BIOLOGICAL TIMEKEEPING

Calendar Description:

An examination of the biological rhythms of cells, tissues and whole animals, the mechanisms of biological timekeeping and how these 'clocks' interact with each other to coordinate physiological events within an animal and with the environment. Prerequisites: SC/BIOL 2020 4.0; SC/BIOL 2021 4.0; one of SC/BIOL 2030 4.0, SC/BIOL 2031 3.0.

Note: Course title to be changed next year to “Physiology of Circadian Timing” to better reflect the course content.

Course Director:

Dr. Colin G. H. Steel
Laboratory: Rooms 010/010A Farquharson
Office: Room 010B Farquharson
Phone: ext. 33437
Email: csteel@yorku.ca

Scheduling:

Room S201, Ross Building

Text:

No required text. Reading will be assigned from books and recent review articles, all of which will be available on line as e-journals (which I will email to the class) or kept on Reserve for this course in Steacie.

Suggested Grading and Dates:

Term Test #1, February 8th = 20%
(on basic concepts and cellular mechanisms)

Term Test #2, March 15th = 30%
(on nervous and hormonal mechanisms and circadian systems)

Final Exam (3 hours), in exam period, April 10-26 = 50%
(on whole course)

TOTAL = 100%
EXPANDED COURSE DESCRIPTION:
Life evolved in a cyclical environment alternating between the freezing darkness of night and the searing radiation of day. Early nucleated cells evolved the ability to time their various activities to occur in the most appropriate portion of daily and seasonal cycles. These cellular biological "clocks" are retained in modern organisms where they coordinate both cellular and physiological activities which are expressed in the whole organism as overt rhythms ranging from hormone secretion rhythms to sleep-wake (activity) rhythms. Interactions between the component "clocks" of an organism, mediated primarily by nerves and hormones, lead to internal temporal organisation of events within it. The fundamental cellular and physiological mechanisms of biological clocks were developed in key animal model systems such as bacteria, molluscs and insects and later applied to mammals and humans. Molecular clocks are now known in nearly all human tissues; new research reveals their importance in synchronizing the functions of various tissues with each other, to produce coordinated functioning of the various body parts. Clocks are master coordinators of physiology.

The analysis of human biological clocks has made extraordinarily rapid advances in recent years at the levels of physiology and cell and molecular biology. Human clocks are critical factors in the development of cancers, heart attacks and a host of other diseases. This knowledge is creating profound changes in numerous medical practices. The subject has acquired a prominence in public awareness (rhythms in human performance, shift-work, jet-lag, etc.). In medicine, treatment of many diseases has been revolutionised by precise timing of administration of medications. Numerous disorders are now recognised as due to malfunctions of human biological "clocks" and are treated by the new techniques of "chronotherapy". Others are simply natural variants of timekeeping genes in humans (eg ‘larks’ and ‘owls’). We will discuss the need for education of society in general regarding the serious dangers to human health of requiring people to adopt work schedules or lifestyles that defy their biological clockwork.

The course will emphasise the physiological mechanisms underlying biological clocks but will also discuss the subject at the level of its cellular and molecular mechanisms and its human and medical implications. Therefore, the course crosses a number of the conventional disciplinary boundaries within biology.

Short Course Lecture Outline

- General concepts and properties of biological clocks
- How cells keep time; cellular basis of 24h rhythms
- Term Test #1
- Neurobiology and endocrinology of circadian clocks in model animals and mammals
- Term Test #2
- Human and medical implications

Students are reminded that the University policies on academic honesty, ethics, conduct, disabilities and religious observance are always in force. For details see:
http://www.yorku.ca/secretariat/senate_etc_main_pages/ccas.htm
LECTURE SCHEDULE

I. Basic Concepts and Properties of Biological Clocks


Circadian rhythms in whole organisms.
   Properties and evidence of endogenous nature.
   What is a circadian clock?

Circadian rhythms in populations.
   Circadian gating: Drosophila eclosion rhythm.
   Genetic control of circadian properties: ‘clock mutants’.

Mechanism of synchronisation of clocks with environmental signals ie Entrainment.
   The phase response curve. Pacemakers and slaves.
   Use of ‘skeleton’ photoperiods.
   Stopping the clock with light: Damping and singularity points.
   Entrainment to temperature cycles.
   Conflict between Zeitgebers.

Reading for the above topics:
1) Chapters 1, 2 and 3 in Saunders, D.S. (1977) “An Introduction to biological rhythms” (3 copies on Steacie Reserves). Basic concepts have not changed despite the age of this book.
2) Slightly more detailed version of the above is in Chapters 1, 2, and 3 of “Insect Clocks” (2002) by D.S. Saunders, C.G.H. Steel, X. Vafopoulou, R.D. Lewis (also on Reserve). All the basic concepts were developed in insects, so this book covers all the same topics. Use it if you find the little book inadequate, otherwise not necessary reading.
3) Pages 1063-1071 of Golombek, D.A. and Rosenstein, R.E. Physiology of circadian entrainment, Physiol. Rev. 90, 1063-1102 (2010). The remaining pages of this review are not very well presented, so you are not encouraged to read the rest!
   From this point on, recent reviews will be used as reading material, available as e-journals I will email these to the class when we need them. Some reviews may be published during the course, so I cannot specify ahead of time what these will be.

II. How Does a Cell Function as a Clock?

   How many clocks in a cell? Unicellular clocks of algae and bacteria.
   Clock genes in bacteria (kai genes).
   The molecular oscillators of Drosophila, Neurospora and mammals.
   Clock gene products and transcription regulators: the transcription/translation oscillator (TTO).
   From the TTO to cellular clock: roles of post-translational factors, membranes, ion fluxes.

**Term Test #1: February 8th** (on basic concepts and cellular mechanisms)
III. Neurobiology and Endocrinology of Circadian Timing Systems.

Structure and function of clocks in the brain and other tissues. Multiple clocks are connected together into a timekeeping system. Discussion of key animal systems:

Invertebrates:
- Molluscan eye clock: a simple neuronal clock.
- Insect neuroendocrine clocks: a model multioscillator system of mammals.

Neuroarchitecture of the clockwork in the brain and how it controls rhythms in behaviour and rhythmic release of hormones.
- Hormones as ‘messengers of time’.
- Discovery of TTOs in many peripheral tissues (peripheral oscillators) of insect models: evidence of hormones and nerves in synchronization of circadian systems.

Birds: Pineal gland as pacemaker and roles of melatonin.

Mammals (including humans):
- The suprachiasmatic nucleus (SCN) in the brain of man and other mammals.
- Mechanisms of rhythm generation by SCN cells.
- Circadian photoreceptors in the eye; melanopsin.
- Melatonin and circadian timing.
- Interaction of SCN with clocks in the retina and the pineal gland (melatonin).

Peripheral oscillators in diverse mammalian tissues including:
  - Clock in the heart (cardiomyocyte clock)
  - Adrenal gland clock and corticosteroid rhythms
  - Food entrainable oscillator

Why are there clocks everywhere and how are they coordinated together??
The emerging new concept of coordination of physiological functions between tissues by circadian rhythms in hormones and nerves, controlled by networks of interacting circadian clocks.

Term Test #2: March 15th (on neurobiology and endocrinology of circadian systems)

IV. Human and Medical Implications.

Health problems resulting from ignoring your clocks.
- Diseases related/cause by circadian defects: cancers, heart attacks, diabetes etc.
- Jet-lag, shift-work, depression, ‘SAD’, consequences of bright lights at night.
- ‘Night owls’, ‘larks’ and natural clock mutations in humans.
- Self help techniques for surviving the 24/7 world: Use of melatonin and phototherapy.

Timing medications for effectiveness; ‘chronopharmacology’.
- Circadian rhythms and cancer; roles in both cause and treatment.

Final exam in exam period April 10-26 (on whole course)