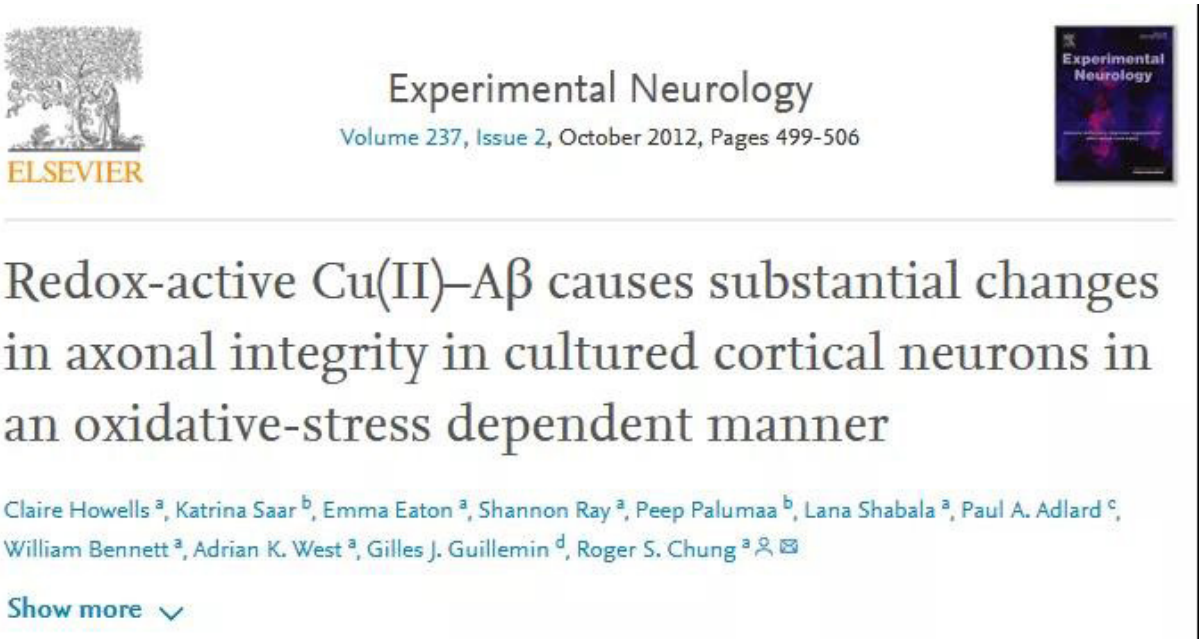
Practical Applications

Medical Applications — Alzheimer's Risk Assessment

Contributed to the editorial department of Zhongguancun NMT Industrial Alliance

The discovery of Cu-induced neuronal K^+ discharge by non-invasive micro-test technology provides evidence for the discovery that Cu and Aβ interact to induce neurodegeneration

Editor's note:
Alzheimer's disease AD, also known as senile dementia, affects about 36.5 million people worldwide, causing economic losses of 250.2 billion US dollars. According to statistics, the number of Alzheimer's patients in China was about 15.07 million in 2020, ranking first in the world. It is estimated that the number of patients will exceed 22 million in 2040, and the younger trend of Alzheimer's disease is obvious. At present, the youngest Alzheimer's patient found in China is only 39 years old. Therefore, it is imminent to carry out large-scale testing and general surveys, provide targeted prevention recommendations, and formulate relevant policies and guidelines. Recently, researchers from the University of Tasmania have made new discoveries in the mechanism of Alzheimer's disease using a non-invasive micro-test technique. The editor hereby shares this document with you.



Date received: 2022-10-10, Date received: 2022-10-10
Editor E-mail: yanhan@nmtia.org.cn

Basic Information

Topic: The discovery of Cu-induced neuronal K^+ discharge by non-invasive micro-test technology provides evidence for the discovery that Cu and Aβ interact to induce neurodegeneration

Journal: Experimental Neurology

Impact factor: 7.299 (2019)

Title: Redox-active Cu(II)-Aβ causes substantial changes in axonal integrity in cultured cortical neurons in an oxidative-stress dependent manner

Authors: Claire Howells, Katrina Saar, Emma Eaton, Shannon Ray, Peep Palumaa, Lana Shabala, Paul A.Adlard, William Bennett, Adrian K.West, Gilles J.Guillemin, Roger S.Chung

Test sample: rat cortical neurons

Ion/molecule detection indicators: K^+

K^+ test liquid composition: 40μM Cu(II)–Aβ real-time processing

K^+ flux experimental treatment method: 150 mM NaCl, 0.5 mM KCl, 0.5 mM $CaCl_2$, 1.5 mM $MgCl_2$, 1.25 mM NaH_2PO_4, 5 mM $NaHCO_3$, 25 mM glucose, pH 7.4

Abstract: The beta-amyloid (Aβ) peptide comprises the amyloid plaques that characterize Alzheimer's disease (AD), and is thought to significantly contribute towards disease pathogenesis. Oxidative stress is elevated in the AD brain, and there is substantial evidence that the interaction between Aβ and redox-active copper is a major contributing factor towards oxidative stress in AD.

The main finding of this study is that redox-active Cu(II)-Aβ causes pronounced axonal pathology in long-term neuronal cultures, including axonal fragmentation and the formation of hyperphosphorylated tau-immunoreactive axonal swellings. Notably, MAP-2 expressing dendritic processes remain largely un-affected by Cu(II)-Aβ treatment. These dystrophic axonal manifestations resemble some of the characteristic neuritic pathology of the AD brain. The present study demonstrates that Cu(II)-Aβ directly causes formation of intra-axonal swellings via the generation of free radicals and subsequent efflux of K^+ out of neurons. In conclusion, this study reports that redox-active Cu(II)-Aβ can induce substantial neurodegenerative changes in mature neurons, and may have an important role to play in the slowly progressing pathogenesis of AD.

Key words: non-invasive micro-test technology; Alzheimer's disease (AD); β-amyloid; neurotoxicity

1. Experimental results of ion/molecule flux

The study used a highly sensitive non-invasive micro-test technique to assess the impact of Cu(II)-$Aβ_{1-40}$ on K^+ ion flux in cultured cortical neurons (Figure 1). It was found that Cu(II)-$Aβ_{1-40}$ caused substantial efflux of K^+ ions (Figure 1). But $Aβ_{1–40}$ alone had no effect on K^+ flux (results not shown). To determine the importance of Cu(II)-Aβ-induced K^+ efflux to cortical neurons, the scientists assessed whether the K^+ channel inhibitor 4-aminopyridine (4-AP) could block Cu(II)-Aβ-induced cytoskeletal disruption. It was found that 4-AP (2 mM) almost completely blocked the Cu(II)-Aβ-induced formation of intra-axonal swellings.

2. Other experimental results

1) Cu(II)–Aβ exerts greater acute neurotoxicity

upon cultured cortical neurons than other biochemical forms of Aβ

2) Chronic exposure to extracellular Cu(II)-$A\beta_{1-40}$ can lead to progressive neurodegeneration in cortical neurons.

3) Chronic exposure to redox-active Cu(II)-$A\beta_{1-40}$ leads to progressive changes in axonal integrity in cortical neurons.

4) Cu(II)-$A\beta_{1-42}$ induced pathological changes in axons of cultured cortical neurons.

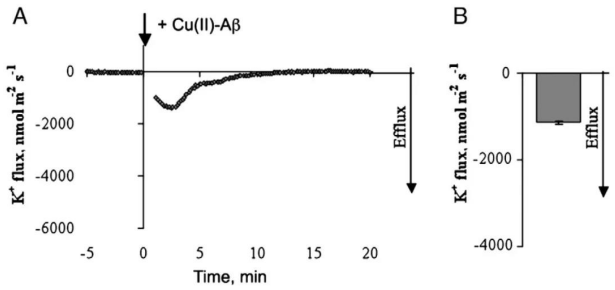


Figure 1. 40 μM Cu(II)-$A\beta_{1-40}$ produced a substantial efflux of K^+ coming out of cortical neurons. Negative values represent K^+ efflux.

3. Conclusion

This study reported that Cu(II)-Aβ can induce substantial neurodegenerative changes in neurons via oxidative stress and K^+ dyshomeostasis pathway, and may play an important role in the slowly progressing pathogenesis of AD.

(Editor in charge: Xuefei Li)