Circadian rhythms: re-setting the clock in type 2 diabetes and metabolic disease

Brendan Gabriel, PhD

2019

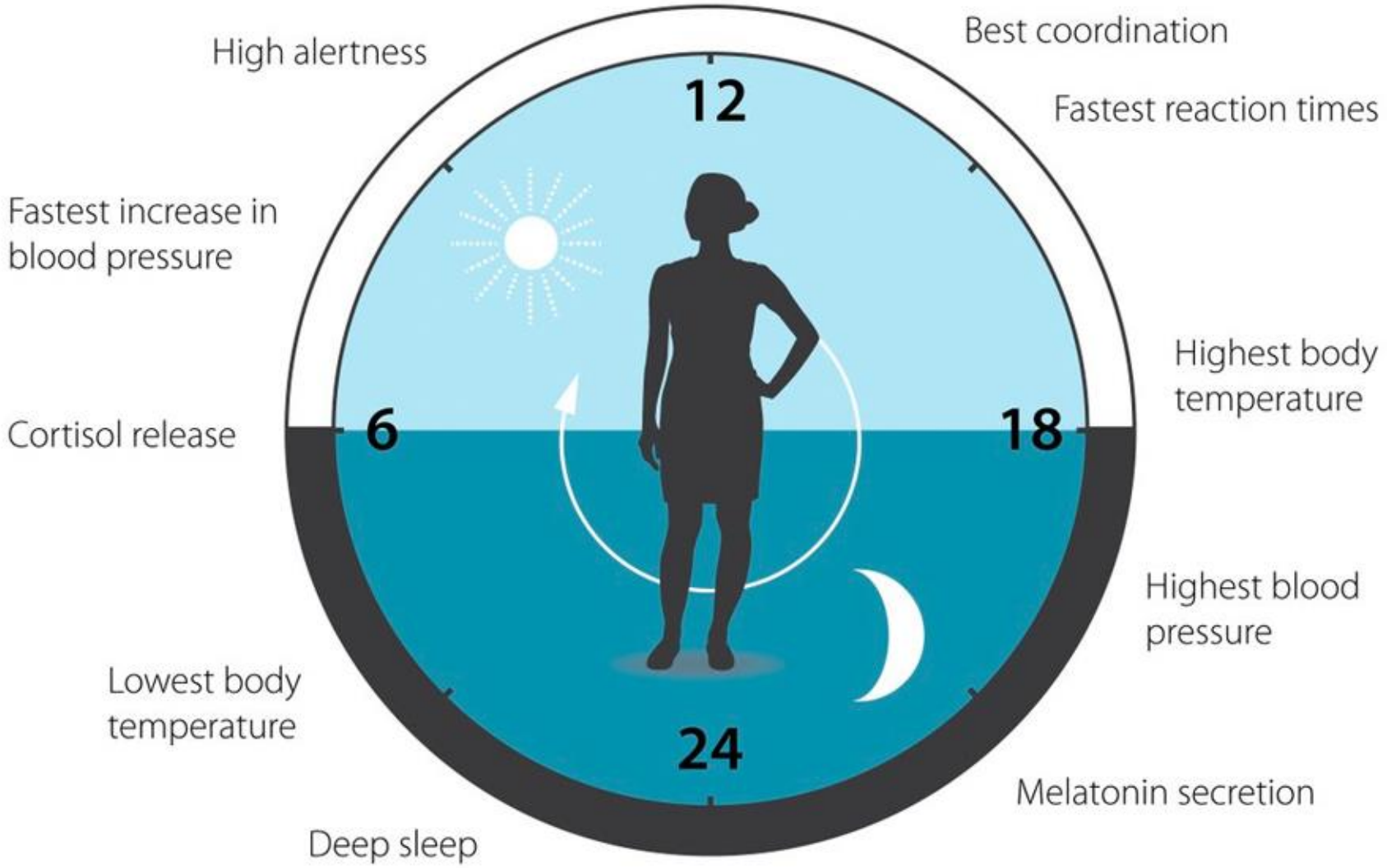
Circadian rhythms evolved as a protection against UV light

Biological rhythms are functionaly important

Nearly all of biology has circadian rhythms

Dysfunctional rhythms are implicated in several diseases

The Circadian Clock Anticipates and Adapts our Physiology to the Different Phases of the Day



Our biological clock helps to regulate sleep patterns, feeding behavior, hormone release, blood pressure, and body temperature.

The Nobel Prize in Physiology or Medicine 2017

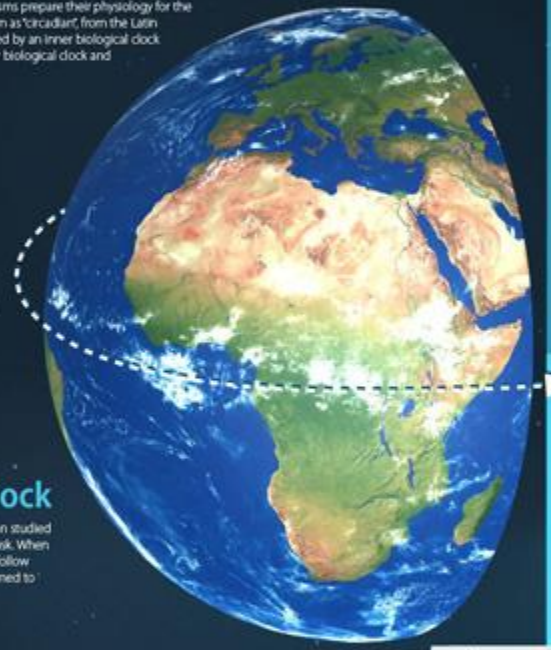
What makes us tick?

The 2017 Nobel Prize in Physiology or Medicine has been awarded to Jeffrey C. Hall, Michael Rosbash and Michael W. Young **for their discoveries of molecular mechanisms controlling the circadian rhythm.**

Life on Earth is adapted to the rotation of our planet. Living organisms prepare their physiology for the fluctuations between night and day. These daily rhythms are known as 'circadian', from the Latin *circadiem*, meaning "around a day". The circadian rhythm is regulated by an inner biological clock in our cells. This year's Nobel laureates were able to peek inside our biological clock and elucidate its inner workings.

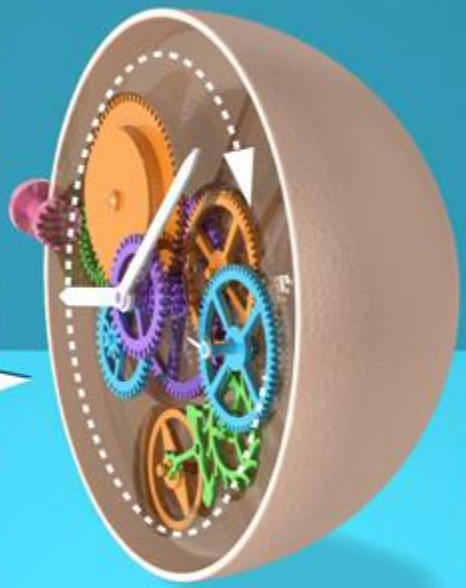
An internal biological clock

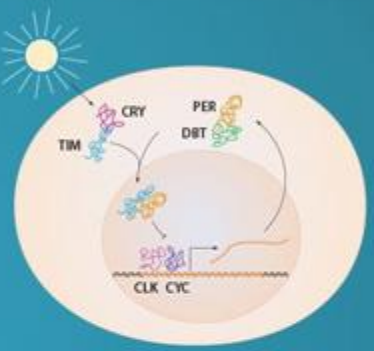
In the 18th century, the astronomer Jean Jacques d'Ortous de Mairan studied mimosa plants, whose leaves open during daytime and close at dusk. When he placed the plant in constant darkness, the leaves continued to follow their normal daily oscillation independent of daily light. Plants seemed to have an inner biological clock.



Cogs and wheels of the biological clock

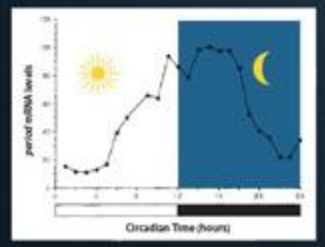
The paradigm-shifting discoveries by the laureates established the key mechanistic principles for the biological clock in fruit flies. The PER protein prevents its own synthesis by blocking the *period* gene and thereby regulates its own level in a continuous, cyclic rhythm. To block the period gene, PER needs to reach the cell nucleus. TIM binds to PER, enabling entry into the cell nucleus where the two proteins inhibit period. Additional proteins are required to stabilize PER (DBT), activate the period gene (CLK and CYC), and to calibrate the clock by light (CRY).





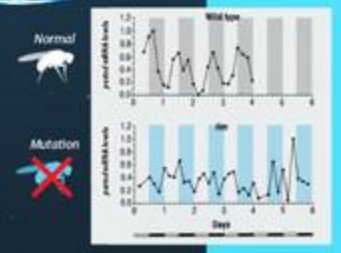
The circadian clock in humans

Biological clocks function by the same principles in other multicellular organisms, including humans. A large proportion of our genes are regulated by the biological clock and, consequently, a carefully calibrated circadian rhythm anticipates and adapts our physiology to the different phases of the day. A precisely calibrated clock regulates many processes including sleep, feeding, hormone levels, blood pressure and body temperature. Since the seminal discoveries by the three laureates, circadian biology has developed into a vast and highly dynamic research field, with implications for our health and wellbeing.



The *period* gene

The Nobel Laureates isolated a gene called *period*, which is required for the circadian rhythm in fruit flies. The gene encodes the PER protein. Jeffrey Hall and Michael Rosbash showed that the *period* gene activity (mRNA levels) followed a 24-hour rhythm.



The *timeless* gene

Michael Young identified a second gene, called *timeless*, encoding the TIM protein. He showed that TIM is essential for a normal circadian rhythm and that TIM is required for the oscillation of *period* mRNA levels.

Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

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Text and scientific advice: The Nobel Committee for Physiology or Medicine
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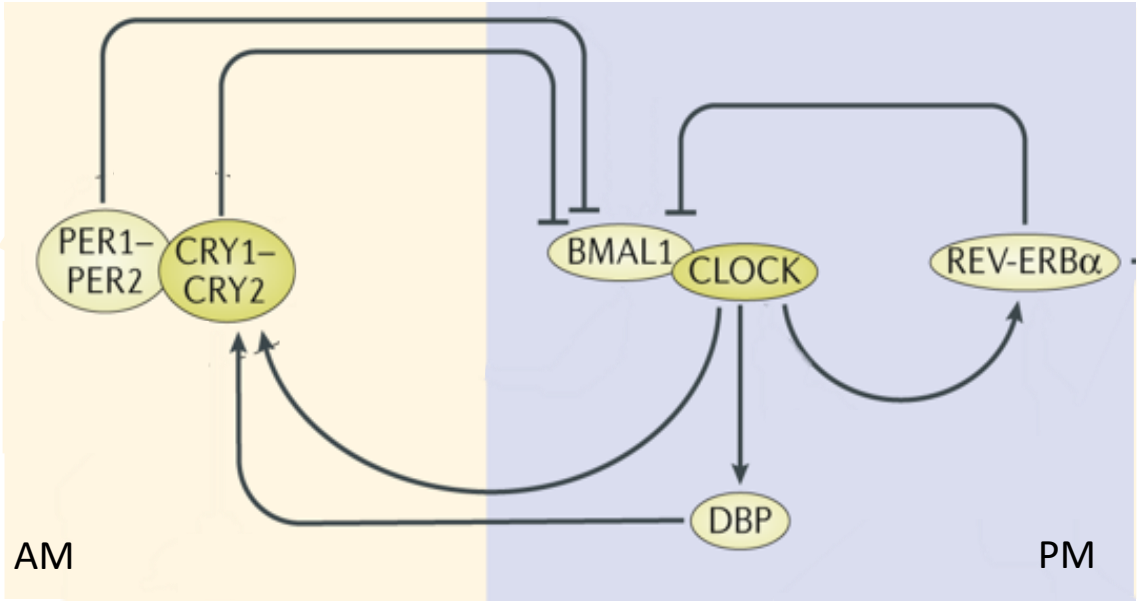
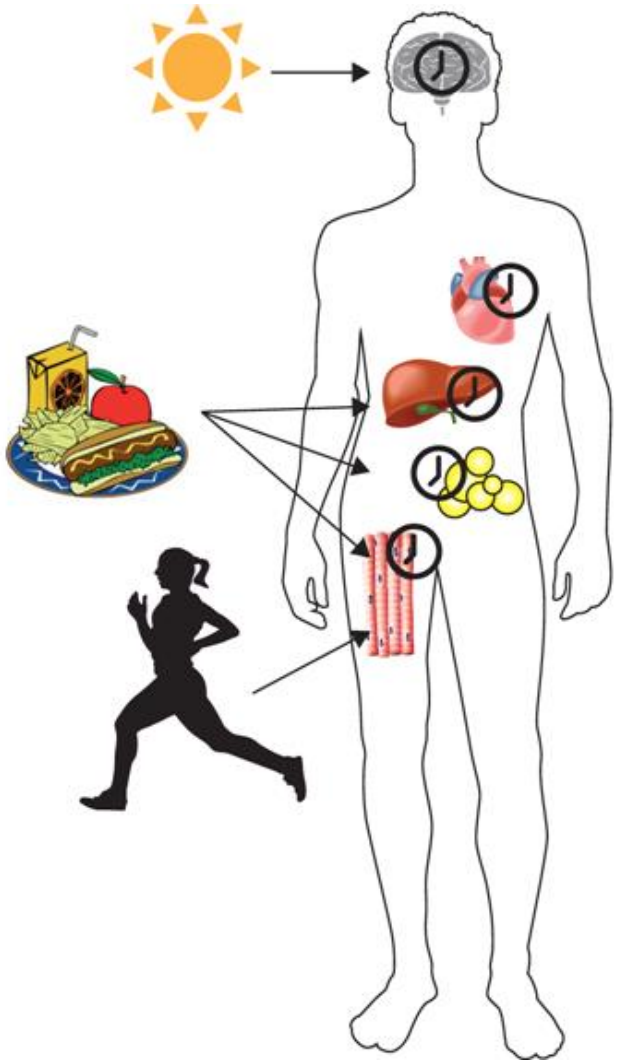
The core-clock machinery

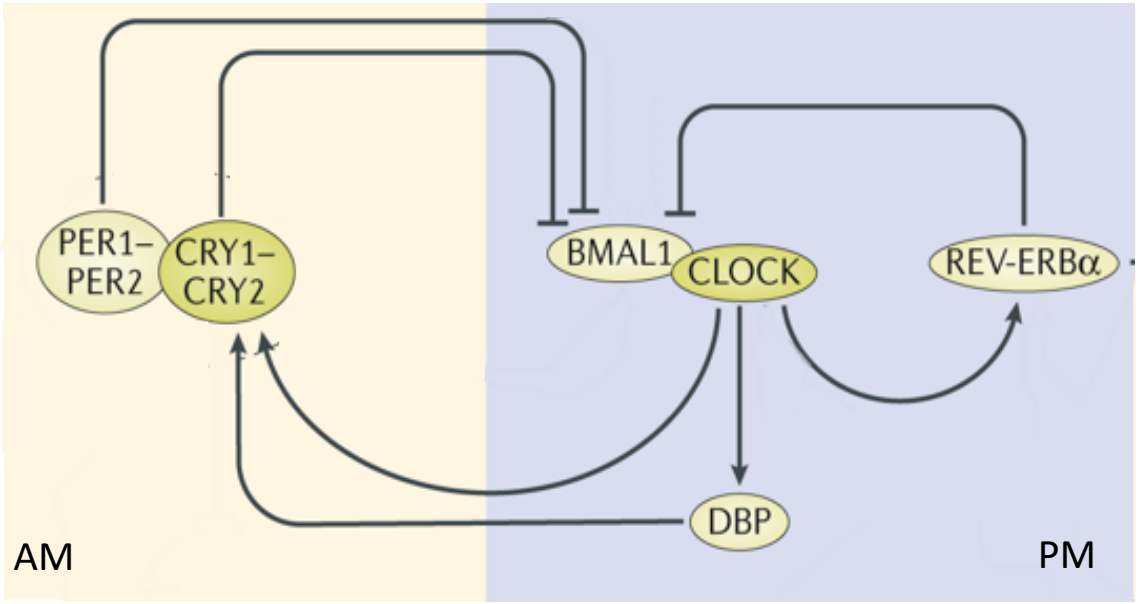
- **Peripheral clocks** are regulated by the central clock, but can also be affected by other cues.
- The number of **clock-controlled genes** is extensive.



Circadian clocks exhibit tissue-specific rhythmicity, orchestrated by the central circadian clock in the suprachiasmatic nucleus.

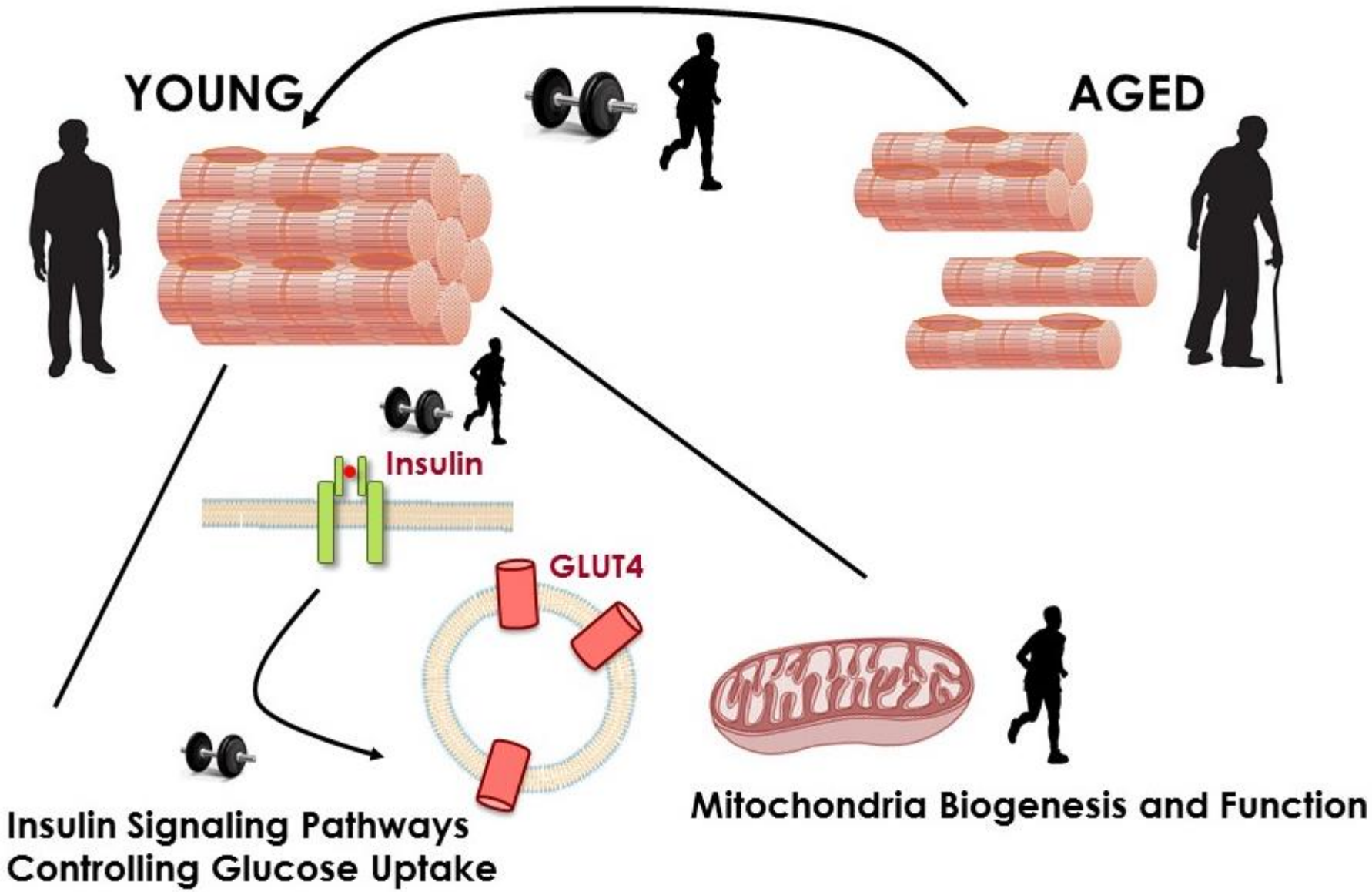
Synchronization takes place via neural, hormonal and behavioral cues.



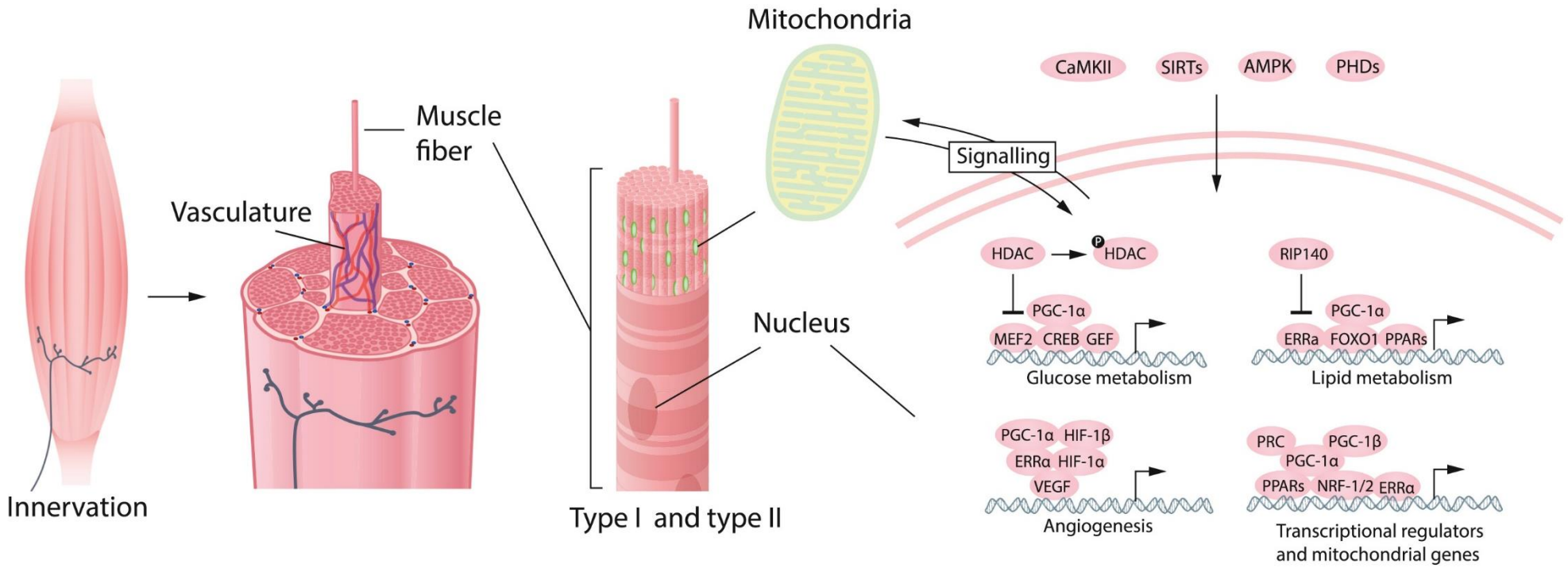


J Mol Endocrinol 60:R115–R130, 2018

Preventing skeletal muscle degradation in disease



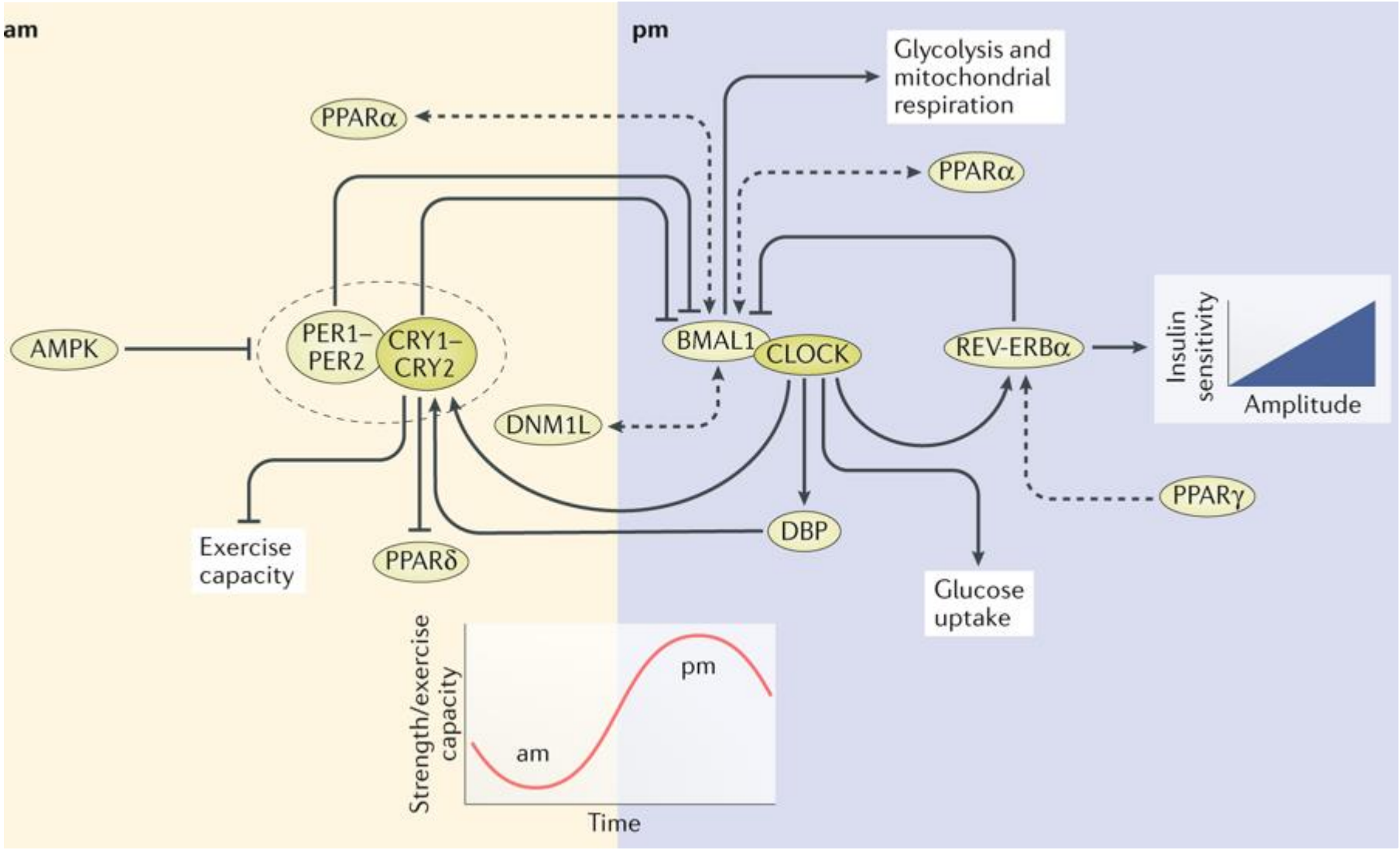
Muscle tissue is a dynamic network



- Metabolic systems are part of dynamic networks, which are often highly plastic.

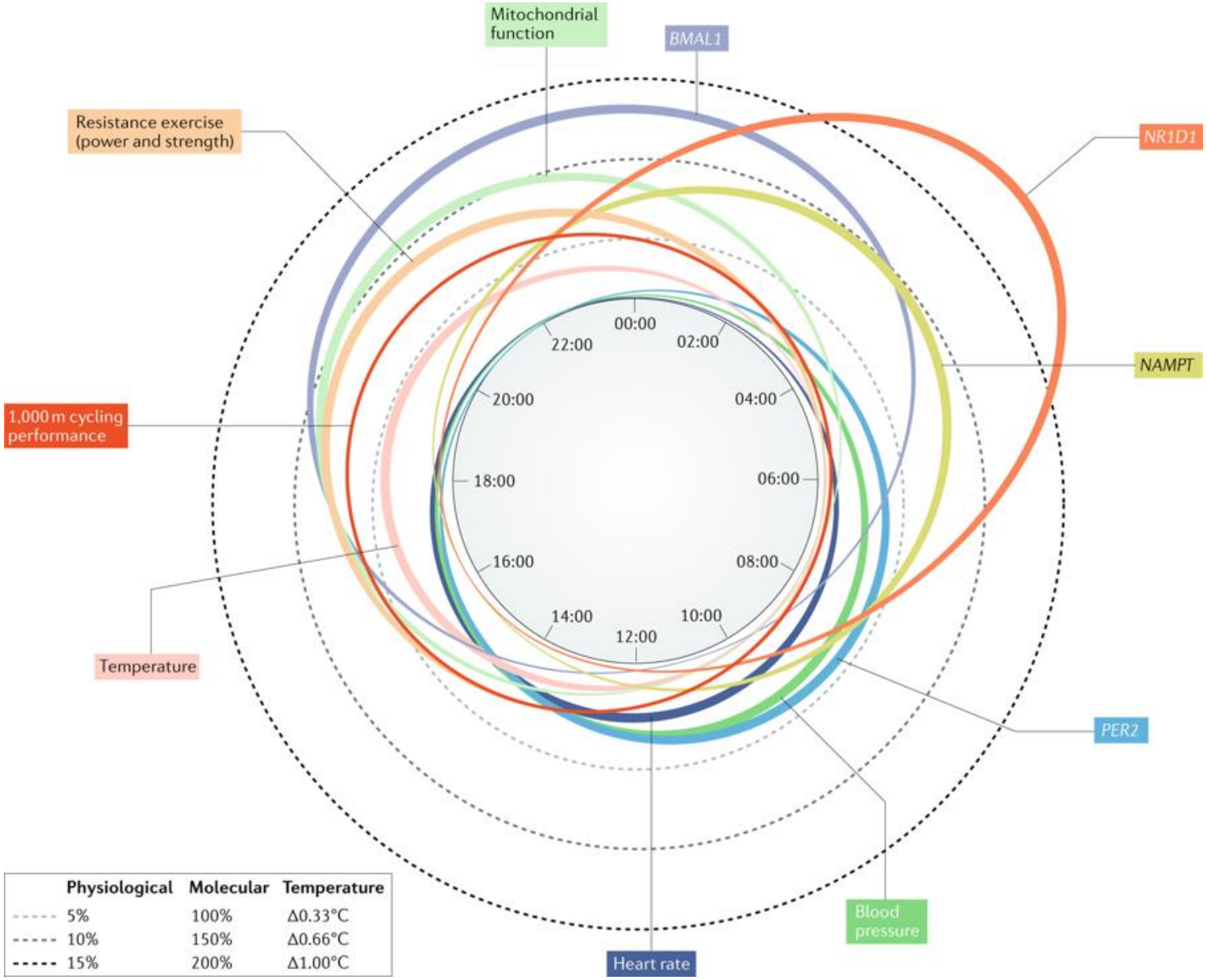
Gabriel & Zierath,
Cell metab. 2017

The intrinsic clock machinery in skeletal muscle



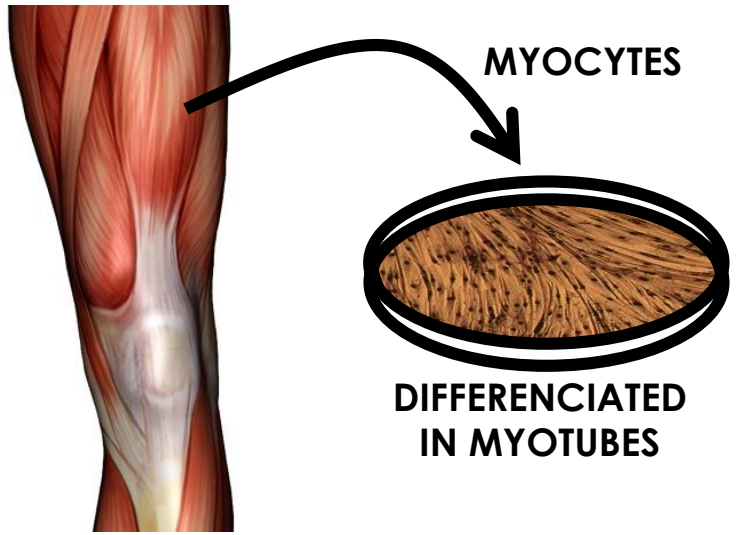
Gabriel & Zierath, 2019
Nat. Rev. Endo

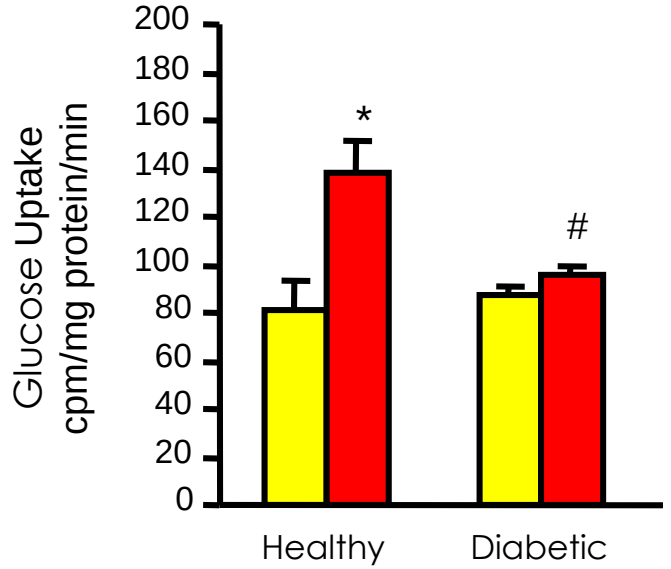
The molecular clock coalesces with physiology



Gabriel & Zierath, 2019 *Nat. Rev. Endo*

Memory of Diabetic Phenotype in Primary Human Muscle Cell Cultures

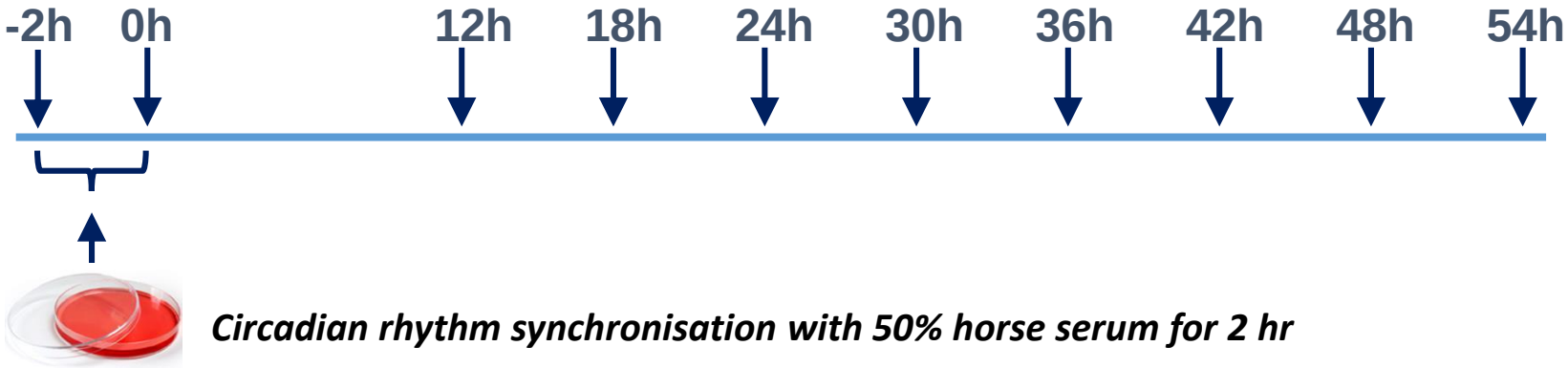




Bouzakri and Zierath, J. Biol. Chem, 2007

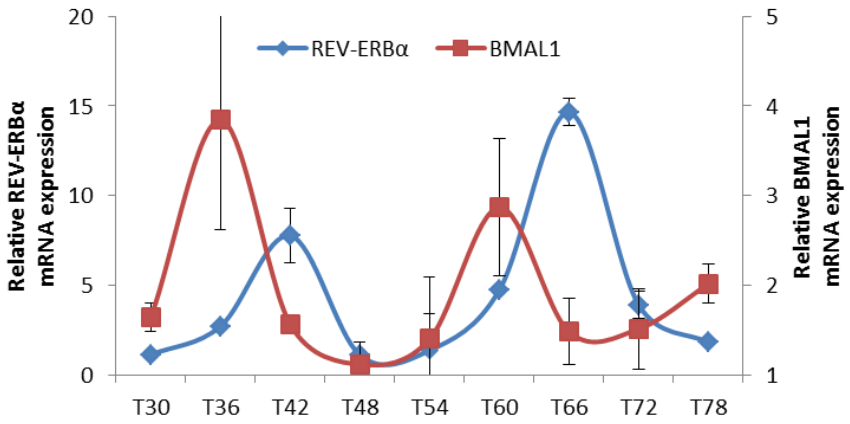
Cultured muscle cells maintain the "insulin resistant phenotype" of the donor, even after several passages

Skeletal Muscle Cells Display Circadian Rhythm in Culture

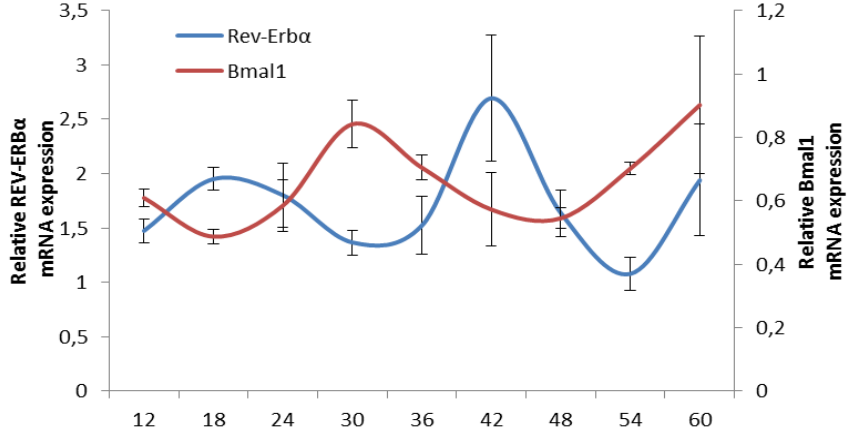


Circadian rhythm synchronisation with 50% horse serum for 2 hr

Human primary myotubes



Mouse C2C12 myotubes



Romain Barrès

Skeletal muscle cell circadian rhythm

2h serum shock 50%FBS

RNA-seq
Mito-Function

Growth → Differentiation → Synchronization → Treatment → Extraction → Analysis

T2D
Diabetic

N=5

NGT
Healthy

N=7

Control

4.5g/L Glucose +
50nM Insulin

Laura Sardón Puig

Nicolas Pillon

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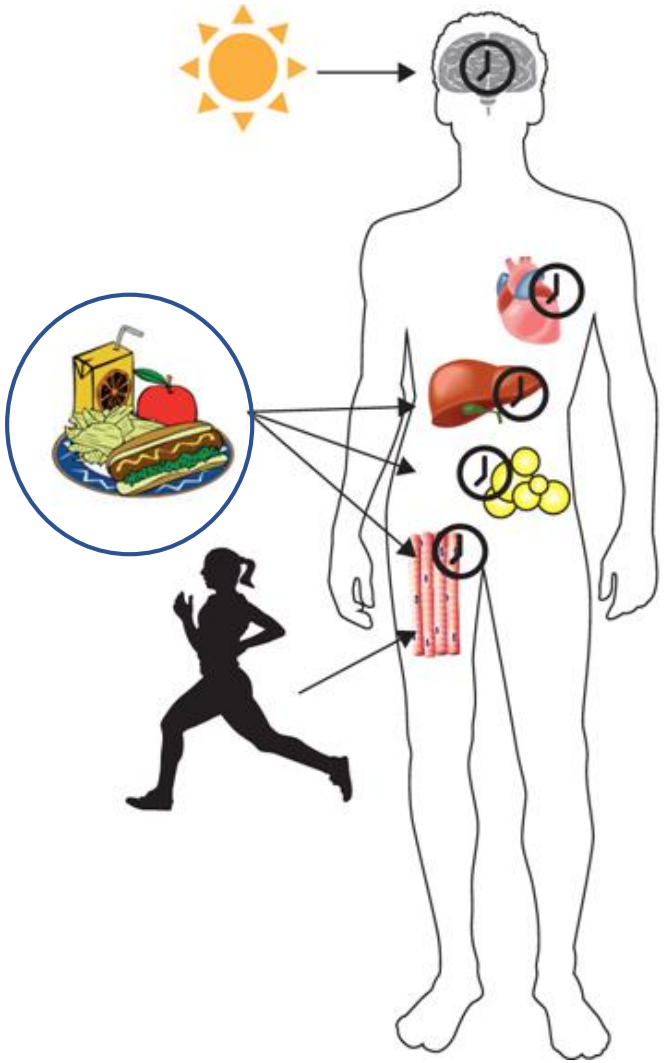
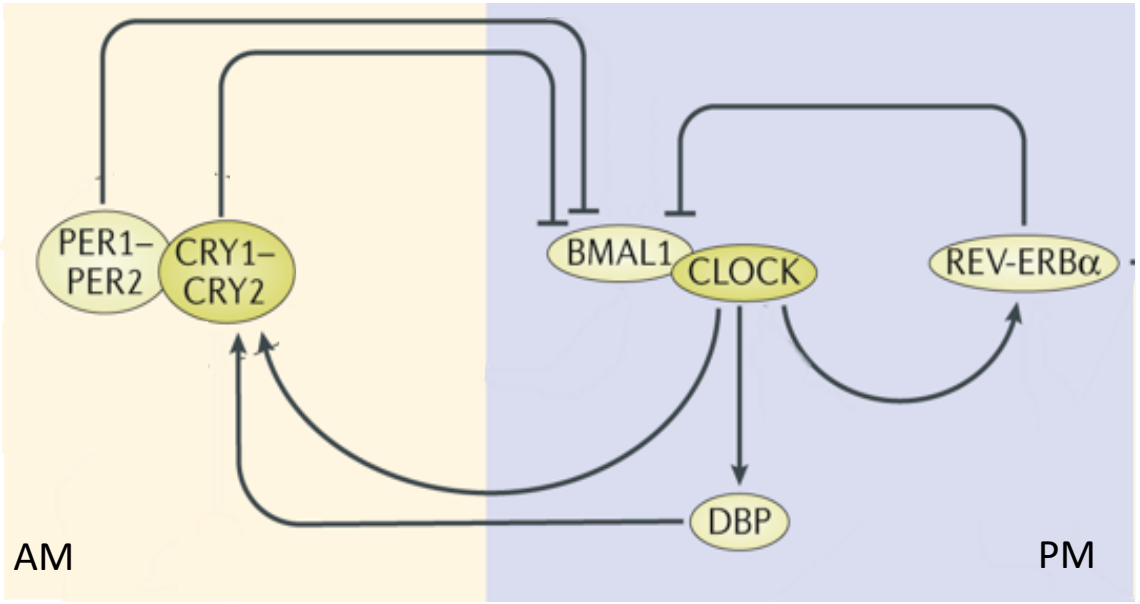
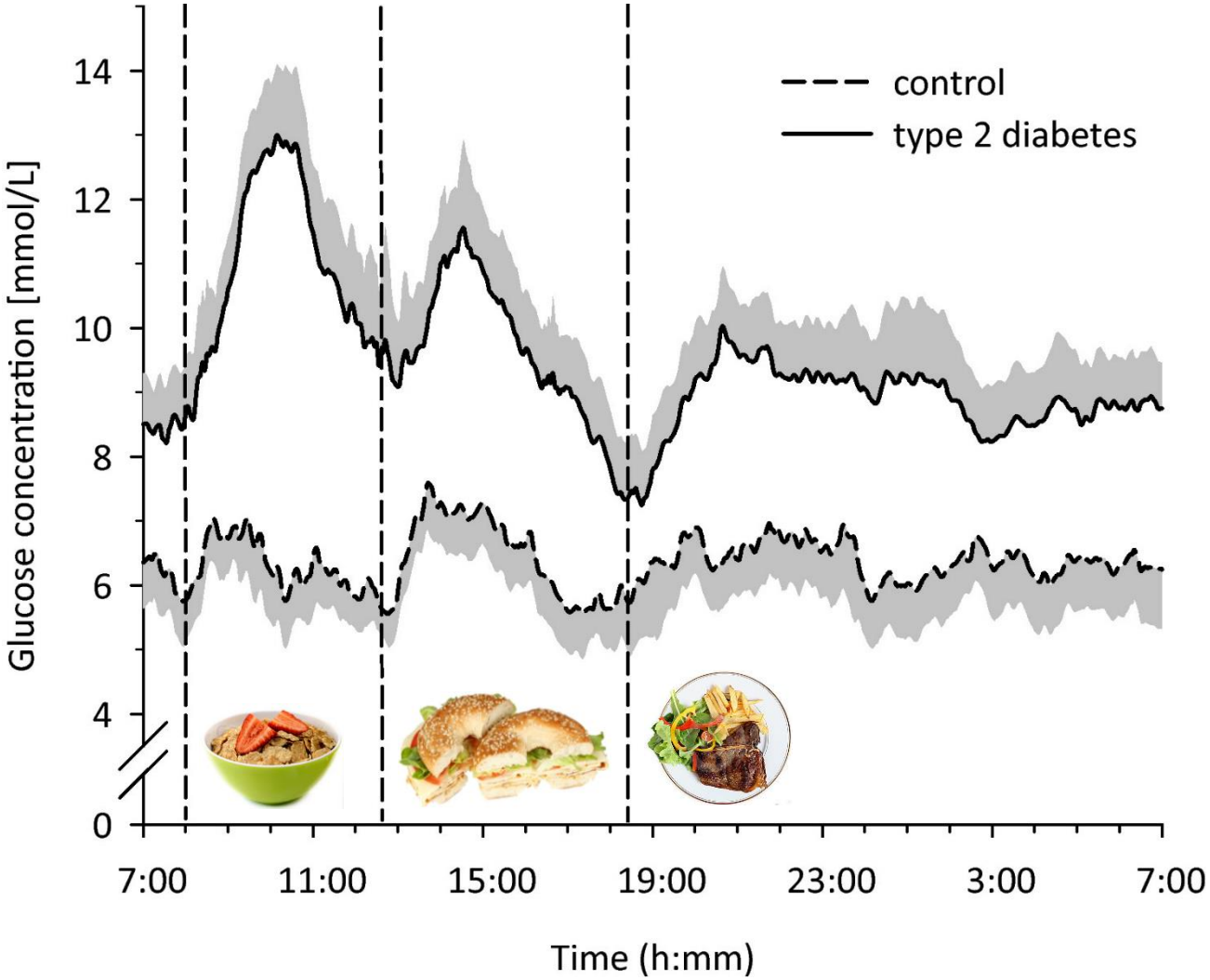




J Mol Endocrinol 60:R115–R130, 2018

Postprandial Hyperglycemia Is Highly Prevalent Throughout The Day in Patients With T2DM



van Dijk JW et al. *Diabetes Res Clin Pract* 93: 31-37, 2011.

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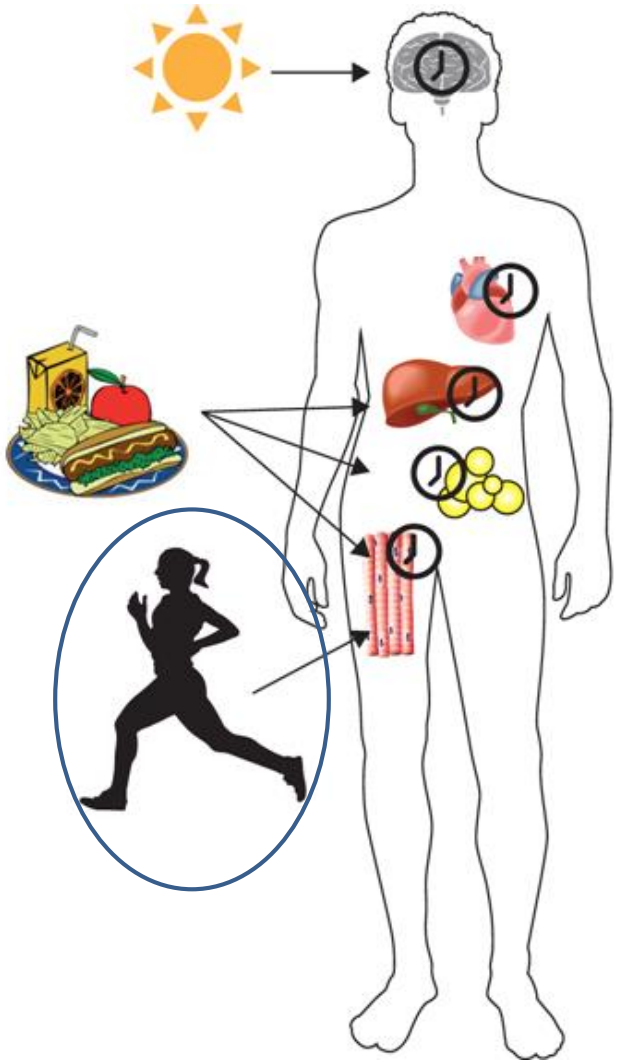
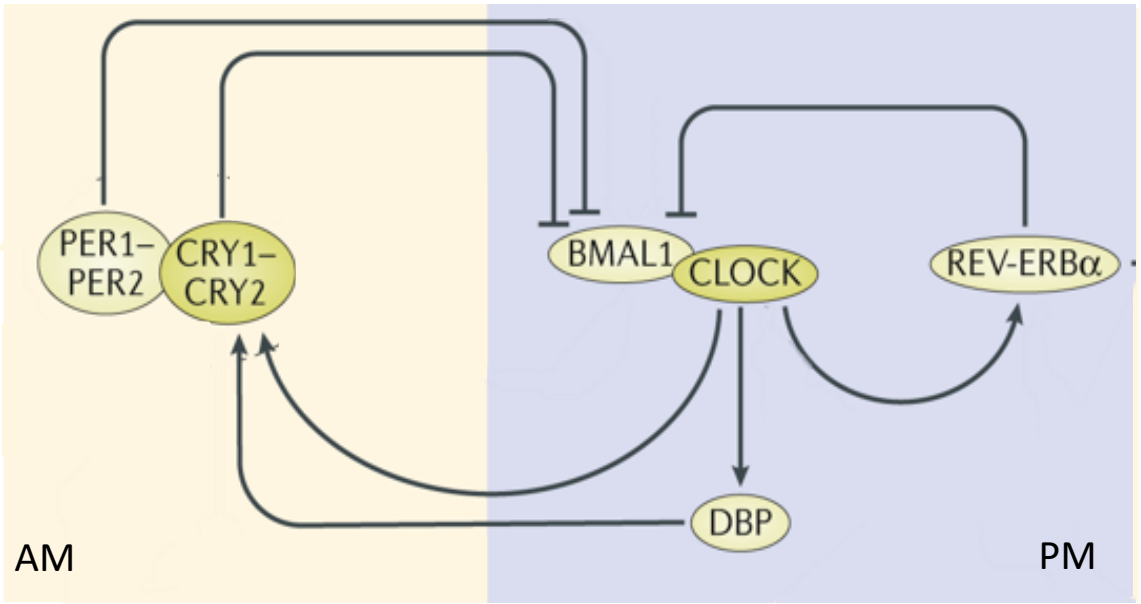
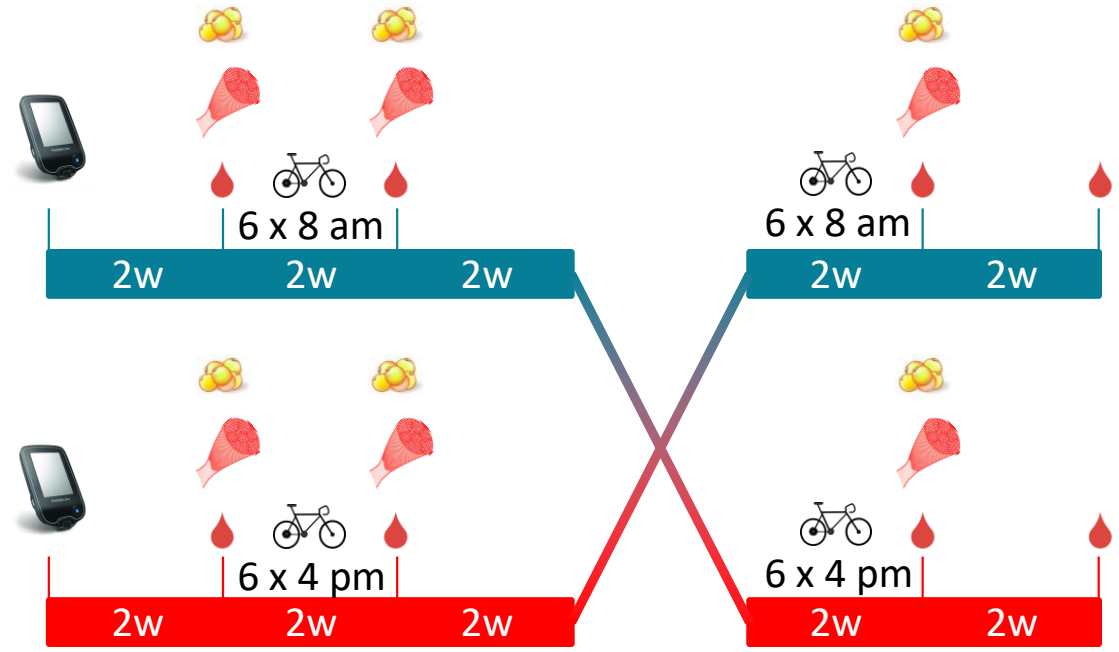




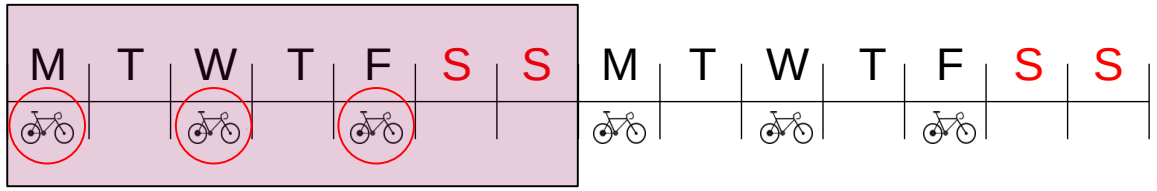
J Mol Endocrinol 60:R115–R130, 2018

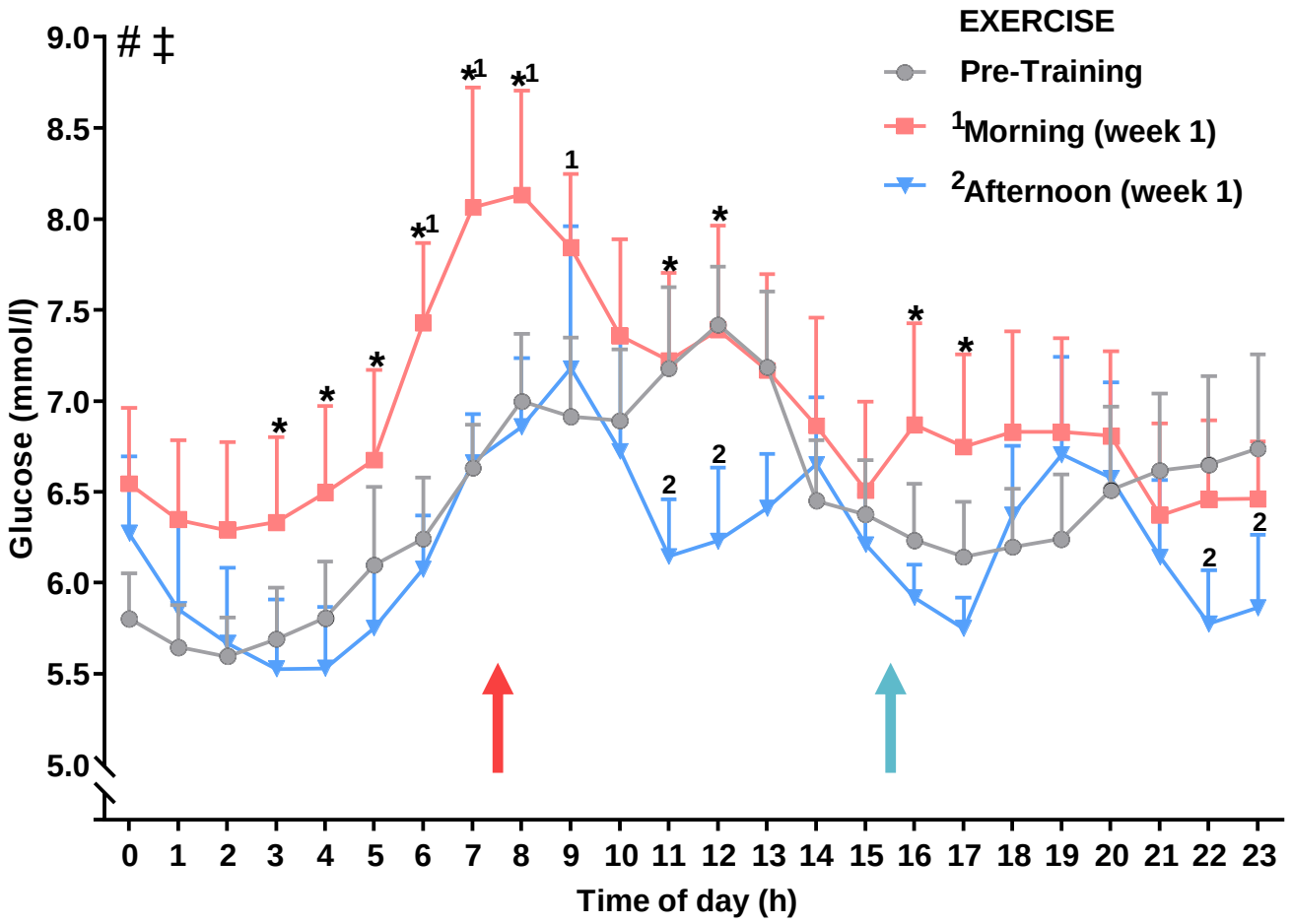
Study design



- CGM
- Blood sampling
- Biopsy (muscle / SAT)
- HIIT

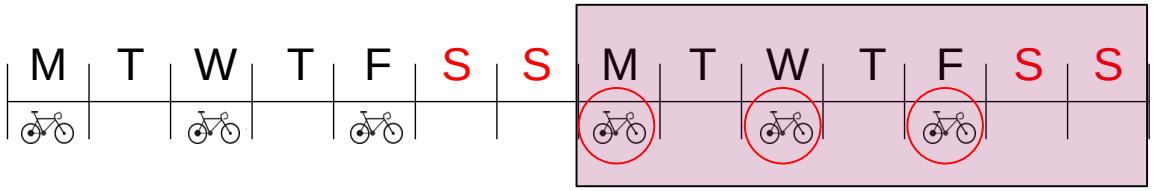
- Morning vs Afternoon high-intensity interval training (HIT)
- Continuous glucose monitor (CGM) based blood glucose levels
- Type 2 diabetes (T2D)
- “Free-living” setting

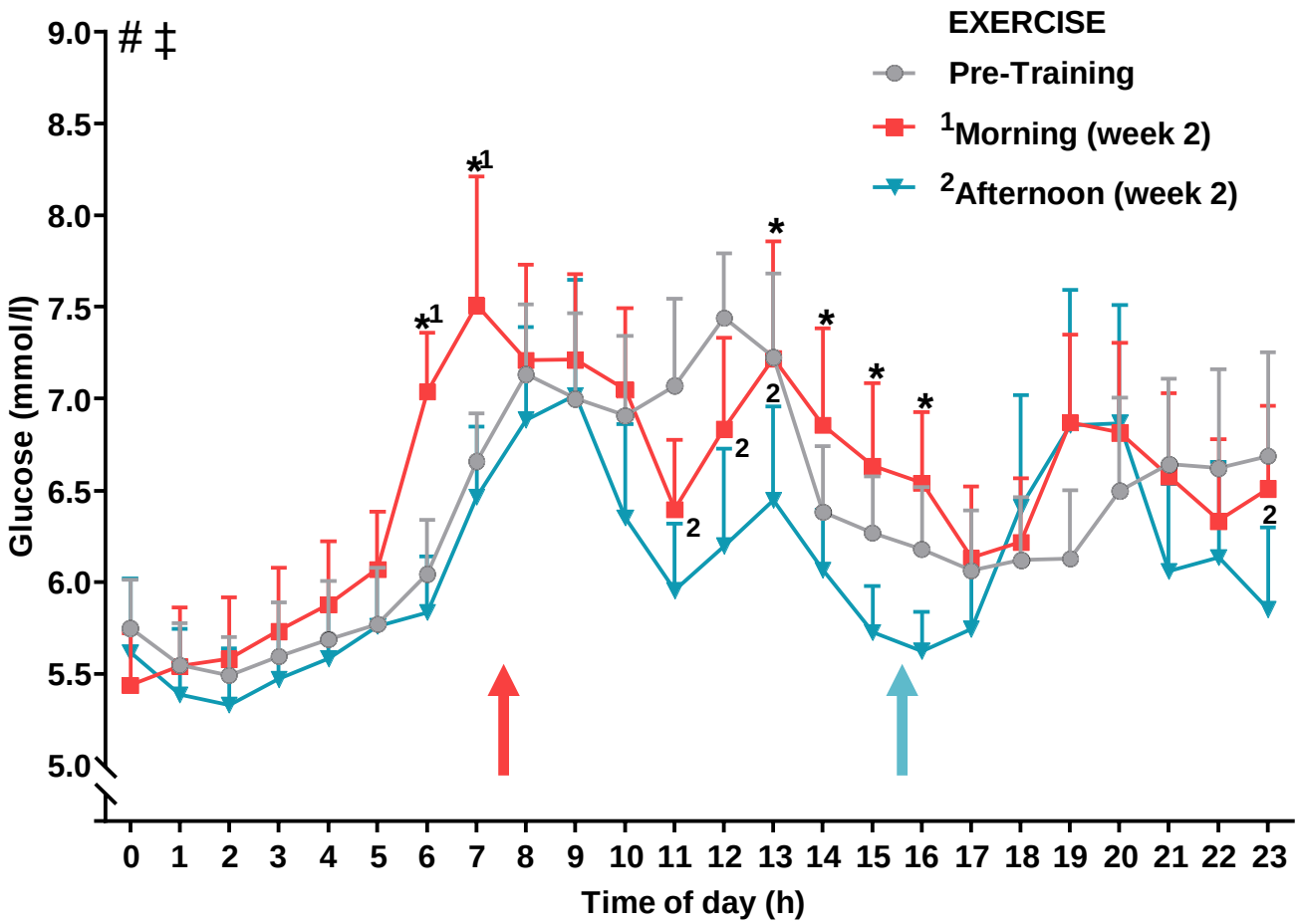




3-day mean, training, week-1

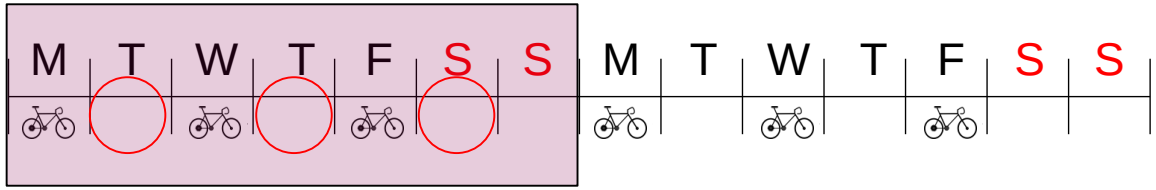
Savikj*, Gabriel* et al., *Diabetologia* (2019)

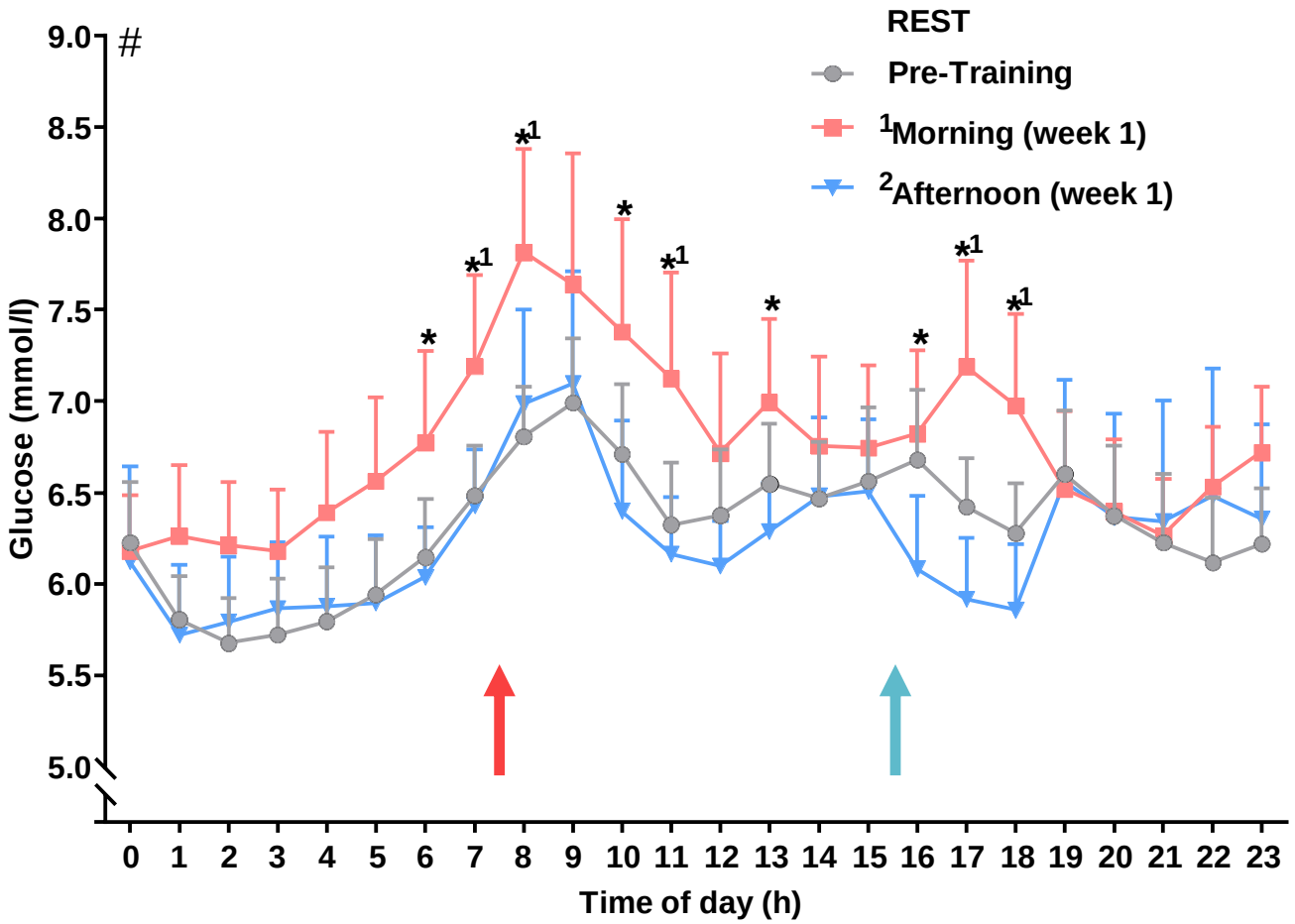




3-day mean, training, week-2

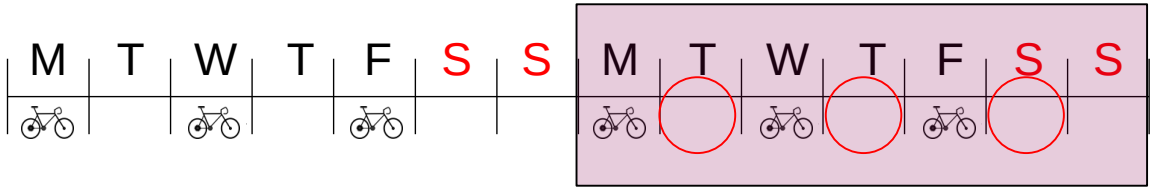
Savikj*, Gabriel* et al., *Diabetologia* (2019)

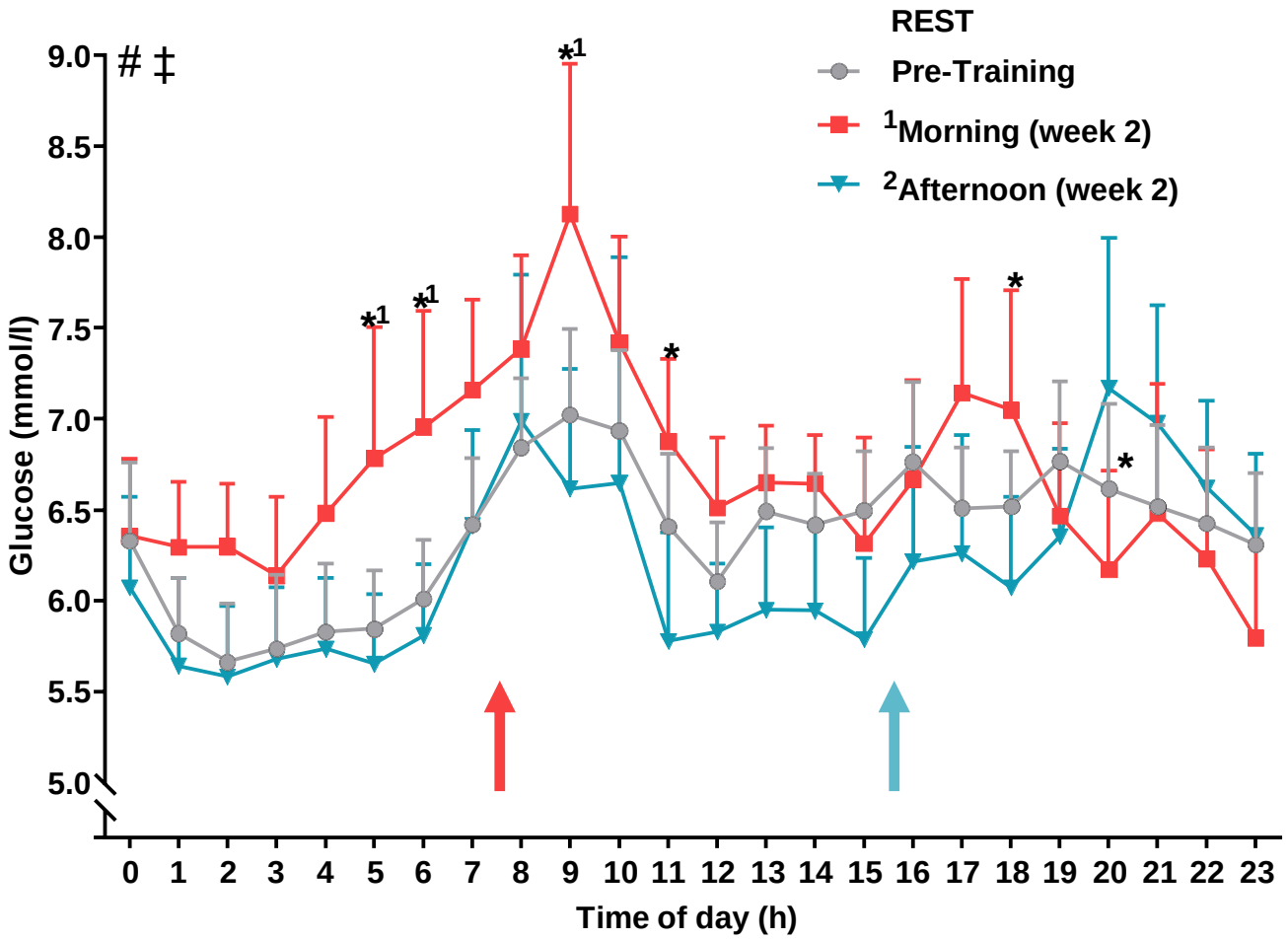




3-day mean, rest, week-1

Savikj*, Gabriel* et al., *Diabetologia* (2019)



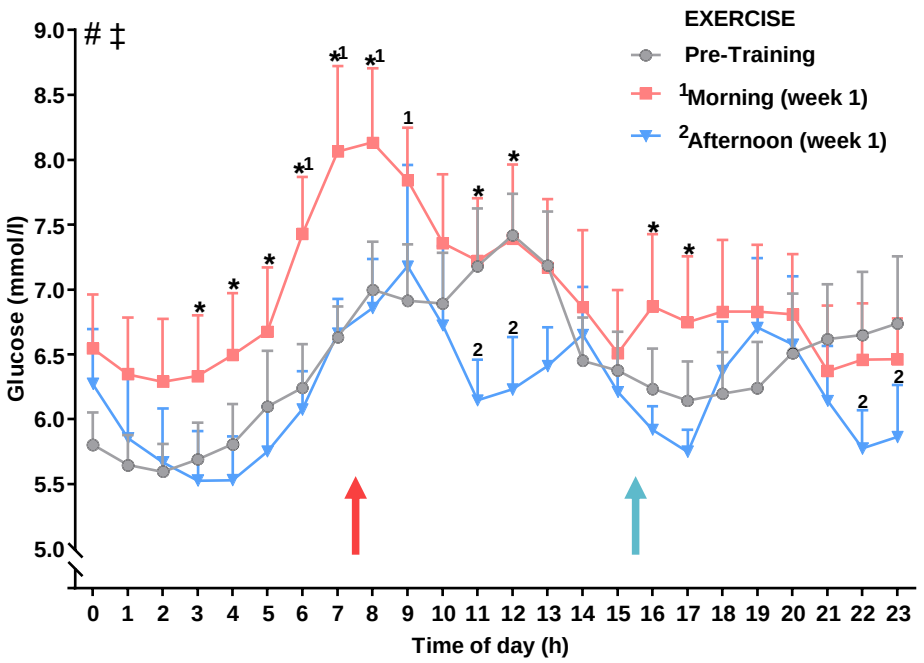


3-day mean, rest, week-2

Savikj*, Gabriel* et al., *Diabetologia* (2019)

Summary

- Afternoon HIT ↘ blood glucose
- Morning HIT ↗ blood glucose
- Mechanism – requires further investigation



Savikj*, Gabriel* et al., *Diabetologia* (2019)

Acknowledgments

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- Astrid Basse
- Ali Altinas

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- Simon Platt

Juleen Zierath

Anna Krook

Jonathon Smith

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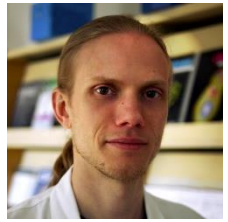

Nicolas Pillon

Karolinska Institutet

novo nordisk fonden

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Wenner-Gren Stiftelserna

BIOCHEMICAL SOCIETY