Effects Of IFN-γ And TNF-α On Spontaneous Sleep In Mice

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Cytokines play important roles in sleep regulation [(1)]. It is hypothesized that sleep responses during infectious diseases are induced by cytokines. Furthermore, some cytokines, such as IL-1, TNF-α and IFN-γ, induce nitric oxide, which is also involved in sleep regulation. TNF-α and IFN-γ potentiate each other's actions in terms of nitric oxide production [(2)] and in other systems. Thus we decided to determine the effects of TNF-α and IFN-γ, plus the combination of both, on sleep.

Eight adult female mice were implanted with EMG and EEG electrodes. The mice were housed in individual cages placed in environmental chambers and kept on a 12:12 light-dark cycle with light onset at 08:00. Sleep recordings began a week after surgeries. Each mouse received 0.2 ml saline (i.p.) at dark onset on the first day as control and the following cytokines in the same volume; 10,000 units IFN-γ on the second day and 1μg TNF-α on the third day. On the fifth day, the combination of 10,000 units IFN-γ and 1μg TNF-α was given. The EEG data were processed by online Fast Fourier Transformation (FFT). Sleep-wakefulness status was scored visually offline using the EEG and EMG. Data were analyzed by two way repeated analysis of variance (ANOVA) followed by Student-Newman-Keuls (SNK) test.

IFN-γ or TNF-α increased non-rapid eye movement sleep (NREMS) during the first six hours after injection. The effects of IFN-γ and TNF-α given together were additive, the time in NREMS was increased by over 55% ($P<0.05$) in the first 6 hours (Fig 1). TNF-α reduced low frequency EEG power but enhanced high frequency power. IFN-γ itself had little effect on EEG power. In contrast, the combination of the IFN-γ and TNF-α significantly decreased the EEG power by 10-19% ($P<0.01$) (Fig 2). No significant effect was found on the rapid eye movement (REM) sleep.

Results suggest that the combination of IFN-γ and TNF-α enhanced sleep in mice and changed the characteristics of the sleep EEG. (Supported by NIH NS 31453, NS 25378 and HD 36520)