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Review

Synaptic pathology: A shared mechanism in neurological disease

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ABSTRACT

Synaptic proteomes have evolved a rich and complex diversity to allow the exquisite control of neuronal communication and information transfer. It is therefore not surprising that many neurological disorders are associated with alterations in synaptic function. As technology has advanced, our ability to study the anatomical and physiological function of synapses in greater detail has revealed a critical role for both central and peripheral synapses in neurodegenerative disease. Synapse loss has a devastating effect on cellular communication, leading to wide ranging effects such as network disruption within central neural systems and muscle wastage in the periphery. These devastating effects link synaptic pathology to a diverse range of neurological disorders, spanning Alzheimer's disease to multiple sclerosis. This review will highlight some of the current literature on synaptic integrity in animal models of disease and human post-mortem studies. Synaptic changes in normal brain ageing will also be discussed and finally the current and prospective treatments for neurodegenerative disorders will be summarised.

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1. Introduction

The approximately one hundred billion neurons found within the human brain act in beautifully intricate arrangements to generate and control our every thought, memory, emotion and dream. They also control our ability to sense the world, to communicate those sensations to others and decide how to plan our lives. These remarkable abilities are only possible if neurons can efficiently coordinate with other cells in the network, and the transfer of information occurs at specialised compartments called synapses (Fig. 1).

Depending on the chemical signal released, synapses can have excitatory or inhibitory effects on the target cell. Excitatory synapses most commonly form on small dendritic protrusions known as spines, where the synapse can be isolated from the main dendritic branch and become highly specialised. Inhibitory synapses tend to form directly onto the dendritic branch or onto the neuronal cell soma, although some exceptions to this general rule do occur. Once formed, these synaptic contacts are not rigid

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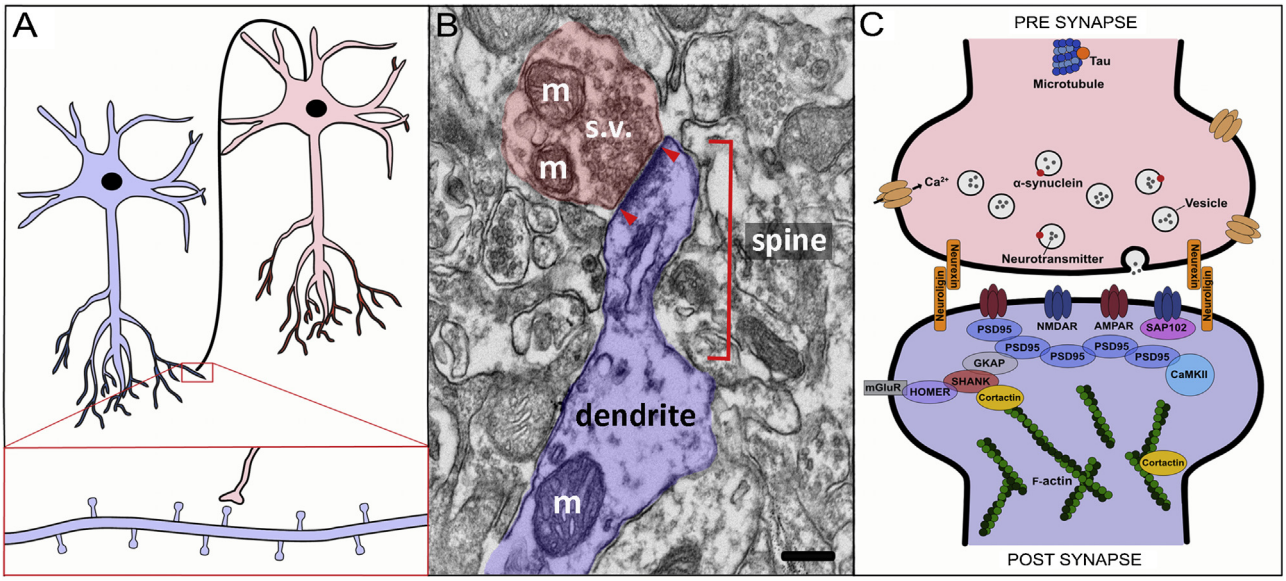

Fig. 1. Synaptic structure (A) Neurons within a network frequently communicate by passing excitatory messages from one cell (pink) to another (blue) at small compartments known as synapses. Excitatory synapses often occur between a presynaptic axon terminal and a postsynaptic dendritic spine (lower panel) and this is known as an axospinous synapse. (B) Electron micrograph from the mouse nucleus accumbens showing an axospinous synapse. The presynaptic terminal (pink) contains the machinery required to release small packets of neurotransmitter inside synaptic vesicles (s.v.) which when released, cross the synaptic cleft and act on the next cell (blue). Synapses require a lot of energy and two small mitochondria (m) can be seen inside the presynaptic terminal. The postsynaptic cell contains a clearly identifiable spine, protruding from the dendritic shaft. The spine head receives the synaptic message from the presynaptic cell at an electron dense accumulation of proteins known as the PSD (within the red arrowheads). Note the dendritic mitochondria (m) in close proximity to the spine. Scale bar = 100 nm. (C) Diagram highlighting a select few of the presynaptic and postsynaptic components of the synapse. Presynaptically, the microtubule-binding protein Tau can be found bound to microtubules and Ca^{2+}-permeable ion channels are located on the terminal's plasma membrane. Synaptic vesicles are presynaptic and contain α-synuclein in the membrane and neurotransmitters within their lumen. Neurexins protrude into the synaptic cleft, looking for their postsynaptic neuroligin partners and help hold the synapse in place. Postsynaptically, ionotropic glutamatergic receptors such as NMDA and AMPA receptors are found directly opposing the presynapse. These are held in place by scaffolding proteins such as PSD95 and SAP102, which form an integral part of the PSD. Other important scaffolding molecules such as Homer, GKAP and Shank combine to hold metabotropic glutamate receptors such as mGluR5 in place, in perisynaptic regions. Spine architecture is maintained by important structural proteins such as F-actin, which are found in the spine neck and base of the spine head. It is believed that interactions between Shank and cortactin allow synaptic changes to influence spine dynamics, via alterations in F-actin.

and can strengthen in response to increased activity or become shrunken and even lost following lack of activity (Trachtenberg et al., 2002). This plasticity is thought to play a fundamental role in the formation, storage and removal of memory (Lamprecht and LeDoux, 2004). Furthermore, spine dynamics can often be used as a quantifiable means of analysing circuit activity as spine number and morphology change in response to fluctuations in neuronal activity (Trachtenberg et al., 2002).

Given the critical role synapses play in normal neurophysiology, it is not surprising that loss of synaptic integrity may underlie many of the most common neurodegenerative diseases. Synaptic dysfunction or synaptic loss often precedes late-stage features of many neurological conditions such as Alzheimer's disease (Selkoe, 2002), Motor Neuron disease (Fischer et al., 2004; Frey et al., 2000), Huntington's disease (Li et al., 2003), Parkinson's disease (Day et al., 2006; Bellucci et al., 2016) and multiple sclerosis (Mandolesi et al., 2015). While synaptic pathology is a common feature of these disorders, the nature of the synaptic change is not necessarily consistent, which illustrates how critical normal neuronal function is for brain health. Given the plasticity of synapses and the malleability of dendritic spines, it raises the possibility of exploiting these features as potential therapeutic targets. If we can prevent synaptic loss or strengthen existing connections between neurons, we may be able to slow or even reverse disease-driven neurological change.

In this review, we will highlight a selection of neurodegenerative disorders that exhibit synaptic dysfunction as an early feature of the disease, discuss the changes that occur during normal brain ageing and discuss the current and prospective ways in which synaptic function can be targeted for therapeutic exploitation.

1.1. Synapse structure

Synapses are the point of contact between two neurons and can exist as either electrical or, more often, chemical synapses. In both cases the cells do not touch, but communicate by passing ions (electrical synapse) or neurotransmitters (chemical synapse) across a small gap known as the synaptic cleft. Adhesion proteins such as neuroligins and neurexins span this cleft, physically holding the synapse in place (Sudhof, 2008) (Fig. 1C). Intriguingly, these cleft-spanning proteins are critical for synaptic integrity and mutations in the genes for these proteins have been implicated in neurological disorders (Sudhof, 2008).

The presynaptic bouton contains the complex machinery required for synthesis, storage and release of neurotransmitters (Südhof, 2012) (Fig. 1C). This is a tightly regulated process, ensuring efficient and accurate transmitter release following action potential propagation. Synaptic vesicles, packed with neurotransmitter, undergo calcium-dependent fusion with the presynaptic membrane and release their contents into the synaptic cleft. Altered protein homeostasis in the presynaptic terminal has been linked to neurological disorders. The abundant presynaptic protein alpha-synuclein forms striking pathological aggregates in a group of neurological disorders known as synucleinopathies (Goedert, 2001).

Once released from the presynaptic terminal, neurotransmitters cross the synaptic cleft and interact with receptors in the postsynaptic membrane. Ligand-gated ion channels (ionotropic receptors) open rapidly upon neurotransmitter binding and allow the direct flow of ions into the postsynaptic neuron, altering the local membrane potential. G-protein coupled receptors (GPCRs; metabotropic receptors) induce an array of downstream signalling cascades fol-