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Biological Psychology 10003

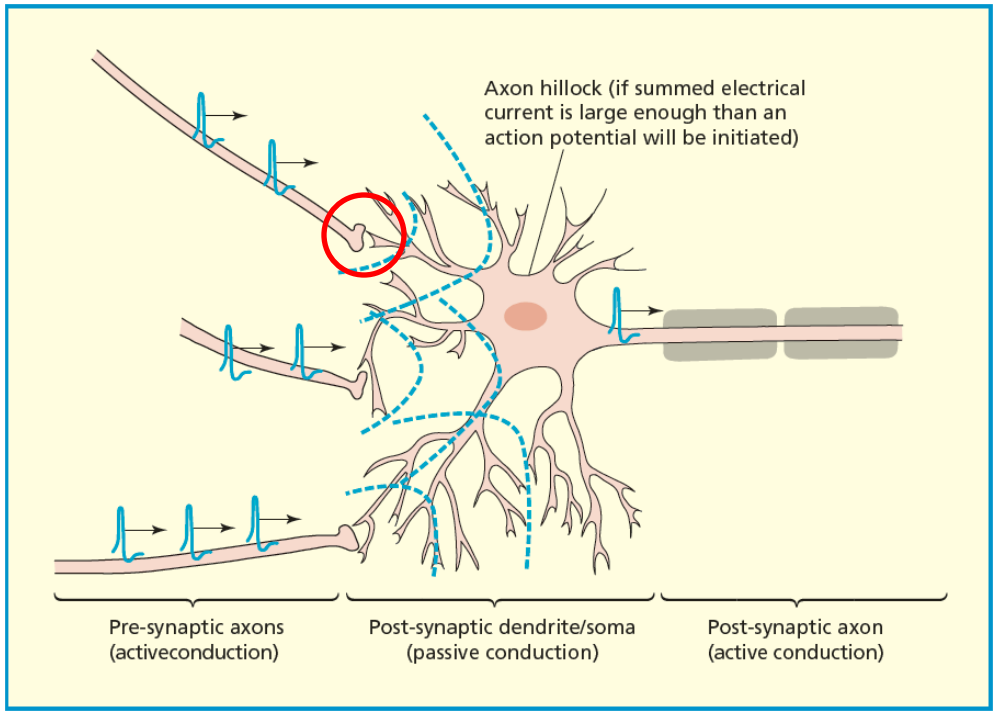
Lecture 3: Neurotransmission

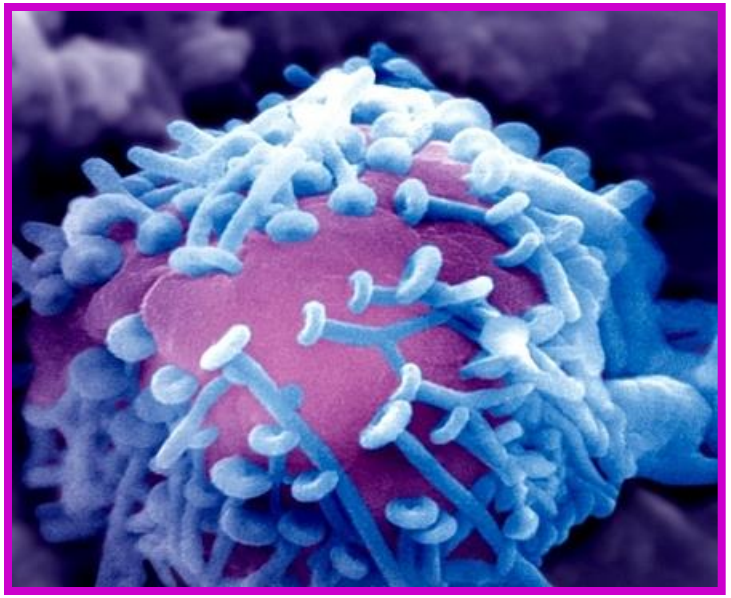
Overview:

- Propagation of action potential to the synapse
- Chemical transmission at the synapse
- Excitation and inhibition of the postsynaptic cell
  - Spatial and temporal summation
- How are neurotransmitters inactivated
- Main types of neurotransmitters
- Drugs and neurotransmitters

The synapse

- **Synapse**: the junction at which the signal is passed from one neuron to another one
  - The neurons are separated by a space or **synaptic cleft** of ~20-30 nm wide (no cytoplasm continuity between neurons – Ramon y Cajal's Neuron Doctrine)

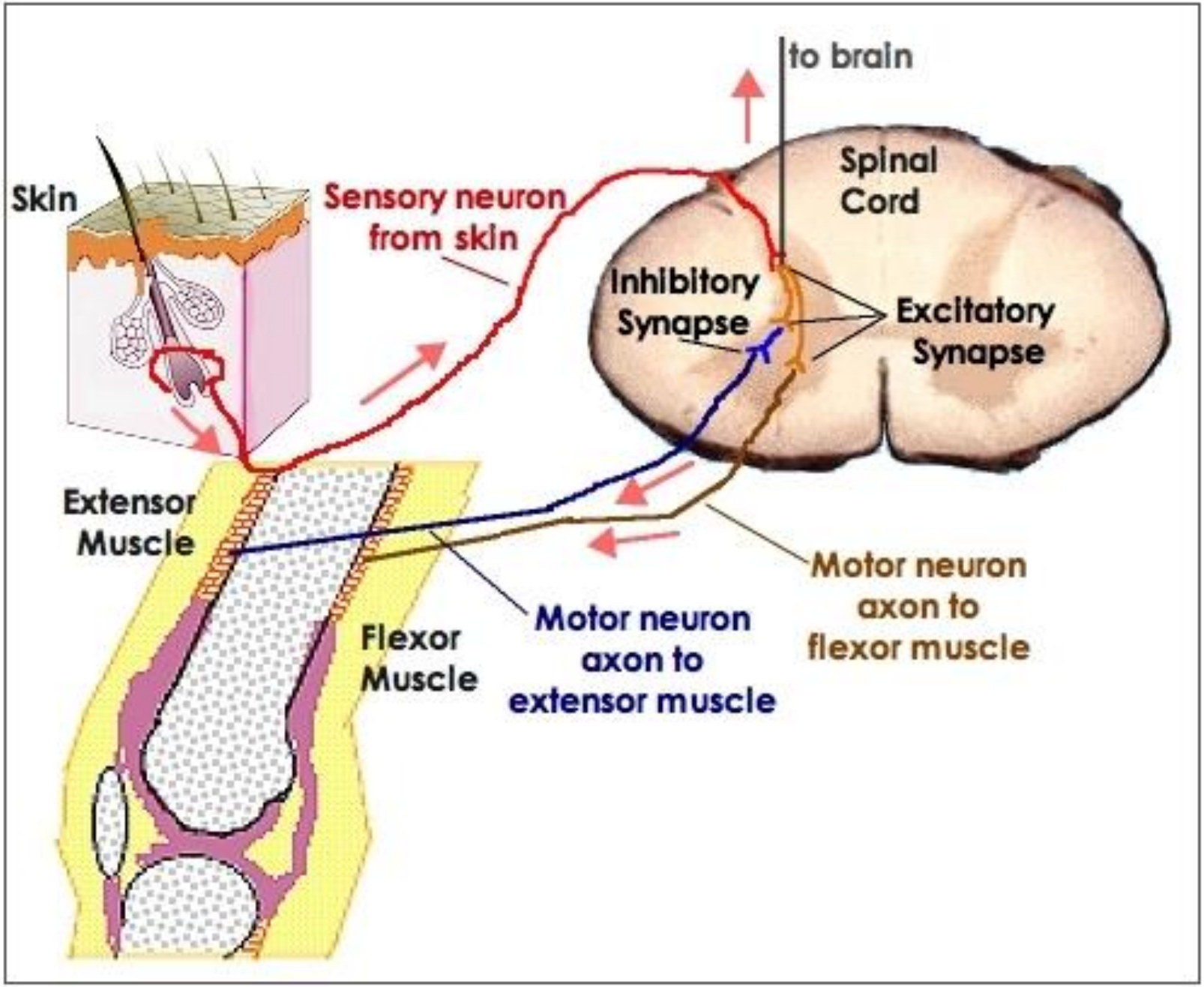




Discovery of Synapse

- Charles Scott Sherrington (1857-1952), Nobel prize 1932
- Reflexes are slower than conduction along the axon:
  - Pinching a dog's foot made the dog flex its leg after a short delay

SIR CHARLES SCOTT SHERRINGTON

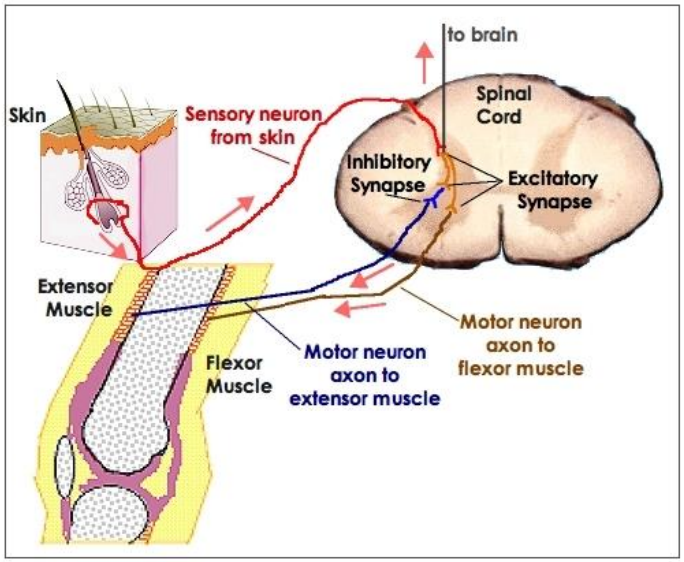

to brain
Skin
Sensory neuron from skin
Spinal Cord
Inhibitory Synapse
Excitatory Synapse
Extensor Muscle
Flexor Muscle
Motor neuron axon to extensor muscle
Motor neuron axon to flexor muscle

Transmission of signal between neurons

- Charles Scott Sherrington (1857-1952), Nobel prize 1932
- Reflexes are slower than conduction along the axon:
  - Pinching a dog's foot made the dog flex its leg after a short delay
  - The speed of impulse in reflexes - 15 m/s (as compared to 40 m/s in individual sensory or motor axons)
- Sherrington supported Ramon y Cajal's claim that there was a small gap between neurons, i.e. synapse. The transmission is delayed at synapses


SIR CHARLES SCOTT SHERRINGTON

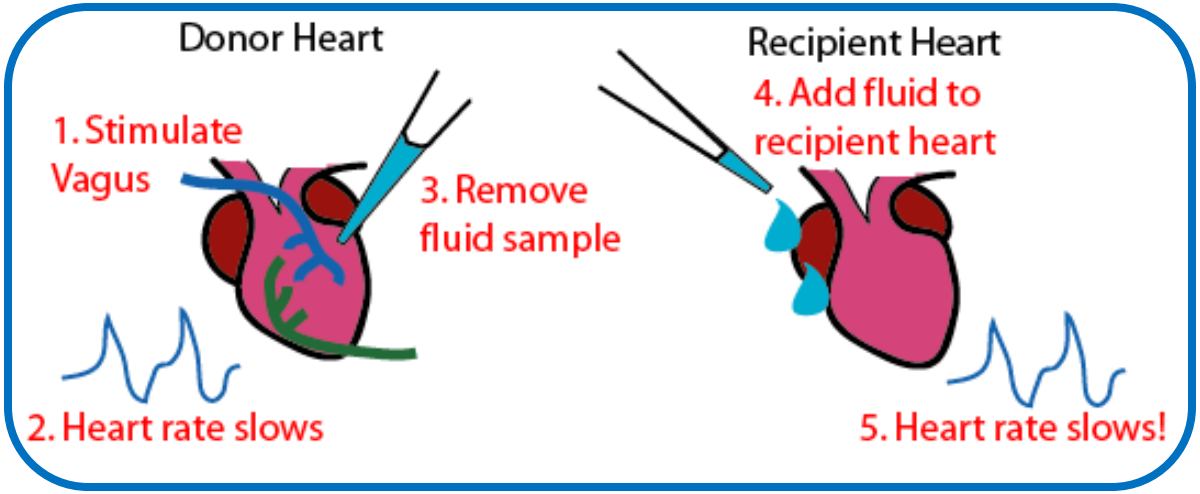
- How is the signal transmitted at synapses?
  - Electrically? Chemically?



Chemical transmission at synapses

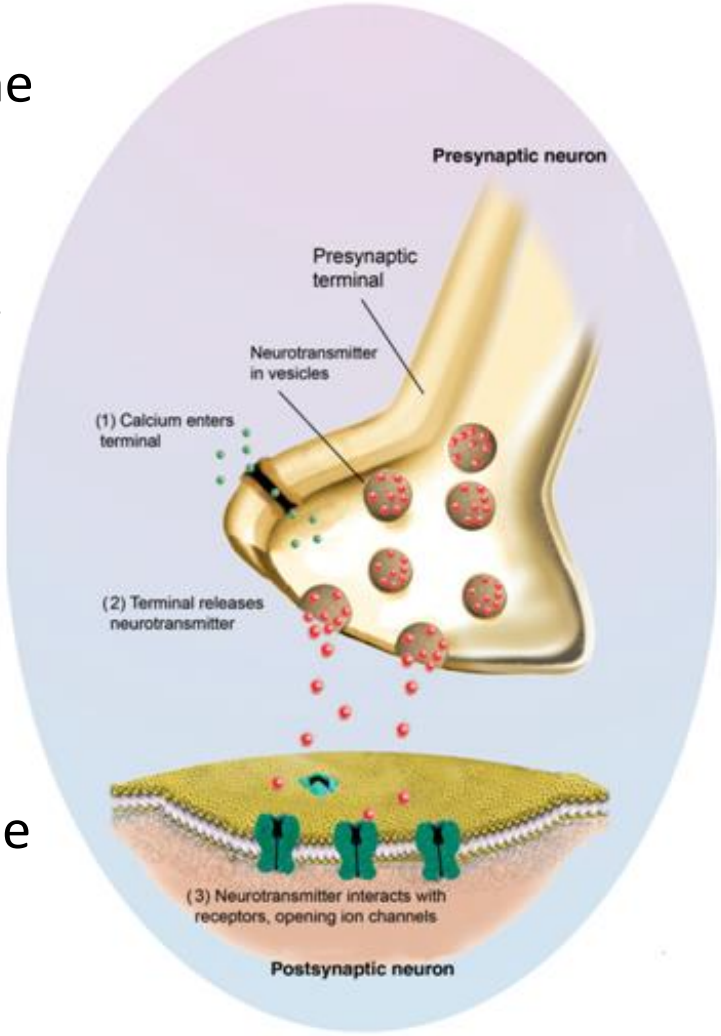
Otto Loewi (1921) isolated two frog hearts

- Stimulating the vagus nerve of the donor heart; the heart beat slowed down. Loewi collected the fluid ('Vagusstoff', later confirmed to be acetylcholine) from the donor heart, transferred to the recipient heart. The recipient heart slowed down
  - The opposite effect from experimenting with the accelerator nerve
- Loewi's conclusion: each nerve released a different chemical into the fluid—one inhibited the heart and one excited it
- → **Synaptic transmission is via chemical neurotransmitters** (though electrical transmission can also occur)



Sequence of Chemical Events at a Synapse

- The neuron synthesizes chemicals that serve as **neurotransmitters**
- Neurotransmitters are stored in **vesicles** in the axon terminals
- When the action potential arrives at the terminals of the presynaptic neuron, voltage-gated calcium channels open due to depolarization → Ca+ enters the neuron
- Within 1-2 ms this leads to release of neurotransmitter into the **synaptic cleft** (the amount varies)
- Neurotransmitters cross the 20-30 nm wide cleft in 0.01 ms and attach to **receptors** on the postsynaptic neuron and alter the neuron's activity
  - Total delay in transmission across the synapse ~2ms



Garrett (2011)

Receptors on the postsynaptic cell

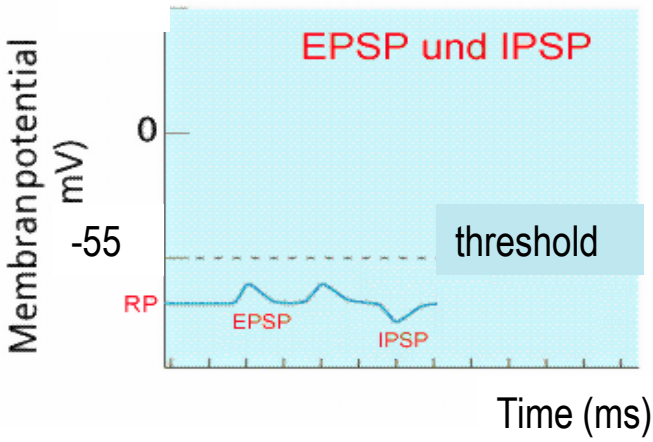
- A **receptor** is a protein embedded in the membrane that matches the molecular shape of a specific neurotransmitter molecule

- **Ionotropic receptors:** neurotransmitter directly opens some type of ion channels. The effect is fast (within a few ms after the release of neurotransmitter) and short-lived (~ 20 ms)
  - Used for visual & hearing inputs, muscle activity (rapid change of information)
- **Metabotropic receptors:** neurotransmitter opens ion channels indirectly & produces slower (after 30+ ms after the synaptic transmission) but longer-lasting (seconds, minutes, or longer) effects
  - Useful for behaviours such as hunger, thirst, fear, anger

Excitatory & inhibitory postsynaptic potentials

Activation of receptors on the postsynaptic neuron has two possible effects on its membrane potential

- **Excitatory postsynaptic potential (EPSP)**
  - Depolarization of the neuron; the postsynaptic neuron more likely to fire (relative to its spontaneous firing rate)
- **Inhibitory postsynaptic potential (IPSP)**
  - Hyperpolarization of the neuron; decreases the rate of action potentials in the postsynaptic neuron

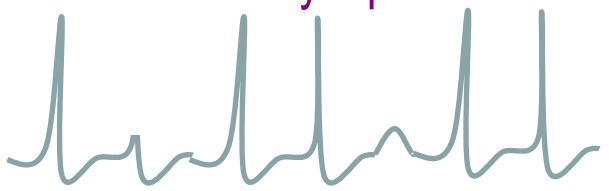


Q: *Do EPSPs/IPSPs always result in a more excited/inhibited behaviour?*
A: No, because an EPSP may activate a neuron which in turn inhibits many other neurons (and vice versa).

spontaneous firing

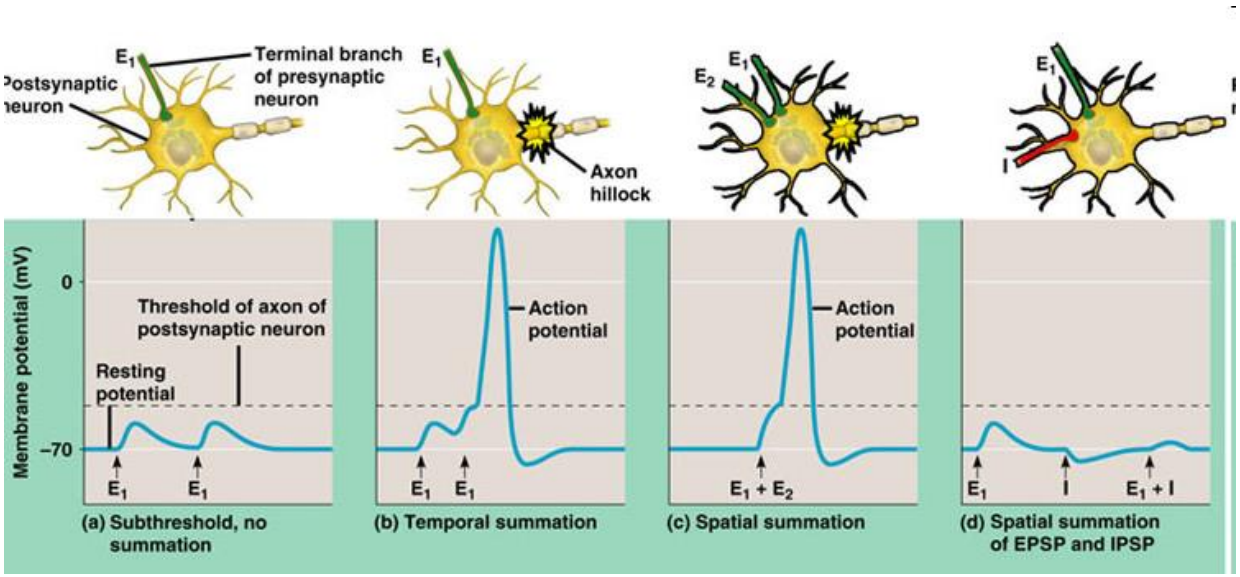
with excitatory input

with inhibitory input



Temporal and spatial summation

- EPSPs and IPSPs are *graded* potentials , i.e., membrane potentials are of varying magnitude (unlike action potentials which are 'all-or-none')
- Their effects can accumulate over a short time ('temporal summation'), i.e., rapid repeated sub-threshold stimulations of a pre-synaptic neuron add together
- Spatial summation: inputs arriving at different locations on the dendrites and cell body (nearly) simultaneously are combined



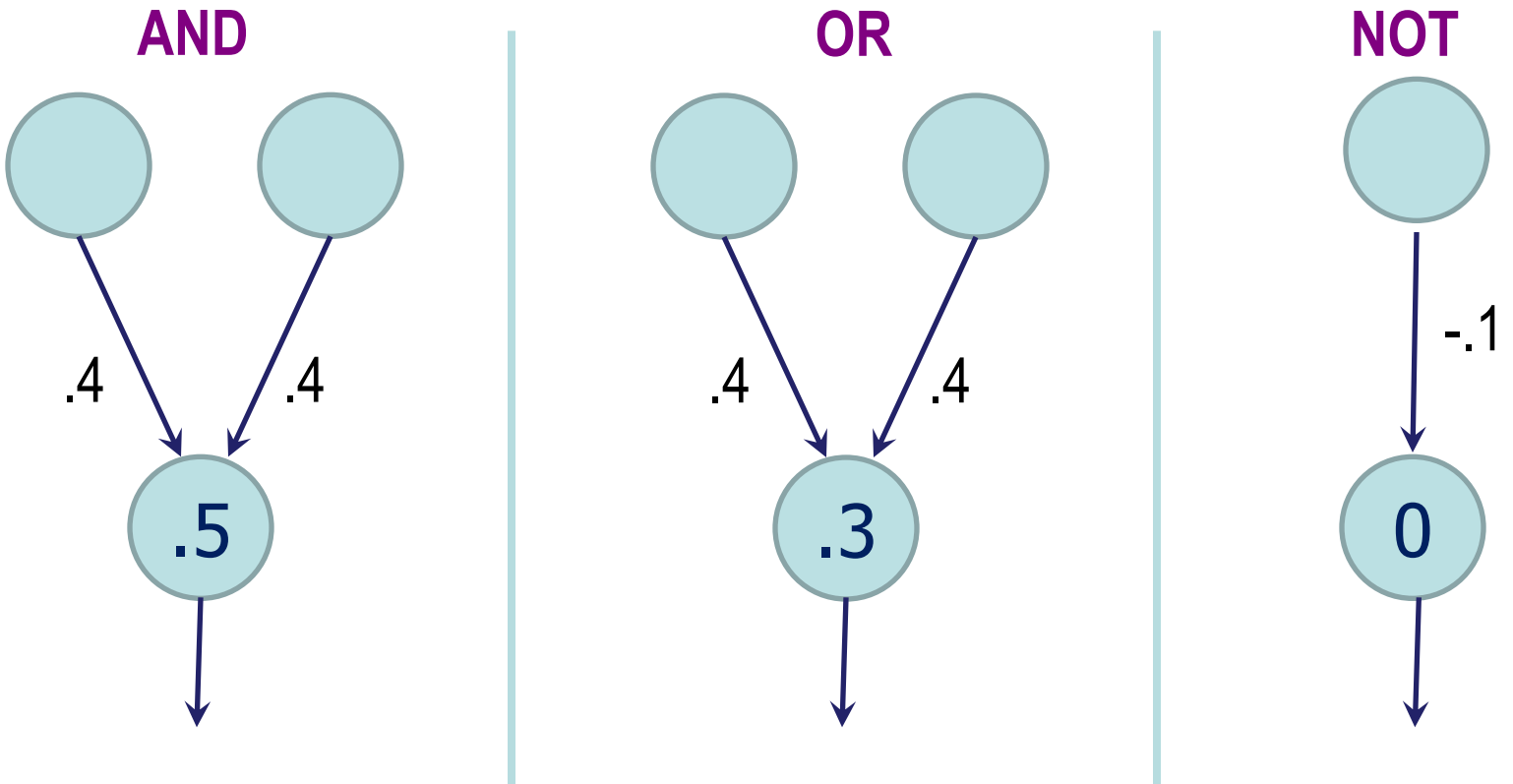
http://porpax.bio.miami.edu/~cmallery/150/neuro/c7.48.18.summation.jpg

The neuron acts as

1. an information integrator (via temporal & spatial summation)
2. a decision maker, by combining excitatory and inhibitory inputs algebraically & determining whether to fire

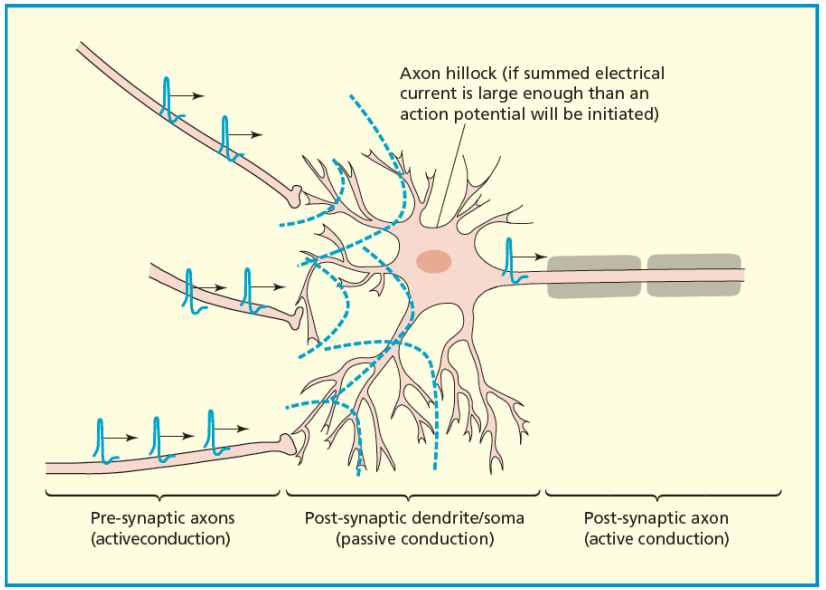
Neuron as Decision Maker

- Any information-processing task can be made up of sets of instructions (a program) that uses the simple logic operators AND, OR, NOT
- Synaptic wiring diagram for simple logic operators:



Synapse & neurotransmission: summary

- **Presyntaptic neuron:**
  - an action potential hops down the axon
  - when it reaches the axon terminal, it opens Ca+ channels → Ca+ ions flow into the neuron and release neurotransmitters from vesicles
- **Synaptic cleft:**
  - neurotransmitters enter the synaptic cleft
  - neurotransmitters roam down to the postsynaptic neuron & attach to its receptors, which opens up ion channels on the post-synaptic neuron
- **Postsynaptic neuron:**
  - becomes either depolarized (more positive than at rest, then the neuron is excited) or hyperpolarized (even more negative than at rest, the neuron is inhibited)
  - In case of multiple synapses: algebraic sum of the activity across synapses
  - if the neuron is sufficiently depolarized, it fires an action potential



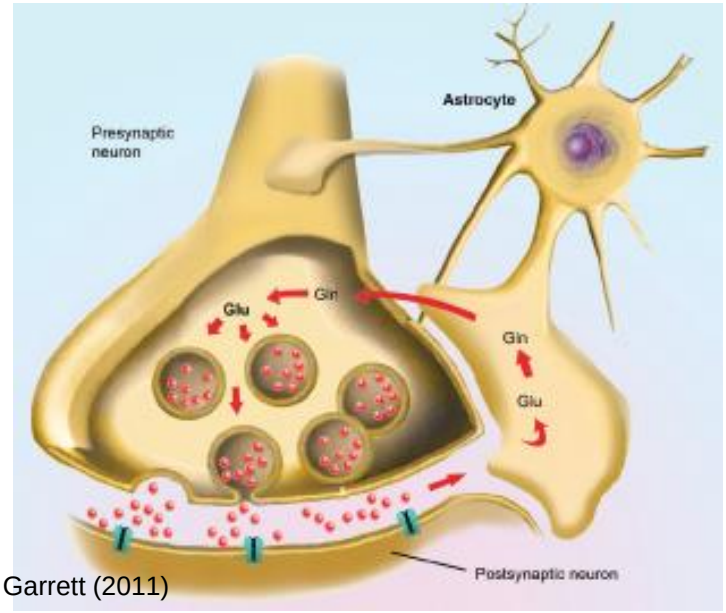
Inactivation and re-uptake of neurotransmitters (1)

- Once the neurotransmitter has activated the receptors, it must be inactivated (in order not to continue exciting/inhibiting the receptor & to allow frequent responding)
- Different neurotransmitters are inactivated in different ways
  1. Acetylcholine is broken down by acetylcholinesterase into acetate and choline

Myasthenia gravis (from Greek μύς "muscle", ἀσθένεια "weakness", and Latin gravis "serious"; abbreviated MG) is an autoimmune neuromuscular disease leading to fluctuating muscle weakness and fatiguability. It is an autoimmune disorder, in which **weakness is caused by circulating antibodies that block acetylcholine receptors at the post-synaptic neuromuscular junction, inhibiting the stimulative effect of the neurotransmitter acetylcholine**. *(from Wikipedia)*

Inactivation and re-uptake of neurotransmitters (2)

2. Serotonin, dopanime, norepinephrine detach from the receptor and are absorbed back by the presynaptic neuron (‘**re-uptake’)** and can be used again later
3. Glial cells can reabsorb transmitters at some synapses (& influence synaptic activity by granting or withholding such absorption)



Garrett (2011)

An astrocyte encloses the synapse where it absorbs the neurotransmitter glutamate (Glu) from the cleft and recycles glutamate into its precursor glutamine (Gln). Glutamine returns to the presynaptic terminal for re-use

Table 3.1 Neurotransmitters and Their Functions (from Schacter et al)

Neurotransmitter	Function	Examples of Malfunctions
Acetylcholine (Ach)	Enables muscle action; regulates attention, learning, memory, sleeping, and dreaming	With Alzheimer's disease, Ach-producing neurons deteriorate
Dopamine	Influences movement, motivation, emotional pleasure, and arousal	High levels of dopamine are linked to schizophrenia. Lower levels of dopamine produce the tremors and decreased mobility of Parkinson's disease.
Glutamate	A major excitatory neurotransmitter involved in learning and memory	Oversupply can overstimulate the brain, producing migraines seizures.
GABA (gamma-aminobutyric acid)	The primary inhibitory neurotransmitter	Undersupply linked to seizures, tremors, and insomnia.
Norepinephrine =noradrenaline	Helps control mood and arousal	Undersupply can depress mood.
Serotonin	Regulates hunger, sleep, arousal, and aggressive behavior	Undersupply linked to depression; Prozac and some other antidepressant drugs raise serotonin levels.
Endorphins	Act within the pain pathways and emotion centers of the brain	Lack of endorphins could lower pain threshold or reduce the ability to self-soothe.

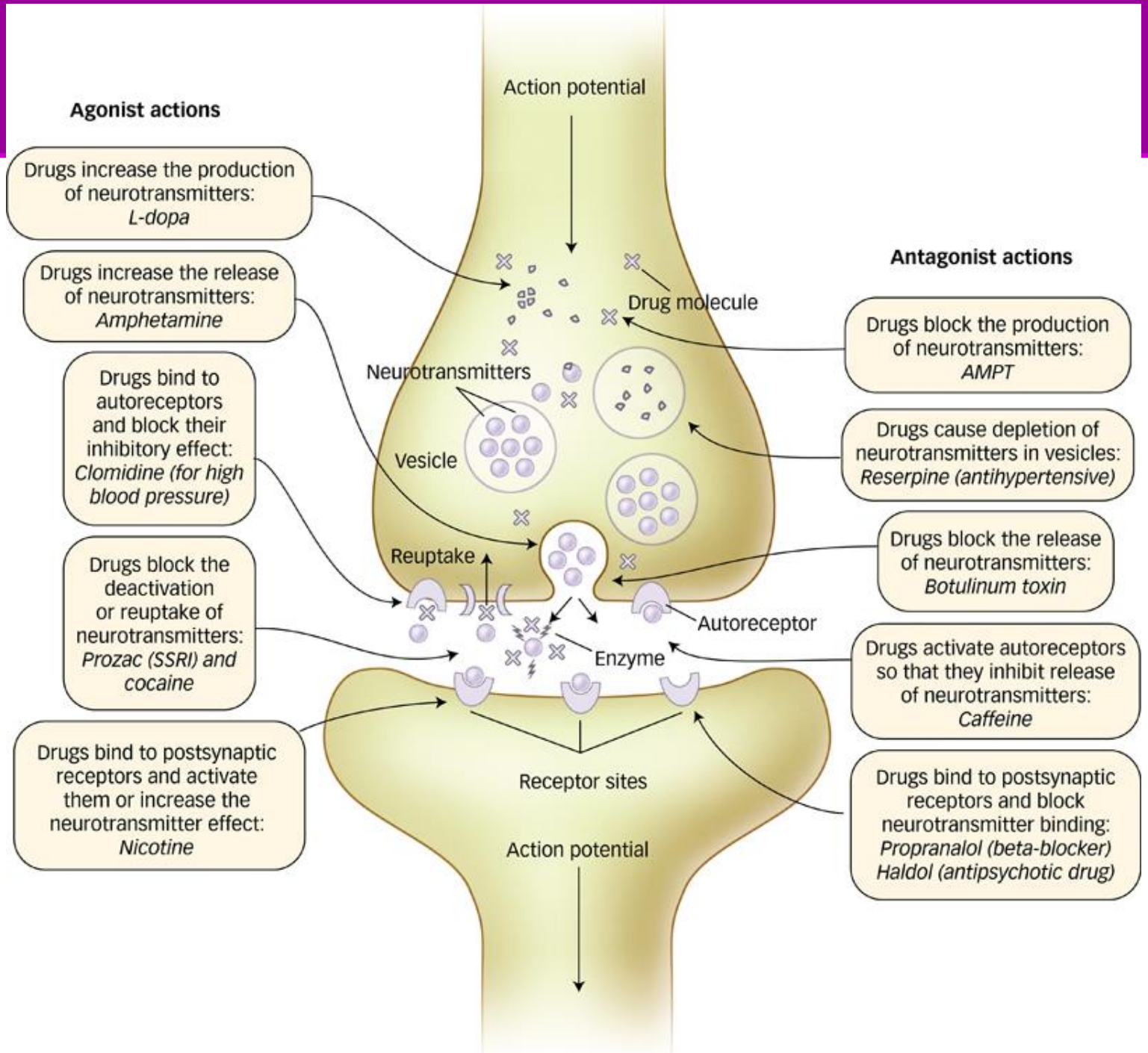
Neurotransmitters & Behaviour

- The neurotransmitters found in humans are virtually the same as in non-human species
- The differences between species are quantitative
  - Variations in the number of synapses
  - The amount of neurotransmitter release
  - Sensitivity of receptors on postsynaptic cells
- These variations yield all the rich variation in behaviour across species

Psychoactive drug mechanisms

- Most psychoactive drugs imitate what the brain produces naturally and takes advantage at mechanisms that handle normal synaptic transmission

- Drugs facilitate or inhibit transmission at synapses
  - **Antagonist**: a drug that blocks the effects of a neurotransmitter
  - **Agonist**: a drug that mimics or increases the effects of a neurotransmitter


Agonist actions
Drugs increase the production of neurotransmitters: *L-dopa*
Drugs increase the release of neurotransmitters: *Amphetamine*
Drugs bind to autoreceptors and block their inhibitory effect: *Clomidine (for high blood pressure)*
Drugs block the deactivation or reuptake of neurotransmitters: *Prozac (SSRI) and cocaine*
Drugs bind to postsynaptic receptors and activate them or increase the neurotransmitter effect: *Nicotine*
Action potential
Drug molecule
Neurotransmitters
Vesicle
Reuptake
Autoreceptor
Enzyme
Receptor sites
Action potential
Antagonist actions
Drugs block the production of neurotransmitters: *AMPT*
Drugs cause depletion of neurotransmitters in vesicles: *Reserpine (antihypertensive)*
Drugs block the release of neurotransmitters: *Botulinum toxin*
Drugs activate autoreceptors so that they inhibit release of neurotransmitters: *Caffeine*
Drugs bind to postsynaptic receptors and block neurotransmitter binding: *Propranalol (beta-blocker)* *Haldol (antipsychotic drug)*

Abused drugs

- Abused drugs differ in their predominant action:
  - amphetamine & cocaine – stimulants
  - morphine & other opiates – narcotics
  - LSD – hallucinogen

- Yet, most of them directly or indirectly stimulate the **release of dopamine**, esp. in nucleus accumbens
  - "The dopamine hypothesis of reward" (Spanagel & Weiss, 1999)

Example: Cocaine

- Cocaine is extracted from the South American coca plant
- Historically used as a topical anesthetic in eye and nasal surgery
  - Cocaine blocks sodium channels, thereby interfering with the propagation of action potentials and acts as a local anesthetic
- Cocaine is a stimulant, i.e., it activates the CNS to produce arousal, increased alertness, and elevated mood
- Cocaine blocks the reuptake of dopamine and serotonin at synapses, potentiating their effect

Summary

- Synapse: the presynaptic cell releases neurotransmitters which cross the synaptic cleft and bind to receptors on the postsynaptic cell
- Neurotransmitters can cause excitatory or inhibitory potentials in the postsynaptic cell (EPSPs or IPSPs)
- Main types of neurotransmitters and their function
- Most psychoactive drugs use mechanisms that handle normal synaptic transmission

Reading material

- SGW, chapter 3 - REQUIRED
- Kalat, chapter 3
- See also Bob Garrett's *Brain & Behaviour*, chapters 2 & 5

- Spanagel R, Weiss F (1999). "The dopamine hypothesis of reward: past and current status". *Trends Neurosci.* **22**(11): 521–7.
- For an in-depth coverage of these and other aspects of neuroscience, check out

  Bear, M.F., Connors, B.W., & Paradiso, M.A. (2006). *Neuroscience: exploring the brain* (3rd edition). Baltimore, MA.