THE EFFECTS OF APOE GENOTYPE ON KAINIC ACID INDUCED NEUROPATHOLOGY

K. Deng¹, M. Monaghan¹, M.-L. Sung², E. Wagner², H.K. Warwick², Z. Lou², Q. Lin¹, M. DenBleyker², M.M. Zaleska¹, M.N. Pangalos¹, P.H. Reinhart², D. Riddell¹

¹Pfizer, Groton, CT, ²Pfizer, Princeton, NJ, USA

Background: Inheritance of the apoE4 allele (e4) is associated with poor outcome after head trauma and stroke and with higher risk of developing Alzheimer's disease. However, the underpinning mechanisms remain elusive.

Methods: Using the human apoE3 and apoE4 targeted replacement mice and apoE knockout mice; we investigated their response to kainic acid (KA) excitotoxic insult.

Results: We observed an exacerbated response of apoE4 and apoE knockout mice to KA stimulation in the measurement of severity and frequency of high level seizure, knockout>>4/4>3/3. KA induced an increase of astrocytes activation in an apoE genotype specific fashion (knockout>>4/4>3/3). The severity of neurodegeneration was further evaluated by immunostaining for MAP-2. KA-challenged apoE knockout and apoE4 mice had a more significant disruption of MAP-2-positive neuronal dendrites in hippocampus in comparing with apoE3 mice. Moreover, we examined the expression of apoE post KA-challenged. Protein levels of apoE is genotype dependent, 3/3>4/4. ApoE was mainly expressed by astrocytes under physiological conditions and after KA treatment. In addition, the C-terminal putative toxic fragments of apoE were not detected in KA treated apoE3 and apoE4 mice, indicating the dissociation of neuronal damage and the production of apoE fragments under physiological expression of apoE.

Conclusions: These data suggest that neuronal vulnerability to KA is apoE genotype dependent. The different sensitivity to the insults appeared to be the major driver of the distinctive responses. Given that apoE knockout mice show the most severe phenotype, our results support the notion that apoE4 is a “loss of function” mutation.