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Title: Rapid variations in glutamate levels across sleep-wake states

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Authors: ***J. JOHN**[1,2], L. RAMANATHAN[1,2], J. M. SIEGEL[1,2,3];
[1]Psychiatry/ Neurobiol Res, UCLA / Sepulveda VA Medical Center, North Hills, CA, [2]Psychiatry, UCLA, Los Angeles, CA, [3]Brain Research Institute, UCLA, Los Angeles, CA.

Glutamate is the most abundant excitatory neurotransmitter. In this study we investigated rapid changes in glutamate release across the sleep-wake cycle with a glutamate biosensor (Pinnacle Technology Inc., Kansas) which allows the measurement of glutamate levels at 1-3 sec resolution, in contrast to the 5 min resolution possible with microdialysis-HPLC. Electrodes for the assessment of sleep-wake parameters and a guide cannula were implanted in male Sprague-Dawley rats (350-450g). One week after surgery the glutamate biosensor, with a 1-mm long active area, was inserted through the guide cannula and EEG and EMG measurements were recorded for state determination. There was a rapid (0.44 ± 1.7s, median 2s) and progressive increase in glutamate levels in the posterior hypothalamus (PH) during REM sleep. Glutamate levels increased by 0.47 ± 0.04 µM. A strong correlation between duration of REM sleep and glutamate levels ($r=0.92$, $df=1,25$, $p<0.0001$) was observed in this region. Long REM sleep episodes were accompanied by increases in glutamate levels which remained above the preceding slow wave sleep level throughout the REM sleep episode. There was a progressive increase in glutamate levels in the cortex and lateral hypothalamus (LH) with spontaneous active waking/ grooming. The level of glutamate increased by 0.40 ± 0.04 µM in the LH and by 0.28 ± 0.03 µM in the cortex. We did not see a comparable increase in the PH. The latency to peak glutamate levels in LH and cortex during active waking ranged from 20-400s. Glutamate levels remained low and constant in quiet waking and slow wave sleep relative to active waking/ grooming (in the cortex and LH) or REM sleep (in the PH). Forced waking /sleep deprivation (20-120 min.) resulted in a gradual increase in glutamate levels in the cortex, PH and LH. The highest level of glutamate was reached 15-20 min. into the forced waking period. In summary, glutamate levels in various brain areas increase in proportion to waking and/or REM sleep duration. Increased glutamate levels may drive or be driven by processes regulating sleep-wake needs.

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