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Exploring the Role of Ubiquitin–Proteasome System in Parkinson's Disease

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Abstract

Over the last decade, researchers have discovered that a group of apparently unrelated neurodegenerative disorders, such as Parkinson's disease, have remarkable cellular and molecular biology similarities. Protein misfolding and aggregation are involved in all of the neurodegenerative conditions; as a result, inclusion bodies aggregation starts in the cells. Chaperone proteins and ubiquitin (26S proteasome's proteolysis signal), which aid in refolding misfolded proteins, are frequently found in these aggregates. The discovery of disease-causing gene alterations that code for multiple ubiquitin–proteasome pathway proteins in Parkinson's disease has strengthened the relationship between the ubiquitin–proteasome system and neurodegeneration. The specific molecular linkages between these systems and pathogenesis, on the other hand, are unknown and controversial. We outline the current level of knowledge in this article, focusing on important unanswered problems.

Keywords α-synuclein · Neurodegeneration · Parkinson's disease · Proteolysis · UPS

Background

Neurodegenerative disorders with an amyloidogenic factor, such as Alzheimer's disease (AD) and Parkinson's disease (PD), are clinically diverse and appear to be separate conditions with common neuropathologic markers [1]. However, selected neuronal populations are often lost in such neurodegenerative disorders. Another distinguishing aspect is the continuous deposition of intraneuronal ubiquitin-positive proteinaceous masses in the above neuronal disorders (Table 1). The research regarding the ubiquitin–proteasome system (UPS) dysfunction associated with PD is growing and becoming clearer. Several lines of research have recently revealed a close link between UPS abnormalities and the aetiology of PD [10, 11]. Although the molecular mechanisms causing neuronal degeneration are still unknown, it is becoming evident that hereditary factors and abnormal proteolytic degradation play a crucial

Highlights
- In the aetiology of Parkinson's disease, the vicious cycle between proteasome failure and protein accumulation is crucial.
- The ubiquitin–proteasome system (UPS) is the primary hydrolytic system involved in the bulk of protein breakdown.
- PROTAC's development brings up new possibilities for treating Parkinson's disease through proteasome modulation.
- Proteasome homoeostasis regulation is a promising treatment for Parkinson's disease.

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Table 1 Neurological disorders having ubiquitin-positive protein inclusions

Disorder	Mutation	Gene involved	UPS direct role (yes/no)	Pathology
Parkinson's disease	Missense	α-Synuclein	No	Lewy bodies [2–4]
		UCH-L1	Yes(DUB)	
	Deletion/Missense	Parkin	Yes(E3)	
		DJ-1		
Alzheimer's disease	Missense	Presenilin 1	No	Neurofibrillary tangles, amyloid plaques [5, 6]
		Presenilin 2	No	
		APP (Amyloid precursor protein)	No	
Amyotrophic lateral sclerosis	Deletion/Missense	SOD1 (superoxide dismutase 1)	No	Inclusions such as Lewy body [7, 8]
Huntington's disease	Polyglutamine tract	Huntingtin	No	Nuclear inclusions [8]
Multiple systems atrophy		α-synuclein	No	Lewy bodies [3]
spinocerebellar ataxia 1/3/7	Polyglutamine tract	Ataxin-1/3/7	No	Nuclear inclusions [9]

part in the neurodegenerative process [12]. In addition to recent improvements in other neurodegenerative disorders, the connection of two genes involved in the UPS in familial PD strongly designates that the UPS plays a crucial role in neurodegeneration. Failure of the UPS to clear undesired proteins, which eventually leads to the deposition and aggregation of harmful proteins, is certainly the main factor in the molecular pathogenesis of PD. Because each of the familial PD-related genes, UCH-L1, parkin, and α-synuclein, has been shown to interfere with normal UPS activity and thus protein degradation, familial PD has now been dubbed the prototype condition connected to UPS failure [1]. Furthermore, sporadic PD patients' brains were found to have proteasomal deficiencies, suggesting that UPS malfunction may be a common link between sporadic and familial PD [13]. A better understanding of the UPS and its components and the precise role the UPS plays in maintaining neuronal viability, and how the UPS reacts to the accumulation of abnormal or toxic proteins will undoubtedly give insight into the molecular pathogenesis of amyloidogenic neurodegenerative disorders [11, 14–16].

Defects in the UPS, which is generally a form of protein degradation system, cause changes in protein homoeostasis, leading to impaired proteins deposition that is harmful to neuronal survival [17]. Several PD models centred on straight interruption of UPS functioning recapitulate the most notable aspects of PD. The UPS's proteolytic destruction of undesirable proteins is essential for the proper regulation of different cellular activities [3, 4, 10]. Environmental neurotoxins and genetic susceptibility have been identified as potential risk factors for PD in epidemiological research. At the same time, the mechanisms leading to selective dopaminergic degradation remain unknown. UPS failure in PD is supported by mutants of α-synuclein, parkin, and ubiquitin carboxy-terminal hydrolase L1 (Uch-L1) [10–13]. The pathways by which the UPS typically degrades damaged proteins, the pathways by which protein deposition can cause neurotoxicity in UPS dysfunction, and the data that impaired protein clearance may be a common aetiopathogenic feature that connects and combines the various causes of PD are all discussed in this review.

Parkinson's Disease (PD)

Neurodegeneration in PD affects several brain regions, including the olfactory nuclei, the locus coeruleus (LC), and the vagus dorsal motor nucleus; the substantia nigra pars compacta (SnPc)-linked dopaminergic neurons loss, resulting in severe striatal dopamine depletion, is the primary neuropathology that causes the wide range of motor deficits [1]. Bradykinesia, rigidity, gait impairment, postural instability, and resting tremor are symptoms of PD, an age-related neurological disease [18]. Recently, there has been increased interest in the notion that protein breakdown dysfunctions play a role in the neurodegenerative processes that result in several aetiological forms of PD. Recent data points to the accumulation of intracellular proteins result from folding or breakdown changes, causing neuronal death in sporadic and familial PD cases [19]. This mechanism, we believe, also explains the age-linked sporadic PD, the initial starting of familial disorder, selective SnPc involvement, and different Lewy bodies in these incidences. The exact cause of sporadic PD is unclear; however, neurodegeneration is linked to many metabolic abnormalities in the SnPc, including dysfunctioning of the mitochondria caused by the inhibition of complex-I and oxidative stress manifested by decreased glutathione and higher iron levels [20]. PD incidences linked to genetic abnormalities are limited and not included in the majority of sporadic cases. However, some familial PD

patients have been linked to genetic mutations that encode UCH-L1, parkin, and α-synuclein, and several other genes [21]. The intracytoplasmic aggregation of proteinaceous inclusions, viz. the Lewy body, is another cause of neurodegenerative disease. As a result, there could be many reasons for PD, and it is unknown how they are related. Extraneous variables, such as changes in proteasomal inhibitor formulation, strain background variances in treated mice and rats, and environmental conditions, are thought to be responsible for the wide range of results. A post-mortem examination by McNaught and colleagues of Sprague–Dawley rats indicated neuronal loss and eosinophilic, synuclein/ubiquitin-positive inclusions in the SN's surviving neurons, and dopamine deficiency in the striatum [22, 23]. Dopamine agonists relieved behavioural symptoms and the gradual pattern of the motor impairment shown by treated rats. They discovered that proteasomal inhibitors' systemic injection caused a behavioural and pathological phenotype similar to PD [22]. Even though two other laboratories were reproduced dopaminergic cell loss after systemic injection of proteasome inhibitors, Zeng and colleagues found synuclein masses in the SnPc, and neither group saw progressive motor impairment [24, 25]. However, this hypothesis has been scrutinised because other laboratories have not replicated similar findings [26]. Many genetic mutations in familial PD suggest a change in protein structure or degradation, which may play a critical role in the onset of neurodegeneration. Moreover, the presence of damaged proteins due to oxidation, higher protein accumulation, and reduced proteolysis in the SnPc of sporadic PD patients supports the theory that defective protein clearance serves a prominent role in the pathophysiology of cell death in PD. The discovery that treatment with the proteasomal inhibitor lactacystin causes degeneration and the production of synuclein and ubiquitin-positive inclusions in rat ventral mesencephalic primary neurons further cemented the relationship between the aetiology of PD and proteasomal inhibition [27, 28].

Ubiquitin–Proteasome System (UPS)

The UPS controls apoptosis, cellular differentiation, cell cycle progression, and signal transmission by regulating the degradation of critical regulatory proteins [14]. The UPS is an internal protein breakdown mechanism that handles most of the cell's protein turnover (Fig. 1). In eukaryotic cells, the UPS is critical for maintaining normal functions and homoeostasis. Although the unambiguous involvement of free 20S proteasome in cellular proteolysis towards native or oxidised proteins has yet to be proven, protein degradation

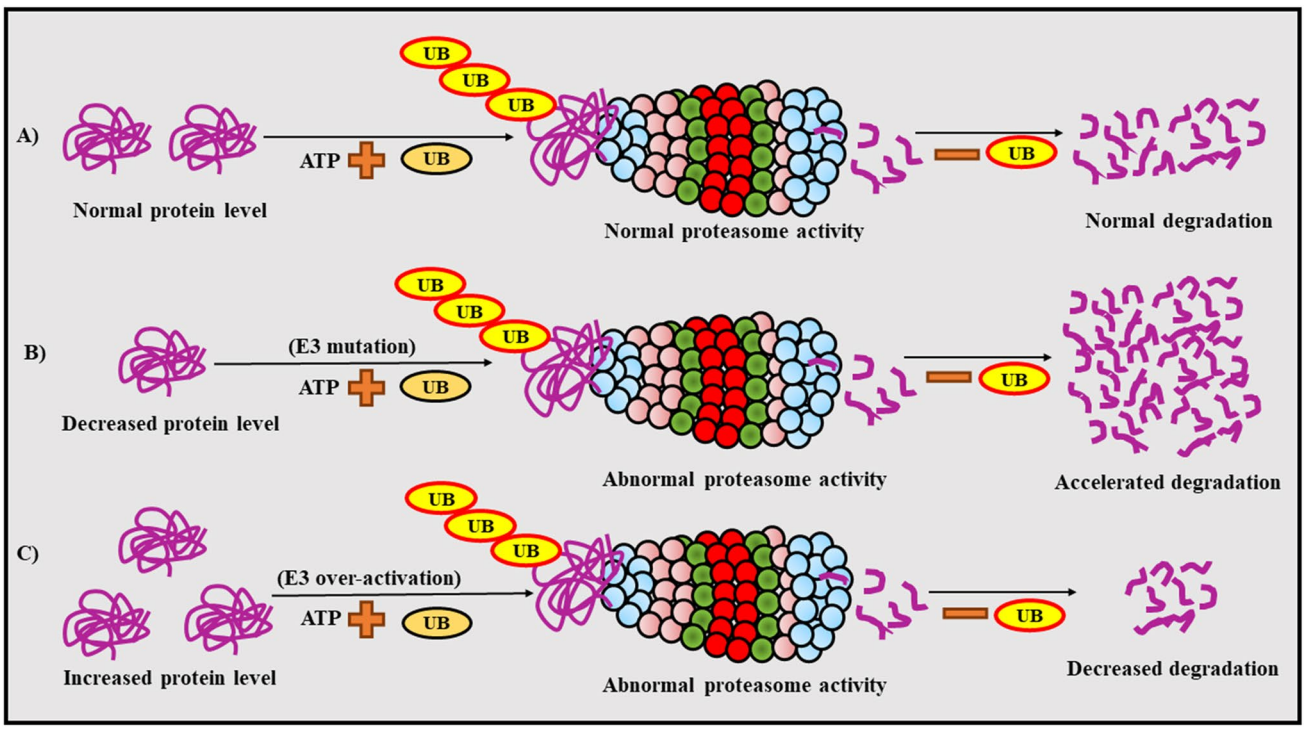

Fig. 1 **A** The steady-state level of cellular proteins is maintained via normal degradation [27]; **B** Reduced degradation and aggregation of the target substrate are caused by a mutation in an E3 enzyme or the substrate's recognition motif [14]; **C** the steady-state level of a protein decreases when degradation is accelerated due to an increase in the level of an E3 (over-activation) or an ancillary protein that binds the substrate and targets it for degradation [29]

by the proteasome may occur through numerous proteasome complexes with varying needs [30]. Proteins designated for breakdown link covalently with a 76 AA residue protein called ubiquitin (Ub) by establishing an iso-peptide bond between the ε-amino group of a lysine residue of the substrate and the C-terminal carboxylate (G76) of Ub [31]. This complex ligation reaction necessitates the activity of Ub activating (E1), conjugating (E2), and ligating (E3) enzymes in order. According to many studies, the proteasomal pathway as a target appears to be a promising strategy for combating various disorders, including neurodegeneration and cancer [15, 16]. Mechanism-based therapies development in various disorders has been aided by a more excellent knowledge of UPS and identifying components responsible for removing critical regulatory proteins. Dysfunction of the UPS can cause various problems, including systemic autoimmunity, neurodegeneration, and cancer. Furthermore, the UPS destroys impaired and mutant proteins, avoiding their aggregation. UPS is a complex, carefully regulated system essential for normal cell homoeostasis, including cellular stress response, inflammatory and immunological response regulation, sodium channel function, DNA repair, and cell cycle regulation [11, 27, 32].

Proteasome Structure

The proteasome is a cylindrical assembly having one or two lids that houses the active proteolytic positions in its constitutive state. Four slanted heptameric rings of α and ß protein subunits form the central cavity to produce the cylindrical core (core particle, CP, or 20S). The CP gate's default state is closed. The N-terminal must be shifted to a continuous channel from their axial orientation to the catalytic site, allowing substrate access and proteasomal breakdown [29]. N-terminal of specific α subunits controls the gating of the core particle. The active sites for proteolytic activity are housed in the ß subunits, which face the CP's inner cavity: ß1 has caspase-like action and cleaves after acidic residues, ß2 has trypsin-like action and cleaves after basic residues, and ß5 has chymotrypsin-like action and cleaves after hydrophobic residues [33]. In eukaryotes, seven separate α subunits form the outer two rings of the barrel, while the two internal rings contain seven distinct ß subunits [34–36].

The members of an ATPase family are involved in a variety of cellular functions. On the other hand, nine non-ATPase subunits constitute the cap. The conventional 26S proteasome is formed when two 19S modules join to 20S core (19S–20S–19S). The CP gate area is near the base subcomplex and consists of a hexameric ring of six regulatory particle triphosphatase (Rpt) proteins. The lid and base are two biochemically separate subcomplexes made up of 19 integral subunits. As depicted in Fig. 2, the regulator assemblies cap the CP's both ends and change the role of activated 20S CP. The 11S regulator (PA28 complex), like the 19S regulator, binds to the α-rings of the 20S proteasome for its activation, and it has ATP-independent functioning. PA700/19S/RP, which can bind to the terminal α-rings of the 20S CP on one or both ends, is the primary partner of 20S CP in the structure of the 26S proteasome [41, 42]. PA700/19S/RP (regulatory particle), PA28/11S protein family activator and the PA200/Blm10 activator are all examples of endogenous modulators. Proteasome activators mediate gate modulation, which is required by the proteolytic chamber for substrate intake. During the late stages of CP assembly, binding of Blm10 to proteasome aids the maturation of CP complexes. Blm10 may play a role in chromosome integrity and DNA or oxidative damage repair, most likely by ATP- and Ub independent acetylated histone degradation in somatic cells [43, 44]. It may also play a function in mitochondrial homoeostasis, according to other research [45]. Binding of PA200/Blm10 to CP's one end and the 19S to another end can result in pure or hybrid complexes. It is occupied by monomeric proteins of less than 250 kDa and is present in yeast to humans. Ribosomal protein genes are regulated by a transcription factor Sfp1 (split-finger protein 1), one physiological target for Blm10–proteasome complexes. PA28 increases its expression in response to stress [15]. It divides into three different forms: PA28α, PA28ß, and PA28γ isoforms, the roles of which are unknown. The 11S–20S–11S complex is assumed to be limited to breaking moderately impaired proteins, while the 19S–20S–19S and 19S–20S–11S can degrade significant complex proteins [45]. PA28α/ß can create hybrid 26S proteasomes with improved proteolytic efficiency in eukaryotic cells [33]. It can also aid protein refolding mediated by heat shock protein 90 (HSP 90). Interferon-γ induces both PA28α and PA28ß units, implying a function for PA28α/ß in antigen appearance of MHC Class I. They are also found in organs that have no immune activities. In the cytosol, PA28α and PA28ß form heteroheptameric rings, whereas PA28γ is present in the nuclei of both vertebrates and invertebrates forming homoheptameric rings [15, 33]. Although the function of PA28γ is unknown, mice lacking PA28γ have smaller bodies and cell cycle abnormalities seen in embryonic fibroblasts of these mice. In an ATP- and ubiquitin-dependent way, the PA700 ATP-dependent proteasome activator detects ubiquitinated proteins for threading, unfolding, and deubiquitination into the proteasome's CP [46].

Protein Inclusions in Parkinson's Disease

Proteins prone to aggregation, such as mutant α-synuclein or polyglutamine repeat (huntingtin fragment), can impede the UPS system, as evidenced by research. UPS activity reduction could result in protein aggregates that could impede

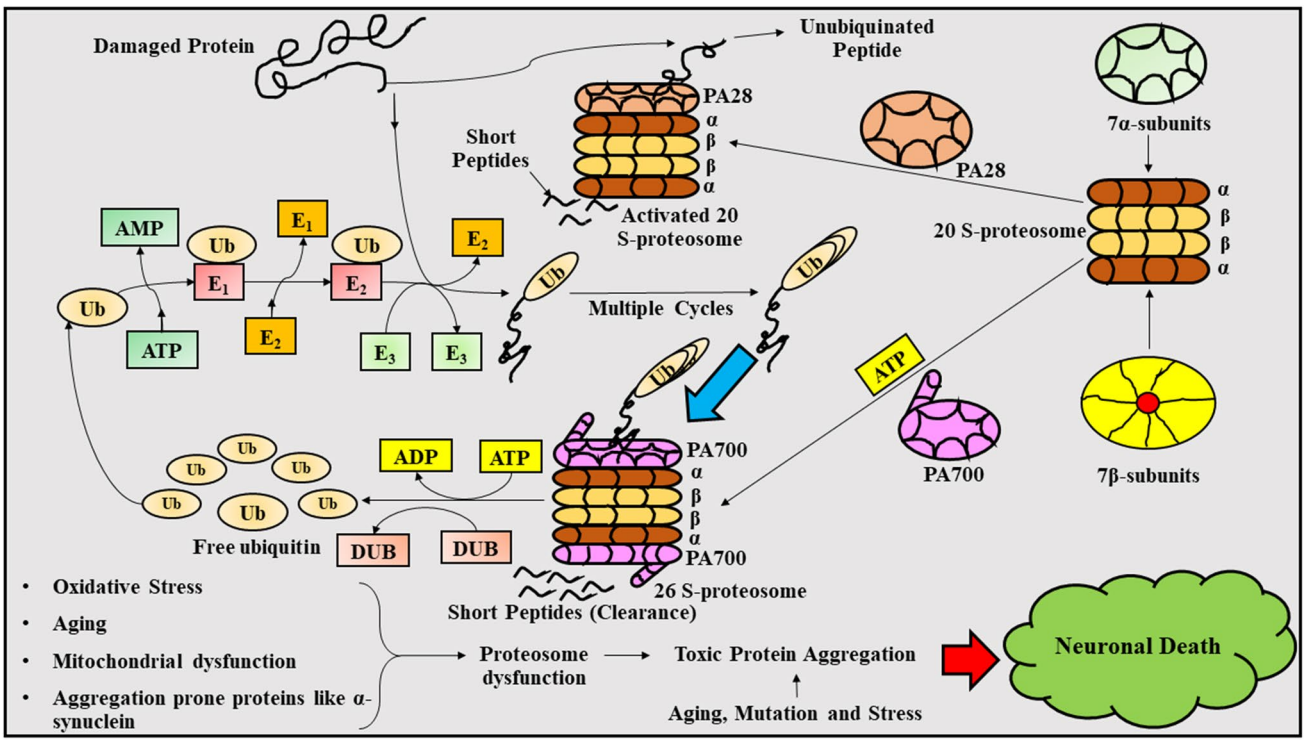

Fig. 2 Ubiquitin–proteasome system (UPS) and Parkinson's disease (PD) [In general circumstances, proteins intended for proteasomal breakdown get attached with the Ub chain by several rounds of a linear reaction catalysed by Ub activating (E1), conjugating (E2), and ligating enzymes (E3). Parkin is an example of E3. Deubiquitylating enzymes (DUBs), UCH-L1, work to reverse ubiquitylation processes. The UPS machinery requires energy in the form of ATP to operate. PD-linked genetic mutations in α-synuclein, UCHL1, and parkin, as well as mitochondrial alterations, exogenous stress, age-related changes, could cause the UPS to be disrupted, resulting in the protein accumulation or abnormal protein intermediates that could be directly detrimental to neuronal survival. The formation of Lewy bodies is assumed to be the outcome of the cell's attempt to sequester these aberrant proteins. The use of chaperones like Hsp70 to improve protein refolding and the stimulation of autophagy to clear protein aggregates could help alleviate UPS defects [37–40]. Such measures may provide novel approaches to the treatment of PD.]

the protein breakdown mechanism themselves. Probably feed-forward cycle exists between defective UPS and protein aggregation, in which one influences the other [47–49]. Excessive accumulation of aggregates can be harmful to cellular processes, triggering a feed-forward cycle that eventually leads to cell death [44, 48]. The critical question is whether Lewy body-like protein inclusions are harmful to neurons, causing them to degenerate, or whether they are cytoprotective, removing dangerous aberrant proteins from sensitive biological systems. Toxic soluble proteins are separated as a protective measure into aggregates, according to the current consensus. Lewy bodies in the outstanding dopaminergic cells of the SnPc are one of the signals that altered protein breakdown may be implicated in PD pathogenesis [50]. Lewy bodies are made up of a diverse combination of lipids and proteins. When the cell's ability to digest abnormal, mutant or oxidised proteins is surpassed, or when proteasomal action is blocked or impeded, abnormal proteins collect and tend to congregate. Proteins such as α-synuclein, several proteasomal elements, neurofilament, and Ub can be oxidatively altered and form the peripheral filamentous elements, whereas inclusions core are formed by the lipids [51, 52]. PD's clinical hallmarks are Lewy bodies; however, the process of the formation of protein aggregates and pathogenic importance is unclear.

Parkinson's Disease (PD) and Ubiquitin–Proteasome System (UPS)

Neurodegenerative diseases are pathologically and clinically diversified disease groups in which symptoms are caused by selective neurons reduction in particular brain parts. The neuropathological hallmark in PD has been reported to have inclusion bodies connected with disease-specific proteins, proteasome, Ub or Ub conjugates. Researchers have discovered a direct pathogenetic relationship between the UPS aberration and the sickness in several diseases [53–56]. The UPS, responsible for most of the cell's protein turnover, is an effective intracellular breakdown system. Figure 2 summarises the elementary steps of the metabolic process, which have been widely described elsewhere [3,

53, 54]. The failure of the UPS has been partially blamed by researchers in the pathophysiology of adult-onset, non-familial PD. Lewy bodies generally show immunoreactivity for ubiquitin. α-Synuclein, uchl1, parkin, dj1, and pink1 are the genes that have been identified as faulty [57–59]. It is worth noting that PD affects α-synuclein on a genetic level, marked by synuclein gene alterations and dupli/triplication. Additionally, the function of macroautophagy and CMA in α-synuclein breakdown or clearance is crucial. Two similar α-synuclein alterations (A53T and A30P) have been discovered to impede CMA degradation [60]. A different finding linking PD to UCHL1, a deubiquitinase enzyme, has a missense alteration (I93M) that lowers its deubiquitinating activity, suggesting that the UPS may play a role in PD [61]. Based on studies that proteasome component Rpt2 depletion promotes α-synuclein deposition and inclusions like Lewy body in mice, α-synuclein is established as a 26S proteasome's substrate [25, 62]. By 19S regulatory unit interaction and blocking the action of 26S proteasome, clumps of misfolded α-synuclein prolong the UPS dysfunction. However, in the 19S RP absence and without previous ubiquitination, α-synuclein monomers might be destroyed by 20S core particles [63, 64]. PINK1 phosphorylates ubiquitin on depolarized mitochondria, and the phosphorylated ubiquitin interacts with Parkin to cause conformational changes, allowing auto-inhibition to be released [65, 66]. As a result, Parkin's ability to act as an E3 without binding to phosphorylated ubiquitin has been demonstrated. Parkin has been identified as a constituent of Lewy bodies, although the predominantly Lewy bodies are associated with structural proteins like α-synuclein, a 14.5-kDa protein. Parkin has an auto-inhibited conformation, to put it simply. Parkin's structure has been solved in both its inactive and active variants. The REP domain binds to the RING1 domain to block its E2–binding interface, whereas the RING0 domain occludes the RING2 domain containing the catalytic core residue Cys431 [66]. A recent mouse study found that lactacystin-mediated inhibition of proteasome causes a limited decline of dopaminergic neurons and loss of striatal DA in the nigrostriatal pathway and Ser129-phosphorylated α-synuclein elevated appearance, supporting PD genesis by the dysfunction of UPS linked with α-synuclein breakdown [67]. A 53-kDa protein, parkin ordinarily diffusely expressed in brain neurons, is missing in individuals with autosomal recessive juvenile PD [68]. Parkin mutations cause up to 77 percent of familial cases with less than 30 years of onset and 10–20 percent of early-onset PD individuals [69]. The discovery of parkin's E3 ligase activity and a mutation in the parkin gene revealed the significance of UPS in PD for the first time. It's unclear how inactive parkin without phospho-ubiquitin may ubiquitylate CDCrel-1 and Pael-R under steady-state conditions, based on the existing molecular structure. Eosinophilic intracytoplasmic inclusions and Lewy bodies accumulated with Pael-R found in SnPc's dopaminergic neurons [70]. Parkin's structural findings suggest that the REP domain binds to the RING1 domain to block its E2–binding interface, while the RING0 domain occludes the RING2 domain containing the catalytic core residue Cys431. Parkin has an auto-inhibited conformation, to put it simply. However, PINK1 phosphorylates ubiquitin on depolarized mitochondria, and the phosphorylated ubiquitin interacts with parkin to cause conformational changes, causing auto-inhibition to be released. As a result, Parkin's ability to act as an E3 without binding to phosphorylated ubiquitin has been confirmed [71, 72]. From the standpoint of the present molecular structure, it is unclear how inactive parkin without phospho-ubiquitin can ubiquitylate CDCrel-1 and Pael-R under steady-state conditions.

Ubiquitin–Proteasome system (UPS) Dysfunction in PD

Protein accumulation serves as a UPS failure in the CNS. Synuclein's neurotoxicity is currently thought to be partially attributable to its suppression of proteasome activity. α-Synuclein neurotoxicity comprises the reduced role due to oligomerisation or alteration, fibrillation, or enhanced cell membrane penetration by oligomerised α-synuclein. In animal models, cell cultures, and cell-free systems, wild-type α-synuclein inhibits the proteasome more efficiently than oxidised, mutant, or oligomeric α-synuclein. In 1998, Leroy discovered a UCH-L1 I93M mutation in a family with PD [73]; Maraganore reported the next year that an S18Y polymorphism in UCH-L1 greatly reduced the risk of PD [74]. PINK1 phosphorylated ubiquitin on damaged mitochondria, and the presence of phosphorylated ubiquitin in the proximity of parkin can trigger parkin conformation alterations that allow it to be activated. As a result, we assume that proteins on the surface of injured mitochondria are actual parkin substrates is more reasonable and credible [75, 76]. UCHL1 is one of a number of DUB proteases that play a key role in the regulation of certain protein pools. Ubiquitin signalling is a dynamic, conserved mechanism in which ubiquitin rapidly modifies protein substrates to affect the stability, localisation, or activity of protein. DUBs regulate this process by eliminating ubiquitin from the substrates produced by ubiquitin conjugates and ligases. Many DUBs use common ubiquitin bond cleavage methods to selectively regulate physiological pathways [77]. Thorough genetic screening, neither the I93M nor other UCH-L1 mutations have been discovered, and UCH-L1 variants have failed to segregate with illness [78]. Against these claims, a 2004 study found that "UCHL1 is a PD susceptibility gene" [79], and this claim was refuted by Healy in 2006 [80]. The Uch-L1 mutation has been demonstrated to make cells more susceptible

to aggresome development due to proteasome inhibition therapy. Uch-L1 oxidation, observed in PD brains, has been linked to reduced hydrolase activity [81, 82]. The role of Uch-L1 in PD, on the other hand, is unknown. Uch-L1 is the only one of the four Uch-L1-4 that has deubiquitination and ligase activity and is neuron-specific [83]. Recently, Uch-L1 mutation was identified in a few cases of familial PD. It is currently unclear that ubiquitination/deubiquitination is intermediated by Uch-L1 or mutations are linked to the dopaminergic deterioration [83]. There is evidence that Uch-L1 hydrolase activity imparts neural resistance and that a mutation that decreases hydrolase activity could be a risk factor for PD development. Fibrillar-synuclein is the main structural component of Lewy bodies in sporadic PD. Variation in α-synuclein levels is most likely to blame for the observed variation, or perhaps another neurotoxic stimulus is required for α-synuclein to cause nigrostriatal degeneration. Upregulation of α-synuclein in MPTP animal models and enhanced MPTP resistance of nigral dopaminergic neurons in α-synuclein KO mice highlight the crucial function of α-synuclein in the physiopathology of PD [84]. Synuclein alterations have also been discovered in few familial PD incidences, including E46K, A53T, A30P, and gene locus triplication [85]. In the nigral dopaminergic cell line, α-synuclein overexpression lowered chymotrypsin-like proteasomal activity and guarded against neurotoxicity induced by chemicals for 12 hours, but later amplified the neurotoxic response [86]. Studies exploring synucleinopathies utilising genetically modified animals or viral-linked overexpression found great diversity in developing the clinical and behavioural abnormalities associated with PD, and not a single model shows nigral cell loss [87, 88]. Thus, the role of the UCH-L1 gene in familial PD is still debated. α-Synuclein is believed to have an essential part in PD pathophysiology. Parkin's altered solubility or nitrosylation likely neutralises parkin's neuroprotective role in sporadic PD; this adds to nigrostriatal dopaminergic deterioration. Parkin promotes neurons resistance to a range of stimuli, including dopamine, proteasome inhibitors, mitochondrial inhibitors, 6-OHDA-synucleinopathies, tauopathies, Pael-R overexpression, p38/JVT-1, and manganese, among others [89]. The functional effects of particular mutations in PD have been discovered using genetically modified and knockout animal models. Parkin-knockout mice and Drosophila models have well-preserved nigral DA neurons, but these animals have several neurochemical, mitochondrial, and behavioural abnormalities significant to PD development [76, 84]. On the other hand, others have not been able to replicate the same behavioural phenotype and neurochemical in mice, revealing that parkin knockout may not be the best mouse model for PD study in future [90]. The exact cause for this divergence between studies is unknown; however, it is possible that substantial neuronal cell loss occurs in parkin-knockout (KO) mice in their later stages of life. This theory could explain why asymptomatic human parkin heterozygotes decrease dopamine uptake in the midbrain and striatum areas deprived of nigral degradation. A ring domain E3 ligase, parkin, has been implicated in 50 percent of autosomal-recessive early-onset PD cases. Various proteins on the surface of damaged mitochondria are known as substrates for parkin [76]. Parkin interacts physically with the S5a (Rpn 10) subunit of the 26S proteasome, which is necessary for recognising ubiquitinated substrates by the proteasome, implying that parkin is involved in UPS dysfunction [91, 92]. The discovery of a link between many genes implicated in the UPS dysfunction and familial PD has offered suitable proof for the possibility of a dysfunctional UPS being involved in the disease.

The presence of ubiquitinated proteins in Lewy bodies indicates that UPS clearance of the target proteins is inadequate. The substantial loss of 20S proteasome core components and proteasome activators PA700 and PA28 may be responsible for proteasomal activity reduction in the SnPc region. Post-mortem investigation of sporadic PD brain tissues revealed comparatively decreased proteasomal activity in the SnPc region, supporting the hypothesis of a dysfunctional UPS in PD pathogenesis [17, 93, 94]. Chaperone proteins, proteasome subunits, ubiquitin, α-synuclein, and neural filament proteins are all found in cytoplasmic protein aggregates called Lewy bodies, which are hallmarked pathology of PD [95]. Misfolded protein accumulation during neurodegeneration is a sign of inefficient protein processing and breakdown, which is a standard defining feature of various neurodegenerative diseases, whereas the significance of protein accumulation to survival or death of neurons is yet unknown [96].

Macroautophagy and Selective Autophagy as a Degradation System in PD

Ubiquitin-binding proteins, ubiquilins, have a role in various neurodegradative processes. Both selective autophagy and macroautophagy abolish ubiquilin1, whose mutations influence PD risk [19]. CMA appears to abolish DJ-1 protein, as well as LRRK2 and α-synuclein; however, macroautophagy is primarily responsible for the elimination of aggregated and mutant proteins. Autophagy processes are affected in a different way by changes in the protein structures of PD-linked genes including DJ-1 and LRRK2, as well as lysosomal abnormalities [19, 39]. Preclinical research has identified numerous therapy methods that may be effective for PD by increasing autophagy [97]. LRRK2 overexpression promotes macroautophagy by increasing the levels of the p62 (an autophagic receptor) and promoting a long-term rise in autophagosome creation via a calcium-dependent route [39].

Throughout the previous decades, it has become obvious that Ub controls not just proteasome-mediated breakdown, moreover it too controls selective autophagy [98]. In selective autophagy, the autophagosomes engulf the injured mitochondria first, generating the mitophagosomes, which subsequently merges with lysosomes, where the lysosomal proteases degrade malfunctioning mitochondria [19, 99]. Ultimately, disintegrated macromolecules are carried back to the cytoplasm for reprocessing, allowing the substance to be reused and newer mitochondria to be generated. To eliminate aberrant mitochondria, MOM-linked Atg32 (receptor on mitochondrial) can interface with a scaffold protein, Atg11 necessary for selective autophagy, as well as an Ub-like protein, Atg8 localised on autophagosomes, in yeast [100]. Above-described processes are complicated, and they interact with one another. They also collaborate to encourage the elimination of malfunctioning mitochondria, ensuring a robust mitochondria reserve (Fig. 3).

Relationship between Ub/Proteasome and Autophagy

Autophagy and the Ub/proteasome are inextricably related. Selective autophagy relies heavily on proteins like GABARAP/LC3/ATG8 [101]. In a pathway with Ub, phosphatidylethanolamine was attached and regulated by LC3-like regulators, which requires the ATG5-12/16 complex's E3-like action [101]. Modified phosphatidylethanolamine and LC3-like regulators are absorbed into the phagophores and work together with autophagic receptors having LC3-interacting domains to mediate selective autophagy [39, 101]. Autophagic receptors identify Ub chains connected to cytoplasmic contents by Ub-binding regions in Ub-reliant selective autophagy, thus attaching selected content to the membrane of autophagosomes [98]. Autophagic receptors straightly attach to intracellular contents like mitochondria in Ub-independent autophagy, often through transmembrane regions. Unique oligomerization regions are used by autophagic receptors to aggregate with their selected contents [78, 102]. In a research by *Shen et al.*, treatment with lactacystin enhanced the Beclin 1 and LC3-I/II expression levels, while reducing the SQSTM1/p62, mTOR, and p-mTOR levels in SH-SY5Y cells and the midbrain of a UPS-impaired animal model of PD [103]. Additionally, lactacystin therapy resulted in a huge deficiency of TH-positive neurons in the SnPc and a huge rise in the quantity of autophagosomes in the left TH-positive neurons in a UPS-impaired mouse model of PD (Fig. 4).

UPS Roles in Motor and Non-Motor Symptoms of Parkinson's Disease

Aggregation prone proteins like α-synuclein, mitochondrial dysfunction, mutation, aging, and oxidative stress all lead to the proteasome dysfunction, which in turn leads to the accumulation of toxic proteins. And, all these has a role in motor and non-motor symptoms of PD [38, 39]. The ageing process, as well as certain age-related disorders like PD, are characterised by mitochondrial and UPS dysfunction. By managing the mitophagy and proteome, the UPS maintains mitochondrial homoeostasis. Mitochondrial failure causes oxidative damage to cellular proteins, disrupting their

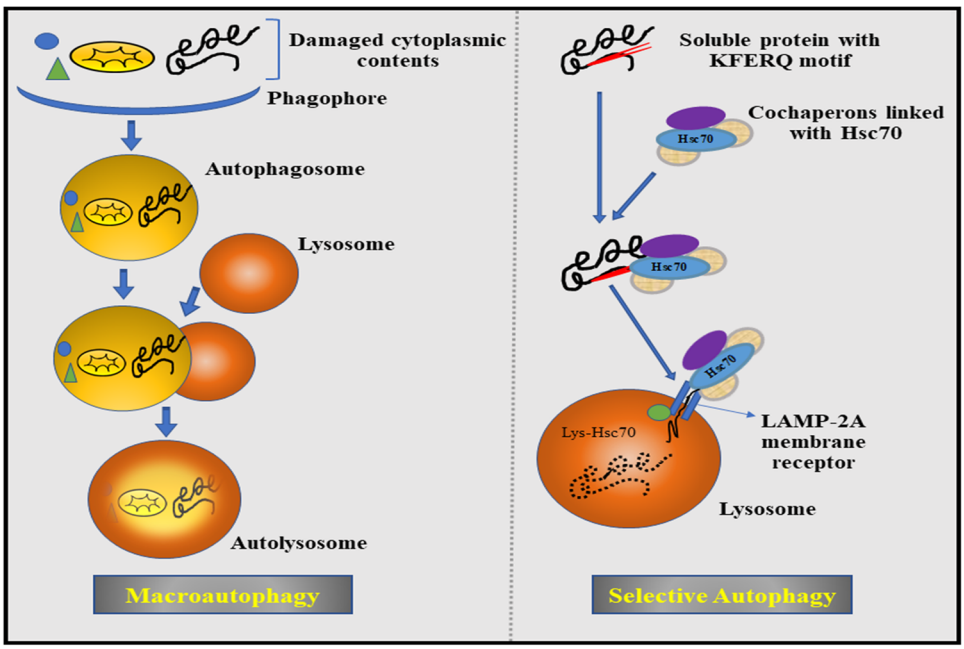

Fig. 3 Implication of selective autophagy and macroautophagy dysregulation in PD [19, 39, 98]. [Selective autophagy: CMA-mediated degradation, wildtype soluble α-syn degradation, inhibited by altered α-syn; Macroautophagy: degradation of impaired mitochondria, wildtype insoluble α-syn degradation, altered α-syn degradation]

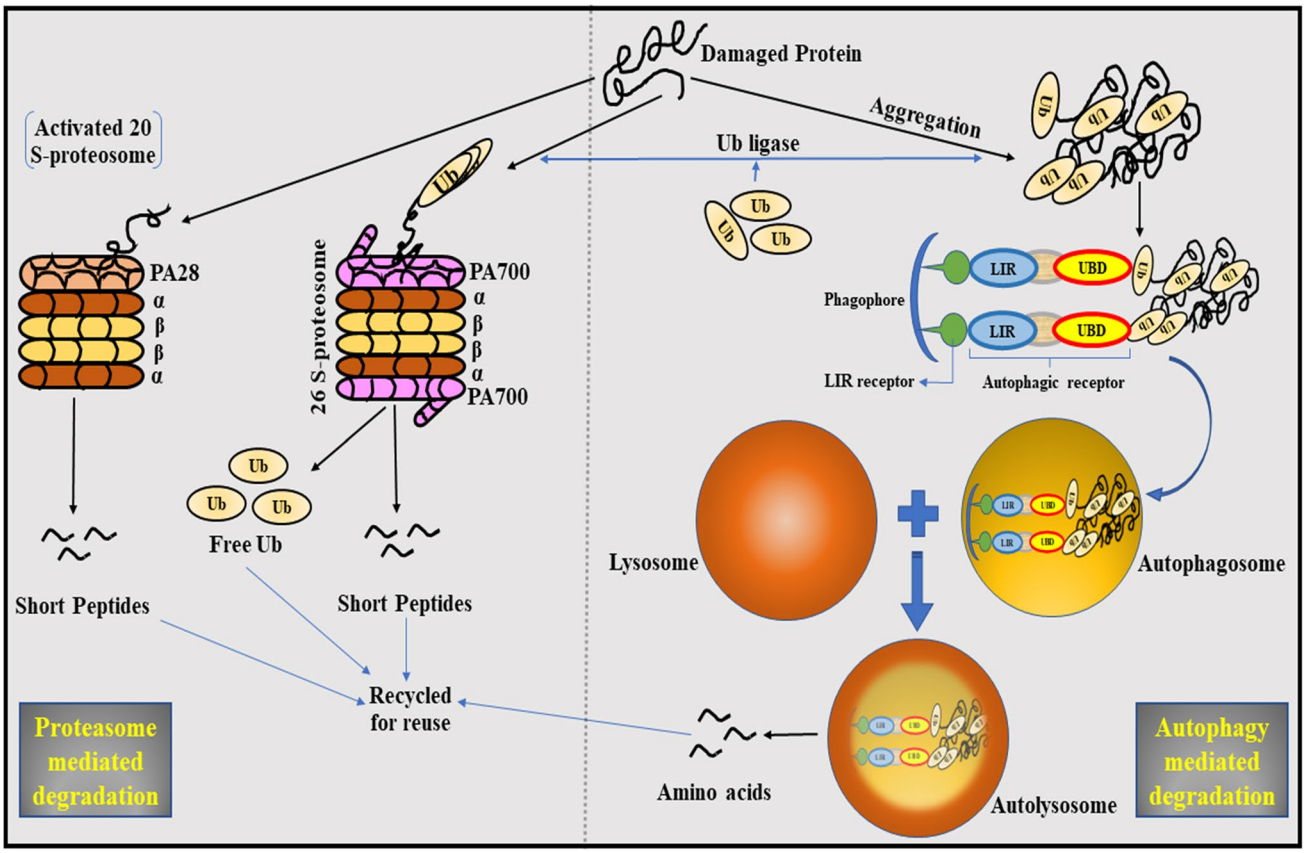

Fig. 4 Illustration showing Ub/proteasome-mediated and autophagy-mediated degradation of damaged or altered proteins [39, 78, 101]

equilibrium. Proteasome activation improves the ageing process in mice by lengthening their lifespan. It is difficult to distinguish mitochondrial dysfunction from UPS malfunction in PD [104]. Protein ubiquitination is important in the progression of neuropathic pain. Deubiquitinating enzyme (DUB), ubiquitin ligase, SUMOylation, and ubiquitination, among other things, govern chronic pain. To impact efficiency and synaptic activity, ubiquitination-modified protein receptors and ion channels perform this role [105]. The UPS has been linked to α-synuclein build-up or aggregates, which has been recognised as a clinical characteristic of PD, a neurodegenerative disease [99]. Ubiquitin, 26S proteasome-mediated signal for proteolysis, and chaperone proteins, which aid in the refolding of misfolded proteins, are frequently found in these aggregates. The discovery of disease-causing mutations in genes coding for multiple UPS pathway proteins in PD has strengthened the relationship between the UPS and neurodegeneration [106]. In the Lewy bodies' ubiquitinated protein aggregates from PD subjects, p62 was frequently found. Because p62 is involved in the destruction of misfolded or unfolded proteins, its dysregulation in the CNS causes a rise in protein aggregates, resulting in neurodegenerative disease. Increased aggregation formation of α-synuclein was also linked to a failure in normal p62 function, which had a toxic effect. Rotenone therapy, for example, increased α-synuclein aggregation and dopaminergic neuron degeneration in the substantia nigra, as well as p62 expression [97]. Ubiquitin marks proteasome substrates, and platelets have a functioning ubiquitination system that altered the proteome through mono- and poly-ubiquitination, which results in the dizziness [107].

UPS Management

During the last 20 years, public perceptions of proteasome function have shifted dramatically. Proteasomal activity and level regulation at many stages, including localisation, assembly, and activity, appear to be exceedingly complex that could help tune up proteasomal function to specific cellular conditions and needs. Even though it is yet unclear how proteasomal deficiencies in brain ailments are the secondary or fundamental cause of another pathogenesis such as oxidative stress, ER stress, or mitochondrial damage, the regulation of proteasomal activity as a treatment measure is gaining attraction for neurodegenerative disorders [108–110]. Table 2 lists some of the investigated medications in this regard where proteasomal inhibitors have

Table 2 Drugs used in neurodegenerative diseases to modulate the proteasomal activity

Category	Drug	Target disease/disorder
β5 activator	Betulinic acid Lithocholic acid derivatives Oleuropein	Autism and other neurodegenerative diseases[111, 112]
20S inhibitor	Paraquat	Parkinson's disease [102]
20S inhibitor (Cu-mediated interaction)	Clioquinol	Huntington's disease [113]
Reversible β5 inhibitor	PSI (Z-Ile-Glu(OtBu)-Ala-Leu-al), ALLN or MG101 (N-acetyl-Leu-Leu-Norleu-al)	Parkinson's disease, Huntington's disease [114, 115]
Non-competitive β5 inhibitor	Cyclosporin A	Parkinson's disease [116]
Covalently binds to the active site of the β subunits	MG132 (Z-Leu-Leu-Leu-al)	Parkinson's disease, Huntington's disease [117]
Reversible β5 and β1 inhibitor	MG115 (Z-Leu-Leu-Nva-al)	Parkinson's disease, Huntington's disease [118]
Irreversible β5=β2= β1 inhibitor	Lactacystin/Clasto-lactacystin β-lactone	Alzheimer's disease, Parkinson's disease, Huntington's disease [119, 120]
Irreversible β5=β2> β1 inhibitor	Epoxomicin	Parkinson's disease [121]
Inhibition of acid-sensing ion channels (ASIC1a)	Benzamil	Huntington's disease [122]
Mitochondrial Complex I inhibitor	MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride)	Parkinson's disease [123]

primarily been used to develop neurodegenerative models, whereas proteasomal activators have been investigated as a potential treatment for neurodegeneration.

Because UPS failure acts to function in PD development, medications focused directly or indirectly on alleviating UPS dysfunction might relieve those suffering from the disease [17, 108]. The following sections explain some ways for resolving UPS issues, which includes parkin therapy, induction of autophagy, management of misfolded protein and aggregation, etc. These approaches focused on regulating UPS activity can be beneficial for the treatment and management of parkinsonian patients. It is vital to remember that sporadic PD is probable complex, and the UPS can be unbiased one of multiple actors involved in the disease's pathophysiology. Given this, it is possible that PD could be healed by a mix of medicines aimed at significant issue sites of pathogenic flow, UPS being one of them.

Intriguingly, glutathione S-transferase S1 (GstS1) was discovered in a recent screen for parkin dysfunction modifiers in flies. In parkin mutant flies, overexpression of GstS1 protects dopaminergic neurodegeneration, suggesting that inducing GstS1 expression can effectively manage PD [124]. In Drosophila, increased parkin expression responds to PD-like signs caused by Pael-R or α-synuclein overexpression [108]. A study found that parkin administration protects against α-synuclein overexpression in a primate (non-human) model [125]. In line with these findings, MPTP- or 6-OHDA-treated and overexpressing α-synuclein rats showed that virus-mediated parkin delivery protects dopaminergic neurodegeneration [123]. Parkin appears to be a broad-spectrum neuroprotectant; parkin gene delivery could be a promising new treatment option for PD [126].

In cell culture models of accumulated protein, mTOR-independent pathways activate autophagy by the lithium action (which inhibits inositol monophosphatase, resulting in autophagy activation) or trehalose (unknown mechanism of activation) improves favourable outcomes [37, 40]. The suppression of mTOR by rapamycin stimulates autophagy and enhances the breakdown of accumulated protein, such as α-synuclein, reducing neurotoxicity. The phosphatidylinositol 3-kinase pathway's mammalian target of rapamycin (mTOR), which generally restrict autophagy, is a proper target for modulating the degradation system mediated by lysosomes. Even though autophagy is a separate degradation system from the UPS, new data reveal that the two systems work together to maintain protein homoeostasis. Both autophagy and UPS appear to be indulged in protein degradation (α-synuclein clearance), which is particularly relevant to PD. In a biological process, autophagy catabolises cytoplasmic components, including organelles. Furthermore, two recent independent papers give significant evidence for autophagy's role in neurodegeneration [78, 102]. Targeting autophagy pathway to treat parkinsonian disease could lead to new treatments [39].

Genetic techniques increasing the levels of chaperone expression to aid protein refolding might be beneficial for PD patients [127]. An anti-inflammatory medicine, dexamethasone sold beneath the brand names Solurex and Decadron, has been shown to boost several UPS constituents expression, together with proteasomal core subunits and PA700 activator [123]. In MPTP-treated mice, these

combined effects could explain the protection of dopaminergic neurodegeneration by dexamethasone [123]. Adeno-associated virus-mediated Hsp70 gene transfer prevents MPTP-induced nigrostriatal deterioration in mice, likely by lowering the quantities of misfolded proteins caused by the neurotoxin. Pharmacologically promoting expression of Hsp70 using available commercial medication Geldanamycin, whose analogues are presently in II Phase clinical trials, reduces neurotoxicity in multiple PD models [128]. In both flies and mice, α-synuclein and Hsp70 co-expression lower α-synuclein accumulation while attenuating dopaminergic neurons death mediated by α-synuclein [37, 38]. Proteasome inhibition causes protein deposition and aggregation, which serves as a possible contribution to pathogenicity. Compounds that directly boost UPS function, in addition to these, are likely to minimise protein accumulation and disease. Several other UPS modulators that are now being researched for various diseases could be relevant to PD. Approaches targeted at lowering proteasome load or increasing proteolysis should theoretically improve PD patient outcomes. This could include using RNA silencing to reduce the burden of harmful proteins.

Proteasome Activation

The UPS can be activated in three ways: endogenous activators, genetic activators, and natural or synthetic substances, as well as tiny molecules. Several tiny compounds capable of activating the proteasome have been discovered over time. The denaturing reagents, lipids, peptides, fatty acids, synthetic peptidyl alcohols, esters, nitrile activators, SDS, polylysine, and linoleic acid all fall under this category. Partially denaturing the proteasome and opening its conformation is the mechanism of action of SDS and fatty acids. Through the PA28 binding site, synthetic peptidyl alcohols, esters, p-nitro aniline, and nitriles activate the proteasome. Betulinic acid and oleuropein, extracted from Betula pubescens and Olea europaea, respectively, are potent proteasome activators [96, 129]. Oleuropein can activate all three proteasomal functions and generate conformational changes in the 20S-ring, whereas betulinic acid predominantly activates chymotrypsin-like activity. Other natural antioxidants, including dithiolethione and sulforaphane, may boost proteasome expression and improve oxidative stress resistance [111]. PA28, PA200, and PA700 are the three primary endogenous 20S proteasome activators known to date [4, 33, 130]. PA28 stimulates peptide hydrolysis by forming a ring with the 20S proteasome [26]. This route, like PA200, is ATP- and ubiquitin-independent and does not participate in the degradation of ubiquitinated proteins. PA28 is often referred to as the 11S regulatory particle (REG) [7]. This regulatory particle is typically a hetero-heptadimer found in the cytoplasm or a homo-heptadimer found primarily on the nucleus. PA28 overexpression was found to improve neuron survival in a Huntington disease cell model [131]. Proteasome activators could therefore be employed as therapeutic targets. PA200 is a nuclear protein with a molecular weight of 200 kDa that interacts with the 20S proteasome [132]. This proteasome activator boosts peptide hydrolysis, especially after acidic residues. PA700-19S is a 19-protein regulatory particle that is 1 MDa in size. In an Ub- and ATP-dependent way, this regulatory particle activates 20S proteasomes. Individual subunits of this particle are involved in protein unfolding, deubiquitination, and the opening of the ß-ring lid, which facilitate substrate access into the proteasome. PA28-20S-PA700 also produces hybrid proteasomes engaged in MHCI antigen presentation with the 26S proteasome [24–26, 132]. Through the breakdown of poly-ubiquitinated proteins, induction of PA700 has been proposed as one of the possible treatment options. Only a few proteasome activators were evaluated for their usefulness in neurodegenerative disorders, even though there is a vast spectrum of them. Table 2 summarises those that were found to be efficacious in experimental models of neurodegenerative illness. Yeast transcriptional regulatory system of the proteasome, a zinc finger transcription factor Rpn4, a proteasome-associated transcriptional regulator bearing proteasome-associated control elements (PACE) sequence, now represents the category of genetic activators. The Nrf1-DDI pathway is the most well-known pathway for the positive transcriptional regulation of the Proteasome [133]. Proteasome maturation protein (POMP) overexpression raises the quantity of functioning and assembled proteasomes and improves the antioxidant ability of cells, and it has been shown to upregulate proteasome activity in a human fibroblast cellular model [129]. Activation of proteasome pathways is still being studied as a possible therapeutic approach for treating PD and AD [130]. Ubiquitin–proteasome system is crucial molecular machinery that keeps cells in physiological settings; it is essential for cell survival; hence, its control must be done with extreme caution, as the regulators' side effects could be fatal.

PROTACs

PROTACs have been discovered with more selectivity than intrinsic inhibitors for targeted protein breakdown, which has lately expanded rapidly. Although p38 MAPK blockade has been linked to a reduction in abnormal protein aggregation in the presence of proteotoxic stress, nobody has yet demonstrated the safety and tolerability necessary for FDA clearance. A recent study used von Hippel–Lindau (VHL), E3 Ub ligase, and foretinib (small-molecule binder) to generate PROTAC, which destroys p38 MAPK via proteasome in a particular way [134–136]. PROTAC works by coupling

E3 Ub ligase to a small-molecule binder via a flexible chemical linker, triggering ectopic ubiquitylation and ultimately leading to the destruction of the proteasome. PROTAC is thought to be involved in the androgen receptor recruitment to the E3 Ub ligase, and degeneration of androgen receptor depends on the proteasome, which is inhibited by proteasomal inhibitors in cells [137]. Stimulation of ubiquitination is another way to improve protein breakdown. Proteolysis targeting chimeric molecules is used in this method of selective ubiquitination and proteasome post-translational destruction of specific substrates (PROTACs) [138]. PROTACs are intriguing hetero-bi-functional molecules that serve as a link between the targeted protein and the E3 ligase. With attached PROTAC, E3 Ub ligase stimulates the formation of polyubiquitin chains on target proteins, facilitating recognition and subsequent destruction by the 26S proteasome [137, 138]. PROTAC development appears to be a potential technique for understanding neurodegenerative disorders and translating those findings into targeted treatments [139, 140]. Off-target effects and proper dosage may be a problem in clinical applications because saturating concentrations of PROTAC might oppose the binding of PROTAC–protein complexes to its ternary partner, a well-known phenomenon known as the hook effect in cell tests. A study develops and formulates QC-01-175 (tau degrader) in which the tau PET tracer 18F-T807 is converted into a toxic tau ligand and linked to the CRL4CRBN E3 Ub ligase group. Surprisingly, QC-01-175 selectively degrades toxic tau, implying that the degrader is disease-relevant and tau-specific [141]. If high-quality PET tracers are accessible, PROTAC could be used to construct a functional α-synuclein degrader to use in PD. Even though nuclear and cytosolic proteins can be regularly digested, PROTAC-mediated protein degradation in the ER and Golgi has not been described. Furthermore, whether a PROTAC is engineered to cause protein breakdown in a unified system, it can be used in various cells without requiring genetic alteration [142].

The UPS uses all of the xenobiotic receptors as protein substrates. After activation by the ligand, the aryl hydrocarbon receptor was found to be rapidly removed [143]. Proteasome inhibitors prevent the degradation of aryl hydrocarbon receptor and are responsible for the stimulation of aryl hydrocarbon receptor target genes in the absence of ligand. In prostate and breast cancer cells, the aryl hydrocarbon receptor is an ubiquitin E3 ligase for the androgen receptor and oestrogen receptor, respectively [143, 144]. The breakdown of ß-catenin in the intestine likewise exhibits this transcription-independent enzymatic activity. The Cullin-really interesting new gene (RING) E3 ligase incorporating aryl hydrocarbon receptor is a conventional Cullin-really interesting new gene (RING) E3 ligase with CUL4B as the scaffold and aryl hydrocarbon receptor as the substrate adaptor [98]. A recent study found that when transcriptional activity is inhibited, E3 ligase activity increases, implying that E3 activity and transactivation are mutually exclusive [144]. The ubiquitylation of the pregnant X receptor is also controlled by multiple E3 ligases, although the ubiquitylation of the constitutive androstane receptor is less well characterised [98, 145, 146]. In conclusion, ubiquitylation-mediated proteolysis is crucial in the xenobiotic response. The UPS appears to be influenced by xenobiotic receptors as well.

Conclusion

The classic neurodegenerative condition, PD, appears to be connected to UPS dysfunction. Indeed, there is now a strong case to be made that UPS dysfunction is a common link across the various genetic causes of familial PD, whereas limited data suggest that proteasomal function is also affected in sporadic PD. According to above-discussed *in vitro* and *in vivo* results, UPS malfunction causes a failure to properly degrade undesired proteins, resulting in aberrant protein build-up and aggregation, the formation of inclusion bodies, and finally, the death of selective dopaminergic neuronal cells. One broad theory that could apply to all neurodegenerative brain amyloidoses is that excess protein accumulation could surpass the UPS's standard degradative capacity, causing cellular and metabolic abnormalities that eventually lead to neuronal malfunction and death. The underlying reason for aberrant protein accumulation could be a malfunction of the UPS, resulting in a positive feedback mechanism. The presence of ubiquitin-positive intraneuronal inclusion bodies in neurodegenerative brain amyloidoses, as well as aberrant aggregation and accumulation of amyloidogenic proteins like α-synuclein or tau, suggests that UPS dysfunction plays a vital role in the molecular pathogenesis of these diseases. Understanding the UPS and its specific involvement in degrading aberrant proteins and the mechanisms by which toxic protein deposition impacts neuronal integrity would hopefully lead to the development of new rational therapeutics for amyloidogenic neurodegenerative diseases. Autophagy, as a defensive measure for removing undesired mitochondria, has a significant relation with PD since it is crucial to PD pathogenesis and related genes, such as parkin and PINK1, are involved in mitophagy regulation. Hence, a better understanding of Ub/proteasome and autophagy/mitophagy mechanisms and their connections to PD may lead to more effective future target for drug development and therapy methods for PD that target mitophagy pathways.

Abbreviations AA: amino acid; AD: Alzheimer's disease; ATG : autophagy-related gene; CDCrel-1: cell division control-related protein; CMA: chaperone-mediated autophagy; CP: core particle; E1: ubiquitin-activating enzyme; E2: ubiquitin-conjugating enzyme; E3: ubiquitin-ligating enzyme; GstS1: glutathione S-transferase S1;

GABARAP: g-aminobutyric acid receptor-associated protein; HSP 90: heat shock protein 90; KO: knock out; LC: locus coeruleus; LC3: microtubule-associated protein 1 light chain 3; Pael-R: parkin-associated endothelial-like receptor; PD: Parkinson's disease; PROTAC : proteolysis targeting chimera; Sfp1: split-finger protein 1; SnPc: substantia nigra pars compacta; Ub: ubiquitin; UCH-L1: carboxyl-terminal hydrolase L1; UPS: ubiquitin–proteasome system

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