Sleep Deprivation is Associated with Neurocognitive Impairment and Immune Activation

Jessica COWDEN[1], Wanwisa PROMSOTE[1,2,3], Kesara CHUMPOLKULWONG[1], Decha SILSORN[1], Luis LUGO-ROMAN[1], Denise HSU[1,2,3]

1 Armed Forces Research Institute of Medical Sciences, Bangkok 10400, Thailand.

2 US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD 20910, USA.

3 Henry M. Jackson Foundation for the Advancement of Military Medicine Inc, Bethesda, MD 20817, USA.

Summary: Sleep deprivation has been shown to reduce cognitive performance and modulate immune responses in humans. Animal models of neuropathogenesis are helpful for understanding the effects of disease processes and therapeutic interventions on the brain, where sampling is usually not feasible in humans. We developed a rhesus macaque sleep deprivation model to evaluate the impact of sleep deprivation on neurocognitive performance and immune functions.

Methods: Six male rhesus macaques (aged 5-12 years) were included in this study. Animals underwent Cambridge Neuropsychological Test Automated Battery (CANTAB) training 3 times per week from week 16 to week 20. Once the study was initiated, animals underwent 3 rounds of sleep deprivation, lasting 48 hours from 7am Monday to 7am Wednesday at weeks 0, 2 and 4. Neurocognitive performance, including performance accuracy and speed on the motor task and self-ordered spatial search task, was assessed using CANTAB at 24 and 48 hours post sleep deprivation. Blood was collected after the CANTAB assessment at 48 hrs. Plasma cortisol level and biomarkers of immune activation were assessed via ELISA, multiplex assay and flow cytometry.

Result: Neurocognitive impairments (defined as individualized z-Score >2.5 standard deviation when compared to baseline mean) were found in all animals following each of the 3 rounds of 48hr sleep deprivation (Figure). Significant transient increases in immune activation were observed in both innate and adaptive peripheral immune cells (including CD69+ CD4+ T cells, $p<0.0001$; CD8+ T cells $p<0.0001$; NK cells $p<0.0001$; monocytes, $p=0.0002$ and granulocytes $p<0.0001$) and a number of plasma biomarkers (including cortisol, $p=0.0124$, C-reactive protein $p<0.0001$; IL-2, $p<0.0001$; TNF-**α**, $p=0.0179$; MCP1, $p=0.0031$; MIP-1**β**, $p<0.0001$; and vascular endothelial growth factor $p<0.0001$). These changes normalized by day 7 post sleep deprivation.

Conclusion: In this rhesus macaque model, sleep deprivation was associated with transient neurocognitive impairment and systemic immune activation. Results established the utility of this model studying the impact of sleep deprivation on neurocognition.