Synapses: sites of cell - cell contact that allows signal transmission between neurons and their target

In the CNS: synapse form between two neurons.

In the PNS: synapse form between two neurons, and between neurons + muscle.

Chemical synapse: type of synapse that release neurotransmittors to transmit signals across the synaptic cleft:

- Asymmetric synaptic terminals: vesicles in the pre-synaptic terminal, bound by synapsin on F-actin
  - During depolarisation synapsin is phosphorylated and releases NT vesicles.
  - Consist of an active zone at the presynaptic membrane containing proteins.
  - Vesicle loading: vesicle contain proton pump to generate gradient, vesicular Ach/Glutamate/GABA transporter exchanges H+ ions and NTs. **Different transporters can be immunofluorescent tagged to identify excitatory/ inhibitory synapses**
- Post-synaptic density in the post-synaptic terminal, contain neurotransmittor receptors.
  - Excitatory post synaptic terminals are found on dendritic spines, compared to inhibitory post synaptic terminals found on dendritic shaft or along the axon.
  - Differences in receptors, AMPA, NMDA, mGluR for excitatory, GABA, glycine for inhibitory
  - Differences in scaffolding proteins: PSD95 in excitatory PSD, Gephryin in inhibitory PSD.

Synaptogenesis in the CNS and PNS:

3-step pathway: Contact initiation between axon and target, differentiation of pre/post synaptic terminals, maturation of synapse.

- Contact initiation: Growth cone of the axon sense signals in the envrionment to make contact with its target
- Differentiation of pre/post synaptic terminals:
  - Differentiation and vesicle formation occur first in pre-synaptic terminals, followed by scaffolding assembly and receptor recruitment in the post-synaptic terminal.
  - **GFP probes show synapsin expression in excitatory pre-synaptic terminal before PSD95 expression**
- Maturation: following synaptogenesis in the CNS, synapses will be pruned by microglia based on their activity.

Factors involved in synaptogenesis: 2 types includes secreted factors and membrane bound factors.

- Secreted factors: e.g. Wnt, FGF, BDNF
  - An example: Wnt7a involved in synaptogenesis in cerebellar granular cells and mossy fibres.
  - In cerebellum, **Wnt7a sfrp1 antagonist lead to reduced growth cone area.**
  - **In hippocampus,** Wnt7a is involved in the formation of excitatory synapses only, **culturing neurons in Wnt7a medium led to increased formation of excitatory synapses, no significant difference in inhibitory synapses. Visualised with fluorescent tags on PSD markers.**
  - Wnt7a receptor: Frizzled-5 (Frz5): **hyperactivation lead to higher number of dendritic spines**
  - Wnt7a downstream protein: dishevelled (Dsh), **KO lead to similar effect as Wnt7a KO, decrease in synapse markers**
- Membrane bound factors: e.g. N-CAM, Neuroligin-neurexin, EphB-Ephrin
  - Neurexin-neuroligin adhesion molecules: **mutation in this adhesion complex associated with autism**
    - Neurexin (ligand), two types α and β, present in presynaptic terminals
    - Neuroligin (receptors), three types NLG1 (excitatory), NLG2 (inhibitory), NLG3 (both)
  - Interaction important for synapse maturation: **overexpression of NLG —increased synapsin marker expression**
  - **KO of three NLG does not affect synapse formation, but decreases firing rate and function.**

Formation of neuromuscular junction

- Before contact initiation, AchR is distributed evenly across muscle cells.
- Contact between presynaptic terminal and muscle causes AchR to aggregate at synapse, later stabilied.
- Agrin released by presynaptic terminal aggregates the AchR, **KO shows dispersed AchR in mice**
- Agrin interact with its receptor MuSK, via LRP4, and stabilised with scaffolding protein Rapsyn.
    - **KO experiments shows Rapsyn required to maintain AchR cluster, Agrin required to localise the nerve ending.**
- Wnt is also involved in AchR localisation
    - Wnt3 released by the postsynaptic terminal, create microclusters later stabilised by agrin
    - In absence of postsynaptic terminal, muscle cells release Wnt3a - inhibit Rapsyn expression via canonical pathway