Noradrenergic neurons of the locus coeruleus are phase-locked to cortical up-down states during sleep

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The activity of all major ascending neuromodulatory arousal systems is greatly reduced during the periods of cortical synchronization that are reflected in EEG as high-amplitude low-frequency waves. Despite the relative silence, neuromodulatory neurons typically switch their firing pattern from a tonic mode during the alert, desynchronized cortical state to a bursting mode during cortical synchronization that is characteristic for slow wave sleep (SWS) or anesthesia. The bursting activity is particularly efficient for a corresponding release of neuromodulators in the target regions. The activity of brainstem cholinergic and dopaminergic neurons correlates with cortical slow oscillations, while activity of the noradrenergic system in this context remains unexplored. We recorded unit activity of the noradrenergic neurons of the locus coeruleus (LC) with simultaneous monitoring of the cortical state by EEG in behaving rats. Here we report that the activity of LC neurons is phase-locked to cortical slow oscillations indicative of up-down states. In addition, we show that LC neurons lock best to slow oscillations advanced by approximately 100 ms, suggesting a possible noradrenergic contribution to generation of cortical up state. These results provide the first strong evidence for a cortico-coerulear interaction during SWS and challenge a conventional dogma about a quiescent state of the LC-noradrenergic system during sleep. The phase-locking of noradrenergic neurons to cortical slow oscillations may have a strong impact on the coordinated activity of neuronal assemblies during up states, which might be relevant for off-line information processing, synaptic plasticity and memory consolidation.

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