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Potential therapeutic role of neurotensin receptor agonists in the treatment of Alzheimer's disease

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Abstract

Progressive deterioration of cognitive performance is a critical characteristic of Alzheimer's disease (AD) and improving cognitive function represents a major therapeutic approach for this disease. Current available therapies for AD including the cholinesterase inhibitors and the partial NMDA receptor antagonist memantine provide only minimal benefit for a limited period to a subset of patients. Finding drugs that can improve memory is still a major method to relieve the symptoms of AD patients. Accumulating evidence demonstrates that neurotensin (NT) and NT receptors are densely distributed in the entorhinal cortex (EC), a structure that is essential for learning and memory and undergoes the earliest pathological alteration in AD. However, the physiological functions of NT in the EC especially in learning and memory and the therapeutic potential of NT receptor modulators for AD have not been determined. Here, we found that activation of NT receptor type 1 (NTS1) induced persistent increases in action potential firing frequency which could last for at least 1h, a novel phenomenon we named as Long-Term Excitation (LTE). NT-induced LTE was mediated by down-regulation of TREK-2 K+ channels and required the functions of phospholipase C and protein kinase C. NT-induced LTE underlies NT-mediated enhancement of spatial learning as assessed by Barnes Maze. Furthermore, microinjection of NT and NTS1 agonist into the EC significantly attenuated the memory impairment of APP/PS1 mice, an animal model of AD. Our results suggest that NTS1 agonists may be a potential drug that can be further developed for AD therapy.

Biography

Saobo Lei has completed his Ph.D from the University of Alberta and postdoctoral studies from the University of Toronto and National Institutes of Health. He is an Associate Professor in the University of North Dakota. He has published more than 40 papers in reputed journals and serves as an editorial board member for 10 journals. His research is focusing on identifying the cellular and molecular mechanisms underlying neuropeptides-induced neural modulation in the brain and testing the possibilities of using modulators of neuropeptide receptors for treating neurological diseases such as anxiety, epilepsy, Alzheimer's disease and schizophrenia.