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Pacemaker Neurons and Neuronal Networks in Health and Disease

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1. Introduction

Neural network activity provides the operational basis for diverse neural circuits to determine temporal windows during which multiple, coherent neuronal assemblies engaged in the generation of specific behaviors can be recruited [1-3]. Neural network activity emerges from the combination of intrinsic neural properties and the synaptic interactions among them [1-5]. However, the relative contributions of intrinsic and synaptic properties to circuit activity are diverse and change, depending on the state of the network, mainly through the action of neuromodulators [6]. On top of this diversity, the intrinsic properties of neurons are also heterogeneous, ranging from silent “linear” neurons (also called followers or non-pacemakers; Fig 1 bottom trace) to “non-linear” intrinsic bursters (also called pacemakers; Fig. 1 upper trace) [7]. The presence of pacemaker neurons and their pivotal role in network activity generation is an accepted fact for invertebrate networks [8]. In the case of mammalian circuits, accumulating evidence supports the presence and participation of these pacemakers in generating network rhythmic activity by several circuits throughout the brain in normal and abnormal conditions [1,4,5, 9-11]. In mammalian networks, bursting has been related to neural network generation [1], induction of synaptic plasticity, [12] as well as to the transition of abnormal neural network states [13,14]. Here, I will review just some examples of neural networks that contain pacemaker neurons, the main ionic mechanisms involved in their bursting generation, and the participation of these pacemakers in generating neural network function under normal and pathological conditions.

For the purpose of this chapter, pacemakers are defined as neurons that can generate oscillatory bursts of action potentials independently of the network, i.e. in the absence of any synaptic input [Fig. 1; upper trace] [1,9]. They do so because they have a mixture of ionic conductances that allow them to produce rhythmic excursions of the membrane

potential on top of which barrages of action potentials are generated [3; 11; Fig. 1; upper trace]. In networks that contain them, pacemaker neurons may act as true pacemakers or as resonators that respond preferentially to specific firing frequencies [1,9]. Non-pacemaker neurons change their firing rate gradually in almost strict correspondence to their synaptic input [1]. In contrast, the nonlinearity of bursting activity enables pacemaker neurons to modulate more abruptly their firing [1]. Moreover, bursting neurons amplify synaptic input and transmit their information more reliably through synaptic contacts [15-17]. As a consequence of these properties, pacemaker neurons can facilitate the onset of excitatory states or synchronize neuronal ensembles involved in diverse functional roles, such as movement control, sleep-wakefulness cycling, perception, attention, etc. [1,9]. The ability of these neurons to generate bursts of action potentials lies in voltage-sensitive ion fluxes, which act in specific voltage- and time-windows and whose activity is regulated by the metabolic state of the neurons, by neuromodulators, and by activity-dependent mechanisms [1, 18-20]. Next, I will describe some examples of mammalian neural networks containing pacemaker neurons.

One of the more popular examples of a mammalian pacemaker neuron is, perhaps, the reticular thalamic neuron (RTN) [22,23]. RTNs are able to generate bursts of action potentials depending on two major inward currents: the low-threshold (T-type) Ca^{2+} channels [22,23] and the hyperpolarization-activated and cyclic nucleotide-gated nonselective cation channel (HCN) [24]. Interestingly, these neurons can switch from the “bursting mode” to a “tonic mode” depending on their membrane potential [25,26]. The transitions between firing modes are determined by the action of several neuromodulators as well as by GABAergic phasic inhibition [25,26]. It has been proposed that the “bursting mode” of these RTNs dominates the generation of slow-wave activity during non-REM sleep, whereas the transition to the tonic firing mode is related to the generation of faster rhythms produced during wakefulness [25,26]. Therefore, it has been proposed that pacemaker RTN neurons are key elements of the cortico-thalamic neural network that gates the transitions among different states of consciousness [i.e. sleep/awakening] [22,23]. From a clinical point of view, it has been reported that an increase during wakefulness of the bursting mode of RTN neurons is related to the generation of absence seizures [27,28]. Accordingly, absence seizures are successfully treated with T-type Ca^{2+} channel blockers such as ethosuximide, which reduces the bursting mode of RTNs [28,29].

Intrinsic bursting neurons have been identified in the neocortex [30-34]. These pacemakers correspond to a subgroup of pyramidal neurons and to a subset of Martinotti-interneuron cells [30-33]. As expected, pacemaker pyramidal cells are functionally and anatomical different from regular spiking (RS) pyramidal neurons. For example, intrinsic bursters have specific morphological features that differentiate them from the typical pyramidal RS neurons [31]. Intrinsic bursters are larger than RS neurons; they have a triangular soma rather than the more rounded soma of RS pyramidal neurons and a more complex dendritic tree [31]. Regarding their projection, intrinsic bursters send collaterals that are limited to layers 5/6, whereas axonal collaterals from RS pyramidal neurons are more pronounced in

In synaptic isolation

Pacemaker

Non-Pacemaker

10 mV

1 seg

Figure 1. Identification of pacemaker and non-pacemaker neurons. Recordings from two neurons in the preBötzinger Complex are shown in conditions where fast synaptic transmission has been blocked using a cocktail of glutamate, GABA, and glycine receptor antagonists (synaptic isolation). Whereas both neurons were originally identified as rhythmic inspiratory neurons, in synaptic isolation pacemakers can be identified by their ability to continue the generation of oscillatory bursts of action potentials independently of the network. In contrast, non-pacemaker neurons become either silent or fire tonically in a non-rhythmic fashion.

the supragranular layers [31, 34, 35]. Moreover, the intracortical circuits for intrinsic bursters are different from those of RS neurons [35]. For instance, intrinsic bursters receive intracolumnar excitatory innervations from all layers, whereas RS neurons receive intracolumnar inhibitory and excitatory inputs from layers 2/3 and 5 [35]. Finally, the extracortical projections of these two types of pyramidal cells differ; for instance, intrinsic bursters project to the thalamus, pons, and colliculus while RS neurons project to cortical and striatal targets [36,37]. Cortical pacemakers have been hypothesized to play a major role in the generation of spontaneous activity [4, 33]. For instance, Cunningham et al. [4] have described a group of intrinsic pacemakers that produce bursts of action potentials in the gamma range, relying on the persistent sodium current (INap), and that their blockade abolishes gamma generation in the auditory cortex. Similarly, other types of intrinsic bursters that also rely on the INap, but that fire their bursts at lower frequencies, have been implicated in the generation of population activity in the somatosensory cortex [38,39]. Based on this and other evidence, it has been proposed that the cortex may act as a central pattern generator [2]. From a pathological point of view, cortical pacemaker neurons play a role in the generation of epileptic network activity [13; 14]. For example, we have found that human cortical epileptic foci have an increased number of cells with INap-dependent pacemaker properties [13,14], which may explain why reducing the INap has an antiepileptic effect [40-42].

Similarly to gamma rhythm, pacemakers involved in theta rhythm generation have been identified in the septohippocampal network [10,43]. These putative theta pacemaker neurons are GABAergic cells that are localized in the medial septum and express parvalbumin and the HCN [44-46]. Interestingly, alterations in the activity of these theta pacemaker neurons might be involved in the pathophysiology of Alzheimer disease (AD), which progresses with a reduction in evoked-theta oscillations [47]. Accordingly, application of the AD-related amyloid-beta peptide reduces the activity of theta-pacemaker neurons and reduces theta rhythm in rats [43, 48-50].

Pacemaker neurons have been reported in the hypothalamic arcuate nucleus, which is responsible for the control of the satiety-hunger cycle [51]. These neurons, which contain neuropeptide Y [NPY], are conditional pacemakers that are activated by orexigens (ghrelin and orexin) and inhibited by the anorexigens (leptin) [51]. The bursting properties of these neurons do not depend on the INap, because their membrane potential oscillations persist in the presence of tetrodotoxin, but are inhibited by blocking the T-type calcium channel [51]. Since these arcuate pacemakers can contribute to balanced food consumption, an alteration in their activity can be associated with eating disorders and obesity [52-54].

Subthalamic neurons can exhibit bursting properties, depending on the state of the network. As RTNs, subthalamic pacemakers can shift from a regular, single-spike mode to a burst-firing mode depending on their depolarization level [55,56]. The bursting mode relies on the L-type and the T-type Ca²⁺ channels, and it is insensitive to tetrodotoxin [55,57]. The subthalamic nucleus is composed of glutamatergic neurons, whose normal transition between tonic and bursting modes controls the circuitry of the basal ganglia by modulating

the activity of the two principal output structures of the network: the internal pallidal segment and the substantia nigra pars reticulata [58, 55, 56]. Interestingly, pacemaker activity of subthalamic neurons has been associated with Parkinson's disease [59]. For instance, an increase in subthalamic burst firing has been found in animal models of parkinsonism [60,61] and in parkinsonian patients [62,63]. Also noteworthy is that high-frequency stimulation of the subthalamic nucleus, which reduces subthalamic burstiness [62,64], produces a reduction in motor impairments associated with parkinsonism and is currently used in the treatment of parkinsonian patients [63,65]. Moreover, modulation of the T-type calcium channel in subthalamic bursters also reduces parkinsonisms [66].

Pacemaker neurons have also been identified in the spinal cord, where they seem to play a major role in its central pattern generators [67-69]. For instance, in the central pattern generator for locomotion, some interneurons exhibit intrinsic bursting activity [67-69] that relies on the INap [67-69]. This mechanism is essential for the activity of the locomotion central pattern generator, since blockade of INap abolishes bursting activity and fictive locomotion [67-69]. Also in the spinal cord, it was recently reported that an increase in pacemaker activity is observed in the dorsal horn of animals that suffer from chronic pain [70]. These intrinsic bursters exhibit an increase in the density of the INap and the HCN [70], which may offer therapeutic targets to treat chronic pain [71,72]. In fact, several blockers of the INap have shown very promising effects against acute and chronic pain [73-75]. Finally, I will review the role of pacemaker neurons in the activity of a vital network: the preBötzinger Complex (preBötC).

2. Role of pacemakers can be state-dependent: An example of the inspiratory rhythm generator

Respiratory rhythm commands are generated by two, interacting oscillators, one controlling inspiration (preBötC) and other, located in the parafacial respiratory group (pFRG), possibly controlling active expiration [76-79]. Neurons with pacemaker properties have been identified in the preBötC [5,80,81; Fig. 1]. However, a rather complex picture has emerged regarding their intrinsic properties. PreBötC pacemakers have been found to show considerable variability in the range of interburst and intraburst frequencies, the amplitude of the plateau potential underlying bursting firing, and the voltage trajectory of this plateau [5, 80-86]. A biophysical and pharmacological characterization of their intrinsic properties have shown us that preBötC pacemakers can be grouped into two major groups: those that rely on the INap and those that rely on a Ca^{2+} -activated non-specific cationic current [ICAN] [5, 82, 84, 86]. Interestingly, the participation of these pacemakers in respiratory rhythm generation is state dependent. We found that blocking either the pacemakers that rely on the INap or the pacemakers that rely on the ICAN is not sufficient to abolish respiratory rhythm generation by the preBötC [5, 87]. However, when both of the two pacemaker populations are blocked, the preBötC ceases the generation of its rhythmic activity [5], and the animals die [87]. This evidence suggests that breathing generation relies on the activity of two distinct pacemaker neurons [5,87]. However, this is not the case when

the preBötC is challenged with hypoxic conditions. During hypoxia, the respiratory network is reconfigured and generates a “last-resort” respiratory rhythm called gasping [79]. Under these conditions the pacemaker neurons relying on the ICAN cease to fire, and the respiratory network relies only on the INap-dependent pacemaker neuron, whose blockade abolishes gasping generation [5,87]. These findings may have clinical relevance since gasping is an important autoresuscitation mechanism that seems to fail in victims of sudden infant death syndrome [SIDS, 88,89]. SIDS victims breathe normally during normoxia, when the respiratory rhythm can be generated by either of the two types of pacemaker, but they do not gasp efficiently in hypoxia [88,89], when the respiratory network relies exclusively on one type of pacemaker neuron.

3. Conclusion

In conclusion, pacemaker neurons are important components of several mammalian neural networks. The presence of pacemaker neurons allows these networks to produce different types of network activities, both in normal and in pathological conditions. Moreover, the contribution of pacemaker neurons to neural network dynamics is not fixed but depends on the action of neuromodulators or the state of the network. I believe that pacemaker neurons provide neural networks with the ability to coordinate population activity and to adjust it in response to several physiological demands. Unfortunately, changes in pacemaker activity can also lead to pathological states associated with several neurological diseases. The study of pacemaker properties, which is a very interesting topic itself, may also identify molecular targets to correct abnormal network activity.

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