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Chronic Stress-Induced Heightened Wakefulness is Modulated by a Paraventricular Thalamus to Central Amygdala Neuronal Pathway

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Abstract

Survival requires increased wakefulness in reaction to stimuli, but this can also result in sleep disorders like insomnia. Both a crucial thalamic area for wakefulness and a stress-sensitive portion of the brain is the paraventricular thalamus (PVT). It is yet uncertain, nevertheless, whether the PVT and its neuronal circuitries play a role in regulating wakefulness under stressful circumstances. Here, we discover that various stresses activate PVT neurons that transmit to the central amygdala (CeA).

Keywords: Sleep; stress; Paraventricular thalamus

Introduction

Animals have developed a wide range of stress-adaptive behavioural responses, including freezing, avoiding, and escaping. Increased wakefulness is a requirement for these adaptive responses to stress because a rapid transition from sleep to wakefulness helps animals deal with difficulties in stressful situations. On the other hand, one of the behaviours that is most susceptible to stress is sleep/wakefulness [1]. Stressful life experiences affect persons' ability to sleep normally and raise their chance of developing insomnia. Particularly, neuropsychiatric illnesses including anxiety, major depressive disorder, and post-traumatic stress disorder that are linked to stress frequently include sleep difficulties.

Acute stress stimulates PVT neurons that project CeA

Using anterograde and retrograde tracing, we looked at the anatomical characteristics of the PVT-to-amygdala projection first. For the purpose of anterograde tracking axonal terminals in the amygdala, adeno-associated virus (AAV) encoding enhanced green fluorescence protein (AAV-CaMKII-EGFP) was injected into the PVT. According to earlier research. Dense EGFP-positive axon terminals were seen in the CeA compared to the basolateral amygdala (BLA) in these experiments. Red fluorescent RetroBeads were inserted into the CeA or BLA, respectively, to retrogradely trace PVT neurons that transmit to the amygdala (Figure S1D). We discovered that there were considerably more RetroBeads-labeled PVT neurons projecting to the CeA than the BLA, indicating that the CeA is preferentially innervated [2, 3].

Previous investigations have shown that stress can activate some of the substrates of the wakefulness-promoting system. Newly discovered wakefulness-promoting nuclei have been found in the thalamus, notably in the midline thalamus. These nuclei also transmit projections to the amygdala. The reaction of the thalamic nuclei to various stressors has not, however, been studied. We first mapped the c-Fos expression of the thalamus under acute stress settings before looking into the specific response of the PVT-CeA circuit to acute stress. Three well-known acute stress paradigms, including the "cage change challenge," "acute restraint," and "predator odour 2,3,5-trimethyl-3-thiazoline," were used to mice (TMT, a component of fox urine). We discovered that numerous thalamic nuclei consistently expressed more c-Fos after exposure to various stressors [4, 5].

The PVT had the highest degree of c-Fos expression among these nuclei (Figure S2 and Table S1). Then, by labelling these neurons with RetroBeads, we looked at the c-Fos expression of CeA-projecting PVT neurons in response to stimuli (Figures S3A and S3B). Only a small percentage of CeA-projecting PVT neurons were c-Fos positive in the control conditions (home cage: 13.88% 1.33%; control: 12.3% 1.67%; saline: 15.34% 1.71%). Acute stress, however, markedly increased the proportion of PVT neurons that project CeA and are c-Fos positive (Figures S3C–S3H, new cage: 24.76% 1.85%; restraint: 21.8% 2.39%; TMT: 24.21% 1.66%) [6, 7].

We next employed fibre photometry recording to track the calcium (Ca2+) activity of CeA-projecting PVT neurons in response to stimuli in order to directly evaluate the temporal dynamics of these neurons (Figure 1A). In order to achieve this, CeA-projecting PVT neurons were labelled using an intersectional strategy41. AAV encoding Cre-dependent Ca2+ indicator (AAV-ef1-DIO-jGCaMp7b) was injected into the PVT of mice (henceforth referred to as PVT-CeAjGCaMp7b mice) together with retrogradely transported AAV encoding Cre recombinase (AAVretro-Syn-Cre) (Figures 1A and 1B). In order to capture the populational Ca2+ fluorescence released by CeA-projecting PVT neurons, an optical fibre was implanted above the PVT (Figures 1A and 1B). During home cage exploration, jGCaMp7b baseline recording of CeA-projecting PVT neurons revealed clear signal variations in the 488-nm channel, but were almost completely absent [8,9].

Discussion

Mice were given isoflurane anaesthesia before having phosphate-buffered saline (PBS) transcardially infused into them, followed by about 100mL of 4% paraformaldehyde (PFA). The brains were post-fixed in 4% PFA for 4 hours before being moved to 30% sucrose, where they sunk to the bottom. Using a freezing microtome, brains were coronally sectioned at a 30 m distance (CM 3050S, Leica). Slices containing the targeted areas of the brain were then mounted on glass microscope slides, dried, and coverslipped with a mounting medium containing DAPI (F6057, Sigma, USA). The brain slices were blocked

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with blocking solution (P0260, Beyotime, China) at room temperature (RT) for 30 min. before being stained with c-Fos. Primary antibody for rabbit c-Fos was diluted with primary antibody (1:1000, AB190289, Abcam, USA).

Conclusion

Neurons that were c-Fos-positive or RetroBeads-labeled were manually counted by an investigator who was unaware of the treatment. The fibre intensity was determined by dividing the fluorescence value of each brain area by the fluorescence value of the BNST in order to quantify the intensity of PVT-innervated CeA neurons' axon fibres. RV-dsRed-labeled neurons were manually registered to the Allen Mouse Brain Atlas at 120 m intervals for quantification in order to trace the presynaptic inputs of CeA-projecting PVT neurons. The ratio of RV-dsRed-labeled neurons in the targeted brain region to all RV-dsRed-labeled neurons in the entire brain, excluding those in the starting cell distribution area, was used to represent the input from this brain region [10].

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Declaration of Interests

The authors declare no competing interests.

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