CNS Neurotransmitter Pathways
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OBJECTIVES

To define the origin, course, and distribution of the major transmitter-specific systems of the CNS: glutamatergic, GABA-ergic, cholinergic (ACh), noradrenergic (NE), dopaminergic (DA), and serotonergic (5-HT). The principal neurotransmitters in the CNS are glutamic acid and GABA.

I. INTRODUCTION:

A. CLASSICAL NEUROTRANSMITTERS

1. Amino Acids:
   Glutamate (Glutamic Acid) - principal excitatory CNS transmitter
   GABA (Gamma-aminobutyric Acid) - principal inhibitory CNS transmitter
   Glycine - inhibitory; predominantly in lower brainstem and spinal cord

   (about 80% of CNS synapses are glutamatergic or GABA-ergic; hard-wired information-processing systems; the remaining 20% affect background CNS activity)

2. Acetylcholine (ACh)

3. Biogenic Amines (Monoamines)
   Catecholamines: Dopamine (DA), Norepinephrine (NE)
   Indoleamines: Serotonin (5-HT)

B. NEUROPEPTIDES - this class of neurotransmitters is probably the most rapidly growing; at least forty are now recognized in the CNS

Simple neurotransmitters are distinguished from neuropeptides because they can be synthesized within the nerve terminal (replaced faster after release).

While simple neurotransmitters can be synthesized in the nerve terminal, neuropeptide synthesis is driven by messenger RNA, and occurs in the cell body. During periods of prolonged release the peptides can be depleted from the nerve terminal, and the replacement can only occur via new synthesis at the level of the cell body and subsequent transport of the peptide down the axon to the nerve terminal.
C. CO-LOCALIZATION OF NEUROTRANSMITTERS WITHIN A NERVE TERMINAL

Two or more neurotransmitters (or neuropeptides) can be present in the same neuron; commonly, a simple neurotransmitter (such as ACh or NE) plus a neuropeptide (e.g., endorphins, enkephalins).

Neurotransmitters (neuropeptides) can be differentially released from the nerve terminal; at low frequency one is released, and at high frequency both are released.

D. MODES OF ACTION/ POST-SYNAPTIC EFFECTS

The interaction of the neurotransmitter with specific receptor/transducers or second messengers within the post-synaptic neuron defines the physiologic action of the neurotransmitter.

**Ionotropic** - opening of specific ion channels in the neuronal membrane that results in certain excitatory (depolarization, EPSP) or inhibitory (hyperpolarization, IPSP) effects.

Examples:
- Glutamate - sodium/calcium channel - excitatory
- ACh - sodium channel - excitatory
- GABA - chloride channel - inhibitory
- Glycine - chloride channel – inhibitory

**Metabotropic** (neuromodulatory response) - receptors are linked to a metabolic response through G proteins/second messengers; require a series of enzymatic reactions (more complex than just opening channels)

Example: When NE binds to the beta-receptor, it then binds to a GTP binding protein which activates adenylate cyclase on inner surface of membrane, which converts ATP to cyclic AMP (second messenger) which activates protein kinases that phosphorylate various proteins in the cell, converting them from an active state to an inactive state.

II. PRINCIPAL AMINO ACID NEUROTRANSMITTERS

A. GLUTAMATE - the principal excitatory CNS neurotransmitter; about 40% of all brain synapses

1. **Associational and Commissural Fibers** - originate from layer III pyramidal cells

2. **Corticofugal Fiber Systems** - originate from layer V pyramidal cells; includes corticospinal, corticobulbar, corticopontine, corticostriate projections, etc.
3. **Thalamocortical Projections** - from specific thalamic relay nuclei (e.g., VA, VL, VP) to layer IV of cerebral cortex

4. **Thalamostriate Projections** - from intralaminar complex of thalamus to the striatum

Note: Release of glutamate produces an excitatory (depolarizing, EPSP) response; activation of NMDA receptor facilitates entrance of calcium into postsynaptic neuron; a continuum may exist from excitation to long term potentiation (LTP) for memory consolidation, to excitotoxicity (with neuronal cell death). It is proposed that traumatic brain injury or stroke may precipitate generalized release of glutamate and/or acetylcholine, producing global excitotoxicity and neuronal death.

B. **GAMMA AMINOBUTYRIC ACID (GABA)** - the principal inhibitory CNS neurotransmitter; about 40% of brain synapses; predominates above pons (glycine below pons); GABA keeps CNS neurons under tonic inhibition; interfering with GABA transmission produces seizures; drugs that enhance GABA are used as anti-convulsants; e.g., barbiturates - prolong opening of chloride channels. Some of the major GABA-ergic cell groups include:

1. **Nigrolectals, Nigrothalamics** - from sub. nigra, pars reticulata to sup. colliculus and vent. thalamus (e.g., tonic inhibition of sup. coll.; pause allows saccades to occur)

2. **Striatopallidal, Striatonigrals** - to ext. and int. segments of the globus pallidus and substantia nigra, pars reticulata (principal efferent neurons of caudate and putamen from medium spiny neurons; also lost in Huntington's Chorea)
3. **Pallidothalamics** - from int. segment of globus pallidus to VA nucleus of thalamus (within fascicularis lenticularis and ansa lenticularis); inhibit VA

4. **Cerebellar Purkinje Cells** - Corticonuclear fibers - to deep cerebellar nuclei (inhibit dentate, globose, emboliform, and fastigial nuclei)

5. **Granule Cells** - layers II and IV of cerebral cortex; short axon, intrinsic Connections within cortical column

C. **GLYCINE** - the simplest of all amino acids, is an inhibitory CNS neurotransmitter which predominates from lower brainstem to spinal cord.

III. **CHOLINERGIC CELL GROUPS AND PATHWAYS**

Ch1 - Ch4 = Basal forebrain nuclei (ACh projections to cortex)
Ch5 - Ch6 = Nuclei in the dorsolateral pontine tegmentum (ACh projections to subcortical structures)

A. **Motor Nuclei of Brainstem** - III, IV, VI, V, VII, nuc. ambiguus, XII project to voluntary striated muscles in head; somatic (GSE), branchiomeric (SVE), and smooth and cardiac muscles (GVE), neuromuscular synapses are cholinergic. No "Ch" classification.

B. **Striatum** - contains small short-axon (Aspiny) cholinergic neurons with conn.'s intrinsic within caudate and putamen (Note: only 10% of striatal neurons; other 90% are GABA-ergic, i.e., principal efferents: striatopallidal and striatonigral neurons); implicated in regulation of movement (anti-cholinergic drugs reduce rigidity and tremor of Parkinson's disease) No "Ch" classification
**Huntington's Chorea** - loss of both ACh and GABA-ergic neurons due to atrophy or lesion in caudate and putamen - dyskinesia characterized by irregular, spasmodic, involuntary (choreiform, i.e., “dance-like”) movements of the limbs and facial muscles.

* Link to Netter Image 11.99

**C. Basal Forebrain** - region of caudal basal frontal lobe below the striatum, including nuclei of the precommissural septum; contains multiple cholinergic cell groups which have been classified by Mesulam as Chl-Ch4.

The **nucleus basalis of Meynert** (Ch4), responsible for the cholinergic innervation of the cerebral cortex. Possible involvement in Alzheimer's disease where nucleus shows a 75% loss of neurons. Patients show a decrease in acetylcholine in the brain which is believed to be associated with the cognitive and mnemonic (memory) deficits in the disease.
D. **Pedunculopontine Nucleus** (Ch5) in rostral dorsolateral pontine tegmentum (dorsolateral pontine reticular formation) surrounding brachium conjunctivum; source of **ACh innervation of subcortical structures**, e.g., to striatum, thalamus, substantia nigra, globus pallidus, superior colliculus.

Cholinergic neurons in the PPN are under inhibitory restraint during the waking state. Activation causes onset of (triggers) REM sleep. Note: this cell group is the origin of ponto-geniculo-occipital (PGO) spikes in EEG during REM sleep.

IV. **NORADRENERGIC CELL GROUPS AND PATHWAYS** - catecholamines, derived from tyrosine, terminals have dense core vesicles; these NE cell groups (A1-A7) are in the lateral brainstem reticular formation.

Note: “A” classification = catecholamines; “B” = indoleamines (serotonin)

The **principal source of CNS norepinephrine is the locus ceruleus** (cell group A6) located in the periventricular gray of the rostral pons. Other cell groups (A1-A5, A7), located in the lateral pontine and medullary reticular formation, also synthesize NE. Central release of NE in generalized sympathetic reaction in response to stress, "fight or flight". Extreme activation of this system will cause arousal, anxiety, and feelings of panic.
A. **Dorsal Noradrenergic Bundle** - from the locus ceruleus (A6); projects rostrally through the midbrain periaqueductal gray and medial forebrain bundle through lateral hypothalamus to reach higher levels of the CNS. Generalized NE projections to entire CNS (except hypothalamus).

B. **Ventral Noradrenergic Bundle** - arises from cell groups A1-A5 and A7 in the lateral medullary and pontine reticular formation; pathway ascends through the reticular formation of the lateral brainstem thru medial forebrain bundle to hypothalamus. Specifically targets hypothalamus (affect of stress, arousal on visceroeendocrine function). Descending projections from these cell groups to the spinal cord (e.g., to intermediolateral cell column) affects sympathetic nervous system (including heart rate and respiration).

![Noradrenergic Projections](Image)

* Link to Netter Image 11.96

V. **DOPAMINERGIC CELL GROUPS AND PATHWAYS** - cell groups located primarily in midbrain; terminals contain spheroidal dense core vesicles;

A. **Substantia Nigra, pars compacta** (A8, A9) source of dopaminergic nigrostriatal system to caudate and putamen; loss of neurons or lesion results in Parkinson's disease (paralysis agitans) with resting tremor, rigidity of movement (bradykinesia), freezing, festinating gait, masked face.
B. **Ventral Tegmental Area** - (cell group A10) located above substantia nigra in ventral midbrain tegmentum. Ascending DA projections target basal forebrain “limbic” areas (mesolimbic) and prefrontal cortex (mesocortical).

**Mesolimbic Projections** - “Reward System”- ascend through medial forebrain bundle to "limbic" basal forebrain, especially **nucleus accumbens** which has been referred to as the “addiction center.” The nucleus accumbens neurons have DA and opiate receptors which mediate the pleasurable reinforcing effects of both cocaine and heroin. It also shows activation in other pleasurable activities (food, sex, music).

**Mesocortical Projections** - ascend through medial forebrain bundle to prefrontal cortex, which has the highest level of DA of any area of neocortex. These non-striatal DA pathways are believed responsible for the effects of dopamine on mood. Schizophrenics have elevated levels of DA in the prefrontal cortex.

* Link to Netter Image 11.98
Human functional MRI studies have shown that cocaine, nicotine, alcohol, amphetamine, heroin, and most other drugs of abuse activate the mesolimbic dopaminergic reward system. After the “rush” (as the euphoria ends and the craving sets in) just a few CNS structures continue to be activated: the nucleus accumbens and the amygdala. Patients report that when they hear, smell, touch, or see things that remind them of cocaine, they describe a feeling of arousal and anticipation. The amygdala (see limbic system) is activated as are parts of the brain that involve emotion and memory. The theory is that the memory alone makes the brain release dopamine in anticipation of the reward.

VI. SEROTONERGIC CELL GROUPS AND PATHWAYS - indoleamine, derived from tryptophan.

A. Brainstem Raphe Nuclei - serotonergic (5-HT) cell groups (B1-B8) are confined to the median reticular formation of the midline brainstem in the raphe nuclei.

Midbrain Raphe: primarily ascending 5-HT projections (join MFB)
Dorsal raphe nucleus (B7) - caudal midbrain/rostral pons
Superior central nucleus (B8)

Medullary Raphe: primarily descending spinal cord projections
Nucleus raphe magnus (B3)
Nucleus raphe obscurus (B2) - medulla
Nucleus raphe pallidus (B1)
B. **Ascending Serotonergic Projections** - originate from caudal midbrain/rostral pontine raphe cell groups (dorsal raphe nucleus, B7, superior central nucleus B8), ascend through medial forebrain bundle; project diffusely to higher levels of the CNS; involved in sleep/waking. Reduction of cerebral serotonin (lesion of midbrain raphe) results in prolonged waking state (EEG desynchronization), Serotonin triggers move into slow wave stages of sleep (EEG synchronization).

Serotonin acts as the brain's "brakes," keeping impulsive, aggressive, violent behavior under control. High 5-HT level is associated with obsessive-compulsive behavior (the brakes lock up) resulting in fear of action. Low 5-HT levels lead to depression and suicide. Note: Prozac increases CNS serotonin levels.

C. **Descending Serotonergic Projections** - originate from medullary raphe cell groups (nucleus raphe magnus, obscurus, pallidus, B1-B3) and project to the spinal cord. NRM involved in CNS anti-nociceptive (analgesic) mechanisms, may terminate on intrinsic dorsal horn (endorphin-producing) neurons in laminae I and V. Since the medullary raphe cell groups receive projections from the hypothalamus, they may provide a "limbic" influence on spinal cord function;

dorsal horn - pain modulation; ventral horn - excitability, readiness for movement.

- [Link to Netter Image 11.97](#)
### SUMMARY OF CNS NEUROTRANSMITTERS: CELL GROUPS AND PATHWAYS

<table>
<thead>
<tr>
<th>TRANSMITTER</th>
<th>NUCLEI/CELL GROUPS</th>
<th>PROJECT TO/TERMINATE IN</th>
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<tbody>
<tr>
<td><strong>Glutamate</strong></td>
<td>Lamina III Pyramidal Cells, Cortex Lamina V Pyramidal Cells, Cortex Thalamic nuclei</td>
<td>Associational and Commissural Fiber Systems Corticofugal Projections (e.g., Corticospinals, corticobulbars, corticopontines, corticostriates) Thalamocorticals, thalamostriates</td>
</tr>
<tr>
<td>(Principal excitatory CNS Neurotransmitter)</td>
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<tr>
<td><strong>Aspartate</strong></td>
<td>Inferior olivary nucleus (olivocerebellars climbing fibers) Granule Cells of cerebellar cortex (parallel fibers)</td>
<td>Purkinje cells, cerebellar cortex Purkinje cells</td>
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<tr>
<td>(excitatory)</td>
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<tr>
<td><strong>Gamma-amino-butyric Acid (GABA)</strong></td>
<td>Purkinje Cells Striatum (Caudate/Putamen) Substantia nigra, pars. reticulata Globus pallidus (pallidothalamics) Granule cells (cerebral cortex)</td>
<td>Deep Cerebellar Nuclei Sub. Nigra, pars reticulata (striatonigralss) Globus pallidus (striatopallidals) Superior Colliculus (nigrocolliculars) Thalamus (nigrothalamics) VA nuc. thalamus within cortical columns</td>
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<tr>
<td>(Principal Inhibitory CNS Neurotransmitter)</td>
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<tr>
<td><strong>Acetylcholine (ACh)</strong></td>
<td>Motor Nuclei (GSE, SVE, GVE) Caudate/Putamen (Intrinsic striatal neurons) Ch1-Ch4 in Basal Forebrain (Ch4 = nuc. basalis of Meynert) Ch5/Ch6 DL Pontine Tegmentum (Parabrachial region)</td>
<td>Somatic, Skeletal (GSE) Muscle Branchiometric (SVE) Muscle Cardiac and Smooth (GVE) Muscle Within Striatum All regions of cerebral cortex, inc. Hippocampus Subcortical areas (e.g., basal ganglia thalamus, brainstem, and spinal cord)</td>
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<tr>
<td>(excitatory)</td>
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<tr>
<td><strong>Norepinephrine (NE)</strong></td>
<td>A6 (Locus ceruleus) A1-A5, A7 (lat. pontine and medullary)</td>
<td>All CNS levels (cerebral cortex, cerebellum, brainstem, spinal cord Ascending-to hypothalamus reticular formation Descending-to spinal cord autonomics</td>
</tr>
<tr>
<td><strong>Dopamine (DA)</strong></td>
<td>A8, A9 (Substantia nigra, pars compacta A10 (Ventral tegmental area reward systems (affect mood) )</td>
<td>Striatum (Caudate/Putamen, nigrostriatal) Basal Forebrain - (Nuc. Acc.) mesolimbic Prefrontal Cortex - mesocortical</td>
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A Self-Assessment is available for this lecture.

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