ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 10 | October - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

RETICULAR ACTIVATING SYSTEM: AN OVERVIEW

Neurology

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ABSTRACT

The reticular activating system is the part of the brain that maintains the sleep- wake cycle. Any damage to this region can cause hypersomnolence and drowsiness, along with altered sensorium [1]. Reticular activating system mainly refers to reticular network and its connections. It extends cranially to the diencephalon (subthalamus, hypothalamus and thalamus) and caudally to the spinal cord in the cervical region. The nerve fibers in these pathways also act in the spinal cord to block the transmission of some pain signals to the brain.

KEYWORDS

Reticular activating system, sleep, arousal, pain.

INTRODUCTION:

Reticular activating system (RAS): It mainly refers to reticular network and its connections. Also known as Extra Thalamic Control Modulatory System. The reticular formation, as its name suggests, resembles a net (reticular) that is made up of nerve cells and nerve fibers. The reticular formation has derived its name from its light microscopic appearance of a vague network of nerve cells and nerve fibres. It has been defined to include all areas within the brainstem, which when stimulated will produce arousal [2]. The net extends up through the axis of the central nervous system (CNS) from the spinal cord to the cerebrum. It receives input from most of the sensory systems and has efferent fibers that descend and influence nerve cells at all CNS levels. The exceptionally long dendrites of the neurons of the reticular formation permit Input from widely placed ascending and descending pathways. Through Its many connections, it can Influence skeletal muscle, activity, somatic and visceral sensations, the autonomic and endocrine systems, and the level of consciousness. Phylogenetically, it represents the old reticular core of brain and contains within it the vital cardiac and respiratory centers which control respiration, heart rate and blood pressure [2].

ANATOMICAL EXTENSION AND RETICULAR NUCLEI:

The reticular formation extends cranially to the diencephalon (subthalamus, hypothalamus and thalamus) and caudally to the spinal cord in the cervical region [3]. Although reticular formation is described to be consisting of network of nerve fibres and scattered neurons, among them a number of regions with fairly localized cell groups called reticular nuclei, have been recognized. **Reticular nuclei** in the brainstem arranged into three longitudinal columns [3].

- **Median column** lies in the midline and consists of intermediate size neurons. The nuclei of this column are termed **raphe nuclei**.
- **Medial column** consists of nuclei which are made up large-size neurons, hence this column is also termed **magnocellular column**.
- **Lateral column** consists of nuclei which are made up of small neurons, hence this column is also termed **parvo-cellular column** (parvus = little, small).

Raphe nuclei (median group of nuclei): The raphe nuclei form a contiguous column in the mid-line. The neurons of raphe nuclei produce serotonin, a substance that they use as a neurotransmitter. The dorsal raphe nucleus located in the midbrain projects to the spinal cord and forms the pain controlling pathway [2]. The nucleus raphe magnus in medulla projects to the caudal part of the spinal nucleus of the trigeminal nerve and influences perception of pain through spinal nucleus. In fact, once the raphe nuclei are activated, the serotogenic neurons inhibit the transmission of pain impulses from dorsal grey horns and spinal nucleus of trigeminal nerve respectively.

Clinical Correlation:

The electrical stimulation of either the dorsal raphe nucleus (the periaqueductal grey matter) or the nucleus raphe magnus results in loss of the ability to experience pain from sites of injury or disease. The former procedure has been used clinically in the management of otherwise intractable pain.

Medial group of nuclei: The medial group of nuclei includes

1. Ventral reticular nucleus (in medulla),
2. Gigantocellular nucleus (in medulla and pons) and
3. Oral and caudal pontine nuclei (in pons).

Nuclei of this group receive afferents from nuclei of lateral group and efferents from these nuclei ascend or descend longitudinally in the brainstem and give collaterals to the other reticular cells, thus forming a polysynaptic pathway—a characteristic of impulse transmission through the reticular formation[3].

Lateral group of nuclei includes:

1. Parvocellular nuclei of medulla and pons,
2. Nucleus locus ceruleus of pons
3. Pedunculopontine nucleus of the midbrain.

These nuclei receive collaterals from several ascending pathways and project to the medial group of nuclei of the reticular formation. They are regarded as an association region of the reticular formation.

Neurotransmitters: The neurotransmitters that these neurons release include dopamine, norepinephrine, serotonin, histamine, acetylcholine, and glutamate [3]. The orexin neurons of the lateral hypothalamus innervate every component of the ascending reticular activating system and coordinate activity within the entire system.

Melatonin: Melatonin, often referred to as the Sleep Hormone, is a central part of the body's sleep-wake cycle [2]. Its production increases with evening darkness, promoting healthy sleep and helping to orient our circadian rhythm. It is produced by pineal gland.

Connections of Reticular Formation

The reticular formation receives information from almost all the principal parts of the nervous system and in turn, projects (directly or indirectly) to all these parts. The reticular pathways are polysynaptic, both ascending, descending, and crossed and uncrossed. As a result, a unilateral stimulation produces bilateral responses [1,3].

Afferent connections

- Afferents from various sensory pathways or systems
- Optic system—through tectoreticular fibres,

- Olfactory and limbic systems—through variety of descending pathways, –
- Auditory system—through tectoreticular fibres, –
- Gustatory system,
- Spinal pathways—through spinoreticular fibres. A considerable number of fibres of spinothalamic tract terminate in the lateral reticular nucleus of medulla, which in turn project to the cerebellum [4]. Spinoreticulo-cerebellar pathway is an important pathway for carrying exteroceptive sensations to the cerebellum,
- Trigeminal pathways.
- Afferent fibres from **other parts of central nervous system**
- Cerebellum from both but mainly from contralateral fastigial nucleus.
- Basal ganglia, mainly from corpus striatum.
- Thalamus, hypothalamus and subthalamus.
- Limbic system, mainly from septal areas, amygdaloid nuclei, and hippocampus.
- Cerebral cortex mainly from motor and sensory areas of the cerebral cortex.
- Red nucleus, substantia nigra and habenular nuclei.
- The efferent connections of reticular formation are to all the parts of CNS from which it receives afferents but mainly to
- Autonomic and locomotor control centres of brainstem and spinal cord.
- Cranial nerve nuclei, e.g. dorsal nucleus of vagus.
- Cerebral cortex—indirectly through diencephalic nuclei.

Red nucleus, substantia nigra and tectum of midbrain.
Functionally the reticular formation is divided into two systems [3]:
(a) Ascending Reticular Activating System (ARAS),
(b) Descending Reticular System (DRS).

The ascending reticular activating system is commonly termed by the clinicians simply as reticular activating system (RAS)[3].Most of the ascending tracts, viz. spinothalamic tract, trigeminal lemniscus, lateral lemniscus and central vestibular pathway, while passing through the brainstem give collaterals to the lateral part of the reticular formation which projects to the intraluminal and reticular nuclei of the thalamus[5].These nuclei in turn project to the widespread areas of the cerebral cortex. When this part of reticular formation is stimulated, the individual becomes alert.

Ascending Reticular Activating System (ARAS) -
The ascending reticular activating system is believed to be responsible for maintaining a state of alertness and consciousness [6].

Functions of RAS:
1. Consciousness : The ascending reticular activating system is an important enabling factor for the state of consciousness. Contributes to wakefulness as characterized by cortical and behavioral arousal [6].

2. Regulating sleep-wake transitions: The main function of the ARAS is to modify and potentiate thalamic and cortical function. The physiological change from a state of deep sleep to wakefulness is reversible and mediated by the ARAS. The ventrolateral preoptic nucleus (VLPO) of the hypothalamus inhibits the neural circuits responsible for the awake state, so the VLPO activation contributes to the sleep onset[6].During sleep, neurons in the ARAS will have a much lower firing rate; conversely, they will have a higher activity level during the waking state.

3. Attention : The ARAS also helps mediate transitions from relaxed wakefulness to periods of high attention [4].There is increased regional blood flow (presumably indicating an increased measure of neuronal activity) in the midbrain reticular formation (MRF) and thalamic intralaminar nuclei during tasks requiring increased alertness and attention.

Clinical significance of the ARAS-
- Mass lesions in brainstem ARAS nuclei can cause severe alterations in level of consciousness (e.g., coma)[1,5].Bilateral damage to the reticular formation of the midbrain, pons may lead to coma.(alpha coma and locked in syndrome)
- Direct electrical stimulation of the ARAS produces pain responses in cats and elicits verbal reports of pain in humans. Ascending reticular activation in cats can produce mydriasis, which can result from prolonged pain. These results suggest some relationship between ARAS circuits and physiological pain pathways.

Pathologies:
Some pathologies of the ARAS may be attributed to age, as there appears to be a general decline in reactivity of the ARAS with advancing years. Specifically, disruption of the ARAS has been implicated in the following disorders.

- **Narcolepsy:** Lesions along the pedunculopontine (PPT/PPN) or laterodorsal tegmental (LDT) nuclei are associated with narcolepsy [5]. 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.
- **Progressive supranuclear palsy (PSP) :** Dysfunction of nitrous oxide signaling has been implicated in the development of PSP.
- **Parkinson's disease:** REM sleep disturbances are common in Parkinson's. It is mainly a dopaminergic disease, but cholinergic nuclei are depleted as well. Degeneration in the ARAS begins early in the disease process [5].

Developmental influences-
There are several potential factors that may adversely influence the development of the ascending reticular activating system:
- **Preterm birth:** Regardless of birth weight or weeks of gestation, premature birth induces persistent deleterious effects on pre-attentional (arousal and sleep-wake abnormalities), attentional (reaction time and sensory gating), and cortical mechanisms throughout development [6].
- **Smoking during pregnancy:** Prenatal exposure to cigarette smoke is known to produce lasting arousal, attentional and cognitive deficits in humans [6].

Descending reticular system (DRS) -
Descending reticular system consists of descending pathways from reticular formation to the autonomic centres in the brainstem and, the lateral and anterior horn cells in the spinal cord.

Clinical Correlation: The descending fibres from reticular formation constitute one of the most important motor pathways. The fibres from reticular formation to autonomic centres in the brainstem are critical in controlling respiratory and cardiac rhythms and other vital functions

[7]. These fibres include -
- Descending reticulospinal tracts
- Spinal cord tracts - reticulospinal tract

- The reticulospinal tracts, also known as the descending or anterior reticulospinal tracts, are extrapyramidal motor tracts that descend from the reticular formation in two tracts to act on the motor neurons supplying the trunk and proximal limb flexors and extensors [7]. The reticulospinal tracts are involved mainly in locomotion and postural control, although they do have other functions as well. The descending reticulospinal tracts are one of four major cortical pathways to the spinal cord for musculoskeletal activity. The reticulospinal tracts works with the other three pathways to give a coordinated control of movement, including delicate manipulations. The four pathways can be grouped into two main system pathways – a medical system and a lateral system [7,8]. The medial system includes the reticulospinal pathway and the vestibulospinal pathway, and this system provides control of posture. The corticospinal and the rubrospinal tract pathways belong to the lateral system which provides fine control of movement

Functions of the reticulospinal tracts-
- Integrates information from the motor systems to coordinate automatic movements of locomotion and posture.
- Facilitates and inhibits voluntary movement; influences muscle tone.
- Mediates autonomic functions.
- Modulates pain impulses

Clinical significance of the reticulospinal tracts-
The reticulospinal tracts provide a pathway by which the hypothalamus can control sympathetic thoracolumbar outflow and parasympathetic sacral outflow. Two major descending systems carrying signals from the brainstem and cerebellum to the spinal cord can trigger automatic postural response for balance and orientation: vestibulospinal tracts from the vestibular nuclei and reticulospinal tracts from the pons and medulla. Lesions of these tracts result in

profound ataxia and postural instability [7]. Physical or vascular damage to the brainstem disconnecting the red nucleus (midbrain) and the vestibular nuclei (pons) may cause decerebrate rigidity, which has the neurological sign of increased muscle tone and hyperactive stretch reflexes [1]. Brainstem damage above the red nucleus level may cause decorticate rigidity. Responding to a startling or painful stimulus, the arms flex and the legs extend. The cause is the red nucleus, via the rubrospinal tract, counteracting the extensor motor neuron's excitation from the lateral vestibulospinal and reticulospinal tracts. Because the rubrospinal tract only extends to the cervical spinal cord, it mostly acts on the arms by exciting the flexor muscles and inhibiting the extensors, rather than the legs. Damage to the medulla below the vestibular nuclei may cause flaccid paralysis, hypotonia, loss of respiratory drive, and quadriplegia [1]. The reticular formation consists of more than 100 small neural networks [2,8], with varied functions including the following:

Functions of reticular system-

- **Somatic motor control –** Some motor neurons send their axons to the reticular formation nuclei, giving rise to the reticulospinal tracts of the spinal cord. These tracts function in maintaining tone, balance, and posture—especially during body movements[3, 4].The reticular formation also relays eye and ear signals to the cerebellum so that the cerebellum can integrate visual, auditory, and vestibular stimuli in motor coordination. Other motor nuclei include gaze centers, which enable the eyes to track and fixate objects, and central pattern generators, which produce rhythmic signals of breathing and swallowing.
- **Cardiovascular control –** The reticular formation includes the cardiac and vasomotor centers of the medulla oblongata [6].
- **Pain modulation –** The reticular formation is one means by which pain signals from the lower body reach the cerebral cortex. It is also the origin of the descending analgesic pathways [6, 7]. The nerve fibers in these pathways act in the spinal cord to block the transmission of some pain signals to the brain.
- **Sleep and consciousness –** The reticular formation has projections to the thalamus and cerebral cortex that allow it to exert some control over which sensory signals reach the cerebrum and come to our conscious attention [4-5]. It plays a central role in states of consciousness like alertness and sleep. Injury to the reticular formation can result in irreversible coma.
- **Habituation –** This is a process in which the brain learns to ignore repetitive, meaningless stimuli while remaining sensitive to others. A good example of this is a person who can sleep through loud traffic in a large city, but is awakened promptly due to the sound of an alarm or crying baby [5].Reticular formation nuclei that modulate activity of the cerebral cortex are part of the ascending reticular activating system.

CONCLUSION

The reticular activating system's fundamental role is regulating arousal and sleep –wake transitions. The ascending reticular activating system is an important enabling factor for the state of consciousness. Contributes to wakefulness as characterized by cortical and behavioral arousal. Clinicians must be aware of detailed clinical correlation of RAS associated clinical disorders for prompt therapy.

REFERENCES-

1. Sadiq W, Subhan M. Ischemic Stroke of Midbrain and Cerebellum Involving Reticular Activating System. Cureus. 2017 Sep 1;9(9):e1637. doi: 10.7759/cureus.1637. PMID: 29119068; PMCID: PMC5665691.
2. Vishram Singh. Textbook of clinical neuroanatomy. 2nd edition. New Delhi: Elsevier, 2010. Chapter 19, 401-405.
3. Snell RS. Textbook of Snell clinical neuroanatomy. 8th edition. China: Wolters Kluwer Health,2018. Chapter 9, 299-300.
4. Kovalzon VM. Ascending Reticular Activating System of the Brain. Translational Neuroscience and Clinics. 2016;2(4):275-285. doi:10.18679/CN11-6030_R.2016.034
5. Jang S, Kwak YH. J Kor Phys Ther. The upper ascending reticular activating system between intralaminar thalamic nuclei and cerebral cortex in the human brain. The Korea Society of Physical Therapy 2017;29(3):109-114.
6. Jang SH, Kwon YH. The relationship between consciousness and the ascending reticular activating system in patients with traumatic brain injury. BMC Neurology 20, 375 (2020). Https://doi.org/10.1186/s12883-020-01942-7.
7. George A. Integrative actions of the reticular formation The reticular activating system, autonomic mechanisms and visceral control. Young University of Nebraska Medical Center. Volume 4, 1964, 5-26.
8. Thome J, Densmore M, Koppe G, et al. Back to the Basics: Resting State Functional Connectivity of the Reticular Activation System in PTSD and its Dissociative Subtype. Chronic Stress. January 2019. doi:10.1177/2470547019873663.