

<http://bacteriality.com/2008/05/05/prions/> **Inflammation and prions: an important connection**

Author: Amy Proal 5 May 2008

Adriano Aguzzi of the University Hospital of Zurich:

"Further research by the team showed that, if inflammation is induced in any excretory organ of the body, prions are excreted in whatever substance the organ excretes. "

<http://www.citeulike.org/user/applebyb/article/7558434>

Characterization of the prion protein in human urine.

by: [Ayuna Dagdanova](#), [Serguei Ilchenko](#), [Silvio Notari](#), [Qiwei Yang](#), [Mark E. Obrenovich](#), [Kristen Hatcher](#), [Peter McAnulty](#), [Lequn Huang](#), [Wenquan Zou](#), [Qingzhong Kong](#), [Pierluigi Gambetti](#), [Shu G. Chen](#)

The Journal of biological chemistry (29 July 2010)

Abstract

The presence of the prion protein (PrP) in normal human urine is controversial and currently inconclusive. This issue has taken a special relevance because **prion infectivity has been demonstrated in urine of animals carrying experimental or naturally occurring prion diseases** but the actual presence and tissue origin of the infectious prion have not been determined. We used immunoprecipitation, one- and two-dimensional electrophoresis and mass spectrometry to definitely prove the presence of PrP in human urine and its post-translational modifications. We show that urinary PrP (uPrP) is truncated mainly at residue 112 but also at other residues up to 122. This truncation makes uPrP undetectable with some commonly used antibodies to PrP. uPrP is glycosylated and carries an anchor which, at variance with that of cellular PrP, lacks the inositol-associated phospholipid moiety indicating that uPrP is probably shed from the cell surface. **The detailed characterization**

of uPrP reported here definitely proves the presence of PrP in human urine and will help determine the origin of prion infectivity in urine.

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<http://www.nature.com/nmeth/journal/v7/n7/full/nmeth.1465.html>

Estimating prion concentration in fluids and tissues by quantitative PMCA

Baian Chen , Rodrigo Morales , Marcelo A Barria & **Claudio Soto**

Abstract

Prions, the proteinaceous infectious agent responsible for prion diseases, can be detected with high sensitivity by protein misfolding cyclic amplification (PMCA) technology. Here we describe a quantitative PMCA procedure to calculate the concentration of very low levels of prions in biological samples.

CHRONIC WASTING DISEASE:

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0004848>

Nicholas J. Haley¹, Davis
M. Seelig¹, Mark D.
Zabel¹, **Glenn C. Telling²,**
Edward A. Hoover^{1*}

**Detection of CWD Prions In
Urine and Saliva of Deer by
Transgenic Mouse Bioassay**

“Chronic wasting disease (CWD) is a prion disease affecting captive and free-ranging cervids (e.g. deer,

elk, and moose). The mechanisms of CWD transmission are poorly understood, though bodily fluids are thought to play an important role. Here we report the presence of infectious prions in the urine and saliva of deer with chronic wasting disease (CWD). "

"These findings help extend our understanding of CWD prion shedding and transmission and portend the detection of infectious prions in body fluids in other prion infections."

[Elk And Deer Hunters Protect Yourself From Chronic Wasting Disease ...](#)

Wasting deer: deer **saliva** and blood can carry **prions**. Correction: Vol. 12, No. 10. Prions in humans and animals. Elk and Deer Hunters Protect Yourself from ...
emeurgencia.com/2011011306-elk-and-deer-hunters-protect-...

[Chronic Wasting Disease \(CWD\) - Ohio Sportsman.com - Hunting and ...](#)

By flounder9

CWD- positive animals can contribute to environmental prion load via biological materials including saliva, blood, urine and feces, shedding several times their body weight in possibly infectious excreta in their lifetime, ...

[Ohio Sportsman.com - Hunting... - http://www.ohiosportsman.com/forum/member.php?u=9604](http://www.ohiosportsman.com/forum/member.php?u=9604)

<http://70.32.81.92/science/1295014024/41>

Prions, which are the cause of fatal neurodegenerative disorders termed transmissible spongiform encephalopathies (TSEs), can be experimentally or naturally transmitted via prion-contaminated food, **blood, milk, saliva, feces and urine.**

<http://vir.sgmjournals.org/cgi/content/short/vir.0.017335-0v1>

Aerosol and Nasal Transmission of Chronic Wasting Disease in Cervidized Mice
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² University of Kentucky Medical Center

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Little is known regarding the potential risk posed by aerosolized prions. Chronic wasting disease (CWD) is transmitted horizontally, almost surely by mucosal exposure, and CWD prions are present in saliva and urine of infected animals. However, whether CWD may be transmissible by the aerosol or nasal route is not known. To address this question, FVB mice transgenetically expressing the normal cervid PrPC protein [Tg(cerPrP) mice] were exposed to CWD prions by either nose-only aerosol exposure or by drop-wise instillation into the nostrils. Mice were monitored for signs of disease for up to 755 days post inoculation (dpi) and by examination of tissues for lesions and PrPCWD after necropsy. In particular, nasal mucosa, vomeronasal organ, lungs, lymphoid tissue, and the brain were assessed for PrPCWD by western blotting and immunohistochemistry. Six of 7 aerosol-exposed Tg(cerPrP) mice developed clinical signs of neurologic dysfunction mandating euthanasia between 411 and 749 dpi. In all these mice, CWD infection was confirmed by detection of spongiform lesions and PrPCWD in the brain. Two of 9 intranasally inoculated Tg(cerPrP) mice also developed TSE associated with PrPCWD between 417 and 755 dpi. No evidence of PrPCWD was detected in CWD-inoculated Tg(cerPrP) mice examined at pre-terminal time points. **These results**

demonstrate that CWD can be transmitted by aerosol (as well as nasal) exposure and suggest that exposure via the respiratory system merits consideration for prion disease transmission and biosafety.

Received 30 October 2009; accepted 15 February 2010.

http://www.cicbiogune.es/uploads/doc/noticias/prion_deer.pdf

Epidemiological data suggest that CWD is a self-sustaining disease and it seems that it can be transmitted horizontally in captive populations. Recent studies indicate that the transmission of prions in wild populations may occur through contaminated urine, faeces and saliva.

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0007990> PMCA

Detection of Sub-Clinical CWD Infection in Conventional Test-Negative Deer Long after Oral Exposure to Urine and Feces from CWD+ Deer

Received: September 29, 2009; Accepted: October 29, 2009; Published: November 24, 2009

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Abstract Top Background Chronic wasting disease (CWD) of cervids is a prion disease distinguished by high levels of transmissibility, **wherein bodily fluids and excretions are thought to play an important role. Using cervid bioassay and established CWD detection methods, we have previously identified infectious prions in saliva and blood but not urine or feces of CWD+ donors. More recently, we identified very low concentrations of CWD prions in urine of deer by cervid PrP transgenic** (Tg[CerPrP]) mouse bioassay and serial protein misfolding cyclic amplification (sPMCA). This finding led us to examine further our initial cervid bioassay experiments using sPMCA.

Excerpt

Discussion Detection of subclinical infection in deer orally exposed to urine and feces (1) suggests that a prolonged subclinical state can exist, necessitating observation periods in excess of two years to detect CWD infection, and (2) illustrates the sensitive and specific application of sPMCA in the diagnosis of low-level prion infection. Based on these results, it is possible that low doses of prions, e.g. following oral exposure to urine and saliva of CWD-infected deer, bypass significant amplification in the LRS, perhaps utilizing a neural conduit between the alimentary tract and CNS, as has been demonstrated in some other prion diseases.

“ These results demonstrate the potential for CWD prion transmission via urine and/or feces, and highlight the application of more sensitive assays such as sPMCA in identification of CWD infection, pathogenesis, and prevalence.”

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2593137/>

Detection of infectious prions in urine

Edited by Aleksander Benjak

Dennisse Gonzalez-Romero^a, Marcelo A. Barria^a, Patricia Leon^a, Rodrigo Morales^a and Claudio Soto^a  

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Received 26 July 2008;
accepted 4 August 2008.
Available online 13 August 2008.

Abstract

Prions are the infectious agents responsible for prion diseases, **which appear to be composed exclusively by the misfolded prion protein (PrP^{Sc}). The mechanism of prion transmission is unknown. In this study, we attempted to detect prions in urine of experimentally infected animals. PrP^{Sc} was detected in ~80% of the animals studied, whereas no false positives were observed among the control animals. Semi-quantitative calculations suggest that PrP^{Sc} concentration in urine is around 10-fold lower than in blood. Interestingly, PrP^{Sc} present in urine maintains its infectious properties. Our data indicate that low quantities of infectious prions are excreted in the urine. These findings suggest that urine is a possible source of prion transmission.**

Keywords: Prion; Transmissible spongiform encephalopathy; PMCA; Diagnosis; Scrapie

(EXCERPT)

[MY comment – the following excerpt explains WHY ending the landspreading of prion infected Class B sewage sludge ‘biosolids’ on grazing lands, hay fields and dairy

pastures is so necessary to prevent infection of livestock and wildlife—both of which ingest significant quantities of soil when they graze] --

“One of the top priorities in the prion field is to minimize further spreading of TSEs to humans or animals by limiting the exposure to contaminated material [7,14]. Our findings suggest that urine is a possible source of prion transmission. Since urine produced by animals potentially infected with prions is permanently released and likely concentrated in environmental samples, such as soil and grass, this route may prove very relevant for spreading of TSEs in wild and captive animals such as cervids, sheep and cattle. It is known that PrP^{Sc} is highly resistant to degradation and infectivity can survive in the environment for a long time [23]. Recent studies have shown that PrP^{Sc} adsorbs efficiently into soil where it remains infectious and that both infectivity and PrP^{Sc} can stay intact in soil for long periods of time [24–26]. Contamination of soil with urinary prions may contribute to spreading prion disease among animals, which are known to ingest large amounts of soil, including cattle, sheep and cervids [24,26,27]. Worryingly, the continuous excretion of urine and the extremely high resistance of prions may lead to a progressive accumulation of infectious material in the environment, with potentially catastrophic consequences in the future.

One of the top priorities in the prion field is to minimize further spreading of TSEs to humans or animals by limiting the exposure to contaminated material [7,14]. This is a difficult problem, because prion diseases have a long clinically-silent incubation period in which infected individuals may unknowingly transmit the disease. In addition, it is possible that many individuals may remain as sub-clinical carriers during their entire life, constituting a permanent source of prions [28]. Therefore, the development and validation of procedures to detect even the tiniest quantities of infectious material is of paramount importance [7,15]. Implementation of a large scale program to screen animals at risk of infection of and diagnosis the human population requires detection of prions in easily accessible samples, such as blood or urine. Our results showing that PrP^{Sc} can be detected in urine of a large proportion of infected animals provide a promising avenue for a sensitive and non-invasive biochemical diagnosis of prion diseases. Adaptation of PMCA for detection of prions in urine of naturally infected animals and humans may offer a great possibility for routine testing of prion infections. “

Analysis of Clusterin Glycoforms in the Urine of BSE-Infected Fleckvieh-Simmental Cows

Authors: Lise Lamoureux^a; Sharon L. R. Simon^a; Margot Plews^a; Michael Stobart^{ab}; Martin Groschup^c; Stefanie Czub^d; Catherine Graham^d; J. David Knox^{ab}

“Previously, to meet the demand for an antemortem test based on a matrix that would permit easy access and repeated sampling, two-dimensional differential gel electrophoresis (2D-DIGE) was used to perform an unbiased screen of bovine urine.

Data demonstrated the altered abundance of particular isoforms of the multifunctional glycoprotein clusterin in urine samples obtained from BSE-infected and age-matched Fleckvieh-Simmental cattle.”

“Biochemical and mass spectrometry analyses in combination with the generation of bovine clusterin subunit-specific antibodies enabled us to demonstrate that it was β -subunits of clusterin possessing N-linked glycans of complex structure that exhibited differential abundance in response to BSE infection. The characteristic highly glycosylated clusterin β -subunit was detectable as early as 16 mo post infection (mpi) by one-dimensional (1D) **Western blot analysis of urine obtained from BSE-infected cattle.**”

<http://ddr.nal.usda.gov/bitstream/10113/34009/1/IND43787291.pdf> J.

Comp. Path. 2006, Vol. 134, 63–69

Experimental Second Passage of Chronic Wasting Disease (CWD_{mule deer}) Agent to Cattle

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Summary

To compare clinicopathological findings in first and second passage chronic wasting disease (CWD) mule deer in cattle, six calves were inoculated intracerebrally with brain tissue derived from a first-passage CWD-affected calf in an earlier experiment. Two uninoculated calves served as controls. The inoculated animals began to lose both appetite and weight 10–12 months later, and five subsequently developed clinical signs of central nervous system (CNS) abnormality. By 16.5 months, all cattle had been subjected to euthanasia because of poor prognosis. None of the animals showed microscopical lesions of spongiform encephalopathy (SE) but PrPres was detected in their CNS tissues by immunohistochemistry (IHC) and rapid Western blot (WB) techniques. Thus, intracerebrally inoculated cattle not only amplified CWD PrPres from mule deer but also developed clinical CNS signs in the absence of SE lesions. This situation has also been shown to occur in cattle inoculated with the scrapie agent. The study confirmed that the diagnostic techniques currently used for diagnosis of bovine spongiform encephalopathy (BSE) in the US would detect CWD in cattle, should it occur naturally. Furthermore, it raised the possibility of distinguishing CWD from BSE in cattle, due to the absence of neuropathological lesions and to a distinctive multifocal distribution of PrPres, as demonstrated by IHC which, in this study, appeared to be more sensitive than the WB technique.

Published by Elsevier Ltd.

PRIONS IN URINE OF sCJD VICTIMS

<http://www.plosone.org/article/info:doi%2F10.1371%2Fjournal.pone.0003870;jsessionid=32E2697A8C4578986FE6A047DF159DB3>

Research Article 2008

Urinary α_1 -Antichymotrypsin: A Biomarker of Prion Infection

Gino Miele^{1*}, Harald Seeger¹, Denis Marino¹, Ralf Eberhard¹, Mathias Heikenwalder¹, Katharina Stoeck¹, Max Basagni², Richard Knight³, Alison Green³, Francesca Chianini⁴, Rudolf P.

Wüthrich⁵, Christoph Hock⁶, Inga Zerr⁷, **Adriano Aguzzi^{1*}**

1 Department of Pathology, UniversitätsSpital Zürich, Institute of Neuropathology, Zürich, Switzerland, 2 Prion Diagnostica Srl, Rho, Italy, 3 The National Creutzfeldt-Jakob Disease Surveillance Unit, Western General Hospital, Edinburgh, United Kingdom, 4 Moredun Research

Institute, Pentlands Science Park, Edinburgh, United Kingdom, 5 UniversitätsSpital Zürich, Clinic for Nephrology, Zürich, Switzerland, 6 Division of Psychiatry Research, University of Zürich, Zürich, Switzerland, 7 National TSE Reference Center, Department of Neurology, Medical Faculty, Georg-August University, Göttingen, Germany

Abstract [Top](#)

The occurrence of blood-borne prion transmission incidents calls for identification of potential prion carriers. However, current methods for intravital diagnosis of prion disease rely on invasive tissue biopsies and are unsuitable for large-scale screening. Sensitive biomarkers may help meeting this need. Here we scanned the genome for transcripts elevated upon prion infection and encoding secreted proteins. We found that α_1 -antichymotrypsin (α_1 -ACT) was highly upregulated in brains of scrapie-infected mice.

Furthermore, α_1 -ACT levels were dramatically increased in urine of patients suffering from sporadic Creutzfeldt-Jakob disease, and increased progressively throughout the disease. Increased α_1 -ACT excretion was also found in cases of natural prion disease of animals. Therefore measurement of urinary α_1 -ACT levels may be useful for monitoring the efficacy of therapeutic regimens for prion disease, and possibly also for deferring blood and organ donors that may be at risk of transmitting prion infections.

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PRIONS IN HUMAN wastes Dr. Adriano Aguzzi - University of Zurich prion expert

"Further research by the team showed that, if inflammation is induced in any excretory organ of the body, prions are excreted in whatever substance the organ excretes. "

[//bacterially.com/2008/05/05/prions/](http://bacterially.com/2008/05/05/prions/)

19. Seeger H, Heikenwalder M, Zeller N, Kranich J, Schwarz P, et al. 2005. Coincident scrapie infection and nephritis lead to urinary prion excretion. *Science* 310:324–26

<http://www.nature.com/embor/journal/v7/n3/full/7400642.html>

What makes a good prion? Conference on Prion Biology Sven J Saupe¹ & Surachai Supattapone²

It has long been observed that scrapie infection of sheep and chronic wasting disease (CWD) infection of deer can be transmitted horizontally, but the mode of horizontal transmission among herbivores remains unclear. A. Aguzzi (Zurich, Switzerland) presented exciting results showing that chronic inflammation of peripheral organs stimulates prion replication within the affected organs in mice (Fig 2). Aguzzi showed that an experimental form of lymphocytic nephritis causes concomitant prion replication in the affected kidney, accompanied by excretion of infectious prions in urine. These findings suggest that treating chronic organ inflammation in farm animals could be a simple strategy for preventing the lateral spread of prion diseases, and therefore might have significant implications for public health.

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<http://jvi.asm.org/cgi/content/abstract/80/9/4546>
February 2006

Prion Infection of Oral and Nasal Mucosa

Crista DeJoia, Brian Moreaux, Kimberly O'Connell, and Richard A. Bessen*
Department of Veterinary Molecular Biology, Montana State University, Bozeman,
Montana 59717

Centrifugal spread of the prion agent to peripheral tissues is postulated to occur by axonal transport along nerve fibers. This study investigated the distribution of the pathological isoform of the protein (PrP^{Sc}) in the tongues and nasal cavities of hamsters following intracerebral inoculation of the HY strain of the transmissible mink encephalopathy (TME) agent. We report that PrP^{Sc} deposition was found in the lamina propria, taste buds, and stratified squamous epithelium of fungiform papillae in the tongue, as well as in skeletal muscle cells. Using laser scanning confocal microscopy, PrP^{Sc} was localized to

nerve fibers in each of these structures in the tongue, neuroepithelial taste cells of the taste bud, and, possibly, epithelial cells. This PrP^{Sc} distribution was consistent with a spread of HY TME agent along both somatosensory and gustatory cranial nerves to the tongue and suggests subsequent synaptic spread to taste cells and epithelial cells via peripheral synapses. In the nasal cavity, PrP^{Sc} accumulation was found in the olfactory and vomeronasal epithelium, where its location was consistent with a distribution in cell bodies and apical dendrites of the sensory neurons. Prion spread to these sites is consistent with transport via the olfactory nerve fibers that descend from the olfactory

bulb. Our data suggest that epithelial cells, neuroepithelial taste cells, or olfactory sensory neurons at chemosensory mucosal surfaces, which undergo normal turnover, infected with the prion agent could be shed and play a role in the horizontal transmission of animal prion diseases.

http://molpath.ucsd.edu/09_PDFs_225/Sigurdson2.pathmechdis.3.121806.pdf

Molecular Mechanisms of Prion Pathogenesis

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In addition, it was hypothesized that inflammatory conditions could result in the shedding of prions via excretory organs (e.g., kidney). To investigate this hypothesis, various transgenic and spontaneous mouse models of nephritis were analyzed to ascertain whether prions could be excreted via urine (19). Indeed, prion infectivity was observed

in the urine of mice with both subclinical and terminal scrapie, and with inflammatory conditions of the kidney (19).

(19). Seeger H, Heikenwalder M, Zeller N, Kranich J, Schwarz P, et al. 2005. Coincident scrapie infection and nephritis lead to urinary prion excretion. *Science* 310:324–26

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2603099/>

DOI: 10.3201/eid1409.080259

Suggested citation for this article: **Gregori L, Kovacs GG, Alexeeva I, Budka H, Rohwer RG.**

Excretion of transmissible spongiform encephalopathy infectivity in urine.

Emerg Infect Dis. 2008 Sep; [Epub ahead of print]

“Although the source of TSE infectivity in urine remains unresolved, these results establish that TSE infectivity is excreted in urine and may thereby play a role in the horizontal transmission of natural TSEs. The results also indicate potential risk for TSE transmission from human urine-derived hormones and other medicines.”

“We found TSE infectivity in the urine of hamsters that had no evidence of kidney or bladder inflammation”

‘That urine titer is similar to that of plasma suggests that urine infectivity may originate from blood (25), but how the infectivity would be excreted is not clear.’ .

Alternatively, TSE infectivity may be excreted by processes analogous to those responsible for the low-level virurias that occur during infections of the nervous system by mumps, measles, and West Nile virus (28-30). To the extent that results from the hamster model can be generalized to other TSE infections (**and it has so far proven highly predictive**), then **even the very low concentrations of infectivity measured here could result in substantial environmental contamination. Several liters of urine and several thousand doses of TSE infectivity may be excreted daily over the course of the illness; even higher titers might be excreted by an animal with nephritis.**

The high stability of TSE infectivity would account for its persistence in pasture years after infected animals are removed (31). Recent studies have shown that infectivity that is adsorbed and immobilized by soil minerals (32) can still infect hamsters by oral exposure 29 months later (33). Our study also Page 11 of 16 warns of a possible risk from TSE contamination to fertility hormones and other medicinal products extracted from human urine. “

“

Recent research by Reichl H, Balen A, Jansen CA. has found prions in urine and blood of both animals and humans who are victims of TSEs (Transmissible spongiform encephalopathies – which would include CJD (and Alzheimer’s ?)

Thus, prions in infected urine of TSE/CJD victims which is discharged to sewers, will be partitioned to the sewage sludge by the wastewater treatment process.

“Evidence is emerging that suggests that the protease-resistant isoform (PrP(sc)) of the normal cellular prion protein (PrP(c)) can be detected in the blood and urine of animals and humans with transmissible spongiform encephalopathies (TSEs).”

“Despite the paucity of evidence to date and its relevance to the infectious spread of TSEs, it is important that robust measures are implemented to either remove or inactivate PrP(sc) in order to minimize contamination.”

Full text article at
humrep.oupjournals.org

Prion transmission in blood and urine: what are the implications for recombinant and urinary-derived gonadotrophins?

Reichl H, Balen A, Jansen CA.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12351519&dopt=Abstract

1: Hum Reprod. 2002 Oct;17(10):2501-8.

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<http://www.bioportfolio.com/resources/pmarticle/39241/Is-The-Urea-Cycle-Involved-In-Alzheimer-s-Disease.html>

Is the Urea Cycle Involved in Alzheimer's Disease?

Summary

Since previous observations indicated that the urea cycle may have a role in the Alzheimer's disease (AD) process, we set out to quantify the expression of each gene involved in the urea cycle in control and AD brains and establish whether these genes could be genetic determinants of AD. We first confirmed that all the urea cycle enzyme genes are expressed in the AD brain. The expression of arginase 2 was greater in the AD brain than in the control brain. The presence of the rare arginase 2 allele rs742869 was associated with an increase in the risk of AD in men and with an earlier age-at-onset for both genders. None of the other genes in the pathway appeared to be differentially expressed in the AD brain or act as genetic determinants of the disease.

Affiliation

INSERM U744, Lille, France Institut Pasteur de Lille, Lille, France Universit  de Lille Nord de France, Lille, France.

Journal Details

Name: [Journal of Alzheimer's disease : JAD](#)

<http://www.biomedcentral.com/1746-6148/6/41/abstract>

Discussion

These new results enable us to confirm confidently the presence of specific abnormal prion protein in the adrenal gland and in the kidney of the **cheetah** affected with FSE. **This question is important because it becomes evidenced that urine may sustain transmission of certain forms of the transmissible spongiform encephalopathy (TSE) diseases,** such as hamsters carrying infectious particles. **More recently the kidney was found to accumulate abnormal PrP in other species too such as sheep [17, 18], and the urinary secretion of pathological form of PrP is seriously considered [19, 20].** Even if the origin of the production of this infectious prion particles are not yet clearly identified, **the specific detection of PrPres within the glomeruli of the kidney of cheetah with FSE is in total accordance with this point.**

snip...see full text ;

<http://www.biomedcentral.com/content/pdf/1746-6148-6-41.pdf>*****

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The identification of disease-induced biomarkers in the urine of BSE infected cattle

Sharon LR Simon¹ ✉, Lise Lamoureux¹ ✉, Margot Plews¹ ✉, Michael Stobart^{1,2} ✉, Jillian LeMaistre³ ✉, Ute Ziegler⁴ ✉, Catherine Graham⁵ ✉, Stefanie Czub⁵ ✉, Martin Groschup⁴ ✉ and J David Knox^{1,2} ✉

1 Prion Diseases Program, Public Health Agency of Canada, Winnipeg, R3E 3P6, Canada

Background

The bovine spongiform encephalopathy (BSE) epidemic and the emergence of a new human variant of Creutzfeldt-Jakob Disease (vCJD) have led to profound changes in the production and trade of agricultural goods. The rapid tests currently approved for BSE monitoring in slaughtered cattle are all based on the detection of the disease related isoform of the prion protein, PrP^d, in brain tissue and consequently are only suitable for post-mortem diagnosis. Objectives: In instances such as assessing the health of breeding stock for export purposes where post-mortem testing is not an option, there is a demand for an ante-mortem test based on a matrix or body fluid that would permit easy access and repeated sampling. Urine and urine based analyses would meet these requirements.

Multivariate analyses of protein expression data identified a single protein able to discriminate, with 100% accuracy, control from infected samples. In addition, a subset of proteins were able to predict with 85% ± 13.2 accuracy the time post infection that the samples were collected.

Conclusion

These results suggest that in principle it is possible to identify biomarkers in urine useful in the diagnosis, prognosis and monitoring of disease progression of transmissible spongiform encephalopathy diseases (TSEs).

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<http://www.informaworld.com/smpp/content~content=a931918953~db=all~jumptype=rss>

Analysis of Clusterin Glycoforms in the Urine of BSE-Infected Fleckvieh-Simmental Cows

Authors: Lise Lamoureux^a; Sharon L. R. Simon^a; Margot Plews^a; Michael Stobart^{ab}; Martin Groschup^c; Stefanie Czub^d; Catherine Graham^d; J. David Knox^{ab}

Abstract

Currently approved tests for bovine spongiform encephalopathy (BSE) monitoring in cattle are based on the detection of the disease-related isoform of the prion protein in brain tissue and consequently are only suitable for postmortem diagnosis. Previously, to meet the demand for an antemortem test based on a matrix that would permit easy access and repeated sampling, two-dimensional differential gel electrophoresis (2D-DIGE) was used to perform an unbiased screen of bovine urine. Data demonstrated the altered abundance of particular isoforms of the multifunctional glycoprotein clusterin in urine samples obtained from BSE-infected and age-matched Fleckvieh-Simmental cattle.

“The characteristic highly glycosylated clusterin β -subunit was detectable as early as 16 mo post infection (mpi) by one-dimensional (1D) Western blot analysis of urine obtained from BSE-infected cattle.”

Tateishi J. Transmission of Creutzfeldt-Jakob disease from human blood and urine into mice. Lancet 1985;2:1074.

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Experimental Biology and Medicine 230:343-349 (2005)

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ORIGINAL RESEARCH ARTICLE

Sensitive Detection of Prion Protein in Human Urine

Harash K. Narang^{*,2}, Ayuna Dagdanova[†], Zhiliang Xie[†], Qiwei Yang[†] and Shu G. Chen^{†,1}

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Transmissible spongiform encephalopathies are a group of infectious diseases typically associated with the accumulation of a protease-resistant and β -sheet-rich prion protein, PrP^{Sc}, in affected brains. PrP^{Sc} is an altered isoform derived from the host-encoded glycoprotein, PrP^C. The expression of PrP^C is the highest in brain tissue, but it can also be detected at low levels in peripheral tissue. However, it is unclear whether a significant amount of PrP^C is released into body fluid and excreted into urine. We have developed a simple, rapid method for the reliable detection of PrP^C in urine from normal subjects by Western blotting. Our method can easily and reliably detect PrP^C in apparently healthy individuals using less than 1 ml of urine in which the amount of urinary PrP^C is estimated to be in the range of low micrograms/liter. <http://www.ebmonline.org/cgi/content/abstract/230/5/343>

<http://pubs.acs.org/cen/topstory/7929/7929notw7.html>

PROBE FOR PRIONS

Diagnostic prions found in urine before disease symptoms appear

STU BORMAN

In a surprising and unexpected discovery, researchers in Israel have found a form of prion in urine that can indicate the presence of disease caused by the mysterious protein even before symptoms appear.

While looking for other substances in hamster urine, she and her coworkers found an isoform (tissue-specific form) of protease-resistant prion protein in the urine of prion-infected hamsters, **and subsequently also in the urine of cattle and humans with prion diseases.** Few researchers had looked for prions in urine before, Gabizon notes, because they generally believed prions would not pass through the kidneys in substantially intact form.

Gabizon is hardly a newcomer to prion research. A decade ago, she worked for neurology professor [Stanley B. Prusiner](#) of the University of California, San Francisco, who won the 1997 Nobel Prize in Physiology or Medicine for discovering that prions cause TSEs.

http://www.priondata.org/data/A_Urinediagnostics.html#Ruth%20Gabizon's

Ruth Gabizon's work

Ruth Gabizon is based in Jerusalem but used to work for Stan Prusiner in California. Her work has shown that, as long as concentration steps can take place in advance, then Western blotting of the urine sample from small quantities will show a prion-like compound present in the urine. **This compound was the prion protein, but in a changed form. It remained proteinase K resistant and could be shown to be associated with the prion infection. She showed it to be present in the urine of animals with scrapie and BSE early in the incubation period of the disease. The work has now become part of a company in Israel.**

<http://www.organicconsumers.org/madcow/early82101.cfm>

In the research in Israel, Gabizon's team also tried to see whether the prion particles in **urine** are infectious, but no cases of prion-induced disease were seen in the hamsters. But there were signs that the prion particles - perhaps incomplete or altered prion particles - got into the animals' brains. So the Hadassah team concluded that "the clinical and epidemiological implications" of its findings are yet to be determined.

Commenting on the Israeli team's work, neuroscientist Huntington Potter, of the University of South Florida College of Medicine, said, "The finding of scrapie-like protein in the **urine** before clinical symptoms is going to be very helpful for both the veterinary and medical diagnosis of these diseases." But he also questioned whether prion-based diseases can be transmitted via **urine**. The Israeli researchers, he said, gave "no data addressing that question." And he called their raising the "alarming possibility" of such transmission a "hyper-scare paragraph" that he found confusing. Nonetheless, Potter said, this idea of disease transmissibility via **URINE** "is definitely worth following up. It has been a **MYSTERY IN SCRAPIE** about how the animals infect each other in the field, and this is as good a hypothesis as any."

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<http://www.organicconsumers.org/madcow/urine71701.cf>

If the rogue proteins are in lymph nodes, Dr. Gabizon said, it stands to reason that they will end up in the bloodstream. Because the abnormal proteins cannot be broken down by enzymes in blood, she said, it also stands to reason that they will be cleared from the body by the **kidneys**.

The rogue proteins are small enough to pass through the kidneys' filtration system, she said, **so they should turn up in urine.**

To find the rogue proteins in urine, Dr. Gabizon and her assistant, Gideon Shaked, came up with a purification scheme. The kidneys contain urea, a compound that disrupts protein folding but does not destroy the proteins. The researchers suspected that the rogue proteins might be altered by urea and excreted in urine as particles that would not be recognized as prions.

To test that idea, the researchers took urine samples from hamsters, humans and cattle infected with known prion diseases, and from healthy controls. The urine was put into a machine that removes urea, a process that allows proteins to fold back into their original shapes. These refolded proteins were then exposed to enzymes that broke down normal proteins, but not prions.

In healthy controls, all proteins were destroyed. But in animals and people with prion diseases, one protein could not be broken down. Dr. Gabizon called that enzyme-resistant protein a URINARY PRION and said it was new. The presence of such a protein is the diagnostic hallmark of prion diseases, she said.

Tests show that the **urinary prion** is not overtly infectious, although it may have some low level of infectivity, Dr. Gabizon said. Hamsters injected with the particles have not developed any signs of disease after 300 days but are still under observation. Other rodents have been shown to harbor infectious proteins without showing signs of disease, she said, and **yet as carriers they can pass on the disease.**

The **urinary prion** seems to be an excellent marker for the progression of prion diseases, Dr. Gabizon said. For example, hamsters were injected with the classic rogue prion that causes scrapie, a sheep disease. For one week, the hamsters excreted the **urinary prion**, then stopped. **Sixty days later, the urinary prion reappeared in increasing amounts. Dr. Gabizon said this suggested that as the infection built up in the body and brain, the amount of urinary prion increased. "It is as if the urine was a mirror to the brain," she said.**

<http://www.jbc.org/cgi/reprint/C100278200v1.pdf>

A protease resistant PrP Isoform is Present in Urine of Animals and Humans affected with Prion Diseases - Gideon M. Shaked, Yuval Shaked, Zehavit Kariva, Michele Halimi, Inbal Avraham and Ruth Gabizon, Dept. of Neurology, the Agnes Ginges Center for Human Neurogenetics, Hadassah University Hospital, Jerusalem, Israel -

http://www.icsi.ws/information/enewsletter/sep_03/kinderwunsch

Position paper on the risks of prions in hormone preparations

The Swiss association Kinderwunsch (child wish) is concerned about recently published articles concerning the risks associated with **prions in urinary hormone products.**

The Kinderwunsch association considers the detection of prions in human urine as a warning sign for the immediate drafting and implementation of precautionary measures.

Following the UK's rapid response and its withdrawal of a urinary hormone product as a precautionary measure, **France's decision to issue warnings for urinary hormone products and Sweden's refusal to license urinary hormone preparations, the Kinderwunsch association is now calling on the relevant Swiss authorities to implement without delay precautionary measures to counter the risk of prions in urinary products.**

In parallel, there needs to be transparency concerning the **origin of the urine used to manufacture the hormone preparations** so that the individuals concerned can make a free and informed choice about products until the registration authorities have taken the necessary action. To enable these individuals to make their decision independently of cost, the pending application for the compulsory subsidizing of in vitro fertilization should now be processed and approved as soon as possible.

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