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Transient Receptor Potential Channels in Alzheimer's Disease

Shinichiro Yamamoto^{1*}, Teruaki Wajima^{1*}, Yuji Hara², Motohiro Nishida³, Yasuo Mori¹

¹Laboratory of Molecular Biology, Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan

²Howard Hughes Medical Institute and Departments of Physiology and Biophysics, Internal Medicine, and Neurology, University of Iowa Roy J. and Lucille A. Carver College of Medicine, Iowa City, IA 52242

³Department of Pharmacology and Toxicology, Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan

*These authors contributed equally to the manuscript

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Address correspondence to: Yasuo Mori, Ph.D. Laboratory of Molecular Biology, Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan

Telephone: +81-75-383-2793

FAX: +81-75-383-2765

E-mail: mori@sbchem.kyoto-u.ac.jp

Summary

Cognitive impairment and emotional disturbances in Alzheimer's disease (AD) result from the degeneration of synapses and neuronal death in the limbic system and associated regions of the cerebral cortex. An alteration in the proteolytic processing of the amyloid precursor protein (APP) results in increased production and accumulation of amyloid β -peptide ($A\beta$) in the brain. $A\beta$ can render neurons vulnerable to excitotoxicity and apoptosis by disruption of cellular Ca^{2+} homeostasis and neurotoxic factors including reactive oxygen species (ROS), nitric oxide (NO), and cytokines. Many lines of evidence have suggested that transient receptor potential (TRP) channels consisting of six main subfamilies termed the TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), and TRPA (ankyrin) are involved in Ca^{2+} homeostasis disruption. Thus, emerging evidence of the pathophysiological role of TRP channels has yielded promising candidates for molecular entities mediating Ca^{2+} homeostasis disruption in AD. In this review, we focus on the TRP channels in AD and highlight some TRP "suspects" for which a role in AD can be anticipated. An understanding of the involvement of TRP channels in AD may lead to the development of new target therapies.

1. Introduction

Alzheimer's disease (AD) is a form of dementia in which patients show neurodegeneration, complete loss of cognitive abilities and prematurely die. Central to the neurodegenerative process is the inability of neurons to properly regulate intracellular Ca^{2+} levels ($[\text{Ca}^{2+}]_i$) [1]. In AD, correlations between the pathological hallmarks of AD (amyloid plaques and neurofibrillary tangles) and perturbed cellular Ca^{2+} homeostasis have been established in studies of patients, and in animal and cell culture models of AD [2]. Specifically, increased levels of amyloid β -peptide ($\text{A}\beta$) induce neurotoxic factors including reactive oxygen species (ROS) and cytokines, which impair cellular Ca^{2+} homeostasis and render neurons vulnerable to apoptosis and excitotoxicity [3]. Studies of the effects of mutations in the amyloid- β precursor protein (APP) and presenilin (PS) 1 and 2 on neuronal plasticity and survival have provided insights into the molecular cascades that result in synaptic dysfunction and neuronal degeneration in AD [4]. PS mutations perturb Ca^{2+} homeostasis that sensitizes neurons to apoptosis and excitotoxicity; links between aberrant Ca^{2+} regulation and altered APP processing are emerging [5].

Neuronal toxicity is not simply attributable to the increase in $[\text{Ca}^{2+}]_i$. In fact, treatment with α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) or with KCl increases $[\text{Ca}^{2+}]_i$ up to 1-2 μM in cortical neurons without showing toxicity, while the equivalent $[\text{Ca}^{2+}]_i$ increase induced by Ca^{2+} influx specifically through the N-methyl-D-aspartate (NMDA) receptors induces cell injury, suggesting that the identity of the Ca^{2+} channel that mediates Ca^{2+} influx is critical for neuronal cell death [6]. It is also important to note that decreasing $[\text{Ca}^{2+}]_i$ is toxic in some neurons, while a modest increase in $[\text{Ca}^{2+}]_i$ is neuroprotective. These results paradoxically suggest that Ca^{2+} has not only deleterious but also protective effects on the neuronal cell [6, 7].

The transient receptor potential (TRP) gene was discovered originally in *Drosophila*, where mutants for the gene showed impaired vision due to the lack of a specific cation Ca^{2+} influx pathway into photoreceptor cells [8]. TRP and its homologues constitute a large and diverse family of channel proteins that are expressed in many tissues and cell types in both vertebrates and invertebrates [9, 10]. Mammalian TRPs are plasma membrane cation channels that have diverse physiological functions [11-13]. The TRP superfamily can be classified into three large subfamilies including

canonical (TRPC), melastatin (TRPM), and vanilloid (TRPV) channels, and three other small subfamilies such as polycystin (TRPP). The TRPC subfamily consists of seven homologues, which are receptor-operated cation channels that play an essential role in intracellular Ca^{2+} homeostasis. Ca^{2+} signaling is initiated by neurotransmitters (e.g., agonists that activate G proteins) via the stimulation of cell membrane receptors linked to phospholipase C (PLC) activation, which leads to production of inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DG). The receptor stimulation eventually induces a biphasic Ca^{2+} signal, which is composed of an initial Ca^{2+} release from the endoplasmic reticulum (ER) followed by a sustained and/or oscillatory $[\text{Ca}^{2+}]_i$ increase due to Ca^{2+} influx across the plasma membrane. Different modes of receptor-operated Ca^{2+} entry include store-operated Ca^{2+} entry (SOC) or capacitative Ca^{2+} entry (CCE), resulting from the depletion of intracellular Ca^{2+} stores [14-16], as well as Ca^{2+} entry activated in a Ca^{2+} depletion-independent manner [17-19]. In the brain, it is generally accepted that TRPC1 channels work as a component of SOC, whereas TRPC6 channels are involved in receptor-operated Ca^{2+} entry, which can be activated independently of Ca^{2+} depletion [14-16]. TRPC3 channels that form receptor-operated Ca^{2+} entry are highly enriched in neurons of the central nervous system (CNS) [20]. TRPC4 channels, detected in the brain of embryonic rats, contribute to receptor-operated Ca^{2+} entry [21]. Recent reports have suggested that TRPC5 channels, predominantly expressed in growth cones and early synapses in young rat hippocampal neurons, participate in receptor-operated Ca^{2+} entry [22-24]. Recently, evidence has been provided for the localization of a number of Ca^{2+} signaling proteins within caveolar lipid raft domains in the plasma membrane [25, 26]. In particular, TRPC1 and TRPC3 are associated with caveolin-1, and are assembled in a protein complex with key Ca^{2+} signaling proteins [27]. Ehehalt et al. have reported that lipid rafts are critically involved in regulating $\text{A}\beta$ production [28]. It can be surmised that TRPC channels and lipid rafts contribute to $\text{A}\beta$ regulation. The TRPM subfamily includes eight mammalian homologues. In particular, TRPM2 and TRPM7 represent a Ca^{2+} -permeable, non-selective cation channel activated by ROS [29, 30]. TRPM2 and TRPM7 are also involved in oxidative stress-induced cell death [30]. The TRPV subfamily, composed of six homologues, is known to participate in nociception, mechano-sensing, osmolarity-sensing, and thermo-sensing [13]. TRPV1 is a modestly Ca^{2+} -selective channel gated by capsaicin, acidosis, and

endogenous ligands, such as anandamide [31, 32]. Interestingly, TRPM2, TRPM7, and TRPV1 have been reported to play pathological roles in the brain [29, 31].

Thus, accumulated evidence suggests that TRP channels play prominent roles in neuronal Ca^{2+} signaling. In addition, ROS involved in various pathological conditions leads to TRP channel activation. However, many pathological aspects of TRPs, particularly in AD, are still very unclear. Therefore, this review will seek the correlation between AD and TRP channels.

2. Ca^{2+} misregulation and TRP channels in AD

Ca^{2+} is essential for neuronal development, synaptic transmission and plasticity, and the regulation of various metabolic pathways in neurons [33]. Accumulating evidence suggests that failure of Ca^{2+} homeostasis plays a critical role in the neuropathology of AD. One of the postulated mechanisms of $\text{A}\beta$ toxicity seems to involve a disturbance of Ca^{2+} homeostasis accompanied by enhanced vulnerability to excitotoxic stimuli [1, 2]. This neurotoxicity activates PLC and produces IP_3 , which in turn stimulates intracellular Ca^{2+} stores [34] and also activates NMDA receptors and VDCC [35, 36]. In fact, both the direct neurotoxicity of $\text{A}\beta$ and the enhanced vulnerability to excitotoxicity were attenuated when cells were incubated in Ca^{2+} -free medium, suggesting the involvement of Ca^{2+} influx in this process [37]. Moreover, the pathogenic mutations in PSs and APP responsible for the early onset of familial AD have been suggested to participate in the perturbation of cellular Ca^{2+} homeostasis [4, 5]. FAD-linked mutant PS1 or PS2 may impair CCE and SOC currents. Interestingly, Yoo et al. provided evidence that inhibition of CCE selectively increases the amyloidogenic $\text{A}\beta$ peptide ($\text{A}\beta_{42}$) [38]. Hence, it is likely that reduced CCE is an early cellular event leading to $\text{A}\beta_{42}$ generation associated with FAD mutant PSs. Other reports have described that Ca^{2+} released from the ER and mitochondria participates in the pathogenesis of neuronal degeneration [39, 40]. In contrast, a study by Chen et al. has demonstrated that Ca^{2+} has both stimulatory and inhibitory roles in the process of cell death [6]. This study represents the important finding of increased $[\text{Ca}^{2+}]_i$ resulting in neuronal cell protection.

Alterations in Ca^{2+} homeostasis contribute to neuronal apoptosis and excitotoxicity, and are linked to AD, suggesting the potential benefits of preventative and therapeutic

strategies that stabilize cellular Ca^{2+} homeostasis. Many studies have shown that $[\text{Ca}^{2+}]_i$ is elevated by enhancing Ca^{2+} influx from voltage-dependent or voltage-independent Ca^{2+} channels, or by stimulating Ca^{2+} release from the ER. Recently, Tu et al. [41] have demonstrated that PS form ER Ca^{2+} leak channels, and the function is disrupted by familial AD-linked mutation. Compared to the general pathophysiological importance of Ca^{2+} influx, Ca^{2+} channels specifically involved in AD are poorly understood. In this section, we review the role of TRPs as Ca^{2+} -permeable channels in mediating the neuroprotective and neurodegenerative effects of Ca^{2+} .

2.1. Neuroprotective role of TRPC1

TRPC1 is abundantly expressed in the brain. Recently, TRPC1 channels have been shown to play pivotal roles in neurodegeneration induced by neurotoxin, 1-methyl-4-phenylpyridinium ion [42]. Bollimuntha et al. have demonstrated that TRPC1 channels are expressed in human neuroblastoma (SH-SY5Y) cells, which have been employed extensively in studies of neurotransmitter release, neuronal apoptosis, neurodegeneration, and Ca^{2+} homeostasis [42]. In this study, SH-SY5Y cells treated with neurotoxin show significant reduction in TRPC1 protein levels, and overexpression of TRPC1 protects SH-SY5Y cells against neurotoxin-induced apoptosis. Importantly, activation of TRPC1 by thapsigargin or carbachol decreases neurotoxicity. Hence, increased cell viability is dependent on the activation of TRPC1, and its protection is partially dependent on external Ca^{2+} , suggestive of the neuroprotective effect of Ca^{2+} influx.

As described above, TRPC1 has been suggested to function as SOC. A recent investigation by Kim et al. has demonstrated that, in SH-SY5Y cells, CCE is involved in regulating the release of the soluble form of non-amyloidogenic APP (sAPP) mediated by muscarinic acetylcholine receptor (mAChR) activation [43]. They have speculated that augmentation or induction of CCE leads to neuroprotection and a reduction in A β generation. In support of this speculation, Yoo et al. have reported that inhibition of CCE by SKF96365 induces an increase in the expression of the toxic peptide, A β 42, that is associated with the increase in the expression of mutant PS1 [38]. These results suggest that the functional reduction in CCE may be a causative element in AD. It has

been reported that TRPC3 and TRPC5 are also expressed in SH-SY5Y cells [42]. However, it remains to be uncovered which TRP subtypes are indeed important in mAChR-mediated CCE and sAPP release in SH-SY5Y cells.

2.2. TRPC3 may be involved in the deregulation of tau protein in AD

Enrichment of TRPC3 is reported in the CNS [20]. In this study, the temporal and spatial distribution of TRPC3 parallels that of the neurotrophin receptor TrkB, and activation of TrkB by brain-derived neurotrophic factor (BDNF) leads to a TRPC3 cation influx that is dependent on PLC. Neurotrophin receptors regulate a variety of effects in the nervous system, including neuronal differentiation, cell proliferation, cell survival, and modulation of neurotransmitter release at developing synapses [44]. It is generally accepted that alterations in the structure and function of tau protein are the primary pathology of a variety of neurodegenerative diseases [45], although the events leading to the deregulation of tau protein in AD are not clear. Recently, severe disturbance of BDNF has been reported in AD [46]. Since BDNF is one of the important neurotrophic factors for the proper functioning of neurons as described above, its alteration can lead to the deregulation of tau protein. Interestingly, increased $[Ca^{2+}]_i$ leads to hyperphosphorylation of tau and enhances vulnerability to cell death and memory-related deficits [47]. Therefore, it can be surmised that abnormality of TRPC3 downstream of BDNF is involved in the deregulation of tau protein in AD.

2.3. PS2 regulates Ca^{2+} entry via the activation of TRPC6

Mutated PS genes account for the majority of cases of familial AD [4, 5]. PSs are integral membrane proteins that are mainly located in the ER of neurons [48, 49], and act mainly as a catalytic subunit of the γ -secretase complex [4]. Recently, it has been shown that PSs are involved in Ca^{2+} signaling in neurons [50-53]. Dysregulation of Ca^{2+} signaling evoked by mutations in PS may play a role in the neurodegenerative and hallmark pathological lesions of AD [54-56]. Elevated $[Ca^{2+}]_i$ can modulate the proteolytic processing of APP and thereby increase the production of neurotoxic A β [57]. Thus, AD-linked mutations in PS are implicated in the attenuation of Ca^{2+} entry and the augmentation of Ca^{2+} release from the ER in various cell types. However, the

mechanisms underlying altered Ca^{2+} signaling remain unknown. A recent report demonstrates that, in HEK293 cells, PS2 influences TRPC6-mediated Ca^{2+} entry [58]. In this study, wild-type PS2 and FAD-linked PS2 variants fail to affect endogenous angiotensin II (AII)-induced Ca^{2+} release or AII-induced Ca^{2+} entry pathways in HEK cells. In contrast, the dominant negative mutant of PS2 enhances AII-induced Ca^{2+} entry, suggesting the PS2 as an endogenous inhibitor of Ca^{2+} entry. Further studies reveal that the coexpression of wild-type PS2 or FAD-linked PS2 mutants with TRPC6 completely abrogates AII-induced Ca^{2+} entry through TRPC6 but not Ca^{2+} release. Interestingly, despite the coexpression of PS2 or the FAD-linked PS2 variants, 1-oleoyl-2-acyl-*sn*-glycerol is still able to activate TRPC6, suggesting that the negative regulation of TRPC6 by PS2 is not due to a cleavage of TRPC6 by PS2. Although more extensive studies are necessary to clarify the mechanisms whereby PS2 regulate Ca^{2+} entry via TRPC6, an intriguing hypothesis is that an intermediary protein influences the AII-induced activation of TRPC6 under the regulatory effect of PS2.

2.4. Neurodegeneration by TRPV1 activation

A neuroinflammatory process triggered by A β 42 is central to the neurodegenerative process [59] (see also Section 3 below). This inflammatory process is driven by activated microglia, astrocytes, and the induction of proinflammatory molecules and related signaling pathways, leading to both synaptic and neuronal damage as well as further inflammatory cell activation. Epidemiologic evidence as well as clinical trial data suggest that non-steroidal anti-inflammatory drug use may decrease the incidence of AD, further supporting the role of inflammation in AD pathogenesis [60-62]. Although the precise molecular and cellular relationship between AD and inflammation remains unclear, it is possible that cytokines may mediate activation of signaling pathways, causing further inflammation and worsening neuronal injury [59].

Capsaicin-sensitive sensory neurons are nociceptive neurons, which have long been considered to be involved in aggravation of inflammation such as tissue hyperemia and edema [63]. TRPV1 channels are activated by vanilloid and capsaicin and are also gated at temperatures higher than 42°C and under acidic conditions (pH<6) [31, 32, 64]. Hence, it is conceivable that activation of TRPV1 is sensitized by signaling pathways

downstream of a variety of receptors involved in inflammation. Recent evidence has indicated a wide distribution of TRPV1 expression in microglia, astrocytes, pericytes, and neurons in the brain [65-67]. Therefore, it is likely that TRPV1 channels contribute to AD-related neuroinflammatory processes. A recent study reported by Kim et al. demonstrated that exposure of mesencephalic dopaminergic (MDA) neurons to the TRPV1 agonist capsaicin triggered cell death [68]. This effect was inhibited by the TRPV1 antagonists capsazepine and iodo-resiniferatoxin, suggesting that this channel is directly involved. TRPV1-induced neurotoxicity was accompanied by increases in $[Ca^{2+}]_i$ and mitochondrial damage, and these effects were inhibited by capsazepine and an intracellular Ca^{2+} chelator, BAPTA-AM. Treatment of cells with capsaicin or an endogenous ligand of TRPV1 anandamide led to an increase in mitochondrial cytochrome c release and enhanced immunoreactivity to cleaved caspase-3. Furthermore, intranigral injection of capsaicin into the rat brain produced cell death through TRPV1. Taken together, these results indicate that activation of TRPV1 channels contribute to DA neuronal damage via Ca^{2+} signaling and mitochondrial disruption. Similar results were obtained from microglia treated under similar conditions [67]. Thus, TRPV1 may be involved in AD.

3. Neurotoxic factors of AD and TRP channels

A β is a 40-43 amino acid peptide that accumulates in the central nervous system plaques, which are a characteristic feature of AD [69]. Since mutations in the APP in some cases of familial AD lead to the overproduction of A β [70-74], and since A β is directly toxic to cultured neuronal cells [75-77], it can be argued that neuronal cell dysfunction and cell death caused by aggregates of A β causally contribute to the pathogenesis and progression of AD. Therefore, biochemical mechanisms that lead to A β -induced neuronal cell death should be investigated for the elucidation of AD. Several mechanisms proposed for A β neurotoxicity include production of ROS such as hydrogen peroxide (H_2O_2) and nitric oxide (NO) as well as excitotoxicity with intracellular Ca^{2+} accumulation.

The impairment of mitochondrial metabolism has been well documented in AD patients [78-86]. In addition, several *in vitro* studies of A β and mitochondrial function have reported that A β affects mitochondrial DNA and proteins, leading to impairment of

the electronic transport chain and ultimately, to mitochondrial dysfunction [87-95]. Recently, Lustbader et al. [96] have reported that A β -binding alcohol dehydrogenase directly interacts with A β in the mitochondria of AD patients and transgenic mice and that the interaction promotes the leakage of ROS. The studies also suggest that A β -induced oxidative stress leads to apoptotic neuronal cell death that can be inhibited by antioxidants.

Various laboratories have shown that A β stimulates microglial and astrocytic NO production [97-104]. In AD, microglia appear to cluster around A β plaques [105-107]. A β activates CD4⁺ T cells, which in turn produce various cytokines — including interferon- γ (IFN- γ) — and subsequent microglial cell activation [101, 108]. The activation of microglia causes inducible NO synthase (iNOS)-mediated NO release [104, 109, 110]. Additionally, activated microglia [111] are known to release cytokines such as interleukin-1 α and β and tumor necrosis factor- α (TNF α) [111-113]. These cytokines can directly induce NO production in cultured astrocytes [114]. In addition, A β acts synergistically with cytokines such as IFN- γ or TNF α to induce the expression of iNOS in astrocyte cell lines *in vitro* [102].

In this section, we focus on TRP channels activated by the neurotoxic factors described above, and discuss the possibility that neuronal cell death is triggered by Ca²⁺ influx via neurotoxic factor-activated TRP channels.

3.1. Oxidative stress-induced neuronal cell death and TRPM2

TRPM2, a member of the TRPM subfamily, is expressed in many tissues and cell types including the brain, pancreatic β -cells, and immunocytes. TRPM2 is a Ca²⁺-permeable, non-selective cation channel activated by ADP-ribose (ADPR), nicotinamide adenine dinucleotide (NAD), ROS such as H₂O₂, and the oxidant tertbutylhydroperoxide [30, 115]. ADPR activates TRPM2 by binding to the TRPM2 C-terminal NUDT9-H domain (Nudix motif), which has homology to NUDT9 ADPR hydrolyase but only a low level of ADPR hydrolase activity [116-121]. While our patch-clamp studies indicate that NAD also can directly induce opening of TRPM2 [30], this may be mediated by conversion to ADPR [116, 121]. Our studies using fura-2 fluorescence to monitor [Ca²⁺]_i changes in intact cells, as well as patch-clamp

experiments, have shown that ROS such as H_2O_2 activates TRPM2 [30]. Despite consensus in the literature about this finding, the potential gating mechanism underlying it has been subject to some controversy and is currently unresolved. The question that remains is whether ROS gating of TRPM2 is due to direct activation at the membrane, or an indirect mechanism via a diffusible second messenger such as ADPR or NAD. Interestingly, recent data suggest that oxidative stress induces production of ADPR within the mitochondria, which is then released in the cytosol to activate TRPM2 [121]. Induction of NUDT9 ADPR pyrophosphatase, which degrades ADPR, suppresses H_2O_2 -induced Ca^{2+} transients, providing strong support for a requirement for ADPR binding in TRPM2 gating.

Ca^{2+} influx via H_2O_2 -activated TRPM2 induces cell death in rat insulinoma RIN-5F cells expressing TRPM2; TRPM2-specific antisense oligonucleotide significantly suppressed Ca^{2+} influx and cell death induced by H_2O_2 . TRPM2-specific antisense almost abolished $\text{TNF}\alpha$ -evoked $[\text{Ca}^{2+}]_i$ oscillation in RIN-5F cells, as observed for omission of extracellular Ca^{2+} , and significantly suppressed $\text{TNF}\alpha$ -induced death in RIN-5F cells [30]. The results suggest important involvement of TRPM2 in $\text{TNF}\alpha$ -activated Ca^{2+} channels that mediate cell death. Therefore, it is possible that $\text{TNF}\alpha$ released from $\text{A}\beta$ -activated microglia triggers neuronal cell death via TRPM2 activation in AD. In fact, TRPM2 expressed in rat cortical neurons is critically involved in H_2O_2 -induced Ca^{2+} influx that causes neuronal cell death [122]. Importantly, Fonfria et al. [123] have suggested that activation of TRPM2, functionally expressed in primary cultures of rat striatum, contributes to $\text{A}\beta$ - and oxidative stress-induced striatal cell death, thereby providing evidence that TRPM2 activity may contribute to neuronal cell death in pathophysiological circumstances in which ROS are generated abundantly.

3.2. Does Ca^{2+} influx via TRPM7 induce neuronal cell death?

TRPM7 functions as an ion channel but also has a C-terminal Ser/Thr kinase domain with homology to the eEF2 α -kinase family [124, 125]. TRPM7 is widely expressed, and electrophysiological analyses of currents in TRPM7-expressing cells have revealed both non-selective conductance of Na^+ and Ca^{2+} [125] and selectivity towards divalent cations [124]. Mg^{2+} permeability is a unique feature of TRPM7 among

known ion channels. TRPM7 currents are activated by a drop of Mg·ATP below a certain level, and are inhibited by Mg^{2+} and Zn^{2+} , blocking monovalent cation flow [124, 126]. Although a question has been raised as to whether the TRPM7 kinase domain is involved in regulating channel activity, recent studies have suggested a model in which the TRPM7 kinase domain is not required for channel activation, but have rather proposed that the linkage between the channel and kinase domain functions to position structures such that they can be influenced by the kinase domain in mediating Mg^{2+} and Mg·ATP suppression. Several studies have shown that TRPM7 plays a critical role in cellular Mg^{2+} homeostasis and the entrance of trace metals into the cell [127, 128]. Moreover, deletion of TRPM7 ultimately leads to cell death, clearly supporting the fact that its activity is essential for survival [124]. It has been also demonstrated that TRPM7 is involved in cell proliferation and cell cycle progression [129].

Aarts et al. [130] have reassessed the established model of *in vitro* ischemic neuronal injury, oxygen-glucose deprivation (OGD). In this model, treatment of primary cortical neurons with glutamate receptor antagonists prevents neuronal death when these are exposed to OGD for up to 1 h. However, anti-excitotoxic therapy becomes ineffective when OGD is extended to 1.5 – 2 h, even in the presence of blockers of excitatory amino acid receptors, Ca^{2+} channels, Na^{+} channels, and all ionic entry pathways. Moreover, cell death in prolonged OGD (>1.5 h) is associated with neuronal Ca^{2+} accumulation and the activation of a cation current having the properties of a Ca^{2+} -permeable, non-selective cation conductance named I_{OGD} . Both I_{OGD} and the neuronal Ca^{2+} uptake caused by prolonged OGD are blocked pharmacologically by compounds that inhibit ROS production through the NO/superoxide free radical pathways, suggesting that the NO-mediated ROS signaling pathway is a key player in activating I_{OGD} . Depletion of TRPM7 by siRNA blocked Ca^{2+} uptake and ROS-mediated activation of I_{OGD} and, most importantly, conferred resistance to cell death in cultured neurons exposed to up to 3 h OGD. In the culture system, TRPM7 gating appears to lie downstream from NMDA-mediated NO free radical production. In this paradigm, excitotoxicity is probably the initiating signal in a cell death cascade that is involved in neuronal NOS activation via NMDA receptor with subsequent peroxynitrite production, which in turn activates TRPM7 channels. Additionally, in neurons treated

with sodium nitroprusside, a chemical NO donor, a steady increase in production of ROS was observed. When TRPM7 expression was knocked down using siRNA, the overall production of ROS was suppressed, indicating that TRPM7, once activated by nitrogen or oxygen free radicals, contributes to the further production of ROS. Ca^{2+} influx through TRPM7 then creates a positive feedback loop of ROS production, which eventually kills the neuronal cell. In primary cortical neurons, knockdown of TRPM7 also results in knockdown of TRPM2, suggesting that the expression of these two proteins in cortical neurons is interdependent. In our recent studies [24], although TRPM7 was activated by H_2O_2 , H_2O_2 -induced Ca^{2+} responses of TRPM7 were very small compared to TRPM2. And NO donor activated TRPM2 only at high concentrations, and did not activate TRPM7. It is possible that the sensitivity of TRPM7 to ROS is enhanced by forming heteromers with TRPM2. Considering that TRPM7 is activated by ROS and critical for the progression of anoxic cell death in a model of *in vitro* ischemic neuronal injury, Ca^{2+} overload via oxidative stress-activated TRPM7 may participate in the development of AD.

Not only Ca^{2+} but also Zn^{2+} is a potentially toxic cation involved in neuronal injury. The mechanisms by which Zn^{2+} exerts its neurotoxicity include mitochondrial and extra-mitochondrial production of ROS and disruption of metabolic enzymatic activity, ultimately leading to activation of apoptotic and/or necrotic processes [131]. It has been suggested that imbalances of Zn^{2+} may be involved in AD [132]. In fact, levels of Zn^{2+} were increased in Alzheimer's subjects compared to normal subjects [133-135]. Additionally, Bush et al. [136] showed that A β specifically binds to Zn^{2+} . Zn^{2+} at high concentrations accelerates aggregation of A β peptide, suggesting a role for Zn^{2+} metabolism in the pathogenesis of A β deposition in AD. Hermosura et al. [137] have reported the identification of a TRPM7 variant in a subset of Guamanian amyotrophic lateral sclerosis and parkinsonism-dementia patients that causes a missense mutation, changing Thr-1482 to isoleucine. In functional studies, it was demonstrated that the channel protein encoded by the variant is more sensitive to inhibition by internal free Mg^{2+} . They proposed the possibility that the mutant impairs cellular ion homeostasis, which leads to Guamanian amyotrophic lateral sclerosis and parkinsonism-dementia. Because it is known that TRPM7 is also permeable to Zn^{2+} , Zn^{2+} homeostasis disruption induced by impairment of TRPM7 may participate in AD.

3.3. Does NO-induced activation of TRPC5 lead to neuronal cell death?

TRPC5 is the canonical TRP channel first cloned from the mouse brain [23], and is known to be expressed widely in the brain, testis, kidney, ovary, adrenal gland, uterus, and endothelial cells. The report describes a Ca^{2+} -permeable, receptor-operated channel activated independently of store depletion. Our recent study has revealed that the basal $[\text{Ca}^{2+}]_i$ act on calmodulin to activate myosin-light-chain kinase, and that the phosphorylation of the myosin light chain maintains cell surface localization of TRPC5 proteins. Thus, TRPC5 proteins are constitutively expressed at the plasma membrane to form channels activatable upon G-protein-coupled receptor stimulation [138]. Additionally, Bezzerides et al. [139] have shown that growth factor initiates the rapid translocation of TRPC5 channels from vesicles just under the plasma membrane to the cell surface through the phosphatidylinositol 3-kinase pathway. In neurons, a dominant-negative mutant of TRPC5 (DN-TRPC5) harboring an substitution of three amino acids between the fifth and sixth predicted transmembrane domain induces an increased length of neurites as well as filopodia, the finger-like projections characteristic of growth cones [22]. The results suggest that TRPC5-mediated Ca^{2+} entry is an important determinant of axonal growth and growth cone morphology. Most recently, we have demonstrated activation of the TRPC5 channel via cysteine S-nitrosylation, and as well a structural motif essential for the activation gating [24]. Among TRPCs, TRPC5 shows prominent sensitivity to NO. Our results also suggest that NO and reactive disulfides selectively modify Cys553 and Cys558 residues that are coupled to the gating apparatus in functionally critical domains of the TRPC5 protein. Because C553S and C558S mutations of TRPC5 only partially suppress receptor-induced TRPC5 responses, the cysteines are not absolute necessities but probably play an important regulatory role in TRPC5 activation. Our experiments provide further evidence for activation of native TRPC5 channels by nitrosylation via endothelial NOS upon ATP receptor stimulation in endothelial cells. Although precise identification of physiological protein interaction between nitrosylated TRP channels and NOSs is necessary, it can be speculated that Ca^{2+} influx via nitrosylated TRPC5 mediates the positive feedback regulation of Ca^{2+} -dependent NO production.

Considering reports from various laboratories showing that $\text{A}\beta$ stimulates microglial

and astrocytic NO production, it is possible that this NO production induces Ca^{2+} influx via TRPC5 in neuronal cells. Neuronal NOS is Ca^{2+} dependent. Therefore, as well in neuronal cells, Ca^{2+} influx via nitrosylated TRPC5 may mediate the positive feedback regulation of Ca^{2+} -dependent NO production, whose dysregulation may underlie Ca^{2+} homeostasis disruption and neuronal cell death in AD. Additionally, the alignment of amino acid sequences surrounding Cys553 and Cys558 of TRPC5 with counterpart sequences shows that TRPC5's closest relatives, TRPC1 and TRPC4, as well as TRPV1, TRPV3, and TRPV4, have cysteines conserved on the N-terminal side of the putative pore-forming region. Notably, TRPC1 and TRPC4 associated with TRPC5, and with TRPV1, TRPV3, and TRPV4, respond well to NO. Thus, it is conceivable these TRP channels may also be involved in Ca^{2+} homeostasis disruption in AD.

It was reported that 7-ketocholesterol, a component of oxidized LDL, treatment induces an increase in $[\text{Ca}^{2+}]_i$ in THP-1 monocytic cells [140]. This increase was correlated with the induction of 7-ketocholesterol-induced apoptosis, which appeared to be associated with the dephosphorylation of the proapoptotic protein Bcl-2 antagonist of cell death. It was also demonstrated that Bcl-2 dephosphorylation results mainly from the activation of Ca^{2+} -dependent phosphatase calcineurin via the oxysterol-induced increase in $[\text{Ca}^{2+}]_i$. Moreover, the $[\text{Ca}^{2+}]_i$ increase was likely to be mediated by the incorporation of 7-ketocholesterol into lipid raft domains of the plasma membrane, followed by the translocation of TRPC1 to rafts. Bezzerides et al. [139] have proposed that the channels may be sequestered into vesicles and inserted into the plasma membrane when and where they are needed to induce spatiotemporally restricted Ca^{2+} entry through TRPC channels and to avoid Ca^{2+} overload. As described above, the activation of TRPC5 is regulated by the translocation of TRPC5 to the plasma membrane. If the mechanism that controls TRPC5 translocation to the plasma membrane as TRPC1 is dysregulated, Ca^{2+} overload leading to AD may be triggered.

4. Conclusions

In this review, we have discussed the involvement of TRP channels in AD. Accumulated evidence indicates that TRP channels mediate physiological responses as multifunctional cellular sensors. Since it is thus obvious that they are implicated in so

many fundamental cell functions, establishing their impact on pathophysiology and disease will become an urgent priority in biomedical sciences. Increasing knowledge regarding the link between TRP channels and AD should lead to a fruitful development of innovative drugs in AD.

Figure 1.

Speculated involvement of neuronal TRP channels in AD. A β activates mitochondrial production of ROS, which is released into the cytosol. ROS can activate TRPM2 and TRPM7, and consequent $[Ca^{2+}]_i$ increases induce NO production. NO and ROS further combine to form the highly reactive species peroxynitrite (ONOO $^-$). ONOO $^-$ triggers Ca^{2+} influx via TRPM7. Microglia and astrocytes activated by A β produce TNF α , which induces TRPM2 activation and NO, which selectively modifies Cys553 and Cys558 residues to activate TRPC5. Ca^{2+} influx via nitrosylated TRPC5 mediates Ca^{2+} -dependent NO production by neuronal NOS. It must be noted that the neuroinflammatory process triggered by A β plays a central role in neurodegenerative process in AD. This inflammatory process is driven by activated-microglia and astrocytes that produce inflammatory molecules. Several inflammatory molecules activate TRPV1.

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Table 1. TRP channels expressed in brain [65, 141-144]

Subfamily	Distribution in brain	Proposed major regulation	Possible function
TRPC1	Cerebrum, cerebellum, forebrain, hippocampus	Store-operated	Neuroprotection
TRPC3	Cerebrum, cerebellum, forebrain, hippocampus	Receptor-operated	Neuroprotection
TRPC4	Cerebrum, cerebellum, forebrain, hippocampus	Receptor-operated	Neuroprotection
TRPC5	Cerebrum, cerebellum, forebrain, hippocampus, hindbrain	Receptor-operated, nitric oxide	Neurodegeneration
TRPC6	Cerebellum, cerebrum, forebrain, hippocampus	Diacylglycerol	Not yet determined
TRPM2	Cerebrum, cerebellum, forebrain, hippocampus	Reactive oxygen species, ADP-ribose, nicotinamide adenine dinucleotide	Neurodegeneration
TRPM7	Cerebrum, cerebellum, forebrain, hippocampus	Reactive oxygen species	Neurodegeneration
TRPV1	Cerebrum, hippocampus, hindbrain	Capsaicin, heat (>43°C), pH (<5.9), bradykinin, nitric oxide	Neurodegeneration

Expression of TRPC1, TRPC3, TRPC4, TRPC5 and TRPC6, TRPM2, TRPM7 and TRPV1 in mice brain was determined by real-time RT-PCR. TRP subfamilies reviewed in this article were described in the list.

