Neurodegenerative Diseases

Subjects: Clinical Neurology

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Neurodegenerative diseases are affecting more and more people around the world. Current therapies only treat the symptoms and not the causes of the disease. However, the pathophysiology of these diseases is now better known. In the case of Alzheimer's disease and Parkinson's disease, some common mechanisms have been identified. One of the first known mechanisms is the accumulation of proteins: α-synuclein (Parkinson's disease), Tau (Alzheimer's disease) and β-amyloid (Alzheimer's disease and Parkinson's disease) proteins. Protein accumulation is related to a disruption of mitochondrial activity associated with cell death and oxidative stress. Inflammation is also another important mechanism, which is disrupted in these pathologies.

Parkinson Alzheimer mitochondria apoptosis inflammation autophagy immunity protein aggregation

1. Mechanisms Common to Neurodegenerative Diseases: Pakinson's and Alzheimer's disease

Protein aggregation connected with dysfunctional protein degradation systems, mitochondrial perturbation related with cell death and oxidative stress were identified as mechanisms common to the two most-frequent neurodegenerative diseases in humans : Parkinson’s and Alzheimer’s disease. In the following paragraphs we will detail these mechanisms present in common in these two pathologies.

2. Protein Aggregation and Dysfunctions of Protein Degradation Systems

In Parkinson’s and Alzheimer’s disease, protein aggregation concerns α-synuclein, Tau and β-amyloid proteins, respectively, although β-amyloid proteins are equally present in Parkinson’s disease.

In Parkinson’s disease, insoluble α-synuclein fibrils compose the Lewy bodies and Lewy neurites. These are mainly detected in the pigmented neurons of the substantia nigra and in other neuronal populations at the peripheral and central levels [1][2][3]. Lewy bodies are existent in the dopaminergic neurons of substantia nigra pars compacta. These Lewy bodies are round intraneuronal and positive round inclusions of α-synuclein and ubiquitin [3]. Lewy neurites are atypical neurites made up of α-synuclein filaments and granular material [4]. These Lewy neurites pile up in the amygdala and striatum of Parkinsonian patients [4]. Lewy neurites can restrain neuronal transport and, thus, compromise neuronal activity and survival. In Alzheimer’s disease, the modifications identified are amyloid

plaques and neurofibrillary degeneration. Two proteins have been identified as participating in these modifications: Tau protein and Amyloid precursor protein (APP). The APP protein can generate the Aβ peptide after proteolysis. Amyloid plaques are formed by aggregation of Aβ peptide[5]. Neurofibrillary degeneration is composed of argentophilic neurofilaments found in the pericaryon of some cortical neurons but is also detected within myelinated axons, dendrites and synapses [6]. The intensity of these neurofibrillary accumulations in the neocortex is directly connected with the severity of the disease [7]. Neurofibrillary tangles are composed of hyper-phosphorylated Tau proteins arranged in paired helical filaments. Extracellular deposits of Aβ peptide compose amyloid plaques. Glial cells containing phagocytic lysosomes, and amyelinic neurites enclose amyloid plaques. These plaques are in preference detected in certain areas of the brain: cortex, striatum and cerebellum. The less mature plaques are described as diffuse plaques, composed of amorphous, low-density aggregates of Aβ peptides. Mature plaques consist of very dense aggregates of the Aβ peptide and are correlated with neurodegeneration and astroglial reactivity.

Two systems are involved in the degradation of α-synuclein: the ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway (ALP)[8][9]. The UPS system recognizes short-lived soluble proteins and the ALP pathway identify long-lived macromolecules, cytosolic components and dysfunctional organelles. In the case of Parkinson's disease, chaperone-mediated autophagy (CMA), pathway belonging to ALP system, is implicated. Indeed, CMA activity is connected to levels of LAMP-2A, this receptor of the CMA pathway attaches to chaperones who have identified proteins having the KFERQ motif. In the substantia nigra of patient brains, a diminution of the expression of LAMP-2A is particularly observed[10][11][12]. This diminution is connected to the accumulation of α-synuclein and nigral cell death [13]. Modifications in enzyme content and acidification of the lysosomes were observed as well as autophagosomes accumulation[14][15][16]. In Alzheimer's disease, the accumulation of Aβ inside cells in multivesicular bodies can be explained by proteasome inhibition[17]. Both in vitro and in vivo, peptide levels Aβ can increase due to proteasome inhibition [18]. Extracellular Aβ can enter the cell and inhibit proteasome activity in cultured neurons, which causes it to accumulate in the cytosol[18].

3. Mitochondrial Dysfunction and Cell Death

In the case of Parkinson's disease, a deficiency in the complex I of the mitochondrial respiratory chain is detected at the level of the patient's black matter in the neurons and in the glia, as well as at the level of skeletal muscle and platelets[19][20][21][22]. This change in the activity of the mitochondrial respiratory chain favors the augmentation of mitochondria-dependent apoptotic processes[23]. On experimental models and in patients, modifications in mitochondrial dynamics, at the bioenergetic level and the decrease of complex I activity of the respiratory chain, have been detected[24][25]. Moreover, a relationship exists between the genes involved in Parkinson's disease and mitochondrial function. Indeed, mutations in the LRRK2 gene are connected with dysfunctions in the mitochondria [26]. The proteins encoded by the PARK2 and PINK1 genes are implicated in the elimination of dysfunctional mitochondria by the process of mitophagy[26]. In patients with Parkinson's disease, it has been observed a reduction of degradation of the MIRO protein. This outer mitochondrial membrane protein allows the

mitochondria to bind to the microtubules. This diminution leads to loss of function in the mitochondria, which can lead to an increase in oxidative stress[27].

In addition to what has just been described, α-synuclein can interact with the mitochondria and change their function. α-synuclein can be found in the outer membrane of the mitochondria. It can interfere with members of the TOM complex (translocase/receptor system) and induce inhibition of mitochondrial import of proteins [28]. Excessive production of oxidative stress can be produced during interactions between mitochondria and α-synuclein [29]. α-synuclein can also disrupt the fusion process, and inhibits complex I [30][31]. Histological experiments demonstrate cell death is the process in charge for Parkinson's disease: detection of fragmented DNA, apoptosis in patients' brains (TUNEL methods), presence of active forms of caspases -1, -3, -8 and -9 at the level of the black substance[32][33]. The intrinsic and extrinsic pathways of cell death are also highlighted in post-mortem studies: implication of mitochondrial pathway (p53-GAPDH-Bax pathway), and Fas/FADD death receptor pathway, (high levels of Fas, FADD and caspase-8 in the brains of Parkinsonian patients)[34].

Loss of neurons in the cortical II layer of the entorhinal cortex is a major feature of Alzheimer's disease[35]. Neurons, in the entorhinal cortex, synthesize acetylcholine and innervate the hippocampus and neocortex. This type of neuron can also be affected by cell death in Alzheimer's disease. The two processes responsible for the cell death of these cells are accumulation of amyloid plaques and neurofibrillary degeneration. In various cell cultures and animal models of Alzheimer's disease, it has been shown exogenous Aβ and pseudo-hyperphosphorylated Tau can induce neuronal death[36], neurons internalizing the extracellular Aβ peptide[37]. The disruption of mitochondrial membranes and of enzymatic activities of the respiratory chain can be induced by Aβ peptide, disturbance that could lead to a production of reactive oxygen species [38]. Induced oxidative stress can activated numerous enzymes, as calpains and caspases, leading to neuronal cell death[39].

4. Oxidative Stress

The exact causes of Parkinson's disease are still being studied, but significant evidence suggests that oxidative stress plays a major role in the degeneration of dopaminergic neurons. Since maintaining a balanced redox potential is crucial for neuron survival, it is unsurprising that any disruption to this balance can interfere with other cellular processes and ultimately lead to cell death. It is also believed that various mechanisms at play can contribute to neurodegeneration in Parkinson's disease, creating a feed-forward scenario where primary insults lead to oxidative stress. This stress can then damage essential pathogenetic proteins and disrupt lipid membranes, producing more ROS and further worsening the condition.[40]

Different free radicals, reactive oxygen species (ROS) and reactive oxygen and nitrogen species (RONS) can induce oxidative stress. Hydrogen peroxide (H_2O_2), in the presence of iron (in ionic form), provides two hydroxyl radicals ($^{\cdot}OH$), nitrogen monoxide ($NO^{\cdot}$) and superoxide ($O_2^{\cdot -}$). Free radicals create damages to proteins, lipids and DNA. This would promote neuronal degeneration.

In postmortem studies in patient'sbrain, damage to proteins, lipids and DNA related to free radicals has been detected at the level of substantia nigra[41]. The dysfunctions of the complex I of the mitochondria lead to an augmentation in the production of free radicals, and inversely, oxidative stress causes dysfunction of the mitochondria[41]. Genetic modifications may also be involved in oxidative stress. The DJ-1 or PARK7 genes code for a protein that might have antioxidant activity. Mutations in these genes are concomitant with the increase of oxidative stress. In DJ-1-deficient mice, increased protein oxidation is present in stressed dopaminergic neurons[42]. Changes in mitochondrial activity and oxidative stress can induce to lysosome depletion and functional impairment of the autophagy/lysosome system. These observations demonstrate the very close relationship between the different processes responsible for the pathology[43].

In Alzheimer's disease, ROS break up the cytoskeleton, unorganized, particularly at the level of dendrites [39] but, also, the plasma membrane and the membranes of the cell organelles. This process induces activation of the BACE protein and, as a result, drives the metabolism of the APP protein towards the amyloidogenesis pathway with increased production of the toxic Aβ peptide. As previously stated in Parkinson's disease, proteins, nucleic acids and lipids have been damaged by oxidative stress[44][45]. The Aβ peptide may also behave as a pro-oxidant or by impacting NMDA receptor-dependent calcium influxes. These actions can induce mitochondrial dysfunction and in turn ROS overproduction[46][47].

5. Inflammation and Immunity

The central nervous system (CNS) has its own immune system coordinated by immunocompetent cells. Microglial cells, glial cells (astrocytes) and, possibly, neurons are the mains actors implicated in the inflammatory process during Alzheimer's disease[48][49]. Both microglial cells and astrocytes change rapidly in morphology, antigenicity and function in response to the disease[50]. Microglial cells are cells with support and protection functions for neurons, acting as immunocompetent defense cells. They orchestrate the endogenous immune response of the CNS. Major histocompatibility complex type II (MHCII) can be express in the cells and these microglial cells produce proinflammatory cytokines, chemokines, ROS and complement proteins. These cells play a major role in the cellular immune response to the various lesions encountered in Alzheimer's disease, such as Aβ and senile plaques[51]. Microglial cells can accumulate around amyloid deposits as a result of attraction and activation by the peptide Aβ. The activation of microglial cells lead to increased MHC II cell expression and increased secretion of proinflammatory cytokines (interleukin-1 (IL-1), interleukin-6 (IL-6) and TNF-α (tumor necrosis factor-α)), as well as chemokines (interleukin-8 (IL-8), MIP-1α (macrophage inflammatory protein-1α) and MCP1 (monocyte chemoattractant protein-1))[52][53]. Following chemokine recruitment, the passage of peripheral circulating macrophages across the blood-brain barrier is promoted by Aβ , which may induce an increase in the extent of inflammation. A phagocytic response can be induce in microglial cells by Aβ in a dose- and time-dependent manner[54]. At the same time as the arrival of microglial cells, there is an internalization and co-localization of the lysosome and Aβ associated with damage to neighboring neurons[55][56]. Reactive astrocytes also participate to neurodegeneration by promoting apoptotic cell death[57]. In Alzheimer's disease, astrocytes are present in amyloid deposits, where they secrete several pro-inflammatory molecules such as interleukins, prostaglandins,

leukotrienes, thromboxanes and complement factors. These molecules are like those secreted by microglial cells, with which they are co-located. In the brain of non-demented elderly people, diffuse plaques consisting of Aβ granules and associated with astrocytes have been observed. Astrocytes could thus be implicated in the phagocytosis of Aβ[58] and that, probably, the pathology of Alzheimer's disease could have as a possible cause a deficit in the elimination of Aβ by astrocytes. In the brain of Alzheimer's disease patients[50] and transgenic models of Alzheimer's disease mice[59], reactive astrocytes are found very close to the plaques, surrounding the Aβ deposits, a mechanism by which the cells could act as a protective barrier between healthy and inflammatory tissues[50]. In addition, the fibrillar form of amyloid peptide operates with complement proteins and in consequence induces the innate immune system[60]. For example, the interelation Aβ/C1q, which implicates the 11 N-terminal residues of Aβ, initiates the classical complement pathway[61]. This phenomenom leads to a cascade of activations that permits the formation of lytic complexes, partly responsible for neuronal death, and inflammatory activation[62]. Neurons can produce certain cytokines such as IL-1[63], IL-6[64], TNF-α[65] and some pentraxins, namely CRP and Ap (amyloid P) and thus participates in the inflammatory process[66]. The mRNA expression levels of proteins of the classical complement pathway are expanded in the brains of Alzheimer's patients compared to those of controls[67].

Neuroinflammation and, more specifically, microglial cells are believed to be involved in the development and progression of the death of the dopaminergic neurons of the substantia nigra[68]. Using positron emission tomography (PET) imaging, microglial activation was observed in the pons, central gray nuclei, striatum and frontal and temporal cortical regions of patients with Parkinson's disease[69][70]. Post-mortem immunohistological analyses show in the CNS an increase in cell density, branch retraction and hypertrophy of the cell body and expression of MHC II molecules, processes that are synonymous with microglial activation[71][72][73][74], just as increased expression of the lysosomal marker CD68[75][72]. The two main functions attributed to microglial cells are phagocytosis and antigenic presentation. In the 6-hydroxydopamine (6-OHDA) model, these two processes can evolve according to independent kinetics as shown by the analysis of the lysosomal marker CD68, reflecting the activity of phagocytosis, and MHC II molecules, reflecting the role of antigen presentation[76][77][78][79]. Optimal phagocytic activity may occur before or after maximum neuronal death as evidenced by the level of CD68 expression[76][80]. Different hypotheses can be made, given the contradictory results obtained, as to the role of microglial activation. A process of deregulation of phagocytic functions could increase the autonomous mechanisms of neuronal death. The main function of microglial cells could also be the removal of neuronal cell debris. Activated microglia could be have the ability to secrete a set of pro-inflammatory or anti-inflammatory cytokines. Potentially neurotoxic pro-inflammatory proteins have been detected in the brains of patients with Parkinson's disease, including COX and iNOS, TNFα, IL1β and IFNγ[81][82]. T lymphocytes are the main cells that produce IFNγ, which is known to induce activation of macrophages (including microglia). The deleterious role of IFNγ in the pathophysiology of Parkinson's disease has been demonstrated in numerous animal studies[83][84][85][86]. It has been suggested that the dialogue between Th1 cells and microglial cells in the substantia nigra of patients with Parkinson's disease could be a key process in dopaminergic neuronal loss. In the MPTP model, the degeneration of dopaminergic neurons is inhibited by regulatory T lymphocytes (Treg) that modify the molecular behaviour of microglial cells[87][88]. As a result, microglial cells may have distinct or even opposite effect actions

depending on the stage of Parkinson's disease, the immunogenetic terrain, and a set of instructional signals delivered by infiltrated T cells, among other factors.

The main signaling pathways implicated in protein aggregation, cell death, oxidative stress and inflammation are summarized in Figure 1.

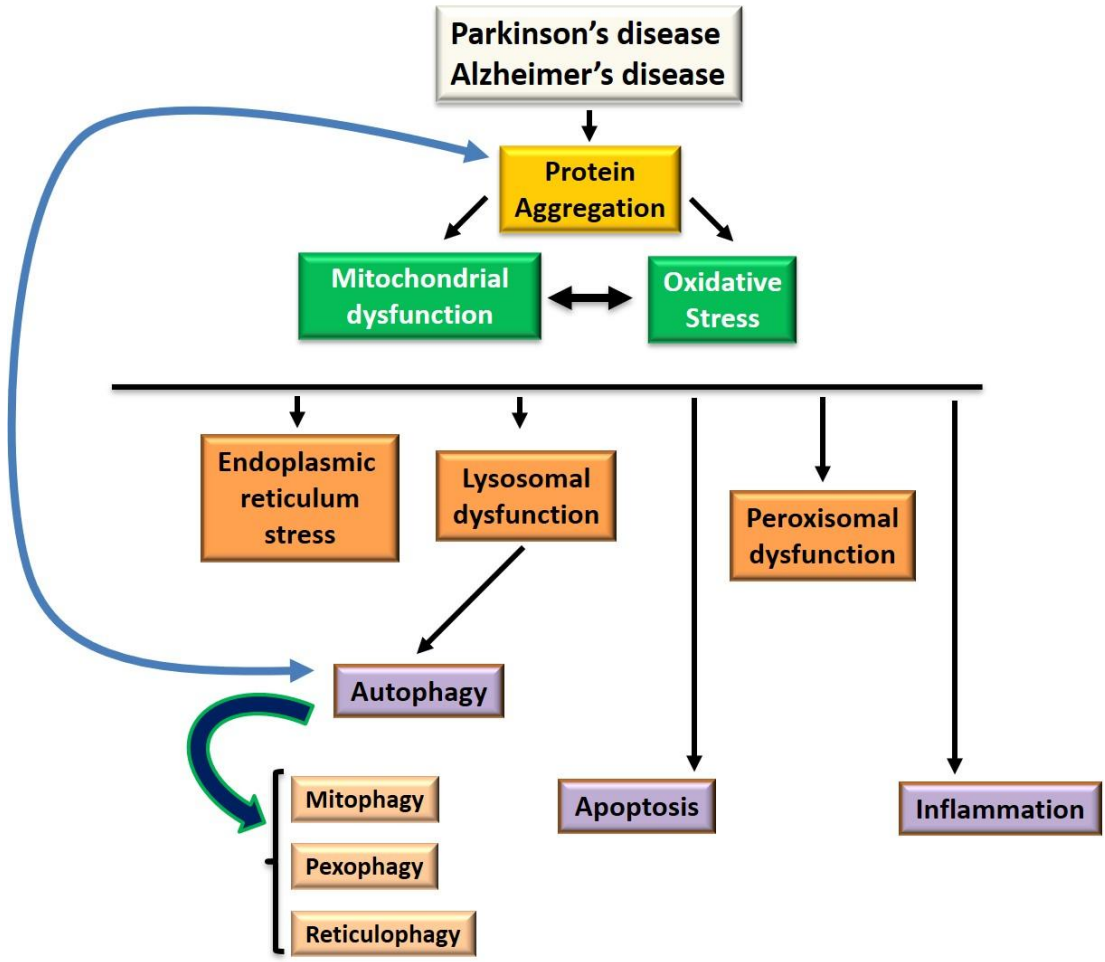

Figure 1: Signaling pathways at the level of target organelles and common processes involved in Parkinson's and Alzheimer's disease: autophagy, apoptosis, oxidative stress and inflammation

The study of these common mechanisms will make it possible to identify natural or synthetic molecules capable of inhibiting them either by using them in natural form or by coupling the compounds of interest to nanoparticles to facilitate their access to the brain.

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