Sleep Cycle Shift and its effects on Cognitive Function

MARY ET BOYLE, PH. D. • DEPARTMENT OF COGNITIVE SCIENCE • UCSD

The Earth Has Rhythm

Why did organisms evolve timekeeping?

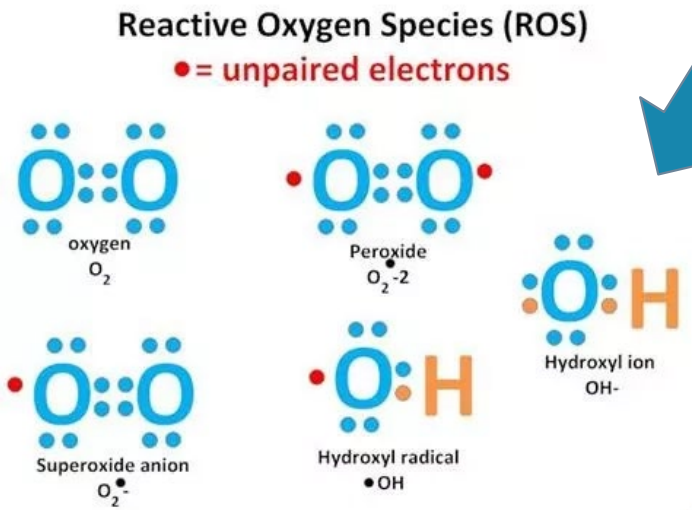
Hypothesis A:

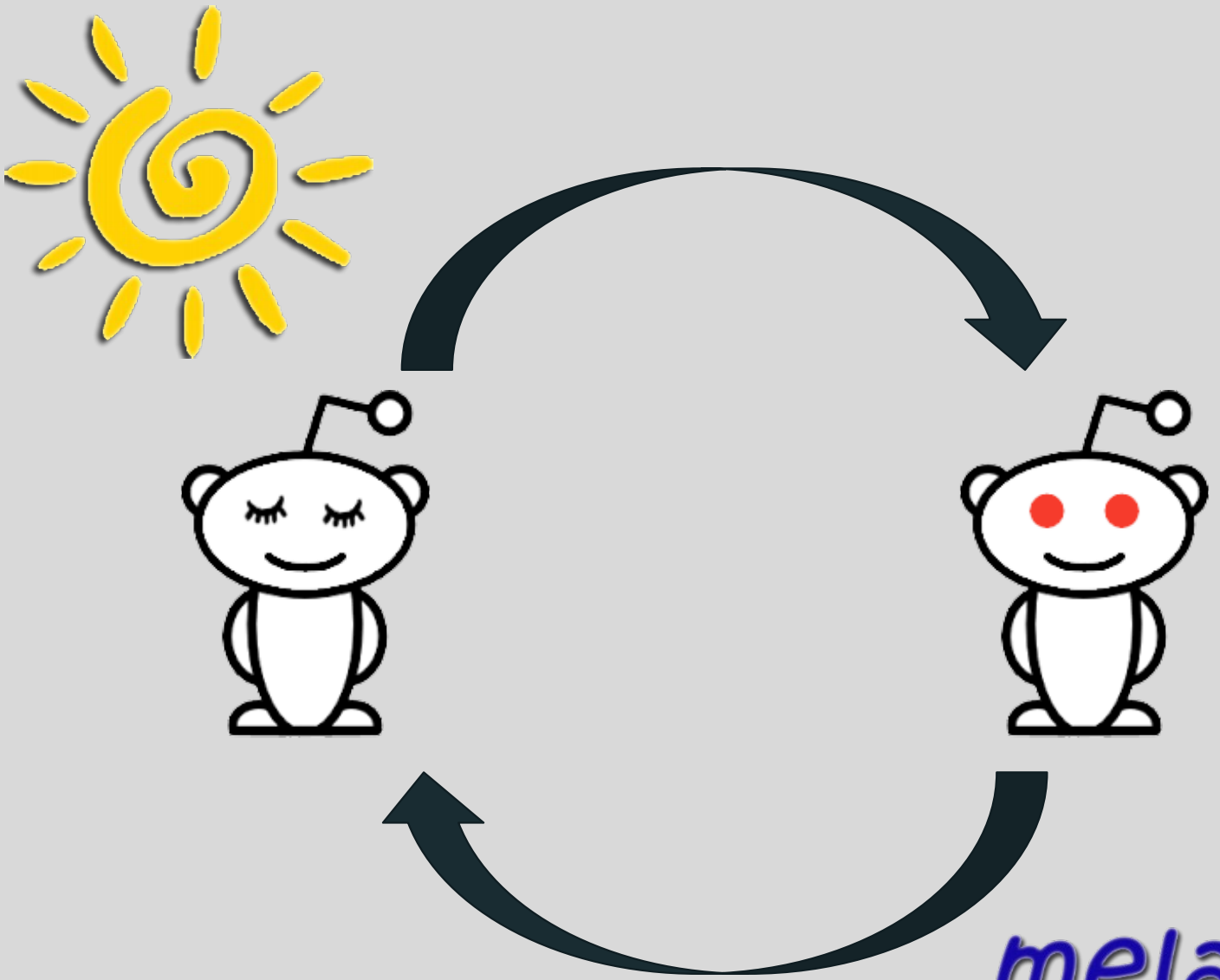
multiple circadian clock systems evolved independently

Protect fragile DNA from sun's UV rays?

Hypothesis B:

one clock evolved - to reduce oxygen damage to cells

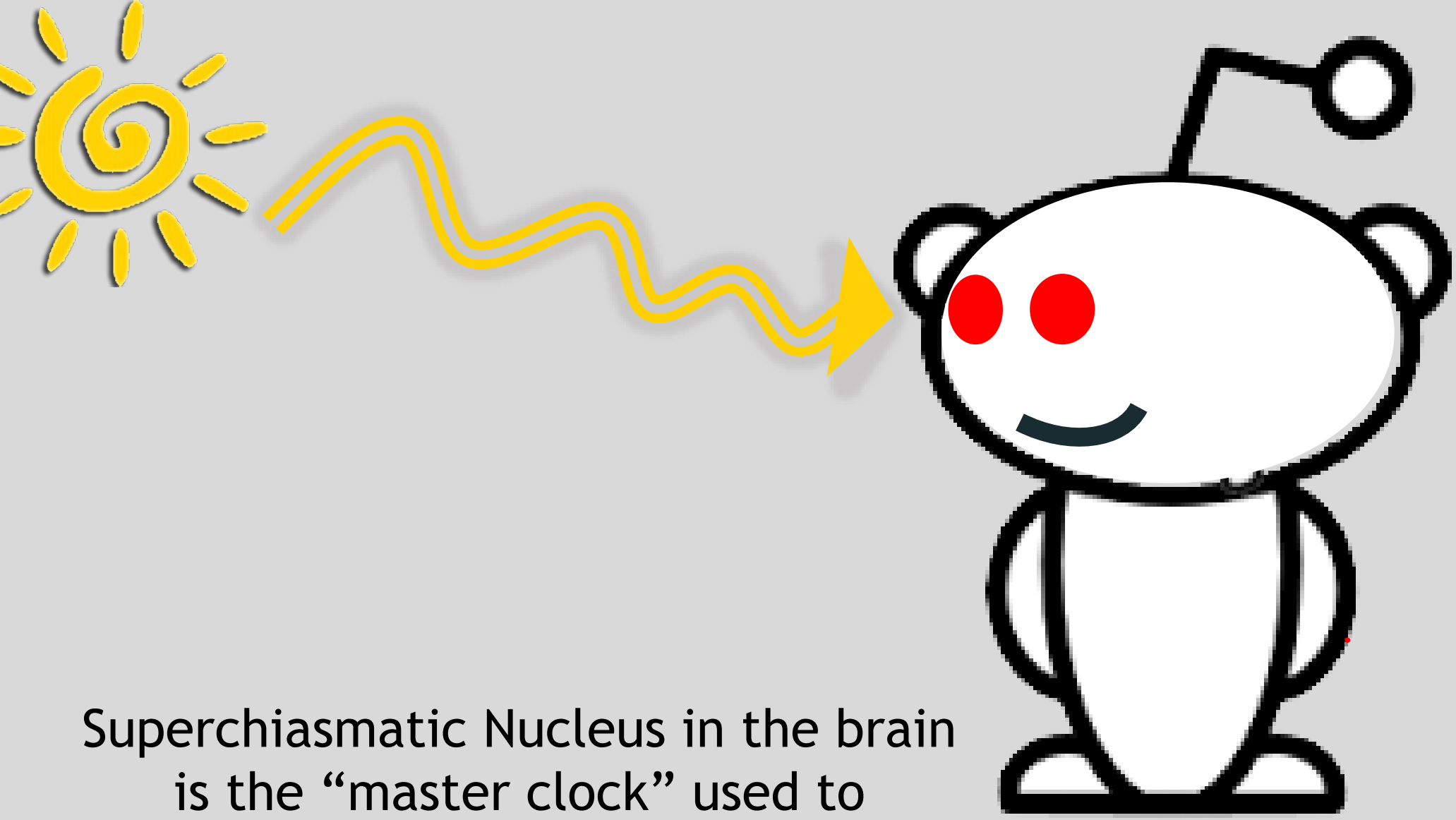




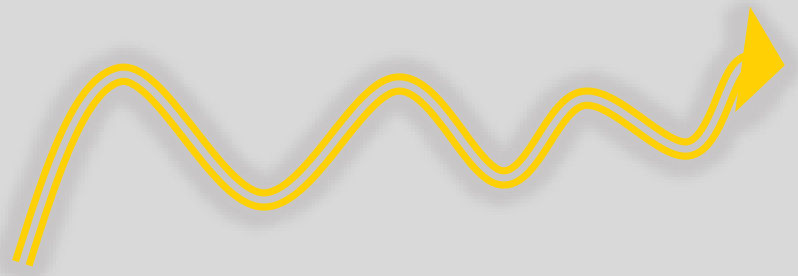
melatonin

Light & Melatonin are the two most influential external cues that synchronize the circadian rhythm

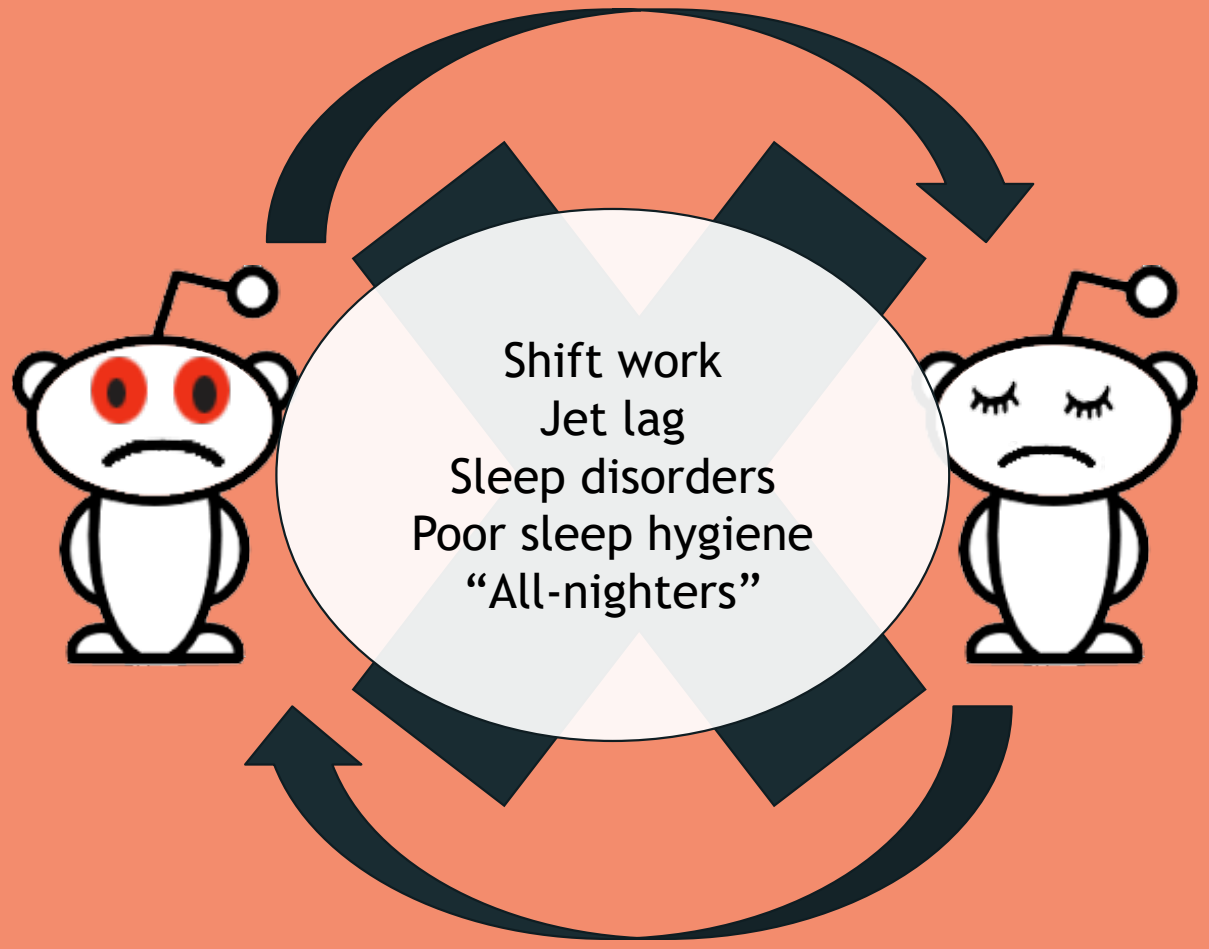
Sleep wake cycle is regulated by the circadian system.



Superchiasmatic Nucleus in the brain is the “master clock” used to coordinate and synchronize most of the body clocks in the periphery.



melatonin



metabolic disruption

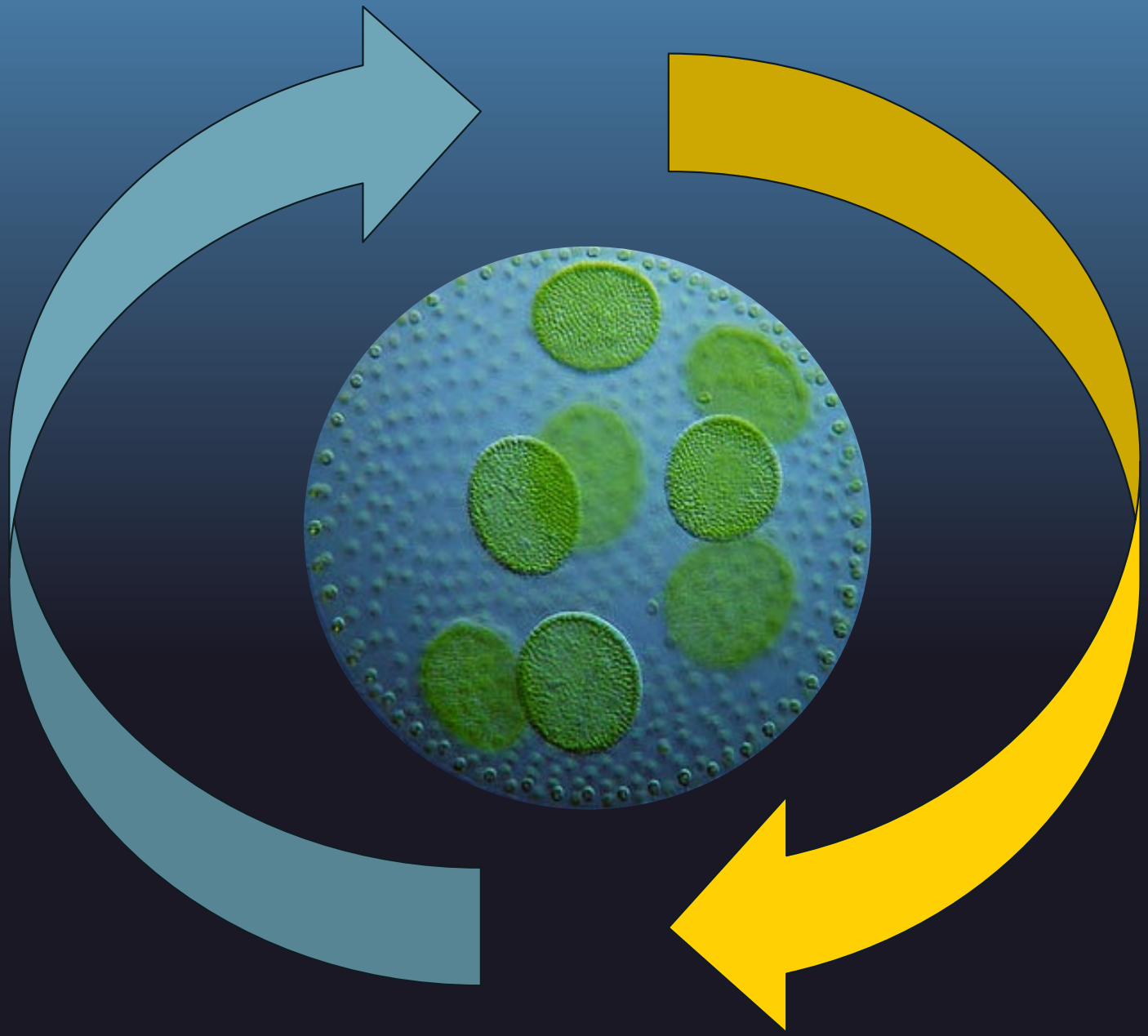
weight gain, obesity

impaired immunity

cognitive malfunction

If the sleep wake cycle is disrupted it can cause metabolic dysregulation

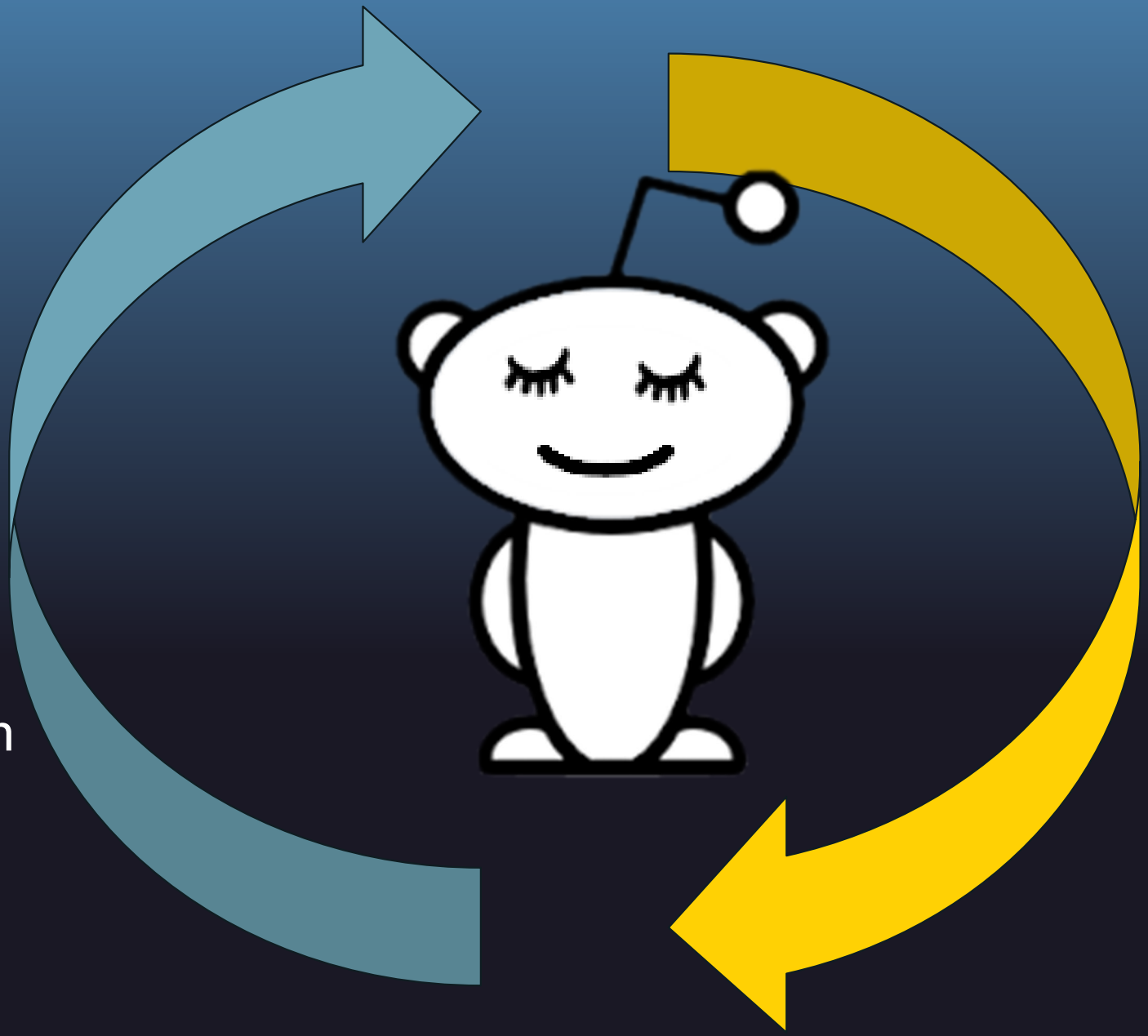
repairs DNA



harvests energy

Cyanobacteria is a photoautotropic organism that has a self-sustained circadian rhythm

- Fasting
- Release of hormones
- Immune system activity
- Resting



Eating

Exercising

Thinking

Working

Our metabolic clocks are based on the diurnal rhythm – it is in our genes.

Shift workers are more prone to developing metabolic disorders

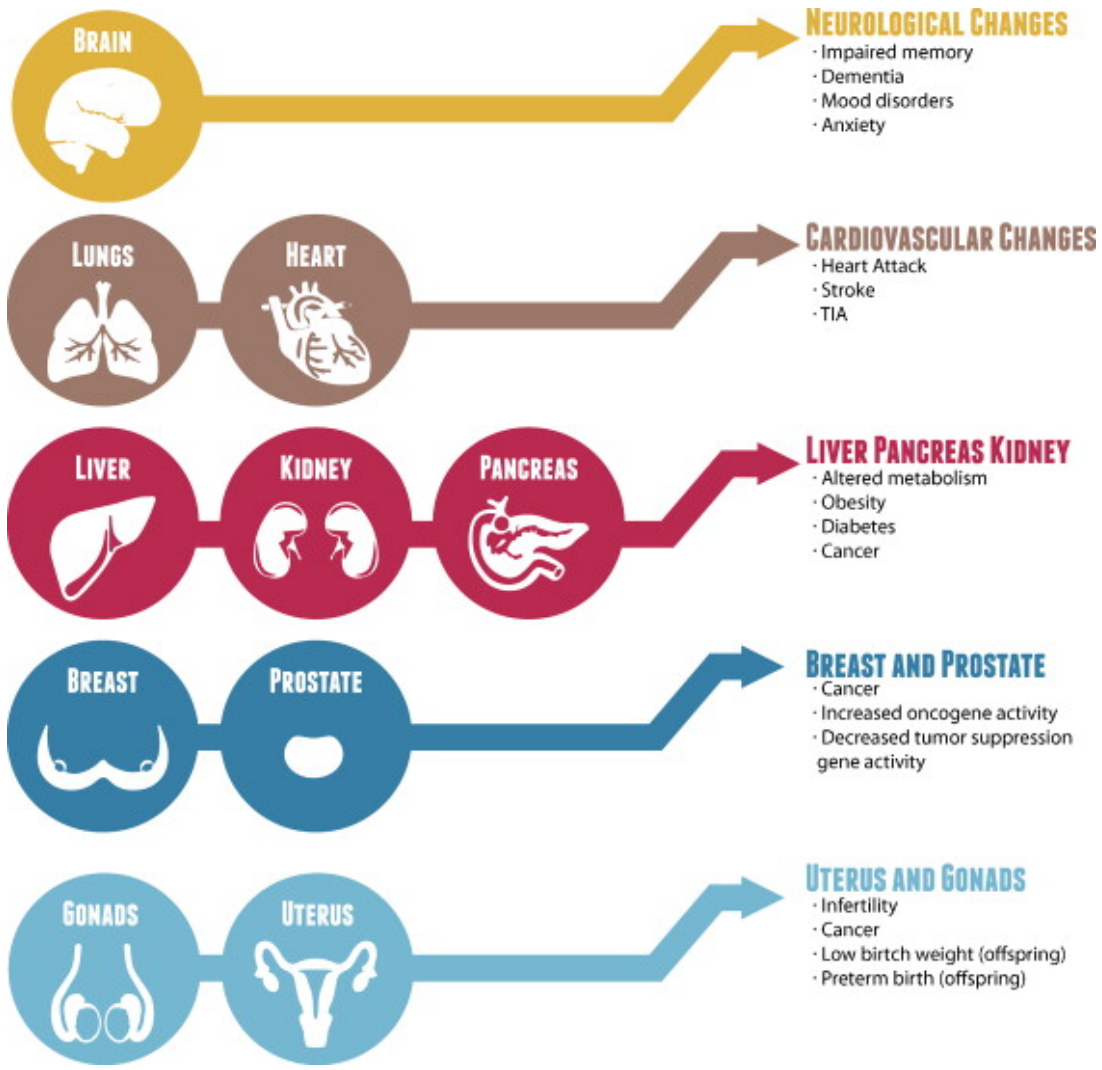
40% more likely to have: cardiovascular disease

Higher incidence of Diabetes Type II

Higher risk of cancer – melatonin disruption

Puttonen S, Härmä M, Hublin C.Scand J Work Environ Health. 2010 Mar; 36(2):96-108. Epub 2010 Jan 20.
The Health Survey for England (2013);
Davis S, Mirick DK.Cancer Causes Control. 2006 May; 17(4):539-45.

Circadian disruption affect multiple organ systems:



"The diagram provides examples of how circadian disruption negatively impacts the brain and the digestive, cardiovascular, and reproductive systems.

Though the diagram displays unidirectional affects, there are various feedback loops that exist within the system and interactions that occur between these systems."

Zelinski, E. L. et al (2014) Neuroscience and Biobehavioral Reviews 40:80–101

Obesity and the circadian clock disruption

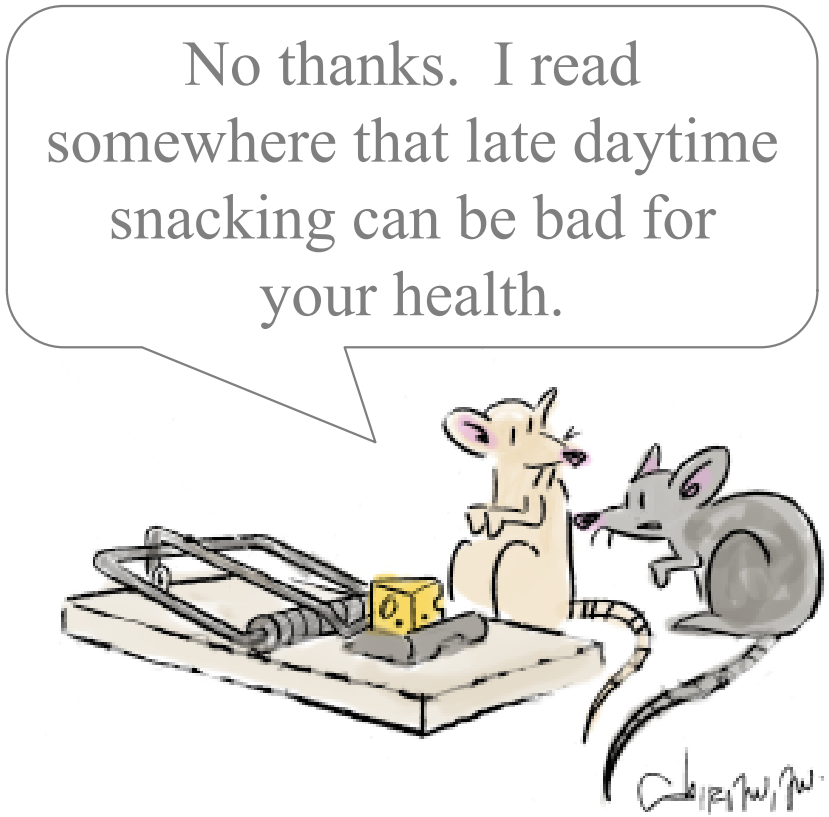
Disrupted circadian clock increases risk of:

- Obesity
- Diabetes
- Heart disease

It’s not only what you eat but when you eat!

Shi, S-H. et. al. (2013) Current Biology 23, 372–381

Insulin sensitivity follows circadian clock:



Other than being nocturnal, mice and men have the same molecular mechanisms underlying circadian rhythm

Insulin action follows a 24 hour clock

Tissue is **resistant to insulin during the fasting phase (night time)** and *sensitive to insulin during the active phase (day time).*

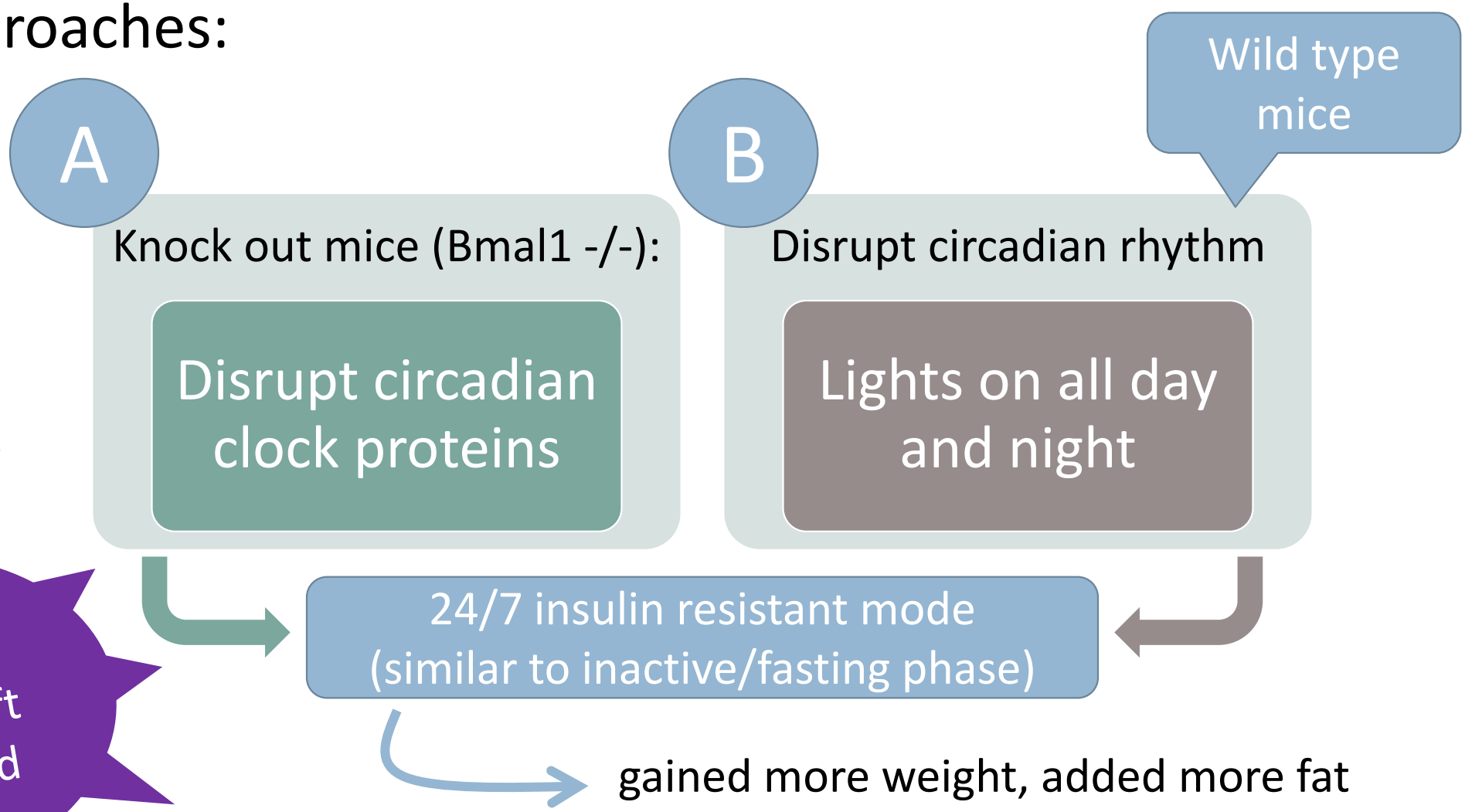
During inactive phase→ glucose is converted to fat.

During active phase → glucose is used for energy and other tissue building

Shi, S-H. et. al. (2013) Current Biology 23, 372–381

What happens to insulin when the circadian clock is disrupted?

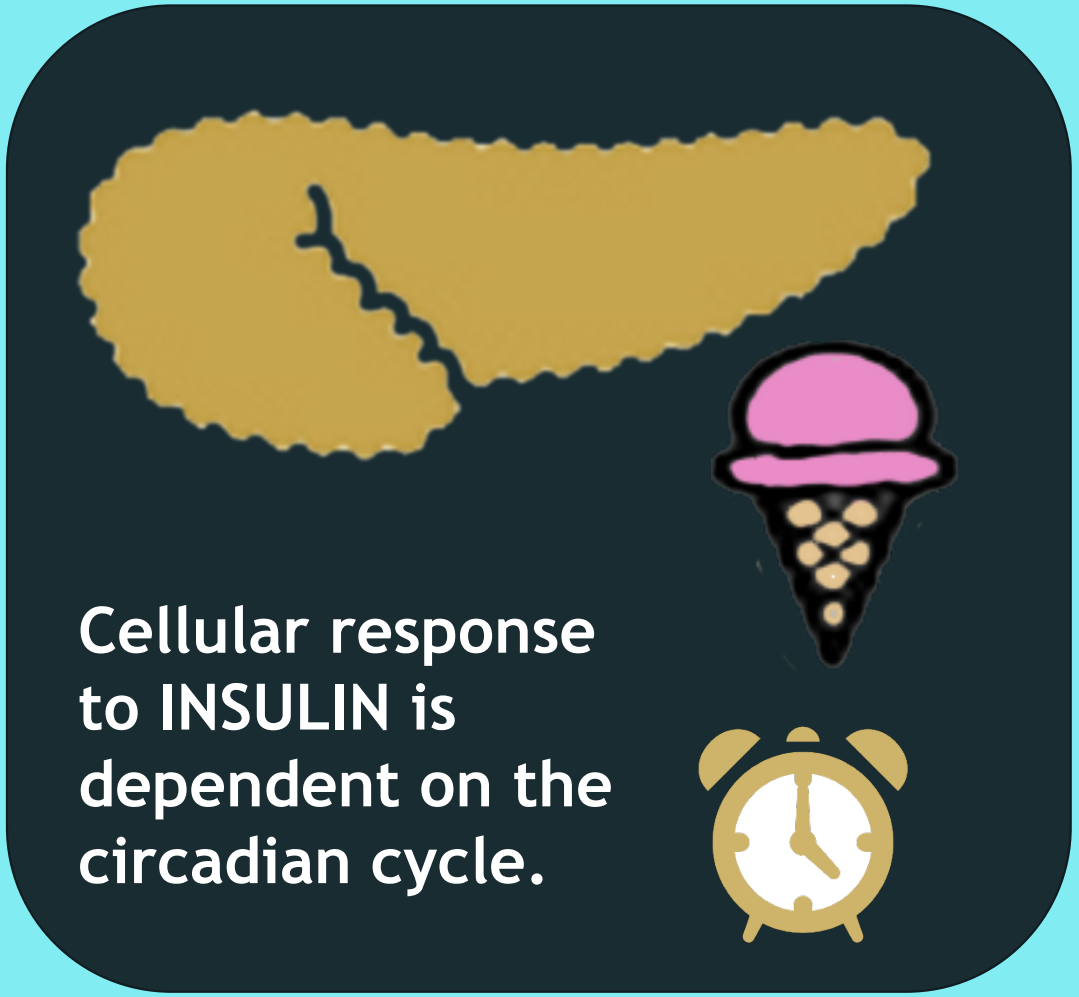
Two approaches:



Helps to explain data on night shift workers and obesity

Shi, S-H. et. al. (2013) Current Biology 23, 372–381

SCN is not the only clock in the body



Time of eating has a huge effect on the liver and insulin efficacy

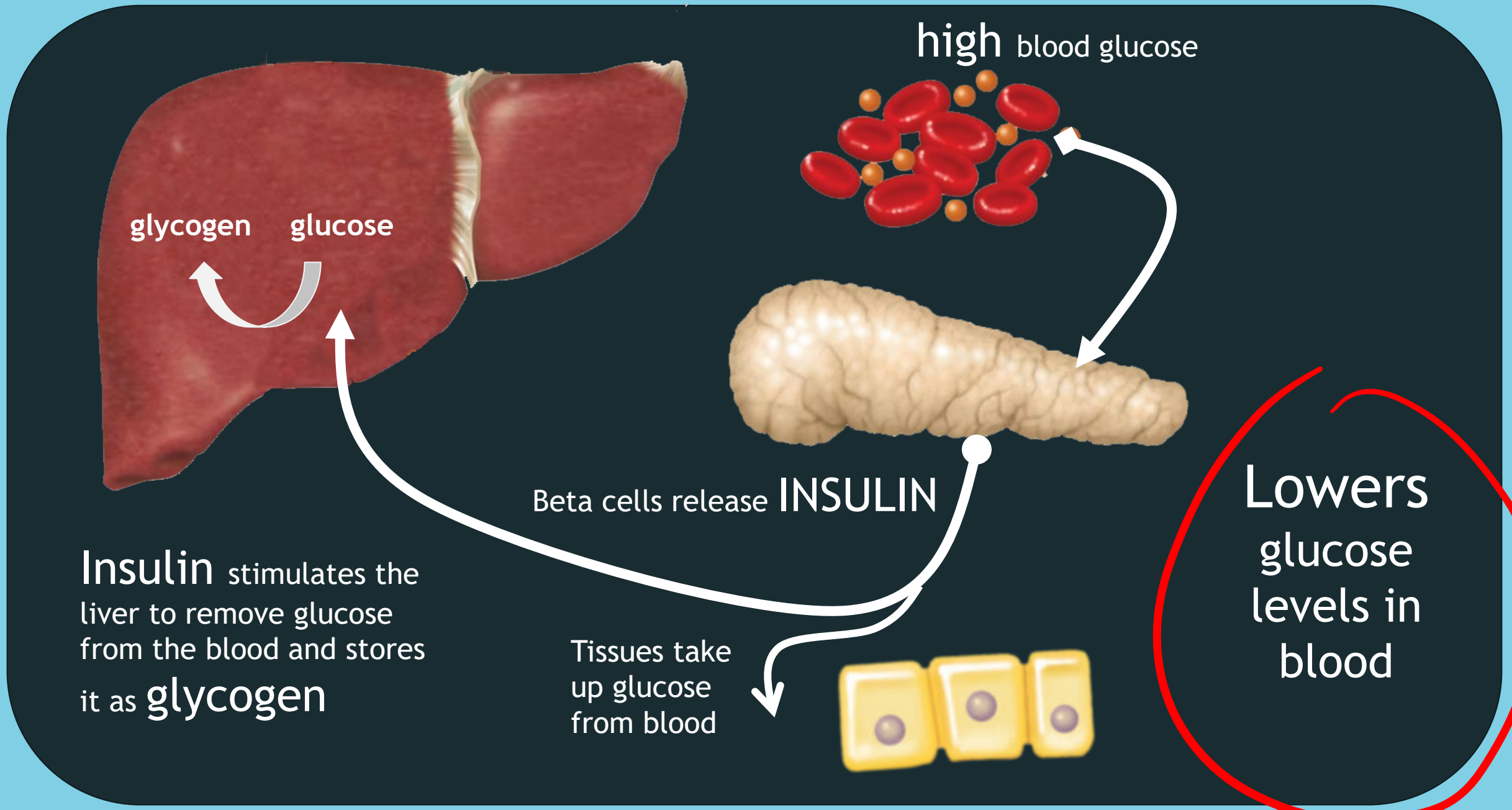


Figure adapted from Kaidanovich-Beilin, O. et al 201

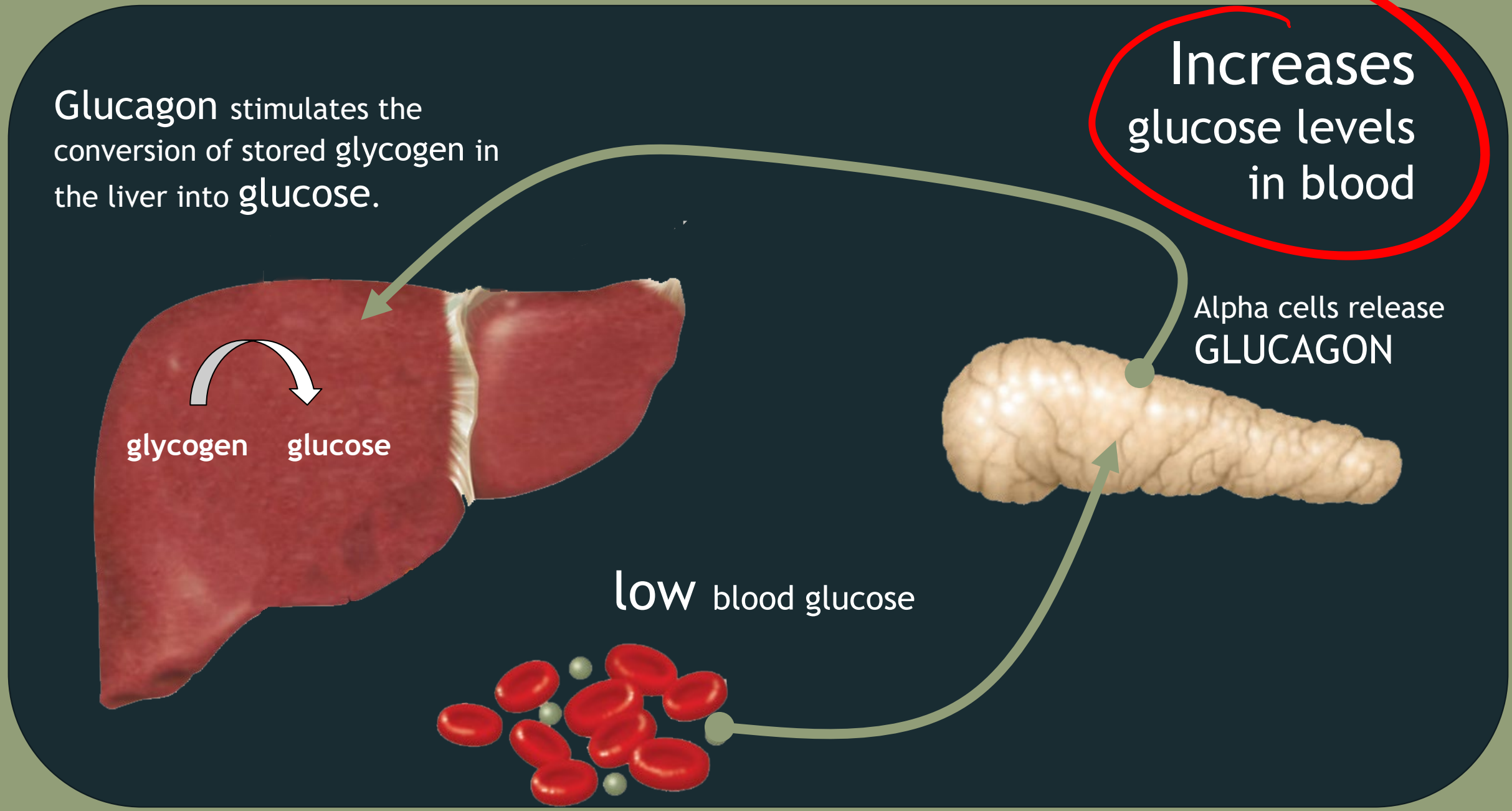
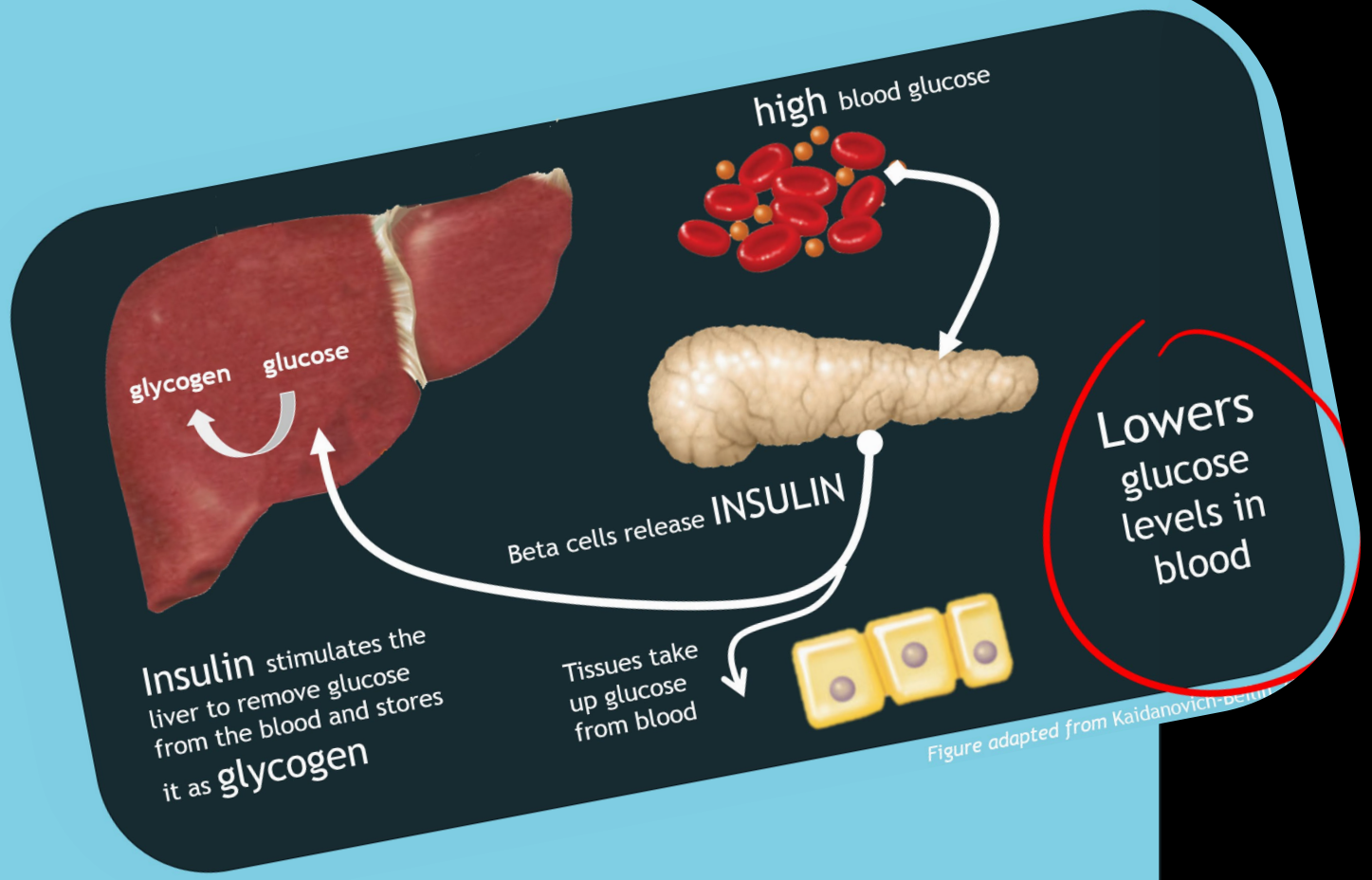


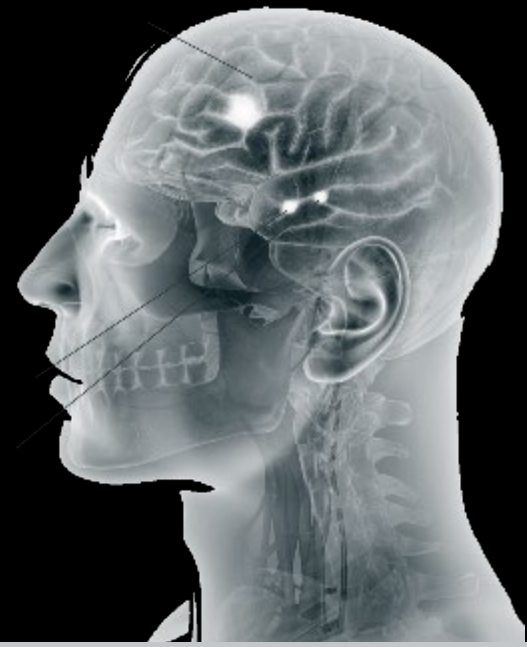
Figure adapted from Kaidanovich-Beilin, O. et al 2012

Insulin-sensitivity is dependent on the peripheral clock in muscle cells.

Glucose uptake in muscle is dependent on the circadian rhythm.



Insulin activates insulin receptors in the brain → affects feeding behaviors, reward, body metabolism, normal emotion & cognitive behaviors.



insulin receptors are found throughout the brain – cortex, midbrain and hypothalamus.

The risk of developing Alzheimer's disease is increased by 50 percent in people with diabetes.

Craft, S. Nat. Rev. Neurol. 8, 360–362 (2012);

Diabetes is a risk factor for dementia

J Neural Transm (1989) 75: 227–232

Journal of Neural Transmission

Cerebral excess release of neurotransmitter amino acids subsequent to reduced cerebral glucose metabolism in early-onset dementia of Alzheimer type

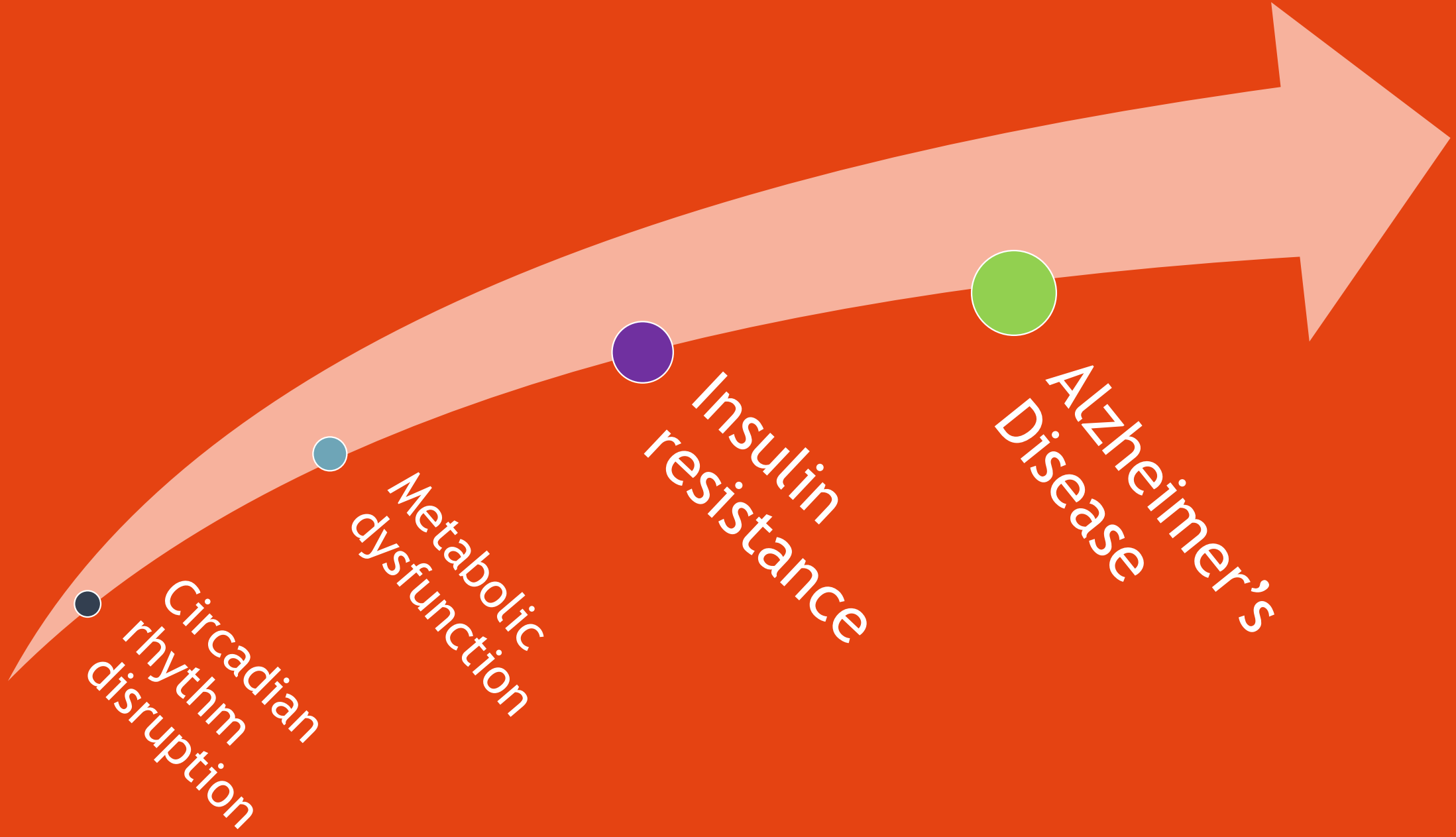
Short Note

S. Hoyer and **R. Nitsch**

Department of Pathochemistry and General Neurochemistry, University of Heidelberg, Heidelberg, Federal Republic of Germany

Accepted November 2, 1988

Summary. A massive cerebral release of amino acids and ammonia was found in early-onset dementia of Alzheimer type. Aspartate and glycine were liberated in high concentrations, whereas glutamate remained rather unchanged. This excess cerebral protein catabolism is due to a 44% reduction in cerebral glucose metabolism. Whereas glutamate and other glucoplastic amino acids may substitute glucose, elevated aspartate may contribute to neuronal damage. The results are discussed with respect to a possible neuronal insulin/insulin receptor deficiency.



Talbot, K. et al. J. Clin. Invest. 122, 1316–1338 (2012).

- Case of Auguste D., 50 year old woman in Germany - 1906
- Her disruptive behavior prompted her husband to see Dr. Alois Alzheimer.

dementia appeared before she was 50 years old

Auguste showed signs of dementia such as:
Loss of memory
Delusions
Temporary vegetative states

insight: dementia is physical

- Alzheimer examined Auguste D.'s brain.
- Discovered plaques and tangles.
- At the time it was thought that dementia was normal aging.

Sleep disturbances:
Trouble sleeping
"drag sheets across the house and scream for hours in the middle of the night."

http://en.wikipedia.org/wiki/Auguste_Deter

eFAD

- Early onset familial Alzheimer disease – symptoms can start in 30's, 40's or 50's

family

- Dominant genetic trait
- One parent had eFAD
- Siblings: 50%

same, (mostly)

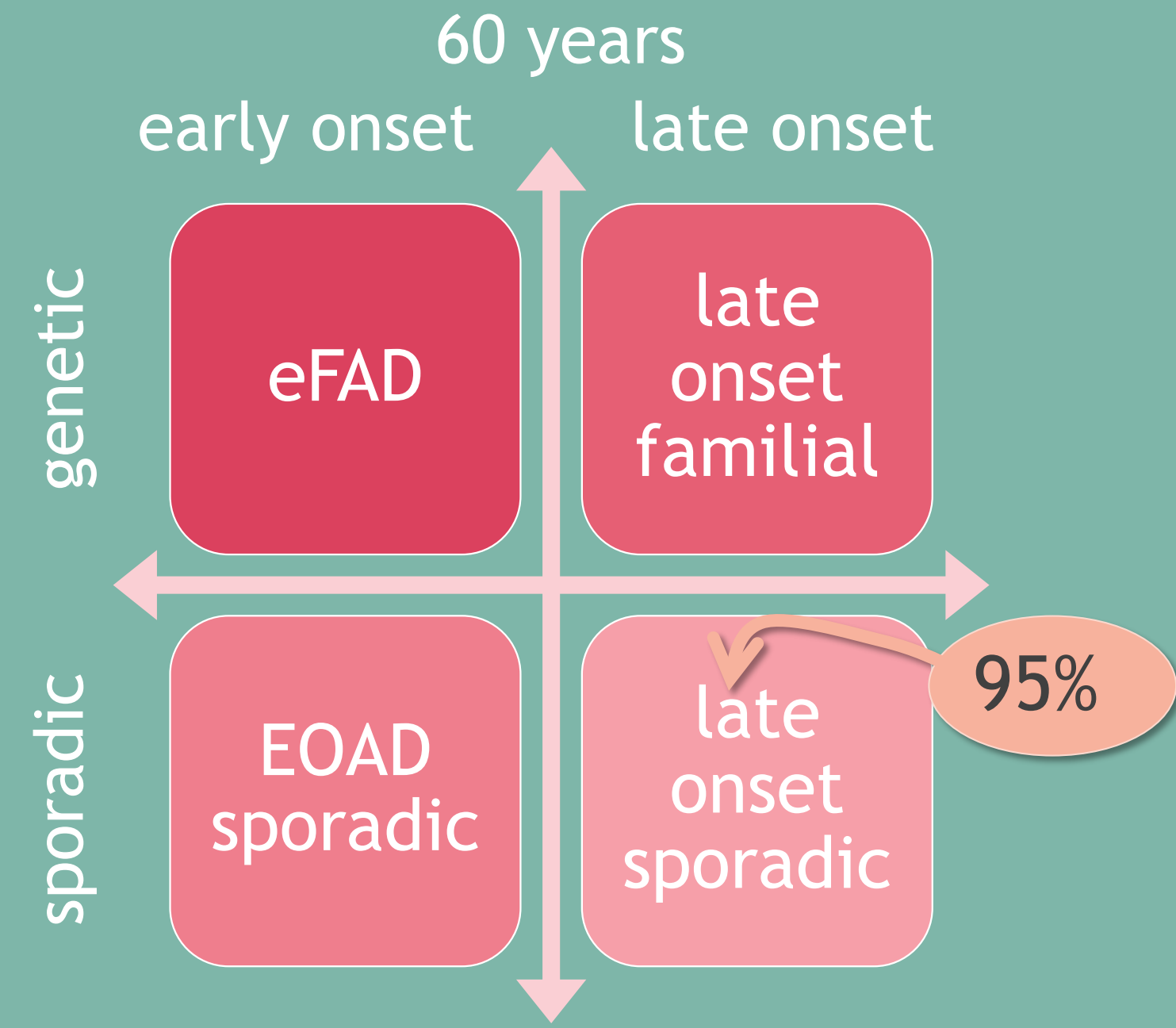
- eFAD and late-onset AD is essentially has the same clinical phenotype – however, they may have different etiologies.

"accounts for less than 1 percent of the 27 million Alzheimer's cases worldwide documented in 2006"

200,000 is the number of people with AD who are younger than 65.

http://www.alz.org/national/documents/topicsheet_alzdisease.pdf

- eFAD is the consequence of mutated genes.
- Late-onset disease is more likely due to a gradual accumulation of age-related malfunctions.



Brickell, K. L. et al *Arch Neurol*. 2006;63(9):1307-1311

these are deterministic mutations

autosomal dominant forms (eFAD)

amyloid precursor protein (APP) Chromosome 21	presenilin-1 (PS1) Chromosome 14	presenilin-2 (PS2) Chromosome 1

Accounts for most eFAD

Brickell, K. L. et al *Arch Neurol*. 2006;63(9):1307-1311

these are genetic **risk** factors

12 to 15 fold increase risk for AD with two copies of ApoE4

Not autosomal dominant

(ApoE)

ApoE4

ApoE4 is thought to lower the age of onset by a decade

Note:
Amyloid-B is cleared from the brain by attaching to ApoE. If it is not attached it can become toxic to the brain

Brickell, K. L. et al *Arch Neurol*. 2006;63(9):1307-1311

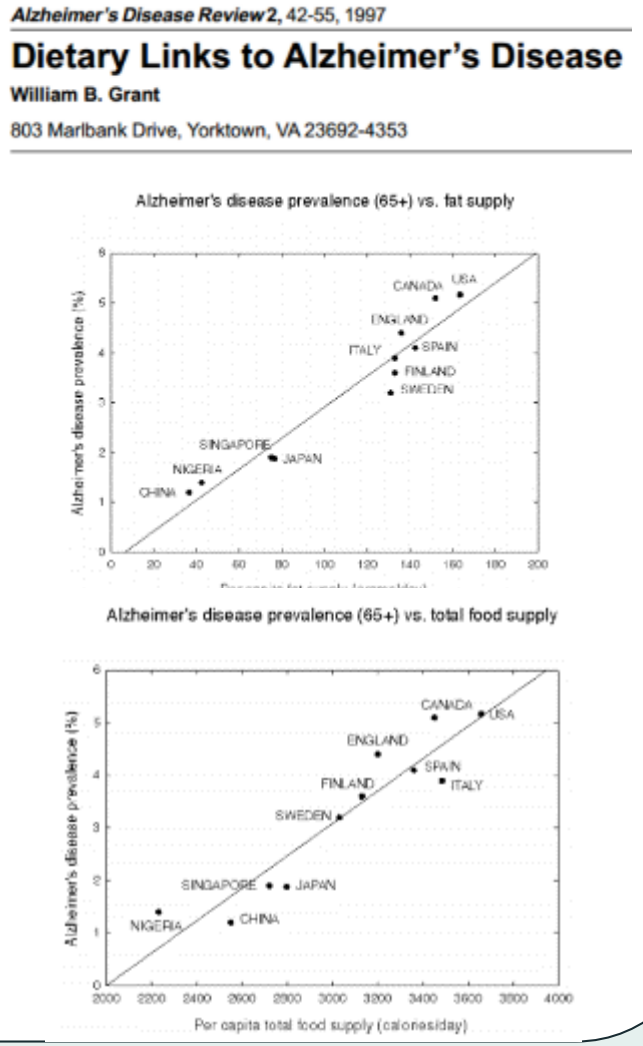
what increases the risk of 95% of the LOAD?

amyloid cascade hypothesis

- peptides generated from APP (amyloid precursor protein) cause AD
- so, reducing the generation or accumulation will treat the disease

diet hypothesis

- 1997 William Grant- correlated food consumption with AD worldwide
- found positive correlation between total calories and total fat in the incidence of AD.



Alzheimer's Disease Review 2, 42-55, 1997

Dietary Links to Alzheimer's Disease

William B. Grant

803 Marlbank Drive, Yorktown, VA 23692-4353

Alzheimer's disease prevalence (65+) vs. fat supply

Alzheimer's disease prevalence (65+) vs. total food supply

Grant, W. (1995) Alzheimer's Disease Review 2, 42-55

lessons

- eFAD
- Test drugs before symptoms

drugs

- Many recent drug candidates have failed in trials.
- Perhaps because the drugs were given too late.

memory

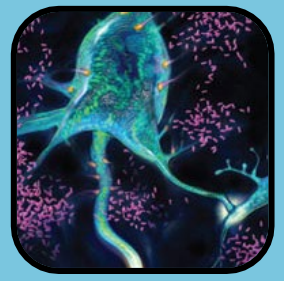
- When a person loses their memory – it is too late.
- The disease has been present for a long time by the time there are symptoms.

lifestyle

- Preventative or delay strategies.

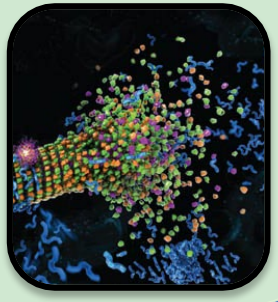
Amyloid accretion

- 5 – 20 years before diagnosis of Alzheimer's dementia
- damages synapses



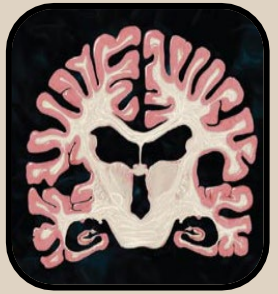
Tau buildup

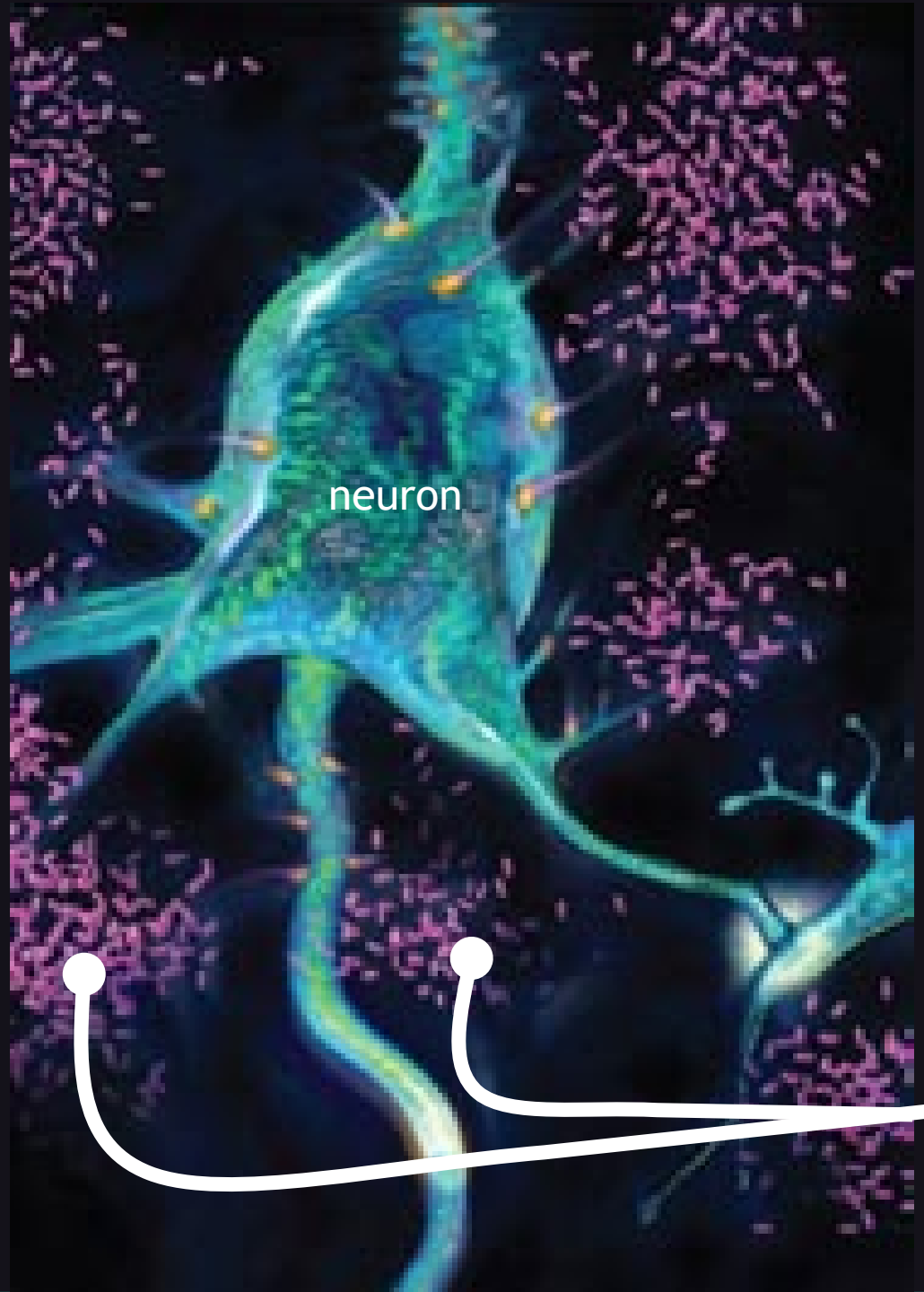
- 1 – 5 years before diagnosis
- Tau protein detaches from the microtubules.



Brain shinkage

- 1 – 3 years before diagnosis
- Cell death shrinks the brain.





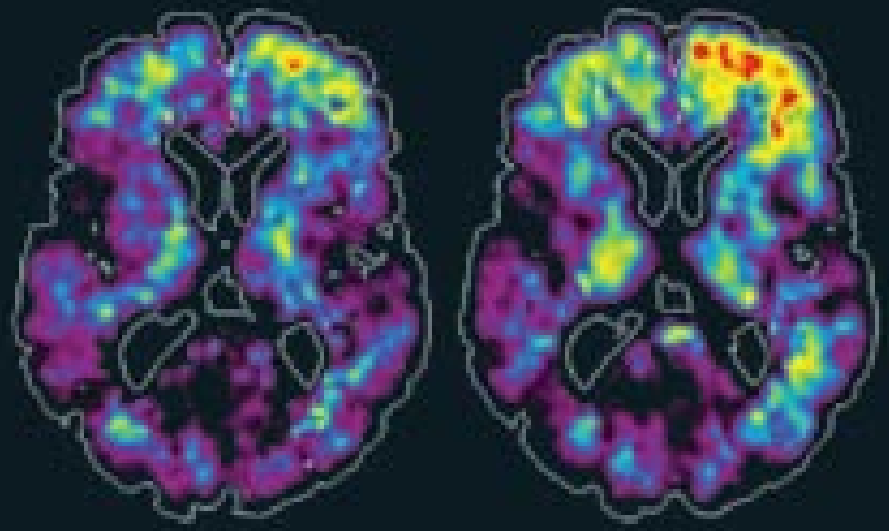
Amyloid Accretion
5–20 years before diagnosis of
Alzheimer's dementia

Scientific American (June 2010)
Alzheimer's: **Forestalling the Darkness**

Amyloid blocks neurotransmitters from reaching the post-synaptic receptors

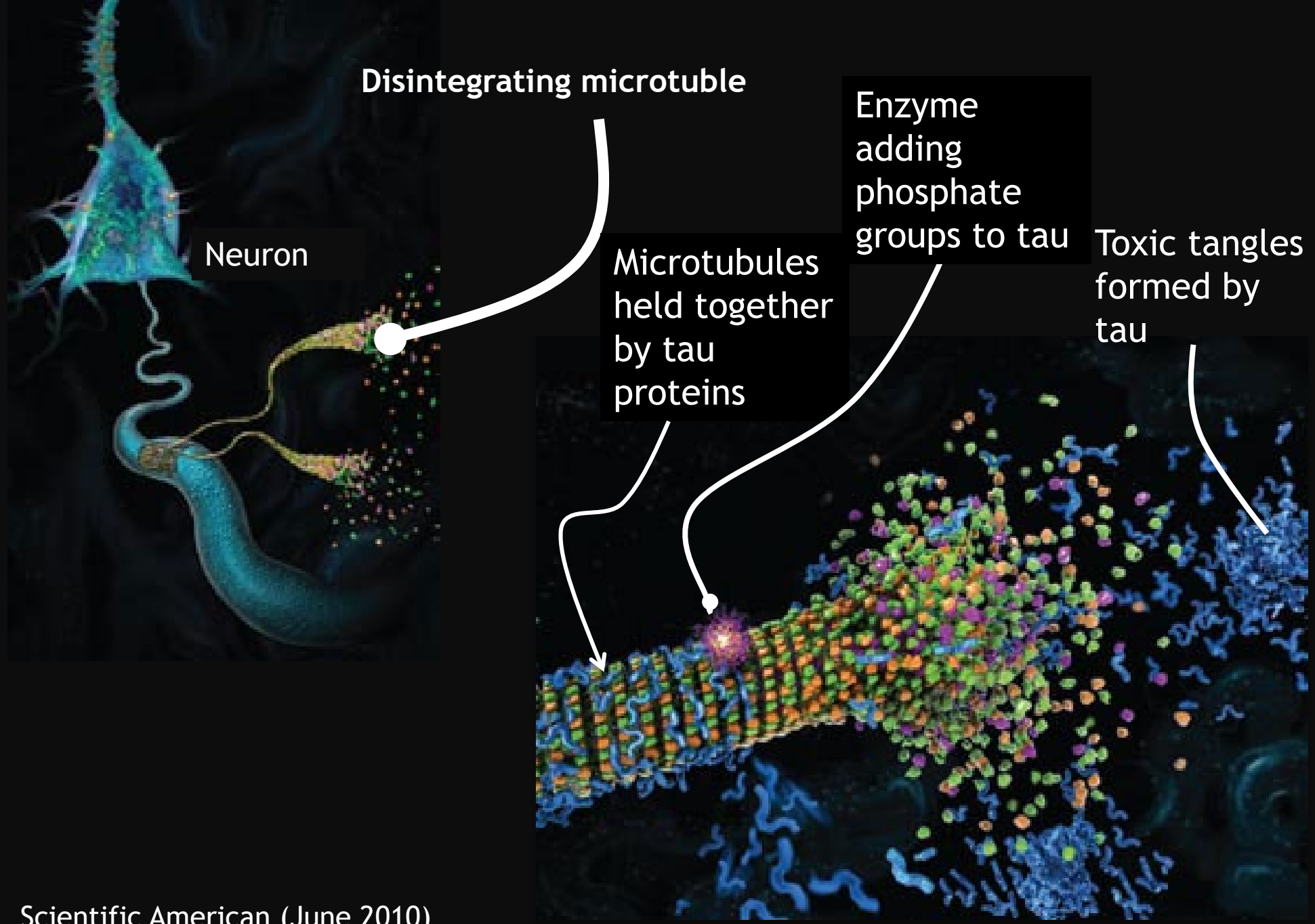
Scientific American (June 2010)
Alzheimer's: **Forestalling the Darkness**

Baseline 24 months



PET scans show increasing retention in the brain's frontal lobes of the amyloid-beta tracer Pittsburg imaging compound-B (PIB) over the course of two years in a 74-year-old, even while the subject remained cognitively normal.

Scientific American (June 2010)
Alzheimer's: **Forestalling the Darkness**



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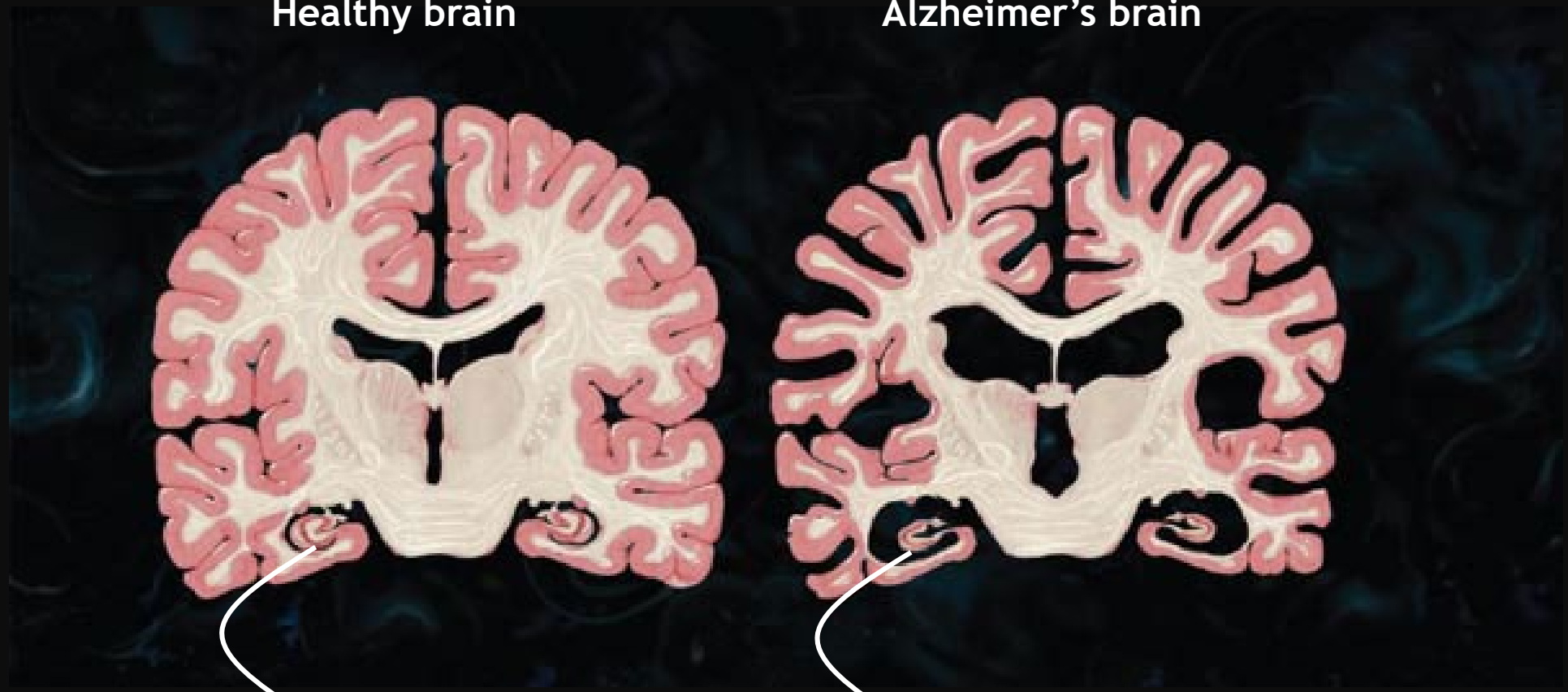


Scientific American (June 2010)
Alzheimer’s: **Forestalling the Darkness**

cascade to AD

- plaques and tangles
  - interact with inflammatory cells in a way that the accumulated plaques and tangles trigger diffuse brain toxicity and neuronal death.
- Measuring amyloid can predict problems even before any mild cognitive impairment (MCI).
- The cognitive decline seems to be triggered when tau protein increases.
- long symptomless amyloid buildup, tau takeover, inflammation and neuron destruction – boom AD.

Medical Hypotheses (2004) 62, 689–700

medical
hypotheses

http://intl.elsevierhealth.com/journals/mehy

High carbohydrate diets and Alzheimer's disease

Samuel T. Henderson*

High carbohydrate intake worsens cognitive performance and behavior in patients with Alzheimer's disease.

Henderson, 2004

Recall, increased risk for LOAD with ApoE4 allele. Why?

1.

ApoE4 protein alters lipid metabolism in a manner similar to high carbohydrate diets.

2.

Prolonged excessive insulin/IGF signaling is toxic to neurons.

Henderson, 2004

with T2D 2x risk of AD

- Patients on insulin therapy 4x risk for AD
- Insulin degrading Enzyme (IDE) → clears out insulin in the brain
- IDE also clears out excess amyloid (in vitro)
- Therefore –insulin resistance in periphery has an effect centrally and it appears that there might not enough IDE to clear out amyloid-B
- Mice without IDE get dementia
- Elderly people get increased amyloid in CSB when insulin is injected into their veins
- AD is the cause of dementia in 82-91% of T2D – greater than the general population
- Genetic predisposition (ApoE4 allele) for Alzheimer's have decreased expression of IDE in the hippocampus.
- Combination of the genetic predisposition to Alzheimer's (carrying the ApoE4 allele) and diabetes could put one at higher risk.

Interaction Between Circadian Rhythm & Metabolic Function

figure: Todd Churin

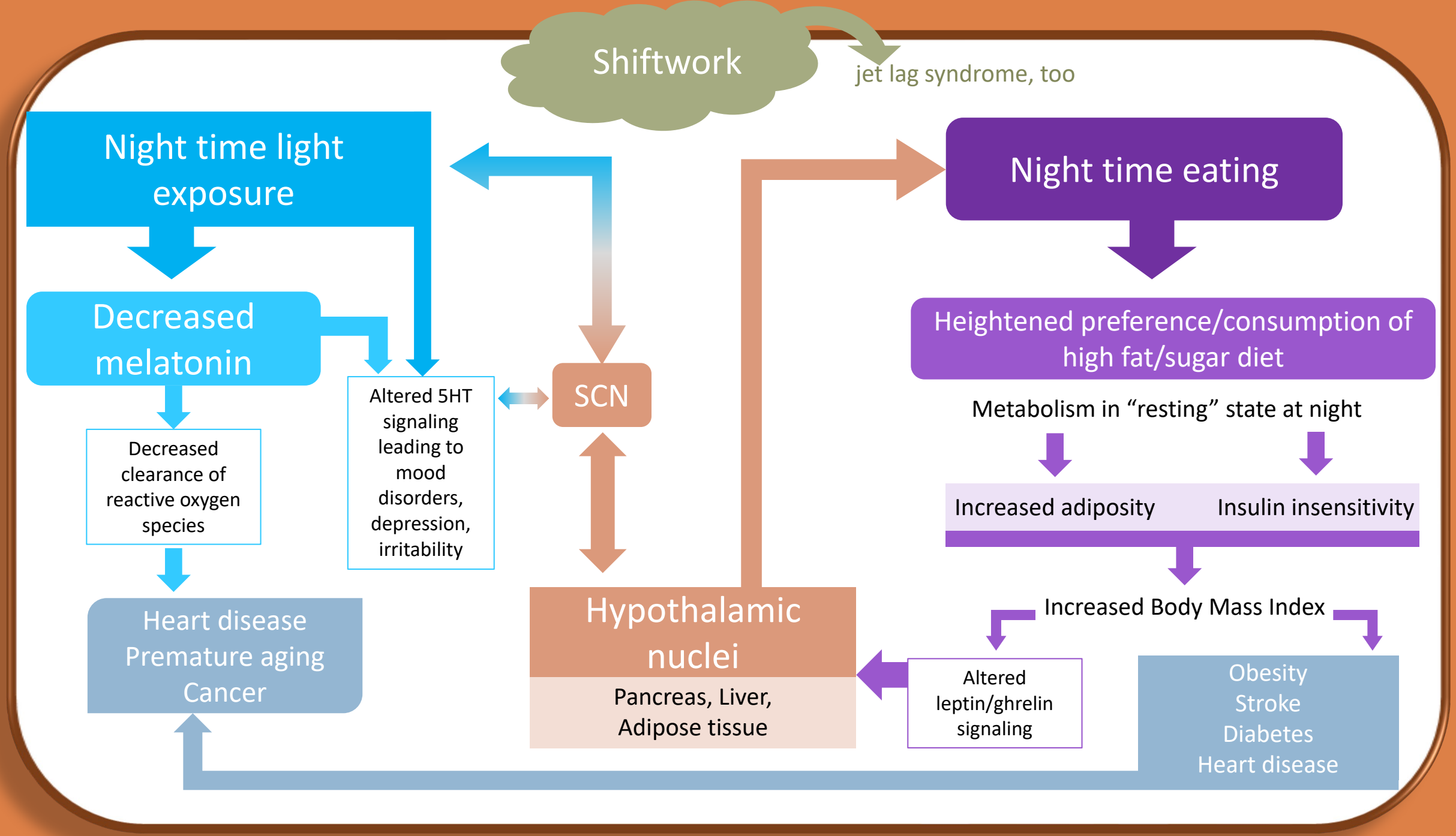


Figure adapted from: Zelinski, E. L. et al (2014) Neuroscience and Biobehavioral Reviews 40:80–101

Signature Hypometabolism in AD

ELSEVIER

Available online at www.sciencedirect.com
ScienceDirect

Experimental Gerontology 42 (2007) 129–138

Experimental Gerontology

www.elsevier.com/locate/expgero

Early detection of Alzheimer's disease using neuroimaging

Lisa Mosconi *, Miroslaw Brys, Lidia Glodzik-Sobanska, Susan De Santi, Henry Rusinek, Mony J. de Leon

Center for Brain Health MHL-400, New York University School of Medicine, 560 1st Avenue, New York, NY 10016, USA

Received 26 April 2006; received in revised form 3 May 2006; accepted 5 May 2006
Available online 12 July 2006

"AD patients show regional metabolic reductions involving the parieto-temporal and posterior cingulate cortices, and the frontal areas in advanced disease."

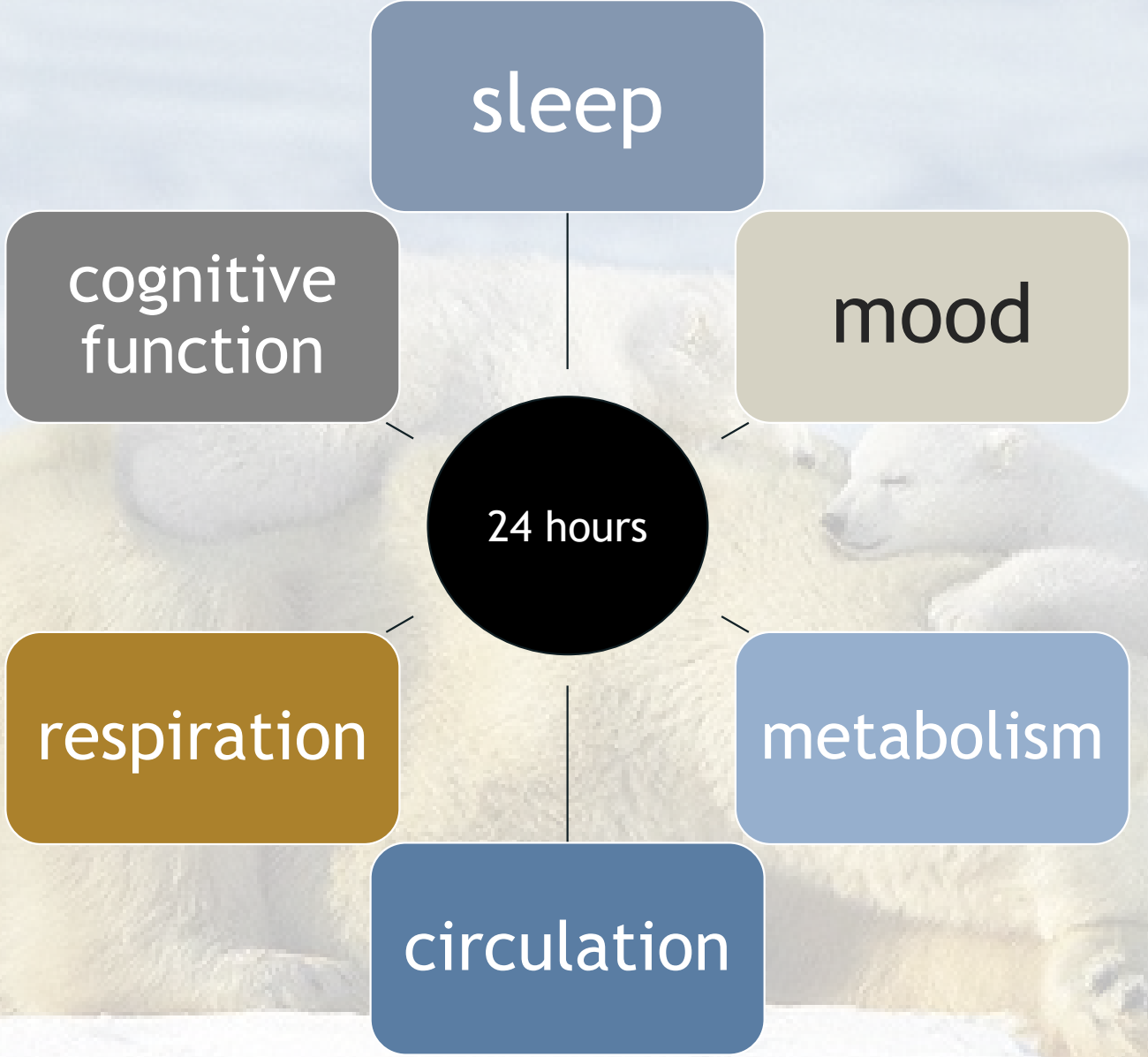
Mosconi, L. et al (2007)

Hypometabolism: Decline in glucose metabolism

Early feature of AD – region specific decline in glucose metabolism

Reduction of glucose metabolism → reduction in function

The circadian clock has a profound effect on the physiology and behavior of organisms.

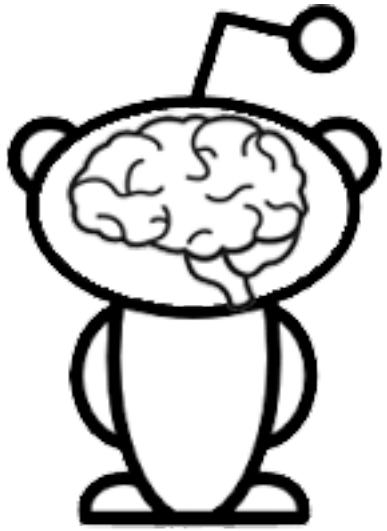


The circadian clock has a profound effect on the physiology and behavior of organisms.

A Single Night of Partial Sleep Deprivation Induces Insulin Resistance in Multiple Metabolic Pathways in Healthy Subjects

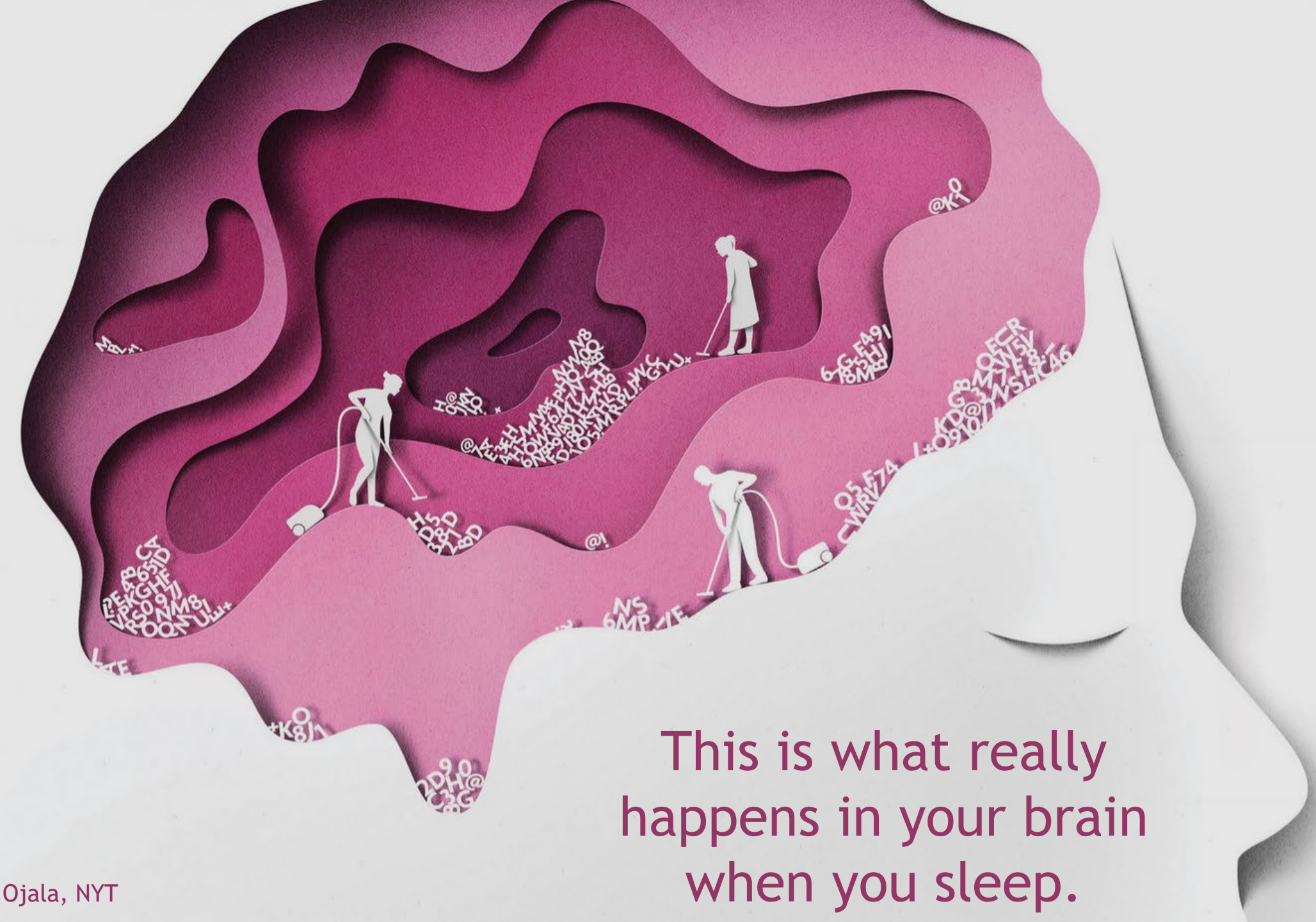
Esther Donga, Marieke van Dijk, J. Gert van Dijk, Nienke R. Biermasz, Gert-Jan Lammers, Klaas W. van Kralingen, Eleonara P. M. Corssmit, and Johannes A. Romijn

Departments of Endocrinology and Metabolic Diseases (E.D., M.v.D., N.R.B., E.P.M.C., J.A.R.), Neurology (J.G.v.D., G.-J.L.), and Pulmonology (K.W.v.K.), Leiden University Medical Center, 2300 RC Leiden, The Netherlands



the effect of a single night of partial sleep on insulin sensitivity

Donga, E., et al. (2010) J Clin Endocrinol Metab 95: 2963-2968



This is what really happens in your brain when you sleep.

Figure: Eiko Ojala, NYT

Nedergaard Lab

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Center for Translational Neuromedicine
Nedergaard Lab intranet

Principal Investigator

Maiken Nedergaard, M.D., DMSc

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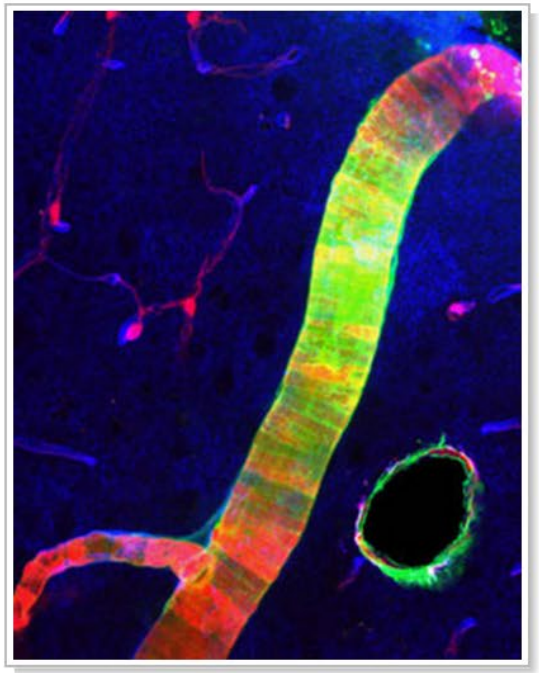
Glymphatic System

Throughout most of the body, a complex system of lymphatic vessels is responsible for cleansing the tissues of potentially harmful metabolic waste products, accumulations of soluble proteins and excess interstitial fluid. But astonishingly, the body's most sensitive tissue –the central nervous system – lacks a lymphatic vasculature. What then accounts for the efficient waste clearance that must occur in order for the neural tissue of our brains to function properly?



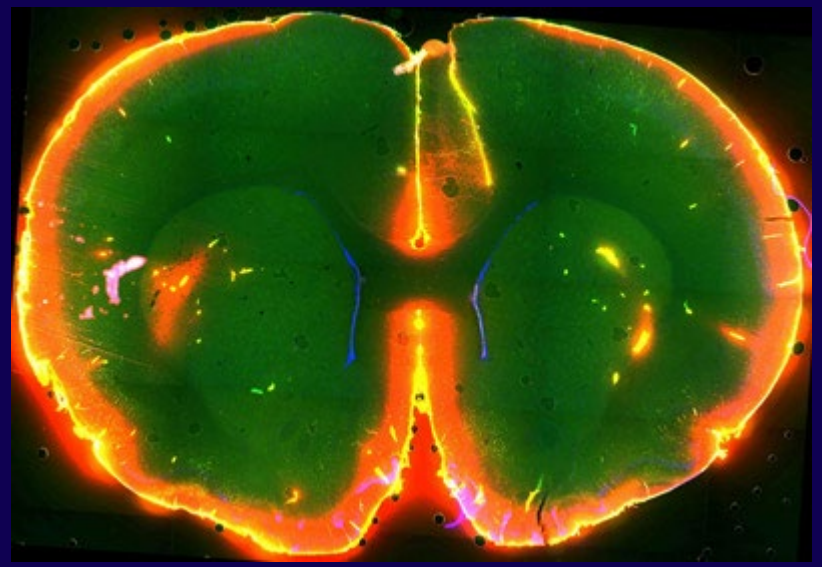
Large (green) and small (red) tracers tagged to soluble proteins in the paravascular cerebrospinal fluid.

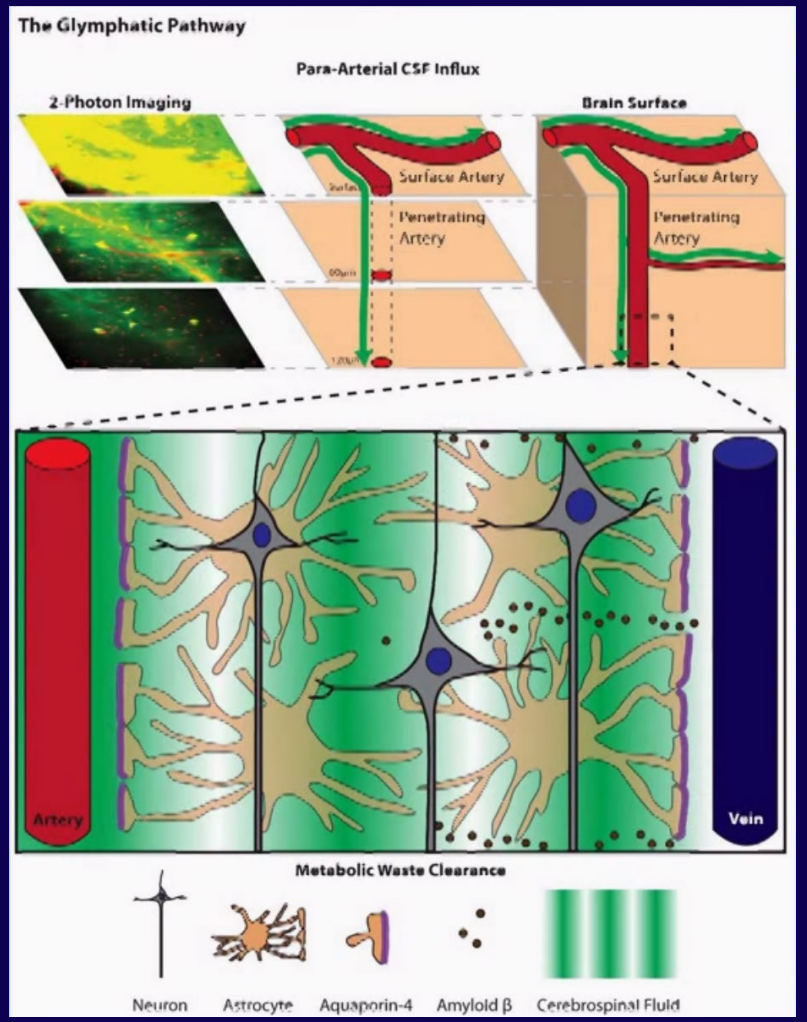
This question has puzzled scientists for centuries. Our group believes that understanding how this process functions in the healthy nervous system holds the key to developing treatment options for a wide variety of neurological diseases, especially those characterized by the improper accumulation of misfolded proteins. The breakdown of the brain's innate clearance system may in fact underlie the pathogenesis of neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's disease, in addition to ALS and chronic traumatic encephalopathy. Past efforts to explain how the brain cleanses parenchymal tissue have suggested that solute and fluid exchange occurs between the interstitial fluid and the cerebrospinal fluid, and that this exchange is driven by diffusion. Yet as many have noted, the distances for diffusion in the brain are too great to explain the highly regulated interstitial environment.

Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie,[1*] Hongyi Kang,[1*] Qiwu Xu,[1] Michael J. Chen,[1] Yonghong Liao,[1] Meenakshisundaram Thiyagarajan,[1] John O'Donnell,[1] Daniel J. Christensen,[1] Charles Nicholson,[2] Jeffrey J. Iliff,[1] Takahiro Takano,[1] Rashid Deane,[1] Maiken Nedergaard[1]†

The conservation of sleep across all animal species suggests that sleep serves a vital function. We here report that sleep has a critical function in ensuring metabolic homeostasis. Using real-time assessments of tetramethylammonium diffusion and two-photon imaging in live mice, we show that natural sleep or anesthesia are associated with a 60% increase in the interstitial space, resulting in a striking increase in convective exchange of cerebrospinal fluid with interstitial fluid. In turn, convective fluxes of interstitial fluid increased the rate of β-amyloid clearance during sleep. Thus, the restorative function of sleep may be a consequence of the enhanced removal of potentially neurotoxic waste products that accumulate in the awake central nervous system.





https://www.youtube.com/watch?v=ci5NMscKJws

Average Number of Hours of Sleep per Night

this is considered to be sleep deprived.

Are you getting enough sleep?

Kripke, D et al (1979) Arch Gen Psychiatry;
Gallup Organization (1995), Sleep in America;
National Center for Health Statistics (1984 & 2004) Morb Mortal Wkly Rep 2005

What would happen if you got one more hour of sleep?

How much can an extra hour's sleep change you?

9 October 2013 Last updated at 04:24 ET

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The average Briton gets six-and-a-half hours' sleep a night, according to the Sleep Council. Michael Mosley took part in an unusual experiment to see if this is enough.

It has been known for some time that the amount of sleep people get has, on average, declined over the years.

This has happened for a whole range of reasons, not least because we live in a culture where people are encouraged to think of sleep as a luxury - something you can easily cut back on. After all, that's what caffeine is for - to jolt you back into life. But while the average amount of sleep we are getting has fallen, rates of obesity and diabetes have soared. Could the two be connected?

We wanted to see what the effect would be of increasing average sleep by just one hour. So we asked seven volunteers, who normally sleep anywhere between six and nine hours, to be studied at the University of Surrey's Sleep Research Centre.

The volunteers were randomly allocated to two groups. One group was asked to sleep for six-and-a-half hours a night, the other got seven-and-a-half hours. After a week the researchers took blood tests and the volunteers were asked to switch sleep patterns. The group that had been sleeping six-and-a-half hours got an extra hour, the other group slept an hour less.

While we were waiting to see what effect this would have, I went to the John Radcliffe hospital in Oxford to learn more about what actually happens when we sleep.

In the Sleep Centre, they fitted me up with a portable electro-encephalograph, a

Go to this website
and read the article.

http://www.bbc.com/news/magazine-24444634