

ALZHEIMER'S and PARKINSON'S DISEASES ARE transmissible prion/protein misfolding/conformational disorders – 2011 UPDATE

ALZHEIMER'S (AD) and PARKINSON'S (PD) -- MANY DESCRIPTIONS:
MISFOLDING PRION/PROTEIN DISEASES – CONFORMATIONAL DISORDERS
– AMYLOIDOSIS - TAUOPATHY – UPDATE 2011

Whatever you call it, the roots of Alzheimer's Disease (and Parkinson's Disease) lie in misfolding prions/proteins (prions ARE proteins)

Posted by Helene Shields, PO Box 1133, Alton, NH 03809 603-875-3842
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First posting December 2010 – “Alzheimer's is a prion disease”:
[http://www.sludgevictims.com/pathogens/ALZHEIMERS is a prion disease.pdf](http://www.sludgevictims.com/pathogens/ALZHEIMERS_is_a_prion_disease.pdf)

This March 2011 update was necessary as there were so many additional and new articles, research papers, reports, confirming the first December 2010 file.

<http://cshperspectives.cshlp.org/content/3/1/a006833.full.pdf+html>

2011;3:a006833 Cold Spring Harb Perspect Biol

David Colby & Stanley Prusiner - Released January 2011

ENLARGING SPECTRUM OF PRION-LIKE DISEASES

The discovery that prions form amyloid prompted one of us to suggest that the common neurodegenerative diseases are also caused by prions (Prusiner 1984; Prusiner 2001) despite the inability to transmit such illnesses to monkeys and apes (Goudsmit et al. 1980). (* see note below)

Brain extracts from either Alzheimer's patients or aged Tg mice expressing mutant APP injected into the brains of Tg mice expressing the amyloid precursor protein (APP) carrying the Swedish point mutation (Haass et al. 1995) accelerated the formation of Ab amyloid plaques (Meyer-Luehmann et al. 2006; Eisele et al. 2009). Brain extracts from Tg mice expressing mutant tau injected into the brains of Tg mice expressing human wt tau produced aggregates of human tau (Clavaguera et al. 2009). Similar results were found for aggregated tau protein added to cultured cells, which induced the aggregation of nascent tau (Frost et al. 2009).

These findings suggest that the tauopathies result from a prion-like process that induces hyperphosphorylation of tau followed by polymerization into filamentous aggregates. The production of hyperphosphorylated tau also appears to be stimulated by oligomers of the Ab peptide, whereas amyloid fibrils comprised of Ab are a much less efficient stimulus (Lambert et al. 1998). An expanded 44-mer polyglutamine repeat of a truncated huntingtin protein was found to stimulate aggregation of a “normal” 25 mer; this aggregated state could be maintained in cell culture over many generations, arguing for prion-like propagation of huntingtin aggregates (Ren et al. 2009).

Patients suffering from Parkinson’s disease who received fetal grafts of substantia nigral cells later showed aberrantly folded a-synuclein in Lewy bodies within the transplanted grafts, arguing that a-synuclein acted like a prion (Kordower et al. 2008; Li et al. 2008; Olanow and Prusiner 2009). Taken together, these findings argue that prion-like, self-propagating states feature in many different, if not all, neurodegenerative diseases.

A general model of propagation of mammalian prion-like conformational states should include the following considerations (Table 2): First, when the precursor protein is converted to a prion, it undergoes posttranslational modification. Such changes generally result in the acquisition of a high b-sheet content. Proteolytic cleavage features in Alzheimer’s disease (AD) (Glennner and Wong 1984; Masters et al. 1985) and hyperphosphorylation occurs in both AD and the tauopathies (Grundke-Iqbal et al. 1986; Lee et al. 1991).

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[note: Researchers injected mice with brain matter from an AD victim and the mouse developed brain lesions.(Jucker, Walker, 2010)
<http://betaamyloidcjd.blogspot.com/2010/08/transcellular-spread-of-cytosolic.html>

* - note: - In the UK, researchers injected marmosets with AD brain homogenates, and some of the animals developed AD-like amyloid plaques (Baker, Ridley, et al 2007)
<http://www.kxnet.com/getForumPost.asp?setCity=bis&ArticleId=113652>

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2010 <http://www.ucsf.edu/about/neurology-neurosurgery/research>

The opportunity for major progress is tremendous,” says [Stanley Prusiner, MD](#), director of the IND and winner of the 1997 Nobel Prize in Physiology or Medicine

for discovering an entirely new class of disease-causing proteins, called prions, that lead to neurodegeneration. Much evidence argues that prion-like proteins feature in Alzheimer's disease and Parkinson's disease.

http://projectreporter.nih.gov/project_info_description.cfm?aid=8168117&icde=6616536

National Institutes of Health - Research Project January 2011

Number:	2P20RR016476-09A1	Sub-Project ID:	7947	Contact Principal Investigator:	WHITWAM, ROSS EDWARD
Title:	PUI-RESEARCH-MUW-WHITWAM	Awardee Organization:	UNIVERSITY OF SOUTHERN MISSISSIPPI		

Category:

Biotechnology; Emerging Infectious Diseases; Genetics; Infectious Diseases; Transmissible Spongiform Encephalopathy (TSE)

Excerpt

“This project is using functional genomics to investigate the genetic interactions involved in the curing, propagation, and spontaneous formation of the [URE3] prion of *Saccharomyces cerevisiae*. [URE3] prion-mediated amyloid formation is believed to involve similar molecular mechanisms as the amyloid formation that is a feature of such mammalian protein misfolding disorders as scrapie, Creutzfeld-Jacob disease, Alzheimer's disease, Parkinson's disease, and others. Results from this project will provide insight into equivalent processes in those diseases.”

<http://www.jbc.org/content/early/2011/03/10/jbc.M110.199356.full.pdf>

AMYLOID- β 42 INTERACTS MAINLY WITH INSOLUBLE PRION PROTEIN IN THE ALZHEIMER'S BRAIN

Wen-Quan Zou, et al - Case Western

excerpts:

1/20

"These are unique neurodegenerative disorders with an infectious, sporadic or genetic etiology, and which are characterized by deposition of misfolded, pathological PrP (PrP^{Sc}) in the brain (2). **Interestingly, a recent interpretation of early and newer observations suggests that PrP C may play a role in the pathogenesis of AD (3).**"

"4). Also, pathological evidence indicates that **PrP deposits often accompany A β plaques in AD (5-7).**

2/20

"PrP^C present an exacerbated A β plaque burden (8). The circumstantial evidence of an association between PrP and A β was greatly strengthened by the recent finding that PrP was the protein that most strongly supported the binding of cells to soluble A β 42 oligomers in a screen of 225,000 murine clones (9). " **"This evidence led the authors to conclude that PrP mediates A β neurotoxicity through direct binding to toxic A β species (3).** "

" **Our study demonstrates that the interaction of huPrP and A β is found exclusively in the AD brain,** and that this interaction principally involves insoluble forms of huPrP and A β ."

5/20

" **Thus, A β is associated with huPrP aggregates only in AD patients,** suggesting that certain A β conformers typical of AD preferentially bind to PrP. Since AD brains are characterized by increases in A β 42, again, the A β conformer co-immunoprecipitated with PrP is most likely A β 42. "

6/20

"The remaining 5% A β was soluble and interacted with soluble PrP^C. The coimmunoprecipitation of PrP and A β observed in both insoluble and soluble fractions indicates that **the association between PrP and A β is specific.**"

8/20

" The remarkable hypothesis that PrP^C may act as a receptor for A β 42 and play a critical role in the pathogenesis of AD has triggered great interest in the fields of Alzheimer and prion diseases while raising high hopes for finding a cure for AD (3, 9). The evidence supporting this new hypothesis isn based on two fundamental observations: the direct binding of A β 42 to PrP and the potential pathophysiological role of PrP in A β 42 neurotoxicity in different AD models. Several groups have independently confirmed the binding of A β 42 to PrP, leaving no question as to the high specificity of this interaction (9, 12, 16). "

"Cumulatively, these findings indicate that A β 42 may bind to huPrP in the AD brain and that there are two types of A β binding sites on huPrP: the oligomer- (A β 42-specific) and monomer-specific (A β 42-nonspecific) binding sites. Furthermore, our findings carry important implications regarding the pathophysiological consequences of A β /PrP interaction."

9/20

" **Soto and coworkers recently reported that an increase in the efficiency of A β 42 aggregation in vitro was dependent on PrP^{Sc} dosage**

10/20

" Similarly, AD mice developed a strikingly higher load of cerebral amyloid plaques that appeared much faster in prion-infected than in uninfected mice (40). Thus, iPrP (the

PrPSc-like forms identified in uninfected human brains) may facilitate fibrillization of A β 42 in AD.

<http://betaamyloidcjd.blogspot.com/2010/12/alimentary-prion-infections-touch-down.html>

Thursday, December 23, 2010

Alimentary prion infections: Touch-down in the intestine, Alzheimer, Parkinson disease and TSE mad cow diseases The Center for Commentary

Alimentary prion infections: Touch-down in the intestine

Volume 5, Issue 1 January/February/March 2011 Bianca Da Costa Dias, Katarina Jovanovic and Stefan F.T. Weiss View affiliations Hide affiliations Bianca Da Costa Dias School of Molecular and Cell Biology; University of the Witwatersrand; Johannesburg, Republic of South Africa Katarina Jovanovic School of Molecular and Cell Biology; University of the Witwatersrand; Johannesburg, Republic of South Africa Stefan F.T. Weiss **Corresponding author: stefan.weiss@wits.ac.za** School of Molecular and Cell Biology; University of the Witwatersrand; Johannesburg, Republic of South Africa Consumer Freedom

Neurodegenerative diseases are caused by proteinaceous aggregates, usually consisting of misfolded proteins which are often typified by a high proportion of β -sheets, which accumulate in the Central Nervous System. **These diseases, including Morbus Alzheimer, Parkinson disease and Transmissible Spongiform Encephalopathies (TSEs) also termed prion disorders**, afflict a substantial proportion of the human population and as such the etiology and pathogenesis of these diseases has been the focus of mounting research. Although many of these diseases arise from genetic mutations or are sporadic in nature, the possible horizontal transmissibility of neurodegenerative diseases poses a great threat to population health.

In this article we discuss recent studies which suggest that the “non-transmissible” status bestowed upon Alzheimer and Parkinson diseases may need to be revised as these diseases have been successfully induced through tissue transplants.

Furthermore, we highlight the importance of investigating the “natural” mechanism of prion transmission including peroral and perenteral transmission, **proposed routes of gastrointestinal uptake and neuroinvasion of ingested infectious prion proteins**. We examine the multitude of factors which may influence oral transmissibility and discuss the zoonotic threats which Chronic Wasting Disease (CWD), Bovine Spongiform Encephalopathy (BSE) and Scrapie may pose resulting in vCJD or related disorders. In addition, we suggest that the 37 kDa/67 kDa **laminin receptor on the cell surface of enterocytes, a major cell population in the intestine, may play an**

important role in the intestinal pathophysiology of alimentary prion infections.

<http://www.landesbioscience.com/journals/prion/article/14283>

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<http://www.ncbi.nlm.nih.gov/pubmed/21045796>

[Nat Rev Neurol](#). 2010 Dec;6(12):702-6. Epub 2010 Oct 12.

Cell-to-cell transmission of non-prion protein aggregates.

[Lee SJ](#), [Desplats P](#), [Sigurdson C](#), [Tsigelny I](#), [Masliah E](#).

Department of Biomedical Science and Technology, Konkuk University, 1 Hwayangdong, Gwangjin-gu, Seoul, Korea.

Abstract

Neurodegenerative disorders such as Alzheimer disease, Parkinson disease, frontotemporal dementia, Huntington disease and Creutzfeldt-Jakob disease (CJD) are characterized by progressive accumulation of protein aggregates in selected brain regions. Protein misfolding and templated assembly into aggregates might result from an imbalance between protein synthesis, aggregation and clearance.

Although protein misfolding and aggregation occur in most neurodegenerative disorders, the concept of spreading and infectivity of aggregates in the CNS has, until now, been confined to prion diseases such as CJD and bovine spongiform encephalopathy.

Emerging evidence, however, suggests that prion-like spreading, involving secreted proteins such as amyloid- β and cytosolic proteins such as tau, huntingtin and α -synuclein, can occur in other neurodegenerative disorders. The underlying molecular mechanisms and the therapeutic implications of the new data are discussed in this article.

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<http://www.pnas.org/content/106/31/12571.full>

Is Parkinson's disease a prion disorder?

C. Warren Olanow and Stanley B. Prusiner

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Excerpts:

“Based on the available evidence, there is much to suggest that α -synuclein behaves like a prion, and that PD might be a prion disorder (Fig. 1). “

“Both α -synuclein and the cellular form of the prion protein (PrPC) adopt an α -helical-rich conformation under physiological conditions, and both are capable of refolding into a β -sheet-rich conformation that readily aggregates into oligomers and amyloid fibrils. Both of these misfolded proteins (especially the oligomers) are thought to be toxic and capable of inducing neurodegeneration. “

”Furthermore, protein aggregates formed from each of these misfolded proteins can promote the misfolding of additional wild-type protein, and in this way, act as prion conformers (5, 19, 20). “

“It is thus possible that PD is a prion disorder resulting from increased production and/or impaired clearance of proteins such as α -synuclein, leading to misfolding and the formation of toxic oligomers, aggregates, and cell death.”

”Further, it is possible that α -synuclein is a prion protein that can self-aggregate and be transmitted to unaffected cells, thus extending the disease process.”

<http://www.ncbi.nlm.nih.gov/pubmed/20846907>

[Lancet Neurol.](#) 2010 Nov;9(11):1128-38. Epub 2010 Sep 16.

Are synucleinopathies prion-like disorders?

[Angot E](#), [Steiner JA](#), [Hansen C](#), [Li JY](#), [Brundin P](#).

Wallenberg Neuroscience Centre, Lund University, Sweden.

Abstract

A shared neuropathological feature of idiopathic Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy is the development of intracellular aggregates of α -synuclein that gradually engage increasing parts of the nervous system.

The pathogenetic mechanisms underlying these neurodegenerative disorders, however, are unknown. **Several studies have highlighted similarities between classic**

prion diseases and these neurological proteinopathies. Specifically, identification of Lewy bodies in fetal mesencephalic neurons transplanted in patients with Parkinson's disease raised the hypothesis that α -synuclein, the main component of Lewy bodies, could be transmitted from the host brain to a graft of healthy neurons.

These results and others have led to the hypothesis that a prion-like mechanism might underlie progression of synucleinopathy within the nervous system. We review experimental findings showing that misfolded α -synuclein can transfer between cells and, once transferred into a new cell, can act as a seed that recruits endogenous α -synuclein, leading to formation of larger aggregates. This model suggests that strategies aimed at prevention of cell-to-cell transfer of α -synuclein could retard progression of symptoms in Parkinson's disease and other synucleinopathies.

http://cordis.europa.eu/fetch?CALLER=EN_NEWS_FP7&ACTION=D&DOC=1&CAT=NEWS&QUERY=012df0e850ce:e7f9:5b6555b6&RCN=33037

Researchers reveal how sick proteins move between cells in Parkinson's sufferers

[Date: 2011-02-04]

An EU-funded study has revealed that the sick proteins that are a key element of Parkinson's disease move between cells slowly, eventually triggering the destruction of the new host cell. They believe the discovery could lead to new therapeutic strategies for neurodegenerative diseases. Presented in the Journal of Clinical Investigation, the research was funded in part by the PROSPECTS ('Proteomics specification in time and space') project, which has received almost EUR 12 million under the EU's Seventh Framework Programme (FP7).

The mis-folding of abnormal proteins in brain cells is a key element in the development of Parkinson's disease. The study showed that the damaged alpha-synuclein proteins can spread in a 'prion-like' manner, an infection model previously described for diseases such as Bovine spongiform encephalopathy (BSE), otherwise known as mad cow disease.

'This is a significant step forward in our understanding of the potential role of cell-to-cell transfer of alpha-synuclein in Parkinson's disease pathogenesis and we are very excited about the findings,' says Professor Patrik Brundin from Lund University in Sweden, who led a team of researchers from Denmark, France and Portugal.

<http://blogs.angelo.edu/headlines/2011/03/16/renowned-biomedical-researcher-headlines-asu-science-lectureship/>

PARKINSON'S – HUNTINGTON'S – PROTEIN MISFOLDING DISEASES

Press Award
Mar 16 2011



[Renowned Biomedical Researcher Headlines ASU Science Lectureship](#)

Dr. Susan L. Lindquist, a member of the Whitehead Institute for Biomedical Research,. . .

"Prior to the public lecture, Dr. Lindquist will also meet with ASU students to discuss "Lamarck Redux: **Prions**, Hsp90, and the Inheritance of Environmentally Acquired Traits" at 2 p.m. Both lectures are open free to the public. "

A pioneer in the study of protein folding, Dr. Lindquist established that the state of protein equilibrium has profound and completely unexpected effects on normal biology and disease. Her work also established the molecular basis for protein-based mechanisms of inheritance. **More recently, she has built tractable genetic models of complex protein misfolding diseases, including Parkinson's and Huntington's, which are providing new insights on the underlying causes of these ailments.**

http://www.eurekalert.org/pub_releases/2011-02/su-hdp021811.php Feb. 18, 2011

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How disordered proteins spread from cell to cell, potentially spreading disease

Excerpts”

“One bad apple is all it takes to spoil the barrel. And one misfolded protein may be all that's necessary to corrupt other proteins, forming large aggregations linked to several incurable neurodegenerative diseases such as Huntington's, Parkinson's and Alzheimer's.”

“Stanford biology Professor Ron Kopito has shown that the mutant, misfolded protein responsible for Huntington's disease can move from cell to cell, recruiting normal proteins and forming aggregations in each cell it visits.”

“But it's clear what happens when these mechanisms stop working – misfolded proteins start recruiting normal versions of the same protein and form large aggregations. The presence of these aggregations in neurons has been closely linked with several neurodegenerative diseases.”

“The ability of these proteins to move from one cell to another could explain the way Huntington's disease spreads through the brain after starting in a specific region. Similar mechanisms may be involved in the progress of Parkinson's and Alzheimer's through the brain.”

“Kopito found that the mutant protein associated with Huntington's disease can leave one cell and enter another one, stirring up trouble in each new cell as it progresses down the line. The spread of the misfolded protein may explain **how Huntington's** progresses through the brain.

This disease, like Parkinson's and Alzheimer's, starts in one area of the brain and spreads to the rest of it. This is also similar to the spread of prions, the self-replicating proteins implicated in mad cow disease and, in humans, Creutzfeldt-Jakob disease. As the misfolded protein reaches more parts of the brain, it could be responsible for the progressive worsening of these diseases. “

<http://www.news9.com/Global/story.asp?S=12091636&clienttype=printable>

Prion disease in mice may help advance Alzheimer's research

FRIDAY, March 5, 2010 (HealthDay News) -- U.S. researchers have discovered a new form of prion disease that doesn't act like related illnesses, such as mad cow disease, brain but instead causes damage similar to that produced by Alzheimer's disease.

the disease does seem to be similar to two newly reported cases of the prion disease known as Gerstmann-Straussler-Scheinker syndrome, according to the researchers from the U.S. National Institute of Allergy and Infectious Diseases (NIAID).

Prion diseases cause a number of unusual killer diseases, including mad cow disease, sporadic Creutzfeldt-Jakob disease and a kind of fatal insomnia, according to background information in a news release from NIAID.

In the new study, the researchers examined mice that were genetically engineered to process prion proteins in a unique way. Then they exposed them to a prion disease known as scrapie.

The mice didn't develop holes in the brain like those typically caused by prion diseases. Instead, they developed plaques that resembled a form of human Alzheimer's disease.

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<http://www.ncbi.nlm.nih.gov/pubmed/20698011>

Prion protein in Alzheimer's pathogenesis: a hot and controversial issue Iryna Benilova 1,2 Bart De Strooper

1,2

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Keywords: Amyloid-beta (Ab); oligomers; Ab receptor; prion protein (PrP); neurotoxicity

See related article in EMBO Mol Med (Calella AM et al (2010) EMBO Mol Med 2: 306–314)

The role for cellular prion protein PrP in b-amyloid (Ab) oligomer-induced synaptic impairment is a topic of great interest and some controversy. In this issue of EMBO Molecular Medicine Aguzzi and co-workers explore the contribution of PrP to deficient long term potentiation (LTP) and soluble Ab levels in an Alzheimer's disease mouse model and show that the role of prions in Ab related toxicity is far from 'black and white' suggesting complex interpretations of the data available thus far.

... snip ...

One of the most spectacular candidates in the series of candidate receptors for these toxic assemblies is, without doubt, the prion protein (Lauren et al, 2009).

Indeed, an interaction between Ab and the prion protein suggests a potential common molecular substratum for the neurotoxicity seen in both diseases. Prion protein (PrP) was identified in an unbiased screening for receptors that could bind Ab42 oligomers prepared according to a particular

protocol to yield Ab-derived diffusible ligands (ADDL) (Lambert et al, 1998). Such ADDLs are neurotoxic, interfere with LTP and are considered a more or less stable form

<http://www.alscience.it/?view=cnews103#c103>

Focus on protein aggregation: is ALS a prion-like disease?

Epidemiological pattern, focal onset, asymmetrically and orderly spreading of neurodegeneration in ALS and selective vulnerability of MNs inspired in the past decades hypothesis of involvement of an infective agent in a disease pathogenesis, but, despite numerous studies aimed at identification of the ALS-related pathogen, the culprit has so far remained elusive. The idea that the pathogenesis of ALS as well of some other common or rare neurological disorders such as Alzheimer's, Parkinson's or Huntington Disease, might involve mechanisms resembling prion diseases, recently gained new attention due to a description of prion-like properties of major disease-related proteins, including amyloid β and Tau in AD, α -syn in PD, Huntington in HD, and SOD1 in ALS.

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http://www.sciencenews.org/view/generic/id/69982/title/News_in_Brief_Body_%2B_Brain
February 2011

ALS on the move

Harmful proteins responsible for progressive, fatal ALS, or Lou Gehrig's disease, can quickly hop from nerve cell to nerve cell, researchers from the Medical Research Council Laboratory of Molecular Biology in Cambridge report online February 14 in the *Proceedings of the National Academy of Sciences*. The team watched as misfolded clumps of the protein, called superoxide dismutase-1, made their way into nerve cells and induced normally harmless versions of the protein to clump up. These misfolded groups then popped out of the infected cell and into neighboring cells. This cycle is similar to how prions — the infectious proteins behind brain-wasting conditions such as Creutzfeldt-Jakob disease — spread through the brain. —Laura Sanders

Prion-like propagation of mutant superoxide dismutase-1 misfolding in neuronal cells.

Proc Natl Acad Sci U S A. 2011 Feb 14. [Epub ahead of print]

Münch C, O'Brien J, Bertolotti A.

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Abstract

Deposition of proteins of aberrant conformation is the hallmark of many neurodegenerative diseases. **Misfolding of the normally globular mutant superoxide dismutase-1 (SOD1) is a central, early, but poorly understood event in the pathogenic cascade leading to familial forms of ALS.**

“In many neurodegenerative diseases, such as Alzheimer’s disease, Parkinson disease, prion disorders, ALS, and polyglutamine (polyQ) expansion disorder, **a specific protein converts from an otherwise soluble and benign conformation into a misfolded one that assembles into an amyloid or amyloid-like state, defined by a common cross- β structure** (1, 2). Aggregation has been well studied in vitro using diverse disease-associated recombinant proteins and proceeds by nucleated growth polymerization, a process that can be accelerated by addition of preformed aggregates or seeds (2).

It is not clear whether this phenomenon occurs naturally in neurodegenerative diseases. In the case of prion disorders, the conformational switch of the cellular protein PrP^c into the misfolded conformation PrP^{sc} is unique because it confers infectious properties to the protein.

PrP^{sc} infects cells and propagates misfolding by converting PrP^c into the pathogenic conformation (3). Curiously, recent studies have indicated that aggregation of A β 42, polyQ peptides, tau, and α -synuclein can be induced experimentally by exogenous seeds (4–10). “

Here we report that aggregates composed of an ALS-causing SOD1 mutant penetrate inside cells by macropinocytosis and rapidly exit the macropinocytic compartment to nucleate aggregation of the cytosolic, otherwise soluble, mutant SOD1 protein.

Once initiated, mutant SOD1 aggregation is self-perpetuating.

Mutant SOD1 aggregates transfer from cell to cell with remarkable efficiency, a process that does not require contacts between cells but depends on the extracellular release of aggregates.

This study reveals that SOD1 aggregates, propagate in a prion-like manner

in neuronal cells and sheds light on the mechanisms underlying aggregate uptake and cell-to-cell transfer.

PMID: 21321227 [PubMed - as supplied by publisher]
<http://www.ncbi.nlm.nih.gov/pubmed/21321227>

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<http://www.ncbi.nlm.nih.gov/pubmed/20029438>

[Nat Rev Neurosci.](#) 2010 Mar;11(3):155-9. Epub 2009 Dec 23.

Prion-like mechanisms in neurodegenerative diseases.

[Frost B](#), [Diamond MI](#).

Department of Pathology, Harvard Medical School, 77 Avenue Louis Pasteur, Boston, MA 02115, USA.

Abstract

Many non-infectious neurodegenerative diseases are associated with the accumulation of fibrillar proteins. These diseases all exhibit features that are reminiscent of those of prionopathies, including phenotypic diversity and the propagation of pathology.

Furthermore, emerging studies of amyloid-beta, alpha-synuclein and tau--proteins implicated in common neurodegenerative diseases--suggest that they share key biophysical and biochemical characteristics with prions. Propagation of protein misfolding in these diseases may therefore occur through mechanisms similar to those that underlie prion pathogenesis. If this hypothesis is verified in vivo, it will suggest new therapeutic strategies to block propagation of protein misfolding throughout the brain.

PMID: 20029438 [PubMed - indexed for MEDLINE]

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[Cushman et al, 2010](#) Prion-like disorders: blurring the divide between transmissibility and infectivity

[J Cell Sci.](#) 2010 Apr 15;123(Pt 8):1191-201.

<http://www.ncbi.nlm.nih.gov/pubmed/20356930>

Prion-like disorders: blurring the divide between transmissibility and infectivity.

[Cushman M](#), [Johnson BS](#), [King OD](#), [Gitler AD](#), [Shorter J](#).

Department of Biochemistry and Biophysics, University of Pennsylvania School of Medicine, 805b Stellar-Chance Laboratories, 422 Curie Boulevard, Philadelphia, PA 19104, USA.

Abstract

Prions are proteins that access self-templating amyloid forms, which confer phenotypic changes that can spread from individual to individual within or between species. These infectious phenotypes can be beneficial, as with yeast prions, or deleterious, as with mammalian prions that transmit spongiform encephalopathies. However, the ability to form self-templating amyloid is not unique to prion proteins. Diverse polypeptides that tend to populate intrinsically unfolded states also form self-templating amyloid conformers that are associated with devastating neurodegenerative disorders. Moreover, two RNA-binding proteins, FUS and TDP-43, which form cytoplasmic aggregates in amyotrophic lateral sclerosis, harbor a 'prion domain' similar to those found in several yeast prion proteins. **Can these proteins and the neurodegenerative diseases to which they are linked become 'infectious' too? Here, we highlight advances that define the transmissibility of amyloid forms connected with Alzheimer's disease, Parkinson's disease and Huntington's disease. Collectively, these findings suggest that amyloid conformers can spread from cell to cell within the brains of afflicted individuals, thereby spreading the specific neurodegenerative phenotypes distinctive to the protein being converted to amyloid. Importantly, this transmissibility mandates a re-evaluation of emerging neuronal graft and stem-cell therapies.** In this Commentary, we suggest how these treatments might be optimized to overcome the transmissible conformers that confer neurodegeneration.

PMID: 20356930 [PubMed - indexed for MEDLINE] PMCID: PMC2848109 [Available on 2011/4/15]

What is " SOD 1" = "The genetic change alters an abundant enzyme within cells called copper-zinc superoxide dismutase (cu-zn superoxide dismutase, now called commonly SOD1). This enzyme serves to keep cells safe from metabolic waste that can do damage if not rendered harmless."

<http://www.alsa.org/research/about-als-research/sod1.html>

[Zhang et al, 2009](#) Abberant cleavage of TDP-43 enhances aggregation and cellular toxicity <http://www.ncbi.nlm.nih.gov/pubmed/19383787>

[Deng et al., 2010](#) FUS-immunoreactive inclusions are a common feature in sporadic and non-SOD1 familial amyotrophic lateral sclerosis

<http://www.ncbi.nlm.nih.gov/pubmed/20517935>

[Johnson et al, 2008](#) A yeast TDP-43 proteinopathy model: Exploring the molecular determinants of TDP-43 aggregation and cellular toxicity

Udan & Baloh, 2011 Implications of the prion-related Q/N domains in TDP-43 and FUS. [ALS & FTLD]<http://www.ncbi.nlm.nih.gov/pubmed/21135580>

Prion. 2011 Jan 1;5(1). [Epub ahead of print]

Implications of the prion-related Q/N domains in TDP-43 and FUS.

[Udan M](#), [Baloh RH](#).

Abstract

Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) are clinically overlapping neurodegenerative disorders whose pathophysiology remains incompletely understood. ALS initiates in a discrete location, and typically progresses in a pattern consistent with spread of the degenerative process to involve neighboring regions of the motor system, although the basis of the apparent "spread" remains elusive. Recently mutations in two RNA binding proteins, TDP-43 and FUS, were identified in patients with familial ALS.

In addition to being involved in numerous events related to RNA metabolism, each forms aggregates in neurons in ALS and FTLD. Recent evidence also indicates that both TDP-43 and FUS contain prion-related domains rich in glutamine (Q) and asparagine (N) residues, and in the case of TDP-43 this is the location of most disease causing mutations. This review discusses the potential relevance of the prion-related domains in TDP-43 and FUS in normal physiology, pathologic aggregation, and disease progression in ALS and FTLD.

PMID: 21135580 [PubMed - as supplied by publisher]

[Yates et al, 2010](#) Motor neuron disease: Misfolded wild-type SOD1 may link sporadic and familial ALS. <http://www.ncbi.nlm.nih.gov/pubmed/21188749>

[Bosco et al, 2010](#) Wild-type and mutant SOD1 share an aberrant conformation and a common pathogenic pathway in ALS.

<http://www.ncbi.nlm.nih.gov/pubmed/20953194>

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<http://www.kxnet.com/getForumPost.asp?setCity=bis&ArticleId=113652>

Posted By Terry S. Singeltary Sr.

Posted On: Apr 26 2007 9:31AM

Subject: TRANSMISSION OF B-amyloidosis TO PRIMATES strengthens the parallels between Alzheimer's disease and CJD - IN CONFIDENCE

Date: April 25, 2007 at 6:25 pm PST

IN CONFIDENCE

TRANSMISSION OF ALZHEIMER-TYPE PLAQUES TO PRIMATES

H F BAKER, R M RIDLEY, L W DUCHEN, T J CROW, C J BRUTON

As part of a larger series of experiments designed to assess the transmissibility of various neurodegenerative disease including the spongiform encephalopathies (eg Creutzfeldt-Jakob disease and BSE we injected several marmosets (*Callithrix Jacchus*) intracerebrally with brain homogenate from :

- 1) a 56 year old patient with severe Alzheimer's disease - B - amyloid plaques and conophilic angiopathy (CAA) and neurofibrillary tangles; and
- 2) a 62 year old patient with Gerstmann-Straussler disease, a spongiform encephalopathy with PrP Plaques and, in this case, B-amyloid plaques and CAA.

These monkeys were killed more than 6 years after inoculation and their brains were found to contain moderate numbers of B-amyloid plaques and CAA but NO neurofibrillary tangles NO PrP. The brains of more than 12 monkeys killed at an older age did not contain these changes. B-amyloid was not found in the brains of monkeys injected with brain material which did not contain B-amyloid. **These results suggest that B-amyloidosis is a transmissible process resembling the transmissibility of PrP amyloidosis in transmissible dementia and strengthens the parallels between Alzheimer's disease and Creutzfeldt-Jakob disease.**

.....

The article, **"Anchorless Prion Protein Results in Infectious Amyloid Disease without Clinical Scrapie"** by Bruce Chesebro, Matthew Trifilo, Richard Race, Kimberly Meade-White, Chao Teng, Rachel LaCasse, Lynne Raymond, Cynthia Favara, Gerald Baron, Suzette Priola, Byron Caughey, Eliezer Masliah, and Michael Oldstone appears in the June 3, 2005 issue of the journal *Science*. See <http://www.sciencemag.org>.

Send comments to: jasonb@scripps.edu

<http://www.sciencemag.org/content/308/5727/1435.abstract>

Scripps Research Scientists Convert Mad-Cow-Like Prion Disease into Something Similar to Alzheimer's

By Jason Socrates Bardi

A group of researchers led by scientists at The Scripps Research Institute have done something unusual with prion proteins, which are the underlying cause of mad cow disease, scrapie in sheep, chronic wasting disease in deer, and variant Creutzfeldt-Jakob Disease in humans. Prion proteins cause these diseases as a misfolded form of the protein accumulates in the brain and interferes with nervous system functions.

In the latest issue of the journal *Science*, the researchers describe the effect of removing a stretch of amino acids at the COOH end of the protein—called the glycoposphoinositol (GPI) anchor. This GPI anchor is essential for anchoring the prion protein into the membranes of cells, where it is believed this host prion protein interacts with the abnormal disease-producing isoform to yield more and more of the disease associated prion protein. Suspecting that this anchor may also be essential to the pathogenesis of prion diseases, the scientists removed it and looked at the effect of the removal on prion disease pathogenesis.

By taking off this anchor, the researchers showed that the prion protein still folded but was no longer able to attach in normal amounts onto the surface of cells. They then looked at the effect of the anchorless prions on the disease *in vivo*, and they found evidence that the GPI anchor plays a role in prion disease pathogenesis. Transgenic mice that express a form of prion protein without the GPI anchor no longer show the normal characteristics of clinical prion disease when they are infected with infectious prions. That is, they do not develop a progressive neurodegenerative disease fatal by 160 to 170 days after infection. Unexpectedly, these mice lived past 600 days with minimal symptoms.

They found that the anchorless prions instead induced a disease that mimicked Alzheimer's—deposits of amyloid fibrils associated with dystrophic neurons were observed. However unlike Alzheimer's, in which a different protein called "Ab" is deposited, there were heavy deposits of the disease-associated prion protein.

"You can convert the normal form of the prion protein and not get classical [prion] disease," says Michael B. A. Oldstone, a professor in the Departments of Neuropharmacology and Infectology at The Scripps Research Institute. **"The protein doesn't cause disease, but it is converted into an amyloid form that gets deposited in a manner similar to Alzheimer's."**

What is the significance of converting prion plaques into amyloid plaques? The results have implications for understanding both diseases, says Oldstone.

"The association with the abnormal prion protein raises the possibility that a similar mutation in human prion gene may lead, in certain instances, to a corresponding amyloid-like disease in humans," Oldstone adds. He and his colleagues are vigorously evaluating this possibility with tissues from a variety of human diseases.

“Significantly, the anchorless prion proteins had a dramatic reduction in their ability to cause prion disease *in vivo*. Transgenic mice that express a form of prion protein without the GPI anchor no longer show the normal characteristics of prion disease when they are infected with infectious prions. In the mice with the GPI anchor removed, inoculation with tissue containing the misfolded "scrapie" form of prions failed to induce the usual clinical manifestations of prion disease, even after 600 days. By comparison, inoculation of normal mice with the same scrapie samples caused disease in 160 to 180 days.

"Intriguingly, the anchorless prions still deposited in the brain, but in different locations as well as being converted into a different type of protein deposit—one that was more characteristic of the deposits seen in amyloid diseases like Alzheimer's. In fact, the brain tissue of the transgenic mice showed similarity to the brain tissue of mice that are used to model Alzheimer's disease. Interestingly the tissue was infectious on transfer into recipient mice."

.....
DR. STANLEY PRUSINER

http://ebookey.org/Prion-Biology-and-Diseases-by-Stanley-B-Prusiner_100538.html

Although prion diseases in humans have thus far been rare, they are among the best-characterized "conformational diseases." Hence, **the mechanisms of and potential therapeutic approaches to prion diseases may be relevant to more common conformational disorders, such as Alzheimer's disease (in which the amyloid (beta)-peptide is deposited as amyloid), Parkinson's disease (involving (alpha)-synuclein deposition in Lewy bodies), and the many neurodegenerative conditions associated with increased CAG repeats (e.g., Huntington's disease).**

.....
<http://www.ncbi.nlm.nih.gov/pubmed/20021333>

[Cent Nerv Syst Agents Med Chem](#). 2009 Mar;9(1):2-11.

Creutzfeldt-jakob, Parkinson, lewy body dementia and Alzheimer diseases: from diagnosis to therapy.

[Dupiereux I](#), [Zorzi W](#), [Quadrio I](#), [Perret-Liaudet A](#), [Kovacs GG](#), [Heinen E](#), [Elmoualij B](#).

Department of Human Histology-CRPP, University of Liège, Sart Tilman, Belgium.

Abstract

Depositions of proteins in form of amyloid and non-amyloid plaques are common pathogenic signs of more than 20 degenerative diseases affecting the central nervous system or a variety of peripheral tissues. Among the neuropathological conditions, Alzheimer's, Parkinson's and the prion diseases, such as Creutzfeldt-Jakob disease (CJD), present ambiguities as regarding their differential diagnosis.

At present, their diagnosis must be confirmed by post-mortem examination of the brain. Currently the ante-mortem diagnosis is still based on the integration of multiple data (clinical, paraclinical and biological analyses) because no unique marker exists for such diseases. The detection of specific biomarkers would be useful to develop a differential diagnostic, distinguishing not only different neurodegenerative diseases but also the disease from the non-pathological effects of aging. Several neurodegenerative biomarkers are present at very low levels during the early stages of the disease development and their ultra-low detection is needed for early diagnosis, which should permit more effective therapeutic interventions, before the disease concerned can progress to a stage where considerable damage to the brain has already occurred.

In the case of prion diseases, there are concerns regarding not only patient care, but the wider community too, with regard to the risk of transmission of prions, especially during blood transfusion, for which, four cases of variant CJD infection associated with transfusion of non-leukocyte-depleted blood components have been confirmed. Therefore the development of techniques with high sensitivity and specificity represent the major challenge in the field of the protein misfolding diseases. In this paper we review the current analytical and/or biochemical diagnostic technologies used mainly in prion, but also in Alzheimer and Parkinson diseases and emphasizing work on the protein detection as a surrogate and specific biomarker in the body fluid of patients (urine, CSF and blood). This review highlights the urgency of the development of early and sensitive diagnostics in terms of therapeutic challenge.

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<http://www.bath.ac.uk/bio-sci/research/profiles/brown-d.html>

- David R. Brown
- Currently Professor of Biochemistry at the University of Bath Email: bssdrb@bath.ac.uk

Molecular Aspects of Neurodegenerative Diseases

[Professor David Brown](#)

Study of molecular aspects of neurodegenerative diseases. Toxicity of proteins such as prion and alpha-synuclein. Role of microglia in aging of the brain.

“Neurodegeneration

“Our research focuses on proteins associated with neurodegenerative diseases including Alzheimer’s disease, Parkinson’s disease and the so called prion diseases. Prion diseases include the notorious Bovine Spongiform Encephalopathy and the human diseases vCJD, sporadic CJD and Fatal Familial Insomnia. However, despite the concern about these disease the prion protein is a harmless neuronal protein expressed in all vertebrates. Our group is concerned with the normal function of this protein. The prion protein is a copper binding protein which appears to be involved in cellular resistance to oxidative stress. Only when the protein is converted to an abnormal isoform is it capable of inducing neuronal death. Alpha-synuclein can also be converted to a toxic form by its interaction with copper. We are currently studying the mechanism of this process.”

Protein Studies

“Research from our group has been instrumental in showing that the prion protein is a copper binding protein. Our current research includes new directions to study other metal binding proteins associated with neurodegenerative diseases. We have been studying the synuclein family of proteins and the copper and iron binding abilities. Additionally, the protein precursor of beta-amyloid, the protein most associated with Alzheimer’s disease, also binds copper. We are further investigating the metal binding of these proteins using exciting techniques such isothermal titration calorimetry, EPR and cyclic voltammetry. In particular, the redox chemistry of these proteins on binding metals is important to determine, as all three diseases are associated with oxidative damage to the brain.”

<http://www.ncbi.nlm.nih.gov/pubmed/21333653>

Received 21 December 2010; revised 9 February 2011; accepted 10 February 2011.
Edited by P. Wright. Available online 17 February 2011

. Radically Different Amyloid Conformations Dictate the Seeding Specificity of a Chimeric Sup35 Prion

Abstract

A remarkable feature of prion biology is that the same prion protein can misfold into more than one infectious conformation, and these conformations in turn lead to distinct heritable prion strains with different phenotypes

http://my.utoronto.ca/cgi-bin/get_article.cgi?section=NEWS&art_id=1298560038&dept=CHEMISTRYDEPARTMENTOF&type=public

Seminar Time: 2011 Mar 3 10:00:00

Speaker: Brad Nilsson, University of Rochester

Abstract:

The self-assembly of peptides and proteins into cross- amyloid structures is a defining characteristic of amyloid pathologies including Alzheimer’s disease, Parkinson’s disease, type 2 diabetes, and prion encephalopathies.

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<http://www.ncbi.nlm.nih.gov/pubmed/20021333>

[Cent Nerv Syst Agents Med Chem.](#) 2009 Mar;9(1):2-11.

Creutzfeldt-jakob, Parkinson, lewy body dementia and Alzheimer diseases: from diagnosis to therapy.

[Dupiereux J](#), [Zorzi W](#), [Quadrio I](#), [Perret-Liaudet A](#), [Kovacs GG](#), [Heinen E](#), [Elmoualij B](#).

Department of Human Histology-CRPP, University of Liège, Sart Tilman, Belgium.

Excerpts”

“Abstract

Depositions of proteins in form of amyloid and non-amyloid plaques are common pathogenic signs of more than 20 degenerative diseases affecting the central nervous system or a variety of peripheral tissues. Among the neuropathological conditions, Alzheimer's, Parkinson's and the prion diseases, such as Creutzfeldt-Jakob disease (CJD), present ambiguities as regarding their differential diagnosis. “

“ In the case of prion diseases, there are concerns regarding not only patient care, but the wider community too, with regard to the risk of transmission of prions, especially during blood transfusion, for which, four cases of variant CJD infection associated with transfusion of non-leukocyte-depleted blood components have been confirmed. Therefore the development of techniques with high sensitivity and specificity represent the major challenge in the field of the protein misfolding diseases. In this paper we review the current analytical and/or biochemical diagnostic technologies used mainly in prion, but also in Alzheimer and Parkinson diseases and emphasizing work on the protein detection as a surrogates and specific biomarker in the body fluid of patients (urine, CSF and blood). This review highlights the urgency of the development of early and sensitive diagnostics in terms of therapeutic challenge. “

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<http://digitalcommons.unl.edu/cgi/viewcontent.cgi?article=1149&context=zoonoticpub>

A prion protein epitope selective for the pathologically misfolded conformation

Dr. James Ironside, et als (pharma researchers)

“Conformational conversion of proteins in disease is likely to be accompanied by molecular surface exposure of previously sequestered amino-acid side chains. We found that induction of β -sheet structures in recombinant prion proteins is associated with increased solvent accessibility of tyrosine. Antibodies directed against the prion protein repeat motif, tyrosine-tyrosinearginine, recognize the pathological isoform of the prion protein but not the normal cellular isoform, as assessed by immunoprecipitation, plate capture immunoassay and flow cytometry. Antibody binding to the pathological epitope is saturable and specific, and can be created in vitro by partial denaturation of normal brain prion protein. Conformation-selective exposure of Tyr-Tyr-Arg provides a probe for the distribution and structure of pathologically misfolded prion protein, and may lead to new diagnostics and therapeutics for prion diseases. “

“In prion disease, the latter, newly recognized molecular species²⁶ is characteristic of certain prion strains²⁷, early prion infection²⁰⁻²² and interspecies prion transmission²⁸. Protease-sensitive PrP^{sc} may represent a transient intermediate between normal structure and the abnormal, misfolded and aggregated PrP isoform that has acquired protease resistance²⁹. The population of misfolded protease-sensitive molecules may also contain PrP*, the hypothetical PrP isoform responsible for the property of prion infectivity³⁰. “

“The prion diseases may provide a prototype for disorders of protein misfolding, including Alzheimer disease, amyotrophic lateral sclerosis and Parkinson disease. We hypothesize that conformational conversion of proteins in disease is accompanied by molecular surface exposure of previously sequestered amino-acid side chains. It is possible that exploitation of this 'side-chain accessibility' hypothesis, applied here to isoform-selective antibodies for PrP, may provide new diagnostic and therapeutic approaches to other post-translational disorders of the proteome. “

.....
<http://www.medicalnewstoday.com/articles/216870.php> February 2011

Improving Understanding Of The Spread Of Infectious Prions

“Researchers at the University of California, San Diego School of Medicine have identified the motors that move non-infectious prion proteins (PrP^C) - found within many mammalian cells - up and down long, neuronal transport pathways. Identifying normal movement mechanisms of PrP^C may help researchers understand the spread of infectious prions within and between neurons to reach the brain, and aid in development of therapies to halt the transport. “

Their study is published in the February 18 edition of the journal *Cell*.

"Our work unraveling the normal mechanism of movement of this prion protein will help us understand how the devastating pathogenic versions found in mad cow disease and other prion diseases are formed and transmitted in the brain.

Intriguingly, our work may also shed light on what goes wrong in other neurodegenerative diseases such as [Alzheimer's disease](#)," said principal investigator Larry Goldstein, PhD, professor of Cellular and Molecular Medicine, Howard Hughes Medical Institute investigator and director of the UC San Diego Stem Cell Program. “

“The UCSD study of the mechanisms behind normal vesicle movement along the axons in mouse cells might also shed light on other neurodegenerative disease. While Alzheimer's is not generally considered an infectious disease like mad cow disease, emerging data suggest that Tau, amyloid-beta, and alpha-synuclein - proteins implicated in Alzheimer's and [Parkinson's disease](#) - have self-propagating fibril structures with prion-like characteristics. “

.....
<http://www.jbc.org/content/early/2011/01/13/jbc.M110.208934.short?rss=1>

Author Affiliations

¹ Chinese Academy of Sciences, China;

² University of Cambridge, United Kingdom

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Relationship between prion propensity and the rates of individual molecular steps of fibril assembly

Abstract

Peptides and proteins possess an inherent propensity to self-assemble into generic fibrillar nanostructures known as amyloid fibrils, some of which are involved in medical conditions such as Alzheimer's disease. In certain cases, such structures can self-propagate in living systems as prions and transmit characteristic traits to the host organism. The mechanisms which allow certain amyloid species but not others to function as prions are not fully understood.

.....
<http://www.landesbioscience.com/journals/prion/article/14367/>

β-amyloid oligomers and prion protein: Fatal attraction?

Gianluigi Forloni and Claudia Balducci

[View affiliations](#)

The relationship between Alzheimer disease (AD) and prion-related encephalopathies (TSE) has been proposed by different points of view. Recently, the scientific attention has been attracted by the results proposing the possibility that PrPc, the protein whose pathologic form is responsible of TSE, can mediate the toxic effect of β amyloid ($A\beta$) oligomers. The oligomers are considered the culprit of the neurodegenerative process associated to AD, although the pathogenic mechanism activated by these small aggregates remain to be elucidated. In the initial study based on the binding screening PrPc was identified as ligand /receptor of $A\beta$ oligomers, while long term potentiation (LTP) analysis in vitro and behavioural studies in vivo, demonstrated that the absence of PrPc abolished the damage induced by $A\beta$ oligomers. The high affinity binding $A\beta$ oligomers-PrPc has been confirmed, whereas a functional role of this association has been excluded by three different studies. We approached this issue by the direct application of $A\beta$ oligomers in the brain followed by the behavioural examination of memory deficits.

Our data using PrP knock-out mice suggest that $A\beta$ 1-42 oligomers are responsible for cognitive impairment in AD but PrPc is not required for their effect. Similarly, in two other studies the LTP alterations induced by $A\beta$ 1-42 oligomers was not influenced by the absence of PrP. Possible explanations of these contradictory results are discussed.

.....

<http://www.ibioseminars.org/user-can-change-their-additional-information/selected-lectureteaching-tools/susan-lindquist/lecture-notes-1>

“Prion formation in vitro

Prions within these foci appear to be comprised of a specific type of protein aggregate known as amyloid. Amyloid is a highly stable and highly ordered fibrillar protein aggregate. It is a one-dimensional polymer of polypeptides – new subunits are templated and added on only at the two ends of the fiber “

"Amyloid was ultimately proven to constitute infectious prion material when amyloid fibers formed from purified Sup35 prion domain were introduced into yeast cells and the cells became [PSI+]. These experiments confirmed the prion hypothesis – that protein conformations can act as genetic elements."

"Amyloid deposits are also commonly observed with prion diseases, indicating that here, too, prion propagation may be related to the unique properties of amyloid. Additionally, the prion domains of both Sup35 and PrP (the mammalian prion protein) contain a series of amino acid repeats. PrP repeat expansions are a familial mutation that predisposes these families to form prion diseases. Analogously, expanding the repeats in Sup35 also causes increased prion appearance. "

"Why are prions toxic to mammals but not to yeast?"

Many proteins when they polymerize into amyloid also form a variety of non-fibrillar oligomeric species. **These intermediates are now thought to be the principal toxic species associated with amyloid diseases.**

.....

http://en.wikipedia.org/wiki/Alzheimers_disease

"One receptor for A β oligomers may be the prion protein, the same protein that has been linked to mad cow disease and the related human condition, Creutzfeldt-Jakob disease, thus potentially linking the underlying mechanism of these neurodegenerative disorders with that of Alzheimer's disease.^[43] "

.....

<http://www.ncbi.nlm.nih.gov/pubmed/21227476>

[Virology](#). 2011 Mar 1;411(1):1-8. Epub 2011 Jan 11.

Extraneural manifestations of prion infection in GPI-anchorless transgenic mice.

[Lee AM](#), [Paulsson JF](#), [Cruite J](#), [Andaya AA](#), [Trifilo MJ](#), [Oldstone MB](#). *Virology*. 2011 Mar 1;411(1):1-8. Epub 2011

Jan 11.

Extraneural manifestations of prion infection in GPI-anchorless transgenic mice.

[Lee AM](#), [Paulsson JF](#), [Cruite J](#), [Andaya AA](#), [Trifilo MJ](#), [Oldstone MB](#).

Abstract

Earlier studies indicated that transgenic (tg) mice engineered to express prion protein (PrP) lacking the glycosylphosphatidylinositol (GPI^{-/-}) membrane anchor formed abnormal proteinase-resistant prion (PrP^{Sc}) amyloid deposits in their brains and hearts when infected with the RML strain of murine scrapie. In contrast, RML scrapie infection of normal mice with a GPI-anchored PrP did not deposit amyloid with PrP^{Sc} in the brain or the heart. **Here we report that scrapie-infected GPI^{-/-} PrP tg mice also deposit PrP and transmissible infectious material in the gut, kidneys, and islets of Langerhans. Similar to previously reported amyloid deposits in the brain and heart, amyloid deposits were found in the gut; however, no amyloid deposited in the islets.** By high-resolution electron microscopy, we show PrP is located primarily in α cells and also β cells. Islets contain abundant insulin and there is no abnormality in glucose metabolism in infected GPI^{-/-} PrP tg mice.

NEUROFIBRILLARY TANGLES are COMMON neuropathology of Alzheimer's disease, Creutzfeldt Jakob Disease, and are also found in Parkinson's Disease, Dementia with Lewy Bodies, and FTLD (frontotemporal lobar degeneration) and ALS - Amyotrophic Lateral Sclerosis . . . and now in autism victims . . .

AUTISM

<http://www.chiroeco.com/chiropractic/news/10212/52/hope-for-autism-announces-bionutritional-care-training-conference/>

A study released in December 2009 by the Centers for Disease Control (CDC) reported that autism prevalence has increased from the 1994 rate of one in 150 to one in 110 for children born in 1998. This is a staggering 57 percent increase in just four years. More children are diagnosed with autism than cancer, diabetes, and AIDS combined.

In 2009, a survey of thousands of primary care physicians was published in the journal Pediatrics. The doctors were questioned about their ability to care for those with autism. The results were a lack of self-perceived competency and a desire for more education. It is a devastating fact to the millions of American families touched by autism that our greatest need in healthcare is also our weakest area of expertise.

.....

<http://www.prioninstitute.ca/index.php?page=webpages&menucat=42&id=26&action=displaypage&side=1>

Funding: \$698,400

Research Lead: Dr. David Westaway, University of Alberta

Project: *"Extending the spectrum of Prionopathies to Amyotrophic Lateral Sclerosis and Autism"*

This project proposes to link the chemistry of the prion protein to the new territory of other nervous system diseases, such as ALS (Lou Gehrig's disease) and the socialization disorder autism-diseases which are at least one thousand times more common than prion diseases. It is believed that a different type or prion protein may operate in other types of brain diseases, which could lead to new ways of thinking about incurable disorders. The project will create changes in the amounts of the various forms of the new membrane protein, and then perform an array of analyses on the behavior and nervous system transmission of laboratory mice. Nervous transmission by electrical impulse can be measured in isolated brain cells, a system that is also convenient to study the effect of stress by adding small amounts of toxins to the fluids bathing the cultures. By these means, the project aims to extend the boundaries of what is considered "prion disease."

- <http://brain.oxfordjournals.org/content/116/1/281.short>
- **Pathological overlap in cases of parkinsonism associated with neurofibrillary tangles**
A study of recent cases of postencephalitic parkinsonism and comparison with progressive supranuclear palsy and Guamanian parkinsonism-dementia complex
- -----
- <http://www.ncbi.nlm.nih.gov/pubmed/20140439>
- frontotemporal lobar degeneration
- **Sporadic four-repeat tauopathy with frontotemporal lobar degeneration, Parkinsonism, and motor neuron disease: a distinct clinicopathological and biochemical disease entity.**
" In addition, the affected regions exhibited neuronal cytoplasmic inclusions resembling neurofibrillary tangles"

Neurofibrillary tangles in ALS and Parkinsonism-dementia complex

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neurofibrillary tangles in ALS <http://www.ncbi.nlm.nih.gov/pubmed/12722830>

"

Abstract

Since first described, amyotrophic lateral sclerosis/parkinsonism-dementia complex (ALS/PDC) of Guam has represented an important model of age-related neurodegenerative disease. ALS/PDC is characterized neuropathologically by severe widespread involvement by neurofibrillary tangles (NFTs). Over the past 30 years there has been a dramatic

decrease in the incidence of ALS and a 10-year increase in the age of onset of ALS and PDC.

"As noted by Anderson et al, the pattern of neuropathologic lesions seen in those with extensive NFT involvement suggests that such cases represent preclinical examples of ALS/PDC in individuals who have yet to accumulate a sufficient burden of pathology to attract clinical attention and diagnostic evaluation."

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of axons and dendrites in the autistic brain. However, this distribution of neurofibrillary tangles in the cerebral cortex of dementia ...
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Interestingly, neurofibrillary tangles have been described in brains of ...
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- [Assessment of Antifungal Drug Therapy in Autism by Measurement of ...](#)

also be due to the pentosidines; neurofibrillary tangles have been reported in the
brain tissue of an individual with autism.⁴³ Since vitamin B₉ reacts with ...
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Dec 7, 2010 ... The two most common physical changes in the brain, secondary to AD, ... clusters of proteins) and neurofibrillary tangles (bundles of ...

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ARE prion diseases such as Alzheimer's and Parkinson's limited to older people? NO - cases of early onset Alzheimer's are soaring in people age 50 - 64. sCJD strikes many victims in their 50s. "ALS usually strikes in late middle age (the late 50s is average) or later, although there have been cases of ALS in young adults and even in children, ..."

NOW we we learn that ADHD may be a early precursor in younger people to prion diseases in later life.

EVEN more concerning is the implication that autism in children and young adults may ALSO be a prion disease:

[A study released in December 2009 by the Centers for Disease Control (CDC) reported that autism prevalence has increased from the 1994 rate of one in 150 to one in 110 for children born in 1998. This is a staggering 57 percent increase in just four years. More children are diagnosed with autism than cancer, diabetes, and AIDS combined.]

Autism – prion disease in children ?

<http://www.prioninstitute.ca/forms/WEBSITE%20AR.pdf>

Dr. David Westaway, University of Alberta

Extending the spectrum of prionopathies to amyotrophic lateral sclerosis (ALS) and autism

Dr. Westaway's study aims to extend the boundaries of what is considered prion disease. His project takes the chemistry of the prion protein into the territory of nervous system diseases such as ALS (Lou Gehrig's disease) and socialization disorder diseases such as autism. These brain diseases are at least 1,000 times more common than diseases currently accepted as prion related.

Dr. Westaway hypothesizes that a different type of protein misfolding may operate in brain diseases such as Lou Gehrig's and autism. This type of protein misfolding may occur in response to stresses in the brain. Unlike misfolded prions, other misfolded proteins may be noninfectious and not viable outside of the affected animal.

Dr. Westaway's research team will investigate these hypotheses by inducing changes in the brain cells of laboratory mice, measuring the resulting electrical impulses in the animals' nervous systems and analyzing the effect on behaviour. Because nervous transmission by electrical impulse can be measured in isolated brain cells, adding small amounts of toxins to the fluids bathing the cell cultures will make it possible to study the effect of stress. The results could lead to new ways of thinking about nervous system disorders.

,