
DESTINATION
PHARMAGENS

Chronopharmacology

Biological clocks and circadian rhythm

Biological rhythms are innately determined rhythmic biological process or function and self-sustaining oscillation with the duration of time between successive repetitions (i.e., the period) being rather non-varying under normal conditions.

Rhythms affecting our body are ultradian cycles shorter than a day e.g. msec. for a neuron to fire; Circadian-Circa- about a day, lasting for about 24 hours,e.g.,sleep and wake cycles; Infradian- cycles longer than 24 hours e.g. menstrual cycle.

Seasonal-like seasonal affective disorder causing depression in people during the short day's of winter.

While 24-hour clock times and sleep/wake rhythms frequently overlap with the internal clock, they do not always match the circadian rhythm.

There are a variety of methods to ascertain the timing of biological clocks.

- **Melatonin** provides the most reliable and consistent measure of the circadian pattern and can be measured in the plasma, saliva, or urine.
- Because secretion of the hormone is acutely suppressed by light exposure, the measurement of the time of onset of the daily melatonin rise during low-light exposure is a more reliable measure of the circadian phase.
- The **dim-light melatonin onset (DLMO)** has been used to assess alterations of circadian phase in a variety of diseases.
- Other markers, such as core body temperature, and **cortisol** may also serve as biomarkers for circadian rhythms.

Circadian rhythms

These are particularly important in medicine. Physiological day is about 25 hours where the clock is reset daily by the environment night day social schedules.

Biologic rhythms are endogenous nature of circadian. Lack of external synchronizers leads to free running rhythms.

The period of free-running rhythms is longer or shorter than 24 hours and is characteristic for each species. Our internal clocks are genetically determined.

An internal biological clock is located in mammals, in the suprachiasmatic nucleus of the hypothalamus (SCN), delivering its message of time throughout the body.

It is responsible for circadian rhythms and annual / seasonal rhythms.

The SCN uses its connections with the autonomic nervous system for spreading its time-of-day message, either by setting the sensitivity of endocrine glands i.e., thyroid, adrenal, ovary) or by directly controlling an endocrine output of pineal gland i.e., **melatonin.**

Mechanism of Chronopharmacology

The basic unit of circadian timekeeping is the cell. Even in very complex organisms, most cells contain autonomous circuitry for circadian oscillations.

Generally speaking, this mechanism is comprised of negative feedback loops of transcription and translation: activation of a repressor gene results in its later repression by its own protein product, and the instability of this repressor insures this repression is short lived, so that a new cycle can begin.

- In mammals, the principal activators within this system are the CLOCK and BMAL1 proteins and their homologs, which dimerize and bind to certain elements to activate transcription of a large number of circadian genes.
- Among these circadian genes are loci encoding the PERIOD and CRYPTOCHROME families of repressor proteins (PER1-3 and CRY1-2), whose products multimerize and suppress the CLOCK: BMAL1 activating complex.

At each of these steps, additional precision and regulatory finesse is achieved through interaction with a wide range of auxiliary proteins: kinases that phosphorylate clock proteins to modify their stability or activity.

Chronopharmacological techniques ensure that drug levels in the blood are within therapeutic ranges during periods of maximal disease severity.

An **example** of this is seen in how evening doses of antihypertensive therapy can be used to prevent morning rises in blood pressure. The evening dose of the drug may thus be well timed with diurnal changes in blood pressure, preventing diurnal worsening of hypertension.

In addition, medications may have a different effect based on the timing of the dose.

for example, efficacy of ketamine, , has been shown to have varying efficacy based on the timing of dose despite reaching equivalent plasma concentrations, giving rise to the theory that some of these diurnal effects may be due to changes in receptors or secondary messenger systems.

Chronotherapy may prevent up- or down-regulation of receptors during periods of lesser need allowing optimal efficacy during periods of disease exacerbation.