Parkinson's Disease Dementia and Potential Therapeutic Strategies

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SUMMARY

Dementia in Parkinson's disease (PD-D) has only been acknowledged in the recent three decades, but research in this field has accelerated. The purpose of this review was to discuss advances in PD-D regarding biomarker correlates and potential therapeutic targets. Attention and executive dysfunction, memory deficits that improve with cueing, and visual hallucinations are characteristic in PD-D. PD-D dramatically increases the disability and misery of the disease. Current treatment for PD-D is symptomatic, modest, and only transiently effective. There is wide agreement that more effective treatment is needed, but this will require more knowledge about PD-D pathophysiology. Advances in the pathogenesis of PD have focused on the substantia nigra, which is the location from where the pathophysiology of motor symptoms primarily arises in initial stages. In contradistinction, pathology studies have suggested that cognitive decline correlates with cortical and subcortical–cortical projection pathway abnormalities. There is evidence that substantia nigra mechanisms, including protein aggregation of α -synuclein (e.g., Lewy bodies) may also play a role in cortical neuron degeneration. Other different mechanisms, such as Alzheimer's disease pathology (e.g., A β aggregation) may be operant for PD-D. Biomarkers of various types are being proposed for the study of PD-D as well as for objective measures of PD-D prediction and progression. Therapeutic targets are currently derived mostly from general PD neurodegeneration research rather than cortical PD neurodegeneration *per se*. Protein aggregation, genes that are associated with PD, oxidative stress, inflammation, and trophic factors constitute the major classes of therapeutic targets for PD-D. More research is needed on the specific aspects of cortical dysfunction and degeneration that create PD-D.

Introduction

In James Parkinson's "Essay on the Shaking Palsy" in 1817, he stated that mentation was preserved in Parkinson's disease (PD). This was widely believed for over 150 years. This view did not change until treatment with levodopa prolonged survival such that cognitive decline could manifest and be more clearly detected. Today, the reported accumulated prevalence for dementia in PD (PD-D) is 15–38% at 4–5 years follow-up and 50–78% at 8–10 years follow-up, with the overall risk of dementia being six times that of controls [1–5]. Risk factors for PD-D have included age of PD onset, and PD duration and severity [5–9]. The occurrence of dementia doubles the mortality risk of PD, and dramatically increases the level of care needed by the PD patient [10].

It is important to note the differences between how motor and cognitive symptoms are produced in PD. The motor problems in PD are thought to be caused primarily by abnormal basal ganglia

outflow that alters the activity of various motor areas of cerebral neocortex via cortical-basal ganglia-thalamo-cortical loops. In contrast, the literature suggests that in PD-D, abnormalities within the cerebral cortex itself and other areas that project directly to the cortex probably play the important roles in PD-D [3,11,12]. A critical barrier to developing more effective treatments for cognitive dysfunction in PD is the lack of understanding about how PD neurodegeneration causes physiologic dysfunction of cortical areas. There has been much research devoted to the neuronal death mechanism in substantia nigra neurons. However, it should not be assumed that identical mechanisms are operant at the cortical level. Although no neuroprotective treatment for PD-D exists, research into molecular pathogenesis has identified numerous potential therapeutic approaches that are currently being investigated. In this article, we will briefly review the clinical foundation of PD-D and focus pathophysiological aspects as well as putative therapeutic targets.

Table 1 Major current medical therapeutic strategies for PD

Current classes of drugs used in PD therapy for motor aspects	
L-DOPA	Supplement levels of dopamine in brain
Dopamine receptor agonists	Directly activate dopamine receptors (particularly D2R)
DOPA decarboxylase inhibitors	Prevent L-DOPA transformation to dopamine in periphery
COMT inhibitors	Prevent breakdown of L-DOPA prior to transformation to dopamine
Monoamine oxidase-B inhibitors	Extends half life of dopamine in brain. Other?
Amantadine	Increases dopamine release, anti-cholinergic, and NMDA antagonist
Anti-cholinergic agents	Blocks inhibitory muscarinic receptors in striatum
Drugs used to treat PD-D	
Rivastigmine	AChE inhibitor that elevates level of acetylcholine.
Donepezil	AChE inhibitor that elevates level of acetylcholine
Galantamine	AChE inhibitor that elevates level of acetylcholine
Memantine	NMDA antagonist

Clinical Aspects and Natural Course

Definition

The most common definition for PD-D has been the presence of PD plus the DSM-IV criteria for dementia. This criterion involves abnormalities in memory and one other domain of cognition, functional decline related to cognitive deficit(s), and preservation of consciousness [13]. Recently, the Movement Disorders Society (MDS) task force defined core criteria for PD-D as PD by UK Brain Bank criteria and a dementia syndrome having impairment in two or more cognitive domains out of attention, executive, visuospatial function, and memory [14]. Together with the consideration of other features, the MDS criteria allow for Probable and Possible PD-D designations. Mostly, Possible PD-D occurs when the neuropsychological profile in one or more of the cognitive domains is considered atypical.

Treatment

Some of the major current drug treatment strategies for the motor and cognitive aspects of PD are shown in Table 1. None of these listed drugs are focused on preventing PD or PD-D; L-DOPA has been used for 40 years as a PD therapy [15,16] and only treats the clinical consequences of the substantia nigra pathology. Current treatment for PD-D is only symptomatic and marginally beneficial at best. Treatment of PD-D should begin by assessing whether there is any reversible medical problems operant. Acute, subacute, or chronic medical problems may significantly contribute to cognitive deterioration in a PD patient. Infections and toxic-metabolic conditions may have to be screened for in order to detect illnesses that require treatment. Sedative and other psychoactive medica-

tions should receive scrutiny for necessity because they may cause the PD brain to decompensate.

Anti-parkinsonian medication tends to exacerbate PD-D symptoms [17]. If there is evidence for overtreatment (e.g., dyskinesias) then medication should be decreased or discontinued. The nondopaminergic PD medications (amantadine, anticholinergics, monoamine oxidase inhibitors) are usually less symptomatically beneficial so are discontinued before changing levodopa or dopamine agonist therapy. In some cases, the patient may need to have levodopa or a dopamine agonist dosing reduced, and while this may improve cognitive function it may also lead to deterioration in motor function. The decreased mobility may lead to further disability, more caregiver burden and increased risk for infections and blood clots. If no concurrent illness or medication-induced worsening of cognitive function is found, then adding an acetylcholinesterase inhibitor can be considered [18]. Acetylcholinesterase inhibitors were first developed for AD, but these agents are known to have modest but significant benefit on cognition in PD. Donepezil, rivastigmine, and galantamine are three acetylcholinesterase inhibitors that have received study in PD cognitive decline [19]. Rivastigmine is FDA approved in the United States to treat PD-D. The chronic progression of the dementia and overall disability makes it difficult to appreciate the ongoing contribution of currently available symptomatic treatments. In double-blind, placebo-controlled studies the benefit from active drug has usually been modest and transient [20–22]. The nucleus basalis of Meynert is affected in PD (as in AD) and provides acetylcholine projections to the cerebral cortex. Acetylcholinesterase inhibitors providing more acetylcholine neurotransmission to cortical neurons deprived of such projection is the theoretical pharmacodynamic reason for their beneficial effect. Memantine, an NMDA antagonist, has shown preliminary evidence for efficacy in PD-D [23].

Many patients with PD-D develop visual hallucinations. While reducing the dose of dopaminergic agents, amantadine, monoamine oxidase inhibitors, anticholinergic drugs may help, at times these can be extremely difficult to manage. In some cases, acetylcholinesterase inhibitors may decrease hallucinations even in the absence of disabling memory deficits [19,24]. If disabling visual hallucinations do not respond to an acetylcholinesterase inhibitor, then quetiapine should be considered [17]. There are numerous other dopaminergic antagonists (olanzapine, risperidol, haloperidol, etc.) that might reduce visual hallucinations, but all have the potential to worsen motor function. In some cases, the use of clozapine may be indicated although the need to monitor for leucopenia has made this drug difficult to use.

Despite all these treatment interventions, PD-D often produces significant functional decompensation, so the physician should always consider whether a social services evaluation is needed for the patient and caregiver.

Neurobiological Basis and Biomarkers of Parkinson's Disease Dementia

The neurobiological basis for the cognitive decline in PD is unknown. Biomarkers need to play a critical role in the elucidation of mechanism as well as for evaluating treatments of PD

Figure 1 Correlation with time of biomarkers, clinical symptoms, and pathology in cortex of PD patients with cognitive decline.

cognitive decline [25]. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention [26]. Certain biomarkers may be a valuable adjunct to clinical cognitive decline scales because of better reliability and a more direct connection to the biologic target for a particular disease manifestation. Predictive biomarkers may be able to enrich a population that is at risk for developing an undesirable clinical manifestation such as dementia. Finally, biomarkers may be the best way to test whether a therapeutic agent is engaging the pathogenic biologic target that is required for a positive response [27]. It is not yet clear which biomarkers would be best to assess progression or prediction of PD-D. Ideally, clinical and pathological changes should correlate with surrogate biomarkers in a sensitive and precise manner over time (Figure 1). Predictive biomarkers will need to identify high-risk PD patients for developing dementia within a short period of time (a few years) so as to allow identification of PD patients at a time when intervention is beneficial. Multiple biomarkers have been proposed but it will take more investigation to determine how they should be applied. Their required level of accuracy and reliability will need agreement from people working in this field.

Neuropsychological Testing

Rating Scales Designed for PD Cognitive Decline

PD-D has some characteristic features that are seen less prominently in Alzheimer's disease (AD). Attention and executive dysfunction, memory deficits that improve with cueing, and visual hallucinations can be affected early in PD-D [28]. Because PD-D and AD seem to have different cognitive profiles, newer cogni-

tive rating scales are being proposed as more appropriate for PD cognitive deficits as compared to those previously available [29]. The Folstein Mini Mental Status Examination (MMSE) seems to be more sensitive to deficits in those domains particularly affected in AD (memory and language). In one study that compared the MMSE to a neuropsychological battery, PD-MCI was found in almost 30% of PD subjects who had a "normal" MMSE score [30]. Similarly, the Montreal Cognitive Assessment (MoCA) was found to detect cognitive impairment in about half of PD cases with "normal" MMSE using a MMSE cutoff score of <26 [31]. Hoops *et al.* also found the MoCA superior to the MMSE for this purpose [32].

A recent study examined numerous tools for assessing cognitive decline in PD. They found that the SCOPA-COG (SCales for Outcomes of PARKinson's disease—Cognition) and the PD-CRS (Parkinson's Disease—Cognitive Rating Scale) may be better suited than other scales [33]. In all the cited studies, there is a common theme that any cognitive scale that is suited for PD must have a broad range of cognitive domains including representation of subcortical-frontal lobe cognition and attention, in addition to memory, language, and visuospatial cognitive function.

Predictive Neuropsychological Testing in PD

Neuropsychological testing abnormalities in nondemented PD patients have been reported to be predictive of subsequent dementia development, but the types of abnormalities reported vary [1,34,35]. Most reports mention impairments in executive function or memory as predictive of dementia development while others mention visuospatial dysfunction [4,35,36]. The construct of mild cognitive impairment (MCI) as a precursor to AD has created a new area of research for AD and a potential new target for therapeutic intervention. Therapeutic intervention at this earlier stage

Figure 2 A Lewy Body stained with α -synuclein antibodies in a cortical neuron. Courtesy of the neuropathology lab of Dr. Tom Beach.

may be more effective at slowing disease progression than when dementia is fully developed [37]. In a similar manner, defining MCI in PD (PD-MCI) should create an opportunity for studying the pre-dementia state in PD and allow targeting of PD cognitive decline at an earlier stage [35].

Pathology

Correlation of the type of neuropathological findings in neocortical areas with PD-D has been variable. In particular, there are different views about which pathology creates dementia or cortical dysfunction in general [38]. Initially, the neuropathological changes associated with Alzheimer's disease (AD), that is plaques and neurofibrillary tangles, were thought to be the dominant determinant in PD-D [39,40]. More recently, positive correlation has been found with cortical α -synuclein positive Lewy bodies (LBs) and/or abundance of α -synuclein dystrophic neurites [12,41,42]. A LB with α -synuclein immunostaining is shown in Figure 2. However, others have presented other recent evidence for the role of AD pathology and a lack of association with cortical LBs [43]. Some studies have suggested that LB and AD pathology may both be important for contributing to PD-D [44,45]. This lack of clarity has contributed to different defined "forms" of cognitive impairment that exist on a spectrum of pathological correlates: (1) A form of PD-D can be considered as "pure PDD" where psychological tests show declines in mental function but these cases do not have significant amounts of AD pathology; it can be expected that these cases have extensive deposition of LB. (2) PD with the development of AD pathology. This is a common feature as both diseases are exacerbated with aging. In PD cases, the development of classical amyloid plaque pathology and neurofibrillary tangles is a common occurrence [46–49]. PD/AD can only be diagnosed with certainty by postmortem examination of the brains. (3) A third form is Dementia with Lewy Bodies (DLB), where an abundance of cortical LB is a pathological feature with the clinical accompani-

ment of early dementia before one year of parkinsonism as defined by consensus criteria [50]. Additional forms of PD with cognitive decline can be associated with vascular causes of dementia occurring at the same time of nigrostriatal degeneration associated with the movement disorders of PD [51].

Neocortical synaptic density demonstrates correlation with cognitive impairment in AD [52–54]. Synaptophysin is a 38 kD Ca^{2+} binding integral protein of vesicle membranes, and thus detecting its presence provides a presynaptic marker [55]. Synaptic density has been rarely studied in LB disorders (PD, PD-D, DLB). Decreases in synaptophysin have been found in the frontal and temporal lobes and hippocampus in LB disorders [56]. In comparative studies, the synaptophysin loss is $\text{AD} > \text{DLB} > \text{PD-D} > \text{PD}$ [57,58]. While the pattern of synaptophysin loss was diffusely distributed across the cortical layers in AD, the loss in PD and PD-D was greatest around layer V. Thus, there are both qualitative and quantitative differences in synaptic density loss between AD and LB disorders.

Acetylcholine and Monoamine Neurotransmitters

It is now appreciated that acetylcholine and monoamine neurotransmitter systems arising from basal forebrain and brainstem project diffusely to neocortical areas [59,60]. These systems project onto all cortical layers but there is a preference to layers I–III [60–62]. Both acetylcholine and monoamine systems project to nonpyramidal interneurons and pyramidal neurons within the cortex, but serotonin contacts mostly interneurons whereas acetylcholine and dopamine contact mostly pyramidal neurons [60]. There is evidence that these systems perform a "modulation influence" by their use of presynaptic and extrasynaptic transmission [60,62]. In PD, the neurons of diffusely projecting acetylcholine, dopamine, and serotonin systems do undergo neurodegeneration, and have been associated with various behavioral changes including dementia, although there are inconsistent results [11,63,64].

Imaging

MRI

MRI studies have shown reduced hippocampal and amygdala volumes in both demented and nondemented PD patients [65]. MRI studies have shown cortical atrophy in PD compared to controls, and PD-D cases had progressive cortical atrophy compared to nondemented PD cases [66,67]. Other MRI studies report conflicting differences in PD and PD-D. One study found hippocampus atrophy in PD and PD-D with no differences in other regions, including total brain volumes [68]. Another study found gray matter volume decreases in the hippocampus, thalamus, and anterior cingulate of PD-D cases, regions known to have high concentrations of LBs, plaques, and tangles [69]. There are also discrepancies in the estimated rate of brain atrophy between controls, PD, and PD-D, that may be related to age of the cases, disease duration, and degree of cognitive impairment [67,70]. Whether increasing rates of atrophy can be used as a predictor of dementia in PD is unclear, although this has been found to occur in AD [71]. Neocortical

changes are also present but such results are more preliminary and mixed [66,72]. Longitudinal changes in cortical areas have been reported and appear to be both different and more severe with cognitive decline [65]. PD-MCI imaging data is minimal. One recent MRI study found that PD-D cases had widespread areas of cortical atrophy compared to controls and that areas of reduced gray matter were found in the left frontal and bilateral temporal lobes in PD-CogNL and PD-MCI [72]. Despite mixed results, the prevalent opinion is that PD brain atrophy more closely reflects cognitive decline rather than motor dysfunction progression [73].

Functional Imaging

While data support the use of [^{18}F]Dopa PET and [^{123}I] β -CIT SPECT as possible biomarkers for PD, there is no established biomarker for the subsequent development of cognitive impairment in PD [74,75]. FDG PET measures regional cerebral glucose metabolism. FDG PET studies in PD-D have shown deficits in frontal and temporoparietal association areas, and these changes are similar to what is seen in DLB but more severe than nondemented PD [75]. A FDG PET study showed decreased prefrontal and parietal metabolism in PD-MCI [76]. A brain perfusion SPECT study showed amnesic PD-MCI subjects have decreased posterior cortical perfusion [77].

A recently applied technology for imaging AD has been the use of ^{11}C -PIB PET, which targets fibrillar amyloid. There have been limited studies of ^{11}C -PIB PET in PD. In PD studies, it has been shown that there are significant but less severe changes in PD-D than DLB [78]. DLB often has co-existent AD changes which may explain this finding. One study found reduced FDG-PET changes in cortical regions of seven PD-D cases compared to eight controls, but no difference in ^{11}C -PIB PET [79]. This same group found an increase in PIB uptake in patients with LB dementia ($n = 13$) but no increase in PD ($n = 10$) or PD-D ($n = 13$) compared to controls ($n = 22$) [80]. Another group reported no difference in PIB uptake in PD ($n = 4$) but an increased PIB level, comparable to AD, in four cases of either PD-D or DLB (not separated out) [81]. The value of PIB PET in predicting development or diagnosis of PD-D is unclear, especially given the lack of detail in the published abstracts. Transcranial sonography has detected increase ventricular dilation in PD-D [82].

It is re-assuring that these imaging techniques correlate with neuropathological changes found in PD-D, but workers in the field acknowledge the need for more study of clinical and neuropathological correlation. The reasons for variable results among investigators need examination. New imaging target methodology, including potential ligands for α -synuclein, will provide exciting possibilities for more specific PD-D biomarkers.

Electrophysiology

Electroencephalography

Electrophysiological studies have potential as biomarkers for cognitive decline in PD but this is generally not discussed in PD-D review articles [83]. The electroencephalogram (EEG) contains abnormally lower brain wave frequencies in some patients with

PD, but only rarely has this issue been studied with quantitative techniques [84–87]. EEG has high test–retest reliability [88,89]. Soikkeli *et al.* used quantitative EEG (QEEG) methods based on the single EEG electrode derivation (T6–O2) [86]. They found differences between demented and nondemented PD subjects, but they did not examine relative power over several EEG electrodes. In another study, Neufeld *et al.* found that relative amplitude in the α (8–13 Hz) band for several individual electrodes was significantly decreased in PD-D and was unrelated to motor disability [87]. Their study showed no significant trends in relative amplitudes at other frequency bands nor at single electrodes. Global relative EEG power measures uses EEG activity across all electrodes, and therefore such a measure may be more discriminating as a biomarker of clinical generalized cognitive decline than using single or a focal group of electrodes. Our cross-sectional study in 2007 showed that such global QEEG parameters could distinguish between cognitively normal PD, PD-MCI, and PD-D groups [90]. Overall, studies using (QEEG) have showed decreased fast frequencies (α and β) and increased slow frequencies (delta and theta) in PD-D (Figure 3) [86,87,90]. Compressed EEG spectral array analysis has been used to distinguish between AD and DLB or PD-D, but confirmation of these results is needed [91]. These studies show that QEEG may be useful as a biomarker for studying cognitive decline in PD, both as a correlation tool and to test therapeutic interventions.

There are multiple possible physiological explanations for EEG changes that correlate with the cognitive status in PD, but the precise circuitry defects responsible for these changes are unknown. The different frequency bands have had various normal functions and anatomical correlates proposed. α Rhythm is a normal EEG activity generated by thalamocortical and local corticocortical circuits [92]. However, those systems may in turn be affected by other connections with other neuronal circuits. β Rhythms, whether diffuse or focal, are thought to represent primarily neocortical activity [93]. From a functional point of view, evidence shows that β activity reflects cognitive processes and correlates with regional cerebral blood flow [94,95]. Thus, the normal α and β rhythms both depend on intact neocortical function and associated circuits [96]. An increase in theta and delta activity is believed to represent dysfunction in diffuse gray matter areas in both cortical and subcortical areas as well as partial deafferentation of cerebral cortex [92]. Studies have associated cholinergic failure with EEG slowing in these frequency ranges [97–99]. In PD, abnormalities in both diffusely projecting systems and intrinsic cortical circuits have been implicated to cause cognitive decline. Acetylcholine and monoamine pathways project to broad neocortical areas and have had decreased levels demonstrated in PD and specifically in PD with dementia [11,64]. Although the relative contributions of LBs and Alzheimer's disease pathology are controversial, such markers of neocortical pathology correlate with dementia in PD [12,40–42]. Some reports have noted a correlation between motor UPDRS and EEG frequency abnormalities, and these authors have suggested that there are similar subcortical systems that account for both the increasing motor disability and EEG abnormalities [100]. However, both phenomena may result from very different mechanisms but still both correlate with disease progression at different brain locations [101]. The accumulated evidence suggests that both the cortical and subcortical pathology of PD have poten-

Figure 3 Raw electroencephalographic tracings from a PD patient with normal cognition (above) and from another PD-D patient (below).

tial roles in causing EEG rhythm abnormalities in PD patients that are associated with cognitive decline.

Evoked Potentials

The results from evoked potential studies regarding cognitive changes in PD have not been as consistent as for QEEG. The evoked potential waves most studied are those that have “middle” or “long” latencies and are thought to represent cortical activation. The most commonly used evoked potential has been the P300. The P300 is a positive potential at approximately 300 ms that is elicited during an “oddball” paradigm. In this paradigm a different stimulus is inserted occasionally into a series of stimuli consisting of an identical stimulus. It is believed that the P300 represents the cor-

tical processing of the “odd” stimulus. This paradigm can be performed with auditory, visual, or somatosensory stimuli, but auditory stimuli have been studied the most in PD [101–104]. Results have been variable, but most studies have demonstrated longer latency for PD patients than for controls with intact amplitude. The latency increases with PD progression but such studies have not always correlated cognitive decline with the latency changes [104]. Studies that have only examined nondemented PD subjects have interpreted prolonged latencies to represent cognitive dysfunction even in the absence of dementia [105,106]. More recently, P300 latencies have been shown to be longer in PD-D than PD [106,107]. A few studies have noted P300 latency prolongation to correlate with neuropsychological testing with attention testing to be particularly affected [108,109]. Earlier peaks have been

studied less frequent but may also show prolongation [105,110]. Some studies have found no change in the P300 in PD-D [111,112]. More study is needed to reconcile the negative findings of some studies and to determine how reliable a P300 biomarker would be for either surrogate or predictive purposes.

Myoclonus

The small amplitude cortical myoclonus of PD represents cortical neuronal physiologic dysfunction in the primary sensorimotor cortex of PD patients [113]. Key properties of this model are (1) positive sign of abnormal primary sensorimotor cortex neuronal physiology, and (2) detection in PD subjects by noninvasive electrophysiology methods (Figure 4). Cortical myoclonus is known to occur in other neurodegenerative disorders in the presence of parkinsonism, but like in PD, the specific disruption of cortical circuitry that causes the cortical discharge is unknown [114]. The cortical myoclonus of PD is not responsive to levodopa, suggesting

a pathophysiology different from the levodopa responsive parkinsonian symptoms [113]. Even though cortical myoclonus in PD localizes to the focal region of the sensorimotor cortex, its presence and severity is increased in those LB disorders that have dementia as part of the clinical syndrome [113–115]. These disorders are DLB and hereditary LB disease due to α -synuclein triplication, both of which have shown identical electrophysiological characteristics to PD-Myoclonus [113–117]. This association of more severe cortical myoclonus with dementia across the spectrum of LB disorders suggests that it may have relevance as a biomarker model for cortical dysfunction in PD cognitive decline.

Molecular Biomarkers

The study of molecular biomarkers in PD is in its infancy with any evidence for a particular biomarker being preliminary. Most studies have examined a biomarker's ability to detect the presence of PD, rather than any particular aspect of PD (e.g., cognition).

Figure 4 Noninvasive neurophysiological findings in a PD-D patient with small amplitude cortical myoclonus. Top panel: Surface electromyogram shows myoclonus muscle discharges at arrows. Bottom panel: Back-averaging of the myoclonus muscle discharges reveals a pre-myoclonus cortical transient indication of a focal cortical source of the myoclonus in this PD-D patient.

Figure 5 Mechanisms and therapeutic targets for PD-D. The phrases in red indicate potential therapeutic mechanisms for treating the molecular pathophysiology of PD-D.

There are genotypes of PD (genetic forms of PD) that have LBs as a pathological hallmark, which commonly have dementia as part of the phenotype. Examples include PARK1, PARK4, and PARK8 [118]. However, for “sporadic” PD, it is not known whether certain genotypes could be used for a biomarker of PD cognitive decline [118,119]. Genetic factors for dementia *per se* could also be valuable biomarkers for cognitive decline in PD but the evidence is not clear. The presence of ApoE4 was initially reported to be associated with PD-D [120]. More recent studies have suggested a lack of association [121–123]. The possibility remains that Apo E4 produces increased risk of dementia in PD in a subset but this possibility needs more study.

CSF τ and A β -42 have been reported as somewhat predictive of cognitive decline in controls, and this would seem to justify their examination in PD cognitive decline [124,125]. CSF F2-isoprostanes (IsoPs) are quantitative *in vivo* biomarkers of oxidative damage to the brain. Although evidence seems weak for their application for the cognitive decline in LB disorders, there are positive findings in AD dementia that may suggest an application for PD-D with AD pathology [123]. Blood assessment of oligomeric α -synuclein has been evaluated in PD, and it would be useful to assess whether differences correlate with cognitive changes [126].

Therapeutic Targets

At the present time, our knowledge is limited about the molecular pathogenesis of neurodegeneration in cortical neurons or in the pathways that project to the cortex. As a result, there is limited insight on which pathways are amenable to direct intervention. Some of the major hypotheses and possible intervention points are depicted in Figure 5. Phrases alongside the arrows refer to possible

intervention mechanisms. Current important aspects are discussed later.

Acetylcholine and Monoamine Neurotransmitters

Although acetylcholine and the monoamines, including dopamine, have a possible neuropharmacologic basis to treat cognitive decline in PD, it is acetylcholine that has so far produced the only class of drugs that have been shown to consistently improve cognitive function, that is, the acetylcholinesterase inhibitors [11]. The Nucleus Basalis of Meynert is affected in PD (as in AD) and provides acetylcholine projections to the cerebral cortex. Acetylcholinesterase inhibitors providing more acetylcholine neurotransmission to cortical neurons deprived of such projection is the theoretical pharmacodynamic reason for their symptomatic treatment effect. Acetylcholinesterase inhibitors were first developed for AD, but these agents are known to have modest but significant benefit on cognition in PD. Donepezil, Rivastigmine, and Galantamine are three acetylcholinesterase inhibitors that have received study in PD cognitive decline [19]. The chronic progression of the dementia and overall disability makes it difficult to appreciate the ongoing contribution of currently available symptomatic treatments. In double-blind, placebo-controlled studies the benefit from active drug has usually been modest and transient [20–22]. Both muscarinic and nicotinic receptors have been reported to be lower in the cortex of PD subjects [127,128]. Because acetylcholinesterase inhibitors presumably act through increased acetylcholine availability, drugs that interact with acetylcholine receptor subtypes are being studied for potential therapeutic effectiveness [129]. Drugs that inhibit butyrylcholinesterase, which has different distribution to neocortex than acetylcholinesterase are being developed [130].

Abnormal Protein Aggregation and Dementia

AD pathology, and pathological mechanisms, are associated with the formation of insoluble aggregates of amyloid β peptide ($A\beta$), and aggregated hyperphosphorylated τ ; frontotemporal dementia (FTD) is associated with abnormal deposits of τ ; whereas PD-D and DLB are associated with abnormal deposits of α -synuclein. The end stage of all diseases is loss of cognitive function due to loss of cortical neuron integrity. It is assumed that the formation of toxic aggregates lead to multiple pathological processes including oxidative stress, inflammation, and neuronal apoptosis, which can, in turn, accelerate abnormal metabolism of α -synuclein (Figure 5). Similar to the formation of $A\beta$ plaques [131–134], it has been suggested that the aggregation of α -synuclein into LB structures is not a toxic event, as these structures might be sequestering toxic species of α -synuclein. It has been shown that soluble oligomers of $A\beta$ are neurotoxic, and similarly, small oligomers of α -synuclein are neurotoxic [131,135,136]. These are intermediate forms of aggregated α -synuclein that proceed to aggregates that form the LB [135,136].

Attempts to inhibit the formation of aggregated protein, to dissociate already formed aggregates or accelerate the formation of inert structures (e.g., consolidated plaques or LB) are the central therapeutic target for each of these diseases (Figure 5) [135]. Drugs aimed to this target are under investigation in multiple experimental and clinical trials, but at present their effectiveness is unclear. For AD, preventing aggregation of $A\beta$ has been the focus of the widely publicized amyloid vaccine approach. In this approach, antibodies against $A\beta$ were induced or injected and these were used to prevent aggregation of $A\beta$ or to dissociate aggregated $A\beta$. Research is ongoing to identify new ways of $A\beta$ vaccination [137]. A similar vaccine approach has been shown to be effective in α -synuclein mouse models of PD/DLB. Surprisingly, as α -synuclein aggregates tend to intracellular, immunization of mice with α -synuclein protein was effective in preventing formation of histological aggregates [138]. Treatments that are directed toward interfering with the molecular pathogenesis of PD-D have the potential to be neuroprotective and or neurorestorative.

α -Synuclein

Research on α -synuclein has taken off since 1997 when an Ala to Thr mutation at position 53 in SNCA gene produced clinical PD in 85% affected [139–141]. This mutation appears to increase the tendency of α -synuclein to aggregate. Additional mutations (A30P and E46K) have been identified. These cases develop pathological PD with widespread cortical LB deposition. At that time, it was demonstrated that α -synuclein was a major component of LBs [142], subsequent work showed that serine-129 phosphorylated α -synuclein was enriched in LB. These two findings have made α -synuclein the major therapeutic target for PD and DLB; however, synucleinopathies are features of many other human neurodegenerative disease including PD, DLB, progressive supranuclear palsy, diffuse LB disease, AD, LB variant of AD, multiple system atrophy (MSA) and even are features of amyotrophic lateral sclerosis, FTD, Pick's disease [143]. A feature of MSA is the prominent presence of α -synuclein deposits in glial cells [143].

α -Synuclein is an abundant 19 kD presynaptic vesicle protein whose normal function is still unclear. In its native form, it is unfolded, but can aggregate down different pathways when exposed to changes in ion concentration, pH, temperature or depending on the cellular environment. Due to abnormal metabolism, primarily due to phosphorylation, but also nitration and oxidation, α -synuclein can form oligomers and aggregates in a manner similar to what has been described for $A\beta$ in AD [143]. It is now believed that aggregated and fibrillar α -synuclein is neuroprotective and it is the soluble oligomeric α -synuclein that is associated with neurotoxicity. α -Synuclein oligomers have been suggested to cause neurotoxicity through calcium influx and seeding [144]. These issues need to be considered when developing therapeutic strategies. Preventing aggregation might be beneficial but one school of thought suggests that accelerating aggregation in LB-like structures, and preventing formation of low molecular weight oligomers might be a better strategy. However, pathological studies show that PD severity and dopaminergic cell loss correlates with numbers of nigra LB; similarly progression to dementia in PD-D and DLB correlates with the formation of cortical LB. Another feature of α -synuclein deposits is its tendency to spread anatomically through different brain regions as disease severity progresses [46,143,145,146].

Agents that Promote α -Synuclein Aggregation

One interesting hypothesis has come from experimental observations that many post-translational modifications (phosphorylation, nitration, dityrosine crosslinking, methionine oxidation, glycosylation, and ubiquitination) can promote α -synuclein aggregation. Serine 129 is the most abundant form of phosphorylated α -synuclein, but serine 87 and tyrosine 125 phosphorylation are features of naturally isolated α -synuclein. Other potential tyrosine phosphorylation sites are present on α -synuclein. A recent study showed that p-129 phosphorylated synuclein promoted toxicity, while p-125 tyrosine phosphorylation prevented aggregation and toxicity. We have described a progressive spread of phosphorylated (p-ser 129) α -synuclein from olfactory bulb to limbic regions to cingulate regions to neocortical regions [146]. There is still controversy whether p-ser-129 synuclein is a suitable therapeutic target. Experimental studies have shown that increased formation of this form of α -synuclein is associated with neurotoxicity [147–149]. However in humans, one could speculate that phosphorylation of α -synuclein at ser129 synuclein becomes more easily accumulated into harmless aggregates that can be sequestered in LB. If inhibiting this form of α -synuclein can positively affect the progression of LB formation, either in the nigrostriatal pathway or in the cortex, this might have an effect on preventing movement changes, mood changes or dementia. Work has focused on identifying the kinase that is principally responsible for the phosphorylation of serine-129 because its inhibition might still be therapeutically effective. One group identified Polo-like kinase 2 (PLK-2) as the major kinase involved [150], while earlier work suggested Casein kinase-2 (CK2) was involved [151]. This issue is still unresolved as recent work suggested LRRK2 might be involved in α -synuclein phosphorylation [152].

Agents that Inhibit α -Synuclein Aggregation

A significant field of research has been on the interactions of dopamine and levodopa with α -synuclein. *In vitro* studies have shown that dopamine can inhibit aggregation of α -synuclein, though dopamine α -synuclein interactions might also promote formation of toxic oligomers [153]. Whether this is a therapeutic target to promote or inhibit is still under investigation [154]. Further studies will involve testing anti-aggregation compounds for α -synuclein in transgenic mouse models.

Increased expression of α -synuclein in experimental systems can result in the increased production of aggregates. For example, transgenic mice overexpressing nonmutated human α -synuclein develop LB-like structures. These are enhanced in mice carry the A30T mutated human α -synuclein [155,156]. This is also illustrated that families with chromosomal trisomy of α -synuclein that develop PD in an autosomal dominant manner [157–159]. Gene duplication of α -synuclein is now being recognized as a feature of sporadic PD [160].

Targets from Genetic Studies

The numbers of PD cases with solely genetic causes are rare but pathological observations of brains from cases with PD associated with mutated α -synuclein (SNCA or PARK1); mutated parkin (PARK2), PTEN-induced putative kinase 1 (PINK1 or PARK6), DJ-1 (PARK7), and leucine rich repeat kinase 2 (LRRK2 or PARK 8) share many common features of pathology although their effects on disease progression differ. Mutations in glucocerebrosidase (GBA) have been linked to early onset PD [161,162]. Most of these forms of genetic PD are associated with PD-D. Although these forms of PD are rare, the roles of these proteins in sporadic PD provide some therapeutic targets for disease modulation. These findings suggest that there is a major role for protein aggregation and neurotoxic α -synuclein oligomeric species in PD and PD-D. These mutations lead to enhanced formation of aggregated α -synuclein due to parkin-driven deregulation of the ubiquitin–proteasome system, resulting in oxidative stress and mitochondrial dysfunction, and altered kinase activity. Genetics and gene expression profiling have been two approaches to understanding the biochemical basis of PD and PD-D. Five genes have now been shown to play a role in PD susceptibility. Mutations in three of these genes, PRKN, PINK1, and DJ1, are important in early onset, recessively inherited PD, while mutations in LRRK2 and SNCA (α -synuclein) result in autosomal-dominant PD. LRRK2 has emerged as the most prevalent genetic cause of PD as different mutations have been identified in this gene associated with both familial and sporadic forms of disease [163,164]. The biochemical properties of LRRK2 are still unclear, but as a serine threonine kinase, it is believed to exert functions early in the disease process, making it a suitable target for therapeutic intervention [165–167].

Gene expression profiling of PD-D using gene “chips” have been used to identify gene expression differences between PD-D, PD, and nondemented. Genes that are differentially expressed between these conditions become new targets for validation. Dunckley *et al.* used laser capture microdissection to compare genes expressed in cases of cognitively normal and PD extracted

neurons with those from PD-D [168]. There was evidence of significant dysregulation of 556 cortical genes in PDD compared to PD and cognitively normal samples; the majority of these genes were downregulated in PD-D. These genes included those involved in axonal transport, neurite outgrowth, cell adhesion, synaptic transmission, oxidative stress, and proteasome function.

Other Targets

There are numerous other targets that have been studied in the context of dopamine containing neurons, but the potential in the treatment of cortical neurons or other substrates of cognitive dysfunction in PD has received little or no study. Nevertheless, potential for their usefulness in treating PD-D exists. Neuroinflammation has been well documented in human PD [169,170]. Peripheral leukocytes from PD patients released spontaneously significant higher levels of inflammatory cytokines and chemokines (MCP-1, MIP-1 α , IL-8, IFN γ , IL-1 β , and TNF- α) in cultures. The levels of these inflammatory mediators were further heightened in response to the challenge of inflammatory stimulus, LPS [171]. These findings had led to suggestion that neuroinflammation is a target for PD treatment [172]. In PD-D, there has not been systematic characterization of neuroinflammation in the affected brain regions. Neurotrophic factors regulating neuronal survival, differentiation, growth, and regeneration has been tested as an alternative for DA neuron-based treatment in PD. Three most studied growth factors are brain-derived neurotrophic factors (BDNF), glial cell line-derived neurotrophic factors (GDNF), and basic fibroblast growth factor (bFGF). These factors have beneficial effects on neuroprotection and neuroregeneration in DA neuronal cultures and animal models of PD. Infusion of bFGF in kainic acid-induced cognitive dysfunction showed functional recovery in hippocampal cholinergic and DA neurons suggesting restorative potential of bFGF in cognitive dysfunctions through mitogenic effects on the progenitor cells [173]. Oxidative stress in PD is believed to have high relevance for substantia nigra pathology [174]. Oxidation with α -synuclein can promote oligomer formation, resulting in proteasome failure, build up of toxic aggregates and cell death. This mechanism might be more responsible for the aggregation and spread of α -synuclein into cortical brain regions, contributing to cognitive decline. Trials have been carried out for anti-oxidants, which can scavenge free radicals, with mixed results [154]. Moderate ingestion of various foods high in anti-oxidants is associated with reduced risk of PD. Promising clinical trials of coenzyme Q10, at high doses, have been reported [154].

Future Needs and Directions

Biomarkers of various types are being proposed for the study of PD-D as well as for objective measures of PD-D prediction and progression. This biomarker research needs to be accelerated because it will play a critical role in both PD cognitive decline pathophysiology and clinical therapeutic trials for PD-D. Currently, there is no agreement among experts as to which biomarkers are acceptable either as predictive or surrogate endpoints.

The need for the prevention and better therapy for the cognitive decline in PD is apparent. Much work needs to be done

before treatments that engage therapeutic targets can be tested in human PD patients. There are major questions that need to be answered:

- What are the important mechanistic differences between the PD neurodegeneration that occurs in the substantia nigra versus cortical neurons and nondopamine subcortical projections?
- What molecular pathways are involved in the toxicity of cortical neurons? What exact role do α -synuclein and A β peptides play?
- How should a therapeutic target that has been developed in an animal model be validated for cognitive decline in human PD?

- How many types of predictive and progression biomarkers are needed to study and evaluate treatments for PD cognitive decline? How do we decide which ones are the best?

One specific critical question is whether preventing the formation of LB, or preventing the formation of oligomeric α -synuclein will prevent PD-D. There may be an interrelationship between α -synuclein aggregation with oxidative stress, inflammation, neuronal cell death, apoptosis, and neurotrophic factor deficits.

Conflict of Interest

The authors have no conflict of interest.

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