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The prion protein as a receptor for amyloid- β

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Increased levels of brain amyloid- β , a secreted peptide cleavage product of amyloid precursor protein (APP), is believed to be critical in the aetiology of Alzheimer's disease¹. Increased amyloid- β can cause synaptic depression^{2,3}, reduce the number of spine protrusions (that is, sites of synaptic contacts)^{4,5} and block long-term synaptic potentiation (LTP)^{6,7}, a form of synaptic plasticity; however, the receptor through which amyloid- β produces these synaptic perturbations has remained elusive. Laurén *et al.*⁸ suggested that binding between oligomeric amyloid- β (a form of amyloid- β thought to be most active^{5,6,9–11}) and the cellular prion protein (PrP^C)⁸ is necessary for synaptic perturbations. Here we show that PrP^C is not required for amyloid- β -induced synaptic depression, reduction in spine density, or blockade of LTP; our results indicate that amyloid- β -mediated synaptic defects do not require PrP^C.

To test whether PrP^C is required for amyloid- β -induced synaptic depression we infected organotypic hippocampal slice neurons with a Sindbis virus driving expression of APPct100, a precursor of amyloid- β , which leads to increased neuronal production and secretion of amyloid- β that does not perturb the health of the neuron, as assessed electrophysiologically³. Synaptic transmission was depressed in neurons expressing APPct100, in both wild-type and *Prnp*^{−/−} mouse slices (where *Prnp* is the gene that encodes PrP^C) 24 h after infection (Fig. 1a). As previously shown for wild-type tissue³, this depression was blocked if *Prnp*^{−/−} slices were maintained during the APPct100 expression period with an inhibitor of NMDA (*N*-methyl-D-aspartate) receptors (Fig. 1a). Thus, synaptic depression after expression of APPct100, an effect of elevated amyloid- β ³, is intact in animals lacking PrP^C.

We next examined the effects of amyloid- β on dendritic spines, sites of excitatory synapses. Overexpression of APP4 (or exposure to oligomeric amyloid- β)⁵ leads to loss of dendritic spines in organotypic slices prepared from wild-type animals, which can be visualized by co-expression of a cytoplasmic marker. The same APP-induced decrease of spines was seen in slices made from mice lacking PrP^C (Fig. 1b). We next determined which species of amyloid- β is responsible for the observed effects. Synthetic amyloid- β (1–40) (A β 40) peptides remain predominantly in monomeric form, and did not affect spine density (Fig. 1c). Amyloid- β (1–42) peptides (A β 42) form oligomers, and when exogenously applied they produced a similar loss of dendritic spines in slices prepared from either wild-type or PrP^C-lacking mice (Fig. 1c). Thus, the loss of dendritic spines produced by oligomeric A β 42 exposure does not depend on PrP^C.

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Author Contributions Experimental work was conducted by H.W.K., L.N.N. and S.N.; designed by H.W.K., L.N.N., S.N. and R.M. The manuscript was written by R.M., H.W.K. and L.N.N.

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We repeated the experiments as described in Laurén *et al.*⁸ that studied PrP^C's role in the A β -mediated blockade of LTP. Acutely prepared hippocampal slices from mature wild-type and *Prnp*^{-/-} mice were exposed to either species of amyloid- β and LTP was induced by theta burst stimulation. We found that A β 42 (but not A β 40) blocked LTP irrespective of whether PrP^C is present or absent (Fig. 1d).

We show that amyloid- β -induced synaptic depression, loss of dendritic spines and blockade of LTP are present in hippocampal slices prepared from PrP^C-deficient animals. In line with our results, amyloid- β oligomers were shown to impair long-term memory equally in PrP^C-lacking and PrP^C-expressing mice¹². Thus, although oligomeric amyloid- β can bind PrP^C, it does not seem to be the receptor responsible for synaptic perturbations caused by oligomeric amyloid- β . Elucidation of the molecular mechanisms by which amyloid- β produces synaptic perturbations remains as a major goal in finding therapeutic treatments of Alzheimer's disease.

METHODS

C57/BL10 and C57/BL10 *Prnp*^{-/-} mice were provided by M. Oldstone (Scripps Research Institute, grant AG04342). Organotypic slice cultures were infected at 7–12 days *in vitro* with Sindbis virus expressing APPct100³. After 24h simultaneous whole-cell paired recordings were obtained as described previously¹³. At 12–17 days *in vitro* slices were infected with Sindbis virus expressing tdTomato or APP plus tdTomato for 48 h, or infected with eGFP and incubated with 1 μ M monomeric A β 40 or oligomerized A β 42¹⁴ for 24 h. Two-photon laser scanning images were taken of dendrites at the site of primary apical dendrite bifurcation. Spine densities were counted as described previously⁴. The protocol for the LTP experiments was as described in Laurén *et al.*⁸.

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Figure 1. PrP^C is not required for amyloid-β-induced synaptic deficits

a, Depression of whole-cell recorded synaptic AMPA receptor currents in a CA1 hippocampal neuron infected with Sindbis virus expressing APPct100 (grey bars) compared to a simultaneously recorded non-infected neuron (white bars) in wild-type (WT; $73 \pm 8\%$, $n = 18$, $P = 0.02$) and *Prnp*^{-/-} slices ($59 \pm 9\%$, $n = 25$, $P = 0.002$). Incubation of slices with 100 μ M D-amino-phosphono-valeric acid (D-APV) during APPct100 expression abolished synaptic depression in WT ($98 \pm 11\%$, $n = 12$, $P = 0.6$) and *Prnp*^{-/-} slices ($105 \pm 13\%$, $n = 13$, $P = 0.6$). EPSC, excitatory postsynaptic current. **b**, Decreased spine density by APP expression in WT ($n = 14$ APP expressing, $n = 9$ control dendrites, $P = 0.03$) and *Prnp*^{-/-} slices ($n = 13$ APP expressing, $n = 9$ control dendrites, $P = 0.01$). Representative images of a dendrite in conditions as indicated. **c**, Spine loss in PrP^C-deficient hippocampal slices is specific to incubation with oligomeric amyloid- β . A β 42, but not A β 40, preparation produced high molecular mass oligomers, as indicated by western blot analysis. WT and *Prnp*^{-/-} slices were incubated with no peptide (ctrl: WT, $n = 22$; *Prnp*^{-/-}, $n = 22$), with A β 40 (WT, $n = 22$; *Prnp*^{-/-}, $n = 20$), or with A β 42 (WT, $n = 22$; *Prnp*^{-/-}, $n = 22$) at 1 μ M peptide concentration for 24 h, and spine densities were analysed blind to the experimenter. Spine densities were unaffected by monomeric amyloid- β incubation (WT, $P = 0.4$; *Prnp*^{-/-}, $P = 0.9$), but significantly reduced by incubation with oligomeric amyloid- β (WT, $P = 0.02$; *Prnp*^{-/-}, $P = 0.03$). Representative images of a dendrite in conditions as indicated. **d**, Oligomeric A β 42 blocks LTP independent of the PrP^C. Hippocampal slices were isolated from 2–3-month-old WT or *Prnp*^{-/-} mice. Field excitatory postsynaptic potentials (fEPSPs) were measured on two independent pathways in the presence of either 500 nM A β 40 or 500 nM A β 42. A control pathway (open circles) was recorded while theta burst stimulation (ten 100-Hz four shock bursts with 200-ms interburst intervals, arrow) was delivered to the second pathway (filled circles) after recording a 15 min baseline. LTP was significantly depressed by A β 42 compared with A β 40 in both WT ($P < 0.001$) and *Prnp*^{-/-} slices ($P < 0.001$). When compared to their corresponding control pathway, LTP was successfully induced in WT ($P < 0.05$) and *Prnp*^{-/-} slices ($P < 0.05$) treated with monomers. Block of LTP was found in both WT ($P > 0.05$) and *Prnp*^{-/-} ($P > 0.05$) oligomer-treated slices when compared to their corresponding control pathway. Statistical comparisons (P) were performed using paired (**a**) or non-paired (**b–d**) two-tailed Student's *t*-test of log-transformed data. All error bars, s.e.m.; asterisk indicates $P < 0.05$.