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RETICULAR FORMATION

Lecture: Douglas Oliver

Readings:

Purves, 2012, 5th edition. p 391 Upper motor neuron control; p 440 Horizontal movement of the eyes; p 464 Central control of visceral motor function; pp 468-462 Autonomic regulation of cardiovascular and bladder function; pp 637-639 Reticular activating system, circuits for sleep; pp 651-652 Integration of emotional behavior

Kiernan JA (2009) *Barr's the Human Nervous System: an Anatomical Viewpoint*, 9th ed., ISBN: 978-0-7817-8256-2.

Allen Brain Atlas, online

Waxman SG (2003) Clinical Neuroanatomy, Lange Med Books

SUMMARY

The reticular formation is in the central part of the brainstem where the neurons and fibers present a netlike (reticular) appearance in transverse sections. All parts of the reticular formation share this property in their appearance. So, it suggests a general or even random organization without distinct nuclear structures or specialized neural circuits. However, this is only partly true. Many parts of the reticular formation form interconnections widely within the central nervous system. On the other hand, other parts of the reticular formation participate in specific neural circuits with specific function.

The clinical significance of the reticular formation is that it is involved in many neural circuits including cranial nerve reflexes, autonomic control of heart rate, breathing, and micturition, gaze control, circuits for attention and sleep, and the general integration of motor and emotional responses.

GENERAL FEATURES OF THE RETICULAR FORMATION

- Diffuse appearance – usually identified as the area between the brainstem nuclei
  - Neuron groups are indistinct
- Cells at raphe
- Very large neurons (gigantocellular) tend to be at paramedian location in medulla and pons
- Smaller cells (parvocellular) tend to be lateral and involve in more local functions

GENERAL ANATOMY OF THE RETICULAR FORMATION

Everyone should be able to identify the location of:

- Mesencephalic RF
- Pontine RF
- Medullary RF

Important Individual Nuclei in the Reticular Formation That You Should Know

- Raphe nuclei at the midline
  - Neurons use <u>serotonin</u> as a neurotransmitter

- Central reticular nuclei, gigantocellular nucleus of the central pons and medulla, not including the midline raphe
  - Includes paramedian pontine reticular formation (PPRF)
  - Neurons use GABA and glutamate as neurotransmitters
- Parvocellular nuclei
  - Medulla, pons, and midbrain
  - Around nucleus ambiguus, facial, trigeminal nuclei, oculomotor nuclei
  - Neurons use GABA and glutamate as neurotransmitters
- Cholinergic nuclei
  - In dorsal and rostral pons
  - Neurons using acetylcholine as a neurotransmitter
  - Not motor neurons (that are also cholinergic)
  - Other important non-motor cholinergic neurons are in the basal forebrain
- Locus coeruleus
  - Rostral pons
  - Catecholamine nuclei
  - Neurons using norepinephrine as neurotransmitter

FUNCTIONS OF THE RETICULAR FORMATION

- Short local connections of the reticular formation
  - Cranial nerve reflexes
  - Central pattern generators
  - Cerebellum input & output
  - Gaze centers within brainstem
- Long connections of the reticular formation
  - Mescencephalic and rostral pontine RF modulates forebrain activity
  - Medullary and caudal pontine RF modulate somatic and visceral motor activity

SHORT CONNECTIONS

Short Local Connections between Cranial Nerves for Reflexes

- Lateral parvocellular reticular formation around cranial nerve nuclei
- Gag reflex – RF connects sensory nerve 9 (spinal trigeminal and solitary tr) with motor 9 (nucleus ambiguous)
- Corneal blink reflex – RF connects spinal trigeminal with facial motor.
- Acoustic startle reflex – input via 8^{th} nerve from ear and output via reticular central pathway. (This one involves some longer pathways mentioned below.)

Central Pattern Generators

- Central Pattern Generator for Chewing control the rhythm of chewing
  - Location in parvocellular RF
    - Surrounds motor trigeminal nucleus
    - Caudal to facial nuc.
  - Central Pattern Generator for Chewing
    - Afferents
      - Trigeminal (lips, oral cavity, muscle spindles in muscles that elevate mandible)
      - Cortical masticatory area in M1

        - Central pattern generator
        - Trigeminal motor for jaw muscles
            - Jaw closing – rostral 2/3 of Motor V
            - Jaw opening – ventromedial middle 1/3 and caudal Motor V
- Central Pattern Generator for Respiration
    - Respiratory regions in parvocellular RF near nuc. Ambiguus
    - Pattern generator controls cycle of active inspiration
    - Inputs modulate breathing pattern
    - Outputs control diaphragm and other muscles

Cerebellar Input and Output: Pre-Cerebellar RF Nuclei

- Inputs to cerebellum from reticular formation
    - Lateral reticular nucleus
    - Paramedian reticular nucleus
    - Pontine reticulotegmental nucleus
- Output from cerebellum
    - To Spinocerebellar tract (Vermal cortex -> Fastigial nucleus -> RF)
    - Vestibulocerebellar (Flocculus-Nodulus -> Fastigial + Vestibular -> RF

Gaze Centers

- Paramedian pontine reticular formation (PPRF)
    - Gigantocellular reticular formation just lateral to midline raphe
    - Horizontal gaze center controlling abducens nucleus motor neurons and intranuclear neurons
- Rostral interstitial midbrain reticular formation (riMRF)
    - Lateral to oculomotor nucleus in rostral midbrain
    - Vertical gaze center controlling muscles of oculomotor nucleus via posterior commissure.

LONG CONNECTIONS

Long Connection Circuitry of RF

- Central Medial Nuclei including gigantocellular, central medullary, caudal pontine, and oral pontine
- Neurons
    - Large dendritic fields
    - Dendritic fields are heavily overlapping
- Inputs
    - Many sources
    - Highly overlapping (not topographic)
- Outputs
    - Axons may be ascending or descending or both
    - Axons make local and long connections
    - Many targets
    - Long distances
- Long connections of the reticular formation
    - Mescencephalic and rostral pontine RF modulates forebrain activity
    - Medullary and caudal pontine RF modulate somatic and visceral motor activity

Whole Body Reactions and Reflexes: Central Group of Reticular Nuclei

- Large neurons in the central reticular nuclei in the pons and medulla. Cuneiform nucleus of the midbrain. Most neurons in the reticular formation use glutamate or GABA as a neurotransmitter. Precise identity not known in human and less known about primate.
- Inputs from all sensory systems, including auditory, somatosensory, superior colliculus
- <u>Origin of the reticulospinal tract – control of muscle tone and posture</u>
- <u>Origin of the reticulothalamic tract. Inputs to intralaminar nuclei and other thalamic nuclei.</u>
- Important for
  - Startle
  - Posture
  - Muscle tone
  - Attention & consciousness

Raphe Nuclei: Serotonergic Neurons

- Raphe nuclei use serotonin as a neurotransmitter. (Barr, Fig 9-8. 9-9)
  - Serotonin is synthesized from the amino acid L-tryptophan. The metabolic pathway consists of two enzymes: tryptophan hydroxylase (TPH) and amino acid decarboxylase (DDC). TPH2 is a brain-specific isoform, and the TPH-mediated reaction is the rate-limiting step.
  - In the Allen brain atlas, see the P56 mouse brain, medulla section 58 and midbrain section 138:
    - http://developingmouse.brain-map.org/data/Tph2/74511925/thumbnails.html
    - Identify the raphe nuclei at the level of the pons and midbrain.
- Inputs from periaqueductal gray and limbic forebrain.
- Outputs
  - Descending outputs to the dorsal horn of spinal cord. This pathway is important for the conscious suppression of pain.
  - Descending modulation of the autonomic nervous system.
  - Ascending outputs of the raphe project to the forebrain and are active in deep sleep. This suggests that they suppress thalamic and cortical activity.

Cholinergic Neurons

- Cholinergic neurons are located in the pedunculopontine nuclei and lateral dorsal tegmental nucleus. (Barr, Fig 9-8. 9-9).
- Acetylcholine is synthesized by the enzyme choline acetyltransferase, Chat. These neurons using acetylcholine as a neurotransmitter.
- In the Allen brain atlas, see the P56 mouse brain sections 85 or 93:
  - http://mouse.brain-map.org/brain/Chat/252/thumbnails.html
  - In the pons and midbrain find the Chat positive neurons. Distinguish the mesencephalic trigeminal neurons from the pedunculopontine nuclei.
- Inputs
  - Reticular formation (raphe and locus coeruleus)
  - Hypothalamus
  - Globus pallidus in basal ganglia
- Outputs
  - RF
  - Forebrain
    - Basal ganglia system

    - Intralaminar thalamic nuclei,
    - Cholinergic basal forebrain
- These neurons are important for maintaining consciousness, but also active during REM sleep.

Catecholaminergic Neurons

- Locus coeruleus is the main source of noradrenergic innervation (Barr, Fig 9-8. 9-9).
- Catecholamines are norepinephrine, epinephrine, and dopamine. Tyrosine hydroxylase or tyrosine 3-monooxygenase is the enzyme responsible for catalyzing the conversion of the amino acid L-tyrosine to dihydroxyphenylalanine (DOPA). DOPA is a precursor for dopamine, which, in turn, is a precursor for norepinephrine (noradrenaline) and epinephrine (adrenaline). In humans, tyrosine hydroxylase is encoded by the *TH* gene.
- In the Allen brain atlas, see the P56 mouse brain, section 87 or section 95:
    - http://developingmouse.brain-map.org/data/Th/100079937/thumbnails.html
    - Find cells in the mouse brain that may synthesize DOPA at the level of the pons and midbrain. These will be in the locus coeruleus.
- Inputs from RF and hypothalamus.
- Locus coeruleus outputs are generally excitatory
    - Projects widely to the forebrain, including the hippocampus, amygdala, and frontal neocortex to modulate activity in the direction of increase excitability.
    - Projects to cerebellum.
    - Projects to brainstem and spinal cord.

Motor Control and Emotion

- Reticular formation integrates voluntary movement with emotional expression
- Part of a “whole body” reaction or expression
- RF inputs from motor cortex
    - Proximal limbs and torso
    - Posture, muscle tone, and general excitability
- RF inputs from limbic cortex & basal forebrain
    - Viscera
    - Heart rate, breathing rate, bladder control, blood pressure, etc.

Sleep and Wakefulness
(See also Lecture 64, McNally for definitive details related to Sleep on the exam)

- Wakefulness
    - Neocortex must be stimulated by thalamus and brainstem for consciousness.
    - Cholinergic RF neurons activate hypothalamus, intralaminar nuclei, and cholinergic basal forebrain
        - Essential for wakefulness
    - Activation of locus coeruleus noradrenergic neurons to activation of cortex important for consciousness
        - Lesions of locus coeruleus do not lead to unconsciousness
    - Central RF nuclei also activate thalamus and basal cholinergic forebrain

- o Orexin –A and –B from lateral hypothalamus activate brain and cholinergic RF during waking.

TABLE 28.1 Summary of the Cellular Mechanisms that Govern Sleep and Wakefulness

BRAINSTEM NUCLEI RESPONSIBLE	NEUROTRANSMITTER INVOLVED	ACTIVITY STATE OF THE RELEVANT BRAINSTEM NEURONS
Wakefulness		
Cholinergic nuclei of pons–midbrain junction	Acetylcholine	Active
Locus coeruleus	Norepinephrine	Active
Raphe nuclei	Serotonin	Active
Tuberomammillary nuclei	Histamine	Active
Lateral hypothalamus	Orexin	Active
Non-REM sleep		
Cholinergic nuclei of pons–midbrain junction	Acetylcholine	Decreased
Locus coeruleus	Norepinephrine	Decreased
Raphe nuclei	Serotonin	Decreased
REM sleep		
Cholinergic nuclei of pons–midbrain junction	Acetylcholine	Active (PGO waves)
Raphe nuclei	Serotonin	Inactive
Locus coeruleus	Norepinephrine	Inactive

***NEUROSCIENCE 5e*, Table 28.1**

- Sleep
  - o Preoptic GABAergic neurons inhibit locus coeruleus and cholinergic RF.
  - o Serotonin and norepinephrine neurons are less active during deep sleep.
  - o Cholinergic RF active during REM sleep

Consciousness and Coma

- What is consciousness?
  - o We have no idea
  - o " Christof Koch lists the following four definitions of consciousness in his latest book,[78] which can be summarized as follows:
    - Consciousness is the inner mental life that we lose each night when we fall into dreamless sleep.
    - Consciousness can be measured with the Glasgow Coma Scale that assesses the reactions of patients.
    - An active cortico-thalamic complex is necessary for consciousness in humans, and
    - Put philosophically, consciousness is what it is like to feel something."
      From Wikipedia and Consciousness, Confessions of a Romantic Reductionist, Christof Koch, 2012, MIT Press
- Loss of consciousness can be caused by lesions
- In general, reticular formation is disconnected from the forebrain with lesions in
  - o Midbrain or rostral pons
  - o Caudal diencephalon
  - o Mass lesions of forebrain
- Glasgow Coma Scale is used clinically to judge level of consciousness
  - o Eye opening
  - o Best motor response

- Verbal response

Waxman SG (2003) Clinical Neuroanatomy, Lange Med Books

Table 18–1. Glasgow Coma Scale. A practical method of assessing changes in level of consciousness, based on eye opening and verbal and motor responses. The response can be expressed by the sum of the scores assigned to each response. The lowest score is 3, and the highest score is 15.

Variable	Examiner's Test	Patient's Response	Assigned Score
Eye opening	Spontaneous	Opens eyes on own.	4
	Speech	Opens eyes when asked to do so in a loud voice.	3
	Pain	Opens eyes when pinched.	2
	Pain	Does not open eyes.	1
Best motor response	Commands	Follows simple commands.	6
	Pain	Pulls examiner's hand away when pinched.	5
	Pain	Pulls a part of body away when pinched.	4
	Pain	Flexes body inappropriately to pain (decorticate posturing).	3
	Pain	Body becomes rigid in an extended position when pinched (decerebrate posturing).	2
	Pain	Has no motor response to pinch.	1
Verbal response (talking)	Speech	Carries on a conversation correctly and tells examiner where and who he or she is and the month and year.	5
	Speech	Seems confused or disoriented.	4
	Speech	Talks so examiner can understand words but makes no sense.	3
	Speech	Makes sounds examiner cannot understand.	2
	Speech	Makes no noise.	1

Slightly modified and reproduced, with permission, from Rimel RN, Jane JA, Edlich RF: Injury scale for comprehensive management of CNS trauma. *JACEP* 1979;8:64.