Lec 1 Nervous System Communication

We can respond to external stimuli voluntarily and involuntarily (autonomic nervous system).

Internal stimuli are sensed by the autonomic nervous system (involuntary). Brain processes sensory input. Understanding the peripheral nervous system (somatic nervous system and autonomic nervous system) helps us understand the central nervous system. The autonomic nervous system is divided into the parasympathetic and sympathetic nervous system.

The 2 divisions of the Autonomic Nervous System: Parasympathetic Vs Sympathetic nervous system

- Ach is the main transmitter in parasympathetic nervous system.

- Noradrenaline is the main transmitter in the sympathetic nervous system. Noradrenaline acts on alpha and beta adrenoceptors.

Evidence of chemical transmission by nerves via neurotransmitters: Generic requirements for neurotransmission

Loewi: Could stimulate the denervated heart in the right container from the chemical produced from the vagus nerve connected to the other heart on the left side.

- Nerves have electrical transmission within them and chemical transmission outside them.

-Ach doesn't just act on muscarinic receptors of the heart, it also acts on nicotinic receptors in the somatic nervous system (voluntary nervous system). It contracts muscles by acting on nicotinic receptors and slows the heart rate through muscarinic receptors.

- ➔ Ligand gated receptors are faster, GPCR are slower.
- ➔ Signalling pathways (Loewi's experiment: one nerve excites, one nerve inhibits)
- ➔ Inactivation (cuz don't want the receptor to be continually stimulated).

Most knowledge about the brain began from analysing the peripheral nervous system.

Insights from peripheral nerves

Transmitters & receptors localize to specific pathways.

- Ach acts on muscarinic receptors of the heart via the parasympathetic nervous system and acts on nicotinic receptors via the somatic nervous system.
- The somatic motor nervous system is a one neuron system that goes to the skeletal muscle, whereas the autonomic nervous system is a 2 neuron system--- the nerve fibre leaving the Central Nervous System along the different parts of the brain and the spinal cord (the preganglionic fibres) which always use Acetylcholine as the neurotransmitter.
- All preganglionic neurons (leaving the central nervous system) use Ach as the neurotransmitter to act on the peripheral nervous system. Ach released from preganglionic neuron always acts on nicotinic receptors.

- Parasympathetic nervous system postganglionic neurons release Ach to act on muscarinic receptors.
- Sympathetic nervous system has short preganglionic fibres. The sympathetic nervous system postganglionic neurons release Noradrenaline to act on alpha and beta adrenoceptors. Noradrenaline acts on beta adrenoceptors of the heart to increase heart rate.

- Exception: Postganglionic neuron of Sympathetic nervous system releases Acetylcholine to act on muscarinic receptors of the sweat glands.

CNS neurotransmitters beyond noradrenaline and acetylcholine

There are over 40 transmitters which variously contribute to central neuronal activity.

- Some of these transmitters are wide spread, others are highly localised (e.g. orexins)
- Recognise CNS transmitter localisation / function

Monoamines:

dopamine, serotonin

Amino acids:

GABA, glutamate, glycine, aspartate

- Amino acids are not just the building blocks of protein, they also function as neurotransmitters.

Peptides:

opioids, NPY, CCK, orexins

- The peptides that amino acids normally make can also function as neurotransmitters.

Other:

ATP, Nitric Oxide

Nerve structure and function

- Enables combination of electrical and chemical signalling

- Damage to the nerve will not only affect the electrical transmission but will also affect the chemical transmission of the nerve terminal at the end.

Electrical signalling along axon

- Common to all nerves

Chemical signalling

- Unique for a given nerve

Signals it recognises:

• Dendritic Receptors

Transmitter it utilises:

• Synthesis, Storage

• Release, Inactivation

• Receptors on target cell

How do drugs act?

"… for chemotherapy the principle is true that corpora non agunt nisi fixata." Ehrlich, 1913

- Drugs do not act unless bound

- Receptors
- Ion channels
- Carrier molecules
- Enzymes
- DNA

- Drugs affect molecules involved in cellular function

Receptor localization and cellular signalling

Ligand-gated ion channels/ ionotropic receptors	**GPCR/ metabotropic receptor**	**Kinase-linked receptors**	**Nuclear receptors**
- allows ion flow - can hyperpolarize (less excitable)/depolarize (more excitable) - Fast response (e.g. Ach nicotinic receptor)	- Slow response (e.g. Ach muscarinic receptor) - Can interact with an ion channel or an enzyme - Activate a signalling pathway that amplifies signals to produce a cellular effect	- The receptors themselves are enzymes which are waiting to be phosphorylated. They are waiting for the drug to bring them together.	- The drug needs to cross the membrane or need a carrier. Not every drug has access to the brain.

- Drugs need to have access to the molecular target to bind to it.

How drugs interact with receptors

➔ Full and partial agonists: Different agonists have different levels of response (i.e. have different levels of efficacy)

➔ Antagonists don't elicit a response; they bind to the receptor to prevent the binding of agonists. They prevent action by binding to the receptor.

➔ Allosteric modulators: E.g. Some drugs regulate the GABA receptor to change the affinity of GABA to the receptor.