Acid-sensing ion channel 1a: a novel target in Alzheimer's disease?

Dalila Mango*, Robert Nisticò

Alzheimer's disease (AD) represents the most common form of dementia and is characterized by a progressive decline of cognitive functions. Complex multifactorial processes underlie AD pathophysiology, including amyloid-beta (Aβ) toxicity, tau protein hyperphosphorylation, synaptic dysfunction, oxidative stress, and neuroinflammation (Ju and Tam, 2022).

The amyloid cascade hypothesis remains the most popular theory to explain AD pathogenesis, even though it is still largely debated. The accumulation of Aβ oligomers promotes several stress responses in neurons among which dysregulation of Ca^{2+} homeostasis, activation of the endoplasmic reticulum stress (ERS) and mitochondria permeability play a critical role (Selkoe and Hardy, 2016).

Endoplasmic reticulum (ER) and mitochondria are vital organelles highly interconnected by a specialized set of proteins. The ER represents the major calcium storage pool, while mitochondria is responsible for energy production within the cell and plays a major role in buffering Ca^{2+} from the ER (Eysert et al., 2020). As a consequence of this interplay, ER and mitochondria reciprocally impact each other both in normal and pathologic states.

Indeed, both ERS activation and mitochondrial dysfunction contribute to AD progression and irreversible neuronal death (Esteras et al., 2020). Prolonged ERS induces the release of apoptotic factors and these were found elevated in the hippocampus of AD patients and also in an AD mouse model (Ismael et al., 2021).

In the past years, the investigation of acid sensing ion channels 1a (ASIC1a) as pH sensors in the brain highlighted a crucial role of these channels in several pathologic processes, such as ischemia, acidosis, neuroinflammation, and neurodegeneration, thereby suggesting a possible involvement also in AD (Mango and Nisticò, 2021). ASIC1a represents a key target for ischemia-induced neuronal damage since it provides a non-voltage-gated pathway for Ca^{2+} entry in neurons (Xiong et al., 2004; Yermolaieva et al., 2004). Using a neuroblastoma cell line, a recent study has demonstrated the implication of ASIC1a in ERS-mediated apoptosis (Pan et al., 2021), a process also observed in the hippocampus of AD patients (Ismael et al., 2021). Another study suggests a role of ASIC1a in mitochondrial Ca^{2+} dysregulation in response to inflammatory stimuli (Liu et al., 2018). These pieces of evidence support the hypothesis that ASIC1a might represent a new target against ERS activation and mitochondrial permeability alteration that occurs in AD.

In particular, the work conducted by Pan et al. (2021) has demonstrated that ASIC1a is involved in ERS-mediated apoptosis. Silencing ASIC1a or inhibiting these channels with the selective inhibitor Psalmotoxin-1 (PcTx-1) was able to reduce the apoptosis induced by the ERS pathway (Pan et al. 2021). This investigation has demonstrated for the first time that ASIC1a plays a permissive role in ERs-mediated apoptosis, thus suggesting ASIC1a as a novel target to afford neuroprotection.

Since ASIC1a is present in the mitochondrial membrane of neurons where it regulates ROS production (Wang et al., 2013), a recent study shed light on the function of ASIC1a protein in mitochondrial membranes permeability during acidosis (Liu et al., 2018). In particular, Liu et al. (2018) have shown that Aβ oligomers induced pH mitochondria acidification and Ca^{2+} overload resulting in neuronal death. Of note, PcTx-1 was able to significantly increase the viability of neurons exposed to oxidative stress or aggregated Aβ while it showed only a tendency to protect neurons from Ca^{2+} overload and mitochondria acidification. A limitation of this study is that PcTx-1 was used at a high concentration (200 nM) possibly leading to off-target effects.

Altogether, the above pieces of evidence linking ASIC1a to ERS and mitochondria dysfunction corroborate the hypothesis that the targeting of ASIC1a might be a viable treatment approach for AD (**Figure 1**).

Noteworthy, berberine, an alkaloid extracted from a variety of herbs, was able to alleviate ERS and oxidative stress and ameliorated cognitive impairment in the AD mouse model (Liang et al., 2021), further confirming that the ERS pathway may represent a potential target in the neurodegenerative process. However, several compounds that target ERS-regulated proteins might also affect their basal physiologic activity hence leading to side effects.

Yet, not many studies have investigated the role of ASIC1a in AD, so more evidence is needed to support this hypothesis. A crucial challenge will be to develop potent and selective blockers for the individual ASIC subunits involved in the pathologic process, while minimizing their impact on physiologic activities.

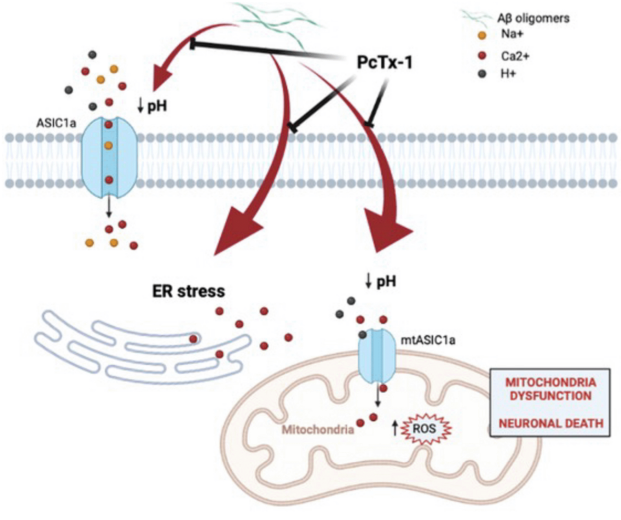

Figure 1 | Cartoon showing the proposed role of ASIC1a in Aβ-mediated neuronal death. In AD, pathological triggers including Aβ-induced cytosolic pH acidification, activation of ER stress, and mitochondria acidification leading to neuronal death. These changes are reversed by the selective ASIC1a inhibitor PcTx-1, thereby suggesting that blocking ASIC1a might be a viable approach to AD therapy. Aβ: Amyloid-beta; AD: Alzheimer's disease; ASIC1a: acid sensing ion channels 1a; ER: endoplasmic reticulum; mt: mitochondrial; PcTx-1: psalmotoxin-1; ROS: reactive oxygen species.

Dalila Mango*, Robert Nisticò
School of Pharmacy, University of Rome "Tor Vergata"; Laboratory of Pharmacology of Synaptic Plasticity, European Brain Research Institute, Rome, Italy
***Correspondence to:** Dalila Mango, PhD, d.mango@ebri.it.
https://orcid.org/0000-0003-3358-4068 (Dalila Mango)

Date of submission: January 30, 2022
Date of decision: March 11, 2022
Date of acceptance: March 21, 2022
Date of web publication: June 2, 2022

https://doi.org/10.4103/1673-5374.346479
How to cite this article: *Mango D, Nisticò R (2023) Acid-sensing ion channel 1a: a novel target in Alzheimer's disease? Neural Regen Res 18(2):324.*
Availability of data and materials: *All data generated or analyzed during this study are included in this published article and its supplementary information files.*

Open peer reviewers: *Dmitry I. Osmakov, Sechenov First Moscow State Medical University, Russia; Stephan Kellenberger, University of Lausanne: Universite de Lausanne, Switzerland .*
Additional file: *Open peer review reports 1 and 2.*

References

Esteras N, Abramov AY (2020) Mitochondrial calcium deregulation in the mechanism of beta-amyloid and tau pathology. Cells 9:2135.
Eysert F, Kinoshita PF, Mary A, Vaillant-Beuchot L, Checler F, Chami M (2020) Molecular dysfunctions of mitochondria-associated membranes (MAMs) in Alzheimer's disease. Int J Mol Sci 21:9521.
Ismael S, Wajidunnisa, Sakata K, McDonald MP, Liao FF, Ishrat T (2021) ER stress associated TXNIP-NLRP3 inflammasome activation in hippocampus of human Alzheimer's disease. Neurochem Int 148:105104.
Ju Y, Tam KY (2022) Pathological mechanisms and therapeutic strategies for Alzheimer's disease. Neural Regen Res 17:543-549.
Liang Y, Ye C, Chen Y, Chen Y, Diao S, Huang M (2021) Berberine improves behavioral and cognitive deficits in a mouse model of Alzheimer's disease via regulation of β-amyloid production and endoplasmic reticulum stress. ACS Chem Neurosci 12:1894-1904.
Liu Z, Pei H, Zhang L, Tian Y (2018) Mitochondria-targeted DNA nanoprobe for real-time imaging and simultaneous quantification of Ca2+ and pH in neurons. ACS Nano 12:12357-12368.
Mango D, Nisticò R (2021) Neurodegenerative disease: what potential therapeutic role of acid-sensing ion channels? Front Cell Neurosci 15:730641.
Pan X, Zhu Y, Wu X, Liu L, Ying R, Wang L, Du N, Zhang J, Jin J, Meng X, Dai F, Huang Y (2021) The interaction of ASIC1a and ERS mediates nerve cell apoptosis induced by insulin deficiency. Eur J Pharmacol 893:173816.
Selkoe DJ, Hardy J (2016) The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 8:595-608.
Xiong ZG, Zhu XM, Chu XP, Minami M, Hey J, Wei WL, MacDonald JF, Wemmie JA, Price MP, Welsh MJ, Simon RP (2004) Neuroprotection in ischemia: blocking calcium-permeable acid-sensing ion channels. Cell 118:687-98.
Yermolaieva O, Leonard AS, Schnizler MK, Abboud FM, Welsh MJ (2004) Extracellular acidosis increases neuronal cell calcium by activating acid-sensing ion channel 1a. Proc Natl Acad Sci U S A 101:6752-6757.
Wang YZ, Zeng WZ, Xiao, X, Huang Y, Song XL, Yu Z, Tang D, Dong XP, Zhu MX, Xu TL (2013) Intracellular ASIC1a regulates mitochondrial permeability transition-dependent neuronal death. Cell Death Differ 20:1359-1369.

P-Reviewers: Osmakov DI, Kellenberger S; C-Editors: Zhao M, Liu WJ, Wang Lu; T-Editor: Jia Y