

## Title: Rapid eye movement sleep is initiated by dopamine signaling in the basolateral amygdala in mice

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The sleep cycle alternates between REM (rapid eye movement) and NREM (non-rapid movement) sleep, which is a highly characteristic feature of sleep. However, the mechanisms by which this cycle is generated are totally unknown. We found that a periodic transient increase of dopamine (DA) level in the basolateral amygdala (BLA) during non-rapid eye movement (NREM) sleep terminates NREM sleep and initiates REM sleep. DA acts on dopamine receptor D2 (Drd2)-expressing neurons in the BLA to induce a transition from NREM to REM sleep. This mechanism also plays a role in cataplectic attack, which is a pathological intrusion of REM sleep into wakefulness in narcoleptics. These results show a critical role of DA signaling in the amygdala in REM sleep regulation and provide a neuronal basis of sleep cycle generation. Sleep and wakefulness states are strongly influenced by activities of monoaminergic neurons in the brain stem/hypothalamus. These neurons diffusely innervate broad regions of the brain including the cerebral cortex, basal forebrain, lateral hypothalamus (LH) and thalamus to maintain wakefulness. Among them, noradrenergic neurons in the locus coeruleus (LC), histaminergic neurons in the tuberomammillary nucleus (TMN) and serotonergic neurons in the dorsal raphe (DR) share similar firing patterns, with generally rapid firing during wakefulness, slow and occasional firing during non-rapid eye movement (NREM) sleep, and almost complete cessation of firing during REM sleep. However, the firing patterns of dopamine (DA) neurons across sleep/wakefulness states are unclear. DA neurons in the substantia nigra and ventral tegmental area (VTA) (DAVTA neurons) have been thought to exhibit different firing patterns across sleep/wakefulness states from other monoaminergic neurons. DAVTA neurons were reported to show burst firing during REM sleep, although another report suggested DAVTA neurons showed no change in mean firing rate across the stages of sleep or wakefulness. Also, a recent state-of-the-art virus-mediated tracing study revealed that DAVTA neurons are comprised of heterogeneous populations with differential input and output organization, suggesting the possible existence of multiple DAVTA neuronal populations with differential roles in sleep/wakefulness regulation with distinct firing patterns across vigilance states. In this study, we first examined the extracellular level of DA across the sleep/wakefulness cycle in several brain regions that receive dense projections of DAVTA neurons using fiber photometry with dopamine sensor to determine the existence of subpopulations of DAVTA neurons with differential roles in sleep/wakefulness regulation. We found that DA level in the BLA started to increase shortly prior to NREM to REM transitions and peaked at the time of the transitions. This characteristic temporal pattern was not observed in other regions including the nucleus accumbens (NAc), medial prefrontal cortex (mPFC) and LH. Optogenetic activation of DA terminals or

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inhibition of D2 dopamine receptor (D2R)-expressing neurons in the BLA during NREM sleep caused transition to REM sleep and increased REM sleep amount. These manipulations were accompanied by increases in Fos-positive neurons in the BLA and central nucleus of the amygdala (CeA). Likewise, inhibition of DA terminals in the BLA markedly decreased REM sleep time. Similar manipulations of DAVTA terminals in the LH, NAc or PFC did not show any effect on REM sleep expression. These results suggest that the transient DA increase, which occurs just before the transition from NREM to REM sleep, inhibits D2R- expressing neurons in the BLA to trigger the NREM-REM transition. Our findings demonstrate that DA signaling in the BLA plays an important role in triggering NREM to REM sleep transitions by signaling through DRD2-expressing neurons.

### Biography

I got my bachelor degree of psychology from university of Tsukuba, and I wanted to enter where I can study medical neuroscience because I wanted to understand complex human mind from the neuroscience perspective. I happened to see the pamphlet of Ph.D. Program in Humanics, and I decided to try this program because I thought this program will fit me and I can get an opportunity to have good supports from various experts in medical science, engineering, and informatics field. I belong to Liu lab in WPI-IIS which aims at revealing the mechanisms of instinctive behavior using state-of-the-art biological techniques. And I study the neuronal mechanisms of sexual behavior, a kind of instinctive behavior. Also I develop an automated annotation system for mice sexual behavior so I study intellectual image processing under prof. Takizawa who specialized in medical image processing.