Hypothalamus

■ INTRODUCTION

Hypothalamus is a diencephalic structure. It is situated just below thalamus in the ventral part of **diencephalon.** It is formed by groups of nuclei, scattered in the walls and floor of third ventricle. It extends from optic chiasma to mamillary body.

■ NUCLEI OF HYPOTHALAMUS

Nuclei of hypothalamus are divided into three groups:

1. Anterior or preoptic group
2. Middle or tuberal group
3. Posterior or mamillary group.

Nuclei of each group are listed in Table 149.1 and represented diagrammatically in Figure 149.1.

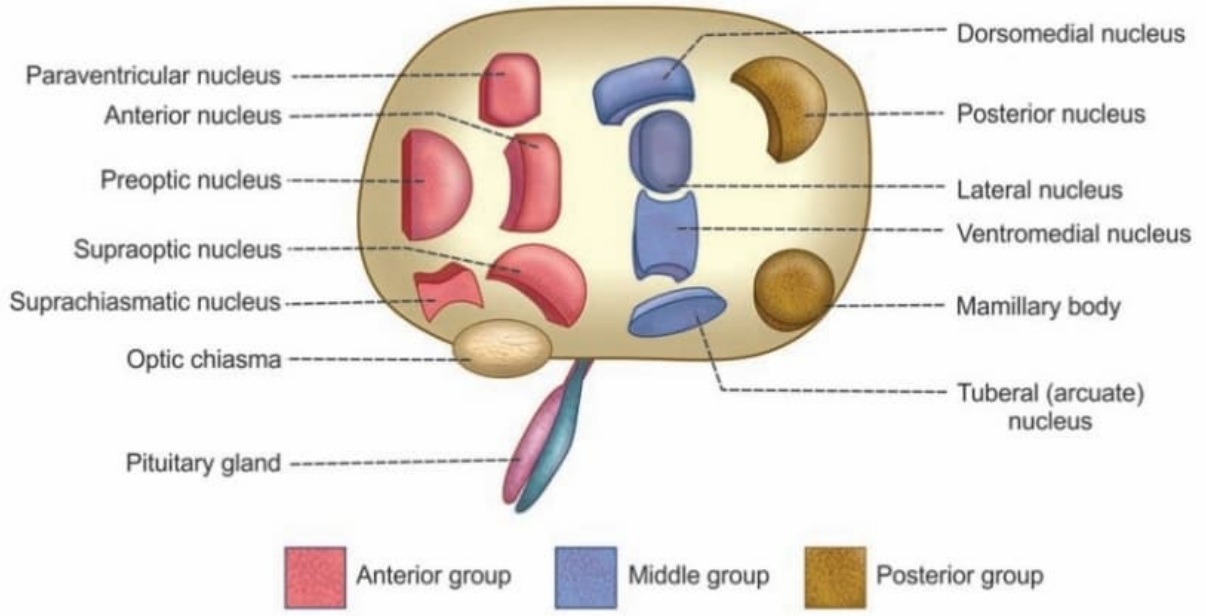

FIGURE 149.1: Nuclei of hypothalamus

TABLE 149.1: Nuclei of hypothalamus

Anterior or Preoptic group	Middle or Tuberal group	Posterior or Mamillary group
1. Preoptic nucleus	1. Dorsomedial nucleus	1. Posterior nucleus
2. Paraventricular nucleus	2. Ventromedial nucleus	2. Mamillary body
3. Anterior nucleus	3. Lateral nucleus	
4. Supraoptic nucleus	4. Arcuate (tuberal) nucleus	
5. Suprachiasmatic nucleus		

CONNECTIONS OF HYPOTHALAMUS

AFFERENT CONNECTIONS TO HYPOTHALAMUS

1. *Medial forebrain bundle:* From rhinencephalon (limbic cortex) to preoptic nucleus, lateral nucleus and mamillary body
2. *Fornix:* From hippocampus to mamillary body
3. *Stria terminalis:* From amygdaloid to preoptic nucleus
4. *Corticohypothalamic fibers:* From prefrontal area (8) and precentral area (6) of cerebral cortex to the supraoptic and paraventricular nuclei of hypothalamus
5. *Pallidohypothalamic fibers:* From globus pallidus to diffused areas of hypothalamus
6. *Thalamohypothalamic fibers:* From dorsomedial and midline nuclei of thalamus to diffused areas of hypothalamus
7. *Reticulohypothalamic fibers:* From reticular formation of brainstem to diffused areas of hypothalamus
8. *Retinohypothalamic fibers:* Fibers from retina to supraoptic, suprachiasmatic and ventromedial nuclei of hypothalamus (Fig. 149.2).

EFFERENT CONNECTIONS FROM HYPOTHALAMUS

1. *Mamillothalamic tract:* From mamillary body to anterior thalamic nuclei
2. *Mamillotegmental tract:* From mamillary body to the tegmental nuclei of midbrain
3. *Periventricular fibers:* Fibers from posterior, supraoptic and tuberal nuclei of hypothalamus pass through periventricular gray matter and reach the following:
   i. Reticular formation in brainstem and spinal cord
   ii. Dorsomedial nucleus of thalamus
   iii. Frontal lobe of cerebral cortex
4. *Hypothalamohypophyseal tract:* From supraoptic and paraventricular nuclei of hypothalamus to posterior pituitary.

■ FUNCTIONS OF HYPOTHALAMUS

Hypothalamus is the important part of brain, concerned with **homeostasis** of the body. It regulates many vital functions of the body like endocrine functions, visceral functions, metabolic activities, hunger, thirst, sleep, wakefulness, emotion, sexual functions, etc. (Table 149.2).

■ 1. SECRETION OF POSTERIOR PITUITARY HORMONES

Hypothalamus is the site of secretion for the posterior pituitary hormones. **Antidiuretic hormone** (ADH) and **oxytocin** are secreted by supraoptic and paraventricular nuclei. These two hormones are transported by means of axonic or axoplasmic flow through the fibers of hypothalamohypophyseal tracts to posterior pituitary. Refer Chapter 66 for details.

■ 2. CONTROL OF ANTERIOR PITUITARY

Hypothalamus controls the secretions of anterior pituitary gland by secreting **releasing hormones** and **inhibitory hormones.** It secretes seven hormones.

i. Growth hormone-releasing hormone (GHRH)
ii. Growth hormone-releasing polypeptide (GHRP)
iii. Growth hormone-inhibiting hormone (GHIH) or somatostatin
iv. Thyrotropin-releasing hormone (TRH)
v. Corticotropin-releasing hormone (CRH)
vi. Gonadotropin-releasing hormone (GnRH)
vii. Prolactin-inhibiting hormone (PIH).

These hormones are secreted by discrete areas of hypothalamus and transported to anterior pituitary by the **hypothalamohypophyseal portal blood vessels.** Refer Chapter 66 for details.

■ 3. CONTROL OF ADRENAL CORTEX

Anterior pituitary regulates adrenal cortex by secreting **adrenocorticotropic hormone** (ACTH). ACTH secretion is in turn regulated by corticotropin-releasing hormone (CRH), which is secreted by the paraventricular nucleus of hypothalamus (Refer Chapter 70 for details).

■ 4. CONTROL OF ADRENAL MEDULLA

Dorsomedial and posterior hypothamic nuclei are excited by emotional stimuli. These hypothalamic nuclei, in turn, send impulses to adrenal medulla through sympathetic fibers and cause release of **catecholamines,** which are essential to cope up with emotional stress (Chapter 71).

■ 5. REGULATION OF AUTONOMIC NERVOUS SYSTEM

Hypothalamus controls autonomic nervous system (ANS). Sympathetic division of ANS is regulated by posterior and lateral nuclei of hypothalamus. Parasympathetic division of ANS is controlled by anterior group of nuclei. The effects of cerebral cortex on ANS are executed through hypothalamus (Chapter 164).

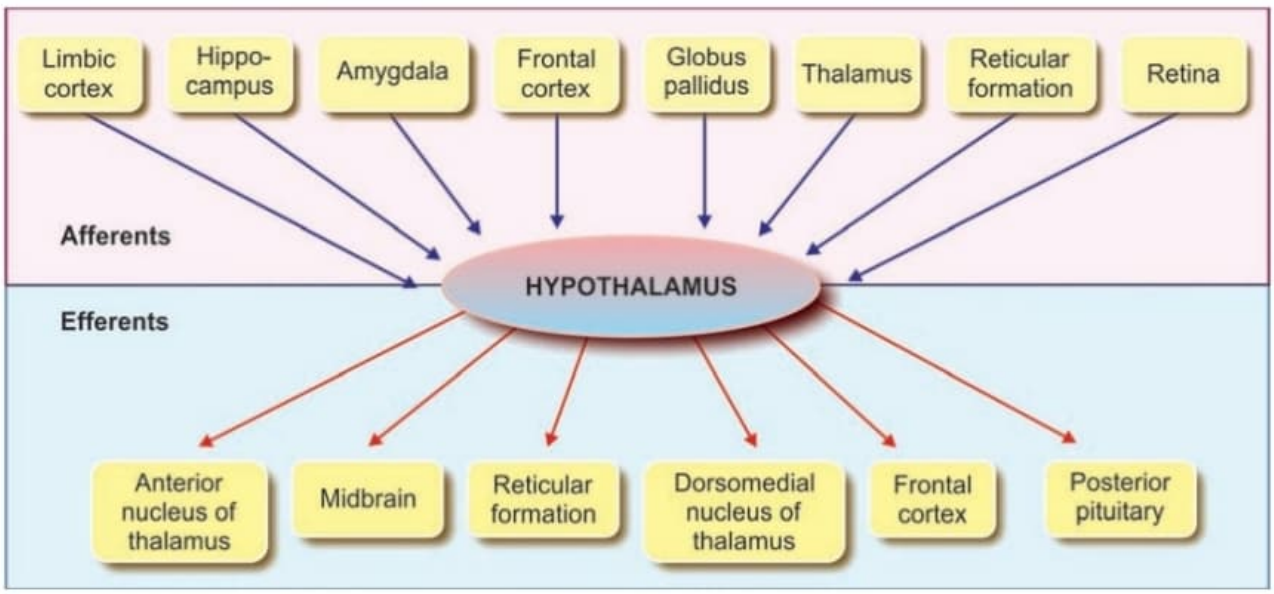

FIGURE 149.2: Connections of hypothalamus

TABLE 149.2: Functions of hypothalamus

Functions	Action/Center	Nuclei/Parts involved
1. Control of anterior pituitary	Releasing hormones Inhibiting hormones	Discrete areas
2. Secretion of posterior pituitary hormones	Oxytocin Antidiuretic hormone (ADH)	Paraventricular nucleus Supraoptic nucleus
3. Control of adrenal cortex	Corticotropin-releasing hormone (CRH)	Paraventricular nucleus
4. Control of adrenal medulla	Catecholamines during emotion	Posterior and dorsomedial nuclei
5. Regulation of autonomic nervous system (ANS)	Sympathetic Parasympathetic	Posterior and lateral nuclei Anterior nuclei
6. Regulation of heart rate	Acceleration Inhibition	Posterior and lateral nuclei Preoptic and anterior nuclei
7. Regulation of blood pressure	Pressor effect Depressor effect	Posterior and lateral nuclei Preoptic area
8. Regulation of body temperature	Heat gain center Heat loss center	Posterior hypothalamus Anterior hypothalamus
9. Regulation of hunger and food intake	Feeding center Satiety center	Lateral nucleus Ventromedial nucleus
10. Regulation of water intake	Thirst center Water retention by ADH	Lateral nucleus Supraoptic nucleus
11. Regulation of sleep and wakefulness	Sleep Wakefulness	Anterior hypothalamus Mamillary body
12. Regulation of behavior and emotion	Reward center Punishment center	Ventromedial nucleus Posterior and lateral nuclei
13. Regulation of sexual function	Sexual cycle	Arcuate and posterior nuclei
14. Regulation of response to smell	Autonomic responses	Posterior hypothalamus
15. Role in circadian rhythm	Rhythmic changes	Suprachiasmatic nucleus

■ 6. REGULATION OF HEART RATE

Hypothalamus regulates heart rate through **vasomotor center** in the medulla oblongata. Stimulation of posterior and lateral nuclei of hypothalamus increases the heart rate. Stimulation of preoptic and anterior nuclei decreases the heart rate (Chapter 101).

■ 7. REGULATION OF BLOOD PRESSURE

Hypothalamus regulates the blood pressure by acting on the **vasomotor center.** Stimulation of posterior and lateral hypothalamic nuclei increases arterial blood pressure and stimulation of preoptic area decreases the blood pressure (Chapter 103).

■ 8. REGULATION OF BODY TEMPERATURE

Body temperature is regulated by hypothalamus, which sets the normal range of body temperature. The set point, under normal physiological conditions is 37°C.

Hypothalamus has two centers which regulate the body temperature:

i. **Heat loss center** that is present in preoptic nucleus of anterior hypothalamus
ii. **Heat gain center** that is situated in posterior hypothalamic nucleus.

Regulation of body temperature is explained in Chapter 63.

■ 9. REGULATION OF HUNGER AND FOOD INTAKE

Food intake is regulated by two centers present in hypothalamus:

i. Feeding center
ii. Satiety center.

Feeding Center

Feeding center is in the lateral hypothalamic nucleus. In experimental conditions, stimulation of this center

in animals leads to uncontrolled hunger and increased food intake **(hyperphagia),** resulting in obesity. Destruction of feeding center leads to loss of appetite **(anorexia)** and the animal refuses to take food.

Normally, feeding center is always active. That means, it has the tendency to induce food intake always.

Satiety Center

Satiety center is in the ventromedial nucleus of the hypothalamus. Stimulation of this nucleus in animals causes total loss of appetite and cessation of food intake. Destruction of satiety center leads to **hyperphagia** and the animal becomes obese. This type of obesity is called **hypothalamic obesity.**

Satiety center plays an important role in the regulation of food intake by temporary inhibition of feeding center after food intake.

Mechanism of Regulation of Food Intake

Under normal physiological conditions, appetite and food intake are well balanced and continues in a cyclic manner. Feeding center and satiety center of hypothalamus are responsible for the regulation of appetite and food intake. These centers are regulated by the following mechanisms:

i. Glucostatic mechanism
ii. Lipostatic mechanism
iii. Peptide mechanism
iv. Hormonal mechanism
v. Thermostatic mechanism.

i. *Glucostatic Mechanism*

Cells of satiety center function as **glucostats** or **glucose receptors,** which are stimulated by increased blood glucose level.

While taking food, blood glucose level increases. Slowly the glucostats are stimulated and satiety center is activated. At one stage, it develops the feeling of 'fullness'. Now, the satiety center inhibits the feeding center and stops the food intake.

After few hours of food intake, the blood glucose level decreases and satiety center becomes inactive. So, the feeding center is no longer inhibited. Now it becomes active and increases the appetite and induces food intake. After taking food, once again blood glucose level increases and the cycle is repeated (Fig. 149.3).

However, glucostats do not give response to very high level of glucose in blood **(hyperglycemia).** So, in conditions like diabetes, hyperglycemia fails to stimulate the satiety center. The satiety center does not inhibit the feeding center, so the frequency of food intake increases (polyphagia).

ii. *Lipostatic Mechanism*

Leptin is a peptide secreted by **adipocytes** (cells of adipose tissue). It plays an important role in controlling the food intake and adipose tissue volume. Details of leptin are given in Chapter 73.

When the volume of adipose tissues increases, adipocytes secrete and release a large quantity of leptin into the blood. While circulating through brain, leptin crosses the blood-brain barrier and enters hypothalamus.

In hypothalamus, leptin inhibits the feeding center, resulting in loss of appetite and stoppage of food intake. It is suggested that the cells present in blood-brain barrier contain many receptor-like proteins, which are responsible for the transport of leptin across the barrier.

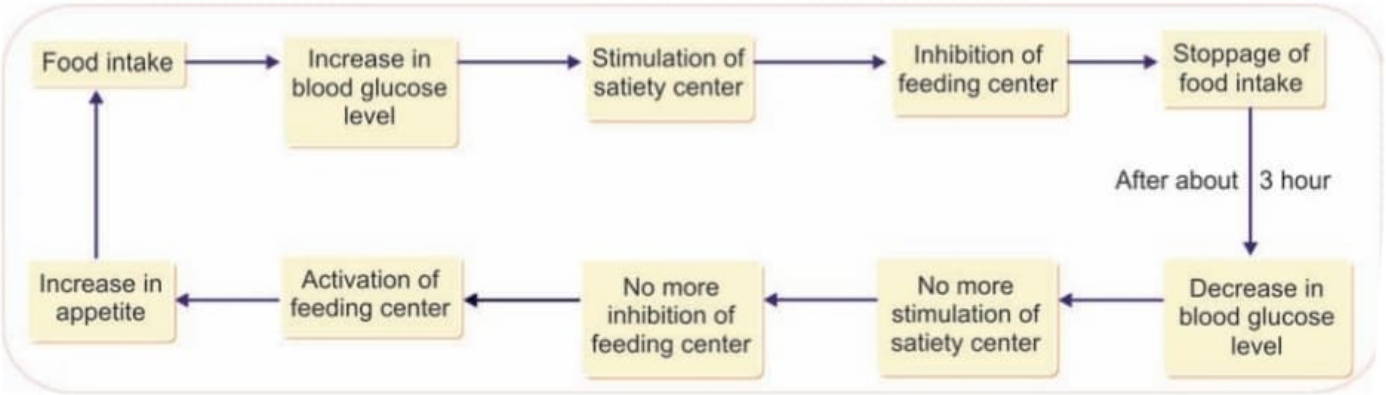

FIGURE 149.3: Glucostatic mechanism

Mode of action of leptin

Leptin acts through some specific neuropeptides in hypothalamus, such as:

a. Neuropeptide Y: It is secreted in small intestine, medulla and hypothalamus. Normally, this peptide stimulates the food intake. But, leptin inhibits neuropeptide Y, leading to stoppage of food intake. Refer Chapters 44 and 141 for details of neuropeptide Y.
b. *Pro-opiomelanocortin (POMC):* It is secreted from anterior pituitary. It is also secreted from hypothalamus, lungs, GI tract and placenta. Normally, it inhibits food intake. Leptin stimulates the secretion of POMC.

Leptin receptor

Many leptin receptors are identified. However, leptin acts via **'LepRb'**, which is the only active receptor present in many nuclei of hypothalamus.

iii. *Peptide Mechanism*

Some peptides regulate the food intake either by stimulating or inhibiting the feeding center, directly or indirectly. The important one among the peptides is ghrelin.

Ghrelin is secreted in stomach (Chapter 44) during fasting. It directly stimulates the feeding center and increases the appetite and food intake. Besides ghrelin, several other peptides are involved in the regulation of food intake.

Peptides, which increase the food intake:

a. Ghrelin
b. Neuropeptide Y.

Peptides, which decrease the food intake:

a. Leptin
b. Peptide YY.

iv. *Hormonal Mechanism*

Some endocrine hormones and GI hormones inhibit the food intake by acting through hypothalamus.

Hormones which inhibit the food intake:

a. Somatostatin
b. Oxytocin
c. Glucagon
d. Pancreatic polypeptide
e. Cholecystokinin.

v. *Thermostatic Mechanism*

Food intake is inversely proportional to body temperature. So in fever, the food intake is decreased. Exact mechanism of this fact is not known. It is suggested that the **preoptic thermoreceptors** (see above) may act via feeding center. The cytokines are also suggested to play a role in decreasing the appetite during fever.

■ 10. REGULATION OF WATER BALANCE

Hypothalamus regulates water content of the body by two mechanisms:

i. Thirst mechanism
ii. Antidiuretic hormone (ADH) mechanism.

i. *Thirst Mechanism*

Thirst center is in the lateral nucleus of hypothalamus. There are some **osmoreceptors** in the areas adjacent to thirst center. When the ECF volume decreases, the osmolality of ECF is increased. If the osmolarity increases by 1% to 2%, the osmoreceptors are stimulated. Osmoreceptors in turn, activate the **thirst center** and thirst sensation is initiated. Now, the person feels thirsty and drinks water. Water intake increases the ECF volume and decreases the osmolality (Fig. 149.4).

ii. *ADH Mechanism*

Simultaneously, when the volume of ECF decreases with increased osmolality, the supraoptic nucleus is stimulated and ADH is released. ADH causes **retention of water** by facultative reabsorption in the renal tubules. It increases the ECF volume and brings the osmolality back to the normal level. On the contrary, when ECF volume is increased, the supraoptic nucleus is not stimulated and ADH is not secreted. In the absence of ADH, more amount of water is excreted through urine and the volume of ECF is brought back to normal.

■ 11. REGULATION OF SLEEP AND WAKEFULNESS

Mamillary body in the posterior hypothalamus is considered as the **wakefulness center.** Stimulation of mamillary body causes wakefulness and its lesion leads to sleep. Stimulation of anterior hypothalamus also leads to sleep.

■ 12. ROLE IN BEHAVIOR AND EMOTIONAL CHANGES

The behavior of animals and human beings is mostly affected by two responding systems in hypothalamus and other structures of limbic system. These two systems act opposite to one another.

The responding systems are concerned with the affective nature of sensations, i.e. whether the sensations

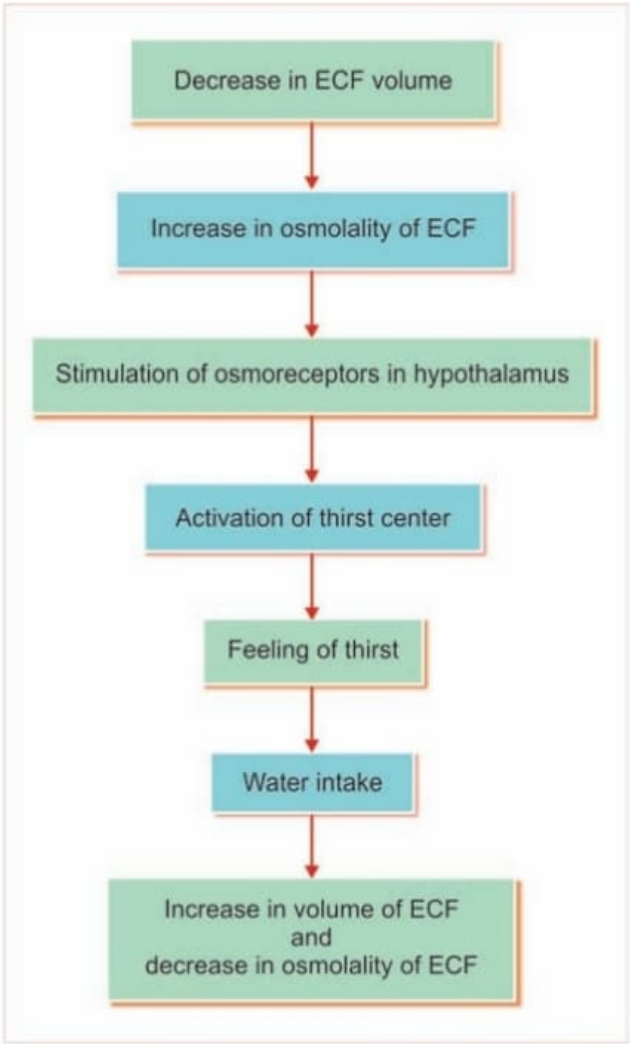

FIGURE 149.4: Thirst mechanism. ECF = Extracellular fluid.

are pleasant or painful. These two qualities are called the reward (satisfaction) and punishment (aversion or avoidance). Hypothalamus has two centers for behavioral and emotional changes. They are:

i. Reward center
ii. Punishment center.

Reward Center

Reward center is situated in medial forebrain bundle and ventromedial nucleus of hypothalamus. Electrical stimulation of these areas in animals pleases or satisfies the animals.

Punishment Center

Punishment center is situated in posterior and lateral nuclei of hypothalamus. Electrical stimulation of these nuclei in animals leads to pain, fear, defense, escape reactions and other elements of punishment.

Role of Reward and Punishment Centers

The importance of the reward and punishment centers lies in the behavioral pattern of the individuals. Almost all the activities of day-to-day life depend upon reward and punishment. While doing something, if the person is rewarded or feels satisfied, he or she continues to do so. If the person feels punished or unpleasant, he or she stops doing so. Thus, these two centers play an important role in the development of the behavioral pattern of a person.

Rage

Rage refers to violent and aggressive emotional expression with extreme anger. It can be developed in animals by stimulating the punishment centers in posterior and lateral hypothalamus. The reactions of rage are expressed by developing a defense posture, which includes:

i. Extension of limbs
ii. Lifting of tail
iii. Hissing and spitting
iv. Piloerection
v. Wide opening of eyeballs
vi. Dilatation of pupil
vii. Severe savage attack even by mild provocation.

Sham Rage

Sham rage means false rage. It is an extreme emotional condition that resembles rage and occurs in some pathological conditions in humans.

In physiological conditions, the animals and human beings maintain a balance between the rage and its opposite state. This balanced condition is called the **calm emotional state.** A major irritation may make a person to loose the temper. However, the minor irritations are usually ignored or overcome. It is because of inhibitory influence of cerebral cortex on hypothalamus. But the calm emotional state is altered during brain lesions. In some cases, even a mild stimulus evokes sham rage. It can occur in decorticated animal also.

Sham rage is due to release of hypothalamus from the inhibitory influence of cortical control.

■ 13. REGULATION OF SEXUAL FUNCTION

In animals, hypothalamus plays an important role in maintaining the sexual functions, especially in females. A decorticate female animal will have regular estrous cycle, provided the hypothalamus is intact. In human beings also, hypothalamus regulates the sexual functions by secreting gonadotropin-releasing

hormones. Arcuate and posterior hypothalamic nuclei are involved in the regulation of sexual functions.

■ 14. ROLE IN RESPONSE TO SMELL

Posterior hypothalamus along with other structures like hippocampus and brainstem nuclei are responsible for the autonomic responses of body to olfactory stimuli. The responses include feeding activities and emotional responses like fear, excitement and pleasure.

■ 15. ROLE IN CIRCADIAN RHYTHM

Circadian rhythm is the regular recurrence of physiological processes or activities, which occur in cycles of 24 hours. It is also called diurnal rhythm. The term circadian is a Latin word, meaning 'around the day'.

Circadian rhythm develops in response to recurring daylight and darkness. The cyclic changes taking place in various physiological processes are set by means of a hypothetical internal clock that is often called **biological clock.**

Suprachiasmatic nucleus of hypothalamus plays an important role in setting the biological clock by its connection with retina via retinohypothalamic fibers. Through the efferent fibers, it sends circadian signals to different parts and maintains the circadian rhythm of sleep, hormonal secretion, thirst, hunger, appetite, etc.

Whenever body is exposed to a new pattern of daylight or darkness rhythm, the biological clock is reset, provided the new pattern is regular. Accordingly, the circadian rhythm also changes.

■ APPLIED PHYSIOLOGY – DISORDERS OF HYPOTHALAMUS

The lesion of hypothalamus occurs due to tumors, encephalitis and ischemia. Following features develop in hypothalamic lesion:

1. Disturbances in carbohydrate and fat metabolisms, when lateral, arcuate and ventromedial nuclei are involved in lesion
2. Disturbance in sleep due to lesion in mamillary body and anterior hypothalamus
3. Disturbance in sympathetic or parasympathetic function occurs due to lesion in posterior, lateral and anterior nuclei
4. Emotional manifestations, leading to sham rage due to lesion in ventromedial and posterolateral parts
5. Disturbance in sexual functions due to the lesion in midhypothalamus.

One or more of the above features can become prominent, resulting in some clinical manifestations such as:

1. Diabetes insipidus
2. Dystrophia adiposogenitalis
3. Kallmann syndrome
4. Laurence-Moon-Biedl syndrome
5. Narcolepsy
6. Cataplexy.

■ DIABETES INSIPIDUS

Diabetes insipidus is the condition characterized by excretion of large quantity of water through urine. Refer Chapter 66 for details.

■ DYSTROPHIA ADIPOSOGENITALIS

This condition is characterized by obesity and sexual infantilism, associated with dwarfism (if the condition occurs during growing period). It is also called **Fröhlich syndrome.** Refer Chapter 66 for details.

■ KALLMANN SYNDROME

Kallmann syndrome is a genetic disorder characterized by hypogonadism, associated with **anosmia** (loss of olfactory sensation) or **hyposmia** (decreased olfactory sensation). It is also called **hypogonadotropic hypogonadism,** since it occurs due to deficiency of gonadotropin-releasing hormones, secreted by hypothalamus. Refer Chapter 66 for details.

■ LAURENCE-MOON-BIEDL SYNDROME

This disorder of hypothalamus is characterized by moon face (facial contours become round by hiding the bony structures), obesity, **polydactylism** (having one or more extra fingers or toes), mental retardation and hypogenitalism.

■ NARCOLEPSY

Narcolepsy is a hypothalamic disorder with abnormal sleep pattern. There is a sudden attack of uncontrollable desire for sleep and the person suddenly falls asleep. It occurs in the daytime.

The sleep may resemble the normal sleep. The duration of sleep is very short. It may be from few seconds to 20 minutes. In night, sleep may be normal but is often disturbed or there may be insomnia (loss of sleep).

■ CATAPLEXY

Cataplexy is the sudden uncontrolled outbursts of emotion associated with narcolepsy. Due to emotional outburst like anger, fear or excitement, the person becomes completely exhausted with muscular weakness. The attack is brief and last for few seconds to a few minutes. Consciousness is not lost.