



RESEARCH HIGHLIGHT

Paraventricular Thalamus as A Major Thalamic Structure for Wake Control

Yu-Feng Shao¹ · Jian-Sheng Lin² · Yi-Ping Hou¹

Received: 20 November 2018 / Accepted: 30 December 2018 / Published online: 16 March 2019
© Shanghai Institutes for Biological Sciences, CAS 2019

The thalamus is the gate of the cerebral cortex, the ultimate target for the neural networks controlling behavioral states and cognitive functions. According to the reticular theory initially proposed by Moruzzi and Magoun, excitatory inputs from large reticular zones of the brainstem *via* widespread intra- and extra-thalamocortical systems finally activate the cerebral cortex to cause generalized cortical activation and wakefulness [1]. This theory proposes a central relay role to the thalamus for cortical activation as supported by early studies using neurodegeneration techniques and by the elegant work of Steriade's group and other investigators illustrating the electrophysiological mechanisms of the thalamocortical system at the cellular level during wakefulness, rapid eye-movement sleep (REMs) and non-REM sleep (NREMs) [2]. Yet, more selective lesion studies conducted between 1960 and the 2000s by many research teams have questioned the importance of the thalamus because these thalamic lesions do not result in loss of cortical activation and wakefulness [3]. Moreover, the identification of other wake-promoting systems, such as those of the hypothalamic hypocretin (Hcrt) and histamine neurons [4], has diverted attention from the thalamus to other structures and thus "dilute" its importance. Recently, the use of innovative approaches such as optogenetics and chemogenetics combined with

transgenic animal models has demonstrated the effects of cell-type-specific and real-time activation and/or inactivation of selective cellular targets along with their pathways. Thus, the time appears opportune to assess whether the previous lesion methods involved large-scale damage of all thalamic cells, leading therefore to biased conclusions on the thalamic control of wakefulness.

It is in this context that Ren *et al.* studied the role of a distinct thalamic structure, the paraventricular thalamus (PVT) in the paramedian region of the thalamus in the wake-control neural network [5]. Indeed, the complex thalamic nuclei involved in sleep-wake control have distinct afferent and efferent connections and participate in various brain functions [6]. Yet, which specific nuclei and circuitry are key in controlling wakefulness remain to be assessed. In this study, the authors first found a markedly greater number of *c-fos*-immunoreactive neurons in the PVT than in the other paramedian thalamic nuclei after wake-enhancement in the mouse. Using *in vivo* fiber photometry and multichannel electrophysiological recordings, they further found that the PVT glutamatergic (Glu) neurons were more active during wakefulness than during sleep. Moreover, the firing of these neurons increased in anticipation of cortical activation and behavioral arousal but decreased prior to sleep onset. These neurons, therefore, have the discharge pattern of a brain arousal system.

Then, the authors questioned the importance of the PVT in wakefulness. On the one hand, when the PVT_{Glu} neurons were chemogenetically inhibited in the early dark phase, NREMs with a high EEG delta power (2–4 Hz) increased markedly. In addition, lesioning PVT_{Glu} neurons by diphtheria toxin A or ibotenic acid equally caused a decrease in wakefulness and an increase in NREMs accompanied by an enhanced EEG delta power. When PVT_{Glu} neurons were optogenetically activated during

✉ Yi-Ping Hou
houyiping@lzu.edu.cn

¹ Departments of Neuroscience, Anatomy, Histology, and Embryology, Key Laboratory of Preclinical Study for New Drugs of Gansu Province, School of Basic Medical Sciences, Lanzhou University, Lanzhou 730000, China

² Integrative Physiology of the Brain Arousal Systems, Lyon Neuroscience Research Center, Lyon 69373, France

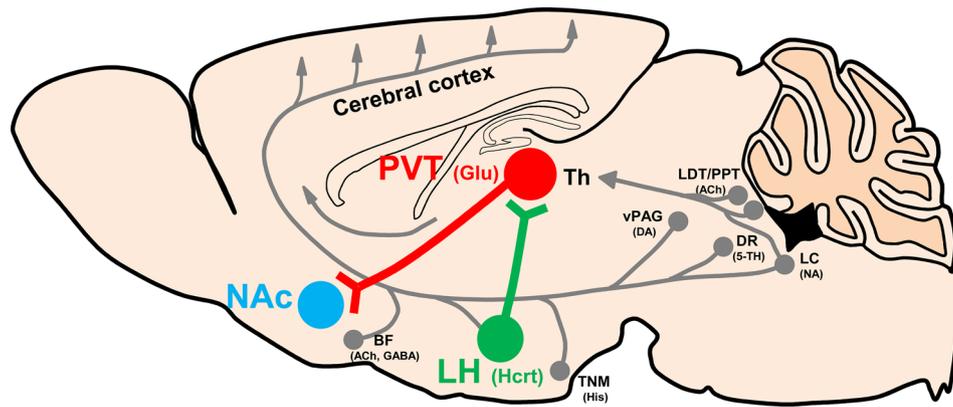


Fig. 1 Schematic parasagittal section of mouse brain summarizing the LH_{Hcrt} - PVT_{Glu} - NAc circuit within the neural network involved in wake control. Many neurotransmitter systems (grey) are involved in the network, such as noradrenergic (NA) neurons of the locus coeruleus (LC), cholinergic (ACh) neurons of the pedunculopontine and laterodorsal tegmentum nuclei (LDT/PPT), serotonergic (5-HT) neurons of the dorsal raphe nucleus (DR), dopaminergic (DA) neurons of the ventral periaqueductal gray matter (vPAG), histaminergic (HA) neurons of the tuberomammillary nucleus (TNM), hypocretin (Hcrt) neurons of the lateral hypothalamus (LH), and ACh- and γ -aminobutyric acid (GABA)-containing neurons of the

basal forebrain (BF). These neuronal systems can activate the cerebral cortex either directly by their widespread ascending projections or indirectly *via* their forebrain or thalamic (Th) relays. The glutamatergic (Glu) neurons of the paraventricular thalamus (PVT) are considered here as a critical thalamic node involved in cortical activation during wakefulness. On the one hand, they receive projections from the hypothalamic wake-promoting system LH_{Hcrt} neurons and, on the other hand, they can directly activate the nucleus accumbens (NAc), which is involved in several behavioral aspects during wakefulness.

NREMs, a reliable transition to wakefulness with a decrease in EEG delta power occurred. Optical stimulation also promoted transitions from REMs to wakefulness and increased the probability of wakefulness at the expense of a decrease in that of both NREMs and REMs. On the other hand, when the PVT_{Glu} neurons were optically activated under general anesthesia, 10-Hz stimulation caused an immediate increase in total EEG burst activity accompanied by a prolonged burst duration. The sustained activation of PVT_{Glu} neurons accelerated the emergence from anesthesia-induced unconsciousness. From these data, the authors suggested that the PVT is both necessary and sufficient for wakefulness. The next question is whether glutamatergic neurons projecting to the cortex from other localized thalamic and extrathalamic structures play roles similar to or distinct from the PVT, although this question has already been partially addressed in this study.

One would wonder then what are the anatomical and functional circuits of PVT_{Glu} neurons that play such a role in wake maintenance. The authors found that PVT_{Glu} neurons send dense projections to the nucleus accumbens (NAc). Optical activation of the PVT_{Glu} -to-NAc projections reliably elicited transitions from both NREMs and REMs to wakefulness, while chemogenetic inhibition reduced wakefulness. This downstream pathway was further confirmed by the compromised wake-inducing effects of the PVT after ablation of NAc neurons using ibotenic acid. Interestingly, NAc neurons expressing dopamine D_1 receptors are thought to be essential in both wake induction and maintenance *via* the lateral

hypothalamus (LH) and midbrain circuits [7]. In terms of afferent inputs, the authors notably demonstrated that LH_{Hcrt} cells directly project to PVT_{Glu} neurons. They found that chemogenetic inhibition of the Hcrt neuronal inputs decreased wakefulness while optical stimulation of Hcrt neuron terminals during NREMs increased the firing rate of PVT neurons. The involvement of the LH_{Hcrt} - PVT_{Glu} pathway in wake control was further confirmed by an increased latency to wakefulness with optogenetic stimulation of Hcrt neurons after ablating PVT_{Glu} neurons. Hcrt neurons strongly excite all brain wake-promoting regions, including the midline and intralaminar nuclei of the thalamus as well as the cortex, and are therefore important for wake stability and consolidation [3, 4]. Moreover, their deficiency is the direct cause of narcolepsy, a sleep disorder characterized by excessive daytime sleepiness and cataplexy in humans. Thus, the LH_{Hcrt} - PVT_{Glu} circuit is likely an important pathway through which Hcrt neurons contribute to wake maintenance. Further studies are required to determine whether other wake-promoting systems, such as aminergic and cholinergic neurons, also constitute excitatory source for the PVT to enhance wakefulness. Since abolition of the PVT enhances sleep, it seems unlikely that its role is limited to relaying lower excitatory sources, as was classically thought for the thalamocortical system, but to intrinsically activate the cerebral cortex.

Collectively, data and evidence provided by this study reveal the PVT as a critical thalamic structure in cortical activation and wakefulness and the LH_{Hcrt} - PVT_{Glu} -NAc

pathway as a critical thalamic node in the neural network for wake control (Fig. 1). Unlike many classical studies investigating the role of the midline and intralaminar nuclei or the thalamocortical system as a whole, one of the original features of this and other recent studies on the paramedian thalamic nuclei is their focus on a specific thalamic nucleus using multiscale functional approaches. Thus, the dorsal medial thalamus, which mainly contains the PVT, summates subcortical arousal information and effectively transfers it to several forebrain regions to modulate the level of arousal [8], whereas spontaneous firing of centromedial thalamic neurons in mice is phase-advanced to global cortical active states and NREMs-wake transitions. Such transitions can be enhanced again by tonic optogenetic activation of centromedial thalamic neurons [9]. More generally, the desynchronized cortical state during active behavior is driven by a centrally-generated increase in thalamic action potential firing which can also be mimicked by optogenetic stimulation of the thalamus [10].

From a clinical standpoint, the role demonstrated here for the PVT explains why patients with a localized lesion of the paramedian thalamus caused by bilateral paramedian artery infarcts show disturbances of consciousness ranging from hypersomnolence to comatose sleep, a clinical feature not observed with other thalamic lesions [11]. Thus, both basic and clinical data appear to point to a critical role of the paramedian thalamus, including the PVT, in setting vigilance states.

Finally, this study together with other recent reports [6, 8, 9] using multiscale approaches to assess the functional roles of the thalamus and its neural circuitry seems to open a new era to reconsider the thalamic control of behavioral states.

Acknowledgements This highlight was supported by grants from the National Natural Science Foundation of China (81471347, 81771426, and 31500853) and by the Talent-Introducing Project of State Administration of Foreign Experts Affairs of China (X2017008).

Conflict of interest The authors declare no potential conflicts of interest.

References

1. Moruzzi G, Magoun HW. Brain stem reticular formation and activation of the EEG. *Electroencephalogr Clin Neurophysiol* 1949, 1: 455–473.
2. Steriade M, Timofeev I. Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. *Neuron* 2003, 37: 563–576.
3. Lee SH, Dan Y. Neuromodulation of brain states. *Neuron* 2012, 76: 209–222.
4. Lin JS, Anacleit C, Sergeeva OA, Haas HL. The waking brain: an update. *Cell Mol Life Sci* 2011, 68: 2499–2512.
5. Ren S, Wang Y, Yue F, Cheng X, Dang R, Qiao Q, *et al.* The paraventricular thalamus is a critical thalamic area for wakefulness. *Science* 2018, 362: 429–434.
6. Gent TC, Bassetti C, Adamantidis AR. Sleep-wake control and the thalamus. *Curr Opin Neurobiol* 2018, 52: 188–197.
7. Luo YJ, Li YD, Wang L, Yang SR, Yuan XS, Wang J, *et al.* Nucleus accumbens controls wakefulness by a subpopulation of neurons expressing dopamine D₁ receptors. *Nat Commun* 2018, 9: 1576.
8. Mátyás F, Komlósi G, Babiczky Á, Kocsis K, Barthó P, Barsy B, *et al.* A highly collateralized thalamic cell type with arousal-predicting activity serves as a key hub for graded state transitions in the forebrain. *Nat Neurosci* 2018, 21: 1551–1562.
9. Gent TC, Bandarabadi M, Herrera CG, Adamantidis AR. Thalamic dual control of sleep and wakefulness. *Nat Neurosci* 2018, 21(7): 974–984.
10. Poulet JF, Fernandez LM, Crochet S, Petersen CC. Thalamic control of cortical states. *Nat Neurosci* 2012, 15: 370–372.
11. Hermann DM, Siccoli M, Brugger P, Wachter K, Mathis J, Achermann P, *et al.* Evolution of neurological, neuropsychological and sleep-wake disturbances after paramedian thalamic stroke. *Stroke* 2008, 39: 62–68.