



**integrando la
Innovación**

**X Congreso Nacional de
ALZHEIMER**
GIJÓN. 8, 9, 10 y 11 /NOV/ 2023

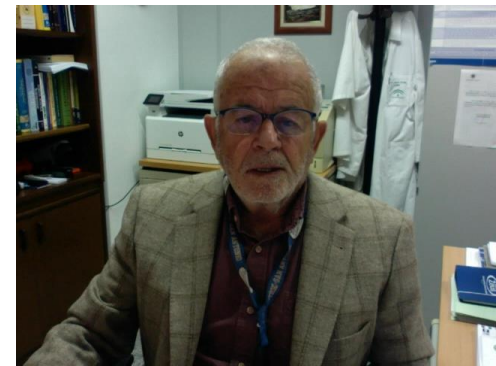
Melatonina y enfermedad de Alzheimer



Darío Acuña Castroviejo

**Centro de Investigación Biomédica
Parque Tecnológico de Ciencias de la Salud
Universidad de Granada
Avda. del Conocimiento s/n
18016 Granada**

Gijón, 10 de noviembre de 2023



IivMEL
Instituto Internacional de la Melatonina

958 241 000 - ext.20169 | Avenida del Conocimiento s/n 18016, Granada | info@institutodemelatonina.com

Inicio | ¿Qué es la melatonina? | ¿Quiénes somos? | Equipo | Nuestros servicios | Noticias | Contacto

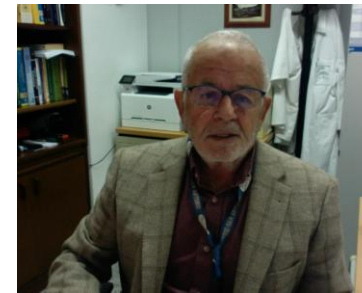
**Instituto
Internacional
de Melatonina**

Covid-19 Research

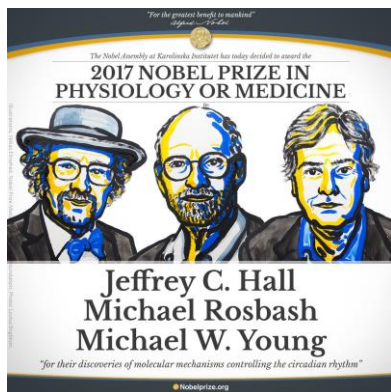
<http://www.institutodemelatonina.com>
info@institutodemelatonina.com



<https://www.salvat.com/neurociencia-y-psicologia/sueno-y-vigilia-3847>



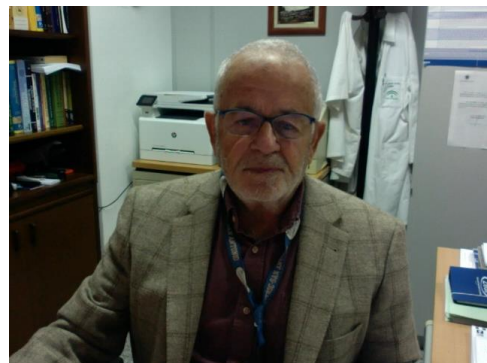
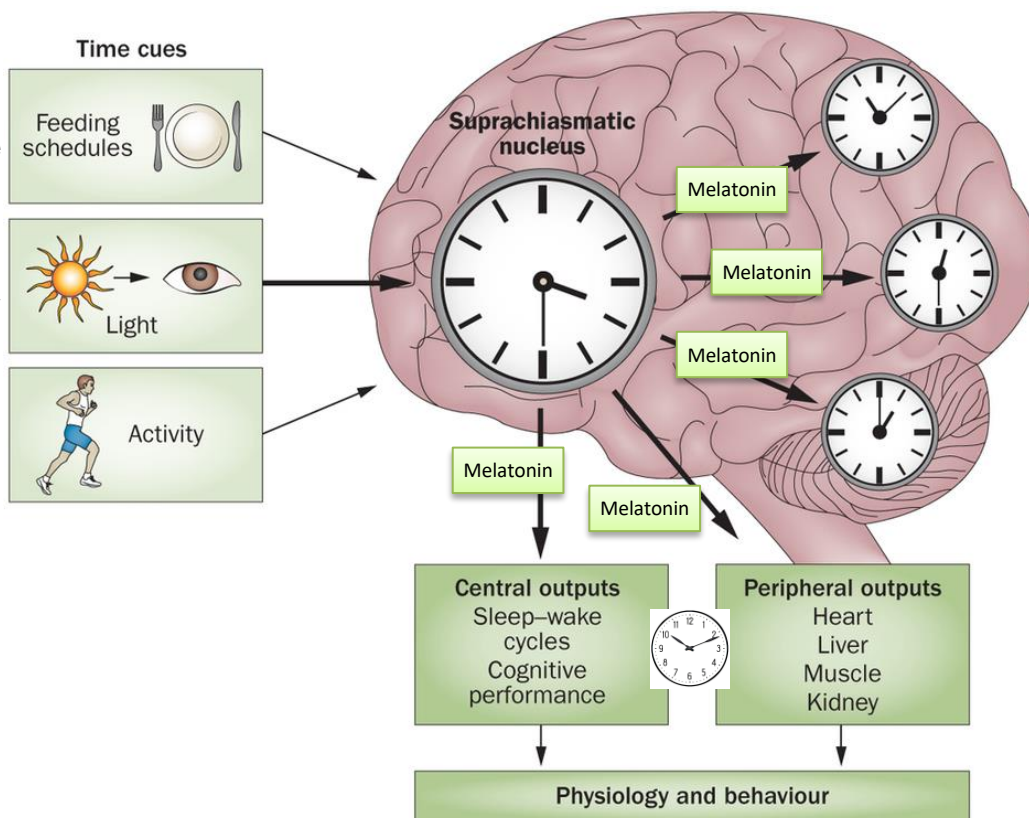
EL SISTEMA CIRCADIANO



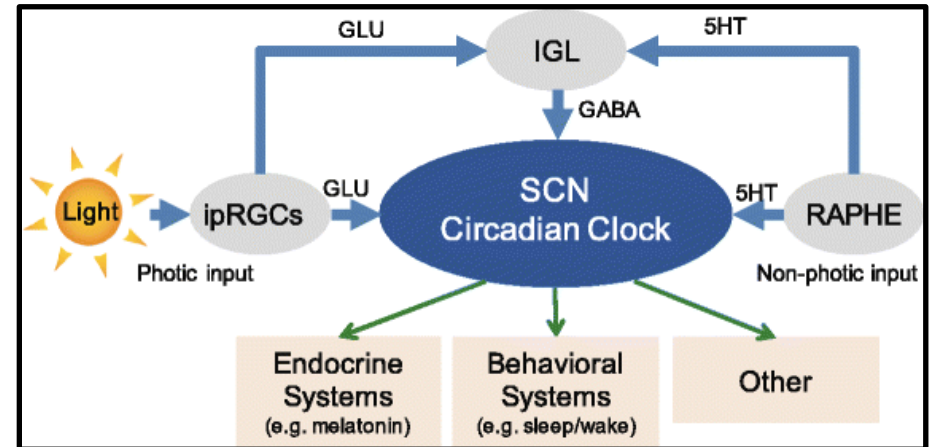
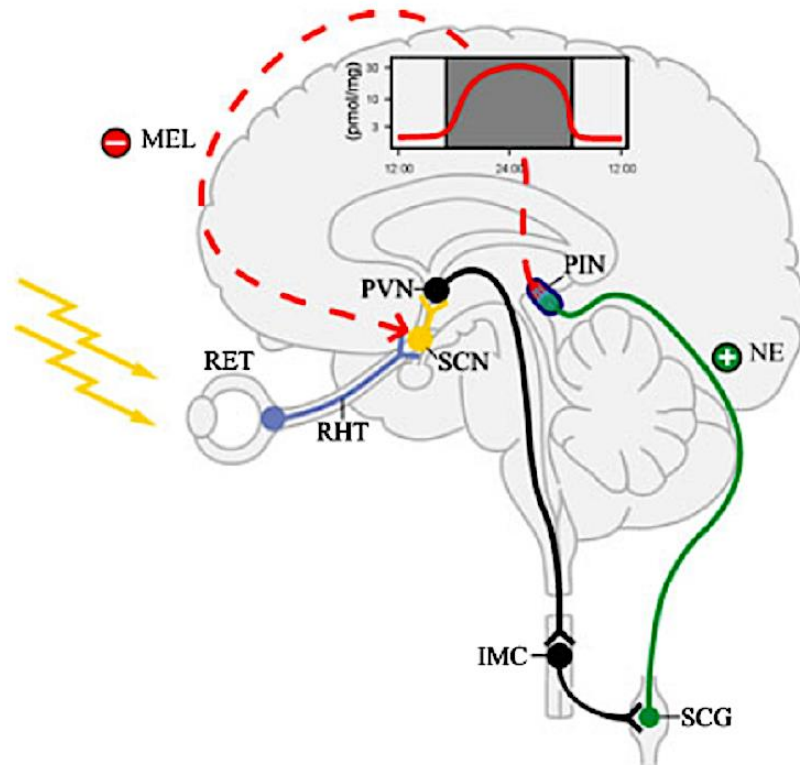
3-4 h antes de acostarse

Máxima luz por la mañana

Mejor por la mañana, no por la tarde



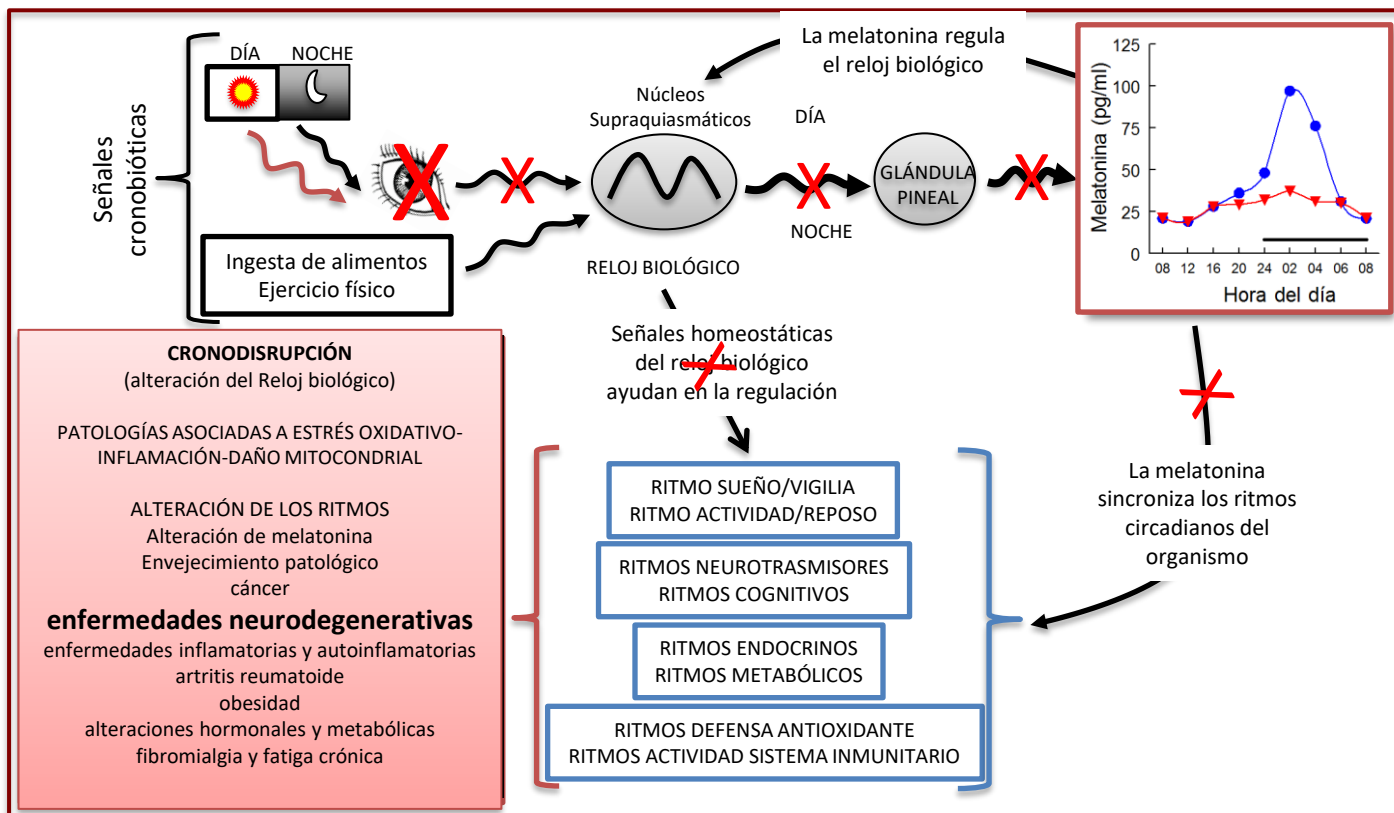
LA MELATONINA PINEAL Y EL CONTROL DE LOS RITMOS



REGULACIÓN DE LOS RITMOS CIRCADIANOS



CONSECUENCIAS DE LA ALTERACIÓN DEL RELOJ



INSOMNIO = SIGNO PRECOZ DE PD/AD



EL sueño es fundamental para la homeostasis cerebral y su déficit es un signo temprano de enfermedades neurodegenerativas

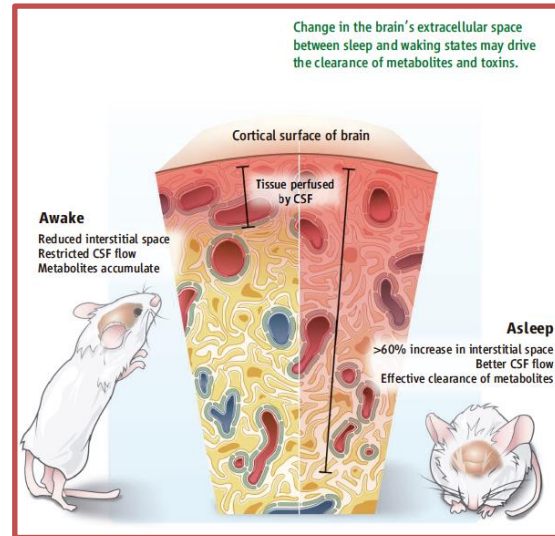
SLEEP CHRONIC DEFICIT



MICROGLIA ACTIVATION
NEURONAL FAGOCITOSIS



INCREASED SUSCEPTIBILITY TO OTHER
FORMS OF BRAIN DAMAGE



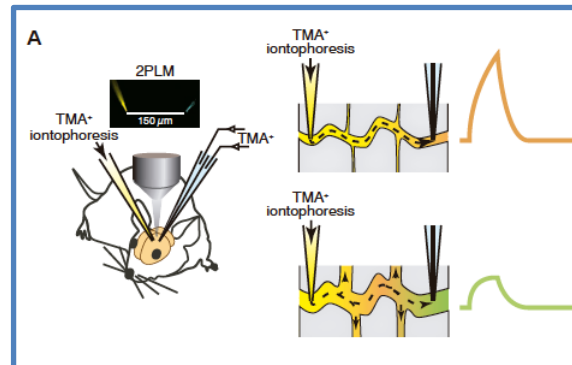
NORMAL SLEEP RHYTHM



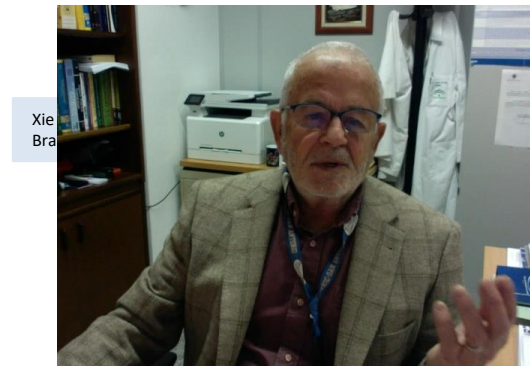
INCREASE OF INTERSTITIAL SPACE
REDUCTION OF INTERSYNAPTIC SPACE



MEMORY CONSOLIDATION
COGNITIVE PERFORMANCE

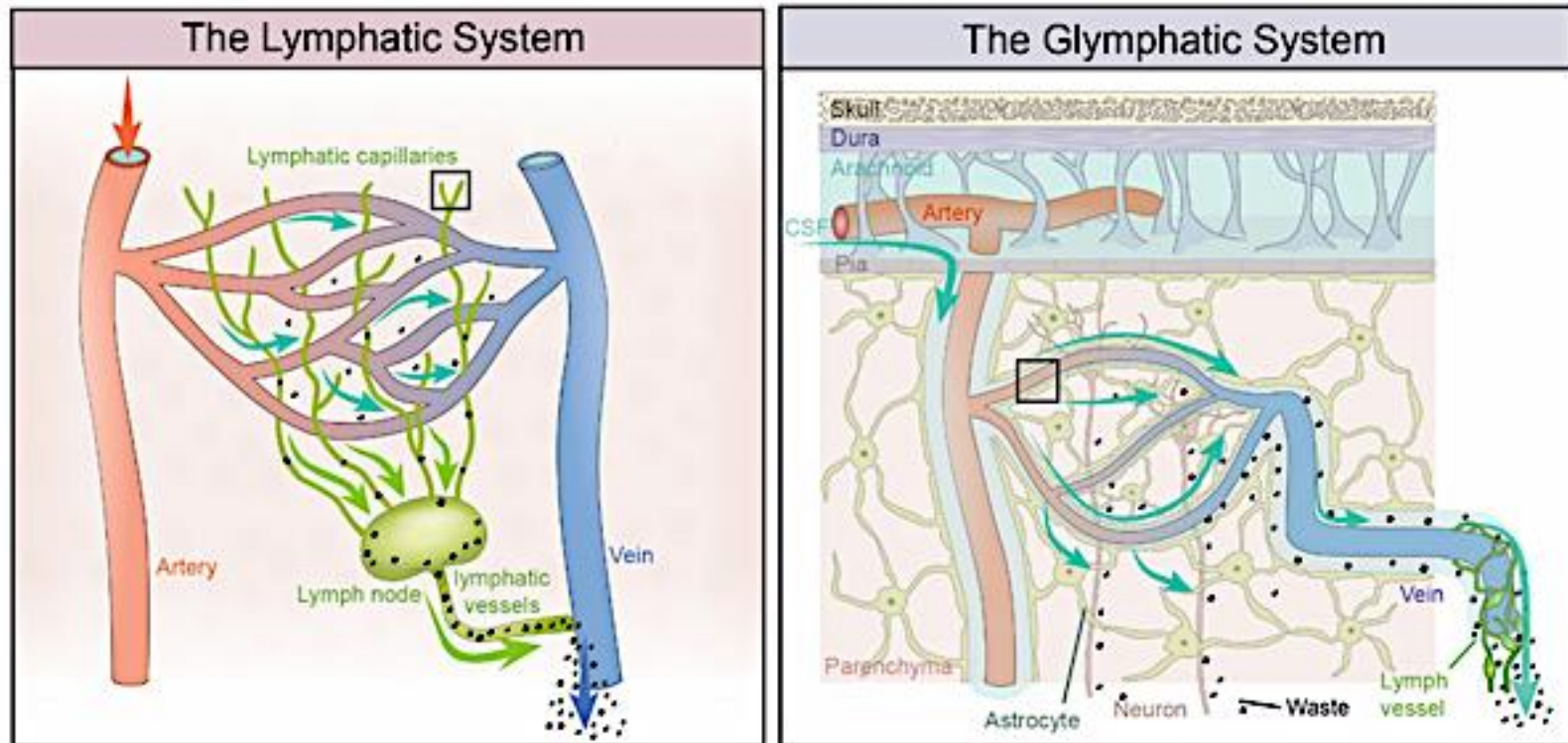


Bellesi et al. Sleep Loss Promotes Astrocytic Phagocytosis and Microglial Activation in Mouse Cerebral Cortex. *J Neurosci* 2017;37:5263-5273.



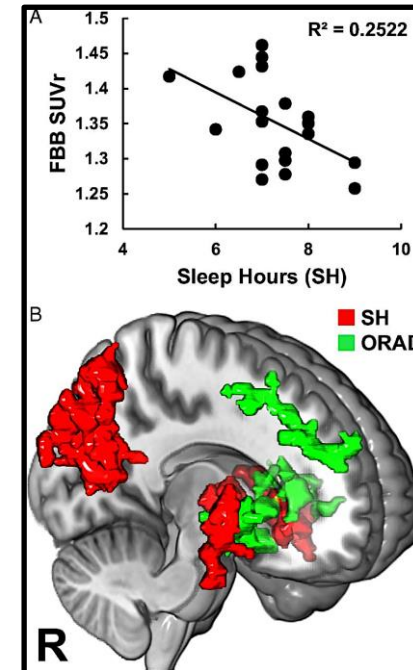
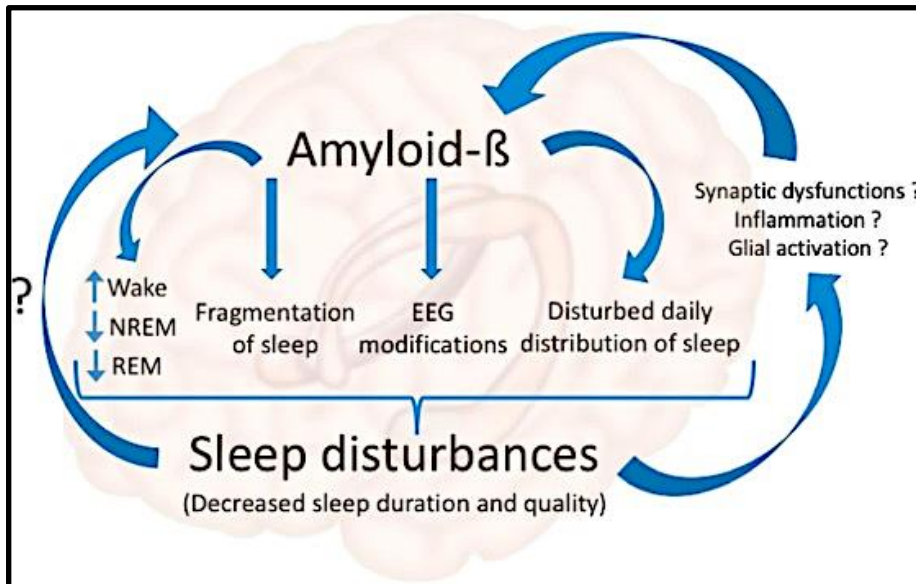
EL sueño es fundamental para la homeostasis cerebral y su déficit es un signo temprano de enfermedades neurodegenerativas

Throughout the body, lymphatic fluid movement supports critical functions including clearance of excess fluid and metabolic waste. **The glymphatic system is the analog of the lymphatic system in the brain.** Because of the functional conservation between these systems, we hypothesize that **both are regulated by circadian rhythms**, and injury within these tissue (such as ischemia or inflammation) may alter interstitial fluid movement and pathology in a similar manner.



The lymphatic system in the periphery (left) and glymphatic system in the brain (right) are functionally homologous, **enabling interstitial fluid movement, waste clearance, and immune surveillance of the tissue.** Hablitz and Nedergaard. Current Biology 2021.

Los niveles más altos de AB cerebral (proporciones AB42/40 más bajas) se relacionan con acortamiento del sueño, destacando la importancia del tiempo total de sueño para eliminar AB durante el sueño de ondas lentas.



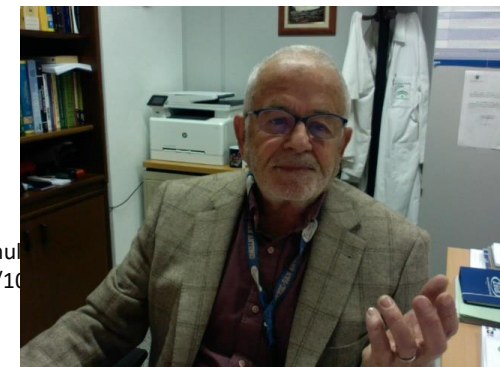
Insel PS, et al. Association of Sleep and β -Amyloid Pathology Among Older Cognitively Unimpaired Adult. JAMA 2021;doi:10.1001/jamanetworkopen.2021.17573

Sadler CR, et al. Connections between ApoE, sleep, and A β and tau pathologies in Alzheimer's disease. J Clin Invest 2023; doi: 10.1172/JCI171838.

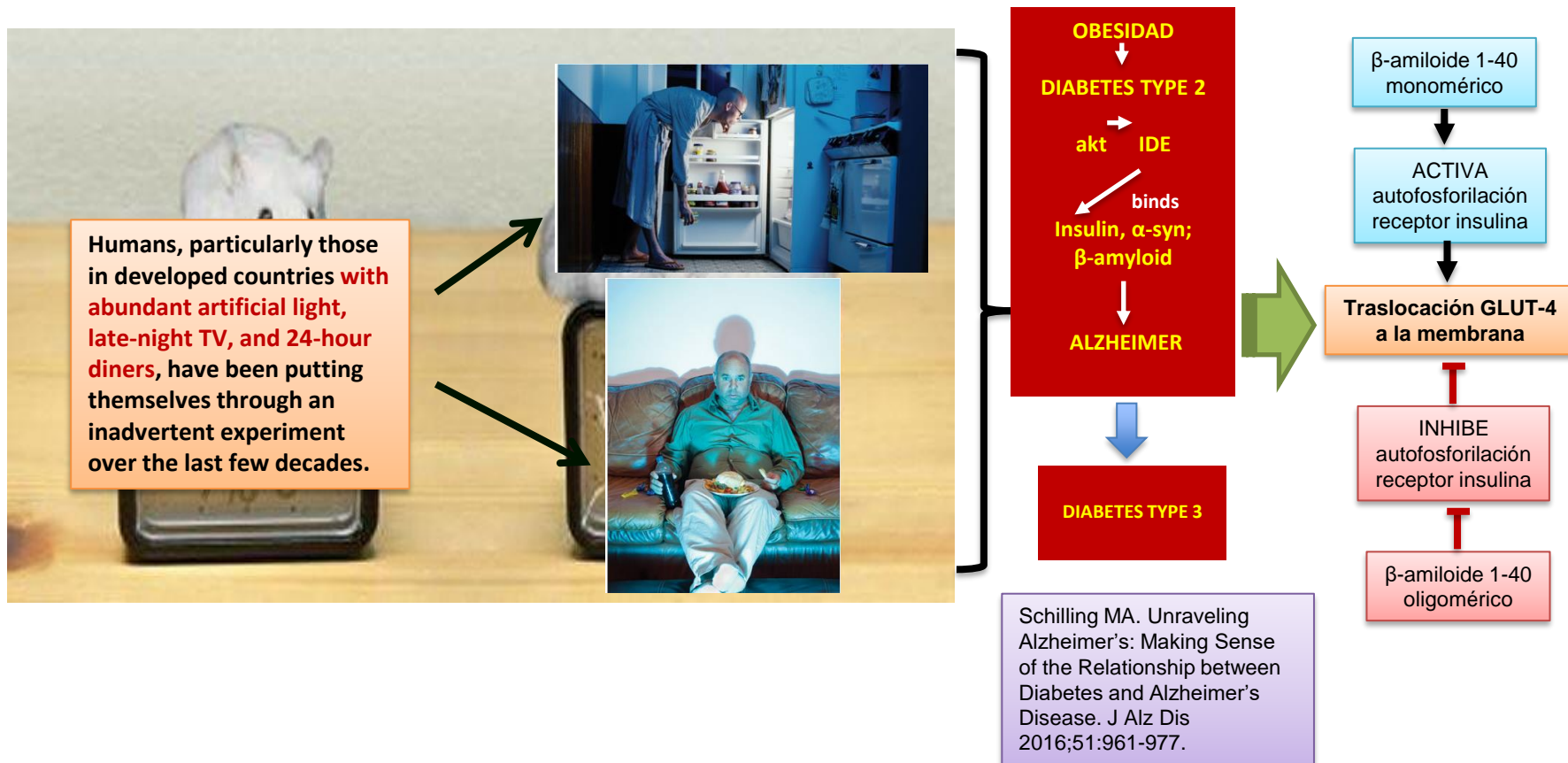
Yoon SH et al. Association of Sleep Disturbances With Brain Amyloid and Tau Burden, Cortical Atrophy, and Cognitive Dysfunction Across the AD Continuum. Neurology 2023; doi: 10.1212/WNL.0000000000207917.

Harenbrock J et al. A meta-analysis of the relationship between sleep and β -Amyloid biomarkers in Alzheimer's disease. Biom Neuropsychiat 2023; /doi.org/10.1016/j.bionps.2023.100068.

Shokri-Kojori E, et al. β -Amyloid accumulation during sleep deprivation. PNAS 2018;doi.org/10.1073/pnas.1711111111



¿Por qué comer en los momentos equivocados está ligado a efectos tan profundos y negativos en nuestro cuerpo?

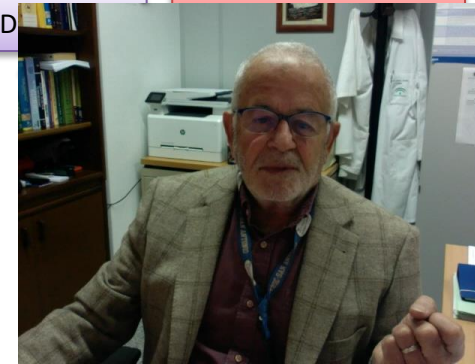
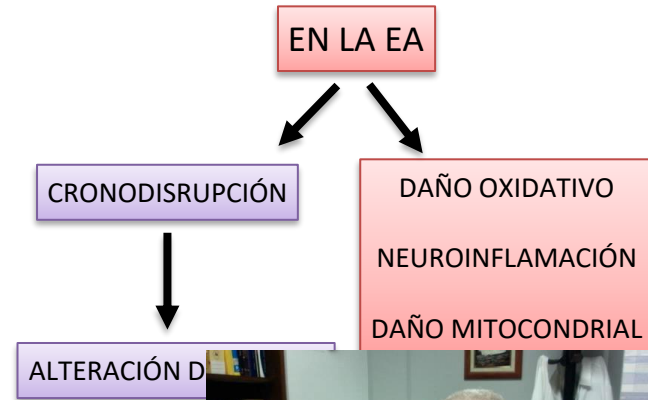
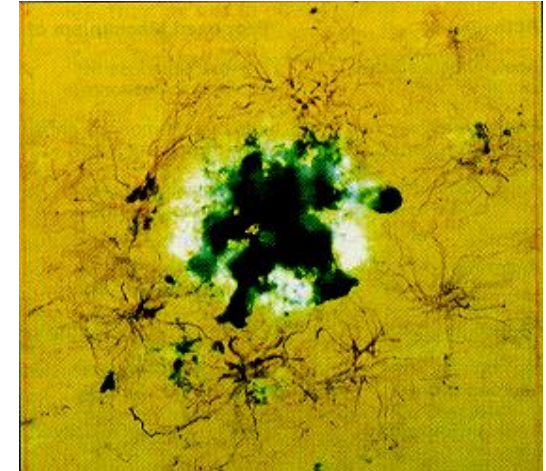
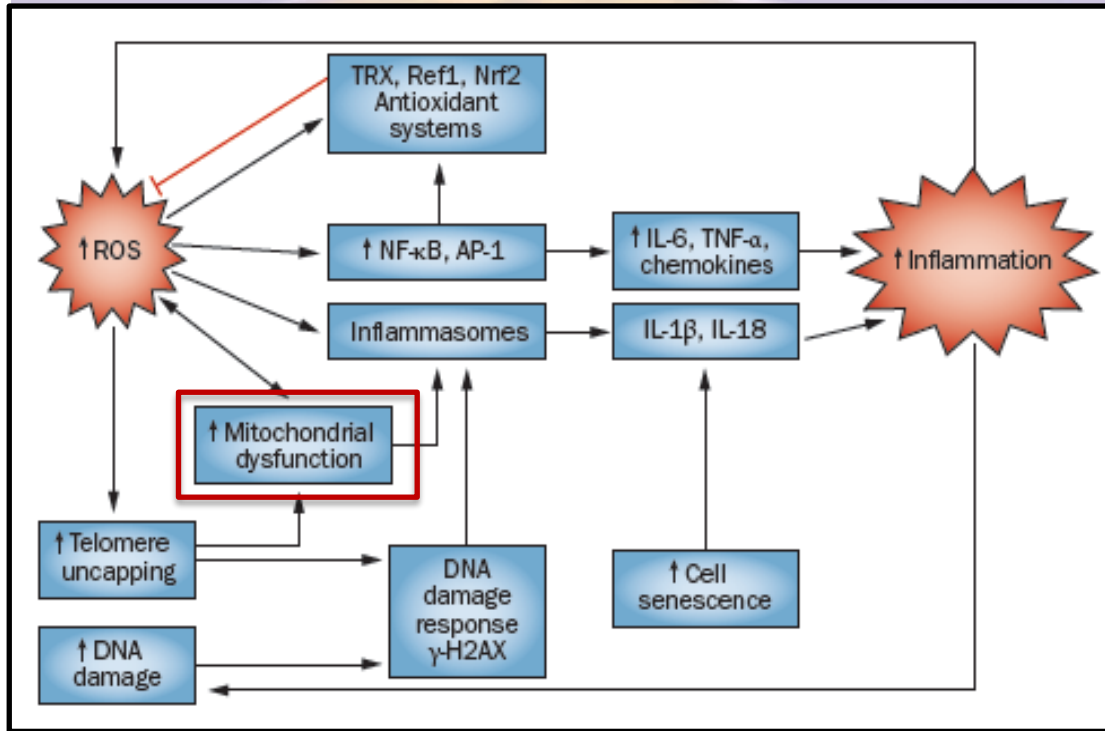


-McMullan CJ, et al. Melatonin secretion and the incidence of type 2 diabetes. JAMA 2013; 309:1388-1396.

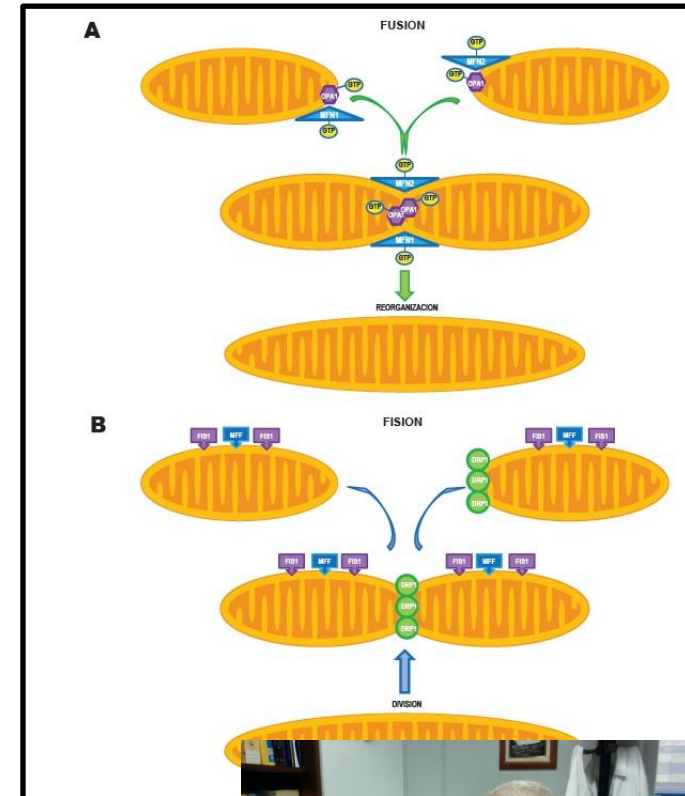
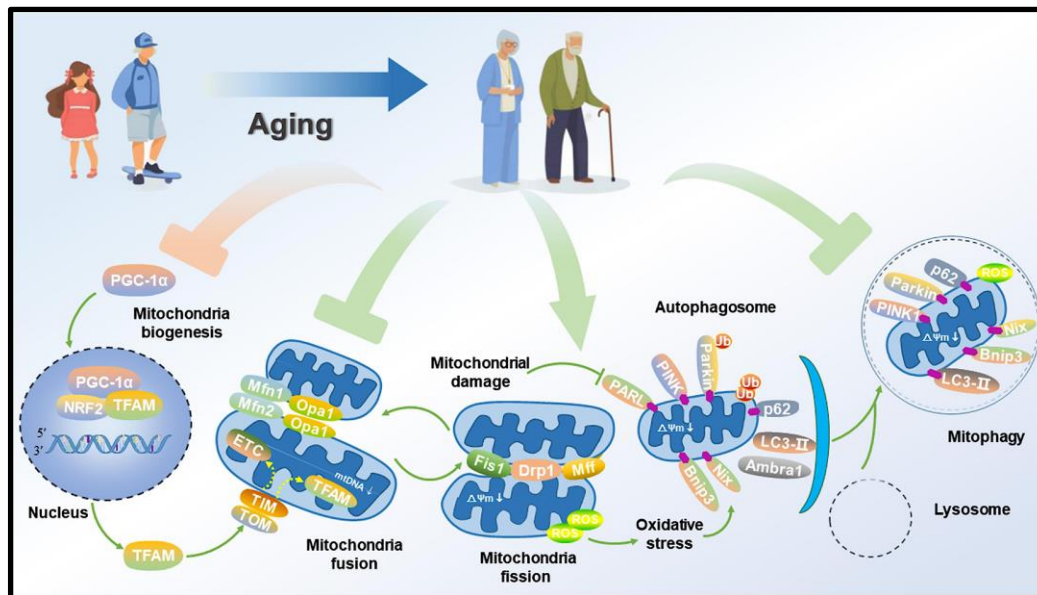
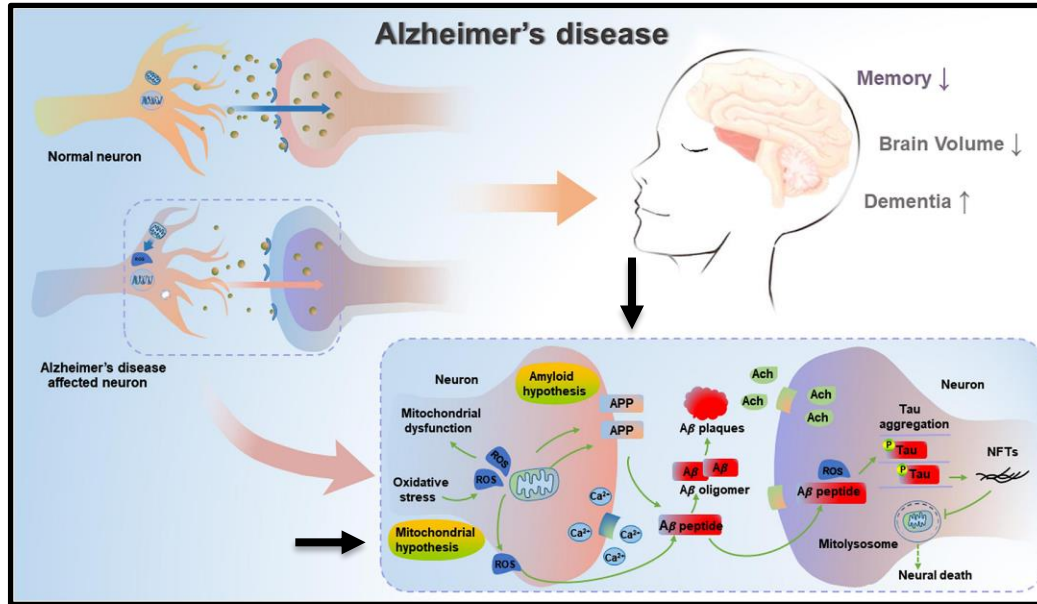
-Karamitri A, et al. Involvement of melatonin MT2 receptor mutants in type 2 diabetes development. Med Sci 2013; 29:778-784.

-McMullan CJ, et al. Association of nocturnal melatonin secretion with insulin resistance in nondiabetic young women. Am J Epidemiol 2013; 178:231-238.

Molina-Fernández R et al. Differential regulation of insulin signalling by monomeric and oligomeric amyloid beta-peptide. Brain Comm 2022; /doi.org/10.1093/braincomms/fcac243.



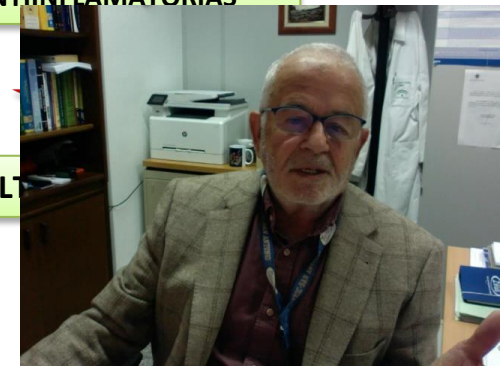
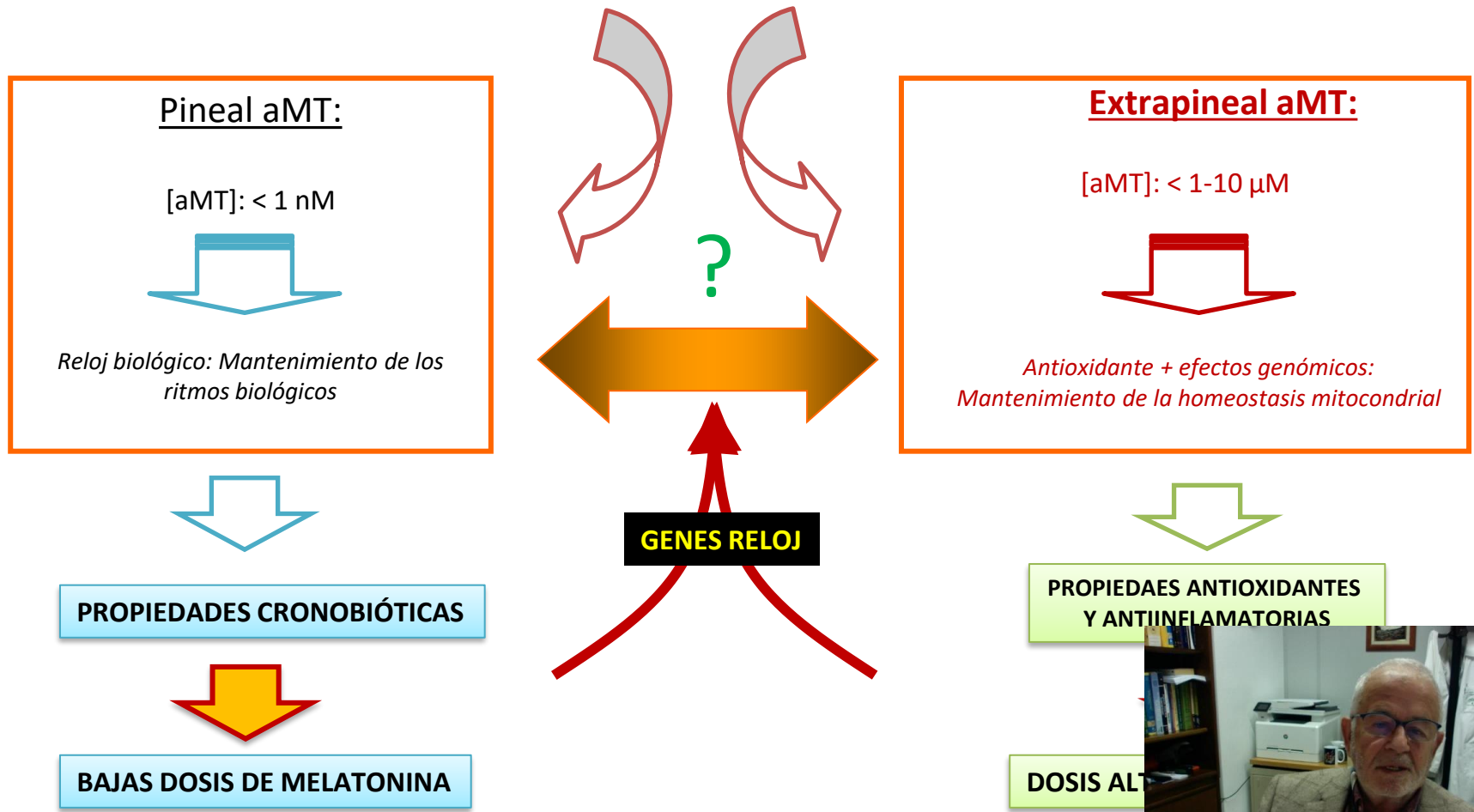
La neurona y sus mitocondrias

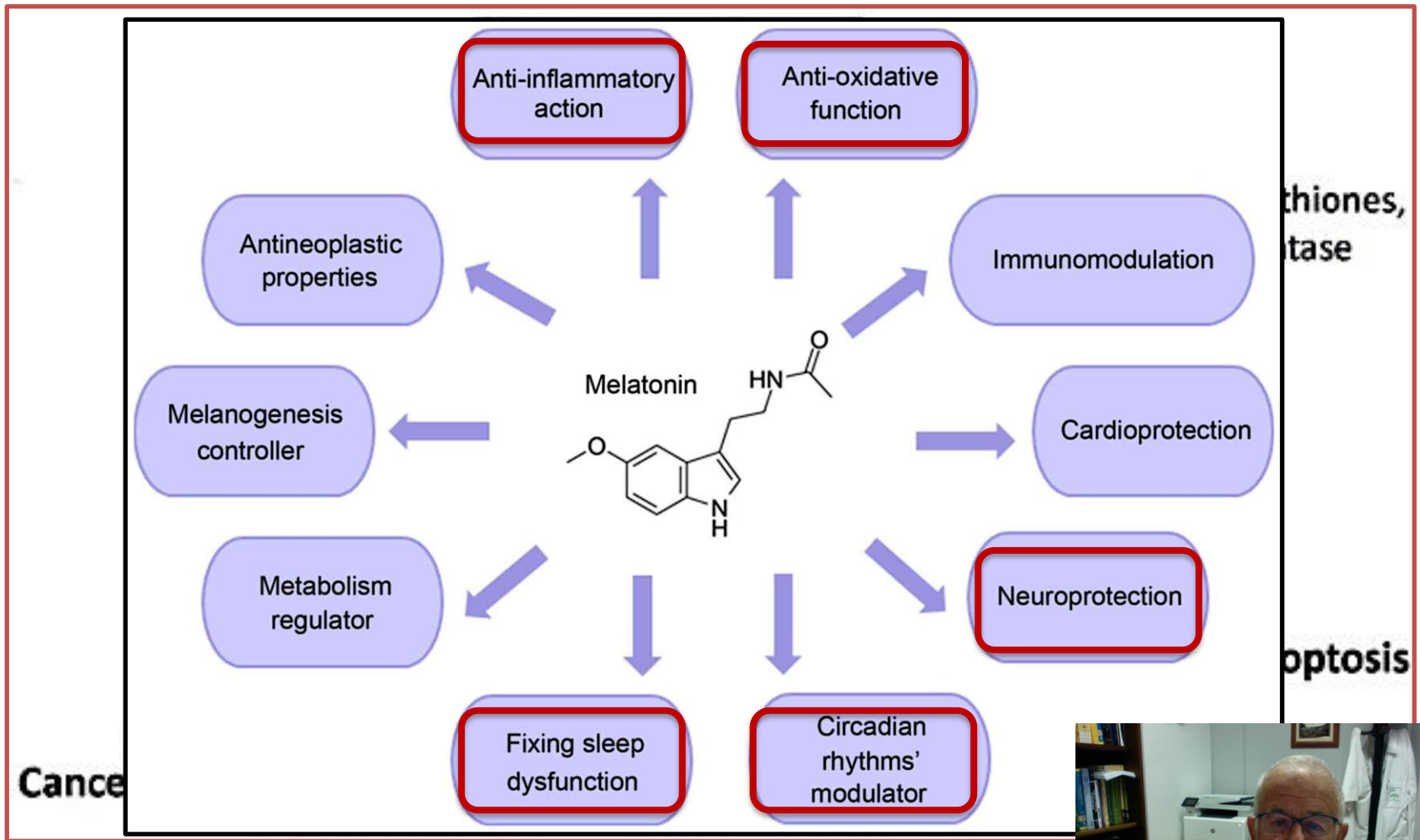


Liang J et al. Exercise-Induced Mitophagy and Improving



MELATONINA PINEAL vs. EXTRAPINEAL

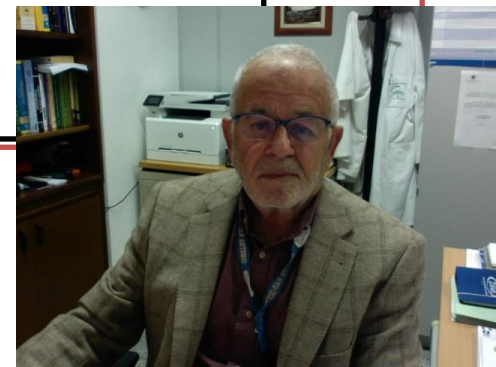




thiones,
tase

optosis

Cance



The FASEB Journal express article 10.1096/fj.99-0865fje. Published online July 24, 2009

Melatonin but not vitamins C and E maintain mitochondrial homeostasis in t-butyl hydroperoxide-induced mitochondrial oxidative stress

J. Pineal Res. 2009; 46:188-198
 Doi:10.1111/j.1600-079X.2008.00647.x

Melatonin protects the reducing oxygen consumption

The FASEB Journal express article

Melatonin controls expression of

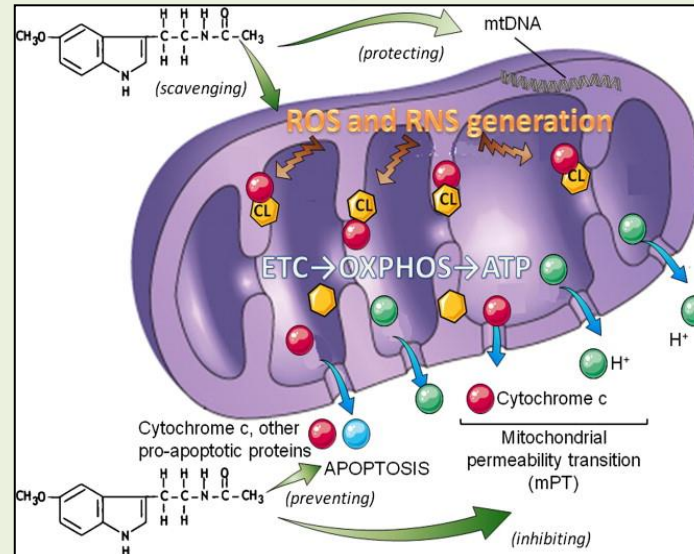
The FASEB Journal express article
 The FASEB Journal

Disruption of the melatonin requirement

J. Pineal Res. 2016; 60:193-203
 Doi:10.1111/jpi.12303

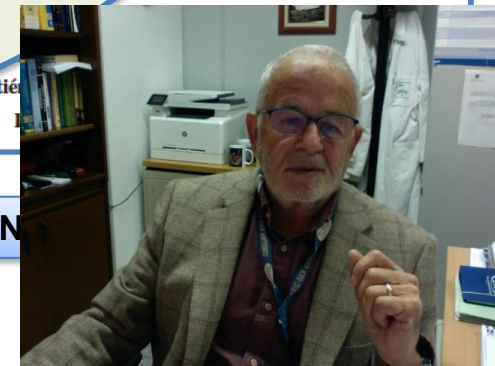
Same molecule but different effects on NLRP3 inflammasome activation, and

LA MELATONINA MANTIENE LA HOMEOSTASIS MITOCONDRIAL



ATP

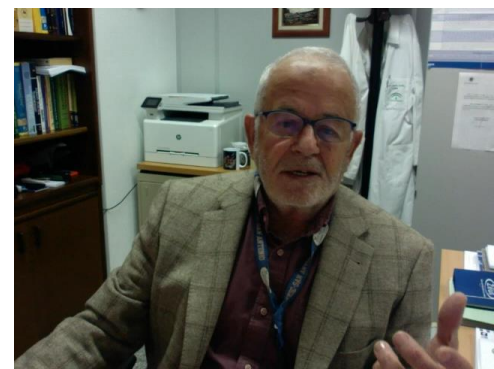
LA MELATONINA REDUCE LA NEUROINFLAMACIÓN



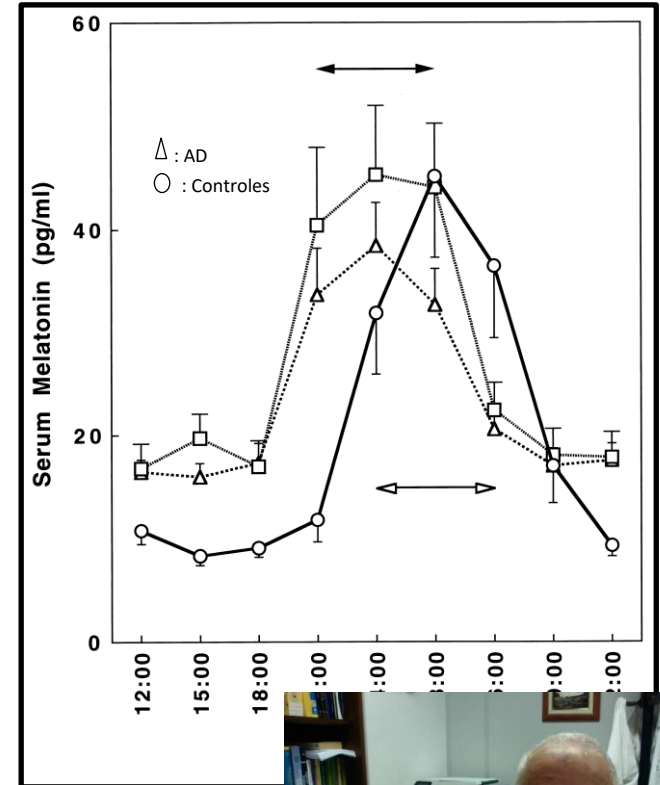
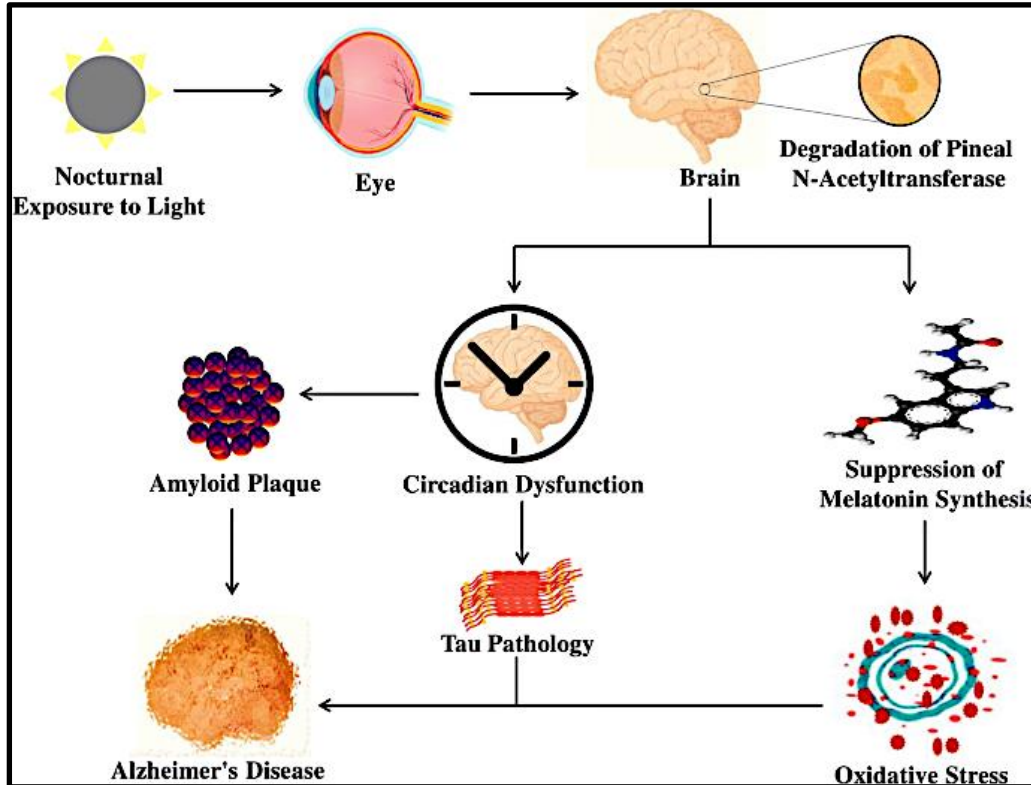


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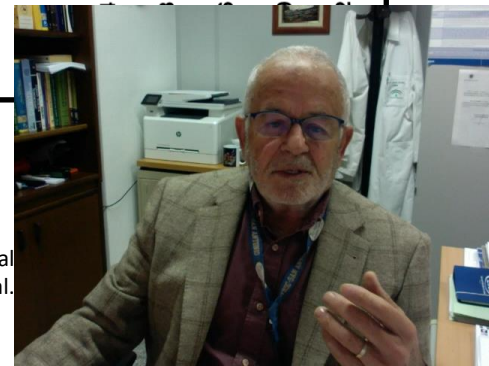
MELATONINA EN LA EA

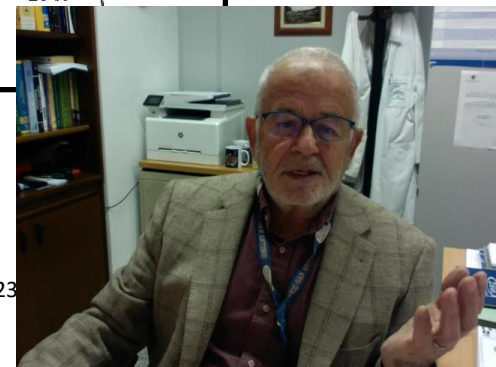
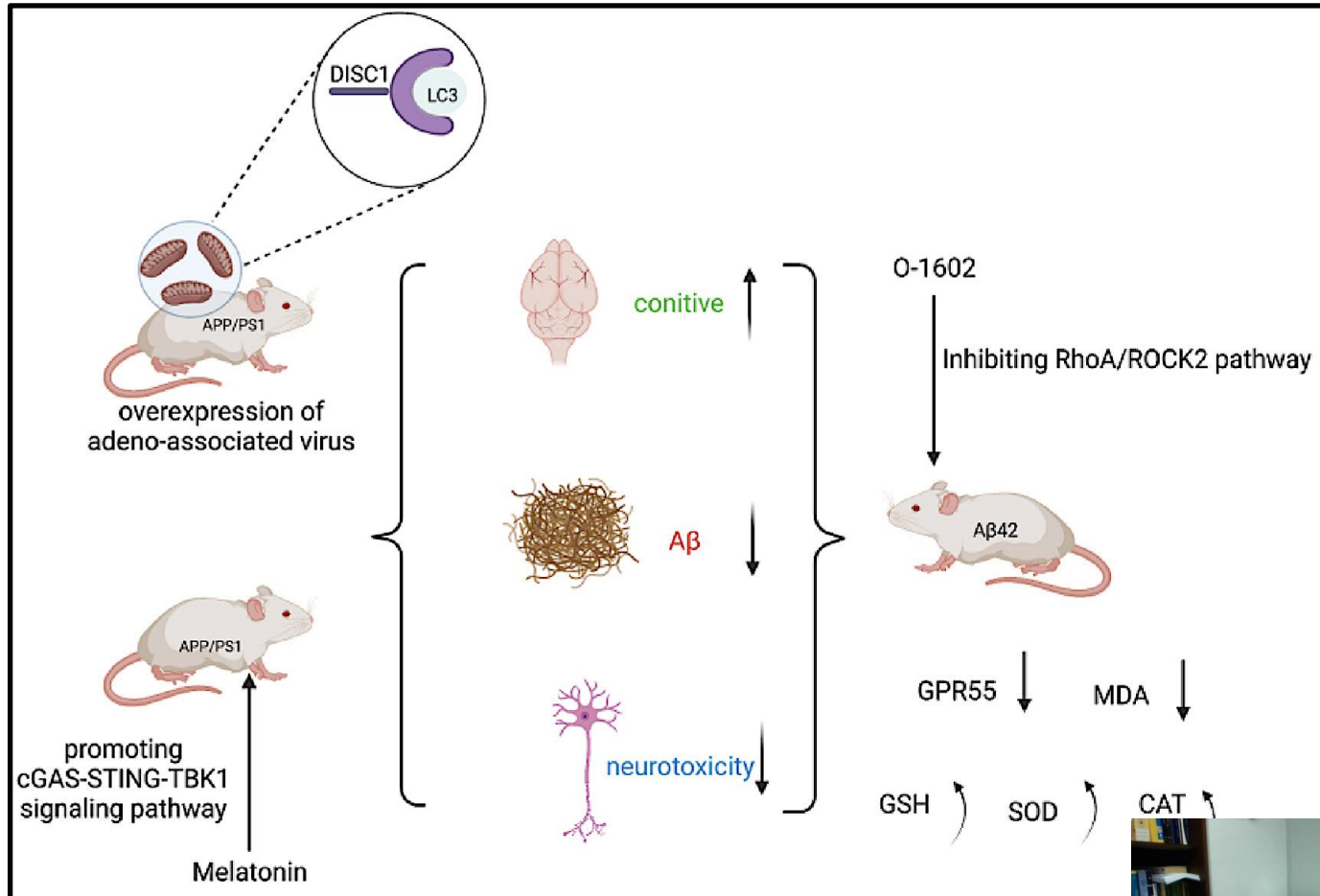


ENFERMEDAD DE ALZHEIMER




Breen DP, et al
Ohashi Y, et al.





BEHAVIORAL AND COGNITIVE PROFILE



ELSEVIER

Neurobiology of Aging 33 (2012) 1124.e13–1124.e29

www.elsevier.com/locate/neuaging

**NEUROBIOLOGY
OF
AGING**

**Melatonin plus physical exercise are highly neuroprotective in the
3xTg-AD mouse**

Yoelvis García-Mesa^a, Lydia Giménez-Llort^b, Luis C. López^c, Carmen Venegas^c,
Rosa Cristòfol^a, Germain Escames^c, Darío Acuña-Castroviejo^c, Coral Sanfeliu^{a,*}

^a Institute of Biomedical Research of Barcelona (IIBB), CSIC, IDIBAPS, Barcelona, Spain
^b Institute of Neuroscience and Medical Psychology Unit, Department of Psychiatry and Forensic Medicine, Autonomous University of Barcelona,
Barcelona, Spain
^c Instituto de Biotecnología, Departamento de Fisiología, Centro de Investigación Biomédica, Parque Tecnológico de Ciencias de la Salud, Universidad

The 3xTg-AD mouse strain harboring familial AD mutations
PS1/M146V, APP^{swe}, and tauP301
(B6;129-Psen1^{tm1Mpm} Tg(APP^{swe},tauP301L)1Lfa/Mmjax)

Furio AM, et al. Possible therapeutic value of melatonin in mild cognitive impairment: a retrospective study. J Pineal Res 2007; 43:404-409.

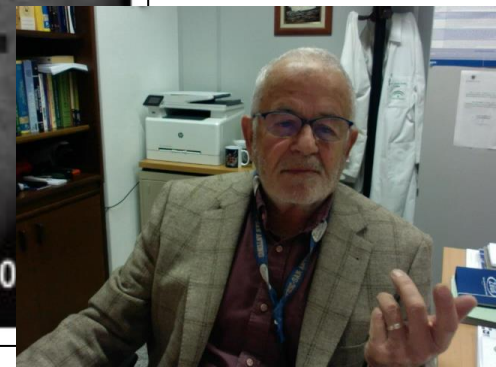
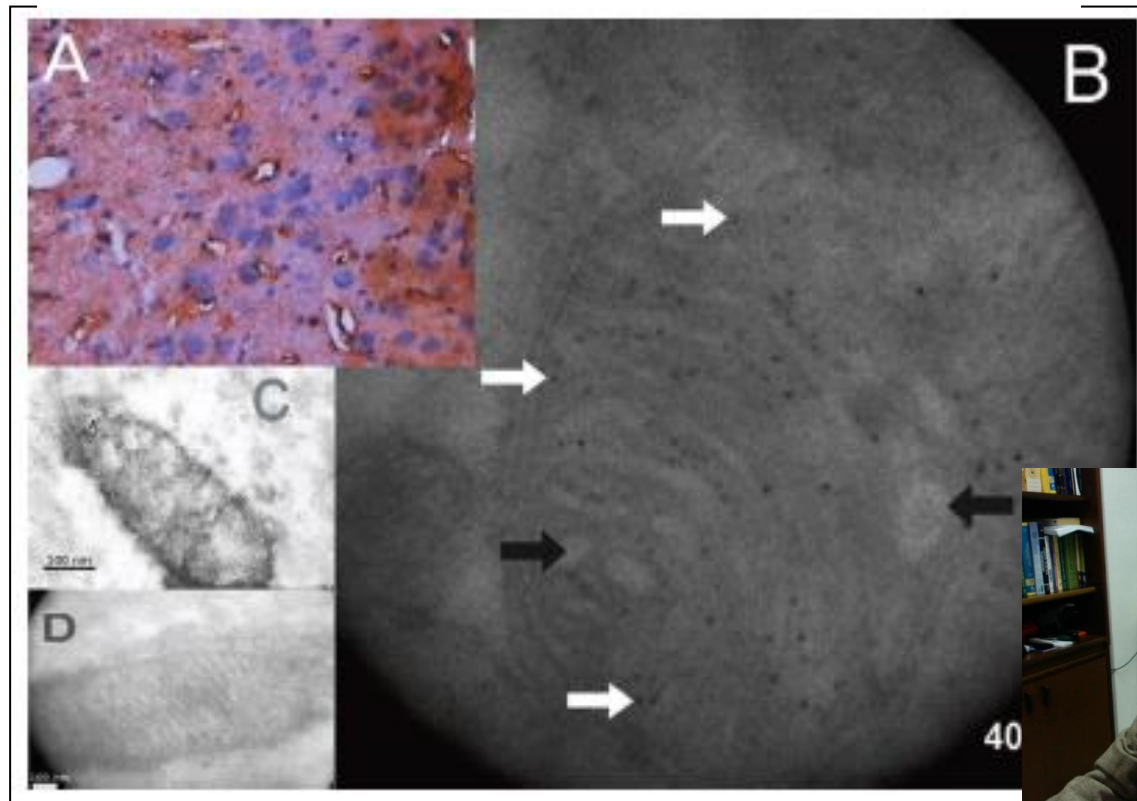
Cardinali DP, et al. Clinical aspects of melatonin intervention in Alzheimer's disease progression. Curr Neuropharmacol 2010; 8:218-227.

Cardinali DP
melatonin in
Neurodegen



A β EN LA MITOCONDRIA*Oxidative Medicine and Cellular Longevity 2012;***Accumulation of Exogenous Amyloid-Beta Peptide in Hippocampal Mitochondria Causes Their Dysfunction: A Protective Role for Melatonin**

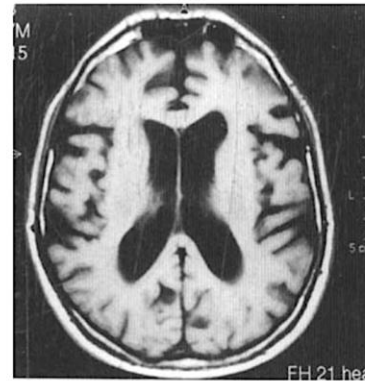
Sergio Rosales-Corral,^{1,2} Dario Acuna-Castroviejo,³ Dun Xian Tan,²
Gabriela López-Armas,¹ José Cruz-Ramos,¹ Rubén Muñoz,⁴ Valery G. Melnikov,⁵
Lucien C. Manchester,² and Russel J. Reiter²



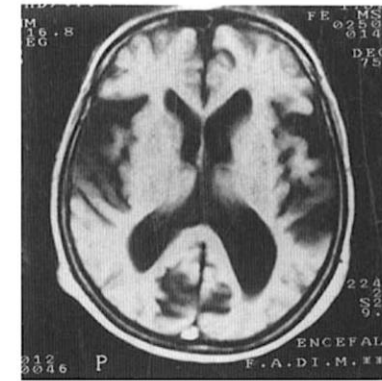
Brusco LI, et al. Monozygotic twins with Alzheimer's disease treated with melatonin: Case report. J Pineal Res 1998; doi: 10.1111/j.1600-079x.1998.tb00396.x

Brusco LI, et al. Melatonin treatment stabilizes chronobiologic and cognitive symptoms in Alzheimer's disease. NeuroEndocrinol Lett 2000;21:39-42

Furio AM, et al. Possible therapeutic value of melatonin in mild cognitive impairment: a retrospective study. J Pineal res 2007; doi.org/10.1111/j.1600-079X.2007.00491.x



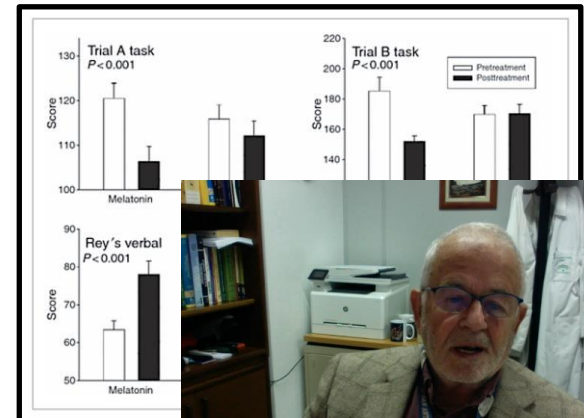
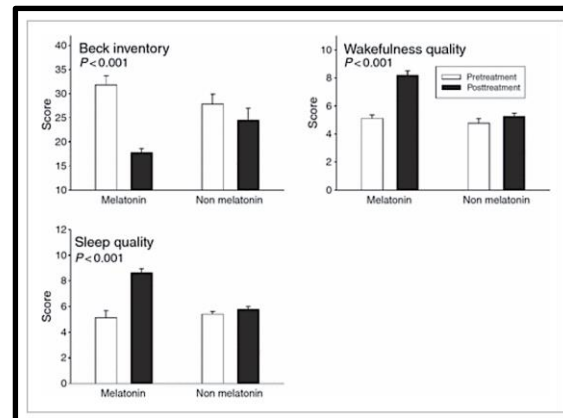
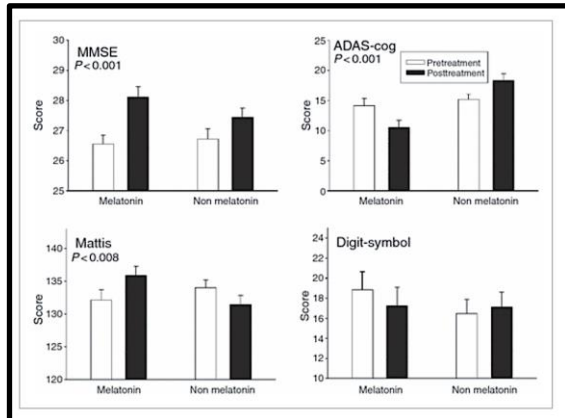
Patient NN



Patient ZZ

Fig. 1. Comparison of MNR of monozygotic twins with Alzheimer's disease of 8 years duration, one of them (patient N.N., left) treated with melatonin (6 mg/day) during 36 months.

A generalized cortical atrophy was found in both patients, with a more important bitemporal atrophy and ventricular enlargement in patient .Z.Z (right) who did not receive melatonin.



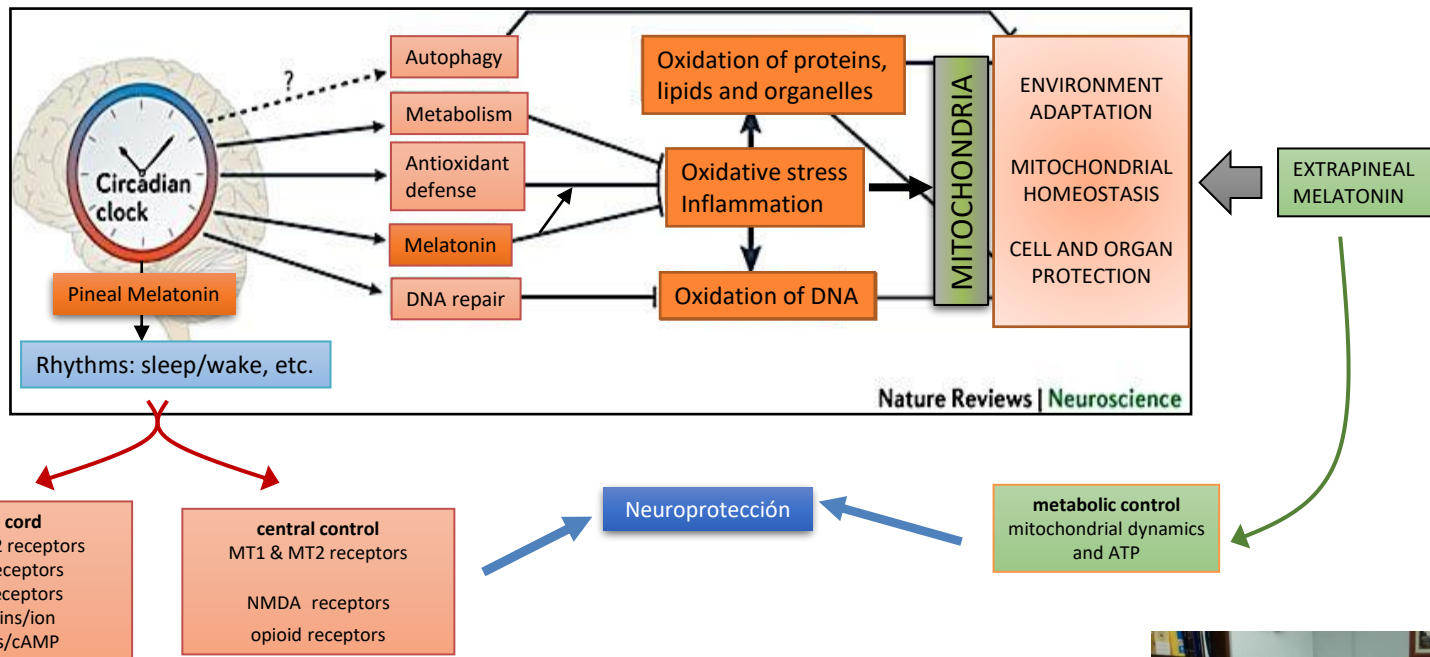
Clinical continuum	CN	MCI	Dementia
NIA-AA 2011	Preclinical	MCI	Dementia
IWG	Asymptomatic at risk	Prodromal AD	Dementia
DSM-5		Mild NCD	Major NCD
NIA-AA syndromes	CU	MCI	Dementia
NIA-AA stages 2018	ST1	ST2	ST3
			ST4, ST5, ST6

La melatonina es altamente efectiva al tiempo del

deterioro cognitivo leve



MELATONINA: VÍA FINAL COMÚN



Anna A. Kondratova & Roman V. Kondratov
Nature Reviews Neuroscience 2012; **13**, 325-331
Clocks not winding down: unravelling circadian
Eric E. Zhang & Steve A. Kay. *Nature Reviews Molecular Cell Biology*

