

Role of TDP-43 in activation of the brain inflammatory response

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Introduction

TDP-43 is associated with fronto-temporal lobar dementia (FTLD) and some cases of Alzheimer's disease. Previous studies have found a role for TDP-43 in regulation of inflammatory markers such as IL-6, but the effect of increased TDP-43 expression on inflammation has not been studied. In order to fill these gaps, we induced peripheral inflammation in WT and TDP-43 overexpressing mice and began profiling changes in inflammatory cytokines, receptors, and kinases, in addition to changes in behavior.

Methods

9-month old WT and TAR4 were given intraperitoneal injections with saline or 500 mcg/kg LPS every three days for 15 days, at which point murine behavior was performed as seen in Figure 1. Brain tissue was collected thereafter for immunohistochemistry and biochemical studies.

Results

Peripheral inflammation coupled with TDP-43 overexpression caused marked deficits in learning and memory, as tested by the radial arm water maze. However it did not worsen TDP-43's effect on locomotor performance.

In the brain, LPS induced neurotoxicity in both WT and TAR4 mice, with TAR4 mice showing increased neurotoxicity.

Changes in several inflammatory receptors and kinases were seen in LPS injected mice, however there was no phenotypic change between WT and TAR4 mice.

Conclusions

LPS exacerbates TDP-43 induced pathology by impairing memory and increasing neurotoxicity in the brain. The neurotoxicity may be explained by microglial activation and differential nucleocytoplasmic shuttling of TDP-43 in neurons, microglia, and astrocytes. Additionally translocation of inflammation associated kinases such as NF- κ B may explain these changes.

Acknowledgements

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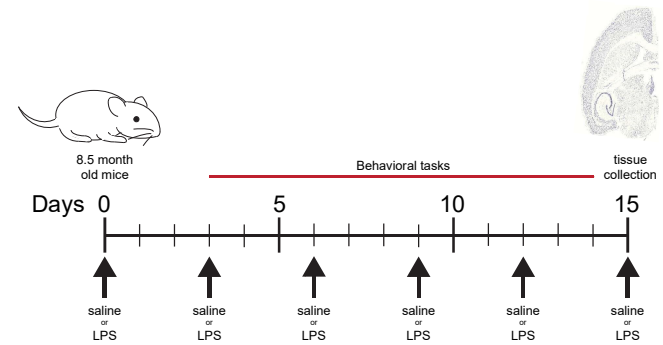


Figure 1. Experimental design to assess effects of peripheral inflammation.

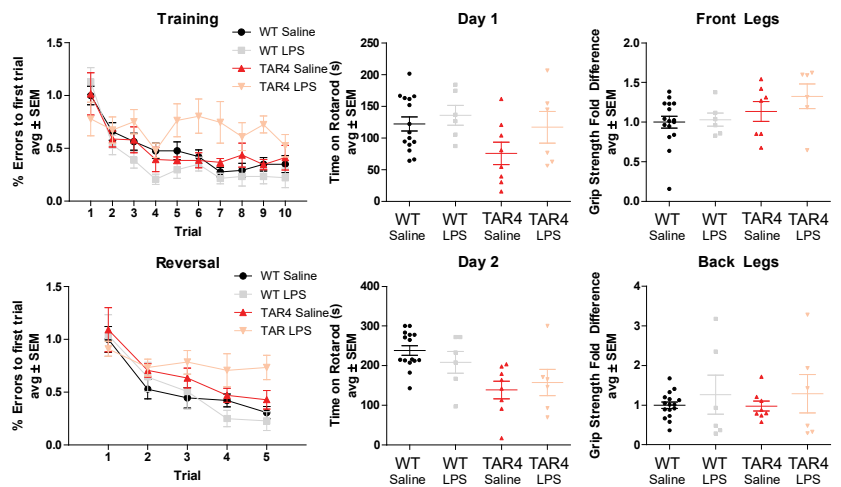


Figure 2. LPS induces TDP-43 dependent changes in learning and memory.

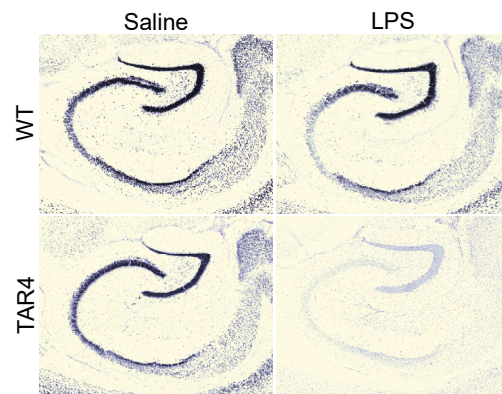


Figure 3. Neuronal loss in the hippocampus of LPS injected mice.

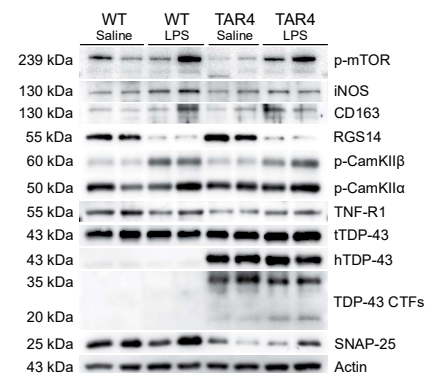


Figure 4. LPS induced changes in inflammatory receptors and synaptic markers.