Food Intake Regulation & the Clock

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Circadian disruption affect multiple organ systems:

- **Brain**
  - Neurological Changes
    - Impaired memory
    - Dementia
    - Mood disorders
    - Anxiety

- **Lungs**
  - Cardiovascular Changes
    - Heart Attack
    - Stroke
    - TIA

- **Liver**
  - Liver Pancreas Kidney
    - Altered metabolism
    - Obesity
    - Diabetes
    - Cancer

- **Kidney**

- **Pancreas**

- **Breast**
  - Breast and Prostate
    - Cancer
    - Increased oncogene activity
    - Decreased tumor suppression gene activity

- **Prostate**

- **Gonads**
  - Uterus and Gonads
    - Infertility
    - Cancer
    - Low birth weight (offspring)
    - Preterm birth (offspring)

“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.”

Obesity and the circadian clock disruption

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

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.

No thanks. I read somewhere that late daytime snacking can be bad for your health.

What happens to insulin when the circadian clock is disrupted?

Two approaches:

A
- Knock out mice (Bmal1 -/-):
  - Disrupt circadian clock proteins
  - 24/7 insulin resistant mode (similar to inactive/fastiging phase)
  - Gained more weight, added more fat

B
- Disrupt circadian rhythm
  - Lights on all day and night

Wild type mice

Shiftwork

Night time light exposure

Decreased melatonin

- Decreased clearance of reactive oxygen species
- Heart disease
- Premature aging
- Cancer

Altered SHT signaling leading to mood disorders, depression, irritability

Hypothalamic nuclei

Pancreas, Liver, Adipose tissue

- Altered leptin/ghrelin signaling

Night time eating

- Heightened preference/consumption of high fat/sugar diet
- Metabolism in “resting” state at night
- Increased adiposity
- Insulin insensitivity
- Increased Body Mass Index

Increased Body Mass Index

- Obesity
- Stroke
- Diabetes
- Heart disease

Figure adapted from: Zelinski, E. L. et al (2014) Neuroscience and Biobehavioral Reviews 40:80–101
Food Intake during the Normal Activity Phase Prevents Obesity and Circadian Desynchrony in a Rat Model of Night Work

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Night worker activity (during normal resting phase)

- Induction of dysynchrony
- Influenced and moved food intake toward the working hours
- Significantly shifted triacylglycerol temperature rhythms
- Abolished general glucose activity rhythm

What would happen if you restricted food intake to the “normal” active phase and did not eat during the “rest” phase?

Experimental design:

Feeding conditions:
- AL = ad libitum
- FD = food restricted during day
- FN = food restricted during night

Note: water was always available

LD: ZT 0-12 (FD had food 0-12)  ZT 12-0 (FN had food 12-0)

WORKING TIME  ZT 2-10

Control (C)
- Left undisturbed during baseline in home cages.
- Undisturbed for 5 weeks during the experiment phase in home cages.
- Weekends undisturbed with food *ad libitum*.
- C-AL n=24
- C-FD
- C-FN

Night Work (W)
- Work protocol for 5 weeks 9-5pm (ZT 2-10)
- 8 hours day/5 days per week in work cages.
- Work protocol for 5 weeks 9-5pm (ZT 2-10)
- 8 hours day/5 days per week in work cages.
- Weekends undisturbed with food *ad libitum* in home cages.
- W-AL
- W-FD
- W-FN

These two groups had food while working

24 HOUR PERIOD

ZT 0-12 (FD had food 0-12)

Left undisturbed during baseline in home cages.

Monitored during baseline 8-10d.

Note: water was always available

ZT 12-0 (FN had food 12-0)

Work protocol:
- Rats were placed in slow rotating wheels which force the rats to stay awake.
- Slow rotating: rats don't need to walk the entire time; can sit and groom & lie down.

AL = *ad libitum*
FD = food restricted during day
FN = food restricted during night
Measurements:

**Food Intake**
- Monitored twice every week during the baseline and during working weeks by weighing separately the nocturnal and diurnal consumption.

**Weight**
- Rats were weighed before starting the baseline and at the end of the fourth week of the working protocol.
- Abdominal fat pads were dissected and weighed.

**Blood samples**
- At the end of the 5th working week blood samples for 2 days every 3 hours.

**Hormone levels**
- Glucose, TAG, Corticosterone
W-AL and W-FD rats exhibited along the weeks a decrease of their nocturnal activity and dampening of the daily activity rhythm. The rats W-FN maintained similar proportions of daily activity as observed in the baseline and the control groups.

Daily rhythms are observed clearly synchronized to the LD cycle without change in the predominating nocturnal patterns of activity in the three groups.

Food ingestion, weight and abdominal fat levels

The groups that ate during the normal resting phase (C-FD, W-AL, and W-FD) showed major body weight gain (B) and higher accumulation of fat (C and D).

FIG 3. Mean daily food intake ± SEM (A), body weight gain (B), and retroperitoneal (C) and peritoneal (D) fat of control (n = 6–7 per subgroup) and working groups (n = 6–7 per subgroup) with food ad libitum (light gray bars), food during the day (white bars), and food during the night (dark gray bars), striped bars = working groups. All the groups showed a similar daily pattern of food consumption (A); however, groups that ate during the normal resting phase (C-FD, W-AL, and W-FD) showed major body weight gain (B) and higher accumulation of fat (C and D). Different letters indicate significant differences among groups (P < 0.05).
Daily values for glucose, TAG, and corticosterone (mean SEM) for control groups (A, C, and E) and working groups (B, D, and F) (n 5–9 per group) after 4 wk with food ad libitum (gray circles), with food during the day (FD; yellow squares), or with food during the night (FN; red triangles).

White and black horizontal bars, LD cycle; striped bar, time in the activity wheel. Asterisk (ad libitum), cross (FD), and (FN) indicate statistical difference between the highest and the lowest values of the same group (P 0.01).
Daily temperature curves (mean SEM) for the control groups and working groups (n = 5–6) with food ad libitum (gray circles, top row), with food during the day (white squares, middle row) and food during the night (gray dark triangles, bottom row) after 4 wk.

White and black horizontal bars, LD cycle; striped bar, food access.

*Bar charts*, Mean values for the day and night temperature.

Control groups are represented by *filled bars* and working groups by *striped bars*.

The *asterisk* indicates statistical difference between day and night temperature (P < 0.01).
Review

The trouble with circadian clock dysfunction: Multiple deleterious effects on the brain and body

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Abstract

This review consolidates research employing human correlational and experimental work across brain and body with experimental animal models to provide a more complete representation of how circadian rhythms influence almost all aspects of life. In doing so, we will cover the morphological and biochemical pathways responsible for rhythm generation as well as interactions between these systems and others (e.g., stress, feeding, reproduction). The effects of circadian disruption on the health of humans, including time of day effects, cognitive sequelae, dementia, Alzheimer’s disease, diet, obesity, food preferences, mood disorders, and cancer will also be discussed. Subsequently, experimental support for these largely correlational human studies conducted in non-human animal models will be described.

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Circadian Disruption Leads to Insulin Resistance and Obesity

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Background: Disruption of circadian (daily) timekeeping enhances the risk of metabolic syndrome, obesity, and type 2 diabetes. While clinical observations have suggested that insulin action is not constant throughout the 24 hr cycle, its magnitude and periodicity have not been assessed. Moreover, when circadian rhythmicity is absent or severely disrupted, it is not known whether insulin action will lock to the peak, nadir, or mean of the normal periodicity of insulin action.

Article

Results: We used hyperinsulinemic-euglycemic clamps to show a bona fide circadian rhythm of insulin action; mice are most resistant to insulin during their daily phase of relative inactivity. Moreover, clock-disrupted Bmal1-knockout mice are locked into the trough of insulin action and lack rhythmicity in insulin action and activity patterns. When rhythmicity is rescued in the Bmal1-knockout mice by expression of the paralogous gene Bmal2, insulin action and activity patterns are restored. When challenged with a high-fat diet, arhythmic mice (either Bmal1-knockout mice or wild-type mice made arhythmic by exposure to constant light) were obese prone. Adipose tissue explants obtained from high-fat-fed mice have their own periodicity that was longer than animals on a chow diet.

Conclusions: This study provides rigorous documentation for a circadian rhythm of insulin action and demonstrates that disturbing the natural rhythmicity of insulin action will disrupt the rhythmic internal environment of insulin sensitive tissue, thereby predisposing the animals to insulin resistance and obesity.
Glucose Clamps – Techniques used to quantify glucose metabolism and insulin resistance:

Hyperglycemic
- Plasma glucose levels are raised to 125mg/dl
- Glucose levels are maintained at a high levels by continuously infusing glucose
- The amount of glucose needed to be infused is a measure of: insulin secretion capacity

Hyperinsulinemic-euglycemic
- 100muU/ml maintaining a constant infusion of insulin into a vein.
- Blood glucose is maintained at normal levels by continuously infusing glucose (due to high insulin)
- The amount of glucose needed is a measure of: glucose metabolism