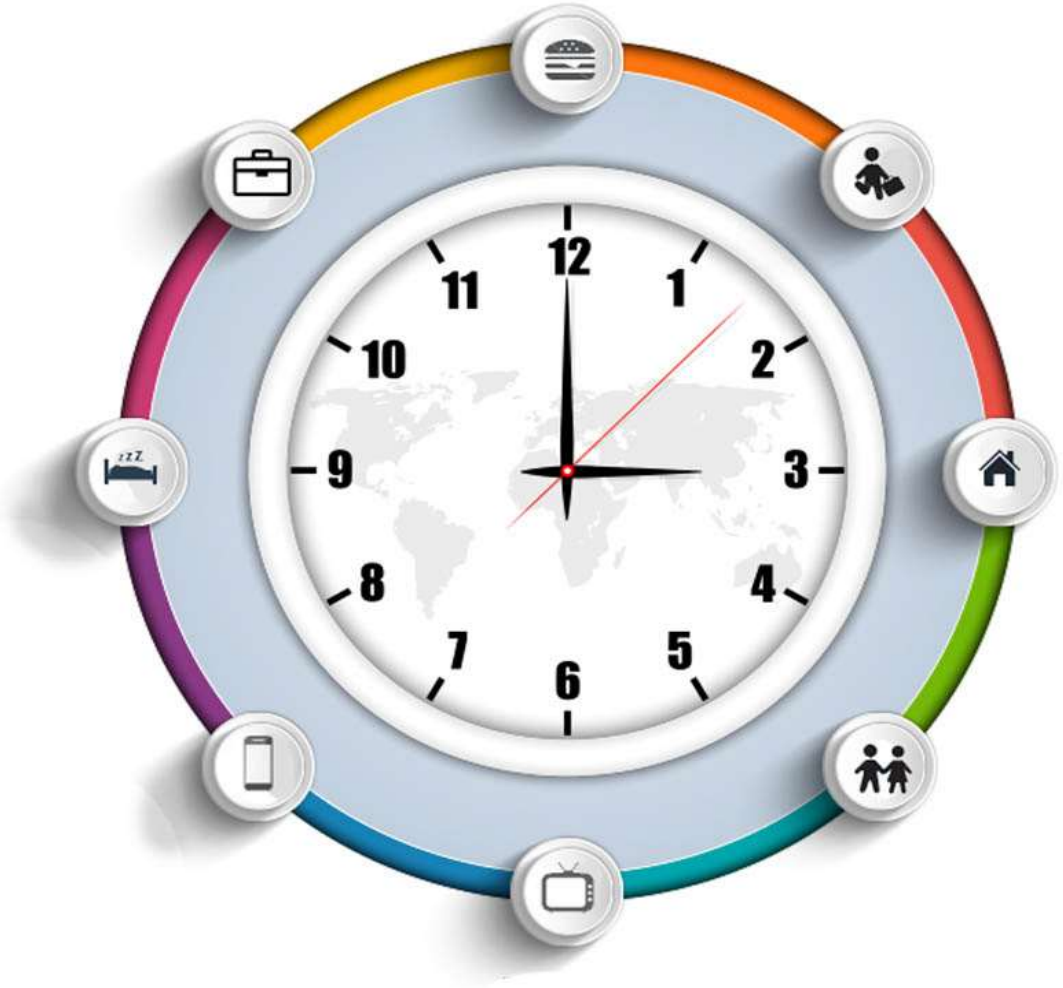
CHRONOPHARMACOLOGY



- Dr Mangala Nischal
- 2nd yr PG
- M D pharmacology

Overview

- Introduction
- History
- Definitions
- Circadian rhythm & clock genes
- Applications of Chronopharmacology
- Chronopharmaceutics
- Conclusion
- References

Introduction :-

- Most facets of mammalian physiology and behavior vary according to time-of-day, thanks to an endogenous “circadian” clock.
- Daily oscillations of proteins is necessary for either drug absorption or metabolism result in circadian pharmacokinetics; and oscillations in the physiological systems targeted by these drugs result in circadian pharmacodynamics.
- Circadian clocks influence all major organ systems, and this influence translates directly into disease pathology that also varies with time of day.

History :

- **Jean-Jaques d'Ortous de Mairan** described circadian rhythms of plants in the 18th century

- **Franz Halberg** coined the term '**Circadian'** in 20th century.
- (circa – about or approximately; dian-day, or about 24 hour).
- Considered as one of the founders of Modern Chronobiology.

Biological rhythms

- Circadian: Lasting for about 24 hours.

  -Sleep wake cycles

- Infradian: Cycles longer than 24 hours.

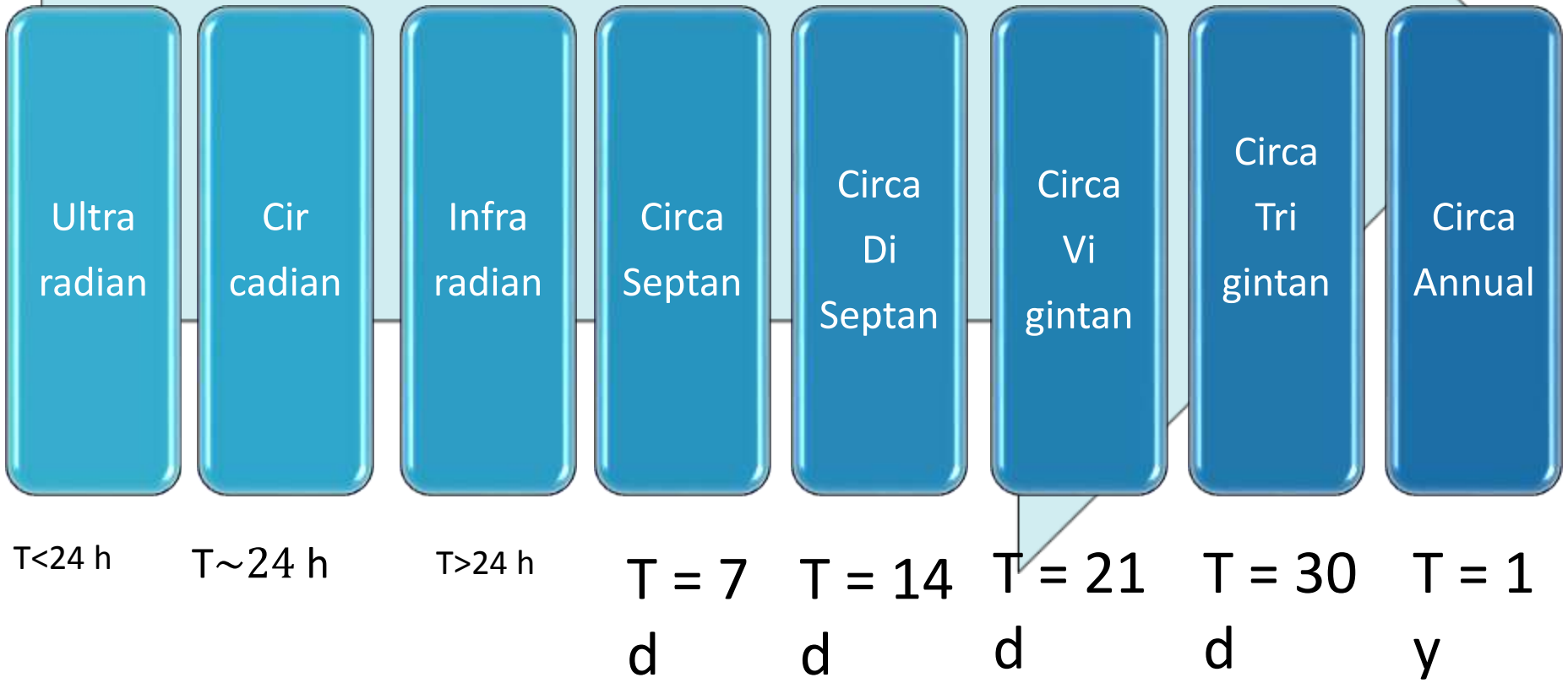
  -Menstrual cycle

- Ultradian: Cycles shorter than a day.

  -Neuronal firing time

- Seasonal: Seasonal affective disorders.

Biorhythms


Ultra radian
Cir cadian
Infra radian
Circa Septan
Circa Di Septan
Circa Vi gintan
Circa Tri gintan
Circa Annual
T<24 h
T~24 h
T>24 h
T = 7 d
T = 14 d
T = 21 d
T = 30 d
T = 1 y

Definitions :

- Chronobiology

  The branch of science focusing on biological rhythms and their mechanisms.

- Chronos (time),
- Bios (life),
- Logos (study).

- Chronopharmacology

Science dealing with optimization of drug effects & minimization of adverse effects by timing medications in relation to biological rhythm. It is concerned with the effects of drugs upon the timing of biological events and rhythms.

- Subdivided into
  - **Chronopharmacokinetics**
  - **Chronotoxicity**
  - **Chronesthesy**
  - **Chronotherapy**

Chronopharmacokinetics :

- It deals with the study of the temporal changes in the pharmacokinetics of the drugs with respective time.
- Study of absorption, distribution, metabolism, and excretion of drug according to the time of the day or year.

- Chronesthesy
- The rhythmic changes in susceptibility or sensitivity of a target system to a drug.

- Chronergy

Rhythmic changes of both the desired [effectiveness] and undesired [toxicity, tolerance] effects on the organism as a whole.

Chronotherapeutics

- Discipline of medical treatment which allows for the consideration of a patient's biological rhythm, changes in the severity of a disease state during the day, and the synchronizing of dosing and delivery of a particular drug to allow for the optimal efficacy in the patient.
- Refers to concept of matching timing of treatment with intrinsic timing of illness.

Advantages

- Prevents over dosage
- Appropriate usage of drug
- Reduce side effects

- ChronoPharmaceutics

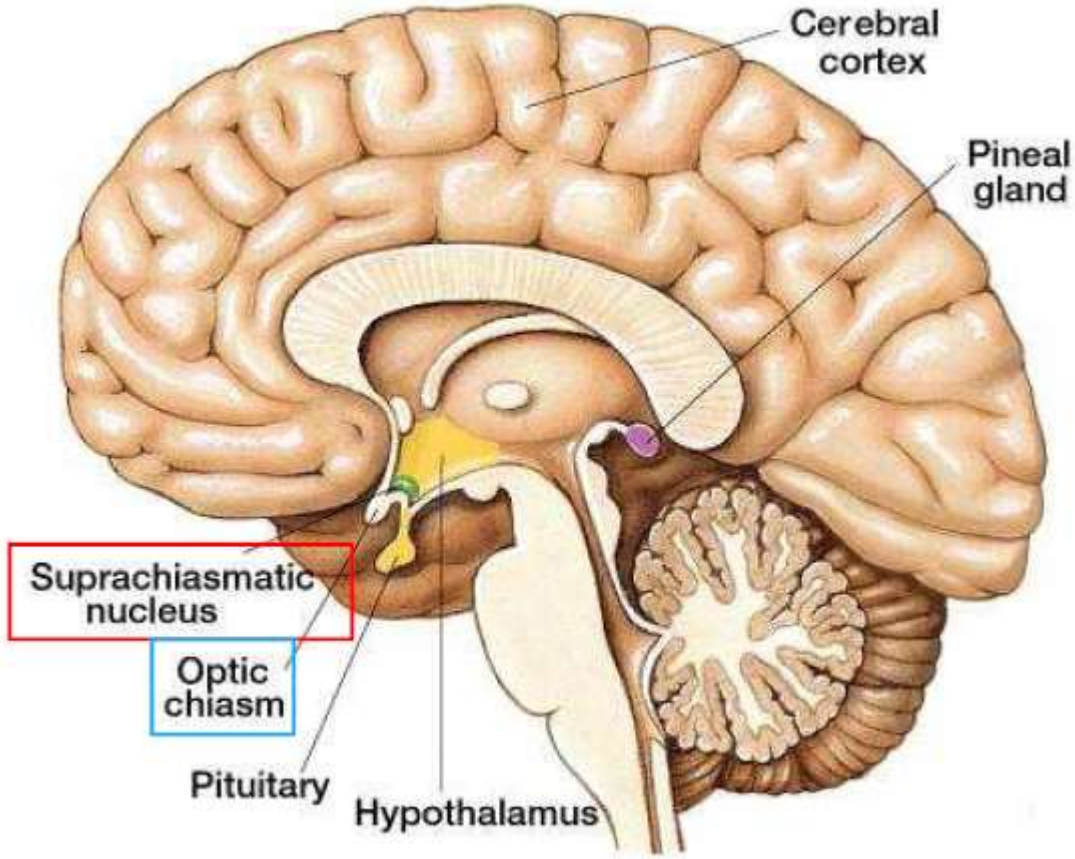
  - Branch which designs and develops a drug delivery system in accordance with biological rhythm to optimize the treatment of disease.

Circadian rhythm

- The basic unit of circadian timekeeping

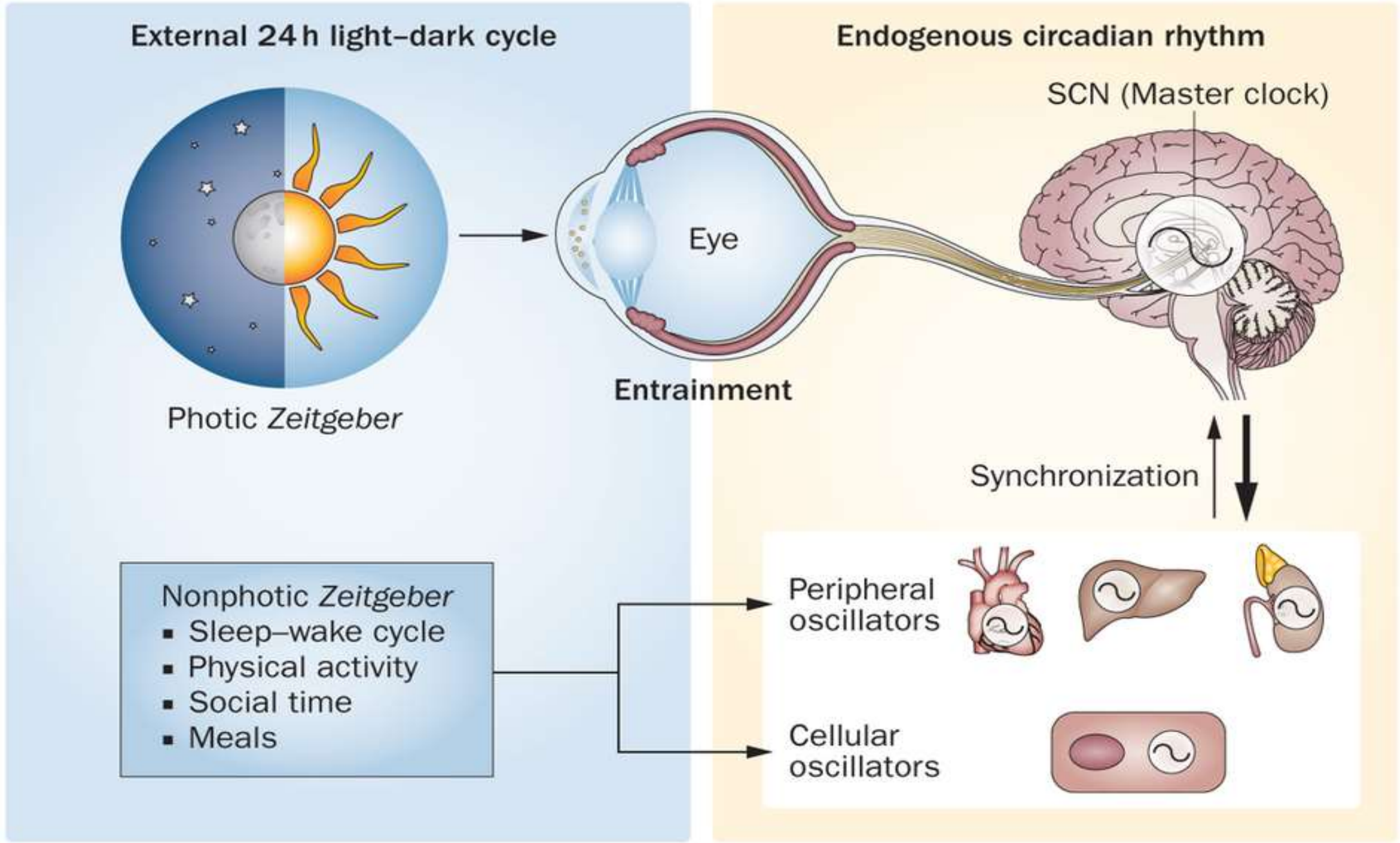
  is the…

- **Supra chiasmatic nucleus**
- **Clock genes**



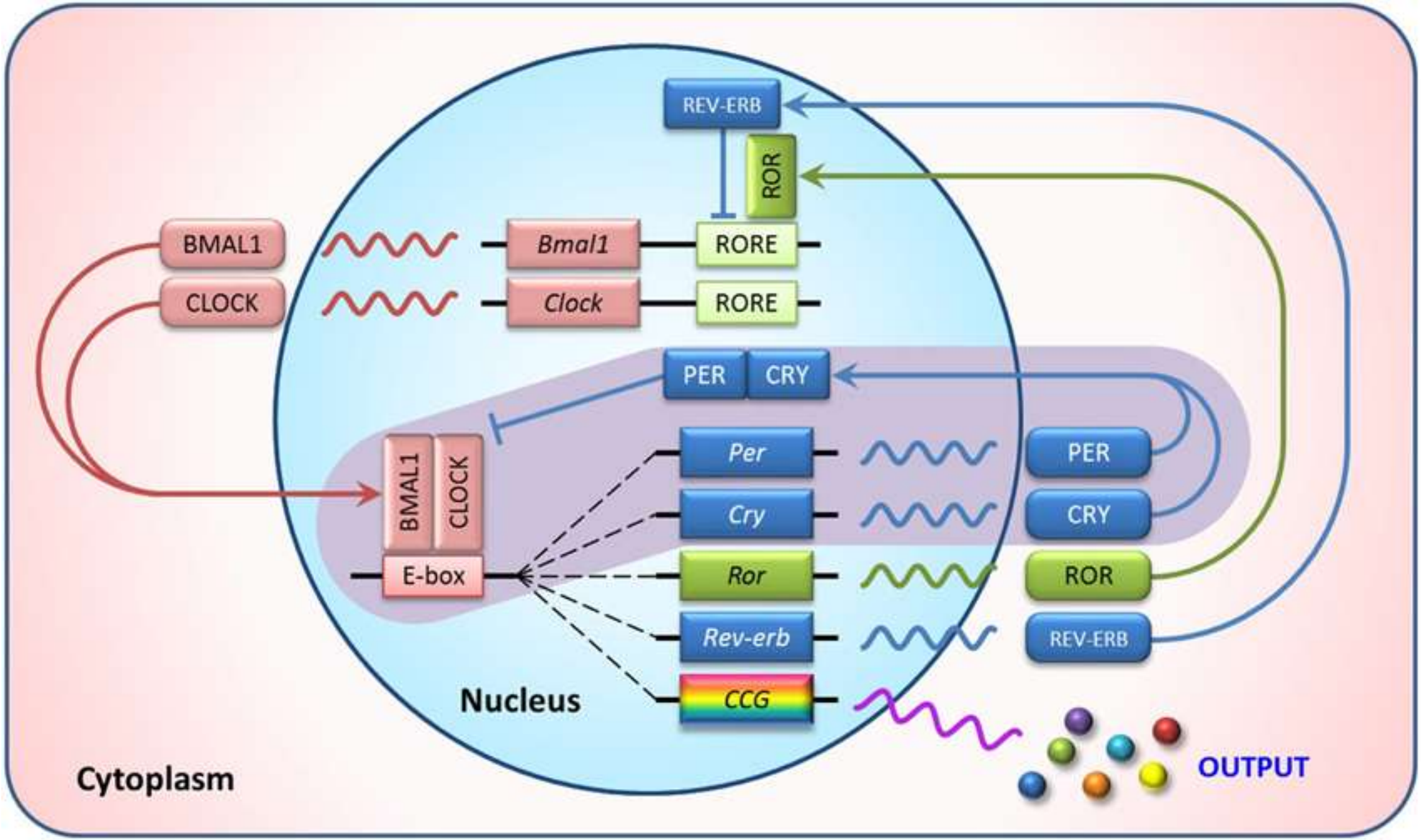
Zeitgeber

Circadian rhythms are driven by endogenous processes, are self-sustaining, and rely upon circadian time cues (**zeitgebers)** to remain appropriately oriented to the individual's environment and desired routine.

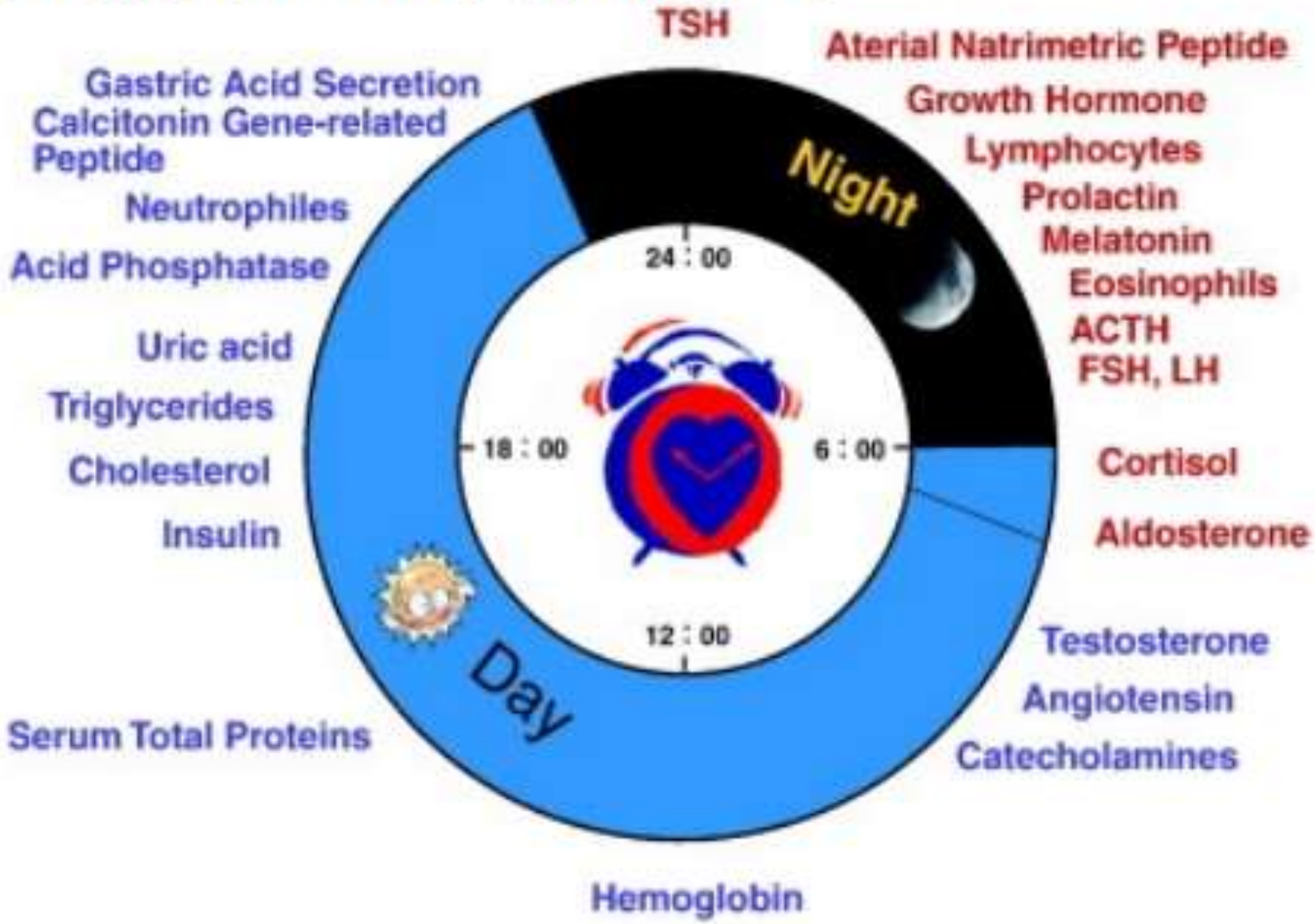

External 24 h light–dark cycle
Endogenous circadian rhythm
SCN (Master clock)
Eye
Photic *Zeitgeber*
Entrainment
Synchronization
Nonphotic *Zeitgeber*
▪ Sleep–wake cycle
▪ Physical activity
▪ Social time
▪ Meals
Peripheral oscillators
Cellular oscillators

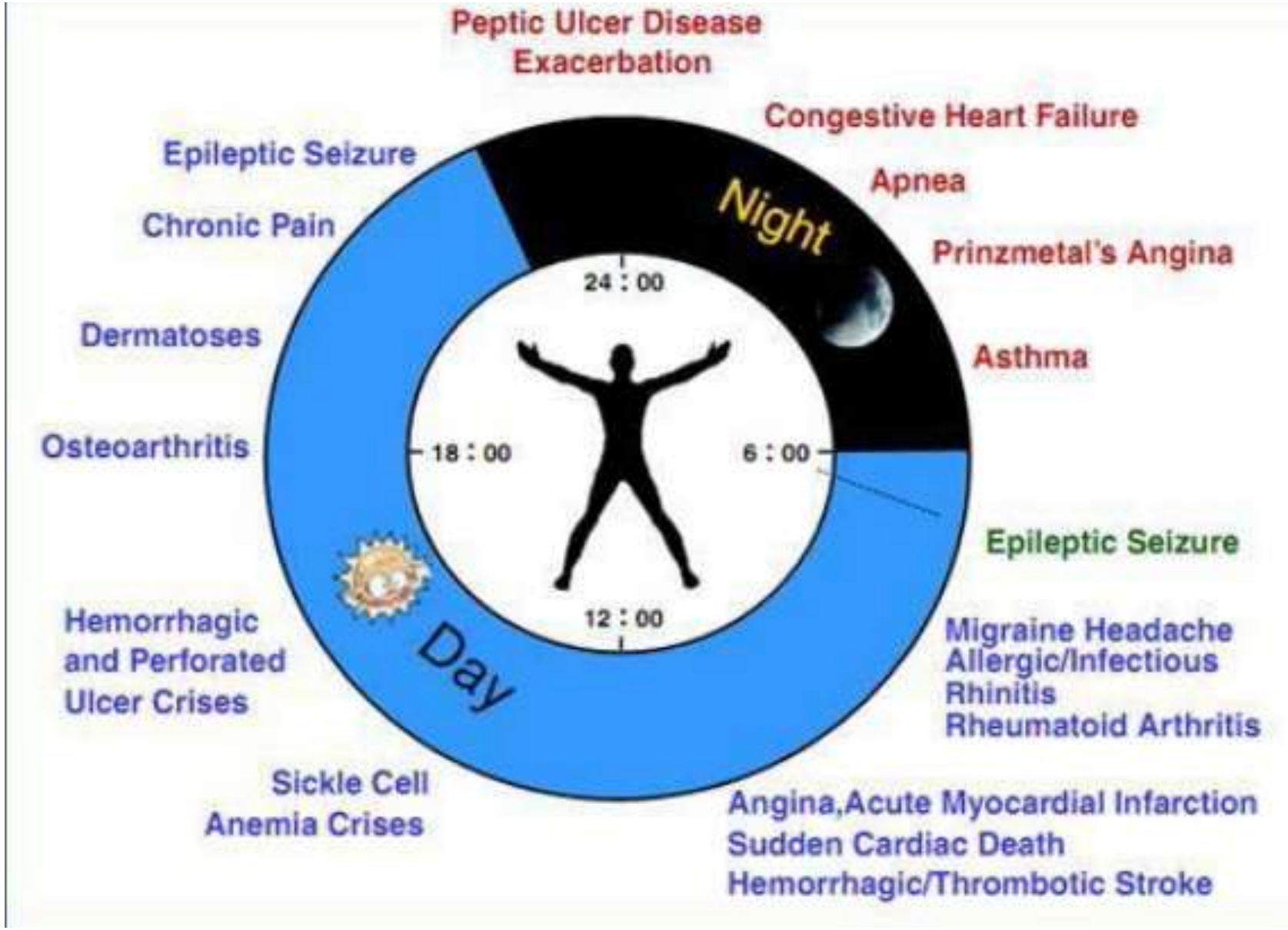
Clock Genes :

- Circadian rhythms are driven by a group of genes called **clock genes.**
- In mammals, the core clock genes consist of **Bmal1** (Brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1), **CLOCK** (Circadian Locomotor Output Cycles Kaput), **Per** (Period), and **Cry** (Cryptochrome).
- They form a tightly regulated system with interlocking feedback and feed-forward loops.


REV-ERB
ROR
BMAL1
CLOCK
Bmal1
Clock
RORE
RORE
PER
CRY
BMAL1
CLOCK
E-box
Per
Cry
Ror
Rev-erb
CCG
PER
CRY
ROR
REV-ERB
Nucleus
Cytoplasm
OUTPUT

Human Circadian Time Structure




Peptic Ulcer Disease
Exacerbation
Congestive Heart Failure
Epileptic Seizure
Apnea
Chronic Pain
Night
Prinzmetal's Angina
24 : 00
Dermatoses
Asthma
Osteoarthritis
18 : 00
6 : 00
Epileptic Seizure
Hemorrhagic
and Perforated
Ulcer Crises
12 : 00
Migraine Headache
Allergic/Infectious
Rhinitis
Rheumatoid Arthritis
Day
Sickle Cell
Anemia Crises
Angina,Acute Myocardial Infarction
Sudden Cardiac Death
Hemorrhagic/Thrombotic Stroke

Applications of Chronopharmacology

Respiratory system

Increased bronchoconstriction at night due to…

↑Parasympathetic tone

↓ Adrenaline

↓ Cortisol at midnight

↑Sensitivity to irritants and allergens at night

→ exacerbations of allergic rhinitis & asthma

Asthma

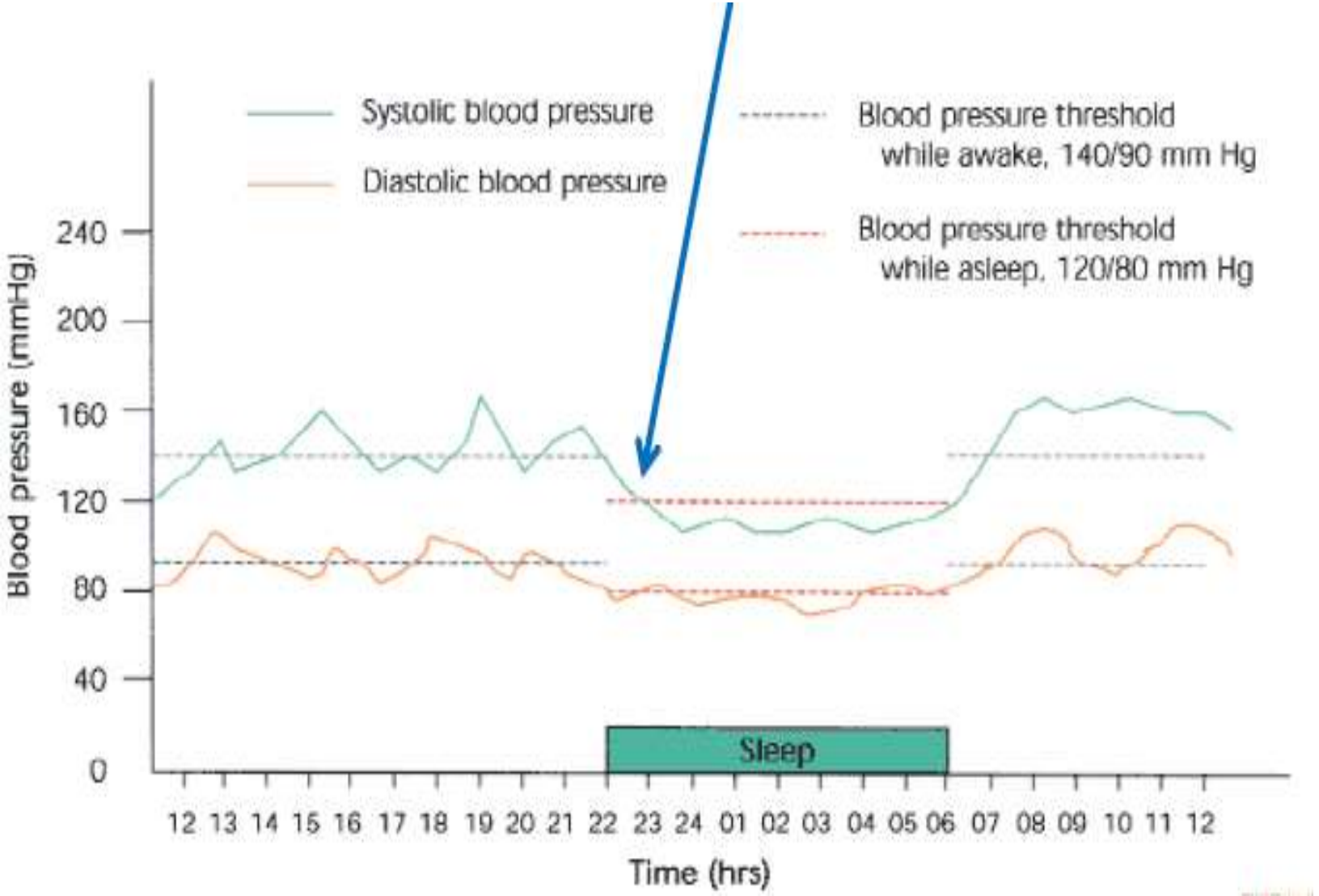
- Acute attack of asthma

  - more common between midnight and 6 am.

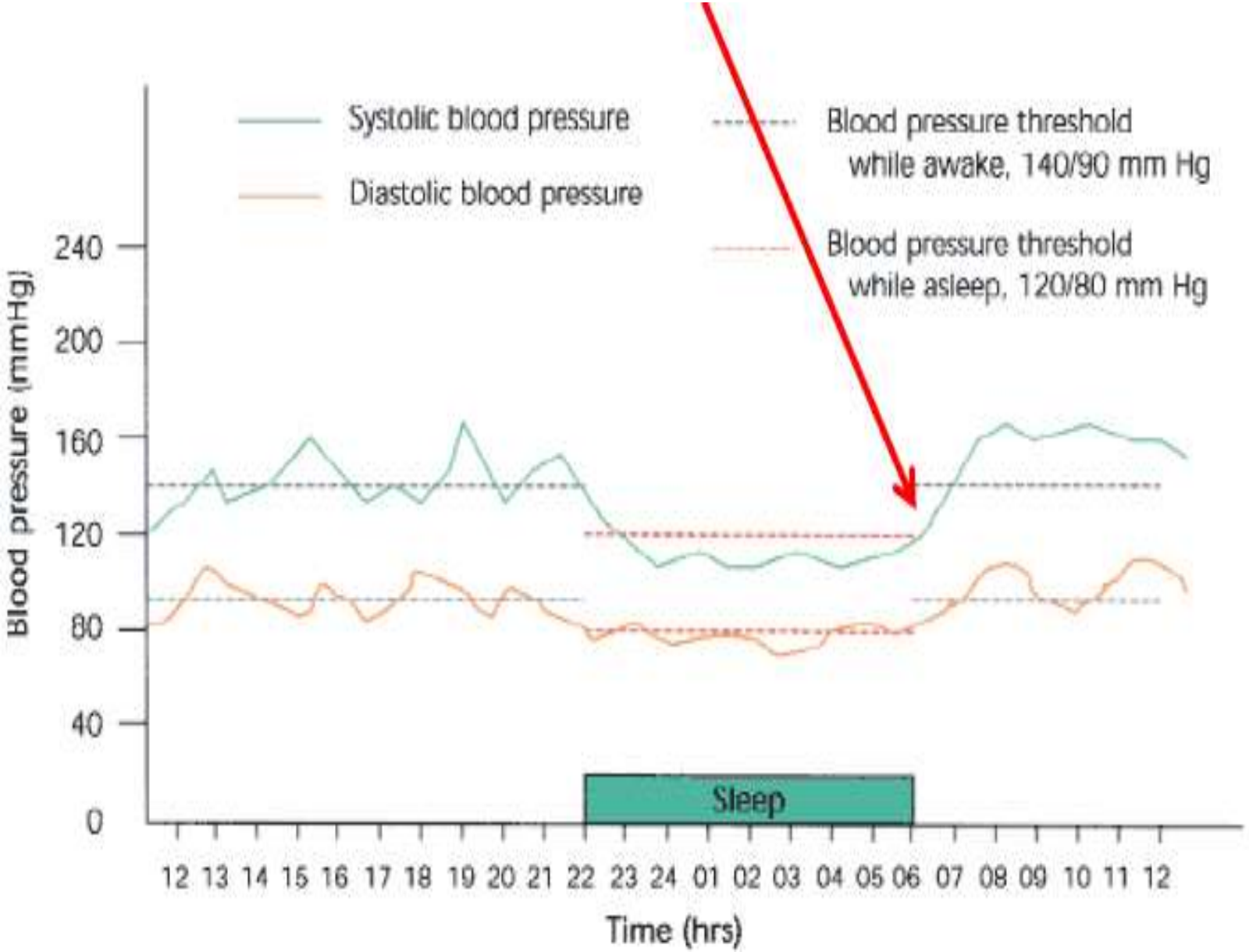
- Rx - Theophylline and Beta 2 agonist is timed at evening

CVS-

Night time dip

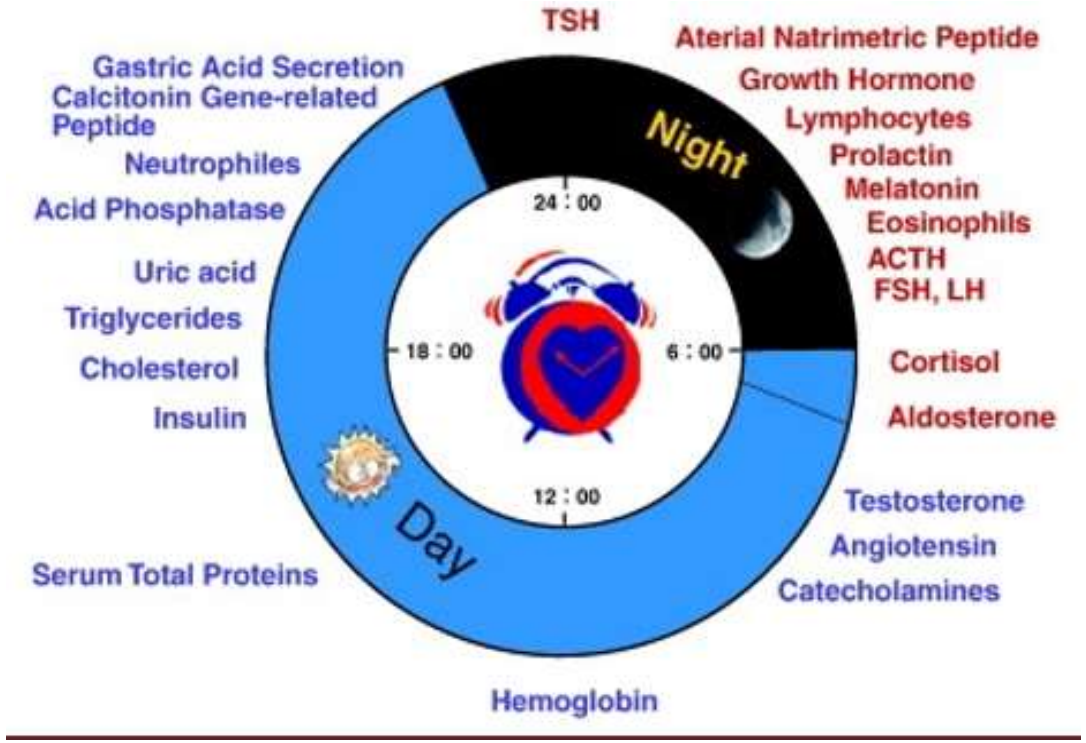


Morning rise



Cardiovascular Disorders

- Myocardial infarction
  Sudden cardiac death
  Angina pectoris
  Transient ischemic attacks / Stroke



High incidence between 6am and 12 noon.

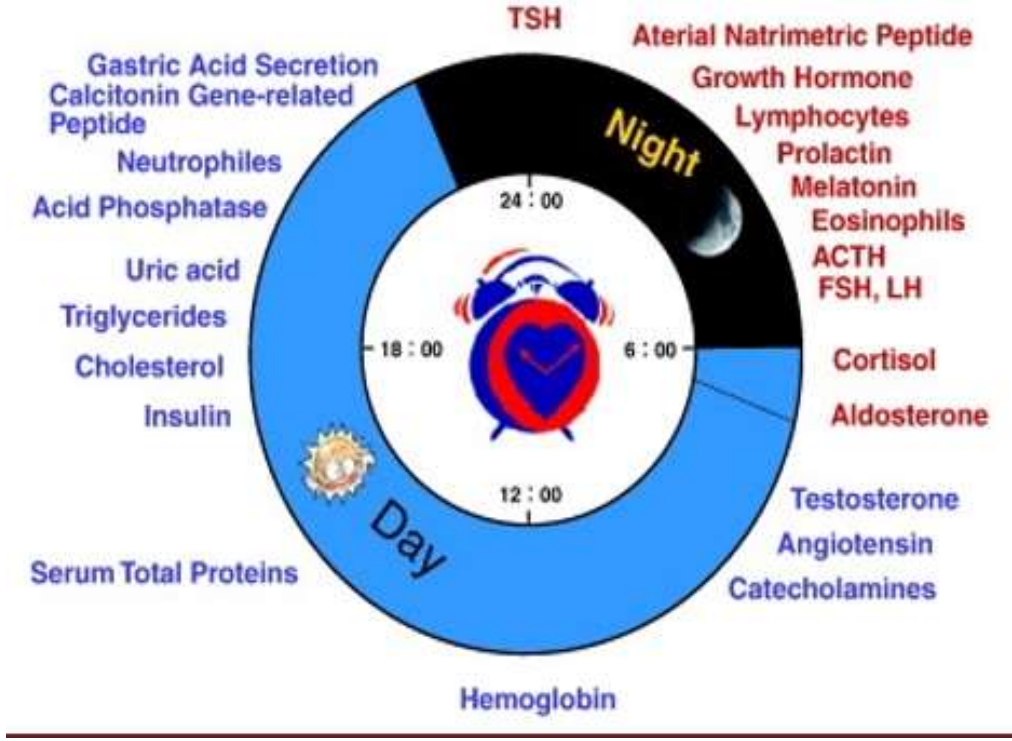
- ↑ Vascular tone
- ↑ Platelet aggregation
- ↓ Intrinsic thrombolytic activity.

Cardiovascular drugs

- Aspirin – maximum antiplatelet effect in the morning.
- Thrombolytics and Heparin – ↓ benefit during early morning hours.
- Atenolol – more effective during day time.
- Labetalol – more effective in early morning hours.
- Enalapril - Peak effect in the afternoon after morning dose.

Endocrine system

- Highest secretion of cortisol early morning.
- Lowest at midnight.
- GH peaks during sleep.
- Testosterone peaks early morning.
- TSH peaks at mid night.
- Corticosteroids given as single morning dose cause less pituitary adrenal suppression



Gastrointestinal tract

- Acid secretion peaks between 10 pm and 2 am.
- Ulcer pain is worst at this time.
- Ulcer healing is directly related to acid secretion inhibition at night.
- Evening dosage of H_2 receptor antagonists or PPI.

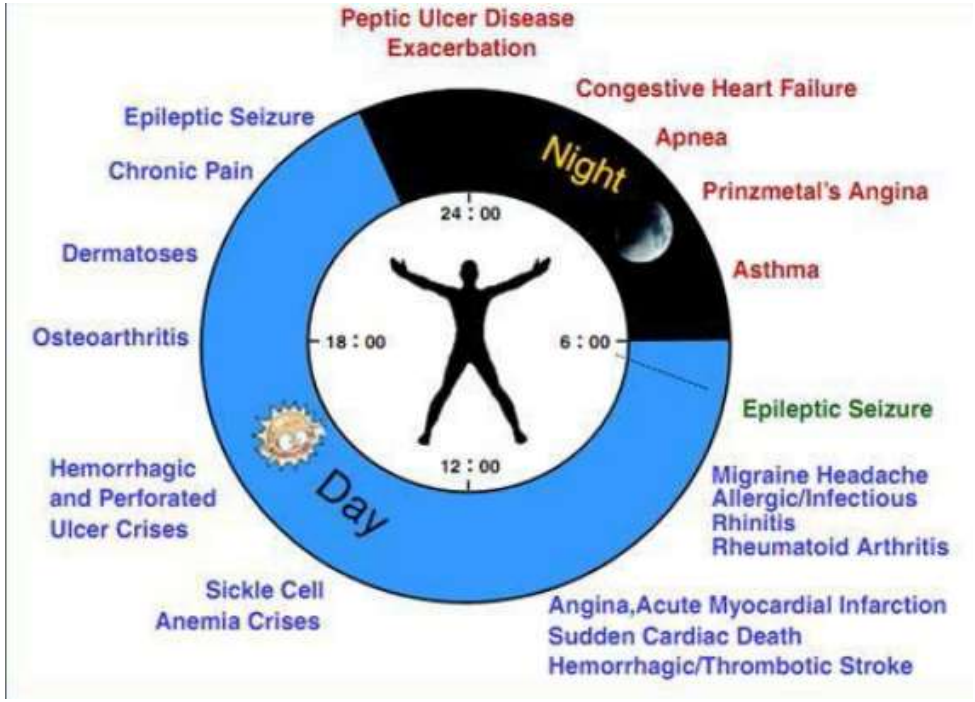
CNS

- Melatonin – secreted at night by pineal gland.
- Function – synchronizes sleep wake cycle with circadian rhythm.
- Melatonin agonist [Ramelteon] – hypnotic for sleep onset insomnia & reduces jet lag symptoms.
- Bedtime administration - more effective.

Musculoskeletal system

Rheumatoid Arthritis

- Symptoms more severe - 8am & 11am.
- Long acting NSAIDS at bed time

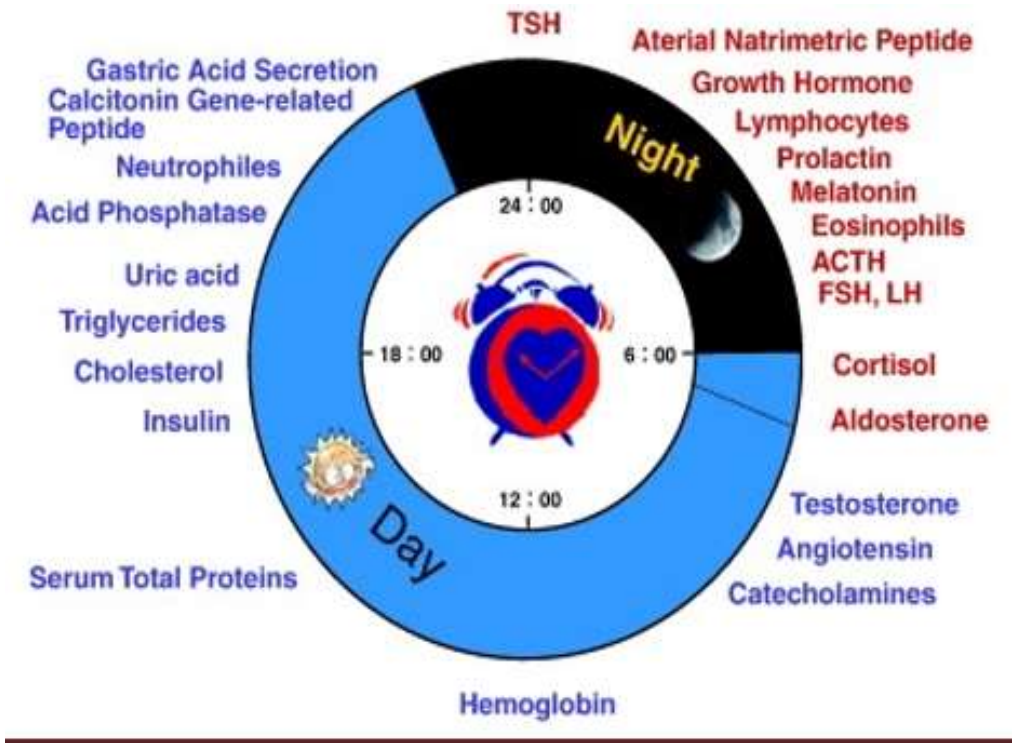


Osteoarthritis

- Pain more intense between 2 pm and 8 pm.
- Morning dose for afternoon worsening, evening dose for night time worsening.

Hypercholesterolemia

- Cholesterol synthesis more at night.



- Evening dose of HMG CoA reductase inhibitors is more effective.

Cancer

- Cancer cells are considered to have lost internal time keeping mechanism.

- Tumor cells and normal cells differ in their chronobiological cycles.

- The basis for the chronopharmacotherapy of cancers...

Lymphoma

- The DNA synthesis in the normal human bone marrow cells has a peak around noon while the peak of DNA synthesis in lymphoma cells is near midnight.

- So, an s-phase active cytotoxic therapy at late nights should be more advantageous

Skin Disorders

- Psoriasis: cell proliferation rate peaks between 9pm & 3am.

-Inflammatory activity highest at night, least in the morning.

- Atopic dermatitis: sensitivity to histamine highest at night.
- Topical corticosteroids: activity in the afternoon higher than that in the morning.

ChronoPharmaceutics

Design and development of Chrono drug delivery system :

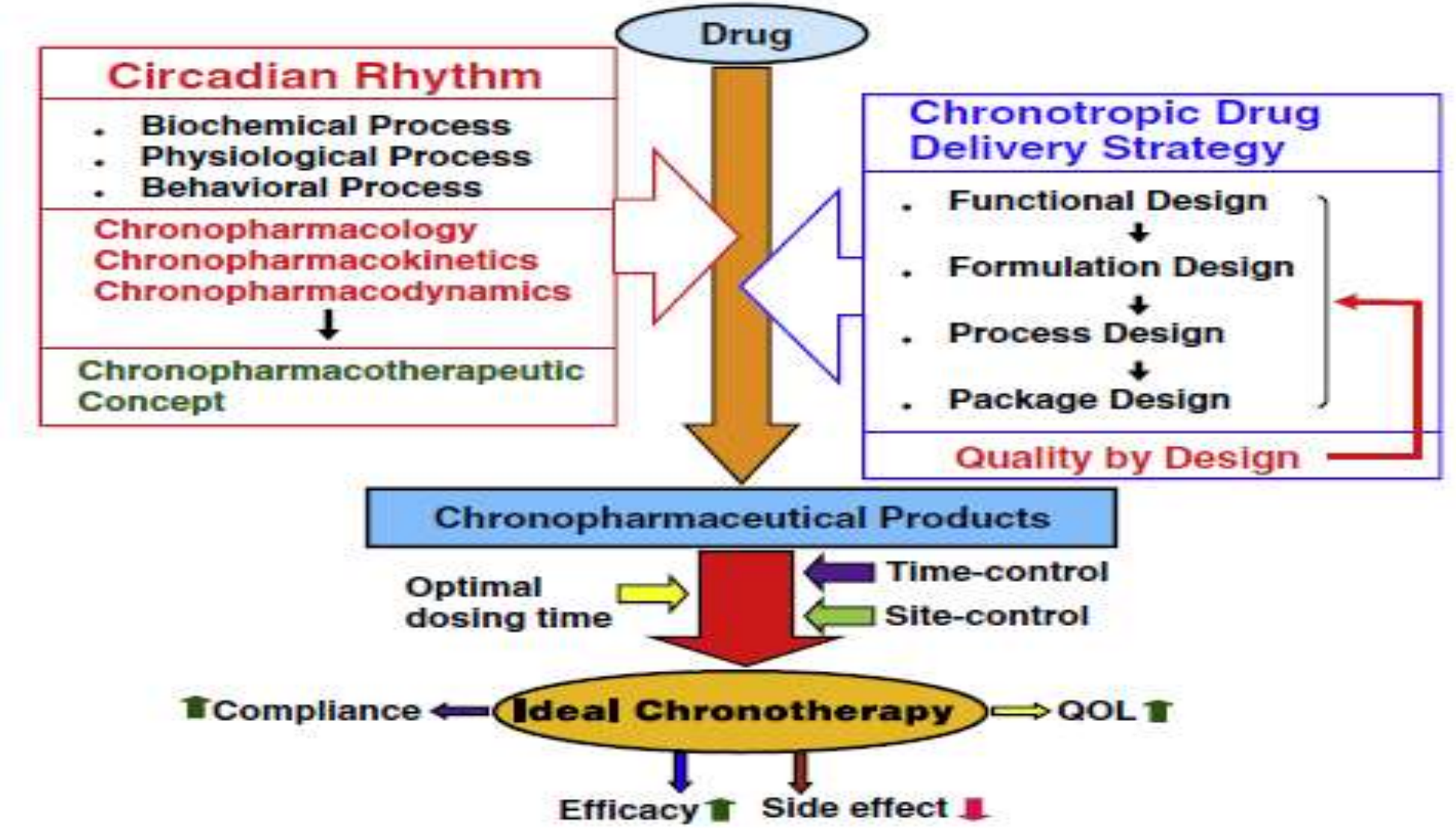
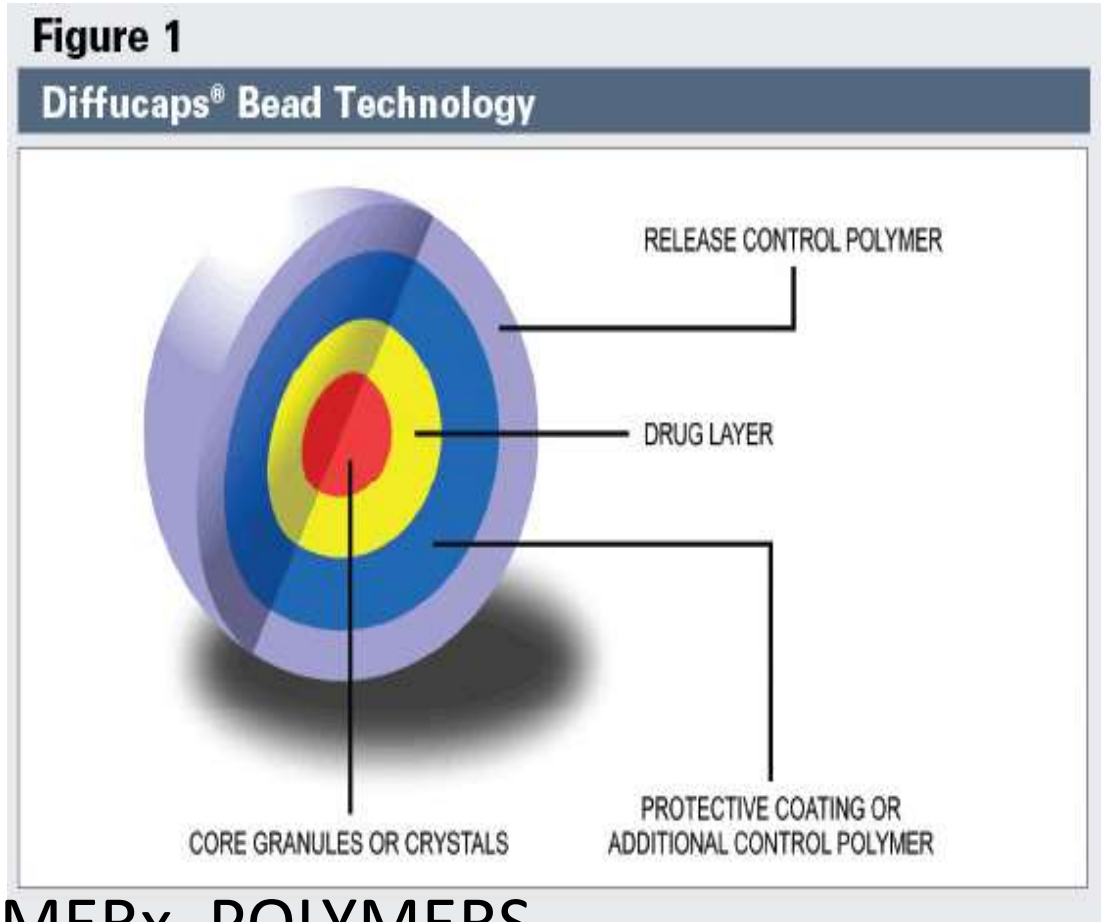


Fig. 2. Design and development of new chronotropic DDSs in accordance with circadian

Chrono Drug Delivery Systems (Chrono-DDS)



OROS, CODAS, CEFORM, TIMERx, POLYMERS, MICROCHIPS, DIFFUCAPS

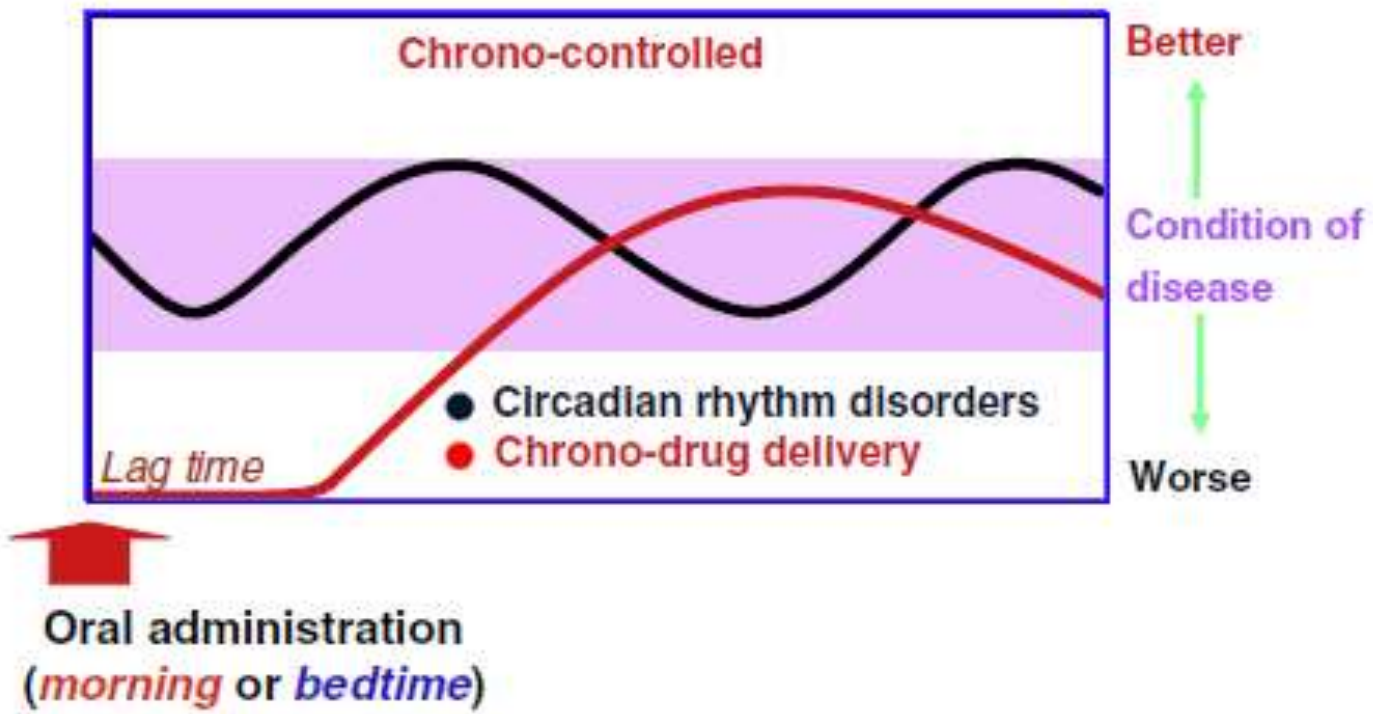


Fig. 22. An ideal chronotheraputic drug delivery according to the circadian rhythm disorders of the patient.

Chronopharmaceutical technologies:

- Parenteral routes in chronotherapy include

  - C**hronomodulating infusion pumps** (i.e. Melodie™, Panomat™ V5, Synchromed™, Rhythmic™)

  - C**ontrolled-release microchips**

- Oral administration include

  - Contin™, Chronset™, Codas™, Ceform™, Diffucaps™, TIMERx®, Chronotopic™, Egalet™, GeoClock™, Port™, Three-dimensional printing (3DP)™

  - methods involve physico-chemical modification of the active pharmaceutical ingredient and/or the use of **controlled-release erodible polymer** .

- **Pulsatile drug delivery systems**: Here a targeted drug is deliverd at specific site due to induction of certain physiochemical stimuli at target site.
- Release of certain enzymes, hormones, antibodies, pH of the site, temperature of the site, presence of certain cells, and concentration of biomolecules (glucose, neurotransmitters, inflammatory mediators) act as stimuli to trigger the release of drug from these types of drug delivery systems.

- Recently, a novel **floating pulsatile system** - high internal phase emulsion based porous material.

Marketed technologies of pulsatile drug delivery

Technology	Mechanism	Proprietary name and dosage form	API	Disease
OROS®;	Osmotic mechanism	Covera-HS® XL tablet	Verapamil HCl	Hypertension
CODOS®	multiparticulate ph dependent system	Verelan® PM; XL release capsule	Verapamil HCL	Hypertension
DIFFUCAPS®	multiparticulate system	Innopran®;XL tablets	Verapamil HCl, propranolol HCl	Hypertension
Three dimensional printing®	externally regulated system	TheirForm®	Diclophenac sodium	Inflammation
Pulsincap™	Rupturable system	PulsincapTM	Dofetilide	Hypertension

Conclusion

- Effectiveness and toxicity of a drug are not constant over 24 hr period.
- Understanding the biological rhythms can optimize and individualize drug therapy to a great extent.
- Thus it can help to decrease the drug related toxicity and enhance effectiveness.

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Thank you