NKMAX

Neuroscience

Neurological Disorder

Neurodegenerative disease

Neurodegeneration is the progressive loss of structure or function of neurons, including death of neurons. Many neurodegenerative diseases including amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD) occur as a result of neurodegenerative processes. Such diseases are incurable, resulting in progressive degeneration and/or death of neuron cells. As research progresses, many similarities appear that relate these diseases to one another on a sub-cellular level.

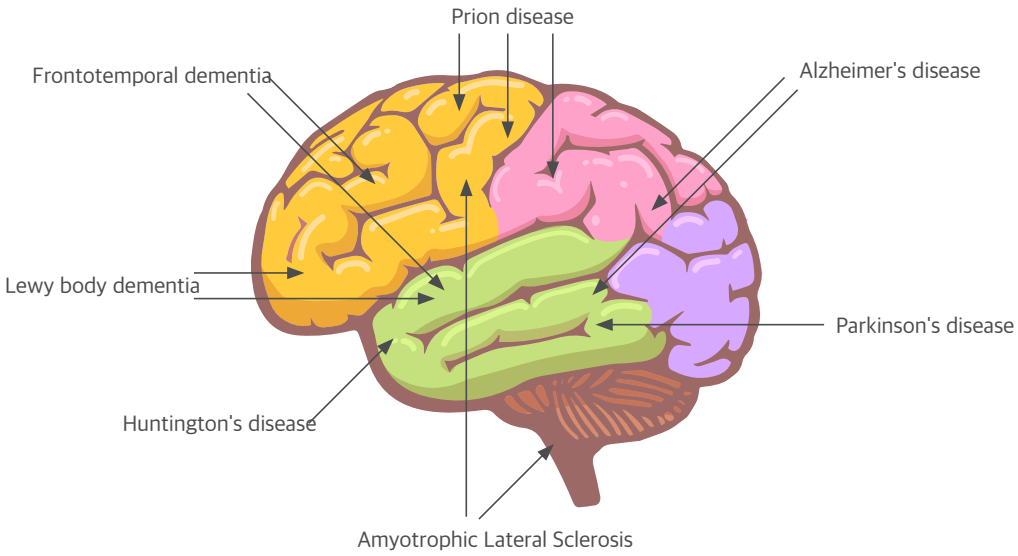

Figure 1. Overview of the anatomical location of the neurodegenerative disorders.

Neurodegeneration can be found in many different levels of neuronal circuitry ranging from molecular to systemic. The most common neurodegenerative disorders are amyloidosis, tauopathies, α-Synucleinopathies, and transactivation response DNA binding protein 43 (TDP-43) proteinopathies. Abnormal protein conformations in these disorders and their cellular and neuroanatomical distribution constitute the major histopathologic features essential in making a specific neuropathologic diagnosis.

Examples of protein accumulations within neurons include tau in neurofibrillary tangles (NFTs) or Pick bodies, α-synuclein in Lewy bodies, and TDP-43 in neuronal cytoplasmic and neuronal intranuclear inclusions. Protein accumulations within astrocytes include tau in tufted astrocytes (TAs), astrocytic plaques (APs), and thorn-shaped astrocytes (TSAs). Protein accumulations within oligodendroglia include tau in coiled bodies and α-synuclein in glial cytoplasmic inclusions. These abnormal protein aggregates are composed of intrinsic neuronal proteins and other cellular components, in contrast to neuronal inclusions found in viral infections where the protein is foreign.

Table 1 Overview of established neurodegenerative disease genes

Disease	Gene	Protein	Inheritance	Relevance to pathogenesis
AD	*APP*	Amyloid β (Aβ) precursor protein	Dominant	Altered Aβ production (Aβ42/Aβ40 ratio ↑) and aggregation
AD	*APOE*	Apolipoprotein E	Risk factor	Unknown
AD	*PSEN1*	Presenilin 1	Dominant	Altered Aβ production (Aβ42/Aβ40 ratio ↑)
AD	*PSEN2*	Presenilin 2	Dominant	Altered Aβ production (Aβ42/Aβ40 ratio ↑)
PD	*SNCA*	α-Synuclein	Dominant	Neurotoxicity by aggregation of α-synuclein
PD	*PRKN*	Parkin	Recessive	Impaired protein degradation via proteasome
PD	*DJ1*	DJ-1	Recessive	Impaired oxidative stress response
PD	*PINK1*	PTEN-induced putative kinase 1	Recessive	Mitochondrial dysfunction
PD	*LRRK2*	Leucine-rich repeat kinase 2; dardarin	Dominant	Unknown
FTD	*MAPT*	Microtubule-associated-protein tau	Dominant	Altered tau-production (tau-isoform 4R/3R ratio ↑), and/or altered binding to microtubules
ALS	*SOD1*	Superoxide dismutase 1	Dominant and Recessive	Protein misfolding/aggregation, and/or impaired oxidative stress response
ALS	*ALS2*	Alsin	Recessive	Impaired neuroprotection
HD	*HD*	Huntingtin	Dominant	Unknown
Prion	*PRNP*	Prion protein (PrP)	Dominant and Risk factor	Transformation of PrP^{c} into PrP^{sc}

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; FTD, frontotemporal dementia; ALS, amyotrophic lateral sclerosis; HD, huntington's disease.

Neuroinflammation

Neuroinflammation is defined as an inflammatory response within the brain or spinal cord. This inflammation is mediated by the production of cytokines [interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)α], chemokines (CCL2, CCL5, CXCL1), reactive oxygen species, and secondary messengers (NO and prostaglandins). These mediators are produced by resident central nervous system (CNS) glia (microglia and astrocytes), endothelial cells, and peripherally derived immune cells. There are immune, physiological, biochemical, and psychological consequences of these neuroinflammatory responses.

Microglial, the innate immune cells of the CNS, is a central player in neuroinflammation. Activated microglia rapidly alter their transcriptional profiles and produce inflammatory cytokines and chemokines. Depending on the context, the production of cytokines and chemokines can facilitate the recruitment of leukocytes to the brain. Besides, the high degree of inflammation has primary and secondary damage and can also have chronic neuroinflammatory components that may never resolve. This degree of neuroinflammation is associated with immune responses induced by autoimmune diseases like multiple sclerosis (MS) and autoimmune encephalomyelitis.

Synaptic Proteins and Receptors

Synaptic Adhesion Molecules

Synapse is basic structural units for communication between neurons and is essential for neuronal function. The cell to cell adhesion system is involved in many aspects of neuronal development including neuronal cell migration, axon bundle formation, synapse formation, and formation of a complex glial networks that surround axons and synapses. The cell adhesion molecule (CAM) proteins are involved in all stages of synapse formation and stabilization, providing 'bridges' between pre- and post-synaptic sites. Alteration of the interactions of CAMs leads to structural and functional impairments, which results in many neurological disorders, such as autism, Alzheimer's disease, and schizophrenia.

Several families of CAM are recognized, including neurexins and neuroligins, leucine-rich repeat transmembrane neuronal proteins (LRRTMs), N-cadherin/β-catenin, ephrins and Eph receptors, synaptic cell adhesion molecule (SynCAM), and integrins. Most CAMs (e.g., neurexins and neuroligins, SynCAMs, and β1 integrin) localize at the center of the synapse whereas others (e.g., the N-cadherin/β-catenin system) are found at the outer rims of presynaptic active zones and postsynaptic regions.

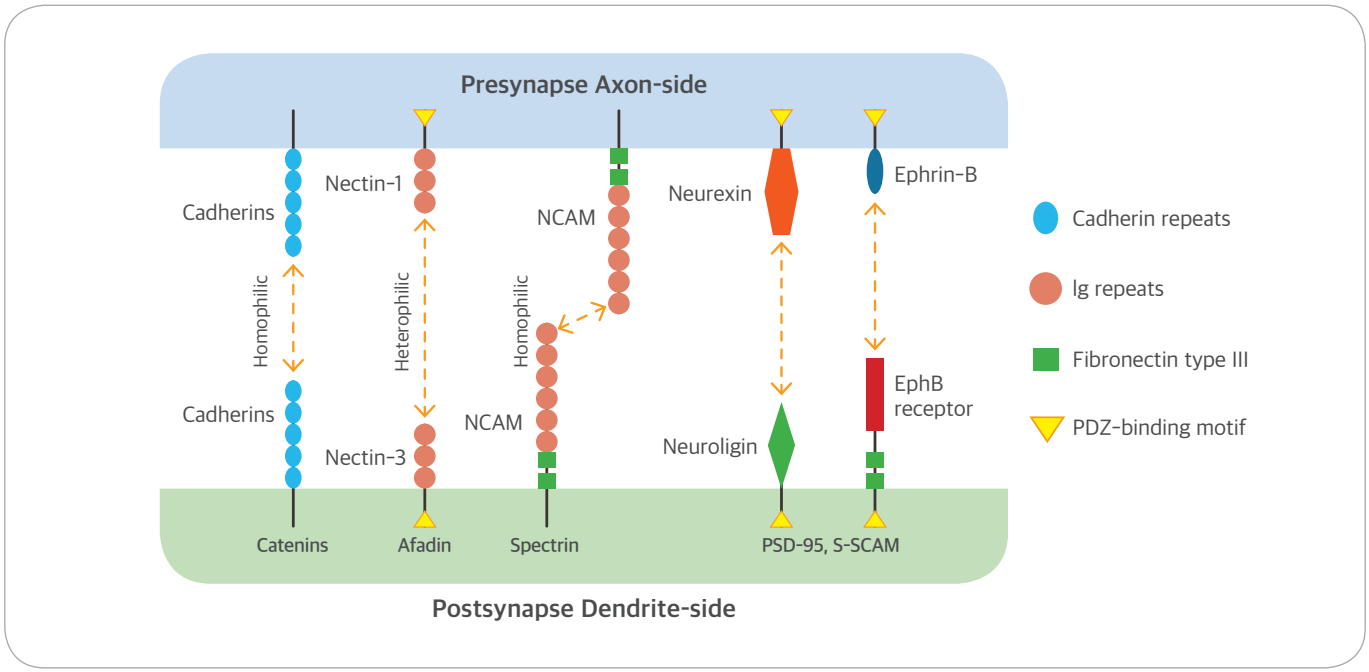

Figure 2. Molecular composition of the synapse.

Synaptic Vesicle Cycle

Presynaptic nerve terminals are highly specialized vesicle-trafficking machines. Neurotransmitter release from these terminals is sustained by constant local recycling of synaptic vesicles independent from the neuronal cell body. This independence places significant constraints on the maintenance of synaptic protein complexes and scaffolds. Key events during the synaptic vesicle cycle such as exocytosis and endocytosis require formation and disassembly of protein complexes.

Neuronal signals travel along axons and trigger the opening of voltage-gated calcium (Ca^{2+}) channels in presynaptic terminals. The influx of Ca^{2+} initiates a series of events leading to the fusion of synaptic vesicles to the presynaptic membrane at active zones. This results in the release of neurotransmitters into the synaptic cleft and the propagation of signals downstream via the actions of various postsynaptic receptors. Synaptic vesicles in the presynaptic terminals are retrieved from the membrane, reacidified, and refilled with neurotransmitters for reuse. This dynamic process of synaptic vesicle recycling is critical for maintaining normal synaptic function.

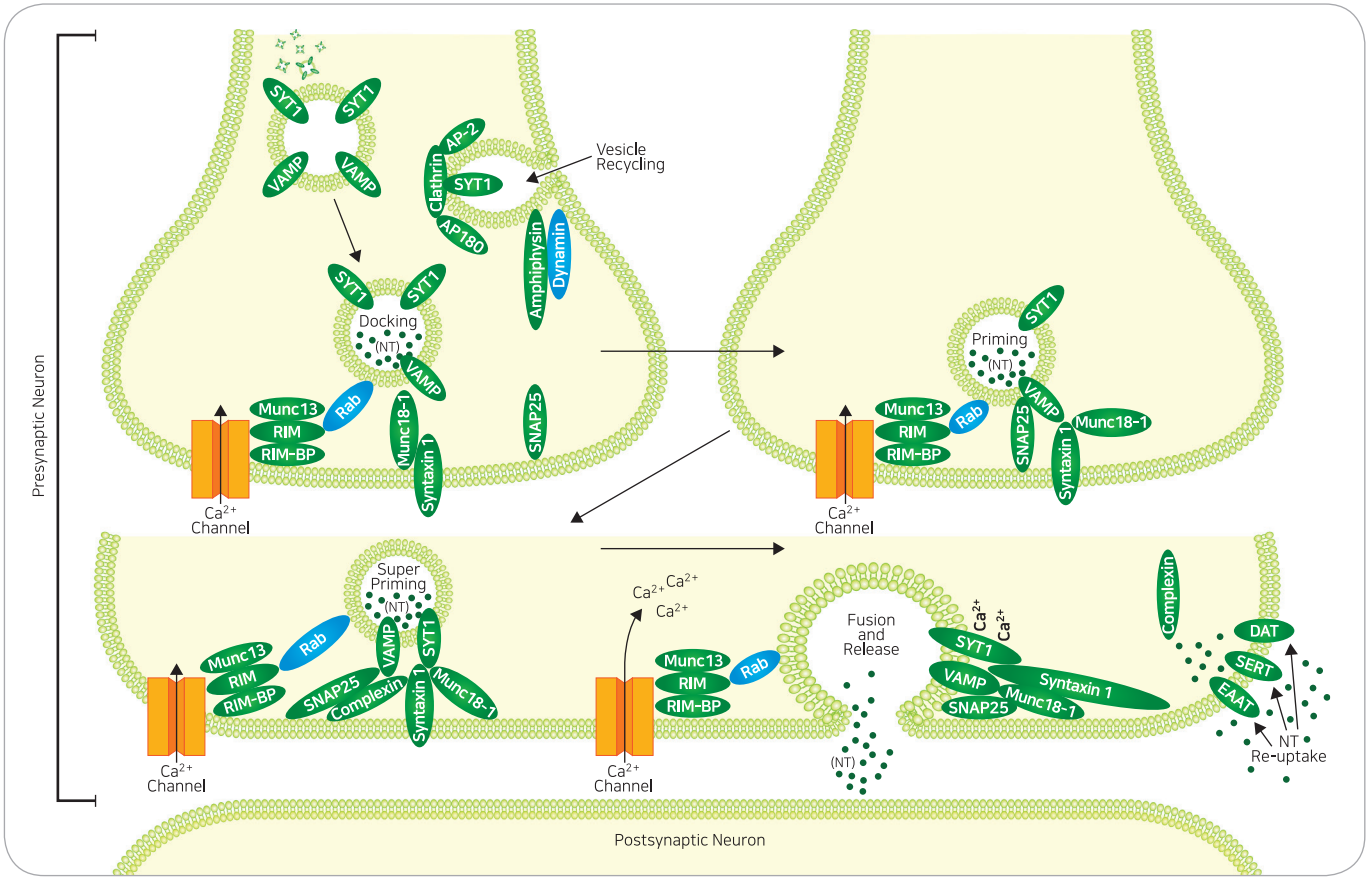

Figure 3. The pathway of a synaptic vesicle (SV) in the nerve terminal is divided into many stages. 1: Empty synaptic vesicles take up neurotransmitters (NTs) by active transport into their lumen using an electrochemical gradient that is established by a proton pump activity. 2: Filled synaptic vesicles are translocated to the active zone. 3: Synaptic vesicle attached to the active zone of the presynaptic plasma membrane but, to no other component of the presynaptic plasma membrane, in a targeted reaction (docking). 4: Synaptic vesicles are primed for fusion to be able to respond rapidly to a Ca^{2+} signal later. 5: Ca^{2+} influx through voltage-gated channels triggers neurotransmitter release in less than 1 msec. Ca^{2+} stimulates the completion of a partial fusion reaction initiated during priming. 6: Empty synaptic vesicles are coated by clathrin and associated proteins in preparation for endocytosis. 7: Empty synaptic vesicles shed their clathrin coat, acidify via proton pump activity, and retranslocate into the backfield of the nerve terminal. This dynamic process of synaptic vesicle recycling is critical for maintaining normal synaptic function. Precise release of neurotransmitters depends on the equilibrium between vesicular fusion during exocytosis and membrane retrieval during endocytosis.

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