

ABSTRACT

Understanding of basic rhythm of human body can enhance health unexpectedly. The science of chronomedicine explores the interaction between biological rhythms, medicine and drugs. Cardiovascular variations can serve as endpoints for preventive as well as curative health care. Endogenously regulated daily cyclic rhythms of body are known as circadian rhythms. Apart from this many biological cycles are exogenously regulated like light and dark or day and night. Many times they are organizing force for endogenous cycles. Everyday human body experiences of being hungry, tired, active, listless or energized at regular interval. Body temperature, heartbeat, blood pressure and urine flow cycle rhythmically change throughout the day. Levels of many hormones, for example ACTH-cortisol, thyroid-stimulating hormone (TSH) and growth hormone (GH), rise and fall in a daily rhythmic pattern. It is relatively predictable too and governed partially by exposure to sunlight and darkness being dependent on melatonin secretion. These daily cycles work to facilitate human body functions. We try to disrupt these cycles in many ways in our modern living and invite illnesses arising out of desynchronization from natural atmosphere. Knowledge of these cycles helps in dispensing medicines at a time when it can be most effective or really needed by human body. Ultimately it contributes in developing effective chronopreventive and chronotherapeutic strategies.

Chronomedicine is best defined as the application of chronobiology in order to understand the pattern of disease, which can be related to disturbances of circadian rhythm. Chronobiology is derived from three different words 'chromos' means 'time'; 'bio' means 'life'; and 'logos' mean 'science'. Thus it can be inferred that chronobiology is the science to discover the variability in the functioning of the human body.

Time is divided into various frames known as chronomes. Chronomes contain the major incidents in that time frame (only the deterministic events are marked) They are mapped by chronomics as the reference values for both an applied chronomedicine and a basic chronobiology. Chronomics quantify health and helps in identifying new disease risks. They are important tool to diagnose predisease and overt illness, enabling timely and timed treatment. They are also instrumental in validating the short- and long-term efficacy of a given treatment on an inferential statistical individualized as well as population basis.

If we can really understand the basic rhythms of human body, we can get our health enhanced in a way never expected before. The field of chronomedicine explores the interaction between biological rhythms, medicine and drugs. Greater extent of cardiovascular variations can also be exploited as endpoints for preventive as well as curative health care. Implementation of chronomedicine with molecular medicine is also being explored.

The founder of chronomedicine was Franz Halberg (1919–2013) he developed the technique of chronobiology which included chronomics, chronoastrobiology, and chronobioethics. He coined the term circadian, after documenting that biologic rhythms tip the scale between health and disease and even between life and death.

The daily peripheral activities of the organs are dependent on the Suprachiasmatic Nucleus (SCN) while interacting with the endocrine and autonomic nervous systems. It is reset by alternating light and dark through the retino-hypothalamic tract. Feeding time and scheduled exercise can also trigger the mammalian circadian system.

WHAT IS CIRCADIAN RHYTHM?

Cyclic changes marked on a daily basis are known as the circadian rhythm. They are regulated endogenously and move through approximately 24-hours. They can be regarded as probably the best known of the natural cycles. They can be further broken down into routine cycles of different time intervals.

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- Nocturnal, which describes organisms active in the night.
- Crepuscular, which describes organisms primarily active during the dawn and dusk hours like certain animals.

Many biological cycles are regulated exogenously, many external factors play an important role in regulating our body rhythms which is evident by the behavior of our body towards heat and cold weathers throughout the year. Researches show that these external forces may have greater influence on the body and may also contribute in the organizing of the body during endogenous cycles. The name given to such external (exogenous) forces is *zeitgebers* (a German word meaning 'time givers'). Rightly said, these forces which include sunlight, noise, social

Some of the other rhythms include:

- **Infradian rhythms:** They are the cycles lasting longer than a day such as the monthly cycle of mensuration in females or start or stop of hormones at a particular age.
- **Ultradian rhythms:** They are the set of cycles which last less than a day such as the 90-minute REM cycle and the 3-hour cycle of growth hormone production.
- **Tidal rhythms:** It is observed in tidal or aquatic life which follow the 12.4 hours cycle between high and low tides.
- **Lunar rhythms:** They follow the cycle of 29.4 days or the monthly e.g. lunar cycle and aquatic life and migration.
- **Gene oscillations:** Some genes are expressed more during certain hours of the day than during other hours.
- **Circasemidian Rhythms:** it is 12 hour cycle. "Post lunch dip" is good example of its loss
- **Circaseptan rhythm:** are weekly rhythms
- **Circasemiseptan:** half-weekly cycles

Acrophase is the period of time when the process is most active, and bathyphase or troughphase when it is least active. The particular moment of highest activity is the peak or maximum; the lowest point is the nadir. How high (or low) the process gets is measured by the amplitude.

The cycles can be huge such as the temperature cycle over the time of an year or small cycles of light and dark over a day. All the cycles are synchronised with other cycles to create a natural rhythm. It can be clearly observed as the body temperature cycle, cardiac cycle is in sync with our sleep-wake cycle. Some of the circadian cycles are controlled by the internal hormonal activities while some others are controlled by the exogenous stimuli. Throughout the animal kingdom, various cycles can be observed and the result of various exogenous and endogenous cycles can be observed.

HOW DO THESE CYCLES INTERACT WITH CIRCADIAN RHYTHM?

The cycles are continuously in motion or keep revolving in order to maintain the circadian rhythm or simply to say that the cycles are the basic defining regularities. Every day we might experience change in body temperature and energy levels, the urination cycle is not exact same for two individuals nor is same for two consecutive days. Levels of many hormones, such as ACTH-cortisol, thyroid-stimulating hormone (TSH) and growth hormone (GH), also rise and fall in this relatively predictable, daily rhythmic pattern. This rhythmic pattern is initiated and

governed in part by exposure to sunlight and darkness. These daily cycles work to our advantage.

ARE WE LOSING THIS INTERACTION?

In the modern world it is very difficult to keep in touch with the regular natural cycles and the circadian cycles are generally ignored or altered to the ease of the individual like women taking birth control pills which also alter their menstrual cycle, or staying awake during night and sleeping/wakening up late. The natural circadian cycles have also been altered due to our changing habitat; we live in era where A/Cs provide cooling during summers and we have heaters to provide warmth during winters, as such the natural cycles of temperature and weather. It can be said that we have started to command our nature and stopped being the slave of our circadian cycles. At first, it might not occur that the body is losing the synchronization but the increasing digestive problems and problems of headache and other mild disease show the impact of the imbalance created by the modern lifestyle.

TRAVELLING ACROSS TIME ZONES

'Jet lag' is a very commonly known desynchronisation which occurs due to imbalance caused by changing of time zones and the light and dark cycles. The symptoms of jet lag are easily evident and very common because the body also loses the synchronization with the earth's spin. Earth spins from west to east taking a flight against this direction i.e. east to west, would lead to far severe disruption of the circadian cycle.

TIRED TEENS

Apart from travelling across time zone, many other things can leave a person out of synchronization like keeping awake up to late hours for partying, studying and working in shift job. It is very commonly seen in teenagers. Evidences suggest it has dumbing-down effect on younger generation. It is a proven fact that age has a significant effect on the number of hours required to sleep, teenagers need almost 9.5 hours while an adult requires not more than 7 hours of sleep. One of the major reasons for such behavior is that teenagers circadian cycle is longer due to higher release of hormones and more physical pressure. Due to change in lifestyles melatonin enzyme to induce sleep is delayed at night due to which loss of sleep is witnessed.

The activity level of teenagers and the daily schedule for academics or purpose of recreation put the children under a lot of pressure and therefore they might not be able to give their 100% in any of the fields. Researchers have proved that the teenagers are deprived of night's sleep by almost three hours per day. It has also been found that change in school timings which allowed students to complete their sleep requirements was reported with higher results and lower behavioral problem.

POST-LUNCH DIP: A LOSS TO CIRCASEMIDIAN RHYTHMS

Post lunch dip (PLD) a common experience of energy dip faced by all of us at some part of the day where you might be under the urge to sleep after lunch and the situation

might be worsen by inappropriate food choices such as high glycaemic index snacks and meals. Research provides enough evidence to support that the brain signals during REM and PLD have significant similarity and it is not just a nutritional phenomenon. This also supports the fact that PLD is a 12 hourly or circasemidian fluctuation in our sleep-wake cycle.

ULTRADIAN RHYTHMS FLUCTUATIONS

Alteration in mood can also be related to the circadian cycle and ultradian rhythm for more significant results. Each circadian cycle consist of much shorter ultradian rhythms, ranging up to 90 minutes. We might experience many peaks and lows of during the day.

Many ultadian cycles are so small that they cannot be noticed but one of such changes can be seen in skin throughout the day.

Many other ultradian rhythms simply get ignored because of the fast-paced lifestyles we like to lead. However when we are asleep they are quite pronounced. Throughout the night or whenever we sleep, our bodies go through an approximately 90-minute cycle involving REM (rapid eye movement, or dream) sleep and non-REM (deep) sleep periods. Disruption of these REM cycles can lead to insomnia, fatigue, loss of concentration and memory and mood disorders.

LONGER CYCLES (CIRCASEPTAN RHYTHM)

There exist longer and more evident rhythms called circaseptan or weekly rhythms. Though the prevalence of the circaseptan rhythms is very low, yet scientists believe that they do occur and have observed higher rate of rejection in transplant patients during seven, fourteen and twenty-one days after surgery.

Some evidences of such responses being governed by geomagnetic activity are present and thus can be related to semi-weekly or circasemiseptan cycles. Some studies show that the blood pressure shows some unknown synchronization with the time of birth and thus this phenomena is named 'locking up' with earth.

SOME LONGER CYCLES

- **Infradian Cycles:** These are the cycles' lasting from 28 days to a month they include the most obvious menstrual cycle with its cyclically fluctuating levels of estrogen and progesterone.
- **Circalunar Cycle:** For some women their monthly menstruation also follows this lunar cycle, though opinion is divided on whether the menstrual cycle will naturally, in the absence of modern disruptions, synchronise with the normal lunar cycle.

SEASONAL CHANGES

There exist a circannual cycle which is revealed by the seasonal change in flowers or behavior of animals.

Seasonal Affective Disorder (SAD, or winter depression) is a disorder which can be related to the length of the day, similarly researchers are trying to prove that melatonin is

secreted exclusively at night and also the level of secretion is affected by the length of day and the season, it is found that the melatonin levels are higher during winters, when days are shorter thus reducing activity and inducing sleep or laziness. Melatonin levels usually decrease with age. But seasonal shifts are also seen in elderly. SAD may worsen with age. Natural or artificial sunlight especially in the early morning, improves mental health as it suppresses melatonin production.

Annual cycles are not only difficult but expensive also to study, than the shorter circadian cycles. However research has proved seasonal fluctuations in other hormones too. Women with breast cancer have abnormal annual fluctuations in level of prolactin hormone if it is compared with healthy women. In another study of 'cancer chromatics', blood samples drawn at different points of year from women have shown not only it was natural annual cycle of prolactin but also thyroid stimulating hormone (TSH) lost in women who developed breast cancer.

HOW DOES IT WORK IN CHRONOMEDICINE?

Medicine dosage is very much dependent on the time during which the drug has been consumed, it has been proved by studies that non-steroidal anti-inflammatory drugs (NSAIDs) may be less dangerous to the stomach lining when taken at night rather than day. In one study of individuals with osteoarthritis the incidence of adverse effects was cut in half when NSAIDs were taken at night instead of in the morning and there is some evidence that morning pain can also be controlled by taking NSAIDs at night.

Profound cardiac rhythms can be observed in frequency and intensity of symptoms in arthritic diseases such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and gout. People suffering from rheumatoid arthritis have reported higher severity of joint pain swelling and stiffness during mornings while those with osteoarthritis reported higher pain during night.

Heartburn and ulcers get worse at night during 10 PM to 2 AM, this can be related to secretion of stomach acid which is 2-3 times higher than during the day. These night-time rises are the result of a circadian rhythm of stomach acid production so if the medicine is given at same time it is more effective.

Synchronization with the circadian rhythms is found to be far more advantageous when compared to other treatments for cardiovascular diseases or certain diseases such as asthma etc.

Most of the medical conditions show a diurnal pattern in clinical features and grave nonfatal and fatal outcomes e.g., respiratory ones of viral and allergic rhinorrhea, reversible (asthma) and non-reversible (bronchitis and emphysema) chronic obstructive pulmonary disease, cystic fibrosis, high altitude pulmonary edema, and decompression sickness; cardiac ones of atrial premature beats and tachycardia, paroxysmal atrial fibrillation, 3rd degree atrial-ventricular block, paroxysmal

418 supraventricular tachycardia, ventricular premature beats, ventricular tachyarrhythmia, symptomatic and non-symptomatic angina pectoris, Prinzmetal vasospastic variant angina, acute (non-fatal and fatal) incidents of myocardial infarction, sudden cardiac arrest, in-bed sudden death syndrome of type-1 diabetes, acute cardiogenic pulmonary edema, and heart failure; vascular and circulatory system ones of hypertension, acute orthostatic postprandial, micturition, and defecation hypotension/syncope, intermittent claudication, venous insufficiency, standing occupation leg edema, arterial and venous branch occlusion of the eye, menopausal hot flash, sickle cell syndrome, abdominal, aortic, and thoracic dissections, pulmonary thromboembolism, and deep venous thrombosis, and cerebrovascular transient ischemic attack and hemorrhagic and ischemic stroke.

Correct knowledge of these temporal patterns not only helps guide patient care but research of their underlying endogenous mechanisms, i.e., circadian and others, and external triggers. At the same time it gives information regarding development and application of effective chronopreventive and chronotherapeutic strategies.

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