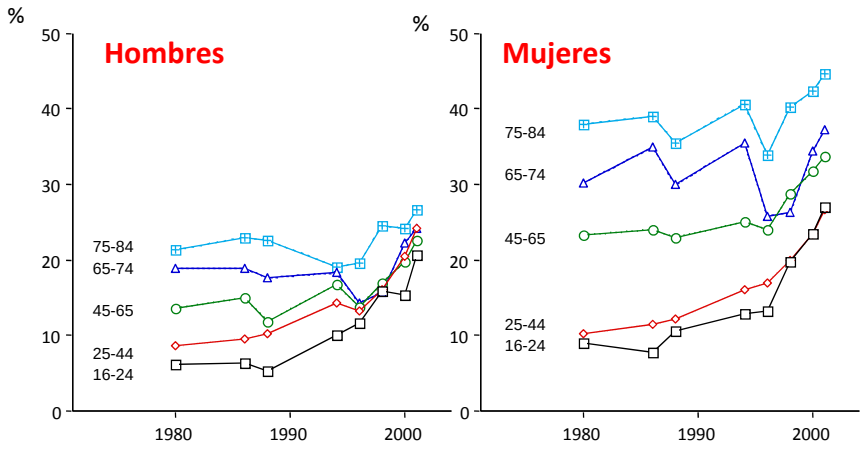
La Prevalencia de Dificultades del Sueño es Alta

- 68% reportan dificultades del sueño, con poca diferencia de sexo o edad.



M. Blanco, N. Kriguer, S. Pérez Lloret, D. P. Cardinali. **BMC Family Practice** 2003, 4:17

Alteraciones del sueño en Suecia



(SCB/ULF, 2003)

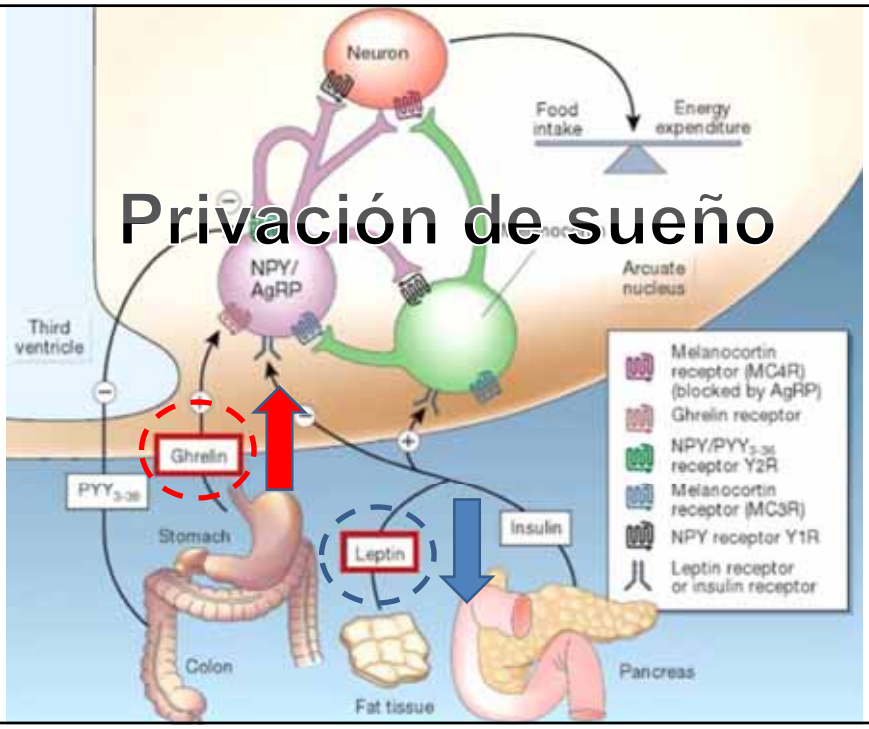

1960
Duración del sueño: 8 h diarias
W
nREM
REM
76 años
50 años
20 años
6 años
Sociedad 24/7
2011
Duración del sueño: 6 h diarias
W
nREM
REM
76 años
55 años
15 años
6 años
CARGA ALOSTÁTICA

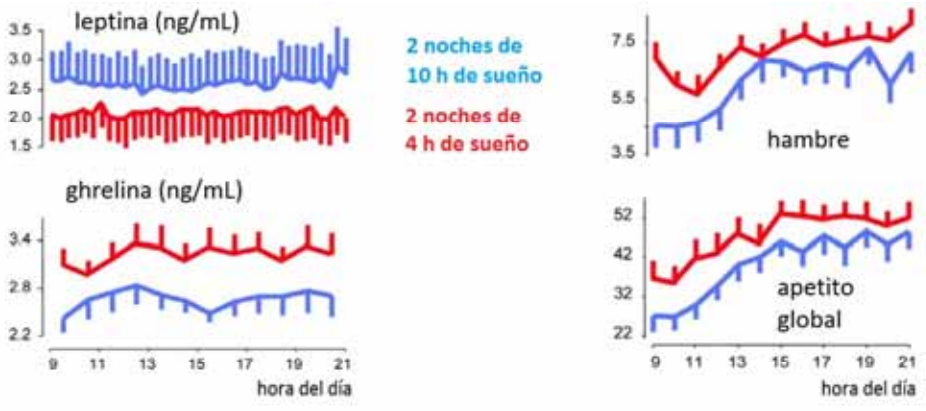

OBESIDAD Y PÉRDIDA DE SUEÑO ¿UNA O DOS EPIDEMIAS?

TRABAJO EN TURNOS

- En una muestra de 27.485 trabajadores se demostró el aumento excesivo de peso y sus comorbilidades (fenotipo de síndrome metabólico) en relación con controles.

Karlsson B, Knutson B, Lindhl B. Is there an association between shift work and having a metabolic syndrome? Results from a population-based study of 27, 485 people. Environ Med 2001; 58:747-52.





Van Cauter et al, 2007

American Journal of Epidemiology

Vol. 164, No. 10
DOI: 10.1093/aje/kwj280
Advance Access publication August 16, 2006

Original Contribution

Association between Reduced Sleep and Weight Gain in Women

Sanjay R. Patel[1], Atul Malhotra[2,3], David P. White[2,3], Daniel J. Gottlieb[4], and Frank B. Hu[3,5,6]

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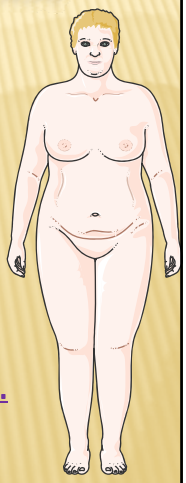
[2] Division of Sleep Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA.
[3] Harvard Medical School, Boston, MA.
[4] Division of Pulmonary and Critical Care Medicine, Boston University and VA Boston Healthcare System, Boston, MA.
[5] Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, MA.
[6] Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA.

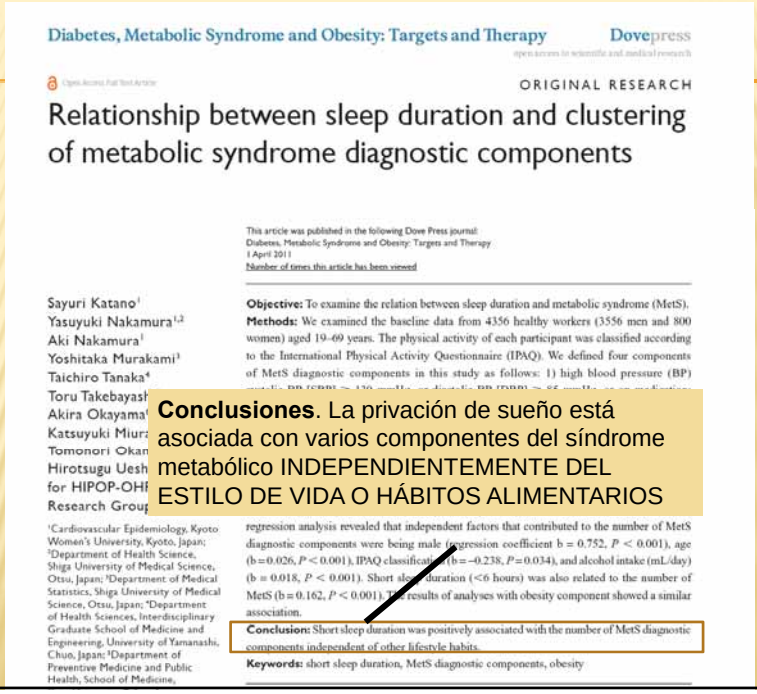
Received for publication February 23, 2006; accepted for publication April 12, 2006.

NURSES' HEALTH STUDY

S PATEL et al., AM J EPIDEMIOL 2006;164:947–954



- 68,183 mujeres seguidas durante 16 años
- Aquéllas que durmieron 5 h diarias o menos tuvieron una probabilidad de sobrepeso 32% mayor y de obesidad15% mayor
- Estas asociaciones se mantuvieron aún luego de ajustar por dieta o actividad física.



Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy Dovepress

ORIGINAL RESEARCH

Relationship between sleep duration and clustering of metabolic syndrome diagnostic components

This article was published in the following Dove Press journal:
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy
1 April 2011
Number of times this article has been viewed

Sayuri Katano[1]
Yasuyuki Nakamura[1,2]
Aki Nakamura[1]
Yoshitaka Murakami[3]
Taichiro Tanaka[4]
Toru Takebayash
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Research Grou

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Objective: To examine the relation between sleep duration and metabolic syndrome (MetS).
Methods: We examined the baseline data from 4356 healthy workers (3556 men and 800 women) aged 19–69 years. The physical activity of each participant was classified according to the International Physical Activity Questionnaire (IPAQ). We defined four components of MetS diagnostic components in this study as follows: 1) high blood pressure (BP)

regression analysis revealed that independent factors that contributed to the number of MetS diagnostic components were being male (regression coefficient b = 0.752, $P < 0.001$), age (b = 0.026, $P < 0.001$), IPAQ classification (b = −0.238, $P = 0.034$), and alcohol intake (mL/day) (b = 0.018, $P < 0.001$). Short sleep duration (<6 hours) was also related to the number of MetS (b = 0.162, $P < 0.001$). The results of analyses with obesity component showed a similar association.

Conclusion: Short sleep duration was positively associated with the number of MetS diagnostic components independent of other lifestyle habits.

Keywords: short sleep duration, MetS diagnostic components, obesity

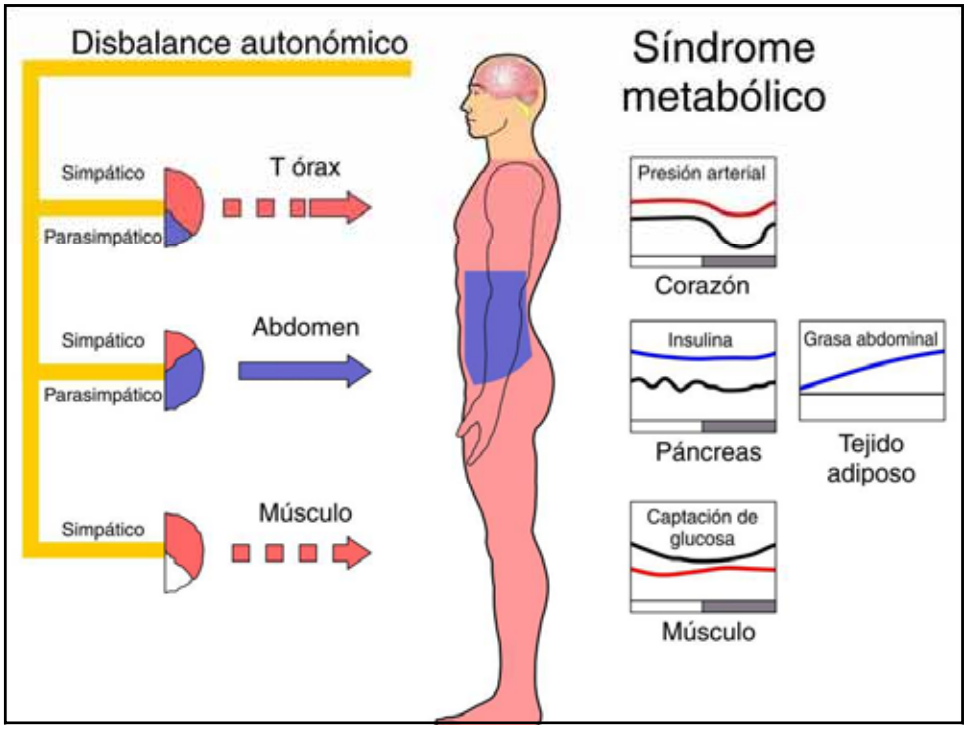
Conclusiones. La privación de sueño está asociada con varios componentes del síndrome metabólico INDEPENDIENTEMENTE DEL ESTILO DE VIDA O HÁBITOS ALIMENTARIOS

- ¿Pueden los cambios hormonales en leptina y ghrelina explicar totalmente la asociación entre sueño insuficiente y obesidad?

SÍNDROME METABÓLICO

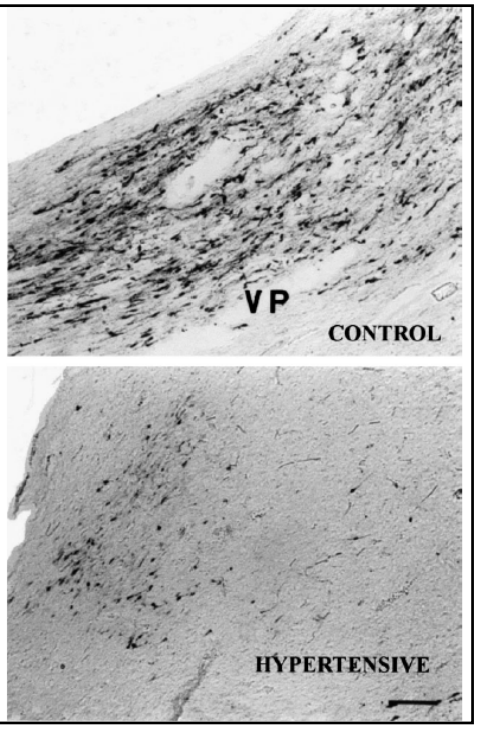
- Disbalance autonómico
- Desequilibrio a favor del parasimpático en el territorio visceral abdominal (GRASA ABDOMINAL)
- Desequilibrio a favor del simpático en el territorio tóraco-muscular (AUMENTO DE LA PRESIÓN ARTERIAL Y DE LA RESISTENCIA A LA INSULINA).

Buijs et al., 2005



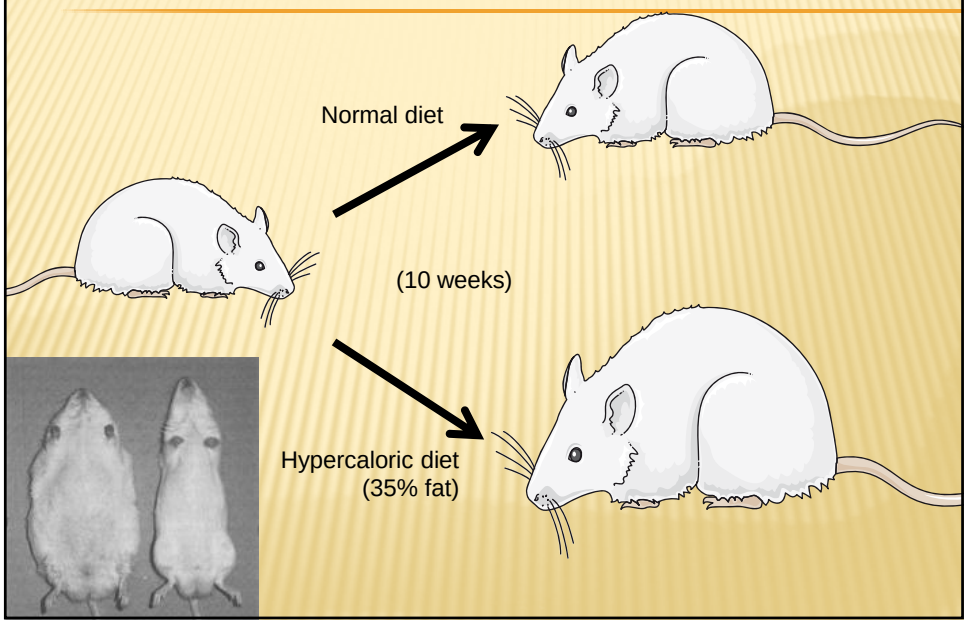
REDUCCIÓN DE NEURONAS VASOPRESINÉRGICAS EN NÚCLEO SUPRAQUIASMÁTICO DE PACIENTES OBESOS E HIPERTENSOS.

Goncharuk et al. 2001



SÍNDROME METABÓLICO.
¿UN DESORDEN CIRCADIANO DEL SUEÑO?

RAT. HIGH FAT FEEDING



Endocr (2008) 33:118–125
DOI 10.1007/s12020-008-9066-x

ORIGINAL PAPER

Effect of a high-fat diet on 24-h pattern of circulating levels of prolactin, luteinizing hormone, testosterone, corticosterone, thyroid-stimulating hormone and glucose, and pineal melatonin content, in rats

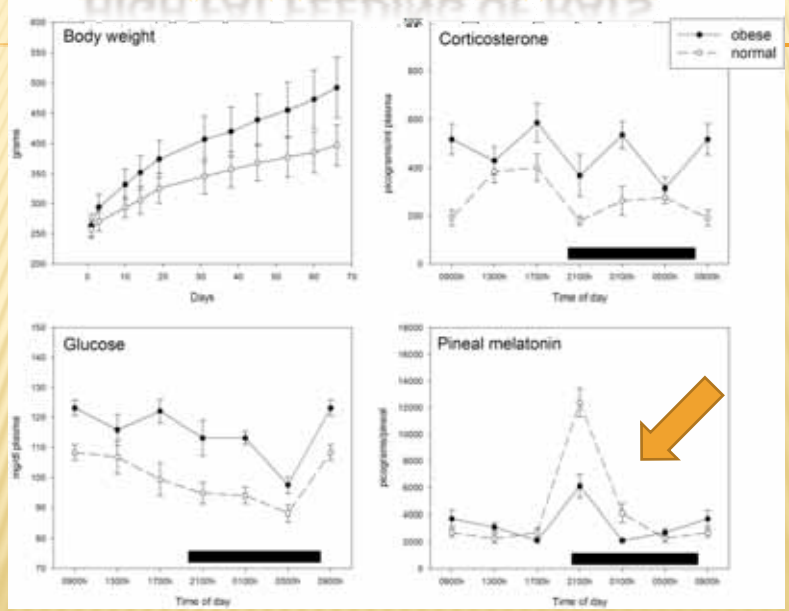
Pilar Cano · Vanesa Jiménez-Ortega · Álvaro Larrad · Carlos F. Reyes Toso · Daniel P. Cardinali · Ana I. Esquifino

Received: 4 February 2008 / Accepted: 4 March 2008 / Published online: 1 May 2008

Abstract Circadian rhythmicity is affected in obese subjects. This article analyzes the effect of a high-fat diet (35% fat) on 24-h changes circulating prolactin, luteinizing hormone (LH), testosterone, corticosterone, thyroid-stimulating hormone (TSH) and glucose, and pineal melatonin content in rats. When body weight of rats reached the results underlie the significant effects that obesity has on circadian organization of hormone secretion.

Keywords Circadian · High-fat diet · Obesity · Hyperglycemia · Melatonin · Prolactin

HIGH FAT FEEDING OF RATS



Esquifino, Cardinali et al., Endocrine 2008

nature publishing group

ARTICLES
INTEGRATIVE PHYSIOLOGY

Effect of a High-fat Diet on 24-Hour Pattern of Circulating Adipocytokines in Rats

Pilar Cano[1], Daniel P. Cardinali[2], María J. Ríos-Lugo[1], María P. Fernández-Mateos[3], Carlos F. Reyes Toso[2] and Ana I. Esquifino[1]

We have shown a significant disruption of 24-h pattern of plasma pituitary, adrenal, and gonadal hormones in high-fat-fed rats. Our objective was to assess the effect of a high-fat diet (35% fat) on mean levels and 24-h pattern of several adipocytokines in rats. A normal diet–fed rats (4% fat) were used as controls. When body weight of high-fat-fed rats attained values about 25% higher than controls (after 66 days of treatment), the animals were killed at six different time intervals throughout a 24-h cycle. Plasma concentrations of insulin, adiponectin, interleukin (IL)-1, leptin, ghrelin, plasminogen activator inhibitor-1 (PAI-1), and monocyte chemoattractant protein-1 (MCP-1) were measured in a multianalyte profiling by using the Luminex-100 system. Tumor necrosis factor α (TNFα) and IL-6 were measured by enzyme-linked immunosorbent assay. A significant hyperglycemia developed in high-fat-fed rats, together with a significant increase in plasma insulin. Mean levels of plasma adiponectin, IL-1, IL-6, TNFα, and leptin augmented, and ghrelin decreased, in high-fat-fed rats. The normal daily pattern of plasma insulin, adiponectin, IL-1, IL-6, TNFα, leptin, ghrelin, and MCP-1 became disrupted in high-fat-fed rats. The results indicate that a high-fat diet may bring about signs of insulin resistance and mild inflammation in rats, together with the disruption in daily variations of circulating insulin and ghrelin, and of several adipocytokines including leptin, adiponectin, IL-1, IL-6, TNFα, and MCP-1.

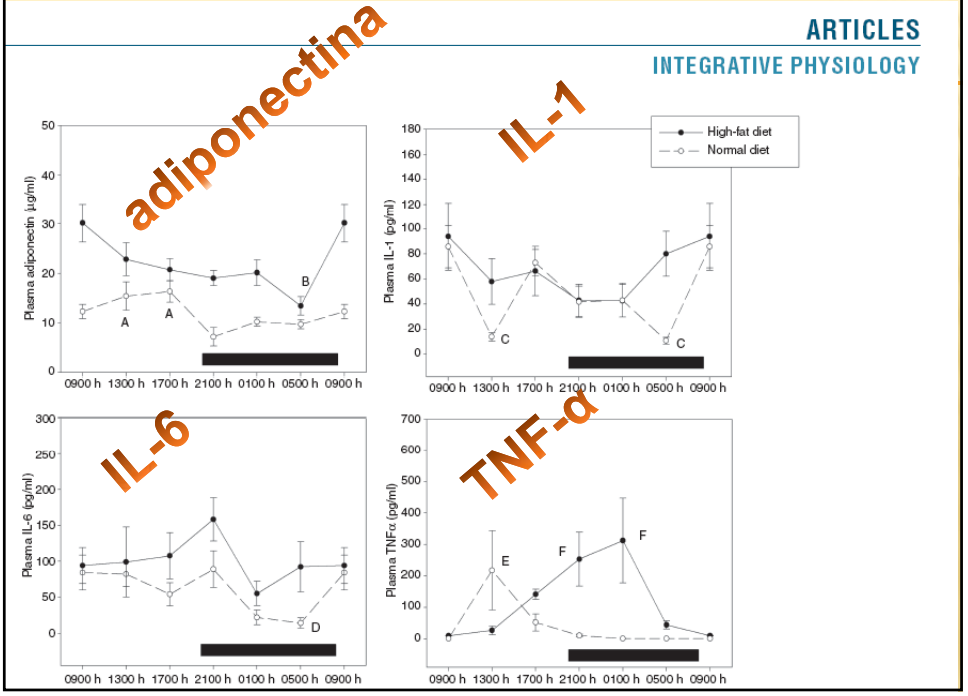
Obesity (2009) doi:10.1038/oby.2009.200

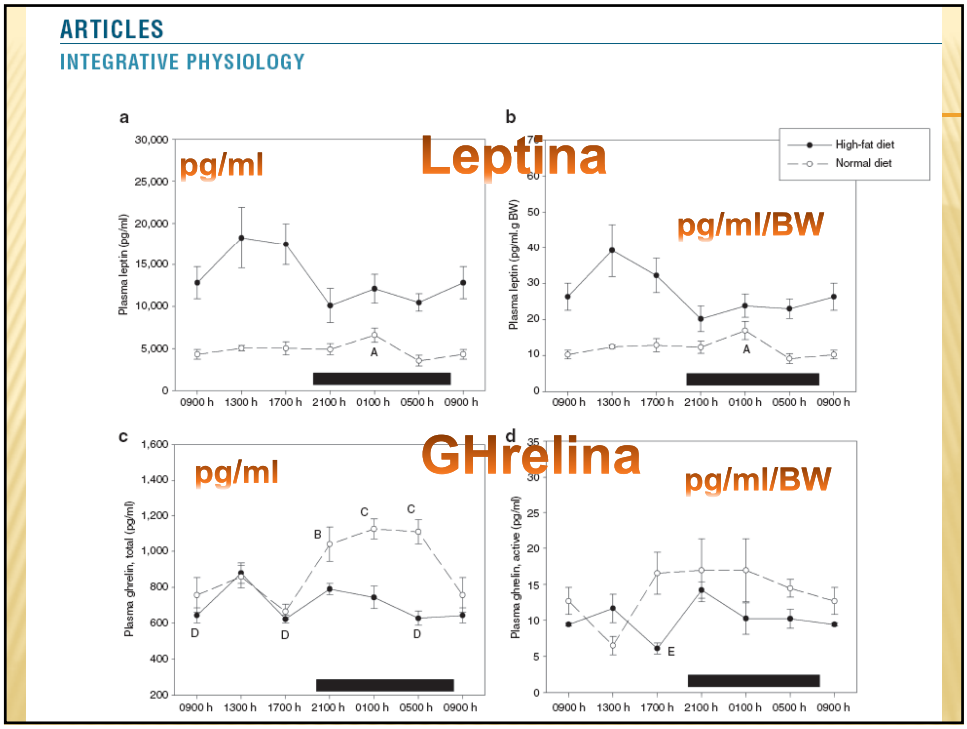
INTRODUCTION

There is a large body of evidence linking feeding regimens and food components with the circadian system (see refs. 1,2). A high-fat diet, that contributes to insulin resistance and inflam-

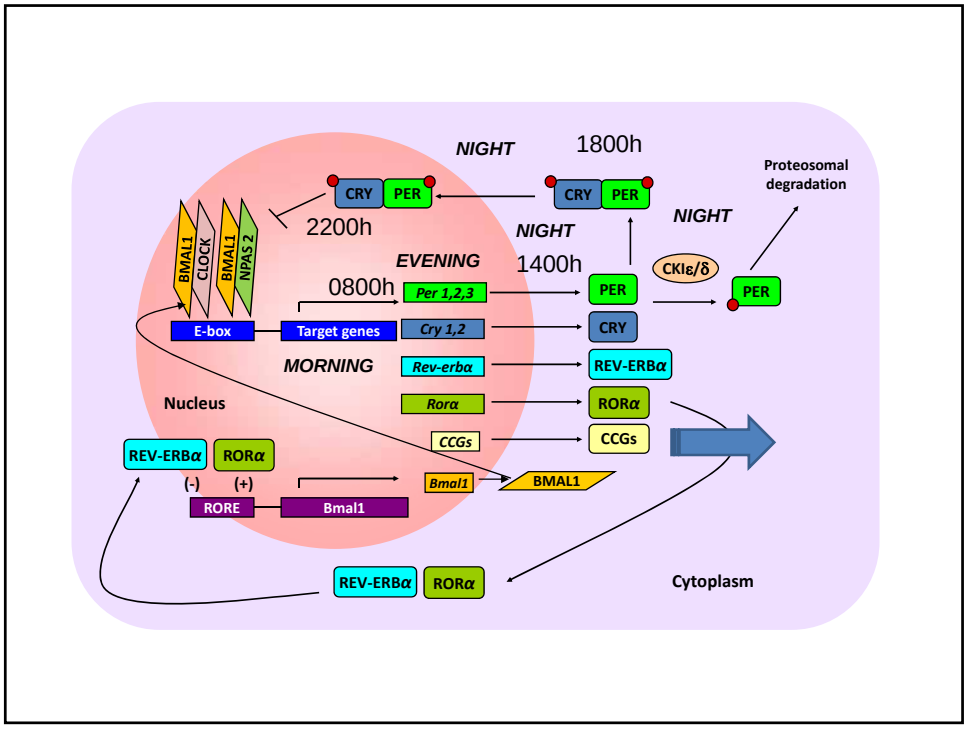
significant disruption of 24-h hormonal pattern seen in high-fat-fed rats coexists with changes in the daily pattern of several circulating adipocytokines.

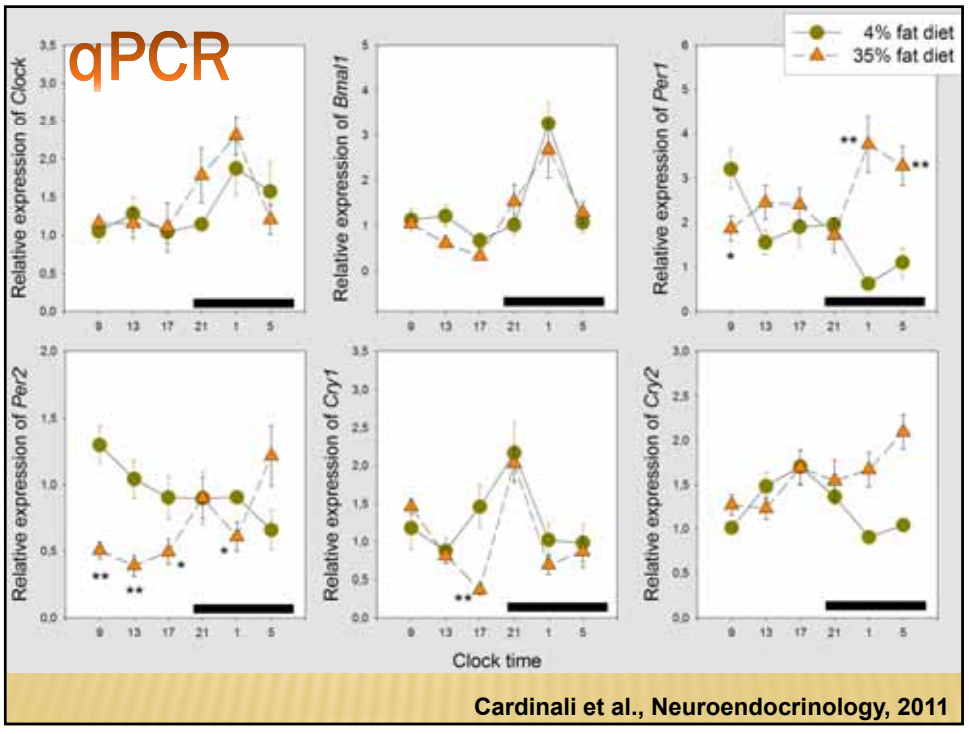
ARTICLES
INTEGRATIVE PHYSIOLOGY




ARTICLES
INTEGRATIVE PHYSIOLOGY
a
pg/ml
Leptina
Plasma leptin (pg/ml)
b
High-fat diet
Normal diet
pg/ml/BW
Plasma leptin (pg/ml.g BW)
c
pg/ml
GHrelina
Plasma ghrelin, total (pg/ml)
d
pg/ml/BW
Plasma ghrelin, active (pg/ml)
0900 h 1300 h 1700 h 2100 h 0100 h 0500 h 0900 h

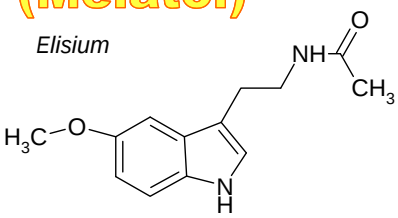

qPCR Technical Guide
SIGMA
SIGMA-ALDRICH
5'
3'


NIGHT
1800h
Proteosomal degradation
CRY
PER
2200h
NIGHT
NIGHT
BMAL1
CLOCK
BMAL1
NPAS 2
EVENING
1400h
CKIε/δ
0800h
Per 1,2,3
PER
PER
E-box
Target genes
Cry 1,2
CRY
MORNING
Rev-erbα
REV-ERBα
Nucleus
Rorα
RORα
CCGs
CCGs
REV-ERBα
RORα
(-)
(+)
Bmal1
BMAL1
RORE
Bmal1
REV-ERBα
RORα
Cytoplasm


qPCR
4% fat diet
35% fat diet
Relative expression of Clock
Relative expression of Bmal1
Relative expression of Per1
Relative expression of Per2
Relative expression of Cry1
Relative expression of Cry2
Clock time
Cardinali et al., Neuroendocrinology, 2011

Melatonina (Melatol)

Elisium

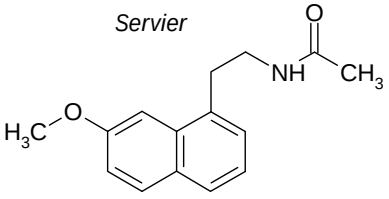


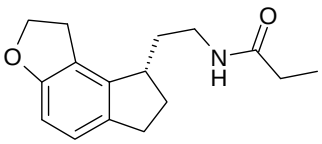
(Circadin)

Neurim; Lundbeck

Agomelatina (Valdoxan)

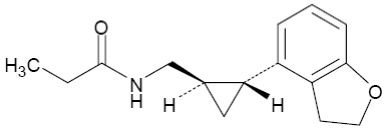
Servier





Ramelteon (Rozerem)

Takeda



Tasimelteon (VEC 162)

Vanda

Journal of Psychopharmacology
http://jop.sagepub.com/

British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders

SJ Wilson, DJ Nutt, C Alford, SV Argyropoulos, DS Baldwin, AN Bateson, TC Britton, C Crowe, D-J Dijk, CA Espie, P Gringras, G Hajak, C Idzikowski, AD Krystal, JR Nash, H Selsick, AL Sharpley and AG Wade

J Psychopharmacol 2010 24: 1577 originally published online 2 September 2010
DOI: 10.1177/0269881110379307

The online version of this article can be found at:
http://jop.sagepub.com/content/24/11/1577

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SAGE
http://www.sagepublications.com

On behalf of:
British Association for Psychopharmacology

2010

Treatment of insomnia in the elderly

2010

What is known about treatment of insomnia in the elderly

- Cognitive behavioural therapy is effective in insomnia in the elderly (Ia)
- Short-acting Z-drugs increase the risk of falls in elderly patients (III)
- Prolonged release melatonin given for 3 weeks improves sleep onset latency and sleep quality in patients over 55 (1b)

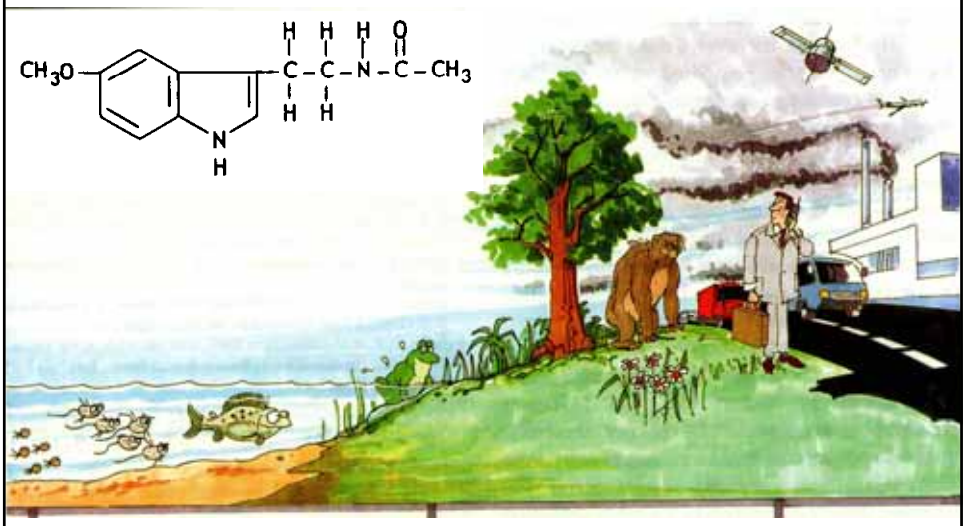
What is not known?

- What is the long-term efficacy and safety of melatonin?

Recommendations

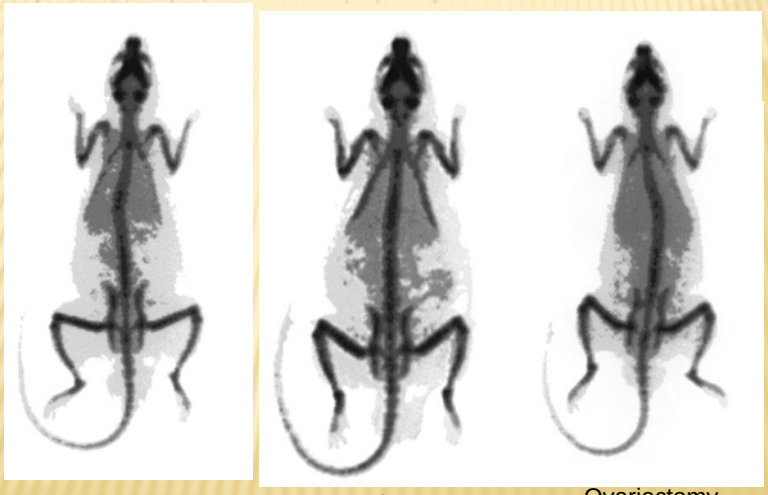
- CBT is effective and should be offered as a first line where available (A).
- When a hypnotic is indicated in patients over 55, prolonged-release melatonin should be tried first (B).
- If a $GABA_A$ hypnotic is used then a shorter half-life will minimize unwanted hangover (A).

Melatonina: Una molécula de 5000 millones de años



1500 millones de años | 400 millones de años | Hoy

MELATONIN AND BODY FAT



Control | Ovariectomy | Ovariectomy + melatonin

Molecular, Biological, Physiological and Clinical Aspects of Melatonin

J. Pineal Res. 2010
Doi:10.1111/j.1600-079X.2010.00798.x

Journal of Pineal Research

Melatonin effect on plasma adiponectin, leptin, insulin, glucose, triglycerides and cholesterol in normal and high fat–fed rats

Abstract: Melatonin effect on body weight progression, mean levels and 24-hr pattern of circulating adiponectin, leptin, insulin, glucose, triglycerides and cholesterol were examined in rats fed a normal or a high-fat diet. In experiment 1, rats fed a normal diet were divided into two groups: receiving melatonin (25 μg/mL drinking water) or vehicle for 9 wk. In experiment 2, animals were divided into three groups: two fed with a high-fat diet (35% fat) and melatonin (25 μg/mL) or vehicle in drinking water for 11 wk, while a third group was given a normal diet (4% fat). At the end of experiments, groups of eight rats were killed at six different time intervals throughout a 24- hr period. Melatonin administration for 9 wk decreased body weight gain from the 3rd wk on without affecting food intake. A significant reduction in circulating insulin, glucose and triglyceride mean levels and disrupted daily patterns of plasma adiponectin, leptin and insulin were observed after melatonin. In high fat–fed rats, melatonin attenuated body weight increase, hyperglycemia and hyperinsulinemia, as well as the increase in mean plasma adiponectin, leptin, triglycerides and cholesterol levels. The high-fat diet disrupted normal 24- hr patterns of circulating adiponectin, insulin and cholesterol, the effects on insulin and cholesterol being counteracted by melatonin. Nocturnal plasma melatonin concentration in control and obese rats receiving melatonin for 11 wk attained values 21–24-fold greater than controls. The results indicate that melatonin counteracts some of the disrupting effects of diet-induced obesity in rats.

María J. Ríos-Lugo[1], Pilar Cano[1], Vanesa Jiménez-Ortega[1], María P. Fernández-Mateos[2], Pablo A. Scacchi[3], Daniel P. Cardinali[3] and Ana I. Esquifino[1]

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Key words: adiponectin, circadian rhythms, high-fat diet, insulin, leptin, melatonin

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Received May 10, 2010;
accepted June 4, 2010.

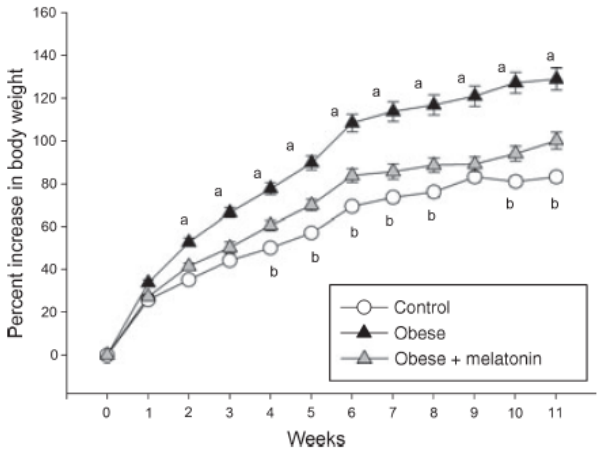
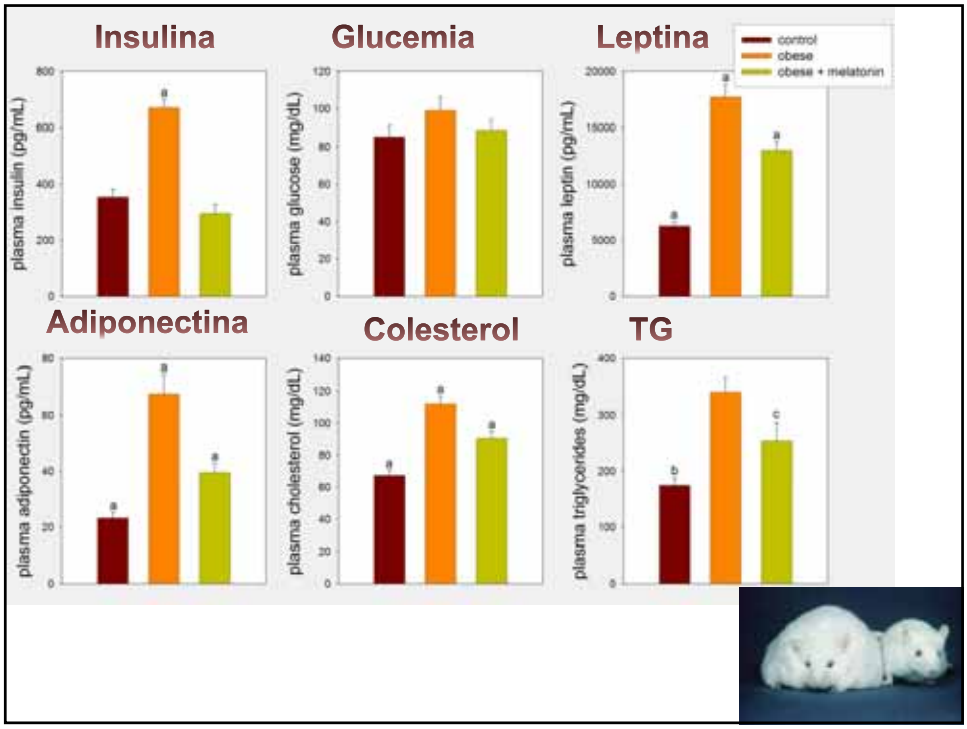


Fig. 3. Percent increase in body weight of rats fed a normal diet (4% fat) or a high-fat diet (35% fat) and melatonin (25 μg/mL) or vehicle in drinking water for 11 wk. Shown are the mean ± S.E.M. (n = 48/group). Letters indicate the existence of significant differences after a one-way ANOVA followed by a Bonferroni's multiple comparisons test and a given week of treatment, $^{a}P < 0.01$ versus the remaining groups. $^{b}P < 0.01$ versus high fat–fed rats receiving melatonin.



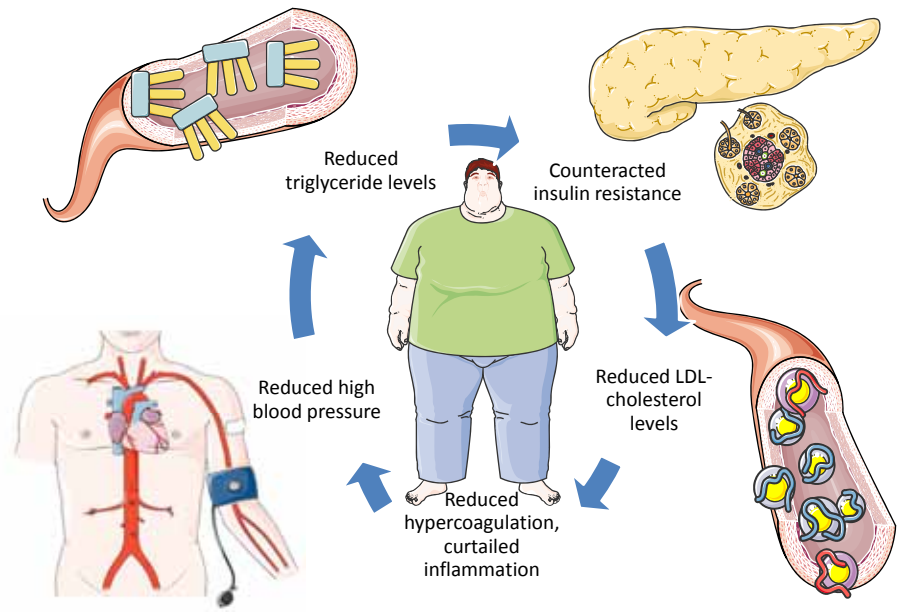
Melatonina y Síndrome Metabólico (I)

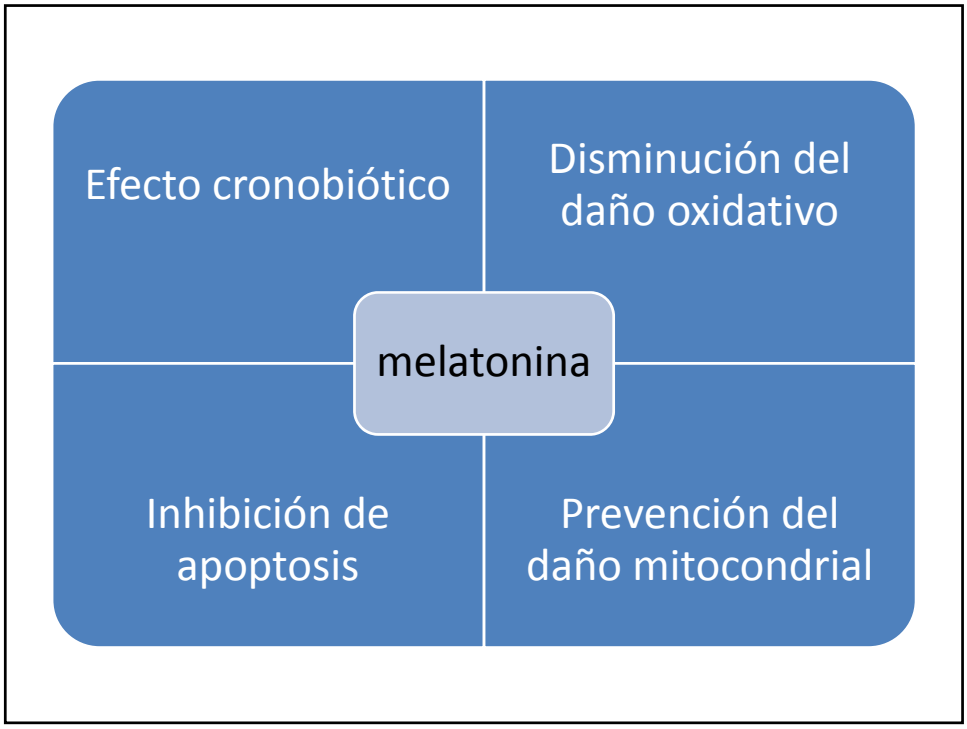
OBSERVACIÓN	REFERENCIA (S)
Niveles bajos de melatonina en diabéticos tipo 2	Tutuncu et al. 2005. J Pineal Res 39, 43-49.
Up-regulation de receptores de melatonina en diabéticos tipo 2	Peschke et al. 2007. *J Pineal Res* 42, 350-358.
El polimorfismo de genes que codifican receptores de melatonina MT1 se asocia con mayor riesgo de diabetes tipo 2	Prokopenko et al., 2009. *Nat Genet* 41, 77-81
Secreción nocturna de melatonina más baja en pacientes coronarios	Sakotnik et al. 1999. *Eur.Heart J* 20, 1314-1317; Girotti et al. 2000. *J Pineal Res* 29, 138-142; Dominguez-Rodriguez et al. 2002. *J Pineal Res* 33, 248-252; Yaprak et al. 2003. *Int J Cardiol*. 89, 103-107.

Melatonina y Síndrome Metabólico (II)

OBSERVACIÓN	REFERENCIA (S)
Tratamiento con melatonina reduce PA elevada en hombres y mujeres con hipertensión arterial	Cagnacci et al. 2005. *Am J Hypertens*. 18, 1614-1618. Scheer et al. 2004. *Hypertension* 43, 192-197. Grossman et al. 2006. *Am J Med*. 119, 898-902
Tratamiento con melatonina reduce PA elevada y mejora dislipemia y daño oxidativo en pacientes con síndrome metabólico	Kozirog et al. *J Pineal Res* 2011 DOI:10.1111/j.1600-079X.2010.00835.x
Tratamiento con melatonina reduce PA elevada en adolescentes diabéticos tipo 1	Cavallo et al. 2004. *J Pineal Res* 36, 262-266.
Tratamiento con melatonina reduce la hipercoagulabilidad inducida por catecolaminas post-estrés en pacientes	Wirtz PH, Spillmann M, Bartschi C, Ehlert U, von Kanel R. 2008. *J Pineal Res* 44, 127-133.
La agregación plaquetaria en voluntarios sanos es inhibida por melatonina con efecto máximo en la mitad de la noche	Del Zar et al. 1990. *Acta Endocrinol. (Copenh)* 123, 453-458; Vacas et al. 1991. *J Pineal Res* 11, 135-139.

Melatonin and the Metabolic Syndrome





LA INCONGRUENCIA DE LAS DOSIS

	Melatonina	Circadin (melatonina)	Ramelteon	Agomelatina	Tasimelteon	TIK-301
Afinidad	MT_1: Ki = 0.080 nM MT_2: Ki = 0.263 nM	MT_1: Ki = 0.383 nM MT_2: Ki = 0.7[illegible] nM	MT_1: Ki = 0.014 nM MT_2: Ki = 0.112 nM	MT_1: Ki = 0.1 nM MT_2: Ki = 0.268 nM	MT_1: Ki = 0.28 nM MT_2: Ki = 0.17 nM	MT_1: Ki = 0.081nM MT_2: Ki = 0.042 nM
Biodispo-nibilidad	15%	15%	< 2%	< 5%	-	-
Vida media	[illegible]	[illegible]	1 2-5	[illegible]	-	-
Unión a proteínas	70%	70%	82%	95%	-	-
Volumen de distribución		-	73.6 L	35 L	-	-
Potencia relativa	MT_1: 1 MT_2: 1	MT_1: 1 MT_2: 1	MT_1: 8 MT_2: 3	MT_1: 1 MT_2: 1	MT_1: 0,25 MT_2: 1	MT_1: 1 MT_2: 5
Dosis	3 mg	2 mg	8 -32 mg	25 – 50 mg	50 mg	
Compañía	Elisium SA	Neurim Pharma-ceuticals	Takeda Pharma-ceutical Company	Servier	Vanda Pharma-ceuticals	Tikvah Pharma-ceuticals

Necesidad de estudios con 50 – 100 mg melatonina por día


www.daniel-cardinali.blogspot.com
¡Muchas gracias!