Synapse Function in Dementia and Neurodegenerative Disorders

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Introduction

Neurons in the brain are connected into networks by specialised contacts, called synapses. Chemical synapses constitute the majority of synaptic contacts in the brain. They consist of the presynaptic bouton, a part of an axon containing vesicles with the neurotransmitter, which is apposed to the postsynaptic part on the dendrite of another neuron containing the neurotransmitter receptors (Fig. 1). Neurons release neurotransmitters at synapses to transmit signals to other neurons in the network. Synapses therefore play a key role in all brain functions including learning and memory. Studies in humans and animal models indicate that synaptic function is affected in a range of neurodegenerative disorders. In this review, we discuss the evidence supporting the idea that synaptic dysfunction is one of the earliest and most common abnormalities preceding neuronal death in neurodegenerative disorders and is a factor which may directly contribute to the pathological processes causing cognitive impairment. Possible mechanisms of synapse dysfunction and future strategies for its treatment are also briefly discussed.

Synaptic Dysfunction Occurs at Early Stages of Neurodegenerative Disorders

The development of functional neuroimaging allowed significant advances in our understanding of impaired synaptic function during the progression of neurodegenerative diseases. Assessment of glucose metabolism using fluorodeoxyglucose F-18 imaged by positron emission tomography (18F-FDG-PET) revealed already impaired neuronal and synaptic activity at early stages of dementia (1). Abnormal network activity has also been found in several studies using functional magnetic resonance imaging (fMRI) to study early functional changes in the brains of patients with mild cognitive impairment (MCI) (2).

Analysis of the correlation between synaptic transmission and morphological changes of synaptic connectivity in animal models of Alzheimer’s disease, which is the most common form of dementia, has shown that synaptic function is affected prior to the actual loss of synaptic connections (3).

Synapse Architecture is Affected in Neurodegenerative Disorders

Synapses may exist for many years and the stability of their well-defined architecture is rendered by a number of scaffold proteins that accumulate at synapses, including cell adhesion molecules and cytoskeletal components (Fig. 1). Changes in the ultrastructure of the synaptic contacts have been observed by electron microscopy in postmortem human brain tissue and mouse models of Alzheimer’s disease (4,5) and Huntington’s disease (summarised in (6)). Furthermore, different modalities of neuroimaging in subjects with early dementia pathology have found that impaired memory is linked with microstructural changes in the brain (7).

Experiments with cultured neurons revealed that changes in the synapse ultrastructure and synaptic cytoskeleton levels occur within hours after exposure of neurons to the amyloid precursor protein (APP) cleavage product Aβ, a peptide that accumulates in brains of individuals affected by Alzheimer’s disease, which plays an important role in disease pathogenesis (8). This observation indicates that alterations in synapse structure are among the first structural changes occurring in neurons exposed to Aβ and suggests that Aβ targets directly the molecular machinery responsible for the maintenance of the synapse architecture.

The synaptic scaffold, consisting of cell adhesion molecules linking pre- and post-synaptic membranes, associated intracellular scaffolding proteins and the actin cytoskeleton, is the major determinant of the synaptic architecture in the brain (9). While this scaffold provides a stable framework, it can undergo profound reorganisation over time, which is found to be critical for synaptic maturation and turnover. Analysis of hippocampal neurons in mice with increased Aβ production showed increased levels of actin filaments at the postsynaptic site of synapses, located in close proximity to Aβ plaques (10), suggesting Aβ-induced alterations in the synaptic architecture in vivo. Together with cell culture experiments and similar observations in human patients, these experiments indicate that the synapse structure is affected at the early stages of the disease and this process could play a direct role in the synapse loss preceding neuronal death.

The mechanisms by which Aβ impacts synapse structure and function in Alzheimer’s disease, and the mechanisms of synapse loss and dysfunction in other neurodegenerative disorders remain poorly understood. Soluble and oligomerised Aβ is found in the diseased brain and forms extracellular plaques. While there is still controversy on the relative contribution of soluble and aggregated Aβ to disease pathology (11), important advances have been made over the last decade by studying Aβ-induced changes to the structure and intracellular signalling pathways at synapses in the brain. A well-established concept is that Aβ alters the localisation of α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors at the postsynaptic membrane,
impacting on synaptic transmission and eventually causing disruption of the postsynaptic integrity (Fig. 1 [1] and [2]) (12). This is believed to be a major contributing factor to the excessive pathologic stimulation of CNS neurons that is observed after the exposure of the neurons to Aβ.

More recent studies have demonstrated the involvement of several signalling pathways at the postsynaptic site in response to Aβ, including EphA4 and AMPK mediated signalling events (13,14).

Synapse Loss

Studies using post-mortem human brain tissue indicate that a cognitive decline in humans correlates best with the loss of synapses in the brain (summarised in (15)), suggesting that early synapse dysfunction is followed by synapse loss. A reduction in synapse density in the brain is already observed in individuals showing a mild cognitive decline, and a further reduction in synapse density is observed in individuals suffering from Alzheimer’s disease (16). Synapse loss was therefore found to be the major correlate of cognitive impairment in neurodegenerative disorders (17). Synaptic dysfunction and synapse loss have been reported not only in Alzheimer’s disease but also in human brain tissues affected by other neurodegenerative disorders such as Parkinson’s disease (18), Huntington’s disease (19) and amyotrophic lateral sclerosis (20). Studies in animal and cellular models analysing different stages of the disease indicate that changes in synapse number and composition occur before neuronal death in Alzheimer’s disease, Huntington’s disease (21), and amyotrophic lateral sclerosis (22). These observations indicate that abnormalities in synapse function occur at the earliest stages of these and probably other neurodegenerative diseases.

Alterations in the synapse architecture outlined above suggest that changes in the synaptic scaffold accompany synapse loss in neurodegenerative disorders. In agreement, biochemical analysis revealed changes in the levels of a number of synaptic proteins involved in synapse formation and maintenance in the post-mortem human brain tissue affected by Alzheimer’s disease and other disorders, including cell adhesion molecules (Fig. 1 [3]) (23-25) and cytoskeletal components (Fig. 1 [4]) (26). Elevated levels of the breakdown products of synaptic cell adhesion molecules and scaffolding proteins, which have been observed in brains of transgenic mouse models of Alzheimer’s disease and in brain tissue and cerebrospinal fluid of patients with Alzheimer’s disease and other dementia syndromes (27) suggest that disassembly of the synaptic scaffold is accompanied by the proteolysis of its components. Aberrant intracellular signalling (13,14) affecting the posttranslational modifications of the synaptic scaffold proteins could be another factor contributing to the synapse disassembly by modifying the interactions between its neurotransmitter receptors, the postsynaptic scaffold and the postsynaptic cytoskeleton (Fig. 1 [5]).

Synapse Loss and Changes in the Synapse Structure Correlate with the Impaired Synaptic Plasticity in Neurodegenerative Disorders

Synaptic plasticity, characterised by the long-term changes in the efficacy of synaptic transmission, plays a key role in learning and memory formation. Changes in the synaptic efficacy depend on the structural reorganisation of the synaptic contacts and adjustments in their numbers.
The long-term potentiation of synaptic transmission has been shown to be inhibited by Aβ (28), suggesting that abnormalities in synaptic plasticity directly contribute to cognitive impairment in Alzheimer’s disease. Changes in the synapse function and their ability to undergo plastic changes have been described in mouse models of Parkinson’s disease (summarised in (29)), amyotrophic lateral sclerosis (30), and Huntington’s disease (6), indicating that they can serve as common targets in designing new treatments for these disorders.

Current and Future Strategies for Treatment of Synaptic Dysfunction in Neurodegenerative Disorders

While there is still no efficient treatment targeting pathogenesis and progression of neurodegenerative disorders, research into a range of treatment strategies is currently being undertaken. These strategies include: targeting pathogenic factors such as Aβ in its soluble or aggregated state, neurofibrillary tangles or tau protein; inhibiting pathological signalling cascades that are activated in response to these pathologic factors, decoupling glutamate-induced excitotoxicity from intracellular responsive cues and structurally protecting synaptic connections by stabilising synaptic architecture.

Drugs targeting neurotransmission are already used to treat Alzheimer’s disease with some limited success. Inhibitors of cholinesterase are aimed at compensating for the loss of basal forebrain cholinergic neurons by prolonging the life time of the neurotransmitters released by the remaining cells. Memantine, a non-competitive NMDA receptor antagonist, is used to reduce overstimulation of NMDA receptors and associated neuronal death in this disease (summarised in (31,32)). The efficacy of these drugs in alleviating synapse dysfunction in other neurodegenerative disorders is under investigation.

These current treatments however only slowly or temporarily alleviate dementia symptoms in Alzheimer’s disease. Hence, other disease modifying drugs that either prevent synapse disassembly or promote the reestablishment of neuronal synapses are urgently needed. The molecular mechanisms of the changes in synapse numbers and structure in neurodegenerative disorders remain in the focus of intense research, which may help to identify new strategies for treatment.

References