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Title: Cross-talk of circadian and immune system in neuropeptide S receptor 1 deficient mice

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Body: Rationale. Polymorphisms in Neuropeptide S (NPS) receptor 1 (NPSR1) are associated with asthma and usual bedtime. Endogenous rhythms are maintained in the hypothalamus by the central pacemaker that synchronizes peripheral clocks. Because circadian rhythms are important modulators of immune functions, we hypothesized that central NPS affects pulmonary immune responses via controlling the molecular clock in the lung. Methods. NPS (1 nM) or vehicle was injected intracerebroventricularly to mice, and lung tissue was collected for mRNA analysis with real-time PCR (n=6/group). A transcriptome analysis was conducted between *Npsr1*^{-/-} mice and their wildtype littermates with and without pre-disposition to exposure of multi-walled carbon nanotubes (MWCNT) on four consecutive days (n=8/group). Results. Central NPS increased expression of circadian genes *Per1* and *Clock*, and reduced tumor necrosis factor alpha (*Tnf-a*) expression in the lungs of wildtype mice 1h after injection. The basal expression levels of pro-inflammatory mediators were increased in the lungs of *Npsr1*^{-/-} mice. This correlated with altered temporal expression of *Tnf-a* in the lung and higher amount of macrophages and lymphocytes in the bronchoalveolar lavage fluid. 24h after last MWCNT exposure, *Npsr1*^{-/-} mice had significantly higher production of inflammatory mediators, such as *Tnf-a* and interleukin 4, in their lungs compared to the wildtype mice. Conclusions. Our results indicate that central NPS/*Npsr1* pathway affects circadian clock gene expression and mediates anti-inflammatory effects in the mouse lung. Lack of *Npsr1* leads to constant expression of pro-inflammatory cytokines in the lung and increased immune responses to MWCNT exposure.