The Psychiatrist: Clinical and Therapeutic Journal

Mini Review Open Access

The Evolution of Mood Disorder Neurological Rehabilitation

Keerthi Kandati*

Department of National Clinical Research, India

Abstract

Proteins in neurodegenerative diseases (NDs) frequently accumulate and are misfolded. There is treatment for NDs, and the molecular processes that lead to this pathological aggregation have been extensively studied. Fibrillary deposits of -synuclein (-Syn), a protein that is thermostable and highly conserved, exacerbate neurodegenerative diseases (NDs) like Alzheimer's, Parkinson's, and Lewy body. As a result, inhibiting -Syn aggregation may be an option for therapeutic treatment. The debasement of target proteins by microscopic particles has gained interest in drug research in recent years as yet another useful method. Functional foods and dietary supplements derived from food's bioactive compounds are also gaining popularity as ND intervention agents. Reports propose that dietary bioactive phospholipids might further develop cognizance and defend neurons because of their capacity to impact psychological wellness and comprehension in vivo and in vitro. However, it is necessary to clarify the mechanisms by which lipids may prevent the pathological aggregation of -Syn. Our investigation of the evidence for the potential instruments that underpin this effect focuses primarily on PLDP-inferred lysophospholipids (LPLs), which have the potential to limit - Syn collection.

Keywords: Lysophospholipids; Neurodegenerative Diseases; Amyloid; A-Synuclein

Introduction

In the majority of brain-related disorders, neurodegeneration has been identified as the pathophysiological hallmark. Misfolding and aggregation of particular proteins into abnormal, toxic species is a common feature of many neurodegenerative diseases (NDs). Planning treatment and ensuring that patients and their families receive the appropriate support can only be accomplished with an early diagnosis. However, drug development faces unique difficulties when developing therapeutic approaches for NDs. Despite the fact that NDs do not have a cure, there are now more options for treatment and support [1]. Multiple system atrophy (MSA), Alzheimer's disease (AD), Lewy body disease (LBD), and Parkinson's disease (PD) are the most prevalent NDs. Since the 1960s, amyloid-like protein aggregation in the brains of ND patients has been observed, and several of these aggregates' three-dimensional structures have been discovered. The development of amyloid-like aggregation protein inhibitors has been aided by these structural data [2]. The presence of amyloids in NDs has only been linked to diseases for decades. Strong evidence also suggests that NDs are characterized by the activation of inflammatory processes. Even in the earliest stages of AD, the brains of patients have elevated levels of pro-inflammatory cytokines and chemokines, activated microglia, and astrocytes. Maturing influences homeostatic cycles that safeguard against protein misfolding and is related with an expansion in oxidative pressure, neuroinflammation, and mitochondrial-lysosomal brokenness, which have been displayed to enact microglia cells and astrocytes straightforwardly [3]. In AD, it has been argued that extracellular amyloid-peptide (A) triggers the activation of microglia and astrocytes, which in turn trigger the release of cytokines such as tumor necrosis factor alpha (TNF-). A production and A-induced neuroinflammation are both enhanced by TNF-signaling. ND progression has been linked to neuroinflammation, oxidative stress, and mitochondrial dysfunction. Resveratrol's neuroprotective effects are said to be due to its ability to control neuroinflammation and inhibit microglial activation. By providing a rich source of phospholipids (PLs) and lysophospholipids (LPLs), our recent study demonstrated that porcine liver decomposition product (PLDP) could improve cognitive function in elderly individuals. Notably, cholesterol and phospholipids are the main lipids in synaptic vesicles. Although LPLs may have anti-neuroinflammatory properties, their concentration of PLDP-derived lipids is not sufficient to provide cognitive benefits. LPLs have been found to be both biologically active molecules and structural components of biological membranes in previous research. A wide range of processes are influenced by LPLs, including neurogenesis in the CNS. These small molecules may have therapeutic potential for NDs, as evidenced by the growing interest in the role of extracellular LPLs in the pathology of NDs [4].

α-Syn Protein, Aggregates, and Inhibitors of Aggregate

α-Syn in Regulating Physiology in the Brain

α -Syn is mostly found in nerve cells in specialized areas called presynaptic terminals in the brain. The equilibrium between the cytosolic and membrane-bound states of -Syn is found in neurons [5]. In the cytosol, -Syn is natively unfolded as a monomer, whereas when it is bound to the membrane, -Syn takes on a helical shape. In early-stage PD-affected regions like the olfactory bulb, dorsal motor nucleus of the vagus, and substantia nigra, Syn is highly expressed in the neuronal cell bodies. -Syn expression is notably regulated throughout development. In rodents, syn mRNA expression begins in the late stages of the embryo and peaks in the first few weeks after birth, after which it decreases. However, it is still unknown how -Syn reaches the synapse and why it prefers synaptic vesicle membranes. For the purpose of reducing the dysfunction that results from protein aggregates in the brain, various therapeutic strategies have been developed, one of which is the direct targeting of proteins that are misfolded. Misfolding and aggregation of specific proteins are hallmarks of NDs. The nervous system of mammals expresses a lot of the -Syn protein, and when too much of it builds up,

***Corresponding author:** Keerthi Kandati, Department of National Clinical Research, India, E-mail: keertthek1andati@gmail.com

Received: 01-Dec-2022, Manuscript No: tpctj-22-83430; **Editor assigned:** 08-Dec-2022, Pre-QC No: tpctj-22-83430 (PQ); **Reviewed:** 22-Dec-2022, QC No: tpctj-22-83430; **Revised:** 26-Dec-2022, Manuscript No: tpctj-22-83430 (R); **Published:** 31-Dec-2022, DOI: 10.4172/tpctj.1000170

Citation: Kandati K (2022) The Evolution of Mood Disorder Neurological Rehabilitation. Psych Clin Ther J 4: 170.

masses called Lewy bodies form. Exosomes, membrane nanovesicles that are secreted by cells in the CNS, have been found to contain -Syn oligomers, which is interesting. Neurons from various brain regions, including the neocortex, hippocampus, substantia nigra, thalamus, and cerebellum, express -Syn at high levels in the central nervous system (CNS). In addition to other synucleinopathies, PD relies heavily on the aggregation of -Syn. Neuronal cell inclusions, axonal spheroids, and oligodendrocyte aggregates (glial cytoplasmic inclusions) that accumulate in MSA are the results of abnormal -Syn, making -Syn fibrils important therapeutic targets in PD and synucleinopathies that are related. With a global prevalence of over 6 million, PD is the second most common ND. Despite the fact that the exact cause of Parkinson's disease (PD) is still unknown, -Syn has emerged as the main molecule in PD pathogenesis. Lewy bodies, which are intracellular inclusions of aggregated -Syn, are a pathological hallmark of PD. The third most prevalent type of degenerative dementia is Lewy body dementia, or dementia with observable Lewy bodies. Visual hallucinations, movement disorders, cognitive issues, difficulty sleeping, erratic attention, and depression are all symptoms of Lewy body dementia, which progresses over time and causes mental function to deteriorate [6].

Ubiquitination and phosphorylation of α-Syn

α -Syn is phosphorylated most frequently in serine and tyrosine residues. It is typically phosphorylated at S129 and S87 in Lewy bodies. Phosphorylation at S129 increases from 5% in healthy brains to about 90% in Lewy bodies, which are strongly linked to Parkinson's disease [7]. However, it is unclear why LBD pathologies like PD and DLB involve extensive phosphorylation. The impact of S129 on -Syn aggregation has been the subject of contradictory in vitro studies. It has been reported that mitochondrial impairment-induced increased Ca2+ influx causes a change in the solubility of -Syn proteins from normally soluble to insoluble and causes Ser129 phosphorylation to produce a signal for proteasomal degradation [8]. -Syn aggregates may continue to undergo phosphorylation because Ser129 phosphorylation contributes to the process of removing excess -Syn. It also interacts with metal ions and various proteins, such as fatty acid-binding protein 3 and lipid membranes. The majority of S87-P-Syn was also found in the membrane fractions of brain homogenates from transgenic animals and diseased human brains. Within the NAC region, S87 is one of the few residues and phosphorylation sites. According to a previous study, S87 phosphorylation destabilizes the helical conformation of membrane-bound -Syn and decreases the protein's lipid-binding affinity around the phosphorylation site, altering its conformation and decreasing its affinity for lipid vesicles. It has been reported that the S87 cryo-TEM structure of -Syn fibrils faces the outside of the fibril; As a result, it can still be used to modify -Syn fibrils in response to disease. The pathogenesis of a number of NDs has been linked to the ubiquitination of protein filaments that have been aggregated or formed [9]. Ubiquitin-Syn is found in Lewy bodies; As a result, their immunoreactivity to anti-ubiquitin antibodies has been demonstrated. -Syn has eight lysine residues that are able to be ubiquitinated, and ubiquitin has multiple internal lysine residues that are able to form polyubiquitin chains. The presence of ubiquitin in synucleinopathies' intracellular inclusions suggests that, like tau in AD's neurofibrillary tangles, abnormally aggregated or misfolded proteins are the target of ubiquitination in these inclusions [10].

The Brain and LPLs

Through the "Lands cycle," PLs and LPLs can join together to maintain lipid homeostasis. As a result of their neurotransmitter and/or neuromodulatory properties, some lipids, like LPLs, may be neuroprotective [11]. Long-chain polyunsaturated unsaturated fats have been found to significantly improve mouse mind phospholipids. According to recent research, LPC is the preferred carrier of polyunsaturated fatty acids into the brain across the BBB. Either the lecithin cholesterol acyltransferase (LCAT) reaction or the hydrolysis of PC by PLA2 (which involves removing a fatty acid group at the sn-2 position) are the processes that result in the production of LPC. According to a Drosophila model, PLA2G6 dysfunction, which causes PARK14-related familial Parkinson's disease, alters the binding affinity between -Syn and the synaptic membrane, causing damage to the phospholipid remodeling pathway and causing -Syn aggregation. The concentration of LPC in healthy individuals' blood plasma typically ranges between 200 and 300 M. Due to its rapid debasement, LPC is readily available and has a short half-life, preventing impairment of various vascular capabilities. Currently, it is thought that activated platelets release LPLs like LPC, LPE, and LPS, which the serum's lyso-PLD turns into LPA. LPC is said to have significant platelet-destroying effects. Several NDs, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and prion diseases, all have impaired platelet function [12]. In NDs, platelet dysfunction is common. Secretory phospholipases' modification of lipoproteins slowed platelet activation and aggregation, according to a recent study. The researchers discovered that LPC is necessary for these effects. LPC is increasingly being recognized as a key factor positively associated with NDs, as evidenced by lower plasma levels of LPC in AD patients [13]. It has been discovered that adult AD patients' blood plasma, cerebrospinal fluid (CSF), and brain tissue contain lower LPC concentrations than healthy adults'. Phosphocholine makes up the headgroup of LPC, and glycerol makes up the backbone. Both of these groups are connected to a variable fatty acid group that can be bound at the sn-1 or sn-2 position. Polyunsaturated fatty acids (PUFAs) are typically bound in tissues and plasma at the sn-2 position, whereas saturated fatty acids (SFAs) are typically bound at the sn-1 position of LPC. The mind gets plasma unsaturated fats principally from two pools: plasma fatty acids without esterification and those with esterification as LPC. According to previous research, FAs bound to LPCs are more efficiently transported across the BBB into the brain than free fatty acids (FAs). containing MFSD2A, a member of the major facilitator superfamily An orphan transporter is a transporter that has been shown to act as a specific LPC receptor, such as the human sodium carbonate electrogenic LPC symporter 1. LPCs carry long-chain PUFAs like DHA across the BBB [14]. According to other studies, the brain can only synthesize a few fatty acids; As a result, the BBB is necessary for the majority of blood-derived fatty acids to enter the brain. However, cholesterol and lipoproteins are unable to cross the BBB under normal physiological conditions. For a little molecule drug to cross the BBB in pharmacologically basic aggregates, the molecule ought to have twofold sub-nuclear characteristics, specifically, a sub-nuclear mass of 400-500 Da and high lipid dissolvability. Accordingly, we conjecture that LPLs could be utilized to make an oral, little atom inhibitor of - Syn misfolding determined to end the movement of infection [15].

Conclusions and prospects for the future

During aggregation in NDs, lipids interact with -Syn, according to a growing number of studies. The formation of amyloids, which are collections of proteins that are associated with each other, is associated with a number of diseases that are frequently associated with older people. The molecular mechanisms that control amyloid formation are still poorly understood. However, when a wide range of molecules,

like lipids, are present in the physiological environment, amyloid formation is clearly visible. Sadly, neither curing nor slowing down the progression of NDs is currently possible. However, numerous novel treatments are currently the subject of clinical research. Understanding the in vitro and in vivo structural properties of -Syn monomers, oligomers, and fibrils is essential for the development of therapeutic drugs. Within PLDP-derived lipids (PEL), we recently discovered functional LPLs. The BBB prevents drugs from passing from the bloodstream to the brain, which is the primary reason why NDs lack effective treatments; New methods for delivering neuro-drugs into the central nervous system have been developed in response to this. As a result, drugs must be altered to improve their delivery. Based on their potential applications and biological activity, LPLs, according to our hypothesis, are extremely appealing research targets. Furthermore, different elements of cell layers (like lipid organization, charge, ebb and flow, and lipid pressing) can regulate the limiting of α-Syn to them. We contend that the association of LPLs and -Syn oligomers at an early stage of the aggregation process is the cause of the observed inhibitory effect on fibril formation. The fact that non-monomeric -Syn structures associate with the LPL aggregates is an essential feature of this mechanism. In vivo amyloid formation, where aggregation takes place in a lipid-rich environment, similar mechanisms of action may be relevant. When bound to lipid interfaces under normal conditions, -Syn takes on a secondary structure that is helical. This could help explain the different ways that LPLs affect the formation of amyloid in different proteins. LPLs' capacity to bind directly to -Syn and prevent its aggregation suggests that they could be useful therapeutic agents for ND prevention. This would prevent the aggregates from spreading from one cell to the next. As a result, the primary phospholipids found in PEL and their effects require additional research.

References

1. McCracken M, DeHaan G, Obedin-Maliver J (2022) Perinatal considerations for care of transgender and nonbinary people: A narrative review. Curr Opin Obstet 34: 62-68.
2. Institute of Medicine, Board on the Health of Select Populations, Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities (2011) The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. National Academies Press (US), Washington (DC), USA.
3. Dragon CN, Guerino P, Ewald E, Laffan AM (2017) Transgender Medicare beneficiaries and chronic conditions: Exploring fee-for-service claims data. LGBT Health. 4:404-411.
4. National Center for Transgender Equality: Washington, DC, USA, 2011.
5. Fredriksen-Goldsen KI, Kim H-J, Bryan AE, Shiu C, Emlet CA (2017)The cascading effects of marginalization and pathways of resilience in attaining good health among LGBT older adults. Gerontologist 57:72-83.
6. Jessen F, Amariglio RE, Van Boxtel M, Breteler M, Ceccaldi M, et al. (2014) A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement10:844-852.
7. López-Sanz D, Bruña R, Delgado-Losada ML, López-Higes R, Marcos-Dolado A, et al. (2019) Electrophysiological brain signatures for the classification of subjective cognitive decline: Towards an individual detection in the preclinical stages of dementia. Alzheimers Res Ther. 11- 49.
8. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, et al. (2011) Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:280-292.
9. Hill NL, Mogle J, Wion R, Munoz E, DePasquale N, et al. (2016) Subjective cognitive impairment and affective symptoms: A systematic review. Gerontologist 56:109-127.
10. Flatt JD, Johnson JK., Karpiak SE, Seidel L, Larson B, et al. (2018) Correlates of subjective cognitive decline in lesbian, gay, bisexual, and transgender older adults. J Alzheimers Dis 64:91-102.
11. Jang Y, Haley WE, Choi EY, Franco Y (2021) Racial/ethnic differences in correspondence between subjective cognitive ratings and cognitive impairment. Am J Geriatr Psychiatry 30: 627-635.
12. O'Shea DM, Dotson VM, Fieo RA, Tsapanou A, Zahodne L, et al. (2016) Older adults with poor self-rated memory have less depressive symptoms and better memory performance when perceived self-efficacy is high. Int J Geriatr Psychiatry 31:783-790.
13. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, et al .(2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:270-279.
14. Chochinov HM, Wilson KG, Enns M, Lander S (1997) "Are you depressed?" Screening for depression in the terminally ill. Am J Psychiatry 154:674-676.
15. Gorman T, Dropkin J, Kamen J, Nimbalkar S, Zuckerman N, et al. (2013) A Controlling health hazards to hospital workers. New Solut. 23:1-167.