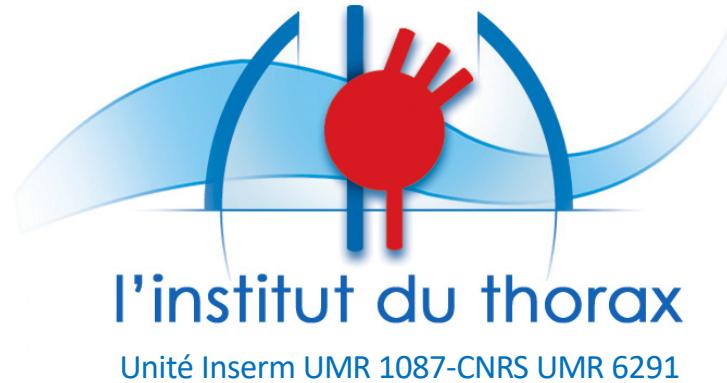


# Rythmes circadiens et Maladies métaboliques



**Pr David JACOBI, PUPH Nutrition**

# **PLAN**

## **PARTIE 1 : physiologie**

1. Introduction sur les rythmes circadiens

## **PARTIE 2 : pathologie**

1. Effet expérimental du régime gras
2. Décalage des rythmes et risque métabolique

## **PARTIE 3 : étude d'article**

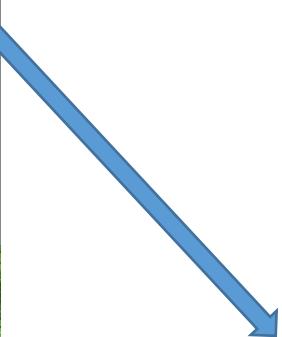


# Le rythme “naturel” humain est de ???

- 1962 : Michel Siffre passe 61 jours sous terre dans le gouffre de Scarasson (Alpes franco-italiennes)
- Emerge le 17 septembre en pensant être le 20 aout
- Mais a garde un rythme endogène de... ~ 24 h

## Marqueurs bio du rythme circadien des mammifères

- Mélatonine basse le jour
- Température centrale minimum at ~5:00, ~2 h avant le lever
- Cortisol plasmatique



## Rythmes circadiens

- 1. Processus bio. endogène avec période ~24 h en libre cours**
  - Persiste en conditions constantes (ex : obscurité continue)
  - A distinguer des rythmes diurnes non endogènes



# Rythmes circadiens

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# Rythmes circadiens

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  - Persiste en conditions constantes (ex : obscurité continue)
  - A distinguer des rythmes diurnes non endogènes
- 2. Compensation pour la température : dans une frange de températures physiologiques**
- 3. Entrainable**
  - Remis à zéro par un stimulus externe (ou Zeitgeber)

# Nycthéméral OU diurne OU circadien ?



## ***Nycthéméral (nycthémère)***

- Grec *nukhthēmeron* : *nuktos* « nuit» et *hēmera* « jour»
- Lie à un cycle physiologique de 24 heures consécutives

## ***Diurne***

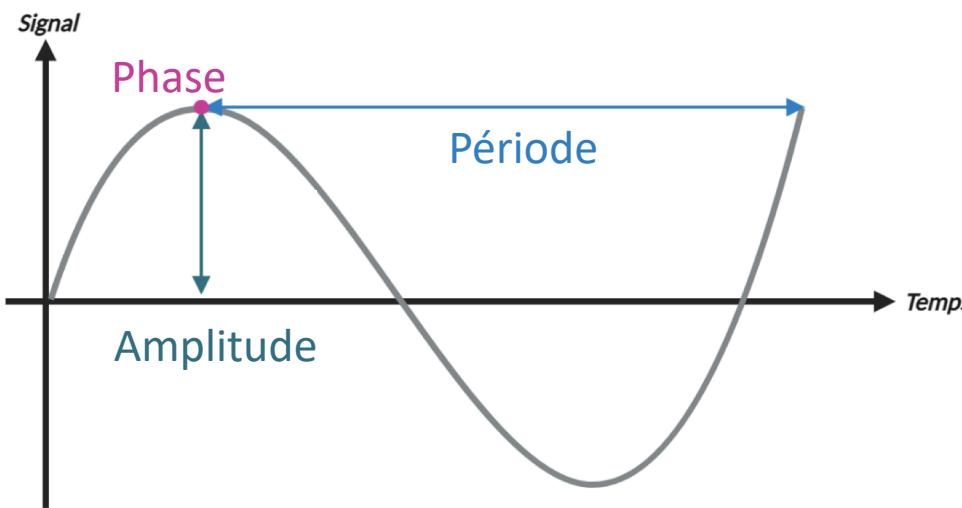
latin *diurnus* « qui se fait tous les jours »

1. tous les jours
2. de ou durant le jour (opposé de nocturne)

## ***Circadien***

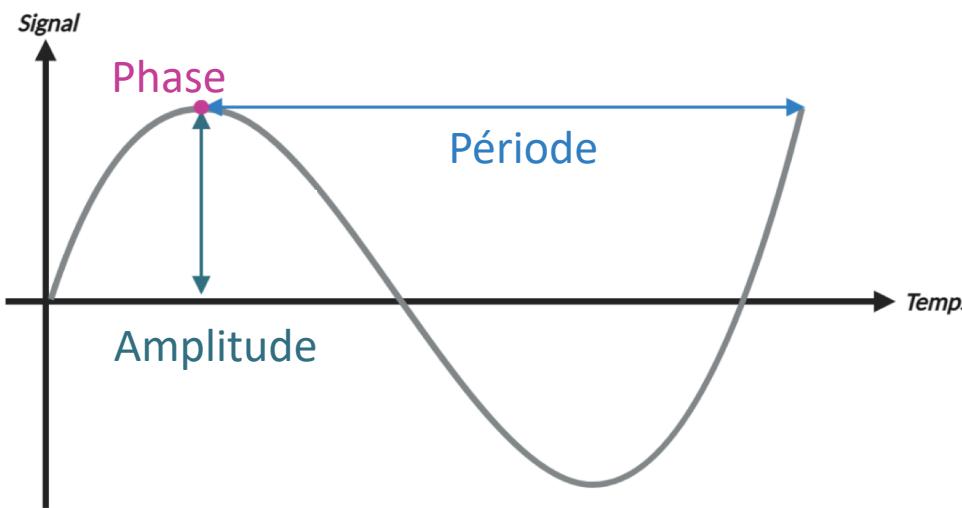
- latin *circa diem*, « environ un jour »

# Rythmes biologiques et horloge circadienne

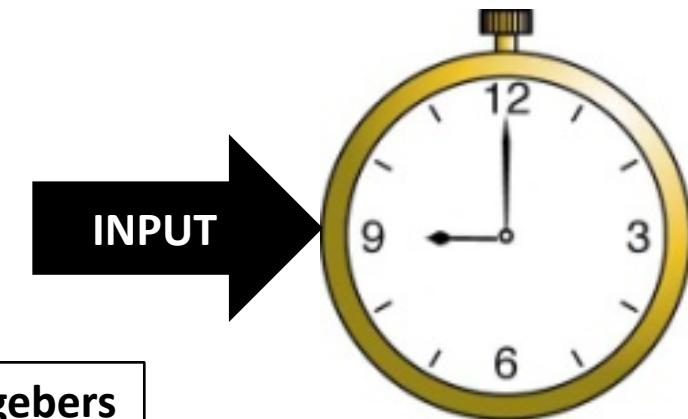


Horloge circadienne

# Rythmes biologiques et horloge circadienne



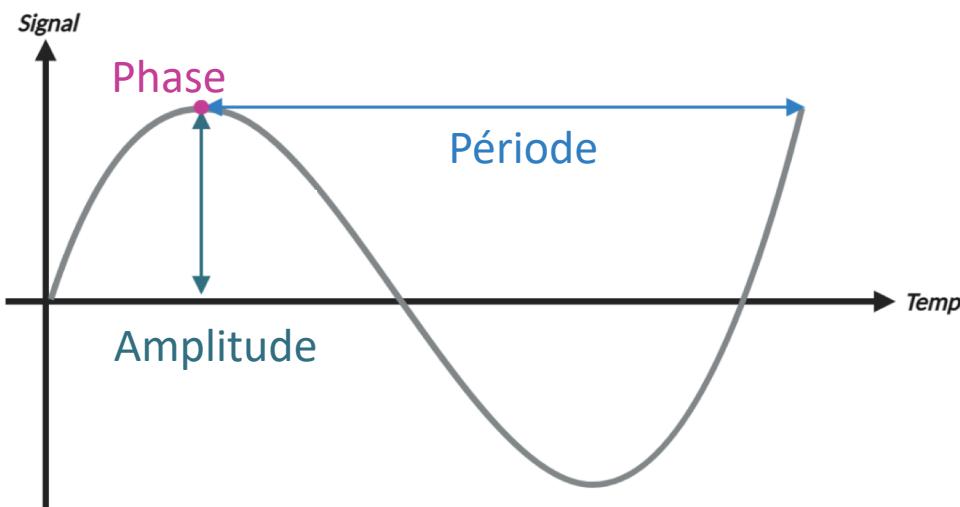
Lumière  
Alimentation  
Température



Synchroniseurs = **Zeitgebers**

**Horloge circadienne**

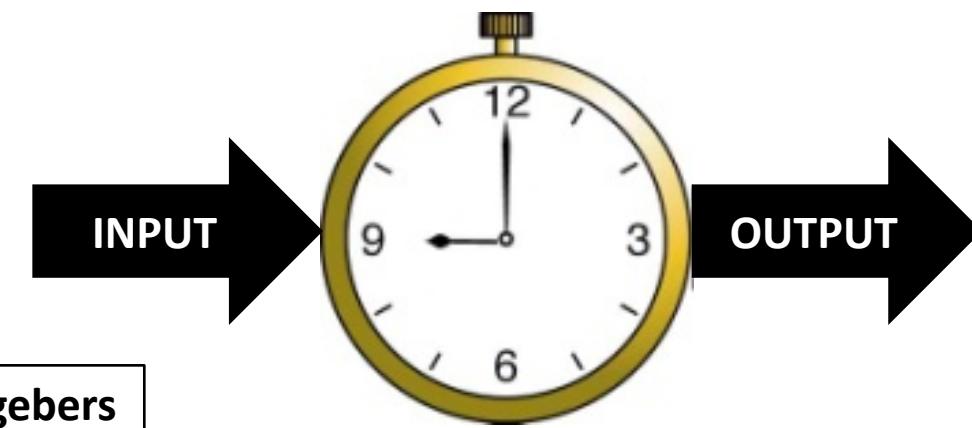
# Rythmes biologiques et horloge circadienne



Lumière  
Alimentation  
Température

INPUT

Synchroniseurs = Zeitgebers

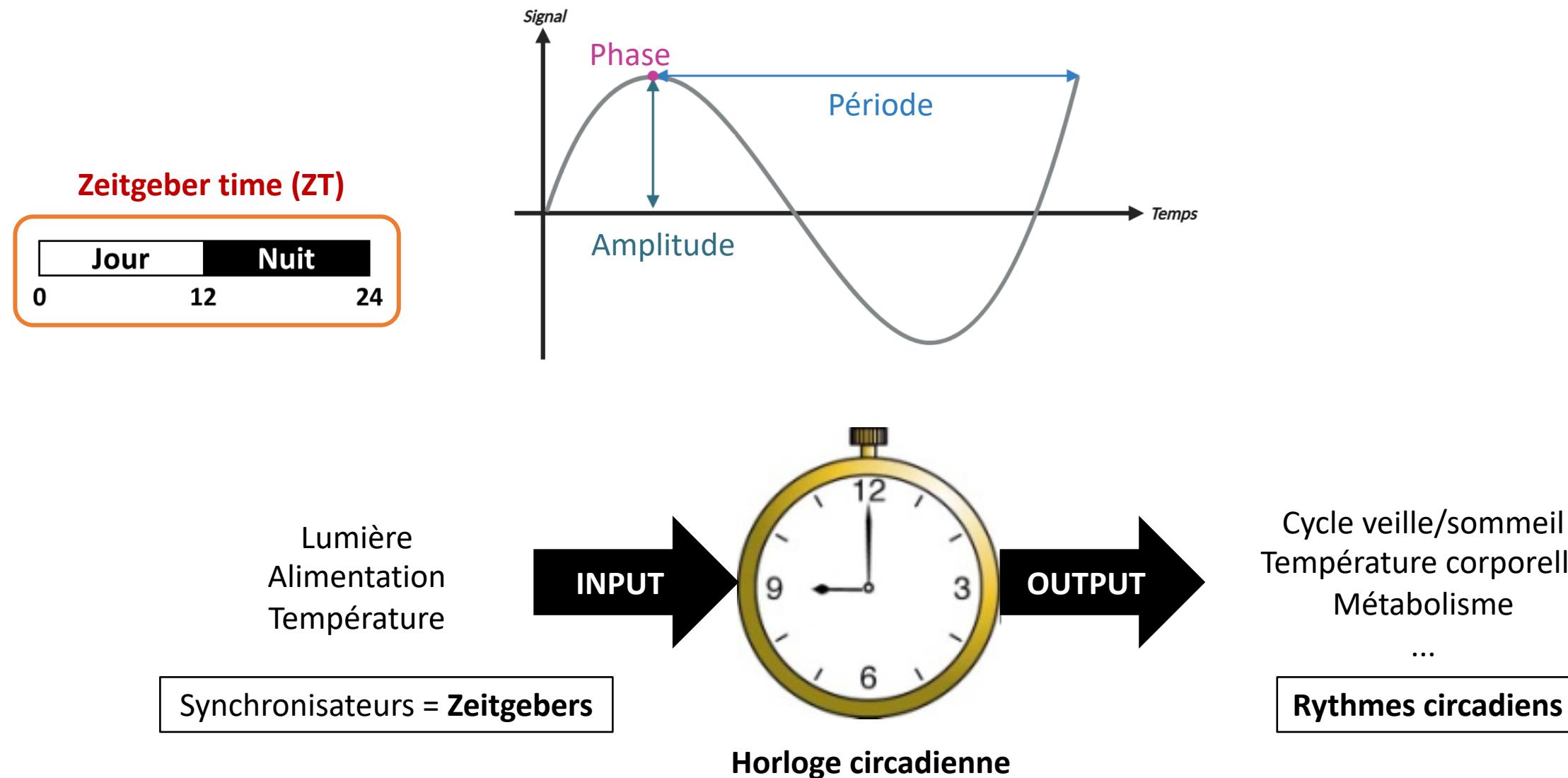


Horloge circadienne

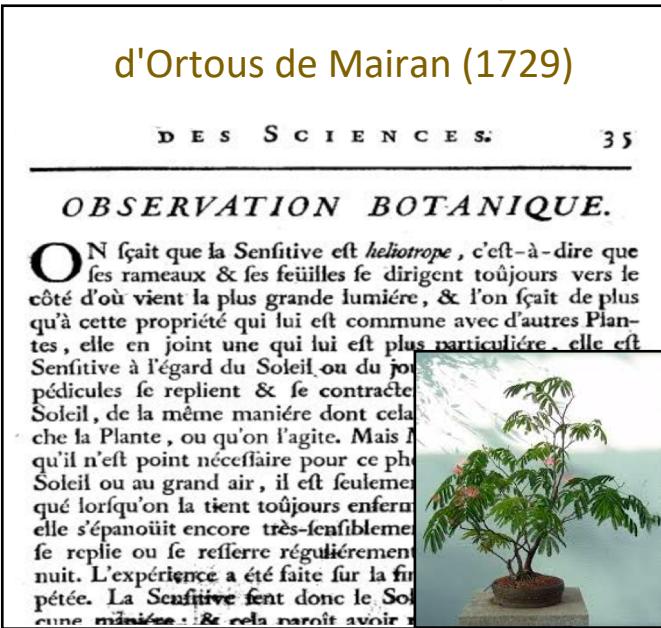
Cycle veille/sommeil  
Température corporelle  
Métabolisme  
...

Rythmes circadiens

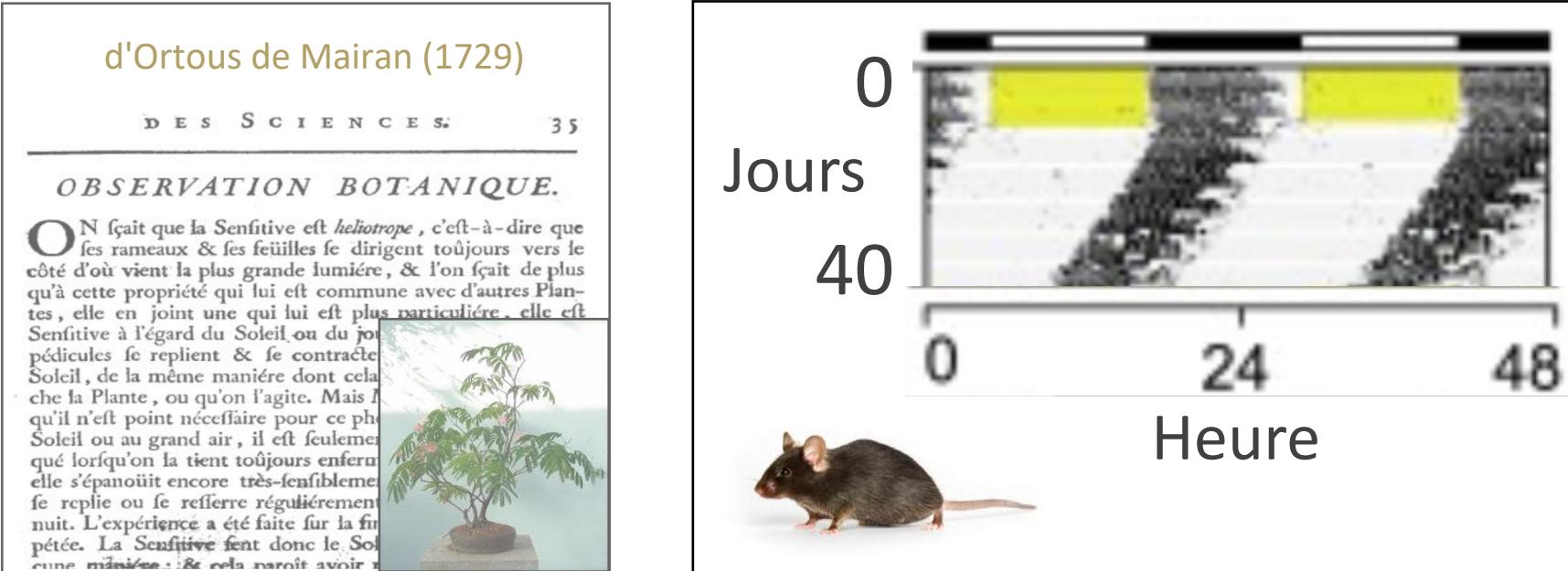
# Rythmes biologiques et horloge circadienne



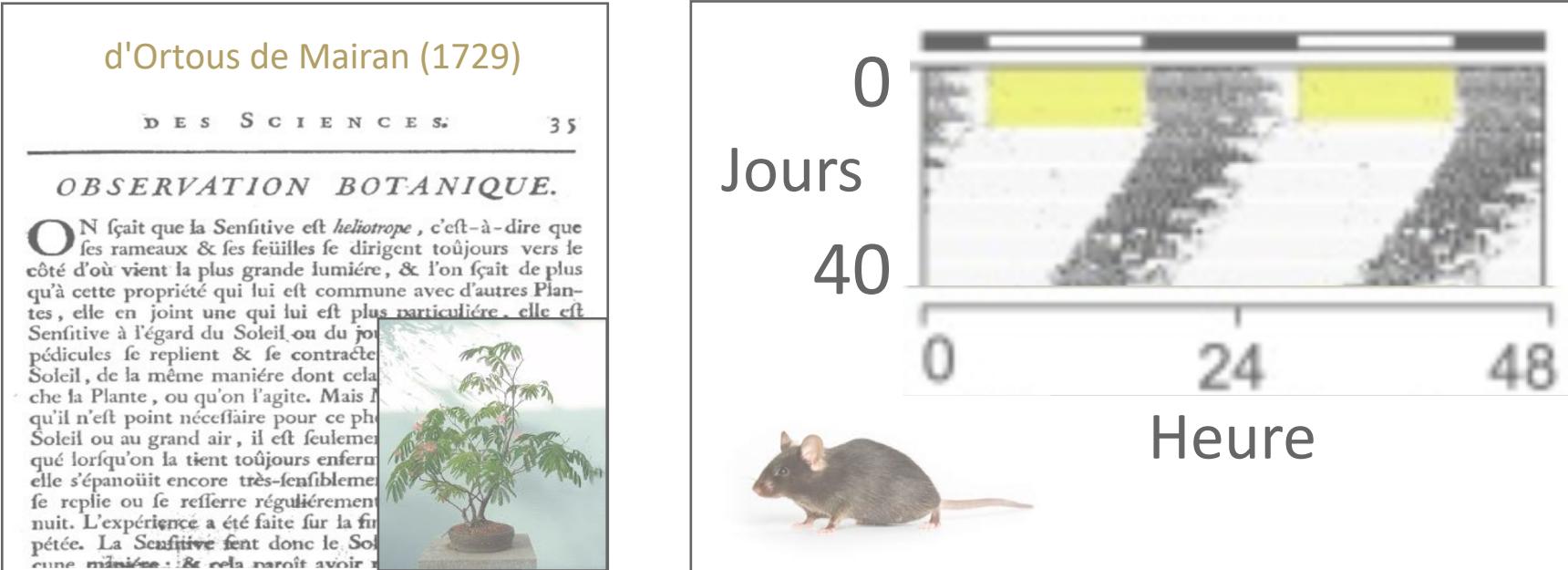
# Les rythmes biologiques endogènes



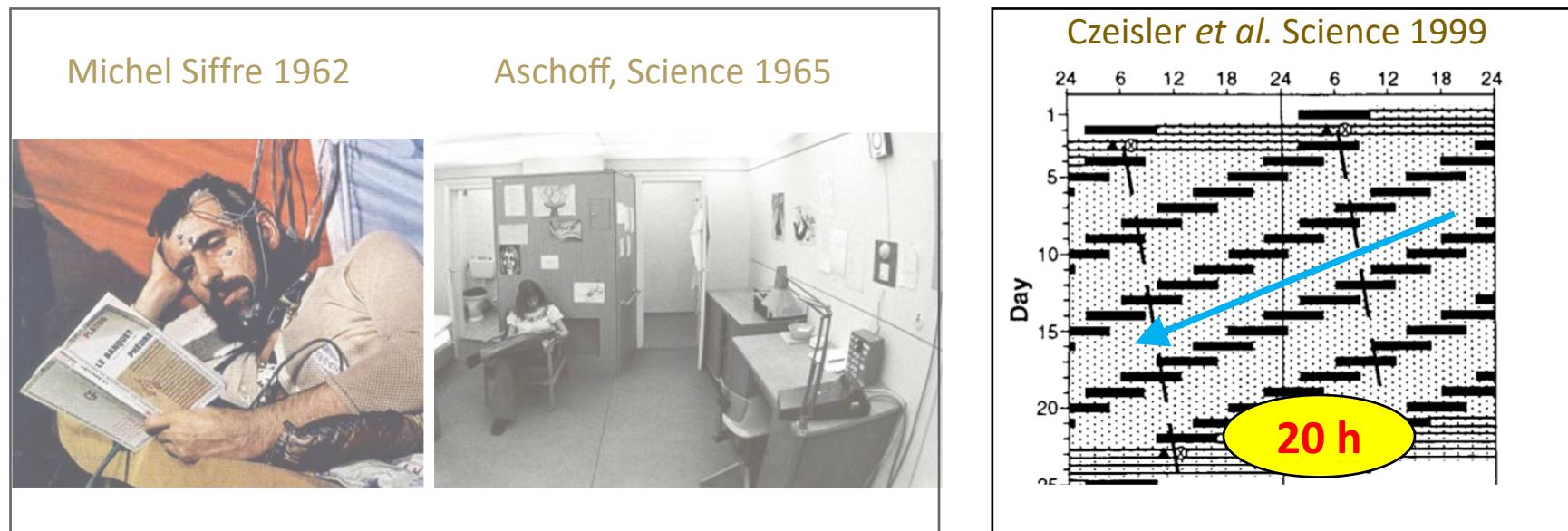
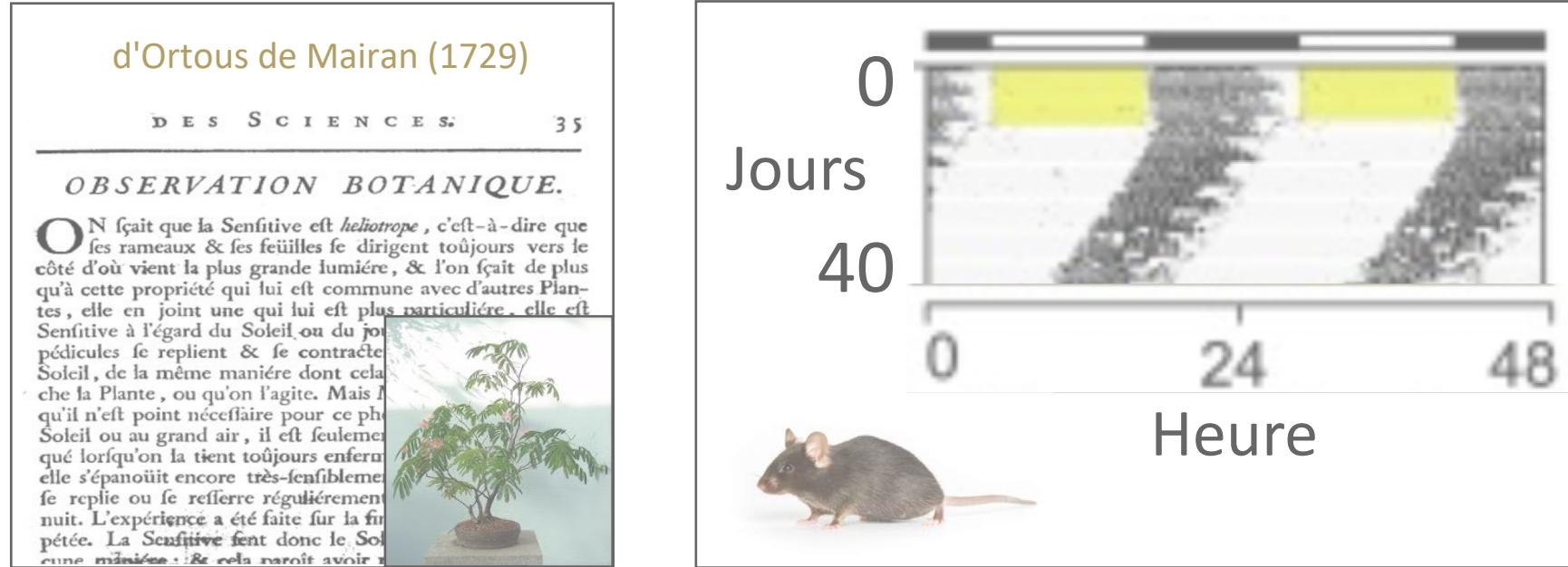
# Les rythmes biologiques endogènes



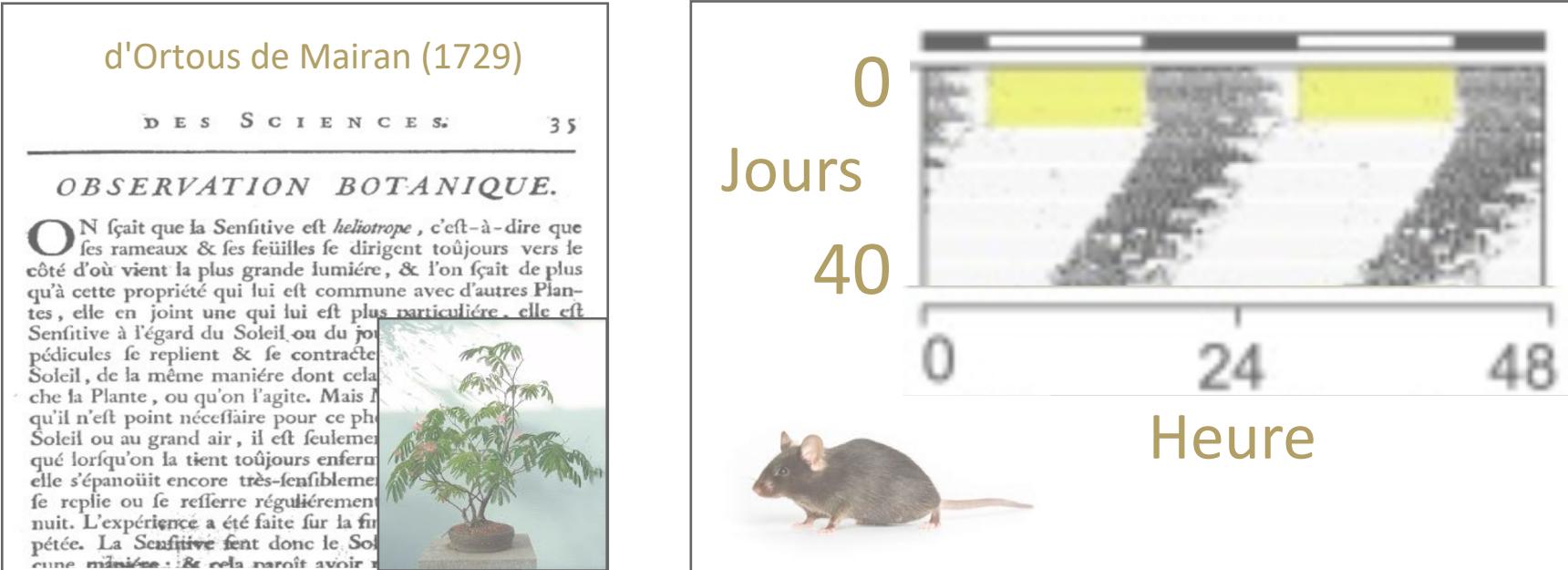
# Les rythmes biologiques endogènes



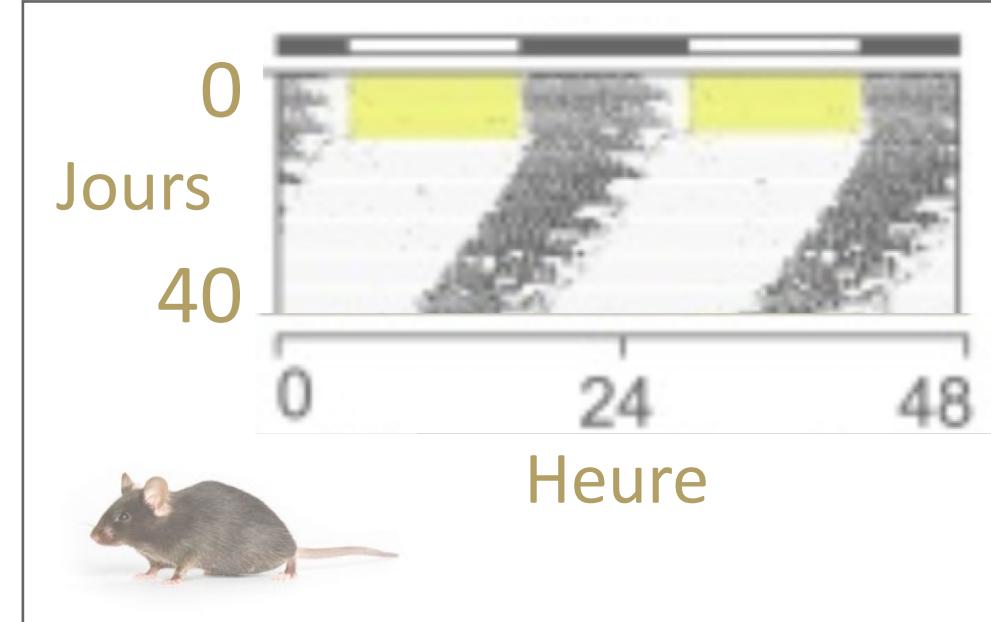
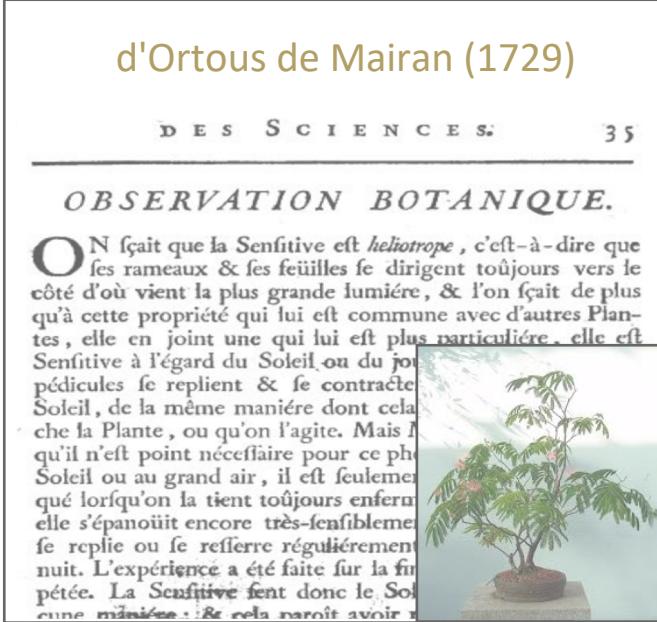
# Les rythmes biologiques endogènes



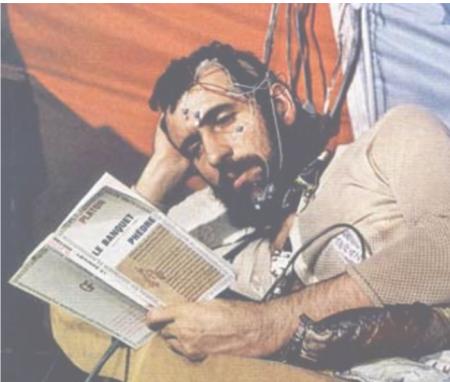
# Les rythmes biologiques endogènes



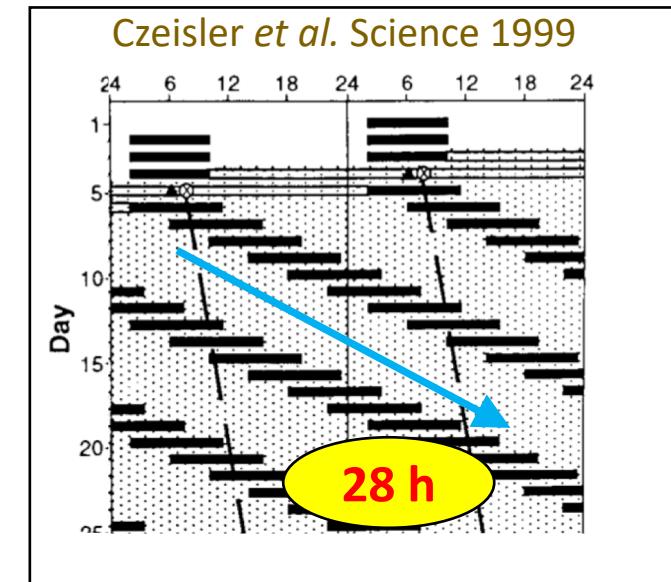
# Les rythmes biologiques endogènes



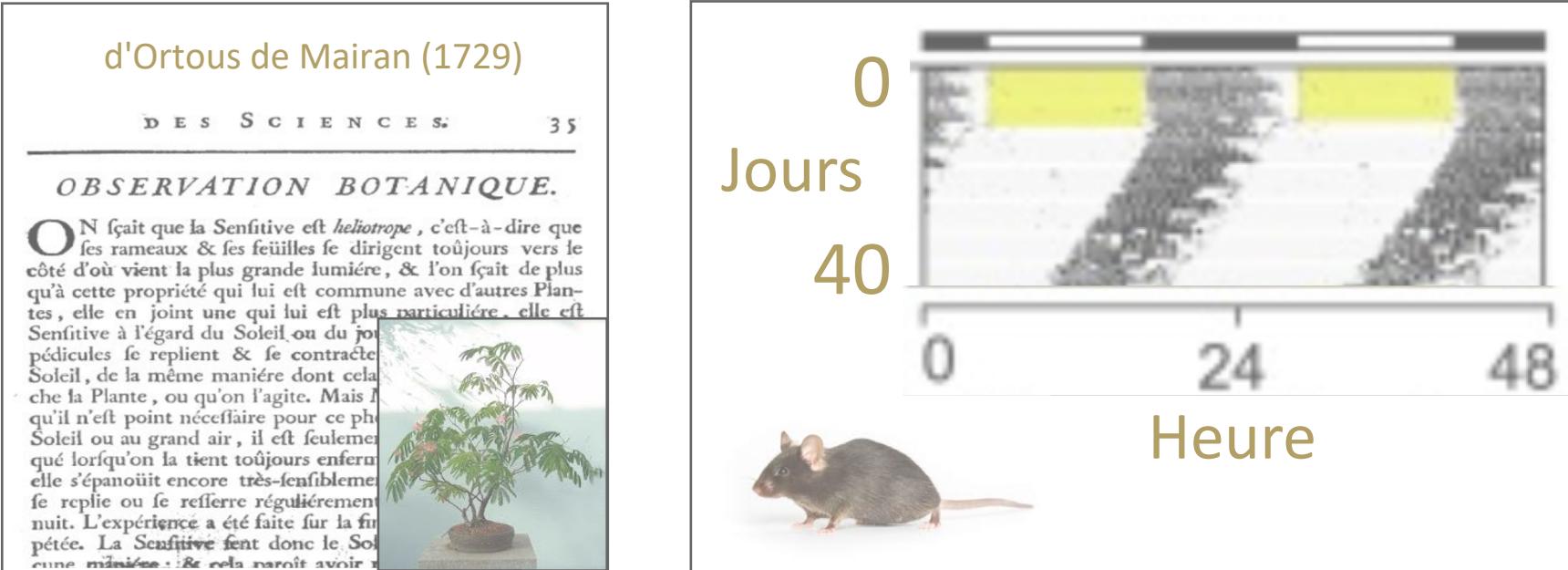
Michel Siffre 1962



Aschoff, Science 1965



# Les rythmes biologiques endogènes



# Les rythmes biologiques endogènes

# d'Ortous de Mairan (1729)

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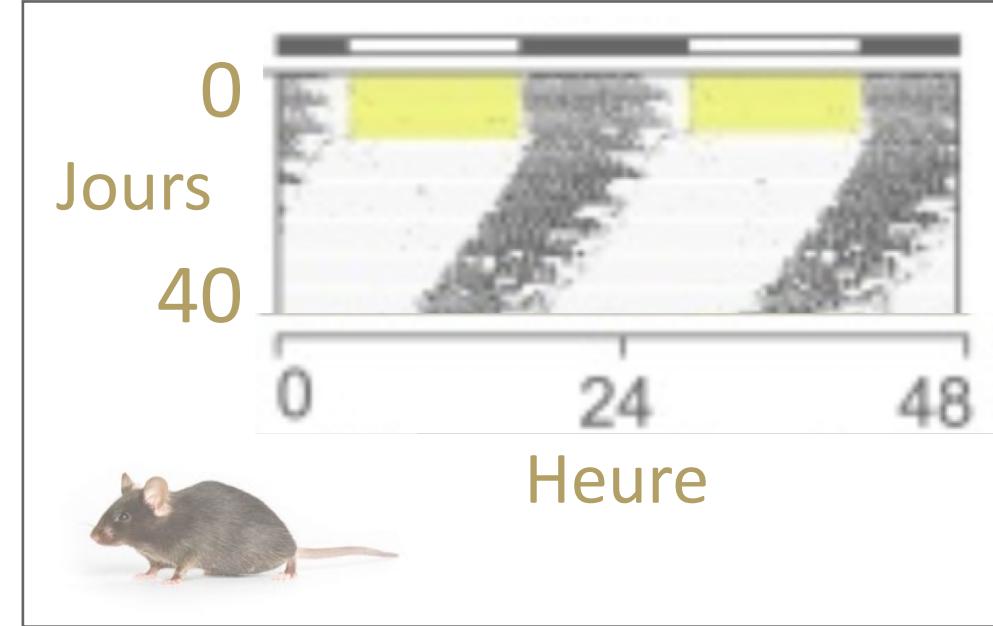
D E S   S C I E N C E S.

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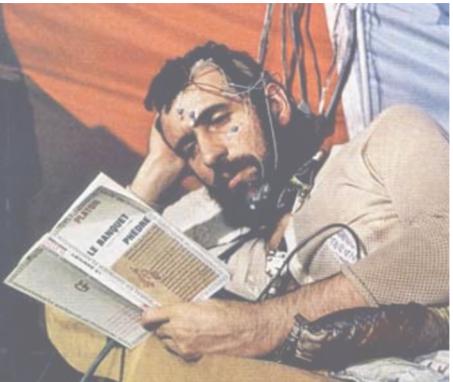
## 35

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### *OBSERVATION BOTANIQUE.*



Michel Siffre 1962



Aschoff, Science 1965



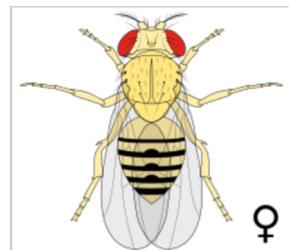
Czeisler *et al.* Science 1999

## Période

	Temp	Mélat.	Cortisol
n	24:10	24:11	24:11
	00:07	00:08	00:09

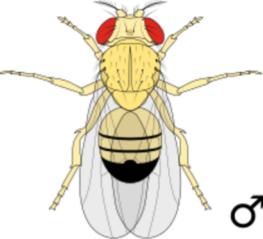
# Konopka RJ and Benzer S, PNAS 1971

*Drosophila melanogaster*  
(mouche des fruits)

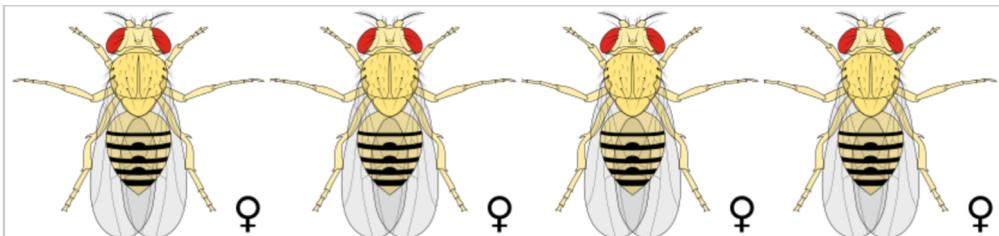


XX

mutagenèse



XY



XX

24 h

XX

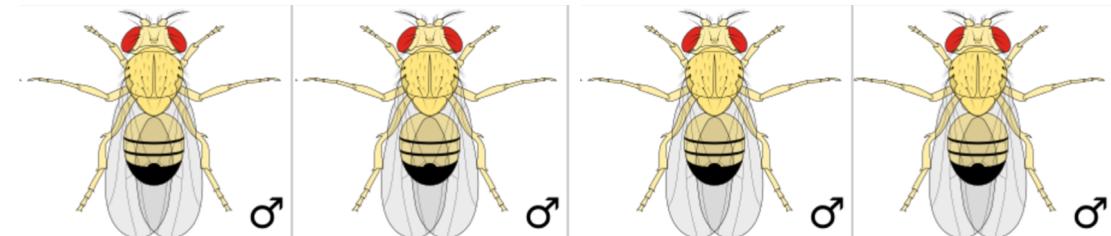
24 h

XX

24 h

XX

24 h



XY

24 h

XY

arrythmicité

XY

19 h

XY

28 h

→ gène Per (period) sur le chromosome X

# Nobel 2017, physiologie et médecine



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Elmehed  
**Jeffrey C. Hall**



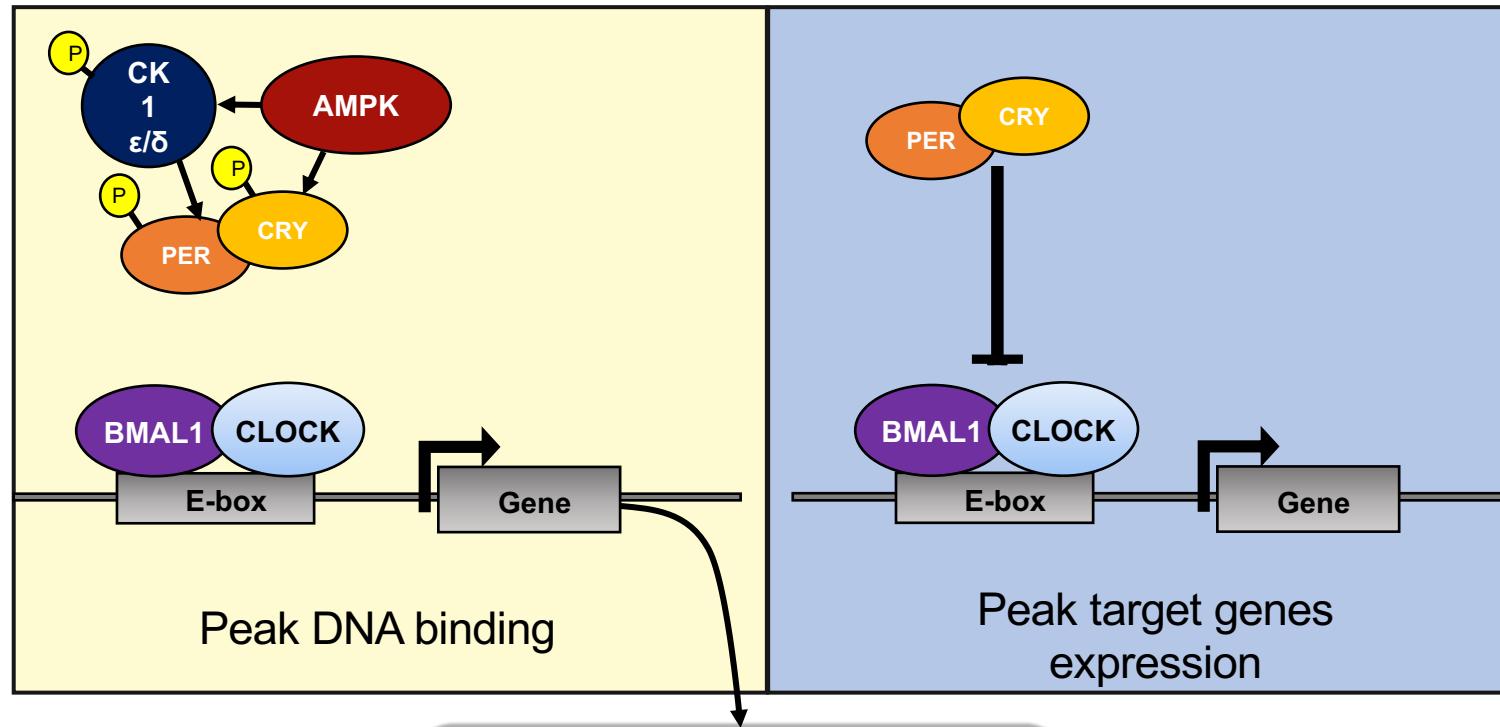
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Elmehed  
**Michael Rosbash**



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Elmehed  
**Michael W. Young**

# L'“horloge circadienne” et comment elle tourne

Les engrenages de la boucle de rétroaction transcription-traduction

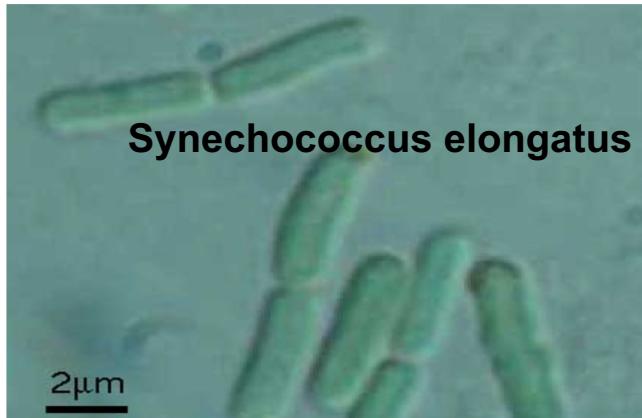


Examples of regulated genes

Per1,2,3 Cry1,2	Ror Rev-erb Ppara/ $\gamma/\delta$	Srebp-1 G6pc Gck
--------------------	--	------------------------

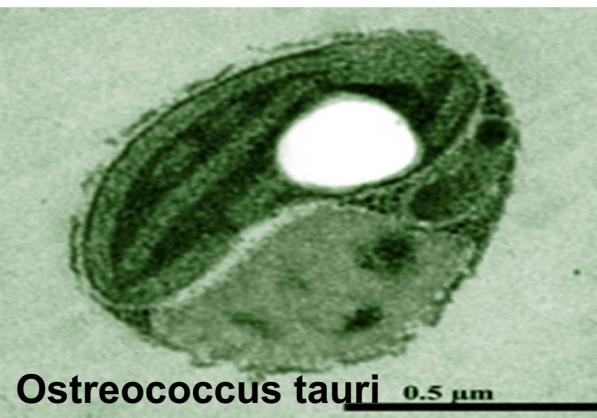
# Les autres rythmes biologiques circadiens

## Procaryotes



Cyanobactérie procaryote  
Phosphorylation de KaiC  
Tomita, Science 2005

## Eukaryotes unicellulaires



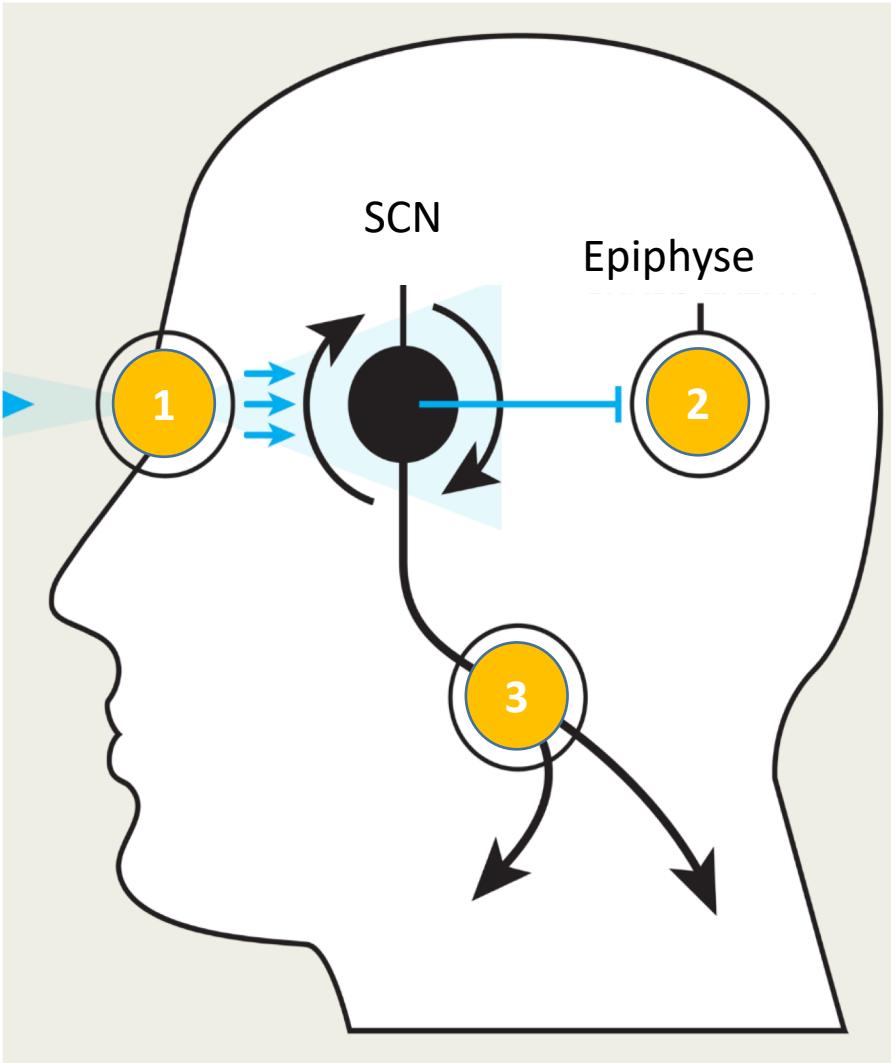
Protiste  
Couple Redox  
O'Neill, Nature 2011

## Eukaryotes multicellulaires

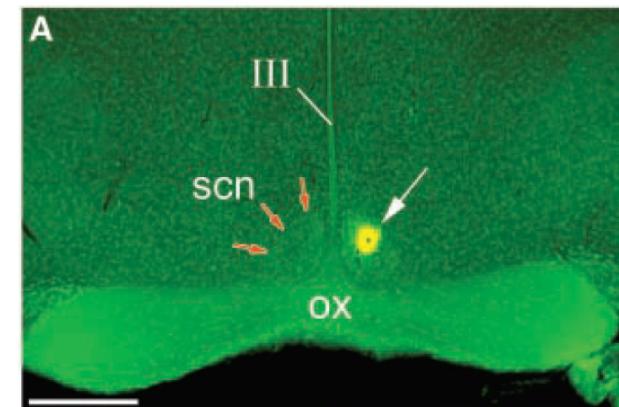


Couple Redox  
O'Neill & Reddy, Nature 2011

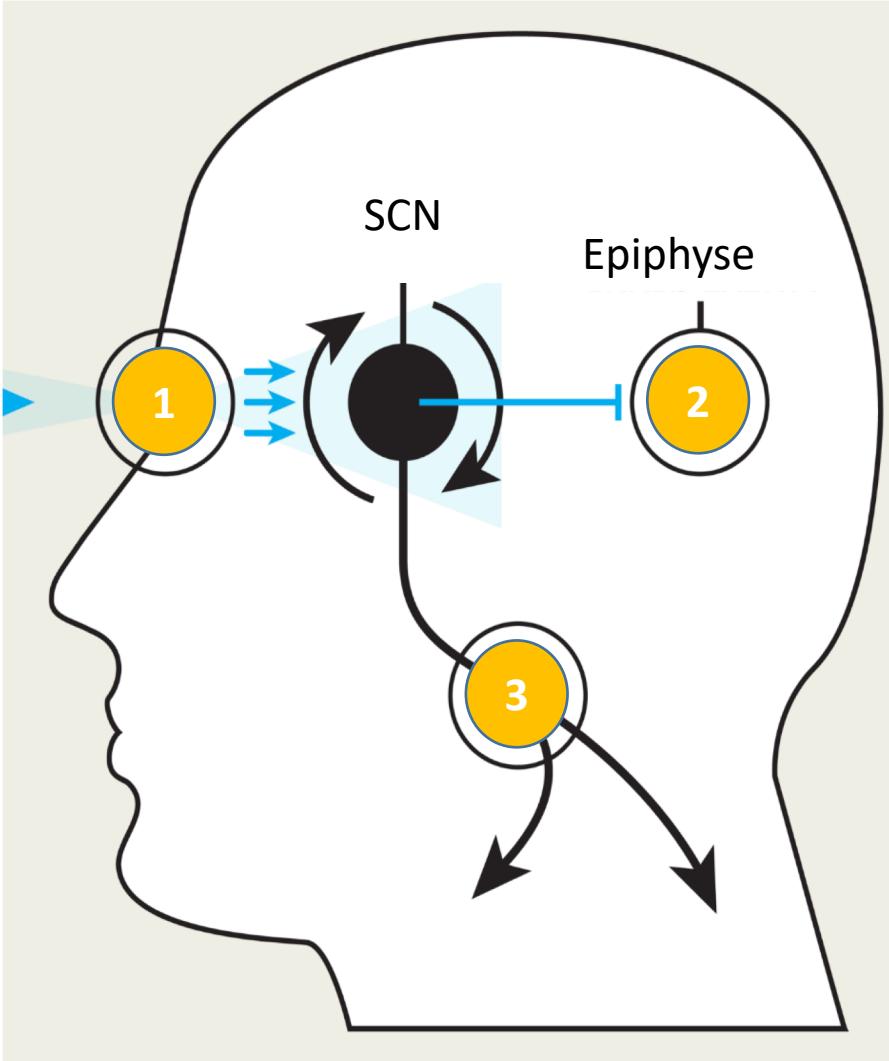
# Horloges centrale et périphériques



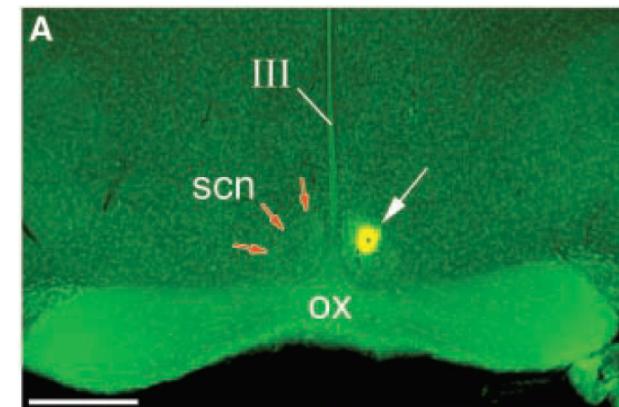
- Origine hypothalamique des rythmes (PNAS 1972)
- Noyaux suprachiasmatiques (PNAS 1979)
- Cellules ganglionnaires rétiniennes à mélanopsine (Science 2002)



# Horloges centrale et périphériques

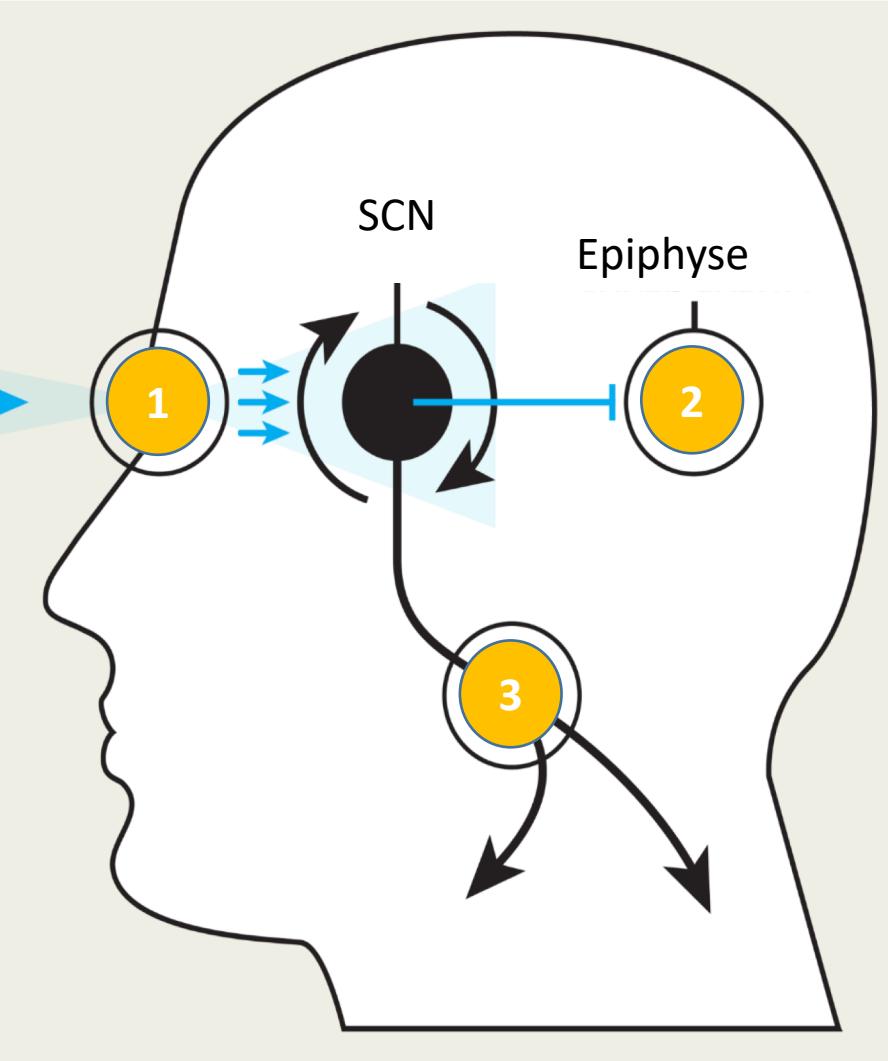


- Origine hypothalamique des rythmes (PNAS 1972)
- Noyaux suprachiasmatiques (PNAS 1979)
- Cellules ganglionnaires rétiniennes à mélanopsine (Science 2002)

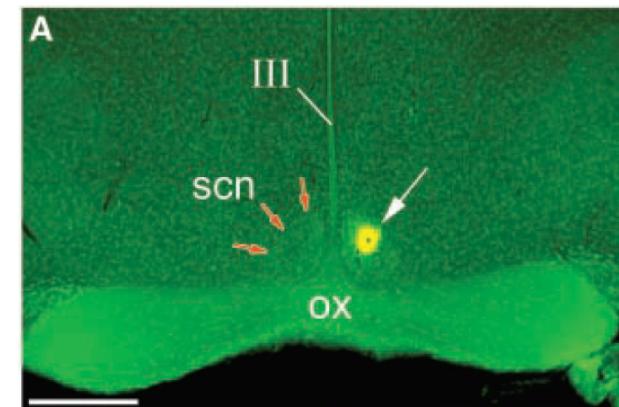


- Entrainment of the circadian clock in the liver by feeding (Science 2001)

# Horloges centrale et périphériques



- Origine hypothalamique des rythmes (PNAS 1972)
- Noyaux suprachiasmatiques (PNAS 1979)
- Cellules ganglionnaires rétiniennes à mélanopsine (Science 2002)



- Entrainment of the circadian clock in the liver by feeding (Science 2001)
- Persistent circadian oscillations in mouse peripheral tissues (PNAS 2004)

# Pourquoi des rythmes circadiens ?

## Hypothèse de l'avantage extrinsèque

1. Conserver un repère temporel sans indications extérieures
2. Réponse plus efficace aux challenges environnementaux grâce à l'anticipation  
→ programmation des fonctions biologiques à des moments favorables de la journée

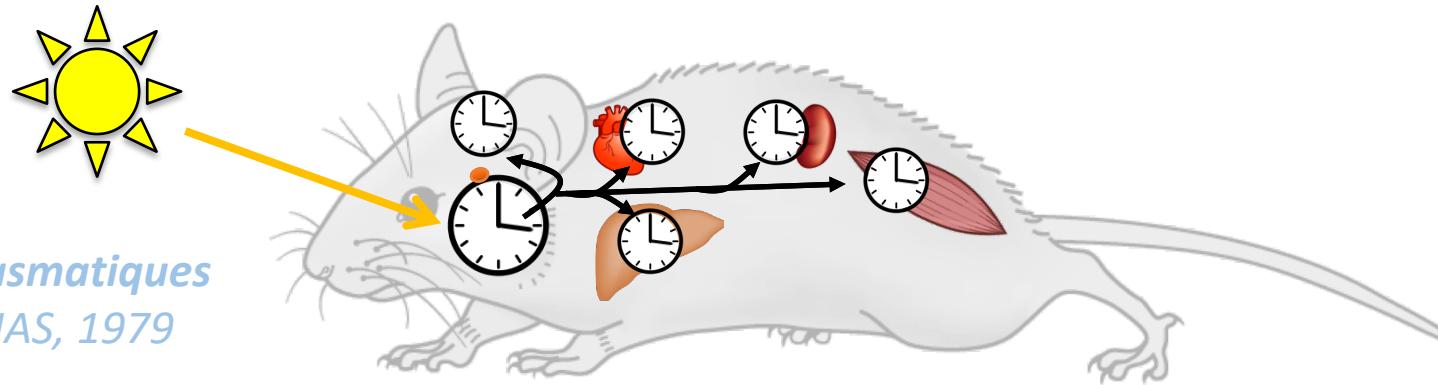
## Hypothèses de l'avantage intrinsèque

1. Organisation circadienne multi oscillatoire en phases mutuelles (cellule, tissu, organisme)  
→ coordination temporelle de la physiologie

# L'horloge centrale est synchronisée par la lumière

*Oscillations persistantes dans les tissus périphériques*  
Yoo et al., PNAS, 2004

*Noyaux suprachiasmatiques*  
Inouye et al., PNAS, 1979

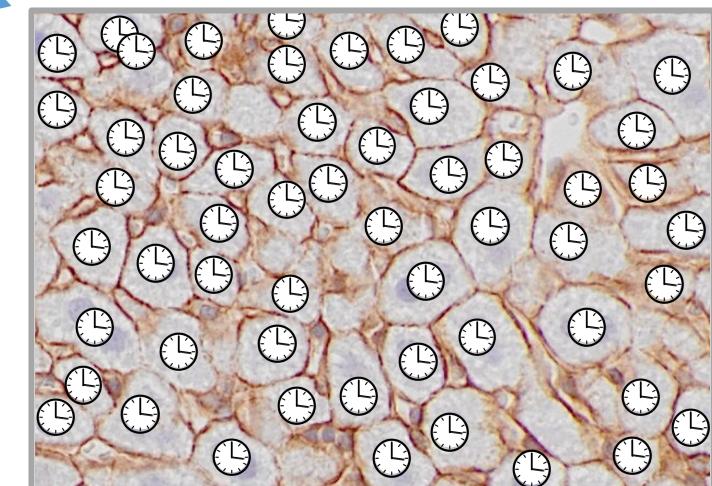
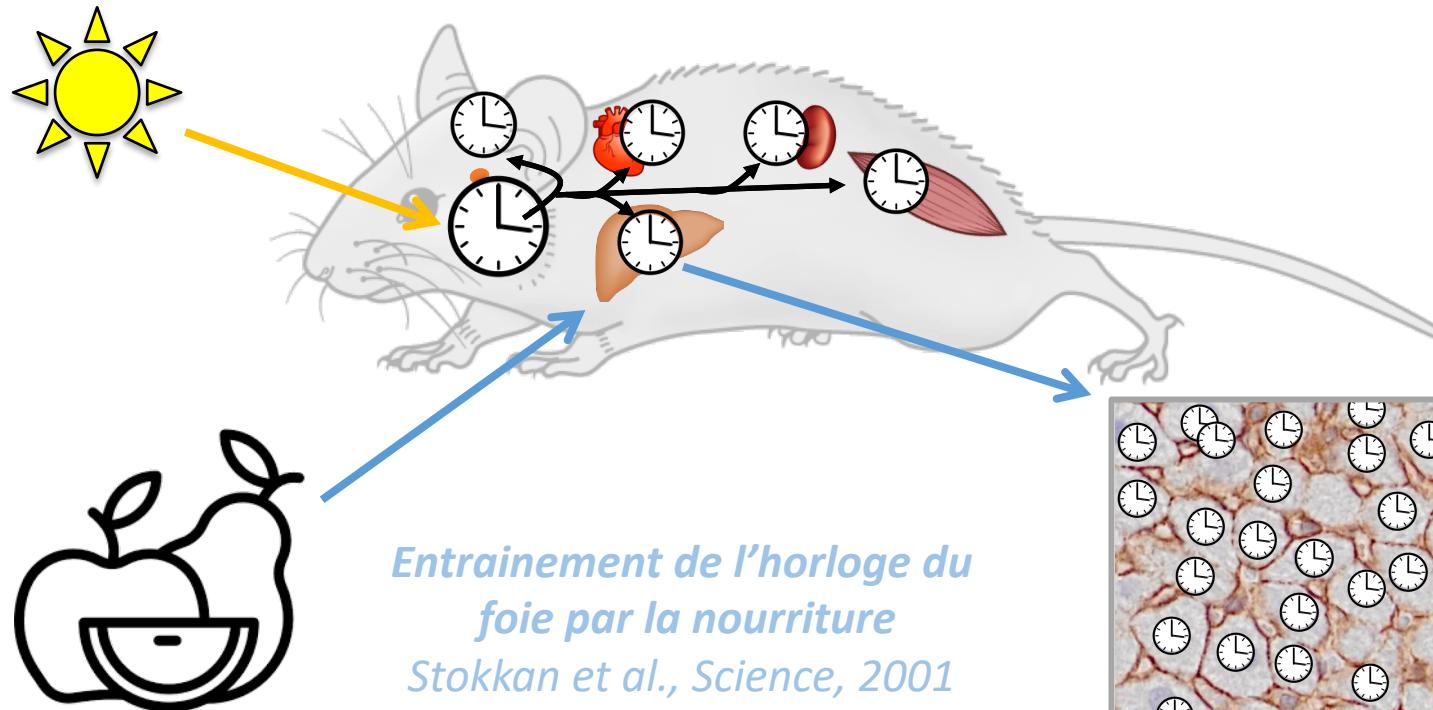


*Cellules ganglionnaires à melanopsine*  
Panda et al., Science, 2002

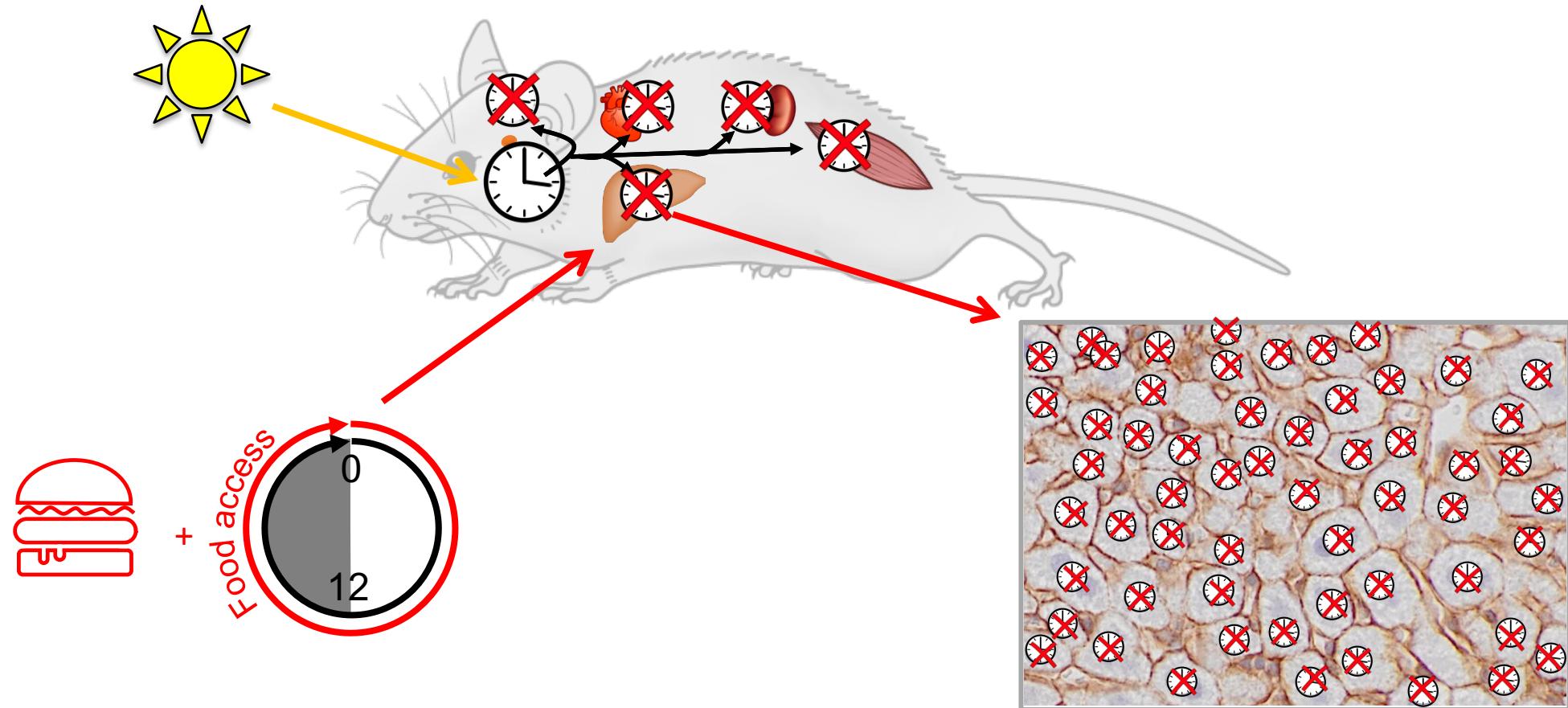
# Les horloges périphériques sont synchronisées par les prises alimentaires

*Oscillations persistantes dans les tissus périphériques*

*Yoo et al., PNAS, 2004*



# Un régime *High Fat* (HF) désynchronise les horloges périphériques

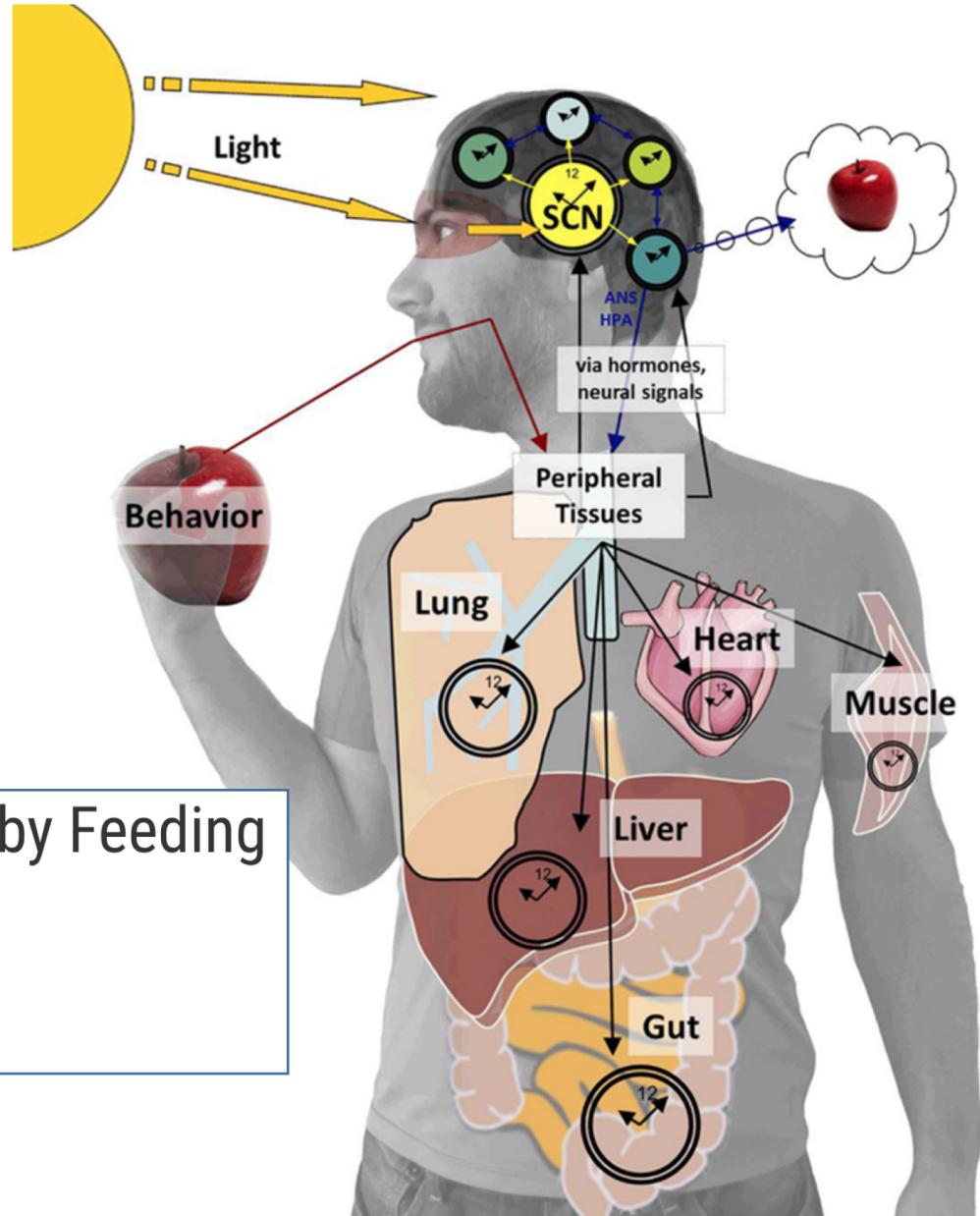


# Horloge biologiques des mammifères → les horloges périphériques

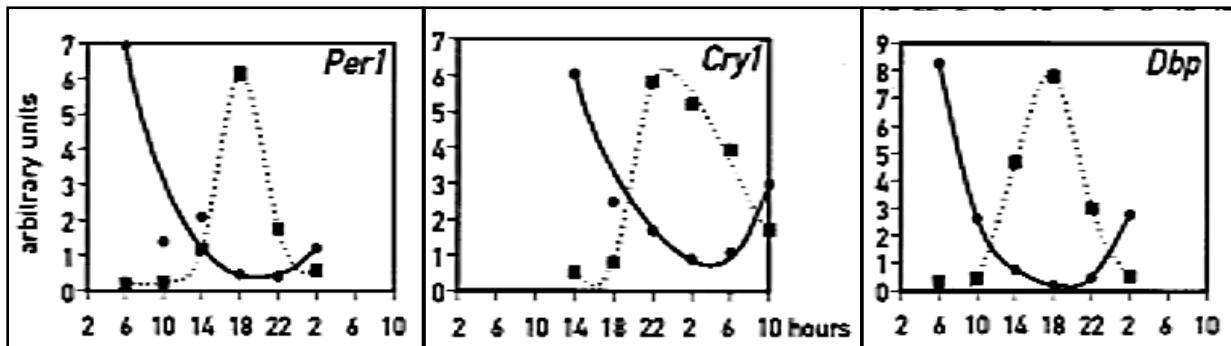
Entrainment of the Circadian Clock in the Liver by Feeding

Karl-Arne Stokkan<sup>1,2,\*</sup>, Shin Yamazaki<sup>1,\*</sup>, Hajime Tei<sup>3</sup>, Yoshiyuki Sakaki<sup>3</sup>, Michael Menaker<sup>1,†</sup>

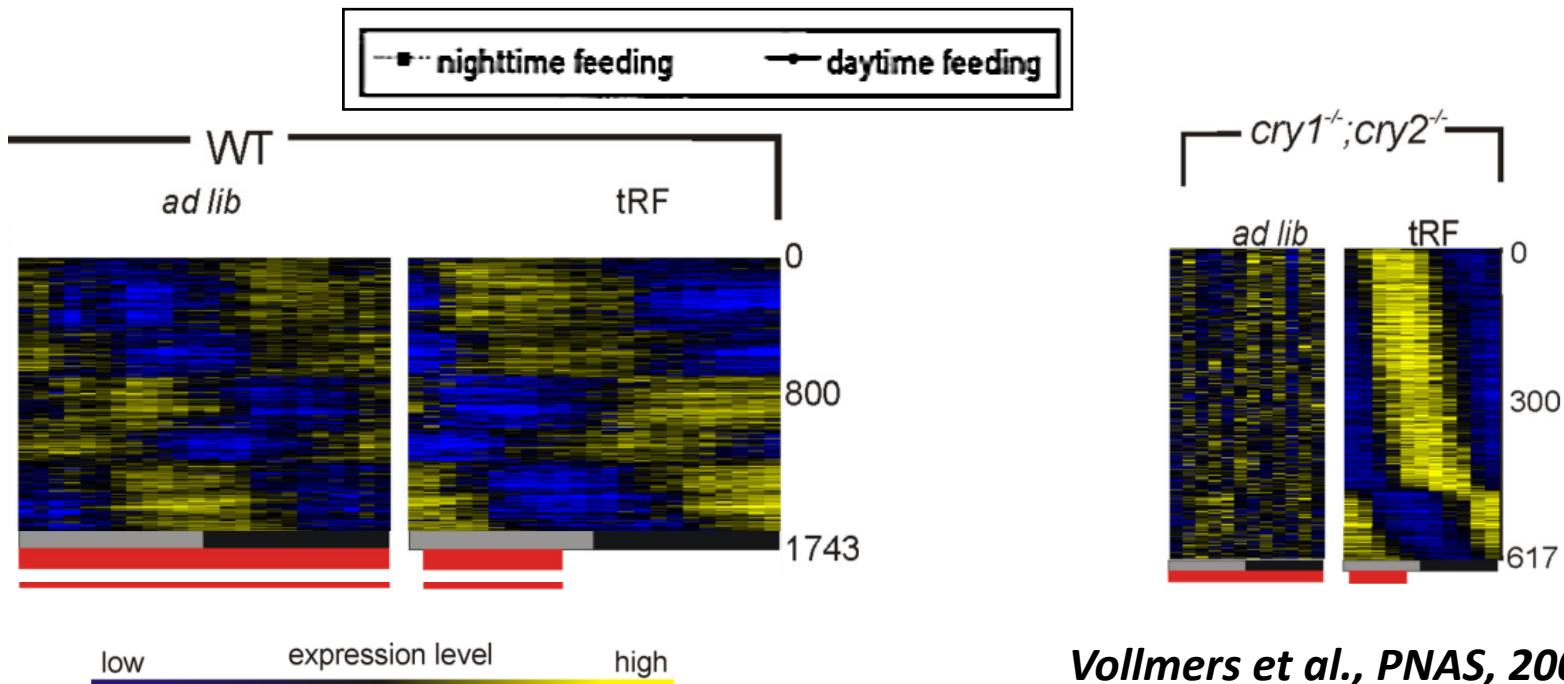
Science 19 Jan 2001:



# Contrôle de l'horloge circadienne hépatique par le rythme alimentaire

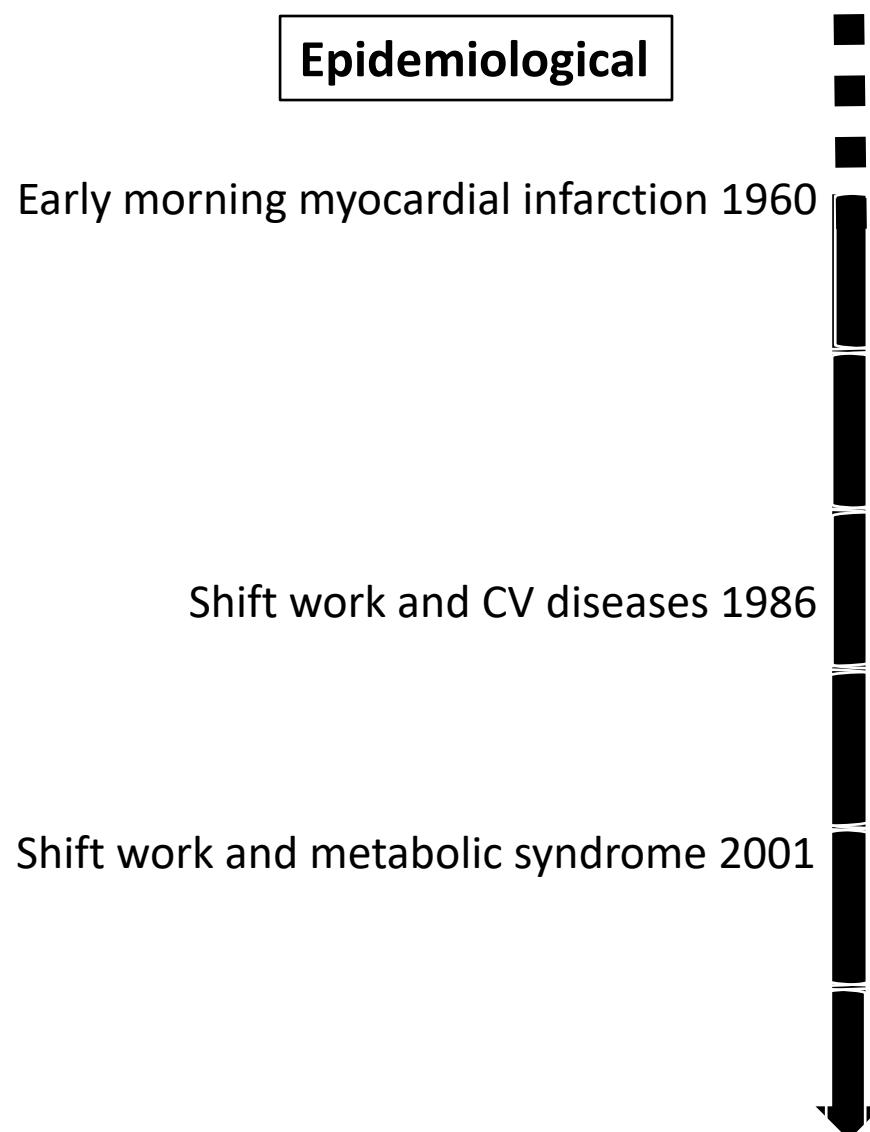


Damiola et al., Genes Dev., 2000

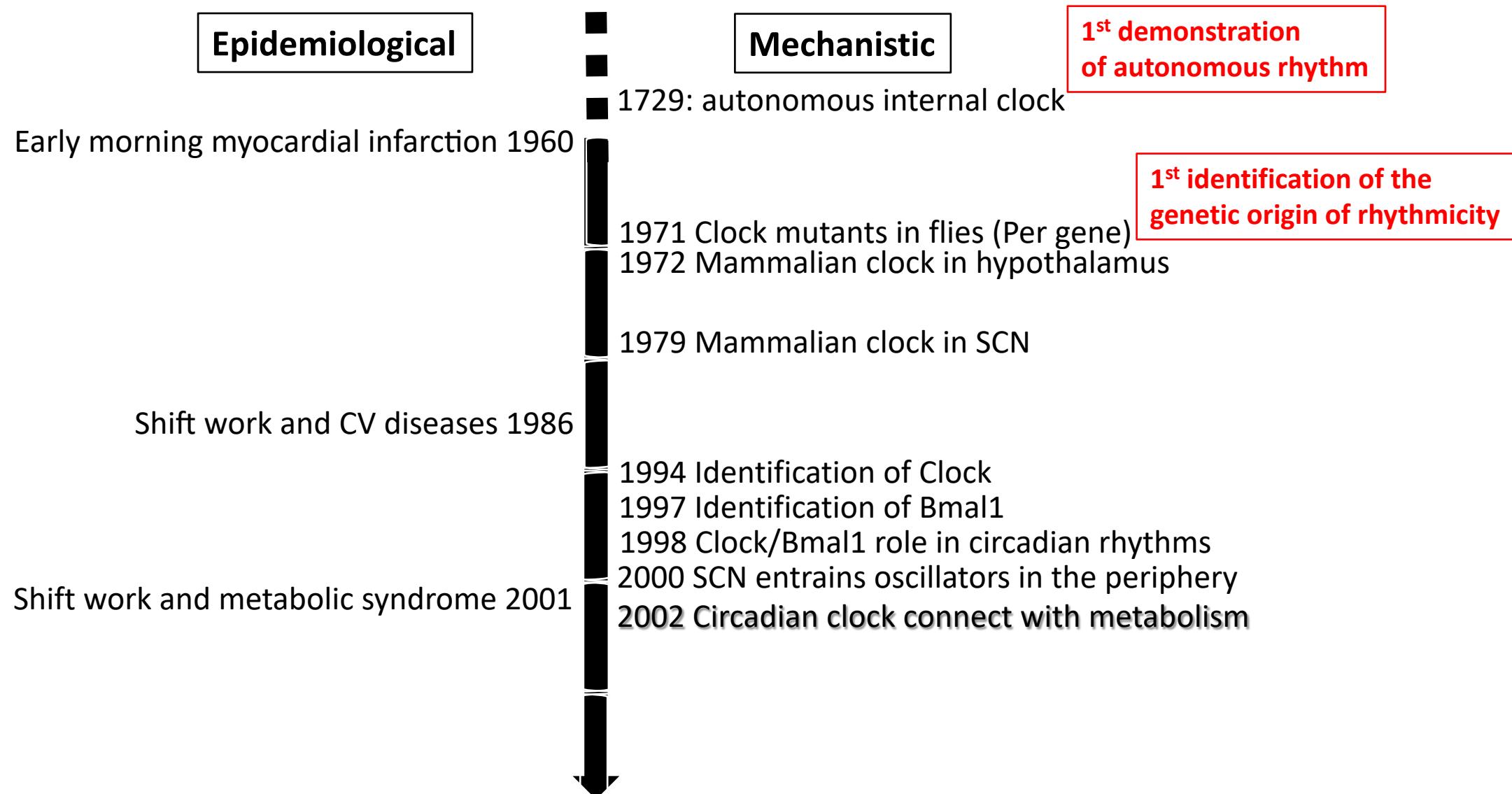


Vollmers et al., PNAS, 2009

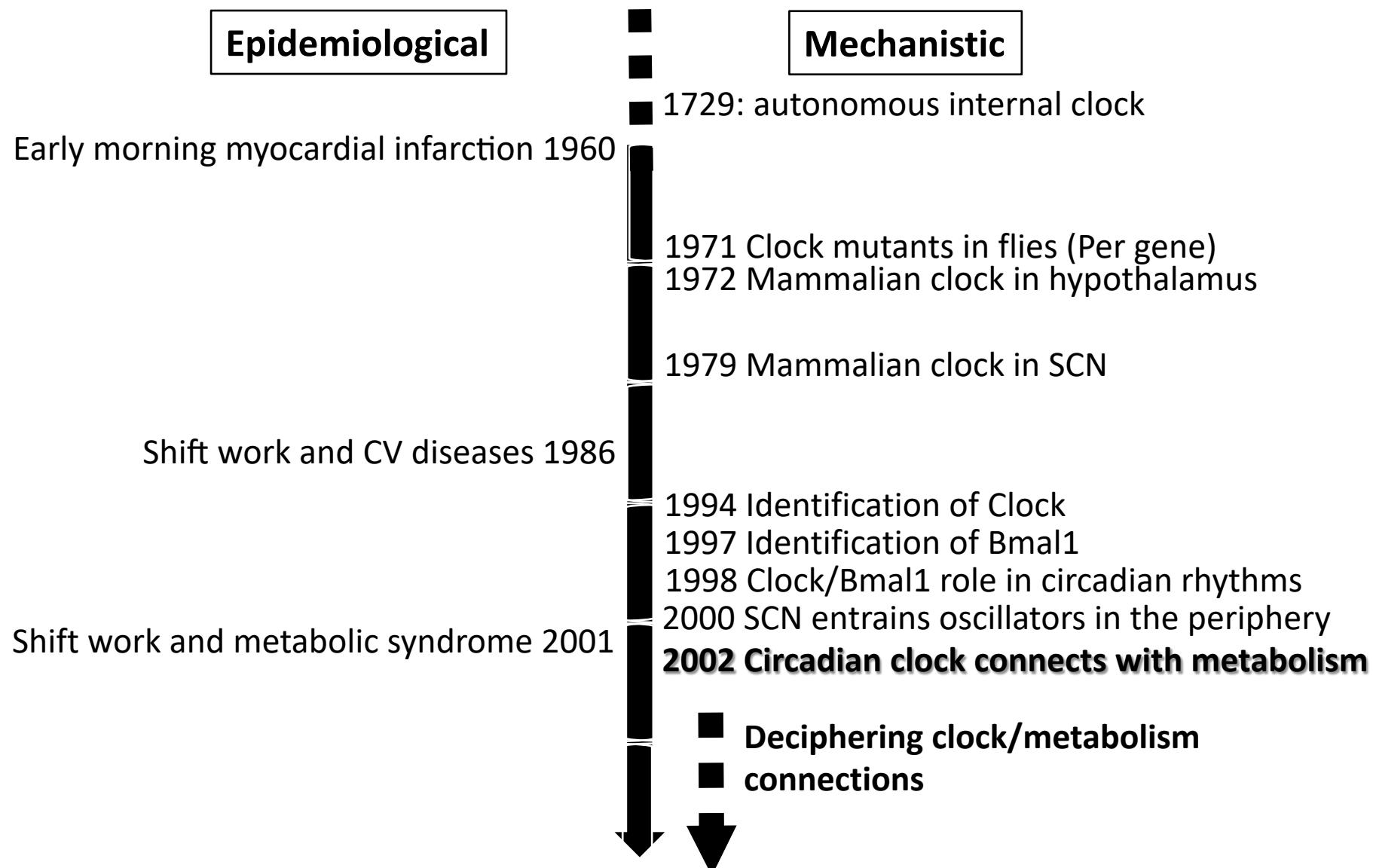
# Lien entre le métabolisme et l'horloge circadienne



# Lien entre le métabolisme et l'horloge circadienne



# Lien entre le métabolisme et l'horloge circadienne



# PLAN

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## PARTIE 2 : pathologie

1. **Effet expérimental du régime gras**
2. Décalage des rythmes et risque métabolique

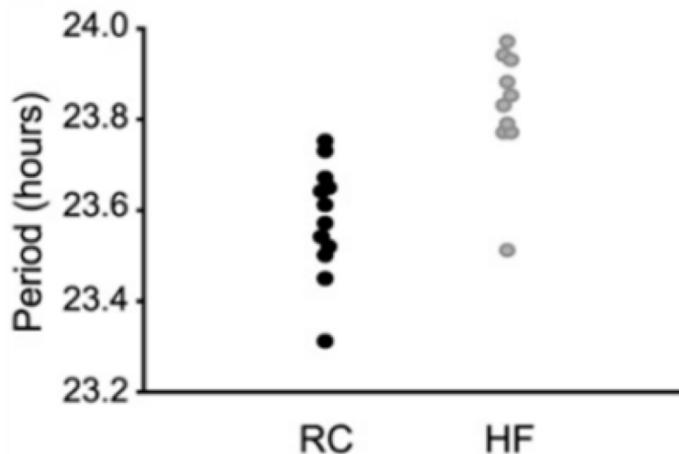
## PARTIE 3 : étude d'article

# Le régime gras altère le comportement de façon précoce



RC : Régime normal (16% gras)  
HF : Régime *High fat* (45% gras)

## Rythme d'activité



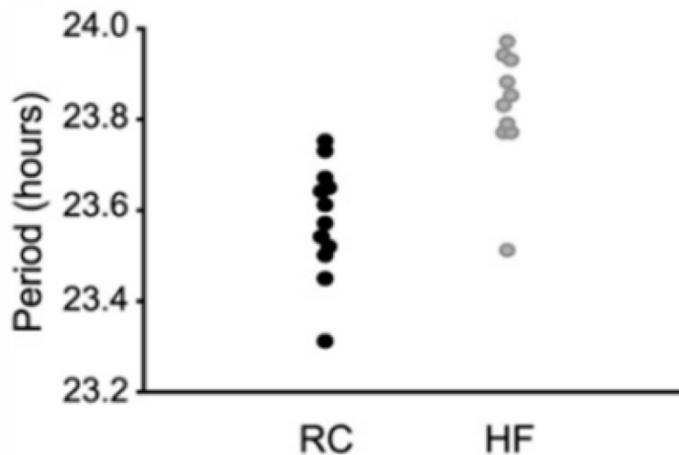
Adapté de Kohsaka et al., *Cell Metabolism*, 2007

# Le régime gras altère le comportement de façon précoce

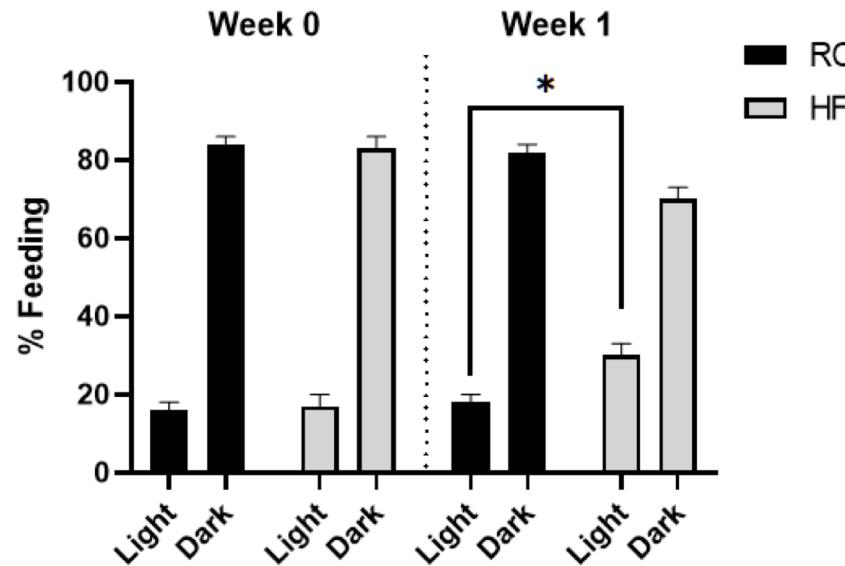


RC : Régime normal (16% gras)  
HF : Régime *High fat* (45% gras)

Rythme d'activité



Rythme alimentaire



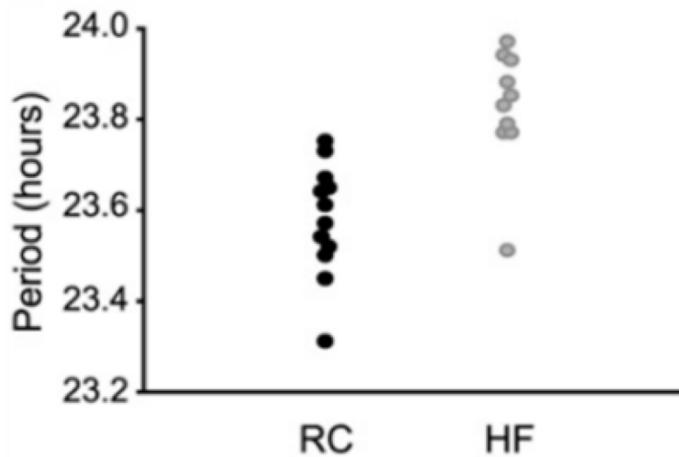
Adapté de Kohsaka et al., *Cell Metabolism*, 2007

# Le régime gras altère le comportement de façon précoce

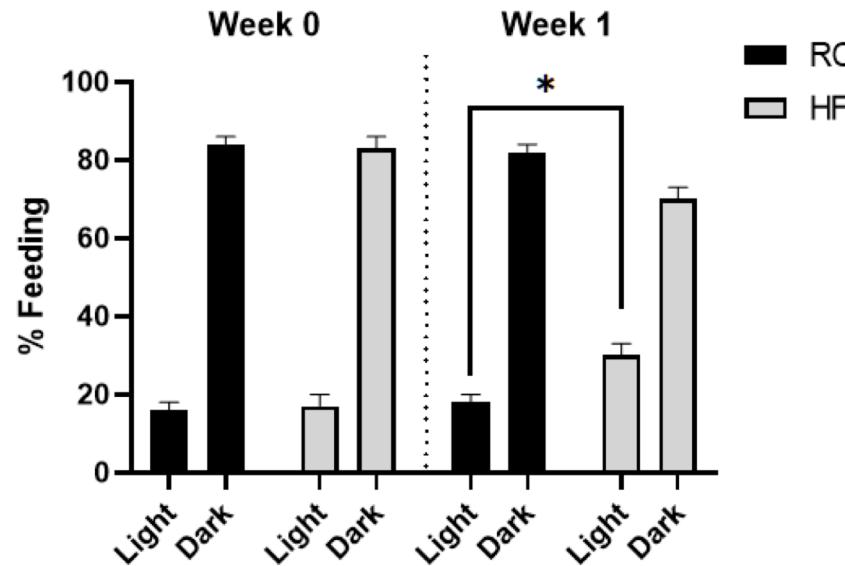


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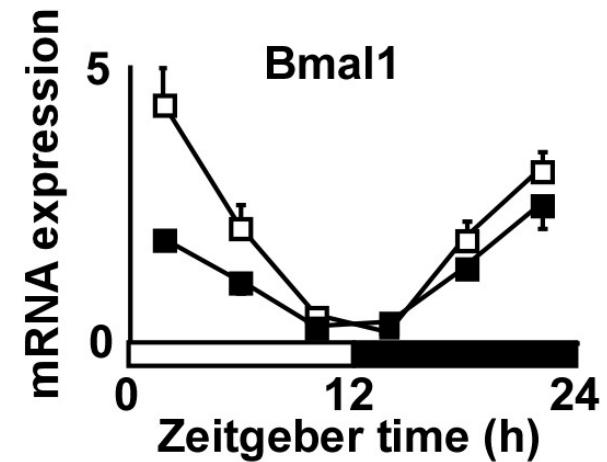
Rythme d'activité



Rythme alimentaire

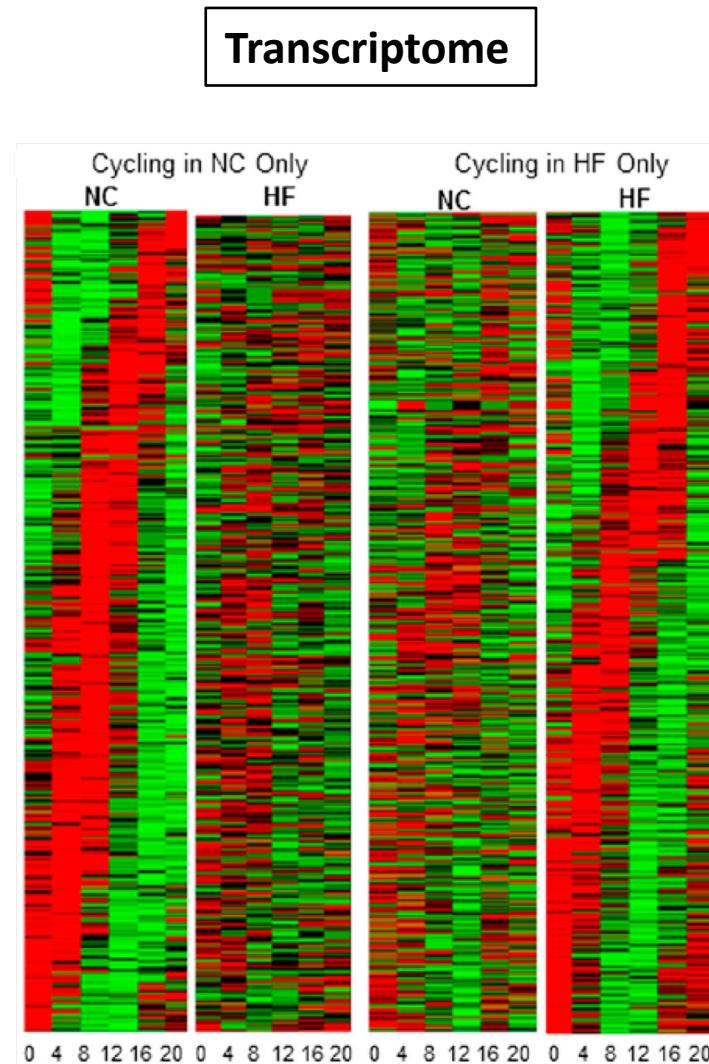


Horloge hépatique



Adapté de Kohsaka et al., *Cell Metabolism*, 2007

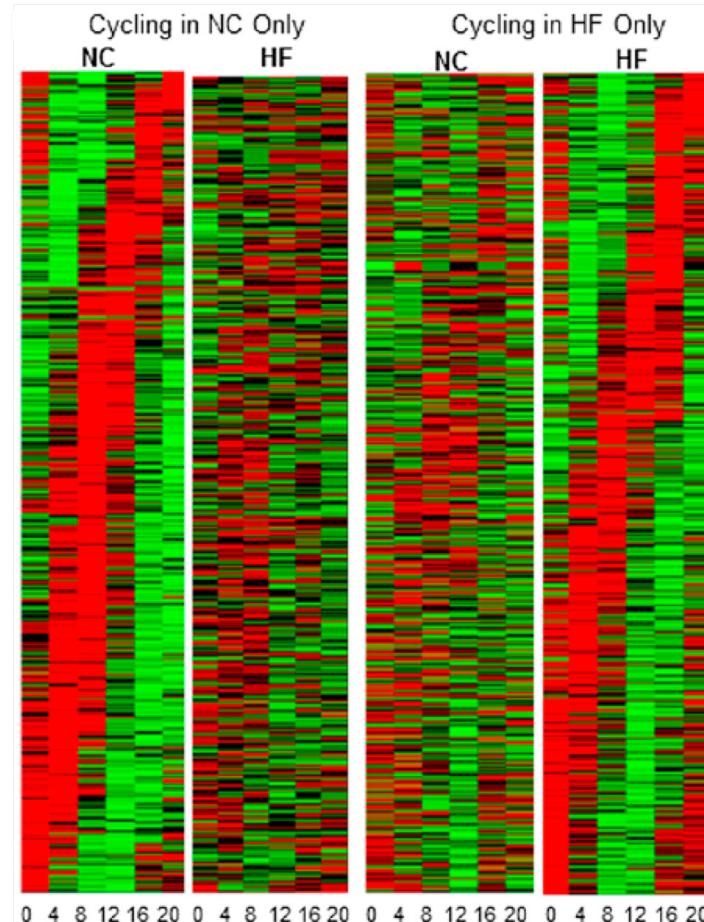
# Le régime gras altère le métabolome et le transcriptome hépatiques



Adapté de Eckel-Mahan et al, Cell, 2013

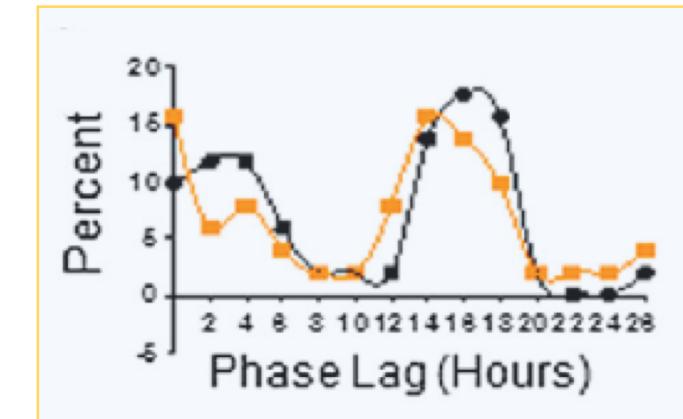
# Le régime gras altère le métabolome et le transcriptome hépatiques

Transcriptome



Métabolomique

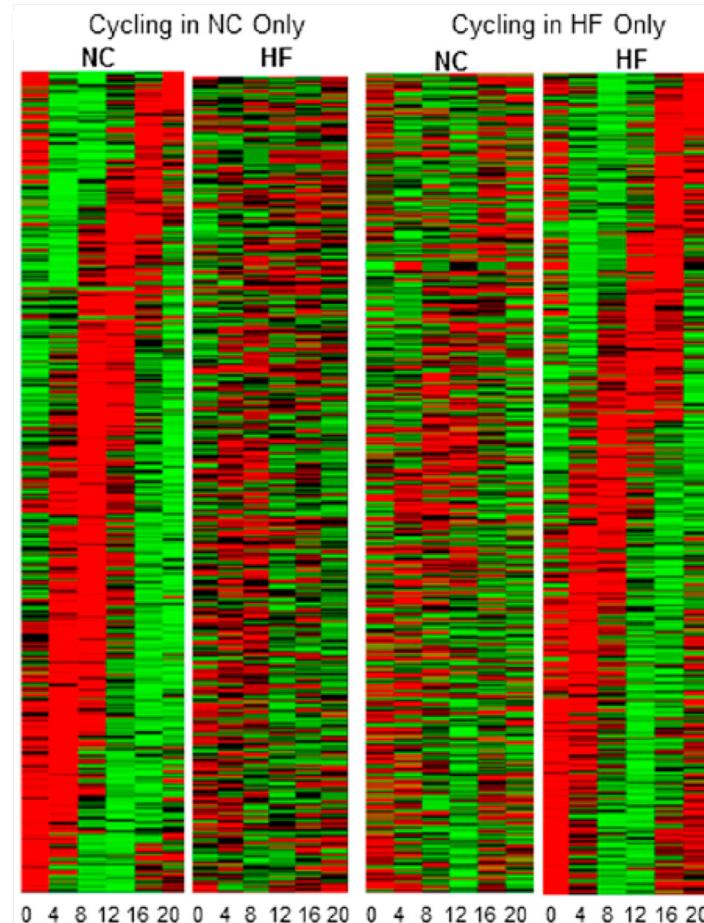
Métabolites rythmique  
dans les deux régimes  
(n=61)



- Régime normal(ND)
- Régime High Fat (HF)

# Le régime gras altère le métabolome et le transcriptome hépatiques

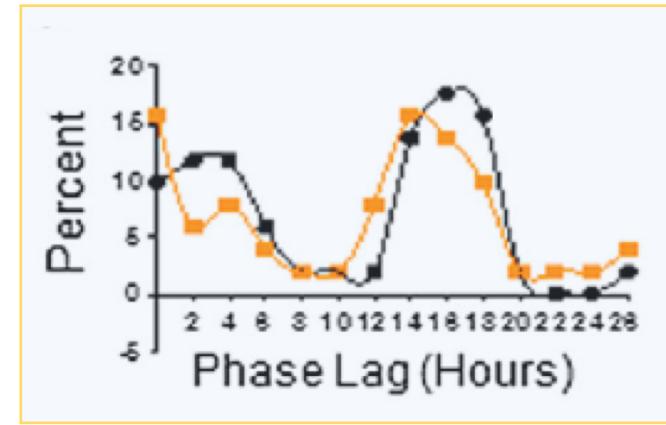
Transcriptome



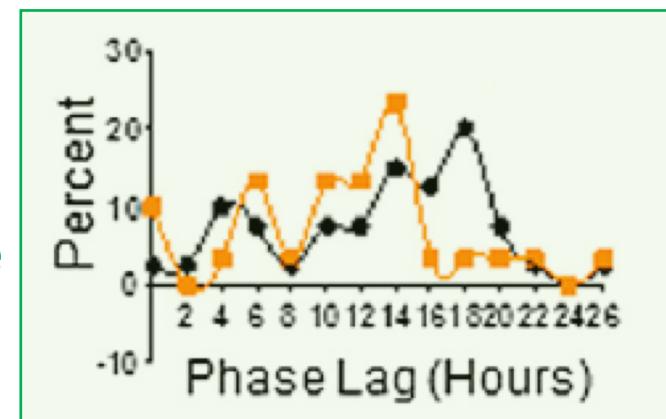
Métabolomique

Métabolites rythmique dans les deux régimes (n=61)

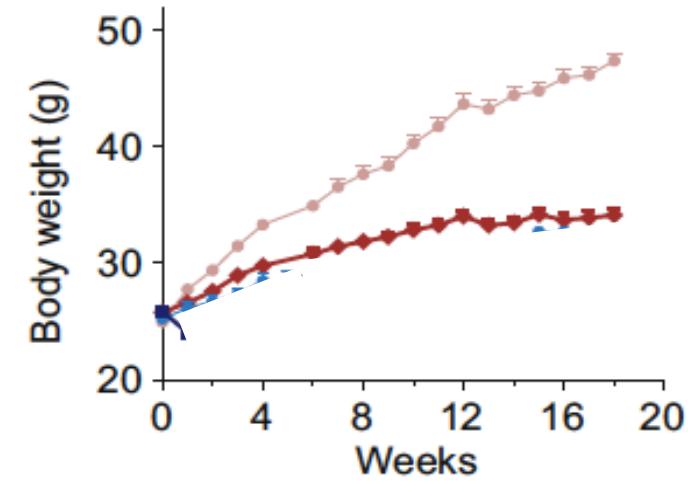
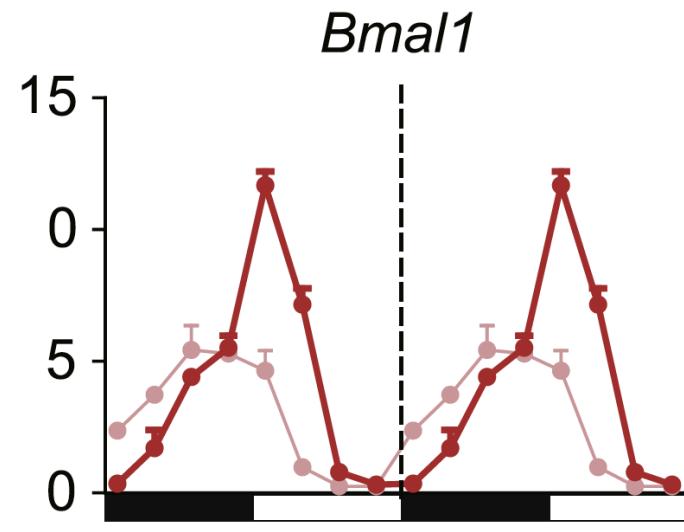
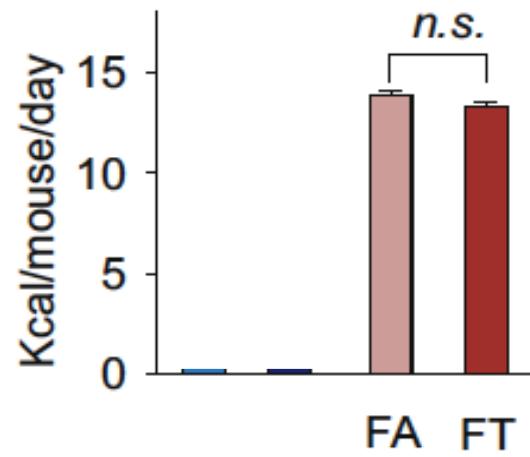
- Régime normal(ND)
- Régime High Fat (HF)



Métabolites rythmique uniquement dans un régime (ND : n=42 / HF : n=38)

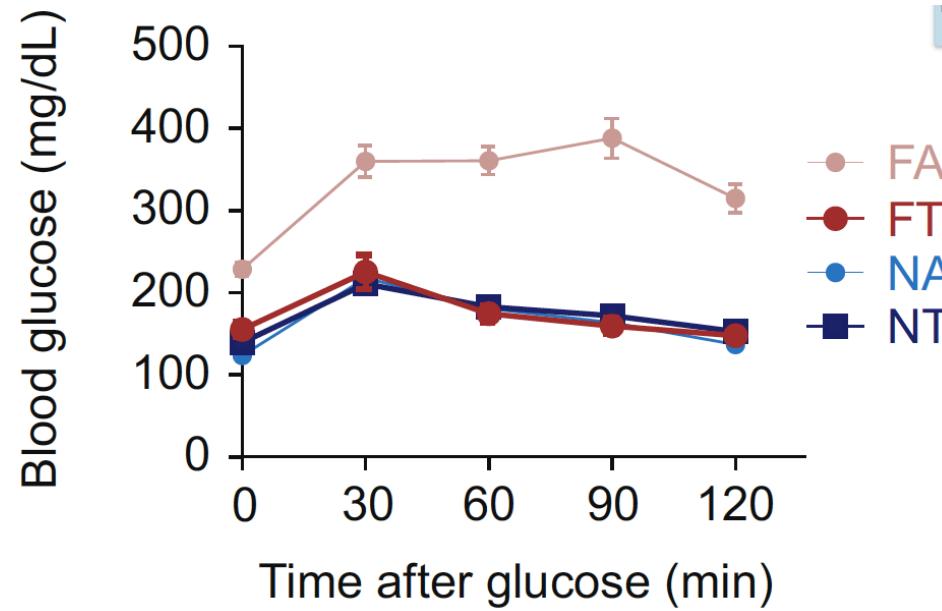
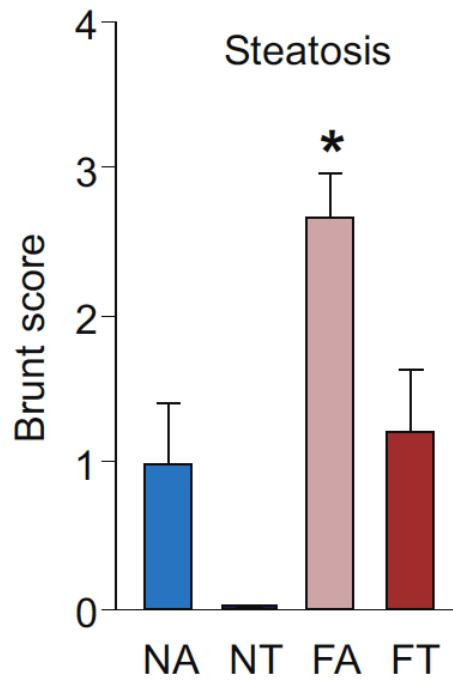


# La restriction alimentaire temporelle synchronise l'horloge hépatique et améliore les pathologies métabolique



Hatori, Cell metab 2012

# La restriction alimentaire temporelle synchronise l'horloge hépatique et améliore les pathologies métabolique



Hatori, Cell metab 2012

# PLAN

## PARTIE 1 : physiologie

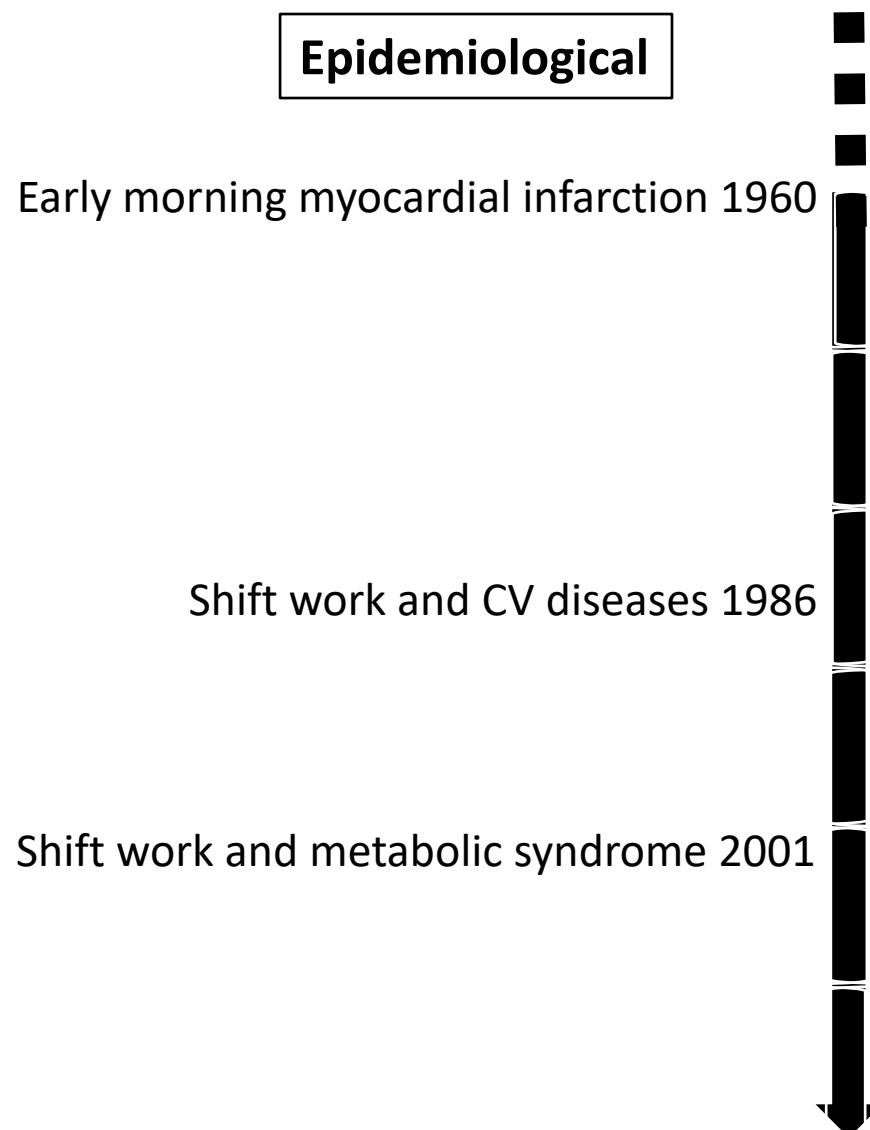
1. Introduction sur les rythmes circadiens

## PARTIE 2 : pathologie

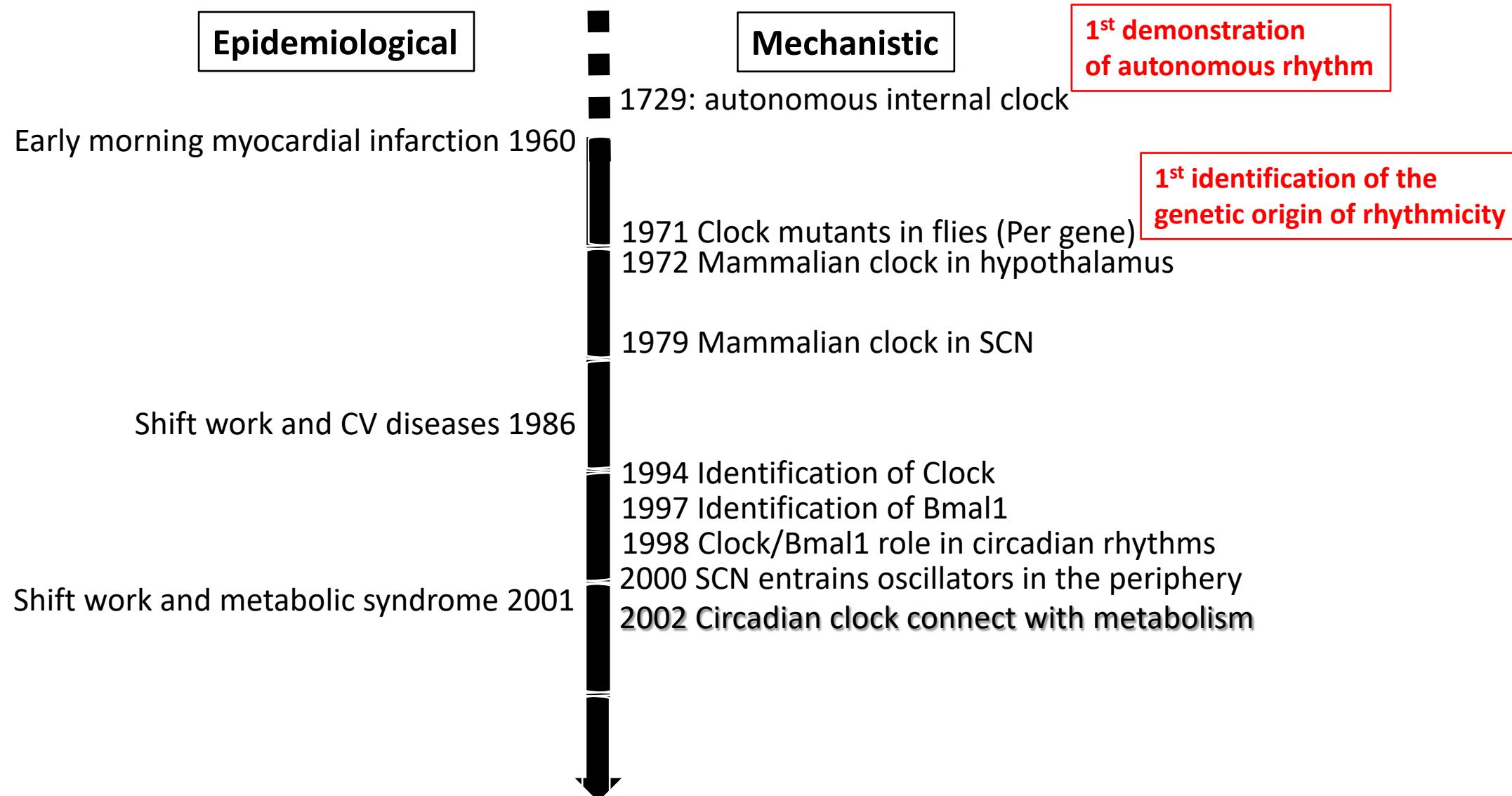
1. Effet expérimental du régime gras
2. Décalage des rythmes et risque métabolique

## PARTIE 3 : étude d'article

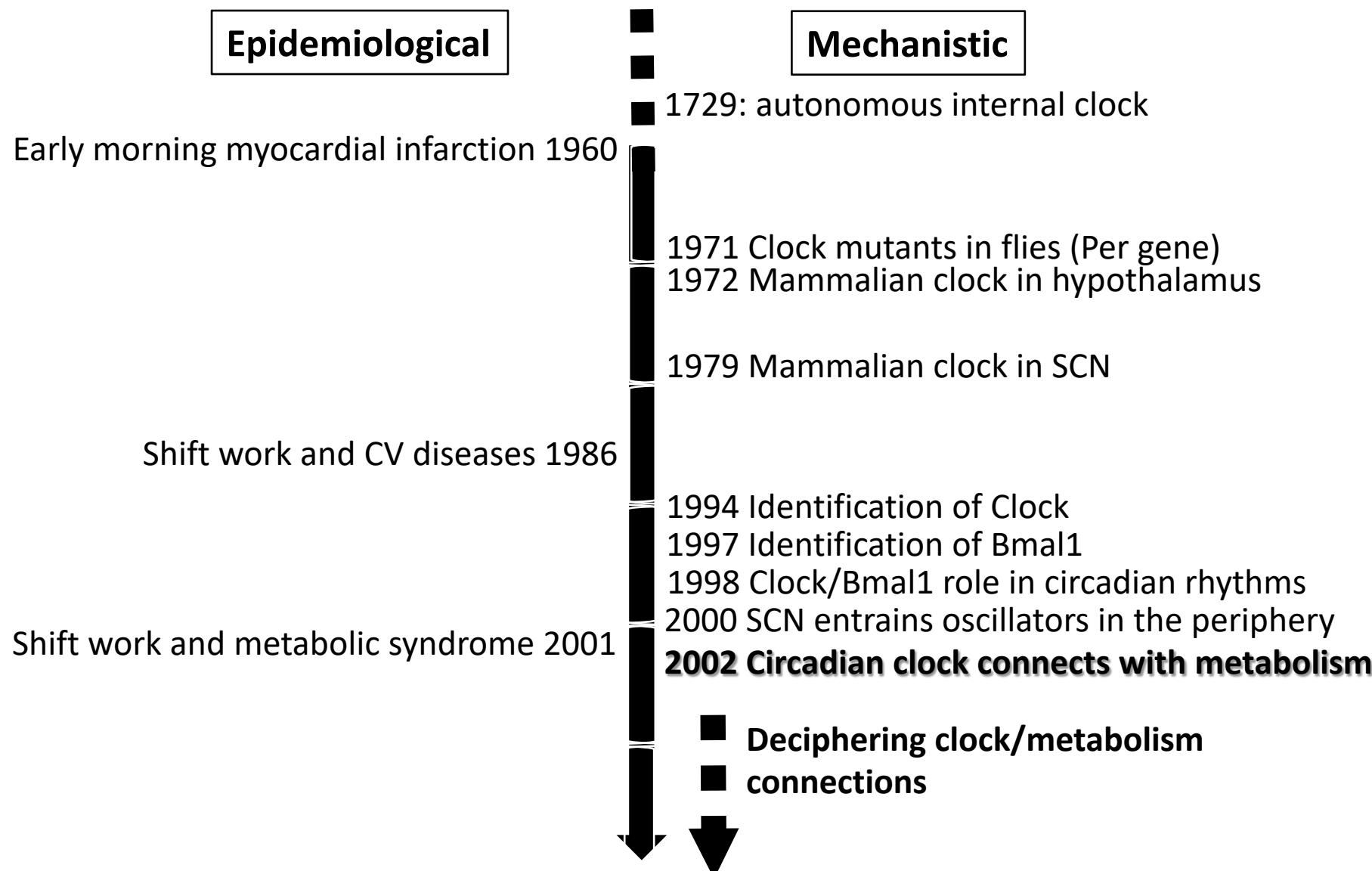
# Lien entre le métabolisme et l'horloge circadienne



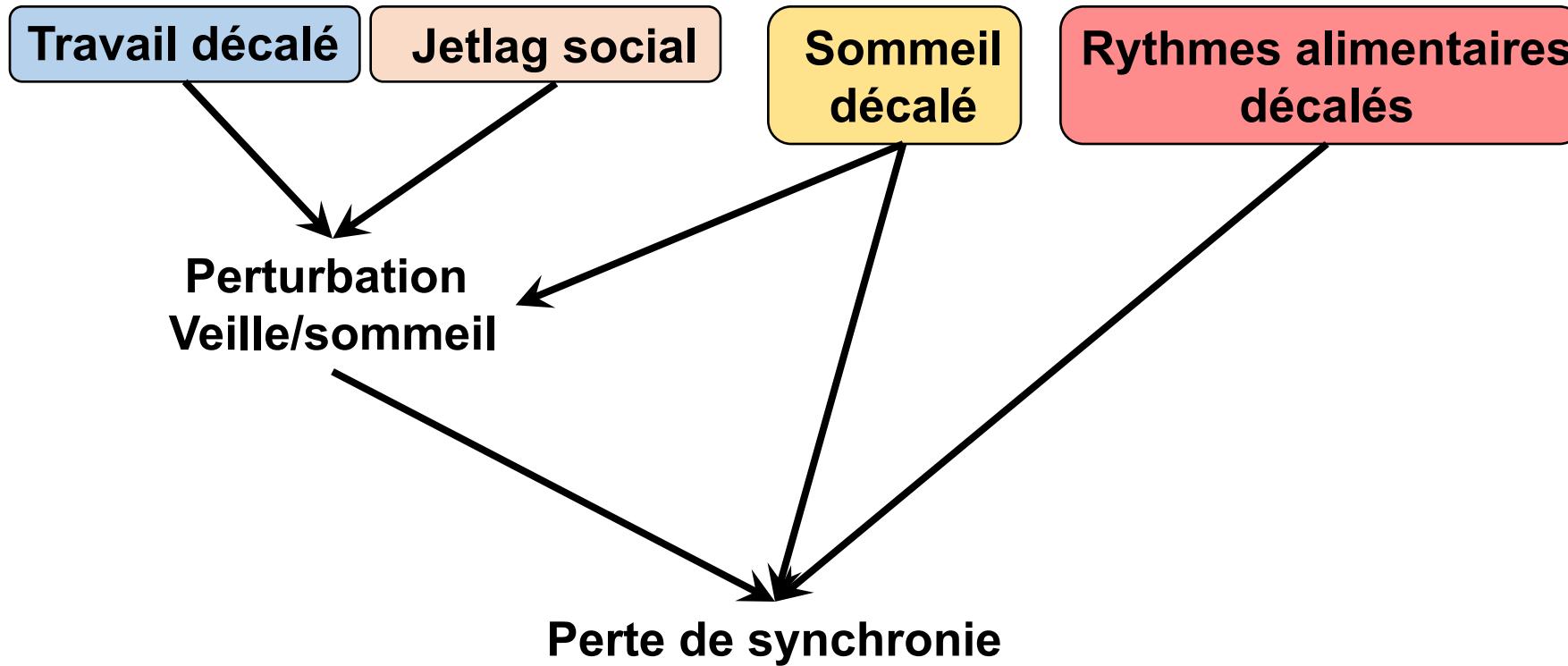
# Lien entre le métabolisme et l'horloge circadienne



# Lien entre le métabolisme et l'horloge circadienne



# Le mode de vie moderne



# Travail décalé



agence nationale de sécurité sanitaire  
alimentation, environnement, travail

Rapport d'expertise collective

Juin 2016

Édition scientifique

Évaluation  
des risques sanitaires  
liés au travail de nuit

**3,5 millions de travailleurs décalés en France  
X 2 en 20 ans**

Et 69% des travailleurs ont >1 h de jetlag social  
*(Roenneberg Handb Exp Pharmacol 2013)*

# Travail décalé

## Etudes expérimentales

- Altère métabolisme du glucose et sensibilité à l'insuline
- Perturbe la régulation pondérale

## En condition de vie réelles

- **Prise de poids** : études cas-témoins positives
- **Diabète de type 2** : études de cohortes; relation dose-réponse avec la durée de travail posté
- **Cardio-vasculaire**: études avec biais de sélection et d'information

# Sommeil décalé

## Etudes expérimentales

- Restriction de sommeil → surconsommation calorique → prise de poids (*Markwald, PNAS 2013*)
- Restriction de sommeil (5 h; 1 semaine) : altération réponse charge IV en glucose (*Buxton, Diabetes 2010*)
- Augmenter le sommeil chez petits dormeurs améliore la sensibilité à l'insuline (*Buxton, Sci Transl Med 2012*)
- Manger pendant le cycle de nuit perturbe le métabolisme glucidique (*Sheer, PNAS 2009*)

# Sommeil décalé

Décalage circadien et coucher tardif s'accompagne souvent d'un sommeil réduit → peut aussi contribuer au risque

## **En condition de vie réelles**

- Risque de diabète de type 2 (*Cappuccio, Diabetes Care 2010*)
- Risque d'obésité (*Patel, Obesity 2007*)

# Chrononutrition

- Risque d'obésité et prise alimentaire le soir (*Wang et al. 2013*)
- Succès de la perte de poids et prise alimentaire le soir  
(*Jakubowicz Obesity 2013*)
- Perte de poids et horaire du repas « du midi » (*Garaulet et Int J obesity 2013*)  
Idem après chirurgie bariatrique (*Ruiz-Lozano Clin Nutr 2016*)

# Certaines populations ont des rythmes alimentaires erratiques

The diagram is divided into two main sections: 'BASELINE EATING PATTERN (3 weeks)' and 'INTERVENTION (16 weeks)'.  
**BASELINE EATING PATTERN (3 weeks):** Shows a group of blue silhouettes representing people. Below the silhouettes, the text reads: 'Erratic daily eating patterns spread over day and night. Weekend eating patterns delayed from weekdays.' To the right of this section is a smartphone displaying a meal on its screen, with a small portion highlighted by a red circle.  
**INTERVENTION (16 weeks):** Shows a group of blue silhouettes representing overweight individuals. To the right, the text reads: 'Overweight, healthy individuals; Eating duration >14h'. Below this, the text says: 'INTERVENTION (16 weeks)', 'Eat within self-selected 10 - 12h every day.', 'Feedback through Feedograms.', and 'No recommendation on nutrition or calories.' An arrow points from the 'INTERVENTION' text to the red-highlighted portion of the smartphone screen. A large downward-pointing arrow is located at the bottom left of this section, pointing towards the text 'WEIGHT LOSS; IMPROVED SLEEP'.

**BASELINE EATING PATTERN (3 weeks)**

Erratic daily eating patterns spread over day and night.  
Weekend eating patterns delayed from weekdays.

**INTERVENTION (16 weeks)**

Overweight, healthy individuals;  
Eating duration >14h

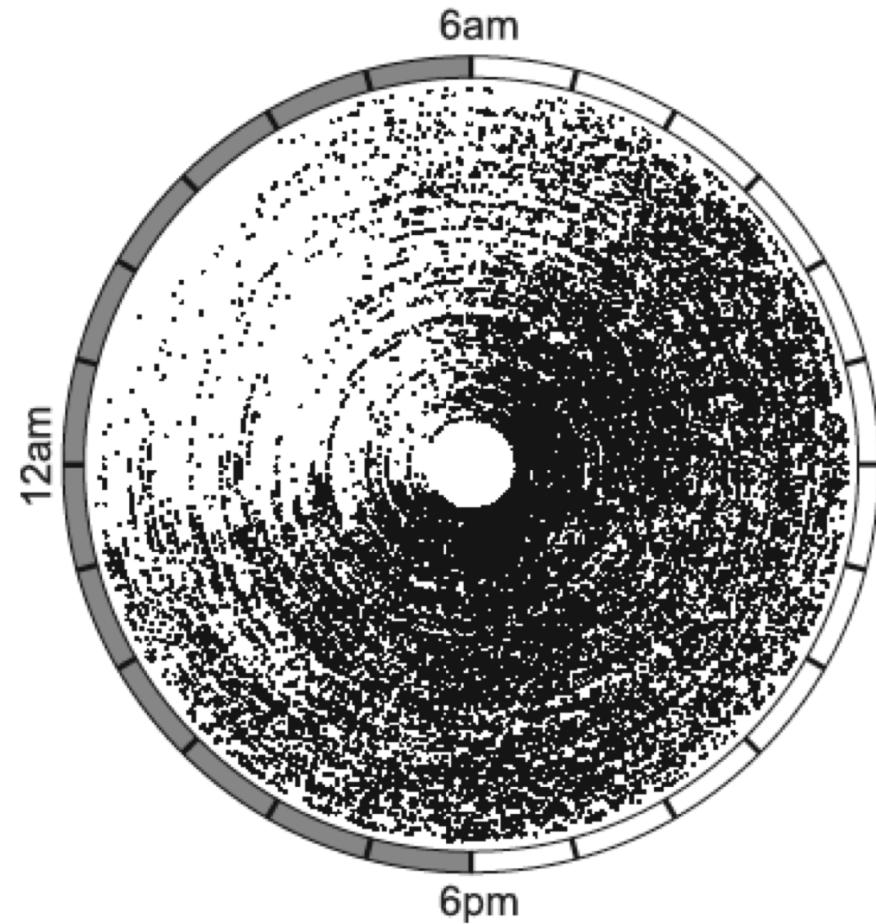
Eat within self-selected 10 - 12h every day.  
Feedback through Feedograms.  
No recommendation on nutrition or calories.

WEIGHT LOSS; IMPROVED SLEEP

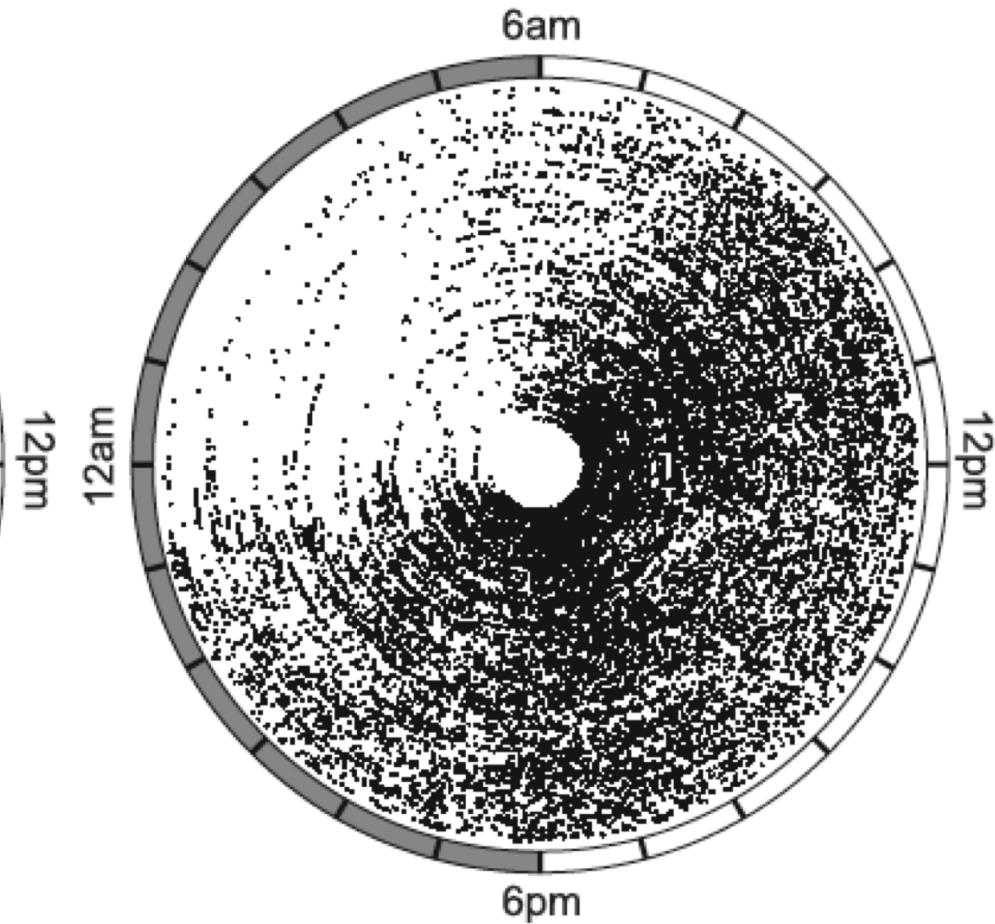
**Gill et al.**

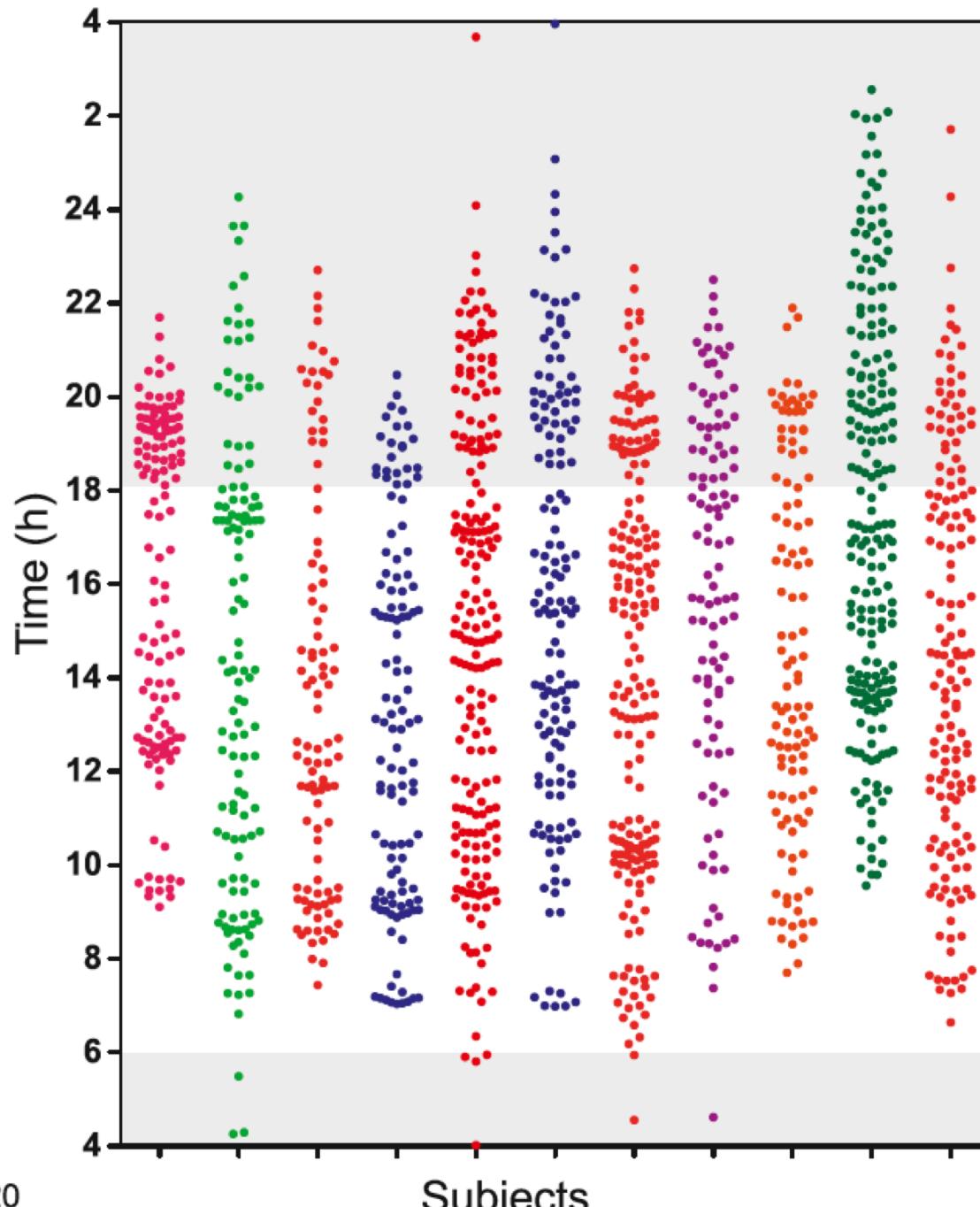
**Cell Metab 2015**

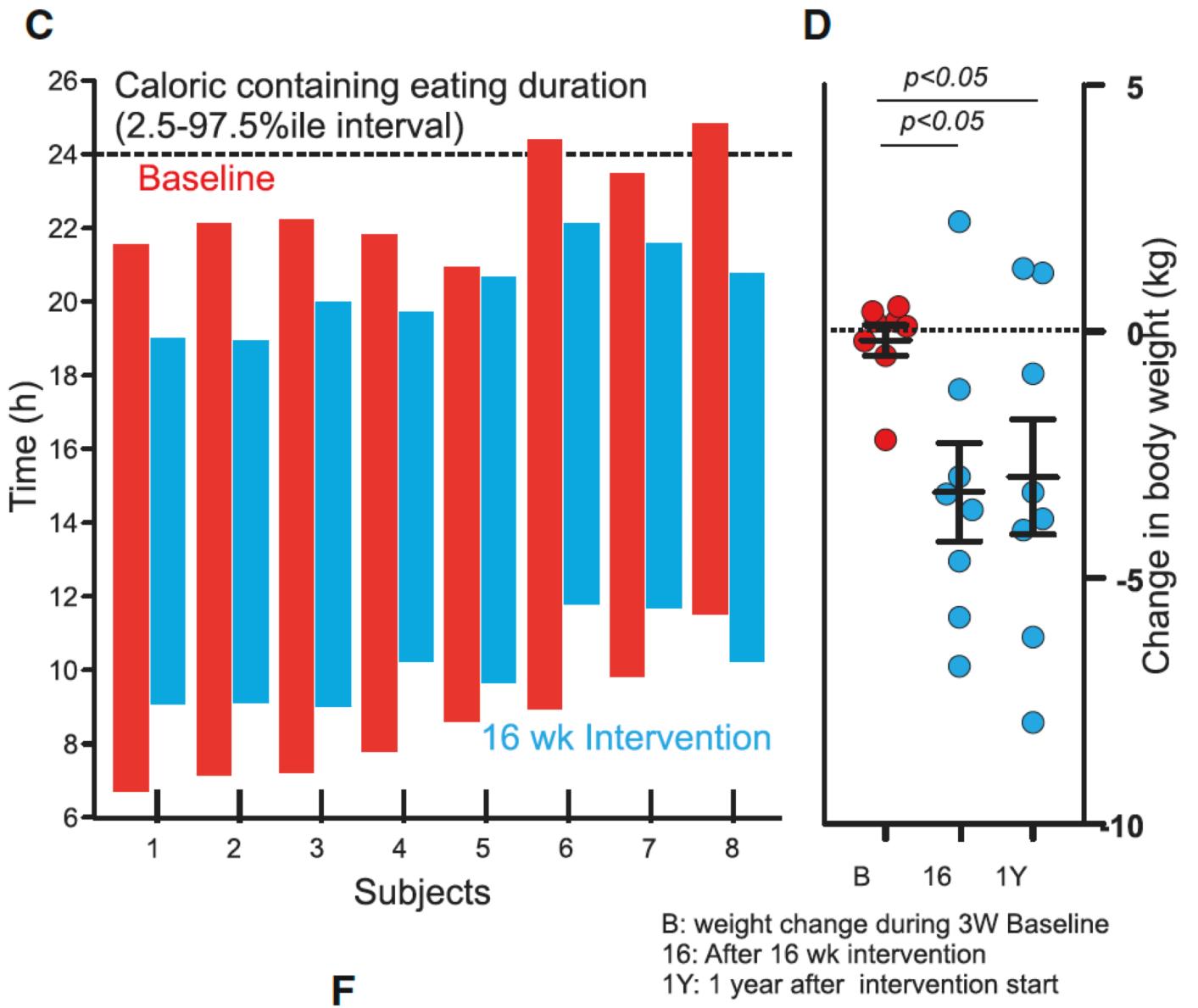
**All events**



**Calorie events**

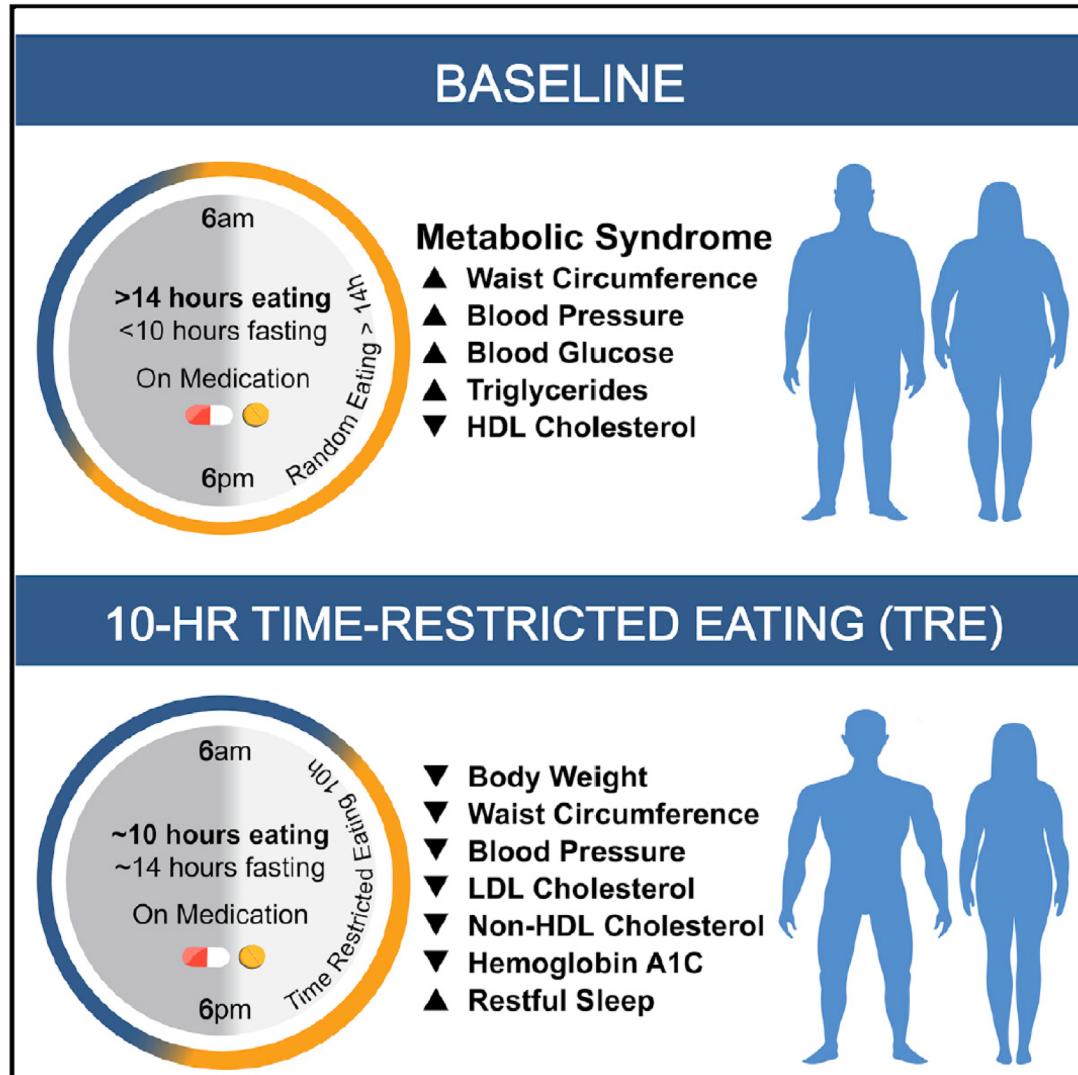






B: weight change during 3W Baseline  
16: After 16 wk intervention  
1Y: 1 year after intervention start

# Etude avant-après : effet du TRF



**Wilkinson et al.**  
**Cell Metab 2020**

14 semaines

**A**

Recruitment,  
Pre-screening,  
Phone-interview

$\geq 14$  hours eating Interval

10 hour eating interval

Baseline/Screening

Intervention

Visit  
Week 0

1<sup>st</sup>

2<sup>nd</sup>

1

2

3

4

5

...

11

12

3<sup>rd</sup>

13

4<sup>th</sup>

14

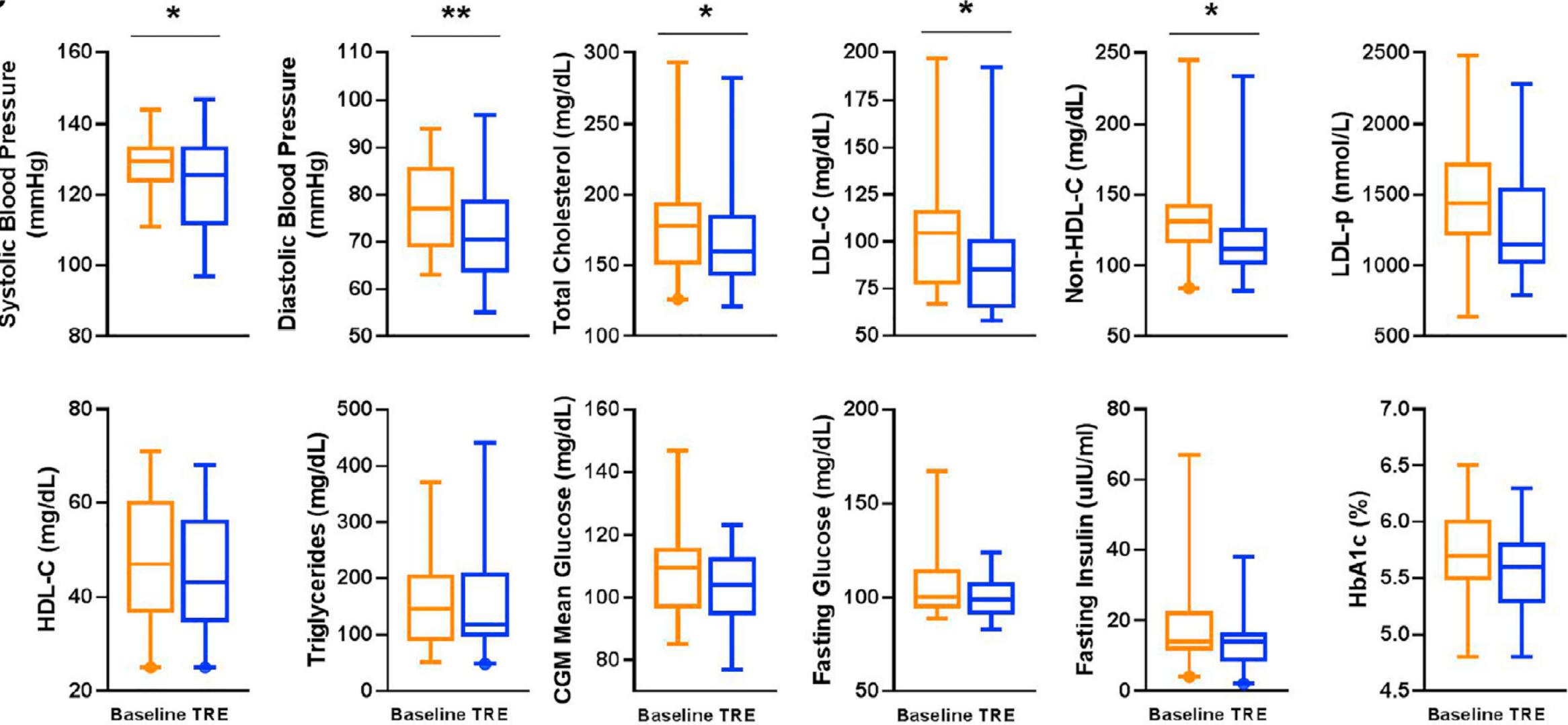
mCC App

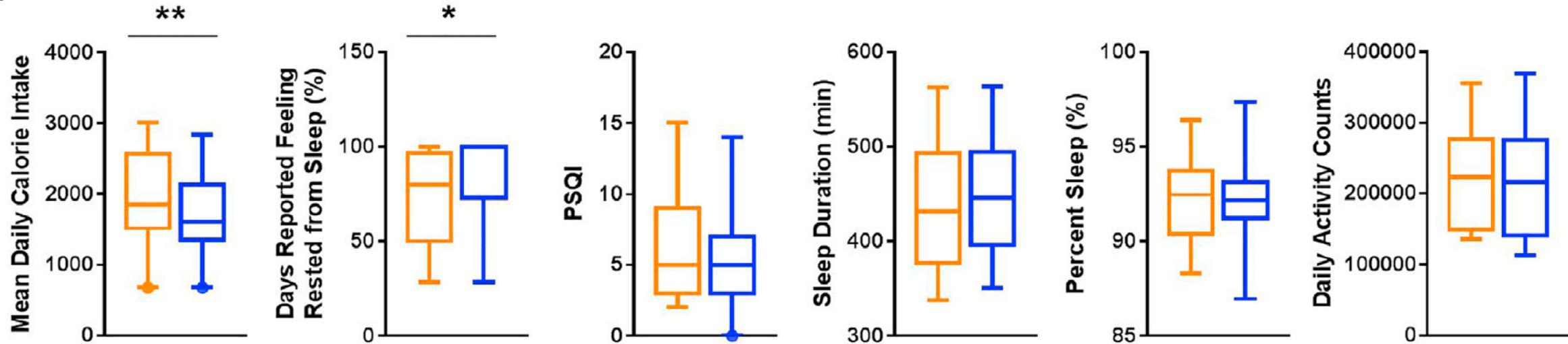
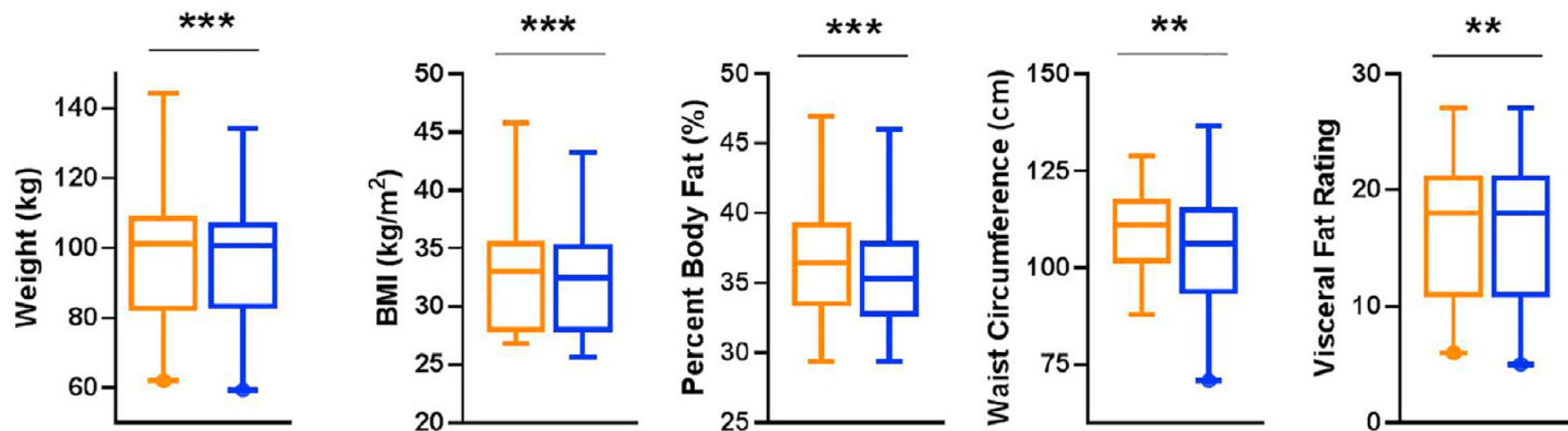
Weight/Body  
Composition

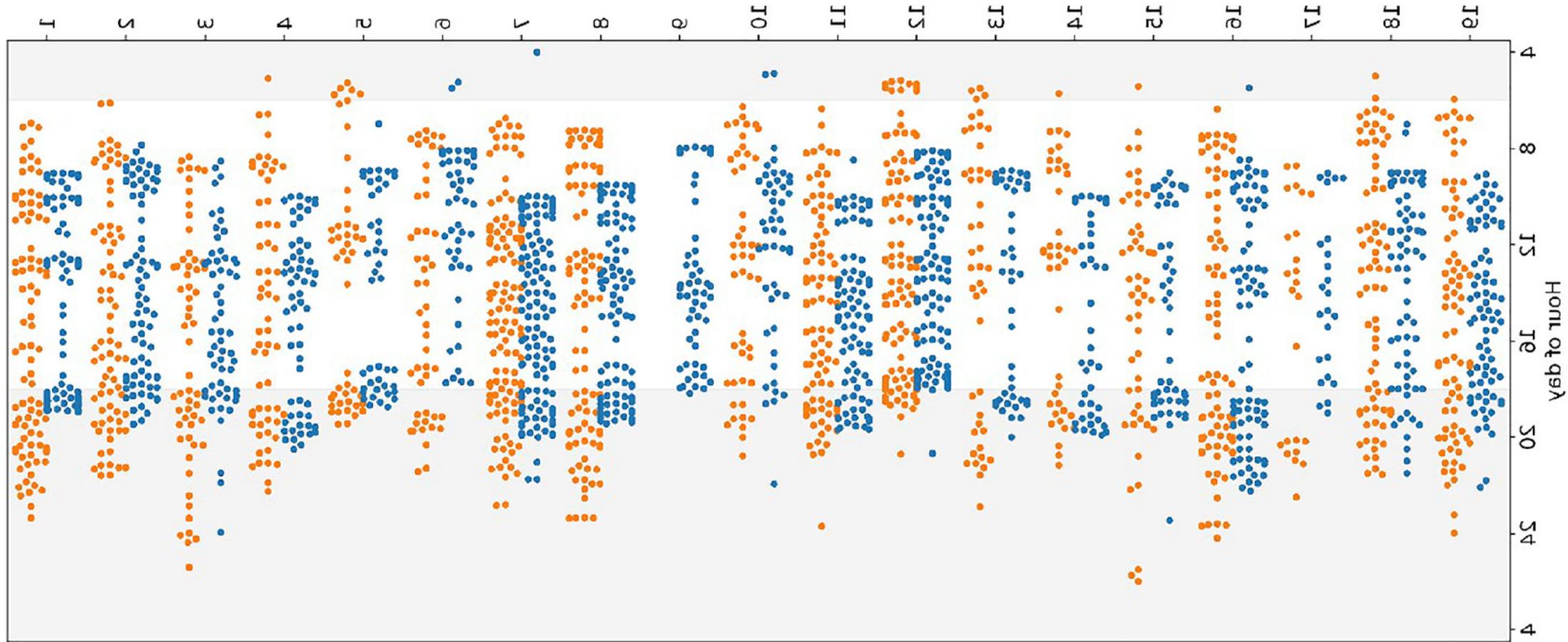
Vitals/  
Blood Draw

CGM

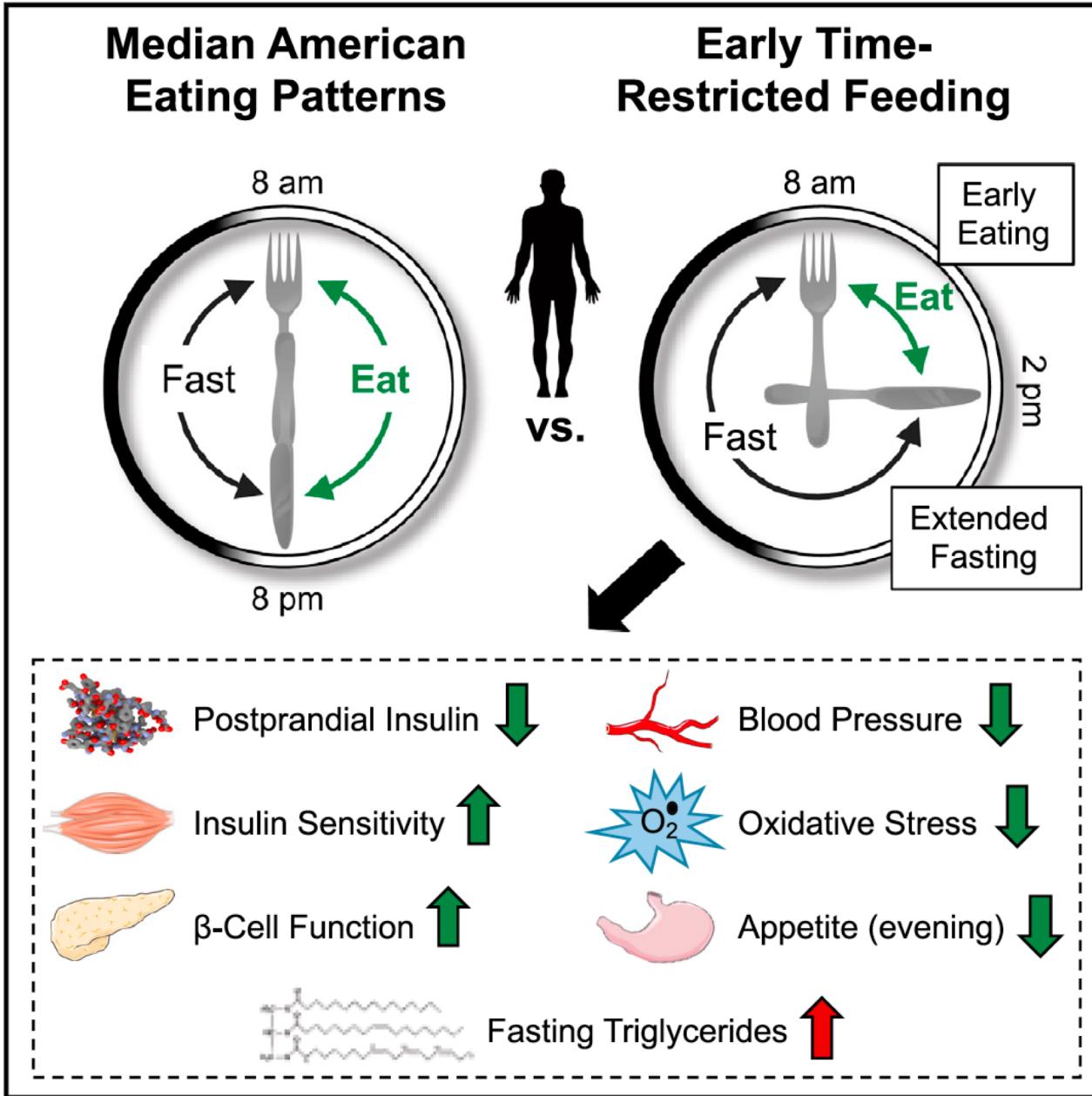
Actiwatch

**C**

**A****B**



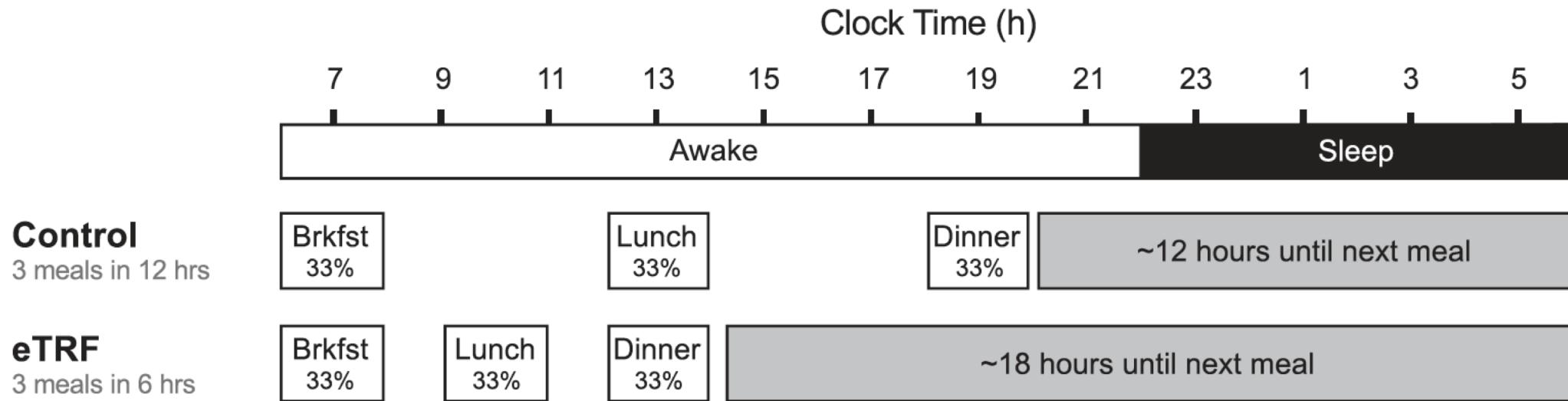
# Etude contrôlée : effet du TRF



Sutton et al.  
Cell Metab 2018

# Randomized, crossover, controlled feeding study

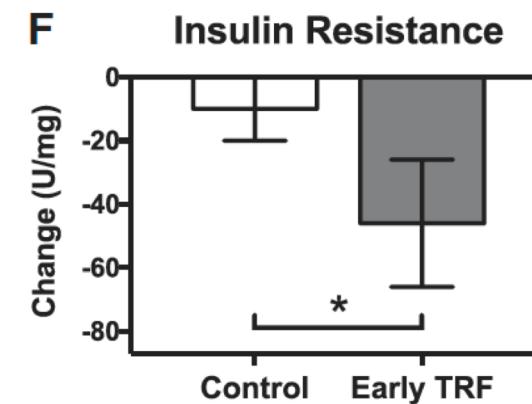
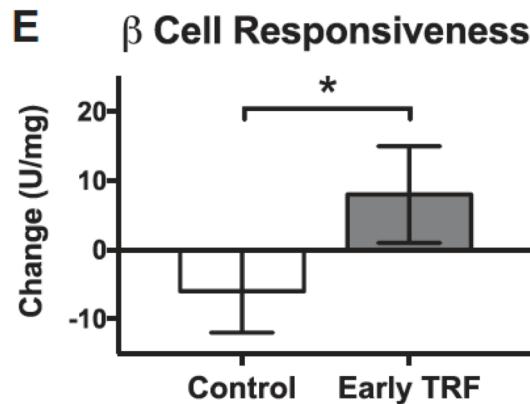
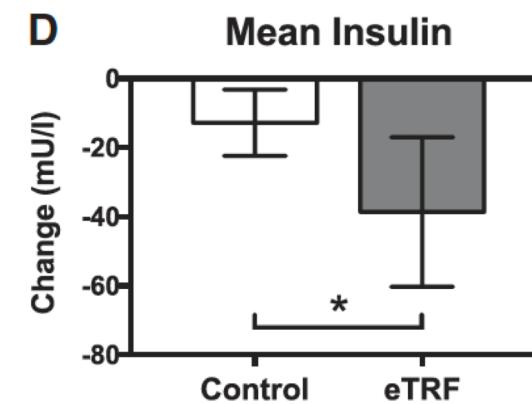
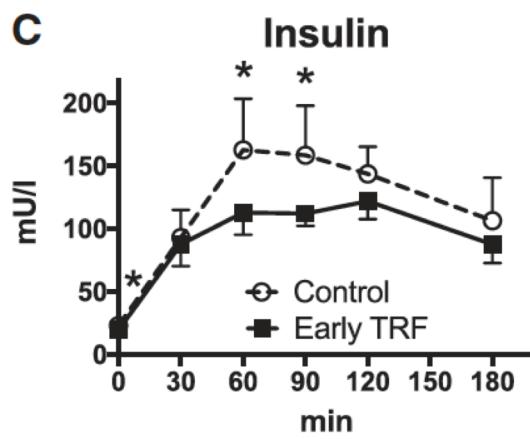
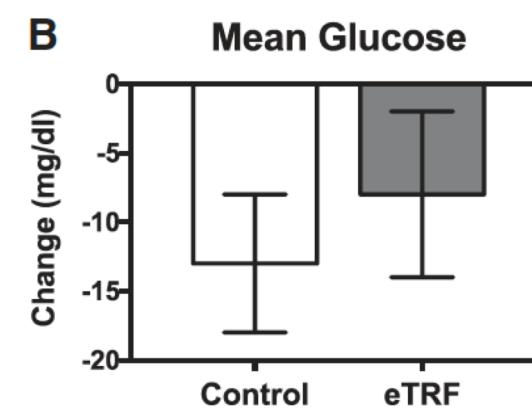
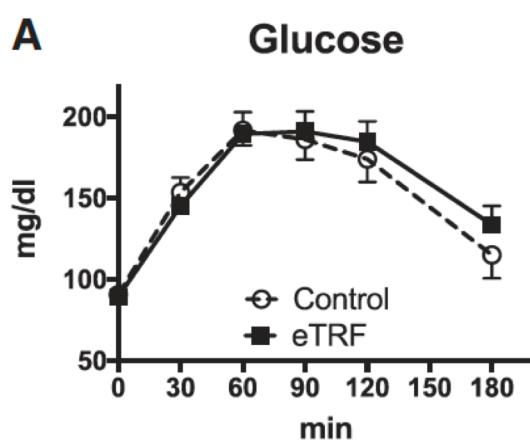
## A Meal Timing Interventions , 5-week for each arm

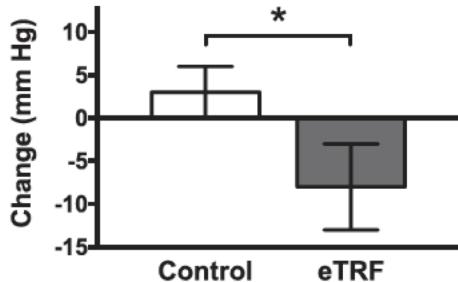
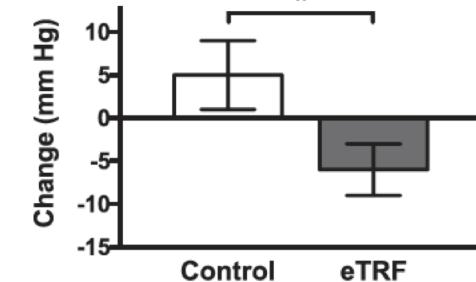
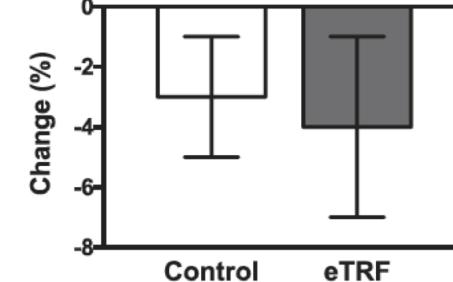
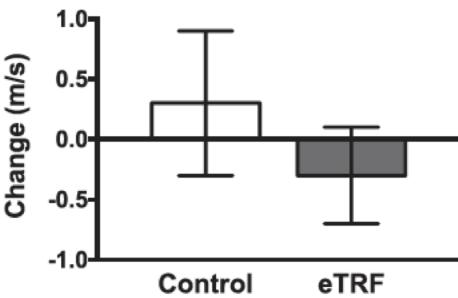
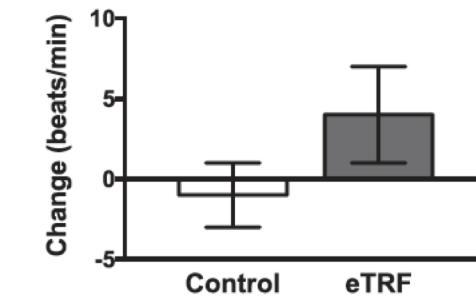
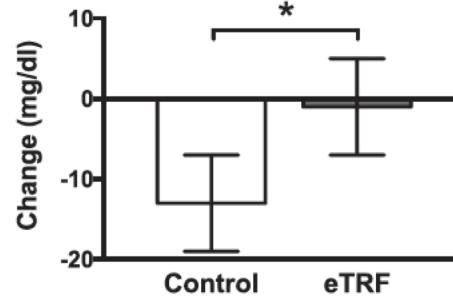
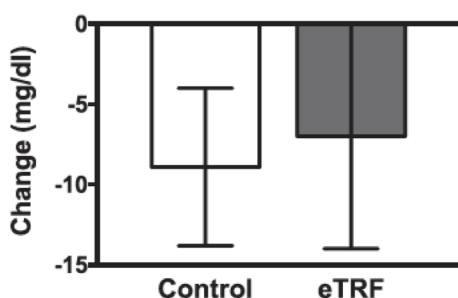
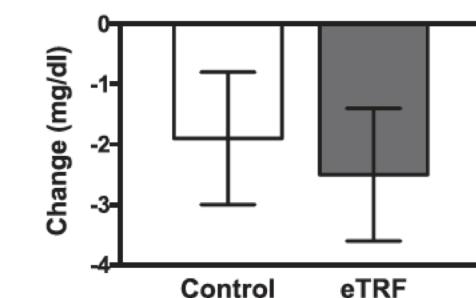
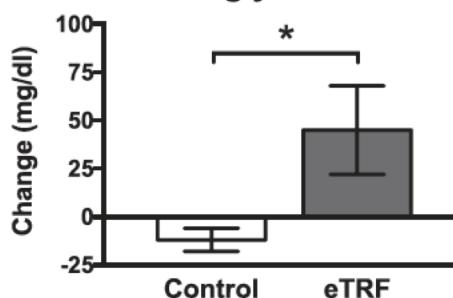


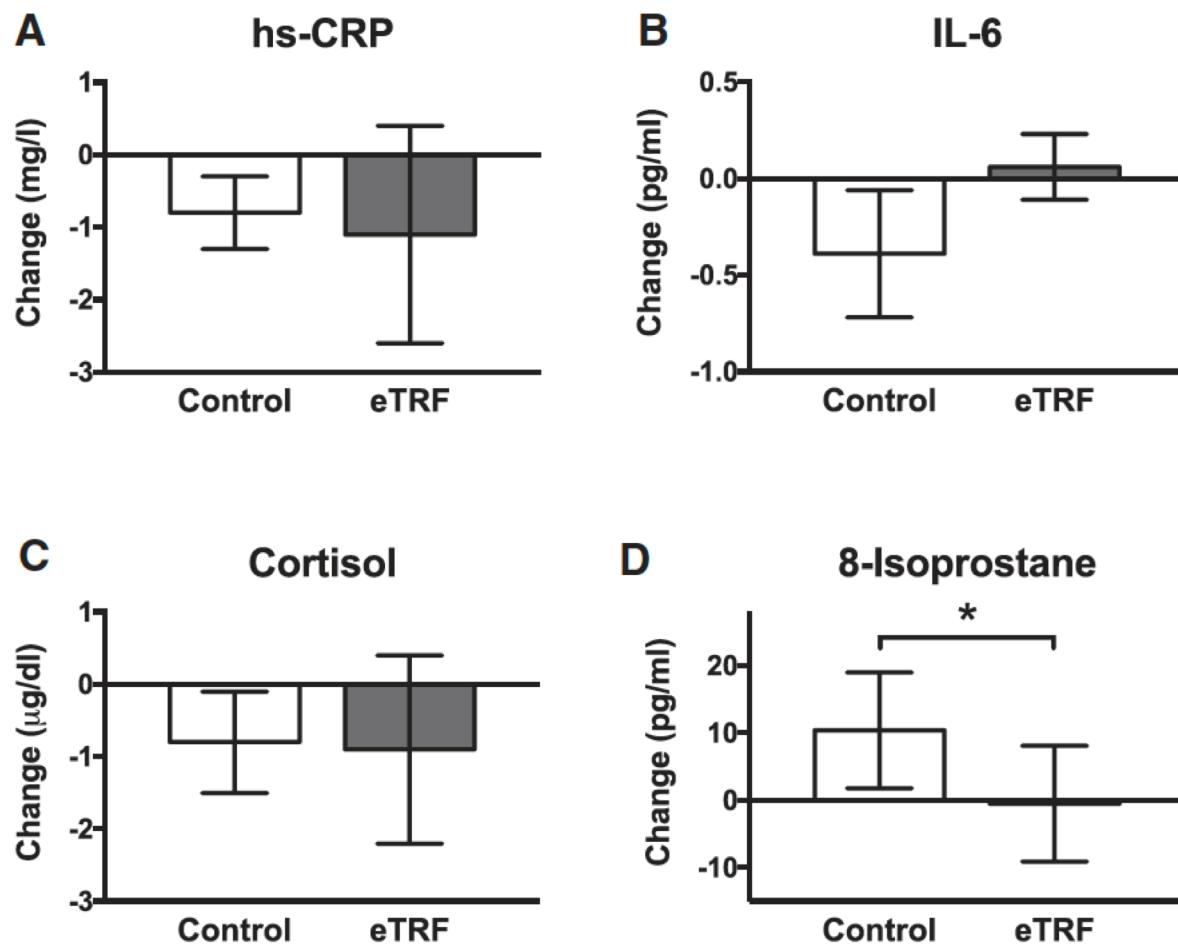
## B Study Menus

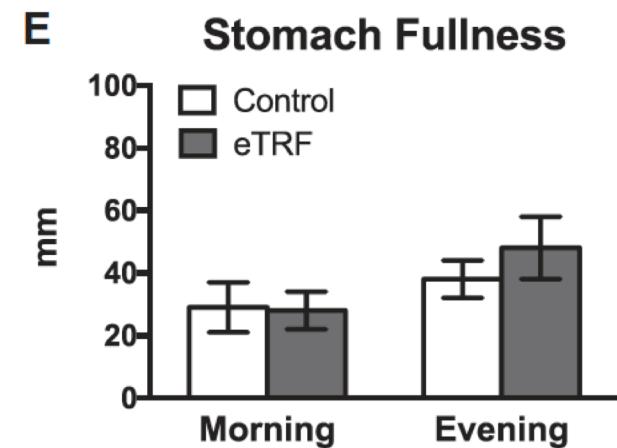
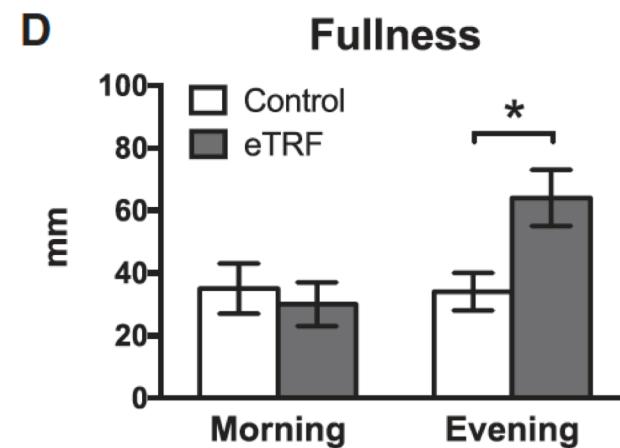
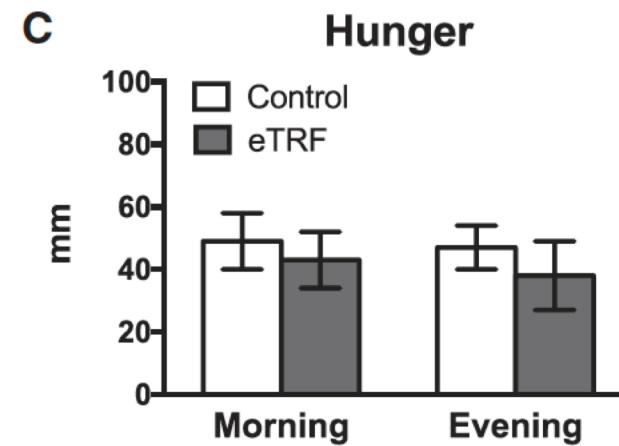
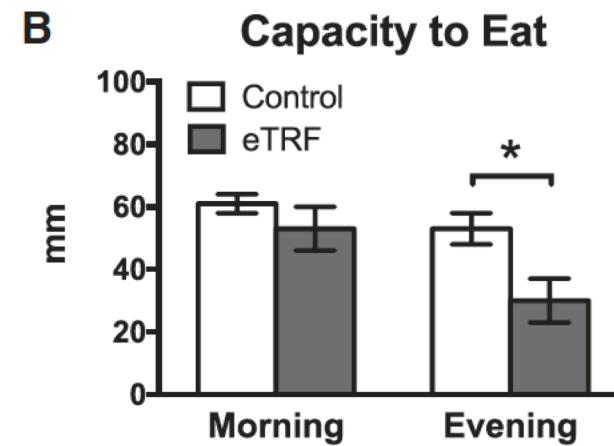
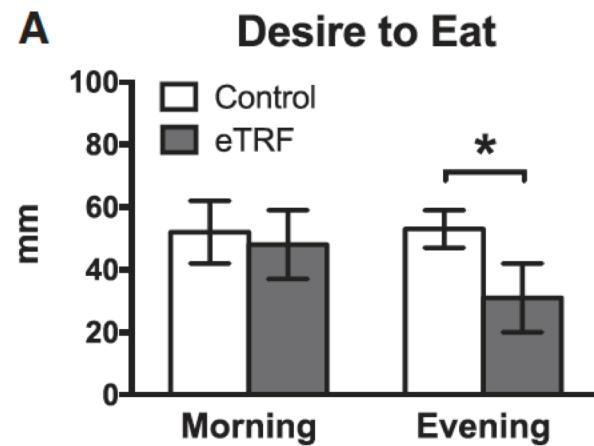
Day 1	Day 2	Day 3	Day 4	Day 5
<b>Breakfast</b>	<b>Breakfast</b>	<b>Breakfast</b>	<b>Breakfast</b>	<b>Breakfast</b>
Bagel Cream Cheese Tropical Fruit Cup 1% Milk *Boiled Egg *Cheddar Cheese	Oatmeal Scrambled Egg Whites 1% Milk Butter Grape Juice Graham Crackers Peanut Butter	Waffles Maple Syrup Butter Blackberries Boiled Egg 1% Milk Pears	Cereal: Honey Nut Cheerios Scrambled Egg Whites Fruit Cocktail 1% Milk Butter Vanilla Wafers	Blueberry Muffin Boiled Egg Tropical Fruit Cup 1% Milk Granola Bar Peanut Butter
<b>Lunch</b>	<b>Lunch</b>	<b>Lunch</b>	<b>Lunch</b>	<b>Lunch</b>
Whole Wheat Bread Ham Lettuce Tomatoes Mayo & Mustard Pretzels Peaches Hummus Dip	Hamburger Bun Grilled Chicken Breast Lettuce Tomatoes Mayo & Mustard Fruit Salad Yogurt (Strawberry) *Cheese Crackers	Whole Wheat Bread Turkey Lettuce Tomatoes Mayo & Mustard *Swiss Cheese Baked Tortilla Chips Salsa with Black beans Sour Cream	Whole Wheat Pita Bread Chicken Salad Lettuce Tomatoes Sun Chips Grapes Chocolate Pudding	Chicken Pesto Pasta Lettuce Tomatoes Fat-free Italian Dressing Pineapple Chunks 1% Milk
<b>Dinner</b>	<b>Dinner</b>	<b>Dinner</b>	<b>Dinner</b>	<b>Dinner</b>
Alfredo Pasta with Chicken Capri Mixed Vegetables Dinner Roll, White Butter Pears	Catfish Almondine Rice Pilaf Green Beans Butter Dinner Roll, Wheat Peaches 1% Milk	Lemon Sage Chicken Wild Rice Blend California Blend Vegetables Butter Dinner Roll, White Pineapple Chunks Mozzerella String Cheese	Spaghetti and Meatballs Broccoli Butter *Dinner Roll, Wheat 1% Milk	Pork Chop Rosemary Garlic Potatoes Carrots Butter Dinner Roll, White *Parmesan Cheese 1% Milk

\* Food was or was not served, depending on participant's calorie level.



**A Systolic Blood Pressure****B Diastolic Blood Pressure****C Augmentation Index****D Pulse Wave Velocity****E Heart Rate****F Total Cholesterol****G LDL Cholesterol****H HDL Cholesterol****I Triglycerides**





# Restriction alimentaire temporelle

## De la recherche pré-clinique sur les animaux à la prescription

2012-

Etudes animales



2015-

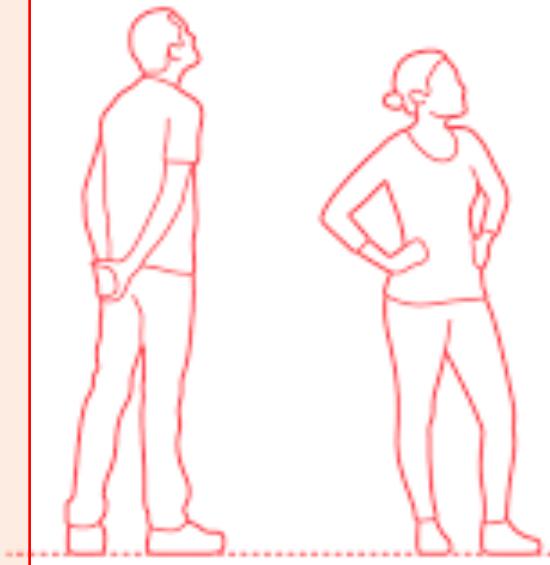
Etudes pilotes

2019-

Etudes d'intervention

2020-

Essais contrôlés  
randomisés



Effets sur le long terme ?

Standards et recommandations ?

Nutrition personnalisée / de précision

# **PLAN**

## **PARTIE 1 : physiologie**

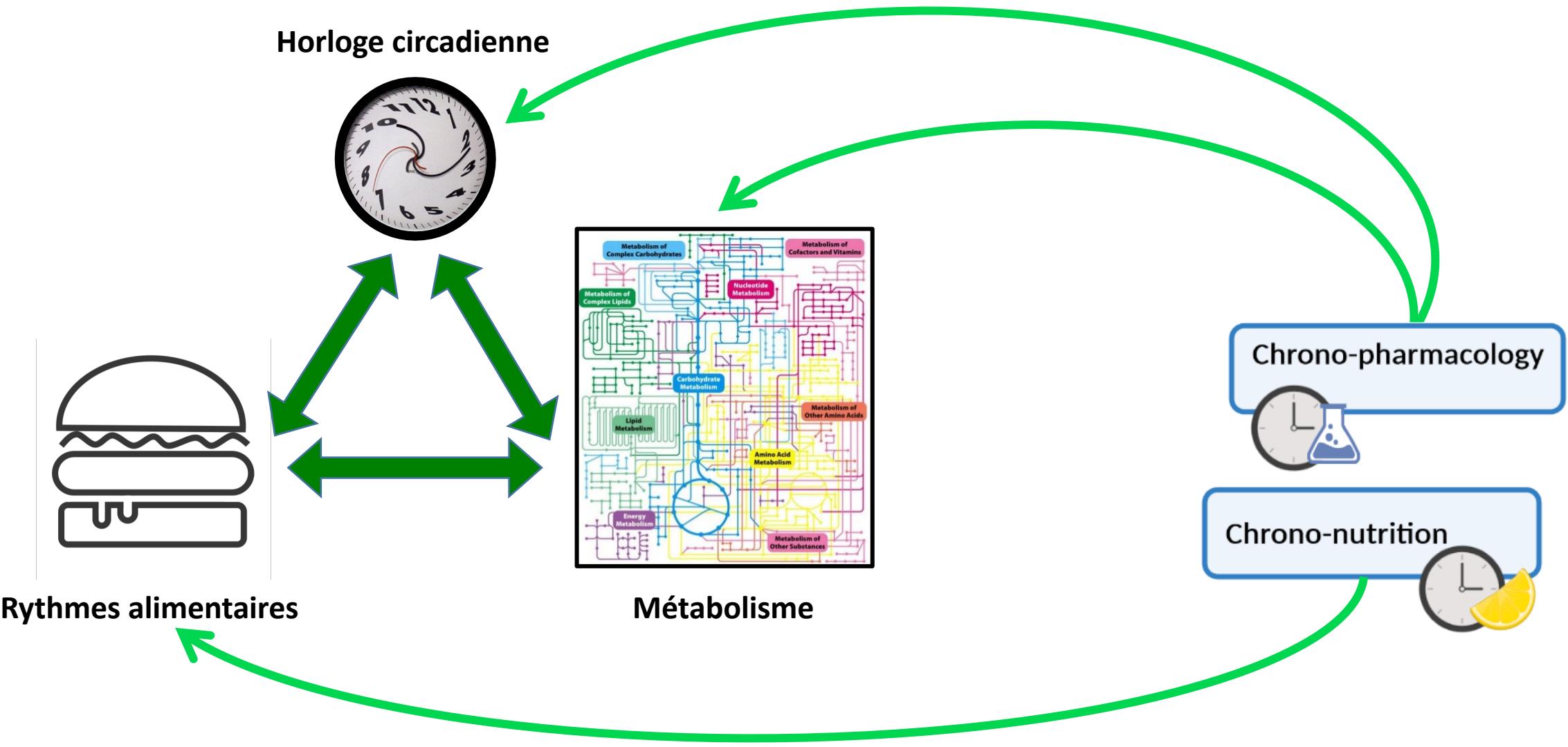
1. Introduction sur les rythmes circadiens

## **PARTIE 2 : pathologie**

1. Effet expérimental du régime gras
2. Décalage des rythmes et risque métabolique

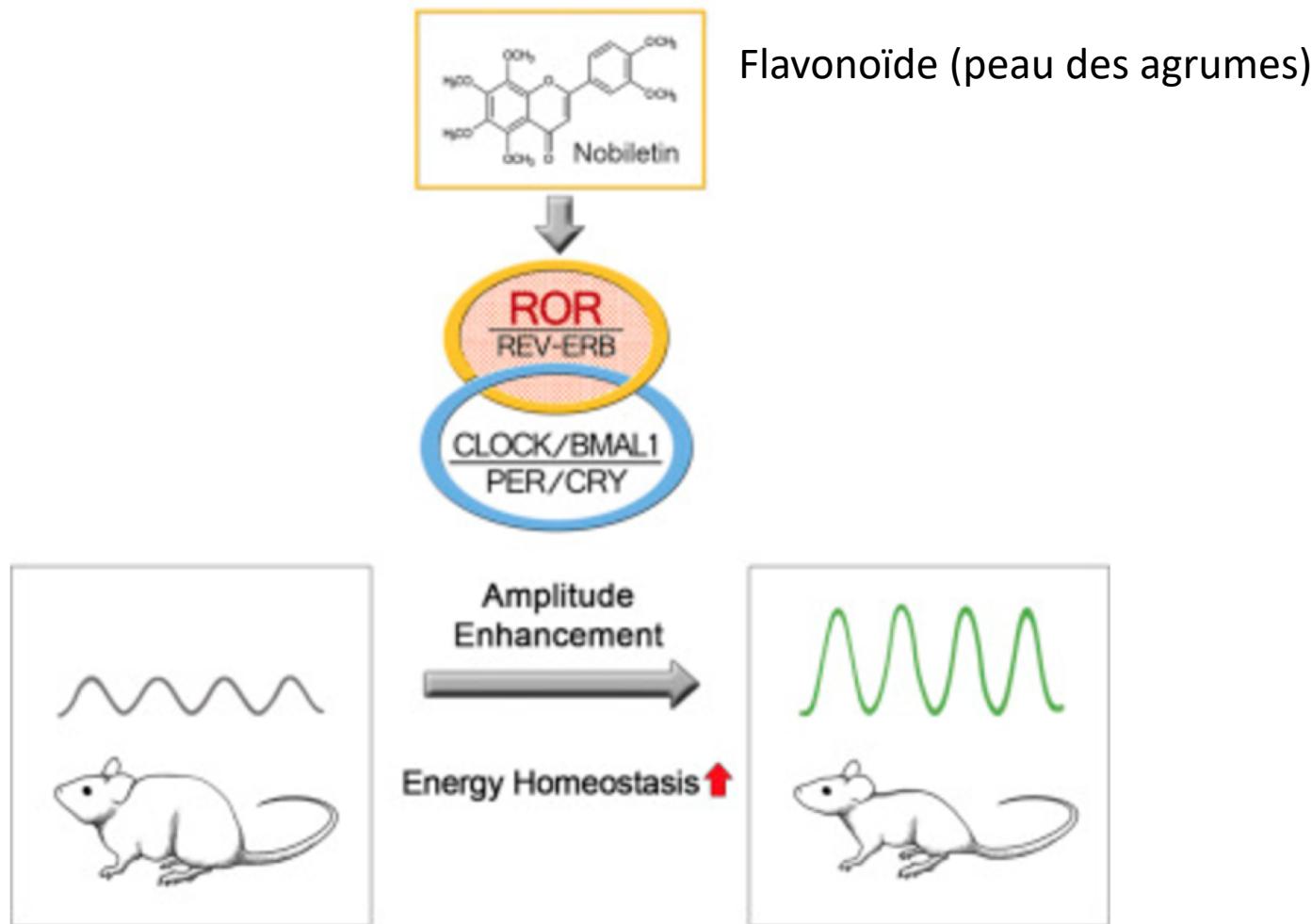
## **PARTIE 3 : étude d'article**

# Intervenir sur les rythmes biologiques pour moduler l'homéostasie métabolique

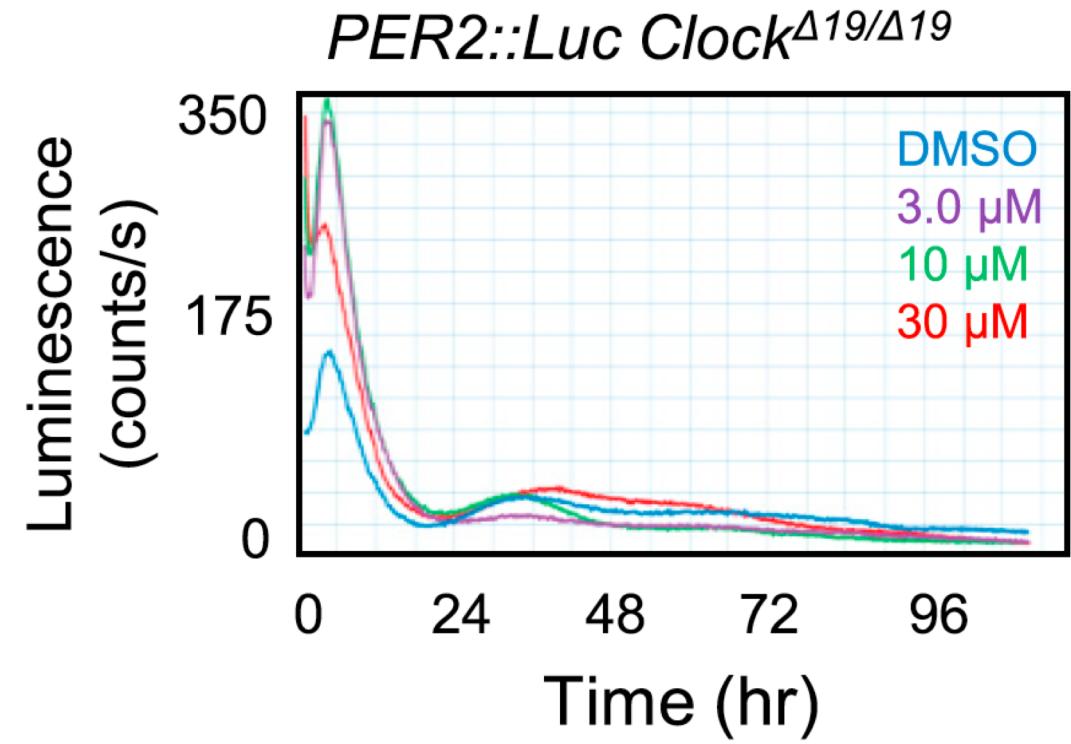
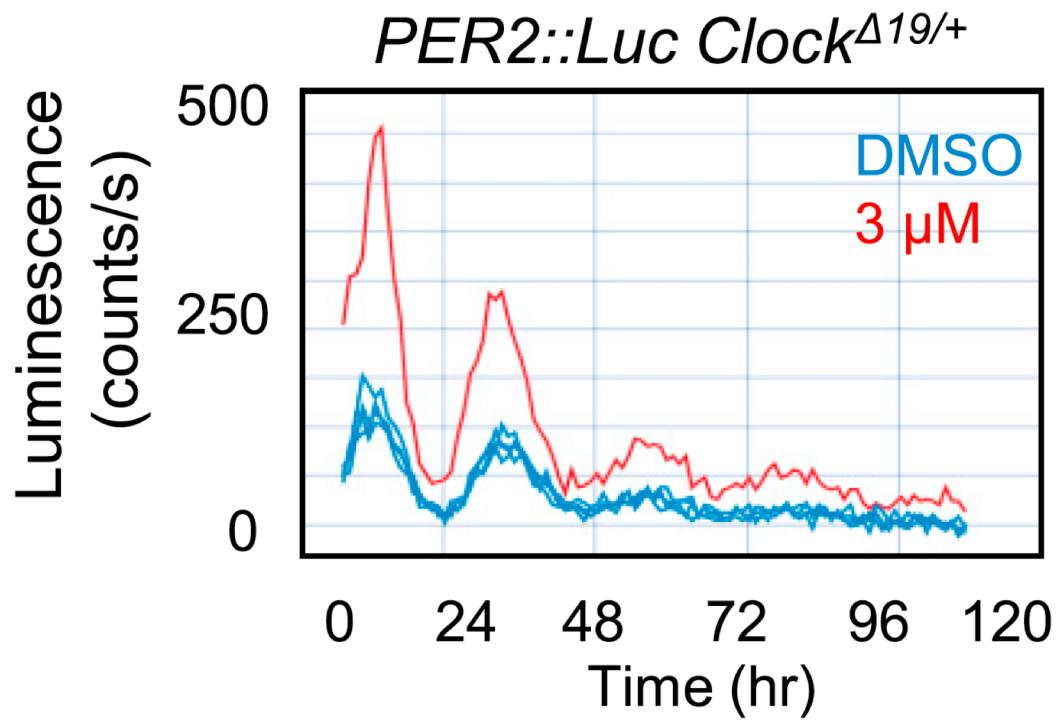


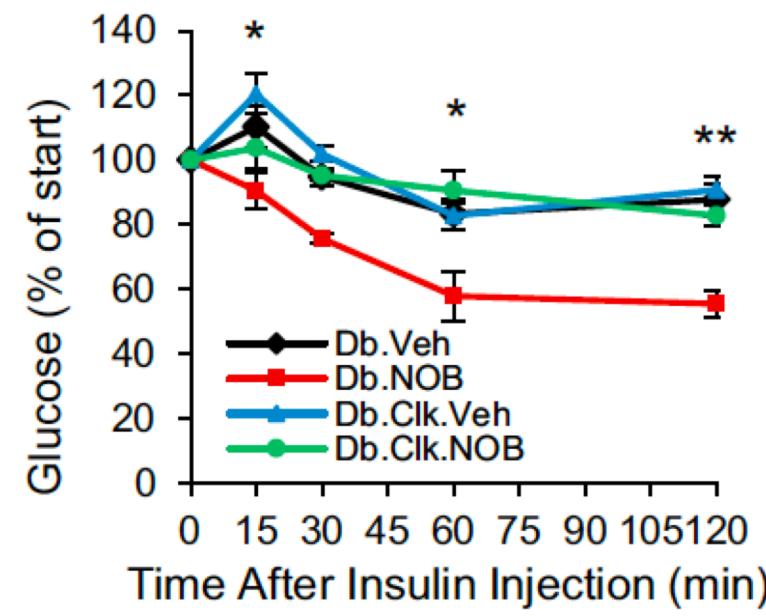
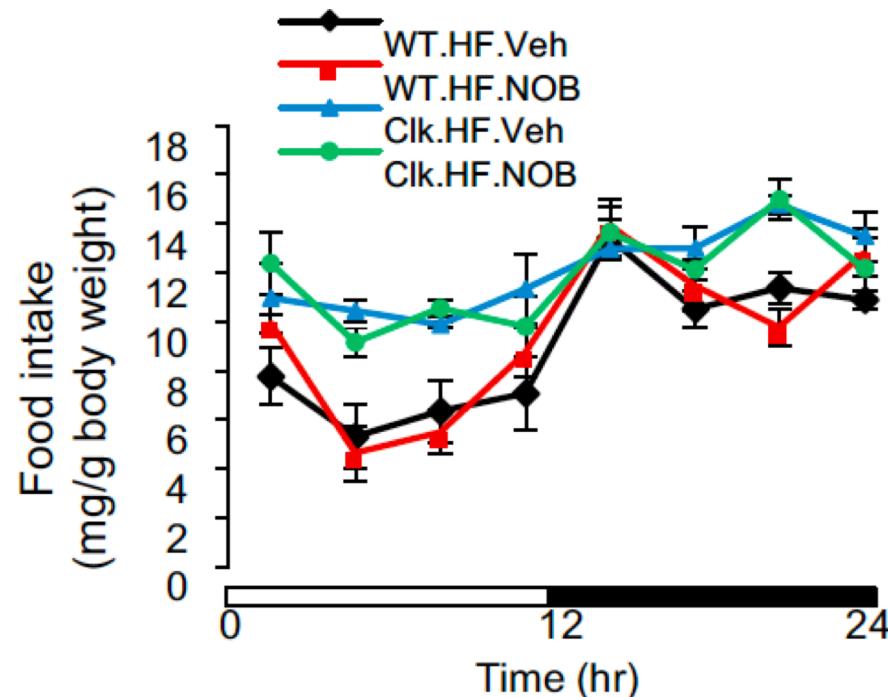
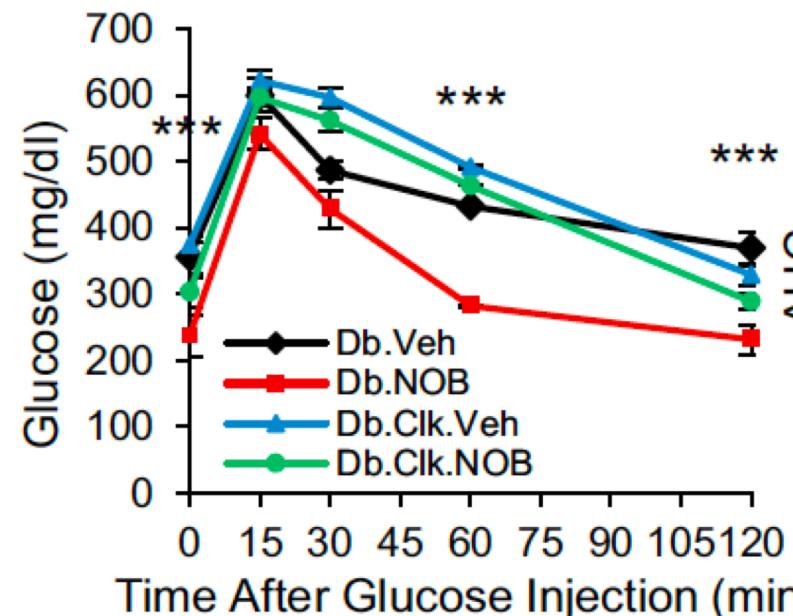
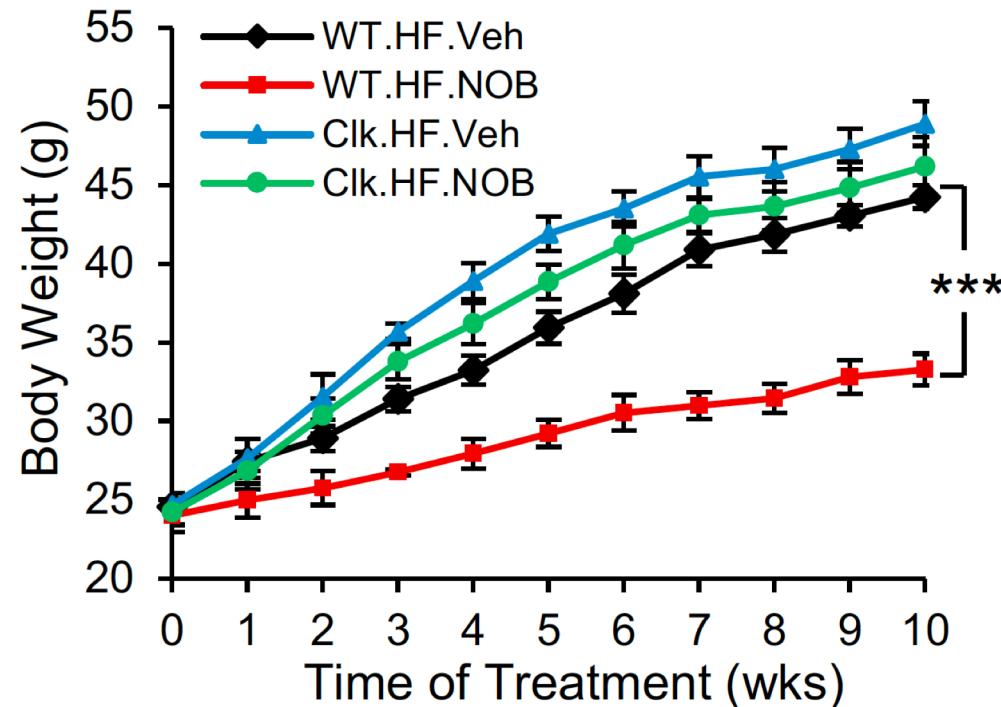
# The Small Molecule Nobiletin Targets the Molecular Oscillator to Enhance Circadian Rhythms and Protect against Metabolic Syndrome

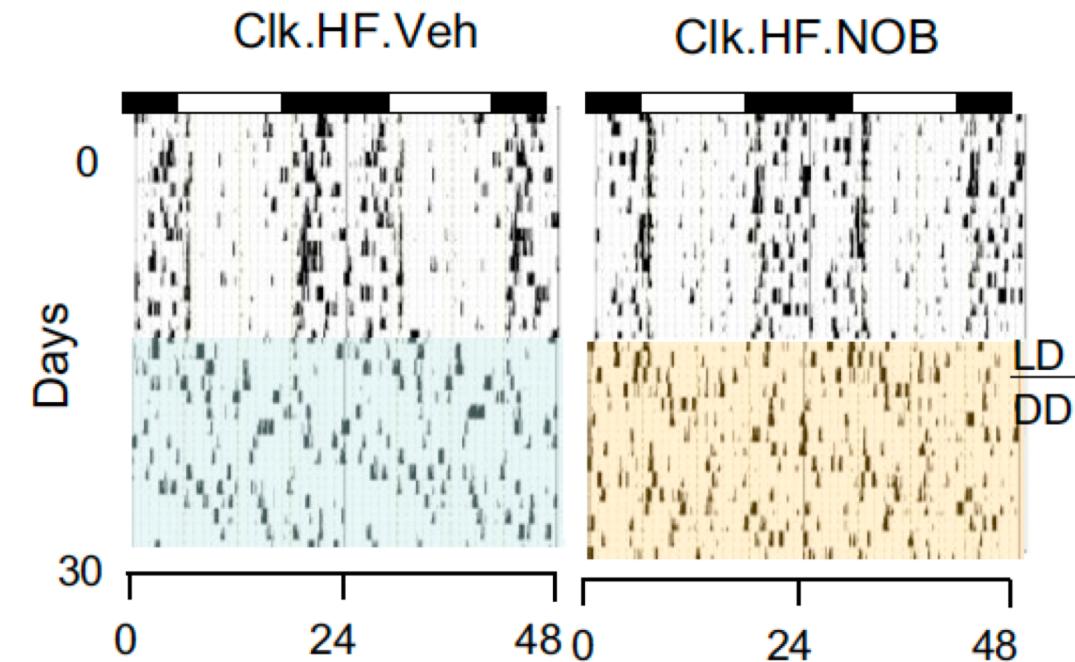
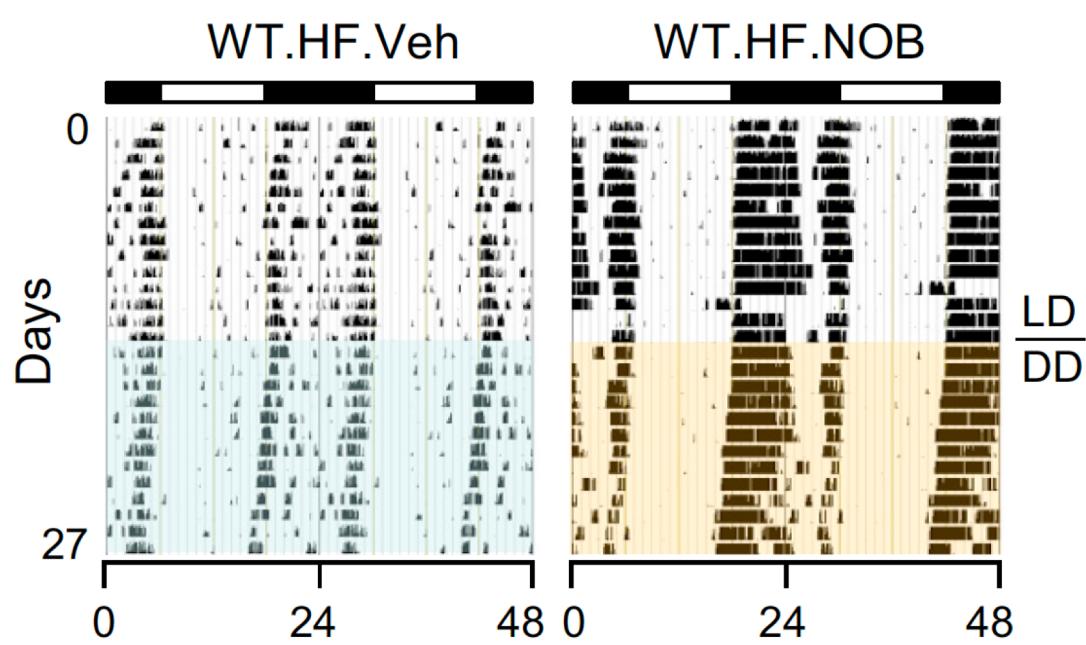
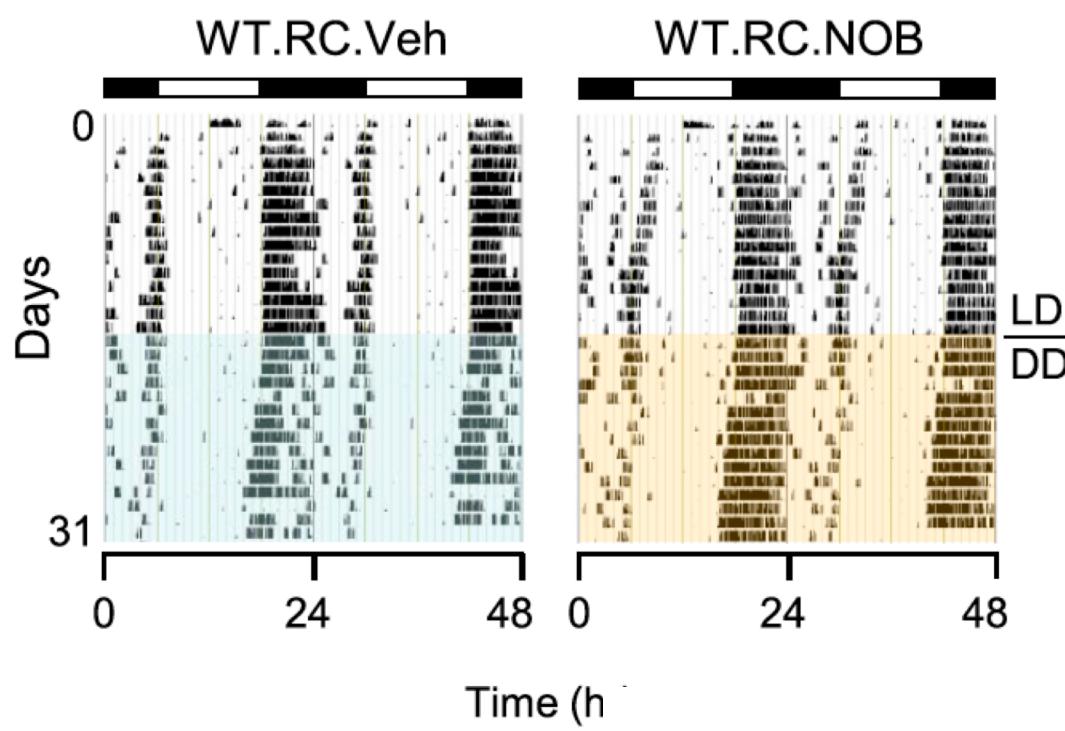
*He et al. Cell Metabolism 2016*

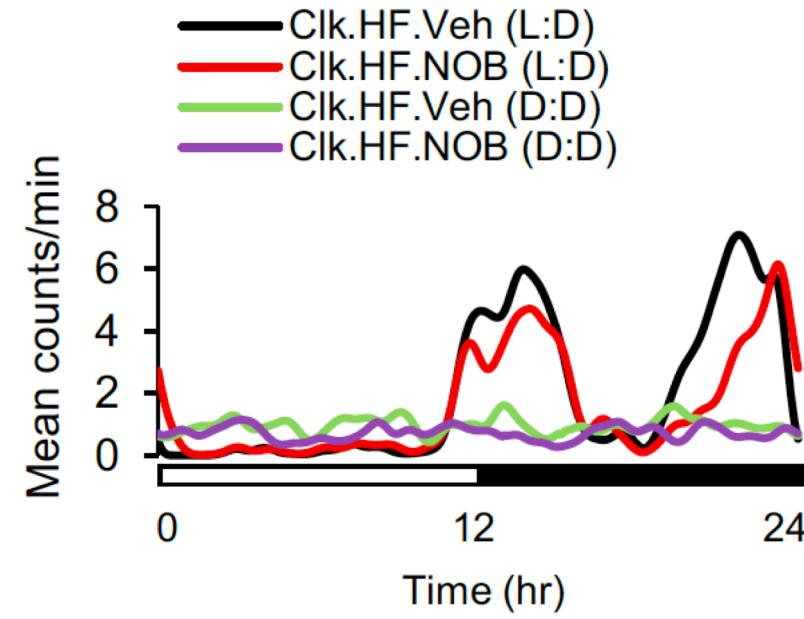
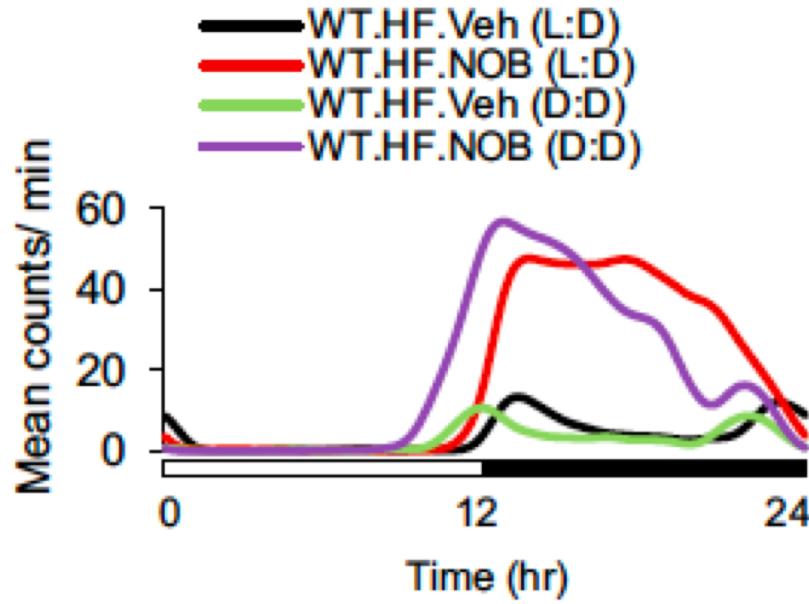
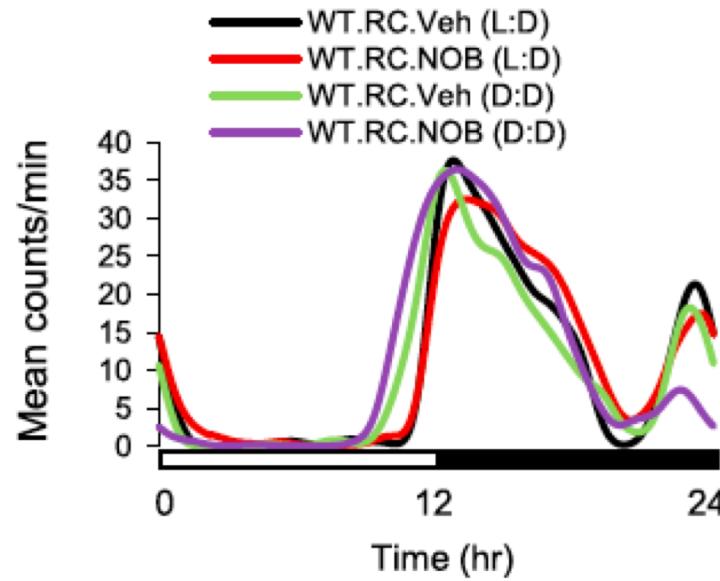


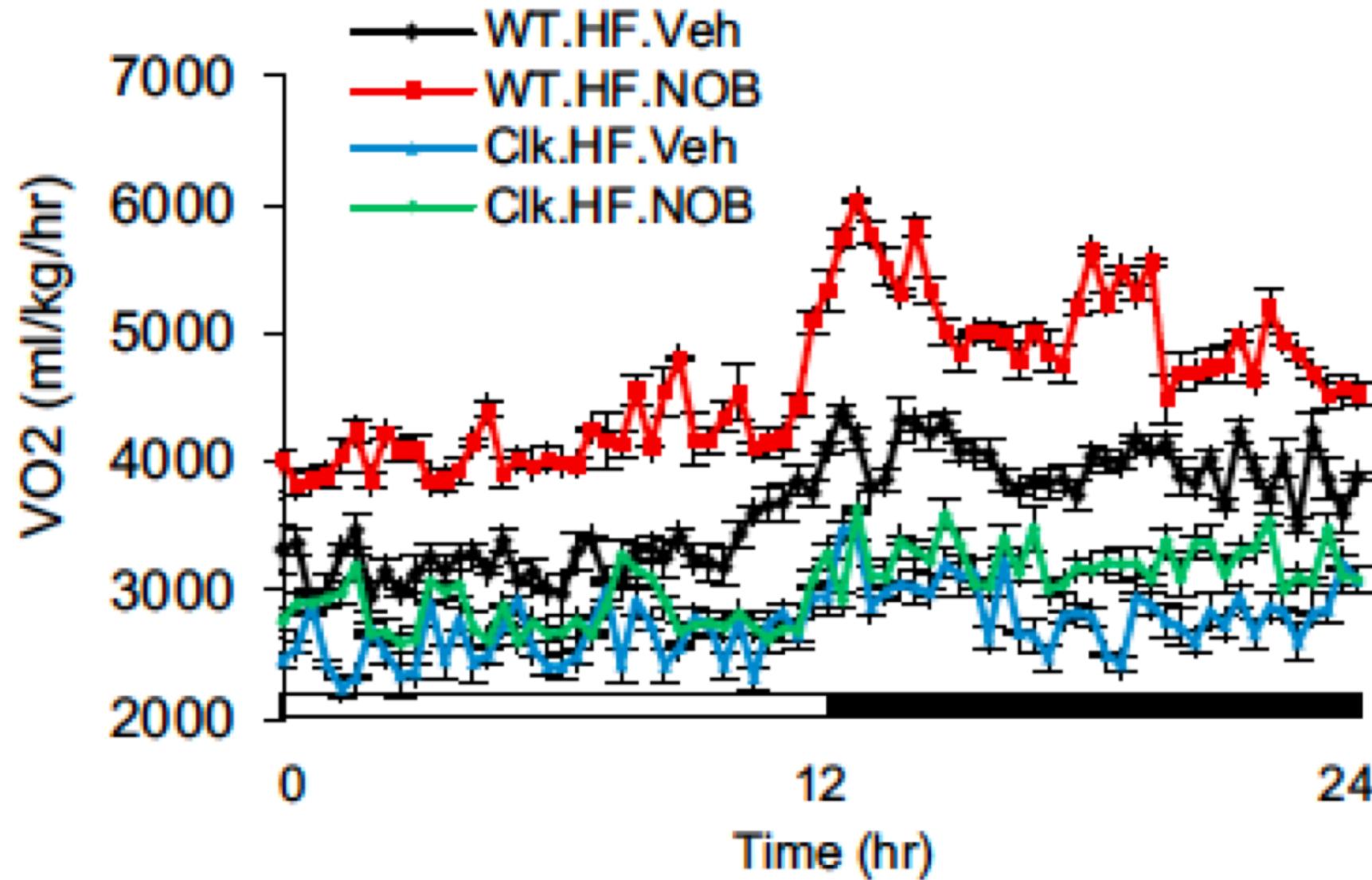
# *IN VITRO*

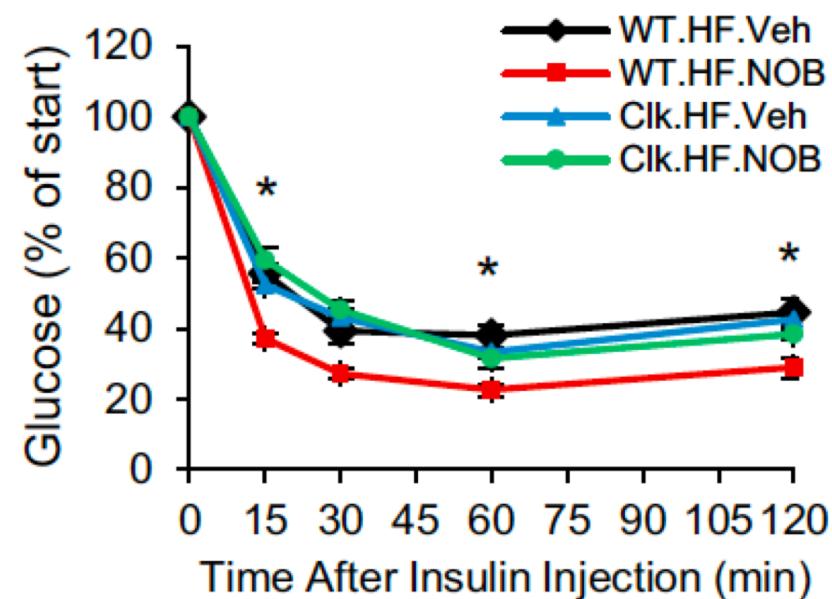
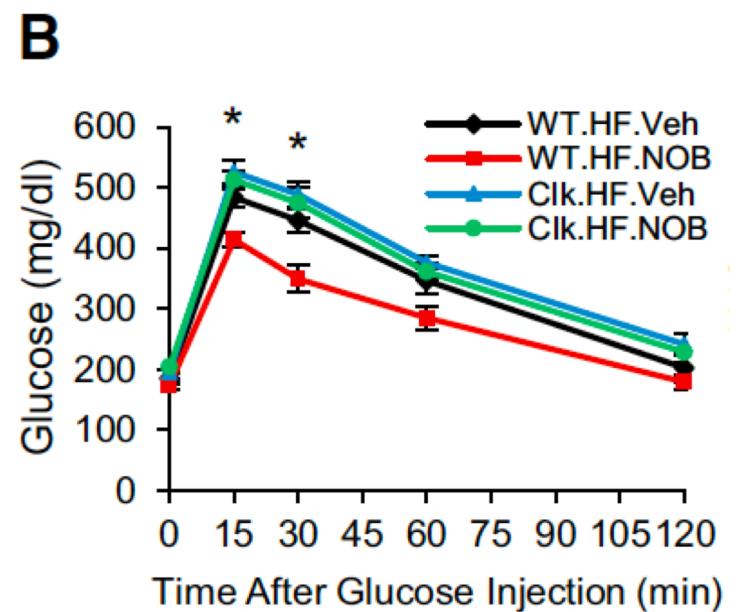
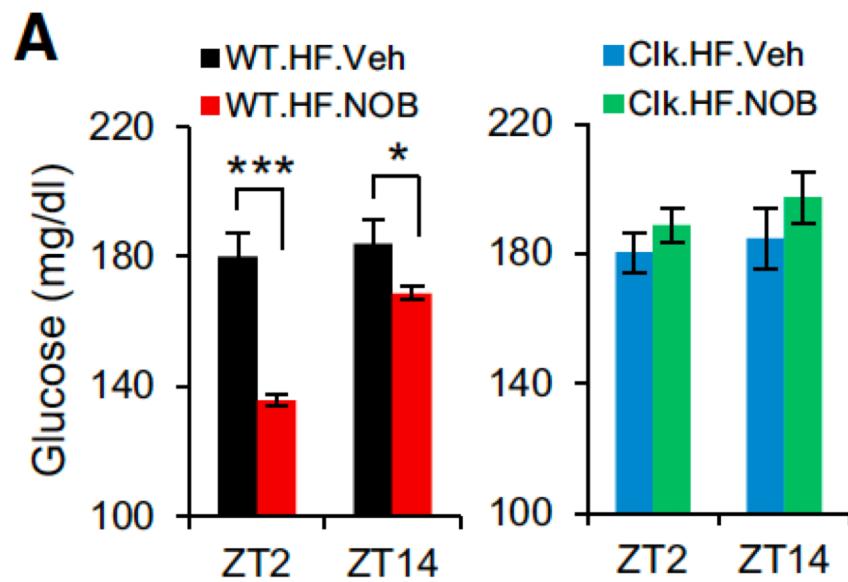


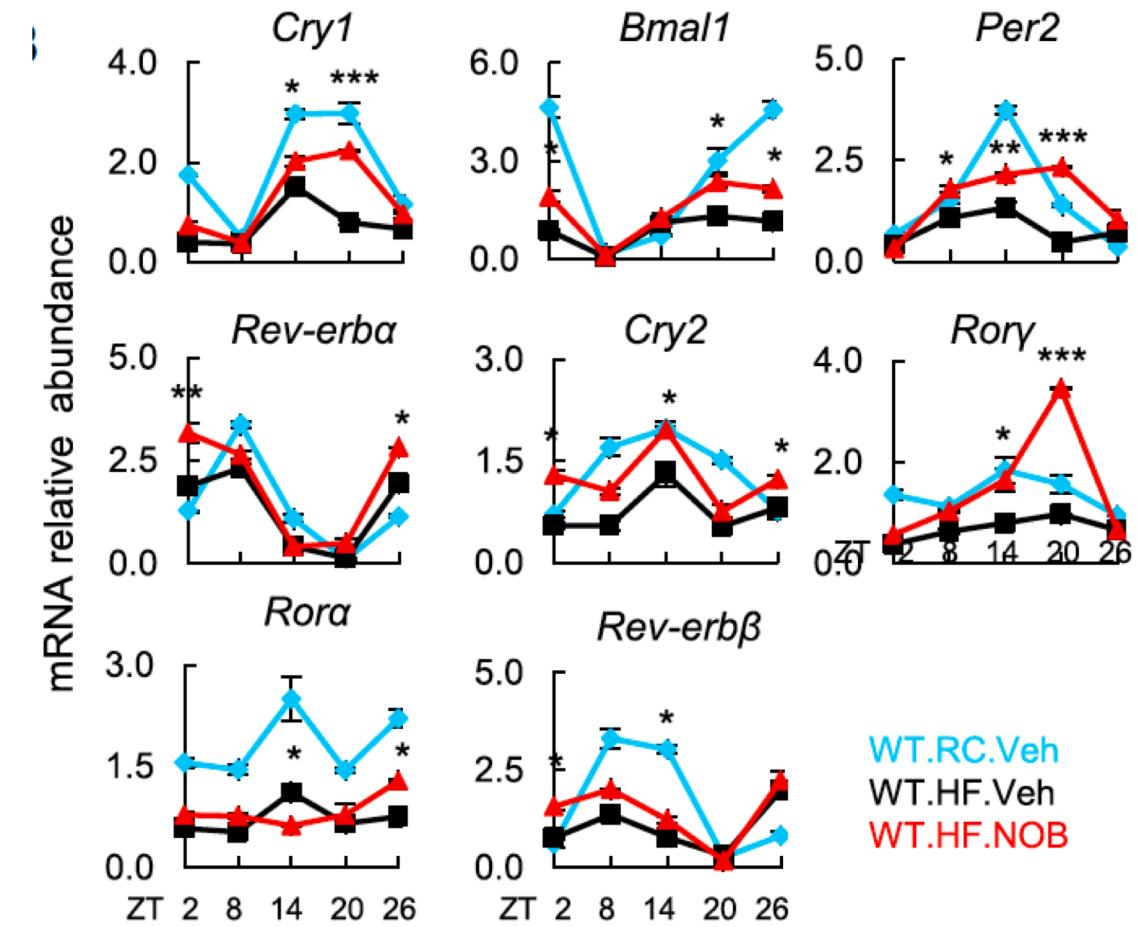
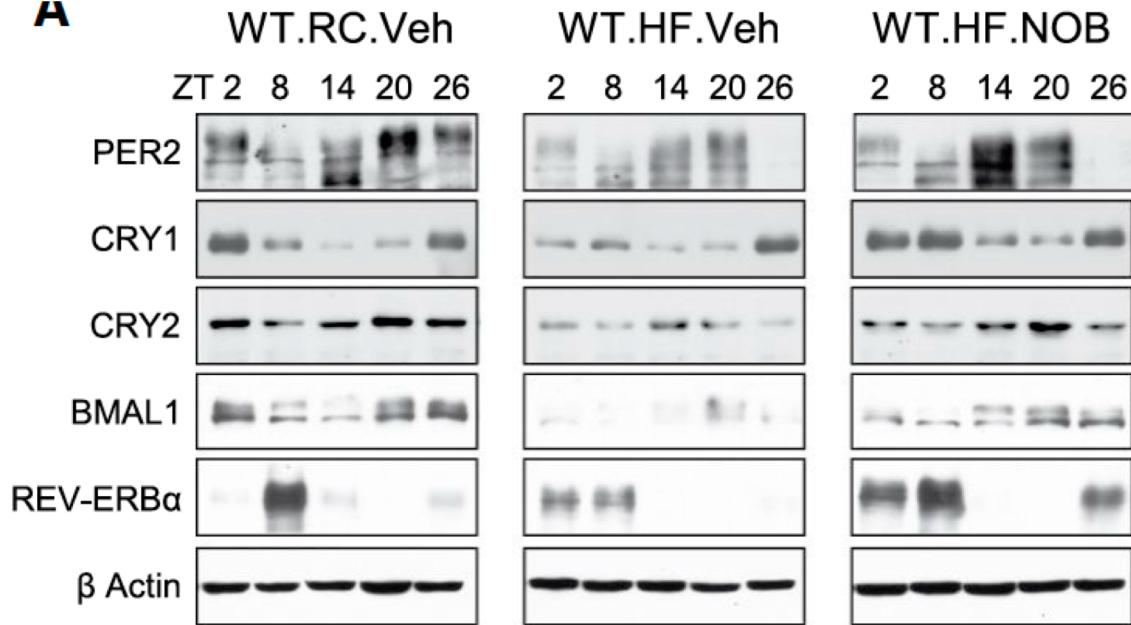




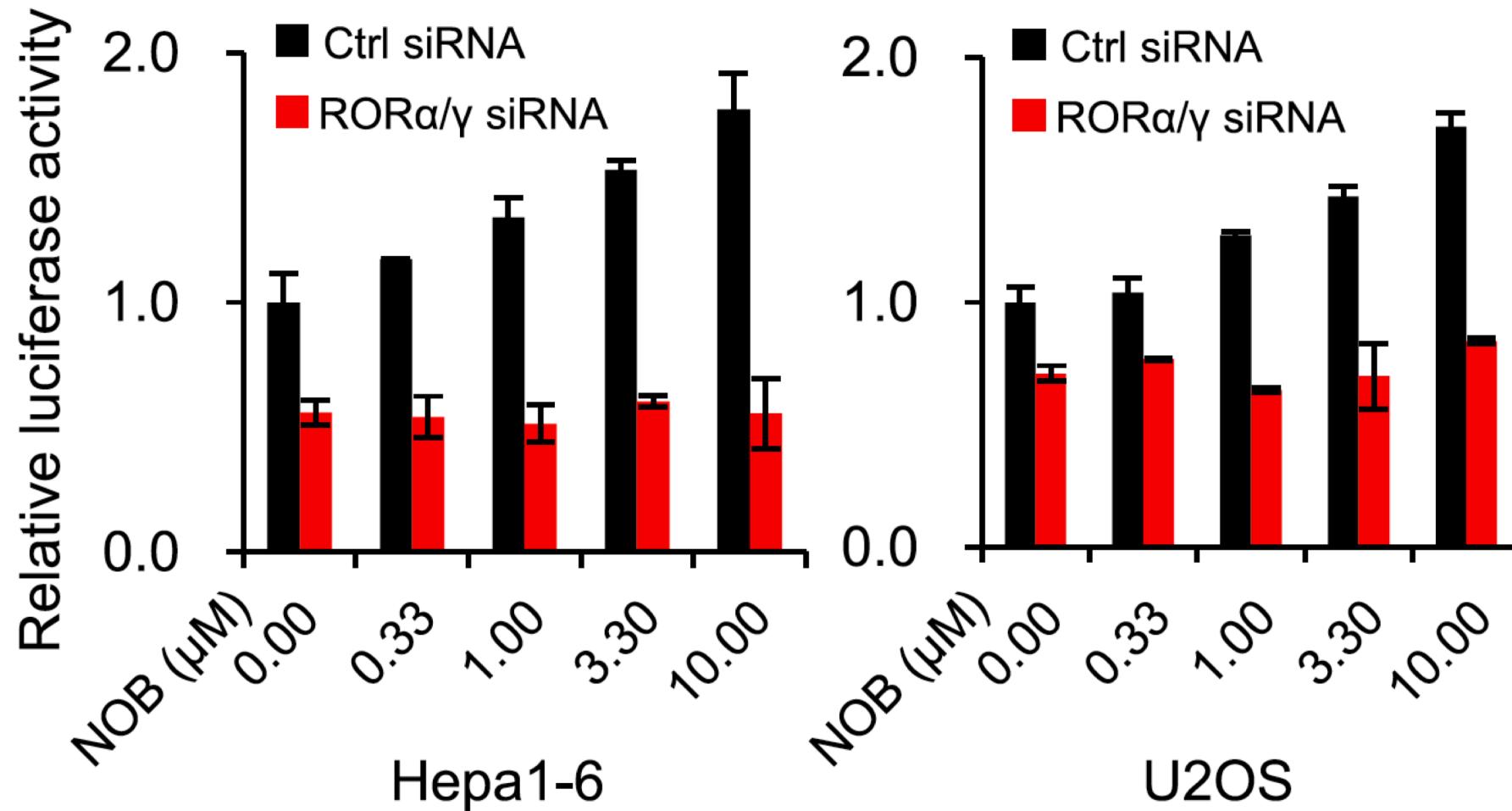






**A**

# Bmal1 promoter-driven luciferase reporter expression



# Rythmes circadiens et Maladies métaboliques



**Pr David JACOBI**  
**PUPH nutrition**