School of Medical Sciences

Physiology 1A

Cell Physiology lecture #6

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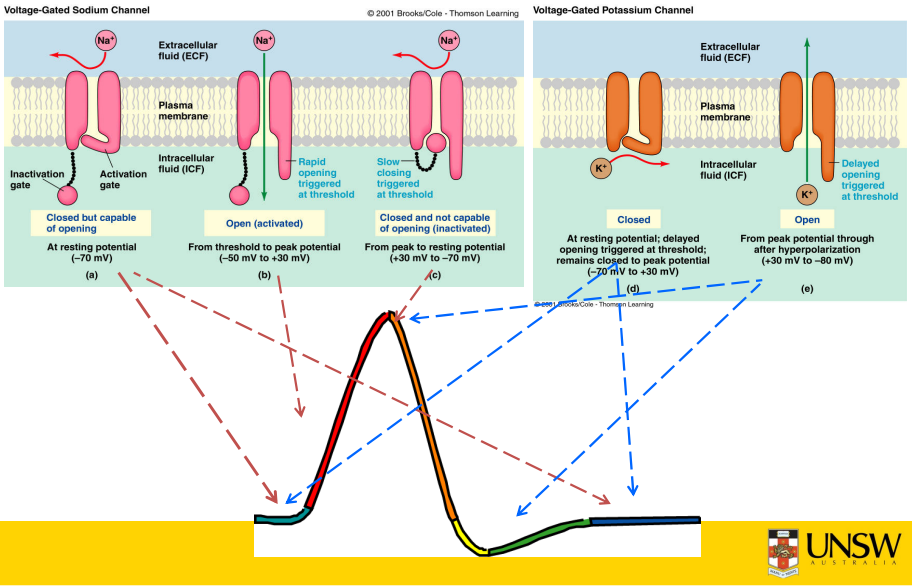
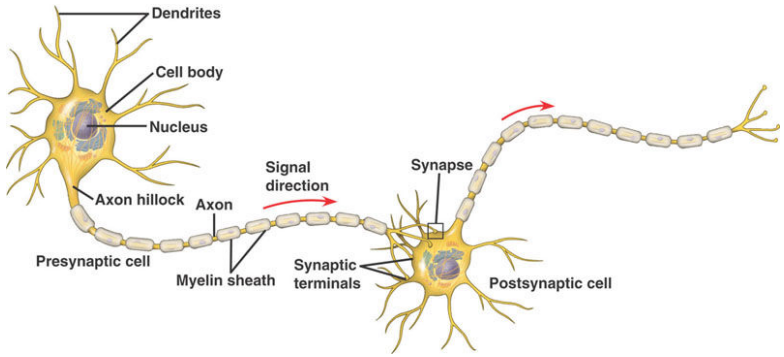
The nerve action potential….summary



The nerve action potential….

- *Generated in a specialised region of high Na+ channel density called the axon hillock. This signal must then be communicated to other nerves.*

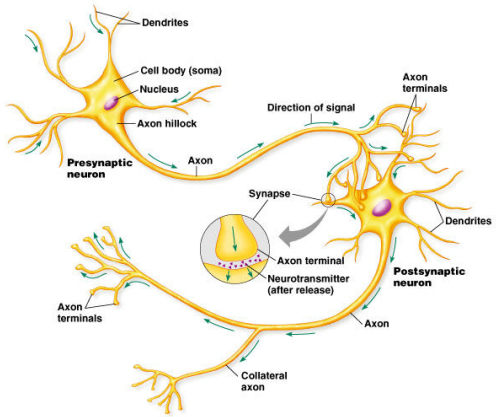


http://hplusmagazine.com/wp-content/uploads/neuron_structure2.jpg

- *How does this signal travel….*

Final Concept:
Communication of Signals from cell to cell

A nerve cell communicates with other nerve cells and with peripheral organs and/or muscle via converting the action potential into a chemical messengers at **synapses**



Learning Aims – lecture 6

- To describe the general features of chemical and electrical communication between cells
- To list the steps involved in synaptic transmission at the neuromuscular junction (as a model synapse)
- To know the transmitters and ionotropic receptors at neuromuscular and central synapses
- To be able to distinguish ionotropic and metabotropic receptor signalling
- To understand the receptors and ionic fluxes involved with excitation and inhibition at central synapses, what EPSP and IPSP mean, and how these EPSPs and IPSPs get integrated by a neuron (i.e., summation) to elicit an action potential response
- To be able to briefly describe how neurotransmitter signalling may be switched off

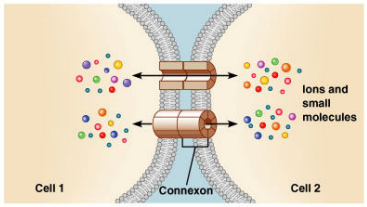
Supporting activities:

- Cell Physiology tutorial #3.
- Stanfield, Chapter 8 (Synaptic Transmission)

Cell communication. Electrical or Chemical

1) Electrical communication

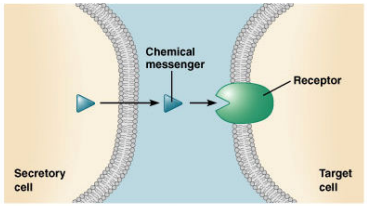
(direct electrically coupling between adjacent cells)



(a) Direct communication through gap junctions

2) Chemical communication

(a chemical released by one cell acts on a receptor in a receiving cell)

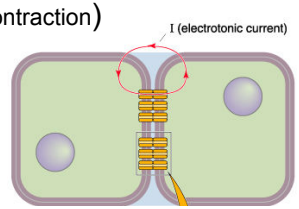


(b) Communication via chemical messengers

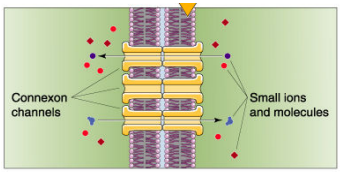
1) Electrical Communication

- **occurs via structures connecting cells known as "Gap junctions"**
- These consist of end-to end connexin proteins to form a connexon channel between adjacent cells
- assists synchronisation of cell activity in an organ

(e.g. peristalsis of smooth muscle in stomach, heart muscle ventricular contraction)



A gap junction: two adjacent cells connected and isopotential via channel pores,



Cell-cell gap junction

A closer look – connexon channels connecting cells

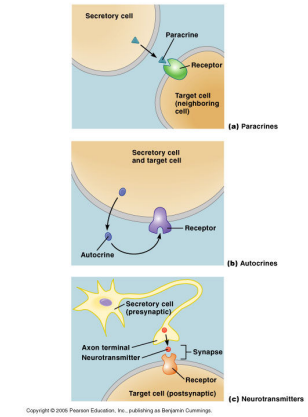
Electrical Communication via Gap junctions

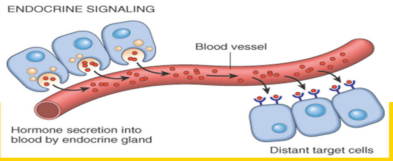
Electrical Communication via Gap junctions

- protein channels between adjacent cells, many cell types
- connexons - comprised of multpile connexins
- channel pore quite large, usually open
- the adjacent cells have same V_m and small solute concentrations
- cells can respond as one (synchronised)
- if found at synapses called electrical synapses; eg retina

eg cardiac muscle; smooth muscle, glands, cochlear, neurons

Chemical Communication via Receptors





General features:

- *common to virtually all cells*
- *one cell releases a chemical that act on another cell*
- *synthesis of chemical*
- ***transport then release of chemical***
- ***getting to the site of action***

(paracrine, autocrine, synapse, endocrine – see Fig.)

- ***binding to specific receptors***
- ***cell response***
- *termination / recycling of chemical*

Chemically-activated Receptors

1) Metabotropic receptors

The membrane receptor and the target /effector protein in the cell (enzyme, ion channel) are separate proteins linked by a 2nd messenger

The Nobel Prize in Chemistry 2012

Photo: U. Montan
Robert J. Lefkowitz
Prize share: 1/2

Photo: U. Montan
Brian K. Kobilka
Prize share: 1/2

The Nobel Prize in Chemistry 2012 was awarded jointly to Robert J. Lefkowitz and Brian K. Kobilka *"for studies of G-protein-coupled receptors"*

Photos: Copyright © The Nobel Foundation

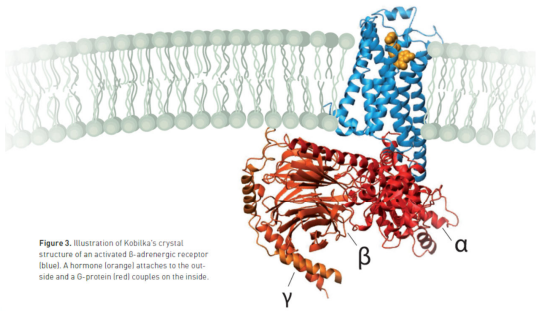


Figure 3. Illustration of Kobilka's crystal structure of an activated B-adrenergic receptor (blue). A hormone (orange) attaches to the outside and a G-protein (red) couples on the inside.

The crystal structure a G-protein coupled receptor, a type of metabotropic receptor.. The membrane receptor is shown in blue, this triggers associated G-proteins (red, 2nd messengers) to activate enzymes and modulate ion channels in the cell)

http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2012/popular-chemistryprize2012.pdf

Chemically-activated Receptors

1) Metabotropic receptors, eg G-protein coupled receptors

Metabotropic Signaling:

- The image shows a schematic of G-protein receptor signaling
- Features of metabotropic signaling include
- Slower signals
- Amplification
- Scope for modulation and cross signaling
- Used by lots of hormones, neurotransmitters and odours

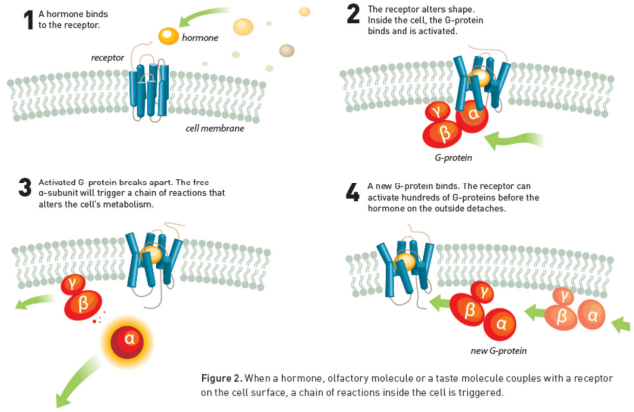
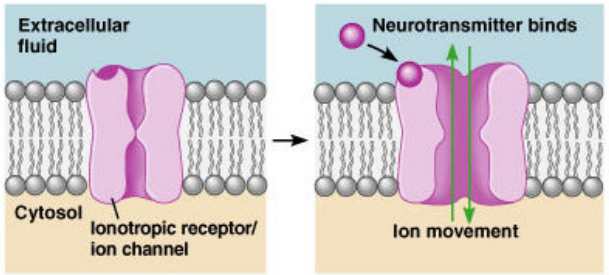


Figure 2. When a hormone, olfactory molecule or a taste molecule couples with a receptor on the cell surface, a chain of reactions inside the cell is triggered.

Chemically-activated Receptors

2)The "ionotropic receptor" subclass



(a) Fast response

Ionotropic Receptors or Ligand-gated Ion Channels:

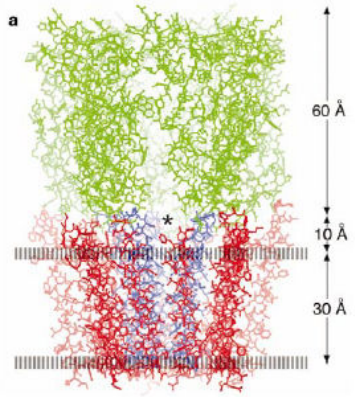
- The Receptor is an ion channel with a gate that is opened by the ligand molecule
- Binding of ligand > channel gate opens > ionic current flow > V_m change
- Fast transmission of signals at central or peripheral synapses
- Different receptors for different ligands, channel pores have different selectivity
- Neurotransmitters and their receptor channels shown later

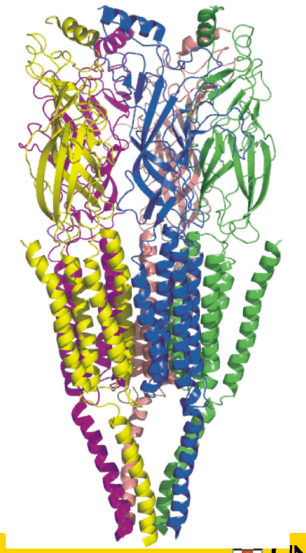
Chemically-activated Receptors

- e.g, The nicotinic ACh receptor

Chemically-activated Receptors

- e.g, The nicotinic ACh receptor

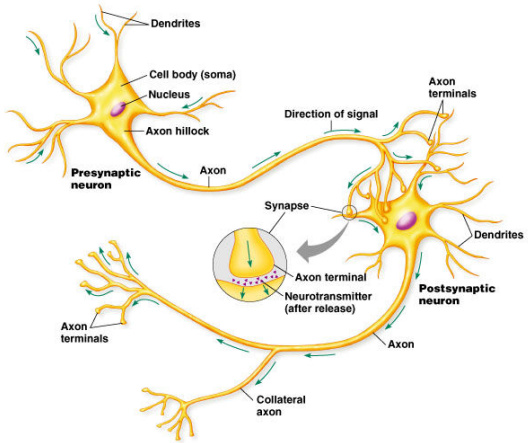




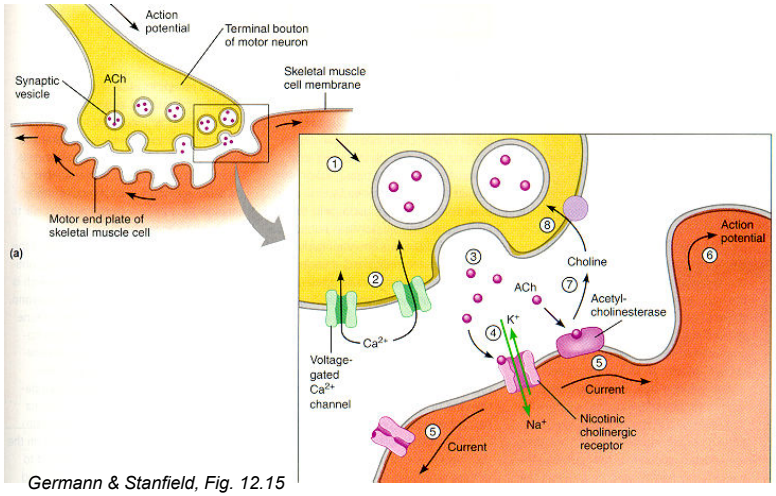
Miyazawa et al., Nature 2003
Unwin, J Mol Biol., 2005

Communication across a synapse

A nerve cell communicates with other nerve cells and with peripheral organs, and does this largely by converting the action potential into a chemical messengers at synapses



Neuromuscular junction – a mode chemical synapse



Germann & Stanfield, Fig. 12.15

Key events in Synaptic Transmission at the Neuromuscular Junction

1) action potential in presynaptic motor nerve terminal causing depolarization

2) activation of presynaptic voltage-dependent Ca^{2+} channels and influx of Ca^{2+} into terminal

3) exocytosis of acetylcholine (ACh) from synaptic vesicles and diffusion of ACh across the synaptic cleft.

4) ACh binds to and gates open / activates the nicotinic ACh receptors at the specialised postsynaptic region known as the endplate. The open receptor-channels allow the influx of Na+ (and a little bit of K+ efflux)

5) The net inflow of Na+ (= an influx of positive current, the end-plate current, EPC) depolarises the post-synaptic membrane (causing the small end-plate potential, EPP). Many small EPPs add together and spread beyond the endplate

6) The depolarization of muscle membrane potential crosses the voltage threshold and causes a muscle action potential

7) Meanwhile, nicotinic ACh receptors close, ACh is degraded to choline and acetate by the enzyme acetylcholinesterase, found at the endplate

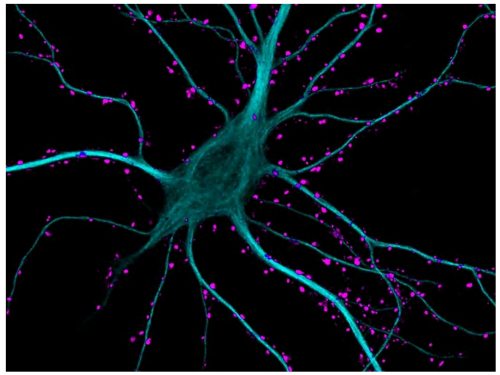
8) Choline is recycled back into nerve terminal where it can be used to resynthesis ACh

Central Synaptic Transmission

Millions of synapses co-ordinating brain activity

Similar mechanisms cf Neuromuscular junction except:

- Each synapse causes a excitatory depolarization or an inhibitory hyperpolarization
- Each postsynaptic response at a single synapse is very small and subthreshold (≈2 mV)
- Synaptic responses must be integrated (summed) to effect action potentials in the soma



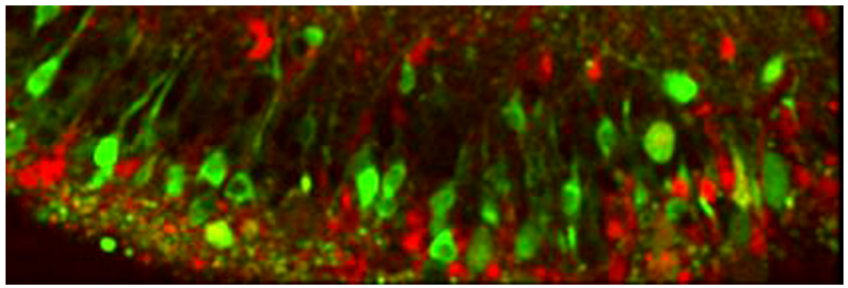
Fluorescence confocal microscope image of excitatory nerve terminals on a single cultured neuron (hippocampal neuron). The blue structure is the neuron with its soma and extensive dendrites or neuronal processes. Each purple dot represents a single synapse.

A neuron may receive up to 1000 single synaptic inputs each with a small EPSP, IPSP and conductance shunt. The cell soma must integrate or add these up to shape an output response. The output will be to activate / switch off or modulate action potentials. The cell summates these signals in time and space.

. Kieran Boyle/ University of Glasgow. Accessed https://www.theguardian.com/science/neurophilosophy/2014/may/29/3d-model-nerve-terminal#img-1, 12/03/2016

Central Synaptic Transmission

This brief movie shows the electrical activity in an isolated brain slice (showing the CA1 pyramidal cell layer of the hippocampus). The green fluorescence represents electrical activity in nerve cells, the red fluorescence represents some associated glial cells (astrocytes). The flashes correspond to bursts of action potentials. The movie indicates that, even in vitro, there is a lot of neural activity and this is often co-ordinated or synchronized. The co-ordination of neural activity is achieved through excitatory and inhibitory synaptic connections between the nerve cells.



Hiro Inada, national Institutes for Physiological Sciences, Japan, unpublished

Central Synaptic Transmission

- Excitatory and Inhibitory synaptic responses via specific ionotropic receptors

Excitatory postsynaptic potential (EPSP, depolarisation)

Table

Table 1 Ligand-gated ion channel neurotransmitter receptors

Neurotransmitter	Receptor type	Channel selectivity
Acetylcholine	Nicotinic (peripheral)	$Na^+/K^+/Ca^{2+}$
	Nicotinic (neuronal)	$Na^+/K^+/Ca^{2+}$
Adenosine triphosphate	$P2X_{1-7}$	$Na^+/K^+/Ca^{2+}$
Glutamate	NMDA	$Na^+/K^+/Ca^{2+}$
	AMPA	$Na^+/K^+/Ca^{2+}$
	Kainate	$Na^+/K^+/Ca^{2+}$
γ-Aminobutyric acid (GABA)	$GABA_A$	Cl^-
	$GABA_C$	Cl^-
Glycine	GlyR	Cl^-
5-Hydroxytrypamine	$5\text{-}HT_3$	$Na^+/K^+/Ca^{2+}$

Same gene family (i.e. common structure & mechanisms)

AMPA, α-amino-3-hydroxy-5-methylisoxazolepropionate; NMDA, *N*-methyl-d-aspartate.

Inhibitory Postsynaptic Potentials (IPSPs, hyperpolarisation)

Stephenson, F Anne and Hawkins, Lynda M (July 2000) Neurotransmitter Receptors in the Postsynaptic Neuron. In: Nature Encyclopedia of Life Sciences. London: Nature Publishing Group. http://www.els.net/ [doi:10.1038/npg.els.0000284]

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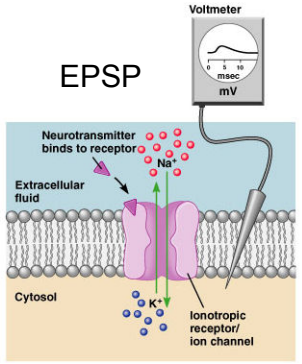
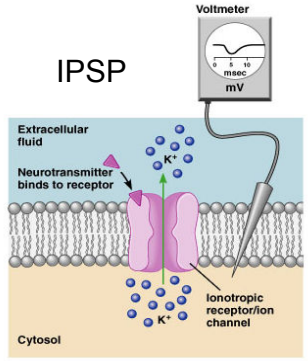
Central Synaptic Transmission

- Excitatory depolarizing and Inhibitory hyperpolarizing synaptic responses

Postsynaptic depolarisations – make it easier to reach threshold and generate an Action Potential hence Excitatory Postsynaptic Responses (EPSPs) , usually mediated by Na+ influx through glutamate-gated cation channels

Postsynaptic hyperpolarisations - make it harder to reach threshold and generate an Action Potential hence Inhibitory Postsynaptic Responses (IPSPs), usually mediated by Cl^- influx through GABA-gated anion channels





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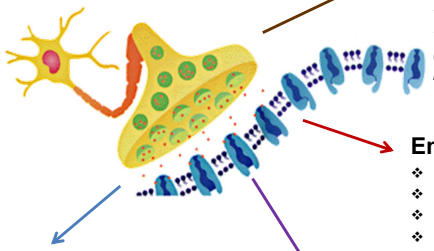
The synaptic response is brief.
General modes to switch off chemical transmission:



Uptake transporters

- Presynaptic, Postsynaptic, Surrounding glial cells
- Secondary active transporters
- Specific for different neurotransmitters
- Common (GABA, glutamate, amines)

(e.g., serotonin, dopamine and noradrenalin uptake Proteins are targets of therapeutic & abused drugs)

Enzyme breakdown

- Enzymes for different transmitters
- Membrane bound or soluble
- ACh broken down by acetylcholinesterase (AChE)
- By products (e.g, choline) may be recycled

(some insecticides and poisons target AChE)

Diffusion or Flow

- Chemical leaves the receptor
- Hormone carried away by blood
- Transmitter diffuses away from synapse

(& may activate extrasynaptic receptors)

Desensitization / Internalisation

- The receptor itself may become less sensitive or change its
- concentration or location in the membrane
- Acute (desensitisation) or chronic (internalisation) effects

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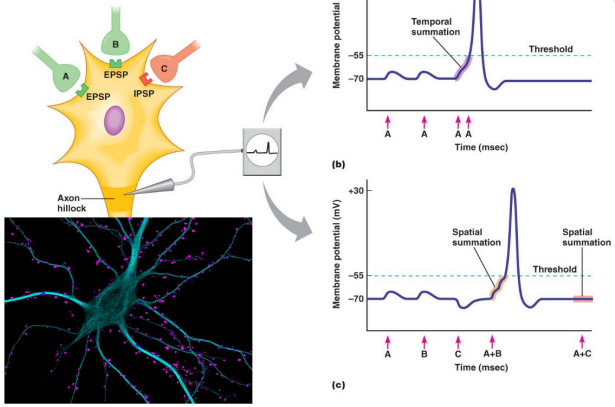
Central Synaptic Transmission

- Postsynaptic Summation of EPSPs and IPSPs



Temporal Summation:

- Repeated activation of the same synapse at brief intervals can produce a larger synaptic response

Spatial Summation:

- Activation of different synapses at around the same time can produce a larger synaptic response (for EPSPs)
- An IPSP can cancel an EPSP if they occur around the same time

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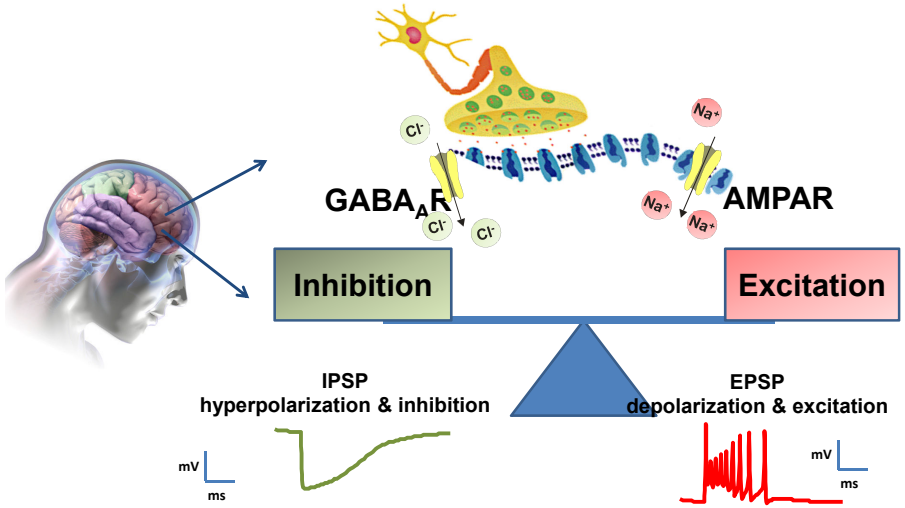
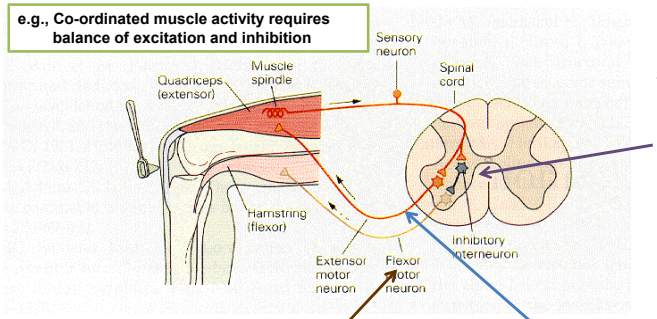
Brain function: A balance of excitation and inhibition



Brain function: A balance of excitation and inhibition

e.g., Co-ordinated muscle activity requires balance of excitation and inhibition



Synapses in the spinal cord

- Excitatory or Inhibitory
- EPSPs or IPSPs
- Glutamate depolarizes (EPSP) extensor motor neuron and also the inhibitory interneuron
- Inhibitory interneuron releases GABA to hyperpolarize (IPSP) flexor motor neuron

Reduced Activation of the flexor muscle

- Less action potentials in the motor neuron axons
- Less depolarisation in the motor neuron cell soma

Increased Activation of the extensor muscle

- More action potentials in the motor neuron axons
- More depolarisation of the motor neuron cell soma

What would happen if GABA or glycine inhibition in the spinal cord was blocked? E.g., a drug called "strychnine"?

I hope you enjoy Phys 1A

& further Physiology and/or

Neuroscience study!

Further study of Neuro Physiology:

- NEUR 2201: Fundamentals of Neuroscience (S2, convenors Dr Goulton, Dr Moorhouse)
- NEUR 3121: Molecular and Cellular Neuroscience (S1, convenor Dr Lewis)
- NEUR 3221: Neurophysiology (S2, convenor Dr Power)
-
- Neuroscience or SOMS honours

(see http://medicalsciences.med.unsw.edu.au/students/soms-honours/overview; http://medicalsciences.med.unsw.edu.au/students/undergraduate/neuroscience/honours)

- Masters, PhD