

## Reticular formation: A Review

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### Abstract

The core reticular formation (RF) is located in the brain stem and is divided into three longitudinal zones: the lateral (sensory), the medial (motor) and the midline (all others) zone. The RF has synaptic connections with many discrete structures of the central nervous system, including the cerebral cortex, cerebellum, lower motor neurons, hypothalamus and limbic system. The RF and its connections constitute the reticular activating system (RAS), which is involved with sleep/wake cycle. The RAS is relatively sensitive to certain drugs, so the effect of anesthetics depends on suppression of this system. The descending fibers from the RF constitute one of the most important motor pathways in controlling respiratory and cardiac rhythms and other vital functions. The study contains compact literature review of reticular formation (RF), to provide basic anatomical structure, functions and disorders of the reticular formation which is important for both anatomists and clinicians. The data was collected from various studies. Early study on the reticular formation has been largely overlooked, and back to the beginning of the 19th century. Recent findings on different functional properties have provided a fundamental understanding for the pathophysiology of the reticular formation disorders..

**Keywords:** Reticular formation; raphe nucle; reticulospinal; reticular activating system; pedunculo-pontine nuclei.

## INTRODUCTION

The term "reticular formation" refers to portions of the brain stem core characterized structurally by a wealth of cells of various sizes and types, arranged in diverse aggregations, and enmeshed in a complicated fiber network. The reticular formation is well developed in all vertebrates and it forms the core of the brain-stem in humans (Brodal, 1981). The brain stem core is located in the central parts of the brain stem, and is continuous with the intermediate grey laminae of the spinal cord caudally and with the lateral hypothalamic and subthalamic region rostrally (Cruce *et al.*, 1984). The reticular (net-like) appearance of the reticular formation is easily appreciated in histologic sections where it can be easily distinguished from surrounding long pathways and specific cell groups such as the red nucleus and the cranial nerve nuclei (Andre, 1996).

Anatomical studies indicate that the brain stem reticular

formation, which extends from the medulla to the midbrain, can be subdivided into regions having distinctive cytoarchitecture, fiber connections and intrinsic organization (Martin *et al.*, 1990). Based on cytoarchitectonic features revealed in Nissl-stained material, anatomists have been able to identify more than 40 nuclei, although their borders are often poorly defined. However, as in many other parts of the brain, modern tracer methods and transmitter-specific techniques have revealed the existence of chemically specific cell groups and anatomic systems that do not always abide by the boundaries that have been identified on purely cytoarchitectonic groups (Lennart, 1995). Five distinct chemo-architectonic cell groups can be recognized within the reticular nuclei including: serotonergic, acetylcholinergic, noradrenergic, adrenergic, and dopaminergic. On the basis of cytoarchitectonic, chemoarchitectonic and functional criteria, the reticular formation is divided into three bilateral longitudinal columns: one median (nuclei of raphe), two medial and two lateral columns (Williams *et al.*, 1999). The reticular activating system (RAS) is an area of the brain (including the reticular formation and its connections) responsible for regulating arousal and sleep-wake transitions (Evans, 2003). The adrenergic neurons of the reticular activating system are active during waking and slow wave sleep but cease

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firing during REM sleep. It has been indicated that the neuronal messenger nitric oxide (NO) may play an important role in modulating the activity of the noradrenergic neurons in the RAS (Vincent, 2000).

The aim of this work is the evaluation of the historical reviews, the components, the connections, and the functional neuroanatomy of nuclei in the brainstem reticular formation and the disorders of the reticular formation.

## Historical reviews

The term "reticular formation" was coined in the late 19th century, coinciding with Cajal (1909) who commented on the extensive multiple branching of the reticular formation neurons as the fibers ascended and descended through the middle of the brain stem. Papez (1926) published a definitive work describing the reticular formation's projections down to the spinal cord in cats. Bremer (1935) found that the reticular formation had ascending projections to higher brain centers. Morison and Dempsey (1942) described the mammalian thalamic projections to the cortex, which were under reticular formation influence and which presumably were responsible for producing the coma. Rhines and Magoun (1946) showed that the electrical stimulation of the reticular formation had an influence on the motor activity in anesthetized cats.

Moruzzi and Magoun (1949) investigated the neural components regulating the brain's sleep-wake mechanisms through the reticular formation in the animals. They discovered series of newly relays in direct electrical stimulation of a cat's brainstem known as "ascending reticular activating system" (RAS), and proposed that a column of cells surrounding the midbrain reticular formation received input from all the ascending tracts of the brain stem and relayed these afferents to the cortex and therefore regulated wakefulness. Olszewski (1954) described and named 98 various nuclear aggregations of the reticular formation which were connected with each other in many different ways.

In the early 1960s, Walbery *et al.* (1962) found that the major reticular formation's inputs in mammals originated from the spinal cord, solitary complex, vestibular nuclei and trigeminal nuclei. Another major input to the reticular formation originated in the tectum to provide visual, auditory, and tactile information. A smaller input arrived from the fastigial nucleus of the cerebellum.

Scheibel and Scheibel (1967) suggested that the functions of the reticular formation included a determination of operational modes, gating mechanism for all sensory influx, modulation and monitor of cortical function. Grillner and Shik (1973) described

the reticular formation region located just below the auditory tectum (inferior colliculus in mammals), called Mesencephalic Locomotor Region (MLR) was responsible for releasing locomotion actions in the cat. Romanes (1986) reported that the brain stem reticular formation received collaterals of ascending pathways from the spinal cord, e.g. spinothalamic tracts, and afferent information from the cranial nerves, e.g. nucleus of tractus solitaries and vestibular nuclei. The reticular formation had extensive reciprocal connections with the cerebellum and with many other parts of the central nervous system. In many vertebrates, the reticular formation produced the main descending pathways from the brain to the spinal cord. Carpenter (1991) recognized 3 principal reticular mesencephalic nuclei: cuneiformis, subcuneiformis, and tegmental pedunculopontine. Mc-Minn (1994) reported that certain cells of the reticular formation, in the region of the vagal nucleus and tractus solitarius, constituted the cardiac, respiratory and vasomotor centres, often known as the "vital centres". They were not anatomically demonstrable as distinct nuclei, but major disturbances of this area resulted in death. Adli *et al.* (1999) reported that over 30 nuclei had been identified in the reticular formation of rats, but only a small number of distinct reticular nuclei had been recognized in frogs.

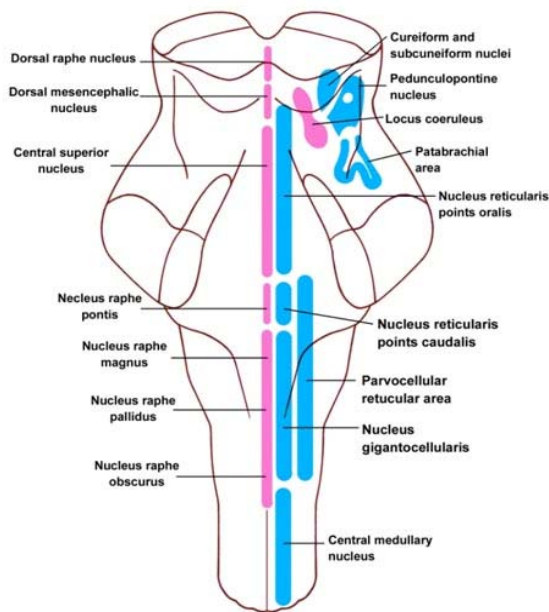
Smith (2000) reported that the reticular formation could be divided into 3 distinct functional zones (lateral, medial, and midline zones). Lateral zone had a role in integration of all sensory information and cortical afferent input. Medial zone had a role in regulation of vital cardiac and respiratory functions and somatic motor activity through the reticulospinal tract. Midline zone had a role in onset of sleep, mood elevation and arousal. McCaffery (2001) described that the reticular formation had 2 components: the ascending reticular activating system, responsible for the sleep-wake cycle and the descending reticular formation, involved in motor movements.

## LOCATION AND COMPONENTS

The reticular formation is a poorly-differentiated area of the brain stem, continuous below with the reticular intermediate spinal grey laminae (laminae V and VI of the cervical region) and project rostrally into subthalamus, hypothalamus, dorsal thalamus, septum, limbic system and neocortex (Williams *et al.*, 1999).

## Columns of the reticular formation

The reticular formation of the brain stem is divided into three bilateral longitudinal columns: median, medial and lateral columns (Fig.1).



**Figure 1:** Diagram showing the nuclear derivatives of brainstem reticular formation: those from median column are in magenta; those from medial and lateral columns are blue.

The median column extends throughout the medulla, pons and midbrain occupying the paramedian zones. Collectively they constitute the raphe nuclei and many neurons are serotonergic. It consists of the following nuclei:

- Nuclei raphes pallidus and obscurus: lie in the upper 2/3 of the medulla crossing the ponto-medullary junction.
- Nucleus raphe magnus: lies partly overlapping the above two nuclei and ascending into the pons.
- Pontine raphe nucleus: lies in the pons above the raphe magnus nucleus.
- Central Superior raphe nucleus: located in the pons.
- Dorsal mesencephalic raphe nucleus: extends throughout the midbrain, expanding cranially and narrowing caudally. (Williams et al; 1999).

The medial column consists of the following nuclei:

- Central nucleus of medulla oblongata: a thin lamina lateral to raphe nuclei in the lower medulla.
- Gigantocellular nucleus: consists of medullary and pontine parts.
- Caudal and oral pontine tegmental reticular nuclei: lie within the tegmentum of pons.
- Cuneiform and subcuneiform nuclei: lie in the midbrain tegmentum.

The lateral column consists of the following nuclei:

- Parvocellular reticular area: lies in the upper medulla and lower lateral pontine tegmentum.
- Superficial ventrolateral reticular area: lying in both medulla and pons.

- Lateral pontine tegmental reticular area: forming the medial and lateral parabrachial nuclei.
- Noradrenergic cell groups: the most important one is the locus ceruleus which lies in the tegmentum of the pons and it functions as an attention centre focusing neural functions to the prevailing needs of the alert person.
- Adrenergic cell groups: lying rostral to noradrenergic group and it function as centre of vasomotor control.
- Cholinergic cell group: lying in the pedunculopontine tegmental nucleus of the mesencephalic tegmental reticular zone.

### Cytoarchitectonic criteria

Del-Tora *et al.*, (2001) reported that early organization of the vertebrate brainstem was characterized by cellular segmentation into compartments, the rhombomeres. Segmentation was a transient feature, and a dramatic reconfiguration of neurons and synapses took place during fetal and postnatal stages. The reticular brainstem core is characterized foremost by loosely arranged small and medium-sized neurons. The main exception occurs in the central parts of the upper medulla and lower pons, where a significant number of large cells intermingle with small and medium sized cells. This region is referred to as the gigantocellular reticular region (Lennart, 1995). Somato-sensory and viscerosensory information reaches the reticular neurons via spinoreticular fibres and sensory cranial nerves. The reticular formation also receives informations from many parts of the CNS (Lennart, 1995). The axons of many reticular neurons remain within the reticular formation, where they take part in multisynaptic pathways and reflex circuits. Other axons form widespread pathways to reach every part of the CNS, including forebrain regions, cerebellum, and all segments of the spinal cord. Locus ceruleus is a group of pigmented cells located near the periventricular grey of the upper part of 4th ventricle. Cells of this nucleus are intermingled with those of the mesencephalic nucleus of trigeminal nerve.

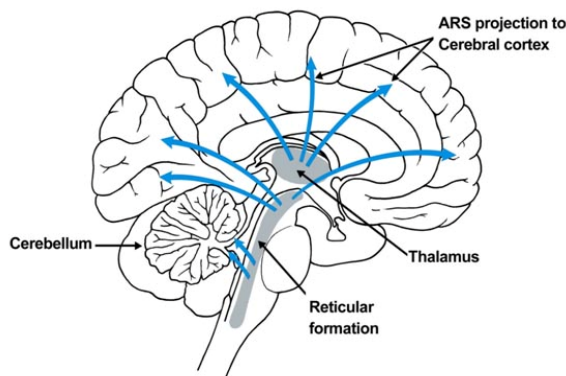
The significance of this nucleus was unknown until it was demonstrated by a florescence technique that its cells contain catecholamine, nearly all of which was norepinephrine (Carpenter, 1991). Locus ceruleus is the principal noradrenergic cell group lying in the brain stem tegmentum of the caudal midbrain and rostral pons. It projects to many areas of the CNS. Ascending fibers project to the cerebellum, hypothalamus, thalamus, limbic structures and cerebral cortex. Descending fibers project widely throughout the brain stem and spinal cord. The locus ceruleus, like the raphe nuclei, has been implicated in the neural mechanisms regulating sleep, particularly REM (rapid eye movement) sleep (Crossman *et al.*, 2000).

## Ascending and descending fibre system

The reticular formation of the brain stem is divided into three bilateral longitudinal columns: median, medial and lateral columns (Fig.1).

### Median Reticular Column

The serotonergic raphe system ramifies extensively throughout the entire CNS. The central superior raphe nucleus projects divergently to all areas of the cortex. Dorsal raphe nucleus not only project to the parietal and occipital cortex but also to the cerebellar cortex (Fig. 2). Carpenter (1991) reported that the dorsal and medial raphe nuclei projected widely to telencephalic structures. Raphespinal serotonergic axons originate mainly from raphe magnus, pallidus and obscures nuclei, project to terminate respectively in the ventral horn and laminae 1,11 and V of the dorsal horns of all segments, and in intermediate (autonomic) horns of thoracolumbar and sacral segments of the spinal cord (Carpenter, 1991). Yates *et al.* (1999) suggested that the raphe nuclei in the medulla and pons influenced the activity of phrenic motoneurons.

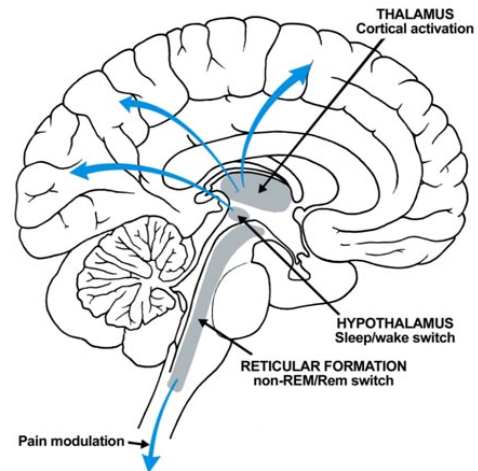


**Figure 2:** Diagram of brainstem reticular formation showing its projections to the cerebral cortex (the reticular activating system) and the cerebellum.

The mesencephalic serotonergic raphe system is principally interconnected rostrally with the limbic system, septum, prefrontal cortex and hypothalamus. Efferent ascending pathway forms a large ventral and a small dorsal pathway. Both originate from neurons in the dorsal and superior central raphe nuclei with small contribution of raphe magnus nucleus. A few fibers of the dorsal pathway terminate in the central mesencephalic grey matter, but most fibers continue into the medial forebrain bundle merging with the axons of the ventral pathway. The fibers of the ventral ascending serotonergic pathway exit rostrally through the ventral tegmentum, substantia nigra and interpeduncular nucleus (Williams *et al.* 1999).

Crossman *et al.* (2000) reported that the axons of the raphe nuclei were widely distributed through the CNS. The ascending fibers to the forebrain were involved in

the neural mechanism of sleep and descending fibers to the spinal cord were involved in the modulation of the nociceptive mechanism (Fig.3).



**Figure 3:** Diagram of brainstem reticular formation showing its role in sleep and pain modulation.

### Medial Reticular Column

It has efferent and afferent components. The descending fibers of the medial reticular zone comprise two major systems:

- Pontospinal (lateral reticulospinal) tract: It is constituted by axons from neurons in the caudal and oral parts of the pontine reticular nuclei which descend un-crossed in the anterior spinal funiculus and terminate in spinal cord laminae VII, VIII and IX.
- Bulbospinal (medial reticular) tract: It originates from the medullary reticular formation and descends bilaterally to terminate in laminae VII, V and VI. Both tracts modulate spinal motor function and segmental nociceptive input (Williams *et al.* 1999).

Specific afferents to the medial reticular zone include:

- Spinoreticular projections: They originate from neurons in the intermediate grey matter of the spinal cord, decussate in the anterior white commissure, ascend in the anterolateral funiculus and terminate in all levels of the medial reticular column and also in the intrathalamic nuclei of the thalamus. Three areas of medial reticular zone receive particularly high densities of termination, gigantocellular nucleus, central nucleus of medulla and caudal pontine reticular nucleus
- Projections from all nuclei of sensory components of the cranial nerves, collaterals of centrally projecting spinal trigeminal, vestibular and cochlear fibers end in the medial reticular formation. Retinotectal and tectoreticular fibers relay visual information and the medial forebrain

bundle transmits olfactory impulses (Williams *et al.*, 1999).

Efferent from the medial column project through a multisynaptic pathway to the thalamus and lateral column of reticular nuclei with cholinergic neurons in the lateral pontine tegmentum. The intralaminar thalamic nuclei project directly to the striatum and neocortex. A direct connection between gigantocellular nucleus of medial reticular column and the cerebellum has been reported by Hassouna *et al.* (2001).

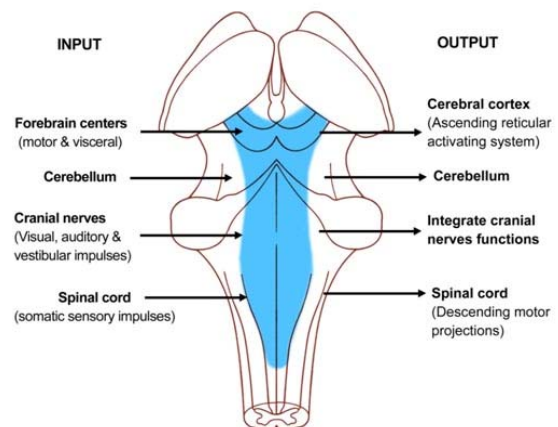
### Lateral Reticular Column

The connections of the lateral column reticular nuclei are complex. The most important nuclei are, parvocellular reticular area, superficial ventrolateral reticular area, noradrenergic group, parabrachial region and locus ceruleus.

- **Parvocellular reticular area:** Their ascending and descending axons constitute bulbar reflex pathways connecting all branchiomotor nuclei and the hypoglossal nucleus with central afferent cranial nerve complexes. It also receives descending afferents from contralateral motor cortex in the corticotegmental tract, and from contralateral red nucleus in the rubrospinal tract (Williams *et al.* 1999). Recent work reported a direct connection between parvocellular reticular area of the lateral reticular column and the cerebellum (Hassouna *et al.* 2001).
- **Superficial ventrolateral reticular area:** It receives afferents from the cardiorespiratory part of the nucleus solitarius. It also receives afferents from the pneumotaxic centre (Kolliker-Fuse nucleus) which projects to the inspiratory centre of nucleus solitarius and a mixed expiratory-inspiratory centre in the superficial ventrolateral reticular area. Efferents from the superficial ventrolateral area synapse on neurons of the supraoptic and paraventricular hypothalamic nuclei. Excitation of these cells causes release of vasopressin from the neurohypophysis.
- **Noradrenergic cell groups:** They innervate directly and indirectly the median eminence and control the release of growth hormone, luteinizing hormone and ACTH (Williams *et al.*, 1999).
- **Lateral pontine tegmentum:** Afferents from insular cortex to the parabrachial region and afferents from hypothalamic nuclei (median preoptic and paraventricular nuclei) project to the lateral parabrachial nucleus and micturition M-region. Reciprocal bulbar projections, from the Kolliker-Fuse nucleus, are projected to the nucleus solitarius and superficial ventrolateral reticular area. Efferents from the lateral pontine tegmentum are

distributed through reticulospinal fibres to all segments of the spinal cord. Efferents from micturition M-region terminate in the preganglionic parasympathetic neurons in the sacral segments of the spinal cord innervating the detrusor muscle (Williams *et al.* 1999).

- **Locus ceruleus (Noradrenergic cells group):** Descending fibers from locus ceruleus project as caudal limb of the dorsal periventricular pathway and also caudal limb of the dorsal noradrenergic bundle (i.e. part of longitudinal catecholamine bundle) to innervate, mainly ipsilaterally:
  - All other rhombencephalic reticular areas.
  - Principal and spinal trigeminal nuclei.
  - Pontine nuclei.
  - Cochlear nuclei and nuclei of lateral lemniscus.
  - Dorsal horns of all spinal segments.
  - Bilaterally to all spinal preganglionic autonomic neurons.
- **Ascending fibers from the locus ceruleus pass in:**
  - **Dorsal noradrenergic bundle :** It is large and joins the medial forebrain bundle in the hypothalamus which connect the locus ceruleus with adjacent structures along its course e.g. central mesencephalic grey matter, dorsal raphe nucleus, superior and inferior colliculi, amygdale, septum, olfactory bulb, interpeduncular nucleus, epithalamus, dorsal thalamus, habenular nuclei, hippocampal formation and neocortex.
  - **Rostral limb of dorsal periventricular pathway,** ascend in ventromedial periaqueductal grey matter to terminate in the paraventricular nucleus in the hypothalamus.
  - **Superior cerebellar peduncle,** the fibers terminate in the deep cerebellar nuclei (Williams *et al.*, 1999).



**Figure 4:** Diagram of brainstem reticular formation showing its input and output. Reticular formation is shown in blue.

## FUNCTIONS OF THE RETICULAR FORMATION

Young and Young (1997) reported that the reticular formation received input from all parts of the central nervous system and in turn exerted wide-spread influences on virtually every function of the central nervous system (Fig.4). The authors reported that the central location of the reticular formation in the brain stem provided with widespread distribution.

The descending raphe system:

- The dorsal mesencephalic raphespinal projections function as a pain control pathway. The dorsal medullary reticular nucleus in rats is involved in the facilitation of nociception after acute thermal noxious stimulation and it plays a major role in the transmission of nociceptive visceral input (Almeida and Lima 1997).
- The intermediate raphespinal projections modulate the sympathetic control of cardiovascular function.
- The ventral raphespinal projections enhance motor responses to nociceptive stimuli and promote the flight and fight response. Neurons of the medial reticular zone in ponto-medullary junction, active during mastication, influenced the motor nucleus of trigeminal nerve in rabbit (Kolta *et al.*, 2000).
- Both medial and lateral reticulospinal tracts modulate the spinal motor function and segmental nociceptive input (Williams *et al.*, 1999).
- The parvocellular reticular area functions as bulbar reflex pathway. Chewing, swallowing, breathing and vocalization in mammals require precise coordination through projection from parvocellular area ipsilaterally to both facial and hypoglossal cranial nerve nuclei (Popratiloff *et al.* 2001).
- The superficial ventrolateral reticular area: Through its connection with nucleus solitarius, it controls cardiovascular baroreceptor, chemoreceptor and respiratory reflexes. It has also connection with pneumotaxic centre to innervate both inspiratory and expiratory muscles. It is also the seat of visceral alerting response. Through its connection with hypothalamus, causes release of vasopressin from the neurohypophysis (Williams *et al.* 1999 and Hanakawa *et al.* 2000).
- The lateral pontine tegmentum:
  - It controls the cardiorespiratory part of the nucleus solitarius (Miller 1999).
  - It innervates the phrenic nerve through its connection with pneumotaxic centre (Williams *et al.* 1999).
  - Micturition M-region innervates the detrusor muscle, while Micturition L-region innervates pelvic floor, anal, and urethral sphincters (Williams *et al.* 1999).

- The taste information from the parabranchial taste area reaches the salivary secretory centre via the reticular formation ventral to the parabranchial nucleus (Mastuo *et al.* 2001).
- Locus ceruleus: (Williams *et al.* 1999)
  - Control of the attentiveness level.
  - Regulation of the cerebral blood flow.
- Control of the sleep - wake cycle, by generation of Rapid Eye Movement (REM) sleep which interrupts the slow-wave sleep. The level and type of sleep depends on a balance between the activity of brain stem reticular activating system which projects to cerebral cortex and causes arousal and wakefulness, and various sleep centers in the brainstem and hypothalamus. An anterior hypothalamic sleep centre may act by inhibiting the reticular activating system. Lesion in anterior hypothalamus leads to insomnia. There is a wake centre in the posterior hypothalamus. Lesion in posterior hypothalamus leads to hypersomnia. Kohlmeier *et al.* (2002) reported that release of acetylcholine within the pontine reticular formation (PRF) from the axon terminals of mesopontine cholinergic neurons plays an important role in REM sleep generation due to substance P (SP) in the cholinergic projections.
- The locus ceruleus may play a role in clinical depression, panic disorder, and anxiety. Psychiatric research has documented that enhanced noradrenergic postsynaptic responsiveness in the neuronal pathway (brain circuit) that originates in the locus ceruleus and ends in the basolateral nucleus of the amygdala is a major factor in the pathophysiology of most stress-induced fear-circuitry disorders and especially in posttraumatic stress disorder (PTSD) (Bracha *et al.* 2005).
- The locus ceruleus is responsible for mediating many of the sympathetic effects during stress. The locus ceruleus is activated by stress, and will respond by increasing norepinephrine secretion, which in turn will alter cognitive function (through the prefrontal cortex), increase motivation (through nucleus accumbens), activate the hypothalamic-pituitary-adrenal axis, and increase the sympathetic discharge/inhibit parasympathetic tone (through the brainstem). (Ramos *et al.* 2007). The locus ceruleus's role in cognitive function in relation to stress is complex and multi-modal. Norepinephrine released from the locus ceruleus can act on  $\alpha 2$  receptors to increase working memory, or an excess of NE may decrease working memory by binding to the lower affinity  $\alpha 1$  receptors (Benarroch *et al.* 2009).

- **Ascending Reticular System:**
  - The reticular formation has both sensory and motor functions; the main sensory function is alerting the cerebral cortex to incoming sensory signals. Part of the reticular formation, called the reticular activating system (RAS), consists of fibers that project to the cerebral cortex directly or via the thalamus (Fig.2). The effect is a generalized increase in cortical activity. The RAS is responsible for maintaining consciousness and for awakening from sleep (Tortora and Grabowski, 2000). Parvizi and Damasio (2001) reported that the reticular activating system modulated the electrophysiological activity of the cerebral cortex. Castro-Alamancos and Calcagnotto (2001) mentioned that the thalamus was the principal relay station of sensory information to the neocortex. Alkire *et al.* (2002) explained the common mechanism through which various anaesthetic agents produce unconsciousness. General anesthesia showed specific suppression of regional thalamic and midbrain reticular formation activity. Evans (2003) proposed that a column of cells surrounding the midbrain reticular formation received input from all the ascending tracts of the brain stem and relayed these afferents to the cortex and therefore regulated wakefulness and was coined the ascending reticular activating system (RAS).
  - Garcia-Rill *et al.* (2007) reported that smoking during pregnancy produces postnatal arousal, attentional and cognitive deficits in humans. This exposure can induce major disturbances on pedunculopontine nucleus (PPN) neurons that may adversely influence the development of the ascending reticular activating system. Hall *et al.* (2008) mentioned that premature birth may influence the development of the reticular activating system inducing persistent deleterious effects on pre-attentional (arousal and sleep-wake abnormalities), attentional (reaction time and sensory gating), and cortical mechanisms.

## DISORDERS OF BRAIN STEM RETICULAR FORMATION

Garge and Pepper (1995) suggested that the basic pathology in essential hypertension might be an inherited defect in the blood supply of that part of reticular formation of rostral ventrolateral medulla which contained the pressor area of vasomotor center. Garcia-Rill (1997) studied the disorders of the reticular activating system, which include:

- Schizophrenia : There is an increase in the number of PPN neurons in areas of RAS.
- Post-traumatic stress disorders, Parkinson's disease: Patients with these syndromes exhibit a significant decrease in the number of locus ceruleus neurons, resulting in increased disinhibition of the PPN.

- Narcolepsy: There is a significant down-regulation of PPN output and a loss of orexin peptides, promoting the excessive daytime sleepiness that is characteristic of this disorder.
- Behavior disorder: Exhibits decreased in the number of neurons in specific part of the RAS.

Aydogdu *et al.* (2001) reported that Wallenberg's syndrome (WS) is well defined clinically, and the lateral medullary infarction (LMI) is its most frequent cause. The lateral medullary syndrome resulted from thrombosis of the posterior inferior cerebellar artery or the vertebral artery. Dysphagia has been reported in 51-94% of patients with WS. Some patients do not clinically demonstrate dysphagia and aspiration from the onset of stroke, although the major swallowing centers of the nucleus solitaries and nucleus ambiguus and the reticular formation around them are located in the dorsolateral medulla oblongata.

Sarphie *et al.* (1999) studied the structural alterations in the region of brainstem respiratory nuclei that might account for immediate post-injury respiratory abnormalities in anesthetized experimental animals. A similar phenomenon could account for the transient or permanent post-injury apnea seen in humans with severe head injury.

Liu and Wong-Riley (2000) utilized cytochrome oxidase (CO) as a marker of neuronal functional activity to examine metabolic changes in brain stem respiratory nuclei of rats from newborn to 21 day of age. This might bear some relevance to our understanding of pathological events during postnatal development such as occurred in sudden infant death syndrome.

Ferini-Strambi and Zucconi (2000) reported that REM sleep behavior disorder (RBD) was characterized by the intermittent loss of REM sleep atonia, indicating that lesions to the perilocus ceruleus disrupted the excitatory connection to the nucleus reticularis magnocellularis in the descending medullary reticular formation. Symptomatic RED cases were associated with several neurologic disorders such as dementia, cerebrovascular diseases, multiple sclerosis and brainstem neoplasm.

Crossman *et al.* (2000) reported that a unilateral brain stem lesion due to stroke, tumor or multiple sclerosis would lead to ipsilateral cranial nerve dysfunction, contralateral spastic hemiparesis, hyper-reflexia and an extensor plantar response (upper motor neurone lesion), contralateral hemisensory loss and ipsilateral incoordination. A bilateral lesion destroyed the "vital centres" for respiration and circulation, leading to coma and death. Multiple sclerosis could affect eye movements producing internuclear ophthalmoplegia.

Mileykovskiy *et al.* (2000) reported that activation of the pontine inhibitory area (PIA) including the middle portion of the pontine reticular nucleus, oral part, or gigantocellular reticular nucleus suppresses muscle tone in decerebrate animals.

Heneka *et al.* (2006) and Heneka *et al.* (2010) reported that there was up to 70% loss of locus ceruleus neurons in Alzheimer's disease (AD). Mouse models of Alzheimer's disease showed accelerated progression after chemical destruction of the locus ceruleus. The norepinephrine from locus ceruleus cells in addition to its neurotransmitter role locally defused from "varicosities". As such it provided an endogenous antiinflammatory agent in the microenvironment around the neurons, glial cells, and blood vessels in the neocortex and hippocampus. It had been shown that norepinephrine stimulated mouse microglia to suppress A $\beta$ -induced production of cytokines and their phagocytosis of A $\beta$ . This suggested that degeneration of the locus ceruleus might be responsible for increased A $\beta$  deposition in AD brains.

Lee *et al.* (2008) suggested that lesions of the subcortical brain areas such as the pyramidal tract and the basal ganglia-brainstem axis, which are involved in motor functions and sleep-wake cycles, may lead to Restless Legs Syndrome (RLS) symptoms in patients after an ischemic stroke.

## SUMMARY

From the findings observed in the present study, it could be concluded that the reticular formation is a diffuse network of neurons and nerve fibres traversing the brain stem. It is discovered early in all vertebrates. It merges upwards to hypothalamus and thalamus and downward to the spinal cord. Reticular formation has different chemo-architectonic nuclear groups; it has 3 bilateral longitudinal columns (median, medial and lateral). The present study evaluated the connections of the reticular formation with the spinal cord, cranial nerve nuclei, thalamus, hypothalamus, limbic cortex and neocortex.

This study revealed 'Locus ceruleus' which probably acts as an attention center focusing neural function of the alert man. The present study also revealed Reticular Activating System (RAS) which projects through thalamic nuclei to the cerebral cortex was involved in arousal and alerting reactions.

Recent studies were done to explain the functions and pathological disorders of the reticular formation because bilateral damage to the reticular formation of the midbrain may lead to a coma or death. This study explains the common mechanism through which various anaesthetic agents produce unconsciousness

through suppression of regional thalamic and midbrain reticular formation activity.

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## Reticular formation: A Review

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