Sleep and Diabetes

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Diabetes Learning Group
February 21, 2018

LEARNING OBJECTIVES

- Become familiar with the molecular clock-control of glucose homeostasis
- Recognize the influence of circadian disruption on glucose management
- Identify the role of melatonin as a regulator of the timing system in the etiology of DM2

BACKGROUND

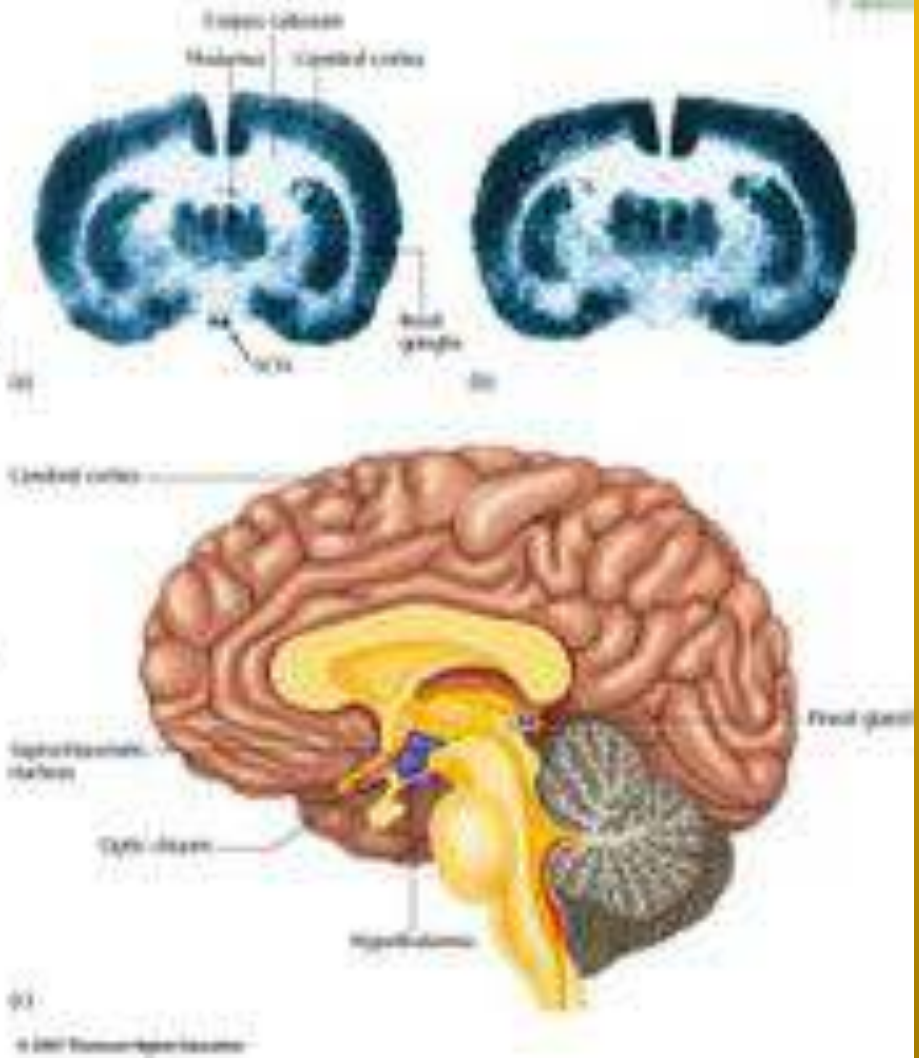
The internal timing system influences (and is influenced by) obesity and metabolic disease (refs 6-10)

It regulates daily rhythms of insulin secretion and glucose metabolism.

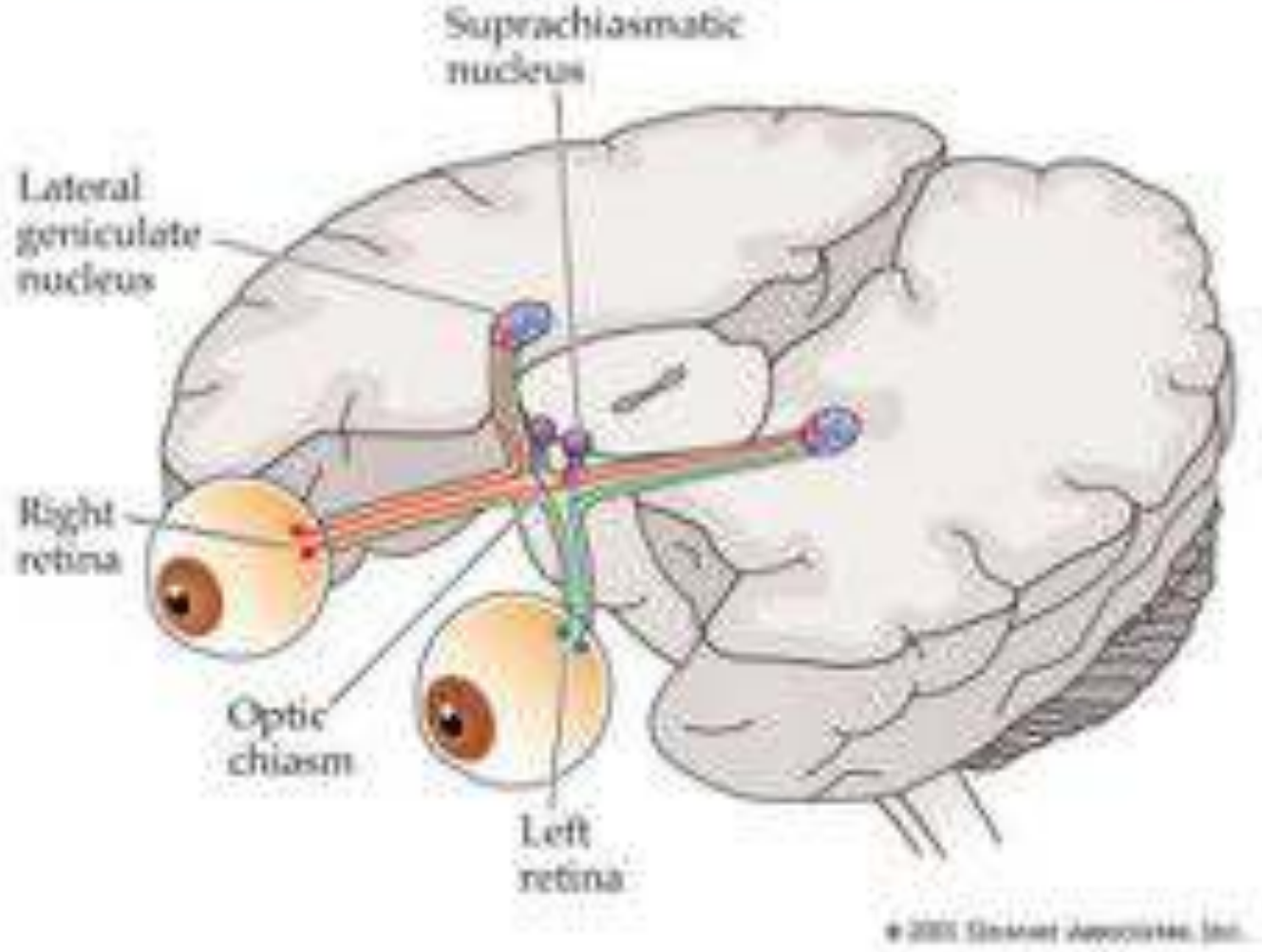
The prevailing view is that the timing system synchronizes your biochemistry with daily variations in the environment in order to optimize energy utilization (ref 22)

Biological Clocks

- **Circadian rhythms** – daily cycles of ~ 24 hours
- **Pineal gland** regulation – releases melatonin
- **Suprachiasmatic Nucleus** (SCN) acts as a biological clock
  - Found in the hypothalamus
  - Just above the optic chiasm
  - Receives info from the retina
- **Retinohypothalamic pathway**
- **GABA** released from the hypothalamus shuts down arousal systems



Retinohypothalamic pathway



Suprachiasmatic nuclei (central oscillator)

- Sleep/ wake cycles
- Body temperature
- Hormonal rhythms

Cellular level molecular clocks (peripheral oscillators)

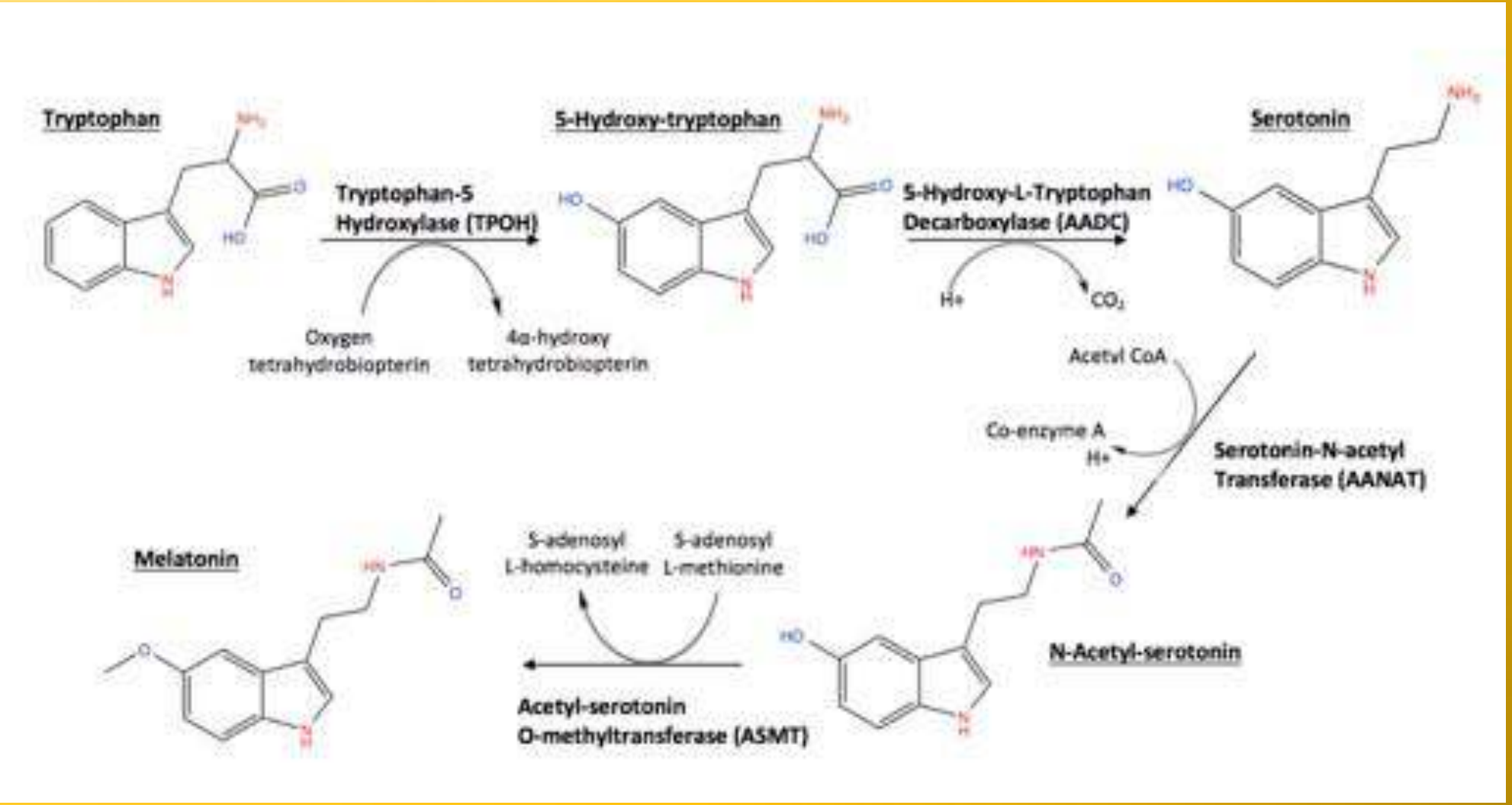
- Autoregulatory feedback loop oscillator of interacting transcription factors known as clock genes

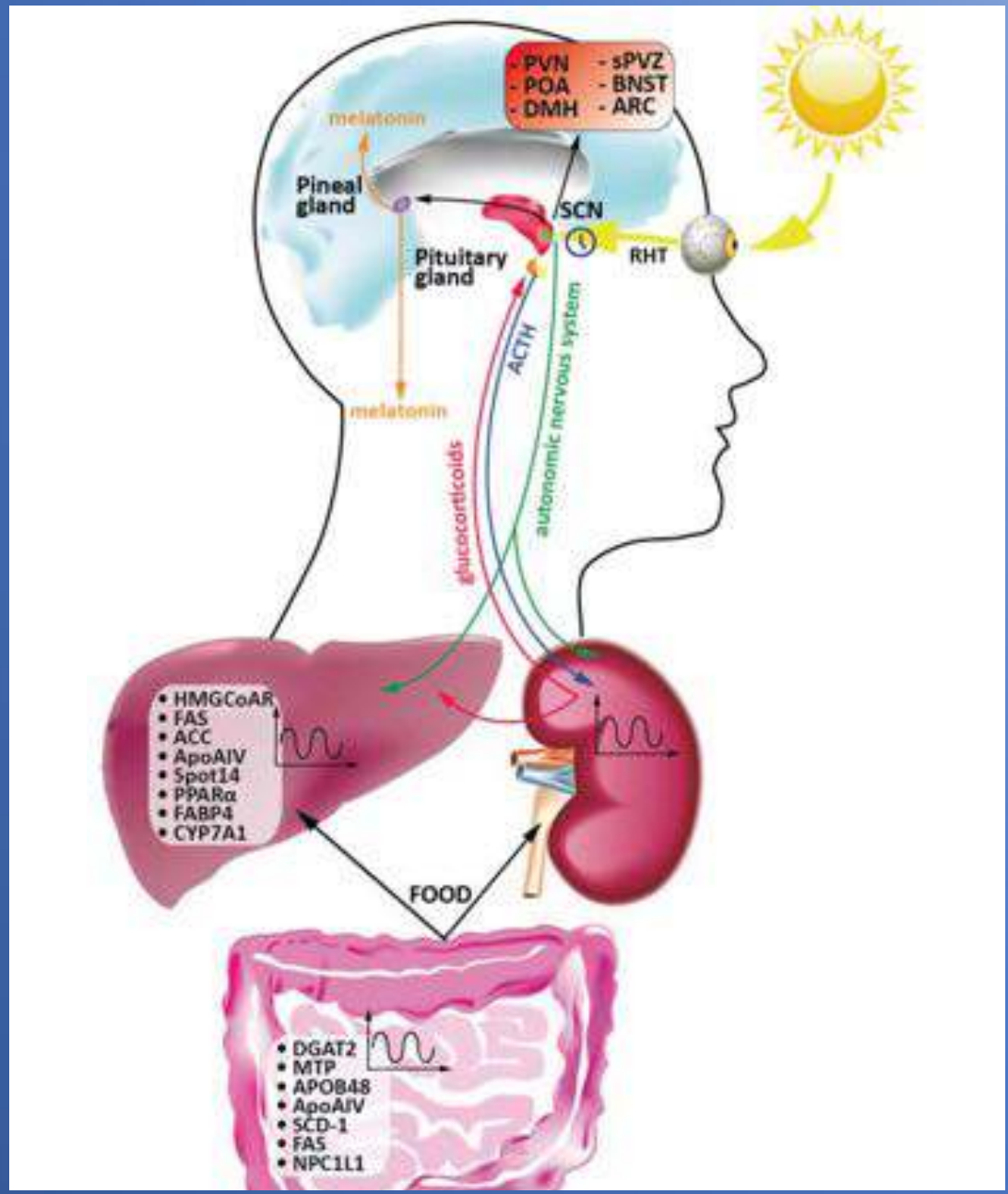
Chronomedicine and type 2 diabetes: shining some light on melatonin.
Diabetologia. 2017 May;60(5):808-822. doi: 10.1007/s00125-016-4175-1. Epub 2016Dec 16.
Forrestel AC, Miedlich SU, Yurcheshen M, Wittlin SD, Sellix MT

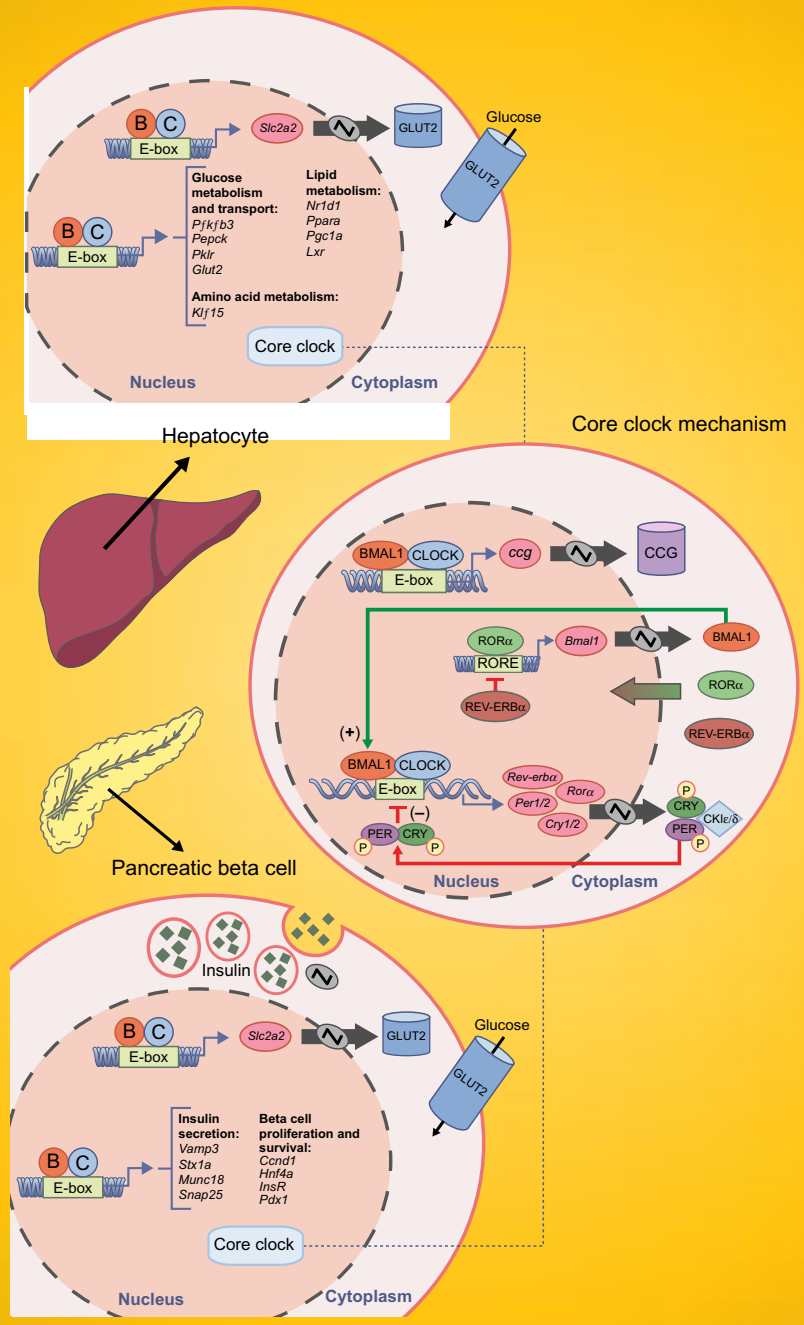
The Pineal Gland synthesizes and secretes melatonin

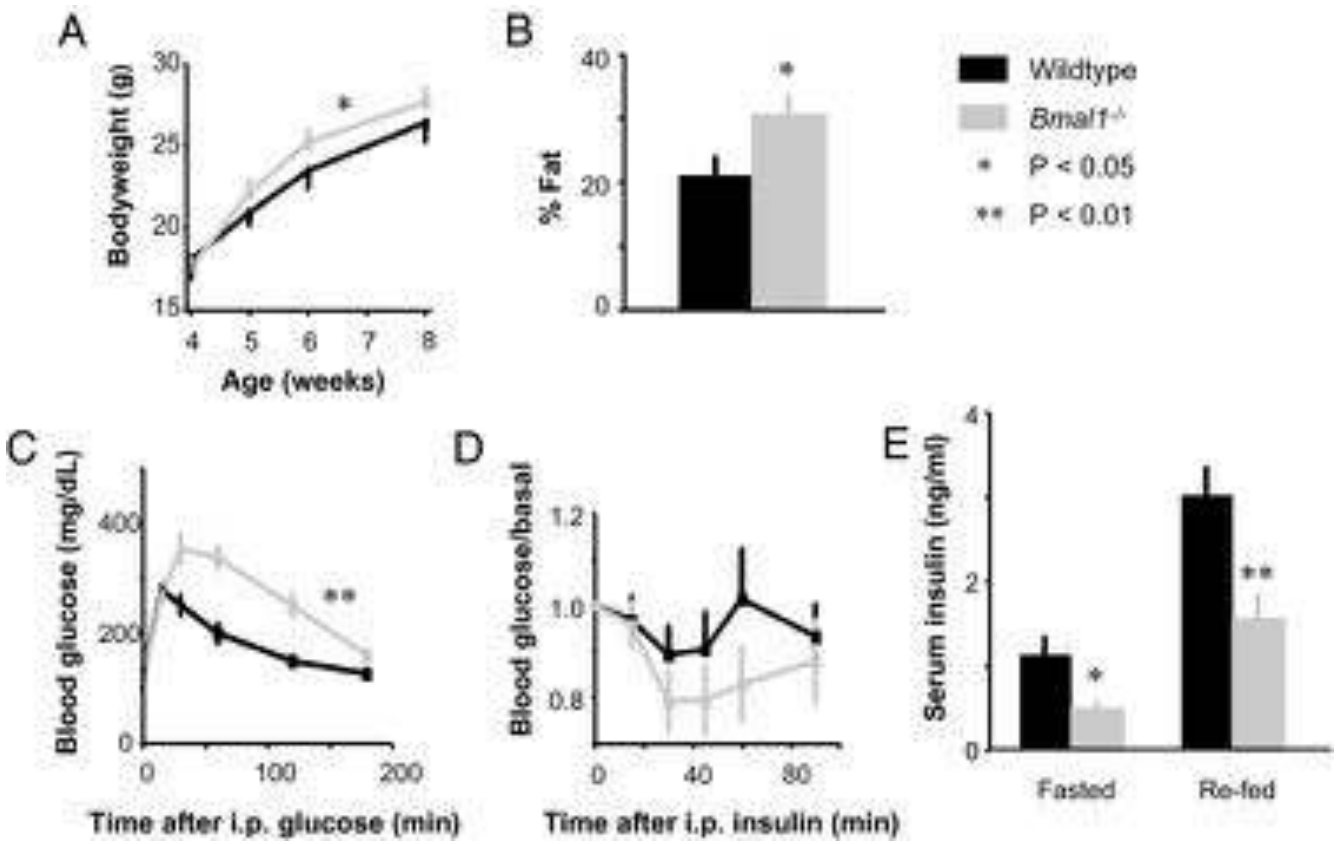
Pineal Gland

Melatonin comes from serotonin



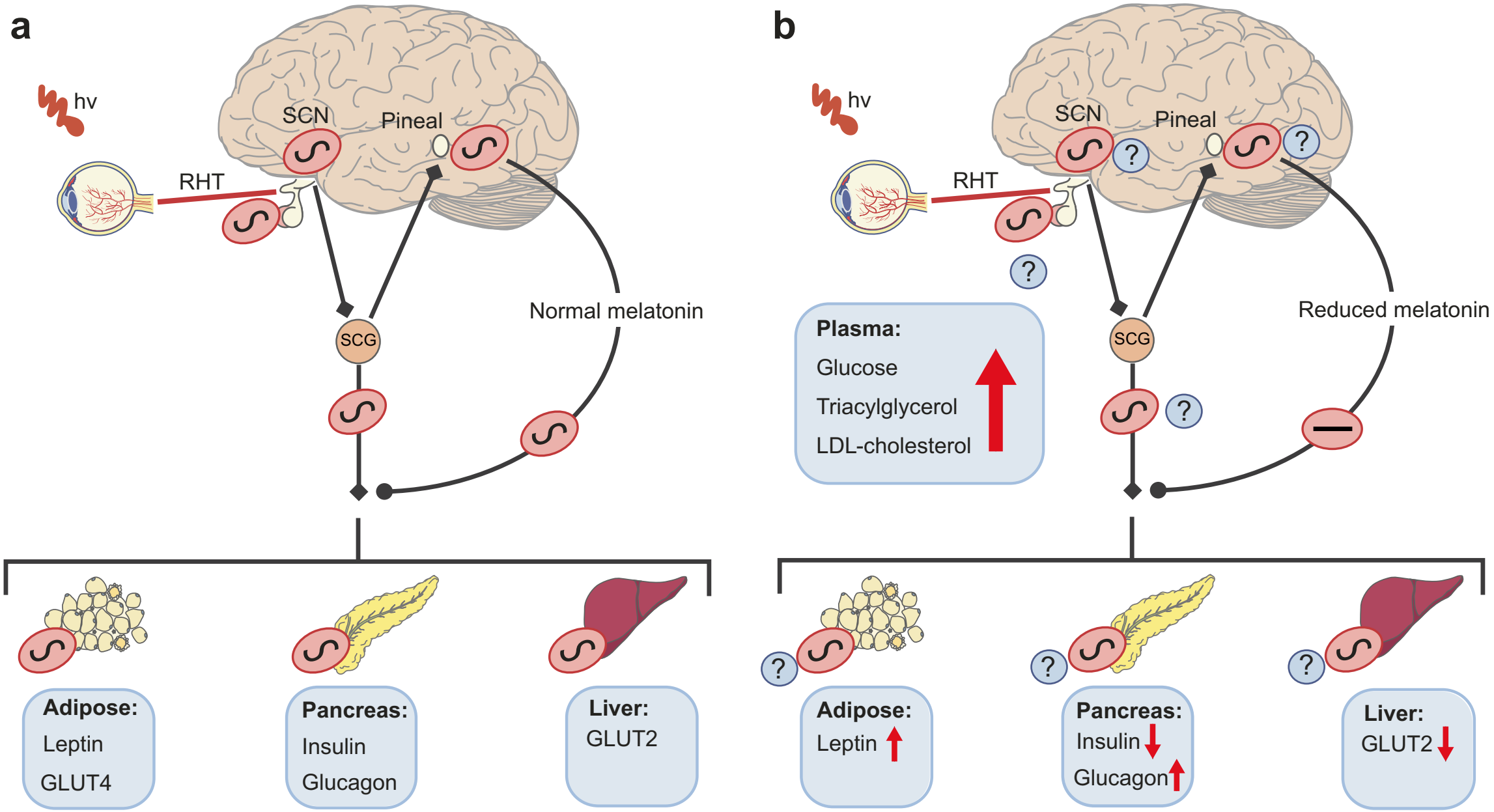

- PVN - sPVZ
- POA - BNST
- DMH - ARC
melatonin
Pineal gland
SCN
Pituitary gland
RHT
melatonin
ACTH
autonomic nervous system
glucocorticoids
• HMGCoAR
• FAS
• ACC
• ApoAIV
• Spot14
• PPARα
• FABP4
• CYP7A1
FOOD
• DGAT2
• MTP
• APO848
• ApoAIV
• SCD-1
• FAS
• NPC1L1


Hepatocyte
B
C
E-box
Slc2a2
GLUT2
Glucose
GLUT2
Glucose metabolism and transport:
Pfkfb3
Pepck
Pklr
Glut2
Lipid metabolism:
Nr1d1
Ppara
Pgc1a
Lxr
Amino acid metabolism:
Klf15
Core clock
Nucleus
Cytoplasm
Core clock mechanism
BMAL1
CLOCK
ccg
CCG
RORα
RORE
Bmal1
REV-ERBα
(+)
(–)
Rev-erbα
Per1/2
Cry1/2
CRY
PER
P
CKIε/δ
Pancreatic beta cell
Insulin
Insulin secretion:
Vamp3
Stx1a
Munc18
Snap25
Beta cell proliferation and survival:
Ccnd1
Hnf4a
InsR
Pdx1



Physiological significance of a peripheral tissue circadian clock

Proc Natl Acad Sci U S A. 2008 Sep 30; 105(39): 15172–15177.
Published online 2008 Sep 8. doi: 10.1073/pnas.0806717105


a
hv
SCN
Pineal
RHT
SCG
Normal melatonin
Adipose:
Leptin
GLUT4
Pancreas:
Insulin
Glucagon
Liver:
GLUT2
b
hv
SCN
Pineal
RHT
SCG
Reduced melatonin
Plasma:
Glucose
Triacylglycerol
LDL-cholesterol
Adipose:
Leptin
Pancreas:
Insulin
Glucagon
Liver:
GLUT2

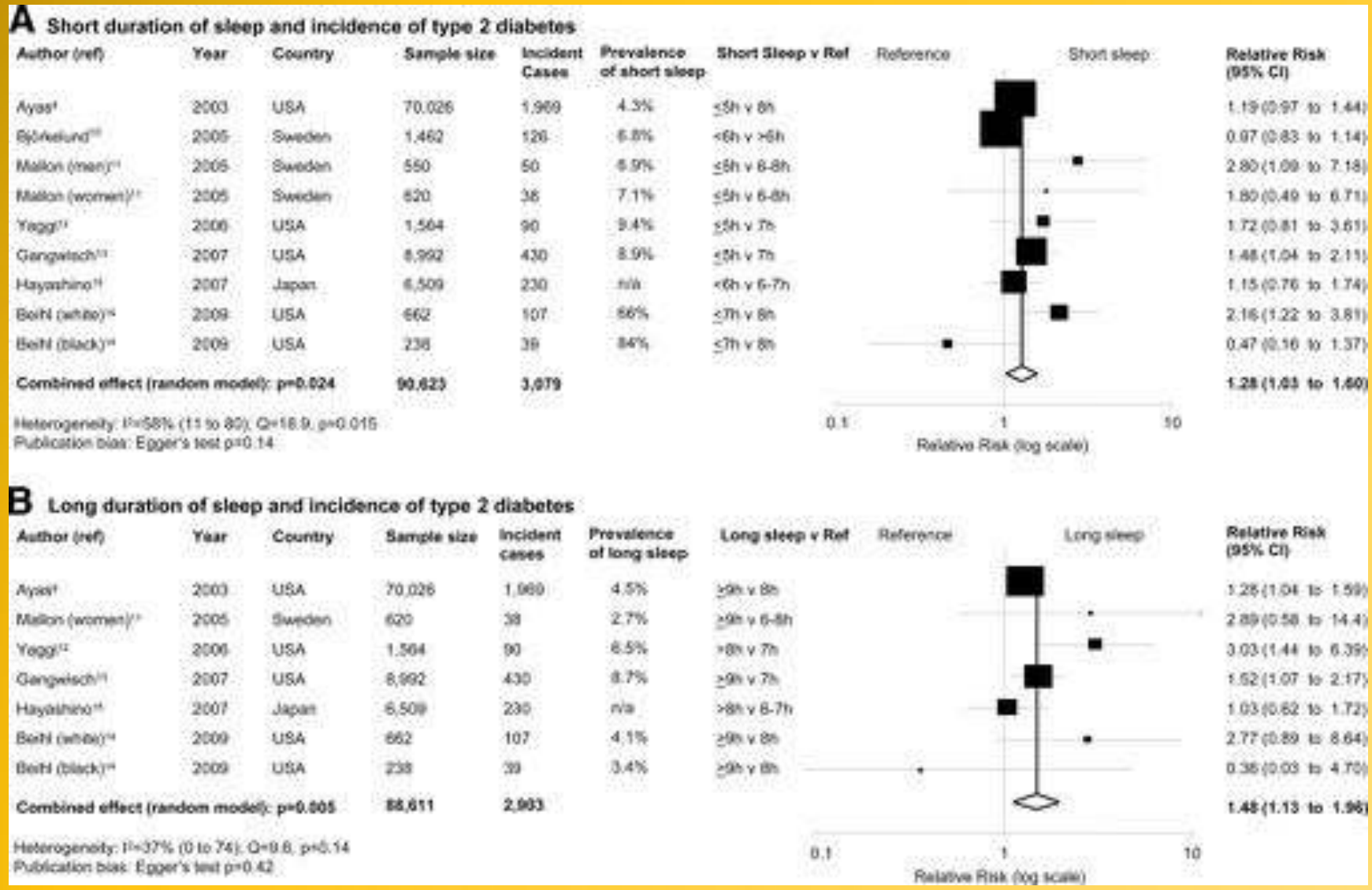


Figure 1—*Quantity of sleep and the risk of developing type 2 diabetes. Results are expressed as RR (95% CI). The size of squares is proportional to the weight of the study.* A: *Forest plot of the risk of type 2 diabetes associated with short duration of sleep compared with the reference group in nine population cohorts from seven published prospective studies.* B: *Forest plot of the risk of type 2 diabetes associated with long duration of sleep compared with the reference group in seven population cohorts from six published prospective studies. n/a, not available.*

Quantity and Quality of Sleep and Incidence of Type 2 Diabetes
Cappuccio, FP, et al; Diabetes Care, vol 33: 414-420, 2010

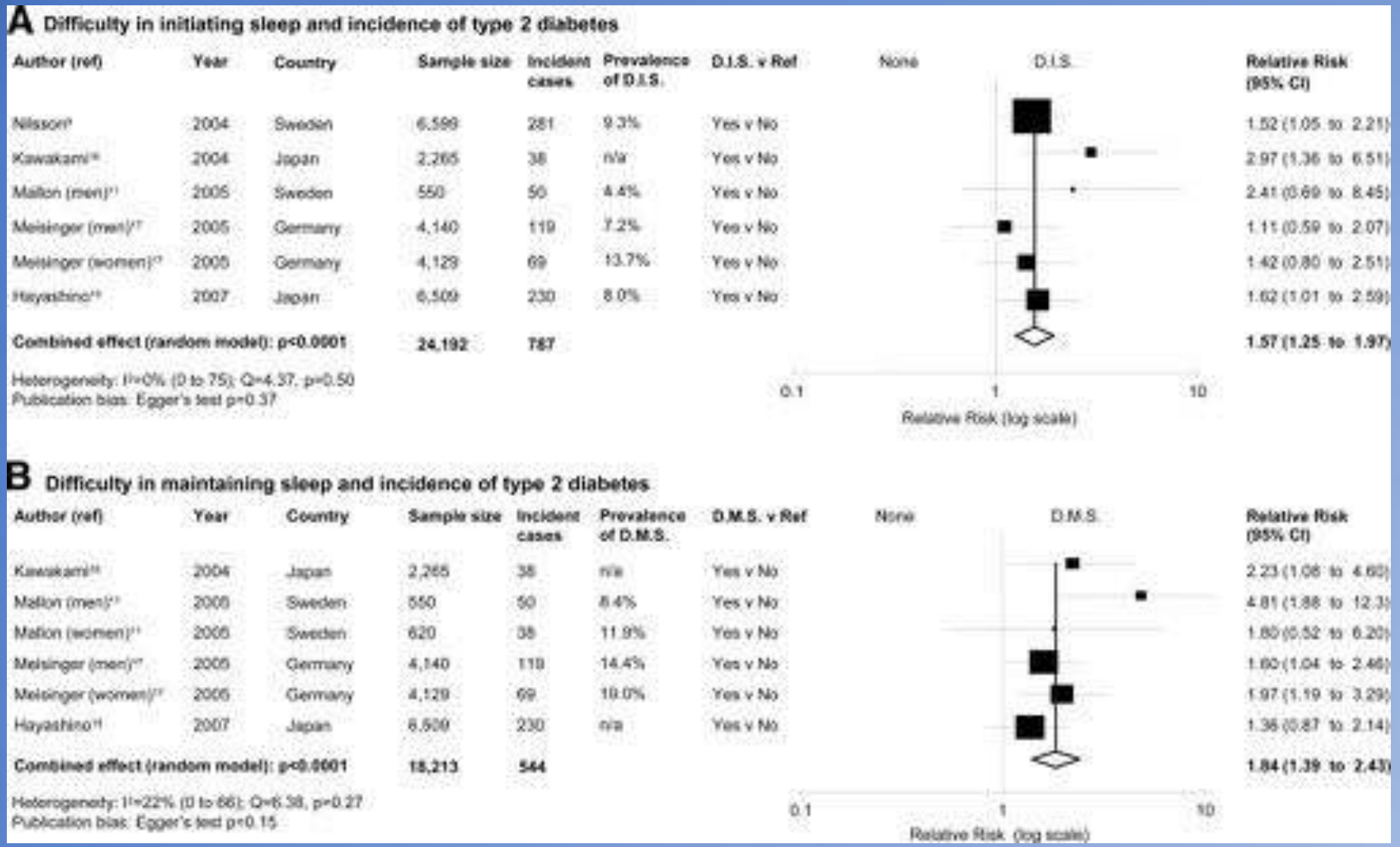


Figure 2—*Quality of sleep and the risk of developing type 2 diabetes. Results are expressed as RR (95% CI). The size of squares is proportional to the weight of the study.* A*: Forest plot of the risk of type 2 diabetes associated with difficulty in initiating sleep (D.I.S.) compared with none in six population cohorts from five published prospective studies.* B*: Forest plot of the risk of type 2 diabetes associated with difficulty in maintaining sleep (D.M.S.) compared with none in six population cohorts from four published prospective studies. n/a, not available.*

Quantity and Quality of Sleep and Incidence of Type 2 Diabetes
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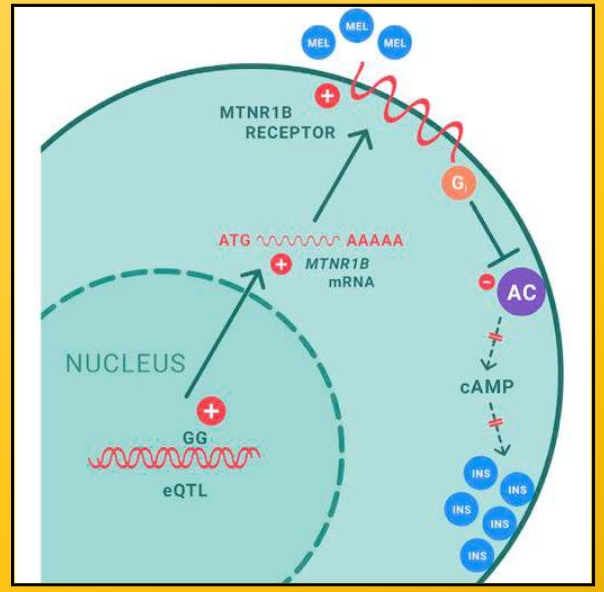
Clinical and Translational Report

Cell Metabolism

Increased Melatonin Signaling Is a Risk Factor for Type 2 Diabetes

Graphical Abstract



Highlights

- rs10830963 is an eQTL in human islets conferring increased *MTNR1B* mRNA expression
- Melatonin inhibits cAMP rises in mouse islets and clonal insulin-secreting cells
- Melatonin blocks insulin release in mouse islets and clonal insulin-secreting cells
- Melatonin's inhibition of insulin release is stronger in risk allele carriers

Authors

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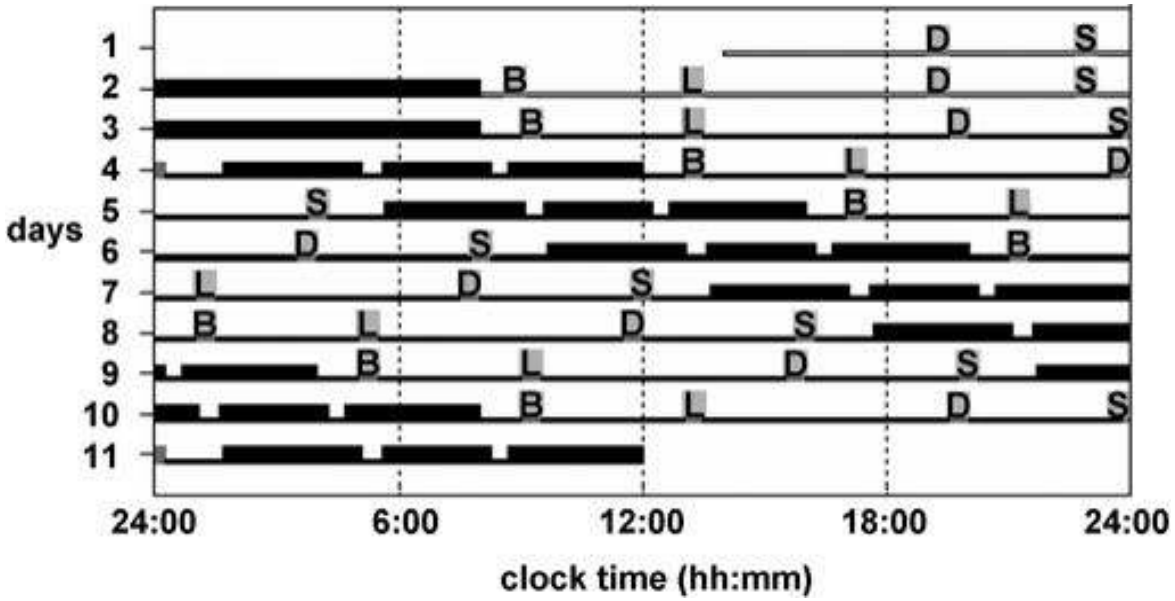
In Brief

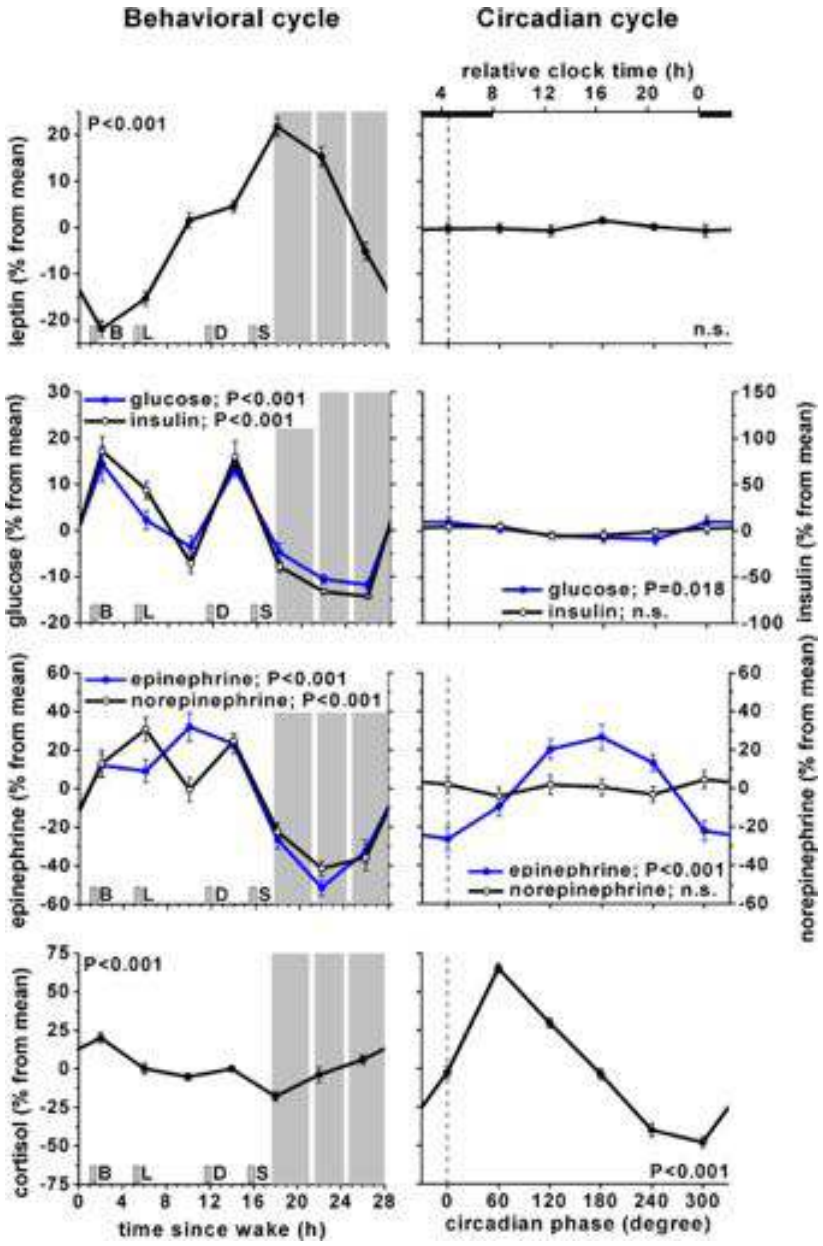
Tuomi et al. show that a common (about 30%) human type 2 diabetes risk variant of the melatonin receptor 1B gene affects insulin release. A recall-by-genotype study demonstrated that melatonin treatment inhibits insulin secretion, with at-risk carriers exhibiting higher glucose levels. Melatonin might have a protective role in preventing nocturnal hypoglycemia.

Tuomi et al., 2016, Cell Metabolism *23*, 1067–1077
June 14, 2016
http://dx.doi.org/10.1016/j.cmet.2016.04.009

CellPress

Disruption of the timing system alone can lead to metabolic dysfunction





Adverse metabolic and cardiovascular consequences of circadian misalignment

Frank A. J. L. Scheer[a,b,1], Michael F. Hilton[a,2], Christos S. Mantzoros[b,c], and Steven A. Shea[a,b]

www.pnas.org/cgi/doi/10.1073/pnas.0808180106

PNAS | March 17, 2009 | vol. 106 | no. 11| 4453-4458

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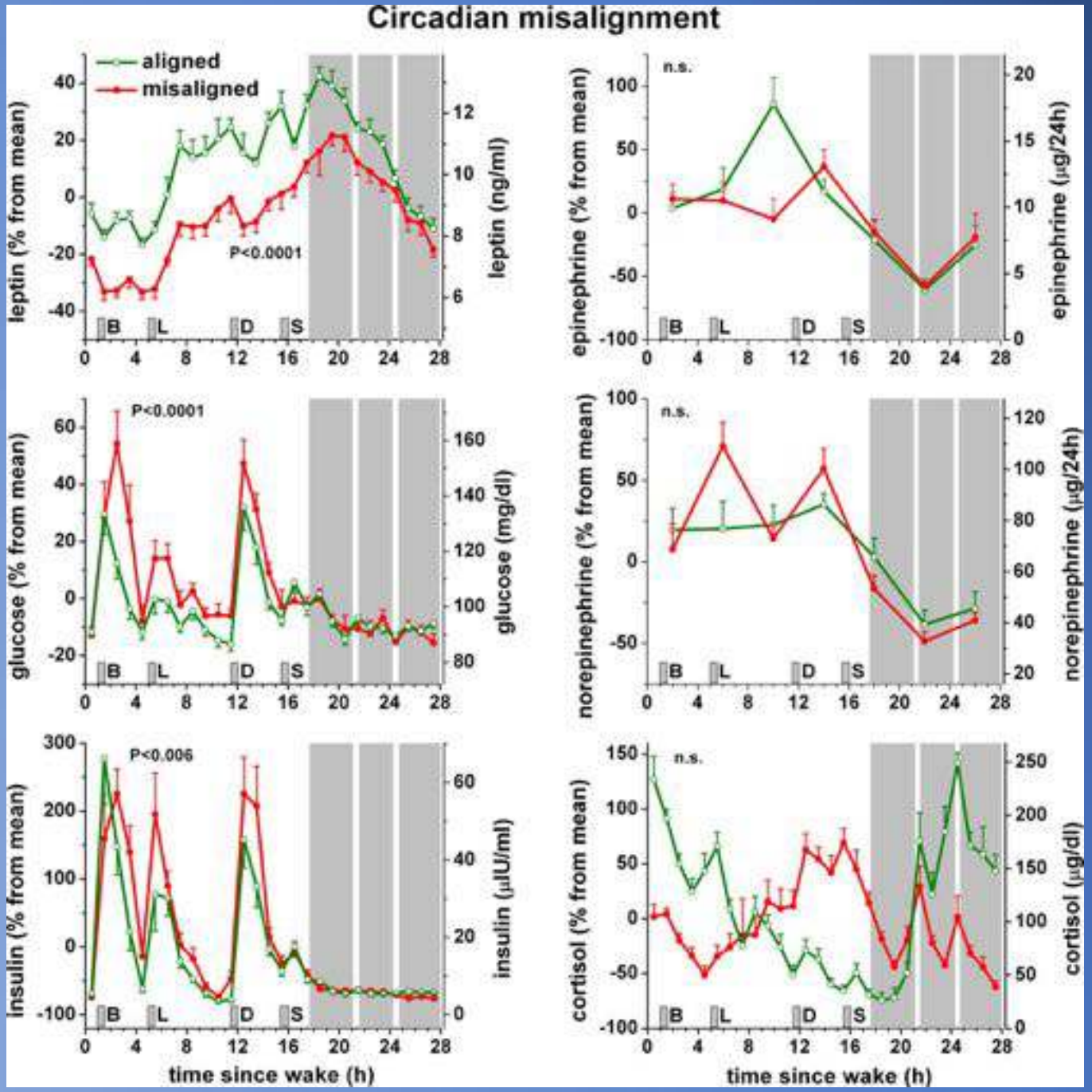

THANK YOU!

QUESTIONS? YOUR THOUGHTS?