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BF Parvalbumin Neurons as Emergency Switches: Linking Arousal from Sleep and Negative Learning

Wenrui Xu

Hamden Hall Country Day School, Hamden, USA
xwrnancyus@gmail.com

Abstract. Rapid arousal from Non-rapid Eye Movement (NREM) sleep is a fundamental survival mechanism that allows animals to respond to life-threatening conditions. Recent studies have demonstrated that the Basal Forebrain (BF) plays a crucial role in regulating cortical activation, and Parvalbumin (PV) neurons are key in amplifying information and facilitating rapid wakefulness. Research used optogenetics, EEG/EMG recording, and stimulus paradigms to demonstrate that BF-PV neurons produce fast, transient arousal. In contrast, inhibiting BF-PV neurons would diminish responses to both internal and external threats.Recent research has expanded the role of BF-PV neurons beyond arousal, demonstrating that they are also crucial in the processing of negative learning and aversive experiences. Moreover, BF-PV neurons may contribute to sleep disturbances, such as nightmare-inducing awakeness, hypervigilance caused by stress, and physiological arousal triggered by emotional or metabolic stress. This paper will review the function of BF-PV in regulating sleep-wake cycles, responding to internal (hypercarbia) and external (auditory stimuli) threats, and mitigating negative learning. It will also explore new directions of BF-PV potential involvement in nightmares, emotional stress, and physiological responses, such as post-exercise heightened arousal.

Keywords: Basal Forebrain, Parvalbumin Neurons, arousal, Negative learning, Sleep-wake regulation

1. Introduction

Sleep is a vulnerable state, and during this period, the animals must retain the ability to respond to danger. Arousal can be triggered by internal physiological stimuli, such as CO_2 accumulation (hypercarbia), or external stimuli, including loud sounds. The Ascending Reticular Activating System (ARAS) regulates wakefulness through multiple pathways, including the thalamus, the brainstem, and the Basal Forebrain(BF). The BF is a major hub that integrates arousal signals and modulates cortical activation.

Among BF, the Parvalbumin-expressing GABAergic (BF-PV) neurons charge at high frequency and enhance cortical processing. As Super emphasized, sleep-promoting and wake-promoting systems mutually inhibit each other to maintain state boundaries [1]. Still, the precise role of different subtype neurons in BF has only become clear recently. With the development of

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optogenetics and Cre-driver mouse lines, researchers have now begun to isolate the function of BF-PV neurons with high specificity.

This paper is to consolidate recent discoveries, and reinforce the idea that BF-PV neurons serve as a quick response 'emergency button' in promoting suvival. The finding integrated findings from optogenetic stimulation and inhibition, calcium imaging during aversive learning, EEG/EMG recordings of sleep-to-wake transitions, transgenic serotonergic manipulations, and auditory/emission-driven arousal tasks. In addition to summarizing laboratory findings, this paper extends BF-PV research into the realm of life, exploring how BF-PV neurons may relate to nightmares, emotional stress, and hyperarousal, as well as physiological responses, such as post-exercise sympathetic activation or cholesterol spikes.

2. BF and sleep-wake regulation

The basal forebrain (BF) contains heterogeneous cell groups, including cholinergic, glutamatergic, and GABAergic neurons. Those neurons play a crucial role in regulating arousal states. Parvalbumin-expressing (PV) GABAergic neurons are well-suited for rapid state transitions due to their fast-spiking properties, allowing control of cortical activation.

Saper has proposed the concept of "behavioral state switching," by which sleep-promoting nuclei (e.g., VLPO) and wake-promoting nuclei (e.g., BF, orexin system, monoaminergic centers) reciprocally inhibit each other to keep the state border between arousal and sleep [1]. While this model accounts for the overall switch in sleep patterns, it is silent on how emergencies—choking, predator noise and internally-induced physiological changes—abruptly puncture NREM stability. Traditional lesion-based approaches have been unable to isolate the contributions of different neurons, thereby limiting our understanding of how rapid arousal occurs.

Recent advances have clarified this gap. Optogenetics and Cre-driver mouse studies enable scientists to target specific subneurons of the BF selectively. Firstly, BF-PV neurons' optogenetic activation quickly desynchronizes EEGs; EEG desynchronization indicates an immediate and potent influence on the activation of cerebral cortex.By contrast, when BF-PV neurons were disabled prolonged wake-up latency from stimulus ultimately increased to nearly twice the normal length [2].Secondly, using both optogenetics and calcium imaging techniques in BF-PV neurons is made feasible by the Cre-driver mouse method [3]. These findings illustrate that BF-PV neurons are fundamental initiators of rapid sleep-wake transitions.

Furthermore, from cross species studies that birds [4] and primates [5] are the same quickly discharge "similar to PV" neurons, such essential electrophysiological features can provide rapid alert waking. As an MRI study in humans, BF activation precedes cortical arousal in response to hypercarbia and loud tones can cause ear pain. All of these fast discharge neurons have both similar functional roles and locations in the periphery.

All in all, BF-PV neurons are critical nodes that primarily respond to dangers during sleep and represent the first step in the "emergency switch."

3. CO_2-induced arousal and serotonin system relates to BF

During sleep, rising CO_2 will disrupt respiratory stability. The brain evolved specialized mechanisms to detect this imbalance during NREM sleep. Buchanan and Richerson demonstrated that serotonin (5-HT) neurons, serving as "the CO_2 alarm," located in the medullary raphe, are essential for detecting hypercarbia. These neurons detect a slight change in CO_2 and signal the brain to initiate breathing restoration. In a transgenic model in which central 5- HT neurons were removed

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selectively, it was demonstrated that 100% of wild-type mice aroused within 30 seconds when exposed to 10% CO_2 whereas under the same condition only one anesthesized 5-HT- deficient (ie partially psychedelic) mouse regained consciousness Thus, as far as survival was concerned, these 5- HT neurons were playing a crucial role [6].

However, detection alone is insufficient. BF-PV neurons rapidly amplify the danger signal, producing cortical activation and behavioral arousal. When hypercarbia is detected by 5-HT neurons, these neurons activate BF-PV neurons, which in turn generate cortical desynchronization, increased gamma-band activity, and immediate arousal. Optogenetic studies demonstrate that stimulating BF-PV neurons alone can mimic the awakening effect of CO_2, whereas inhibiting BF-PV neurons delays the arousal induced by CO_2. Arousal caused by CO_2, therefore, relies on cooperation between serotonergic monitoring of internal threat and BF-PV execution of rapid wakefulness.

Current human research shows a link between 5-HT neurons and BF-PV neurons [7].In individuals with sleep apnea, the overactivity of BF can cause sleep fragmentation, indicating that chronic hypercarbia might repeatedly bring BF-PV neurons into play and raise their threshold for arousal [8].In an infant, some abnormality in 5-HT neurons is related to sudden infant death syndrome (SIDS), showing that this circuit has a basic role in necessary survival [9].

4. BF-PV and auditory arousal

Sensory information is dampened during sleep. To quickly respond to danger signals, BF-PV neurons, with their fast spiking and strong inhibitory control, amplify auditory inputs.

Experiments show that chemogenetic activation of BF-PV neurons increases the probability of awakening induced by noise by ~35%, whereas inhibition significantly reduces responses, doubling the latency to awaken [2]. These findings suggest that BF-PV neurons enable the brain to shift rapidly from sleep to wakefulness when external danger arises.

The response of BF-PV neurons to danger signals has implications for sleep disorders, including insomnia, sleep obstacles caused by anxiety, and hypervigilance. Chronic stress increases amygdala excitability, leading to hypervigilance [10], and elevates cortisol levels, thereby heightening the sensitivity of the arousal system [11].

Although no study has directly tested the relationship between chronic stress and BF-PV neurons specifically, much evidence shows that stress amplifies threat processing pathways and lowers arousal thresholds. According to Saper and Fuller, stress increases the likelihood of the awakening system, including the BF, being activated [12]. Because BF-PV neurons are an integral part of the rapid arousal circuit, they are hypothesized to become more readily activated when upstream neurons are stimulated by stress.

Therefore, BF-PV neurons can be positioned as a target affected by hyperarousal, induced by chronic stress.

5. BF-PV neurons and negative learning

Recent research has shown that BF-PV neurons are not only involved in rapid arousal but also contribute to defensive learning. Hegedűs and colleagues provided evidence that BF-PV neurons play a role beyond rapid arousal. By employing calcium imaging and optogenetic technology, they found that PV neurons in the BF showed twice the activity level to indicate a footshock than at any other trial stage. The animals made evident behavioral deficits in avoidance learning tasks when

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these cells were inactivated [3]. That means PV neurons in the BF may assist an animal to change its behavior as response to a warning signal--a kind of defensive learning.

Compared between positive experiences and negative experiences, BF-PV neurons' responses are brief, strong, and closely tied to negative experiences. This pattern suggests that these neurons may detect situations with potential danger.

The additional research on PV interneurons in cortical circuits gives a new sight. Kim reported that PV neurons modulate negative learning through cortical inhibitory control [13]. Although the research focused on cortical PV neurons, the fundamental principles of PV-mediated inhibitory gating can generalize to BF. These studies claimed that the role of BF-PV neurons extends beyond immediate arousal to include long-term survival learning.

5.1. BF-PV neurons and nightmare

Nightmares are internal threat experiences that engage limbic networks. These dreams, including scenarios of pursuit, suffocation, and other danger stimuli, activate the amygdala and other fear-processing regions. Due to the sensitivity of BF-PV neurons to threatening signals, intense nightmares may activate BF-PV neurons via the ARAS pathway.

5.2. BF-PV neurons and emotional stress

Emotional stress alters arousal regulation by increasing the excitability of the amygdala, elevating cortisol levels, and enhancing the sensitivity of threat monitoring. These physiological changes make the brain more reactive during sleep, which reduces its stability and makes it easier to be awakened by minor internal signals. Because BF-PV neurons are located in the system of arousal, the change of stability induced by stress lowers the BF-PV neurons' threshold of activation.

5.3. BF-PV neurons and physiological stress

Physiological stress, including heavy exercise, can also influence arousal systems. Intense physical activities produce short-term increases in sympathetic nervous system activation and metabolic demand. Signals related to heart rate, breathing, and chemical neurotransmitters may reach the basal forebrain via these pathways. Thus, BF-PV neurons may become more likely to be used to explain why vigorous late-evening workouts sometimes lead to difficulty falling asleep or sudden, light awakenings. These internal changes can quickly activate neural circuits involved in vigilance.

6. Conclusion

BF-PV neurons have been termed neural "emergency switches", amassing survival functions of multiple systems which embody sleep-wake regulation, internal threat responsiveness, external danger process, and emotional learning. Connecting swift cortical activation with memory of danger, they make sure animals are not just free to act on an immediate threat but also have enough sense not to walk into one again in future. Expanding BF-PV research into real-life situations reveals their potential involvement in awakening induced by nightmares, hypervigilance related to stress, emotional arousal, and post-exercise physiological activation. Since the upstream system causes these changes, position BF-PV as one of the nodes associated with sleep instability and emotional instability. In the future, investigations should explore how chronic stress affects the excitability of BF-PV. Those findings may build new strategies for treating insomnia, panic awakening, and hyperarousal.

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