Circadian Rhythms



Controlling the timing of behaviour by anticipating the environment



- Circadian = circa + dium
- Exists in most if not all unicellular and multicellular organisms

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The Circadian Circuit



Health consequences of circadian misalignment



Roenneberg et al. (2012) Current Biology

Shift Work



Increased risk of:

- Obesity
- Diabetes
- Cancer
- Mental Illness



Historical Perspective





Jean-Jacques d'Ortous de Mairan (1678 – 1771)

Hist de l'Acad Royal Sci (Paris), 1729

"...Il est seulement un peu moins marqué lorsqu'on la tient toujours enfermée dans un lieu obscur..."

"The sensitive plant hence perceives the sun without seeing it"

Rhythms in leaf-opening persist even in the absence of sunlight

Historical Perspective

Rat







Nathaniel Kleitman (1895 – 1999)

Historical Perspective

'Founders of Chronobiology' 1960





Colin Pittendrigh (1918 – 1996)

Jürgen Aschoff (1913 – 1998)



- Conceptual framework of circadian rhythms
- Long before any genes or neural circuits were identified



Cold Spring Harbor Symposium on Quantitative Biology, Vol. XXV *Biological Clocks*

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What would a circadian pacemaker look like?

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Output Rhythms Hormonal Cycles Rest/Wake Feeding

The Molecular Clock

Circadian behaviour has a genetic component

Drosophila period (per)



B. arrhythmi	24 hours — C mutant	>	
C. short-pe	riod mutant		

------ 28 hours ------>

Konopka & Benzer, PNAS 68:2112, 1971



Ron Konopka & Seymour Benzer

eclosion

Identification of the molecular mechanisms controlling circadian rhythms

Core clock genes in drosophila





Jeffrey C. Hall Michael Rosbash Michael W. Young

"for their discoveries of molecular mechanisms controlling the circadian rhythm"

Nobelprize.org

Similar molecular mechanisms generate circadian rhythms in flies and mammals

Core clock genes in drosophila



Core clock genes in mammals



Transcription-translation feedback loop

Deleting the circadian clock causes arrhythmicity

Wildtype	Heterozygous	Homozygous KO _{Hours}		
Hours	Hours			
8 16 24 32 40 48	0 8 16 24 32 40 48	0 8 16 24 32 40		
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• Global Bmal1 KO

48

• Fully deleting any of the 4 key components of the molecular clock causes behavioural arrhythmicity

The core circadian clock genes are expressed throughout the body

Expression of Bmal1



However, one area of the brain was particularly enriched in clock genes

The Master Pacemaker

In mammals, the suprachiasmatic nucleus (SCN) is the master circadian pacemaker





The SCN is necessary and sufficient for circadian rhythms



The SCN has self-sustained rhythms in gene expression, firing activity and neurotransmitter release



Individual SCN neurons have circadian oscillations in gene expression driven by the 'molecular clock'

Core Clock genes create a ~24-h transcription-translation feedback loop







The SCN is Composed of Multiple Autonomous Single-Cell Oscillators



Self-sustained rhythms is a unique feature of the SCN



Yamazaki et al (2009) JBR

In vivo rhythms in firing activity and gene expression



Many open questions remain about SCN function



- How neurons in the SCN respond during different lighting conditions (e.g. seasons) and disease-states (e.g. Alzheimer's)
- How individual SCN neurons couple together?
- How input information is processed within the SCN
- How circadian information is communicated to the rest of the brain

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Photic Information

Blocking the input pathway to the SCN should result in a free-running organism

- Ennucleated mice show free-running circadian rhythms
- However, mice that lack both rods and cones show intact circadian rhythms

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Melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs) are necessary for circadian entrainment





ipRGCs project to the suprachiasmatic nucleus as well as other brain regions



Pretectal region

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How does the SCN communicate circadian information to the rest of the brain?

SCN largely innervates hypothalamic areas



SCN transplants only partially recover circadian rhythms



Meyer-Bernstein et al. (1999) Endocrinology

Guo et al. (2006) J Neurosci

Timed firing of SCN can shift circadian rhythms in locomotor activity





Mazuski et al

SCN circuits that can modulate other behaviours





SCN VIP neurons can regulate the timing of aggression

SCN vasopressin neurons can regulate the timing of thirst

Circadian regulation of key behaviours remains unexplained



Many questions remain about how the SCN communicates timing information



- Diffusable factor, neuronal communication or both?
- What about non-brain areas?
- Differences between diurnal/nocturnal animals?
- How is timing communicated?

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