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Review

Neurodegenerative disorders share common features of "loss of function" states of a proposed mechanism of nervous system functions

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ABSTRACT

Neurodegenerative disorders are highly heterogeneous for the locations affected and the nature of the aggregated proteins. Nearly 80% of the neurodegenerative disorders occur sporadically, indicating that certain factors must combine to initiate the degenerative changes. The contiguous extension of degenerative changes from cell to cell, the association with viral fusion proteins, loss of dendritic spines (postsynaptic terminals), and the eventual degeneration of cells indicate the presence of a unique mechanism for inter-cellular spread of pathology. It is not known whether the "loss of function" states of the still unknown normal nervous system operations can lead to neurodegenerative disorders. Here, the possible loss of function states of a proposed normal nervous system function are examined. A reversible inter-postsynaptic functional LINK (IPL) mechanism, consisting of transient inter-postsynaptic membrane (IPM) hydration exclusion and partial to complete IPM hemifusions, was proposed as a critical step necessary for the binding process and the induction of internal sensations of higher brain functions. When various findings from different neurodegenerative disorders are systematically organized and examined, disease features match the effects of loss of function states of different IPLs. Changes in membrane composition, enlargement of dendritic spines by dopamine and viral fusion proteins are capable of altering the IPLs to form IPM fusion. The latter can lead to the observed lateral spread of pathology, inter-neuronal cytoplasmic content mixing and abnormal protein aggregation. Since both the normal mechanism of reversible IPM hydration exclusion and the pathological process of transient IPM fusion can evade detection, testing their occurrence may provide preventive and therapeutic opportunities for these disorders.

Contents

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; AMPAR, AMPA receptor; ADEM, acute disseminated encephalomyelitis; APP, amyloid precursor protein; CBD, cortico-basal degeneration; DHA, docosahexaenoic acid; EEG, electroencephalogram; EFA, essential fatty acid; EM, electron microscopy; ECM, extracellular matrix; EPSP, excitatory postsynaptic potential; FTD, fronto-temporal dementia; GABA, gamma-aminobutyric acid; GluR, glutamate receptor; GluR1, GluA1 subunit of AMPAR; HIV, human immunodeficiency virus; HSV1, herpes simplex virus 1; IPL, inter-postsynaptic functional LINK; IPM, inter-postsynaptic membrane; LBD, lewy body disease; L-DOPA, L-3 4-dihydroxyphenylalanine; LINK, inter-postsynaptic functional link; LTP, long-term potentiation; MCI, mild cognitive impairment; MSA, multi-system atrophy; NMDA, *N*-methyl-D-aspartic acid; PC, phosphatidyl choline; PD, Parkinson's disease; PE, phosphatidyl ethanolamine; PIP2, phosphatidylinositol 4,5-bisphosphate; PLS, primary lateral sclerosis; PrP^{C}, prion protein cellular; PrP^{SC}, prion protein scrapie; PSP, progressive supranuclear palsy; Postsynapse, postsynaptic terminal or dendritic spine; SNARE, SNAP (soluble NSF attachment protein) receptor; SNPc, substantia nigra pars compacta; Spine, dendritic spine or postsynaptic terminal; TDB, trans-active response DNA binding protein (TARDBP); VTA, ventral tegmental area.

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1. Introduction

It is not yet known how the nervous system operates to produce internal sensations of various higher brain functions such as perception, memory and consciousness. Parallel to this, the underlying mechanism that leads to a large number of neurodegenerative disorders has remained enigmatic. There may be a relationship between these two. This situation is reminiscent of the pre-DNA era when a lack of knowledge of both the normal genetic mechanism and that of the genetic disorders existed at the same time. Observations about the autosomal recessive nature of inheritance of the "inborn errors of metabolism" by Archibald Garrod in 1908 alone was sufficient to indicate the existence of the genetic material in pairs. However, working back from the observed loss of function states towards the functional units was delayed for several reasons [181,230]. Taking lessons from this historical context, the examination of various neurodegenerative disorders can be carried out first to enlist their common features and examine whether they match the "loss of function" states of any proposed mechanism of nervous system functions. Since in the case of the nervous system a very large number of observations can be made from both the normal and pathological conditions at multiple levels, this is a feasible approach. In this context, the present work examines the semblance hypothesis [212,215], which explains the nervous system features observed both from the third- and first-person frames of reference. Due to biological variations, overlapping findings from different neurodegenerative disorders are used for this purpose and are listed below.

A systematic examination of a large number of neurodegenerative disorders enabled the identification of the following common features. (1) Many disorders exhibit contiguous lateral spread of pathology between neurons within the same neuronal order that cannot be explained by trans-synaptic spread alone [9,53]. In primary lateral sclerosis (PLS), which affects cortical motor neurons, nearly half of the cases show contiguous spread [63]. Amyotrophic lateral sclerosis (ALS) frequently initiates with local spread of pathology [179,119], that still lacks a cellular-level explanation [20]. Animal models of tau pathology have shown lateral spread between adjacent neurons [46,53]. In synucleopathies, α-synuclein spreads to the neighboring cells [118,133,55]. Other examples are also reviewed [148,79]. (2) The abnormally expressed proteins both within the cytoplasm and in some cases outside the cells often become aggregated [114]. Electron microscopic (EM) examinations have shown the presence of protein aggregates of enriched β-pleated sheet structures of β-amyloid, tau and α-synuclein [75,182], non-amyloid granular fibrils of TDP43 inclusions [210,138], prion proteins, ubiquitin and other proteins. (3) Considerable heterogeneity has been observed in the genetic factors [25,176,191] and in the nature of mis-folded proteins expressed in various neurodegenerative [179] and neurodevelopmental [186] disorders. (4) Severe heterogeneity in clinical features makes these disorders part of a spectrum of disorders [185,123]. In addition, multiple disease types can occur in one patient. (5) 80% of these disorders occur sporadically [174] indicating the possibility of a unique combination of conditions triggering the pathology. (6) Cognitive defects and hallucinations are common features of advanced neurodegenerative diseases. (7) Dopamine, known to promote motivation-induced associative learning [233,234] is associated with various neurodegenerative disorders. Artificially increasing dopamine relieves symptoms of hypokinetic movements and dopamine blockers are used to prevent hallucinations in neurodegenerative disorders. (8) Dendritic spine loss and eventual neuronal death are common features [80]. (9) Glial cells are involved in different neurodegenerative disorders [141,86]. (10) Infections, particularly by enveloped viruses, are associated with neurodegenerative changes [54,108,238,88]. (11) Aging is an important etiological factor associated with different primary neurodegenerative disorders [153].

The lateral spread of protein aggregates between the cells necessitates pathology to cross the bilayers of two adjacent lipid membranes, requiring the formation of at least a tunneling nanotube between the cells [128], which is demonstrated only in a few conditions. This led to the search for prion-like activity of different proteins [195,121,127,67,102,175]. However, except for a few disorders, evidence for prion-like proteins having self-

templating replication is lacking. These difficulties have led to the proposal of a new term "propagons" for the mechanism of spread of pathology [59]. The unsettled issues in understanding pathogenesis indicate the presence of a yet undiscovered mechanism [3,223,122,204]. Specifically, the need for examining common factors to identify the triggering mechanisms [76] and the importance of understanding interconnections of the normal neural networks were highlighted [2]; with the specific example of Alzheimer's disease (AD) [120]. In these contexts, a proposed mechanism that explains both first-person internal sensations of higher brain functions and third-person observations at various levels is examined to determine whether the loss of function states of its key operational mechanism can explain the above common features of the neurodegenerative diseases.

2. Proposed cellular changes that induce internal sensations

The nervous system has synaptically-connected neurons with a widely varying number of input (postsynaptic terminals or dendritic spines or spines) and output (presynaptic terminals) terminals. There is general agreement that the internal sensations of higher brain functions emerge from the nature of the connections between the neurons within the network. Experiments attempting to verify the synaptic strengthening hypothesis [85,198,190,26] and neural network studies [155,187,222] have provided valuable information from multiple levels. However, the challenge in identifying the nodal points and the specific conditions necessary for the emergence of the first-person internal sensations of various higher brain functions remains.

Diverse findings about the normal functioning of the nervous system at different levels indicate that the central basic cellular mechanism that interconnects all these findings is likely a unique one. In this context, a theoretical examination was carried out to derive a feasible cellular mechanism that can explain both the first-person internal sensations of various higher brain functions such as perception and memory and third-person observed behavioral motor activities. This is the basis of the semblance hypothesis [212,215] and is summarized in Fig. 1. A cellular mechanism occurring during associative learning that can enable the induction of the virtual internal sensation of memory in response to a cue stimulus was searched for. In summary, during the process of associative learning between two sensory stimuli, an inter-postsynaptic functional LINK (IPL) is expected to form at the locations of convergence of these stimuli. These IPLs are reversible, stabilizable by repeated learning, and reactivatible in

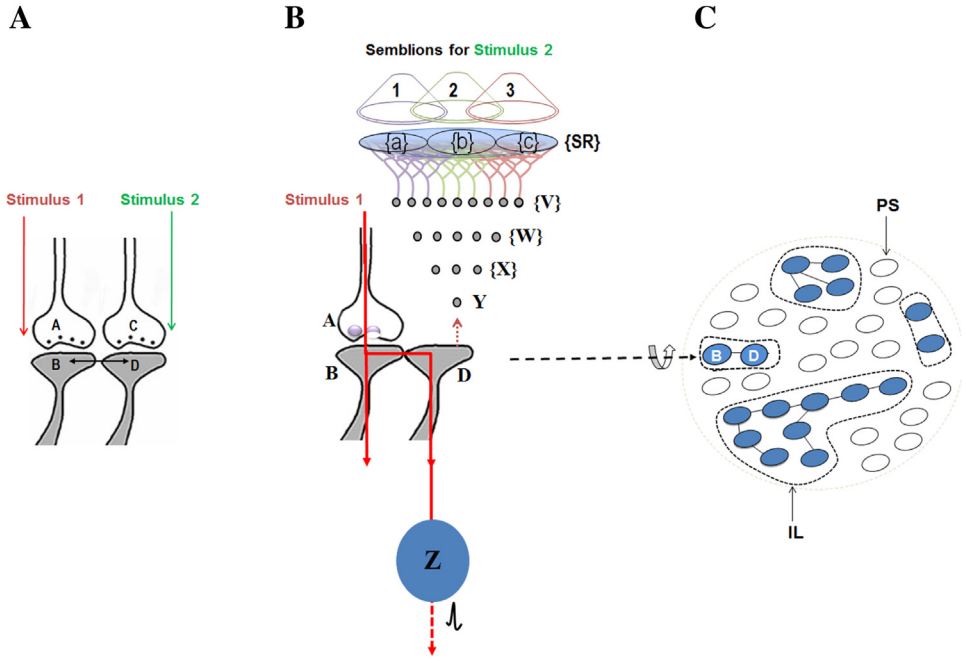

Fig. 1. Formation and reactivation of an inter-postsynaptic functional LINK (IPL). (A) During associative learning, two sensory stimuli arriving at their locations of convergence induce the formation of an IPL B-D between two abutted postsynaptic terminals B and D. (B) During memory retrieval, when stimulus 1 (cue stimulus) arrives at the synapse and depolarizes postsynaptic terminal B, it reactivates the IPL formed during associative learning and activates LINKed postsynaptic terminal D. Postsynaptic terminals are being continuously depolarized by quantal release of neurotransmitter molecules from their presynaptic terminals. The lateral activation of postsynaptic terminal D through the IPL induces a semblance (sensory hallucination) of arrival of activity from its presynaptic terminal C. The sensory content of the semblance can be estimated by estimating the nature of the sensory stimuli that can activate postsynaptic terminal D. This can be arrived by extrapolating backwards from postsynaptic terminal D towards the sensory receptor level. Postsynaptic terminal D is activated by firing of neuron Y. All the sets of dendritic inputs that can activate neurons at each of the lower orders ({X}, {W}, {V}) are listed. This extrapolation towards the sensory receptor level identifies a set of sensory receptors {SR}. {a}, {b}, and {c} are subsets of {SR} whose activation is capable of independently activating postsynaptic terminal D. 1, 2 and 3 are hypothetical packets of sensory stimuli activating sensory receptor subsets {a}, {b}, and {c} respectively and are called semblions. Thus, stimulus 1 (cue stimulus) induces virtual internal sensation of semblions 1, 2, 3 or their integral, which forms the semblance for stimulus 2. This is the basis of the induction of the internal sensation of memory of stimulus 2. The lateral spread of activity through IPL B-D contributes to the horizontal component of extracellularly-recorded oscillating potentials. The activation of postsynaptic terminal D may reach the soma of its neuron Z. If neuron Z is already at a threshold-activated state short of very minimal voltage, then it can cross the threshold and elicit an action potential. If neuron Z is a motor neuron, it contributes towards behavioral motor activity that occurs concurrently with the formation of internal sensations of memory of stimulus 2. (**C**) A cross-section through inter-LINKed postsynaptic terminals B and D at one region of the nervous system. It is imagined that large number of postsynaptic terminals are in one plane as that of postsynaptic terminals B and D. The sectioned area is rotated 90 degrees to show the cut surfaces. Due to continued learning, more postsynaptic terminals are LINKed together to form islets of inter-LINKed postsynaptic terminals. Islets with two, four and nine inter-LINKed postsynaptic terminals are shown. A and C: Presynaptic terminals. B and D: Postsynaptic terminals. PS: Postsynaptic terminal; IL: Islet of inter-linked postsynaptic terminals (figure modified from [215]).

either direction in response to specific cue stimuli. Later, during the arrival of the cue stimulus that reactivates the IPL, units of internal sensations at the LINKed postsynaptic terminal get induced as a systems property when the lateral entry of activity through the IPL contributes to the horizontal component of the extracellularly-recorded oscillating potentials. The computational product of all the induced units of internal sensations in response to a specific cue stimulus forms the memory. Both the potentials arriving through the inter-LINKed postsynaptic terminal activating several sub-threshold activated motor neurons and the removal of inhibitory inter-neuronal activities can lead to third-person observed behavioral motor actions. Continued associative learning between different sensory stimuli eventually leads to the formation of a large number of inter-LINKed postsynaptic terminals (Fig. 1C). Many of them get stabilized due to repeated learning and related learning events. Different cellular mechanisms for the IPL formation were described previously [217]. The present work examined various possible pathological changes of different types of IPLs for matching findings of their loss of function states among different neurodegenerative disorders.

2.1. Possible types of inter-postsynaptic functional LINKs

Different biological mechanisms that can provide this operation include (1) Close contact between the postsynaptic membranes by hydration exclusion from the extracellular matrix (ECM) space [131,178,98,105] (Fig. 2A, B), (2) Reversible partial inter-postsynaptic membrane (IPM) hemifusion (Fig. 2C), and (3) Reversible complete IPM hemifusion (Fig. 2D). The nature of different types of IPLs was previously explained [217] (Fig. 1; Table 1). The conditions that induce these LINKs are important in determining their possible pathological states.

2.2. Inter-membrane hydration repulsion

Lipid bilayers naturally repulse each other mainly due to electrostatic and hydration repulsion forces [188]. This is of importance at locations where a large number of inputs converge to form a congested environment with minimal ECM volume. Hydration repulsion is considered a fundamental force in structural biology that prevents the collapse of the lipid membrane-bound cells [98] and has been studied using phospholipid bilayer membranes [131,168]. Hydration repulsion exhibits an exponential decay with a decay length of a few Ångstrom [178]. Modeling and experiments suggest that hydration repulsion occurs when two bilayers approach closer than 15–20 Å [39]. Further estimations showed that very high pressure of nearly more than 100 atmosphere is necessary to merge the outer leaflets of two membranes [150]. These factors indicate that lipid-bilayer fusion has a very high kinetic barrier (~50 kcal/mol) [177].

Factors that that can overcome the repulsive forces between the lipid membranes [47] are expected to form IPLs. Due to the requirements for high energy, the interaction between the lipid bilayers is restricted to changes ranging from close contact by excluding the water of hydration to reversible intermediate stage of hemifusion and is expected to take place in very small areas of nearly 10 nm^2 [130]. In pathological states where hydration repulsion cannot be maintained either due to reduction in ECM hydration state due to conditions such as hyponatremia or dendritic spine expansion, the membranes can come in close contact with each other. This may lead to ephaptic transmission of potentials between them. The reversible nature of these changes was explained as one key change in seizure disorders [218]. It is possible that the loss of hydration repulsion leads to close contact between the postsynaptic membranes, resulting in non-specific IPL formation and the induction of non-specific semblances, leading to the transient events of cognitive impairment, hallucinations and unconsciousness [213–215]. The symptoms occurring from the loss of hydration repulsion may be reversed by optimizing electrolyte balance and by preventing dopamine-induced dendritic spine expansion using dopamine blockers.

2.3. Inter-membrane hemifusion

Membrane hemifusion is an intermediate stage in the process of membrane fusion [43] and is observed in a large number of cellular processes [161]. Details of the kinetics and energetics of these inter-membrane interactions were reviewed previously [217]. Repeated activation of IPLs can lead to the stabilization of the IPM hemifusion by methods such as the

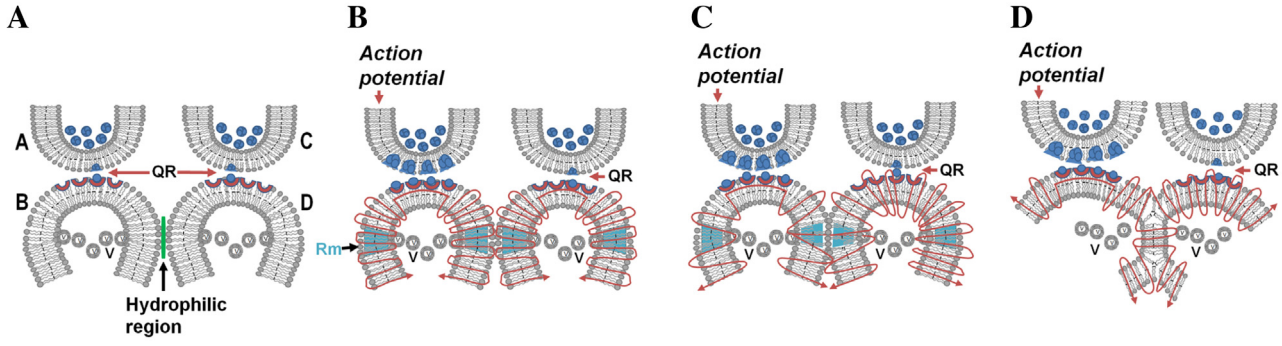

Fig. 2. Normal inter-postsynaptic space and different types of inter-postsynaptic functional LINKs (IPLs). (A) Presynaptic terminals A and C with synaptic vesicles inside (in blue). Normal quantal release of neurotransmitter release is represented by release of the contents from one vesicle from each of these terminals. This is a continuous process that induces very small potentials at postsynaptic membranes B and D. Postsynaptic terminals contain membrane-bound vesicles inside them marked (V) with GluR1 α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor subunits. Water of hydration (in green) is present between the postsynaptic membranes. (B) Simultaneous arrival of activity at the synapses leads to the removal of the hydrophilic region between the postsynaptic membranes and and allow the membranes to come in close contact with each other forming an IPL. Note the transfer of potentials from the postsynaptic membrane B to D through the IPL. Since the process of removal of water of hydration is a process that requires a great deal of energy, this IPL reverts rapidly. Rm: the membrane segment marked in blue where membrane reorganization occurs. (C) Reversible partial hemifusion between the abutted postsynaptic membranes. The exocytosis of AMPA receptor vesicles (V) occurring from two abutted postsynaptic terminals [146] makes the areas adjacent to the synapse more favorable for membrane reorganization and favors membrane hemifusion. This is reversible. (D) Complete hemifusion between the postsynaptic terminals. Dopamine, known to increase dendritic spine (postsynaptic terminal) enlargement is expected to favor complete hemifusion, which is also reversible. Various factors can stabilize the hemifused area for varying periods of time. QR: Quantal release (Figure modified from [216]).

Table 1
Different types of inter-postsynaptic functional LINKs (IPLs) based on the reversibility and their stabilization. The duration of stabilization of IPLs depends on the continued activation of the inter-LINKed postsynaptic membranes and the life-span of the stabilizing mechanism. IPM: Inter-postsynaptic membrane.

IPL mechanism	*Stabilization*	*Reversibility*
Loss of hydration repulsion	*No*	*Readily reversible*
Partial IPM hemifusion	*Unlikely*	*Readily reversible*
Complete IPM hemifusion	*Yes; for variable duration*	*Reversible. Continuous activation by repeated learning, events of related learning and reactivation promote stabilization of hemifused membrane segments*

insertion of trans-membrane proteins across the IPM hemifusions to obtain long-term stability. Once the stabilizing factors are removed, the hemifused area can reverse back to the independent membranes.

2.4. Effect of membrane composition

The nature of the reversible IPLs depends on the membrane composition. In the membranes, saturated fatty acids with an even number of carbon atoms (such as palmitic or stearic acid) attach to the first (*Sn-1*) and unsaturated fatty acids (such as oleic acid, docosahexaenoic acid (DHA) and arachidonic acid) attach to the second (*Sn-2*) carbon atoms of the glycerol molecule. DHA and arachidonic acid are the main polyunsaturated fatty acids (PUFAs) in the brain. The *Sn-3* position hydroxyl group of the glycerol molecule bonds with phosphoric acid to form phosphatidic acid, which then bonds with one of the molecules—serine, ethanolamine, choline, inositol, sphingosine, or ethanolamine. There is a consensus that the distribution of phospholipids across most eukaryotic membranes has a high degree of asymmetry with regards to their presence in the bilayer [18]. For example, in mammals, phosphatidyl serine (PS) and phosphatidyl ethanolamine (PE) are concentrated in the cytoplasmic leaflet; whereas phosphatidyl choline (PC) and glycosphingolipids are concentrated in the outer leaflet of the membranes of the red blood cells [24,237,151].

Various factors that control membrane fusion are reviewed [112]. High PE content promotes membrane fusion [57]. The lipid bilayer of rapidly fusing synaptic vesicles at the presynaptic terminals have a high cholesterol content, a high proportion of the plasmalogen form of PE and low phosphatidyl inositol [207]. Depletion of cholesterol inhibits both soluble NSF (N-ethylmaleimide sensitive fusion protein) attachment protein receptor (SNARE)- and viral-mediated membrane fusions [134,139]. Phosphatidylinositol 4,5-bisphosphate (PIP_2) present at high concentration at the sites of vesicle fusion of synaptic membranes is likely to interact with Ca^+ with its three negative charges and facilitate localized dehydration followed by stalk formation [6]. In these contexts, combinations of different factors are expected to control the formation of different IPLs.

3. Pathological conditions of IPLs

3.1. Conversion of IPLs to membrane fusion

Since there are different types of possible IPLs [217] (Fig. 2), their disorders can lead to different types of pathologies with characteristic features. Membrane fusion occurs through a series of membrane-coupled conformational rearrangements [82] that include destabilization of the membranes through the insertion of amphipathic protein segments and lipid reorganization via hemifusion [171]. Unlike stabilized hemifused areas, changes in membrane lipid composition can predispose non-stabilized hemifused areas of the membrane to advance towards a fused state [107]. This change of the lipid membrane composition in turn depends on the dietary availability of essential fatty acids, the integrity of expression of the enzymes for lipid synthesis, elongation, desaturation, and membrane lipid assembly. For example, arachidonic acid, one of the main PUFAs in the brain that usually comes from dietary animal sources or form from modification from linoleic acid, prevents the conversion of hemifused membranes to a fusion state [41]. Certain fusogenic proteins can reduce the energy barrier that prevents membrane fusion. For example, viral fusion proteins can induce the distortion needed to form a hemifusion stalk and further lead to membrane fusion changes [171,231,152,83].

Any factor that can lead to the enlargement of the dendritic spines can augment IPL formation by overcoming the repulsive forces [47]. Dopamine is known to produce enlargement of the dendritic spines during a critical time period [234] and is a expected mechanism that can promote IPL formation when two abutted postsynaptic membranes (dendritic spines) get activated simultaneously [215]. Several regions of the nervous system such as the frontal cortex, hippocampus, amygdala and nucleus accumbens receive dopaminergic inputs from the ventral tegmental area (VTA) and the striatum receives dopaminergic inputs from the substantia nigra pars compacta (SNPc) [184]. The dendritic spines at these locations are vulnerable to IPM fusion if factors that prevent the conversion of hemifusion to fusion are disturbed. Uncontrolled enlargement of the abutted spines in the context of membrane lipid compositional changes can promote the pathological conversion of hemifusion to fusion (Fig. 3). Other factors that affect membrane composition are ATP-dependent transmembrane proteins that translocate phospholipid molecules between the outer and inner lipid membrane bilayers called flippases, floppases and calcium-dependent scramblases [18,64].

Most of the IPM fusions are expected to be small and reverse back to normal single membranes immediately. Therefore, it is reasonable to expect that mixing of the cytoplasmic content is of transient occurrence unless the IPM fusion pore size is large. Since areas of IPM fusion maintain the electrical continuity between the postsynaptic membranes, it will continue to allow propagation of depolarization potentials similar to the normal IPLs. However, IPM fusion between the dendritic spines is likely to cause the spread of pathology laterally from the affected neuron to the unaffected neurons within the same neuronal order. This can explain the observations made during the experimental neurodegeneration [145,94].

3.2. Consequences of inter-spine fusion

IPM fusion is likely to occur between similar neurons of the same neuronal order. Will mixing of their cytoplasmic contents through the IPL fusion pore induce any cellular response? It is known that gene expression profiles of two adjacent CA1 neurons differ in their expressed proteins [104,37]. Therefore, fusion between any two neurons is expected to result in cytoplasmic content mixing that initiates cellular responses. The expression of abnormal proteins can be a cellular response to foreign proteins arriving at the cytoplasm and can in turn lead to the disturbance of lipid structure and integrity. Both the unusual proteins in the non-matching solvent conditions of

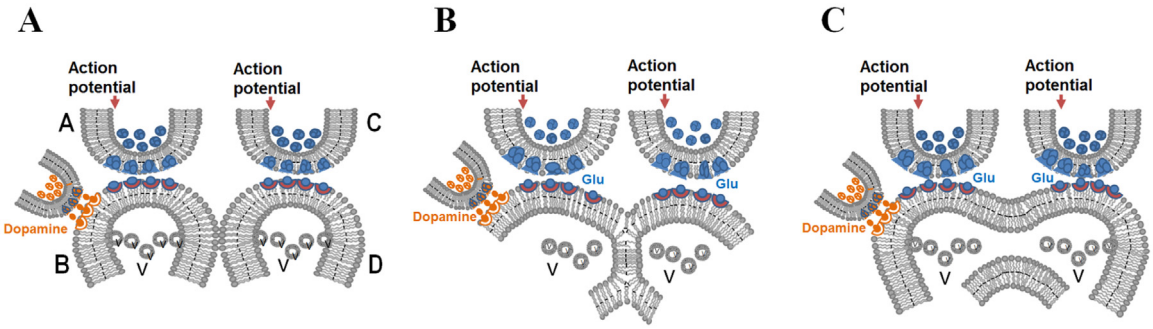

Fig. 3. Dopamine-induced postsynaptic enlargement that leads to inter-postsynaptic membrane (IPM) fusion. (A) Inter-postsynaptic functional LINK (IPL) formation at locations where one of the postsynaptic terminals receives dopaminergic innervation. Dopamine can lead to enlargement of postsynaptic terminal C that can augment IPL formation. (B) IPM hemifusion augmented by dopamine-induced dendritic spine enlargement. Since hemifusion is reversible, this can be considered a normal mechanism. (C) Pathological IPM fusion secondary to the spine enlargement by dopamine. This is expected to occur when other factors favouring fusion such as the lack of checkpoint mechanisms preventing hemifusion to fusion and changes in membrane lipid composition are present simultaneously. Most of these fusion changes are expected to revert if they span only for short lengths. A and C: Presynaptic terminals; B and D: Postsynaptic terminals. Glu: Glutamate; V: Membrane-bound vesicles with GluR1 α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor subunits (figure modified from [216]).

the normal cytoplasm and eventual changes in solvent conditions of the cytoplasm for normal proteins can lead to denaturation and precipitation of proteins.

Incorrectly folded proteins are eliminated from the cell through robust mechanisms such as unfolded protein response (UPR) and autophagy [12,40]. During cellular stress, the endoplasmic reticulum (ER) responds through the UPR mechanism that controls the accumulation of protein aggregates. In severe cellular stress, this mechanism fails to operate to its fullest extent and leads to the accumulation of protein aggregates. In these conditions, autophagy is initiated for protein degradation, recycling and elimination of unwanted damaged cell debris.

3.3. Role of SNARE proteins in hemifusion

Once the hydration repulsion force (explained in Section 2.2) is overcome and the membranes are in close contact with each other, fusogenic factors can trigger the formation of different types of IPLs. One such protein is the SNARE protein, whose function is critical in synaptic vesicle fusion within the presynaptic terminal [203]. Based on the present work, SNARE proteins at the postsynaptic terminals are expected to limit IPL changes to IPM hemifusion, which is an intermediate stage in the membrane fusion process. Studies were carried out to estimate the short-range repulsive force that is necessary to bring the vesicle membranes in close contact with each other prior to fusion and has been quantified by the hydration force parameters. Using membranes of specific composition and vesicle diameter, it was postulated that the effect of SNARE complex formations at the periphery of the membranes may lead to dehydration at the point of contact between the membranes [1]. It was found that SNARE proteins can produce reversible hemifusion intermediates preceding the fusion state [140]. Moreover, hemifusion and fusion are found to be definitive endpoints in SNARE protein-mediated inter-membrane interaction [71]. It is known that SNARE proteins form a very tight alpha-helical bundle that can pull two membranes together to initiate membrane fusion [52,240]. All the above findings indicate that SNARE proteins can provide an ideal candidate mechanism for the IPL formation. It is necessary to examine the nature of the postsynaptic SNARE proteins and the factors that restrict their action to IPM hemifusion.

Postsynaptic SNARE proteins have been studied in the context of long-term potentiation (LTP), an experimental electro-physiological finding that shows correlation with behavioral markers indicative of the internal sensation of retrieved memories [143,17]. It was possible to explain LTP based on the formation of IPLs, especially IPM hemifusion [215]. Specific SNARE proteins are necessary for LTP [103]. The role of SNARE proteins in the exocytosis of GluR1 subunit of AMPA receptors is known [144,109,103]. The merging of the GluR1 containing vesicle lipid membranes with the postsynaptic membrane leads to the continuous reorganization of lipid membranes at the extra-synaptic locations close to the synapse. This is evidenced by the observation that GluA1 AMPA subunits are located 25 nm from the synaptic borders on the postsynaptic membranes [100]. Both SNARE protein transmembrane segment self-interaction [92] and peptides mimicking transmembrane segments of the SNARE protein [124] were shown to induce membrane fusion. In this context, the regulation of SNARE fusion machinery by the fatty acids [52] indicates that alterations in lipid composition can convert hemifusion to a pathological fusion state and initiate neurodegenerative changes. Experiments showing that a single SNARE molecule can lead to membrane fusion between two liposomes [219], whereas three molecules are necessary for fusion between two living cells [158] indicates the effect of membrane compositional changes on the efficiency of SNARE molecules in membrane fusion. All the above evidence strongly suggests that SNARE proteins form a suitable candidate mechanism for the normal IPL formation. Since reversible IPM hemifusion is a possible IPL mechanism and since SNARE proteins have an inherent property for membrane fusion, it is reasonable to expect the presence of strong checkpoint mechanisms in place to prevent the SNARE proteins from converting normal reversible IPM hemifusion state to fusion. The loss of these checkpoint mechanisms can also act as etiological factors that lead to neurodegenerative changes.

3.4. Extra-postsynaptic membrane fusion

It is known that the neurodegenerative changes spread from the neurons to involve astrocytes and microglia [192]. For example, astrocytic pedocytes surround nearly more than half of the synapses examined at the stratum radiatum of the hippocampal area CA1 [224]. In this context, the late consequences of loss of regulation of IPM hemifusion can lead to fusion between the postsynaptic terminals and adjacent glial cell membranes (type 6, Table 2). Pathological changes resulting from cell-cell fusion can lead to reactive cellular responses among different glial cells that lead to the formation of tau-positive glial cells in PSP, CBD and Pick's disease [116], thorny astrocytes in AD [159], tufted astrocytes in PSP [236], astrocytic plaques in CBD [236] and glial cytoplasmic α-synuclein in PD, MSA and LBD [28]. In addition, membrane fusion pathology can also lead to cellular mechanisms that try to remove deleterious protein precipitates from the cells through the formation of

Table 2
Table showing different types of inter-postsynaptic functional LINK (IPL) pathologies. These depend on the nature of onset and speed of spread of pathology. Since various factors can influence the formation of different types of normal IPLs, their defects can lead to this spectrum of IPL pathologies. IPM: Inter-postsynaptic membrane.

Type	Nature of IPL	Consequences
1	Acute reversible non-specific IPL formation	Non-specific semblances resulting in reduced memory, hallucinations, seizures and loss of consciousness.
2	Acute non-reversible IPM fusion	E.g. HSV encephalomyelitis, Acute disseminated encephalomyelitis (ADEM).
3	Subacute non-reversible IPM fusion	Continuous formation of IPM fusion and spread of pathology. E.g. Prion disease, Rasmussen's encephalitis.
4	Chronic intermittent IPM fusion	Frequent occurrence of IPM fusions. E.g. Autism spectrum disorders with developmental regression.
5	Stabilized IPM fusion	IPL function of spread of EPSPs occurs continuously. In addition, degenerative changes will continue through the IPM fusion pore.
6	Extra-postsynaptic membrane fusion	Extension of IPM fusion with glial cells and presynaptic terminals.
7	Dopamine-induced fusion	Spine enlargement can lead to IPM fusion in the presence of membrane lipid changes.

extracellular vesicles called exosomes [48]. Neurotubes also form between the postsynaptic and presynaptic terminals [79].

4. Associated findings

4.1. LTP, memory, kindling, seizures and neurodegeneration

Following the finding that the hippocampus is an important area for memory, experiments were carried out using the hippocampus to discover electrophysiological correlates for memory. This led to the discovery that LTP [143,17] is correlated with behavioral markers indicative of the internal sensations of memory retrieval. During LTP induction, high-frequency impulses are applied at a group of axons whose terminals form a group of densely packed synapses that are separated by negligible ECM. Following this, stimulation by a regular impulse at the same location becomes sufficient to elicit long-lasting increased potentials recorded either from the soma of the postsynaptic neurons or extracellularly. LTP is explained as a function of formation of different IPLs by the semblance hypothesis [215,217]. The basis of this include dendritic spine enlargement [234] and GluR1 AMPA receptor subunit exocytosis [169,117] at the inter-postsynaptic locations that lead to membrane reorganization that are expected to induce different types of reversible, stabilizable and reactivatible IPLs [217]. The expected common IPLs induced by LTP are reversible changes such as the formation of close contact between the postsynaptic membranes by hydration exclusion between the membranes and IPM hemifusion. Small areas of reversible membrane fusion that reverse back slowly over time are also expected to form during LTP. Prolonged duration of LTP and its slow reversibility indicate that reversible IPM hemifusion and fusion are the most probable underlying changes.

The correlation between LTP and behavioral markers indicative of memory retrieval indicates that IPL mechanisms are involved during associative learning and memory retrieval. Details are described previously [215,217]. The reactivatible IPLs at the time of arrival of the cue stimulus induce units of internal sensations, whose computational product forms the memory. Several IPLs that are formed during previous learning events will be shared during every new learning event. Therefore, a new associative learning need to induce only a new set of IPLs that are unique for the new learning. Duration of stabilization of the IPLs depends on the motivation-induced dopamine-associated spine enlargement and determines the duration of storage of associatively learned information. At the arrival of the cue stimulus, reactivation of the existing IPLs that are more widely spread within the hippocampus and cortex occurs. In contrast, LTP artificially induces a set of IPLs at a specific location. Since the energy barrier for spontaneous membrane hemifusion and fusion is very large [150,177,130,47,39],*in vitro* fusion assays are carried out by incorporating fusogenic molecules into the membranes or by increasing the membrane's tension [111]. This can explain the requirement for high frequency stimuli to artificially generate IPLs at a specific location during LTP induction.

In comparison, kindling is induced by stronger stimulating conditions than LTP that leads to afterdischarges and shows several similarities to human seizure disorders [15]. Based on the present work, kindling is expected to induce primarily large IPM fusions, most of which remain non-reversible. This supports the finding that spatial memory performance gets disrupted by kindling and not by hippocampal CA1 LTP [132]. Seizures that are comparable to kindling are expected to induce large number of IPLs, most of which include IPM fusions and lead to excessive lateral spread of activity contributing to the slowing of the EEG waveform [218]. This may explain both the occurrence of seizures in several neurodegenerative disorders and the eventual neurodegenerative changes in primary seizure disorders.

4.2. Infection and neurodegenerative diseases

A large number of studies have shown infection as an etiological factor in AD and other neurodegenerative disorders [54,108,238,88]. The role of herpes simplex virus 1 (HSV1) in neurodegenerative disorders is highlighted in several studies [202,14,11,99,170]. What factor do these different infective agents have in common that can lead to neurodegenerative changes? It is known that several enveloped viruses release proteins responsible for inducing membrane fusion [231,152,83]. These viral proteins can overcome the kinetic barrier [177] and lead to cell-to-cell fusion [171]. Specific examples of enveloped viruses causing membrane fusion include the herpes virus [49,60], the cytomegalovirus [113], the Epstein-Barr virus [44], the flavivirus [199,200], the human immunodeficiency virus (HIV) [157,21], the rabies virus [180] and the influenza virus [42]. The Zika virus of the family flavivirus, which is an enveloped virus is implicated in the development of microcephaly [189,241]. The potential role of flaviviral fusion proteins that leads to membrane fusion [193] may explain neuronal destruction and loss of brain volume and can be subjected to further verification.

4.3. Heterogeneity of protein aggregates

Since the cells involved and the direction of spread of the membrane fusion process between the cells vary, both the brain locations affected and proteins that get precipitated also vary. A large number of combinatorial probabilities for fusion between the dendritic spines of similar types of neurons expressing slightly different proteins can contribute to the heterogeneous nature of expressed proteins. The postsynaptic terminals of the excitatory synapses in the brain regions that also receive dopaminergic inputs can undergo IPM fusion in an augmented fashion due to the effect of dopamine on dendritic spine enlargement. Since the locations of IPLs between the dendritic spines of different neurons at a given time depend on previous associative learning events, the IPM

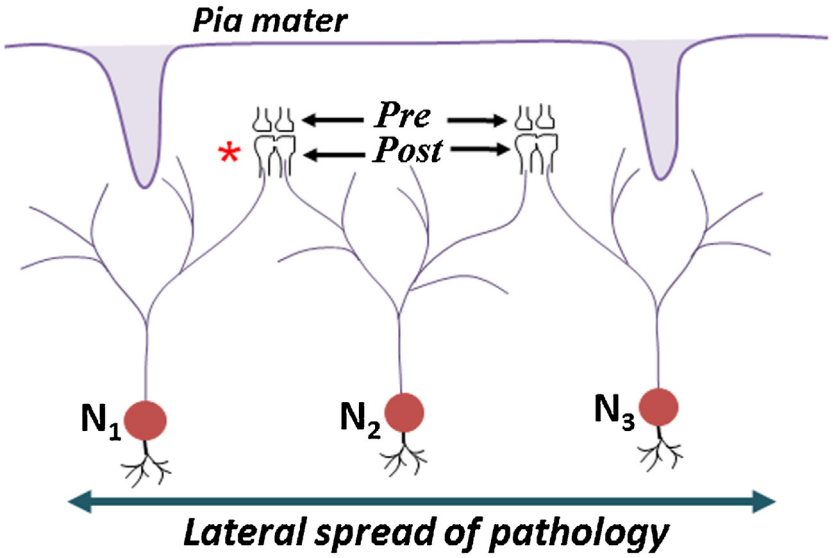

Fig. 4. Lateral spread of pathology at the initial stages of neurodegenerative disorders mediated through inter-postsynaptic membrane (IPM) fusion. The figure shows lateral spread of pathology in the cortex from neuron N_1 to neuron N_2 and then to neuron N_3. IPM fusion events are formed by the pathological conversion of the normal IPLs (Fig. 3) between the dendritic spines of neurons N_1, N_2 and N_3. Initial formation of IPM fusion takes place between neurons N_1 and N_2 (marked by red star). Once cytoplasmic contents get transferred between neuron N_1 and neuron N_2, through the IPM fusion pore, both these neurons mount certain cellular responses that alter their gene expression that can lead to the precipitation of abnormal proteins (figure modified from [218]).

fusion changes of the existing IPLs are individual-specific. This significant variation of IPL locations between individuals can also contribute to the observed heterogeneity of the disease process. Interaction between different proteins at different levels can explain why some patients have features of different types of neurodegenerative diseases [126].

4.4. Rate of progression

Depending on the strength of the etiological factors, different types of pathological changes can lead to different types of IPLs and explain the observed differences in the speed of progression of different neurodegenerative disorders. For example, in acute HSV encephalitis, the severity and locations affected depend on the extent of the membrane fusion caused by the fusogenic proteins released by the virus. This in turn will depend on the viral load and the starting time of effective treatment with antiviral medications. The size of the IPM fusion pore can vary depending on several factors. Small fusion pores are expected to reverse quickly, making the pathological changes to reverse as well, if other factors that trigger the pathology are stabilized. In conditions where recurrent formation of fusion pores occur, pathological changes are induced intermittently. Large fusion pores remain irreversible and induce rapid changes in pathology causing rapid progression of cellular death.

4.5. Pattern of spread of neurodegenerative changes

The finding that most neurodegenerative disorders have clusters of inclusions regularly distributed parallel to the pia mater [9] indicates a mechanism for the lateral spread of pathological processes from neuron to neuron within the same neuronal order, which is expected to occur by a mechanism other than the expected trans-synaptic spread [53]. Contiguous lateral spread of pathology to the adjacent cortices is present in PLS that specifically affects the neurons of the motor cortex [63] and in ALS [179,119]. The spread of α-synuclein to the neighboring cells [118,133,55] and the spread of tau pathology to the adjacent neurons explained in animal models [46,53] are other examples. The IPM fusion demonstrated in the present work can provide a feasible explanation for the lateral spread of pathology (Fig. 4). Following initial local inter-postsynaptic lateral spread between the neurons, the pathology can spread via postsynaptic membrane fusion with other cell types and the presynaptic terminals (Fig. 5). This can explain heterogeneous nature of spread of pathology in different neurodegenerative diseases.

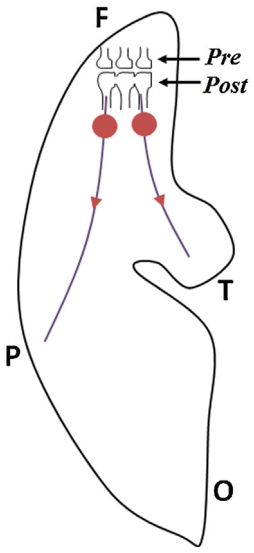

Fig. 5. Inter-postsynaptic membrane (IPM) fusion between the dendritic spines of frontal cortical neurons that project to other cortices. The IPM fusion at frontal cortex (F) leads to the mixing of the cytoplasmic content between the neurons that trigger neurodegenerative changes. The axonal terminals of different neurons that project to temporal (T) and parietal (P) cortices where they can lead to the spread of pathology (type 6, Table 2). Once the neurons at the temporal and parietal cortices are affected, then neuron to neuron spread can take place through IPM fusion between their dendritic spines, when global factors promoting fusion are present. This can explain a possible mode of spread of neurodegeneration from the frontal cortex to other cortices in frontotemporal dementia. O: Occipital region (figure modified from [218]).

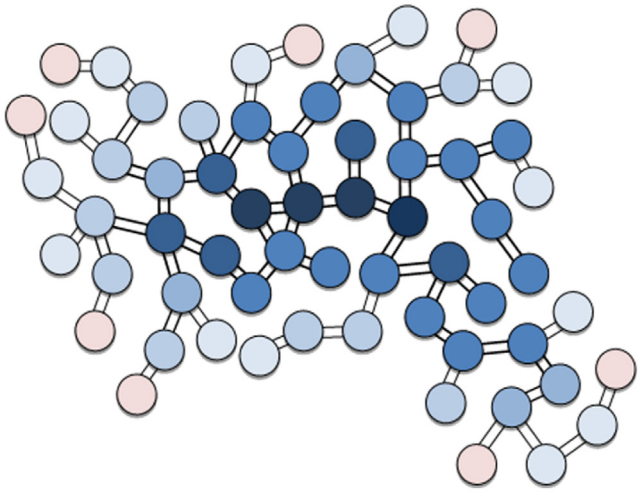

Fig. 6. A large islet of inter-LINKed postsynaptic terminals with stabilized IPLs at the central region. This figure shows large islet of inter-LINKed postsynaptic terminals compared to the small ones shown in Fig. 1C. The expansion of the islet of inter-LINKed postsynaptic terminals is expected to occur by continued associative learning events. Note that the IPLs at the central region of the islet (in dark blue) are stabilized and are resistant to get converted to an IPM fusion state. However, those newly formed IPLs at the peripheral regions of the islet (in light blue and pink), which are not stabilized, are prone to undergo fusion under pathological conditions.

4.6. Resistance to membrane fusion at the stabilized IPLs

Conversion of IPLs, especially IPM hemifusion to a pathological fusion state depends on whether the hemifused segments are stabilized or not. Stabilized IPM hemifusions are expected to resist further transition to their fused states. At brain regions where a large number of postsynaptic terminals form islets of inter-LINKed postsynaptic terminals (Fig. 1c), IPLs are most likely well-stabilized due to the continued arrival of stimuli from shared common physical properties of the environment in which the animals live. Since the IPLs at the peripheral regions of the islets of inter-LINKed postsynaptic terminals are comparatively recent in their formation and likely lack stabilizing mechanisms, they will be more prone to undergo IPM fusion (Fig. 6). Similarly, IPLs that are responsible for innate behaviors are also expected to remain stabilized throughout the life of the animals and are unlikely to undergo IPM fusion during the neurodegenerative process at least at the initial period. Continuous associative learning and memory retrieval events that help maintain the IPLs in their stabilized states may be used to prevent IPM fusion, if pathogenic factors are controlled.

4.7. Neurodegeneration and homeostatic mechanisms

The fused cells are expected to initiate homeostatic cellular mechanisms for protecting themselves from injury (Fig. 7). The expected changes include (1) Mechanisms for closure of the inter-membrane fusion by reversal of the fusion process. (2) If this fails, then it is possible to seal the fusion pore by inducing certain cellular mechanisms. (3) If the above mechanisms fail, removal of the fused dendritic spine from the neuron can stop the ongoing cytoplasmic mixing between the neurons. The observed reduction in dendritic spine stability followed by loss of spines in different neurodegenerative disorders [115,87] can explain this. (4) If the fused dendritic spines cannot be removed, it leads to the accumulation of increased levels of mis-folded proteins that will cause defects in the structural integrity of the neuron. The normal ubiquitination process will become inadequate for the removal of excessively accumulated misfolded proteins, which can lead to cell damage. Ultimately, the function of the endoplasmic reticulum is affected and mechanisms for programmed cell death will be triggered [23]. This last step may protect other neurons that are at early stages of fusion with the neuron that is already undergoing apoptosis.

5. Neurodegenerative disorders

5.1. Parkinson's disease

Microstructural brain alterations are observed during the early stages of PD [22] and are associated with the accumulation of α-synuclein in the neurons. There are several first- and third-person findings in PD that need a common mechanism at the cellular level for explaining them in an interconnected manner. The following are some of these findings in PD that are pieces of a puzzle requiring a solution.

- Current primary treatment of bradykinesia, tremor and rigidity in PD is dopamine precursor drug, L-3, 4-dihydroxyphenylalanine (L-DOPA) that increases dopamine in the brain. How does dopamine relieve motor symptoms in PD?
- Dopamine can induce dystonia as a side effect. How can this be explained?

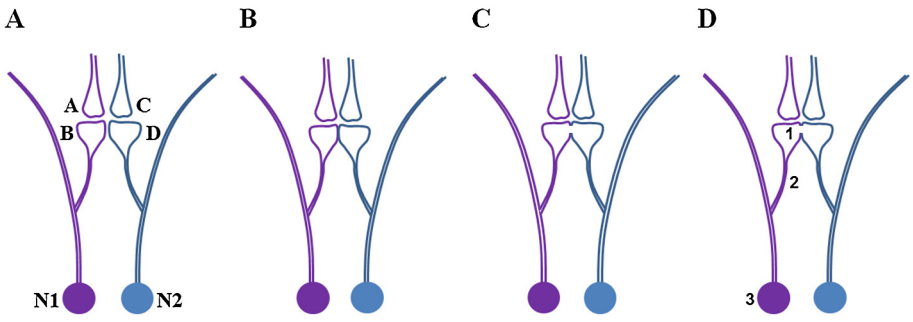

Fig. 7. Stages towards fusion between the postsynaptic terminals and homeostatic protective mechanisms. (A) Two neurons N1 and N2, with one each of their dendritic spines (postsynaptic terminals B and D) abutted to each other. (B) Inter-postsynaptic functional LINK (IPL) between dendritic spines B and D. Complete inter-postsynaptic membrane (IPM) hemifusions can get stabilized. (C) Non-stabilized IPM hemifusion can undergo pathological changes when fusion-favourable conditions such as changes in membrane lipid composition, lack of checkpoint mechanisms that prevent conversion of hemifusion to fusion state and fusion proteins or chemicals are present. The cytoplasmic content mixing will lead to triggering of cytotoxic response within the neuron. (D) Different homeostatic cellular mechanisms. Initial change is closure of the inter-spine fusion pore (1). If the fusion pore cannot be closed and if the cytoplasmic content mixing continues, it will trigger cellular mechanisms for the removal of the dendritic spine at the narrowest region of the spine neck (2). This can explain spine loss observed in neurodegenerative disorders. If these mechanisms fail and if the mixing of cytoplasmic content continues, then programmed cell death is initiated (3). This may save the less affected neuron. 1: Sealing of the fusion pore. 2: Removal of the dendritic spine. 3: Apoptosis of one of the neurons. A and C: Presynaptic terminals (figure modified from [218]).

- How does dopamine's efficiency decrease over time [72]?
- Why L-DOPA treatment cannot prevent disease progression?
- How to explain rigidity, bradykinesia and simultaneously ongoing neurodegenerative changes in PD?
- L-DOPA induces hallucinations as a side effect. How are the first-person internal sensations of hallucination induced by dopamine? How does D2 receptor blockers prevent these hallucinations?
- How does the disease pathology lead to memory problems? Why don't the current medications improve memory deficits?
- Why DBS is effective only in those patients who respond well to L-DOPA?

In normal conditions, it is expected that the basal ganglia provides sufficient drive for the motor cortex to initiate and maintain motor activity. A large number of motor neurons are finely-controlled for the execution of behavioural motor activities in response to a cue stimulus. A mechanism for achieving this fine-control by IPL-induced framework of mechanisms was previously explained [217]. This is by maintaining the neurons at sub-threshold levels and activating them at the arrival of a few additional postsynaptic potentials from the cue stimulus. This can operate in addition to the known controls by the inhibitory neuronal activities and maintenance of intrinsic inhibitory voltage-dependent conductances such as I_h, I_A and conductance through the SK-type calcium channels [91,30]. A cue stimulus from the environment reactivates the IPLs and induces various internal sensations of higher brain functions (Fig. 1B). During this process, the potentials arriving through the inter-LINKed postsynaptic terminals lead to the firing of the sub-threshold activated motor neurons explaining behavioural motor activity. This provides a mechanism to explain the occurrence of motor movements at the time of induction of internal sensations of a decision to move.

Medium spiny projection neurons are the major neuronal types affected in the striatum in PD. They comprise 95% of the striatal neurons that undergo changes during the learning of a motor task and are GABAergic [235]. The inhibitory outputs from these neurons are used to regulate the excitatory thalamic outputs to the motor cortex through both the direct and indirect pathways [33]. A robust fine-control of the thalamic excitatory neuronal activity can be achieved through an IPL-mediated mechanism. Dendritic spines of medium spiny projection neurons receive inputs from (a) the cortex through glutamatergic cortico-striatal axonal terminals, and (b) the dopaminergic SNPc neurons through their axonal terminals. Dendritic spines from different medium spiny neurons in the striatum are abutted to each other with minimal ECM space, which provide provision for the formation of IPLs between them. Blockage by Mg^+ continues to prevent activation of several of the glutamatergic synaptic inputs of the cortico-striatal pathway. Once the arrival of activity removes the Mg^+ block, activation of the postsynaptic terminals (dendritic spines) can lead to the formation of IPLs. This is reflected by the ability to induce LTP in the striatum [32].

Based on the semblance hypothesis, the strength of LTP that can be induced at a location depends on the convergence of inputs at that location between the stimulating and recording electrodes, which increases the number of IPLs formed. This is reflected on the ability to induce LTP by stimulating the cortico-striatal pathway that involve the striatal medium spiny neurons [142]. The presence of IPLs will allow the medium spiny neurons to be held at sub-threshold potentials that allow them to get activated at the arrival of a very minimal stimulus. It is experimentally shown that dopamine causes enlargement of the dendritic spines during a critical time period [234]. Dopamine released at several areas of the brain [201] can lead to dendritic spine enlargement and promote the formation of reversible IPLs. The enlargement of the abutted dendritic spines of the medium spiny neurons by dopamine from SNPc neuronal terminals is expected to overcome the inter-postsynaptic membrane repulsive forces [150,177,130,47,39] between the spine membranes. This can initiate cellular changes for the formation of different IPLs between their membranes and can also explain the role of dopamine in LTP induction observed in striatal medium spiny neurons [38,164].

The normal dopamine-augmented IPL formation in the striatum reduces the required potentials from the frontal cortex for activating the striatal medium spiny neurons. Changes in the membrane lipid composition, removal of the checkpoint mechanisms that prevent conversion of IPM hemifusion to fusion, and insertion of certain chemicals and viral fusion proteins can lead to inter-spine fusion, triggering the neurodegenerative process in PD (Fig. 8). This will lead to the observed loss of dendritic spines of medium spiny neurons and eventually cause reduction in dendritic length [56,226]. These changes eventually will reduce the activity of striatal medium spiny neurons and is a possible explanation for bradykinesia observed in the early stages of PD. The additional loss of spines will reduce the baseline sub-threshold activation of the medium spiny neurons to further low values such that more frontal cortical inputs will become necessary to activate them. This explains the need for increased mental effort and repeated

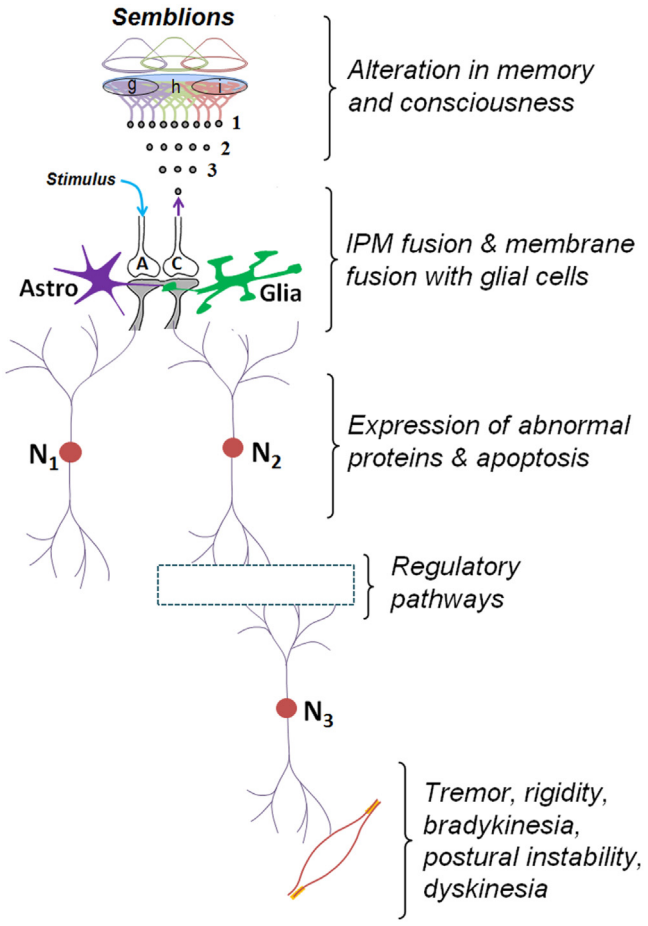

Fig. 8. Diagrammatic representation of effects of degenerative changes on cognitive functions and motor activity. Formation of non-specific inter-postsynaptic functional LINK (IPL) results in induction of large number of non-specific semblances resulting in cognitive changes. Arrival of potentials through the non-specific IPLs to the motor neurons can initially lead to homeostatic mechanisms to control their firing. Later, when the arrival of activity crosses the limits of feedback control by inhibitory interneurons, it can lead to symptoms such as tremor, rigidity and dyskinesia. Fusion-induced neuronal death can contribute to the symptoms of bradykinesia and postural instability. Eventually, the fusion process can involve astrocytes and microglial cells. N_1, N_2 and N_3 are neuronal somata. A and C are presynaptic terminals whose postsynaptic terminals have undergone fusion. Astro: Astrocyte. Semblions are the units of internal sensations (see Fig. 1).

attempts to increase the temporal summation of potentials to overcome the inertia of movements at the early stages of the disease.

The axonal terminals of the SNPc neurons synapse with the striatal medium spiny neurons. SNPcs undergo degenerative changes in PD. The spread of degenerative changes from the striatal medium spiny neurons can occur by type 6 changes (Table 2) at the synapses formed by the dendritic spines of these neurons and the presynaptic terminals from the SNPc neurons. Even though both medium spiny neurons and SNPc neurons can be affected by membrane fusion, the ability to lose dendritic spines can provide an advantage to the medium spiny neurons to limit the damage quickly; whereas SNPc neurons that lack this ability to quickly terminate the fusion may undergo severe damage. When IPM fusion changes spread to include the presynaptic terminals from the SNPc neurons, any cytoplasmic content mixing can become severely toxic to the SNPc neurons and can eventually lead to their death. Therefore, these changes may initiate at a very early stage of the disease process, several years before the movement problems begin.

When dopamine release from the SNPc presynaptic terminals is reduced, artificially elevating the dopamine level by treatment with L-DOPA allows neighbouring dendritic spines of medium spiny projection neurons to enlarge and generate IPLs at the arrival of stimuli from the frontal cortex (Fig. 3). This can facilitate smooth voluntary movements with L-DOPA treatment. The IPLs formed secondary to dopamine-induced spine enlargement reverse back when the concentration of the available dopamine reduces. This explains the reversal of the L-DOPA effect after few hours. Excessive L-DOPA treatment can lead to dyskinesia, which can be explained by the formation of an excessive number of IPLs between the dendritic spines of different medium spiny projection neurons. When the abnormalities in the membrane lipid composition or other fusogenic factors persist, treatment with L-DOPA can have a dual effect. The maintenance of electrical continuity through the hemifused postsynaptic membranes continue to provide the functions of the IPLs; but in a non-reversible manner. Moreover, the fusion pores continue to promote neurodegenerative changes. These can explain the rigidity in PD along with the continuation of neurodegenerative changes.

Continued loss of dendritic spines of the striatal medium spiny projection neurons will lead to a further reduction in the dendritic spine density to such levels that even spine enlargement with dopamine will not allow many of these spines to get close to each other for IPL formation and summating the EPSPs to keep the medium spiny neurons at sub-threshold activated state and to fire them. Therefore, simple efforts that provide only limited potentials will not be sufficient to cross the threshold for triggering action potentials to mediate downstream effects. In the absence of dendritic spines at LINKable distances, administration of L-DOPA gradually loses effect over a period of few years. Even though L-DOPA produces symptomatic relief, the continuous dendritic spine expansion can promote IPM fusion in the presence of other fusion-promoting factors and lead to eventual spine loss and disease progression. In the absence of dendritic spines at LINKable distances, deep brain stimulation will be ineffective in treating PD patients who do not show a good response to L-DOPA. Both cognitive and neuropsychiatric impairments are reported in PD, which can be explained in terms of reduced number of available dendritic spines for IPL formation in different parts of the nervous system, and the formation of excessive non-specific IPLs, especially in the presence of exogenous dopamine along with other fusogenic factors.

5.2. Alzheimer's disease

Dendritic spine loss is a significant finding in AD and has been examined from different aspects [58]. Both amyloid-β and hyperphosphorylated tau are contributing factors towards the dendritic spine damage [81,97]. An early form of amyloid in the ECM volume occurs as extracellular loose aggregates, that later form diffuse plaques. Amyloid-β are expected to cause three different types of changes. They may induce IPM fusion similar to that observed by vesicle fusion experiments [225]. They may directly disrupt the integrity of lipid bilayer by interacting with phospholipids [84]. In addition, extracellular amyloid aggregates occupying the ECM space between the postsynaptic membranes can inhibit the formation of normal IPLs (Fig. 9). Due to these reasons, clearing of the excessively formed extracellular amyloid can reverse some of the adverse effects. However, concerns raised about the amyloid cascade hypothesis [209,8] indicate that a still unknown mechanism leads to the pathogenesis. Since hyperphosphorylated tau protein accumulates in the cytoplasm of large number of neurons globally, it supports the predictions made by the present work that the pathological changes due to IPL fusion continue even after the removal of amyloid from the ECM space.

It has been shown that amyloid-β is capable of binding specifically to the phospholipid membranes with relatively high affinity, and that the modulation of the composition of the membrane can alter both membrane-amyloid interactions and produce toxic effects [232]. Treatment with antibodies to amyloid-

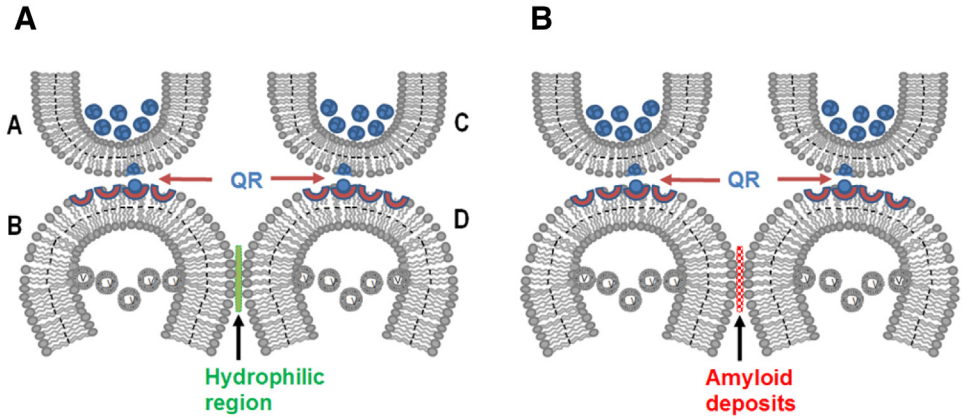

Fig. 9. Intercellular changes that prevent normal formation of inter-postsynaptic functional LINK (IPL). (A) Two synapses A-B and C-D with their postsynaptic terminals B and D abutted to each other. Normal hydrophilic region at the inter-postsynaptic membrane (IPM) extracellular space is shown. (B) Deposition of amyloid in the IPM extracellular matrix space can prevent the normal mechanism of formation of different types of IPLs. QR: Quantal release. A and C: Presynaptic terminals; B and D: Postsynaptic terminals.

β did not show the expected effects in the recent clinical trials [29]. In mice that overexpress mutant human amyloid precursor proteins (Tg2576 mice), amyloid-β is likely to induce IPM fusion as observed by vesicle fusion experiments [225]. This may explain the increased baseline cortical neuronal activity in the Tg2576 mice. Even though the antibody to amyloid- β removes the extracellular amyloid that prevents IPL formation, the pathological mechanism of IPL fusion that has already triggered alteration of gene expression can persist. Both IPL fusion formation and the precipitation of abnormal proteins are likely to continue. Since the fused inter-postsynaptic terminals can transmit potentials between them, similar to other IPLs, it will continue to activate several cortical neurons non-specifically even after the amyloid antibody treatment. This may explain the increased cortical hyperactivity observed in these studies [29].

One study has shown changes in peripheral blood plasma samples in a group of cognitively normal older adults that predicted their phenoconversion to either amnestic mild cognitive impairment (MCI) or AD within a two- to three-year timeframe with over 90% accuracy [149]. This indicates that a certain relationship exists between the plasma lipid composition and early neurodegenerative changes. A major role for APOE in the brain is to maintain a constant supply of neuronal lipids for rapid and dynamic membrane synthesis [10]. APOE4 allele, a well-established risk factor for AD [51] likely causes defects in maintaining normal membrane lipid composition, which in turn promotes IPM fusion. A significant decrease in phosphatidylcholine (PC) and phosphatidylethanolamine (PE) in the plasma membranes is observed in AD [162]. There is a significant decrease in the PE and phosphatidyl inositol (PI)-derived total fatty acids in the hippocampus of AD subjects [173]. An alteration in lipid concentrations is found in the prefrontal cortex of the AD patients that can possibly lead to extensive membrane remodeling and instability [95].

Age is the most important etiological factor for AD. Based on the present work, different factors can contribute to age-related pathophysiology. Age-dependent alteration in the optimal expression of a small subset of enzymes among the large number of enzymes involved in multiple steps in the synthesis, elongation and desaturation of various fatty acids and membrane lipid assembly can lead to alteration in membrane lipid composition. This can predispose the dendritic spines to undergo fusion and initiate neurodegenerative changes. Reduced reactivation of IPLs can eventually lead to removal of the stabilizing factors, which will predispose the spines to undergo IPM fusion that results in neurodegenerative changes under favourable conditions. Since the internal sensations of all the primary sensations are expected to operate mainly through the pre-existing IPLs that are stabilized at birth, primary sensory modalities remain unaffected until the last stages in most of the neurodegenerative disorders, unless the changes directly affect the primary sensory cortical areas. Since smell is affected early in AD and PD, it provides an opportunity to examine the IPL pathologies along the neuronal circuitry for the propagation of the smell stimuli and the locations of IPLs where internal sensation of perception occurs.

5.3. Prion disorders

Glycosylphosphatidylinositol (GPI)-anchored cellular prion protein PrP^{C} is particularly expressed in neuronal cells [196]. In prion disease, normal prion proteins change their conformation from PrP^{C} to PrP^{SC}. The GPI membrane anchor directs prion protein to lipid rafts that are rich in cholesterol and have lipids with saturated acyl chains, mainly PC and sphingomyelin and was found to be involved in the conformational change to PrP^{SC} [27,160]. The depletion of cholesterol from the cell membranes is known to lead to the disruption of raft micro-domains [93] and prevent PrP^{SC} formation [208]. These indicate that prion disease resulting from the conformational change from PrP^{C} to PrP^{SC} bears a strong relationship to the membrane lipid composition.

PrP^{SC} is found mainly on the neuronal plasma membranes with a predilection to the sites of cell-to-cell contact [74]. It is also known that the prion pathology starts at the dendritic spines leading to a loss of spines [68,89]. Experiments carried out in search of a mechanism for inter-cellular spread using cultured cells showed the formation of tunneling nanotubes of 50–200 nm diameter made of actin-rich hollow filaments between the interconnected cells that act as transport conduits for prion-like protein aggregates [77]. These changes indicate the presence of type 6 changes (Table 2) expected from the inter-membrane fusion. The microscopical finding of status spongiosus with coarse vacuolation of the cortex indicates that groups of neurons undergo cell death.

The fact that majority of prion disorders are sporadic in occurrence indicates that several factors need to occur together to induce the specific pathogenic mechanism for the degenerative changes. The presence of amyloid plaques in the transmissible spongiform encephalopathies [135] indicates that the presence of IPM fusion can lead to shared pathological changes similar to that observed in AD. Periodic sharp waves in EEG are characteristic of prion disease. Continued IPM fusion may explain how it can increase the horizontal component of the oscillating potentials and how they can be responsible for the slowing of the normal oscillatory waveforms as explained previously [218]. The disease kuru known to occur in people who consume human brain tissue shows the possibility for the incorporation of modified forms of certain human brain lipids into the lipid membranes that may predispose IPLs to undergo membrane fusion.

5.4. Seizure disorders

Early stages of AD can be associated with seizures [166,227]. Experimentally it was shown that animal models induced by overexpressing mutant amyloid precursor protein (APP) manifest seizures [165]. Diseases where neurodegenerative changes are observed such as HSV1 encephalopathy, prion disease and fronto-temporal dementia are associated with seizures. Based on the present work, the formation of a large number of IPLs that increase the lateral spread of activity can explain (a) the increase in the amplitude observed in spikes, sharps and slow waves recorded during the inter-ictal period and, (b) the increased horizontal component of oscillating potentials contributing to the slowing of the frequency of oscillating potentials [218]. The IPM fusion can explain the observed dendritic spine loss [78] and neurodegenerative changes in seizure disorders.

5.5. Schizophrenia

Schizophrenia affects several domains such as subjective experience, cognition, affect and behavioral expression [167]. Difficulties were found in identifying schizophrenia as a pure neurodegenerative or a neurodevelopmental disorder [154,183]. Even though views towards neurodegenerative pathology may be gaining more attention [7], the absence of convincing evidence for gliosis typically seen in classical neurodegenerative disorders is viewed as a hindrance for considering schizophrenia as a neurodegenerative disorder [45]. Since the disease shows a certain potential to achieve long-term remission and functional recovery [239], it indicates that some reversible changes are responsible for the disease symptoms. Even though antipsychotics relieve the first-person internal sensations of delusions and hallucinations, these medications do not improve the associated cognitive deficits.

An explanation for these features was provided in terms of the possible reversible IPL changes [214].

Several studies have observed excessive loss of grey matter in schizophrenia [34,36]. The development of schizophrenia is associated with a progressive reduction in the number of dendritic spines of the cortical pyramidal neurons [35]. Post-mortem studies in schizophrenic patients showed reduced dendritic spine density in the glutamatergic pyramidal cells [70,73]. A meta-analysis showed reduced whole brain and hippocampal volumes and an increased ventricular volume relative to the healthy controls [197]. A recent 5-year follow up study showed subcortical volume loss in schizophrenic patients who also had significantly smaller hippocampal volume at base line than the controls [221]. All the above results indicate loss of brain tissue, which can be explained in terms of neurodegenerative changes.

The long-term remission and functional recovery seen in schizophrenia [239] indicate the possibility that these changes occur due to the reversible nature of the IPLs and that any irreversible pathology may be terminated by the removal of the affected spines. Reversal of the symptom of hallucinations by treatment with dopamine blockers indicates the possibility that they prevent dendritic spine enlargement induced by dopamine [234] and stop eventual non-specific IPL formation. Both the formation of non-specific functional LINKs and the lack of formation of specific IPLs at locations of convergence of associatively learned sensory inputs can explain cognitive defects. Based on the present work, the aggressive synaptic pruning observed in schizophrenia [62,156] may be resulting from a homeostatic mechanism in response to the IPM fusion changes. The lack of availability of effective treatment for negative symptoms indicates that they may result from loss of spines that lead to lack of formation of specific IPLs required for the induction of internal sensations of normal mental functions and associated motor activity.

One study reported altered fatty acid absolute concentrations, particularly within the cholesteryl esters in the prefrontal cortex of schizophrenic patients [205]. Changes in peripheral blood cell membranes have been observed in schizophrenia. Two recent meta-analyses have discovered substantial evidence for decreased levels of PUFAs such as DHA and arachidonic acid in erythrocyte membranes in schizophrenia patients [220,90]. The role of long-chain omega-3 fatty acids in preventing the development of psychotic disorders in adolescents presenting at the prodromal stage of schizophrenia [4] indicates the possibility that these fatty acids can likely change the membrane lipid composition and prevent the formation of non-specific IPLs that leads to the disease symptoms.

5.6. Other disorders

Changes in membrane lipid composition may explain both cognitive defects and changes in red cell membranes in neuroacanthosis, a disorder associated with abetalipoproteinemia [106]. Mutant proteins in inherited forms of neurodegenerative disorders [136] can contribute towards the IPL fusion. Even though neurodevelopmental disorders are found to have neurodegenerative changes [110,228], a common etiological reason leading to neurodegenerative changes is still not known. Since dopamine receptor blockers are used to reduce motor stereotypies and hyperactivity in children with autism [5,147], dopamine-induced IPL mechanisms at certain levels is likely contributing to the pathology. Overactivation of NMDA receptors can lead to overactivation of the IPLs and in turn can lead to IPM fusion. This along with other contributory factors can lead to neurodegenerative changes [242].

Recent findings regarding the neurodegenerative process in multiple sclerosis [31] may be attributed to changes in the structural integrity necessary for maintaining optimal IPL mechanisms in these disorders. In traumatic brain injury, expression of both amyloid and hyper-phosphorylated tau is reported [211]. Chronic traumatic encephalopathy (CTE), a form of tauopathy, is a progressive degenerative disease found in people who have suffered repetitive brain trauma. Tau-linked neurodegenerative changes observed in CTE are indistinguishable from that in AD [194,16,163]. All the above may be explained in terms of shear injury-mediated cell swelling and disruption of IPLs that can lead to cytoplasmic content mixing.

6. Lipids and membrane stability

6.1. Role of lipids in membrane hemifusion and fusion

The role of lipids in normal membrane fusion steps taking place routinely during synaptic vesicle recycling is reviewed [125]. Based on the semblance hypothesis, the IPL mechanism at the postsynaptic terminal is expected to be limited to the IPM hemifusion stage with strong blockage for its conversion to IPM fusion. Any dysregulation of this checkpoint mechanism or changes in the membrane lipid composition is expected to result in pathological changes of IPM fusion.

6.2. Potential role of dietary lipids

Humans and likely all vertebrates are unable to synthesize n-6 PUFA or n-3 PUFA from the 18-carbon monounsaturated fatty acids due to specific enzyme deficiencies. Humans are also unable to interconvert n-6 PUFA and n-3 PUFA, making these PUFAs independent essential dietary requirements [101]. Different studies have shown direct effect of a dietary deficiency of n-3 fatty acids on impaired learning and memory and other brain disorders [96,13]. Since n-3 fatty acid deficiency is implicated in neurodegeneration [19] and a large number of studies support the protective role of n-3 fatty acids or its derivatives in preventing neurodegeneration [66,206,61], it is likely that these fatty acids have a direct role in maintaining lipid membrane structure. It was reported that consumption of a diet low in n-3 PUFA increases the expression of SNARE complex proteins in the rat hippocampus [172], even though its significance is not yet known.

It is reported that n-3 fatty acids in the diet prevent anesthetic-induced neurodegeneration [129]. This is significant in the context of the present work and that the mechanism of anesthetic action can be explained in terms of the formation of a large number of non-specific IPLs [216]. Chronic dietary deprivation of n-6 fatty acids leads to the rapid loss of docosahexaenoic acid (DHA), which is a major PUFA in the brain [137]. All the above features indicate that essential fatty acids have a major role in maintaining normal membrane lipid composition and in preventing neurodegenerative changes in the absence of other known membrane fusogenic factors.

7. Future directions

The dynamics of the lipid composition of lipid bilayers of the lateral postsynaptic membranes can be undertaken to fully understand the IPL mechanism. The normal IPL mechanism of formation of close contact by hydration exclusion will require new experimental approaches to confirm its occurrence *in vivo*. Since the pathological occurrence of intermittent reversible IPL fusion can evade detection by using the current tools, methods to identify their occurrence by constant real-time monitoring is required. The IPM hemifusion can be studied using new methods [65]. Since age

is a determining factor in many of these disorders, age-related changes in the stability of genes, messenger RNA and proteins required for fatty acid synthesis, elongation, desaturation and the membrane lipid assembly within different neuronal cell types can be carried out. In the light of the previous observations that SNARE proteins can promote hemifusion and complete fusion as alternative outcomes [71], factors that determine the function of this protein need further study.

The differences in locations of D1 and D2 receptor-expressing neurons in the striatum [69] can be used to understand the nature of the IPLs affected in these disorders. Pathological mechanisms for neurodegeneration observed in disorders of gray matter such as neuronal ceroid lipofuscinosis [50] can be studied. Examination of the lipid membrane bilayers of single dendritic spines is currently limited due to several reasons. Information obtained from virtual ultrathin sections of electron tomography ($\sim 5 \times 10^{-9}$ m) necessitates large-scale reconstruction to examine a single dendritic spine of the size nearly 5×10^{-7} m. This will allow identification of the small areas (nearly 10 nm^2) [130] where IPM hemifusion events are expected to take place. These studies can be extended to examine the large number of IPM hemifusion and fusion expected to form during LTP induction and kindling experiments respectively. The effect of cytoplasmic content mixing that may lead to abnormal protein expression and aggregation can be studied using the artificial transfer of cytoplasmic contents using cultured cells. These experiments can be valuable in examining whether self-propagating prion proteins can be induced by cytoplasmic mixing between certain cell types under conditions of altered membrane lipid composition.

8. Conclusion

Since the nervous system generates most of its major functions as internal sensations, it has been very difficult to understand the system operation by examining third-person-accessible features at biochemical, cellular, electrophysiological, and behavioral levels. By keeping the specific mechanism of induction of internal sensation as the single unknown factor, it was possible to build a hypothesis that can provide interconnecting explanations for almost all the third-person findings through the semblance hypothesis. Many findings within different neurodegenerative disorders have provided a sufficiently powerful puzzle for examining the loss of function states of the proposed normal mechanism of the nervous system operations. When common features found in neurodegenerative disorders are organized, they match with the loss of function states of different types of IPLs, the key structural mechanism for the structure-function units of the semblance hypothesis. A summary is shown in Fig. 10.

If this theoretically fitting mechanism is correct, the following therapeutic opportunities are likely feasible. Infection with enveloped viruses that release membrane fusion proteins can be prevented through the development of vaccines against these viruses. Dietary deficiency of lipid precursors can be managed through diet modifications depending on the membrane lipid composition of the individuals. Since aging is a factor associated with neurodegeneration and since stabilized IPLs are resistant to IPM fusion, continued learning can be used as a method to prevent neurodegenerative disorders. Aging-associated reduction in expression of certain proteins (enzymes) in lipid pathways can be studied. It may become possible to replenish these enzymes or the lipid byproducts catalyzed by them. Methods for dendritic spine enlargement to achieve IPL effects such as treatment with L-DOPA may be undertaken safely only when the lipid membrane composition changes and other factors that predispose to IPM fusion are reversed back to near-normal levels. Both the homeostatic mechanism of dendritic spine removal and the

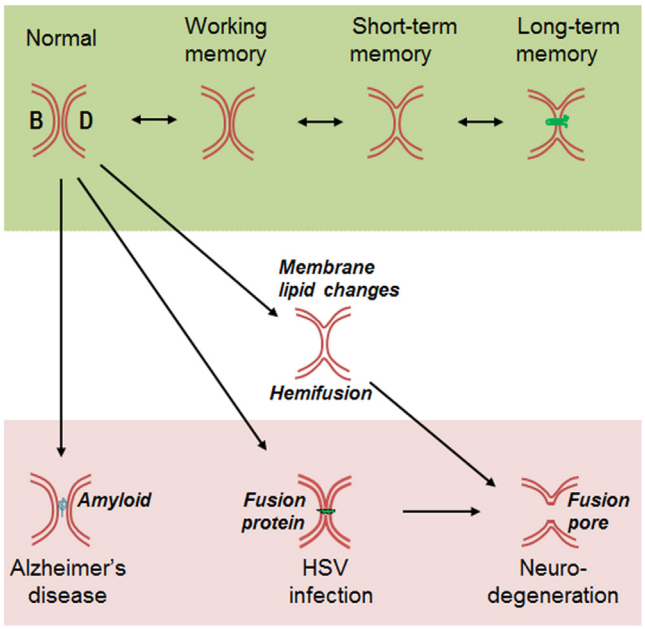

Fig. 10. A summary diagram of the inter-relationship between the inter-postsynaptic functional LINKs (IPLs) in normal functions and neurodegenerative diseases. Most IPLs responsible for working memory reverse back leading to the forgetting of these memories. Working, short- and long-term memories can be explained in terms of the duration of different IPLs (Fig. 2). Amyloid deposition at the inter-postsynaptic membrane (IPM) extracellular matrix space prevents formation of new IPLs. Fusion proteins of enveloped viruses such as herpes simplex virus1 (HSV1) and changes in membrane lipid composition can cause generation of non-specific hemifusion and fusion in the presence of conditions that are favorable for membrane fusion. IPM fusion leads to neurodegenerative changes. B and D are the postsynaptic terminals.

neuronal apoptosis secondary to IPM fusion can be verified when the pathophysiological mechanism leading to microcephaly observed in Zika virus infection will be investigated.

Both the normal intermittent reversible IPM hydration exclusion and the reversible pathological IPM fusion processes taking place at areas smaller than 10 nm^2 are transient in nature. Since both these processes can evade detection, dedicated experiments to capture their occurrence in real time are necessary to confirm the findings made by the present work. In the interim, it is possible to examine whether preventive measures emerging from this work can reduce the incidence of neurodegenerative disorders. Since the present work provides mechanisms that are useful in both preventing and halting the neurodegenerative disorders, an urgent examination of the proposed pathophysiology may save valuable time in understanding these disorders and consequently the mechanism of normal nervous system functions. Based on the present work, understanding the neurodegenerative disorders is likely to require incorporation of lipidomic studies with a special focus at the level of the postsynaptic membranes. The proposed mechanism of loss of function states of normal IPLs should be treated as unproven until further experimental verifications are carried out.

Conflict of interest

U.S. patent application 14/068,835 pertains to an electronic circuit model of the inter-postsynaptic functional LINK.

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