Abstract: The prion protein PrPC is infamous for its role in disease, but its normal physiological function remains unknown. Here we found a previously unknown behavioral phenotype of Prnp-/- mice in an odor-guided task. This phenotype was manifest in three Prnp knockout lines on different genetic backgrounds, which provides strong evidence that the phenotype is caused by a lack of PrPC rather than by other genetic factors. Prnp-/- mice also showed altered behavior in a 2nd olfactory task, suggesting that the phenotype is olfactory specific. Furthermore, PrPC deficiency affected oscillatory activity in the deep layers of the main olfactory bulb, as well as dendrodendritic synaptic transmission between olfactory bulb granule and mitral cells. Notably, both the behavioral and electrophysiological alterations found in Prnp-/- mice were rescued by transgenic neuronal-specific expression of PrPC. These data suggest that PrPC is important in the normal processing of sensory information by the olfactory system.]

[And from the same issue of Nature Neuroscience. See below - Mod.CP]

******
[5] Prion protein function
Date: Sun 21 Dec 2008
Source: Nature Neuroscience 12, 7 - 8 (2009) [edited]
<http://www.nature.com/neuro/journal/v12/n1/full/nn0109-7.htm>

Title: Sniffing out a function for prion proteins

Abstract

When prion proteins go wrong, they can do serious damage, but little is known about their normal function, despite their ubiquitous expression in the brain. A new report in this issue [see above] suggests a critical role for prions in olfactory discrimination.

Introduction

Although the word prion was coined by Stanley Prusiner to describe the "proteinaceous infectious particle" that causes a family of fatal neurodegenerative diseases known as transmissible spongiform encephalopathies more than 20 years ago, little is known about the normal function of prion proteins. Most of what is known about them comes from studies of their involvement in these devastating diseases, which include Creutzfeld-Jakob disease, bovine spongiform encephalopathy ('mad-cow disease') and chronic wasting disease in elk and deer. These diseases are distinguished by rapidly progressive neurological deterioration and a pattern of neurodegeneration that is characterized by prominent vacuolization of neuronal cytoplasm, which gives the brain a sponge-like histological appearance. The key pathogenic event in these diseases is the conversion of an endogenous cell-surface glycoprotein, the prion protein (PrPc), to a pathological isoform (PrPsc) that has an abnormal conformation and an unusual resistance to proteolytic degradation. PrPsc accumulates in cells and plaque-like extracellular deposits, converting more PrPc into the pathogenic form and triggering neurodegeneration by mechanisms that are still not fully understood. Conversion of PrPc can be a result of inherited mutations, infection of the

host with a prion-infected tissue or rare sporadic events. Although the formation of PrPsc is believed to result in a gain of toxic function, a loss of function of PrPc has not been excluded as being involved in prion disease PrPc is most abundantly expressed in the brain and it would be expected that the loss of this protein would result in substantial neurobehavioral modifications. However, the specific role of PrPc in neural function and behavior is far from clear. In fact, previous work suggests that the most robust phenotype of PrPc loss in transgenic mice is protection from prion diseases. Although changes in PrPc expression influence a variety of critical cellular processes in neurons, including cell survival, synaptic maintenance and plasticity, and axonal maintenance, data on these issues have occasionally been contradictory. Thus, 'elusive' remains one of the descriptors most commonly attached to this protein in papers and reviews on PrPc. Fortunately, a clue to the elusive prion function may lie right under, in, our noses. Le Pichon and colleagues have begun this investigation in this issue [see proceeding report].

There are several major hurdles to learning about the function of a particular protein. One of these is knowing where the protein resides in cells. This localization can help narrow down the potential functions of the protein. Earlier this year [2008], it was demonstrated, using new highly specific antibodies, that PrPc in the olfactory system is localized to the axons of both peripheral olfactory sensory receptor neurons and central neurons such as the mitral cells of the olfactory bulb. Glia or support cells in the olfactory bulb or olfactory epithelium were not detectably labeled. In addition to axons, PrPc was also observed in the dendritic spines of axonless olfactory bulb granule cells. These spines are both pre- and postsynaptic to mitral cells, forming reciprocal synapses. Combined with the axon staining, this suggests a potential role for PrPc in presynaptic function. However, given how widely expressed PrPc is throughout the brain, simply showing its presence in the olfactory system was only circumstantial; further tests were required to determine whether it has a functional role in olfaction.

The observation that PrPc is expressed in olfactory sensory neurons, mitral cells and granule cells raises the possibility that it is important for the local circuit function of the olfactory bulb. Olfactory sensory neurons in the nose send axons directly into the brain, terminating on mitral cells, which send their axons directly to olfactory cortex. In the olfactory bulb, local circuits, which include granule cells, refine spatiotemporal patterns of sensory neuron input, and this local circuit function can be monitored electrophysiologically through oscillations in local field potentials. Previous work in a variety of laboratories has demonstrated that manipulation of local circuit function in the olfactory bulb can modulate various aspects of odor perception, 7). Thus, the stage was set to ask whether loss of PrPc affects normal olfaction. Le Pichon and colleagues provide a convincing affirmative answer and with it a clue to PrPc function. Specifically, the loss of PrPc in neurons of the olfactory system of transgenic mice impairs odor-guided behaviors such as finding buried food and simple odor discrimination. The deficit was expressed

regardless of the genetic background of the mice and was not a simple anosmia but was rather an apparent impairment in odor discrimination per se. Although PrPc is found in olfactory sensory neurons, the behavioral deficits were not associated with detectable changes in receptor function. In fact, the sense of smell could be rescued by selectively replacing PrPc in olfactory bulb neurons alone, suggesting a central brain site of action.

Given that PrPc deletion disrupted odor-guided behavior, the final question is raised of whether or not there are neural correlates of this behavioral change in the olfactory bulb. Using electrophysiological recordings, Le Pichon et al. demonstrated specific changes in local circuit function in the olfactory bulb in the PrPc knockouts. For example, using in vivo electrical stimulation to assay local circuit interneuron function, the authors found a decrease in inhibition of mitral cells by granule cell interneurons. This mitral cellgranule cell reciprocal interaction has been hypothesized to be important for everything from lateral inhibition to odor memory to state-dependent modulation of olfactory bulb function. Physiologically, activity in this local feedback circuit underlies high-frequency oscillations in olfactory bulb activity in response to odor stimulation. These olfactory bulb local field potential oscillations may facilitate temporal coding and/or binding of disparate odor features by target neurons in the olfactory cortex. Le Pichon et al. found that these odor-evoked high-frequency oscillations were abnormal in PrPc knockout mice.

The results suggest that PrPc may be important in local circuit function in the olfactory system and may in turn influence odor perception. There has been some debate over whether neural damage done by prion diseases is solely caused by the buildup of PrPsc or whether the concomitant loss of PrPc may also be involved. By demonstrating a systems-level effect of PrPc loss, Le Pichon et al. suggest that both may be important.

[Byline: Donald A Wilson1 and Ralph A Nixon2
1 Donald A Wilson is at the Emotional Brain Institute, Nathan Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Orangeburg, New York 10962, USA, and the Department of Child and Adolescent Psychiatry, New York University School of Medicine, 215 Lexington Avenue, New York, New York 10016, USA.
2 Ralph A Nixon is at the Center for Dementia Research, Nathan Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Orangeburg, New York 10962, USA, and the Departments of Psychiatry and Cell Biology, New York University School of Medicine, 550 1st Ave, New York, New York 10016, USA. <dwilson@nki.rfmh.org>]

--
Communicated by:
ProMED-mail
<promed@promedmail.org>

[The references cited in the text can be found by accessing the original text of tis report in Naute Neuroscinece using the URL at the beginining of the report. - Mod.CP]

******
[6] CJD Update
Date 12 Dec 2008
Source: Health Protection Agency Report, Emerging Infections/CJD [abbreviated and edited]

<http://www.hpa.org.uk/hpr/infections/ei_cjd>.htm>

Creutzfeldt-Jakob disease (CJD) update report

This 6-monthly report provides an update on reports of incidents of potential iatrogenic (healthcare-acquired) exposure to CJD via surgery, and on the National Anonymous Tonsil Archive. Data are correct as of 5 Dec 2008. For numbers of CJD case reports, readers should consult data provided by the national CJD Surveillance Unit (NCJDSU), Edinburgh [1], and the ProMED-mail monthly Prion Disease Updates]. The latest yearly analysis of vCJD reports (onsets and deaths) is also available from the NCJDSU Web site [2], and the ProMED-mail monthly Prion Disease Update.

Reports of incidents of potential iatrogenic exposure to CJD via surgery: 1 Jan 2000 to 30 Jun 2008

There were a total of 350 incidents reported during this period (tabulated in the original text). 12 surgical incidents were reported between 1 Jan and 30 Jun 2008. A surgical incident occurs when a patient undergoes surgery but is only identified as having CJD or being at risk of CJD at a later date. (This means that the ACDP TSE Working Group infection control guidelines would not have been followed). The surgery carried out on an index patient with, or at risk of CJD, may result in contamination of the instruments with abnormal prion protein. (A table in the original text gives the number of CJD surgical incidents reported to the CJD Incidents Panel from January 2000 to June 2008 by the diagnosis of the index patient.)

Investigation of surgical incidents may result in advice to remove surgical instruments from clinical use (to quarantine, destroy, or donate for research). Such advice is generally only given for instruments considered to be potentially contaminated with the CJD agent that have not undergone a certain number of cycles of use and decontamination since their use on an index patient. Hospitals are asked to consider sending any instruments to be permanently removed from use to the Surgical Instrument Store (held by the Health Protection Agency, Porton Down) for research. In the 2nd half of 2007, there were no incidents in which instruments were permanently removed from use.

The Panel may advise contacting and informing some patients of their possible exposure to CJD in a surgical incident. Such advice is generally only given for patients who have definitely been exposed to potentially contaminated instruments which have been used on risk tissues in certain index patients. The Panel may advise that some of these patients should be considered "at-risk of CJD for public health purposes" and asked to take certain precautions (i.e., not to donate blood or other tissues and to inform their medical and dental carers prior to any invasive procedures) in order to reduce the risk of transmitting the CJD agent further. Since 2000, 20 incidents have given rise to such advice (tabulated in the original text). One of these incidents was reported in the 1st half of 2008. The Panel has so far categorised 64 patients as "at-risk"; 13 of whom died before notification. 3 patients have not been notified due to local, clinical decisions. (One index patient undergoing a cataract operation was also a blood component

recipient with evidence of vCJD infection.)

National anonymous tonsil archive for studies of detectable abnormal prion protein

The National Anonymous Tonsil Archive (NATA) continues to receive approximately 400 tonsil pairs per week. The archive had received a total of 67 696 tonsil pairs up to the end of October 2008 from hospitals in England and Scotland. A further 3000 tonsil pairs have been received from the Medical Research Council Prion Unit. Therefore the total number of tonsil pairs in the archive was 70 696.

Testing of homogenates of the tonsil tissue from the archive began at the end of January 2007. 2 enzyme immunoassays (EIAs) are being used for the initial screening of the homogenates for the presence of abnormal prion protein. These EIAs allow the identification of any tonsils that need to be investigated further by the more specific tests of Western blotting (WB) and immunohistochemistry (IHC) [4].

References:

[1] The National Creutzfeldt-Jakob Disease Surveillance Unit, The University of Edinburgh. CJD statistics. CJD figures. Edinburgh: NCJDSU, 3 May 2005. Available at <http://www.cjd.ed.ac.uk/figures.htm>.

[2] The National Creutzfeldt-Jakob Disease Surveillance Unit, The University of Edinburgh. Incidence of variant Creutzfeldt-Jakob Disease Onsets and Deaths in the UK January 1994 - March 2005.Edinburgh: NCJDSU, 14 Apr 2005. Available at <http://www.cjd.ed.ac.uk/vcjdqdec06.htm>.

[3] HPA CJD Incidents Panel [online]. London: HPA. Available at <http://www.hpa.org.uk/web/HPAweb&Page&HPAwebAutoListName/Page/1204031511121>

[4] Spongiform Encephalopathy Advisory Committee. Combining evidence from tissue surveys to estimate the prevalence of subclinical vCJD. SEAC, 2008. Available at <http://www.seac.gov.uk/papers/paper100-2.pdf>.

--
Communicated by:
Terry S. Singeltary Sr.
<flounder9@verizon.net>

[see also:
2008

Prion disease update 2008 (14): new vCJD wave imminent? 20081218.3980
Prion disease update 2008 (13) 20081201.3780
Prion disease update 2008 (12) 20081103.345
Prion disease update 2008 (11) 20081006.3159
vCJD, mother & son - Spain: (Leon) 20080926.3051
Prion disease update 2008 (10) 20080902.2742
Prion disease update 2008 (09) 20080805.2402
Prion disease update 2008 (08) 20080707.2058
Prion disease update 2008 (07) 20080604.1793
Prion disease update 2008 (06) 20080506.1555
vCJD - Spain: susp. 20080410.1311
Prion disease update 2008 (05) 20080408.1285
Prion disease update 2008 (04) 20080303.0878
Prion disease update 2008 (03) 20080204.0455
Prion disease update 2008 (02) 20080107.0087
Prion disease update 2008 (01): correction 20080104.0046
Prion disease update 2008 (01) 20080102.0014
2007

Prion disease update 2007 (08) 20071205.3923
Prion disease update 2007 (07) 20071105.3602
Prion disease update 2007 (06) 20071003.3269

Prion disease update 2007 (05) 20070901.2879
Prion disease update 2007 (04) 20070806.2560
Prion disease update 2007 (03) 20070702.2112
Prion disease update 2007 (02) 20070604.1812
Prion disease update 2007 20070514.1542
CJD (new var.) update 2007 (05) 20070403.1130
CJD (new var.) update 2007 (04) 20070305.0780
CJD (new var.) update 2007 (03) 20070205.0455
CJD (new var.) update 2007 (02): South Korea, susp 20070115.0199
2006

CJD (new var.), blood transfusion risk 20061208.3468
CJD, transmission risk - Canada (ON) 20061207.3457
CJD (new var.) update 2006 (12) 20061205.3431
CJD (new var.) update 2006 (11) 20061106.3190
CJD (new var.) update 2006 (10) 20061002.2820
CJD (new var.) - Netherlands: 2nd case 20060623.1741
CJD (new var.) - UK: 3rd transfusion-related case 20060209.0432
CJD (new var.) update 2006 (02) 20060206.0386
CJD (new var.) update 2006 20060111.0101
2005

CJD (new var.) update 2005 (12) 20051209.3547
CJD (new var.) update 2005 (11) 20051108.3270
CJD (new var.) update 2005 (10) 20051006.2916
CJD (new var.) update 2005 (02) 20050211.0467
CJD (new var.) - UK: update 2005 (01) 20050111.0095
2004

CJD, genetic susceptibility 20041112.3064
CJD (new var.) - UK: update 2004 (14) 20041206.3242
CJD (new var.) - UK: update 2004 (10) 20040909.2518
CJD (new var.) - UK: update 2004 (02) 20040202.0400
CJD (new var.) - UK: update 2004 (01) 20040106.0064
CJD (new var.) - France: 8th case 20041022.2864
CJD (new var.) - France: 9th case 20041123.3138
CJD (new var.), blood supply - UK 20040318.0758
CJD (new var.), carrier frequency study - UK 20040521.1365
2003

CJD (new var.) - UK: update 2003 (13) 20031216.3072
CJD (new var.) - UK: update 2003 (01) 20030108.0057
2002

CJD (new var.) - UK: update Dec 2002 20021207.5997
CJD (new var.) - UK: update Jan 2002 20020111.3223
2001

CJD (new var.), incidence & trends - UK (02) 20011124.2875
CJD (new var.), incidence & trends - UK 20011115.2816
CJD (new var.) - UK: reassessment 20011029.2671
CJD (new var.) - UK: update Oct 2001 20011005.2419
CJD (new var.) - UK: regional variation (02) 20010907.2145
CJD (new var.) - UK: update Sep 2001 20010906.2134
CJD (new var.) - UK: update Aug 2001 20010808.1872
CJD (new var.) - UK: 9th Annual Report 20010628.1231
CJD (new var.) - UK: update June 2001 20010622.1188
CJD (new var.) - UK: update 3 Jan 2001 20010104.0025]
.....cp/ejp/dk

Visit ProMED-mail's web site at <http://www.promedmail.org>.
Send all items for posting to: promed@promedmail.org
(NOT to an individual moderator). If you do not give your
full name and affiliation, it may not be posted. Send
commands to subscribe/unsubscribe, get archives, help,
etc. to: majordomo@promedmail.org. For assistance from a
human being send mail to: owner-promed@promedmail.org.
##
##

Back to Search | Back to Result List

about ISID | membership | programs | publications | resources
14th ICID | site map | ISID home