ORIGINAL RESEARCH

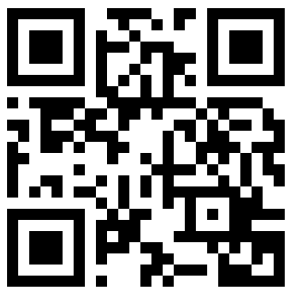# Evaluation of α-synuclein and apolipoprotein E as potential biomarkers in cerebrospinal fluid to monitor pharmacotherapeutic efficacy in dopamine dictated disease states of Parkinson's disease and schizophrenia

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Background and objective: Dopamine plays an important role in the disease pathology of Parkinson's disease and schizophrenia. These two neuropsychiatric disorders represent disease end points of the dopaminergic spectrum where Parkinson's disease represents dopamine deficit and schizophrenia represents dopamine hyperactivity in the mid-brain. Therefore, current treatment strategies aim to restore normal dopamine levels. However, during treatment patients develop adverse effects due to overshooting of physiological levels of dopamine leading to psychosis in Parkinson's disease, and extrapyramidal symptoms in schizophrenia. Absence of any laboratory tests hampers modulation of pharmacotherapy. Apolipoprotein E and α-synuclein have an important role in the neuropathology of these two diseases. The objective of this study was to evaluate cerebrospinal fluid (CSF) concentrations of apolipoprotein E and α-synuclein in patients with these two diseases so that they may serve as biomarkers to monitor therapy in Parkinson's disease and schizophrenia.

Methods: Drug-naïve Parkinson's disease patients and Parkinson's disease patients treated with dopaminergic therapy, neurological controls, schizophrenic patients treated with antidopaminergic therapy, and drug-naïve schizophrenic patients were recruited for the study and CSF was collected. Enzyme-linked immunosorbent assays were carried out to estimate the concentrations of apolipoprotein E and α-synuclein. Pathway analysis was done to establish a possible role of these two proteins in various pathways in these two dopamine dictated diseases.

Results: Apolipoprotein E and α-synuclein CSF concentrations have an inverse correlation along the entire dopaminergic clinical spectrum. Pathway analysis convincingly establishes a plausible hypothesis for their co-regulation in the pathogenesis of Parkinson's disease and schizophrenia. Each protein by itself or as a combination has encouraging sensitivity and specificity values of more than 55%.

Conclusion: The dynamic variation of these two proteins along the spectrum is ideal for them to be pursued as pharmacotherapeutic biomarkers in CSF to monitor pharmacological efficacy in Parkinson's disease and schizophrenia.

Keywords: cerebrospinal fluid, Parkinson's disease, schizophrenia, dopamine, apolipoprotein E, α-synuclein, biomarkers, treatment monitoring

Introduction

Parkinson's disease is a progressive neurodegenerative disorder diagnosed based on the presence of motor symptoms like tremor, rigidity, bradykinesia, and postural

instability.[1] The prevalence increases with age and around 1–2% of the population over the age of 60 years is affected by Parkinson's disease.[2,3] Schizophrenia is a chronic mental disorder characterized by delusions, hallucinations, disorganized speech, or behavior and impaired cognitive ability.[4] The worldwide prevalence of schizophrenia is 1%.[1,5,6] Dopamine is an important neurotransmitter produced in the substantia nigra and ventral tegmental regions of the brain and its dysfunction plays a crucial role in both Parkinson's disease and schizophrenia.[7] In Parkinson's disease, the decrease in dopamine in the substantia nigra of the mid-brain caused by selective loss of dopaminergic neurons has been implicated in disease pathology.[8] On the contrary, dopamine hyperactivity is associated with schizophrenia.[9] The treatment strategies for both the diseases exploit the difference in dopamine level from the baseline. In Parkinson's disease, clinical intervention is aimed at increasing the concentration of dopamine in mid-brain.[10] On the other hand, in schizophrenia, neuroleptics are prescribed which block dopamine receptors and decrease overall dopamine activity.[11] However, there is a strong chance that during the treatment period patients develop symptoms related to the other extreme of dopamine spectrum, wherein Parkinson's disease patients tend to develop psychosis, and schizophrenia patients tend to develop extrapyramidal side effects.[12] This clinical scenario is depicted by the patients recruited in this study (Table 1).

Currently, there is no definite parameter to monitor the treatment and assist the clinicians to modulate therapy to avoid adverse effects. In this regard, biomarkers provide a convenient tool that can be objectively evaluated and used as an indicator of biological processes and pharmacologic response in the human body.[13–15] Biomarker discovery for various diseases including neurological conditions has provided an efficient medium to monitor various disease conditions.[16–18] Despite the discovery of many protein biomarkers for diagnosis or prognosis of Parkinson's disease and schizophrenia, there is no significant clinical proteomic study to monitor drug therapy in these two diseases.[19,20] The unavailability of reliable biomarkers to monitor drug therapy in Parkinson's disease and schizophrenia provides opportunities for clinical proteomic-based biomarker discovery in this field. In the recent past, our group has been dedicatedly involved in protein biomarker discovery to assess treatment in both Parkinson's disease and schizophrenia.[21,22]

Apolipoprotein E is a ligand for low-density lipoprotein receptors and is the most important lipid transport protein

Table 1 Clinical profile of patients receiving pharmacological therapy and showing side effects

Patient ID	Age (years)	Gender	Clinical phenotype	Treatment (Generic)	Side effects
01MA	48	Female	Schizophrenia	Olanzapine, risperidone	Tremor of hands, slow walking, no proper body balance for 4 years
02RA	34	Male	Schizophrenia	Olanzapine, pramipexole, haloperidol	Impaired voice, body stiffness, fatigue, dizziness, slow body movements for 1.5 years
03MA	45	Female	Schizophrenia	Olanzapine, risperidone	Unable to write, tremor of hands, dizziness, poor balance for 3 years
04SH	56	Male	Schizophrenia	Olanzapine, haloperidol	Fatigue, daytime sleepiness, difficulty in walking, jaw stiffness for 3 years
05AM	79	Male	Parkinson's disease	Levodopa, carbidopa ropinirole, rasagiline	Depression and visual hallucinations for 2 years
06TA	56	Male	Parkinson's disease	Levodopa, carbidopa, ropinirole	Auditory hallucinations for 2 years
07LA	58	Female	Parkinson's disease	Levodopa, carbidopa, ropinirole	Claustrophobia, auditory hallucinations and delusions for 2.5 years
08SI	52	Female	Parkinson's disease	Levodopa, carbidopa, ropinirole	Visual hallucinations for 1 year
09SA	57	Male	Parkinson's disease	Levodopa, carbidopa, ropinirole	Delusion and hallucinations for 1 year

present in the brain.[23] The gene is located on the chromosome19q13.2 with three alleles e2, e3, and e4.[24] It is involved in many complex biological processes such as regulation of intracellular signaling, lipid metabolism, modulation of nitric oxide synthase-mediated cell proliferation, immune system regulation, and extracellular signaling.[25–27] Apolipoprotein E is mainly synthesized by astrocytes in the brain and is known to be associated with various neurodegenerative disorders including Alzheimer's disease and Parkinson's disease.[28,29] It is a predominant genetic risk factor for Parkinson's disease as it imparts vulnerability to early semantic memory impairment.[30] In schizophrenia, aberrant apolipoprotein E signaling and the evidence of common receptors with schizophrenia susceptibility gene, reelin, supports its role in the disease pathology.[31]

α-synuclein is encoded by the *SNCA* gene located on the chromosome 4q22.1.[32] It is abundantly expressed in the brain and is known to interact with lipids, presynaptic vesicles, and plasma membrane by lipid rafts.[33–35] It is a core component of Lewy bodies which is a clinical hallmark for Parkinson's disease.[36] In addition, point mutations in the *α-synuclein* gene are known to be a risk factor for Parkinson's disease.[37] The association between α-synuclein expression and schizophrenia has been shown by a previous study.[38] *α-synuclein* expression at the mRNA level is down regulated in lymphocytes of schizophrenic patients.[39]

The intricate association of apolipoprotein E and α-synuclein, with neuropsychiatric disorders, prompted us to study the expression of these proteins in cerebrospinal fluid (CSF) along the clinical dopaminergic spectrum, with a view to developing them as therapeutic efficacy monitoring biomarkers in Parkinson's disease and schizophrenia.

Methods
Ethics, patient selection criteria, and consent
The study was approved by the ethics committee of All India Institute of Medical Sciences, New Delhi (Reference no.: IESC/T-418/26.08.2015), and the methods followed were as per the ethical standard formulated in the Helsinki declaration. The Parkinson's disease and schizophrenia patients were screened and recruited for the study at the Department of Neurology and Department of Psychiatry, All India Institute of Medical Sciences, New Delhi, respectively. The neurological control group comprised of patients with bladder, prostate, and uterine pathologies, who were screened at urology and gynecology clinics at

the institute. These patients were recruited for surgeries under spinal anesthesia. Before enrolling the patients in the study written informed consent was obtained. Briefly, 1.5 mL of CSF was collected under sterile conditions in microfuge tubes and was centrifuged at 4°C for 5 min at 3,000 rpm. The supernatant was taken in a separate microfuge tube and stored in −80°C until further experiments. Proper care was taken while collecting the CSF samples to avoid blood contamination, and samples with even minute contamination with blood were excluded from the study.

Patient inclusion and exclusion criteria
Inclusion criteria: The Unified Parkinson's Disease Rating Scale was used for screening patients with Parkinson's disease according to which a score of zero represents no disability and a score of 199 represents complete disability.[40] For describing the progress of symptoms in Parkinson's disease patients, the Hoehn and Yahr scale was used and was graded from stage 1 to stage 5.[41] ICD 10 was used to diagnose schizophrenia.[42] Exclusion criteria: The patients with other disease or coexisting pathology or those under any therapeutic interventions were excluded from the study.

Enzyme-linked immunosorbent assay (ELISA)
The estimation of apolipoprotein E and α-synuclein in the recruited patients was done using ELISA kits (Elabscience, China). The methodology used was as per the manufacturer's instruction protocol. The concentrations of apolipoprotein E and α-synuclein were extrapolated from the standard curves.

Statistical analysis
The mean concentrations for all the five groups were plotted and a linear curve with line equations and R^2 value was obtained. Correlation coefficient and *p*-value (<0.05) for CSF apolipoprotein E and α-synuclein were obtained using Student's *t*-test. Receiver operating characteristic (ROC) curve was obtained using GraphPad Prism (GraphPad Prism software, San Diego, CA, USA) to derive cut-off levels and area-under-the-curve for apolipoprotein E and α-synuclein in Parkinson's disease and schizophrenia.

Pathway analysis
The entire information of genes corresponding to the identified proteins, their related functions were obtained from UniProt and from published literature in PubMed.

Using this information, the proteins were analyzed for their biological interactions in Parkinson's disease and schizophrenia pathways using KEGG and Schizo-Pi database.[43] For visualizing the interaction and pathways of identified proteins and its interactors Cytoscape v2.8.0 software was used.[44,45] Michigan Molecular Interactions plugin was used to collect the human gene regulatory interactome obtained from the public databases including STRING, MINT, MENTHA, and HPRD and merge the information.[46–50] From this complete network, sub-networks for Parkinson's disease and schizophrenia were obtained up to the first neighboring nodes using the plugin BiNoM v2.5. The resulting networks were merged using Cytoscape. Venn/Euler diagram was used to analyze the intersection between Parkinson's disease and schizophrenia. The corresponding interactions of the identified proteins were noted and analyzed.

Results
Clinical profile

A total of 61 CSF samples of patients with Parkinson's disease and schizophrenia were obtained from the neurology and psychiatry out-patient departments. The sample group included drug- naïve patients and those treated for Parkinson's disease and schizophrenia and neurological controls. The demographic profile of the patients recruited for the study is mentioned in Table 2. The sex distribution of the patients has fewer females as compared to males. Also, the mean age of Parkinson's disease patients is almost twice that of schizophrenia patients, and the mean age of the neurological control group is 61.4 years.

Apolipoprotein E and α-synuclein expression in CSF of Parkinson's disease and schizophrenia

ELISA was done to determine the CSF concentrations of apolipoprotein E and α-synuclein across five groups; (1) drug-naïve Parkinson's disease, (2) treated Parkinson's disease, (3) neurological controls, (4) drug-naïve schizophrenia and, (5) treated schizophrenia. The relationship between apolipoprotein E and α-synuclein concentrations and dopamine level in CSF is represented in Figure 1. It should also be noted that the concentrations of both apolipoprotein E and α-synuclein correlate with each other as indicated by a positive correlation coefficient value of 0.5 in Figure 2. ROC curve was plotted for apolipoprotein E and α-synuclein levels in CSF in Parkinson's disease,

neurological control, and schizophrenia as shown in Figure 3. Individual values corresponding to the cut-off values, sensitivity, and specificity are given in Table 3. It can be observed that when either of the two proteins, apolipoprotein E and α-synuclein, were considered for evaluation with the individual estimated cut-off values, the sensitivity and specificity values ranged from 53.3% to 79.3%.

Pathway analysis

Pathway analysis was carried out to study the interactions of these proteins in these dopamine dictated diseases. A total of 25 proteins were found to be directly interacting with apolipoprotein E and α-synuclein in Parkinson's disease, and 18 proteins were found to be directly interacting with apolipoprotein E and α-synuclein in schizophrenia, with 13 proteins being common amongst the two groups (Figure 4). The functions of these proteins and their relevance in this study have been delineated in Table 4. A hypothesis has been proposed based on the ELISA results, highlights of the pathway analysis, information from previous studies, and the same has been diagrammatically represented in Figure 5.

Discussion
Clinical profile

The incidence of Parkinson's disease and schizophrenia majorly affects the male population; therefore, the sex distribution of the patients has fewer females as compared to males.[69] Secondly, the mean age of Parkinson's disease patients is almost double that of schizophrenia patients because the incidence of Parkinson's disease increases above the age of 60 years, with only 4% of the affected being under the age of 50 years.[70] On the other hand, the

Table 2 Demographic profile of patients recruited in the study

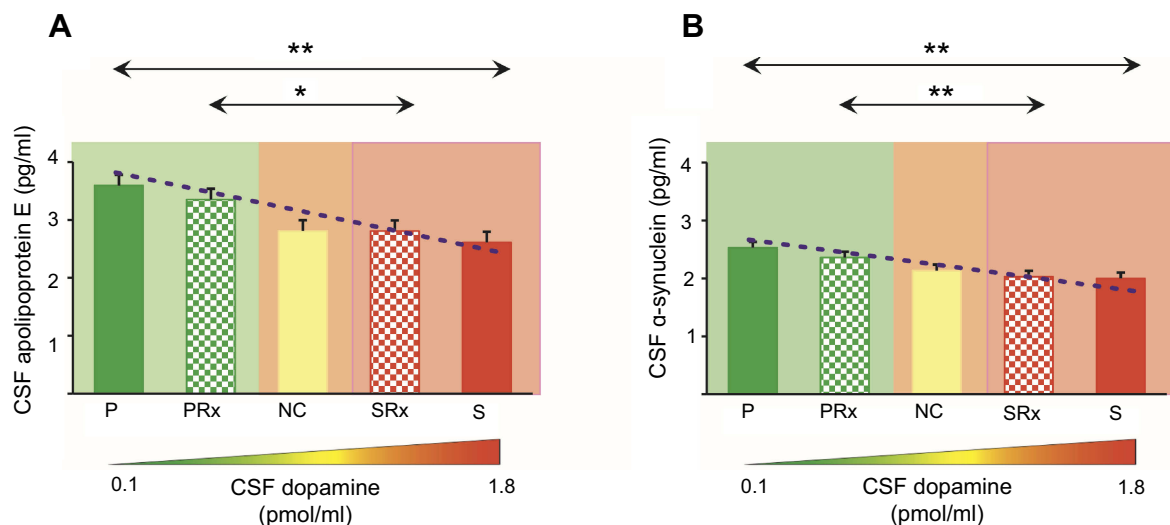| Clinical phenotype	Average age (years)	Gender		Total
		Female	Male	
Parkinson	47.25	1	7	8
Parkinson Treated	52.75	3	25	28
Neurological Control	61.4	6	9	15
Schizophrenia Treated	27	1	5	6
Schizophrenia	25	0	4	4
Total				**61**

Figure 1 ELISA for expression of (**A**) apolipoprotein E and (**B**) α-synuclein in the cerebrospinal fluid (CSF) of Parkinson's disease, neurological controls, and schizophrenia patients. Clinical phenotypes comprise of Parkinson's disease naïve (P), Parkinson's treated (PRx), neurological controls of patients with urological and gynecological diseases needing surgical intervention (NC), schizophrenia treated (SRx), and schizophrenia naïve patients (S). Mean ± Standard error of mean of the values is shown by horizontal lines. The bars represent the concentrations as the average of duplicate readings of each patient sample. Trend lines of apolipoprotein E ($y=-0.25x+3.78$; $R^2=0.91$) and α-synuclein ($y=-0.14x+2.63$; $R^2=0.94$) across the five clinical phenotypes is shown as a blue dotted line in (**A**) and (**B**), respectively. Diagrammatic representation of the dopamine concentration in cerebrospinal fluid (CSF) is shown along the x-axis. Concentrations of dopamine in the CSF across the clinical phenotypes has been estimated in Gao et al and Jensen et al.[47,48] * indicates statistical significance with $p<0.05$.
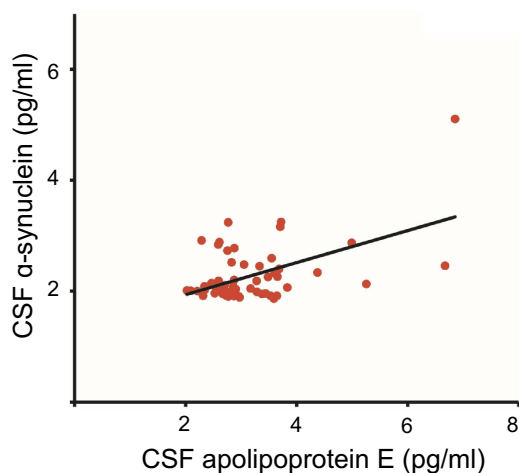

Figure 2 Correlation analysis for apolipoprotein E expression and alpha-synuclein. The correlation coefficient (R^2) has a value of 0.5 and a statistical significance (*p*) of 0.05.
Abbreviation: CSF; cerebrospinal fluid.

incidence of schizophrenia occurs between 16 and 25 years.[71] The mean age of the neurological control group is 61.4 years since the patients selected as neurological controls were those requiring surgical intervention for urological disorders which presents around this age.[72] The drug-naïve patients of Parkinson's disease and schizophrenia represent the extreme end points of dopamine spectrum, patients who have been treated represent time frames within this spectrum, and neurological controls

represent the mid-point of the spectrum that defines the physiological range of dopamine.

Correlation of apolipoprotein E and α-synuclein expression in CSF of Parkinson's disease and schizophrenia

The concentrations of both apolipoprotein E and α-synuclein inversely correlate with the dopamine concentrations. It is higher in drug-naïve Parkinson's disease patients and linearly decreases through treated Parkinson's disease, neurological controls, treated schizophrenia patients and drug-naïve schizophrenia patients. Such a relationship of apolipoprotein E and α-synuclein concentrations with the dopamine levels provides a window of opportunity to modulate treatment in a way that patients do not develop side effects. According to the ROC curve each protein, apolipoprotein E and α-synuclein, individually or as a combination has sensitivity and specificity values of around 54%. This would, therefore, mean that using these protein biomarkers for monitoring therapeutic efficacy would help to reduce the number of patients affected by drug-induced side effects in these two diseases by more than half. These results and data are very encouraging from a translational point of view in the field of neuropsychiatry. It may be noted that though the patients were phenotypes and grouped based on certain clinical criteria,
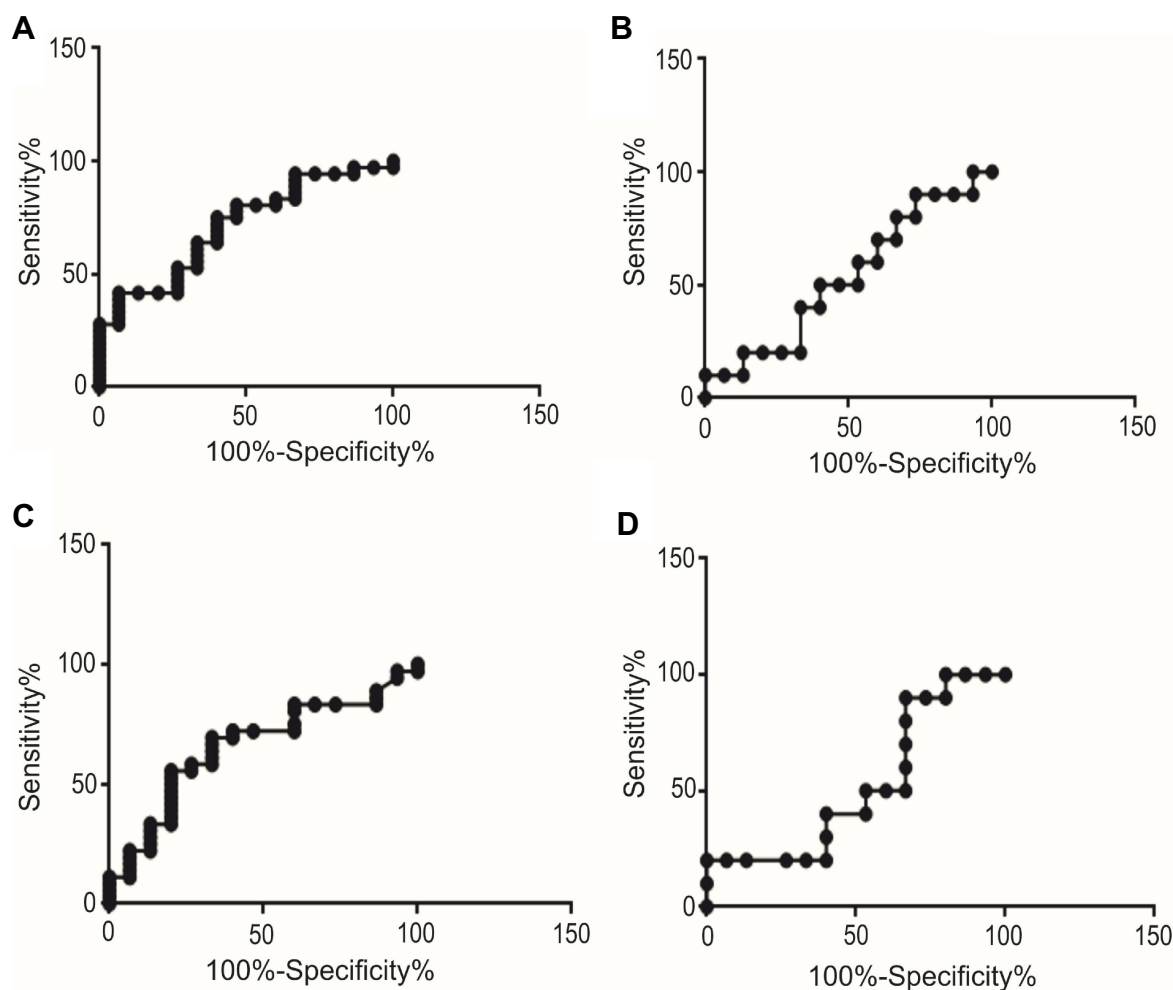
Figure 3 Receiver Operating Characteristic (ROC) for cut-offs that best differentiate disease from controls. (**A**) Apolipoprotein E for Parkinson's disease and neurological control; (**B**) Apolipoprotein E for schizophrenia and control; (**C**) α-synuclein for Parkinson's disease and control; and, (**D**) α-synuclein for schizophrenia and control.

there exists a vast heterogeneity among the patients with respect to the age of onset of the disease, stage of the disease, quality of drug intervention, duration of therapy, personal habits, and habitat. This explains the subtle variations in the concentrations of these two proteins.

Interaction-based pathway analysis involving apolipoprotein E and α-synuclein in Parkinson's disease and schizophrenia

In order to understand the role of apolipoprotein E and α-synuclein in the pathogenesis of Parkinson's disease and schizophrenia, it becomes important to study the interaction of these proteins in the dopaminergic pathway and subsequent cellular damage. Based on these interactions, pathway analysis was carried out to place the observed experimental outcomes in the right perspective. The protein interactions and cellular

mechanisms explaining the observed results are shown in Figure 5 and is discussed below.

(A) Apolipoprotein E is the most abundant apolipoprotein present in the brain and is mostly synthesized by the astrocytes.[73] It is a cholesterol transport protein which is found associated with high-density lipoprotein (HDL).[74,75] The most common apolipoprotein E receptor is low-density lipoprotein receptor-related protein (LRP) which is involved in its uptake across the plasma membrane.[25] Apolipoprotein E and LRP play a major role in cholesterol regulation which affects processes related to abnormal turnover of synaptic proteins.[76] This turnover is a response mechanism to counter the damage at synaptic terminals because of inflammation or oxidative stress, both of which are elevated in Parkinson's disease.[77]

Table 3 Pharmacotherapeutic monitoring value of Apolipoprotein E and α-synuclein in Parkinson's disease and schizophrenia

Biomarker	Cut-off values to differentiate neurological controls from the disease	Parameters	
		Sensitivity (%)	Specificity (%)
Apolipoprotein E	>3.4 pg (Parkinson's disease)	41.7	86.7
Apolipoprotein E	<2.6 pg (Schizophrenia)	50.0	60.0
α-synuclein	>2.2 pg (Parkinson's disease)	55.6	80.0
α-synuclein	<1.9 pg (Schizophrenia)	20.0	93.3
Apolipoprotein E or α-synuclein	>3.4 pg (Parkinson's disease) >2.2 pg (Parkinson's disease)	79.3	66.6
Apolipoprotein E or α-synuclein	<2.6 pg (Schizophrenia) <1.9 pg (Schizophrenia)	60.0	53.3
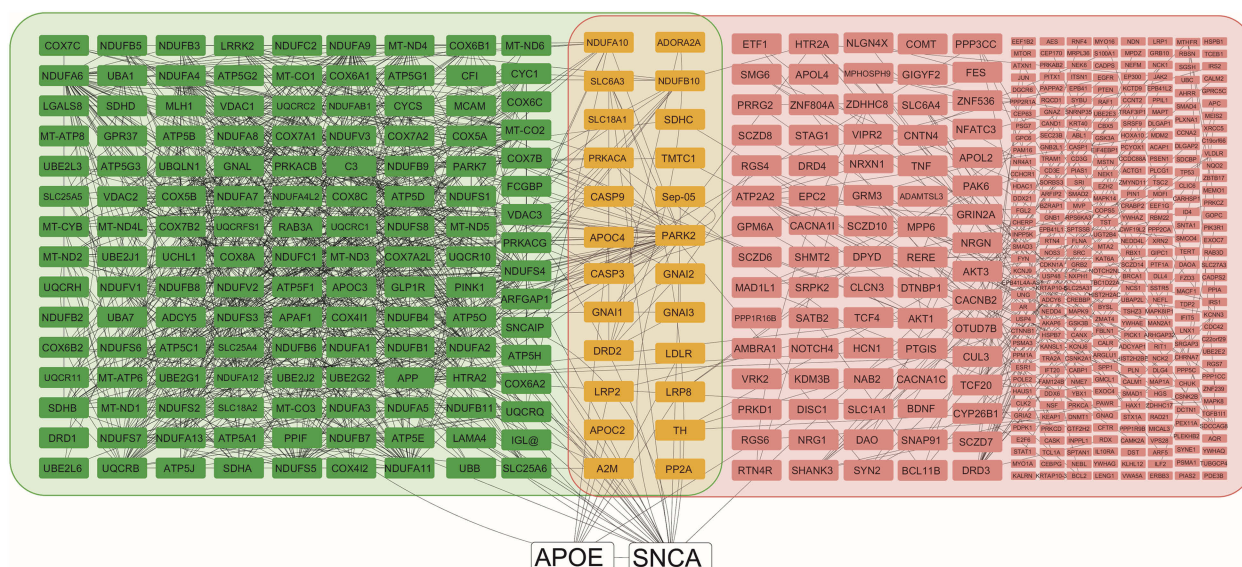
Figure 4 Pathway analysis shows apolipoprotein E and alpha-synuclein, and their respective interactions. apolipoprotein E and alpha-synuclein are shown in white nodes, interacting nodes in Parkinson's disease pathway are highlighted in green, interacting nodes in schizophrenia pathway are highlighted in pink, and nodes that common to both the groups are highlighted in yellow. Those nodes in the schizophrenia group that have four or more than four interactions are indicated in larger size boxes and those less than four are indicated by smaller boxes. All the interactions are shown by gray lines.

In a previous study by our group, the level of alpha-2-macroglobulin was found to be elevated in Parkinson's disease as compared to schizophrenia.[22] Interestingly, LRP is a common receptor for apolipoprotein E, alpha-2-macroglobulin and amyloid precursor protein.[78] This further strengthens the combined role of neuronal damage induced compensatory response involving LRP, apolipoprotein E, and α-synuclein.

(B) α-synuclein is majorly a cytosolic protein; however, its secretion into extracellular space has been established.[79] Extracellular α-synuclein has a heterogeneous population including both monomeric and oligomeric forms that interact with Toll-like receptor 2 which is involved in its uptake.[80,81] Cell surface heparan sulfate proteoglycans are also known to be involved in apolipoprotein E-mediated uptake of α-synuclein.[82] α-synuclein binds to cholesterol and modulates α-synuclein aggregation and its association with HDL.[83–85] Apolipoprotein E increases aggregation of α-synuclein which is a known component of Lewy bodies and promotes neurodegeneration.[86]

(C) α-synuclein also interacts with protein phosphatase 2A (PP2A) and increases its activity, activated PP2A is involved in dephosphorylation of tyrosine hydroxylase, which is a critical enzyme in dopamine metabolism, therefore leads to a reduction of dopamine levels.[66] α-synuclein is also known to bind to

Table 4 Interactions of apolipoprotein E and α-synuclein in the pathogenesis of Parkinson's disease and schizophrenia

| Protein	Function	Relevance in this study	References
Voltage-dependent anion channels	• Transport ATP, small metabolites across the outer mitochondrial membrane • Calcium signaling pathway • Cholesterol metabolism • Parkinson's disease	• Over-expression of α-synuclein causes the degeneration of dopaminergic neurons through and interaction with mitochondrial VDAC, which leads to mPTP activation, mitochondrial uncoupling, and cell death	51–57
NADH:ubiquinone oxi-doreductase subunit S3	• Part of the multisubunit NADH: ubiquinone oxi-doreductase (complexI) • Involved in transfers electrons from NADH to the respiratory chain • Directly involved in electron transfer and coupling	• Increases ROS generation causes oxidative stress and cellular damage • Increased ATP production or elevated complex I activity	58
Synphilin-I	• In neuronal tissue plays a role in the formation of cytoplasmic inclusions and neurodegeneration	• Synphilin-I interacts with alpha-synuclein and promote the formation of lewy body	59, 60
ADP-ribosylation factor GTPase-activating protein I	• Involved in membrane trafficking vesicle transport.	• LRRK2-dependent neurodegeneration in Parkinson	61
Protein phosphatase-2A	• Role in directing signaling toward survival or degeneration • Inhibition of tyrosine hydroxylase	• α- synuclein normally stimulates PP2A activity and reduces phosphorylation of tyrosine hydro-xylase through regulating the methylation of PP2A	62–64
Sodium-dependent dopa-mine transporter	• Terminates the action of dopamine by its high affi-nity sodium-dependent reuptake into presynaptic terminals	• Along with α-synuclein it forms complex that facilitates the membrane clustering of dopamine transporter thereby accelerating dopamine-induced apoptosis	65, 66
Microtubule-associated protein tau	• Promotes microtubule assembly and stability • Maintenance of neuronal polarity	• Along with-α synuclein it aggregate to form lewy body	67
AKT_Serine/threonine kinase-I	• TOR signaling • Regulate many processes including cell survival, growth, apoptosis	• Akt inhibition cause decrease in receptor level, hence disrupting the normal feedback mechanism of dopamine production	68
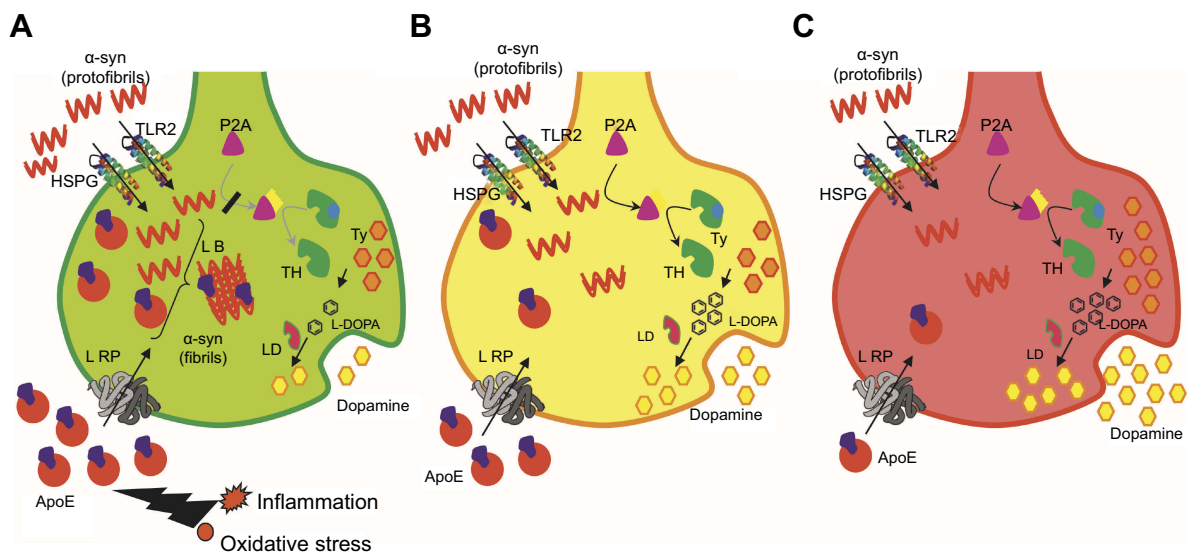
Figure 5 Diagrammatic representation of neuronal synapse depicting experimental result-based hypotheses that explain molecular events in Parkinson's disease, neurological controls, and schizophrenia.
Abbreviations: HSPG, Heparan Sulphate Proteo-Glycan; TLR2, Toll-Like Receptor 2; LRP, Low density lipid Receptor Protein; L-DOPA, Levo-Dopa; P2A, phosphatase 2A; LB, Lewy body; LD, L-decarboxylase; TH, tyrosine hydroxylase; Ty, tyrosine.

tyrosine hydroxylase gene promoter and down regulate its expression.[87] This is substantiated by the fact that there is a decreased level of tyrosine hydroxylase mRNA in Parkinson's disease.[88]

(D) The inverse relationship between apolipoprotein E and α-synuclein to the dopamine spectrum represented by clinical phenotypes including Parkinson's disease, neurological controls, and schizophrenia is very interesting. β2-adrenergic receptor agonists (β2AR) are known to mimic endogenous catecholamines like dopamine, norepinephrine, and epinephrine.[89] β2AR activation decreases histone acetylation of the α-synuclein gene and suppresses its transcription.[90] α-synuclein in association with ATP-binding cassette sub-family A member 1 (ABCA1), a plasma membrane transporter protein, is known to increase the cholesterol efflux mechanism.[91] In the brain, deficiency of ABCA1 which is required for cholesterol efflux to apolipoprotein E leads to reduced lipidation and an overall decrease of apolipoprotein E levels.[92]

(E) In addition, psychotropic drugs up-regulate the expression of apolipoprotein E by activation of sterol regulatory element-binding protein transcription factors through an intracellular oxysterol sensor, liver X-receptor.[93] Liver X-receptor has been shown to positively regulate α-synuclein expression.[94] On the contrary, levodopa-induced lipogenesis inhibition has only been shown in certain non-neurological tissues.[95]

(F) Oxidative stress is another important parameter that regulates apolipoprotein E and α-synuclein in Parkinson's disease and schizophrenia. Oxidative stress is known to be elevated in Parkinson's disease and is decreased in schizophrenia.[96] The increased formation of reactive oxygen species in dopaminergic neurons in Parkinson's disease leads to the formation of cholesterol aldehydes that enable α-synuclein aggregation, leading to a pathologic cycle.[97] Alterations in lipid metabolism have an important role in the pathogenesis of Parkinson's disease since there is direct cross-talk between lipids and α-synuclein, influencing both lipid metabolism and α-synuclein aggregation.[98,99] In the brain, apolipoprotein E is expressed by astrocytes and perivascular cells under normal conditions. However, it has also been found to be intra-neuronally expressed. Such a pattern of apolipoprotein E expression is seen when neurons are under stress conditions.[100] Increased apolipoprotein E formation under such conditions can affect neuronal survival due to the formation of a C-terminal truncated form which causes mitochondrial impairment in neurons.[101]

Conclusion

Apolipoprotein E and α-synuclein CSF concentrations have an inverse correlation along the entire dopaminergic clinical spectrum comprising of Parkinson's disease and schizophrenia. Each protein by itself or as a combination

has the ability to differentiate either of the pathological states from the physiological state. Pathway analysis supports the mechanism of coregulation in the pathogenesis of the two diseases. The dynamic variation of these two proteins along the spectrum is ideal for them to be pursued as pharmacotherapeutic biomarkers in CSF to monitor pharmacological efficacy in Parkinson's disease and schizophrenia with a reasonable accuracy. Outcome of this study will be helpful for the clinicians and patients to monitor pharmacotherapy and make informed treatment decisions in Parkinson's disease and schizophrenia.

Acknowledgments

Disclosure

The authors report no conflicts of interest in regard to this work.

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