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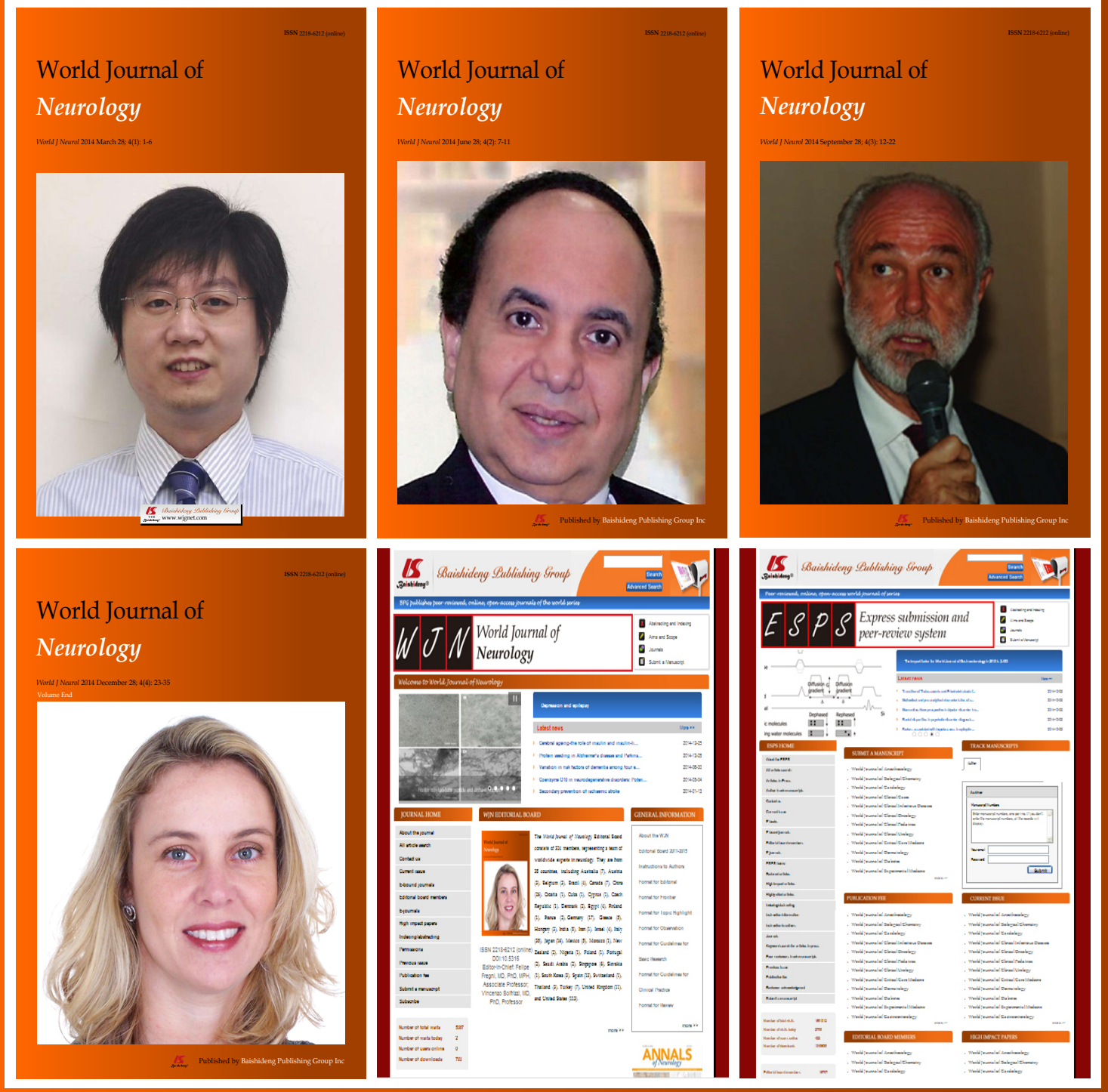

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EDITORIAL

Coenzyme Q10 in neurodegenerative disorders: Potential benefit of CoQ10 supplementation for multiple system atrophy

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Abstract

Coenzyme Q10 (CoQ10) is an essential cofactor in the mitochondrial respiratory pathway and also functions as a lipid-soluble antioxidant. CoQ10 deficiency has been implicated in many clinical disorders and aging. Primary CoQ10 deficiency is a group of recessively inherited diseases caused by mutations in any gene involved in the CoQ10 biosynthesis pathway. Although primary CoQ10 deficiency is rare, its diagnosis is important because it is potentially treatable with exogenous CoQ10. Multiple system atrophy (MSA) was recently shown to be linked to mutations in the *COQ2* gene, one of the genes involved in the CoQ10 biosynthesis pathway. MSA is relatively common in adult-onset neurodegenerative diseases characterized by Parkinsonism, cerebellar ataxia and autonomic failures. Because COQ2 mutations are associated with an increased risk of MSA, oral CoQ10 supplementation may be beneficial for MSA, as for other primary CoQ10 deficiencies. Statins are 3-hydroxy-3-methylglutaryl coenzyme A inhibitors that inhibit the biosynthesis of cholesterol, as well as the synthesis of mevalonate, a critical intermediate in cholesterol synthesis. Statin therapy has been associated with a variety of muscle complaints from myalgia to rhabdomyolysis. Statin treatment carries a potential risk of CoQ10 deficiency, although no definite evidence has implicated CQ10 deficiency as the cause of statin-related myopathy.

Key words: Primary coenzyme Q10 deficiency; Multiple system atrophy; Cerebellar ataxia; *COQ2* gene; Statin; Coenzyme Q10 supplementation; Reduced coenzyme Q10

Core tip: Recently, multiple system atrophy (MSA), relatively common in adult-onset neurodegenerative diseases, was shown to be linked to mutations in the *COQ2* gene, one of the genes involved in the Coenzyme Q10 (CoQ10) biosynthesis pathway. Neurologists so far have not paid much attention to CoQ10 because primary CoQ10 deficiency caused by mutations in the CoQ10 synthesizing genes is very rare. The most important message is that primary CoQ10 deficiency is treatable with exogenous CoQ10 and that oral CoQ10 supplementation might be also beneficial for patients with MSA.

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INTRODUCTION

Coenzyme Q10 (CoQ10), or ubiquinone, is a lipophilic

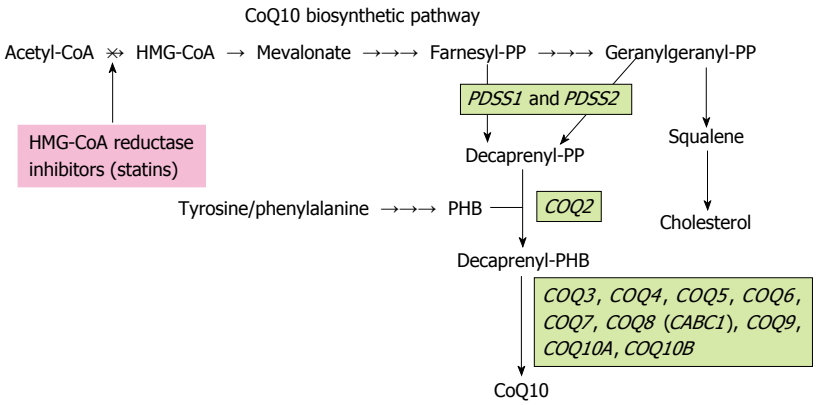

Figure 1 Coenzyme Q10 biosynthesis pathway. Enzyme and human gene symbols are shown in italics. HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; PDSS: Prenyldiphosphate synthase subunit; PP: Pyrophosphate; PHB: Para-hydroxy-benzoate; CoQ10: Coenzyme Q10; CABC: Chaperone-activity of bc1.

molecule present in cell membranes that functions as an essential cofactor for electron transport in the mitochondrial respiratory chain and as an endogenous antioxidant[1]. CoQ10 is synthesized in all cells from tyrosine (or phenylalanine) and mevalonate, with its highest levels found in tissues with high energy turnover, including the heart, brain, liver and kidneys[2]. Levels of CoQ10 are known to decrease with age in various tissues of healthy normal humans and rats[1,3,4].

CoQ10 may be used to improve mitochondrial dysfunction and act as an antioxidant in various clinical conditions[5]. Although CoQ10 has been approved in some countries to treat conditions such as congestive heart failure, it is generally classified as a dietary supplement in most countries and can be purchased over the counter. Interest is particularly keen in the United States where CoQ10 is available in more than 100 single and combination ingredient products, although it has not been approved by the Food and Drug Administration for the medical treatment of any condition.

Primary CoQ10 deficiency is a group of rare, recessively inherited diseases. Its recognition is very important because it is potentially treatable with exogenous CoQ10[6,7]. A study by the multiple system atrophy (MSA) Research Collaboration, published in a recent issue of the New England Journal of Medicine, reported a link between MSA and mutations in the *COQ2* gene, which encodes one of the proteins involved in the CoQ10 biosynthesis pathway[8]. MSA is relatively common in adult-onset neurodegenerative diseases characterized by Parkinsonism, cerebellar ataxia and autonomic failures. This discovery prompted the reconsideration of the roles of mitochondrial function and oxidative stress in the pathogenesis of these neurodegenerative diseases and the potential benefit of CoQ10 supplementation in patients with MSA and related diseases. In this mini review, we also discuss the potential risk in these patients of statins, a group of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, because statin inhibition of mevalonate synthesis not only inhibits the biosynthesis of cholesterol, but may also inhibit the biosynthesis of CoQ10.

BIOSYNTHESIS OF COQ10

CoQ10 is a vital component of the mitochondrial respiratory chain, with de novo biosynthesis of CoQ10 occurring mainly in the mitochondria. CoQ10 biosynthesis is a complex biological process that is not completely understood in humans[9]. Therefore, its biosynthesis pathway has been elucidated in other organisms, including yeasts and bacteria. CoQ10 consists of a benzoquinone ring and a polyprenyl side chain; the benzoquinone ring is synthesized from tyrosine or phenylalanine and the polyprenyl side chain from intermediates in the mevalonate pathway[9].

As shown in Figure 1, decaprenyl diphosphate (decaprenyl-PP) is synthesized from mevalonate by the PDSS1-PDSS2 enzyme complex *via* the intermediates farnesyl-PP and geranylgeranyl-PP. Para-hydroxybenzoate-polyprenyl transferase, or COQ2, subsequently catalyzes the condensation of decaprenyl-PP with para-hydroxybenzoate, synthesized from tyrosine or phenylalanine. At least eight more COQ enzymes (COQ3-COQ10A, B), which catalyze methylation, decarboxylation and hydroxylation reactions, are required to produce functional CoQ10.

COQ10-DEFICIENT DISEASES AND COQ10 SUPPLEMENTATION

Primary CoQ10 deficiency is caused by mutations in any of the *COQ* genes, whereas secondary COQ10 deficiency is caused by genetic defects independent of the CoQ10 biosynthesis pathway or by other inhibitors of the CoQ10 biosynthesis pathway[6,10,11].

Ten genes implicated in the biosynthesis of CoQ10 have been characterized in yeast and 16 human homologs of these genes have been identified in the human genome database[10]. To date, primary CoQ10 deficiency has been linked to 7 of the 16 human genes, *PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ6*, *COQ8* (*ADCK3*/*CABC1*) and *COQ9*[12-24] (Table 1). CoQ10 deficiency has been associated with five major clinical phenotypes: (1) encephalomyopathy; (2) severe infantile multisystemic disease;

Table 1 Genotype-phenotype correlation in primary coenzyme Q10 deficiencies

	Clinical features	Age at onset	Response to CoQ10 supplementation	Ref.
PDSS1	Severe infantile multi-systemic disease	1-2 year	Improved and alive	[12]
PDSS2	Severe infantile multi-systemic disease Leigh syndrome	3 mo	No clinical response	[13]
COQ2	Nephropathy	Infantile-or early childhood-onset	Dramatic improvement of neurological manifestations and nephritic syndrome	[12,14-17]
	Severe infantile multi-systemic disease			
	Multiple system atrophy	Adult-onset	Unknown	[8]
COQ4	Encephalomyopathy	< 3 yr	Significant improvement of neuromuscular symptoms	[18]
COQ6	Nephropathy with sensorineural deafness	Infantile-or early childhood-onset	Improvement of nephritic syndrome and hearing loss	[19]
	Severe infantile multi-systemic disease	< 3 yr		
COQ8 (*CABC1*)	Cerebellar ataxia	Juvenile-or adult-onset	Severe neurological deficit with epilepsy ~mild improvement of ataxia	[20-23]
COQ9	Severe infantile multi-systemic disease	Birth	No clinical response	[24]

CoQ10: Coenzyme Q10; PDSS: Prenyldiphosphate synthase subunit; CABC: Chaperone-activity of bc1.

(3) cerebellar ataxia; (4) isolated myopathy; and (5) nephropathy[25]. Primary CoQ10 deficiency is clinically and molecularly heterogeneous and phenotypes differ even in patients with the same gene mutation. Importantly, primary CoQ10 deficiency is generally responsive to CoQ10 supplementation (Table 1).

Primary CoQ10 deficiency is unique among mitochondrial diseases because an effective therapy is available, at least for some patients. Early and sufficient administration of primary CoQ10 is considered important for good outcomes[25]. Early administration of CoQ10 was found to resolve renal symptoms and prevent neurological damage in a patient with a COQ2 mutation[26]. In contrast, a patient with a COQ9 mutation and severe infantile multisystemic disease did not respond to CoQ10 treatment[24]. The reason that patients with a CoQ10 deficiency vary in response to CoQ10 treatment is not completely understood. Insufficient improvement may be due, however, to the occurrence of irreversible disease manifestations prior to diagnosis and treatment. Therefore, correct and timely diagnosis allows prompt treatment with exogenous CoQ10 and may improve the outcome of these otherwise devastating and potentially fatal disorders.

The amount of CoQ10 in the diet is not sufficient to significantly increase the serum CoQ10 level[9,27]. Rather, a significant increase in its serum level requires supplementation with about 100 mg/d CoQ10[5]. Patients with CoQ10 deficiency have been treated with 100-3000 mg/d of this agent[25]. High doses and long-term administration of exogenous CoQ10 are considered necessary for patient benefit. The bioavailability of different CoQ10 formulations should also be considered[28]. Although CoQ10 is present as both oxidized and reduced forms in the body and both forms are commercially available, the absorption rate of the reduced form is higher than that of the oxidized form because the oxidized form must be reduced upon absorption from the gastrointestinal tract[29].

CoQ10 content in various tissues increases after CoQ10 supplementation. Oral administration of CoQ10 was found to increase CoQ10 levels in both the brain and brain mitochondria[30]. Transfer of exogenous CoQ10 across the blood-brain barrier may require higher CoQ10 doses, perhaps explaining why cerebellar ataxia in patients with primary CoQ10 deficiency shows variable responses to exogenous CoQ10 treatment.

No absolute contraindications are known for CoQ10. Adverse effects with CoQ10 are rare, with fewer than 1% of patients reporting mild gastrointestinal discomfort[29]. Even oral administration of 3000 mg/d for 8 mo was reported to be safe and well tolerated in patients with amyotrophic lateral sclerosis[31].

COQ2 GENE MUTATIONS IN MSA

MSA is an adult-onset, progressive, neurodegenerative disorder that clinically presents as autonomic failure and cerebellar ataxia and/or parkinsonism[32,33]. To date, few symptomatic therapies are available. L-dopa therapy has been shown to be effective for motor symptoms of Parkinsonism for a limited period and several drugs have been used to treat autonomic failure, such as orthostatic hypotension and urinary bladder disturbance[34]. Symptoms in MSA progress rather rapidly and its prognosis is relatively poor; overall survival after disease onset is less than 10 years on average[35,36].

MSA is generally considered a sporadic disease but several familial cases have been reported, suggesting that some genetic factors are associated with susceptibility to MSA[37]. Using linkage analysis and whole genome sequencing, the Multiple System Atrophy Research Collaboration team in Japan identified mutations in the *COQ2* gene in members of two multiplex families with autopsy-proven MSA[8]. These mutations include a homozygous mutation (M78V-V343A/M78V-V343A) and compound heterozygous mutations (R337X/V343A). Moreover, a common variant (V343A) and multiple rare variants in the *COQ2* gene were found to be associated with sporadic MSA. The frequency of the V343A allele

is significantly higher in MSA patients than in controls (4.8% *vs* 1.6%-2.2%). The V343A variant has been found exclusively in Japanese individuals. Thus, this variant represents a susceptibility factor rather than a causative factor for MSA.

Each variant of COQ2 was functionally impaired in yeast complementation assays. Intracellular CoQ10 levels and COQ2 enzyme activities in lymphoblast cell lines established from MSA patients with the two variant alleles were substantially lower than those in controls. Intracellular levels of CoQ10 in the brain tissue of individuals with the homozygous mutation (M78V-V343A) were much lower than in controls. A previous study revealed that the activity of mitochondrial complex I was significantly lower in muscle mitochondria from patients with MSA than in mitochondria from age-matched controls[38]. Because COQ2 mutations are associated with an increased risk of MSA, oral CoQ10 supplementation may be beneficial for patients with MSA, similar to findings in other primary CoQ10 deficiencies.

EFFECT OF STATINS ON COQ10

Statins are the most effective medications currently in use for reducing low-density lipoprotein cholesterol levels. Statins competitively inhibit HMG-CoA reductase, thereby blocking the synthesis of mevalonate, a critical intermediate in the cholesterol synthesis pathway (Figure 1). Although statins have revolutionized clinical cardiology and are generally safe, statin therapy has been associated with a variety of muscle complaints from myalgia to life-threatening rhabdomyolysis[39-41]. The mechanism of statin-related myopathy is unknown but may involve mitochondrial dysfunction resulting from intramuscular CoQ10 deficiency which, in turn, may be due to statin interference with CoQ10 biosynthesis in the same mevalonate pathway.

Statins have been found to reduce circulating CoQ10 levels in humans but low-dose statin treatment does not appear to reduce intramuscular CoQ10 levels. Studies using muscle biopsy materials from patients with statin-related myopathy have yielded conflicting results, with one study suggesting that morphological changes are consistent with mitochondrial dysfunction, while another found that the muscle CoQ10 level is mildly decreased but there was no biochemical or histochemical evidence of mitochondrial myopathy[42,43]. CoQ10 supplementation can increase circulating CoQ10 levels but it is not clear whether this relieves muscle complaints.

Collectively, no definite evidence has implicated CoQ10 deficiency as the cause of statin-related myopathy. However, case reports have described patients with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes whose symptoms were temporally related to statin therapy[44-46], suggesting that statins may provoke mitochondrial diseases in susceptible individuals. The same may be true for individuals susceptible to MSA as well as to other primary and secondary CoQ10 deficiencies.

CONCLUSION

CoQ10 deficiencies are clinically and genetically heterogeneous. Although they are rare, their recognition is important because clinical improvement after CoQ10 supplementation has been repeatedly documented in many patients. The discovery of a link between a CoQ10 synthesizing enzyme and MSA provides new insights into the pathogenesis of MSA and suggests the potential benefit of CoQ10 supplementation. Further studies may lead to effective therapies for MSA and other CoQ10 deficiencies.

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OBSERVATIONAL STUDY

Variation in risk factors of dementia among four elderly patient cohorts

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Abstract

AIM: To examine variation in risk factors that contributed to dementia among four elderly cohorts by race and gender.

METHODS: We examined 2008 Tennessee Hospital Discharged database for vascular factors that play a role in both stroke and dementia. Risk factors for dementia were examined for black and white patients aged 65+. Four race-gender groups of patients-white males (WM), black males (BM), white females (WF), and black females (BF) were compared for prevalence of dementia and stroke. A logistic model predicting dementia in each group separately used several vascular factors affecting dementia directly or indirectly through stroke.

RESULTS: Three point six percent of patients hospitalized in 2008 had dementia and dementia was higher among females than males (3.9% *vs* 3.2%, $P < 0.001$), and higher among blacks than whites (4.2% *vs* 3.5%, $P < 0.000$). Further, BF had higher prevalence of dementia than WF (4.2% *vs* 3.8%, $P < 0.001$); similarly BM had more dementia than WM (4.1% *vs* 3.1%, $P < 0.001$). In logistic regression models, however, different patterns of risk factors were associated with dementia in four groups: among WF and WM, hypertension, diabetes, congestive heart failure, and stroke predicted dementia. Among BF and BM, only stroke and diabetes were related to dementia.

CONCLUSION: Aggressive management of risk factors (hypertension and diabetes) may subsequently reduce stroke and dementia hospitalization.

Key words: Dementia; Race; Gender; Stroke; Vascular factors

Core tip: Large medicaid in-hospital database that examines the differences in prevalence of dementia amongst blacks and white population and by gender. Clear differences emerge; blacks have greater burden of dementia including both genders. Risk factors leading to dementia differed between groups. White males and females had a higher association with stroke, hypertension, heart failure and diabetes while blocks had stroke and diabetes only as risk factors. This difference allows us to target these 2 groups with aggressive management early on to reduce the risk of dementia. The strength lies in analyzing a very large database to derive these conclusions.

Husaini B, Cain V, Novotny M, Samad Z, Levine R, Moonis M.

Variation in risk factors of dementia among four elderly patient cohorts. *World J Neurol* 2014; 4(2): 7-11 Available from: URL: http://www.wjgnet.com/2218-6212/full/v4/i2/7.htm DOI: http://dx.doi.org/10.5316/wjn.v4.i2.7

INTRODUCTION

Dementia is among the most common neuropsychiatric disorder, which afflicts 5% to 10% of American elderly populations over the age of 65, and it accounts for a third of all psychiatric diagnoses among the elderly[1-4].

Previous studies have reported on the role of cardiovascular (CVD) factors that contribute to dementia and dementia differences by race and gender. Dementia is higher among blacks and females[5-17]. The role of these CVD factors among elderly cohorts by race-gender remains unknown. Since strokes occur more often among older people, older age possibly contributes to both stroke and dementia[10-15]. Further, older age is also reported to be correlated with higher rates of hypertension (HTN), diabetes mellitus (DM), myocardial infarction (MI), stroke recurrence[15], and congestive heart failure (CHF)[16]. The risk of stroke increases with age in the presence of diabetes[10-19].

While age is related to all cardiovascular risk factors, stroke, and dementia, it remains unclear whether these risk factors are related to dementia across four elderly race-sex cohorts either directly or indirectly through stroke. Thus, in this study, we explore two issues: (1) Do rates of dementia and cardiovascular risk factors vary by race-gender cohorts? (2) Do cardiovascular risk factors that may influence dementia (directly or indirectly) vary by race-gender cohorts?

MATERIALS AND METHODS

Data

We used Tennessee Hospital Discharge Data files on elderly patients (aged 65+; n = 154945) discharged in 2008. These files are administrative files submitted for reimbursement; they do not provide clinical data but only ICD-9 diagnoses for which a patient was treated. The attending physicians give diagnoses. Since the Tennessee population is largely composed of whites and blacks, we used four race-sex cohorts of dementia patients (n = 5556): White Males (n = 1778), White Females (n = 3069), Black Males (n = 253), and Black Females (n = 456). While the dementia patient's sample had only 11% black patients, this proportion is a good representation of black population in Tennessee, which is approximately 14%. The number of black males in the dementia group, though small with limitations on generalizability, is based on those who received the dementia diagnosis by the attending physicians. For the diagnosis of dementia, we used ICD-9 codes of 290.00, 290.20, 290.40-290.42, 291.2, 294.10, 294.11, and 294.20. Data on risk factors hypertension (HTN), diabetes mellitus (DM), hyperlipidemia (CHOL), cardiac arrhythmia (CA), stroke, congestive heart failure (CHF), and MI were also extracted for each patient. All discharge diagnoses in our analyses included a combination of both primary and secondary diagnoses. The dementia sample of patients (n = 5556) included whites (89%), blacks (11%), females (63%) and males (37%). The mean age of dementia patients was 82.5 years (SD = 9.1). Black males were younger in age (78.4 years, SD = 8.8) compared to other cohorts (Table 1). Finally, age-adjusted (per age 65+) dementia prevalence rate (of 690.6 per 100000 elderly) was developed per CDC methodology[20].

Statistical analysis

Prevalence of hospitalized dementia patients (per 100000) was directly age-adjusted and indexed to the Year 2000 Census per methodology provided by CDC for the population at risk[20]. Prevalence of dementia risk factors by race and gender were evaluated with Pearson χ^2 and the Fisher's Exact Tests. We also used multivariate logistic regression models to examine both the direct and indirect effects of all risk factors impacting dementia. We used logistic models (controlling age) for each race-gender cohort separately to examine the likelihood of dementia associated with each risk factor (Figure 1). Estimating separate equations for each race-gender cohort allowed for the effects of each risk factor to vary across four cohorts.

RESULTS

Prevalence of dementia and cardiovascular risk factors

Our analyses indicate that both dementia and stroke prevalence increased significantly ($P < 0.001$) with increasing age: dementia increased from 1.6% among 65-74 years old to 4.2% among 75-84 years old, to 6.6% among elderly aged 85+. Similarly, stroke prevalence increased from 13.1% among 65-74 years old to 17.3% among 75-84 years old, to 18.0% among elderly older than 85 years of age. Further, blacks have higher prevalence of dementia than whites (4.2% *vs* 3.5%, $P < 0.001$) and so do females than males (3.9% *vs* 3.2%, $P < 0.001$) (not shown). Among four cohorts, dementia prevalence was significantly higher ($P < 0.001$) in black females (4.2%), compared to black males (4.1%), white females (3.8%) and white males (3.1%). The overall diagnosis of dementia was 3.6% (n = 5556) of all elderly patients hospitalized in 2008 (n = 154945).

As a second trend, while one third of dementia patients had DM, CA, CHF, nearly 60% had stroke and 80% had hypertension (Table 1, col. 7). These risk factors varied across four dementia cohorts in that black patients had higher prevalence of HTN, DM, and Stroke (Table 1, col. 6), whereas white patients had higher prevalence of CA than blacks (Table 1, col. 3). Further, prevalence of MI was higher among males (combined cols. 1 + 4) compared to females (combined cols. 2 + 5). Some of these findings are consistent with those reported previously on risk factors.

Table 1 Clinical characteristics of dementia patients by race and gender cohorts

Variables	White males *n* = 1778	White females *n* = 3069	All white *n* = 9847	Black males *n* = 253	Black female *n* = 456	All black *n* = 709	All dementia age 65+ *n* = 5556
Column→	1	2	3	4	5	6	7
Mean age (SD)	80.6 (8.4)	83.9 (9.0)	82.7 (9)	78.4 (8.8)	82.3 (9.4)	80.9 (9.4)	82.5 (9.1)
HTN (%)	81.8	83.1	82.6	85.8	91.7[1]	89.6[2]	83.5
DM (%)	38.1	30.6	33.4	47.2	52.6[1]	50.6[2]	35.6
Chol (%)	11.3[1]	8.5	9.6	8.7	9.4	9.2	9.5
CA (%)	42.4[1]	36.3	38.6[1]	35.6	32.5	33.6	37.9
MI (%)	7.6	5.3	6.2	7.9[1]	5.7	6.5	6.2
CHF (%)	36.7[1]	32.6	34.0	32.4	36.2	34.8	34.2
Stroke (%)	63.1	54.9	57.9	72.7[1]	63.4	66.7[1]	59.0
Dementia (%)	3.1	3.8	3.5	4.1	4.2[1]	4.2[1]	3.6

[1]Differences across cohorts significant at $P < 0.001$; [2]Differences between two racial groups (cols. 3 and 6) are significant at $P < 0.001$. HTN: Hypertension; DM: Diabetes mellitus; Chol: Hyperlipidemia; CA: Cardiac arrhythmia; MI: Myocardial infarction; CHF: Congestive heart failure; Stroke: Prior stroke.

Table 2 Odds ratios showing direct effect of risk factors on dementia by race-gender cohorts

Risk factors	White males	White females	All white	Black males	Black females	All black	All dementia patients
Column→	1	2	3	4	5	6	7
HTN	1.22[2]	1.10[1]	1.15[2]	0.72	1.04 ns	0.88	1.13[3]
DM	1.16[2]	1.16[2]	1.16[2]	1.17 ns	1.28[3]	1.24[3]	1.17[2]
Chol	0.78	0.73	0.75	0.81	0.89	0.85	0.76
CA	0.91	0.89	0.89	1.05 ns	1.03 ns	1.04 ns	0.91
CHF	1.44[3]	1.16[2]	1.26[2]	1.14 ns	1.19 ns	1.17 ns	1.25[3]
MI	0.84	0.83	0.83	1.11 ns	0.8	0.92	0.84
Stroke	9.9[3]	7.8[3]	8.23[3]	13.3[3]	9.2[3]	10.39[3]	8.5[3]

[1]Each logistic analysis included age in model, OR significant at $P < 0.05$; [2]OR significant at $P < 0.01$, [3]OR significant at $P < 0.000$; HTN: Hypertension; DM: Diabetes mellitus; Chol: Hyperlipidemia; CA: Cardiac arrhythmia; MI: Myocardial infarction; CHF: Congestive heart failure; Stroke: Prior stroke.

Cardiovascular predictors of dementia (direct and indirect effects)

Table 2 shows direct effects of CVD factors on dementia as odd ratios for each elderly race-sex cohort. Figure 1A shows both direct effects (in black lines) and indirect effects (in red lines) of risk factors through stroke on dementia.

The direct effect of risk factors on dementia show that among whites (Table 2, col. 3; Figure 1A and B black lines), four risk factors, namely HTN [odds ratio (OR), 1.15, 95%CI: 1.06-1.25], DM (OR, 1.16, 95%CI: 1.08-1.23), CHF (OR, 1.26, 95%CI: 1.18-1.35); and Stroke (OR, 8.23, 95%CI: 7.7-8.74) predicted onset of dementia. Among black males (Table 2, col. 4; Figure 1C), only stroke (OR, 13.3, 95%CI: 9.92-17.16) predicted dementia; and among black females (Table 2, col. 5; Figure 1D) dementia was predicted by two factors, namely DM (OR, 1.28, 95%CI: 1.04-1.57) and stroke (OR, 9.2, 95%CI: 7.4-11.22).

For indirect effect through stroke (red lines), Figure 1A and 1B show that among white patients (combined males and females), five risk factors (HTN, DM, Hyperlipidemia, CA, and CHF) were all related to stroke which in turn predicted dementia. Among blacks (both males and females in Figure 1C and D), only two factors (HTN, DM) were related to stroke, which in turn predicted dementia. Overall, the indirect effects of HTN, DM, CA and HF on dementia through stroke remain intact for the total sample (Figure 1E).

DISCUSSION

Our findings indicate that the risk of both stroke and dementia increases with increasing age. For our study, prevalence of dementia among the elderly (aged 65+) was estimated at the rate of 690.6 per 100000 elderly population and this rate per 100000 elderly varied significantly among four cohorts: black males had the highest rate (902.2), followed by black females (811.4), white males (619.9), and white females (617.5). Further, since diabetes almost doubles the risk of dementia[21], and stroke were more prevalent (with increasing age) among blacks, it appears that dementia among blacks, (who survived stroke and thus are in the sample) may largely result from a combination of both diabetes[19,21] and recurring stroke[15].

The influence of stroke on dementia appears to be consistent with previously reported findings of both increasing age, and stroke associated with HTN and DM[15-23]. Since hypertension and diabetes are highly prevalent in all cohorts, additional investigation is needed

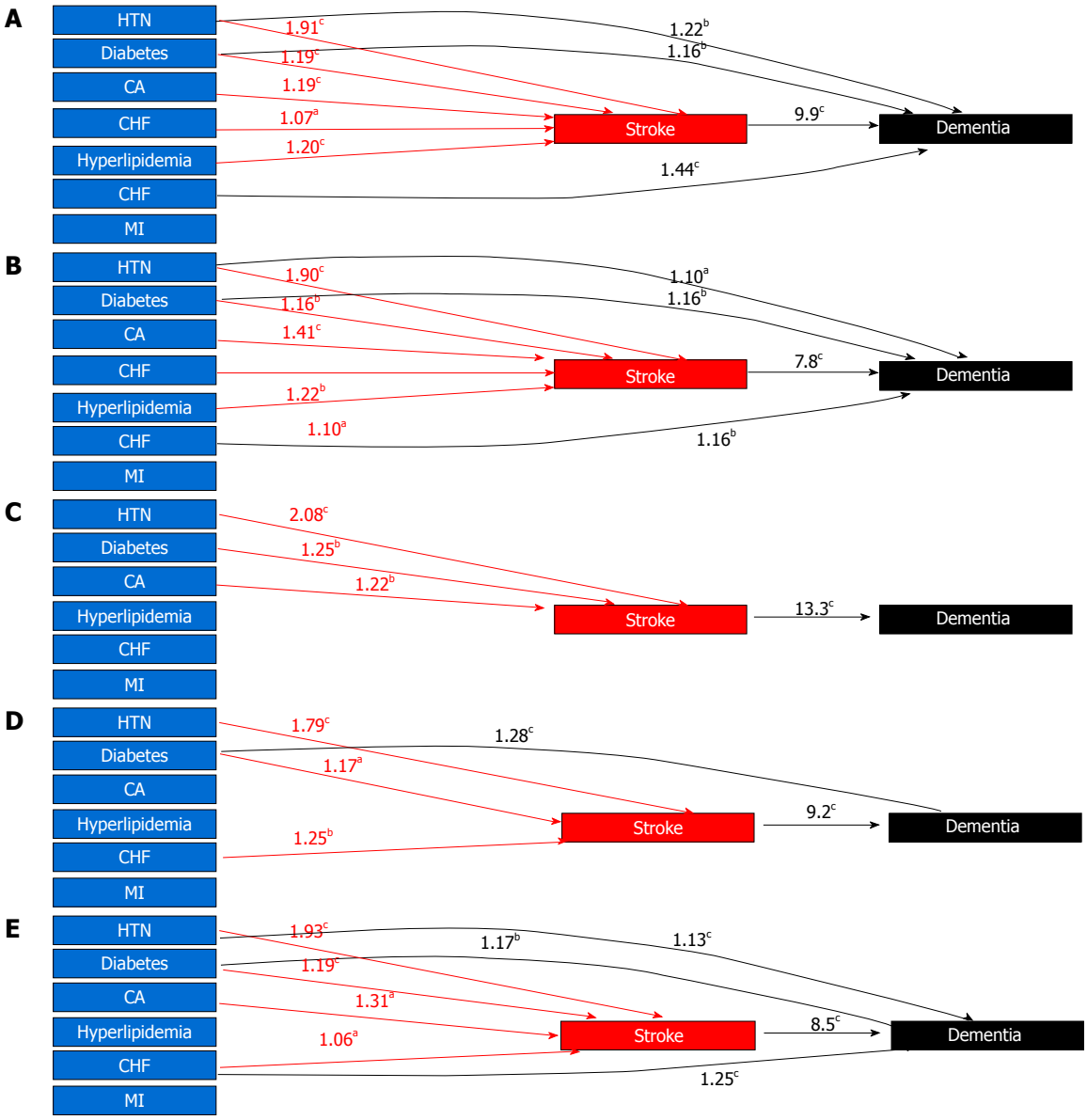

Figure 1 Odd ratios for risk factors predicting stroke and dementia. A: White males (aged 65+ yr); B: White female (aged 65+ yr); C: Black males (aged 65+ yr); D: Black females (aged 65+ yr); E: All dementia patients (aged 65+ yr). Each logistic analysis included age in model; [a]OR significant at $P < 0.05$; [b]OR significant at $P < 0.01$; [c]OR significant at $P < 0.000$. HTN: Hypertension; CA: Cardiac arrhythmia; MI: Myocardial infarction; CHF: Congestive heart failure.

to examine the role of small versus large vessel strokes in dementia. It is plausible that repeated small vessel infarction among the surviving stroke patients might contribute to the beginning of dementia with large vessel infarcts that may bring dementia to a recognizable level. Further, our data have not supported the previously reported role of hyperlipidemia in elevated levels of dementia. A plausible explanation for the lack of finding regarding hyperlipidemia in our study could be due to an effective treatment of this condition that may have neutralized the effect of hyperlipidemia on dementia.

We recognize that the effect of risk factors on dementia is not as robust as anticipated, particularly among black males. This is possibly due to a small number of black male patients in our sample. We recognize but would remiss, if we do not note that these black males are those who are stroke survivors and thus they show a strong effect of stroke on dementia. It may also be noted that there is a higher mortality among older stroke male patients, and thus fewer number of surviving males, particularly black males in our sample, appears to be consistent with the longevity of black population in Tennessee (72.5 years) where black females live longer (longevity of 76 years) than black males (longevity of 68.7 years). Hence the number of black males in our dementia sample, though small, appears to be consistent with the longevity data for the African American population.

Finally, since DM, and stroke predict dementia across most race-gender cohorts, both primary and secondary preventive measures need to be aggressively pursued since most of these risk factors are amenable to effective management strategies aimed at reducing hospitalization for both stroke and dementia among the elderly.

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COMMENTS

Background

This paper addresses issues of worldwide importance to the field of neurology.

Research frontiers

The methods are sound as they utilize administrative files of discharged patients with dementia.

Innovations and breakthroughs

The paper presents extensive, populationbased information regarding patients with a discharge diagnosis of dementia. It presents evidence to show possible variations in risk factors according to gender and race. This information is highly useful for planning public health responses to this important problem.

Terminology

The paper represents a useful scientific contribution to the neurologic literature.

Peer review

In this paper, the authors report about the risk factors of dementia among four elderly groups. This is an interesting study. The paper is well written.

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REVIEW

AIM AND SCOPE

World Journal of Neurology (*World J Neurol*, *WJN*, online ISSN 2218-6212, DOI: 10.5316) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJN covers topics concerning neuro-oncology, electroneurophysiology, cerebrovascular diseases, epilepsy, cognitive impairment, myopathy and peripheral neuropathy, degenerative diseases, infectious diseases, demyelinating diseases, immunological diseases, genetic/metabolic diseases, affective disorders, headaches, sleep disorders, interventional neuroradiology, minimally invasive therapy, rehabilitation, diagnostic imaging, evidence-based medicine, epidemiology and nursing. Priority publication will be given to articles concerning diagnosis and treatment of neurological diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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REVIEW

Cerebral ageing-the role of insulin and insulin-like growth factor signalling: A review

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Abstract

Cerebral ageing is a complex biological process associated with progressing cerebrovascular disease and neuronal death. It does not always, however, associate with a functional decline, as the ageing mammalian brain retains considerable functional plasticity which supports successful cerebral ageing where age-related cognitive decline is modest. On the contrary, pathological cerebral ageing results in memory impairment and cognitive deterioration, with Alzheimer's disease (AD) being a florid example. Trophic/growth factors promote brain plasticity; among them are peptides which belong to the insulin family. Preclinical research suggests that the evolutionarily conserved brain insulin/insulin-like growth factor-1 (IGF-1) signalling system controls lifespan and protects against some features of AD such as neurodegeneration-related accumulation of toxic proteins and cognitive deficiencies, as observed in animal models. Insulin and IGF-1 activate cell signalling mechanisms which play protective and regenerative roles; abnormalities in the insulin/IGF-1 system may trigger a cascade of neurodegeneration in AD. AD patients show cerebral resistance to insulin which associates with IGF-I resistance and dysregulation of insulin/IGF-1 receptors as well as cognitive deterioration. This review is focused on the roles of the insulin/IGF-1 signalling system in cerebral ageing and its potential involvement in neurodegeneration in the human brain as seen against the background of preclinical evidence.

Key words: Brain; Insulin; Insulin receptor; Insulin-like growth factor; Longevity; Alzheimer's; Diabetes mellitus; Inflammation

Core tip: Age itself is a major risk factor for the development of age-related cognitive decline, Alzheimer's and cerebrovascular diseases. Increased life expectancy necessitates the need to understand the processes that underlie successful *vs* pathological brain ageing in order to develop early interventions which may assist in delaying if not reversing the detrimental effects of brain ageing. This review focuses on the signalling system of insulin and insulin-like growth factor-1 (IIS) and its roles in cerebral ageing; it highlights some conflicting literature opinions and incomplete understandings of the roles and mechanisms of the IIS system.

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INTRODUCTION

Ageing is a complex biological process that affects all species ranging from invertebrates through to non-human mammals and humans, being underpinned by alterations at molecular and cellular levels[1,2] that compromise the organism's physiological homeostasis, induce susceptibility to disease and accelerate death[3-5]. The cellular and anatomical changes that occur in the course of brain ageing contribute to cerebrovascular disease[6], impact motor performance and learning and memory functions[7,8], thus leading to cognitive decline and dementia[9]. As human life span is growing and the proportion of the elderly is increasing in most societies, the prevalence of age-dependent diseases such as Alzheimer's disease (AD), Parkinson's disease and stroke is also on the increase world-wide. Consequently, understanding the biological and molecular mechanisms of what constitutes "successful" *vs* pathological cerebral ageing is critical to both delaying the ageing process, enhancing the quality of life in the elderly, and alleviating the already overburdened health care systems, from the cost component involved in treating age-related diseases.

In view of the above points, research on brain-ageing has generated a pool of information regarding the potential mechanisms, which underpin cognitive decline. Advancements in molecular and cell technology, have been instrumental in identifying factors such as oxidative stress[10,11], epigenetic changes[12], mitochondrial dysfunction, inflammatory response[13], impaired cell signalling and gene expressions[14], autophagy and protein turnover, target of rapamycin (TOR) and insulin/insulin-like growth factor (IGF) signalling as potential mechanisms that contribute to alterations observed in brain ageing[9].

This review will first discuss what constitutes "successful" *vs* pathological brain ageing. Within this context, the review will then focus predominantly on the evolutionarily conserved insulin/IGF-signalling (IIS) system, and its roles in cognitive decline, dementia, AD and neuroinflammation.

It has been postulated that the IIS system plays a regulatory role in organismal ageing, lifespan and longevity[15,16], and a reduced expression of its components under experimental conditions has been linked to amelioration of amyloid-β accumulation, the latter being one of the key features of AD[17-19], and cognitive impairment[20]. The IIS system merits an arduous and in depth investigation into the role and the extent of its involvement in cerebral aging, as targeting its components may pave the way to designing novel pharmacological approaches to early interventions and facilitate reversal or delay of cognitive decline in human patients.

SUCCESSFUL *VS* PATHOLOGICAL CEREBRAL AGEING

Defining successful cerebral ageing has been both challenging and controversial and to date there is no scientific consensus defining normal ageing in older age. Despite the lack of an operational definition, it is generally agreed that successful cerebral ageing is a multi-dimensional process, characterized by the absence of cognitive impairment and preservation of mental faculties, which allows for social functioning and independence in older age[21]. This suggests that beyond the neurophysiological and psychological functions, equally vital are some esoteric elements such as wisdom and resilience, which together with lifestyle factors may contribute towards the variability, detected in cognitive abilities amongst "successful" *vs* "unsuccessful" elderly individuals and groups[22,23].

Current research postulates that the ageing mammalian brain retains a considerable functional plasticity, which is activity-related and thus it depends on the lifestyle of the individual (*e.g.*,[24]). There is evidence that human age-related diseases can be delayed by a healthy lifestyle which includes stress management, physical exercise and caloric restriction[24,25]. Thus, although genes are important determinants of longevity, an individual's lifestyle is a powerful instrument that can delay the development of age-related diseases and lead to the path of ageing successfully[25-27].

Functional imaging studies on ageing human brains, suggest that in the absence of pathology, age-related cognitive decline is rather modest and varies amongst individuals[9]. It is characterized by anatomical and functional changes, which are associated with neuronal-synaptic molecular substrates specific to brain area[28,29]. These changes may be attributed to synaptic connectivity rather than neuronal and white matter losses[30,31].

In contrast, the pathologically ageing brain, as that in AD, exhibits marked cognitive decline, which is associated with a significant loss of synapses[32]. Although the molecular mechanisms underlying this synaptic impairment are not fully understood, dysfunction of γ-secretase is evident in many cases of early onset of AD[33], and the gamma-secretase-mediated EphA4 signalling system may be involved in the synaptic pathogenesis of AD[32,33]. Equally, apolipoprotein E4 can increase the presence of amyloid beta (aβ) oligomers in the brain, which in turn may increase the loss of dendritic spines and accelerate memory decline in AD[34].

Of the regions associated with memory and learning, the hippocampal formation exhibit age-related decrease in volume, which may be a consequence of a decrease in neuronal and synaptic density[28,30]; prefrontal cortex (PFC) also shows reductions in grey matter[35,36]. The PFC is implicated in higher executive functions, involving explicit, implicit and spatial memories[28,37,38]. Its decreased grey matter diffusivity may be a potential biomarker for early

AD[39].

Similarly, the posterior cingulate, which is both anatomically and functionally connected to PFC and medial temporal lobe (MTL)[40,41], and which plays a vital role in encoding and retrieval of information[42,43] is also affected in ageing. Interestingly, it is one of the first structures to be affected in AD[44,45] but has not yet been explicitly studied in conjunction with PFC to establish associations between task-related and cognitive task activation[46].

These associations may be modifiable in healthily aged individuals[46-48] in contrast to AD patients[48-50]. PFC grey matter loss may trigger plasticity, which is dependent on the MTL function for memory tasks[51], and consequently, those individuals with functionally intact grey matter/MTL ratio, may make a greater use of the PFC[52].

The hippocampal region implicated in memory function shows age-related atrophy[53], and a decline of working memory function is often observed in healthy ageing[54]. In AD pathology, impaired hippocampal function is detectable even before the formation and accumulation of plaques[55] and volume analysis by means of MRI has been used as diagnostic tool in distinguishing AD patients and healthy age-matched subjects by measuring the grey matter volumes in the lateral temporal and parietal cortices[56]. Furthermore, the AD brain is characterized by ventricular enlargement[57-60], consistent with a considerable loss of grey and white matter[61].

The above alterations may be attributed to age-related neuronal loss, and/or compensatory plasticity, and future studies are needed to test how these three way structure-function-behaviour associations impact the grey matter loss and PFC activation in successful ageing[46]. Equally, stress-related hormonal changes[9] or compromised calcium homeostasis[38,62] can play a role too as prolonged increases of intracellular calcium concentrations may cause neurite degeneration and cell death in ageing[63].

In addition to the observed anatomical, functional and cellular changes, the brain's neurochemistry is also affected, with dopaminergic, noradrenergic and cholinergic systems exhibiting deficits[60,64-69]. Studies on human and rhesus monkey PFC indicate that the balance between inhibitory and excitatory neurotransmission is decreased[70] as an effect of reduced gene expression, which may compromise neural activity resulting in excitotoxicity and neurodegenerative pathology. Positron emission tomography scans in ageing humans show a reduction in dopamine synthesis in the striatum, of relevance to frontal lobe cognitive function[71], and a marked decrease in dopamine receptor binding within caudate and putamen nuclei[66,72].

Reductions in serotonin synthesis, reuptake and receptor binding have also been noted in the caudate nucleus, putamen and PFC of ageing brains[67], and glutamate decreased levels in grey and white matter, basal ganglia have been reported[69,73].

It is of significance that all the pathological features of AD such as neuronal loss, neurofibrillary tangles and plagues may be present in the brains of elderly who may never show the full extent of cognitive deterioration observed in AD[9]. This resilience to cognitive decline in the presence of AD pathology may be attributed to "cognitive reserve", which may reduce the risk of dementia in ageing[74]. It further suggests that the hallmarks of AD may be secondary to ageing.

One of the cellular mechanisms regulating ageing processes is the insulin and IIS system, which is described below with regard to its role and those of its components in cerebral ageing. This system, extensively studied in model organisms, appears to underpin the innate resilience that is essential in successful ageing; it may also present therapeutic potential in the treatment of debilitating neurodegenerative and cerebrovascular diseases.

INSULIN, INSULIN GROWTH FACTORS AND THEIR RECEPTORS

Insulin and the IGF-1 and IGF-2 constitute a family of structurally similar peptides[75,76], which have been preserved in most organisms through evolution[77]. Peripherally, insulin is synthesized and secreted into blood by pancreatic cells, whereas IGF-1 and IGF-2 by the liver in response to the pituitary growth hormone[78].

Insulin is a powerful player in glucose homeostasis, *e.g.*,[79,80], which targets the liver, muscle, and adipose tissue[81], and also the vasculature and the brain[82]. The IGF-1 in contrast, is implicated in foetal and postnatal development, with a role in cellular survival of adult tissues[82]. The circulation and delivery of IGF-1 to the tissues is aided by IGF-1 binding proteins 1-6 in contrast to insulin, which circulates freely[82].

The transportation of insulin and IGF 1 into the brain is achieved through a saturable mechanism within the blood-brain barrier (BBB)[78,82,83], although there is evidence of their *de novo* synthesis in the central nervous system (CNS)[84-86]. Insulin's ability to cross the BBB[83,87-89] depends on a number of factors such as age, fasting or obesity[88]. Under experimental conditions, insulin administered directly into the CNS, decreases body weight by suppressing appetite, lowers serum insulin levels and increases serum glucose[90,91]. An increase in peripheral insulin levels leads to increased cerebrospinal fluid (CSF) insulin, whereas chronic insulin resistance impairs cerebral transportation by down regulating insulin receptors (IR) at BBB[92]. Brain activity in healthy individuals subjected to direct determination of insulin sensitivity with the hyperinsulinemic-euglycemic clamp technique, has been shown to be affected by increased levels of circulating insulin[93].

BBB uptake of IGF involves a lipoprotein receptor-related protein 1, the respective receptor (IGF-1R) and other transport mechanisms, enabling IGF access to

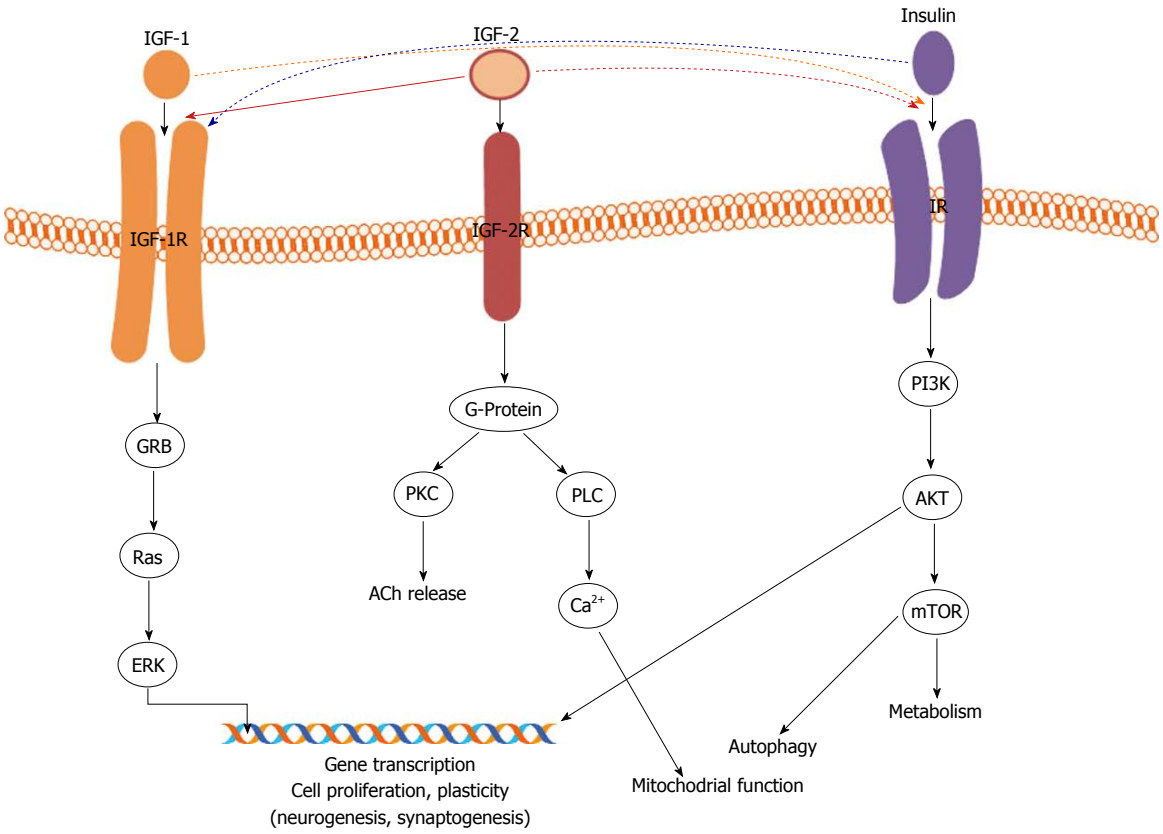

Figure 1 Insulin and insulin-like growth factor signalling pathways-a simplified outline as based on ref. [77]. Low affinity binding between insulin and IGF-1R, and IGF-1 and IR, and IGF-2 and IR is represented by dashed lines. ACh: Acetylcholine; ERK: Extracellular signal-related kinase; GRB: Growth factor receptor-bound protein; IGF-1: Insulin-like growth factor 1; IR: Insulin receptor; IGF-1R: IGF-1 receptor; mTOR: Mammalian target of rapamycin; PLC: Phospholipase C; PKC: Protein kinase C; PI3K: Phosphoinositide 3-kinase; Ras: Signalling proteins involved in cell proliferation (name derived from rat sarcoma).

CSF, and hypothalamic and hippocampal regions[82]. Insulin and IGFs activate signalling systems through their respective receptors, which belong to the tyrosine kinase receptor family[77]: IR, IGF-1R and IGF-2R (Figure 1). Low affinity binding can take place between insulin and IGF-1R, and IGF-1 and IR using the phosphoinositide 3-kinase (PI3K)/AKT pathway**,** while IGF-2 signals downstream not only *via* IGF-2R but also IGF-1R[77]. It should be mentioned that IGF-2R mainly controls the uptake and activation/destruction of extracellular of IGF-1/2 IGF2[94]; the present review is focused on IGF-1R (Figure 1).

IR and IGF-1R differ in their respective functions and tissue expressions[82] being present in the brain within neuron rich structures[95-97] and glial cells[18,98,99]; they are different entities expressed in diverse brain regions. The IR is highly expressed in the anterior thalamic and hypothalamic nuclei, olfactory bulb, hippocampus, cerebral cortex[100,101] and promotes plasticity through supporting synaptogenesis and synaptic remodelling[102,103], and metabolic homeostasis[75,104]. IGF-1R signalling supports normal brain development with its neurogenesis, and successful ageing, consistent with the roles of its agonist neurotrophins (see review[77]). A genetic modification, which results in IGF-1R deletion, causes microcephaly and death in experimental animals[105,106].

INSULIN AND IGF-1 IIS AND ITS ROLES IN COGNITIVE FUNCTION, BRAIN AGEING AND LONGEVITY

The IIS system has been probably the most widely studied conserved mechanism that extends lifespan in worms, flies and mammals[16], linking longevity and successful ageing across the species[107,108]. It has been suggested that although insulin does not directly influence cerebral glucose transport, it appears to influence regionally the distribution of glucose transporter (GLUT) isoforms such as GLUT 4 and GLUT 8; the former being expressed in the cerebellum, hippocampus, pituitary and hypothalamus[109] whereas the latter in the hippocampus and hypothalamus[110]. This selective stimulation of glucose uptake in the brain areas implicated in learning and memory renders the hormone a potent player in potential therapeutic use to restore or enhance impaired cognitive functions[111]. In addition, insulin's indirect role in hippocampal functioning *via* the long-term potentiation cascade, involving the N-methyl-D-aspartate receptor[112] further suggests that insulin can be implicated in synaptic remodelling which is vital for the formation of new memories.

Similarly, insulin's ability to modulate CNS levels of acetylcholine and norepinephrine, known to influence

cognitive function[113,114], may further substantiate its role in neural activity and potential neural protection against the effects of oxidative stress[115].

Studies in animals and humans have suggested that deficiency or reduced effectiveness of insulin is a contributing factor to cognitive decline, impacting memory functions and brain ageing[116-118]. Insulin resistance has been positively correlated with neurodegeneration observed in AD and mild cognitive impairment[118,119]. Patients with type Ⅱ diabetes mellitus, hypertension and chronic hyperinsulinemia show impaired verbal memory while enhanced memory function has been observed upon intranasal insulin administration[120,121].

In preclinical studies, liver-specific IGF-1-deficient (LID) mice, deficient in liver-derived IGF-1 exhibit impaired spatial learning and memory functions[122], demonstrating that this peptide is vital in mediating exercise-induced effects on the adult brain, thus suggesting promotion of neurogenesis[123,124]. In addition, IGF-1 appears to possess neurotrophic properties and plays a role in the amelioration of age-related reduction in hippocampal neurogenesis and behavioural deficits[125,126]; it also improves regional cerebral blood flow in normal rats[127]. It targets brain neurones and glia implying a trophic action on glutamatergic synapses, modulating hippocampal circuitries that are involved in learning and memory[116].

Within this context, research on brain ageing suggests that IGF-1 has potent effects on brain function, and that its reduced signalling during ageing may contribute to cognitive deterioration and compromise the organism's ability to deal with age-associated cerebral pathologies[19]. Similarly, impaired insulin signalling in the brain has been linked to cognitive decline associated with pathological brain ageing[111,128]. Epidemiological studies suggest that individuals with type Ⅱ diabetes and obesity may be at higher risk of developing vascular dementia[129].

On the other hand, centenarian studies provide evidence of correlation between reduced IIS activity and extreme human longevity. Ashkenazi centenarians have been found to have mutations in the IGF-1R that leads to lower activity of the respective signalling pathway[107], and centenarians' offspring had lower peripheral IGF-1 activity when compared with appropriately matched-controls[130]. Of significance, in the same sample of centenarians' offspring, IGF-1 was inversely related to insulin sensitivity[130], and an Italian cohort study reported an IR variant to be associated with longevity[131]. The above findings suggest that in humans the IIS system is a complex determinant of lifespan[132].

PRECLINICAL *VS* CLINICAL STUDIES ON THE ROLE OF THE IIS SYSTEM IN AD

The importance of IR, IGF-1R and their respective agonist peptides has been underscored by data postulating the involvement of the IIS system in AD, which is characterized by amyloid-dependent neurodegeneration and late onset progressive cognitive decline. AD sufferers display impaired cerebral glucoregulation[133], reduced brain insulin receptor activity, reduced insulin concentrations in cerebrospinal fluid, peripheral hyperinsulinemia[134] and reduced insulin and IGF-1 expression[135], together with synaptic loss associated with the accumulation and formation of aggregate amyloid plagues (aβ) and neurofibrillary tangles (tau protein) as measured post mortem[136-138]. The above suggests that the IIS system may play a significant role in the loss of memory functions associated with AD and a reduction of its activity may reduced toxicity, delay aβ accumulation and improve cognitive functions[18,139-143].

In the preclinical approaches, mouse models of AD with a knockout of IGF-1 receptor exhibit reduced cognitive impairment, neurodegeneration and longer lifespan. The findings from the above studies, point to aβ oligomers as the toxic species associated with AD, and the ageing process to be associated with the organism's exposure to their toxicity, leading to age-related neurodegenerative diseases[132]. Consequently, the IIS system was mechanistically linked to neurone-associated toxic protein accumulation and ageing, as reduced signalling is thought to protect the brain and slow the progression of AD[132]. It has been shown to activate the PI3K/AKT and Ras pathways (Figure 1). The former leads to the activation of mammalian TOR (mTOR), and rapamycin-treated mice have been shown to increase their lifespan and ameliorate age-related cognitive deficits[141,144]. The latter activates extracellular signal-regulated kinase-1/-2, which has been implicated in plasticity, including long-term potentiation, and memory formation in the CNS[145]. Although no data as yet exist to support the involvement of both pathways in the pathogenesis of AD, it may present an interesting direction for future research.

A number of current preclinical studies on the animal models of AD suggest that genetic reduction of the signalling pathway may protect against the AD pathology[18,20] while older studies seem to postulate that its reduction is associated with the age-related pathologies[146]. These conflicting views may arise from the use of different experimental approaches[19], or as it has been suggested, reduced IGF-1 peripheral bioactivity may not necessarily induce the same results in brain IGF-1 levels[147], postulating an independent regulatory activity.

It is important to appreciate the complexity of this relationship as human studies which try to correlate peripheral levels of IGF-1/2 with cognitive functioning in health and disease, report disparate finding, as illustrated below. Of the most recent publications in this area, a large scale long-term study on a community sample of over 3500 participants of middle and old ages has demonstrated that lower serum levels of IGF-1 associate with an increased risk of developing AD dementia while higher levels of IGF-1 associate with greater brain volumes in middle-aged participants free of stroke and dementia. The authors conclude that elevated levels of

IGF-1 may protect against neurodegeneration[148]. On the other hand, the Caerphilly Prospective Study on 746 men has not found associations between age-related cognitive decline and IGF-1, contrary to IGF-2 which was associated with both normal age-related and pathological cognitive decline[149]. Furthermore, offspring from families with a parental history of AD appear to have higher serum IGF-1 levels in middle age when compared with appropriate controls, leading to a conclusion that elevated peripheral IGF-1 associates with an increased risk of AD[150].

Despite the existence of opposing views in the field, epidemiological evidence postulates a strong association between type Ⅱ diabetes (T2D) and AD occurrence as AD patients exhibit higher rates of diabetes and impaired fasting glucose levels[151-153], and although the molecular mechanisms underlying this association are not yet clearly understood[82] impaired insulin signalling, amyloid-genesis and inflammation appear to be heavily implicated in the aetiology of diabetes, AD and consequently cerebral ageing[154].

IIS SYSTEM AND INFLAMMATION

Inflammation is seen a key player in obesity, insulin resistance and diabetes, as based on elevated levels of pro-inflammatory cytokines in the circulation and pancreatic islets of T2D patients[155]. Similarly, elevated levels of pro-inflammatory proteins and chemokines have been detected in post-mortem AD patients' brains, *e.g.*,[156]. This was further substantiated by findings from studies on AD mouse models suggestive of inflammation as key to early and/or intermediate stages of the neurodegenerative condition[157]. There is consensus that cerebrovascular inflammation and neuroinflammation, along with an increased accumulation of toxic aβ, all result in a disruption of synaptic activity, which according to some theories is a trigger in AD pathophysiology, *e.g.*,[158].

Studies investigating IGF-1 and IGF-2 peptides' expression in human microglia *in vivo* and *in vitro* suggest that both peptides are expressed in microglia, conferring vital protection against cytokine-mediated neuronal death. It should be mentioned here that microglial activation is associated with increased activities of inflammatory cytokines, *e.g.*, interleukin (IL)-1β and IL-6 which itself can disrupt neural signalling, *e.g.*,[159].

Chronic inflammation increases the production of inflammatory cytokines in the long-term, which contributes to the suppression of neurotrophic factors, including the IGFs, and leads to progressive tissue damage, thus accelerating the onset of clinical manifestations of AD and metabolic disorders including T2D[160,161], and may contribute to neurodegeneration[162].

CONCLUSION

Research on brain ageing suggests that age itself is a major risk factor for the development of age-related cognitive decline, Alzheimer's and cerebrovascular diseases. The increased life expectancy observed in most societies has further necessitated the need to understand the processes that underlie successful *vs* pathological brain ageing such that early interventions through lifestyle modifications or pharmacological agents may assist in delaying if not reversing the detrimental effects on brain pathology.

Within this context, this review examined the role of an evolutionarily conserved signalling pathway, IIS, with the focus on insulin and insulin-like growth factor IGF-1 and their roles in cerebral ageing. Translation of data derived from animal models allow for linking the IIS pathway with its supporting longevity, protein homeostasis, learning and memory, and delayed ageing. The above is also consistent with the human studies, which find evidence of reduced messaging for insulin, IGF-1 and their receptors in post mortem brains of patients with AD. While the link between insulin as such and brain ageing has been recognised, the IIS pathway in its entirety deserves more attention; our still incomplete understanding of the roles and mechanisms of this pathway calls for more translational research to explore novel treatments for cognitive decline through delaying cerebral ageing.

Some conflicting literature opinions and incomplete understanding of the roles and mechanisms of the IIS system demand novel approaches and directions in this field. The IIS system clearly lends itself to the ongoing search for modifiable physiological factors which may delay the onset of cognitive decline and cerebral ageing.

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REVIEW

Protein seeding in Alzheimer's disease and Parkinson's disease: Similarities and differences

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Abstract

Neurodegenerative pathology can be seeded by introduction of misfolded proteins and peptides into the nervous system. Models of Alzheimer's disease (AD) and Parkinson's disease (PD) have both demonstrated susceptibility to this seeding mechanism, emphasizing the role of misfolded conformations of disease-specific proteins and peptides in disease progression. Thinking of the amyloidogenic amyloid-beta peptide (Aβ) and alpha-synuclein (α-syn), of AD and PD, respectively, as prionoids requires a comparison of these molecules and the mechanisms underlying the progression of disease. Aβ and α-syn, despite their size differences, are both natively unstructured and misfold into β-structured conformers. Additionally, several studies implicate the significant role of membrane interactions, such as those with lipid rafts in the plasma membrane, in mediating protein aggregation and transfer of Aβ and α-syn between cells that may be common to both AD and PD. Examination of inter-neuronal transfer of proteins/peptides provides evidence into the core mechanism of neuropathological propagation. Specifically, uptake of aggregates likely occurs by the endocytic pathway, possibly in response to their formation of membrane pores *via* a mechanism shared with pore-forming toxins. Failure of cellular clearance machinery to degrade misfolded proteins favours their release into the extracellular space, where they can be taken up by directly connected, nearby neurons. Although similarities between AD and PD are frequent and include mechanistically similar transfer processes, what differentiates these diseases, in terms of temporal and spatial patterns of propagation, may be in part due to the differing kinetics of protein misfolding. Several examples of animal models demonstrating seeding and propagation by exogenous treatment with Aβ and α-syn highlight the importance of both the environment in which these seeds are formed as well as the environment into which the seeds are propagated. Although these studies suggest potent seeding effects by both Aβ and α-syn, they emphasize the need for future studies to thoroughly characterize "seeds" as well as analyze changes in the nervous system in response to exogenous insults.

Key words: Alzheimer's disease; Parkinson's disease;

Prionoid; Seeding; Propagation; Protein misfolding

Core tip: The disease-specific proteins of Alzheimer's and Parkinson's disease show many similarities as prion-like seeds in the brain. In addition to sharing structural features as misfolded proteins, the interactions and mechanisms that underlie the propagation of these proteins may also be shared, hijacking natural cellular responses in ways not unlike those of pore-forming toxins. Differences in temporal and spatial patterns of disease progression stems from the existence of conformational variants. Misfolded proteins that can be generated *in vitro*, can seed widespread pathology in non-transgenic animal models and question our understanding of disease progression in neurodegenerative diseases.

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INTRODUCTION

The purpose of this review is to examine patterns that are present in the progression of Alzheimer's disease (AD) and Parkinson's disease (PD), with a focus on identifying parallel mechanisms that underlie disease as well as differences that characterize each disease classified as neurodegenerative diseases, both exhibit neuronal loss/dysfunction in various regions of the central nervous system (CNS). Observations made from analyses of tissue from patients as well as animal models continue to provide evidence that the pathological route taken by both AD and PD is related to their disease-specific proteins. The amyloidogenic proteins, amyloid beta peptide (Aβ) in AD and alpha-synuclein (α-syn) in PD[1], have recently been shown to propagate throughout cerebral networks as misfolded seeds. This has likened the spread of pathology to that of prion diseases, which exhibit templating[2], a process where misfolded proteins can induce endogenous protein to misfold.

AD and PD are the two most prevalent neurodegenerative diseases worldwide. Neither race nor gender is spared by either disease and cures for both have remained elusive. By 2010, 35.6 million people were living with AD, a number that is expected to double in the following two decades. PD has a worldwide prevalence estimated at 7 million patients.

AD is the most common cause of dementia and is characterized by a progressive loss of cognitive function, most noticeably in the form of memory loss. This can be followed by further dysfunction in language, visuospatial and executive systems. Hallmarks of AD include the presence of Aβ-containing amyloid (senile) plaques in the extracellular milieu of the CNS and surrounding blood vessels as well as neurofibrillary tangles (NFT) produced by intracellular aggregation of the microtubule associated protein Tau. PD is the most common cause of movement disorders and exhibits clinical symptoms that can be divided into two groups: the more apparent motor symptoms such as resting tremors, bradykinesia and loss of postural reflexes; and the non-motor symptoms such as olfactory dysfunction, sleep disturbances and depression[3]. The pathology is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) of the midbrain and decreased levels of dopamine in regions of the striatum where SNpc neurons project. PD is also characterized by formation of α-syn-containing intracellular inclusions known as Lewy bodies and Lewy neurites[4]. The detection of a combination of amyloid plaques, neurofibrillary tangles and Lewy bodies in patients, signifying overlapping pathology of AD and PD, have led to the classification of the conditions Dementia with Lewy Bodies and Parkinson's Disease Dementia; Dementia with Lewy Bodies patients demonstrate clinical dementia within 1 year of being diagnosed with PD while PD Dementia patients exhibit dementia at later stages of PD[5]. Both AD and PD are chronic illnesses in which clinical symptoms may manifest many years after pathology has commenced. In AD, the accumulation of Aβ protein in the brain primarily occurs before the appearance of the first clinical symptom[6,7]. Lewy bodies of PD also typically appear before the appearance of a classic motor symptom[8,9]. Despite linkage of both diseases to mutations in certain genes, the majority of cases are sporadic in nature.

AMYLOIDOGENIC PROTEINS

Protein folding is a fragile event that requires specific environmental conditions. Subcellular processes exist to regulate and to ensure the folding and stabilization of newly generated proteins into native conformations. Maintenance of pH, temperature and osmolarity as well as ensuring appropriate post-translational modifications of folded proteins ensure the stability required to perform the intended function. Disruption of these processes enhances the rate at which proteins adopt alternate secondary and tertiary structures, which in turn may favor the production of misfolded conformers. It is now thought that subpopulations of misfolded proteins can act as pro-aggregatory seeds that initiate a cascade of pathology in susceptible neuronal populations and may represent the catastrophic event from which many neurodegenerative pathologies progress[10]. Misfolded structures accumulate leading to their deposition into insoluble lesions that spread throughout the central nervous system over time. These lesions can appear both intracellularly and extracellularly and are implicated in the development of neurodegenerative disease states. Diseases such as AD, PD and Amyotrophic lateral sclerosis are characterized by the presence of these deposits which are thought to spread in a prion-like manner[11].

In AD and PD, supramolecular structures, amyloid

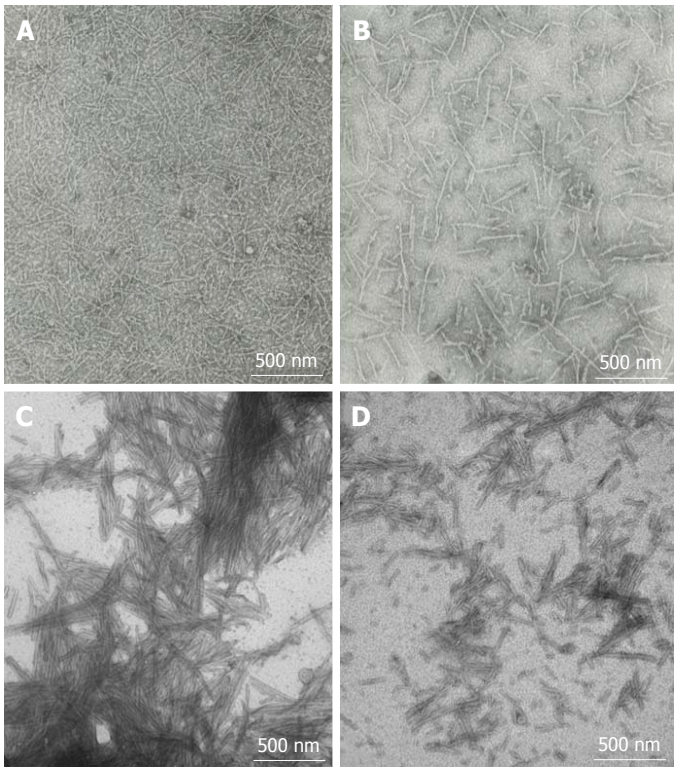

Figure 1 Fibrillar amyloid-beta peptide and alpha-synuclein. A and B: Amyloid-beta (10 mg/mL) was aggregated at room temperature for 72 h with shaking; C and D: α-synuclein (2 mg/mL) was aggregated by incubation at 37 ℃ for 144 h with shaking. Aggregation leads to formation of fibrils with varying structures. Fibrils were negatively stained with 2% phosphotungstic acid and their formation was confirmed using Transmission Electron Microscopy at 75 kV. Images display 40000 × magnification.

fibrils, are formed through the accumulation of subunits rich in β-pleated sheet secondary structure (Figure 1). The disease-specific proteins, Aβ[12] and α-syn[13] have been shown to adopt secondary structures that allow for the formation of the cross β-structure characteristic of amyloid[1]. The monomeric proteins undergo a nucleation-dependent mechanism of aggregation to form oligomers, protofibrils and other intermediate structures. Oligomers formed on the amyloid aggregation pathway will eventually reach a fibrillar state while off-pathway aggregates typically reach equilibrium and terminate aggregation in a prefibrillar state. Physicochemical properties such as hydrophobicity, secondary structure propensities, charge and aromatic interactions underlie the propensity of these proteins and peptide fragments to aggregate[14]. For both Aβ and α-syn monomers, stabilization of a partially folded pre-molten globule-like state, either by lowering of pH or increase in temperature[15,16], is believed to be the critical first step in the formation of the fibrils[17]. Fibrils are metastable structures that, once formed, may represent lower energy states than the native protein structure. The stability is strengthened by dehydration of misfolded species, a process promoted by binding of ligands that render the protein less solvent-accessible[18]. Surfaces that promote clustering of Aβ and α-syn, then, likely promote fibrillization. Several events promote protein misfolding and must be actively countered.

Aβ ranges in length from 36-43 amino acid residues and is formed by the cleavage of the single transmembrane protein amyloid precursor protein (APP). The actions of two proteolytic events, the enzyme beta (β) secretase and the complex gamma secretase, generate $A\beta_{40/42}$. These sequential cleavage events are localized to lipid bilayers where APP and the proteases are present; the plasma membrane as well as the membranes of golgi apparatus and endoplasmic reticulum have been shown to generate Aβ peptides[19-21]. As $A\beta_{42}$ is more hydrophobic and, as such, more fibrillogenic[22] than $A\beta_{40}$, processes that lead to higher ratios of $A\beta_{42}$:$A\beta_{40}$ promote the development of amyloid. Mutations in several genes encoding proteins involved in the production of Aβ, including APP, PS1 and PS2, promote this pathological ratio and are linked to familial, early-onset AD. Aβ fibrils cluster to form the extracellular cerebral amyloid plaques that are observed in AD[23].

α-Syn differs from Aβ in that it is a full length protein and is significantly larger (14 KDa *vs* 4 KDa for Aβ). It consists of 140 amino acid residues and is localized to the presynaptic terminals of neurons in most brain regions[24]. Missense mutations in the α-syn gene, *SNCA*, (A53T, A30P and E46K) are linked to autosomal dominantly-inherited early-onset PD[25-27]. Furthermore, overexpression of α-syn by multiplication of *SNCA*, showed accelerated formation of Lewy-like structures in SHSY-5Y neuroblastoma cells, of which fibrillar α-syn is the main component[28]. *In vivo* mouse models of α-syn overexpression have been developed. Mice

primarily display an increase in Lewy body formation in neuronal populations that are dictated by the nature of the transgene incorporation[29]. Models with higher levels of α-syn overexpression may also display dopaminergic cell loss in the SNpc and motor deficits associated with this loss[29]. Models of transgenic mice expressing human α-syn with the A53T mutation display α-syn aggregation and inclusion formation; however, these mice do not show any degeneration in dopaminergic populations in the SNpc[30]. Although the native functional role of α-syn is currently unknown, many studies have pointed to the involvement of α-syn in synaptic transmission by regulating neurotransmitter release[31]. Involvement in synaptic transmission has also been suggested for Aβ where it may be involved in feedback regulation of neuronal activity and modulation of glutamatergic and cholinergic inputs[32,33].

In addition to Aβ and α-syn, aggregation of tau protein is implicated in neurodegeneration seen in AD and other tauopathies. Hyperphosphorylation of tau leads to formation of intracellular insoluble neurofibrillary tangles, the presence of which correlates with the clinical manifestation of dementia in AD[6]. The colocalization of α-syn inclusions and tau neurofibrillary tangles in some neurodegenerative diseases may be due to a common mechanism. *In vivo* studies have suggested seeding of both proteopathic species occurs by specific strains of fibrillar α-syn[34]. Mouse models have also shown acceleration of neurofibrillary tangles formation by injections of fibrillar Aβ[35] and overexpression of mutant APP[36,37]. Interestingly, prior studies have also established an interaction between α-syn and Aβ. Both Aβ and α-syn have been shown to seed each other's aggregation *in vitro*[38] and a stretch of hydrophobic amino acid residues (61-95) found in the central portion of α-syn has been termed the non-Aβ component of AD amyloid (NAC) after discovery in Aβ plaques[39]. Both are thought to be natively unstructured and flexible monomers with brief but residual secondary structure[40-42]. Aβ has a central hydrophobic region (17-21) that permits strong intermolecular interactions between monomers and provides the peptides with an enhanced propensity to aggregate[40]. α-Syn contains the central hydrophobic NAC region, which forms intermolecular interactions[43]. Despite a lack of homology in amino acid sequence, several amyloidogenic proteins and peptide fragments are thought to share common structural features as oligomers[44]. This commonality is supported by the inhibition of amyloid formation of many peptides/proteins by a single compound. Inositol stereoisomers such as *scyllo*-inositol have been shown to stabilize non-toxic forms of $A\beta_{42}$[45,46] while also attenuating Aβ[47] and α-syn[48] mediated toxicity *in vitro*. Polyphenols have also been shown to inhibit fibrillogenesis through aromatic interactions[14] that prevent conversion of large oligomer into fibrils or further elongation of pre-existing fibrils[14]. Many additional classes of inhibitors have been shown to promote oligomeric forms of both Aβ and α-syn that do not effect cell viability[49].

HISTOLOGICAL SPREAD

Histological studies of tissue from AD and PD patients have identified patterns of pathology that can be classified by a staging scheme[6,8]. Despite notable inter-individual variation at early stages of AD, a three stage scheme was established following the consistent spread of amyloid deposition from basal isocortical areas to the hippocampal formation[6]. Also developed was a six stage scheme that correlates the preclinical and clinical progression of dementia with the increasing presence of NFTs[6]. Current AD diagnoses take measures of amyloid load into account along with NFT spread and the extent of dementia symptoms exhibited. These measures are compared to reference ratios that are predicted by age to diagnose individuals as having a high, intermediate or low likelihood of AD[7]. For PD, Braak *et al*[8] developed a six stage scheme for disease progression starting with the presence of intraneuronal inclusions in the dorsal (X) motor nucleus and proceeding upward through the midbrain culminating in the cortex. There is no standard diagnostic test for PD, with diagnoses typically relying on a combination of neurological examination to confirm α-syn pathology and SNpc dopaminergic neuron loss along with examination of motor symptoms. Currently there is intensive research on identifying accurate biomarkers for early detection of AD and PD[3,4,50-52].

Both AD and PD pathology follows a pattern of progression that is spatiotemporally regulated with pathological spread into interconnected regions. As pathological hallmarks of AD and PD increase within the brain, patterns of spread for each disease rarely differ in origin and direction, especially in familial forms of disease. This has lent credence to the recent hypothesis that Aβ and α-syn pathology spreads by transfer of aggregates to interconnected regions. Newly taken up aggregates, whether oligomeric or fibrillar, can then induce templating of endogenous peptide/protein and lead to elevated levels of pathological conformers that alter cellular homeostasis. This is in line with the proposal that Aβ and α-syn should be termed "prionoids"[53,54]; amyloids that exhibit prion-like transmission from cell-to-cell but have not yet proven transmissible between individuals and are not tractable by microbiological techniques[54].

MOLECULAR INTERACTIONS

The lipid bilayer of the plasma membrane exhibits dynamic features that are responsible for interaction with the extracellular environment. The composition of the plasma membrane is heterogeneous and is known to contain specialized domains that play a significant role in neuropathological mechanisms due to protein-lipid interactions. Protein-lipid interactions can modulate aggregation by recruiting proteins to increase local

concentration, favoring conversion into a partially-folded state (aggregation prone) and by modulation of the depth that the protein/peptide penetrates the membrane affecting nucleation propensity. Anionic charges on surface head-groups first attract these peptides and act as conformational catalysts for amyloidogenic fibrillization. Polyunsaturated fatty acids concomitantly enhance interactions by increasing membrane fluidity, favoring association and insertion of peptides/proteins such as Aβ/α-syn[55] into the transmembrane. Initially, Aβ[46] and α-syn[56,57] were shown to interact with phosphatidylinositols, aiding in the binding to the membrane and enhancing aggregation[57]. More recent studies highlighted the importance of lipid rafts in the aggregation pathway, specialized micro-domains that are rich in cholesterol and sphingolipids such as gangliosides[58]. Gangliosides-Aβ interaction drives aggregation into toxic oligomers[59] by promotion of α-helical secondary structure that eventually converts to β-sheets[60]. The ganglioside GM1, the most abundant ganglioside in lipid rafts, is enriched in neuronal membranes, and compared to other gangliosides, demonstrated the greatest seeding of Aβ oligomers[60]. Seeding was potentiated by clustering of the lipid moiety, which was further stabilized by increasing cholesterol concentrations in the membrane[61,62]. Surprisingly, the more recent literature argues for the protective role of sterols through inhibition of Aβ fibrillization and toxicity[63,64] (reviewed by Bucciantini)[65]. As cholesterol decreases membrane fluidity, it likely hinders insertion and nucleation of Aβ and α-syn at the surface[65]; although these effects are not sufficient to counter GM1 interactions[66]. α-Syn interacts with GM1, which promotes conversion into an oligomeric α-helix rich structure, but in contrast to Aβ, prevents α-syn from aggregation into fibrils[67]. GM1 is also involved in endocytotic internalization of monomeric α-syn into microglial cells similar to previously described internalization of bacterial toxins[68]. Together, it is apparent that membranes play an important role in the misfolding of amyloidogenic proteins.

CELL TO CELL TRANSFER

Consistent evidence of spread of AD and PD pathology to interconnected regions of the CNS suggested cell-to-cell transfer of disease-related proteins. The presence of Aβ and α-syn in extracellular fluids supports the existence of mechanisms that release protein/peptides extracellularly. *In vivo* dialysis of human CNS revealed the presence of Aβ in the CSF[69]. Furthermore, Aβ is present in blood plasma[70] and recent studies suggest that pathological forms of Aβ ($Aβ_{42}$) in the CSF have predictive value as biomarkers[51]. α-Syn monomers are also detected in extracellular biological fluids like the cerebrospinal fluid[71] and blood plasma and oligomeric forms show elevated levels in the fluids of PD patients[50]. Careful understanding of the mechanisms that underlie how or why cells react to pathological forms of Aβ and α-syn may explain this spread and identify methods to limit it.

In vitro studies have shown that small amounts of Aβ can be transported outside cells *via* fusion of peptide containing multivesicular bodies (MVBs) with the plasma membrane followed by the release of Aβ-carrying exosomes[72]. More recent evidence showed that soluble oligomeric forms of Aβ undergo cell-to-cell transfer between directly connected rat primary neurons and human SHSY-5Y cells in donor-acceptor co-culture models[73]. Transfer failed when cells didn't form direct connections, identifying the importance of connectivity and supporting observations that prion-like transfer *in vivo* occurs between interconnected neuronal networks[74-76]. Although differing oligomeric Aβ isoforms ($Aβ_{40}$/$Aβ_{11-42}$/$Aβ_{42}$/$Aβ_{3(pE)-40}$), including amino-terminally truncated pyroglutamylated Aβ (pE-Aβ) were transferred between cells, the more cytotoxic $Aβ_{42}$ was transferred to a greater extent[77]. This transfer appeared to be an early response to stress in degradation and clearance pathways and occurred more robustly with increased accumulation of non-degradable forms of the peptide[77]. Interestingly, protofibrillar/fibrillar forms of Aβ were more easily degraded and cleared by the lysosomal machinery and thus undergo less transfer than oligomeric forms[77]. Earlier studies also showed that the majority of internalized Aβ was found in compartments that compose the endocytic pathway, specifically late endosomes and lysosomes, and that uptake is dependent on endocytosis[19]. Despite these results, there remains many questions in regard to the mechanisms that underlie Aβ transfer and release into the extracellular milieu.

More progress has been accomplished in elucidating mechanisms of α-syn transfer between neurons. Several studies have shown that exocytotic/endocytotic mechanisms[78-80] as well as exosomes[81,82] are used by cells to externalize and internalize α-syn. Lee *et al*[80] showed that despite α-syn generally being localized within the cytosol, small amounts of α-syn are constitutively released extracellularly, in both native and pathological forms. Exocytosis of α-syn is *via* a non-classical vesicular transport system independent of the endoplasmic reticulum and Golgi apparatus. Prior to release, α-syn was detected in the lumen of intracellular large core dense vesicles where the intravesicular α-syn fraction was more aggregation-prone than the cytosolic fraction[80]. Another study by Desplats *et al*[79] demonstrated α-syn transfer between co-cultured neuronal populations in the absence of membrane leakage, although, transfer was more robust in the presence of neuronal degeneration. Furthermore, α-syn uptake was mitigated in dominant negative mutant acceptor cells that cannot form endocytotic vesicles[79]. Co-localization of internalized α-syn with endosomal markers was detected *in vitro*[79] and *in vivo*[78] and provided support for the reliance of cells on endocytosis for uptake of extracellular α-syn. Vesicular export of α-syn was further studied *in vitro* and demonstrated that, similar to Aβ, exosomes were responsible for the release of a portion

of the α-syn detected extracellularly[82,83]. Exosomes were found to be contain oligomeric α-syn both bound to the outer membrane and within lumenal fractions. Exosomes containing α-syn were more readily taken up by cells than lipid-free α-syn oligomers[83]. Additionally, induction of lysosomal dysfunction, using lysosomal inhibitors, potentiated the release of exosomes associated α-syn oligomers[81,83] while enhancement of autophagy diminished α-syn release[83]. Cellular conditions that lead to accumulation of α-syn, particularly pathological forms, favors extracellular release. Conversely, packaging in vesicles may explain how misfolded proteins enter naïve cells undetected.

Since the discovery of Lewy bodies in long-term fetal nigral tissue grafted into the striatum of PD patients[84-86], studies have subsequently shown α-syn transfer in rat models of PD. Angot *et al*[78] injected a viral vector into the SNpc of Sprague-Dawley rats to overexpress human α-syn in local neurons. Three weeks post-transfection, dopaminergic neurons were grafted intrastriatally and showed uptake of human α-syn one week later. Uptake was more robust in rats sacrificed at later time points (2 and 4 wk post-graft)[78]. The study also demonstrated, *in vivo*, the presence of human α-syn in endosomal compartments as well as core regions of cytoplasmic inclusions[78], supporting previous *in vitro* results that exogenous α-syn recruits endogenous protein to aggregate[87]. It has become apparent that trans-synaptic interneuronal transfer of Aβ and α-syn occurs in various conformations and structures. This identifies a relatively similar mechanism by which amyloidogenic proteins may propagate through the nervous system in AD and PD. Further investigation into whether this process is exclusive to pathological states, as in, whether this transfer is a cellular response to aberrant structures, is important for the development of therapeutic strategies targeting amyloid transfer.

MECHANISM OF TRANSFER

Transfer of proteins between cells is common however the mechanism that underlies transfer of pathologic species is not fully elucidated. Notably, certain forms of both Aβ and α-syn have been identified as stressors of the lysosomal degradation pathway. Emerging data implicate this stress in the extracellular release of aggregates. Lysosomal stress by Aβ is not fully understood but recent observations that oligomeric Aβ accumulated in lysosomes[88-90], induced abnormal lysosomal morphology and increased the size of the lysosomes suggests a similar mechanism as that reported for α-syn[77,91]. Internalized α-syn was shown to induce lysosomal rupture and it was suggested that this rupture is a mechanism that contributes to the release of α-syn[91]. Small fractions of these proteins in the cell may be diverted from the lysosomal degradation pathway to MVBs and exosomes for transport out of the cell. This diversion is likely a cellular attempt to rid itself of potentially toxic accumulations and is supported by the highly cytotoxic fractions of α-syn and Aβ located within exosomes[83]. Recent reports have shown that exosomes contain only 1.5% of the released α-syn[14] and as such, it is not the primary route for α-syn release from cells. These results point to the hijacking of toxin-induced cellular responses as a method for the further spread of amyloidogenic toxic species *via* a mechanism similar to the pore-forming toxins released by the bacterium *Staphylococcus aureus* (*S. aureus*)[92] and *Bacillus anthracis*[93]. *S. aureus* releases α-hemolysin to form heptameric pores in the membrane, and cellular survival depends on internalization of these pores. Once internalized, non-degraded fractions are sorted into MVBs to be released as exosomes, toxin-carrying exosomes[92]. Anthrax toxin is an AB toxin that relies on its two components, lethal factor and protective antigen, to infiltrate cells and compromise their function[93]. Protective antigen and lethal factor interact at plasma membranes, are endocytosed and interact with the limiting and intraluminal membranes of endosomes, delivering lethal factor to the cytosol and lumen of intraluminal vesicles. This loading partially allows lethal factor to be released within exosomes to deliver the toxin to nearby cells where it enters and rapidly attacks its targets. These mechanisms are analogous to aggregated forms of Aβ and α-syn interacting with plasma membranes, entering cells, and being loaded into exosomes for extracellular release.

Furthermore, pores formed by amyloidogenic proteins are similar in structure to the β-barrels formed by pore-forming toxins[94]. Antibodies that recognize the structure of Aβ and α-syn annular protofibrils also bind heptameric β-barrels of α-hemolysin, indicating that Aβ and α-syn protofibrils share a conformational state with this pore-forming toxin[95]. Formation of these small pores by bacterial toxins elicits endocytosis in an attempt by the cell to maintain survival. Endocytosed toxins are targeted for autophagy but as these pores are resistant to degradation, cells then exocytose vesicles as a protection method. Removal of these membrane interactions is intended to restore homeostasis and prevent cytotoxicity. Studies of Aβ transfer suggest that propagation is not secondary to cytotoxicity and instead occurs as an early response to failure of the cell's clearance machinery[77]. Endocytosis of membrane disrupting agents, mainly those that form small (approximately 2 nm in diameter) pores, occurs on the scale of hours to remove the pores from the surface[96]. The similarity by which many non-endogenous interactions manipulate a cell's natural response systems suggests that the propagation of amyloidogenic proteins is aided by lipid membrane interactions that enhance association with the endocytic pathway (Figure 2).

ANIMAL MODELS

Propagation of amyloid proteins, as measured by the presence of amyloid plaques and Lewy bodies and Lewy

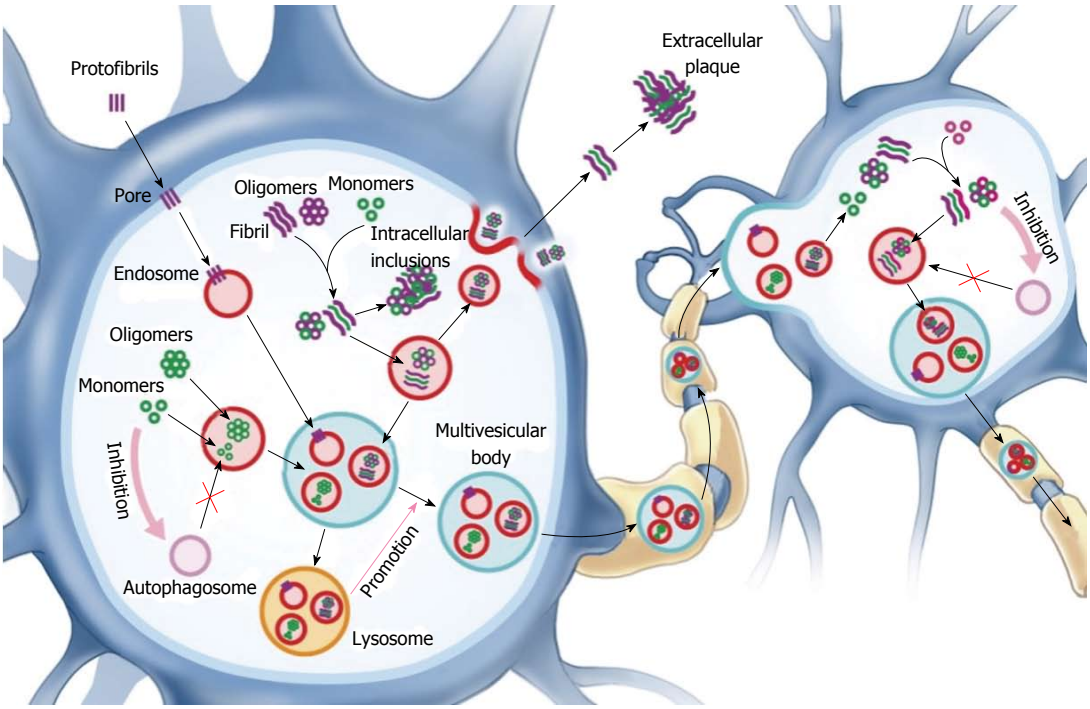

Figure 2 Several mechanisms are proposed to underlie the extracellular release of amyloidogenic proteins from neurons. Lysosomal dysfunction due to uptake and accumulation of proteopathic species that are not degraded promotes the release of misfolded species by exosomes and exocytosis. Uptake by nearby neurons likely occurs *via* an endocytic mechanism and allows proteopathic species (oligomers and fibrils) to seed the templating of endogenous protein into a misfolded conformation. Pore formation by insertion of protofibrillar amyloid-beta and alpha-synuclein prompts a cellular response to undergo endocytosis and degradation. Inhibition of autophagosome formation may contribute to amyloid deposition as well as transfer of amyloidogenic species.

Table 1 Seeding of Alzheimer's disease and Parkinson's disease-like pathology in mice

	AD	PD
Misfolded peptide/protein	Aβ peptide τ protein	α-syn protein
Pathological deposits	Intracellular (neurofibrillary tangles) Extracellular (amyloid plaques)	Intracellular (lewy bodies/lewy neurites)
Exogenous seeding of brain homogenates		
Transgenic mouse models	Human AD brain extracts into APP23[98,103,105], P21[102] and HuAPPwt[101] Rodent APP brain extracts into APP23[98,100,103], APP-PS1[98]	No reports Rodent α-syn brain extracts into M83[75,106]
Non-transgenic mice	Human AD brain extracts into Fischer 344 rats-no seeding[102]; into mice-no seeding[97] Rodent APP brain extracts into C57BL/6 J-no seeding[98]	Human Dementia with Lewy Bodies brain extracts into C57BL/6 J mice[76]
Exogenous seeding of synthetic peptides/protein		
Transgenic mouse models	Aβ40 and AβS26C into APP23[100] Aβ40/42 into APP23-no seeding[98]	Mouse α-Syn Fibrils into M83[75] Human α-Syn Fibrils into M83 and M47[108,109]
Non-transgenic mice	No reports	Mouse α-Syn Fibrils into C57BL/6 J[74,76,107,108] Human α-Syn Fibrils into C57BL/6 J[76,107,108]

Aβ: Amyloid-beta; τ: Tau; α-Syn: Alpha-synuclein; AD: Alzheimer's disease; APP: Amyloid precursor protein; PD: Parkinson's disease.

neurites, follows a stereotypical pattern[6,8] in AD and PD patients. To explain this, it is hypothesized that Aβ and α-syn transfer through neuronal networks and seed the misfolding of endogenous protein in naïve cells. Several experimental paradigms support this hypothesis, particularly, seeding and propagation of pathology in animals treated with exogenous misfolded protein (Table 1). Prion-like seeding of Aβ was demonstrated by injection of AD brain homogenates into APP-overexpressing mice leading to senile plaque formation near the injection site, 5 mo post-injection[97]. Although this provided the first evidence of Aβ seeding *in vivo*, it did not provide unequivocal evidence that Aβ was responsible for the seeding of pathology. Contamination of homogenate tissue with other seeding agents such as gangliosides and/or other molecules implicated in amyloid

aggregation may have accelerated the aggregation kinetics of endogenous Aβ. Meyer and colleagues, demonstrated the necessity for Aβ peptide after immunodepletion of Aβ from the injected extracts, protein denaturation, or Aβ immunization of APP23 mice attenuated seeding activity in the injected hosts[98]. Use of extracts from different AD mouse models, APP23 mice carrying the Swedish mutation and APP-PS1 mice carrying the Swedish and PS-1 L166P mutations, leads to differing seeding patterns in the hippocampus; APP23 extracts promote formation of primarily diffuse and filamentous lesions while APP-PS1 extracts promote formation of compact, punctate lesions[98]. Synthetic or cell-culture derived Aβ failed to demonstrate seeding altogether. The failure of synthetic Aβ aggregates generated in an *in vitro* environment to seed was attributed to Aβ peptide polymorphism and the possibility of differing strains of Aβ exhibiting different seeding potential[98]. Langer *et al*[99] characterized these proteopathic species and revealed that both fibrillar proteinase K-resistant and lower order soluble, proteinase K sensitive Aβ species from the same AD brain extract show seeding activity *in vivo*. Since different forms of Aβ found in AD brain extracts show more robust induction of pathology compared to synthetic Aβ fractions, it was proposed that endogenous Aβ species contain a structural feature capable of templating endogenous Aβ that is not generated in synthetic Aβ oligomers/protofibrils *in vitro*. Additionally, the soluble and insoluble fractions of brain extracts differ in the distribution pattern and morphology of aggregates formed within the brain; this is hypothesized to be due to differing propagation/transfer of both species *in vivo*. Stöhr *et al*[100] was able to show that fibrillized synthetic $A\beta_{40}$ and $(A\beta S26C)_2$, a mutant $A\beta_{40}$ peptide that forms covalent dimers and aggregates into neurotoxic fibrils, induced amyloid plaques that propagated throughout the brain from a single ipsilateral injection. Albeit, it was noted that synthetic fibrils were less potent than both AD brain lysates and Aβ purified from these extracts. Purified Aβ reduced seeding time by 40% and was attributed to 10-fold higher levels of pure Aβ than those in extracts, which suggested that the effect was concentration-dependent. Nonetheless, purification of Aβ from *in vivo* homogenates and recapitulation of results generated by injection of total homogenates demonstrated that Aβ alone was sufficient to generate seeding *in vivo*. More importantly, seeding by synthetic fibrils indicates that cofactors of aggregation found *in vivo* are not critical for induction of proteopathic conformations.

More recently, induction of Aβ aggregation in mouse[101] and rat[102] models that express human APP, but never develop AD pathology, was shown after injection of brain extracts from advanced AD patients. Despite never developing pathology during normal aging, the rat model (APP21-transgenic line) expresses a human *APP* gene carrying the Swedish and Indiana mutations and represents a model of AD-susceptibility. HuAPPwt mice, express the wildtype human *APP* gene, demonstrated that susceptibility to templating was not dependent on the presence of pathological mutations in Aβ. These results also suggest that murine APP retains resistance to templating, strengthening the importance of identifying conformational variants of amyloid (strains) for future propagation studies. Evidence for the existence of conformational variants of misfolded Aβ was demonstrated when brain extracts from AD patients carrying different mutations (Arctic *vs* Swedish) or with sporadic AD displayed different patterns of pathology in inoculated APP23 mice[103]. Extracts from all AD cases led to similar deposition of parenchymal Aβ plaques but differences were detected in cerebrovascular deposition. Patterns of Aβ deposition that surround blood vessels and spread into the parenchyma in mice inoculated with Arctic mutation-containing extracts; contrastingly, extracts from sporadic and Swedish mutation-carrying cases displayed a thin, compact layer of Aβ surrounding vessels, with the exception of a sporadic case displaying a combination of phenotypes[103]. These differences were maintained when homogenates from mice that had developed pathology post-inoculation were injected into younger mice, demonstrating serial transmission of seeding that was dependent on the properties of the seeds[103]. Interestingly, transgenic mice overexpressing the Arctic and Swedish mutations show the spreading cerebral amyloid angiopathy phenotype as compared to mice carrying only the Swedish mutation, which show thin, compact layers of Aβ perivascularly[104]. This suggests that the Arctic mutation promotes a dominant phenotype of cerebral amyloid angiopathy. Fritschi *et al*[105] further supported the existence of Aβ variants when it was shown that Aβ seeds derived from soluble AD brain extracts, but not Aβ CSF fractions, led to Aβ plaque deposition in APP transgenic mice. Despite Aβ levels being significantly higher in the CSF, they failed to seed pathology and this was attributed to their processing; CSF Aβ was not N-terminally truncated like Aβ peptides found in the soluble brain extract[105].

Propagation studies investigating prion-like behavior of α-syn have also demonstrated seeding properties. Mougenot *et al*[106] injected M83 mice (mouse model of PD expressing α-syn with the *A53T* mutation) with brain homogenates from older M83 mice that developed intracellular α-syn inclusions and showed that this inoculation accelerated the appearance of synuclein pathology while shortening lifespan. Luk *et al*[75] showed that young M83 mice inoculated with both lysates of aged M83 mice and synthetic α-syn fibrils developed accelerated pathology, further demonstrating that seeding of pathology was solely dependent on α-syn *in vivo*. Unilateral injections into the neocortex and striatum led to formation of inclusions containing phosphorylated endogenous α-syn in regions directly and indirectly connected to the injection sites such as the frontal cortex, thalamus, hypothalamus, substantia nigra pars compacta, locus coeruleus, cerebellar nuclei, and the spinal cord. The pathology was bilateral and phosphorylation of

α-syn at serine 129 (pSer129) was used as an indicator of pathological fibrillar α-syn. Hyperphosphorylated α-syn-containing inclusions were detected in the SNpc and were accompanied by diminished tyrosine hydroxylase staining. These observations suggested that misfolded wildtype α-syn underwent interneuronal transfer, seeded the formation of intracellular inclusions by recruiting endogenous α-syn, and initiated neuronal degeneration in dopaminergic neurons. It was also demonstrated that induction and propagation of PD-like pathology occurs in wildtype mice[74]. Pathology, as measured by inclusion formation and dopaminergic neurodegeneration, was detected as early as 30 d post-injection and was progressive becoming more severe at 90 d in both transgenic and wildtype mice[74,75]. Masuda-Suzukake *et al*[76] used human synthetic α-syn fibrils and insoluble fractions of α-syn from patients with Dementia with Lewy Bodies for injection into SNpc of wild type mice. Pathology was detected in regions connected to the injection site, starting at 90 d post-injection and showing maximal severity at 15 mo. Injection of fibrils into the SNpc led to intracellular inclusions appearing in the striatum, amygdala, stria terminalis and dentate gyrus[76]. Masuda *et al*[76] suggests that the detection of pathology in hippocampal regions, unlike mice injected into the neocortex and striatum, which do not display pathology in the hippocampus, are likely dependent on the injection site. Masuda-Suzukake *et al*[107] confirmed the importance of the injection site in determining regional transfer of pathology by injecting wildtype mice in three different regions and showing differential spread of pathology. Within one month of inoculation, α-synuclein spread from the substantia nigra to the amygdala and stria terminalis; from the striatum to the amygdala, substantia nigra and throughout the cortex; and from the entorhinal cortex to the dentate gyrus and CA3 regions of the hippocampus, the fimbria and the septal nucleus[107]. Other differences, such as rate of inclusion formation and degeneration of SNpc neurons may be linked to fibril length. Luk *et al*[75] used fibrils fragmented by sonication whereas Masuda and colleagues initially used full-length fibrils. Masuda-Suzukake *et al*[107] used fragmented fibrils in later experiments and see pathology as early as 1 mo post-injection. Shorter fragments may increase the surface area available for interaction with the cell leading to accelerated seeding process. Interestingly, in both studies, wildtype mice presented with very similar pathological distribution regardless of whether disease brain lysates or synthetic fibrils were used. This suggests that, in contrast to Aβ, α-syn fibrils displayed limited conformational heterogeneity since *in vitro* conditions are sufficient to create seeds with equivalent potency to those generated *in vivo*. Interestingly, a study by Sacino *et al*[108] questions the propagation of pathology in wildtype mice by injection of wildtype α-syn preformed fibrils. Initially, it was shown that injecting human α-syn preformed-fibrils in M83 mice hippocampi led to widespread inclusion formation throughout the CNS, including the hippocampus, striatum and cortex, three regions that typically do not develop pathology in M83 mice. However, detection of pathological α-syn in white matter tracts was absent conflicting with previous observations[74-76]. Furthermore, injection of both human and mouse α-syn fibrils into non-transgenic mice led to limited inclusion formation that was restricted to the injection sites. Inoculations were bilateral into the hippocampi and cortices of 2 mo old mice and detection of pathology at increasing time points post-injection showed decreasing immunoreactivity of pathological α-syn specific antibodies. The study attributes previously seen widespread staining to cross-reactivity of phospho-specific antibodies targeting phosphorylated α-syn (pSer129) with phosphorylated neurofilament-L (pSer473 NFL)[108]. More recently, Sacino and colleagues injected soluble (Δ71-82) and fibrillar human α-syn into M20 mice (overexpressing Human wildtype α-syn) that do not typically develop Parkinson-like pathology, as measured by presence appearance of Lewy bodies, in their lifespan[109]. By 4 mo post-injection, inoculated mice developed α-syn pathology at the injection site, the hippocampus, as well as the cortex, striatum, midbrain, and brainstem[109]. Induction of Lewy body formation using soluble species that do not fibrillize, implicates mechanisms other than templating in the disturbance of protein homeostasis. Furthermore, results suggest that overexpression of WT α-syn compromises resistance to templating and transmission since similar inoculations into non-transgenic mice failed to show spread to other regions[108]. As such, replication of studies between laboratories will be necessary to distinguish pathological seeding with α-syn.

The variability in results reported by different groups attempting to induce propagation of pathology by exogenously added seeds indicates that the mechanisms of propagation are likely complex. Sacino *et al*[108] suggests that conformational variations are a major factor explaining some of the inconsistencies seen in literature. Additionally, Sacino *et al*[108] suggests that seeding/transfer of α-syn possibly occurs as a result of the neurotoxic effects of the injected aggregates as well as the disruption of normal proteostatic mechanisms[108], neuroimmune activation and/or injury response[109]. Guo *et al*[110] reinforce the need for biochemical identification of conformational variants of amyloidogenic peptides and proteins, such as seen with Aβ[111] and α-syn[112,113]. Future studies should not only thoroughly characterize/profile the species prior to injection, but should extensively analyze changes that occur *in vivo* as a result of amyloidogenic seeds.

AD and PD exhibit many similarities in mechanisms potentially linked to their etiology. As it stands, strong evidence supports amyloidogenic structures seeding native peptides/proteins to pathologically misfold, facilitating the progression of disease. The neurotoxic effects of various aggregate subpopulations have not been characterized sufficiently to understand whether the mechanisms underlying toxicity contributes to the propagation of

pathology during disease progression. As well, oligomers, protofibrils and fibrils have been shown to display overlapping functions, such as membrane disruption, despite differences in structure. Different members of the aggregation pathway may share extensive β-sheet structure, but understanding molecular variations in the tertiary and quaternary structures may help in the understanding of their structure-function relationships and how this relationship progresses during aggregation.

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