Published in final edited form as:

Curr Alzheimer Res. 2020 ; 17(4): 311–312. doi:10.2174/156720501704200520094610.

New Approaches to Develop Drug Treatment for Alzheimer's Disease: Targeting Calcium Dysregulation

Huafeng Wei, MD, PhD [Guest Editor]

Department of Anesthesiology and Critical Care, University of Pennsylvania Perelman School of Medicine, 305 John Morgan Building, 3620 Hamilton Walk, Philadelphia, PA 19104, USA

There are about 44 million patients with dementia worldwide which is expected to increase to 135 million by the year 2050. Alzheimer's Disease (AD) is the number one cause of dementia, with prevalence doubling every five years between ages 50 to 80 years. Unfortunately, there are no disease modifying drugs available for AD treatment. Several factors that may contribute to the failure of advancement in new drug development on AD treatment include: 1). Most drug development target the amyloid pathology. Although amyloid pathology may contribute to the development of AD pathology partially, it is likely not the primary root cause or main mechanism for AD dementia; 2). There is no well accepted animal model for sporadic AD (SAD) which constitutes more than 95% of AD patients, so drugs that work well in familiar AD (FAD) animal models may not be effective in patients with SAD; 3). There may be multiple pathways or mechanisms of neurodegeneration, synapse and cognitive dysfunction in AD patients, so a single drug targeting one pathological pathway may not be fully effective. A combination of drugs targeting different pathways may provide effective therapeutic effects.

Among alternative approaches to study mechanisms of AD pathology and dementia, disruption of intracellular Ca^{2+} homeostasis has been increasingly recognized as a major upper stream pathological mechanism of AD, with many recent studies demonstrating the efficacy of old or new drugs and compounds targeting correction of Ca^{2+} dysregulation for AD treatment [1–3]. This thematic issue aims to illustrate the mechanisms and features of Ca^{2+} dysregulation in each major intracellular Ca^{2+} store in AD. Various Food and Drug Administration (FDA) approved clinically available drugs and novel compounds targeting different sites of pathological Ca^{2+} dysregulation were developed as potential new treatments of AD.

Chami and Checler have discussed in detail the molecular structure, function and Regulation of Ryanodine Receptor (RyR) Ca^{2+} channel located on the ER membrane and its contribution to ER Ca^{2+} homeostasis and cell function [4]. The leaky type 2 RyR (RyR-2) mediated Ca^{2+} dysregulation results in worsened amyloid pathology, mitochondria

Tel: 215-746-8704, Fax: 215-349-5078, weih@uphs.upenn.edu.

CONFLICT OF INTEREST

Dr. Huafeng Wei was one of inventors in a US provisional patent application titled "Intranasal Administration of Dantrolene for Treatment of Alzheimer's Disease" filed on June 28, 2019 (Serial number 62/868,820) by the University of Pennsylvania Trustee. The patent application is also part of the research collaboration agreement between University of Pennsylvania and Eagle Pharmaceutical Company, which produce and sale of Ryanodex, a new formula of dantrolene for treatment of malignant hyperthermia.

dysfunction, synapse, and cognitive dysfunction. Pathological activation of Protein Kinase A (PKA) associated with β_2 adrenergic signaling and the subsequent phosphorylation of RyR-2, as well the oxidation and nitrosylation of RyR-2 *via* different mechanisms, contribute to the excessive RyR-2 activation and associated AD pathology, which can be inhibited by the compounds that stabilize RyR-2 and minimize the pathological Ca^{2+} leak.

Abou *et al.*, summarized the studies demonstrating therapeutic effects of RyR, antagonist dantrolene, a clinically available drug to treat malignant hyperthermia or muscle spasms, on amelioration of Ca^{2+} dysregulation and associated AD pathologies, synapse and cognitive dysfunction in various cell and animal models [1, 5]. Wang *et al.* also proposed a novel approach to administer dantrolene intranasally in order to increase brain concentration and duration [6], which has been demonstrated to be more effective than the subcutaneous approach in ameliorating memory loss in 5xFAD mice, even as a disease modifying drug, with tolerable side effect after about 8 months treatment [7]. Nasal administration of dantrolene may further decrease the overall minimal effective therapeutic dose for treatment of AD or other neurodegenerative diseases such as stroke, spinal ischemia, seizure, Huntington's disease and spinocerebellar ataxia *etc.* [8], with reduced side effects of dantrolene after chronic use.

Wu *et al.*, discussed the physiological regulation of mitochondrial Ca^{2+} homeostasis, especially its close relationship with the ER and the mechanisms of pathological mitochondrial Ca^{2+} overload, as important AD pathology and etiology. Potential targets to correct mitochondrial Ca^{2+} dysregulation and particular compounds were proposed and discussed [9].

Popugaeva *et al.*, summarized the overall Ca^{2+} dysregulation in both familiar and sporadic AD and its essential role in many proposed AD pathology, as the potential targets and compounds for treatment of AD [10]. In particular, they explained the important role of Store Operated Ca^{2+} Entry (SOCE) in maintaining physiological ER Ca^{2+} homeostasis. Both impairment and excessive function of SOCE have been demonstrated in AD, depending on the AD mutation sites of presenilin 1 [10].

In short, this thematic issue summarized previous studies using clinically available drugs or new compounds ameliorating pathological Ca^{2+} dysregulation as new treatments of AD. We have proposed new approaches for future drug development based on the Ca^{2+} dysregulation mechanisms in AD. We thank all authors, reviewers, journal's editorial team and publisher (Bentham Science).

FUNDING

Supported by grants to HW from the NIH (R01GM084979, R01AG061447).

REFERENCES

- [1]. Peng J, Liang G, Inan S, et al. Dantrolene ameliorates cognitive decline and neuropathology in Alzheimer triple transgenic mice. *Neurosci Lett* 2012; 516(2): 274–9. doi: 10.1016/j.neulet.2012.04.008. [PubMed: 22516463]

- [2]. Chakroborty S, Briggs C, Miller MB, et al. Stabilizing ER $\text{Ca}^{(2+)}$ Channel function as an early preventative strategy for Alzheimer's disease. PLoS One 2012; 7(12): e52056. [PubMed: 23284867]
- [3]. Oules B, Del Prete D, Greco B, et al. Ryanodine receptor blockade reduces amyloid-beta load and memory impairments in Tg2576 mouse model of Alzheimer disease. J Neurosci 2012; 32(34): 11820–34. doi:10.1523/JNEUROSCI.0875-12.2012 [PubMed: 22915123]
- [4]. Chami M, Checler F. Targeting Post-translational remodeling of ryanodine receptor: A new track for Alzheimer's disease therapy? Curr Alzheimer Res 2020; 17(4): 313–23. doi: 10.2174/1567205017666200225102941. [PubMed: 32096743]
- [5]. Abou MB, Sun L, Wei H. Approaches to optimizing dantrolene neuroprotection for treatment of Alzheimer's disease Curr Alzheimer Res 2020; 17(4): 324–328.
- [6]. Wang J, Shi Y, Yu S, et al. Intranasal administration of dantrolene increased brain concentration and duration. PLoS One 2020; 15(3): e0229156. doi: 10.1371/journal.pone.0229156. [PubMed: 32160210]
- [7]. Shi YZL, Gao X, Zhang J, et al. Intranasal dantrolene as a disease-modifying drug in Alzheimer 5XFAD mice. Alzheimer Dementia 2019; 19(7): P597.
- [8]. Inan S, Wei H. The cytoprotective effects of dantrolene: A ryanodine receptor antagonist. Anesth Analg 2010; 111(6): 1400–10. doi: 10.1213/ANE.0b013e3181f7181c. [PubMed: 20861418]
- [9]. Wu AJ, Tong BC, Huang AS, Li M, Cheung KH. Mitochondrial calcium signaling as a therapeutic target for Alzheimer's disease. Curr Alzheimer Res 2020, 17(4): 329–43 doi: 10.2174/1567205016666191210091302. [PubMed: 31820698]
- [10]. Popugaeva E, Chernyuk D, Bezprozvanny I. Reversal of calcium dysregulation as potential approach for treating Alzheimer's disease. Curr Alzheimer Res 2020; 17(4): 344–54. [PubMed: 32469698]