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Review

Thalamic Inhibition: Diverse Sources, Diverse Scales

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The thalamus is the major source of cortical inputs shaping sensation, action, and cognition. Thalamic circuits are targeted by two major inhibitory systems: the thalamic reticular nucleus (TRN) and extrathalamic inhibitory (ETI) inputs. A unifying framework of how these systems operate is currently lacking. Here, we propose that TRN circuits are specialized to exert thalamic control at different spatiotemporal scales. Local inhibition of thalamic spike rates prevails during attentional selection, whereas global inhibition more likely prevails during sleep. In contrast, the ETI (arising from basal ganglia, zona incerta (ZI), anterior pretectum, and pontine reticular formation) provides temporally precise and focal inhibition, impacting spike timing. Together, these inhibitory systems allow graded control of thalamic output, enabling thalamocortical operations to dynamically match ongoing behavioral demands.

Introduction – General Questions

While several studies have elegantly delineated roles for the thalamus in relaying sensory inputs to the neocortex, the extensive reciprocal connections between thalamic nuclei and all cortical regions suggest that the function of the thalamus extends beyond sensory processing and simple relay. Thalamic nuclei are integral to processes involving motor control [1], memory [2], and arousal [3]. In one of the best studied cases, the visual thalamus, the retinal signal experiences substantial transformation on its way to the cortex that involves contrast- and context-dependent gain modulation [4], as well as temporal structuring [5]. Because these operations are prevalent across nonsensory systems as well, analogous thalamic circuits and computations are likely to subserve multiple cognitive functions [6–8].

The aforementioned thalamic operations require complex inhibitory control. Unlike cortex, striatum, and cerebellum, the thalamus lacks a variety of interneuron types that provides spatiotemporally diverse and precise GABAergic input to its projection neurons (Box 1). The best-studied source of thalamic inhibition derives from a thin sheet of cells, the TRN, which innervates all its individual nuclei [9]. Although some heterogeneity has been described among TRN neurons, their morphology and neurochemistry appear to be less diverse than those of cortical interneurons [10,11]. Nevertheless, thalamic operations are under similar constraints as those of the neocortex, requiring inhibitory control across multiple spatial and temporal scales (Box 1).

Given this challenge, the central question we pose here is how does heterogeneity of inhibition arise in the thalamus? In other words what specialized GABAergic mechanisms enable thalamic circuits to differentially process information streams in both space and time, and according to ongoing behavioral demands?

In this review, we discuss two putative solutions to this problem: (i) structural and physiological features of TRN allow its circuits to shift the spatial and temporal scales of inhibition under various

Trends

Thalamic inhibition is a critical element of normal TC interactions and evidence for its perturbation is found in many diseases.

Compared to their cortical, striatal, and cerebellar counterparts, little is known about the circuit and computational principles of thalamic inhibition.

Thalamic inhibition encompasses diverse circuits acting in various spatial and temporal domains.

The thalamus receives inhibitory afferents from the TRN as well as from extrathalamic sources. These two types of inhibition display major differences in connectivity, synaptic organization, and physiology, suggesting distinct functions.

TRN inhibition is a scalable system that controls spike rates across behavioral states and cognitive needs, whereas extrathalamic inhibition impacts spike timing in well-defined thalamic regions and limited behavioral contexts.

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Box 1. Scales of Inhibition

The nervous system needs to organize neuronal activity across multiple spatial and temporal scales. The spatial domain ranges from local cell populations to the entire brain, the time domain from slow oscillations (0.1–1 Hz) to high γ activity (up to 250 Hz) [81]. In several brain regions (cortex, hippocampus, striatum, and cerebellum), one solution to cope with these the wide range of scales is the emergence of distinct interneuron classes [82–85]. For example, the size of axon arbors in cortical interneurons ranges from small, dense (e.g., neurogliaform cells) through mid-range, covering roughly a cortical column (e.g., basket cells) to long-range interneuron selective cells that can simultaneously affect the activity of large cortical territories [86]. The size of axon arbor, thus, physically determines the spatial scale of action. Along the temporal dimension, the firing rate of the interneurons, as well as the exact mechanism of GABAergic action, determines the scale of action in time. The slow firing rate, sluggish kinetics of receptor activation, as well as the extrasynaptic mode of action, enables neurogliaform cells to act in the time domains of slow oscillations [87]. In contrast, high firing rate and fast GABA-A receptor-mediated inhibition of basket cells allows them to control γ oscillations [86].

The question we pose here is how can the thalamus cope with these variable spatiotemporal scales? A substantial proportion of cortical operations involve interactions with the thalamus, therefore, thalamic inhibition needs to operate across a similar spatiotemporal range to that of the cortex. In addition, various inputs parcellate the thalamus into distinct nuclei and subnuclei, which, in some situations, need to be controlled separately, while in others synchronously. So, what are the inhibitory mechanisms that enable different scales of control in the thalamus?

behavioral conditions; and (ii) powerful ETI systems [12–16] provide heterogeneous, nucleus-specific inhibitory control of the thalamus involved in a well-defined set of nuclei.

We should note here that while many of the experimental data informing our view of the thalamus are derived from studies of rodent brains, we have tried to focus on principles that are likely to be universal to mammalian thalamic function. In line with this approach, we indicate when comparative data on rodents and primates (including humans) are available.

We also note that thalamic interneurons as a third form of inhibition in the thalamus are outside the scope of the present account. These cells are found in variable numbers and distributions across distinct mammalian species [17]. Outside of their function in vision (as local spatial contrast-enhancement elements [4]), there is little information about their role in other parts of the thalamus. From our perspective, their peculiar anatomical connectivity pattern (forming dendrodendritic contacts in triadic arrangements) represents a spatially restricted form of inhibition, acting on a single excitatory input. This may, therefore, add yet another level of complexity to thalamic inhibition.

TRN

General Overview

The TRN is a shell of GABAergic neurons that covers the lateral and anterior aspects of the mammalian thalamus (Figure 1A). TRN-like structures exist in reptiles [18] and fish [19], suggesting an evolutionarily conserved origin. Compared to the knowledge we have about the development of cortical interneuron classes, we know surprisingly little about the developmental origins of the TRN. Early reports refer to the origin of the TRN as ventral (or rostral) thalamic, but more recently, the term prethalamic has been introduced [20]. In adult life, the question of how exactly the TRN regulates thalamic function is an open one. Our thesis is that the TRN can operate at variable spatiotemporal scales to modulate thalamic processing according to behavioral needs. This would require specialized TRN connectivity, intrinsic properties, and synaptic outputs. In the following sections, we discuss these putative mechanisms and their contribution to a spatiotemporal sliding scale of thalamic inhibition.

TRN Connectivity That Enables Variable Scales of Action

While the sole recipients of TRN output are thalamic projection neurons (TC cells; also called relay neurons), TRN neurons receive excitatory inputs from both thalamus and cortex. Based on pioneering anatomical studies, a sectorial organization of the TRN has been known for several