

ORAL PRESENTATION

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# TNF gene deletion prevents lipopolysaccharide-mediated sensitisation of the neonatal mouse brain to hypoxic-ischaemic insult

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## Introduction

An increasing body of evidence suggests a synergistic link between infection/inflammation and hypoxia-ischaemia in the pathogenesis of perinatal brain injury. Deletion of the TNF cytokine gene cluster (TNF, LT $\alpha$  and LT $\beta$ ) has previously been shown to abolish lipopolysaccharide (LPS)-mediated sensitisation of the developing brain to hypoxic-ischaemic (HI) insult. In this study, I investigated if single TNF and LT $\beta$  gene deletions prevented LPS-sensitised HI brain injury.

## Methods

Postnatal day 7 mice homozygous for either TNF or LT $\beta$  cytokine gene deletions received either 0.3mcg/g LPS or saline by intraperitoneal injection 12 hours prior to 30-minute HI insult. Coronal forebrain sections were examined for brain injury using Nissl stain and microglial activation using the activation marker  $\alpha$ M $\beta$ 2 intergrin ( $\alpha$ M). Injury was scored in ipsilateral grey matter regions and external capsule white matter (ipsilateral and contralateral). Values given are mean  $\pm$  SEM and data was analysed for significant differences using unpaired two-tailed Student's t-test.

## Results

Pre-treatment with LPS in wild-type mice (n=13) resulted in significantly increased overall brain injury ( $0.96 \pm 0.17$  v  $3.11 \pm 0.44$ ,  $p < 0.05$ ) and  $\alpha$ M expression across all assessed ipsilateral forebrain regions ( $p < 0.05$ ) compared to saline pre-treated controls (n=13). TNF knockout animals pre-treated with LPS (n=14) did not show a significant difference in overall brain injury ( $2.82 \pm 0.50$  v  $2.90 \pm 0.57$ ,

$p = 0.91$ ) or regional  $\alpha$ M expression compared to saline controls (n=13). Wild-type animals from the LT $\beta$  breeding group did not exhibit increased overall brain injury in response to LPS pre-treatment (n=4) compared to saline controls (n=4).

## Conclusions

Deletion of the TNF cytokine gene prevents lipopolysaccharide-mediated sensitisation of the neonatal brain to hypoxic-ischaemic insult. Sensitisation to LPS was not seen in the wild-type animals in the LT $\beta$  strain, which could suggest possible spontaneous mutation of the gene (s) responsible for LPS response in the strain used. Future work into the effects of LT $\alpha$  and LT $\beta$  gene deletions, cell-specific gene deletions and pharmacological inhibition of cytokines may help further the understanding of the mechanisms involved in endotoxin-sensitised HI brain injury and provide possible therapeutic options to minimise injury to the developing nervous system.

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