A β Inhibition of Ionic Conductance in Mouse Basal Forebrain Neurons Is Dependent upon the Cellular Prion Protein PrP^C

Kwai Alier,^{1*} Li Ma,^{1*} Jing Yang,² David Westaway,^{1,2} and Jack H. Jhamandas¹

¹Department of Medicine (Neurology), University of Alberta, Edmonton, Alberta T6G 2S2, Canada, and ²Centre for Prions and Protein Folding Diseases, University of Alberta, Edmonton, Alberta T6G 2M8 Canada

Current therapies for Alzheimer's disease (AD) address a loss of cholinergic neurons, while accumulation of neurotoxic amyloid β (A β) peptide assemblies is thought central to molecular pathogenesis. Overlaps may exist between prionopathies and AD wherein A β oligomers bind to the cellular prion protein PrP^C and inhibit synaptic plasticity in the hippocampus (Laurén et al., 2009). Here we applied oligomeric A β to neurons with different PrP (*Prnp*) gene dosage. Whole-cell recordings were obtained from dissociated neurons of the diagonal band of Broca (DBB), a cholinergic basal forebrain nucleus. In wild-type (wt) mice, A β_{1-42} evoked a concentration-dependent reduction of whole-cell outward currents in a voltage range between -30 and $+30$ mV; reduction occurred through a combined modulation of a suite of potassium conductances including the delayed rectifier (I_K), the transient outward (I_A), and the iberitoxin-sensitive (calcium-activated potassium, I_C) currents. Inhibition was not seen with A β_{42-1} peptide, while A β_{1-42} -induced responses were reduced by application of anti-PrP antibody, attenuated in cells from *Prnp*^{0/+} hemizygotes, and absent in *Prnp*^{0/0} homozygotes. Similarly, amyloidogenic amylin peptide depressed DBB whole-cell currents in DBB cells from wt mice, but not *Prnp*^{0/0} homozygotes. While prior studies give broad support for a neuroprotective function for PrP^C, our data define a latent pro-pathogenic role in the presence of amyloid assemblies.

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease and is characterized by loss of cognitive function leading to frank dementia. Amyloid β (A β), a secreted peptide cleavage product of amyloid precursor protein (APP), is thought to be important in mediating synaptic disruption, neuronal dysfunction, and cell death (Walsh et al., 2002; Palop and Mucke, 2010). Intermediate-sized, soluble assemblies of A β are implicated in synaptotoxicity more so than large fibrillar assemblies or plaques (Bitan et al., 2003; Kirkitadze and Kowalska, 2005; Teplow et al., 2006). For prion diseases, the cellular prion protein PrP^C precursor, encoded by the *Prnp* gene, is a membrane-anchored glycoprotein that is remodeled to a β -sheet-enriched

isoform, PrP^{Sc} (Prusiner, 1991). Recently, soluble forms of A β have been reported to bind PrP^C, resulting in suppression of synaptic plasticity in hippocampal slices (Laurén et al., 2009). Further, transgenic (Tg) mice expressing familial AD-associated mutant forms of β APP (TgAPP mice) are rescued from memory impairment and early death following ablation of PrP^C (Gimbel et al., 2010). While some other studies are in broad accord with these notions (Barry et al., 2011; Freir et al., 2011), others have disputed an obligatory role for PrP^C in A β -induced impairment of synaptic structure and function, and in AD-related behavioral endpoints (Balducci et al., 2010; Calella et al., 2010; Kessels et al., 2010; Cissé et al., 2011) yet have confirmed physical interactions between A β and PrP (Balducci et al., 2010; Chen et al., 2010; Bate and Williams, 2011). We investigated this provocative area. Our prior studies have defined neuronal excitability-modifying properties of PrP (Alier et al., 2010) focusing on the 105–125 region (mouse PrP numbering) immediately adjacent to a putative 95–105 A β binding site. Here we measured the actions of oligomeric A β and human amylin—another amyloidogenic peptide that shares some biophysical and neurotoxic properties with A β —on forebrain neurons from the nucleus of the diagonal band of Broca (DBB). Using mice of different *Prnp* genotypes, our data implicate a requirement for PrP^C in A β and amylin depression of specific potassium conductances.

Materials and Methods

Mouse strains. All procedures were complied with Canadian Council for Animal Care guidelines. Congenic *Prnp*^{0/+} mice (Zrch 1 allele, 17 back-

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*K.A. and L.M. contributed equally to this work.

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Correspondence should be addressed to either of the following: Dr. Jack H. Jhamandas, 530 Heritage Medical Research Centre, Department of Medicine (Neurology), University of Alberta, Edmonton, AB T6G 2S2, Canada, E-mail: jack.jhamandas@ualberta.ca; or Dr. David Westaway, Centre for Prions and Protein Folding Diseases, 204 Environmental Engineering Building, University of Alberta, Edmonton, AB T6G 2M8, Canada, E-mail: david.westaway@ualberta.ca.

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crosses to C57BL/6 stock, Taconic) were intercrossed to yield *Prnp*^{0/0}, *Prnp*^{0/+}, and wild-type (wt) genotypes (of either sex), with additional wt mice purchased for some experiments (Taconic Farms, “C57BL/6Tac”). (Janus et al., 2000; Chishti et al., 2001).

Acutely dissociated cells and whole-cell recordings. These procedures were as described previously (Jhamandas et al., 2001, 2011). Data are presented as mean ± SE. Student's two-tailed *t* test (paired when appropriate) was used for determining significance of effect in electrophysiological measurements.

Reagents. Oligomeric form of Aβ_{1–42} peptide (rPeptide), Aβ_{42–1}, and human amylin (American Peptide) were prepared as described previously (Stine et al., 2003, 2011; Jhamandas et al., 2011). Peptides were diluted in external perfusion medium just before application. PrP antibody Sha31 (Medicorp) was diluted to a concentration of 300 ng/ml before use. All drugs and chemicals were applied via bath perfusion (3–5 ml/min), which allowed complete exchange in less than half a minute.

Results

Recordings from DBB neurons

Dissociated neurons from the DBB contain a variety of potassium conductances: transient outward (*I*_A), delayed rectifier (*I*_K), and calcium-activated potassium (*I*_C). The effect of Aβ on this ionic conductance was investigated in mice of different *Prnp* genotypes. Average membrane capacitance (*C*_m) was estimated on an Axopatch-1D amplifier: wt mice had a *C*_m of 8.75 ± 0.59 pF (*n* = 8; C57BL/6) or 9.75 ± 0.56 pF (*n* = 10; C57BL/6Tac), while *Prnp*^{0/+} mice and *Prnp*^{0/0} mice had *C*_m values of 12 ± 0.76 pF (*n* = 9) and 8 ± 0.60 pF (*n* = 10), respectively. Under control conditions without drug, the average input conductance measured from the slope of the current–voltage (*I*–*V*) relationships between –60 and –110 mV was 1.05 ± 0.22 nS (C57BL/6), 0.93 ± 0.12 nS (C57BL/6Tac), 0.93 ± 0.19 nS (*Prnp*^{0/+}), and 0.77 ± 0.18 nS (*Prnp*^{0/0}). Application of 1 μM oligomeric Aβ_{1–42} (Stine et al., 2003, 2011) had no significant effect on conductance in this voltage range compared to that under control conditions (1.34 ± 0.22 nS, *p* > 0.05, *n* = 8, C57BL/6; 0.94 ± 0.13 nS, *p* > 0.05, *n* = 10, C57 BL/6Tac; 0.91 ± 0.13 nS, *p* > 0.05, *n* = 9, *Prnp*^{0/+}; 1.07 ± 0.28 nS, *p* > 0.05, *n* = 10, *Prnp*^{0/0}).

Effects of oligomeric Aβ_{1–42} on the whole-cell currents

Whole-cell currents (WCC) were investigated in *Prnp*^{+/+}, *Prnp*^{0/+}, and *Prnp*^{0/0} cells under control conditions and in the presence of Aβ_{1–42} (1 μM). Aβ_{1–42} inhibited whole-cell currents in the range –30 to +30 mV. In C57BL/6Tac wt mice, Aβ_{1–42} significantly reduced WCC (control = 5.60 ± 0.26 nA, Aβ_{1–42} = 4.84 ± 0.28 nA at +30 mV, **p* < 0.05, *n* = 8) (Fig. 1A). Aβ_{1–42} inhibited peak whole-cell currents of DBB neurons in a dose-dependent manner (Fig. 1C). Inverse Aβ, Aβ_{42–1}, peptide (1 μM) had no effect on WCC (control = 4.76 ± 0.51 nA, Aβ_{42–1} = 4.51 ± 0.47 nA at +30 mV, *p* = 0.36, *n* = 6) (Fig. 1B). In the C57BL/6 wt mice at +30 mV, application of Aβ_{1–42} significantly decreased WCC from 3.72 ± 0.27 nA to 3.08 ± 0.27 nA, a reduction of 15.21 ± 1.2%, **p* < 0.05, *n* = 8) (Fig. 2A). Aβ_{1–42} had no significant effect on the WCC of *Prnp*^{0/+} mice (control = 3.94 ± 0.27 nA, Aβ_{1–42} = 3.63 ± 0.26 nA at +30 mV, *p* = 0.19, *n* = 9) (Fig. 2B) and *Prnp*^{0/0} mice (control = 3.65 ± 0.44 nA, Aβ_{1–42} = 3.57 ± 0.42 nA at +30 mV, *p* = 0.41, *n* = 10) (Fig. 2C). We also investigated whether the anti-PrP^C antibody (Sha31) is able to inhibit the Aβ_{1–42}-evoked reduction of WCC on the DBB neurons in *Prnp*^{+/+} mice. Seventy-five percent (6 of 8 cells) of DBB neurons responded to Aβ_{1–42} in the usual manner. However, in the presence of anti-PrP^C antibody Sha31, Aβ_{1–42} (1 μM)-evoked depression of WCC in wt DBB neurons was markedly reduced, compared to control conditions (Fig. 2D).

Figure 1. Effects of Aβ_{1–42} on DBB WCC in wt mice. **A**, Aβ_{1–42} (1 μM) significantly depresses WCC (**p* < 0.05, *n* = 8 at +30 mV), inset shows the voltage ramp protocol applied for 10 s. **B**, Reversed oligomers Aβ_{42–1} (1 μM) peptide had no effect on WCC (*p* = 0.36, *n* = 6 at +30 mV). **C**, Dose–response relationship for Aβ_{1–42}-evoked inhibition of peak WCC at +30 mV (*n* = 5 at each dose).

Outward potassium currents in DBB neurons are a mixture of calcium and non-calcium-activated components (Jhamandas et al., 2001). The non-calcium-activated component consists primarily of the *I*_K and the *I*_A currents, while the calcium-dependent component of potassium currents includes voltage-sensitive conductances, *I*_C (BK channels). The effects of oligomeric Aβ_{1–42} on these conductances were further investigated in wt (i.e., *Prnp*^{+/+}) mice.

Effects of Aβ_{1–42} on *I*_A and the *I*_K potassium currents in wt mice

Both *I*_A and *I*_K currents are voltage sensitive, and their activation and inactivation are strongly voltage dependent. *I*_A requires the holding potential to be relatively hyperpolarized (approximately –110 mV) for removal of its inactivation, whereas it is inactivated at –40 mV. On the other hand, *I*_K is not inactivated at –40 mV. Hence, the difference in the biophysical properties of *I*_A and *I*_K was used to isolate these two currents. Application of a conditioning pulse to –40 mV will activate *I*_K without any significant

Figure 2. Effect of *Prnp* gene dosage and PrP blockade on Aβ inhibition of DBB whole-cell currents. **A**, Aβ₁₋₄₂ significantly reduces WCC of DBB neurons from C57BL/6Tac wt mice ($p < 0.05$, $n = 8$ at +30 mV). **B**, Effects of Aβ₁₋₄₂ on DBB whole-cell currents of heterozygous (*Prnp*^{0/+}) mice. Current–voltage (*I*–*V*) plot of slight reduction in WCC following application of Aβ₁₋₄₂ ($p > 0.05$, $n = 8$ at +30 mV). **C**, Effects of Aβ₁₋₄₂ on DBB whole-cell currents of homozygous (*Prnp*^{0/0}) mice. *I*–*V* plot of slight reduction in WCC following application of Aβ₁₋₄₂ ($p > 0.05$, $n = 10$ at +30 mV). **D**, In the presence of anti-PrP antibody Sha31, Aβ₁₋₄₂ reduction of WCC in DBB neurons from wt mice is markedly blunted compared to control conditions (no antibody). Inset shows reduction of WCC by Aβ₁₋₄₂ without and in the presence of the anti-PrP antibody Sha31 ($p > 0.001$, $n = 9$ at +30 mV).

contamination by I_A (Connor and Stevens, 1971). A conditioning pulse to -120 mV will activate both I_A and I_K . Difference currents obtained by subtracting the currents evoked by depolarizing pulses following a conditioning pulse to -40 mV from those

evoked following a conditioning pulse to -120 mV provide an estimate of I_A . The currents were recorded from a neuron with a conditioning pulse to -40 mV for 150 ms, representing mainly I_K , under control conditions, and in the presence of oligomeric Aβ₁₋₄₂ (1 μM). Aβ₁₋₄₂ reduced I_K by $20.08 \pm 1.86\%$ compared to the control (control = 4.82 ± 0.29 nA, Aβ₁₋₄₂ = 3.66 ± 0.18 nA, at +30 mV, $p < 0.05$, $n = 5$) (Fig. 3A). Figure 2B shows difference currents recorded from the same neuron representing mainly I_A , under control conditions, and in the presence of Aβ₁₋₄₂. Aβ₁₋₄₂ significantly reduced I_A by $20.4 \pm 4.6\%$ compared to control (control = 1.90 ± 0.10 nA, Aβ₁₋₄₂ = 1.44 ± 0.10 nA, at +30 mV, $p < 0.05$, $n = 4$).

Effects of Aβ₁₋₄₂ oligomers on calcium-activated potassium currents in wt mice

Calcium-activated currents include the voltage-sensitive conductances called maxi gK(Ca) (I_C or BK) and the voltage-insensitive ones that underlie action potential afterhyperpolarization (I_{AHP}). Of the two main Ca^{2+} -activated potassium currents, under whole-cell recording conditions from DBB neurons, the apamin-sensitive slow I_{AHP} (SK) makes little contribution, and the majority of the currents flow through I_C channels (Jhamandas et al., 2001). Indeed, as in rat DBB neurons (Jassar et al., 1999), we observed no apamin-sensitive currents in DBB cells from C57BL/6Tac wt mice (data not shown). To determine the degree to which Aβ₁₋₄₂ oligomer (1 μM) effects are mediated via I_C , we examined actions of Aβ₁₋₄₂ under conditions where cells from C57BL/6Tac mice were perfused with iberiotoxin (IBTX), a specific blocker of I_C channels. Figure 3C shows the average of current–voltage relationships obtained from six neurons under control conditions, in the presence of IBTX (50 nM) alone, and upon application Aβ₁₋₄₂ in the presence of IBTX. IBTX applied alone reduced outward currents. Application of Aβ₁₋₄₂ in the presence of IBTX resulted in an additional, but smaller, reduction of the currents than evoked by Aβ₁₋₄₂ alone (control = 5.18 ± 0.19 nA, IBTX = 4.55 ± 0.25 nA, IBTX and Aβ₁₋₄₂ = 4.42 ± 0.26 nA at +30 mV, $p < 0.05$ compared to control, $n = 6$). Thus, Aβ effects on I_C type of K^+ channels contribute to the overall reduction in whole-cell currents that is observed in peptide-treated DBB neurons.

Human amylin peptide reduces whole-cell currents in wt DBB neurons

Effects of human amylin on WCC were examined on DBB neurons from wt and *Prnp*^{0/0} mice. Application of human amylin (1 μM) in DBB neurons from C57BL/6Tac wt mice resulted in a significant reduction in WCC in the voltage range -30 to $+30$ mV (control = 6.83 ± 0.95 nA, human amylin = 5.77 ± 0.78 nA at +30 mV, $p < 0.05$, $n = 7$) (Fig. 4A). Human amylin had no significant effect on the WCC of *Prnp*^{0/0} mice (control = 5.02 ± 0.40 nA, human amylin = 4.81 ± 0.35 nA at +30 mV, $p = 0.7$, $n = 5$) (Fig. 4B, inset).

Discussion

Using Aβ₁₋₄₂ multimeric assemblies—visualized as spheroidal structures by electron microscopy (Jhamandas et al., 2005, 2011)—we have documented inhibition of a suite of potassium conductances, i.e., I_K , I_A , and I_C . The effect was observed in dissociated neurons derived from the DBB, a cholinergic forebrain nucleus (Jhamandas et al., 2001). In heterozygous mice, there was an insignificant suppression of whole-cell currents, while in the homozygous null *Prnp*^{0/0} mice, there was no suppression. To confirm that these effects upon Aβ₁₋₄₂ action were mediated directly by PrP^C protein, rather than reflecting a secondary ge-

Figure 3. $A\beta_{1-42}$ significantly reduces the I_K , I_{KA} , and I_C currents in DBB neurons. **A**, Voltage protocol for recording I_K is depicted on the left with a holding potential of -80 mV and a 150 ms conditioning pulse to -40 mV. Top, The effect of $A\beta_{1-42}$ on I_K . Bottom, $I-V$ plot of the peak I_K current indicating a reduction of the I_K current after 5 min perfusion of $A\beta_{1-42}$ (1 μ M) ($*p < 0.05$, $n = 5$ at $+30$ mV). **B**, Top, I_A obtained as difference currents by subtracting the currents obtained by the voltage protocol in **A** from that obtained by applying the voltage protocol shown here (cells held at -80 mV and a conditioning 150 ms pulse applied to -120 mV). Bottom, $I-V$ plot of the I_A current indicating a reduction of the peak I_A current after 5 min perfusion of $A\beta_{1-42}$ (1 μ M) ($*p < 0.05$, $n = 4$ at $+30$ mV). **C**, $I-V$ relationship from DBB neurons under control conditions, in 50 nM IBTX, in 1 μ M $A\beta_{1-42}$ in IBTX ($*p < 0.05$ compared to control, $n = 6$ at $+30$ mV). Inset shows reduction of WCC under control conditions by $A\beta_{1-42}$ and in the presence of the IBTX ($p > 0.05$, $n = 6$ at $+30$ mV). All recordings were made from wt cells.

Figure 4. Effect of *Prnp* gene dosage on human amylin (hAmylin) inhibition of DBB whole-cell currents. **A**, hAmylin (1 μ M) depresses WCC in a DBB neuron from C57BL/6Tac wt mice. **B**, Application of hAmylin to a DBB neuron from *Prnp*^{0/0} does not result in WCC reduction. Inset shows histograms depicting hAmylin-evoked reduction of WCC at $+30$ mV in *Prnp*^{+/+} (wt) and *Prnp*^{0/0} mice ($*p > 0.001$).

netic mechanism (for example, a functional polymorphism in linkage disequilibrium with the *Zrch1 Prnp* null allele), we also examined the effects of $A\beta_{1-42}$ on DBB neurons from wt mice in the presence of a PrP antibody. For this purpose, we used the monoclonal antibody reagent Sha31. No significant reduction in WCC was identified following perfusion of DBB neurons with Sha31, thus supporting the notion that $A\beta_{1-42}$ effects require PrP^C.

In wt mice, $A\beta_{1-42}$ preparations induced a decrease in whole-cell currents that was nearly abolished by iberitoxin, a specific blocker of I_C . This supports an involvement of calcium-activated potassium channels in mediating, in part, the cellular effects of $A\beta_{1-42}$ on DBB neurons. I_C currents have been shown to be responsible for the repolarization phase of the action potential and, hence, play a role in the process of spike frequency adaptation (accommodation) (Vergara et al., 1998; Kim and Hoffman, 2008). The effect of $A\beta_{1-42}$ on depressing outward currents through I_C channels could result in an increased excitation of DBB neurons. Functionally, I_K channels augment action potential repolarization, and therefore $A\beta_{1-42}$ reduction of I_K currents, in wt mice, would also be expected to result in an increase in the action potential width, potentially playing a role in regulation of cell excitability. Physiologically, I_A produces its effect by increasing the rate of both action potential repolarization and accommodation (Viana et al., 1993; Zhang and McBain, 1995; Gu et al., 2007). Blockage of I_A by $A\beta$ could lead to increased duration of depolarization during an action potential and consequently increase Ca^{2+} influx into DBB neurons. We have previously observed that $A\beta$ and human amylin demonstrate identical

electrophysiological effects on cholinergic neurons of the DBB, and moreover share a similar profile of neurotoxicity on primary cultures of neurons from this basal forebrain nucleus (Jhamandas et al., 2001, 2003; Jhamandas and MacTavish, 2004). A recent report also suggest that PrP^C may also serve as a target for the expression of biological effects of amyloidogenic peptides besides A β (Resenberger et al., 2011). We therefore examined the electrophysiological effects of human amylin on DBB neurons from wt and *Prnp*^{0/0} mice, where we observed that human amylin effects were markedly blunted in *Prnp*^{0/0} cells in a manner akin to oligomeric A β . While the mechanism tying A β - or human amylin-docked PrP^C to potassium conductances remains to be established, A β binding sites have been mapped to distinct N-terminal regions within PrP^C (Laurén et al., 2009; Balducci et al., 2010; Chen et al., 2010; Freir et al., 2011), but a functional effect of antibodies binding to the α -helical C-terminal region is not without precedent. Thus ICSM18 antibody binds to helix 1 residues 146–159 (White et al., 2003) and had efficacy on hippocampal cells when administered at a concentration of 2 μ g/ml (Freir et al., 2011), whereas Sha31 used here binds to residues 145–152 (Féraudet et al., 2005) and had efficacy on DBB cells at 0.3 μ g/ml (Fig. 2D). These “distal” effects are compatible with the notion that PrP undergoes interactions in *cis*- between the flexible N-terminal region and the globular C-terminal domain (Qin et al., 2000), and clues as to how PrP^C might impact potassium channels may lie within an interactome derived from the adult mouse brain (Schmitt-Ulms et al., 2004).

In addition to variable results emerging from different laboratories (see Introduction), the pro-pathogenic response of PrP^C to amyloid assemblies seems at odds with neuroprotective activity. Go-forward studies to reconcile these issues will need to focus upon reliable traits present within a spectrum of phenotypically divergent TgAPP mice (Phinney et al., 2003; Ashe and Zahs, 2010; Wisniewski and Sigurdsson, 2010) and avoid the diverse effects that can be driven by different types of A β assemblies (Sakono and Zako, 2010). Divergent target cell populations under study (e.g., hippocampus vs basal forebrain) also need to be considered. When these variables are isolated, the protective and pathogenic properties of PrP^C may be discerned reliably. In turn, it may be possible to test the hypothesis that pro-pathogenic effects of PrP^C reflect a subverted physiological function that is poorly adapted to deal with chronic exposure to amyloid assemblies, as would be found in AD. If the basal neuroprotective activity of PrP^C can be separated in dose–response properties from pro-pathogenic effects, then PrP^C-directed anti-amyloid therapies may warrant closer consideration.

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