MODEL ANSWER

PHYSIOLOGY HYONOURS/6TH SEM PHYA

DSEB3 PAPER (CHRONOBIOLOGY & STRESS PHYSIOLOGY)

1. WHAT IS REM AND NON-REM SLEEP?

Sleep, a normal, reversible, recurrent state of 'reduced responsiveness' to external stimulation. It is different from states of coma, hibernation, and death by the fact that it can be rapidly reversed. The human body cycles through two phases of sleep, -Rapid eye movement (REM) and Non-rapid eye movement (NREM) sleep, which is further divided into three stages, N1, N2 and N3.

REM Sleep:

- REM sleep is associated with rapid movements of the eyes, dreaming and irregular muscle movements.
- The EEG recording shows beta waves - like brain waves during wakefulness. The brain is highly active throughout REM sleep, increasing brain metabolism by up to 20%.
- But at the same time, skeletal muscles are atonic and without movement, except for the eyes. That is why it is known as paradoxical sleep.

NON-REM SLEEP:

- There is no rapid eye-movement in NREM sleep. It is further sub-divided into N1, N2 and N3 sleep.
- N1 Stage: This is the lightest stage of sleep and begins when more than 50% of the alpha waves are replaced with low-amplitude mixed-frequency (LAMF) activity in EEG. Muscle tone is present in the skeletal muscle, and breathing tends to occur at a regular rate. This stage lasts around 1 to 5 minutes, consisting of 5% of total sleep time.
- N2 stage: This stage represents deeper sleep, in which heart rate and body temperate drops. It is characterized by the presence of sleep spindles, K-complexes, or both in EEG. It plays an important role in memory consolidation. It lasts around 25 minutes in the first cycle and lengthens with each successive cycle, eventually consisting of about 45% of total sleep.
- N3 Stage: N3 is also known as slow-wave sleep (SWS). This is considered the deepest stage of sleep and EEG is characterized by delta waves with much lower frequencies and higher amplitudes. This is the stage when the body repairs and regrows tissues, builds bone and muscle, and strengthens the immune system.

2. WHAT DO YOU UNDERSTAND BY SEASONAL BREEDING?

- Seasonal breeders are animal species that actively and successfully breed only during certain times of the year. This is to maximize the survival of their offspring by overcoming the different climatic conditions and taking into consideration the availability of feed and fodder. Example- horses, dogs, goat, sheep etc.

- Duration of photo period plays a critical role in the onset of breeding season for seasonal breeders. The changing photoperiod acts as a bioregulator of reproductive activity and fertility through the mediation of central nervous system, hypothalamus, anterior pituitary, and the pineal gland. The pineal gland translates the visual signal into hormonal signal thereby showing fluctuation in secretion of melatonin which alters the pulsatile secretion of GnRH/LH.

3. WHAT DO YOU UNDERSTAND BY EXTERNAL AND INTERNAL ENVIRONMENT?

- The internal environment refers to the 'internal milieu' of a multicellular organism, a concept first given by the French physiologist Claude Bernard (1813–78). Every cell of a multicellular organism must regulate its surroundings to keep a relatively stable internal environment. The fluid outside the cells in the body is the extracellular fluid (ECF). The internal environment is thus equivalent to the extracellular fluid. Extracellular fluid is found in three extracellular compartment- plasma, interstitial fluid, and lymph. The internal environment is important for all normal cell function.

- The surrounding environment in which a living organism lives forms the external environment. It pertains to the physical, chemical, biological, and social conditions surrounding the organism.

- Animal organs and organ systems constantly adjust to internal and external changes through a process called homeostasis ("steady state"). The goal of homeostasis is the maintenance of equilibrium around a set point. Any change in the internal or external environment (stimulus) is detected by a receptor. If there are normal fluctuations from the set point, the body's systems will usually attempt to go back to this point. For instance, if the body becomes too warm, adjustments are made to cool the animal. If the blood's glucose rises after a meal, adjustments are made to lower the blood glucose level etc.

4. DISCUSS THE EFFECT OF HYPOBARIC ENVIRONMENT ON HUMAN BODY. HOW IT CAN BE PREVENTED?

High-altitude environments expose travelers to cold, low humidity, increased UV radiation, and decreased air pressure, all of which can cause health problems. The biggest concern, however, is hypoxia, due to the decreased partial pressure of oxygen (PO2). For example, the PO2 at the altitude of Everest Base Camp (5,300 m) is about one-half of the sea-level value.

Altitude illness is divided into 3 syndromes: acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE).

a) **Acute mountain sickness (AMS):** The hallmark of AMS is a headache, with other symptoms including nausea, vomiting, loss of appetite, fatigue, sleep disturbance, and dizziness**.** The condition is typically self-limited, developing and resolving over 1–3 days. Men are at greater risk of altitude sickness than women

b) **High altitude pulmonary edema (HAPE):** HAPE can occur by itself or in conjunction with AMS and HACE. HAPE can be more rapidly fatal than HACE. Initial symptoms include chest congestion, cough, exaggerated dyspnea on exertion, and decreased exercise performance. If unrecognized and untreated, HAPE progresses to dyspnea at rest often with bloody sputum. Symptoms of HAPE commonly appear at night and can worsen during exertion. Symptoms include chest tightness or fullness, blue or gray lips and fingernails, coughing when breathing, etc.

c) **High altitude cerebral edema (HACE:** HACE is considered as "end stage" of AMS. HACE is associated with altered mental status, ataxia, confusion, and drowsiness, just like alcohol intoxication. In this state, brain accumulates extra fluid, swells, and stops working properly. Symptoms may include worsening headache, vomiting, Exhaustion, Visual hallucinations, Changes in behavior Coma.

Prevention:

- it is advisable to slow down the rate of ascent. The optimal rate of ascent should be no more than 500 m per day at levels greater than 2500 m.
- Avoiding exercise and alcohol for the first 48 hours until acclimated.
- If Acute Mountain Sickness does occur, further ascent is not advisable until acclimated.

5. DISCUSS RESPIRATORY CHANGES DUE TO ACCLIMATIZATION IN HIGH ALTITUDE.

[please follow text books]

6. DEFINE HYPOXIA.

Hypoxia is a state in which oxygen is not available in sufficient amounts at the tissue-level to maintain adequate homeostasis. It can result from inadequate oxygen delivery to the tissues or due to low oxygen content in the blood (hypoxemia). There are four main types of hypoxia: Hypoxic, Hypemic, Stagnant and Histotoxic hypoxia.

- Hypoxic Hypoxia: Also referred to as altitude hypoxia. It is the lack of oxygen absorbed by the body due to atmospheric conditions. As altitude increases, the partial pressure of oxygen decreases along with blood oxygen saturation.
- Hypemic Hypoxia: It occurs when the blood is not able to carry enough oxygen to the body's cells, usually caused by anemia, blood loss, deformed blood cells, or carbon monoxide (CO) poisoning and in smoking.

- Stagnant Hypoxia: Oxygen deficiency in the body due to poor circulation of the blood. It Can occur from pulling of blood due to gravity or cold (constricting blood vessels) which may reduce blood to extremities.
- Histotoxic Hypoxia: It is the inability of the body to use oxygen. It is caused by alcohol and other drugs such as narcotics and poison.

7. DISCUSS AGE RELATED CHANGES IN BIOLOGICAL CLOCK.

Aging is characterized by a gradual decline in numerous physiological systems. Physiological rhythms are known to deteriorate with aging and show a phase-advance towards early morning wakening.

a) Age impacts sleep timing, duration, and consolidation. Elderly adults exhibit increased sleep latency, increased night-time awaking, and excessive daytime sleepiness. Overall sleep decreases and tends to be more fragmented in the elderly.
b) Similarly, the amplitude and magnitude of the rhythms of eating and of hormone secretion are also reduced with age. Daily rhythms of melatonin and cortisol are decreased. Body temperature also appears to show an age-related reduction in circadian amplitude.
c) Change in SCN: The electrical properties of SCN neurons change with age, with older neurons showing a reduction in the circadian amplitude of resting membrane potential. In addition, there are age-related reduction in synaptic spines and a shortening of dendrites, suggesting a loss of neuronal connectivity with age. SCN also shows reductions in the expression of two major peptides, vasoactive intestinal polypeptide (VIP) and arginine-vasopressin (AVP). Furthermore, GABAergic signaling appears to be disrupted in the aged SCN. The expression of PERIOD genes like PER1 and PER2 become flat and phase-advanced by approximately 4 to 6 hours in older animals. Expression of CRY1 and BMAL-1 also become arrhythmic.
d) Change in peripheral oscillator: Peripheral oscillators also dampen with age. This results in desynchronization and decreased amplitude of rhythms at the network level.

8. WHAT ARE SOMNOGENS?

A somnogen is any substance that causes or induces sleepiness. Examples- melatonin, adenosine, GABA, norepinephrine, orexin (hypocretin), acetylcholine, histamine, cortisol, serotonin etc.

9. WHAT IS CHRONOTYPING?

"Chrono" means "time". A chronotype is a classification system to understand the sleep and productivity schedules of human beings. It is a person's circadian typology i.e., the individual differences in activity and alertness in the morning and evening. Most research breaks human chronotypes into morning type, evening type and intermediate types. Chronotyping is highly beneficial as it can predict the time of the day in which an individual reaches his/her peak physical/cognitive performance.

10. WHAT IS CHRONOTHERAPY?

Chronotherapy is a therapeutic intervention which aims to reset a dysregulated circadian rhythm of an individual to normal sleep/wake cycles. It is a method used to treat sleep disorders (Insomnia, DSP etc.) using external stimuli to gradually adjust a person's sleep patterns. There are 4 types of chronotherapy:

- **Bright light therapy**: Bright light therapy involves receiving high-intensity, fluorescent illumination coming from a specially designed light box for 10 – 90 minutes each morning. Bright light therapy is the first-line treatment for seasonal mood disorders.
- **Sleep deprivation therapy:** it involves completely avoiding sleep for one to three cycles (whole night and the following day) mixed with nights of recovery sleep. It is highly efficient in diminishing depressive symptoms.
- **Sleep phase advance therapy:** involves moving bedtime and wake time forward (for instance, 5 pm to 12 am midnight) until a normal sleep/wake cycle is achieved and maintained. This therapy has been used in

conjunction with the sleep deprivation therapy to alleviate depressive symptoms and proved to be highly efficient to reset the circadian clock in patients with delayed sleep phase disorder (DSPD).

- **Triple/combined therapy:** It is a combination of above three therapies which particularly helps to reduce suicidal and depressive symptoms in a rapid and sustainable manner.

11. WHAT IS ROS? HOW THEY ARE FORMED?

Oxygen is required for all living organisms for their survival. But at the same time, **oxygen is potentially toxic**. It is considered as a double-edged sword. The concept of oxygen toxicity is due to the formation of oxygen free radicals or reactive oxygen species (ROS).

Free Radicals: A free radical is defined as **a molecule or a molecular species that contains one or more unpaired electrons and is capable of independent existence**. Examples- Superoxide radical ($O2^-$), Hydroxyl radical (OH^-), Hydro-peroxy radical (HOO^-), Nitric oxide radical (NO^-), Peroxynitrite radical ($ONOO^-$) etc. All these free radicals are highly reactive, have very short half-life, can generate new radicals by chain reaction and cause damage to biomolecules, cells, and tissues.

Reactive Oxygen species: Free radical and ROS are not synonymous. Free radicals contain one or more unpaired electrons. (E.g., $O2^-$, OH^-, HOO^- etc). But there are some non-radical derivatives of O_2 which do not contain unpaired electrons. (E.g., Hydrogen peroxide (H_2O_2) Singlet Oxygen ($^1O_2$). The term **ROS is used in a broader sense to collectively represent all free radicals and highly reactive non-free radicals of biological system.**

Formation of Free radicals or ROS:

1. Molecular oxygen (O_2) is para-magnetic and contains two unpaired electrons. During metabolic reactions, molecular oxygen is completely reduced and converted to water. If the reduction is incomplete, a series of reactive radicals are formed.
2. When an oxygen molecule takes up one electron it becomes **superoxide anion. ($O_2^{-\cdot}$).** Superoxide anion can accept H+ and form **hydroperoxy radical (HOO·)** which finally forms **hydrogen peroxide (H_2O_2)**.

(1) $O_2 + e^- \Rightarrow O_2^{-\cdot}$

(2) $O_2^{-\cdot} + H^+ \Rightarrow HO_2^{\cdot}$

$2HO_2^{\cdot} \Rightarrow H_2O_2 + O_2$

3. **Fenton reaction**: Fenton's response starts with the oxidation of the ferrous ion (Fe2+ cation) to the ferric ion (Fe3+ cation). This results in the formation of a hydroxide ion (OH^-) and a hydroxyl free radical (HO•).

4. **Haber-Weiss reaction:** Hydrogen peroxide can further react with superoxide anion in presence of Fe++ to form hydroxide ion (OH^-) and a hydroxyl free radical (HO•).

$Fe^{3+} + O_2^{\cdot-} \longleftrightarrow Fe^{2+} + O_2$

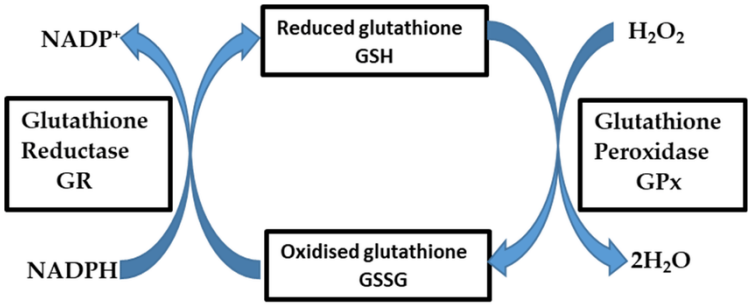
$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + HO^{\cdot} + OH^-$ (Fenton reaction)

$O_2^{\cdot-} + H_2O_2 \longleftrightarrow O_2 + HO^{\cdot} + OH^-$ (Haber-Weiss reaction)

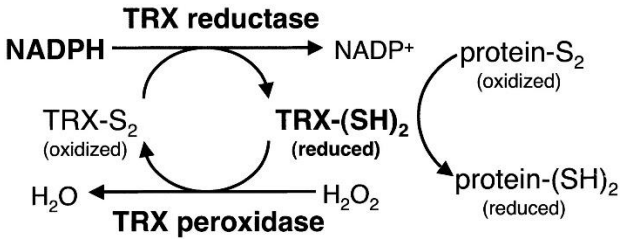
12. NADPH PLAYS CRUCIAL ROLE IN REPLENISHING THE ANTIOXIDANT RESERVE-JUSTIFY.

NADPH increases the antioxidant status of the body. The production of glutathione (GSH), an important antioxidant, requires NADPH. NADPH also plays important roles in the function of two other antioxidant systems- thioredoxin and catalase.

a) NAD(P)H acts as a hydride (hydrogen anion) donor in a variety of enzymatic processes. One example is the re-reduction of GSSG (oxidized glutathione) to GSH, catalyzed by glutathione reductase. Because of this reaction, NADPH has been suggested to also act as an indirectly operating antioxidant, thus maintaining the antioxidative power of glutathione.



b) Thioredoxin reductase (TRX reductase) utilizes NADPH as an electron donor to maintain the reduced form of thioredoxin (TRX-SH), which contributes to scavenge H2O2.



c) Catalase is one of the crucial antioxidant enzymes that mitigates oxidative stress. NADPH binds to catalase, and reactivates it when it has been inactivated by H2O2. In the process, the bound NADPH becomes NADP+. it is essential to prevent the enzyme denaturation.