THE DUAL ACTION OF MEMANTINE ON ALZHEIMER'S DISEASE

T.-Y. Wu¹, Y.-J. Chen¹, C.-Y. Teng¹, T.-R. Jinn²

¹Department of Bioscience Technology, Chung Yuan Christian University, Chung Li, ²Graduate Institute of Chinese Medical Science, China Medical University, Taichung, Taiwan R.O.C.

Alzheimer’s disease (AD) is the most common neurodegenerative disease in the modern but senile society and this senile dementia attacked more than 20 million people worldwide. The inhibition of APP and tau expression may be the strategy that can defeat Alzheimer's disease. It has been demonstrated that the expression of APP and tau proteins can be mediated through the internal ribosome entry site (IRES), an atypical translational initiation mechanism, as well as the cap-dependent translation initiation. In previous studies, it had shown that amantadine can inhibit the translation activity of IRES derived from hepatitis A viruses enterovirus 71 or encephalomyocarditis virus. It is interesting that the chemical structure of amantadine is similar to memantine, a therapeutic drug in moderate to severe AD, both are tricyclic symmetric amine. Transient transfection assays showed that both the IRES of APP or Tau had higher translational activity in the neuron derived cell line N2A than that in the non-neuronal cells, CHO or COS-1 cells. This result was consistent with the tissue tropism of APP or Tau IRES. More interestingly, the IRES activity of APP or Tau IRES can be inhibited by the memantine but without interfering the cap-dependent translation activity when the concentration of memantine was lower than 10 uM. These results suggest that the NMDA receptor antagonist, memantine can suppress the expression of neuronal APP and tau proteins through a novel cap-independent translational initiation mechanism.