

TIME COURSE EXPRESSION OF PLASMA CYTOKINE LEVELS FOLLOWING ACUTE HYPOTENSION AND ASSOCIATED COGNITIVE DYSFUNCTION IN MICE

E. Garcia¹, Michael Haile, M.D.¹, J. D'Urso¹, D. Quartermain², S. Galoyan¹, A. Bekker¹

¹Anesthesiology, New York University, New York, NY, ²Neurology, New York University, New York, New York

Introduction: Hypotension has been implicated in the development of cognitive dysfunction (CD). Nitroglycerin induced hypotension (NTG-IH) to below the range of cerebral autoregulation causes a transient delayed impairment of short-term memory that was attenuated by the NSAID Meloxicam (MEL) given at 24h1. Mice had intact memory on day 1, impaired memory on day 5, and recovered memory on day 9. We tested the hypothesis that plasma cytokine levels would be associated with CD.

Method: After IACUC approval, 30 Swiss-Webster, 30-40 g mice (6-8 weeks) were randomized into six groups: 1) no treatment; 2) i.p. NTG (60 mg/kg) tested at 8h; 3) NTG at 24h; 4) NTG at 72h 5) NTG on Day 5; 6) NTG then i.p. MEL (60mg/kg) at 24h tested on Day 5; 6) NTG on Day 9. Subjects were anesthetized with i.p. Ketamine (90mg/kg)/Xylazine (10mg/kg) before cardiac puncture with powdered-heparin syringes (Smiths, UK). Plasma levels of TNF- α , INF- γ , IL-1 α , IL-1 β , IL-2, IL-6, and IL-10 were determined by ELISA with MILLIPLEX Multi-Analyte Profiling (Billerica, MA). Data was analyzed using Kruskal-Wallis One-Way ANOVA and compared against baseline using Mann-Whitney post-hoc tests with Bonferonni correction. Concentration values below or above the assay standards were assigned their respective min or max detectable value.

Results: After box-plot adjustment for outliers, 1 sample each from groups 2; 5; 6 and 2 samples from group 4 were excluded from analysis. There were no significant differences in any markers for NTG and 24h delayed MEL treatment groups at day 5 compared to baseline.

A time course analysis of cytokine expression following NTG-IH showed that at 8h IL-1 β is down-regulated while IL-10 is up-regulated ($p < .00167$); IL-6 showed trends of up-regulated expression at 8h, albeit not significant ($p = .286$). At 24h cytokine expression returned to basal levels and did not significantly differ from baseline at tested intervals up to day 9. At day 9 a significant down-regulation of IL-1 β and IL-6, and an up-regulation of IL-10 was observed compared to baseline ($p < .00167$). No significant changes were observed in TNF- α , INF- γ , IL-1 α , or IL-2 at any time after NTG-IH.

Conclusion: CNS inflammation and cytokine expression have been implicated in the development of cognitive dysfunction². The observed time course expression pattern of IL-1 β , IL-6, and IL-10 are strongly suggestive of inflammation and resolution brought on by acute hypotension. However, we did not observe any conclusive evidence of cytokine-dependent short-term memory function associated with Meloxicam treatment or NTG-IH at any interval. This suggests that secondary mechanisms dependent on cytokine expression might be involved with cognitive function in the setting of inflammation.

References:

1. Garcia et al. Meloxicam Prevents Transient Cognitive Dysfunction in Mice after Nitroglycerin Induced Hypotension. *Journal of Neurosurgical Anesthesiology*: October 2009 – Volume 21 – Issue 4 – pp 367-426 (Abstract).
2. Goshen et al. In: R. Ader, Editor, *Psychoneuroimmunology*, Elsevier AP 2007; pp. 337-377.

