Neuroendocrine control

It is thought that circadian regulation of physiology and behavior imparts survival advantages to organisms that use clocks. In mammals, a master clock resident in the SCN synchronizes other central and peripheral oscillators to evoke this regulation.

This master oscillator consists of interlocking transcriptional-translational feedback loops, and it regulates both core clock genes necessary for oscillator maintenance as well as specific output genes that directly or indirectly mediate physiology under circadian control.

It is now clear that both neuroanatomical and molecular outputs of the clock are necessary for proper circadian clock function.

Neuroendocrine control

Sensor integration center (concept vs anatomy)

Afferent "story line"

Efferent "story line"

Sensor

Effecter

Negative feedback "story line"

E.g. °C/F

Neuroendocrine control

Sensor integration center (concept vs anatomy)

Afferent "story line"

Efferent "story line"

Sensor

Effecter

Negative feedback "story line"

E.g. °C/F

"Anticipation"
Neuroendocrine control

- Afferent “story line”
- Efferent “story line”
- Integration center (concept vs anatomy)
- Feedback

Sensor e.g. 1°C/F

What if …

“Homeostatic control”

Example

If glucose is detected in the blood ???
Glycemia up
Insulin up
Glycemia down

E.g. glucose on β-cells
Neuroendocrine control

Theoretically, a feedforward mechanism anticipates the logistics needed to carry on a specific physiological effect.

Keep this thought in mind for the rest of this lecture.
Chronobiology, or the study of biological rhythms, concerns itself with the timing of events within and external to animals.

Single cells and animals have evolved timing systems that are important for every type of behaviors and physiology.

**examples**

Migration and hibernation versus day and night

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The golden hamster is the chronobiologists’ favorite animal subject because of their impressive daily rhythms in their use of a running-wheel kept in their cage. They sleep during the day and run all night.

**methods**
Biological rhythms - a clock

But, what happens if you do not know if it is day or night??
Biological rhythms - a clock

Effect of constant darkness or constant light. Both conditions are free running conditions.

activity rhythms

splitting rhythm after prolonged exposure to constant light

(each horizontal line represents two days of data)

activity rhythms

Effect of constant darkness or constant light. Both conditions are free running conditions.
Biological rhythms - a clock

Evening (E) / morning (M) oscillators in mammalian photoperiodism.

A, oscillators entrained to a short night rhythm
B, as nights get longer (PRC) the oscillators drift apart since their free running rhythms differ
C, in long nights oscillators adopt an entrainment pattern where they overlap minimally

entrainment (zeitgebers)

Biological rhythms - PRC

effect of a light pulse

all individuals are running in constant darkness, a free running condition.
Melatonin is derived from the amino acid tryptophane, the same as the NT serotonin.

Melatonin is released from the pineal gland into the CSF and blood during the night.
Biological rhythms - Melatonin

L:D Summer condition

- e.g. long day vs short night

L:D Winter condition

- e.g. short day vs long night

Melatonin light induced Summer vs Winter condition

exogenous melatonin induced Summer vs Winter condition
Biological rhythms - Melatonin

Free running rhythm of drinking behavior in rats

- exogenous melatonin entrained rats to the period of the injection regime

Blinded rat with intact SCN

- All individuals are blind, thus they are running in constant darkness, a free running condition

So, light may not be necessary ...
Suprachiasmatic nucleus

Blinded rat with intact SCN

Blinded rat with a lesioned SCN

SCN

All individuals are blind, thus they are running in constant darkness, a free running condition

Suprachiasmatic nucleus

A. 

So, what might be the relationship among biological rhythms, light, the SCN and melatonin ??? ...

B.
So, what might be the relationship among biological rhythms, light, the SCN and melatonin???

SCN

Melatonin is released from the pineal gland into the CSF and blood during the night.
Theoretically, a feedforward mechanism anticipates the logistics needed to carry on a specific physiological effect.

The PVN or “integrator” concept and the SCN or “anticipation” concept.
SCN - repro rhythm to clock

- Blinded rat with intact SCN (have repro rhythm)
  - Individuals are blind, thus they are running in constant darkness, a free running condition

- Blinded rat with a lesioned SCN (do not have repro rhythm)

The SCN is responsible for the precise timing of the LH surge:

1. SCN lesions eliminates the ovarian cycle (behavior & LH surge).
2. The LH surge maintains its exact relationship to the locomotor activity in a constant light environment, suggesting they are controlled by the same circadian mechanism.
3. Lengthening / shortening of activity cycle by pharmacological treatment or light entrainment alters the estrous behavior and the LH surge.
4. Pentobarbital in proestrous AM temporarily blocks the LH surge, which occurs at precisely the normal time the next day.

... and how would you use this knowledge to make a clock??
DNA → cAMP ----> PKA ----> channel / enzyme

Steroid S + R ----> SR

Protein synthesis

mRNA

Cellular response

Na / K pump

e.g. repro rhythm to clock

... a hint ... how would you use this knowledge to make a clock ??? ...

SCN - repro rhythm to clock

... and what the hell is this supposed to mean ??? ...
SCN - repro rhythm to clock

... a negative feedback

SCN - repro rhythm to clock

... a negative feedback
SCN - repro rhythm to clock

e.g. repro rhythm to clock. A ‘circle’ intersecting a ‘circle’

SCN - repro rhythm to clock

signal transduction

SCN neuron

SCN clock neuron

Target cell

nuclear responses

neurogenic or paracrine

“CCG”

“CG”

“CCGs”

cytoplasmic responses

“CCG”

retinal ganglion cell

glutamate

SCN clock neuron

photoreceptor

SCN - repro rhythm to clock
Phosphorylation of CREB signal transduction

SCN - repro rhythm to clock

SCN times rhythmic events:
1. SCN lesions eliminates rhythmic events. Fetal SCN transplantation to SCN lesioned rats restore rhythmic activities.
2. The restored rhythm depends on donor SCN (exp: 22h vs 24h rhythm).
3. In some cases, this restoration does not depend on re-establishment of synaptic connections since encapsulated SCN (allows diffusion of small chemicals but not neuronal outgrowth) is able to restore activity rhythms.
4. However, in some other cases, neuronal connections may be necessary to restore rhythmic events.

Oscillators (SCN & others)
Oscillators (SCN & others)

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and ... how do oscillators get entrained or reseted (zeitgeber)? ...

Oscillators (SCN & others)

Light resetting kinetics

Delayed induction of Per in shell by peptidergic signals from core

Rapid induction of Per in core by retinal innervation

Retina
Oscillators (SCN & others)

Its all in the timing
Its all in the timing
So, reproductive cyclicity in both humans and farm production animals might be a function of the neuroendocrine control associated with clock genes.

So, … ovulation in humans and egg production in laying hens might be a function of the neuroendocrine control associated with clock genes.
**Clocks and Ovulation Induction**

So, ... ovulation induction by light in humans (e.g. puberty) and mares might be a function of the neuroendocrine control associated with clock genes.

**Clocks and Lactation**

So, ... lactation in humans and milk production in farm production animals might be a function of the neuroendocrine control associated with clock genes.
So, ... reproductive aging in humans and farm production animals might be a disfunction of the neuroendocrine control associated with clock genes.

So, ... hypertension in humans might be a disfunction of the neuroendocrine control associated with clock genes.