Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Is PrP^C a Mediator of Aβ Toxicity in Alzheimer's Disease?

Diego Peretti

Medical Research Council Toxicology Unit, Hodgkin Building, University of Leicester, Leicester LE1 9HN, United Kingdom

Review of Gimbel et al.

The amyloid hypothesis proposes that the abnormal accumulation of amyloid β peptide (Aβ) in the brain is a direct cause of neurodegeneration and cognitive decline in Alzheimer's disease (AD). This hypothesis is supported by the occurrence of pathogenic mutations in amyloid precursor protein (APP) and presenilin proteins in autosomal-dominant AD that increase Aβ generation, especially the toxic $A\beta_{42}$ form (for review, see Hardy and Selkoe, 2002). More recently, soluble Aβ oligomeric species have been linked to synaptic dysfunction and learning and memory deficits, including long-term potentiation (LTP), *in vitro* and *in vivo* (for review, see Haass and Selkoe, 2007). Indeed, synaptic loss is an early event and the major structural correlate of cognitive impairment in patients with AD. Hence, major efforts have been directed to elucidate the pathways involved in Aβ toxicity.

Recently, an expression cloning screen for proteins that interact with Aβ oligomers identified the cellular prion protein, PrP^C, as binding synthetic Aβ oligomers with high affinity *in vitro*. Further, this interaction was necessary for the inhibitory effects of Aβ oligomers on LTP *in vitro* (Laurén et al., 2009). Thus, in the absence of PrP^C, Aβ oligomers did not impair LTP, suggesting a role for PrP^C in mediating memory impairment in AD. PrP^C is an interesting candidate. It is a highly conserved protein, with high levels of expression in neurons, but of unclear function. PrP-null mice are essentially phenotypically normal, but misfolded PrP^C is central to the pathogenesis of prion disorders, which are also neurodegenerative diseases. If PrP^C is a major player in memory impairment in AD, it could become a therapeutic target.

The role of the PrP^C–Aβ interaction *in vivo* is the subject of a recent paper in *The Journal of Neuroscience*. Gimbel and colleagues (2010) address the role of PrP^C in mediating the effects of brain-derived Aβ oligomers on memory *in vivo*, using a mouse model of AD. They tested the toxicity of Aβ oligomers in the presence and absence of PrP^C in APP/PSen mice, which express two AD causal mutations, the Swedish mutation in APP and an exon-9-deleted variant of presenilin 1. APP/PSen mice have both elevated steady-state levels of $A\beta_{42}$, which directly correlates to the rate of amyloid deposition, and age-dependent episodic-memory deficits without concurrent LTP impairment (Jankowsky et al., 2004; Volianskis et al., 2010). The mice also have some neuropathological changes, including degeneration of forebrain monoaminergic neurons (Liu et al., 2008) and a marked incidence of unexplained sudden death (Halford and Russell, 2009). The authors addressed the role of PrP^C in these processes by crossing the APP/PSen mice to homozygous PrP-null mice of matched genetic background, thus generating APP/PSen mice with and without PrP^C expression.

First, the authors analyzed whether PrP^C affected the levels of APP and its products. They found no major differences with or without PrP^C. These results are in contrast to reported negative regulation of β-secretase (which cleaves APP to form Aβ) by PrP^C, which resulted in increased Aβ levels in PrP-null mice (Parkin et al., 2007). But APP/PSen mice express two- to fourfold more APP than wild-type mice, so this might obscure any effect of PrP^C on β-secretase regulation (Jankowsky et al., 2004). What it is not clear, however, is whether APP/PSen/PrP-null crosses in this paper produce a progeny indeed devoid of all PrP^C. The authors presented no data showing absence of PrP^C in APP/$PSen^+$/PrP^- mice (PrP-deficient APP/PSen mice). This appears to be a critical omission. Nonetheless, even if the animals are in fact hemizygous for wild-type PrP^C, the reduced PrP^C levels may still give relevant functional readout for Aβ toxicity.

Next, the authors analyzed degeneration of the forebrain monoaminergic neuron afferents, an early symptom of AD that occurs in this mouse model. They found that reduced length of serotonin fibers was rescued in PrP-deficient APP/PSen mice compared with APP/PSen controls at 12 months. There were also slight but significant increases in the presynaptic and postsynaptic markers synaptophysin and PSD-95 in PrP-deficient APP/PSen mice compared with APP/PSen controls. Thus, PrP^C deficiency appears to be neuroprotective in this model.

Another parameter analyzed was survival during the first year of age. APP/

Received June 23, 2010; revised July 23, 2010; accepted July 26, 2010.

I thank members of the laboratory for their insightful discussions and comments.

Correspondence should be addressed to Diego Peretti, Medical Research Council Toxicology Unit, Hodgkin Building, University of Leicester, PO Box 138, Lancaster Road, Leicester LE1 9HN, United Kingdom. E-mail: dap22@le.ac.uk.

DOI:10.1523/JNEUROSCI.3235-10.2010

Copyright © 2010 the authors 0270-6474/10/3011883-02$15.00/0

PSen mice showed a 60% survival rate at 12 months. This result is consistent with previous findings in the same model (Halford and Russell, 2009). The reason for this is not understood, but it also occurs with other APP mutations in transgenic mice and it is highly dependent on genetic background (Carlson et al., 1997). The phenotype was dramatically reduced in PrP-deficient APP/PSen mice, which had a survival rate of >96% at one year. This rescue is so striking that it is surprising the authors did not explore it further. It would have been interesting to analyze whether the effect on survival depends on the level of PrP^C.

Next, the authors examined spatial learning and memory using the Morris water maze test. Here, mice rely on distant visual cues to navigate from a start location at the perimeter of an open swimming arena to reach a submerged (hidden) escape platform. After a set of trials, the platform location was reversed for a second set of trials, a procedure called reversal learning. The test was performed at 3 and 12 months of age. No differences were observed in control conditions of cued learning across all groups of mice. A deficit was detected in APP/PSen animals at 12 months at the end of the spatial learning (trials 5 and 6) and in reversal learning. Loss of reversal learning suggests that the animals cannot efficiently extinguish their initial learning and acquire a path to the new goal position. The deficits observed were rescued in PrP-deficient APP/PSen mice. In addition, memory was tested in the absence of a hidden platform 2 d after the last learning trial and the 12-month-old APP/PSen mice showed no preference for the location of previously learned hidden platform. The preference was rescued in PrP-deficient APP/PSen mice. PrP^C deficiency also rescued the latency of APP/PSen mice to enter a dark compartment in which an aversive stimulus was delivered during a training session in the passive avoidance paradigm, based on associative emotional learning.

This work therefore appears to show a significant rescue of learning/memory deficits in APP/PSen mice in the absence of PrP^C, as well as subtle neuropathological rescue and striking effects on survival. Interestingly, putting Aβ oligomers into wild-type and PrP-null mice produced an apparent impairment of memory independent of PrP^C (Balducci et al., 2010). The age of the mice and the tests used here were different, but any interaction of Aβ and PrP^C might be more complex than suggested.

Thus, the central hypothesis proposed by Gimbel et al. (2010) is that Aβ toxicity, not just in memory but also in sudden death and neuropathology, is mediated through PrP^C. The APP and PS1 mutations in the mice used here are both under the control of prion promoter. This generates an experimental condition of Aβ production, which perfectly matches with endogenous PrP^C expression. Thus, the role of PrP^C as a downstream effector in the Aβ-dependent pathological cascade might be overestimated. Testing other AD transgenic mouse models in which mutations are expressed under the control of promoters not related to PrP^C would be important to exclude this possibility. Further, PrP^C knock-out would be predicted to rescue the phenotypes in all AD (Aβ-based) transgenic models, if indeed Aβ acts via PrP^C as the authors propose. A systematic analysis of several of the other mouse models would be needed before PrP^C blockade could be supported as a therapy in AD, as the authors suggest. Another approach would be to test whether expressing mutant PrP^C that lacks the Aβ binding site prevents Aβ toxicity.

In conclusion, the authors showed a role for PrP^C in Aβ-mediated memory impairment in this specific model. However, further studies will be required to understand the precise role of PrP^C in a more realistic *in vivo* scenario of multiple target mediators of Aβ oligomers toxicity. Another interesting course to explore would be the understanding of common pathways among neurodegenerative disorders. Future work should screen for common downstream pathways activated. An important, unanswered question in prion disease is the identification of PrP^C intermediate toxic elements and the pathways activated by them. Do the events induced by Aβ through PrP^C depend on generation of a toxic PrP element? Are the pathways activated by Aβ oligomers through PrP^C binding similar to those induced by PrP^C binding to infectious isoform PrP^{Sc}? In a broader view, these findings and others open a window for searching for common underlying processes required for synaptic function that might be at the core of many neurodegenerative diseases with a synaptic dysfunction component.

References

Balducci C, Beeg M, Stravalaci M, Bastone A, Sclip A, Biasini E, Tapella L, Colombo L, Manzoni C, Borsello T, Chiesa R, Gobbi M, Salmona M, Forloni G (2010) Synthetic amyloid-beta oligomers impair long-term memory independently of cellular prion protein. Proc Natl Acad Sci U S A 107:2295–2300.

Carlson GA, Borchelt DR, Dake A, Turner S, Danielson V, Coffin JD, Eckman C, Meiners J, Nilsen SP, Younkin SG, Hsiao KK (1997) Genetic modification of the phenotypes produced by amyloid precursor protein overexpression in transgenic mice. Hum Mol Genet 6:1951–1959.

Gimbel DA, Nygaard HB, Coffey EE, Gunther EC, Laurén J, Gimbel ZA, Strittmatter SM (2010) Memory impairment in transgenic Alzheimer mice requires cellular prion protein. J Neurosci 30:6367–6374.

Haass C, Selkoe DJ (2007) Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. Nat Rev Mol Cell Biol 8:101–112.

Halford RW, Russell DW (2009) Reduction of cholesterol synthesis in the mouse brain does not affect amyloid formation in Alzheimer's disease, but does extend lifespan. Proc Natl Acad Sci U S A 106:3502–3506.

Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297:353–356.

Jankowsky JL, Fadale DJ, Anderson J, Xu GM, Gonzales V, Jenkins NA, Copeland NG, Lee MK, Younkin LH, Wagner SL, Younkin SG, Borchelt DR (2004) Mutant presenilins specifically elevate the levels of the 42 residue beta-amyloid peptide *in vivo*: evidence for augmentation of a 42-specific gamma secretase. Hum Mol Genet 13:159–170.

Laurén J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM (2009) Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers. Nature 457:1128–1132.

Liu Y, Yoo MJ, Savonenko A, Stirling W, Price DL, Borchelt DR, Mamounas L, Lyons WE, Blue ME, Lee MK (2008) Amyloid pathology is associated with progressive monoaminergic neurodegeneration in a transgenic mouse model of Alzheimer's disease. J Neurosci 28:13805–13814.

Parkin ET, Watt NT, Hussain I, Eckman EA, Eckman CB, Manson JC, Baybutt HN, Turner AJ, Hooper NM (2007) Cellular prion protein regulates beta-secretase cleavage of the Alzheimer's amyloid precursor protein. Proc Natl Acad Sci U S A 104:11062–11067.

Volianskis A, Køstner R, Mølgaard M, Hass S, Jensen MS (2010) Episodic memory deficits are not related to altered glutamatergic synaptic transmission and plasticity in the CA1 hippocampus of the APPswe/PS1DeltaE9-deleted transgenic mice model of beta-amyloidosis. Neurobiol Aging 31:1173–1187.