Neurotransmitters

neurotransmitters are the language of the nervous system

one type of chemical signaling

chemical signaling is the main way cells talk to each other

Many different kinds of chemicals can be used for signaling:

a. paracrine regulators (tissue hormones)
   effects only on neighboring cells
   distributed by simple diffusion through interstitial fluids
   don’t enter blood
   rapidly inactivated by enzymes after triggering receptor
   protein on target cell

   eg. histamine

b. neurotransmitters
   secreted by neurons in response to electrical stimulus
   very short range → cell to cell across synapse

c. neurohormones
   released into blood by neurons

d. hormones
   long range
   secreted into blood by endocrine gland

specific chemicals bind to receptors on or in cell to cause change in cell function

→ some receptor proteins are enzymes that cause reactions

→ some open and close gated membrane channels

cell only responds to a chemical if it has the correct receptor protein
= target cell for that chemical

Neurotransmitters are released at most synapses

100’s of neurotransmitters have been identified
   some are excitatory
   some are inhibitory

some neurons produce and release a single NT
most make 2 or more and can release one or all at the same time

different cells respond in different ways to same chemical
	eg. ACh  $\rightarrow$ stim skeletal muscle cells
       $\rightarrow$ inhibits heart muscle cells

the same NT may have different effects in different parts of body
eg. excitatory one place, inhibitory another

**The effect of a NT on a postsynaptic neuron depends on:**

the properties of the **receptor protein**

*not on* the nature of the NT

a variety of different kinds of chemicals have been found to act as neurotransmitters:

1. acetylcholine
2. protein & peptides
3. amino acid derivatives
   - biogenic amines
   - amino acids
4. Inorganic gasses
5. ATP

synapses in PNS release only a few different neurotransmitters

eg. Somatic Motor Neurons $\rightarrow$ ACh,
eg. Autonomic Motor Neurons $\rightarrow$ Epinephrine, NE

most of the diversity is in the CNS, esp the brain

**Neuromodulators**

other chemicals can be released at synapse in addition to neurotransmitters:
  = **neuromodulators**

neuromodulators can influence the release of NTs or the post synaptic neuron’s response to the NT

NM are usually peptides = **neuropeptides**

a chemical may be both a NT and NM
neuromodulators function in 2 different ways:

1. have **direct effect** on membrane potential by opening and closing chemical gates
2. have **indirect effect** on membrane potential thru “second messenger” inside the cell

   eg. receptor on cell membrane
   ↓
   adenylate cyclase
   ↓
   cyclic AMP

**Effects of Drugs on Nervous Transmission**

many drugs (both prescription and illegal) have their effects on the body because they either mimic or somehow modify the action of neurotransmitters or neuromodulators at synapses

knowing receptor types is clinically important → allows selection of drugs that can affect specific organs in ways desired

The end result of these actions:

**A. enhance** the action of the neurotransmitter
   1. drugs mimic specific neurotransmitters
   2. speed up the rate of NT synthesis or release
   3. prevent neurotransmitter inactivation

**B. inhibit (block)** the action of neurotransmitter
   1. reduce synthesis of the NT in axonal end bulbs
   2. prevent binding of NT to receptor
   3. slow down rate of synthesis or release

**PNS Neurotransmitters**

relatively few NT are found in PNS, most diversity is in CNS

Two main Neurotransmitters in PNS:

- **Acetylcholine**
- **Nor Epinephrine**

→ neurons that release ACh are called **cholinergic**
→ neurons that release NE are called **adrenergic**
PNS synapses occur in **somatic** and in **autonomic** branches

**Somatic Neurotransmitters**

**acetylcholine** at all NM junctions

was the 1st NT to be identified

always stimulatory → causes muscle contractions

removed from synapse by **acetylcholinesterase** enzyme

in ACh can be affected at these NM jcts by:

1. **Botulism Toxin**
   blocks release of ACh → paralysis

2. **Black Widow Toxin**
   stimulates massive release of ACh
   → intense cramping and muscle spasms

3. **Nicotine**
   mimics ACh: binds to receptor and activates it but no enzyme to remove it
   → prolonged hyperactivity

4. **atropine, curare**
   binds to receptor but does not induce muscle contractions
   since ACh cant bind, muscle cells cannot be stimulated
   → paralysis

5. **nerve gas, malathione**
   block the breakdown of ACh (=cholinesterase inhibitors)
   → extended, extremely strong contractions

**Autonomic Neurotransmitters**

autonomic synapses produce **Acetylcholine** or **Norepinephrine**

synapses at ganglion and at effector organ:

   at ganglion (preganglionic fibers), neurons secrete **acetylcholine**

synapses at end organs
in parasympathetic branch, most fibers also secrete **ACh** at effector organ

in sympathetic branch most fibers secrete **NE** at effector organ

different neurotransmitters of post synaptic neurons are responsible for each branches’ different effects on same target organ:

but same NT can have **excitatory** effect on some organs and **inhibitory** effect on other organs

**Acetylcholine (Cholinergic Fibers)**

secreted by all autonomic preganglionic fibers → always excitatory

secreted by most parasympathetic postganglionic fibers
   → usually excitatory
     a few are inhibitory

due to two major kinds of NT receptors:

**1. Nicotinic ACh Receptors**
   (named for drug that binds to receptor and mimics ACh)

   most ACh receptors in body:

   a. Neuromuscular jcts of somatic motor neurons
   b. all ganglionic receptors (sym & parasym)
   c. also secreted by sym branch at adrenal medulla

   **always causes stimulation**

**2. Muscarinic ACh Receptors**
   ( = “mushroom” named from source of drug that binds to these receptors)

   can cause stimulation or inhibition of effector organs

   **stimulatory**
   all parasympathetic effectors except the heart

   a. parasympathetic synapses stimulate
b. parasympathetic synapses stimulate bronchial constriction

c. parasympathetic synapses constrict iris circular muscle to constrict pupil
d. in sym branch
  \(\rightarrow\) ACh activates sweat glands

eg. **Atropine** blocks stimulatory muscarinic effects:
  \(\rightarrow\) used in preop to suppress salivation and respiratory secretions
  \(\rightarrow\) used to dilate pupils

**inhibitory**

a. parasympathetic synapse at heart
decreases force and rate of heart beat

b. in sym branch
  \(\rightarrow\) ACh inhibits (dilates) blood vessels in skeletal muscles

**NorEpinephrine (Adrenergic Fibers)**

secreted by most sympathetic postganglionic fibers at effector organ
can be excitatory or inhibitory depending on receptor type:

1. **Alpha Receptors**
   (alpha 1 & alpha 2)

   usually **stimulatory**

   in sym branch, NE:
   \(\rightarrow\) constrict blood vessels of skin
   \(\rightarrow\) constricts visceral organ sphincters
   \(\rightarrow\) causes contraction of radial muscles in iris to dilate pupils

   **eg. Ephedrine**
   in OTC cold, cough & allergy medications
   \(\rightarrow\) stimulate alpha receptors to cause:
   constriction of blood vessels serving skin, mucosa, salivary glands, etc
eg. Alpha blockers (Vioxx, Celebrex)
  \(\rightarrow\) dilates blood vessels to lower blood pressure

2. Beta Receptors
  \((\beta_1, \beta_2, \beta_3)\)

usually **inhibitory**: dilation or relaxation of effector muscles, stops glandular secretion

in sym branch, NE:
  \(\rightarrow\)relaxes muscles to dilate coronary arterioles (\(\beta_1\))
  \(\rightarrow\)relaxes muscles to dilate bronchioles (\(\beta_2\))
  \(\rightarrow\)relaxes muscles in walls of digestive and urinary organs (\(\beta_2\))

a few are **stimulatory**: constriction, glandular secretion

in sym branch, NE:
  \(\rightarrow\)increases heart rate (\(\beta_1\))
  \(\rightarrow\)stimulates renin release by kidneys (\(\beta_1\))
  \(\rightarrow\)stimulates secretion of insulin by pancreas (\(\beta_2\))
  \(\rightarrow\)stimulates lipolysis of fat cells (\(\beta_3\))

eg. Beta blockers
  \(\rightarrow\) reduce heart rate without interfering with other sympathetic functions

**CNS Neurotransmitters**

most of the diversity is in the CNS, esp the brain

several hundred neurotransmitters & neuromodulators have been identified so far

many hormones act as neurotransmitters in the brain

a variety of different chemicals have been found to act as neurotransmitters in the CNS:

1. acetylcholine
2. proteins & peptides
3. amino acid derivatives
   biogenic amines (=catecholamines)
   amino acids
4. Inorganic gasses
5. ATP
1. **Acetylcholine (ACh)**
   also at all NM jcts and in Autonomic NS

   **in CNS:**
   1. inadequate amt ACh → correlated with Alzheimer’s
   2. ACh receptors destroyed in Myasthenia gravis
      an autoimmune disease

2. **Proteins & Peptides**
   broadly distributed in brain
   affect behavior, moods, sleep, thought

   some examples:

   eg. **Substance P**
   peptide (chain of amino acids)
   mediates pain transmission in PNS
   in CNS affects mood
   also involved in respiratory and cardiovascular control

   eg. **endorphins & enkephalins**
   peptides
   in limbic system and related structures
   natural opiates
   reduces pain perception
   “runners high”

   1. **morphine, heroin, methadone**
      binds to enkephalin receptors
      → mimicks effects of endorphins

   eg. **cholecystokinin**
   peptide
   may be related to feeding disorders

3. **Amino Acid Derivatives**
   unaltered amino acids or modified ones, eg. catecholamines

   eg. **aspartate**
   amino acid
   only in CNS
   excitatory

   eg. **glutamate**
   amino acid
only in CNS
excitatory
important in learning and memory

1. released in large quantities after stroke
   → increases damage to nervous tissue

eg. **glycine**
   amino acid
   in spinal cord
   inhibitory

1. strychnine blocks receptors → causes convulsions

eg. **histamine**
   produced in hypothalamus
   in immune system is powerful vasodilator

eg. **GABA**
   modified amino acid
   most abundant inhibitory NT in brain (~1/3\(^{rd}\) of all)
   → inhibits skeletal movements

1. deficiency: Huntington’s disease → jerky movements
2. **alcohol**
   enhances its inhibitory effects
   → slowed reflexes
   → reduced coordination
3. **tetanus toxin** blocks CNS synapses that release
   inhibitory NT such as GABA and glycine
   → results in overstimulation of muscles

also affects mood
   excess: less anxiety
   deficiency: more anxiety

1. **Valium**
   binds to GABA receptors
   mimics or enhances its effects → less anxiety

eg. **dopamine**
   a catecholamine synthesized from tyrosine
   esp in substantia nigra of basal ganglia (midbrain)
affects coordination of skeletal muscles
also a “feel good” NT
1. Parkinson’s Disease
deficiency \rightarrow \text{tremors (no inhibition of basal nuclei)}

2. schizophrenia
correlated with excess of dopamine

3. amphetamines
    enhance its “feel good” effects

4. cocaine
    blocks its uptake \rightarrow \text{enhances “feel good”}

\text{eg. norepinephrin}
also released by some neurons in autonomic NS

esp in brain stem
another “feel good” NT
affects mood: arousal, dreaming

1. generally: excess \rightarrow \text{mania}
deficiency \rightarrow \text{depression}

2. Cocaine & amphetamines
    prevents inactivation of norepinephrin \rightarrow \text{enhances its effect}
    (amphetamines and cocaine have similar effect as on dopamine)

\text{eg. serotonin}
indolamine, synthesized from tryptophan or histidine
in brain stem (reticular system)
    induces sleep, temp regulation, appetite
also affects mood and aggression

1. LSD
    binds to serotonin receptors
    \rightarrow \text{prevents its effect or counteracts its function in brainstem (RAS)}

2. Prozac
    prevents its uptake
    \rightarrow \text{relieves anxiety and depression}

3. linked to migraine headaches

4. Inorganic Gasses

\text{eg. NO (nitric oxide)}
toxic gas
short lived
is synthesized on demand
not stored in axonal vesicles
in CNS may be involved in learning and memory
in PNS causes relaxation of smooth muscle

eg. **CO (carbon monoxide)**
in CNS
similar physiology as NO

4. **ATP**
now recognized as a major neurotransmitter in both CNS and PNS
produces fast excitatory response at certain receptors