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Research report

Effect of amyloid β on capacitive calcium entry in neural 2a cells

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ABSTRACT

We studied the direct role of amyloid β (Aβ) in regulating capacitive calcium entry (CCE), an important refilling mechanism for depleted intracellular calcium stores. For the first time, we found that Aβ can potentiate CCE. Neural 2a cells stably expressing Swedish mutant APP (APPswe), which can secrete large amounts of Aβ, have stronger CCE than its wild-type controls. Either reducing the Aβ in the medium by antibody binding or decreasing Aβ production by γ secretase inhibitor treatment could significantly depress CCE in APPswe cells. The results demonstrated that the CCE potentiation in APPswe cells was caused by Aβ over-expression. Our research also revealed that the effect of Aβ on CCE potentiation could be decreased by Aβ channel blocker, which showed that the channels formed by Aβ are one of the ways through which Aβ causes CCE potentiation.

1. Introduction

Alzheimer's disease (AD) is a progressive dementia affecting a large proportion of aging people. AD is characterized by two hallmark brain lesions, i.e. extracellular deposits of amyloid β (Aβ) and intracellular neurofibrillary tangles. Aβ is 40–42 amino acids in length and is proposed to be central in the pathology of Alzheimer's disease (AD) [5,6,16]. It is derived from the processing of Amyloid Precursor Protein (APP) by β secretase and γ secretase [12]. Familial APP mutations increase Aβ production or lead to an increased proportion of Aβ ending at residue 42 [4,28]. The Swedish mutation of APP, which can cause an overproduction of Aβ, is a double mutation at codons 670 and 671 (APP 770 transcript) in exon 16. It has been found to be correlated with the disease in two large families with early-onset Alzheimer's in Sweden [1,17].

Calcium plays a very important role in a great variety of life processes. Calcium dyshomeostasis is an important molecular defect in AD [3,13]. Degenerated neurons in the brains of AD patients showed increased levels of calcium [18] and increased activation of Ca^{2+}-dependent enzymes [20]. Sustained disturbance in calcium homeostasis might be the primary cause of neurodegeneration in Alzheimer's disease.

Capacitive calcium entry (CCE), which is also called store-operated calcium entry (SOCE), is calcium influx activated by depletion of calcium stores [22]. It has been reported that CCE is involved in AD pathology. Mutations of presenilin 1, which is one of the γ secretase components, leads to diminished CCE [9,14,33]. It seems clear that one cellular consequence of Alzheimer's disease-associated presenilin mutations is diminished CCE, which in some way could contribute to the associated neuropathology. In contrast to presenilin mutations, surprisingly few direct studies have addressed the effect of Aβ on CCE.

Here, we used neural 2a (N2a) cells stably expressing Swedish mutant APP, which over produces Aβ [30], as model cells to study the effect of Aβ on CCE. Our results showed that the Swedish mutant APP can cause significant potentiation of CCE in N2a cells. This kind of potentiation could be antagonized either by the removal of Aβ by Aβ antibodies or by the inhibition of Aβ production by DAPT, a γ secretase inhibitor. Our research also showed that the channels formed by Aβ on the cell membrane contribute to Aβ caused CCE potentiation.

2. Materials and methods

2.1. Antibodies and chemicals

Mouse monoclonal antibody 6E10 against APP was purchased from Signet Laboratories (Dedlam, MA), and 4G8 against $Aβ_{17–24}$ was from Sigma (St. Louis, USA). Mouse anti-$Aβ_{1–42}$ antiserum was made by ourselves. *N*-[*N*-(3,5-

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difluorophenacetyl)-L-alanyl]-sphenylglycinet-butyl ester (DAPT), thapsigargin and tromethamine were obtained from Sigma.

2.2. Cell cultures

Murine N2a cells and their derivative clones stably expressing Swedish mutant APP (APPswe) and wild-type human APP695 (APPwt) were generous gifts from Dr. Huaxi Xu of the Burnham Institute, USA. Cells were maintained in medium containing 50% DMEM and 50% Opti-MEM (Gibco, USA), supplemented with 5% FBS, 250 μg/ml G418 and 0.1% antibiotics (penicillin and streptomycin).

2.3. Western blot

For APP concentration detection, adherent cells were collected and further lysed using cell lysis buffer. Protein concentrations were determined using a BCA kit (Pierce, USA). Samples were eluted by cell lysis buffer to get the same concentration. Proteins were further eluted by adding 4 × sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) sample buffer and boiled at 100 °C for 5 min. Proteins were separated by 10% SDS-PAGE and were electrotransferred onto nitrocellulose membrane (pore size 0.45 μm). The membrane was incubated with anti-APP antibody 6E10 (1:1000 dilution) at 4 °C for more than 4 h. Detection was performed using alkaline phosphatase conjugated goat-anti-mouse IgG (1:10000). The bands on the membrane were scanned and analyzed.

2.4. Calcium measurements

If not specifically mentioned, most of the [Ca^{2+}] measurements in the cells were performed using the indicator Fluo3/AM (Calbiochem, USA). Fluo3/AM was solubilized in DMSO. Cells were loaded with 5 μM Fluo3/AM in HBSS (145 mM NaCl, 2.5 mM KCl, 1 mM $MgCl_2$, 20 mM HEPES, 10 mM gluocose, 1.8 mM $CaCl_2$) containing bovine serum albumin (1%) at 37 °C for 30 min [8]. After 30 min of washing, they were viewed using an upright microscope (BX61, Olympus). Measurements were acquired at 3 s intervals. If not specially mentioned, the digital images were collected by CCD camera (Coolsnap HQ) using a 20 × water immersion objective, and subsequently analyzed using MetaMorph (Molecular Devices). Some of the images were collected by a confocal microscope (FV500, Olympus), using a 60 × water immersion objective and further analyzed by Fluoview (Olympus). For Ca^{2+}-free experiments the same buffer was used, but $CaCl_2$ was replaced with 50 μM EGTA.

Fura2/AM was also used to confirm the data obtained from Fluo3/AM. Cell treatment was as same as that in the Ca^{2+} measurement using Fluo3. The cells were viewed using an inverted microscope (IX71, Olympus). The excitation wavelengths of Fura2/AM are 340and 380 nm, while the emission wavelength is 510 nm. Digital images were collected by a CCD camera using a 40 × oil immersion objective (Olympus, Japan). Measurements were acquired at 3–5 s intervals at both excitation wavelengths (340 and 380 nm). Digital fluorescence images were constructed and displayed as pseudo-color images and subsequently analyzed (Aquamos). Ratio of a Fura2 emission at 510 nm evoked by 340 and 380 nm light using a digital imaging system (Hamayatsu, Japan) was used to represent the intracellular Ca^{2+} concentration.

Each experiment was performed for at least three cultures, and the values for each group were expressed as mean ± SD. Statistical analyses were carried out by two-tailed unpaired *t*-test. $P < 0.05$ was considered to be significant. Data was collected using a CCD system except where noted otherwise. Cells were stained with fluo3 except specially noted. Data was collected using a CCD system and cells were stained with Fluo3/AM unless noted otherwise.

2.5. Aβ measurement

Aβ levels were determined using a commercially available sandwich enzyme-linked immunoabsorbant assay (ELISA) kit which specifically recognizes Aβx-40 (Wako, Japan). Briefly, to measure Aβ levels in the cell culture medium, 100 μl of undiluted medium or standards included in the kit were applied to microtiter plates pre-coated with antibody and preserved in refrigerator overnight. Second conjugate was applied to incubate for 2 h. The wells were then washed and substrate solution was applied. The reaction was stopped with stop solution, and the color reaction was read at 450 nm. Each experiment was performed for three cultures, and the values for each group were expressed as mean ± SD. Statistical analyses were carried out by student's *t*-test. $P < 0.05$ was considered to be significant.

3. Results

3.1. CCE is increased in APPswe cells

To investigate the effect of Swedish mutant APP on CCE, we compared the CCE of N2a cells stably expressing Swedish mutant APP (APPswe) with wild-type N2a cells (WT) (Fig. 1A). CCE was induced by a published protocol [9,23,33]. Briefly, after preincubation in Ca^{2+}-free media containing cyclopiazonic acid (CPA) for depletion of the ER Ca^{2+} stores, the cells were replenished with Ca^{2+}-containing media (1.8 mM). An increase of CCE was observed in APPswe cells as compared to the WT cells (Fig. 1B, C). This result was further confirmed using a confocal laser microscope system (Fig. 1D, E) with Fluo3/AM as well as using an inverted microscope with another calcium indicator Fura2/AM (Fig. 1F,G). As CCE was depressed in N2a cells transfected with wild-type human APP (APPwt) (Fig. 1B, C), it excluded the possibility that wild-type APP is playing a role in the CCE potentiation process.

3.2. CCE potentiation in APPswe cells is caused by Aβ overproduction

The most significant difference between Swedish mutant APP and wild-type APP is that Swedish mutant APP can be overprocessed by β secretase and secrete much more Aβ (Fig. 2A) [17]. To verify if Aβ was the cause of CCE potentiation in APPswe cells, 0.05% Aβ antibody 4G8 was added to the culture medium of APPswe cells. Twenty-four hours after the treatment, the CCE measurements were carried out. The results showed that Aβ antibody can decrease CCE in APPswe cells (Fig. 2B, C). Similar results were obtained by treating the cells with anti-$Aβ_{1–42}$ antiserum (Fig. 2B, C). The results suggest that Aβ was one of the main causes of CCE potentiation in the APPswe cells.

To further confirm the role of Aβ in CCE potentiation, Aβ production inhibitor was added. We added 2 μM DAPT, a well-known γ secretase inhibitor, into the culture medium of APPswe cells. Twenty-four hours later, CCE was measured. It was shown that DAPT could depress CCE in the APPswe cells, but not in the wild-type cells (Fig. 2D, E, F). This result further confirmed the key role of Aβ in CCE potentiation. Although the Aβ production was also inhibited, there was no remarkable change of CCE in the wild-type cells. This may be because that the CCE potentiation is a pathological symptom caused by high concentrations of Aβ, and low concentrations of Aβ in wild-type cells do not disturb normal CCE.

3.3. ER calcium stores increased in APPswe cells

It is suggested that CCE operates through a putative connection between ER calcium stores and plasma membrane CCE channels [22]. The depletion of ER calcium stores triggers an influx of extracellular calcium into the cytosol through store-operated calcium channels on the plasma membrane. Here, we investigated if ER calcium store was changed in APPswe cells. The analysis was performed by measuring the response to thapsigargin in APPswe and WT cells. Application of thapsigargin blocks SERCA Ca^{2+} pump activity, leading to leakage of Ca^{2+} from the ER to the cytosol via the endogenous ER Ca^{2+} leakage pathway [29].

It was shown that application of 1 μM thapsigargin caused a larger cytosolic Ca^{2+} elevation in APPswe cells than in WT cells. The results showed that the ER calcium stores increased in APPswe cells compared to that in WT cells (Fig. 3A, B).

3.4. CCE in APPswe cells can be decreased by Aβ channel blocker

To further define the mechanism underlying the enhanced CCE in APPswe cells, we focused our research on the cell membrane. It has been reported that Aβ can form calcium-permeable channels in cell membrane. This might be the basis of Aβ neurotoxicity [15,25]. To verify if CCE potentiation in APPswe cells is caused by the channel formation in the cell membrane, tromethamine, an Aβ channel blocker [26], was used. After 20 mM tromethamine treatment for 24 h, the CCE in the APPswe cells was decreased (Fig. 4A, B). This

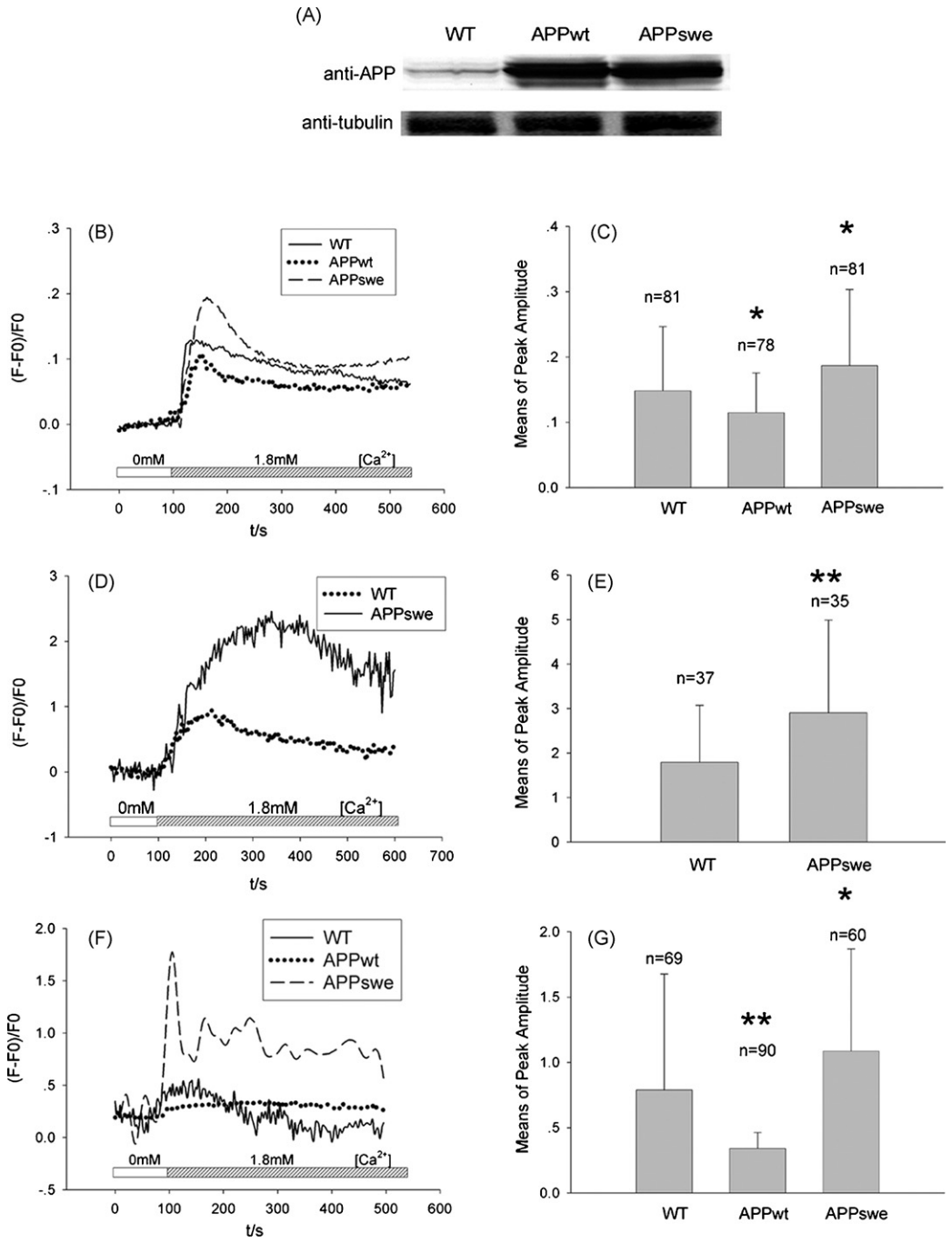

Fig. 1. CCE in N2a cells (WT) and its derivatives stably expressing human APP 695 (APPwt) and Swedish mutant APP (APPswe). (A) APP expression levels were higher in APPwt and APPswe cells than in WT cells. Cell lysates from different cells were analyzed by Western blotting with anti-APP monoclonal antibody (6E10) (upper panel). Tubulin was detected as loading control (lower panel). (B) The time course of CCE in representative WT, APPwt and APPswe N2a cells. (C) The average peak amplitude of CCE in WT, APPwt and APPswe N2a cells. (D) The time course of CCE in representative WT and APPswe N2a cells. Data was collected using confocal microscope system. (E) The average peak amplitude of CCE in WT and APPswe N2a cells. Data was collected using confocal microscope system. (F) The time course of CCE in representative WT, APPwt and APPswe N2a cells. Cells were stained with Fura2/AM. (G) The average peak amplitude of CCE in WT, APPwt and APPswe N2a cells. Cells were stained with Fura2/AM (n = number of cells) ($^{*}p < 0.05$, $^{**}p < 0.01$). Data was collected using a CCD system and cells were stained with Fluo3/AM unless noted otherwise.

suggests that Aβ channels formed in the cell membrane contribute to the effect of Aβ on CCE potentiation.

4. Discussion

Calcium dyshomeostasis is an important molecular defect in AD [13]. Several calcium signals were found to be changed in AD. Disruption of calcium regulation in the ER mediates significant signal-transduction cascades that are associated with Alzheimer's disease [25]. We investigated the role of Aβ on ER calcium and CCE. Our results demonstrated that overproduced Aβ in APPswe cells leads to not only higher CCE but also increased ER calcium store compared to that in its wild-type counterparts. The CCE elevation can be decreased in the presence of Aβ antibody or γ secretase inhibitor. It demonstrated that CCE potentiation in APPswe cells was mainly caused by Aβ overproduction.

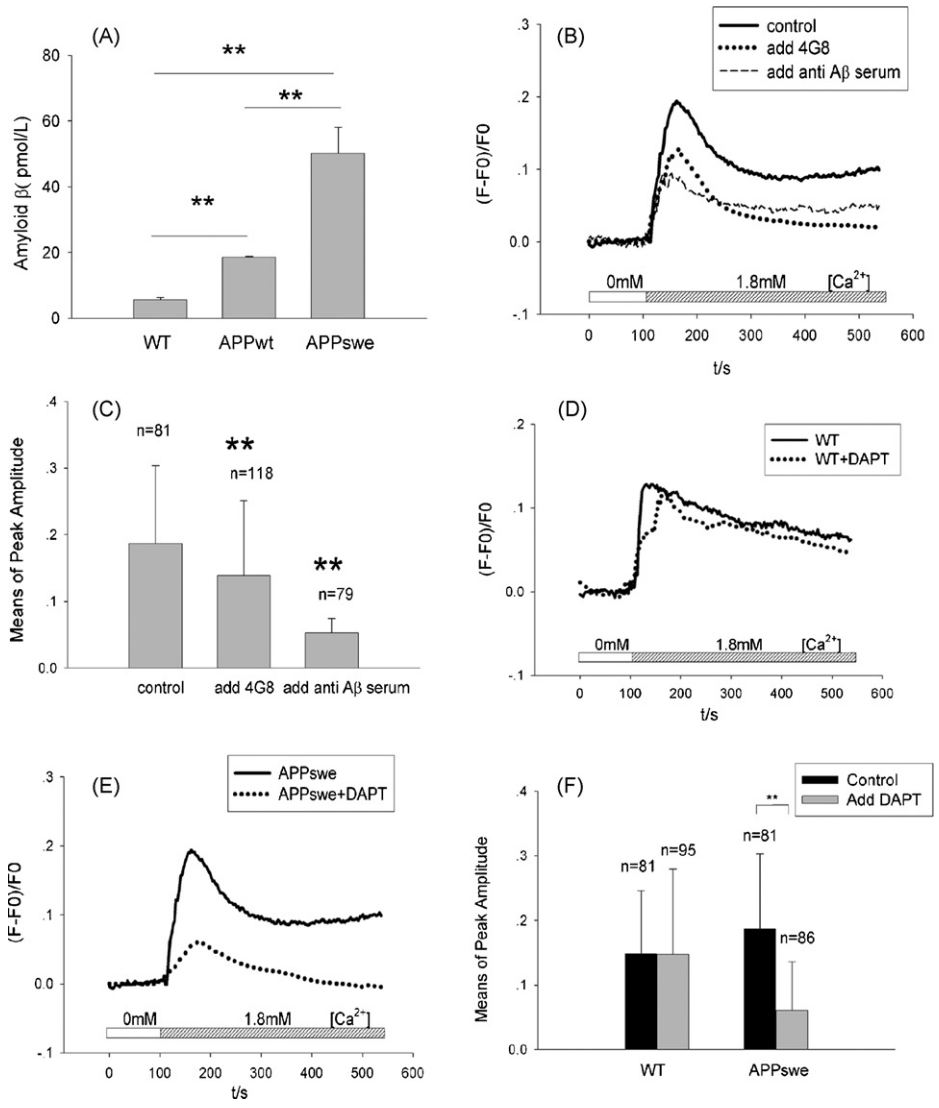

Fig. 2. CCE can be depressed in APPswe cells by removal of Aβ. (A) Levels of secreted Aβ in WT, APPwt, and APPswe cells. The culture medium was collected for measurement of Aβ by commercially available ELISA kit which specifically recognizes Aβx-40. The chemically synthesized Aβ fragments in the kit were used as standards (**$p < 0.01$). (B) The time course of CCE in representative APPswe cells with or without Aβ antibody treatment. (C) The average peak amplitude of CCE in APPswe cells with or without Aβ antibody treatment. (D) The time course of CCE in representative WT cells with or without DAPT treatment. (E) The time course of CCE in representative APPswe cells with or without DAPT treatment. (F) The average peak amplitude of CCE in WT and APPswe cells with or without DAPT treatment (n = number of cells) (**$p < 0.01$).

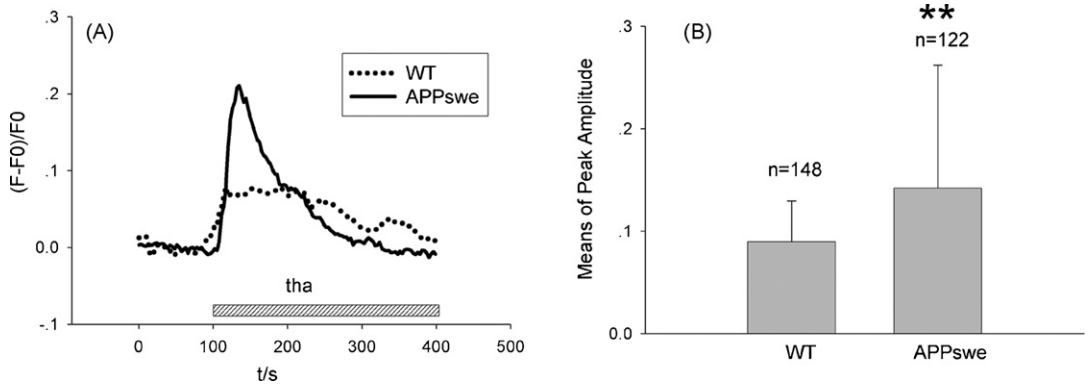

Fig. 3. ER calcium store was increased in APPswe cells. (A) The time course of CCE in representative wt and APPswe cells treated with 1 μM thapsigargin. (B) The average peak amplitude of CCE in WT and APPswe cells treated with 1 μM thapsigargin (n = number of cells) (**$p < 0.01$). "tha" represented "thapsigargin".

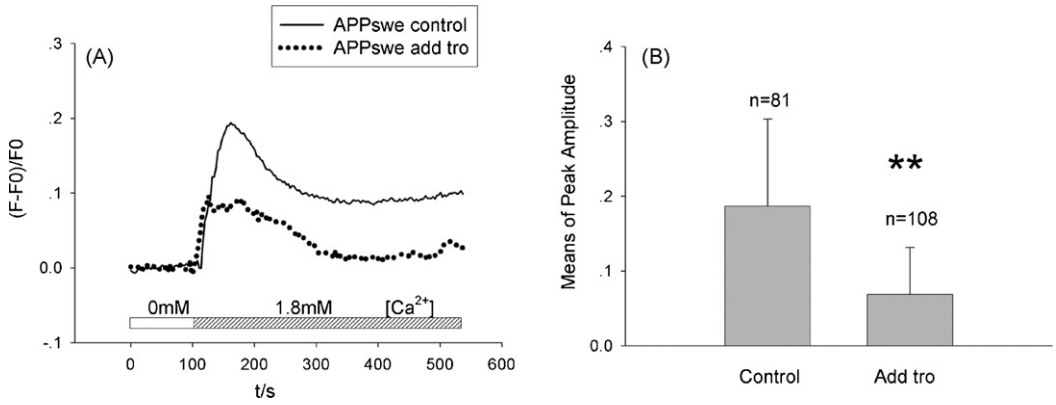

Fig. 4. Tromethamine can depress CCE in APPswe cells. (A) The time course of CCE in representative APPswe cells with or without 20 mM tromethamine treatment. (B) The average peak amplitude of CCE in APPswe cells with or without 20 mM tromethamine (n = number of cells) ($^{**}p < 0.01$). "tro" represented "tromethamine".

Our result also showed a depression of CCE in APPwt cells. The different effect of APPwt and APPswe cells on CCE is because of the different segmentation of them. As APPwt cells do not secret as much Aβ as APPswe cells and other fragments of APP which is overproduced in APPwt cells may play CCE depression roles, the integrated effect of different fragments of APPwt cells is the depression of CCE.

CCE is the primary mode of regulated calcium influx into the cytoplasm [22]. CCE disturbance can cause several physiological changes, and in some way could contribute to the associated neuropathology [22]. The CCE potentiation we found here in the APPswe cells could be used to explain several molecular mechanisms of Aβ toxicity such as apoptosis, cell cycle disturbance and the change of calcium oscillation [21,31,32].

Our results also showed that the Aβ-caused CCE potentiation is connected with the channels formed by Aβ. Aβ channel blocker can decrease the CCE potentiation in APPswe cells. The concept that Aβ can insert into the cell membrane and form ion channel has been supported by several studies and is thought to be the way through which Aβ takes its toxic effect. The interaction of Aβ with cell membrane may result in the activation of a chain of biological processes that, when long enough, induces cell apoptosis [2,19]. Our research suggested that ion channels formed by Aβ are involved in CCE regulation. Blockage of Aβ channels can antagonize CCE potentiation caused by Aβ, which indicates that Aβ channel blocker could be used for AD therapy. While Aβ affects calcium entry through the cell membrane, presenilins exert their effect on the interior membrane. It has been reported that presenilins form ER calcium leakage channels [29]. The channels formed by Aβ in the outer membrane and the channels formed by presenilins in the inner membrane jointly regulate the cytosol calcium level in Alzheimer's disease. Aβ channels might regulate CCE through two pathways. One is that Aβ channels can cause some changes in the cell signaling pathway of CCE. Another is that Aβ channels directly play the role of store operated calcium channels. Further experiments are needed to define the mechanism. Although we have shown the effect of Aβ channels on CCE, considering the complicated mechanism of CCE, we cannot exclude other possibilities through which Aβ causes CCE potentiation.

Aβ can take various forms of aggregates: monomers, oligomers, protofibrils, fibrils and plaques. While fibril formation is linked to neurotoxicity, evidence points to globular oligomers as the toxic species [7]. Considering the low concentration of Aβ in the cell culture medium here, it is difficult to detect its aggregation states, and therefore it is hard to decide which structures contribute to Aβ caused CCE potentiation. However, we can deduce the suggestion by combining previous studies with our results. Our results show that Aβ channels contribute to Aβ caused CCE potentiation. Several reports suggested that it is oligomer (rather than fibrils) that forms Aβ channels on the membrane [24,27]. This viewpoint was supported by structural data [10,11]. Therefore, oligomers may play important roles in Aβ caused CCE potentiation.

In conclusion, our results demonstrate the role of Aβ in CCE in AD model cell. Furthermore, we have established that these phenomena are connected with the channels formed by Aβ. This suggests a new effect of Aβ channels in AD. Our work also provides a possibility of using Aβ channel blocker for AD therapy.

Conflict of interest

None

Acknowledgements

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References

[1] N. Arispe, J.C. Diaz, O. Simakova, Aβ ion channels prospects for treating Alzheimer's disease with Aβ channel blockers, Biochimica et Biophysica Acta 1768 (2007) 1952–1965.
[2] N. Arispe, E. Rojas, H.B. Pollard, Alzheimer disease amyloid beta protein forms calcium channels in bilayer membranes: blockade by tromethamine and aluminum, Proc. Natl. Acad. Sci. USA 90 (1993) 567–571.
[3] M. Brzyska, D. Elbaum, Dysregulation of calcium in Alzheimer's disease, Acta Neurobiol. Exp. (Wars) 63 (2003) 171–183.
[4] M. Citron, T. Oltersdorf, C. Haass, L. McConlogue, A.Y. Hung, P. Seubert, C. Vigo-Pelfrey, I. Lieberburg, D.J. Selkoe, Mutation of the beta-amyloid precursor protein in familial Alzheimer's disease increases beta-protein production, Nature 360 (1992) 672–674.
[5] G.G. Glenner, C.W. Wong, Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein, Biochem. Biophys. Res. Commun. 122 (1984) 1131–1135.
[6] G.G. Glenner, C.W. Wong, Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein, Biochem. Biophys. Res. Commun. 120 (1984) 885–890.
[7] Y. Gong, L. Chang, K.L. Viola, P.N. Lacor, M.P. Lambert, C.E. Finch, G.A. Krafft, W.L. Klein, Alzheimer's disease-affected brain: presence of oligomeric A beta ligands (ADDLs) suggests a molecular basis for reversible memory loss, Proc. Natl. Acad. Sci. USA. 100 (2003) 10417–10422.
[8] M.B. Hallett, R. Hodges, M. Cadman, H. Blanchfield, S. Dewitt, E.J. Pettit, I. Laffafian, E.V. Davies, Techniques for measuring and manipulating free Ca^{2+} in the cytosol and organelles of neutrophils, J. Immunol. Methods 232 (1999) 77–88.
[9] J. Herms, I. Schneider, I. Dewachter, N. Caluwaerts, H. Kretzschmar, F. Van Leuven, Capacitive calcium entry is directly attenuated by mutant presenilin-1,

independent of the expression of the amyloid precursor protein, J. Biol. Chem. 278 (2003) 2484–2489.
[10] Y. Hirakura, I. Carreras, J.D. Sipe, B.L. Kagan, Channel formation by serum amyloid A: a potential mechanism for amyloid pathogenesis and host defense, Amyloid 9 (2002) 13–23.
[11] H. Jang, J. Zheng, R. Lal, R. Nussinov, New structures help the modeling of toxic amyloidbeta ion channels, Trends Biochem. Sci. 33 (2008) 91–100.
[12] J. Kang, H.G. Lemaire, A. Unterbeck, J.M. Salbaum, C.L. Masters, K.H. Grzeschik, G. Multhaup, K. Beyreuther, B. Muller-Hill, The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor, Nature 325 (1987) 733–736.
[13] F.M. LaFerla, Calcium dyshomeostasis and intracellular signalling in Alzheimer's disease, Nat. Rev. Neurosci. 3 (2002) 862–872.
[14] M.A. Leissring, Y. Akbari, C.M. Fanger, M.D. Cahalan, M.P. Mattson, F.M. LaFerla, Capacitative calcium entry deficits and elevated luminal calcium content in mutant presenilin-1 knockin mice, J. Cell. Biol. 149 (2000) 793–798.
[15] H. Lin, Y.J. Zhu, R. Lal, Amyloid beta protein (1-40) forms calcium-permeable, Zn^{2+}-sensitive channel in reconstituted lipid vesicles, Biochemistry 38 (1999) 11189–11196.
[16] C.L. Masters, G. Simms, N.A. Weinman, G. Multhaup, B.L. McDonald, K. Beyreuther, Amyloid plaque core protein in Alzheimer disease and Down syndrome, Proc. Natl. Acad. Sci. U.S.A. 82 (1985) 4245–4249.
[17] M. Mullan, F. Crawford, K. Axelman, H. Houlden, L. Lilius, B. Winblad, L. Lannfelt, A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N-terminus of beta-amyloid, Nat. Genet. 1 (1992) 345–347.
[18] F.E. Murray, J.P. Landsberg, R.J. Williams, M.M. Esiri, F. Watt, Elemental analysis of neurofibrillary tangles in Alzheimer's disease using proton-induced X-ray analysis, Ciba. Found. Symp. 169 (1992) 201–210.
[19] N. Arispe, O. Simakova, Aβ ion channels. Prospects for treating Alzheimer's disease with Aβ channel blockers, Biochimica et Biophysica Acta 1768 (2007) 1952–1965.
[20] R.A. Nixon, K.I. Saito, F. Grynspan, W.R. Griffin, S. Katayama, T. Honda, P.S. Mohan, T.B. Shea, M. Beermann, Calcium-activated neutral proteinase (calpain) system in aging and Alzheimer's disease, Ann. N. Y. Acad. Sci. 747 (1994) 77–91.
[21] I.G. Onyango, S.M. Khan, Oxidative stress, mitochondrial dysfunction, and stress signaling in Alzheimer's disease, Curr. Alzheimer. Res. 3 (2006) 339–349.
[22] A.B. Parekh, J.W. Putney Jr., Store-operated calcium channels, Physiol. Rev. 85 (2005) 757–810.
[23] R.L. Patterson, D.B. van Rossum, D.L. Gill, Store-operated Ca^{2+} entry: evidence for a secretion-like coupling model, Cell 98 (1999) 487–499.
[24] A. Quist, I. Doudevski, H. Lin, R. Azimova, D. Ng, B. Frangione, B. Kagan, J. Ghiso, R. Lal, Amyloid ion channels: a common structural link for protein-misfolding disease, Proc. Natl. Acad.Sci. U.S.A. 102 (2005) 10427–10432.
[25] S.K. Rhee, A.P. Quist, R. Lal, Amyloid beta protein-(1-42) forms calcium-permeable, Zn^{2+}-sensitive channel, J. Biol. Chem. 273 (1998) 13379–13382.
[26] O. Simakova, N.J. Arispe, Early and late cytotoxic effects of external application of the Alzheimer's Abeta result from the initial formation and function of Abeta ion channels, Biochemistry 45 (2006) 5907–5915.
[27] Y. Sokolov, J.A. Kozak, R. Kayed, A. Chanturiya, C. Glabe, J.E. Hall, Soluble amyloid oligomers increase bilayer conductance by altering dielectric structure, J. Gen. Physiol. 128 (2006) 637–647.
[28] N. Suzuki, T.T. Cheung, X.D. Cai, A. Odaka, L. Otvos Jr., C. Eckman, T.E. Golde, S.G. Younkin, An increased percentage of long amyloid beta protein secreted by familial amyloid beta protein precursor (beta APP717) mutants, Science 264 (1994) 1336–1340.
[29] H. Tu, O. Nelson, A. Bezprozvanny, Z. Wang, S.F. Lee, Y.H. Hao, L. Serneels, B. De Strooper, G. Yu, I. Bezprozvanny, Presenilins form ER Ca^{2+} leak channels, a function disrupted by familial Alzheimer's disease-linked mutations, Cell 126 (2006) 981–993.
[30] Z.F. Wang, H.L. Li, X.C. Li, Q. Zhang, Q. Tian, Q. Wang, H. Xu, J.Z. Wang, Effects of endogenous beta-amyloid overproduction on tau phosphorylation in cell culture, J. Neurochem. 98 (2006) 1167–1175.
[31] J. Woods, M. Snape, M.A. Smith, The cell cycle hypothesis of Alzheimer's disease: suggestions for drug development, Biochim. Biophys. Acta 1772 (2007) 503–508.
[32] R.L. Yanfang Rui, L. Yifu, Z. Shaoqing, Y. Xinzhu, S. Zhonghua, X. Zuoping, Acute effect of b amyloid on synchronized spontaneous Ca^{2+} oscillations in cultured hippocampal networks, Cell Biol. Int. 30 (2006) 733–740.
[33] A.S. Yoo, I. Cheng, S. Chung, T.Z. Grenfell, H. Lee, E. Pack-Chung, M. Handler, J. Shen, W. Xia, G. Tesco, A.J. Saunders, K. Ding, M.P. Frosch, R.E. Tanzi, T.W. Kim, Presenilin-mediated modulation of capacitative calcium entry, Neuron 27 (2000) 561–572.