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The reticular nucleus revisited: Intrinsic and network properties of a thalamic pacemaker

Pablo Fuentealba, Mircea Steriade *

Laboratoire de Neurophysiologie, Faculté de Médecine, Université Laval, Québec, Que., Canada G1K 7P4

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Abstract

The intrinsic and network properties of thalamic reticular (RE) neurons, which release the potent inhibitory neurotransmitter γ-aminobutyric acid (GABA), endow them with oscillatory properties within the frequency range of sleep spindles (7–15 Hz), a hallmark brain rhythm that characterizes early sleep stages. The original hypothesis that RE neurons are pacemakers of spindles, based on absence of this oscillation in thalamocortical (TC) systems after disconnection from RE nucleus and presence of spindle rhythmicity in the deafferented RE nucleus, is supported by new experimental results in vivo, in vitro and in computo showing that interactions through chemical synapses as well as electrical coupling among inhibitory RE neurons lead to generation and synchronization of spindle sequences within the nucleus. Besides their pacemaking role in spindle generation, RE neurons are crucially implicated in the inhibition of TC neurons during cortically generated spike-wave (absence) seizures, which may explain the obliteration of signals from the external world and unconsciousness during these epileptic fits.

Contents

Abbreviations: AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EPSC, excitatory postsynaptic current; EPSP, excitatory postsynaptic potential; FPP, fast prepotential; GABA, γ-aminobutyric acid; $I_{Na(p)}$, persistent Na^+ current; IPSP, inhibitory postsynaptic potential; LTS, low-threshold spike; NMDA, *N*-methyl-D-aspartate; PDS, paroxysmal depolarizing shift; PSW, polyspike-wave; RE, thalamic reticular; SW, spike-wave; TC, thalamocortical; V_m, membrane potential

* Corresponding author. Tel.: +1 514 343 6370; fax: +1 514 343 2111.
E-mail address: mircea.steriade@phs.ulaval.ca (M. Steriade).

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1. Background

This article addresses a hotly debated issue, namely, to what extent the thalamic reticular (RE) neurons possess intrinsic properties and participate in local network operations allowing them to generate and synchronize a hallmark oscillation that characterizes early sleep stages, spindle waves (7–15 Hz). First discovered during the 1980s, the cardinal role played by the RE nucleus in spindles' induction was shown by abolition of this rhythm in thalamocortical (TC) systems after lesions of RE neurons (Steriade et al., 1985) and, more importantly, by the property of in vivo deafferented RE neurons to generate spindles in the absence of cortex and the remaining thalamus (Steriade et al., 1987a). Those data led us to postulate that RE nucleus is the pacemaker of spindle oscillations. This idea was challenged by the absence of spindles in slices from the posterior (perigeniculate) part of the RE nucleus, maintained in vitro (von Krosigk et al., 1993). However, in a *Science* article (Steriade et al., 1993), the authors of the discrepant results obtained in vivo and in vitro concluded that ‘‘spindle oscillations are generated in the reticular thalamic nucleus disconnected from dorsal thalamic and cortical inputs'' (p. 684) and, concerning the failure of experiments on RE in vitro slices to find spindles, proposed that ‘‘a larger and more intact collection of reticular thalamic cells may be able to generate spindle waves autonomously'' (p. 684). More recent experiments and computational studies on isolated RE-cells' networks (see Section 4) congruently led to the conclusion that spindle rhythmicity can be produced within the RE nucleus, without necessarily requiring inputs from TC and cortical neurons. The idea of RE-induction of spindle generation transcends the mechanism of this major sleep oscillation, as it sheds further light on differences between the intact and sliced brain (Steriade, 2001a,b, 2004).

The importance of recent investigations on RE neurons, particularly those that demonstrate the prevalent synaptic weight of neocortical inputs on these cells (Golshani et al., 2001; Jones, 2002), also relates to the role played by RE neurons in inhibiting target TC neurons during cortically generated spike-wave (SW) seizures (Steriade and Contreras, 1995; Crunelli and Leresche, 2002; Steriade, 2003). Seizures with ‘‘spike'' and ‘‘wave'' complexes at 3–4 Hz are observed in absence epilepsy, associated with loss of consciousness. The cortical origin of a majority of SW seizures casts doubt on earlier hypotheses claiming that such paroxysms are generated by ‘‘centrencephalic systems'' (Penfield and Jasper, 1954) and on more recent in vitro data implicating TC neurons in the generation of such seizures (von Krosigk et al., 1993; Huguenard, 1999). The powerful inhibition of TC neurons during SW seizures is also relevant to mechanisms that underlie obliteration of signals from the external world and unconsciousness during such paroxysms.

We first show the place of the RE nucleus in thalamic and cortical circuitry (Fig. 1A). The modulation of RE neurons by some neurotransmitters may partially explain the differences in their behavior between isolated thalamic slices and the intact brain. Next, we deal with the intrinsic properties of RE neurons and their synchronization, which provide the substrate for spindle generation within this nucleus. Finally, we present recent in vivo and in computo data demonstrating the generation of spindles within the RE nucleus and the RE-induced inhibition of TC neurons during SW seizures (see Fig. 1B). Here, we mainly refer to data relevant to the two major topics of this article, spindle oscillations and SW seizures. For other morphological and physiological features of the RE nucleus, such as the topographical organization of different RE sectors and their relations to dorsal thalamic nuclei, the reader may consult previous monographs and reviews (Steriade et al., 1990, 1997; Jones, 2002, 2005).

2. Morphology, immunoreactivity and connections of thalamic reticular neurons

The RE nucleus is a derivative of the ventral thalamus (Jones, 1985) and is entirely composed of GABAergic cells (Houser et al., 1980). It is a relatively thin sheet of neurons that surrounds the anterior, lateral and to some extent ventral surfaces of the dorsal thalamus. Because of its anatomical position, the RE nucleus is traversed by virtually all axons connecting the dorsal thalamus with the neocortex, giving the nucleus its reticulated appearance and name. RE neurons have long dendrites (Fig. 2), whose secondary and tertiary branches possess vesicle-containing appendages that form synapses on the dendrites of neurons in the same nucleus. The presynaptic dendritic appendages are common in cats (Deschênes et al., 1985; Yen et al., 1985), present but rare in monkeys (Williamson et al., 1993), and reportedly absent in rats (Ohara and Lieberman, 1985).

The cells of the RE nucleus have soma diameters of 20–50 μm, and are generally ovoid, with relatively long dendritic branches emerging from the poles of the soma (Fig. 2). Even though RE neurons seem to be relatively homogeneous from the morphological point of view, there is evidence for functional differences. As yet, there are no morphological correlates of the two neuronal populations of the RE nucleus, one of which generates low-threshold spikes (LTSs) and is able to switch from tonic to burst firing, the other apparently lacking the low-threshold Ca^{2+} conductance and firing only tonically (Contreras et al., 1992). The latter group is similar to the overwhelming majority of neurons in the ventral lateral geniculate nucleus (Crunelli et al., 1987) that share a common embryological origin with the RE nucleus and similarly do not project to cortex (Jones, 1985). Another example of functional, but not related to morphological, diversity is the presence of a subgroup of RE neurons which display intrinsic membrane bistability, likely due to the functional expression of a persistent Na^+ current, $I_{Na(p)}$ (Fuentealba et al., 2005) (see details in Section 3.1).