Part II: SYNCHRONICITY - Synchronizing Biological Rhythms for Slower Aging, Preventing Illness and Optimal Performance

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I. Understanding the Circadian System

The Cycles of Life
Internal and External Biological Rhythms
The Circadian Rhythm Profile
The Daytime Energy Cycle
The Nighttime Sleep Cycle
Factors making Body Rhythms Go Out of Sync

II. Biology of the Circadian System

Biological Clocks of the Circadian System
Hypothalamus and Homeostasis
The Suprachiasmat Nucleus – the Central Circadian Clock
Feedback Control of the Circadian System for Homeostasis
The Pineal Gland - a Neurochemical Rhythm Transducer
Neurotransmitter Regulation of Daytime Energy Cycle & Nighttime Sleep & Repair Cycle
Neuroendocrine Deviation, Loss of Homeostasis and Aging

III. Problems of Circadian Dysfunction

Factors making Body Rhythms Go Out of Sync
Aging, Senescence and Degenerative Disease
Circadian Rhythm Sleeping Disorders
Affective Disorders
Cancer
Dementia
Weather Sensitivity
Jet Lag, Shift Work and Late Night Living

IV. Chronobiotics and Chronotherapy

What are Chronobiotics
How Chronobiotics alter Timekeeping
Chronotherapy Treatment of Disease

V. References

I. Understanding the Circadian System

The Cycles of Life

Medicine has traditionally viewed the healthy body as a homeostatic steady state. But recent scientific evidence reveals that the steady state is really an integrated, rhythmic ebb and flow of hormones, neurotransmitters, enzymes, receptors sensitivities, and internal functions that affect every cell in the body.

Every living creature has normal daily (circadian) rhythms, such as the sleep/wake cycle, that are keyed to the earth's daily rotation. There are also daily rhythms that affect the function of the lungs, cardiovascular system, kidneys, blood flow, muscular activity, and cognitive function. Human females, of course, have monthly menstrual cycles. There are even subtle weekly and yearly cycles of life that affect reproduction, immune function, and the aging process. .

Health and Wellness can be viewed as a state when all the body's biological rhythms are closely in sync. Many illnesses including allergy, arthritis, asthma, cardiovascular disease, depression, and even cancer, are affected by bodily clocks. Desynchronization of these internal clocks can initiate accelerate aging, physical problems, and mental disorders and A short list includes depression, mental fogginess, memory loss, headaches, moodiness, short temper, tension, poor appetite, slow reflexes, fatigue, weakness, and off-schedule bowel movements.

Internal and External Biological Rhythms

Essentially, there are two types of biological rhythms: "external-derived rhythms" and "internally-derived rhythms". The externally-derived rhythms reflect responses to periodic changes in the environment such as a change in the seasons, or the transition from day to night. The internally-derived rhythms originate within the person from biological clocks. Under normal situations these internally derived clock rhythms are entrained (co-ordinated) and synchronized by exposure to the daily pattern of light and darkness as well as other environmental cues. .

The temporal organization of our biological rhythms reflect a genetic program which serves the adaptive functions of 1) creating internal order of our biological functions and behavior and 2) coordinating our biological functions with changes in the environment.

The Circadian Rhythm Profile

Each person shows highly characteristic, profile of their biological rhythms over a 24 hour circadian cycle. This is known as a "chronotype "the scientific name for your individual circadian rhythm pattern and reflects a person's molecular and physiological properties

Under normal timing of the daily 24 hour light /dark cycle from sunrise to sunset, human physiological and behavioral rhythms exhibit consistent peaks (acrophases) and troughs in either the day or the night. Rhythms that include body core temperature, blood pressure, heart rate, adrenalin and noradrenalin production, exercise capacity, vigilance, decision making, problem exhibit peaks in the daytime light phase of our 24 hour day. Other rhythms such as the hormone melatonin, growth hormone, exhibit peak during the night phase of the 24 hour day cycle.

Over the course of our 24 hour day, there is a circadian switching in the human body from a **Daytime Energy Cycle** to a **Nighttime Sleep & Repair Cycle.** The midpoint for this shift is about 4 pm, the traditional English tea time. At this time chronobiotic agents that normally advance or delay the circadian phase produce minimum effects.

Healthy, stable and perhaps longest living people are expected to have consistent time characteristics between their **Daytime energy cycle** and **Nighttime Sleep & Repair Cycle** of biological functions such as body temperature, hormone secretions, feeding behavior over the course of day and throughout their life.

THE DAYTIME ENERGY CYCLE

At sunrise we switch on our conscious mind to begin our daily activities. Our brain, nerves and hypothalamus gland increase their output neurotransmitter for conscious thinking, coordinated movement and the metabolic processes required for activities during our waking hours.

The Time for Expending Energy to Survive

During the day, our body expends a great amount of energy to insure our survival and overcome stresses of life. Our sympathetic nerves are prepared to release powerful stimulants like adrenalin for emergency situations. We burn up more calories, generate more heat, create more waste, have a higher blood pressure, a stronger heart rate and a greater pain tolerance during the day.

Normally, fluctuations in the level of the hormone cortisol are highest in the early morning , lowest in the evening. This help explain why symptoms of asthma and some forms of arthritic, and other inflammatory diseases are typically better in the morning and worse in the evening.

Daytime when Stress is Most Destructive

Daytime is when we're most vulnerable to the damaging effects of excess stress. Chronic mental and physical stress that is beyond your capacity to handle can be extremely damaging to health. Uncontrolled stress releases excessively high amounts of cortisol and related hormones from the adrenal glands that are precursors to many minor problems and serious disorders, including immune depression, ulcers, acne, high blood pressure, strokes, mental depression, psychosis, diabetes, heart disease and premature aging.

It is well-known that most heart attacks and strokes occur between 7 am and noon. This coincides with a sharp increase in pulse rate, blood pressure, and platelet aggregability (an important stage in clot formation), while plasma fibrinolytic (clot-dissolving) ability is at its lowest level of the day.

THE NIGHTTIME SLEEP CYCLE

At night we switch off our conscious mind and drift gradually to sleep. When darkness falls, eyes inform your biological time-clock, the Pineal Gland to secrete the sleep-including hormone Melatonin. This starts a chain of events that put you to sleep. As you lie in bed, your brain waves pass from the active Beta State to the slower, brain wave meditative Alpha State, into a pre-sleep creative Theta State and finally into the slow wave Delta State of sleep. Like consciousness, sleep is an active mental process. Each night you have four to five 90-minute cycles of intense brain activity and dreams.

The Time for Physical and Mental Repair

Sleeping and dreaming are essential for good health. During sleep your body releases hormones for physical repair and creates dreams for mental repair. Dreams harmonize your mind with your outer environment and enable you to cope with stressful events when you are awake. In fact, you can program your dream state to find answers to problems that you could not solve during the day and wake up with the answer.

Sleeping disorders are the most commonplace expression of circadian disturbance. Over 60 million Americans have a sleeping disturbance and the most common problem is insomnia. An inability to sleep causes wear and tear, slower body repair, decreased performance and mental distress.

Factors Making Body Rhythms Go Out of Sync

The human body depends upon internal clocks and their responses from the signals of external cues for smooth transition from your Daytime Energy Cycle to Nighttime Sleep Cycle and for the circadian system to function correctly. But many factors of modern living can desynchronize your inner time clocks that result in problems during the day and sleeping disorders at t night:

- Abnormal patterns of light
- Excess mental and physical stress
- Social isolation
- Long distance East-West jet travel
- Uneven work schedule
- Insufficient, excessive or irregular sleep
- Improper eating
- Taking drugs and psychoactive medicines
- Spending most time indoors without natural daylight
- Living an abusive and erratic lifestyle

When the entraining cues are removed or presented at abnormal times or phases of our 24 hour Circadian cycle a wide range of behaviors and functions are changed. Other factors may damage the circadian central clock, cellular clocks and clock genes. Plus impairments in the sensory signal generators, transmission pathways, the neuroendocrine system, homeostatic feedback control and cell receptors can cause the circadian system to malfunction.

Chronic phase shifts and deteriorations in circadian system functioning can severely impair daytime physical and mental performance. Individuals with chronically disrupted circadian sleep cycles from modern working schedules and lifestyles, have a greater frequency of accidents, illnesses and behavioral disorder. Individuals that continually fail in matching the phase of their biological rhythmic functions with environmental cues may become chronically desynchronized, adapt poorly to physiological challenges, and suffer the ultimate insult of a premature death.

II. The Biology of the Circadian System

Biological Clocks are behind the Circadian System

Circadian clocks are molecular time-keeping systems that underlie daily biological rhythms in anticipation of the changing light and dark cycles. These clocks mediate daily rhythms in physiology and behavior that are thought to confer an adaptive advantage for our survival. Circadian Cycles established by biological clocks occur throughout nature and have a period of approximately 24 hours.

The master clock of the human circadian system is located in the suprachiasmatic nucleus (SCN) of the hypothalamus coordinates the timing of circadian rhythms, including daily control of hormone secretion. The SCN drives hormone secretions in the brain, set the phase of "clock genes" that regulate circadian function at the cellular level and signals endocrine glands via the autonomic nervous system, allowing for rapid regulation and synchronization circadian rhythms via multisynaptic pathways. The circadian system is synchronized via temporal regulation of endocrine gland function by a combination of genetic, cellular, and neural regulatory mechanisms that ensure that each response occurs in its correct time niche.

Researchers believe cur cell cycle checkpoints are gated to our intrinsic circadian clocks to protect DNA against mutation and acquired damage that would lead to genome instability and premature aging. Peak DNA repair capacity is normally synchronous to the crest of mutagenic stress as they oscillate with respect to time.

Hypothalamus and Homeostasis

The hypothalamus is the body's primary organ of homeostasis. It maintains the equilibrium of most biological processes within a fairly narrow range. Releasing factors (small protein-like molecules) from the hypothalamus initiate hormonal changes in the pituitary (formerly considered the master gland). Hypothalamic secretions keep internal temperature, blood pressure, thirst, hunger, sexual appetites, chemical and water balances, menstrual cycles, and numerous other activities functioning normally. For the hypothalamus to do this, it must be sensitive to biochemical changes that signify slight deviations in these functions. Too much or too little of a particular hormone in the tissues influences the hypothalamus to secrete more or less specific releasing factors and inhibiting factors which bring about the adjustment by the mechanism known as negative feedback.

The Suprachiasmat Nucleus: Our Central Circadian Clock

It's now accepted that the Suprachiasmat Nucleus (SCN) of the hypothalamus acts as the central pacemaker or clock for the internally-derived biological rhythms. It is the primary source of rhythmic temporal information (circadian pacemaker) for controlling all physiologic processes including the modulations of sleep and wakefulness, cell division, detoxification and nutrient metabolism

The SCN clock is a remarkable and very rare piece of neurobiology because the behavioral phenomenon observed at the level of the entire organism, circadian timekeeping, can be seen not only at the level of a tissue but also within individual neurons. The SCN consist of neuron clusters whose electrical potential frequency fluctuates spontaneously with an approximate 24-hour periodicity that peaks during the biological daytime of diurnal cycle. Each SCN neuron functions autonomously, generating its own spontaneously oscillating electrical potential. Synchrony of neuronal activity is partially achieved through the mediator vasoactive intestinal polypeptide acting through its receptor.

The SCN regulates the circadian expression of genes in peripheral tissues through a mixture of neural pathways, neurohormones and neuropeptides. SCN neurons project directly to the several nuclei and the subparaventricular zone of the hypothalamus, the basal forebrain and thalamus. Secondary projections of SCN fan out to the neocortex, limbic system, hippocampus, anterior pituitary, hypothalamus and reticular activating system (RAS). This enables the SCN to modify wakefulness via the RAS, thermoregulation & feeding via the hypothalamus, memory & learning via the hippocampus, mental performance via the neocortex and endocrine secretion via the pituitary. The SCN neurons contain numerous neuropeptides and neurohormones that act as signal messengers.

In the brain SCN signals set the phase of "clock genes" that regulate circadian function at the cellular level within neurosecretory cells. The protein products of these clock genes exert direct transcriptional control over neuroendocrine releasing factors. Clock genes and proteins expressed in peripheral endocrine organs providing additional modes of temporal control

Molecular timekeeping in SCN neurons is synchronized and sustained by inputs from different pathways and interneuronal neuropeptide signals. The SCN receive afferent projections from the retina via a monosynaptic pathway, the retinohypothalamic tract which arises from photoreceptors and retinal ganglion cells that are specialized for sensitivity to light. The SCN also receives input through the geniculohypothalamic tract from the intergeniculate leaflet of the thalamus and serotonergic input from midbrain raphe neurons. These may allow non-photic (light) entrainment cues, such as feeding, exercise and social cues to influence the SCN.

A molecular clock mechanism similar to the SCN is found in most major organ systems. These tissue clocks are synchronized by endocrine, autonomic and behavioral cues that depend on the SCN, and in turn drive the circadian expression of local transcriptomes, that co-ordinate circadian metabolism and physiology. These local SCN-synchronized clocks control vital processes that include detoxification of foreign substances, cell division and nutrient metabolism.

The SCN signals endocrine glands via the autonomic nervous system that for rapid regulation and adjustments through via multisynaptic pathways. Thus, the circadian system under the guidance of the SCN regulates the temporal functioning of endocrine system function by a combination of genetic, cellular, and neural regulatory mechanisms to ensure that each response occurs at its correct time niche of the day.

Not only does the SCN regulate endocrine rhythms but hormones feed back to the SCN that fine tune the temporal pattern of endocrine secretion for current conditions. For example, dedicated melatonin receptors are localized to the SCN, and ingesting melatonin can alter SCN phase.

Numerous other “clock” genes and regulatory enzymes work in circadian timekeeping at the cellular level. Within a cell, circadian rhythms are produced by an autoregulatory transcriptional negative feedback loop that takes approximately 24 hours. Peripheral clock cells normally receive their phase information from the SCN to synchronize individual oscillators to each other. The SCN sets the phase of peripheral circadian rhythm clocks and coordinates the activity of tissues and organs of the body relative to one another, thereby maintaining homeostasis.

Feedback Control of the Circadian System for Homeostasis

The SCN and the hypothalamus maintain equilibrium of most biological processes through a sophisticated system of negative feedback controls. They monitor the levels of hormones that circulate in the bloodstream. When the peripheral hormones increase above a certain levels, the hypothalamus reduces the output of releasing factors and hormones by negative feedback

The hormones released from the hypothalamus in turn cause the pituitary gland to release stimulating hormones. These stimulating hormones cause the peripheral endocrine glands (thyroid, adrenals, ovaries and testes) to secrete their hormones (i.e. thyroxin, cortisone, estrogen, progesterone, and testosterone, to name a few). In this fashion, this system is controlled by negative feedback—i.e., as the blood level of a peripheral hormone (like thyroxin or testosterone) rises, it causes feedback to the hypothalamus and pituitary, signaling them to reduce their output of stimulatory releasing factors and hormones

The Pineal Gland - a Neurochemical Rhythm Transducer

Recent research indicates that the hypothalamus is itself influenced by another structure in the brain known as the pineal gland. The pineal gland controls the regular cyclical functioning of the entire neuroendocrine system, most notably our 24-hour sleep-wake cycle, as well as many other chronobiological functions. A daily infusion of the pineal gland melatonin entrains circadian rhythms to stay synchronized and provides internal feedback cues to the SCN.

The pineal gland receives signals from the hypothalamus and acts as neurochemical transducer. The hypothalamus gland signals sympathetic nerve endings to release catecholamine neurotransmitters that cause the pineal gland to synthesize the indoleamine melatonin from serotonin by the action of several enzymes. During the daylight hours the actions of these enzymes is lowest and serotonin accumulates in the pineal gland. At nighttime the levels of serotonin drop in the pineal gland and melatonin increases.

The pineal gland appears to be a coordinator between the internal-derived and external derived body rhythms from information it receives about environmental lighting from the retina via a multi-synaptic pathway. Since the pineal gland indoleamine cycle persists in continuous darkness, this suggests that it’s driven by the SCN central clock in that originates in the hypothalamus. When you block the catecholamine secretions and neural activity of the hypothalamus, the pineal gland’s indoleamine cycle ceases.

Neurotransmitter Regulation of “Daytime Energy Cycle” and “Nighttime Sleep & Repair Cycle”

Over the course of our 24 hour day, there is a circadian switching in the human body from a catecholamine-driven pathway**,** the “**Daytime Energy Cycle”,** to an indoleamine-driven pathway, the **“Nighttime Sleep & Repair Cycle”.**

Catecholamines (dopamine, norepinephrine and epinephrine) are the hormones of the arousal system. Their activities include raising blood pressure, increasing heart rate, opening airways, increasing alertness, and generally preparing the body for fight-or-flight.

Indoleamines (serotonin, melatonin) generally reach their peak levels in the evening. They are concerned primarily with maintenance functions, including sleep, cardiovascular activity, and appetite control. Unlike catecholamines, which tend to wake you up and make you more alert, indoleamines tend to lower your arousal level and make you more relaxed, less anxious, and sleepy.

The peaking of the Catecholamine Pathway and Indoleamine Pathway are 180 degrees out of phase (12 hours apart) and coupled to the coordinated activity of the SCN clock genes and peripheral clock cells that control the pathway of choice. An important function of switching pathways is to conserve and preserve energy. The Indoleamine pathway synthesizes and stores glycogen at night for energy production during the day from activity of the catecholamine pathway.

Starting around age 25, there's a lifelong decline in catecholamine neurotransmitters of the "**Daytime Energy Cycle",** (epinephrine, norepinephrine, and dopamine), a slower decline in the indoleamine neurotransmitter "**Nighttime Sleep & Repair Cycle",** (serotonin, melatonin) **"**, This decreases ration of catecholamine to indoleamine transmitters as one ages.

Neuroendocrine Deviation, Loss of Homeostasis and Aging

According to Dr. Vladimir Dilman's *Neuroendocrine Theory of Aging, c*atecholamine deficiencies and neurotransmitter imbalances are a principal cause of loss of "hypothalamic sensitivity" for the progressive metabolic shifts that produce aging and the diseases of aging,

According to Dr. Dilman, a renowned Russian biogerontologist, aging is caused by a progressive loss of sensitivity by the hypothalamus (and related structures in the brain) to feedback inhibition from hormones and neurotransmitters. Throughout your lifespan, this loss of sensitivity produces a progressive los of internal balance and temporal organization of our biological rhythms of Circadian Cycles maintaining control of our biological processes, The result are progressively increasing undesirable changes in the amplitudes, time of their secretion, relative levels and metabolic effects of, neurotransmitters, hormones and cell signalers and transducers. Essentially your body goes out of sync and aging accelerates.
This is considered a cause of many post-maturational diseases, accelerated aging, and earlier death. *The Neuroendocrine Theory of Aging* explains in detail how this causes the major diseases of aging, which contribute to over 85% of early deaths of middle-aged and elderly individuals.

To correct catecholamine deficiencies to help delay aging, prolong life span, prevent aging disorders, and restore youthful biological functions, Dr. Dilman and other aging researchers have suggested: (1) Increase neurotransmitter production and activity; (2) Decrease catecholamine breakdown from MAO-B enzymes; (3) Correct neurotransmitter deficiency and imbalance of the catecholamine/serotonin ratio; (4) Inhibit neurotransmitter re-uptake, to increase intersynaptic neurotransmitter levels; and (5) Correct the decrease in receptor sensitivity and responsiveness of target cells and tissues to neurotransmissions.

III. Problems of Circadian Dysfunction

Aging, Senescence and Degenerative Disease

The process of aging decreases the adaptability of the body rhythms to new schedules so the elderly tend to become chronically desynchronized. (It's as though a person is in a constant state of jet lag.) The result of chronic phase shifts and deteriorations in the circadian cycle is functional decline in physical and mental performance, illness and aging disorders.

Animal studies have shown the adverse effects of circadian rhythm dysynchrony on lifespan. Human studies demonstrate that the age-related disruption of biological rhythms play a role in age related decline and pathology. Heart disease, cancers, immune dysfunctions, endocrine gland disorders, affective disorders, loss of mental acuity and other ailments result when biological rhythms become desynchronized over the course of life.

Circadian Rhythm Sleeping Disorders

Circadian rhythm sleep disorders are persistent or recurring pattern of sleep disruption resulting either from an altered sleep-wake schedule or an inequality between a person's natural sleep-wake cycle and the sleep-related demands. There is a mismatch mis-matching between the sleep/wake schedule required by a person's environment and their circadian sleep-wake pattern. The sleep disruption leads to insomnia or excessive sleepiness during the day, resulting in impaired functioning.

There are six distinct CRSDs currently recognized in the International Classification of Sleep Disorders: 1) delayed sleep phase type, 2) advanced sleep phase type, 3) irregular sleep-wake phase type, 4) free-running type, 5) jet lag type, and 6) shift work type.

- **Delayed sleep phase disorder -** Sleep onset and final awakening are delayed with respect to the desired clock time. Therefore you fall asleep late (for example, between 4 a.m. and 6 a.m.) every night. As a result you awaken at noon or in the afternoon every day.
- **Advanced sleep phase disorder** - The major sleep episode is advanced in relation to the desired clock time. Therefore you fall asleep early (for example at 6 p.m.) every night. As a result you awaken early every day (for example at 2 a.m.).
- **Irregular sleep-wake rhythm** - Your sleep pattern is broken up into short pieces. You sleep off and on in a series of naps over a 24-hour period.
- **Free-running (nonentrained) type** - Your sleep time happens later and later every day
- **Jet Lag type -** Individuals demonstrate sleepiness during the desired wake portion of the day due to the change in time zone. They have difficulty sleeping during the desired sleep portion of the day.
- **Shift Work type -**. Because of night shift work or frequently changing job shifts, the person experiences excessive sleepiness during major periods of wakefulness or insomnia during major sleep period. The disruptions result in inconsistent circadian schedules and an inability to adjust to the changes consistently.

Affective and Psychiatric Disorders

Affective and psychiatric disorders are linked to disturbances of sleep and circadian rhythms on many different levels, including epidemiological studies, clinical symptoms, responses to treatment and common neurobiological mechanisms.

Affective Disorders are mental disorders illnesses characterized by dramatic changes or extremes of mood which also have an effect on thoughts, behaviors and emotions. They include:

- Depressive disorder or unipolar depression;
- Bipolar disorder or manic-depression;
- Anxiety disorders including Panic disorder and Postpartum disorders;
- Seasonal Affective Disorder.

Individuals with mood disorders almost universally complain of disturbed sleep that can be part of a larger disturbance in the regulation of circadian rhythms. Approximately two-thirds of patients with depression have some type of insomnia, with about 40% complaining of the specific symptoms of sleep onset difficulty, frequent awakenings, and early morning insomnia. Plus a high percentage of individuals with sleep complaints also have a mood disorder.

The cause of Affective Disorders is clearly multifactorial. But a primary cause of affective disorders the excesses, deficits, and temporal desynchrony in the activity of catecholamine and indoleamine neurotransmitters secreted between neurons. Catecholamines (norepinephrine, epinephrine, and dopamine) are the hormones of the daytime arousal system. Indoleamines (serotonin, melatonin), that generally reach their peak levels in the evening are concerned primarily with maintenance functions, including sleep.

Levels of the catecholamines neurotransmitters and indoleamines that rise and fall on a cyclic basis throughout the day may help color the mood from bright and cheery to the darkest depths of depression. Imbalances in both the amplitude (hypo- or hyper-secretions) and phase (wrong time for secretions) of these neurotransmitters disrupt internal biological clocks that result in circadian desynchrony affective disorders.

In the winter, millions of people who spend most of their time indoors suffer depression with fatigue, sleepiness, carbohydrate cravings and weight gain. It is called Seasonal Affective Disorder (SAD). Indoleamine (serotonin, melatonin) neurotransmitter imbalances in the brain brought on by the shortening of daylight hours and lack of sunlight exposure in winter upset your sleep-wake cycle and desynchronizes circadian rhythms. A 2008 study indicates that SAD may be linked to a genetic mutation in the eye that makes a SAD sufferer less sensitive to light.

Cancer

Cell cycle checkpoints are gated to the circadian cellular clocks to protect DNA from daily exposure to mutagens. Peak DNA repair capacity is normally synchronous to the crest of mutagenic stress as they oscillate with time. Increased vulnerability to genotoxic stress appears to develop when the circadian pattern of cell cycle control, DNA repair or apoptotic response are phase-shifted relative to the circadian rhythm of mutagenic stress. As a result, accumulating can mutations lead to accelerated aging, genome instability and cancer.

Tumor cell circadian clock genes are rhythmically expressed in coordination with rhythmic circadian growth and jamming that clock may be a new way to fight cancer. At least eight central 'clock' genes coordinate cancer related functions such as cell proliferation and apoptosis within the circadian time each day. Plus, Tumors were shown to shrink faster when chemotherapeutic agents were given in the sweet spot of a patient's *circadian* cycle.

Diabetes

Diabetes and high levels of blood sugar may be linked to abnormalities in a person's body clock and Circadian rhythm sleep patterns, Insulin levels and the hormones that work against the actions of insulin are, influenced by the circadian rhythm. These hormones which include glucagon, epinephrine, (adrenaline), cortisol, and growth hormones raise blood sugar levels when they need to be raised. During the middle of the nighttime hours there are increases in blood glucose production by the liver. These processes are offset by the increase in insulin secretion by the pancreas. Blood glucose then, remains stable.

Circadian disturbances during the sleep cycle of diabetics can cause blood glucose to go out of control. In diabetics, the liver may not respond to insulin to stop glucose production during sleep causing excessive blood sugar levels in the morning. Researchers discovered a genetic abnormality affecting melatonin levels and circadian sleep patterns that disturbs the levels of insulin in the blood and prevents the body from maintaining control of blood sugar levels.

Dementia

People with dementia are characterized by impairments in memory and other cognitive functions. They often display fragmentation in their sleep/wake circadian pattern, such as frequently wake up during the night and frequently fall asleep during the day. Individuals with more severe dementia exhibit a greater loss of normal circadian rhythms functioning. It remains unclear how the circadian dysfunctions from dementia follow deterioration of circadian clocks from neurological damage due to the pathology of the disease.

Obesity

Broken biological clocks may cause obesity. Researchers found key proteins in the hypothalamic region of the brain that manages feeding, energy balance and sleep-wake regulation. Defective clock genes in the brain and throughout the body of mice was found to a create cacophony of physiological changes that produced obesity and metabolic deregulation. In people, similar changes in body fat and metabolic activity are known as "metabolic syndrome", which can lead to cardiovascular disease and type 2 diabetes.

Weather Sensitivity

About half the U.S population is sensitive to changing weather conditions. Fatigue, ill-humor, headaches, insomnia, dislike of work, depression, difficulty concentrating, nervousness, and forgetfulness are the most common affections form weather sensitivity. The human body adjusts to changing weather by secreting different hormones and activating the nervous system that desynchronize the circadian system.

Jet Lag, Shift Work and Late Night Living

Individuals often lose the comfort of internal and external body rhythm synchronization in situations that require an alteration in their daytime activity and nighttime rest cycle. Individuals who engage in rapid transmeridian flight crossing three or more time zones undergo alterations in the timing of their circadian system These changes manifest in the desynchronization of physiological and behavioral rhythms. Upon arrival, travelers encounter a new rhythm of sunrise and sunset and a time-altered activity and social schedule.

The impact of these circadian changes on body physiology results in several days of fatigue, sleepiness, lethargy, insomnia, gastrointestinal track disorders, and poorer mental agility and performance while the body resynchronize its biological rhythms to the new time zone.. The syndrome is commonly known as jet lag.

Similarly, people working night shifts or living late night lifestyles that alter their work/activity schedule to include nighttime hours of activity disrupt the synchronization of the circadian system with results resembling jet lag. These disruptions of the timing of sleep and activity can produce detrimental effects on alertness, cognitive, physical activity and mental stability.

IV. Chronobiotics and Chronotherapy

What are Chronobiotics

A chronobiotic is an agent that acts on the circadian clock or its inputs to alter timekeeping function. They can be a nutraceutical, drug, food chemical or other agent. For example melatonin directly alters circadian signals of the central clock for synchronizing the sleep/wake circadian cycle. Caffeine and amphetamines lengthen the circadian period. The anti-aging agent GH3 is a buffered procaine preparation that works by increasing the level MAO (monoamine oxidase) inhibitors that decline with advancing age. This helps prevents the age-related increase breakdown of catecholamines and indoleamines to maintain the temporal organization of biological rhythms.

How Chronobiotics alter Timekeeping

There are basically three ways that a chronbiotic alters circadian timekeeping:

1. A chronobiotic can modulate the input from photic (light sensitive) afferents to affect entrainment and phase of the circadian biological rhythm.

2. A chronobiotic can act directly on circadian clocks to alter the intrinsic time period. This would be manifested as an alteration in the phase relationship between the circadian rhythm and entrainment to the light-dark cycle.

3. A chronobiotic can act on the oscillator to change the amplitude of clock output. This can have complex effects on different driven rhythms such a hyper-or-hypo secretion of endocrine gland hormones. In the case of the sleep-wakefulness rhythm, that an augmentation of circadian clock amplitude would improve nocturnal sleep and increase daytime alertness.

It is often very difficult to distinguish a direct effect of a chronbiotic on the circadian clock from an effect on a driven circadian process. This is the case for sleep and wakefulness where the exact nature of the relationship between the clock and sleep-wake processes remains unclear and non-circadian and homeostatic, processes play a pivotal role in the timing of sleep-wake cycle. Even a phase-altering circadian effect of from an agent such as hypnotic drug does implicate the circadaian clock as the site of its actions.

Chronotherapy Treatment of Disease

The chronotherapeutic treatment of disease is based on understanding that the effects of many drugs, chemicals are cell-cycle dependent and regulated by circadian clocks. As a result, cells show varying levels of sensitivities to drugs, toxins and chemical substances at different times of the day .

Diseases such as cardiovascular disorders, hypertension, depression, asthma, cancer, and arthritis are influenced by circadian rhythms. For instance, osteoarthritis worsens during the day and is most bothersome in the evenings. But for people with rheumatoid arthritis, the pain usually peaks in the morning and decreases as the day wears on. Cardiovascular diseases such as hypertension and angina, or chest pain, also follow a definite circadian rhythm. Epidemiologic studies document the heightened morning-time risk of angina, myocardial infarction, and stroke.

Cancer

Cancer chronotherapy times the administration of toxic cancer chemotherapeutic agents according to circadian rhythms to produce the greatest action at killing cancer cells without killing the patient and producing minimal side effects.

Arthritis

Arthritic diseases such as rheumatoid arthritis, osteoarthritis, and gout exhibit profound circadian rhythms in the manifestation and intensity of symptoms. The chronotherapeutic treatment of arthritic conditions uses medicines that fight joint swelling, stiffness, and pain.

Studies clearly show that the time when NSAIDs and other anti-arthritic medicines are taken is critical. Taking the medicines at the wrong time of day compromises their effectiveness and increases the risk of side effects. Chronotherapy provides ways of increasing the effectiveness and safety of arthritis medications. Taking long-acting NSAIDs like ketoprofen and indomethacin at bedtime optimizes their therapeutic effect and minimizes their side effects.

Skin Aging

Many skin functions are circadian rhythmic. The proliferation of skin cells varies by up to 30-fold in the 24 hours, being greatest at midnight and least at noon. Circadian rhythms in skin biology give rise to day-night differences in the texture, radiance and overall appearance of facial skin.

The topical application of anti-aging cosmetics to the face for preventing moisture loss, reducing the depth of wrinkles and giving the skin a more youthful look work in relation to the circadian rhythms of facial skin biology. When applied during the day, these cosmetic agents can be significantly less effective.

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