

Lecture 30: Brain Stem: Reflexive Behavior & Neuromodulatory Pathways
By Dr. Hen, 4.30.02
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Note: some of the slides Hen used were not in found in the text. I tried to refer to complementary pictures whenever possible. I also want to refer everyone to last year's transcript, lecture 29. Though Dr. Hen organized his lecture differently this year than last year, the transcript from last year is well done and categorizes things well. This lecture was basically transcribed verbatim from the lecture & tape.

Dr. Hen gave a few introductory notes before starting his presentation of the lecture:

When we are talking about the brainstem, we are actually talking about part of the brain that in lower vertebrates constitutes 90% of the CNS. In higher vertebrates, it is only 10% of the brain's volume but it is a very important part. Most of the behaviors that are found across phylogeny are behaviors that are organized in a reflexive manner by the brainstem. For example, most of the behaviors in a newborn baby are organized by the brainstem. In the sad cases of babies born without diencephalons (as is the result of hydrocephalous), it is virtually incapable to distinguish them from "normal" babies until about 2-3 weeks of age. All of the reflexive behaviors that newborn babies perform such as crying, feeding, facial expressions, swallowing, mastication, and so on, are all organized by the brainstem. **Thus, the brainstem is involved in reflexive, unconscious behavior.**

The brainstem is also involved in the modulation of the conscious states that are organized by the forebrain and the diencephalon.

Thus, the brainstem has two functions:

- 1) Reflexive function. Similar to reflexes organized by the spinal cord.
- 2) Modulation of various arousal & conscious states.

I. Anatomical considerations: cranial nerves & nuclei

Figure 44-1, p. 876

The brainstem serves as a transition zone. It starts with a structure very similar to spinal cord and enlarges into forebrain. The three divisions of the brainstem are the midbrain, pons, and medulla.

Cranial nerves convey sensory information coming from all over the body into the brainstem and also convey motoric information emanating from the brainstem and directed either toward the head muscles, the spinal cord, or a number of relay stations to other skeletal muscles. The various types of cranial nerves can be found on Table 44-1, p. 874 (Hen projected this table in his slide presentation) and are divided into two different families: one of sensory/afferent fibers and one of motoric fibers.

Among sensory nerves, we are dealing with all the somatic and special senses (touch, pain, temperature, proprioception, hearing, vision, olfaction, taste), and also visceral sensory sensations (such as mechanical sensation, temperature, proprioception, and feelings that we may have from our viscera).

In terms of motoric function, there are also 2 divisions: somatic (skeletal muscle) & visceral (smooth muscles & autonomic functions to glands and various structures found in the periphery).

Figure 44-2, p. 877

There are 12 cranial nerves. Some of them have exclusively **sensory** modalities so carry information from periphery inward. Exclusively sensory information can be found by nerves that are responsible for the main senses.

Ex: olfactory nerve, optic nerve, auditory nerve

Some of them have exclusively **motoric** information, sending information to various skeletal or smooth muscles.

Ex: oculomotor nerve, abducens nerve, trochlear nerve (They all carry motoric information to muscles surrounding the eye. They are also involved in various types of eye movements, types of gazes, and lid movements that we perform in daily life).

And, some of them are **mixed**; they carry sensory information in some of their fibers and motor in others.

Ex: trigeminal nerve (sensory from skin, mouth, & teeth; motoric to muscles of mastication).

Ex: vagus nerve (sensory information from muscles of pharynx & larynx, sends voluntary & involuntary motoric information to muscles of pharynx & larynx, and also sends exclusively involuntary motoric (autonomic) information to many other muscles such as the heart, lung, stomach, adrenal medulla, pancreas, blood vessels, large & small intestines. The only organs that are not innervated by the vagus are the genitalia & bladder).

II. Reticular formation, ascending, and descending afferents to forebrain & spinal cord for reflexive behavior and modulation

Since the brainstem is a transition zone between the brain and spinal cord, we are finding particularly in the lower parts (the ones connected with spinal cord), an organization that is very similar to the spinal cord. The nuclei that receive information and carry information of the cranial nerves are organized in columns. These columns are segregated as to whether the nuclei are dealing with sensory or motoric information. So, just like in the spinal cord where there is a dorsal part that carries sensory information and a ventral part that carries motoric information, the nuclei that carry these modalities in the brainstem are also organized in a **dorsal-ventral gradient** (dorsal = sensory; ventral = motoric). *Please look at Figure 44-6, p. 881 (VERY IMPORTANT).*

In the middle of brainstem (and this differs from the spinal cord), there is an area that is much bigger (which would be equivalent of the intermediate gray matter of the spinal cord). This is called the **reticular formation**, and it carries the most complex sets of information.

Figure 44-8, p. 884. One will see different nuclei depending on where one cuts at the brainstem.

At the level of midbrain, we see the **red nucleus, substantia nigra, and mesencephalic reticular formation**. Also, we will find reticular nuclei at different levels, depending on where one cuts. These are the ones that carry two types of information:

- 1) information organized in **local reflexive circuits**. These will coordinate various motor nuclei. Examples of the various types of behavior that can be coordinated by these local circuits within the reticular formation are behaviors such as chewing and swallowing.
- 2) There is also the case where these neurons send **descending projections**, coordinating more complex behaviors such as walking, postural control, gait control. If one stimulates particular sets of neurons within the reticular nuclei, then one can elicit all sorts of behaviors such as stepping motion. Other behaviors include mastication and swallowing, which can be stimulated with the absence of any food or sensory stimulus by stimulation of these local circuits.

So, when dealing with reticular formation, we are dealing with 3 types of neurons:

- 1) **local circuits neurons** that organize the activity of various sensory or motoric nuclei to basically coordinate these reflexive behaviors
- 2) other circuits **neurons that send projections downstream** towards lower parts of spinal cord that organize movements, posture, gait that require activation of leg or arm muscles. This enables them to organize motions (such as the stepping motions).
- 3) **relay neurons** that are contained within nuclei that act as relay stations for sensory information coming from the forebrain.

So, if one thinks of sensory information such as sensory modalities represented in cortex, some information goes directly to spinal cord while other information is interrupted by relay stations in the brainstem, allowing the organism to filter and organize the sensory information in such a way that it can be used to produce simple behavior or responses

II. Neuromodulatory Pathways

The most wide reaching part of the reticular formation not only organizes reflexive behaviors but also carries various neuromodulatory systems that we possess. This is the nuclei that carry either **monoaminergic** information and **cholinergic** information.

Examples of these nuclei include the dorsal raphe nucleus (serotonergic neurons), substantia nigra (dopaminergic neurons), locus ceruleus (noradrenergic neurons).

The most important function of the brainstem is that carrying neurons that all hold neuromodulatory substances allows the brain to modulate any particular arousal or

functional state that we are performing. Secreting different substances in different parts of the brain at different times allows the organism to adapt to particular environmental situations.

Neuromodulatory substances include amines, catecholamines, and cholinergic systems. We are dealing with neuromodulation rather than fast neurotransmission so, as a result, the type of receptors that are activated by neuromodulatory substances are slow-acting receptors. Most of them belong to family of G-protein coupled receptors, which are fundamentally different in the mechanism of action than are receptors that interact with GABA or glutamate (these are fast acting neurotransmitters that act on ion channels and allow the conduction of information to be extremely fast). Neuromodulatory receptors that belong to the G-protein coupled receptor family have a **slower mode of action** and **more diffuse mode of action**.

Two examples:

1) **Dopaminergic systems** *Please look at Figure 45-3, p. 892*

This is composed of a number of nuclei. The main one is the **substantia nigra** that sends projections to the basal ganglia, mostly to the dorsal striatum. Also, there is the **ventral tegmental area (VTA)**, which is located more ventrally than the substantia nigra, and sends information to ventral part of striatum (aka nucleus accumbens) and to a number of cortical structures. Finally, we have dopaminergic neurons in hypothalamus that regulate autonomic functions as well as the activity of the HPA axis.

Ex: substantia nigra – modulates movement

A dysfunction of the substantia nigra circuit results in **Parkinson's disease**, where one has a progressive degeneration of dopaminergic neurons within the substantia nigra and, as a result, experiences all impairments of movement. Dopamine in insufficient levels will result in profound alterations in movement control and the therapies that are currently being used are attempting to increase dopaminergic activity within the striatum.

Also, in the target area, **Huntington's disease** is manifested by a degeneration of neurons that receive dopamine (such as striatal neurons), resulting in profound movement alternations and exacerbated movements. This illustrates that the nigro-striatal pathway connecting the dopaminergic neurons in the substantia nigra to the striatum is critical for proper movement control.

Ex: VTA – modulates hedonic/rewarding states

All the things that are pleasurable (food, sex, drugs of abuse) increase dopamine in nucleus accumbens and, as a matter of fact, most drugs of abuse interact with levels of dopamine in nucleus accumbens. Cocaine blocks uptake of dopamine by dopaminergic neurons emanating from the VTA, increasing levels of dopamine in nucleus accumbens and this underlies some of the reinforcing properties of cocaine. Another example is opiates; μ -opiate receptors are very abundant in the VTA and projections coming from nucleus accumbens to the VTA. Also,

nicotine: nicotine-acetylcholine receptors are abundant in VTA & nucleus accumbens. Finally, alcohol exerts its reinforcing effects possibly via the GABA receptors located in the VTA.

How much dopamine is secreted in nucleus accumbens is critical for the sensation of reward and reinforcement that we experience in normal rewarding situations and abused ones (taking drugs of abuse). In all of these systems, we are dealing with a circuit that is centered around the VTA and nucleus accumbens, and also for the conscious aspects of this experience, we have projections to the prefrontal cortex and limbic cortical structures.

2) **Serotonergic systems** *Please look at figure 45-4, p. 893*

Serotonin is more pleiotropic than dopamine because it is produced by 9 main nuclei (while dopamine only has 3). Three of them are the raphe magnus, raphe pallidus, and raphe obscurus nuclei. They project towards the spinal cord and are the descending projections. This is another difference with dopaminergic system; most of the dopaminergic projections (with the exception of dopaminergic neurons located in hypothalamus) have only ascending projections. Meanwhile, half of serotonin projections are descending while the other half are ascending.

The main ascending projections are the **dorsal raphe projections** and the **median raphe projections**. In all of these nuclei, even though they project to large parts of the CNS, they have very different patterns. The dorsal raphe projects mainly to cortex and stratum while the median raphe projects mainly to the hippocampus.

These neuromodulators can project to the entire CNS (slide shown with ability to diffuse and be found all over the CNS). Most of these neuromodulators interact with many receptors. In the case of serotonin, there are 15 of these **G-protein coupled receptors** with which serotonin could interact. Not only do we have many receptors but also, these receptors can couple with many different signal transduction pathways. This is through a variety of G-proteins and effectors of G-proteins; effectors can be enzymes, ion channels that can activate a variety of second messengers, which in turn can activate a number of kinases, that can phosphorylate a variety of membrane-bound targets or nuclear targets (ion channels & transcription factors), and so on. By using a combination of all the receptors, all of the G-proteins, all the effectors, 2nd messengers, etc. found downstream of serotonin and depending on the battery of signal transduction machinery a particular cell has, it is possible to generate extremely different effects. Effects can be short-lived (such as changes in ion conductances that allow a neuron to respond more or less to changes in incoming stimulus) but also long-lasting changes (such as those involving transcription and translation). Thus, they are extremely wide-ranging in their effects as a **short-term modulator** and a **long-term modulator** (that can underlie long-lasting changes.)

It is no surprise that many of the changes elicited are long-lasting changes. To treat some of the disorders of these neuromodulators, one cannot just take a drug for a day or two but needs to take it for months at a time: anti-depressants (restore normal levels of serotonin), anti-psychotics (restore normal levels of dopamine).

Different examples of functions that serotonin have been implicated in include depression, anxiety, schizophrenia, aggression, etc.. Most of these are a result of lower levels of serotonin (measured by indirect markers). Patients with low levels of serotonin are predisposed to these conditions. Situations such as panic disorder, appetite disorders, anxiety disorders are treated in the same way as depression by using serotonin-uptake inhibitors. These drugs increase serotonin levels and include Prozac, Zoloft, etc., that block serotonin transporter and allow more serotonin to be working at the postsynaptic level. It is an indirect way of increasing serotonin levels. Moreover, treatments for migraines are selective agonists of the particular serotonin receptor 5-HT_{1B/1D}.

Deficits of the serotonergic system can have an effect on many different functions (such as cognitive, reflexive, migraines, gastro-intestinal disorders) because it secreted all over CNS and periphery and modulates the functions of a wide range of structures.

3 elements critical for pleiotropy of neuromodulators:

- 1) **wide distribution**
- 2) **large number of receptors and signal transduction** elements that they modulate
- 3) **complexity** of their pattern of expression

We are dealing with an intricate network and when neuromodulators are released, we are coordinating changes in the CNS and periphery.

Other neuromodulators:

Norepinephrine – main center of production is the locus ceruleus. It has a wide range of projections (both ascending and descending) and deals with wide-ranging functions. Norepinephrine-reuptake inhibitors are another family of anti-depressants, whose goal is to increase norepinephrine levels. *See figure 45-1, p. 890.*

Cholinergic System – less restricted to the brainstem. We have important nuclei in the pontine tegmentum that secrete acetylcholine and send projections to many parts of the brain. Not exclusively localized in the brainstem as is with serotonin, dopamine, and norepinephrine. *See figure 45-5, p. 894.*

Histaminergic System – produced at edge of brainstem in tuberomammillary nucleus, which is part of the hypothalamus that also sends projections both in an ascending and descending manner to many parts of the brain. Histamine is involved in controlling sleep-wake cycles and also levels of consciousness, arousal, alertness. *See figure 45-6, p. 895.*

The “brain arousal system” comprises hypothalamus, thalamus, and upper part of brainstem; it seems that a conjunction of influences from these different elements contributes to the state of arousal or consciousness that we are experiencing. “Consciousness” is difficult to classify in biological terms so we use physiological

recordings such as the EEG. This gives us a first glance at global activity of brain and how it may relate to states of wakefulness and consciousness.

Synchronized state found in sleep. Unsynchronized state found in wakefulness. If one transects brain downstream of brainstem (**between brainstem & spinal cord**), one will still have an animal that is perfectly conscious. It can respond to visual information and tactile information of the skin, and it can follow objects. It is in a state of consciousness that is undistinguishable of the wakeful state in the EEG. If one transects **at the level of the midbrain** and isolates the forebrain from its descending connections, one will have an EEG pattern characteristic of synchronized pattern of sleep, and the animal in this condition is totally unconscious. It cannot respond to any sensory information.

What is believed to be critical to the generation of the wave patterns in the EEG is the way in which the thalamus transmits information to the cortex. These two types of states (synchronized & desynchronized states) have been correlated with 2 types of firing modes of thalamic neurons.

- 1) **Burst mode characteristic of sleep**, where the thalamic neurons in hyperpolarized state and when they fire, they fire in bursts. Don't have single spikes but have groups of spikes together.
- 2) **Transmission mode characterized of wakefulness**, where neurons fire in single spikes.

These two states are responsible for the ability of the thalamus to be more or less responsive to sensory information that comes from the various sensory nerves towards the thalamus. *Please see figures 45-8 & 45-9, p. 898-899.*

Example: fight or flight response.

Emotional response goes to the sensory thalamus, which can transmit information directly to the amygdala through the "low road" or **unconscious** path. The sensory thalamus can also convey information to the amygdala through the "high road" proceeding through the sensory cortex or **conscious** path. The amygdala organizes the defensive and fear reaction, and many of the targets of the amygdala are located in the brainstem. This enables the individual to run away and control other activities (stomach, bladder, heart, lungs, etc.). Interaction with the VTA and dopaminergic system also enables increased arousal.

Many of the ways we respond to environmental stimuli are not just environmental but also have a very strong genetic component. We've seen this in mice and twin studies.