Chapter 6

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) Ca2+ 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 Ca2+ 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

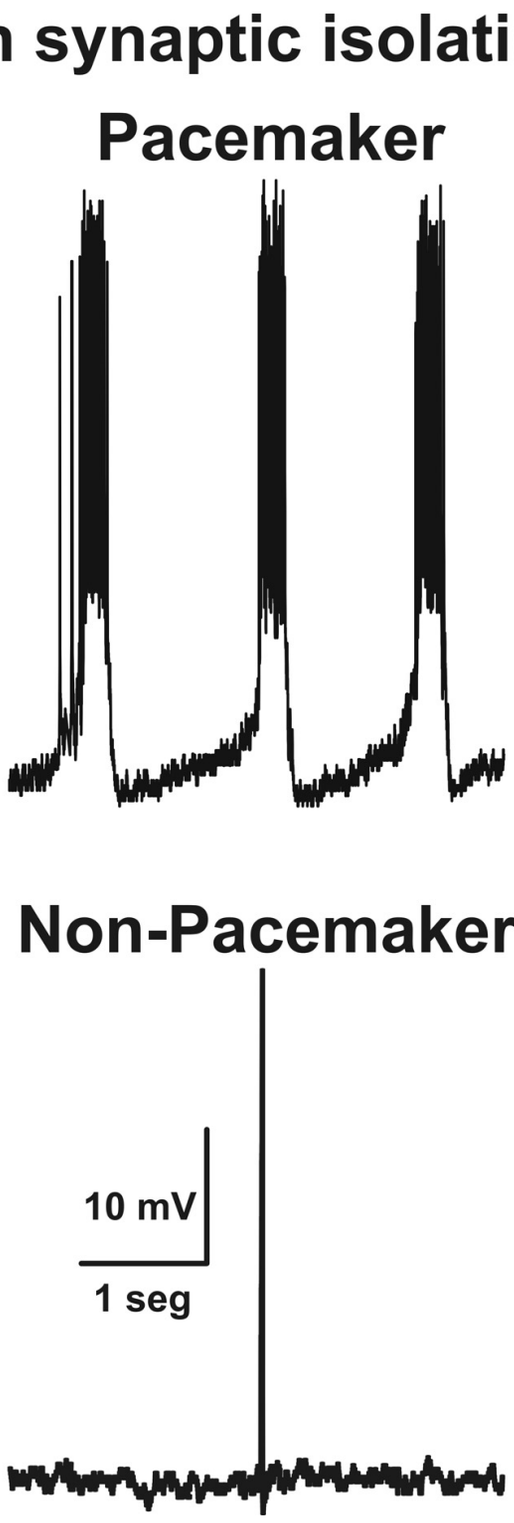

Figure 1. Identification of pacemaker and non-pacemaker neurons. Recordings from two neurons in the preBötzinger Complex are shown in conditions where fast synaptic transmission has been blocked using a cocktail of glutamate, GABA, and glycine receptor antagonists (synaptic isolation). Whereas both neurons 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 busting 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 busrstiness [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 busrters 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 Ca2+-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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4. References

[1] Ramirez JM, Tryba AK, Peña F (2004) Pacemaker neurons and neuronal networks: an integrative view. Curr. Opin. Neurobiol. 14:665-674.
[2] Yuste R, MacLean JN, Smith J, Lansner A (2005) The cortex as a central pattern generator. Nat. Rev. Neurosci. 6:477-483.

[3] Peña-Ortega F (2011) Possible role or respiratory pacemaker neurons in the generation of different breathing patterns. En: Pacemakers, Theory and Applications. Transworld Research Network., pp. Intech Open Acces Publisher
[4] Cunningham MO, Whittington MA, Bibbig A, Roopun A, LeBeau FE, Vogt A, Monyer H, Buhl EH, Traub RD (2004) A role for fast rhythmic bursting neurons in cortical gamma oscillations in vitro. Proc. Natl. Acad. Sci. U. S. A. 101:7152-7157.
[5] Peña F, Parkis MA, Tryba AK, Ramirez JM (2004) Differential contribution of pacemaker properties to the generation of respiratory rhythms during normoxia and hypoxia. Neuron. 43:105-117.
[6] Doi A, Ramirez JM (2010) State-dependent interactions between excitatory neuromodulators in the neuronal control of breathing. J. Neurosci. 30:8251-8262.
[7] Butera RJ Jr, Rinzel J, Smith JC (1999) Models of respiratory rhythm generation in the pre-Bötzinger complex. I. Bursting pacemaker neurons. J. Neurophysiol. 82:382-397.
[8] Marder E, Manor Y, Nadim F, Bartos M, Nusbaum MP (1998) Frequency control of a slow oscillatory network by a fast rhythmic input: pyloric to gastric mill interactions in the crab stomatogastric nervous system. Ann. N. Y. Acad. Sci. 860:226-238.
[9] Llinás RR (1988) The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. Science. 242:1654-1664.
[10] Wang XJ (2002) Pacemaker neurons for the theta rhythm and their synchronization in the septohippocampal reciprocal loop. J. Neurophysiol. 87:889-900.
[11] Peña F. Contribution of pacemaker neurons to respiratory rhythms generation in vitro. Adv. Exp. Med. Biol. 2008 605:114-118.
[12] Pike FG, Meredith RM, Olding AW, Paulsen O (1999) Rapid report: postsynaptic bursting is essential for 'Hebbian' induction of associative long-term potentiation at excitatory synapses in rat hippocampus. J. Physiol. 518:571-576.
[13] Marcuccilli CJ, Tryba AK, van Drongelen W, Koch H, Viemari JC, Peña-Ortega F, Doren EL, Pytel P, Chevalier M, Mrejeru A, Kohrman MH, Lasky RE, Lew SM, Frim DM, Ramirez JM (2010) Neuronal bursting properties in focal and parafocal regions in pediatric neocortical epilepsy stratified by histology. J. Clin. Neurophysiol. 27:387-397.
[14] Tryba AK, Kaczorowski CC, Ben-Mabrouk F, Elsen FP, Lew SM, Marcuccilli CJ (2011) Rhythmic intrinsic bursting neurons in human neocortex obtained from pediatric patients with epilepsy. Eur. J. Neurosci. 34:31-44.
[15] Snider RK, Kabara JF, Roig BR, Bonds AB (1998) Burst firing and modulation of functional connectivity in cat striate cortex. J. Neurophysiol. 80:730-744.
[16] Csicsvari J, Hirase H, Czurko A, Buzsáki G (1998) Reliability and state dependence of pyramidal cell-interneuron synapses in the hippocampus: an ensemble approach in the behaving rat. Neuron. 21:179-189.
[17] Williams SR, Stuart GJ (1999) Mechanisms and consequences of action potential burst firing in rat neocortical pyramidal neurons. J. Physiol. 521:467-482.
[18] Zhang W, Linden DJ (2003) The other side of the engram: experience-driven changes in neuronal intrinsic excitability. Nat. Rev. Neurosci. 4:885-900.
[19] Harris-Warrick RM (2002) Voltage-sensitive ion channels in rhythmic motor systems. Curr. Opin. Neurobiol. 12:646-651.

[20] Harris-Warrick RM (2011) Neuromodulation and flexibility in Central Pattern Generator networks. Curr. Opin. Neurobiol. 21:685-692.
[21] Williams SR, Stuart GJ (1999) Mechanisms and consequences of action potential burst firing in rat neocortical pyramidal neurons. J. Physiol. 521:467-482.
[22] Zhang L, Renaud LP, Kolaj M (2009) Properties of a T-type Ca2+channel-activated slow afterhyperpolarization in thalamic paraventricular nucleus and other thalamic midline neurons. J. Neurophysiol. 101:2741-2750.
[23] Astori S, Wimmer RD, Prosser HM, Corti C, Corsi M, Liaudet N, Volterra A, Franken P, Adelman JP, Lüthi A (2011) The Ca(V)3.3 calcium channel is the major sleep spindle pacemaker in thalamus. Proc. Natl. Acad. Sci. U. S. A. 108:13823-8.
[24] Lüthi A, Bal T, McCormick DA (1998) Periodicity of thalamic spindle waves is abolished by ZD7288,a blocker of Ih. J. Neurophysiol. 79:3284-3289.
[25] Leresche N, Jassik-Gerschenfeld D, Haby M, Soltesz I, Crunelli V (1990) Pacemaker-like and other types of spontaneous membrane potential oscillations of thalamocortical cells. Neurosci. Lett. 113:72-77.
[26] McCormick DA, Williamson A (1991) Modulation of neuronal firing mode in cat and guinea pig LGNd by histamine: possible cellular mechanisms of histaminergic control of arousal. J. Neurosci. 11:3188-3199.
[27] Zhang Y, Vilaythong AP, Yoshor D, Noebels JL (2004) Elevated thalamic low-voltage-activated currents precede the onset of absence epilepsy in the SNAP25-deficient mouse mutant coloboma. J. Neurosci. 24:5239-5248.
[28] Broicher T, Seidenbecher T, Meuth P, Munsch T, Meuth SG, Kanyshkova T, Pape HC, Budde T (2007) T-current related effects of antiepileptic drugs and a Ca2+ channel antagonist on thalamic relay and local circuit interneurons in a rat model of absence epilepsy. Neuropharmacology. 53:431-446.
[29] Tringham E, Powell KL, Cain SM, Kuplast K, Mezeyova J, Weerapura M, Eduljee C, Jiang X, Smith P, Morrison JL, Jones NC, Braine E, Rind G, Fee-Maki M, Parker D, Pajouhesh H, Parmar M, O'Brien TJ, Snutch TP (2012) T-type calcium channel blockers that attenuate thalamic burst firing and suppress absence seizures. Sci. Transl. Med. 4:121ra19.
[30] Agmon A, Connors BW (1992) Correlation between intrinsic firing patterns and thalamocortical synaptic responses of neurons in mouse barrel cortex. J. Neurosci. 12:319-329.
[31] Chagnac-Amitai Y, Luhmann HJ, Prince DA (1990) Burst generating and regular spiking layer 5 pyramidal neurons of rat neocortex have different morphological features. J. Comp. Neurol. 296:598-613.
[32] Zhu JJ, Connors BW (1999) Intrinsic firing patterns and whisker-evoked synaptic responses of neurons in the rat barrel cortex. J. Neurophysiol. 81:1171-1183.
[33] Le Bon-Jego M, Yuste R (2007) Persistently active, pacemaker-like neurons in neocortex. Front. Neurosci. 1:123-129.
[34] Jacob V, Petreanu L, Wright N, Svoboda K, Fox K (2012) Regular spiking and intrinsic bursting pyramidal cells show orthogonal forms of experience-dependent plasticity in layer V of barrel cortex. Neuron. 73:391-404.

[35] Schubert D, Staiger JF, Cho N, Kötter R, Zilles K, Luhmann HJ (2001) Layer-specific intracolumnar and transcolumnar functional connectivity of layer V pyramidal cells in rat barrel cortex. J. Neurosci. 21:3580-3592.
[36] Gao WJ, Zheng ZH (2004) Target-specific differences in somatodendritic morphology of layer V pyramidal neurons in rat motor cortex. J. Comp. Neurol. 476:174-185.
[37] Le Bé JV, Silberberg G, Wang Y, Markram H (2007) Morphological, electrophysiological, and synaptic properties of corticocallosal pyramidal cells in the neonatal rat neocortex. Cereb. Cortex. 17:2204-2213.
[38] Mao BQ, Hamzei-Sichani F, Aronov D, Froemke RC, Yuste R (2001) Dynamics of spontaneous activity in neocortical slices. Neuron. 32:883-898.
[39] van Drongelen W, Koch H, Elsen FP, Lee HC, Mrejeru A, Doren E, Marcuccilli CJ, Hereld M, Stevens RL, Ramirez JM (2006) Role of persistent sodium current in bursting activity of mouse neocortical networks in vitro. J. Neurophysiol. 96:2564-2577.
[40] Taverna S, Mantegazza M, Franceschetti S, Avanzini G (1998) Valproate selectively reduces the persistent fraction of Na+ current in neocortical neurons. Epilepsy Res. 32:304-308.
[41] Taverna S, Sancini G, Mantegazza M, Franceschetti S, Avanzini G (1999) Inhibition of transient and persistent Na+ current fractions by the new anticonvulsant topiramate. J. Pharmacol. Exp. Ther. 288:960-8.
[42] Stafstrom CE (2007) Persistent sodium current and its role in epilepsy. Epilepsy Curr. 7:15-22.
[43] Villette V, Poindessous-Jazat F, Simon A, Léna C, Roullot E, Bellessort B, Epelbaum J, Dutar P, Stéphan A (2010) Decreased rhythmic GABAergic septal activity and memory-associated theta oscillations after hippocampal amyloid-beta pathology in the rat. J. Neurosci. 30:10991-11003.
[44] Simon AP, Poindessous-Jazat F, Dutar P, Epelbaum J, Bassant MH (2006) Firing properties of anatomically identified neurons in the medial septum of anesthetized and unanesthetized restrained rats. J. Neurosci. 26:9038-9046.
[45] Varga V, Hangya B, Kránitz K, Ludányi A, Zemankovics R, Katona I, Shigemoto R, Freund TF, Borhegyi Z (2008) The presence of pacemaker HCN channels identifies theta rhythmic GABAergic neurons in the medial septum. J. Physiol. 586:3893-915.
[46] Hangya B, Borhegyi Z, Szilágyi N, Freund TF, Varga V (2009) GABAergic neurons of the medial septum lead the hippocampal network during theta activity. J. Neurosci. 29:8094-8102.
[47] Cummins TD, Broughton M, Finnigan S (2008) Theta oscillations are affected by amnestic mild cognitive impairment and cognitive load. Int. J. Psychophysiol. 70:75-81.
[48] Peña F, Ordaz B, Balleza-Tapia H, Bernal-Pedraza R, Márquez-Ramos A, Carmona-Aparicio L, Giordano M (2010) Beta-amyloid protein (25-35) disrupts hippocampal network activity: role of Fyn-kinase. Hippocampus. 20:78-96.
[49] Colom LV, Castañeda MT, Bañuelos C, Puras G, García-Hernández A, Hernandez S, Mounsey S, Benavidez J, Lehker C (2010) Medial septal beta-amyloid 1-40 injections alter septo-hippocampal anatomy and function. Neurobiol. Aging. 31:46-57.

[50] Peña-Ortega f, Bernal-Pedraza R (2012) Amyloid beta slows down sensory-induced hippocampal oscillations, International Journal of Peptides, In press.
[51] van den Top M, Lee K, Whyment AD, Blanks AM, Spanswick D (2004) Orexigen-sensitive NPY/AgRP pacemaker neurons in the hypothalamic arcuate nucleus. Nat. Neurosci. 7:493-494.
[52] Davidowa H, Plagemann A (2000) Decreased inhibition by leptin of hypothalamic arcuate neurons in neonatally overfed young rats. Neuroreport. 11:2795-2798.
[53] Davidowa H, Plagemann A (2007) Insulin resistance of hypothalamic arcuate neurons in neonatally overfed rats. Neuroreport. 18:521-524.
[54] Mirshamsi S, Olsson M, Arnelo U, Kinsella JM, Permert J, Ashford ML (2007) BVT.3531 reduces body weight and activates K(ATP) channels in isolated arcuate neurons in rats. Regul. Pept. 141:19-24.
[55] Beurrier C, Congar P, Bioulac B, Hammond C (1999) Subthalamic nucleus neurons switch from single-spike activity to burst-firing mode. J. Neurosci. 19:599-609.
[56] Kass JI, Mintz IM (2006) Silent plateau potentials, rhythmic bursts, and pacemaker firing: three patterns of activity that coexist in quadristable subthalamic neurons. Proc. Natl. Acad. Sci. U. S. A. 103:183-188.
[57] Baufreton J, Garret M, Rivera A, de la Calle A, Gonon F, Dufy B, Bioulac B, Taupignon A (2003) D5 (not D1) dopamine receptors potentiate burst-firing in neurons of the subthalamic nucleus by modulating an L-type calcium conductance. J. Neurosci. 23:816-825.
[58] Albin RL, Young AB, Penney JB (1989) The functional anatomy of basal ganglia disorders. Trends Neurosci. 12:366-375.
[59] Bevan MD, Atherton JF, Baufreton J. (2006) Cellular principles underlying normal and pathological activity in the subthalamic nucleus. Curr. Opin. Neurobiol. 16:621-628.
[60] Hollerman JR, Grace AA (1992) Subthalamic nucleus cell firing in the 6-OHDA-treated rat: basal activity and response to haloperidol. Brain Res. 590:291-299.
[61] Hassani OK, Mouroux M, Féger J. (1996) Increased subthalamic neuronal activity after nigral dopaminergic lesion independent of disinhibition via the globus pallidus. Neuroscience. 72:105-115.
[62] Benazzouz A, Boraud T, Féger J, Burbaud P, Bioulac B, Gross C (1996) Alleviation of experimental hemiparkinsonism by high-frequency stimulation of the subthalamic nucleus in primates: a comparison with L-Dopa treatment. Mov. Disord. 11:627-632.
[63] Rodriguez MC, Guridi OJ, Alvarez L, Mewes K, Macias R, Vitek J, DeLong MR, Obeso JA (1998) The subthalamic nucleus and tremor in Parkinson's disease. Mov. Disord. 3:111-118.
[64] Ammari R, Bioulac B, Garcia L, Hammond C (2011) The Subthalamic Nucleus becomes a Generator of Bursts in the Dopamine-Depleted State. Its High Frequency Stimulation Dramatically Weakens Transmission to the Globus Pallidus. Front. Syst. Neurosci. 5:43.
[65] Garcia L, D'Alessandro G, Bioulac B, Hammond C (2005) High-frequency stimulation in Parkinson's disease: more or less? Trends Neurosci. 28:209-216.

[66] Tai CH, Yang YC, Pan MK, Huang CS, Kuo CC (2011) Modulation of subthalamic T-type Ca(2+) channels remedies locomotor deficits in a rat model of Parkinson disease. J. Clin. Invest. 121:3289-3305.

[67] Zhong G, Díaz-Ríos M, Harris-Warrick RM (2006) Intrinsic and functional differences among commissural interneurons during fictive locomotion and serotonergic modulation in the neonatal mouse. J. Neurosci. 6:6509-6517

[68] Zhong G, Masino MA, Harris-Warrick RM (2007) Persistent sodium currents participate in fictive locomotion generation in neonatal mouse spinal cord. J. Neurosci. 27:4507-18.

[69] Tazerart S, Vinay L, Brocard F (2008) The persistent sodium current generates pacemaker activities in the central pattern generator for locomotion and regulates the locomotor rhythm. J. Neurosci. 28:8577-8589.

[70] Song Y, Li HM, Xie RG, Yue ZF, Song XJ, Hu SJ, Xing JL (2012) Evoked bursting in injured Aβ dorsal root ganglion neurons: a mechanism underlying tactile allodynia. Pain. 153:657-665.

[71] Yao H, Donnelly DF, Ma C, LaMotte RH (2003) Upregulation of the hyperpolarization-activated cation current after chronic compression of the dorsal root ganglion. J. Neurosci. 23:2069-2074.

[72] Jiang YQ, Sun Q, Tu HY, Wan Y (2008) Characteristics of HCN channels and their participation in neuropathic pain. Neurochem. Res. 33:1979-1989.

[73] Yang RH, Xing JL, Duan JH, Hu SJ (2005) Effects of gabapentin on spontaneous discharges and subthreshold membrane potential oscillation of type A neurons in injured DRG. Pain. 116:187-193.

[74] Yang RH, Wang WT, Chen JY, Xie RG, Hu SJ (2009) Gabapentin selectively reduces persistent sodium current in injured type-A dorsal root ganglion neurons. Pain. 143:48-55.

[75] Xie RG, Zheng DW, Xing JL, Zhang XJ, Song Y, Xie YB, Kuang F, Dong H, You SW, Xu H, Hu SJ (2011) Blockade of persistent sodium currents contributes to the riluzole-induced inhibition of spontaneous activity and oscillations in injured DRG neurons. PLoS One. 6:e18681.

[76] Smith JC, Ellenberger HH, Ballanyi K, Richter DW, Feldman JL (1991) Pre-Bötzinger complex: a brainstem region that generate respiratory rhythm in mammals. Science. 254:726-729.

[77] Onimaru H, Homma I (2003) A novel functional neuron group for respiratory rhythm generation in the ventral medulla. J. Neurosci. 23:1478-1486.

[78] Janczewski WA, Feldman JL (2006) Distinct rhythm generators for inspiration and expiration in the juvenile rat. J. Physiol. 570:407-420.

[79] Peña F (2009) Neuronal network properties underlying the generation of gasping. Clin. Exp. Pharmacol. Physiol. 36:1218-1228.

[80] Thoby-Brisson M, Ramirez JM (2001) Identification of two types of inspiratory pacemaker neurons in the isolated respiratory neural network of mice. J. Neurophysiol. 86:104-112.

[81] Del Negro CA, Morgado-Valle C, Feldman JL (2002) Respiratory rhythm: an emergent network property? Neuron. 34(5):821-830.

[82] Del Negro CA, Morgado-Valle C, Hayes JA, Mackay DD, Pace RW, Crowder EA, Feldman JL (2005) Sodium and calcium current-mediated pacemaker neurons and respiratory rhythm generation. J. Neurosci. 25(2):446-453.
[83] Viemari JC, Ramirez JM (2006) Norepinephrine differentially modulates different types of respiratory pacemaker and nonpacemaker neurons. J. Neurophysiol. 95:2070-82.
[84] Tryba AK, Peña F, Ramirez JM (2006) Gasping activity in vitro: a rhythm dependent on 5-HT2A receptors. J. Neurosci. 26:2623-2634.
[85] Mellen NM, Mishra D (2010) Functional anatomical evidence for respiratory rhythmogenic function of endogenous bursters in rat medulla. J. Neurosci. 30:8383-8392.
[86] Ben-Mabrouk F, Tryba AK (2010) Substance P modulation of TRPC3/7 channels improves respiratory rhythm regularity and ICAN-dependent pacemaker activity. Eur. J. Neurosci. 31:1219-1232.
[87] Peña F, Aguileta MA (2007) Effects of riluzole and flufenamic acid on eupnea and gasping of neonatal mice in vivo. Neurosci. Lett. 415:288-293.
[88] Poets CF, Meny RG, Chobanian MR, Bonofiglo RE (1999) Gasping and other cardiorespiratory patterns during sudden infant deaths. Pediatr. Res. 45:350-354.
[89] Sridhar R, Thach BT, Kelly DH, Henslee JA (2003) Characterization of successful and failed autoresuscitation in human infants, including those dying of SIDS. Pediatr. Pulmonol. 36:113-122.