Inositol’s Unproper Metabolism Impact on Neurodegenerative Process

Subjects: Neurosciences

Contributor: Maria Derkaczew , Piotr Martyniuk , Adam Osowski , Joanna Wojtkiewicz

One of the most common cyclitols found in eukaryotic cells - Myo-inositol (MI) and its derivatives play a key role in many cellular processes such as ion channel physiology, signal transduction, phosphate storage, cell wall formation, membrane biogenesis and osmoregulation.

myo-inositol d-pinitol inositol phosphates neurodegenerative disorders

1. Introduction

In the brain, constant changes in inositol levels in extracellular and intracellular compartments regulate the activity of neuronal and glial cells [1]. MI and scyllo-inositol (SI) are the most common forms of inositol found in the brain. MI is found in large amounts in the glial cells and acts as an osmolyte. The concentrations of MI and SI are several times higher than the values found in the blood serum and are on average 100 times higher [2][3]. In the nervous system, the highest concentration of inositol is in the brain - 6 mM. Then, MI occurs in cerebrospinal fluid (0,2 mM) and plasma of nervous cells (0.03 mM) [4][5][6]. SI is found in relatively high concentrations in the human brain than in other tissues, although it has a 12 times lower concentration than mI [7][8]. In nervous system diseases, researchers notice the occurrence of unproper MI’s metabolism to phosphates and its secondary accumulation. MI has been found to be a marker of gliosis in demyelinating lesions. Elevated levels of MI have also been documented in glioblastomas. MI is also involved in the phosphatidylinositol secondary messenger system, which is associated with depression (91). Disorders in MI’s metabolism and distribution have been found in many neurodegenerative diseases.

2. Alzheimer’s Disease

Alzheimer’s Disease (AD) is a chronic, progressive, neurodegenerative disease of the brain that causes nerve cell atrophy. AD is characterized by the occurrence of progressive dementia and at the same time is the most common cause of dementia among the elderly [9]. In the course of AD, researchers can distinguish symptoms such as memory loss and the progressive loss of cognitive functions [10]. Common neuropathological features of AD are neuronal loss, the aggregation of insoluble forms of β-amyloid (Aβ) forming plaques in extracellular spaces and microtubule τ protein hyperphosphorylation in the form of neurofibrillary tangles (NFTs) located in neuronal cells. Changes are usually located firstly in the cortex of frontal and temporal lobes and then slowly spread to the other parts of the brain tissue [11]. Researchers can distinguish the sporadic form of AD (Sporadic Alzheimer’s Disease -

SAD) and the familial form (Familial Alzheimer's disease - FAD). FAD occurs much less frequently in about 5% of AD patients [12]. SAD tends to occur in the elderly and is the most common form of AD, while FAD will appear more frequently in middle age and is associated with mutations in the genes encoding the presenilin 1 and 2 proteins (PS 1,2) and the amyloid precursor protein (APP) [10][13][14][15][16]. APP is normally transformed through several reactions of proteolysis into two types of Aβ - Aβ40 and Aβ42.

In AD researchers can observe the unfavourable ratio of Aβ42 and Aβ40 levels, with a predominance of Aβ42 - the more neurodegenerating one [17][18]. In AD patients according to the literature inositol metabolism is disturbed in several ways. It was proven that AD patients have higher concentrations of MI and SI in their brains compared to healthy people, despite of pathogenesis of the illness [19][20][21]. In Firbank et al. paper AD patients' MI levels seemed to be raised by about 15% but with no evidence for an increase in any particular brain region. Higher MI levels are also seen in adults with Down's syndrome and it has been shown that these patients will mostly develop AD in the future [22]. High MI levels are also detected in presymptomatic patients and those with mild cognitive impairment (MCI), which indicates the possibility of using MI as a marker of the early stages of AD [19][23][24][25]. The metabolism of inositol in AD patients can be impaired at every stage causing the deregulation of Ca^{2+} neuronal homeostasis which leads to neurodegenerative disorders. The intracellular calcium concentration must be constantly maintained at the appropriate level for all processes to take place properly. Disturbances in calcium levels can lead to serious malfunctions in its functioning. Calcium regulates the processes of growth, development and apoptosis, and its inadequate level can even lead to cell death [26][27][28][29]. In human cells, the level of calcium is regulated by several mechanisms. Calcium can enter cells from the extracellular space or it can be taken from the intracellular calcium store, which is the ER. Many studies indicate the enormous role of MI derivatives in regulating these processes. The role of IP3 in the elevation of intracellular calcium levels by releasing it from ER was described, but it is also worth mentioning that the activation of calcium influx from the extracellular space - the so-called Ca-influx also plays a significant role in the pathomechanism of AD and other neurodegenerative disorders [30][31]. There are reports indicating that Ca-influx can be as well stimulated by another MI derivative - Inositol 1,3,4,5-tetrakisphosphate (IP4) [32][33]. Many papers considering this topic focused on disruptions to the function of IP3R. Former literature report a decreased level of binding sites of IP3R in AD patients [34][35] and more recent studies highlight the over-activation of these channels. There is a strong correlation between the overactivity of IP3R and mutations in the presenilin genes [36][37][38]. In presenilin transgenic mice (PS1 FAD mutant mice) increased activity of IP3R was observed which subsequently enhances IICR and leads to increased intracellular calcium levels. Under conditions of increased Ca^{2+} levels, together with the additional oxidative stress characteristic of AD, a non-specific pore in the inner mitochondrial membrane is opened, known as the mitochondrial permeability transition pore (mPTP). The opening of mPTP allows the passage of molecules smaller than 1.5 kDa, and therefore, also protons. Consequently, this leads to the depletion of ATP stores and cell death [13][39][40][41]. It was proven that genetic modifications including the reduction of IP3R1 contributed to the equalization of Ca^{2+} levels [13][42]. Moreover, elevated levels of calcium activate calpain - a protein belonging to the family of calcium-dependent, non-lysosomal cystine proteases. Calpain has many isoforms, but to date, two of them have been most extensively studied - μ-calpain and m-calpain, otherwise known as calpain 1 and calpain 2, respectively. Both of them are activated by calcium ions and inhibited by a specific endogenous inhibitor - calpastatin (CAST).

Calpain regulates many processes inside the cell, including the proper course of the cell cycle, cell proliferation, signal transduction, proper functioning of key protein kinases and phosphatases, apoptosis, memory, learning and in neurons - long term potentiation (LTP) which is a specific function for this type of cell [43][44]. With increasing age and in the course of neurodegenerative disorders such as AD, there is an excessive, uncontrolled activation of calpain, as a response to higher levels of intracellular Ca^{2+}. It was shown that CAST concentrations are additionally lowered in the prefrontal cortex in AD patients, thus, apart from the over-stimulation of calpain by calcium, its inhibition also does not work properly [45][46]. Overly elevated calpain promotes the aggregation of Aβ and NFTs, as well as induces the dephosphorylation (deactivation) of cAMP-response element-binding protein (CREB) - a key protein essential for converting a short-term memory to a long-term memory and other memory and learning processes [47]. Opinions about the role of calcium in the process of direct cell damage are divided, and the authors now tend to emphasize the subtle effects of calcium on the slow progression of neurodegenerative changes, rather than the rapid process leading to cell death [48][49]. Another interesting linkage between disturbances in MI metabolism and the presence of AD is MI's influence on catalase. Catalase allows the H_2O_2 to break down to harmless water and oxygen, and thus, together with other antioxidants such as glutathione peroxidase, reduces the formation of reactive oxygen species (ROS) and saves the cells from oxidative stress [50]. One of the most recent works on the influence of MI on the course of AD focuses on the inhibition of catalase function by MI, while other polyols such as mannitol, sorbitol and glycerol have been shown to have an activating effect on catalase. Researchers suggest that the inhibitory effect of MI may be due to MI binding to an active site of catalase or that MI causes conformational changes in the structure which can result in loss of activity. The loss of the antioxidant capacity of catalase may result in the occurrence of oxidative stress in cells, which was proven to be significantly increased in the course of AD and other neurodegenerative diseases [24][51]. On the other hand, previous reports suggest that MI supplementation results in an increase in the activity of antioxidant agents. Jiang et al. research has shown that antioxidative enzymes' activity such as catalase, glutathione peroxidase and glutathione reductase were improved along with the increasing MI levels in the diet of juvenile Jian carp (*Cyprinus carpio* var. *Jian*) [52].

3. Parkinson's Disease

Parkinson's Disease (PD) is the second most common neurodegenerative disease after AD, occurring in about 2–3% of people over the age of 65. In its course, there is a gradual loss of substantia nigra neurons leading to a decrease in dopamine levels in the striatal brain regions and the deposition of intracellular aggregates of α-synuclein. Many researchers also emphasize the important role of progressive dysfunction of mitochondrial function and the resulting increase in oxidative stress and increase in ROS. Clinical manifestations of PD include bradykinesia and at least one of the additional motor impairments: rigidity or rest tremor. Motor disorders usually occur asymmetrically [53].

Research on animals and cells has shown that IP6 has a protective effect on nerve cells in models of Parkinson's disease. Researchers have demonstrated significant protection against ROS and lipid peroxidation product malondialdehyde (MDA) in PD's model cells - 6-OHDA (6-hydroxydopamine) previously exposed to IP6. IP6 was

shown to inhibit the activation of key proteins involved in apoptosis. Therefore, IP6 due to its anti-apoptotic effect is proven to be neuroprotective against the loss of dopaminergic neurons in PD model cells [54][55].

Considering PD, the researchers also focused on examining the levels of receptors for IP3 and, as in older studies on AD, showed reduced levels of IP3 binding sites. A 50% reduced level of IP3 binding sites in the caudate nucleus, putamen and pallidum with no differences in the frontal cortex at the same time [56].

PD is still diagnosed based on the presence of characteristic clinical symptoms when the disease is already at a significant stage. Many authors have searched for potential diagnostic biomarkers of PD and other neurodegenerative diseases. Magnetic resonance spectroscopy (MRS) is a useful tool that allows for quantitative, non-invasive analysis of selected brain region biochemistry [57]. Of the substances present in the brain that have been studied, many researchers have focused on evaluating the concentration of MI. In Mazuel et al.'s research PD patients and healthy controls were examined with the use of hydrogen 1 proton magnetic resonance spectroscopy (^{1}H-MRS) for the assessment of the metabolic profile in the putamen. As a result, the MI was significantly lower in drug-off PD patients and the MI level did not change even when the therapy was reintroduced [58]. Gröger et al. also used ^{1}H-MRS to investigate the distribution of brain metabolites and focused on the ratios between different substations. It has been shown that the rostral substantia nigra regions of PD patients showed a trend towards decreased MI and total creatine (creatine + phosphocreatine, tCr) ratio compared with healthy controls whereas in the caudal substantia nigra regions the MI/Cr ratios were increased in PD patients compared with healthy controls [59][60].

Progressive Supranuclear Palsy (PSP) also known as Steele–Richardson–Olszewski syndrome is a chronic neurodegenerative disorder also involving the deposition of Tau protein aggregates, clinically resembling PD, and therefore, was often being misdiagnosed for this reason in the past. Typical symptoms of PSP include bradykinesia with disproportionate postural instability, upright posture with neck stiffness, frontal behavioral and cognitive changes, vertical gaze palsy and other brainstem deficits [61]. One of the areas of the brain affected by the disease is the Supplementary Motor Area (SMA). An Italian group of researchers focused on demonstrating PSP-specific neurobiochemical changes within the SMA using ^{1}H-MRS [8]. Research has shown reduced scyllo-inositol levels in the SMA portion of the brains of PSP patients. The researchers stress that there are reports stating the SI's neuroprotective ability against the deposition of protein aggregates in neurodegenerative diseases. In another paper, researchers administered 12 g of inositol daily to nine PD patients. They showed no significant positive MI effects but suggested possible beneficial effects of supplementation in patients with additional depressive symptoms and anxiety [62].

4. Huntington's Disease

Huntington's disease (HD) is a progressive, autosomal-dominant neurodegenerative disorder, manifested by chorea, dystonia, decreased motor coordination, cognitive decline and behavioral changes. Usually, the first symptoms of the disease appear in middle age but may occur at any stage of the patient's life [63][64]. The genetic basis of HD is an occurrence of expanded CAG repeat in exon 1 of the huntingtin gene (polyglutamine, polyQ

expansion) causing the formation of mutant huntingtin (mHtt) protein. mHtt occurs is found in all types of cells, but it appears to be toxic only for neurons of specific brain regions: cortex, caudate nucleus and putamen [13]. Many reports confirm, that in HD deregulation of IP3R also takes place, this time due to the direct binding of mHtt protein to IP3R1 in its C-terminal region [48]. It was proven that mHtt sensitized activation of IP3R by IP3 in medium spiny striatal neurons (MSNs), while normal huntingtin protein showed no such ability. HD transgenic model mice used in research considering alterations in IP3R functions are yeast artificial chromosome (YAC) and mice with a targeted disruption of both Htt-associated protein-1A (HAP1) gene alleles. HAP1 was the first Htt-binding protein to be found. It was shown that HAP1 is present in MSNs and it intensifies the action of mHtt, resulting in increased IICR and elevated calcium levels [65]. Moreover, IP3R is an allosteric protein and its function can be disrupted by changes in its conformation. One of the enzymes that can disturb IP3R's allostery is transglutaminase type 2 (TG2) and its regulation is based on the covalent posttranslational modification of the Gln2746 residue which TG2 tethers to the communicating subunit [66]. Both Gln2746 changes and IP3R dysregulation were detected in HD models, confirming the involvement of IP3R dysregulation in disease pathogenesis [48][67]. TG2 ablation in model mice prolonged their lifespan and improved motor function [13]. Other researchers report that in the course of HD, there is an increase in the activity of inositol hexakisphosphate kinase type 2 (IP6K2), which, among other things, leads to a reduction in Akt phosphorylation, which may lead to cell death and promotes autophagy. Upon activation, IP6K2 is released from the nucleoplasm into the cytoplasm. It was shown that in HD lymphoblasts IP6K2 was present mainly in the cytoplasm of the cell, while in control cells it remained in the nucleus. IP6K2 catalyzes the reaction of transforming IP6 into inositol pyrophosphate diphosphoinositolpentakisphopshate (IP7; PPIP5). In HD lymphoblast cells, increased levels of IP7 were detected compared to control cells, and IP7 promotes cell death [68][69].

5. Spinocerebellar Ataxias

Another neurodegenerative disorder group that will be discussed is Spinocerebellar Ataxias (SCAs). SCAs are a group of hereditary autosomal dominant neurodegenerative disorders characterized by progressive ataxia. To date, there are more than 40 identified types of SCA [70]. Each of the SCA types are based on a mutation, deletion or polyglutamine (poly-Q) expansion at a different gene locus [71]. The characteristic symptoms in the course of SCA include loss of balance and coordination, dysarthria and nystagmus [72]. SCAs cause damage to the brain tissue and mostly affects the cerebellar Purkinje neurons, leading to cerebellar cortex atrophy, neuronal loss, and irreversible degeneration of spinocerebellar tracts, dentate nucleus and pontine[73]. There are many reports in the literature on the relationship between SCAs and dysregulation of IP3R function. Some papers indicate that reduced IP3R abundance is observed in SCAs, while others emphasize the phenomenon of hypersensitivity of IP3R for its ligand—IP3, and excessive IP3R activation [74].

SCA1, SCA2 and SCA3 are caused by intracellular poly-Q (CAG) expansions of cytosolic ataxin protein. It is already known that researchers are looking for potential diagnostic biomarkers for the effective detection of neurodegenerative diseases. In the Oz et al. paper, researchers focused on the analysis of levels of total NAA (*N*-acetylaspartate + *N*-acetylaspartylglutamate, tNAA), glutamate, glutamine, tCr and MI. The levels of tNAA and

glutamate were decreased, while glutamine, tCR and MI levels were elevated. Along with increased neuronal loss and astrocytosis, elevated levels of MI were detected in the pons and cerebellar hemispheres of SCA 1 patients. Differences in MI levels in the study groups allowed for the complete separation of patient and healthy controls (104). In SCA2 there is the occurrence of Purkinje cells depletion and degeneration of the inferior olives, pontine nuclei, as well as pontocerebellar fibers. Ataxin protein-2 specifically binds the IP3R and increases IP3R sensitivity to its activation by IP3. Due to the IP3R overactivation supranormal calcium release from Purkinje cells’ endoplasmic reticulum can be observed, elevated levels of Ca^{2+} play a key role in the development of neurodegenerative pathologies. In the paper by Kasumu et al., the authors present a study on a SCA2-58Q transgenic mouse model. In SCA2-58Q mice the IP3R activation is chronically downregulated consequently lowering related calcium signaling. This downregulation is obtained through overexpression of the Inositol 1,4,5-phosphatase enzyme (5PP) in Purkinje cells of SCA2 transgenic mice. Their results supported the hypothesis that 5PP overexpression suppresses InsP3-induced Ca^{2+} release, and moreover, that Ca^{2+} release suppression prevents the progressive dysfunction of Purkinje cells in SCA2 mice [71]. SCA-3 is less severe than SCA-2 (25).

The deletion of the IP3R1 gene located on chromosome 3 leads to SCA type 15/16 with late/adult onset, SCA 29 with an early onset type, and also sporadic infantile-onset SCA [75][76][77][78]. Researchers suggest that deletion of the IP3R/ITPR1 gene leads to impaired IP3R function. A Western blot of lymphoblastoid cell line proteins confirmed reduced IP3R levels. In conclusion, gene mutations in the course of SCAs lead to reduced activity, as well as IP3R levels.

References

1. López-Gambero, A.J.; Sanjuan, C.; Serrano-Castro, P.J.; Suárez, J.; De Fonseca, F.R. The Biomedical Uses of Inositols: A Nutraceutical Approach to Metabolic Dysfunction in Aging and Neurodegenerative Diseases. Biomedicines 2020, 8, 295.
2. Haris, M.; Cai, K.; Singh, A.; Hariharan, H.; Reddy, R. In Vivo Mapping of Brain Myo-Inositol. Neuroimage 2011, 54, 2079–2085.
3. Thomas, M.P.; Mills, S.J.; Potter, B.V.L. The “Other” Inositols and Their Phosphates: Synthesis, Biology, and Medicine (with Recent Advances in Myo-Inositol Chemistry). Angew. Chem. Int. Ed. 2016, 55, 1614–1650.
4. Owczarczyk-Saczonek, A.; Lahuta, L.B.; Ligor, M.; Placek, W.; Górecki, R.J.; Buszewski, B. The Healing-Promoting Properties of Selected Cyclitols—A Review. Nutrients 2018, 10, 1891.
5. Seaquist, E.R.; Gruetter, R. Identification of a High Concentration of Scyllo-Inositol in the Brain of a Healthy Human Subject Using 1H- and 13C-NMR. Magn. Reson. Med. 1998, 39, 313–316.
6. Spector, R.; Lorenzo, A.V. Folate Transport in the Central Nervous System. Am. J. Physiol. 1975, 229, 777–782.

7. Choi, J.-K.; Carreras, I.; Dedeoglu, A.; Jenkins, B.G. Detection of Increased Scyllo-Inositol in Brain with Magnetic Resonance Spectroscopy after Dietary Supplementation in Alzheimer’s Disease Mouse Models. Neuropharmacology 2010, 59, 353–357.
8. Barbagallo, G.; Morelli, M.; Quattrone, A.; Chiriaco, C.; Vaccaro, M.G.; Gullà, D.; Rocca, F.; Caracciolo, M.; Novellino, F.; Sarica, A.; et al. In Vivo Evidence for Decreased Scyllo-Inositol Levels in the Supplementary Motor Area of Patients with Progressive Supranuclear Palsy: A Proton MR Spectroscopy Study. Park. Relat. Disord. 2019, 62, 185–191.
9. Cummings, J.L.; Cole, G. Alzheimer Disease. Jama 2002, 287, 2335–2338.
10. Gaugler, J.; James, B.; Johnson, T.; Scholz, K.; Weuve, J. 2016 Alzheimer’s Disease Facts and Figures. Alzheimers Dement. 2016, 12, 459–509.
11. Masters, C.L.; Bateman, R.; Blennow, K.; Rowe, C.C.; Sperling, R.A.; Cummings, J.L. Alzheimer’s Disease. Nat. Rev. Dis. Prim. 2015, 1, 15056.
12. Harman, D. Alzheimer’s Disease: Role of Aging in Pathogenesis. Ann. N. Y. Acad. Sci. 2002, 959, 384–395.
13. Egorova, P.A.; Bezprozvanny, I.B. Inositol 1,4,5-Trisphosphate Receptors and Neurodegenerative Disorders. FEBS J. 2018, 285, 3547–3565.
14. Cruts, M.; Hendriks, L.; Van Broeckhoven, C. The Presenilin Genes: A New Gene Family Involved in Alzheimer Disease Pathology. Hum. Mol. Genet. 1996, 5, 1449–1455.
15. Cruts, M.; Van Broeckhoven, C. Presenilin Mutations in Alzheimer’s Disease. Hum. Mutat. 1998, 11, 183–190.
16. Hutton, M.; Hardy, J. The Presenilins and Alzheimer’s Disease. Hum. Mol. Genet. 1997, 6, 1639–1646.
17. Hansson, O.; Lehmann, S.; Otto, M.; Zetterberg, H.; Lewczuk, P. Advantages and Disadvantages of the Use of the CSF Amyloid β (Aβ) 42/40 Ratio in the Diagnosis of Alzheimer’s Disease. Alzheimers Res. Ther. 2019, 11, 34.
18. O’Neill, C.; Cowburn, R.F.; Bonkale, W.L.; Ohm, T.G.; Fastbom, J.; Carmody, M.; Kelliher, M. Dysfunctional Intracellular Calcium Homoeostasis: A Central Cause of Neurodegeneration in Alzheimer’s Disease. Biochem. Soc. Symp. 2001, 67, 177–194.
19. Huang, W.; Alexander, G.E.; Daly, E.M.; Shetty, H.U.; Krasuski, J.S.; Rapoport, S.I.; Schapiro, M.B. High Brain Myo-Inositol Levels in the Predementia Phase of Alzheimer’s Disease in Adults with Down’s Syndrome: A 1H MRS Study. Am. J. Psychiatry 1999, 156, 1879–1886.
20. Chen, S.Q.; Wang, P.J.; Ten, G.J.; Zhan, W.; Li, M.H.; Zang, F.C. Role of Myo-Inositol by Magnetic Resonance Spectroscopy in Early Diagnosis of Alzheimer’s Disease in APP/PS1 Transgenic Mice. Dement. Geriatr. Cogn. Disord. 2009, 28, 558–566.

21. Griffith, H.R.; den Hollander, J.A.; Stewart, C.C.; Evanochko, W.T.; Buchthal, S.D.; Harrell, L.E.; Zamrini, E.Y.; Brockington, J.C.; Marson, D.C. Elevated Brain Scyllo-inositol Concentrations in Patients with Alzheimer’s Disease. NMR Biomed. Int. J. Devoted Dev. Appl. Magn. Reson. In Vivo 2007, 20, 709–716.
22. Firbank, M.J.; Harrison, R.M.; O’Brien, J.T. A Comprehensive Review of Proton Magnetic Resonance Spectroscopy. Dement. Geriatr. Cogn. Disord. 2002, 14, 64–76.
23. Jaworska, A.; Dzbek, J.; Styczynska, M.; Kuznicki, J. Analysis of Calcium Homeostasis in Fresh Lymphocytes from Patients with Sporadic Alzheimer’s Disease or Mild Cognitive Impairment. Biochim. Biophys. Acta Mol. Cell Res. 2013, 1833, 1692–1699.
24. Ali, F.; Manzoor, U.; Bhattacharya, R.; Bansal, A.K.; Chandrashekharaiah, K.S.; Singh, L.R.; Saraswati, S.M.; Uversky, V.; Dar, T.A. Brain Metabolite, Myo-Inositol, Inhibits Catalase Activity: A Mechanism of the Distortion of the Antioxidant Defense System in Alzheimer’s Disease. ACS Omega 2022, 7, 12690–12700.
25. Doraiswamy, P.M.; Charles, H.C.; Krishnan, K.R.R. Prediction of Cognitive Decline in Early Alzheimer’s Disease. Lancet 1998, 352, 1678.
26. Wang, X.; Zheng, W. Ca2+ Homeostasis Dysregulation in Alzheimer’s Disease: A Focus on Plasma Membrane and Cell Organelles. FASEB J. 2019, 33, 6697–6712.
27. Huang, H.M.; Toral-Barza, L.; Thaler, H.; Tofel-Grehl, B.; Gibson, G.E. Inositol Phosphates and Intracellular Calcium after Bradykinin Stimulation in Fibroblasts from Young, Normal Aged and Alzheimer Donors. Neurobiol. Aging 1991, 12, 469–473.
28. Berridge, M.J. The Inositol Trisphosphate/Calcium Signaling Pathway in Health and Disease. Physiol. Rev. 2016, 96, 1261–1296.
29. Seo, M.D.; Enomoto, M.; Ishiyama, N.; Stathopulos, P.B.; Ikura, M. Structural Insights into Endoplasmic Reticulum Stored Calcium Regulation by Inositol 1,4,5-Trisphosphate and Ryanodine Receptors. Biochim. Biophys. Acta Mol. Cell Res. 2014, 1853, 1980–1991.
30. Hinterberger, M.; Fischer, P. Folate and Alzheimer: When Time Matters. J. Neural Transm. 2013, 120, 211–224.
31. Blanchard, B.J.; Thomas, V.L.; Ingram, V.M. Mechanism of Membrane Depolarization Caused by the Alzheimer Aβ1-42 Peptide. Biochem. Biophys. Res. Commun. 2002, 293, 1197–1203.
32. LÜckhoff, A.; Clapham, D.E. E. Inositol 1, 3, 4, 5-Tetrakisphosphate Activates an Endothelial Ca2+-Permeable Channel. Nature 1992, 355, 356–358.
33. Tsubokawa, H.; Oguro, K.; Robinson, H.P.C.; Masuzawa, T.; Rhee, T.S.G.; Takenawa, T.; Kawai, N. Inositol 1,3,4,5-Tetrakisphosphate as a Mediator of Neuronal Death in Ischemic Hippocampus. Neuroscience 1994, 59, 291–297.

34. Haug, L.S.; Østvold, A.C.; Cowburn, R.F.; Winblad, B.; Bogdanovich, N.; Walaas, S.I. Decreased inositol (1, 4, 5)-trisphosphate receptor levels in Alzheimer’s disease cerebral cortex: Selectivity of changes and possible correlation to pathological severity. Neurodegeneration 1996, 5, 169–176.
35. Young, L.T.; Kish, S.J.; Li, P.P.; Warsh, J.J. Decreased Brain Inositol 1,4,5-Trisphosphate Binding in Alzheimer’s Disease. Neurosci. Lett. 1988, 94, 198–202.
36. Mak, D.O.D.; Cheung, K.H.; Toglia, P.; Foskett, J.K.; Ullah, G. Analyzing and Quantifying the Gain-of-Function Enhancement of IP3 Receptor Gating by Familial Alzheimer’s Disease-Causing Mutants in Presenilins. PLoS Comput. Biol. 2015, 11, e1004529.
37. Cheung, K.H.; Mei, L.; Mak, D.O.D.; Hayashi, I.; Iwatsubo, T.; Kang, D.E.; Foskett, J.K. Gain-of-Function Enhancement of IP3 Receptor Modal Gating by Familial Alzheimer’s Disease-Linked Presenilin Mutants in Human Cells and Mouse Neurons. Sci. Signal. 2010, 3, ra22.
38. Toglia, P.; Ullah, G. The Gain-of-Function Enhancement of IP3-Receptor Channel Gating by Familial Alzheimer’s Disease-Linked Presenilin Mutants Increases the Open Probability of Mitochondrial Permeability Transition Pore. Cell Calcium 2016, 60, 13–24.
39. Elder, G.A.; Sosa, M.A.G.; De Gasperi, R.; Dickstein, D.L.; Hof, P.R. Presenilin Transgenic Mice as Models of Alzheimer’s Disease. Brain Struct. Funct. 2010, 214, 127–143.
40. Halestrap, A.P. What Is the Mitochondrial Permeability Transition Pore? J. Mol. Cell. Cardiol. 2009, 46, 821–831.
41. Baumgartner, H.K.; Gerasimenko, J.V.; Thorne, C.; Ferdek, P.; Pozzan, T.; Tepikin, A.V.; Petersen, O.H.; Sutton, R.; Watson, A.J.M.; Gerasimenko, O.V. Calcium Elevation in Mitochondria Is the Main Ca2+ Requirement for Mitochondrial Permeability Transition Pore (MPTP) Opening. J. Biol. Chem. 2009, 284, 20796–20803.
42. Shilling, D.; Müller, M.; Takano, H.; Mak, D.O.D.; Abel, T.; Coulter, D.A.; Foskett, J.K. Suppression of InsP3 Receptor-Mediated Ca2+ Signaling Alleviates Mutant Presenilin-Linked Familial Alzheimer’s Disease Pathogenesis. J. Neurosci. 2014, 34, 6910–6923.
43. Nixon, R.A.; Saito, K.I.; Grynspan, F.; Griffin, W.R.; Katayama, S.; Honda, T.; Mohan, P.S.; Shea, T.B.; Beermann, M. Calcium-Activated Neutral Proteinase (Calpain) System in Aging and Alzheimer’s Disease. Ann. N. Y. Acad. Sci. 1994, 747, 77–91.
44. Sorimachi, H.; Hata, S.; Ono, Y. Calpain chronicle—An enzyme family under multidisciplinary characterization. 2011, 87, 287-327. Proc. Jpn. Acad. Ser. B 2011, 87, 287–327.
45. Higuchi, M.; Tomioka, M.; Takano, J.; Shirotani, K.; Iwata, N.; Masumoto, H.; Maki, M.; Itohara, S.; Saido, T.C. Distinct Mechanistic Roles of Calpain and Caspase Activation in Neurodegeneration as Revealed in Mice Overexpressing Their Specific Inhibitors. J. Biol. Chem. 2005, 280, 15229–15237.

46. Rao, M.V.; Mohan, P.S.; Peterhoff, C.M.; Yang, D.S.; Schmidt, S.D.; Stavrides, P.H.; Campbell, J.; Chen, Y.; Jiang, Y.; Paskevich, P.A.; et al. Marked Calpastatin (CAST) Depletion in Alzheimer’s Disease Accelerates Cytoskeleton Disruption and Neurodegeneration: Neuroprotection by CAST Overexpression. J. Neurosci. 2008, 28, 12241–12254.
47. Mahaman, Y.A.R.; Huang, F.; Afewerky, H.K.; Maibouge, T.M.S.; Ghose, B.; Wang, X. Involvement of Calpain in the Neuropathogenesis of Alzheimer’s Disease. Med. Res. Rev. 2019, 39, 608–630.
48. Takada, S.H.; Ikebara, J.M.; de Sousa, E.; Cardoso, D.S.; Resende, R.R.; Ulrich, H.; Rückl, M.; Rüdiger, S.; Kihara, A.H. Determining the Roles of Inositol Trisphosphate Receptors in Neurodegeneration: Interdisciplinary Perspectives on a Complex Topic. Mol. Neurobiol. 2017, 54, 6870–6884.
49. Frazier, H.N.; Maimaiti, S.; Anderson, K.L.; Brewer, L.D.; Gant, J.C.; Porter, N.M.; Thibault, O. Calcium’s Role as Nuanced Modulator of Cellular Physiology in the Brain. Biochem. Biophys. Res. Commun. 2017, 483, 981–987.
50. Sepasi Tehrani, H.; Moosavi-Movahedi, A.A. Catalase and Its Mysteries. Prog. Biophys. Mol. Biol. 2018, 140, 5–12.
51. Nandi, A.; Yan, L.J.; Jana, C.K.; Das, N. Role of Catalase in Oxidative Stress-and Age-Associated Degenerative Diseases. Oxid. Med. Cell. Longev. 2019, 2019, 9613090.
52. Jiang, W.D.; Feng, L.; Liu, Y.; Jiang, J.; Zhou, X.Q. Myo-Inositol Prevents Oxidative Damage, Inhibits Oxygen Radical Generation and Increases Antioxidant Enzyme Activities of Juvenile Jian Carp (Cyprinus Carpio Var. Jian). Aquac. Res. 2009, 40, 1770–1776.
53. Poewe, W.; Seppi, K.; Tanner, C.M.; Halliday, G.M.; Brundin, P.; Volkmann, J.; Schrag, A.E.; Lang, A.E. Parkinson Disease. Nat. Rev. Dis. Prim. 2017, 3, 17013.
54. Ibrahim, T.; McLaurin, J.A. α-Synuclein Aggregation, Seeding and Inhibition by Scyllo-Inositol. Biochem. Biophys. Res. Commun. 2016, 469, 529–534.
55. Zhang, Z.; Hou, L.; Li, X.; Ju, C.; Zhang, J.; Li, X.; Wang, X.; Liu, C.; Lv, Y.; Wang, Y. Neuroprotection of Inositol Hexaphosphate and Changes of Mitochondrion Mediated Apoptotic Pathway and α-Synuclein Aggregation in 6-OHDA Induced Parkinson’s Disease Cell Model. Brain Res. 2016, 1633, 87–95.
56. Kitamura, N.; Hashimoto, T.; Nishino, N.; Tanaka, C. Inositol 1,4,5-Trisphosphate Binding Sites in the Brain: Regional Distribution, Characterization, and Alterations in Brains of Patients with Parkinson’s Disease. J. Mol. Neurosci. 1989, 1, 181–187.
57. Novotny, E.; Ashwal, S.; Shevell, M. Proton Magnetic Resonance Spectroscopy: An Emerging Technology in Pediatric Neurology Research. Pediatr. Res. 1998, 44, 1–10.

58. Mazuel, L.; Chassain, C.; Jean, B.; Pereira, B.; Cladière, A.; Speziale, C.; Durif, F. Proton MR Spectroscopy for Diagnosis and Evaluation of Treatment Efficacy in Parkinson Disease. Radiology 2016, 278, 505–513.
59. Ciurleo, R.; Di Lorenzo, G.; Bramanti, P.; Marino, S. Magnetic Resonance Spectroscopy: An in Vivo Molecular Imaging Biomarker for Parkinson’s Disease? Biomed Res. Int. 2014, 2014, 519816.
60. Gröger, A.; Chadzynski, G.; Godau, J.; Berg, D.; Klose, U. Three-Dimensional Magnetic Resonance Spectroscopic Imaging in the Substantia Nigra of Healthy Controls and Patients with Parkinson’s Disease. Eur. Radiol. 2011, 21, 1962–1969.
61. Morris, H.R. Progressive Supranuclear Palsy. Blue Books Neurol. 2010, 34, 361–374.
62. Mishori, A.; Levine, J.; Kahana, E.; Belmaker, R.H. Inositol Is Not Therapeutic in Parkinson’s Disease. Hum. Psychopharmacol. 1999, 14, 271–272.
63. Walker, F.O. Huntington’s Disease. Lancet 2007, 369, 218–228.
64. Finkbeiner, S. Huntington ’ s Disease. Cold Spring Harb. Perspect. Biol. 2011, 3, a007476.
65. Tang, T.S.; Tu, H.; Orban, P.C.; Chan, E.Y.W.; Hayden, M.R.; Bezprozvanny, I. HAP1 Facilitates Effects of Mutant Huntingtin on Inositol 1,4,5-Trisphosphate-Induced Ca2+ Release in Primary Culture of Striatal Medium Spiny Neurons. Eur. J. Neurosci. 2004, 20, 1779–1787.
66. Hamada, K.; Terauchi, A.; Nakamura, K.; Higo, T.; Nukina, N.; Matsumoto, N.; Hisatsune, C.; Nakamura, T.; Mikoshiba, K. Aberrant Calcium Signaling by Transglutaminase-Mediated Posttranslational Modification of Inositol 1,4,5-Trisphosphate Receptors. Proc. Natl. Acad. Sci. USA 2014, 111, E3966–E3975.
67. Post, J.I.; Leergaard, T.B.; Ratz, V.; Walaas, S.I.; Von Hörsten, S.; Nissen-Meyer, L.S.H. Differential Levels and Phosphorylation of Type 1 Inositol 1,4,5-Trisphosphate Receptor in Four Different Murine Models of Huntington Disease. J. Huntingtons Dis. 2019, 8, 271–289.
68. Nagata, E.; Nonaka, T.; Moriya, Y.; Fujii, N.; Okada, Y.; Tsukamoto, H.; Itoh, J.; Okada, C.; Satoh, T.; Arai, T.; et al. Inositol Hexakisphosphate Kinase 2 Promotes Cell Death in Cells with Cytoplasmic TDP-43 Aggregation. Mol. Neurobiol. 2016, 53, 5377–5383.
69. Nagata, E.; Saiardi, A.; Tsukamoto, H.; Okada, Y.; Itoh, Y.; Satoh, T.; Itoh, J.; Margolis, R.L.; Takizawa, S.; Sawa, A.; et al. Inositol Hexakisphosphate Kinases Induce Cell Death in Huntington Disease. J. Biol. Chem. 2011, 286, 26680–26686.
70. Sun, Y.M.; Lu, C.; Wu, Z.Y. Spinocerebellar Ataxia: Relationship between Phenotype and Genotype—A Review. Clin. Genet. 2016, 90, 305–314.
71. Kasumu, A.W.; Liang, X.; Egorova, P.; Vorontsova, D.; Bezprozvanny, I. Chronic Suppression of Inositol 1,4,5-Triphosphate Receptor-Mediated Calcium Signaling in Cerebellar Purkinje Cells

Alleviates Pathological Phenotype in Spinocerebellar Ataxia 2 Mice. J. Neurosci. 2012, 32, 12786–12796.

72. Tipton, P.W.; Guthrie, K.; Strongosky, A.; Reimer, R.; Wszolek, Z.K. Spinocerebellar Ataxia 15: A Phenotypic Review and Expansion. Neurol. Neurochir. Pol. 2017, 51, 86–91.
73. Klockgether, T.; Mariotti, C.; Paulson, H.L. Spinocerebellar Ataxia. Nat. Rev. Dis. Prim. 2019, 5, 24.
74. Brown, S.A.; Loew, L.M. Integration of Modeling with Experimental and Clinical Findings Synthesizes and Refines the Central Role of Inositol 1,4,5-Trisphosphate Receptor 1 in Spinocerebellar Ataxia. Front. Neurosci. 2015, 8, 453.
75. Novak, M.J.U.; Sweeney, M.G.; Li, A.; Treacy, C.; Chandrashekar, H.S.; Giunti, P.; Goold, R.G.; Davis, M.B.; Houlden, H.; Tabrizi, S.J. An ITPR1 Gene Deletion Causes Spinocerebellar Ataxia 15/16: A Genetic, Clinical and Radiological Description. Mov. Disord. 2010, 25, 2176–2182.
76. Sasaki, M.; Ohba, C.; Iai, M.; Hirabayashi, S.; Osaka, H.; Hiraide, T.; Saitsu, H.; Matsumoto, N. Sporadic Infantile-Onset Spinocerebellar Ataxia Caused by Missense Mutations of the Inositol 1,4,5-Triphosphate Receptor Type 1 Gene. J. Neurol. 2015, 262, 1278–1284.
77. Obayashi, M.; Ishikawa, K.; Izumi, Y.; Takahashi, M.; Niimi, Y.; Sato, N.; Onodera, O.; Kaji, R.; Nishizawa, M.; Mizusawa, H. Prevalence of Inositol 1, 4, 5-Triphosphate Receptor Type 1 Gene Deletion, the Mutation for Spinocerebellar Ataxia Type 15, in Japan Screened by Gene Dosage. J. Hum. Genet. 2012, 57, 202–206.
78. van Dijk, T.; Barth, P.; Reneman, L.; Appelhof, B.; Baas, F.; Poll-The, B.T. A de Novo Missense Mutation in the Inositol 1,4,5-Triphosphate Receptor Type 1 Gene Causing Severe Pontine and Cerebellar Hypoplasia: Expanding the Phenotype of ITPR1-Related Spinocerebellar Ataxia’s. Am. J. Med. Genet. Part A 2017, 173, 207–212.

Retrieved from https://encyclopedia.pub/entry/history/show/98967