NUS-03 Reducing calcium-mediated endoplasmic reticulum stress could attenuate beta-amyloid peptide neurotoxicity

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Introduction: Beta-amyloid peptide (Ab) has been proposed to play an important role in the pathogenesis of Alzheimer's disease. Exposure of Abeta could trigger disturbance of cellular calcium homeostasis in cultured neurons. Calcium depletion in the endoplasmic reticulum (ER) is one of the major causes of calcium toxicity. Since Ab could trigger ER stress in neurons, we hypothesize that modulation of calcium-mediated ER stress could protect neurons from Abeta neurotoxicity.
Methods: Primary cultures of cortical neurons from 17-day-old embryos of Sprague-Dawley rats were set up. The neurons were pretreated with three ER calcium release modulators, 2-aminoethoxydiphenyl borate (2APB), Xestospongin C (XeC) or FK506 for 2 hours, followed by the treatment with Abeta. In order to assess their neuroprotective effects against Abeta, the release of lactate dehydrogenase, quantification of apoptotic nuclei stained with 4',6'-diamidino-2-phenylindole (DAPI) and assessment of PARP cleavage were examined. Intracellular free calcium levels, expression of ER stress proteins and caspase-3 activity were also monitored so as to understand the mechanism underlying the neuroprotective effects of the three drugs.
Results and Conclusion: Our results showed that 2APB, XeC and FK506 significantly attenuated Abeta neurotoxicity. These drugs could reduce calcium depletion-induced ER stress and subsequent caspase-3 activation. Taken together, these results reveal that the modulation of ER calcium release may be a pharmacological target in future therapeutic approaches of Alzheimer's disease
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NUS-04 Delayed application of GDNF can decrease the NOS expression and rescue injured motor neurons in adult rat with C7 spinal root avulsion

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Introduction: Our previous studies have shown that spinal motoneurons express neuronal NOS and then die following root avulsion injury. Expression of nNOS and death of spinal motoneurons due to root avulsion can be prevented if GDNF is applied intrathetically on the lesion site immediately after avulsion. It is unknown whether delayed treatment with GDNF could still prevent the death of motoneurons after root avulsion. This hypothesis is examined in the present study.
Method: At 2 weeks after avulsion of C7 spinal root, the laminectomy was made at the C-7 segment and a small piece of gelfoam pre-soaked in the solution of 2 microliters normal saline or GDNF at 10 microgram/microliter was placed in contact with C7 segment. At different surviving days, the nNOS expression rate and motor neuron survival rate were detected by NADPH-histochemistry and neutral red counter stain.
Results: NOS expression rate of the motor neurons was 36.46%, 56.49%, 32.73% or 15.13% at 2 weeks, 3 weeks, 4 weeks or 6 weeks after avulsion. With a single dose GDNF, started at 2 weeks after avulsion, the NOS expression rate was markedly reduced to 7.30%, 7.99% and 9.24% at 3 weeks, 4 weeks or 6 weeks. In lesion animals, the motor neuron survival rate was 85.95%, 80.5%, 59.66% or 36.32% at 2 weeks, 3 weeks, 4 weeks or 6 weeks after avulsion. But in lesion animals treated with GDNF, the survival rate was increased to 94.33%, 93.75% or 91.83% % at 3 weeks, 4 weeks or 6 weeks.
Conclusion: Our data show that during a 6 week process of neurodegeneration a single dose GDNF treatment, though delayed up to 2 weeks, can still inhibit the expression of nNOS and allow substantial rescue of injured motor neurons.