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General Principles of Rhythmogenesis in Central Pattern Networks

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Abstract

The cellular and ionic mechanisms that generate the rhythm in central pattern generator (CPG) networks for simple movements are not well understood. Using vertebrate locomotion, respiration and mastication as exemplars, I describe four main principles of rhythmogenesis: (1) rhythmogenic ionic currents underlie all CPG networks, regardless of whether they are driven by a network pacemaker or an endogenous pacemaker neuron kernel; (2) fast synaptic transmission often evokes slow currents that can affect cycle frequency; (3) there are likely to be multiple and redundant mechanisms for rhythmogenesis in any essential CPG network; and (4) glial cells may participate in CPG network function.

The neural basis for rhythmogenesis in simple behaviors has been studied for almost 100 years, yet we cannot identify with certainty the detailed mechanisms by which rhythmic behaviors are generated in any vertebrate system. Early studies focused on whether locomotor rhythms were generated by a chain of coupled reflexes that require sensory feedback, or by a central neural network. By now there is general agreement that for the major rhythmic behaviors (including locomotion, respiration, and mastication, the subjects of this book), there exist CPG networks within the central nervous system that are able to drive the basic rhythmic behavior in the complete absence of sensory feedback. This of course does not eliminate an important role for sensory feedback, which certainly affects cycle frequency and for some behaviors determines the timing of one phase of the behavior. Given the existence of CPGs, the question of rhythmogenesis can be rephrased to ask how these networks determine the timing of the rhythmic behavior. In this chapter, I focus on cellular and molecular mechanisms that could underlie rhythmogenesis in CPG networks, especially those that drive locomotion, respiration, and mastication.

Keywords

Central Pattern Generator; rhythmogenesis; bursting; modulation; ion channel; receptor; calcium

Neuronal or network oscillators?

Two competing mechanisms have been proposed to underlie rhythmogenesis in central pattern generator (CPG) networks, often presented in an either/or manner: either rhythms are driven by endogenously oscillatory neurons which serve as “pacemaker neurons,” or rhythms are generated by the pattern of synaptic connections within the network, forming a “network pacemaker” mechanism. The central point of the “pacemaker neuron” hypothesis is that the CPG network contains neurons that, even when completely isolated from all

synaptic input, continue to oscillate and fire rhythmic bursts of action potentials. Further, these pacemaker neuron oscillations provide the rhythmic synaptic drive to the “follower” neurons to generate the rhythm. A corollary is that if the pacemaker neurons were blocked from oscillating, or eliminated, the rhythmic output from the CPG would halt. In contrast, the “network pacemaker” hypothesis has no requirement for oscillatory neurons at all in the network; if they exist, they are not necessary to generate the rhythm (i.e., eliminating them does not alter the rhythm), or they are driven by synaptic input to fire in patterns or phases that are not controlled by their intrinsic rhythmicity. Instead, it is the pattern of synaptic connectivity between otherwise tonically active or silent neurons that generates the rhythmic output. The half-center model, for example, generates rhythmic bursting and alternation by a pattern of reciprocal inhibition between two otherwise tonically active neuron pools; one pool fires tonically and inhibits the other pool until it fatigues or the inhibited pool escapes from inhibition, and then the pools reverse their activity. In the CPG networks that are discussed in this book, inhibitory synaptic input plays a critical role in shaping the frequency and phasing of the rhythmic motor pattern, but is not essential for rhythmogenesis: blockade of GABA and glycine inhibition alters but does not abolish the rhythm-generating ability of the CPG, showing that they are not organized entirely on a simple half-center model. Alternative models for network pacemakers are based on networks of mutually excitatory interneurons that receive tonic input to initiate a burst, and terminate it by some fatigue mechanism.

In my opinion, these models are not as far apart as they seem, and it is unnecessary to place them in an “either/or” dichotomy. Indeed, there are a number of common features that underlie both the “pacemaker neuron” and “network pacemaker” models for rhythmogenesis. These features arise out of new research, in part reported in this book, describing the neuronal mechanisms in CPG networks. Below I describe four general principles of rhythmogenesis that could serve to guide future research in this area.

Principle I: instead of thinking about rhythmic neurons or circuits, consider rhythmogenic ionic currents

The research described in this volume describes the ubiquitous activity of a number of ionic currents which can participate in generating rhythmic outputs from both bursting pacemaker-based and network pacemaker-based CPG circuits. These currents have relatively slow kinetics and can help to maintain neurons in a prolonged depolarized or hyperpolarized state. Regardless of the model for rhythmogenesis, these currents appear to be critical components.

Persistent sodium current or $I_{Na(P)}$

The persistent sodium current is the slowly or noninactivating component of the fast voltage-dependent sodium current. It can be selectively reduced by low concentrations of riluzole, though this drug is less specific at higher concentrations. $I_{Na(P)}$ appears to be involved in rhythmogenesis in most of the neural networks discussed in this volume. Blockade of $I_{Na(P)}$ has been shown to abolish fictive respiration in the isolated pre-Bötzinger complex (PBC) slice (Del Negro et al., 2002; Koizumi and Smith, 2008), although there is argument over whether this effect is directly on the PBC itself (Koizumi and Smith, 2008) or on adjacent nuclei (Pace et al., 2007b). Blockade of this current abolishes bursting in one major class of pacemaker neurons in the PBC (Del Negro et al., 2002; Pena et al., 2004), but also weakens or abolishes repetitive spiking in many neurons, and thus would also weaken any network-based oscillator (Kuo et al., 2006). In summary, it is not clear whether riluzole blocks the respiratory rhythm via its effects on pacemaker neurons or the network, but $I_{Na(P)}$ is clearly important.

In the mouse spinal locomotor CPG, blockade of $I_{Na(P)}$ by low concentrations of riluzole in normal Ringer solution abolishes fictive locomotion evoked either by transmitter application (*N*-methyl-D-aspartic acid [NMDA] and 5-HT) or by caudal spinal cord stimulation (Tazerart et al., 2007; Zhong et al., 2007). In both of these studies, the cycle frequency was not affected by riluzole; instead, the strength of the motor output became weaker and weaker, at the same cycle frequency, until the pattern was not detectable. This result was explained by riluzole's effect to reduce repetitive firing in both motoneurons and CPG inter-neurons, which would weaken synaptic drive at each point in the network until it ceases to function. Interestingly, riluzole has no detectable effect on fictive locomotion evoked in the salamander spinal cord by NMDA and d-serine (Chapter 10).

As described by Kolta (Chapter 9), the CPG network driving rhythmic mastication is thought to be centered in the trigeminal sensory nucleus. A subset of neurons in this nucleus fire rhythmic bursts of action potentials upon depolarization; such bursting is significantly enhanced in low-calcium saline, which enhances $I_{Na(P)}$ (Li and Hatton, 1996; Tazerart et al., 2008). This bursting in low calcium, as well as bursting evoked by NMDA, is blocked by riluzole. Kolta and colleagues suggest that high levels of activity in the nucleus may activate a mechanism to reduce extracellular calcium, thus activating $I_{Na(P)}$ -dependent pacemaker neurons which drive the masticatory rhythm. While this hypothesis has not yet been tested, it raises the very interesting question of whether significant changes in extracellular ion concentrations can arise during normal motor network activation. In mouse spinal cord slices, zero calcium solutions can also evoke riluzole-sensitive bursting in interneurons thought to be part of the locomotor CPG (Tazerart et al., 2008). Tazerart et al. also argue that significant reductions of calcium might arise normally during locomotion, and that the locomotor CPG may be driven by bursting pacemaker neurons whose rhythmicity is activated by a calcium-dependent shift in the voltage dependence of $I_{Na(P)}$ activation; however, this appears to conflict with experiments in normal calcium Ringer, where the locomotor CPG works well and its cycle frequency is not affected by riluzole (Tazerart et al., 2007; Zhong et al., 2007). These interesting hypotheses will need to be tested by using ion-selective micro-electrodes to measure activity-dependent changes in extracellular ion concentrations in normal calcium-containing solutions.

Calcium-activated nonselective current or I_{CAN}

I_{CAN} has no intrinsic voltage dependence, but is activated by increases in intracellular Ca^{2+} with very slow activation and deactivation kinetics. With these properties, it can support prolonged plateau potentials (Zhang et al., 1995) or rhythmic bursting in neurons. In the respiratory CPG, Ramirez and colleagues identified a set of Cd^{2+} -sensitive bursting pacemaker neurons in mice older than P5 and suggested that these neurons use I_{CAN} to provide some of the rhythmic drive for respiration under normal conditions; in contrast, during gasping evoked by hypoxia, rhythmogenesis is entirely dependent on riluzole-sensitive currents (Pena et al., 2004). An alternative role for I_{CAN} has been proposed by Del Negro and colleagues (2008) (Rubin et al., 2009): in this "group pacemaker model," a set of mutually excitatory neurons all contain significant densities of I_{CAN} ; a small increase in spike activity in a subset of neurons could initiate firing in all of them, which in turn activates I_{CAN} , providing the prolonged depolarizing drive for the burst. Thus, in both pacemaker-based and network-based models, some of the drive that holds the neurons depolarized during an inspiratory burst is mediated by I_{CAN} .

Other inward currents

In addition to these two important inward currents, several others have been implicated in rhythm generation. NMDA is often used, with other transmitters, to activate fictive motor patterns in rhythmic CPG networks. In the lamprey spinal cord, NMDA-activated inward

currents have been hypothesized to participate in swimming rhythm generation, though whether the current's ability to evoke intrinsic bursting is necessary or not may depend on the cycle frequency (see below). The hyperpolarization-activated inward current, I_h , can be activated by the accumulated hyperpolarization separating bursts of action potentials, and provides a depolarizing ramp current to drive the next cycle of activity. Blockade of I_h significantly slows the frequency of fictive locomotion in the salamander spinal cord (Chapter 10), as well as the well-studied pyloric CPG in the lobster stomatogastric ganglion (Peck et al., 2006). In addition, low-threshold, slowly deactivating calcium currents are thought to support repeated firing in many neurons, and these currents could also provide a depolarizing ramp to sustain rhythmic bursting in CPG networks.

Outward currents

The other essential component of a rhythmic system is a mechanism to terminate the burst of action potentials. A number of outward currents play roles in both ending bursts and shaping the spike frequency within the burst; modification of these currents often changes the cycle frequency of the rhythm.

Calcium-dependent potassium current, $I_{K(Ca)}$

$I_{K(Ca)}$ is thought to be the most common current to terminate spike bursts. During a burst of action potentials, calcium channels are activated, resulting in an accumulation of intracellular calcium and increasing activation of $I_{K(Ca)}$; this current eventually outweighs the inward currents (synaptic or intrinsic) that maintain the burst, causing the neurons to fall silent. This in turn closes the $I_{K(Ca)}$ channels either through their intrinsic voltage dependence (BK-type) or as a result of the fall in intracellular calcium during the quiet period (SK-type), allowing synaptic or intrinsic ramp currents to reexcite the neurons and initiate the next burst. $I_{K(Ca)}$ is thought to be the burst-terminating current in the swim CPG in the lamprey spinal cord, as the SK channel blocker apamin reduces the neuronal postburst afterhyperpolarization and slows the fictive locomotor pattern by prolonging each burst (El Manira et al., 1994). Similar effects of apamin are seen in the rat spinal locomotor CPG (Cazalets et al., 1999) and in the masticatory system (Del Negro et al., 1999). Interestingly, blockade of $I_{K(Ca)}$ can stabilize a weak locomotor rhythm in the salamander spinal cord, suggesting that too much $I_{K(Ca)}$ can disrupt the rhythm-generating mechanism (Chapter 10).

Other currents that have been implicated in regulation of cycle frequency include the hyperpolarizing current generated by the electrogenic sodium–potassium ATPase as a consequence of the accumulation of intracellular sodium during the burst (Rubin et al., 2009), and A-type transient potassium currents, which help set the rate of repolarization after a spike or burst. Hess and Manira (2001) described a catechol-sensitive high-threshold A-type current in lamprey neurons. This current plays an important role in spike termination: during catechol application, motoneuron spikes are significantly broadened. This in turn causes enhanced sodium channel inactivation, and reduced repetitive spike ability. When the A-current is blocked during fictive locomotion, the neurons fire fewer spikes per burst, reducing crossed inhibition and accelerating the cycle frequency. The potassium-dominated leak current can also play an important role in regulating cycle frequency. Smith and colleagues have demonstrated both computationally (Smith et al., 2000) and experimentally (Koizumi and Smith, 2008) the importance of the leak in regulating cycle frequency in the inspiratory rhythm generated in the PBC. Reduction of the leak (by application of substance P) causes bursting neuron depolarization and an acceleration in the cycle frequency (Koizumi and Smith, 2008).

Roles of these currents in rhythmogenesis

These examples show the varied but ubiquitous functions of intrinsic ionic currents in shaping rhythmogenesis. By evoking nonlinear responses to subthreshold voltage changes, these currents enable prolonged firing that would sustain a burst, and then burst termination, that are essential for rhythmic motor pattern generation. The appropriate balance of currents is critical for rhythmogenesis to occur (Purvis et al., 2007; Rubin et al., 2009; Smith et al., 2000); this might be modified by modulatory inputs that enable or disable network function. Note that the subthreshold currents that activate these rhythmogenic currents could be endogenous (thus from pacemaker neurons) or synaptic (thus from a network-based oscillator); the requirement for nonlinear enhancement of the subthreshold voltages is the same for both models of rhythmogenesis. Blockade of these currents dramatically affects neurons' abilities to remain depolarized and fire prolonged burst, regardless of whether they are activated by endogenous mechanisms or by synaptic drive. Models such as Del Negro's "group pacemaker" model (Chapter 8; Rubin et al., 2009) are starting to combine the previously separate models by allowing synaptic drive to initiate the burst-generating intrinsic currents for each burst. Ramirez (this volume) has said that the importance of synaptic or intrinsic drive to initiate a burst may vary from burst to burst: "Each breath is a new breath." The critical point is that these rhythmogenic currents are present to amplify the subthreshold input into full bursts of neuronal firing.

Principle II: synaptic currents do not simply depolarize or hyperpolarize the cell by rapid synaptic action, but can also evoke nonlinear membrane responses

Pure "network-based" models for rhythmogenesis try to generate a motor rhythm based solely on the rapid transmitter actions of the main transmitters (glutamate, GABA, and glycine) and the spike-generating mechanisms in the neurons. This is very oversimplified because the "standard" fast synaptic transmitters do far more than simply activating ligand-gated ion channels to depolarize or hyperpolarize the cell. The ionic currents that flow through these channels can in turn activate other currents by methods not simply related to membrane potential. In addition, all neurotransmitters except for glycine also activate slow metabotropic receptors that trigger second messenger pathways to modify ionic currents for prolonged times. Thus, synaptic release of glutamate, for example, need not only cause a simple depolarization.

Multiple actions of glutamate in the lamprey spinal cord

Excellent examples of this principle have been demonstrated by El Manira and colleagues studying the multiple actions of glutamate in the swimming CPG of the lamprey spinal cord (Chapter 7). Glutamate activates NMDA receptors, which as described above have been implicated in rhythmogenesis. Glutamate also activates α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors, rapidly depolarizing the neurons, via sodium entry into the cell. Nanou et al. (2008) showed that this sodium entry in turn activates a Slack-type sodium-activated potassium current, $I_{K(Na)}$, which generates a prolonged outward current following AMPA receptor activation. This secondary and delayed effect of AMPA receptor activation causes an accumulated diminution of synaptic strength through shunting during a burst of excitatory postsynaptic potentials (EPSPs). Wallen et al. (2007) showed that $I_{K(Na)}$ is also activated by sodium entry during a train of action potentials, and contributes to the postburst hyperpolarization amplitude. The hyperpolarization increases with increasing spike frequency, and could participate (with $I_{K(Ca)}$) in regulation of burst frequency. These experiments clearly show that the glutamate-evoked AMPA current can, by increasing intracellular sodium, evoke prolonged outward currents that outlast the transmitter action.

In addition to activating ionotropic receptors, glutamate also activates metabotropic metabotropic glutamate receptor (mGluR) in the lamprey spinal cord (for review, see LeBeau et al., 2005). mGluR1 activation leads to a variety of effects. Postsynaptically, it excites the neuron by reducing a leak K^+ current, and increasing the current and calcium influx through NMDA receptors. In addition, it activates endocannabinoid synthesis; these molecules diffuse from the cell and bind to presynaptic CB1 receptors on glycine nerve terminals, reducing glycine release. The combined increase in EPSP and decrease in inhibitory postsynaptic potential response reduces mid-cycle inhibition during fictive locomotion, increasing the cycle frequency (El Manira et al., 2008; Kyriakatos and El Manira, 2007).

Glutamate actions in the respiratory network

Similar secondary actions of glutamate have been seen in the inspiratory CPG in the PBC. According to the group pacemaker model of Del Negro and colleagues (Chapter 8; Rubin et al., 2009), mutual synaptic excitation between network neurons is thought to initiate each burst of activity, but alone cannot sustain the full inspiratory burst. Instead, glutamate acts through both AMPA receptors and mGluR to activate I_{CAN} , which provides the sharp rise to the burst. AMPA receptor activation depolarizes the cell, which in turn activates voltage-gated calcium currents. mGluR5 activates a PLC-based mechanism resulting in release of calcium from IP_3 -sensitive intracellular stores. These two sources of calcium provide the drive to activate I_{CAN} , which then rapidly depolarizes the neuron and increases its spike frequency during the burst.

These examples show the general principle that rapid synaptic events cannot be easily separated from slower intrinsic neuronal currents. Intrinsic currents are triggered by the synaptically evoked change in membrane potential or intracellular ion concentration. In addition, metabotropic glutamate and GABA receptors transform the responses to these traditionally rapid receptors into slow changes in neuronal excitability. Katz and Frost (1995) first described the phenomenon of “intrinsic neuromodulation” of neural networks which contain neurons releasing neuromodulators as well as other transmitters; if the expression of metabotropic glutamate and GABA receptors is common in CPG networks, then intrinsic neuromodulation would be a ubiquitous feature to be taken into account in all models of rhythmogenesis.

Principle III: there are multiple mechanisms for rhythm generation in any system, which could vary with age, species, and modulatory state

Given the central significance of respiration, locomotion, and mastication, it is very unlikely that a single mechanism accounts for rhythm generation in any of these systems. It is more likely that multiple and redundant rhythmogenic mechanisms cooperate with one predominating under some conditions, while another may predominate at other times. For example, in the lamprey spinal cord, there appear to be two modes of rhythmogenesis. A slow mode, which is seen in the isolated hemicord activated with NMDA, depends on slow bursting sustained by the voltage-dependent activation of NMDA receptors, while a fast mode is seen during application of D -glutamate and does not require NMDA voltage-dependent activation (Cangiano and Grillner, 2003). In the inspiratory network of the PBC, the relative importance of different currents varies under many conditions. For example, I_{CAN} -based oscillatory neurons are very rare before P5, though of course younger animals breathe well (Pena et al., 2004). Under normoxia, I_{CAN} is thought to be an important driver for the eupneic rhythm (Pace et al., 2007a; Pena et al., 2004). However, both *in vitro* (Pena et al., 2004) and *in vivo* (Paton et al., 2006), hypoxia evokes a much slower gasping motor pattern which is entirely dependent on I_{NaP} . Ramirez and colleagues have elegantly shown

how neuromodulators can dramatically alter the cycle frequency as well as the regularity and amplitude of the inspiratory rhythm, due to differential effects on I_{NaP} and I_{CAN} , as well as other currents (Ramirez, this volume). In the masticatory CPG, there is a parallel between the development of I_{NaP} and depolarization-evoked bursting in neurons in the trigeminal main sensory nucleus, and this in turn correlates with the switch from suckling to chewing (Chapter 9).

The principle of multiple and redundant mechanisms for rhythmogenesis is clear even in the most well-studied CPG, that driving the pyloric rhythm in the crustacean stomatogastric ganglion. This 14-neuron network is considered the prototype of an oscillatory neuron-driven rhythmic pattern, where a single neuron, the Anterior Burster (AB) is the pacemaker for the rhythm. However, in the earliest chapter to test the essential role of the AB neuron, Miller and Selverston (1982a) photoinactivated the AB neuron; the remaining network was still able to generate a rhythmic motor pattern, upon stimulation of modulatory inputs, though it had different phasing than the normal rhythm. Only when modulatory inputs were removed did the rhythm stop (Miller and Selverston, 1982a; Russell and Hartline, 1978); this has been shown to be due to the loss of rhythmogenic currents in the absence of neuromodulators. Even under these basal non-modulated conditions, two of the neurons could form a mutually inhibitory half-center oscillator provided that one of the neurons was slightly depolarized to make it active (Miller and Selverston, 1982b). Even for the single AB neuron, there are multiple and redundant ionic mechanisms for generating oscillations. We have shown that dopamine and serotonin can each evoke rhythmic bursting in a synaptically isolated AB neuron, but use different sets of currents to drive the burst (Harris-Warrick and Flamm, 1987). Dopamine-induced bursting is abolished by removal of calcium or block of release of calcium from intracellular stores, and depends on a flufenamic acid (FFA)-sensitive I_{CAN} to drive the oscillations; DA-evoked bursting is insensitive to blockade of I_{NaP} by riluzole or tetrodotoxin (TTX). In contrast, serotonin-evoked bursting is insensitive to FFA, but is blocked by low concentrations of either riluzole or TTX, as well as reductions in extracellular sodium (L. Kadiri and R. Harris-Warrick, unpublished). Thus, depending on the modulatory milieu, this neuron can burst by a calcium-based or a sodium-based mechanism; presumably both mechanisms contribute in varying degrees as the modulatory milieu is changed.

Principle IV: it may not be only neurons: the possible role of glial cells

Glial cells constitute the majority of the cells in the brain. It has been known for years that glia can express voltage-activated ion channels as well as transmitter receptors and pumps (for review, see Baker, 2002; Sontheimer, 1994), yet these cells are routinely ignored as possible participants in active networks. Kolta (Chapter 9; Kolta et al., 2007) has raised the very interesting hypothesis that glial regulation of extracellular calcium may play a critical role in maintenance of rhythmogenesis in the masticatory system. According to this hypothesis, during chewing, glial mechanisms reduce extracellular calcium and thereby enhance I_{NaP} . This allows bursting of neurons in the trigeminal principal sensory nucleus, which drives the masticatory rhythm. Although this hypothesis remains untested, it emphasizes the possible active participation of glial cells in setting the conditions under which rhythmogenesis can be initiated or modulated. This could be a fruitful area for research in the future.

Conclusion

While the neural mechanisms underlying rhythmogenesis have been studied for many years, the chapters in this volume demonstrate how much recent progress has been made in understanding how simple rhythmic behaviors are generated. These mechanisms appear

quite varied, but this is not unexpected. Indeed, multiple mechanisms for rhythmogenesis have been demonstrated in simple invertebrate CPGs, and are very likely in vertebrate networks as well. We may be approaching a synthesis of the traditionally competing models of rhythmogenesis by cellular versus network mechanisms: since all the networks described here depend on boosting by rhythmogenic currents such as I_{NaP} or I_{CAN} , it may be a small difference (perhaps enough to vary on a cycle-by-cycle basis) between a burst that is initiated by synaptic input and one that is initiated by intrinsic burst currents. Traditional network oscillator models ignore the many nonlinear sequelae of traditional rapid synaptic input, including activation of ion-sensitive currents such as $I_{K(Na)}$ and I_{CAN} as well as the participation of metabotropic receptors at many if not most synapses. With the possible participation of glial mechanisms to regulate neuronal excitability by altering extracellular ion concentrations or other mechanisms, we have a new area of research into the mechanisms of rhythmogenesis. The next decade should be an exciting time for research into the cellular and molecular mechanisms of rhythmogenesis in locomotor, respiratory and masticatory CPGs.

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Abbreviations

AB	anterior burster neuron
CPG	central pattern generator
FFA	flufenamic acid
PBC	pre-Bötzinger complex
PLC	phospholipase C
TTX	tetrodotoxin

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