

Title: Dopamine signaling in the amygdala plays a causative role in Muscle atonia during rem sleep and cataplexy in mice

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Cataplexy is one of the cardinal symptoms of narcolepsy, which is characterized by sudden loss of muscle tone usually triggered by emotion with positive valence. We found that reward perception triggered a transient elevation of dopamine (DA) level in the basolateral amygdala (BLA) in narcoleptic mice, which was followed by cataplexy in narcoleptic mice. Optogenetic induction of a transient elevation of DA level in the BLA causes cataplexy-like episodes (CLE). Inhibition of dopamine D2 receptor (DRD2)-expressing neurons in the BLA decreased optogenetically-induced CLE as well as naturally-occurring cataplexy in narcoleptic mice. Local field potential in the BLA showed a positive correlation between theta frequency and muscle atonia in optogenetically induced CLE as well as in cataplexy and REM sleep. Our findings suggest that a DRD2-mediated neural pathway in the BLA plays an important role in evoking muscle atonia during cataplexy as well as in REM sleep. Emotional events trigger behavioral change along with alteration of muscle tone. Animals that encounter fearful situations sometimes show freezing behavior, which is accompanied by increased excitability of α -motor neurons that drives an increase in tone of specific muscles. Emotion sometimes results in rather a decrease in muscle tone, such as phenotypes reflecting the expressions like “knees giving away” and “jaw-dropping”. However, the mechanism that links the limbic system and motor system that controls muscle tone remains poorly understood. Narcolepsy patients sometimes exhibit attacks called cataplexy, which is a sudden weakening of muscle tone, usually induced by strong emotions. Cataplexy might be an exaggerated expression of muscle tone alteration triggered by emotion and might provide a useful model for elucidating the mechanism that regulates muscle tone in response to emotion. Cataplexy is also usually considered to be a pathological intrusion of REM sleep into wakefulness, because loss of muscle tone is also physiologically seen in REM sleep (REM-atonia). Solving the mechanisms that induced cataplexy might allow us to understand the link between the limbic system and motor system, as well as the role of the limbic system in regulating REM sleep, or REM-atonia. Cataplexy is usually triggered by emotion with positive valence. This led us to hypothesize that dopamine (DA) signaling originating from the ventral tegmental area (VTA) is involved in loss of muscle tone in cataplectic attacks. In addition, since many studies have suggested involvement of amygdala function in cataplexy, we first examined DA dynamics in the amygdala during cataplectic attacks in orexin-ataxin 3 transgenic mice, in which orexin neurons are genetically ablated. Previous studies suggested involvement of the central nucleus of the amygdala (CeA) in evoking cataplexy, but since the CeA is the output nucleus of the amygdala, we focused the basolateral amygdala (BLA), since BLA to CeA circuit plays an important role in appetitive behaviors. Using fiber photometry with a genetic DA sensor (GRABDA), we found that each cataplexy attack seen in narcoleptic orexin-ataxin 3

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3 transgenic mice, in which orexin neurons are genetically ablated. Previous studies suggested involvement of the central nucleus of the amygdala (CeA) in evoking cataplexy, but since the CeA is the output nucleus of the amygdala, we focused the basolateral amygdala (BLA), since BLA to CeA circuit plays an important role in appetitive behaviors. Using fiber photometry with a genetic DA sensor (GRABDA), we found that each cataplexy attack seen in narcoleptic orexin-ataxin 3 mice was always preceded by a transient increase of DA level in the basolateral amygdala (BLA). Mimicking the DA increase in the BLA by optogenetic manipulation induced muscle atonia with behavioral arrests in wild type mice, which was similar to cataplexy. We found that inhibition of dopamine D2 receptor (DRD2)-expressing cells in the BLA by expressing tetanus toxin light chain (TeTxLC) decreased optogenetically-triggered cataplexy-like atonia as well as cataplexy in orexin-ataxin 3 mice. Chronic inhibition of DRD2-expressing cells in the BLA also decreased theta frequency of local field potential (LFP) in the amygdala, impaired muscle atonia during REM sleep and inhibited cataplexy. These results suggest that DA signaling in the BLA plays a critical role in cataplexy as well as physiological muscle atonia during REM sleep.

Biography

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