

POSTER PRESENTATION

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NO/cGMP/pCREB re-activation reverses cognition deficits and attenuates amyloid- β neuropathology in transgenic models of Alzheimer's disease

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From 6th International Conference on cGMP: Generators, Effectors and Therapeutic Implications Erfurt, Germany. 28-30 June 2013

Background

An early event in Alzheimer's Disease (AD) is synaptic failure, making the disease fundamentally a disorder of impaired cognition and memory. Synaptic plasticity requires activation of gene expression programs with dysfunction of the transcription factor cAMP-response element binding protein (CREB) strongly implicated in AD etiology.

Results and Conclusion

The hypothesis that activation of CREB through NO/cGMP signaling might modify the amyloid- β ($A\beta$) neuropathology, linked to AD pathogenesis, was demonstrated in both APP/PS1 and 3xTg transgenic mouse models of AD using small molecules, termed nomethiazoles, also designed to provide neuroprotection and attenuate pro-inflammatory cytokine release. Functional restoration of long-term potentiation was shown in hippocampal slices from AD transgenic mice in accord with observation of restoration of cognitive function *in vivo*, and was dependent upon soluble guanylyl cyclase (sGC) activation. Levels of pCREB and BDNF were significantly elevated, whereas TNF α , $A\beta$, oligomeric $A\beta_{1-42}$, and also tau protein were significantly lowered after drug treatment. In the absence of neuronal loss in animal models of AD, neuroprotection was demonstrated in rat primary neurons after oxygen-glucose deprivation or application of oligomeric $A\beta$. The lead nomethiazole was also studied in a novel transgenic mouse model,

E4FAD, which incorporates familial AD mutations, but also has targeted replacement of mouse apolipoprotein-E with human ApoE4, the major genetic risk factor for sporadic and age-related AD.

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Published: 29 August 2013

doi:10.1186/2050-6511-14-S1-P72

Cite this article as: Thatcher et al.: NO/cGMP/pCREB re-activation reverses cognition deficits and attenuates amyloid- β neuropathology in transgenic models of Alzheimer's disease. *BMC Pharmacology and Toxicology* 2013 **14**(Suppl 1):P72.

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