

Orexin mediates neuromodulation during sleep

G. Broglia¹, P.-H. Prouvot Bouvier¹, G. Corsi¹, M. Tafti¹, M. Bandarabadi¹

¹University of Lausanne, Lausanne, Switzerland

Background: Orexin (hypocretin) neurons are important for sustaining long periods of wakefulness and their activity is linked to a variety of behaviors including feeding, motivation, and reward processing. However, the role of orexin in the regulation of sleep and its components remains elusive as it was hypothesized that orexin neurons are silent during sleep.

Methods: We investigated orexin neurons of the lateral hypothalamus using *in vivo* fiber photometry imaging in Hcrt-IRES-Cre mice (n = 8), noradrenergic activity of locus coeruleus (LC) in Dbh-IRES-Cre mice (n = 6), and LC noradrenergic activity in orexin-knockout/Dbh-Cre mice (n = 4), combined with EEG/EMG recordings, during baseline and after sleep deprivation.

Results: We found that the activity of orexin neurons correlates with the phasic components of REM sleep, in particular at enhanced power and faster frequency of theta rhythm, and reaches its highest levels prior to the termination of REM sleep episodes. Furthermore, we found that LC noradrenergic system is periodically reactivated during NREM sleep, as reported recently by other groups, but LC reactivations during NREM sleep are more frequent in orexin-knockout mice compared to controls. Additionally, the duration of each NREM LC reactivation after sleep deprivation is several-folds longer than during baseline NREM sleep.

Conclusions: Our results suggest a strong correlated activity of the orexin system with theta oscillations during REM sleep and prior to its termination, as well as mediating neuromodulatory effects during NREM sleep.