Parkinson's Disease: Genetics and Beyond

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Abstract: Parkinson's disease (PD) is characterized clinically by resting tremor, rigidity, bradykinesia and postural instability due to progressive and selective loss of dopamine neurons in the ventral substantia nigra, with the presence of ubiquitinated protein deposits called Lewy bodies in the neurons. The pathoetiology of cell death in PD is incompletely understood and evidence implicates impaired mitochondrial complex I function, altered intracellular redox state, activation of proapoptotic factors and dysfunction of ubiquitin-proteasome pathway. Now it is believed that genetic aberration, an environmental toxin or combination of both leads to a cascade of events culminating in the destruction of myelinated brainstem catecholaminergic neurons. Also the role of production of significant levels of abnormal proteins, which may misfold, aggregate and interfere with intracellular processes causing cytotoxicity has recently been hypothesized. In this article, the diverse pieces of evidence that have linked the various factors responsible for the pathophysiology of PD are reviewed with special emphasis to various candidate genes and proteins. Furthermore, the present therapeutic strategies and futuristic approaches for the pharmacotherapy of PD are critically discussed.

Key Words: Parkinson's disease, lewy bodies, protein aggregation, pathophysiology, α -Synuclein, Parkin, Mitochondrial dysfunction.

INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative motor disorders affecting 1% of the population over age 50. PD was first described by James Parkinson in 1817 and characterized by resting tremor, rigidity, bradykinesia and postural instability (collectively called parkinsonism). The disease is progressive and the pathologic features of classical PD are the selective loss of dopamine neurons in the ventral substantia nigra with the presence of ubiquitinated protein deposits in the cytoplasm of neurons (Lewy bodies), and thread like proteinaceous inclusions within neuritis (Lewy neuritis). The pathoetiology of cell death in PD remains incompletely understood, but evidence implicates impaired mitochondrial complex I function, altered intracellular redox state, activation of proapoptotic factors, and dysfunction of ubiquitin-proteasome pathway. The resultant state of dopamine deficiency results in disequilibrium of the extrapyramidal motor circuits and development of parkinsonism [14, 208, 225].

EPIDEMIOLOGY

The prevalence of PD in industrialized countries is estimated to be 0.3% of the general population [44, 217]. The disease increasingly strikes with age affecting about 1% of 65-year individuals and rising to 5% by 85-years of age [179]. The annual incidence of PD ranges between 16 and 19 individuals per 100, 000 [265]. PD occurs throughout the world in all ethnic groups and affect both sexes roughly equally or with slight predominance among males [289]. The lowest reported incidence is among Asian and African blacks where as the highest is among European and North Americans [124].

PD greatly shortens life-mortality upto 2-5 % [170]. PD along with other neurodegenerative diseases is projected to be the second most common cause of death among elderly by the year 2040 [154]. PD not only shortens the life expectancy but also causes debility during life affecting quality of life [278]. Mean age of onset of PD was estimated to be in the late 50s [111], however now it is thought to be in the early-to-mid 60s [121]. In 5-10% of the patients initial symptoms arise between age 10 and 40 (sometimes 50) years, hence is termed as young onset PD [85]. However the first symptoms of juvenile onset PD occur before the age of 20 years [187]. Young onset and juvenile onset PD are familial PD since family history is found in these patients. Idiopathic PD or typical sporadic PD is the term probably reserved for PD cases without or known etiology or familial connection [225].

CLINICAL FEATURES

PD is characterized clinically by three motor symptoms such as resting tremors, rigidity and bradykinesia. The fourth symptom postural instability is non-specific and is usually absent in early disease especially in the younger patients [224]. The motor abnormalities are many times accompanied by various non-motor symptoms including autonomic dysfunction[50], depression [105], other psychiatric changes such as cognitive deficit, anxiety, psychosis, hallucinations [32, 57, 166], dementia [66], sensory symptoms [141] and disturbed sleep [1, 251].

A resting tremor with a frequency of 3-5 Hz (classically resembling pill-rolling) is the first symptom in 70% of PD patients. Tremor is usually asymptomatic at disease onset and worsens with anxiety, contralateral motor activity and during ambulation. Resting foot tremor is much less common than hand tremor as a presenting sign [24, 122]. Rigidity is the raised resistance noted during passive joint movement that is uniform throughout the range of motion of the joint. Rigidity is enhanced by contralateral motor activity or mental task performance [168].

Bradykinesia is the most disabling symptom of early PD. It initially manifests by difficulties with fine motor tasks such as handwriting and reduced arm swing while walking. Limb bradykinesia can be tested by finger tapping alternating forearm pronation or supination, foot tapping and fist closing and opening [168].

Postural instability refers to the gradual development of poor-balance, leading to an increased risk of falls. Gait becomes slower with shuffling and turning is en bloc. Freezing is characterized by difficulty initiating gait or striking gait hesitation on arriving at a real or perceived obstacle. Postural and gait abnormalities are rarely prominent early in the course of PD [225].

Over the course of PD, more than 90% of patients experience symptoms of autonomic dysfunction [50]. Depression is common, affecting nearly half of the patients [105]. Other psychiatric symptoms associated with PD are cognitive deficit, anxiety, psychosis, hallucinations etc [32, 57].

Sensory symptoms arise in PD in various patterns [216]. Disturbed sleep is common in PD and has many different causes, including nocturnal stiffness, nocturia, depression, restless leg syndrome and REM sleep behavior disorder [1, 251].

DIFFERENTIAL DIAGNOSIS

The resembling clinical features are shown by normal aging, essential tremors, progressive supranuclear palsy, multiple system atrophy, dementia with Lewy bodies, cortico-basal degeneration, basal ganglia vascular disease, normal pressure hydrocephalus and

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other Parkinson plus syndromes [24, 122]. Less common entities with PD include dopa-responsive dystonia [79], juvenile onset Huntington's disease, pallidopontonigral degeneration and drug induced PD [130, 167]. Drug induced PD usually arises after exposure to neuroleptics, antiemetics and promotility agents (promethazine, prochlorperazine, metoclopramide), reserpine, tetra-benzazine and some calcium channel blockers. The pathologies underlying these diseases are different [244].

Hughes and colleagues as well as many others described differential criteria for diagnosis of PD [80, 116]. The supportive criteria described by Hughes included an asymmetric onset, progression, persistent asymmetry as an excellent response to L-DOPA treatment (dyskinesia). The exclusion criteria include corticospinal tract signs, severe dysautonomia, moderate to severe gait disturbance, and the presence of more than one clinically affected relative history of encephalitis and hydrocephalus and exposure to PD inducing drugs [225]. The exclusion criteria are designed to remove cause of an akinetic rigid syndrome not due to Lewy body nigral degeneration [116].

ETIOLOGY

The bicentenary of James Parkinson's original description of the disease will be marked in ten years, still the etiology debate of PD being environmental caused or genetically determined continues [167].

Environmental

Numerous studies have presented evidences suggesting the role of well water consumption [88, 89], toxic substances exposure as manganese, copper and other heavy metals [88, 89], 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) [148], dopamine derivatives as 6-hydroxy dopamine, salsonilol [163, 177], herbicides and pesticides as paraquat, rotenone [201, 230], endotoxins as lipopolysaccharide by *Salmonella minnesota* infections [183], frontal lobe tumors, defects or variation in metabolic pathways [7, 245] in development of parkinsonism. However, epidemiological studies that evaluated the association between environmental factors and risk of PD have reported inconsistent results for rural residence, drinking well water and exposure to pesticides [6].

Genetic

The role of genetic factor was suggested as early as 1880s, by observations made by Charcott and Gower separately of positive family history in patients of PD. The suggestion is supported by number of studies [207]. Approximately 15% of cases have first and second degree relatives [164]. Yet in the light of modern epidemiology techniques many of these studies appear to have been methodologically flawed, failing to examine affected family member to account for other factors such as family bias [223], hence cannot be considered conclusive.

It was hypothesized that, if PD has strong genetic determinant, concordance in monozygotic twins, who are genetically identical, should be greater than in dizygotic twins. However results of twin study, a frequently used tool to study the role of genetics, showed little difference in concordance in twins when PD develops after age of 50 years, whereas complete concordance was shown in monozygotic twins for PD with onset before 50 years of age. This finding suggests that genetic factors play a more significant part in the young-onset than late-onset or typical sporadic PD [260]. Finding of many other twin studies do not show enhanced concordance in monozygotic twins [132, 277]. Data from cross sectional studies was consistently refuted by longitudinal twin studies using 18F-DOPA positron emission tomography [146]. A large difference in concordance rates of monozygotic and dizygotic twins was observed by one of such studies [213]. With the identified gene mutations in familial PD and common genetic risk factors for idiopathic PD, the genetic basis for the pathophysiology of PD has gained its

place over the environmental factors, even though no gene has been identified so far as being solely responsible for idiopathic PD (Table 1).

In the patient population of PD there were less than 5% patients with monogenetic inheritance of the disease, 10-15% patient with familial history and vast majority of patients about 80% were essentially sporadic or idiopathic with complex etiology [147]. Current information suggests that PD is likely to result from a combination of both genetic and environmental factors [99].

MOLECULAR PATHOGENESIS

Whichever the etiological factor to initiate PD, be it a genetic aberration, an environmental toxin or combination of both, there follows a cascade of events culminating in the destruction of myelinated brainstem catecholaminergic neurons particularly dopaminergic neurons of SNpc. There is no clear explanation for selective neurodegeneration. One possible answer may lie in the ability of these neurons to take up both endogenous and extrinsic toxic compounds through selective carrier mechanisms such as dopamine transporter. Other possible explanations include increased metabolic stress, high physiologic rates of protein oxidation, selective generation of potential toxins or failure to detoxify or dispose off them (possibly because of the presence of neuromelanin) and specific requirement for neurotrophic support. Irrespective of above factors, the death of dopaminergic neuron is prevalent in PD. The symptoms of PD are caused by a >50% loss of dopaminergic neurons in the SNpc leading to >80% reduction in dopamine levels in the striatum [47]. The underlying mechanisms that provoke cell death in PD are largely unknown. The mechanism that has been implicated in neuronal degeneration and now gaining support is protein mishandling (as aberrant degradation) and subsequent accumulation of proteins [94].

PROTEIN AGGREGATION

The production of significant levels of abnormal proteins (as incomplete, mutant, misfolded, denatured, oxidized or otherwise damaged proteins) is associated with normal cellular functions. These abnormal proteins may misfold, aggregate and interfere with intracellular processes causing cytotoxicity. Hence their production should be limited or their clearance must be rapid for survival of cell [87, 235]. The production of abnormal proteins is prominent in the CNS due to high oxidative metabolism in neuronal cells [8, 97] and may be triggered or promoted by iron toxicity [18], glutathione deficiency [18], oxidative stress [64, 290], proteasomal dysfunction [46], mitochondrial impairment [234] and inflammation [196]. The limited ability of neuronal cells to repair/regenerate and their long life span demands equilibrium between the production and degradation of abnormal proteins for cell survival.

Ubiquitin proteasome system (UPS) is the main pathway that mediates the degradation of abnormal and soluble proteins as well as short lived regulatory functional proteins in cytoplasm, nucleus and endoplasmic reticulum [17]. The other system, autophagy uses cathepsins and cysteine proteases to degrade membrane and extracellular components following endocytosis into the lysosome [17]. If the production of abnormal proteins overwhelms, the protein degradation mechanism is inhibited or impaired, there occurs the accumulation and aggregation of these proteins [235]. This adverse state is called proteolytic stress [174]. In PD, where proteolytic stress is a key factor, inclusion bodies are seen in the cytoplasm and axons of neurons at various pathological sites. These inclusion bodies are termed as Lewy bodies (LB) and Lewy neuritis since they were originally described by Fredrich Lewy in 1912 [74].

All forms of familial and idiopathic PD have LBs with the exception of autosomal recessive form [74]. LBs are found in surviving neurons and nigrostriatal pathway as well as extranigral neurons as in dorsal mater nucleus of the vagus, substantia innominata,

Table 1. Genes Involved in Parkinson's Disease

Gene	Chromosome Locus	Gene Product	Age Onset	Clinical Features	Reference
PARK1	4q21-q23	α -synuclein	Late	Rapid progression, tremor uncommon	[242]
PARK2	6q25-q27	parkin	Early/Juvenile	Slow progression, dystonia or dyskinesia	[156]
PARK3	2p13	-	Late	Cognitive decline	[156]
PARK4	4p15	α -synuclein	Late	Postural tremor; dementia with weight loss	[242]
PARK5	4p14	UCHL1	Late	Similar to idiopathic PD	[153]
PARK6	1p35-p36	PINK1	Early	Slow progression, tremor at rest	[223]
PARK7	1p36	DJ-1	Early	Focal dystonia, psychiatric symptoms	[45]
PARK8	12p11.2-q13.1	LRRK-2	Late	Similar to idiopathic PD	[222]
PARK10	1p32(Icelandic)	-	Late	Similar to idiopathic PD	[108]
PARK11	2q(USA)	-	Late	Similar to idiopathic PD	[200]

thalamus, hypothalamus, amygdala, piriform cortex and olfactory bulb [74]. LBs are also seen in extracellular space following destruction of the host neurons [134].

LBs are cytoplasmic rounded inclusions of 8-30 μ in diameter with spherical dense core and peripheral halo radiating filaments of diameter 7-20 nm. The LBs in cortical region are diffuse since they frequently lack a distinct peripheral halo. The LBs contain heterogeneous mixture of insoluble proteins and lipids [48]. Among proteins α -synuclein (α SN) derivatives are the major proteins [48, 250]. Apart from α SN, LBs contain various proteins [14, 49, 149, 250]. These proteins include 1) proteins related to UPS as ubiquitin, ubiquitinated proteins, ubiquitin carboxyterminal hydrolase (UCHL1), ubiquitin ligase, elements of proteasomes, ubiquitin binding protein, parkin and DJ-1 2) cytoskeletal proteins as neurofilaments, intermediate filaments, tubulins, microtubule associated proteins, tropomyosin family, gelsolin (actin disassembling protein, septin) 3) protein kinases and phosphatases 4) chaperones as heat shock proteins (HSP70, HSP90) 5) $\alpha\beta$ crystalline, torsin A, 14-3-3 6) proteins associated with inflammation as various complements 7) α SN binding proteins as synphilin, MAP1B 8) Alzheimer's disease related proteins as tau, apoJ, cdk5, β -amyloid precursor proteins 9) proteins associated with apoptosis, Bcl-2 associated death proteins, extracellular regulated kinase 10) other proteins as glutathione peroxidase, transglutaminase, cytochrome C. These proteins may be oxidized, nitrated, phosphorylated and/or ubiquitinated [14, 49, 249, 250].

α -synuclein

Structure

α SN gene spans about 111 kb, contains 6 exons and encodes 140 amino acid protein that has a molecular weight of ~14 kDa. This extremely heat resistant small acidic protein remains uncoiled in solution but assumes α -helical configuration within lipid containing vesicles and β -sheet at high concentration [220]. The sequence of α SN can be subdivided into three distinct domains i) The highly conserved amino terminal domain of residues 1-65, containing six imperfect repeats with KTKEGV consensus motif. This domain is unordered in solution but can shift to an α -helical confirmation of two distinct helices interrupted by a short break [28, 81]. The amino terminus can bind to lipids and play role in association with lipid micelles, synaptic vesicles, lipid bilayer [63, 131] ii) The central portion of α SN known as non A β component of plaque (NACP) has residues 61-95 and is responsible for various conformations of α SN [266] NACP helps to attain random coil, β sheet or single cylindrical β -sheet or protofibrils and fibrils [53, 61, 82] iii) The acidic C-terminal of residues 97-140 appears critical for other pro-

tein binding and chaperone like activity [138, 202]. The C-terminal has several phosphorylation sites as Y125, 133, 136 and S129 [77]. α SN in LB is extensively and specifically phosphorylated at S129. Whereas post translational modifications in the C-terminal include glycosylation at S129 [236], oxidation [27] and nitration at Y125, 133, 136 [259]. These modifications affect chaperone-like activity.

α SN Protein Functions

Potential Loci for Pathology: The functions ascribed to α SN include physiological regulation of certain enzymes, transporters, neurotransmitter vesicles as well as roles in neuronal survival. α SN has been demonstrated to inhibit protein kinase C [197], phospholipase D2 [123], tyrosine hydroxylase [208]; to down regulate extracellular signal regulated kinase (ERK) [100], Bcl2 associated death protein (BAD) [151]. Also α SN facilitates an increase in the number of plasma membrane dopamine transporter (DAT) molecule. Phospholipase D2 triggers secretory vesicle production by catalyzing hydrolysis of phosphatidyl choline to phosphatidic acid [5]. Tyrosine hydroxylase is rate limiting enzyme in dopamine synthesis. DAT regulates dopamine uptake.

α SN, in addition to binding to lipids, binds to variety of ligands and has been reported to interact with more than 200 proteins [5] and functions as a chaperone. The various proteins with which α SN interacts include synphilin, parkin, UCHL1, 14-3-3, tubulin and many others [5, 237]. Parkin, UCHL1 are involved in UPS whereas 14-3-3 regulates cell growth and neuronal development, antagonizes BAD and increases tyrosine hydroxylase activity [286].

The changes in cellular conditions such as pH, temperature and oxidative stress, mutations and aging could trigger changes in α SN gene expression as well as post translational and/or conformational protein modifications. The changes in the proteins make it more prone to self aggregation hence more difficult to destroy or alternatively the production of misfolded proteins that cannot be degraded [22, 276]. The undegraded α SN accumulates in cytoplasm. This causes molecular crowding or formation of spherical protofibrils, a process that involves β -sheet formations, oligomers and subsequently chains and annular/ring protofibrils [53, 275]. The generated annular protofibrils would exert toxicity due to their binding and permeabilization of vesicles and formation of amyloid pores [149, 275]. α SN fibrils are thought to act initially as protective sink i.e. protofibrils are consumed for formation of fibrils therefore cell gets temporarily relieved from α SN toxicity. However the accumulation of fibrils eventually results in toxicity. Indeed studies using cultured human dopaminergic neurons suggests that mutant α SN triggers an elevation in cytosolic dopamine, oxidative stress and dopamine-dependent toxicity [281]. The mutant α SN causes an

increase in toxicity probably *via* a reduction in synaptic storage of dopamine [257]. The putative toxic forms of α SN, apart from fibrillar aggregates (Lewy bodies, Lewy neuritis, cytoplasmic glial inclusions), amorphous aggregates, oligomers & protofibrils include soluble forms as partially folded intermediates, S129 phosphorylated α SN, phosphorylated, nitrosylated, glucosylated, ubiquitinated α SN species [53].

Soluble forms of α SN complex with different chaperones as 14-3-3 an anti-apoptotic protein [281] and hasten apoptosis. Protein confirmation dependent neurotoxicity is seen as increased propensity of partially folded intermediates to aggregate and oligomerise and act as chaperone [138, 185]. Various non-genetic etiological factors as pesticides, metal ions, oxidized trimethyl-N-oxide have shown to make α SN acquire increased level of secondary structure [211, 267-270]. Oxidative stress conditions facilitate catecholamines including dopamine to be readily converted in the presence of iron to highly reactive metabolites such as dopamine-quinone [37, 211, 267-270], these can bind to α SN. Adducts of dopamine quinone α SN block α SN fibril formation and stabilizes the potentially most toxic α SN protofibrils at the expense of fibrils [37]. The toxicity of dopamine quinone adduct have a role in dopamine dependent toxicity that involves α SN proteins complexes such as with 14-3-3 [281], interacting possibly with various functions of 14-3-3 [157]. Other derivatives as Ser/Tyr phosphorylated α SN, Tyr-nitrosylated α SN, Tyr-phosphorylated α SN perhaps affect vesicle movement and potentiate fibril formation [157, 158]. In addition to α SN overexpression in cultured cells, particularly of mutant forms has been linked to mitochondrial deficit [114], defective cellular trafficking [91], impaired chaperone-mediated autophagy [39] and increased sensitivity to oxidative stress [140].

Mutations in α SN

Three missense mutations have been identified with autosomal dominant inheritance pattern as A53T [140], A30P [140, 143], E46K [287]. These missense mutations develop Parkinson's disease at 40-60 years of age with typical PD symptoms. Genomic duplication [29] and triplication [242] are also identified. Genetic polymorphism in the promoter of α SN gene have been identified as PD susceptibility markers [70, 71, 112] which implicates that variability of α SN levels can predispose individuals to disease [199].

UPS, PARKIN, UCHL 1, PROTEASOMES

Ubiquitin proteasome systems are responsible for rapid degradation control of 30% or more of newly made proteins within the cell [239]. This process plays a crucial role in a number of cellular events such as cell-cycling, protein trafficking, antioxidant defense mechanisms, mitochondrial function, inflammatory response, immune response, apoptotic signaling, synaptic function and neurotransmission, signal transduction, gene transcription, cell development and differentiation [176].

The UPS comprises two sequential processes: marking of target proteins with ubiquitin-ubiquitination and proteolytic action by proteasome, on marked proteins. The ubiquitination is a highly ordered ATP dependant process catalyzed by three enzyme systems viz. E1 (ubiquitin activating enzyme), E2 (ubiquitin conjugating enzyme), E3 (ubiquitin ligase) [107]. For mammalian cells only a single E1 is known to exist at present, whereas E2 family consists of over 20 members as UbcH7, UbcH8 and E3 family consist of hundreds of members, parkin is one of them of importance [214].

In the first step of ubiquitination, molecules of ubiquitin (a 76 amino acid, 8.5 KDa polypeptide) are activated by E1. In the second step, the activated ubiquitin is transferred to E2. In the third step, target protein is recognized by E3 which then catalyses the transfer of ubiquitin from E2 to target protein *via* a covalent bond between carboxyl group of C-terminal residue and internal Lys residue/s of the target protein [214].

Subsequent cycles of covalent addition of Ub molecules result in addition of many Ub molecules to target proteins. A minimum of 4 Ub moieties are required for efficient marking for the proteasome. The marked proteins are degraded by 20/26S proteasomes to small peptides as of 2-24 amino acid residues that are further degraded by peptides to their constituent amino acids ready to be recycled and then hydrolysed by ubiquitin carboxy terminal hydrolase (UCHL 1) to monomeric ubiquitin [118]. Chaperones like heat shock proteins function significantly with UPS, in several ways, notably in their ability to facilitate the recognition and entry into 20/26S proteasomes [118]. Small ubiquitin modifiers (SUMO) may undergo similar and similarly varied reactions with targeted proteins [212].

The dysfunction/inhibition of the protein/s operating in UPS could cause aggregation of unwanted proteins resulting in toxicity. For example, pathogenic species of α SN are more resistant to proteasomal degradation and can directly bind to 20/26S proteasomal subunit and impair proteolytic activity [13, 155, 246]. Over expression of mutant α SN also sensitizes cultured cells to the toxicity associated with proteasome inhibitors, suggesting a prior levels of proteasome impairment [261].

PARKIN

Structure

Parkin, an E3 ligase, gene spans about 1.5Mbp contains 12 exons and encodes a 465 aminoacid protein that has a molecular weight of ~52KDa. Parkin contains i) An amino acid terminal (residues 1-76) ubiquitin homology domain UHD that shares 62% homology to Ub and may be involved in substrate recognition and proteasome binding ii) a central domain (residues 145-232) with unknown function iii) a carboxy terminal RING (RING-Really Interesting New Gene) box (residues 237-449) involved in substrate and E2 interaction. A RING box is composed of two RING-finger motifs. RING1 and RING2 and a cys rich domain termed in between RING (RING1-IBR-RING2) [49, 171].

Parkin Functions

Potential Loci for Pathology: Parkin, the E3 ubiquitin-protein ligase is found to be localized in mitochondria [145]. Numerous substrates that are identified and recruited by parkin in UPS include CDCrel (cell division control related), Pael R (parkin associated endothelial like receptor), O-glyco-sylated α SN, synphilin, cyclin E, CHIP, CASK, septin, α/β tubulin, aminoacyl tRNA synthetase cofactor, p38/JIV 1 and others [49, 171].

The substrate CDCrel is synaptic vesicle associated protein suggested to regulate synaptic vesicle release of cytokines. Parkin mutations could affect CDCrel-1 modulation of dopamine release which may contribute to PD [42]. The second substrate of parkin Pael R is related to aggregation and cell death *via* stress response in endoplasmic reticulum [120, 237]. Parkin suppresses Pael R induced toxicity by ubiquitination and degradation of this protein and can protect dopaminergic neurons against various insults [119].

Interaction of parkin with α SN, synphilin suggests parkin may play role in vesicle transport and LB associated autosomal PD [35, 237]. Over expression of parkin can rescue cells from proteolytic stress [119] as with mutant α SN induced toxicity. Parkin also has been suggested to play a protective role in apoptosis cell death by delaying mitochondrial swelling and reducing cytochrome C release [41].

Mutations in Parkin

Mutations in parkin are associated with autosomal recessive juvenile parkinsonism (ARJP) characterized by early onset disease mostly before 40 years of age. Parkin mutations have been found in about 60% familial cases and about 20% of cases without positive family history [184]. More than 40 different mutations have been identified globally in varied ethnic populations as European, Japa-

nese, Indian, German etc. These mutations include missense mutations, nonsense mutations, frame shift mutations, deletions, insertions, duplications etc [34, 75, 159, 171, 209]. Lack of parkin function due to mutation has been suggested to lead to toxic accumulation of substrate proteins or indeed itself. Over expression of mutated forms of parkin cause oxidative stress, excessive nitric oxide production and lead to cell death probably *via* proteasomal inhibition.

Mutations in parkin can disrupt interaction of parkin with E2s and impair substrate recognition such as Q311stop, T240R abrogate interaction between parkin and UbcH7 [236, 237]. Mutation of R42P does not affect UbcH7 interaction still abolishes ubiquitination [236, 237]. T415N and Q311 stop mutations eliminate UbcH8 binding to parkin and T240 R, W453stop reduces the binding [288]. Wild type parkin can promote the ubiquitination of α SP22 (O-glycosylated α SN) but the R42P and T240R mutants do not display this activity [288]. Exon 3-4 deletion (parkin without aminoacids 58-178) prevents interaction of parkin UbcH7,8 and loss of E3 ligase [288, 119]. The mutations lying in Exon 7 leading to R256C, R275T, C253Y, D280N are especially predisposing to the late onset form of PD due to variable functional reduction in parkin [194]. The Lewy body pathology has been found in a ARJP case with R275 W substitution and exon 3 deletion [70]. As in the case of α SN, the parkin gene promoter has several functional variants and those that of lower transcriptional activity have been reported to be associated with increased risk of PD [279].

DJ-1

Structure

DJ-1 gene spans about 24 kb contain 8 exons and encodes 189 amino acid protein that has a molecular weight of ~20KDa [115]. The crystal structure shows that DJ-1 exists as a homodimer *in vitro*. Dimerization of protein appears to be critical for its normal cellular function, the failure of dimerization results in increased degradation and hence loss of function [115].

DJ-1 Functions

Potential Loci for Pathology: DJ-1 expression is ubiquitous in the brain with higher levels of the transcript in subcortical regions such as the caudate nucleus, thalamus, substantia nigra and hippocampus which are more often affected in PD [9]. Unlike α SN and parkin, DJ-1 is not an essential component of Lewy bodies. DJ-1, which belongs to DJ-1/Thi J/Pfp 1 super family, participates in multiple protein-protein interactions. The important proteins with which DJ-1 interacts are PIAS α (protein inhibitor of activated STAT (signal transducer and activator of transcription)) and DJBP (DJ-1 binding protein) [190, 259]. Both these proteins bind to DNA binding domain of androgen receptor controlled genes. The exact function of DJBP is unknown, while PIAS α , is a member of PIAs family of proteins known as SUMO 1, ligases and regulates various transcription factors such as p53 and steroid hormone receptors [115].

DJ-1 may have a role in sensing and protecting neurons from oxidative stressors and/or protecting against mitochondrial damage. For example in cell culture studies and under stress conditions, wild type DJ-1 appears to translocate to the outer mitochondrial membrane and has shown to confer protection against some toxins such as MPTP [25].

DJ-1 demonstrates an acidic shift in isoelectric point in cultured cells following oxidative stress owing mainly to oxidation of cysteine residues, particularly Cys106, which can be converted to cysteine sulfinic acid (CysSO₂OH) [25]. In cultured cells, overexpression of DJ-1 protects against oxidative harm whereas breakdown of DJ-1 by small interfering RNA (siRNA) enhances the susceptibility to oxidative stress [258]. DJ-1 has been found to shift to more acidic isoforms (pH 5.8) after treatment of cells with herbicide

paraquat causing α SN upregulation and aggregation by oxidizing proteins [162]. DJ-1 may also confer protection against endoplasmic reticulum stress, proteasomal inhibition and the toxicity induced by over expression of PaelR [284].

Mutations in DJ-1

DJ-1 mutations are rare cause of early onset autosomal recessive parkin-like parkinsonism. The frequency of DJ-1 mutations in early onset familial disease is approximately 1-2 %. To date no mutations have been described in idiopathic PD. The identified DJ-1 mutations include L166P, 14kdel, M26I, D149A [2], Ivs6-1G→C, c56 del Cc.56G→A, A104T [96], Ex 5-7 del, IV S5+2-12 del [103]. L166P mutant DJ-1 exists as a monomer instead of dimer because of impaired ability to self-interact. As a result the mutant protein is highly unstable and is degraded by 20/26S proteasome [183]. Wild type DJ-1 over expression can rescue cells from H₂O₂ induced oxidative stress but L166P mutant DJ-1 cannot do this [284]. The effect of other potent mutations remains to be identified. The majority of mutations result in aberrant protein transcription and truncation causing loss of functionality of the protein.

DARDARIN OR LRRK2

Structure

LRRK2 (Leucine Rich Repeat Kinase 2) or dardarin (in Basque dardara means tremor) gene spans about 14 kb contains 51 exons and encodes 2527 amino acid protein that has molecular weight of about 286 KDa [198].

The LRRK2 belong to ROCO protein that contains numerous highly conserved domains as Leucine-rich repeat LRR; Ras of complex proteins (Roc) a Ras-like/small GTPase superfamily domain of mitogen activated protein kinase (MAPK), a tyrosine kinase like domain and WD 40 domain [198].

Very little is known about the normal functions of LRRK2. It functions as kinase and kinase activity most closely resembles the family tyrosine like kinases that phosphorylate serine/threonine residues and lie upstream of MAPK pathways. These receptor interacting protein (RIP) kinases activate downstream pathways by scaffolding function, in addition to and independent of their kinase activity [262].

Mutations in LRRK2

Mutations in LRRK2 tend to be distributed throughout these functional domains and are responsible for $\leq$ 7% of familial autosomal dominant late onset PD and account for 0.5-3% of sporadic PD [51, 83, 198]. The mutations found include R1441C [198, 291], Y1699C [198, 291], G2019S [83], I1122 V [291], I2020T [78]. Many more putative amino acid substitutions have been identified [15, 137]. At present it is unclear how mutations in LRRK2 cause PD, but it will be of particular interest to determine whether LRRK2 is related to other gene products or molecular pathways associated with PD. It is tempting to speculate that the putative kinase activity may be involved in the phosphorylation of protein implicated in PD pathogenesis such as α SN [182].

In contrast to mutations in parkin and DJ-1 which likely cause PD by loss of function mechanisms the I2020T mutation within kinase domain of LRRK2 has been found to increase the kinase activity of LRRK2 by 40% *in vitro* suggesting that increased LRRK2 kinase causes PD [86].

PINK1

Structure

PTEN [(phosphatase and tensin homolog deleted on chromosome ten)] induced putative kinase, PINK1 gene spans about 18 kb contains 8 exons and encodes 581 amino acid protein that has a molecular weight of about ~63KDa. The N-terminus of PINK1 protein has a mitochondrial targeting motif at N-terminus with 34

amino acid and a highly conserved protein kinase domain (amino acid 156-509) homologous to serine/threonine kinases of Ca^{2+} -calmodulin family [241].

Studies of PINK1 are at an early stage and currently little is known about the physiological functions of PINK1. PINK1 is found to be localized in mitochondria and suggested to have mitochondrial function in phosphorylating mitochondrial proteins in response to cellular stress [241]. Although the kinase activity of PINK1 has been demonstrated and as such no putative mitochondrial substrates or interacting proteins have been found. *In vitro* studies suggest that PINK1 may afford some protection against mitochondrial dysfunction and apoptosis induced by proteasomal inhibition, although the mechanism for this action is not understood [241].

Mutations in PINK1

Mutations in PINK1 probably account for only 1-2% of early onset cases of Parkinson's disease [101]. Mutations in PINK1 are thought to cause PD through loss of function with most mutations clustering in and around putative kinase domain. Several mutations reported in PINK1 include W437stop, G309D [234], H271Q, E417G etc [101]. Reports show that loss of *Drosophila* PINK1 leads to defects in mitochondrial function resulting in male sterility, apoptotic muscle degeneration, and minor loss of dopamine neurons that is rescued by overexpression of the ubiquitin E3 ligase, parkin. Thus, PINK1 and parkin appear to function in a common pathway suggesting a convergence of the two genes most commonly associated with autosomal recessive PD [101].

OTHERS

Several other genes have been implicated in the pathology of PD or have been re-examined. These are genes for UCHL-1, synphilin-1, NR4A2 and glucocerebrosidase. UCHL-1 protein functions in the UPS of protein degradation and is also found in LBs. An I93M mutation in gene encoding UCHL-1 resulting in reduced enzymatic activity is thought to cause autosomal dominant PD in one family of German descent [153]. NR4A2 protein acts as a transcription factor required for the differentiation and maintenance of dopaminergic neurons and heterozygous mutations were identified in multiple PD families [150].

Synphilin-1 has been implicated in the pathogenesis of PD after one group identified heterozygous mutations and because it may interact with both α SN and parkin [169]. For all three genes there has been little or no replication of the original study in independent populations.

Mutations are found in gene for glucocerebrosidase and the findings have been replicated by most studies [4, 160].

MITOCHONDRIAL DYSFUNCTION

The link between Parkinson's disease and mitochondria was first established with the identification of a deficiency in the activity of complex I (NADH ubiquinone reductase) in PD substantia nigra and subsequently in the peripheral tissues of patients. Inhibition of complex I results in increased free radical generation and could contribute to the oxidative mediated damage seen in the PD affected substantia nigra. Inhibition of mitochondrial respiration reduces the levels of ATP required for normal UPS function of protein degradation and oxidative stress adds to the substrate load. These changes in turn may induce protein damage and misfolding [26]. The neurotoxic compounds as MPTP, rotenone which selectively damage dopaminergic neurons and cause PD like clinical features are selective inhibitors of complex I of mitochondrial respiratory chain [93]. There is 30-40% decrease in complex I dysfunction in PD which could thus play a role in oxidative stress, free radical mediated protein damage, impaired proteasomal function and protein accumulation [232]. Mitochondria are also intimately involved with both necrotic and apoptotic cell death. Recently identified nuclear gene mutations of mitochondrial proteins include

mutations of PINK1, DJ1 causing Parkinson's disease, and mutations of MtDNA polymerase γ (POLG) causing parkinsonism. The relation between mitochondrial dysfunction PD has been highlighted further by the recent description of mtDNA abnormalities in PD patients. Occasional mtDNA point mutations have been identified in PD but these have not been present in the general PD population. Thus, their association with PD might merely represent part of the wide clinical spectrum of mtDNA mutations and not necessarily imply a more common role in sporadic PD. POLG mutations have been described in patients with PD with ragged red fibres and multiple mtDNA deletions, but mutations of this gene have not been found in sporadic PD [256]. A mutation in the mtDNA 12S RNA was identified in a patient with maternally inherited early onset PD, deafness, and neuropathy. Several studies that have sequenced mtDNA in PD patients have not identified any consistent mutations. Two studies have shown a link between mtDNA haplotypes and the risk for developing PD. The first showed a reduced risk for PD in individuals with haplotypes J and K and the second a 22% decrease in PD risk in those with the UKJT haplotype cluster. In contrast, a smaller study reported an increased risk for PD with haplotypes J and T.

Inhibition of mitochondrial respiration causes the release of reactive oxygen species from the respiratory chain and reduces the levels of ATP required for normal ubiquitin-proteasome system function of protein degradation. These changes in turn may induce protein damage and misfolding [26]. The neurotoxic compounds as MPTP, rotenone which selectively damage dopaminergic neurons and cause PD like clinical features are selective inhibitors of complex I (NADH ubiquinone reductase) of mitochondrial respiratory chain [93]. There is 30-40% decrease in complex I dysfunction in PD which could thus play a role in oxidative stress, free radical mediated protein damage, impaired proteasomal function and protein accumulation [232]. Mitochondria are also intimately involved with both necrotic and apoptotic cell death.

Oxidative Stress

Oxidative stress develops from increased production of highly reactive free radicals, decreased scavenging of these reactive species, increased generation of oxidatively damaged proteins, lipids, DNA and decreased clearance of oxidized products that could be toxic for cells [233].

Signs of oxidative stress are abundant in the substantia nigra of patients of PD [128]. These include reactive oxygen species (ROS) such as hydrogen peroxide, hydroxyl, superoxide and peroxy radicals. Other oxidants are reactive nitrogen species (RNS) as nitric oxide. These strong oxidants react with DNA, protein and lipid altering their structure and causing cellular damage [127]. The oxidants as ROS are produced by dopamine metabolism, the electron transport chain of mitochondria, iron metabolism and inflammation (Fig. 1).

The enzymatic metabolism or auto-oxidation of dopamine generates free radicals [97]. Dopamine metabolism by MAO-A leads to production of dihydroxy phenylacetic acid (DOPAC) and H_2O_2 with the consumption of O_2 and H_2O . Intracellular auto-oxidation of dopamine generates dopamine-quinone and H_2O_2 . Dopamine-quinone participates in nucleophilic reaction with sulfhydryl groups of protein leading to structural modification and reduced glutathione levels [253], and is shown to inhibit glutamate and dopamine transporter function in synaptosome [16], inhibit tyrosine hydroxylase [144] in cell free systems and promote H^+ leakage from mitochondria resulting in uncoupling of respiration to ATP synthesis [137]. H_2O_2 produced can be converted to hydroxyl radical by Fenton reaction in presence of ferrous ion. Hydroxyl radical can react with virtually every cellular macromolecule. In the presence of ferrous ion, the superoxide anion and H_2O_2 two weakly reactive free radical species can combine in the Haber-Weiss reac-

Fig. (1). Putative roles of various candidate genes and other factors on abnormal mitochondrial ATP synthesis in PD.

tion to produce the more reactive OH radical [15, 110]. Reactive oxygen species inhibit complex I and provoke mitochondrial dysfunction.

The iron mediated catalysis of hydroxyl radical generation could be a key mechanism in pathogenesis mediated by oxidative stress. Elevation of iron levels are detected in the SNPC in patients of PD [15, 110]. The iron levels are increased by 35% in PD patients compared to age matched control [247]. Glutathione (GSH) is a major cellular antioxidant counteracting oxidative stress. The oxidative stress indeed is reflected by low levels of GSH and its transfer enzyme glutathione transferase (GST). The depletion of GSH has shown to enhance toxicity of dopamine and H_2O_2 . It is worth to note that, the depletion of GSH and reduced GST activity is reported in PD [243].

Excitotoxicity

The concept of excitotoxicity has been applied to a number of neurodegenerative diseases including PD [92]. Glutamate is the principal excitatory neurotransmitter and mediate its action by interacting with receptors such as NMDA (N-Methyl D-Aspartate), AMPA (α -amino-3-hydroxy-5-methyl 4-isoxalopropionate) and kainate receptors. Persistent activation of the glutaminergic NMDA receptor increases intracellular levels of Ca^{2+} ions potentially leading to activation of proteases, endonucleases, phospholipases and NO synthase with resulting generation of reactive NO. The process, furthermore releases iron from ferritin induces lipid peroxidation and impairs mitochondrial function. Increased intracellular Ca^{2+} concentration and the subsequent events leading to cell death is supported by the observation that dopaminergic neurons expressing calcium binding protein calbindin may be selectively preserved in PD [109]. Glutamate can inhibit the uptake of cysteine which is required for intracellular synthesis of glutathione [186]. Persistent glutamate activation may occur by overactivity of subthalamic glutamate neurons or impairment of complex I activity in SNPC leading to partial depolarization dopaminergic neurons, relieving the voltage dependant blockade of NMDA receptors by Mg^{2+} , making them susceptible to damage consequent to normal physiological levels of glutamate [12, 43]. Glutamate mediated excitotoxicity may contribute to the protein aggregation *via* nitration [58].

Inflammation

Gliosis in the substantia nigra and striatum is a prominent feature of sporadic PD [228]. Activation and neuronal homing of microglia occurs prior to the death of dopaminergic neuron [195]. The

massive microglial activity is reported in PD [151, 152, 173], which may be a general consequence of neuronal death or may be implication of active participation of microglia in the neurodegeneration. Activated microglia release proinflammatory molecules as interleukin 1β (IL- 1β), tumor necrosis factor α (TNF α), interferon γ (IFN γ), which can stimulate the expression of nitric oxide synthase (NOS) and increase nitric oxide production. Cytokines such as TNF α , and IL- 1β trigger the microglial activation and increased levels of these cytokines are observed in the substantia nigra of sporadic PD. Also there is an increased expression of glial inducible NOS and nitrites has been observed in substantia nigra of PD [180]. NO readily reacts with superoxide radical, also produced by activated microglia to produce highly reactive peroxy nitrite anions $ONOO^-$. The $ONOO^-$ can lead to DNA damage, enzyme dysfunction, disruption of structural protein integrity, the events that trigger cellular apoptosis or necrosis [136, 290].

Lipopolysaccharide activated microglia exhibits increase in cyclooxygenase 2 (COX2) synthesis [113]. COX toxicity is mediated by prostaglandins and reactive oxygen species generated through arachidonic acid cascade and inhibition of glutamate uptake causing excitotoxicity [263].

Deficiency of Neurotrophic Factors

Neurotrophic factors such as glial-derived neurotrophic factors (GDNF) and brain derived neurotrophic factors (BDNF) have shown to produce potent protective and regenerative effects on dopaminergic neurons. Delivering GDNF directly into the putamen of PD patients greatly improves their symptoms and significantly increases putaminal dopamine uptake and storage [84]. BDNF appears as an important determinant of dopamine cell survival and D_3 receptor expression [95]. The beneficial effects of BDNF and GDNF raises the possibility that the supply of these or other neurotrophic substances may be limited or that their down stream signaling path may be dysfunctional in PD leading to degeneration of dopaminergic cells.

CURRENT TREATMENT STRATEGIES

The management of PD can be subdivided into three categories as symptomatic treatment, protective or preventive treatment restorative or regenerative treatment. At present only symptomatic treatments are proven efficacy [225]. The treatments encompass pharmacotherapy with levodopa, dopaminergic agonists, MAO inhibitors, COMT inhibitors, anticholinergics etc to support or restore dopaminergic functions (Table 2).

Table 2. Therapies for Parkinson's Disease

Agent	Pharmacological Class	Adverse Effects
Levodopa (with carbidopa and benserazide)	Dopamine precursors	Central side effects (motor fluctuations, dyskinesia, psychiatric disturbances) and peripheral side effects (nausea, vomiting, orthostatic hypotension)
Seligiline	MAO-B inhibitors	Insomnia, neuropsychiatric side effects. Dopaminergic effects of the other drugs may be accentuated.
Tolcapone, Entacapone	COMT inhibitors	Hepatotoxicity, diarrhea, potentiation of levodopa side effects
Ergot derivatives (Bromocriptin, pergolide, lisuride, cabergoline)	Dopamine agonists	Peripheral and central dopaminergic side effects, pedal edema, pleuropulmonary reaction retroperitoneal fibrosis, erythromelalgia, Raynaud's phenomenon, postural hypotension
Ropinirole, Pramipexole	D2/D3/D4 agonist	Somnolence, nausea, vomiting, dyspepsia, abdominal pain, hypotension, confusion, hallucination and dyskinesia
Apomorphine	D1/D2 agonist	Nausea and injection site reactions, neuropsychiatric side effects
Benztrapine, procyclidine etc	Anticholinergics	Peripheral effects (dry mouth, blurred vision, constipation, difficulties with urination) and central effects (confusion, hallucinations, memory problems)
Amantadine	NMDA receptor antagonist	Confusion, hallucination, pedal edema, livedo reticularis

Levodopa

The most reliable and effective symptomatic treatment of PD makes use of levodopa in combination with a peripheral dopa-decarboxylase inhibitors such as carbidopa, benserazide. Unfortunately chronic levodopa treatment is accompanied by motor complications as motor fluctuations (end of dose deterioration, on-off phenomenon, dystonia, athetosis). The motor side effects are compounded by treatment induced psychiatric disturbances such as psychosis, mania or delirium [238]. After 5 years of treatment about 50% of the patients taking levodopa develop motor fluctuations and 30-40% develop dyskinesia. The prevalence is higher in young patients. The occurrence of both motor fluctuations and dyskinesia being almost inevitable after 5 years of treatment [264]. Moreover, there have been suggestions about toxicity of levodopa and its potentiating effects on disease progression [67, 68]. However there is no evidence as yet to support these suggestions [3]. The mechanisms of motor response fluctuations are not completely understood and still a matter of debate. These motor side effects may be caused by alterations in dopamine receptor expression due to progression of the disease process and/or adaptive response of the drug [38]. This may arise from pulsatile delivery of levodopa to striatal neurons, since levodopa has a short plasma half-life of about 90-120 minutes [192]. To take care of this probable cause, prodrugs of levodopa as ethyl ester or methyl ester of levodopa are developed [54].

MAO Inhibitors

The dopamine deficiency can be countered by inhibiting metabolism of dopamine by means of inhibitors of metabolizing enzymes as monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT). The specific MAO enzyme MAO-B catalyses the breakdown of dopamine in the basal ganglia. MAO-B inhibitors such as selegiline and rasagiline both improve motor function in early and advanced PD. Although there was some concern regarding the long term safety of selegiline, several studies have allayed these fears and shown this drug to be both effective and safe for PD patients. Selegiline is a clinically used irreversible MAO-B inhibitor. Other MAO-B inhibitors as rasagiline, lazabemide appear to be promising compounds for the management of PD [205, 252]. Besides decreasing the degradation of dopamine the MAO-B inhibitors possibly possesses neuroprotective properties [226] and are used as adjunct therapy.

COMT Inhibitors

The newly developed catechol-O-methyltransferase (COMT) inhibitors increase the availability of levodopa to the brain, and their action is complementary to that of the dopa decarboxylase

inhibitors. There are concerns about the hepatotoxicity of tolcapone, whereas entacapone, another catechol-O-methyltransferase inhibitor, seems safer in this respect [192]. These compounds however, accentuate side effects of levodopa.

Dopaminergic Agonists

Dopamine-replacement therapy has dominated the treatment of motor symptoms of PD since the early 1960s. The effects are predictable and so are the side effects. None of the more recently introduced synthetic dopamine agonists has surpassed the clinical benefit derived from levodopa [218]. Dopamine agonists, although are less effective, avoid some of the motor complications associated with chronic use of levodopa. The multiplicity of dopamine receptors such as D1-like (D1 and D5) and D2-like (D2, D3 and D4) in the brain offers a range of potential targets [248]. Most currently used drugs however activate D2 and D3 dopamine receptors only [188]. So far exploitation of drugs acting on specific receptor subtypes has been disappointing and no major advance has been made in producing D1 dopamine agonists, a known target for anti-Parkinsonian agents [129]. Partial D2 dopamine agonists are being developed as they might treat the motor symptoms of Parkinson's disease while suppressing both psychosis and dyskinesia. The most important DA receptor agonists which are currently approved are ergolinederivatives such as bromocriptine, lisuride, pergolide, cabergoline as well as the non-ergoline derivatives like pramipexole, ropinirole and apomorphine.

Theoretically, the advantage of being both D1 and D2 agonist such as lisuride seems to be of better therapeutic index [271]. The non-ergoline derived dopaminergic agonists have preferential affinity for D2-like receptors except apomorphine which is active at both D1 and D2 receptors [125]. Ropinirole, pramipexole bind preferably to D3 receptors [36, 181]. A novel compound sumanirole with a 200 fold selectivity for D2 receptor over D3 receptor was recently been shown to be effective in reversing motor symptoms in animal models of PD and did not cause dyskinesia [175]. The D1 specific agonists such as SKF-81297, SKF-82958, ABT-431 are under investigation [65]. A novel mixed dopamine D1/D2/D3 agonist roligotine has proven to be effective antiparkinsonian agent in clinical trials [126]. Recently, non-oral delivery has provided more long-lasting anti-Parkinsonian activity through the subcutaneous or intravenous infusion of apomorphine and transdermal patch technology with roligotine or lisuride. Valvular Heart Disease is observed with the use of dopamine agonists [135].

Anticholinergic Agents

Dopamine deficiency in PD results in overactivity of acetylcholine. The symptoms of excess cholinergic activity can be overcome

by anticholinergic drugs such as benztropine, trihexylphenidyl, procyclidine etc [104].

Others

Amantadine, an antiviral agent was found by chance to be effective in PD and is particularly effective in reducing dyskinesia [20]. This antidyskinetic effect is likely to be mediated by NMDA receptor antagonistic action [254].

EMERGING THERAPIES

Supporting Reduced Dopaminergic Functions

Traditionally, this approach makes use of levodopa, MAO-B inhibitors, COMT inhibitors and dopamine agonists. The novel compounds based on diverse therapeutic strategies are developed as SIB1508Y, an agonist selective for specific nicotinic acetylcholine receptor subtype which enhances release of dopamine from striatum *in vivo* [274, 280]. Other compounds such as NS-2214, NS-2380 which are tropane derivatives of cocaine block the dopamine transporter (DAT) and increase endogenous dopamine levels in the synaptic cleft [280].

INTERVENTION TO PREVENT DEVELOPMENT OF MOTOR COMPLICATIONS

NMDA Receptor Agonists

Dopamine depletion and dopamine replacement strategies result in substantial alteration in basal ganglia NMDA receptor structure, localization and function [30]. With the help of this knowledge and experience of amantadine, a number of studies have examined the efficacy of antagonists of NMDA receptor such as remacemide, however remacemide showed no clear effects in PD [203]. A non-selective, non-competitive antagonist of NMDA receptor is MK-801 which is found to be well tolerated in rodents (but not in primates) can improve akinesia and can have synergistic action with dopaminergic drugs [165]. To avoid the sedative adverse effects of MK-801 selective NMDA receptor antagonists are under development. For example NR2B subunit containing NMDA selective antagonists are ifenprodil, CP101606, Co101244, CI1041 and NRI/NR2B antagonist MDL100453 have been examined in animal studies [98]. Alternative to traditional antagonists other strategies such as drugs that alter the trafficking and regulation of NMDA receptors are also worth exploring. These might include drugs with actions at the phosphatase and kinase systems that modulate NMDA receptor or perhaps drugs acting at upstream modulatory systems such as metabotropic glutamate receptors [161].

AMPA Receptor Antagonists

An excitatory amino acid glutamate acts on another ionotropic receptor AMPA receptor. Stimulation of NMDA and AMPA receptor seems to considerably contribute to motor complications and levodopa induced dyskinesia [23]. Hence AMPA receptor antagonist could be of use in PD as NMDA receptor antagonists. Many of the homophthalazine derivatives as GYKI52466, GYKI53655, GYKI54015, GYKI53405, and GYKI54065 have been developed as AMPA antagonists. Of these talampanel (GYKI53405) has shown promise in decreasing or abolishing levodopa caused dyskinesia [255].

Serotonergic Agents

Advances in knowledge of 5-HT receptors and its subtypes suggests putative role of these receptors in the control of movement and possible novel intervention strategies for modulating dopaminergic and nondopaminergic systems in PD [19]. Based on the distribution, localization and function in the basal ganglia, the subtypes 5-HT_{1A}, 5-HT_{1B/1D}, 5-HT_{2A} and 5-HT_{2C} receptors are clearly linked with modulation of nigrostriatal pathway [10]. Therefore, receptor subtype specific serotonergic agents can act at several sites to modify dopaminergic activity. Sarizotan (EMD12830), a 5-HT_{2A}

inverse agonist has been reported to exhibit encouraging results in phase II trials. Other agents being developed with this strategy include SR46349D (5-HT_{2A} antagonist), ACP103 (5-HT_{2A} inverse agonist), SB206553 (5-HT_{2C/2B} antagonist), SB 242084 (5-HT_{2C} antagonist) and mCPP, MK 212, RO 600175 (5-HT_{2C} antagonists) [11].

A_{2A} Receptor Antagonists

Adenosine, an endogenous purine nucleoside acts as a homeostatic modulator by controlling neurotransmitter release or post-synaptic neuronal response [40]. These actions are mediated by receptors A₁, A_{2A}, A_{2B} and A₃. Among these adenosine receptors, A_{2A} receptors appear to play the most important role in the control of motor behavior and in the modulation of dopamine mediated responses since A_{2A} receptor is enriched in striatum compared with other brain regions [55, 73]. There exists a functional antagonistic interaction between A_{2A} and D₂ receptors as their co-localization in striatopallidial neurons. Stimulation of A₂ receptor has shown to decrease the affinity of D₂ receptors in striatal membrane preparation [73]. This functional interactions has suggested new therapeutic approach for PD based on the use of selective A_{2A} receptor antagonists. Several A_{2A} receptor antagonists have been developed as xanthine derivatives KF-17837, istradefylline, triazoloquinazoline CGS15943, triazolopyrimidine SCH5826, triazolotriazine ZM241385 and VER 2006 [133]. Among the most advanced molecules, istradefylline has moved successfully to phase III clinical evaluation [102].

Interacting with Crucial Steps in Neuronal Death

Programmed cell death, one of the processes of neuronal death occurs by two ways, apoptosis and autophagy. Apoptosis is catalyzed by aspartate proteases called caspases. About 14 different caspases have been identified in mammalian nervous tissue and separated into apoptotic initiators [62]. Selective caspase inhibition would reduce neuronal apoptosis and is considered as a potential therapeutic strategy to develop drugs [221]. This strategy includes caspase inhibitors, p53 inhibitors, JNK inhibitors and GAPDH ligands.

Caspase Inhibitors

The second generation tetracycline derivatives minocycline is referred as caspase inhibitor. Minocycline inhibits immunologic processes for example inhibition of matrix metalloproteases p38-mitogen activated protein kinase, reactive oxygen species release from neutrophils, inducible nitric oxide synthases and complexes with Ca²⁺ [52, 276]. It also inhibits caspase 1 and 3 presumably by interacting with upstream activation [276].

p53 Inhibitors

A synthetic inhibitor of p53 induced transcriptional activation, pifithrin α , was originally developed to protect non-cancerous cells in cancer therapy, but has been also found as protective in the mouse MPTP PD model [56]. However, the long term application of p53 inhibitors as in PD could prove problematic due to its anti-cancer activity.

JNK Inhibitors

The compound presently in clinical trial is CEP-1347 a staurosporin derivative. It inhibits the jun-N-terminal kinase (JNK) pathway by inhibition of mixed-linkage kinase [206].

GAPDH Ligands

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), an enzyme in glycolytic pathway is implicated in p53 dependant apoptosis. TCH 346 binds to GAPDH stabilizes the dimeric form of the protein and prevents apoptosis related up regulation and prevents nuclear translocation of GAPDH known to be involved in the mediation of p53 dependent apoptosis [56]. TCH346 (previously known as CGP3466p), a tricyclic propargylamine derivative has

shown inhibition of apoptosis in various cell lines and its systemic administration prevented motor symptoms and nigrostriatal degeneration induced by MPTP in primates. However in a double-blind, randomised, controlled trial TCH346 did not show evidence of a neuroprotective effect. The discrepancy between the pre-clinical promise of TCH346 and the clinical outcome could have arisen because of the use of laboratory models that do not accurately reflect the pathogenesis of Parkinson's disease, the doses of study drug used, insensitive clinical endpoints, and the patient population selected for study [196].

HALTING OR SLOWING THE PROGRESSION OF NEURONAL LOSS

Induction of Autophagy

Malfunction of UPS or chaperone mediated autophagy (CMA) results in toxic accumulation of proteins leading to cell death. This toxic accumulation of proteins can be circumvented by inducing autophagy. Rapamycin, one such autophagy inducer, suppresses the inhibitory activity of the mammalian target of rapamycin (mTOR) an autophagy protein. Use of rapamycin has demonstrated to reverse pathology in a model of Huntington's disease [219]. Although this is a promising approach, it should be remembered that autophagy also constitutes a non-apoptotic, caspase-independent form of programmed cell death, a significant site of Alzheimers A β peptide generation and inducing autophagy might increase the production of this neurotoxic peptide [285].

Addressing Mitochondrial Dysfunction

The positively confirmed links of mitochondrial dysfunction and protein aggregation causing PD provides a rationale for the use of antioxidants such as vitamin C and E as conjunctive therapies. The result of studies carried to check the validity of the rational gave ambiguous results. One study including vitamin C and E delayed the use of levodopa or dopamine agonists for 2 years. However, the results were not confirmed by further studies [205,227]. Coenzyme Q10 is an intrinsic component of mitochondrial respiratory chain and use of this might be beneficial as suggested by reduced rate of deterioration in motor functions found in double blind placebo controlled pilot studies with longer follow-up [240].

Reducing Oxidative Stress

Oxidative stress caused by increased free radical generation as observed in PD can be reduced by use of spin-trapping compounds such as nitrones. One such compound developed is stibazulenylnitron [283]. These developments of new antioxidants will broaden the therapeutic strategies for PD. Since iron plays a pivotal role in the process of oxidative stress, inflammatory process and cell death, it is apparent that reducing iron-induced oxidation is protective to the neurons and renders iron-chelators as an approach to combat neurodegeneration in PD. VK28, a quinoline compound and its derivatives are developed as iron-chelators and tested in rats [231]. Depletion of an endogenous antioxidant glutathione is one of the important pathogenic factors of PD. Hence it is plausible that one of the ways to counteract this problem is to replenish glutathione pool either by increasing synthesis of glutathione or by slowing its degradation or by administering glutathione or administering precursors of glutathione or its analogues [229, 282]. A GSH analogue YM737 has been tested in animal PD model [282].

Inhibiting α SN/Protein Aggregation

The association of α SN aggregation with PD has led to efforts to develop inhibitors of α SN aggregation, both as peptide based and dopachrome based and proven effective *in vitro* [60, 191]. Geldanamycin, a naturally occurring benzoquinone ansamycin, has been shown to inhibit α SN aggregation and toxicity in cultured cells and in *Drosophila* [174]. However, it should be taken into account that inhibiting α SN aggregation is not without risk. If

protein aggregation is protective mechanism as suggested by protofibril formation, then aggregation inhibitors might liberate toxic oligomeric species and aggravate rather than inhibit the disease process.

Immunotherapy

Therapeutic antibodies can be used to target α SN, however α SN is primarily an intracellular cytosolic protein and as a result might be less accessible to antibodies. An intrabody approach has been reported in which the expression of single-chain Fv antibody inhibits the formation of α SN aggregates [178]. More recently immunization of α SN transgenic mice with α SN has been reported to inhibit the aggregation of α SN in neuronal cell bodies and synapses and increased levels of synaptophysin suggesting recovery from a neurodegenerative process [170]. The use of antibodies might cause immune mediated cellular response also.

Inhibiting Inflammatory Process

Microglia mediated deleterious inflammatory reactions controlled by anti-inflammatory therapy. The anti-inflammatory drugs may inhibit COX2 and COX2 mediated dopamine oxidation and may scavenge hydroxyl radical and NO [31, 72, 263]. Agonists of peroxisome proliferator activated receptor γ (PPAR γ), which has been reported to possess anti-inflammatory qualities is found to attenuate glial activation and rescue dopaminergic cells of substantia nigra in MPTP treated mice [21].

Inducing Recovery of Surviving Dysfunctional Neurons: Neurotrophic Factors

A neuroprotective approach to treat PD is the use of neurotrophic factors to nourish and enhance the survival of dopaminergic cells in the substantia nigra. Several of these factors including neurotrophin4/5, BDNF, GDNF have been shown to be promising in animal models [117, 142]. Unfortunately, results from a recent controlled clinical study delivering GDNF directly into brain did not demonstrate efficacy and safety of such a treatment. A critical review of available data suggests that there are questions that need to be answered before the future of GDNF as a therapy for PD can be determined. Exhaustive human trials should be undertaken with proper route of administration.

Gene Therapy

Gene therapy is considered as one of the most promising approaches to develop a novel effective treatment for PD. Among the candidate genes that have been tested include genes for enzymes of dopamine synthesis such as tyrosine hydroxylase, guanosine triphosphate cyclohydrolase 1, aromatic-L-amino acid decarboxylase and genes for neurotrophic factors [33]. The genes encoding vesicular monoamine transporter-2 and glutamic acid decarboxylase have also produced therapeutic effects in animal models of PD [59]. The important factor to be addressed in gene therapy is regulation of gene expression for its clinical use.

Replacing Lost Neurons by Transplantation

The idea of replacing the dead dopaminergic neurons of the substantia nigra has emerged more than 20 years ago and is tried now for the treatment of PD [106, 210]. The cells used for transplantation are human primary cells, porcine primary cells, expanded stem cells and neural progenitor cells [76]. Promising results have been achieved in clinical trials but much remains to be done before cell based therapies can be practiced extensively such as addressing adverse effects of dyskinesia; improvements in reproducibility of the transplantation; robust solutions to various safety issues, regulatory and ethical consideration.

CONCLUDING REMARKS

Though our knowledge and understanding of the pathophysiology of disease process has been improved with the advent of molecular pharmacological tools, the precise etiology of PD is still a

matter of debate. However, now it is generally agreed that, the genetic factors lead to various protein aggregation and subsequent loss of dopamine neurons. The role of candidate genes and the plausible therapies to target them are the exciting current interest of researchers worldwide. The unmet needs of PD therapy still exist as it is a disorder with variety of complex etiologies. It remains the hope of research scientists that in the not-too-distant future we shall see a new class of drugs arising logically from the understanding of molecular pathophysiology of PD.

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