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Review

Limbic thalamus and state-dependent behavior: The paraventricular nucleus of the thalamic midline as a node in circadian timing and sleep/wake-regulatory networks

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A B S T R A C T

The paraventricular thalamic nucleus (PVT), the main component of the dorsal thalamic midline, receives multiple inputs from the brain stem and hypothalamus, and targets the medial prefrontal cortex, nucleus accumbens and amygdala. PVT has been implicated in several functions, especially adaptation to chronic stress, addiction behaviors and reward, mood, emotion. We here focus on the wiring and neuronal properties linking PVT with circadian timing and sleep/wake regulation, and their behavioral implications. PVT is interconnected with the master circadian pacemaker, the hypothalamic suprachiasmatic nucleus, receives direct and indirect photic input, is densely innervated by orexinergic neurons which play a key role in arousal and state transitions. Endowed with prominent wake-related Fos expression which is suppressed by sleep, and with intrinsic neuronal properties showing a diurnal oscillation unique in the thalamus, PVT could represent a station of interaction of thalamic and hypothalamic sleep/wake-regulatory mechanisms. PVT could thus play a strategic task by funneling into limbic and limbic-related targets circadian timing and state-dependent behavior information, tailoring it for cognitive performance and motivated behaviors.

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1. Introduction

The midline nuclei of the thalamus have received in the last years sudden, unprecedented attention as substrates of cognitive functions, as well as mood, emotions, and reward (e.g. Hamlin et al., 2009; Price and Drevets, 2010; Saalmann, 2014; Sengupta and McNally, 2014; Varela, 2014). This may seem surprising given that the midline nuclei, together with the intralaminar nuclei, have historically represented the core of the “nonspecific thalamus”, involved in a general role of diffuse activation of the cortical mantle.

Furthermore, on the basis of studies in different species and with different methodological approaches, a functional subdivision between the dorsal and ventral groups of the midline thalamic nuclei seems to be currently delineated. Thus, data indicate that cell groups of the ventral thalamic midline are implicated in memory processes (e.g. Cassel et al., 2013; Vertes, 2006; Xu and Südhof, 2013). On the other hand, the dorsal thalamic midline, whose main component is the paraventricular nucleus of the thalamus (PVT), has been implicated in the response to psychoactive drugs (Cohen et al., 1998; Deutch et al., 1995, 1998), adaptation to stressful conditions, modulation of viscerosensory stimuli, positive and negative emotional states, drug-seeking and reward mechanisms (e.g. James and Dayas, 2013; Martin-Fardon and Boutrel, 2012; Hsu et al., 2014; Sengupta and McNally, 2014).

Other sets of findings indicate that neurons of the dorsal thalamic midline, and especially PVT neurons, could play a role in the modulation of state-dependent behavior. We here focus on this aspect, to discuss the neural and functional links of the dorsal thalamic midline with circadian timing and sleep/wake regulation, in which all behavioral performances are inscribed.

1.1. *From the “nonspecific thalamus” to the “midline and intralaminar thalamus”*

The subdivision of thalamic nuclei into the broad categories of “specific” and “nonspecific” nuclei dates back several decades, to the beginning of the modern era of neurophysiology and neuroanatomy, which was then based on anterograde and degeneration techniques for the study of neuronal connections. The functional properties and organization of neural circuits was subsequently re-examined with the advent of single unit recording and tract tracing based on the anterograde and retrograde axonal transport of tracers. A treatise on the itinerary of knowledge on the different categories of thalamic nuclei goes beyond the limits and scope of the present review. It is, however, of interest that this matter is still debated.

The concept of “nonspecific” thalamus, as well as the designation of the midline nuclei as “nonspecific” (see Bentivoglio et al., 1991), originated from different sets of data. We will here mention only two of them. So-called recruiting responses were recorded over a large cortical expanse after low frequency stimulation of thalamic domains in the cat, which included the intralaminar nuclei and, at the midline, the nucleus reuniens and the rhomboid nucleus (Morison and Dempsey, 1942). Furthermore, The diffuse projections, widely distributed upon different cortical areas, were supposed to derive from these “nonspecific” thalamic nuclei (see Jones, 2007; Macchi et al., 1996). The medial core of the “nonspecific” thalamus was thus viewed as the collector transmitting upon the cortical mantle the activation conveyed from the brain stem through the ascending arousal system electrophysiologically identified by Moruzzi and Magoun (1949). While a diffuse thalamocortical system seemed to have been delineated, such “cinderella-like diffuse projection system” (Jasper, 1949) seemed to perform less “elegant” and punctual operations than those of the “specific” thalamic relay nuclei. Altogether, however, this view emphasized a role of medial thalamic cell groups in what would be defined nowadays as state-dependent behavior.

The “nonspecificity” of the “nonspecific” thalamus was challenged in the 1990s on the basis of data accumulated in the meantime, including the definition of discrete, rather than diffuse, cortical targets (e.g. Bentivoglio et al., 1991; Groenewegen and Berendse, 1994; Macchi and Bentivoglio, 1999). Novel views were developed. The concept and anatomical organization of the brain stem reticular formation were revised on the basis of the discovery of monoaminergic systems. Even the role of the reticulo-thalamo-cortical pathway in arousal has been recently reconsidered (Fuller et al., 2010). Thalamic nuclei were subdivided into “first order” and “higher order” nuclei on the basis of their driving input (Guillery, 1995; Guillery and Sherman, 2002). Thalamocortical neurons were subdivided into “core” (“specific”), and “matrix” (“nonspecific”) neurons, distributed in different thalamic nuclei, as key players in the synchrony of cortical activity (Jones, 2001, 2007).

One of the results of this wealth of data and of the relevant theoretical debates is the recent, frequent “upgrading” of the “nonspecific” medial thalamus to the cautious, topographical designation of “midline and intralaminar nuclei” (e.g. Benarroch, 2008; Sengupta and McNally, 2014; Van der Werf et al., 2002; Varela, 2014). It remains that these cell groups differ from sensory and motor relay nuclei of the dorsal thalamus in their effect on sleep and arousal, function in cognitive tasks, mechanisms of temporal synchronization and temporal binding in the cerebral cortex (e.g. Benarroch, 2008; Llinás et al., 2002; Llinás and Steriade, 2006; Van der Werf et al., 2002). Concerning the cortical targets, given that all thalamic nuclei reach more than one cortical area (Jones, 2007; Macchi et al., 1996), the concept of diffuse thalamocortical projections was revised, and the task of a diffuse cortical innervation was passed on to aminergic systems, and, more recently also to orexinergic innervation (see Section 3.4). Solidly grounded is instead the concept of the midline and intralaminar nuclei as source of thalamic output to the striatal complex. In addition, as dealt with below, it has been assessed that the midline nuclei are the source of thalamic output to limbic and limbic-related targets.

2. The modest puzzle of the thalamic midline

Relatively small in rodents, relatively small and thin in nonhuman primates and humans, partitioned into cell groups traversed by fibers with a variety of neurochemical phenotypes (how many do terminate there or are simply passing by?), the collection of cell groups located along the midline of the thalamus appears as an unassuming “puzzle” among the midline structures of the cerebral hemispheres. In the human brain, in which the third ventricle may completely divide the two halves of the thalamus when the massa intermedia is absent, the midline nuclei are located on each side along the ventricle.

The midline thalamic nuclei are composed dorsally by PVT (Pa in the abbreviations used in Olszewski’s nomenclature of the macaque thalamus; Olszewski, 1952) and the paratenial and intermediodorsal nuclei, and ventrally by the rhomboid nucleus and the nucleus

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