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The Cellular Building Blocks of Breathing

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Abstract

Respiratory brainstem neurons fulfill critical roles in controlling breathing: they generate the activity patterns for breathing and contribute to various sensory responses including changes in O_2 and CO_2. These complex sensorimotor tasks depend on the dynamic interplay between numerous cellular building blocks that consist of voltage-, calcium-, and ATP-dependent ionic conductances, various ionotropic and metabotropic synaptic mechanisms, as well as neuromodulators acting on G-protein coupled receptors and second messenger systems. As described in this review, the sensorimotor responses of the respiratory network emerge through the state-dependent integration of all these building blocks. There is no known respiratory function that involves only a small number of intrinsic, synaptic, or modulatory properties. Because of the complex integration of numerous intrinsic, synaptic, and modulatory mechanisms, the respiratory network is capable of continuously adapting to changes in the external and internal environment, which makes breathing one of the most integrated behaviors. Not surprisingly, inspiration is critical not only in the control of ventilation, but also in the context of "inspiring behaviors" such as arousal of the mind and even creativity. Far-reaching implications apply also to the underlying network mechanisms, as lessons learned from the respiratory network apply to network functions in general.

Introduction

The enormous metabolic costs associated with endothermy and the need to maintain the brain and most other organs active continuously made mammals entirely dependent on a continuous supply of oxygen, a highly energetic element which is acquired through breathing (433). Without breathing, mammals typically survive for only a few minutes. Moreover, breathing needs to be continuously adapted to the metabolic needs of the behaving organism, making breathing one of the most integrated behaviors. Various metabolic and behavioral conditions modulate breathing including vocalization, sleep, arousal, fear, exercise, hypoxia, and hypercapnia. Breathing also modulates behaviors such as fear, arousal, and cognitive states. "Being inspired" or "having an inspiration" are commonly used expressions that reflect the close interaction between breathing and higher brain functions. The abilities to breathe, regulate gas exchange, and adapt to various metabolic and behavioral challenges critically depend on the cellular properties of the respiratory neurons within the brainstem. As elegantly researched by the French Professor Francois Clarac (78), the concept that the brainstem plays a crucial role in controlling breathing was first proposed by the English Professor Thomas Willis (599). In 1812, the French physiologist Julien-Jean-Cesar Legallois performed transections at various brainstem levels and was the first to conclude that only a very small circumscribed area in the medulla

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is critical for breathing (286). This observation was subsequently confirmed by Mary Jean-Pierre Flourens, who named this small circumscribed area the noeud vital, to reflect the fact that this area is of vital importance (153, 432). In 1991, Smith et al. identified a very circumscribed area in the ventrolateral medulla, which when lesioned in the isolated brainstem-spinal cord of neonatal rats abolished respiratory activity. This area continued to generate respiratory rhythmic activity even when isolated in thin medullary slices (Fig. 1). Smith et al. (516) termed the area responsible for respiratory rhythm generation the pre-Bötzinger complex (preBötC, Fig. 1A). More recently, the preBötC was identified in humans and it was demonstrated that anatomical alterations in the preBötC were associated with distinct breathing abnormalities (488).

The isolated preBötC generates three physiologically distinct respiratory activity patterns. These activity patterns are similarly seen *in vivo* and in the so-called working heart brain-stem preparation, and are referred to as normal respiratory activity pattern (or eupneic activity, Figs. 1B, 2A,B), sigh-activity pattern (Figs. 1B, 2C-2E), and gasping pattern (299). Mapping the pattern of these three activities reveals a complete anatomical overlap within the preBötC (Fig. 1B). The ability to isolate the preBötC in a functional manner provided rigorous insights not only into the cellular mechanisms that are critical for rhythm generation but also the mechanisms that govern the reconfiguration of the respiratory network to generate the three different activity patterns under different metabolic conditions. These *in vitro* studies were paralleled by studies performed in a variety of *in vivo* preparations. The first demonstration that lesioning of the preBötC indeed abolishes breathing *in vivo* (440), was followed by numerous studies that continue to confirm its importance for various aspects of breathing in health and disease (36, 184, 194, 334, 335, 337, 432, 489, 520, 537, 544, 545, 555, 594). However, it must be emphasized that the preBötC is embedded in a larger neuronal network that is distributed throughout the nervous system. Thus, brainstem respiratory neurons are not only present within the preBötC but different types of cellular properties found in different brainstem areas contribute to different aspects of the breathing rhythm, as well as chemosensation (67, 98, 145, 168, 195, 197, 217, 236, 237, 277, 336, 360, 463, 515, 528). Selective lesion experiments and the ability to preserve specific respiratory functions following experimental isolation have helped not only to better define the role of the preBötC, but there are also various other areas that have benefited from *in vitro* approaches. For example, the experimental isolation of areas such as the retrotrapezoid nucleus (RTN) (193, 196, 284), the locus ceruleus (LC), (13, 133, 370, 620, 621), raphe nucleus (87, 586), and the nucleus tractus solitarius (NTS) (85, 96, 370) have helped us to gain insights into the cellular mechanisms contributing to chemosensation. One important next challenge will be to understand how these cellular properties are integrated into a larger network, to understand how breathing behavior with all its complexity and adaptability is produced. In this review, we will discuss the cellular properties that are known to be critical for various aspects of breathing, based on studies in various *in vitro* and *in vivo* preparations. These studies have not only provided important insights into the neuronal control of breathing, but they have also led to the formulation of principles that govern network interactions and behavioral control in general. It is these general implications that make the respiratory network a great model for understanding how the nervous system generates behavior. Thus, we hope that this review can provide insights that are not only of interest for those working in the field of breathing, but also for anyone interested in neuronal network functions and behavior in general.

The Building Block Hypothesis for Generating Respiratory Network Activity

The search for common principles that underlie the generation of activity patterns, of complex behaviors and processes such as sensori-motor integration, and of learning and memory has led to the important realization that neuronal networks are not hard-wired. The

respiratory network is no exception. Synaptic, cellular, and modulatory processes that define network functions are continuously changing and homeostatically regulated. The availability of modern tools and initiatives that may allow the identification of all synaptic connections in a “connectome” of the brain will provide important insights into the architecture of neuronal networks (294, 295, 526, 527). But understanding the wiring of neuronal networks is just one aspect that defines a functioning network. A network connection is not just excitatory or inhibitory; it is also defined by its iono- and metabotropic mechanisms, its many pre- and post-synaptic ionic currents, its surface receptors, and its complex intracellular mechanisms that are dynamically regulated in an activity-, state-, time-, and context-dependent manner. In this scenario, reciprocally organized inhibitory connections, recurrent excitation, persistent sodium currents, calcium activated nonspecific cation currents, neuromodulators acting on G-protein coupled receptors, and second messenger pathways interacting intracellularly are all building blocks that are dynamically arranged in many different ways to produce a network output. Similar network outputs can be assembled by many different combinations of these building blocks. Removing any of these building blocks may alter the overall output. The network will continue to operate in a manner that is difficult to predict, since these building blocks are not simple “Lego” blocks that have different colors and forms. These building blocks follow many nonlinear rules with regard to the effects that they exert and the conditions during which they are activated. These ideas are by no means novel. More than 20 years ago, Peter Getting wrote a very influential review on the emerging principles governing network operation, and he spelled out the concept that synaptic and intrinsic properties need to be considered as building blocks of a neuronal network (173). The review by Peter Getting is still as relevant today as it was 20 years ago. What has changed is the increased understanding of the molecular and cellular determinants of these building blocks. The respiratory network is a good example for which there has been an explosion in our understanding of the cellular properties of respiratory brainstem neurons. Yet, our understanding of how these properties interact to form a breath is still limited. While it is relatively easy to synthesize the available information into a framework that could explain how the respiratory network generates the respiratory rhythm, the emerging picture will always be incomplete and may even be misleading. But, it seems obvious that the respiratory network does not depend on only one building block, but rather on multiple intrinsic, synaptic, intracellular, and modulatory processes that interact with each other (Fig. 3). Figure 3 can only provide an overview of some of the cellular mechanisms involved in the neuronal control of breathing. A more complete account of the mechanisms involved will be given in the context of this review. But, it is important to emphasize that the combination of these building blocks is not always the same, and different configurations define different states of the respiratory network. Moreover, even the simplest behavioral state is not determined by only one network state. For example, the apparently simple “gasping” state is the result of different network states, as is suggested by the different types of known gasping behaviors (180). Similarly, what is defined as “eupneic breathing” is not generated by a fixed network state, but may differ from species to species and preparation to preparation, causing much confusion in the field of respiration (435). The “eupneic” breaths of a cat, rat, or human, of a neonate or adult, of a mammal living at low or high altitude will all differ. Even within the same species there are individual differences in eupneic breathing and the same individual will not generate every eupneic breath in the same manner.

From a historical perspective, our understanding of neuronal network function has been driven by numerous debates over the most important principles or building blocks that determine network functions and behaviors. Whether the field of respiration received more than its fair share of divisive debates compared to other fields of network functions is irrelevant, but there have been many debates beginning with the discussion of central pattern generators (CPGs) versus chains of reflexes (182, 183, 506, 507), the debates over the

importance of reciprocal synaptic inhibition versus recurrent synaptic excitation, pacemaker versus network properties, *in vitro* versus *in vivo* (467) persistent sodium current versus calcium-activated nonspecific current (CAN) (390), and individual pacemakers versus group pacemakers (106). Perhaps it is time to accept the conclusion that networks are not functioning based on single mechanisms, and that a behavior, even if it looks the same, is not the result of a single network configuration (422), that networks depend not only on CPGs, but also on numerous interacting reflexes, and that they involve persistent sodium and CAN currents, and single and group pacemakers. If we can lay these debates aside, we can begin to better appreciate the dynamic principles that govern not only the respiratory network and breathing, but also all networks and behaviors in general. In this review, we will describe many of the cellular properties that constitute some of the building blocks that govern the respiratory network. We will also discuss some of the interactions that make this network so dynamic and adaptable.

Determinants of Autonomous Activity and Excitability

Overview

The ability of respiratory brainstem neurons to autonomously (=intrinsically) generate action potentials (=spiking) and bursting has received considerable attention in the field of respiration (243, 434, 442, 516) (Fig. 4). Yet, autonomous discharge properties are not a unique feature of the respiratory network. Autonomous neuronal activity is found virtually everywhere in the nervous system, including the neocortex, subthalamic nucleus, amydgala, nucleus basalis, globus pallidum, LC, raphe nuclei, hippocampus, inferior olive, thalamus, suprachiasmatic nucleus, substantia nigra (SNc), ventral tegmental area, and the cerebellum (57, 68, 95, 115, 147, 181, 249, 251, 304, 394, 414, 430, 431, 458, 472, 543, 574). Indeed, autonomously generated activity provides an important intrinsic drive for many behavioral functions, a concept that was first proposed more than a century ago (182, 183). Intrinsic activity is now considered as an important driving principle, not only for all rhythmic motor patterns including breathing, but is also critical for the generation of higher brain functions (31, 206, 279, 429, 617). Indeed, accepting that the brain is an intrinsic activity generator has provided novel ways to characterize the neuronal substrate of complex behaviors and to explain and diagnose the neuronal basis of many neurological disorders (188, 355, 524, 596, 617). Thus, understanding the cellular properties that underlie the intrinsic activity that gives rise to respiratory activity has implications that go far beyond its immediate relevance for breathing. Conversely, the intrinsic ionic currents involved in the generation of the respiratory rhythm play critical roles, not only within the respiratory network, but also in driving other networks throughout the nervous system.

Neuronal activities are commonly defined as “autonomous” if these activities do not require synaptic input to be generated (434, 539). According to this nomenclature, autonomously active neurons are also referred to as pacemakers. Among the autonomously active neurons there are two general types: (a) neurons that are generating intrinsically *spiking activity* (i.e., are not silent) (434, 539). These neurons will be referred to as *autonomous spiking pacemakers* (539). (b) Neurons that are capable of *bursting* in the absence of synaptic input, which will be defined as *autonomous bursting pacemakers* (213). In this review, we will make no distinction between the term “intrinsic” or “autonomous.” Both terms indicate that this activity pattern emerges as a cellular property within an individual neuron without the need of extrinsic drive. But, there are several considerations that are important to emphasize.

Autonomously bursting and spiking neurons may not constitute different neuron types

Autonomously bursting and spiking may characterize different activity states of the same neuron (Fig. 4). The biophysical mechanisms underlying the dynamic transitions between

spiking and bursting have been extensively studied in other model networks using a variety of computational approaches (91, 509, 522). Within the respiratory system as well as other known rhythm generating networks, neuromodulators play critical roles in transforming spiking into bursting neurons and vice versa (442, 578). Specific examples within the respiratory network are neurons that transition from a bursting into an autonomously spiking state following the blockade of endogenous 5-HT_{2A} receptor activation (405) or that transition from autonomously spiking to bursting in the presence of norepinephrine (NE) (578) or substance P (405). The role of thyrotropin-releasing hormone (TRH) in inducing bursting has been elegantly demonstrated in the NTS (99).

Autonomously active and silent neurons may not constitute different neuron types

Again, computational models and various experimental approaches can demonstrate how neurons transit into the different states of activity (522). Whether a neuron is autonomously active or silent depends on various factors, including the types of modulatory inputs, but to a large degree also on the details of the synaptic inputs. Depending on the amount and type of inward current or the balance between inward and outward currents, a neuron may not be sufficiently depolarized in its resting state to be autonomously active in the absence of synaptic input. For such a neuron, synaptic excitatory inputs are required to drive the membrane potential into the voltage range that will activate a burst or spiking activity. But this is also the case when bursting neurons are embedded into the functional network. In this case, synaptic inhibition can suppress autonomous bursting, and synaptic excitatory input is required to activate bursts [Fig. 5; (434, 564)].

Synaptic isolation is an experimental tool to characterize activity state

It is important to emphasize that synaptic isolation is only an experimental tool to better define the mechanisms that underlie bursting and spike generation (554). The fact that pacemaker neurons were more frequently identified within the *in vitro* network than in the *in vivo* network has no functional implications. Irrespective of the *in vitro* or *in vivo* condition, in the intact network these pacemaker mechanisms will be integrated in the synaptically active rhythmic network (Fig. 5). As will be discussed in more detail in later sections, the cellular mechanisms that underlie pacemaker bursting and autonomous spiking will regulate synaptic activity and in turn are regulated by synaptic activity.

The same types of ionic currents can lead to autonomous bursting, spiking, or silence

A neuron's activity is determined by the balance of its inward and outward currents and different ratios of the same currents can generate different neuronal activities. Any modulatory change in the ratio of inward and outward currents and any synaptically evoked change in a neuron's membrane potential will alter the propensity to burst and transform an autonomously bursting neuron into a silent neuron or vice versa (306). Thus, the same neuron can autonomously burst under certain conditions, but it may require synaptic activation in other conditions. Moreover, conditions that alter the degree of synaptic inhibition will affect the ability of the neuron to autonomously burst (Fig. 5). Changes in the ratio of inward and outward currents can not only be caused acutely via neuromodulators or synaptic inputs, but it is likely that it could also be changed in a long-term manner through various forms of plasticity that includes homeostatic plasticity and long-term facilitation. However, such long-term effects on the propensity to burst have not been studied in the respiratory network, but they are well known in other systems (261).

Autonomously bursting neurons in the functional network

First described in *in vitro* preparations, autonomously spiking and bursting respiratory neurons (103, 268, 338, 404, 554) have also been observed in the so-called *in situ*

preparation (531). However, it remains unknown whether autonomously bursting neurons also burst in the intact alert animal. Bursting may be suppressed and/or enhanced by synaptic and/or neuromodulatory inputs. The fact that this is still unknown should not imply that bursting does not exist in intact animals. Unfortunately, demonstrating bursting in intact animals will continue to be challenging, since synaptic isolation of a neuron from an area as critical as the preBötC will inevitably lead to the death of the animal (440, 544). Yet, irrespective of the uncertainty as to whether respiratory neurons burst more strongly or more weakly in the intact animal, the types of inward currents that are acutely identified in pacemaker neurons under *in vitro* conditions are likely also present in the intact animal. These inward currents will interact with synaptic and modulatory inputs, following principles that can in part be studied more rigorously in reduced preparations.

Two types of bursting mechanisms in the preBötC

In neurons of the respiratory network, two types of inward currents have received considerable attention (554): the persistent sodium current (I_{NaP}) and the CAN cation current (I_{CAN}). Both currents give rise to autonomous spiking and bursting activity and both currents interact with synaptic and modulatory inputs, which in the functional network contribute to respiratory rhythm generation. The two inward conductances significantly differ, not only in their activation and inactivation properties, but most likely also in their contributions to the formation of the respiratory rhythm (578). Pharmacological approaches help to better define how these conductances contribute to generation of autonomous and synaptically evoked bursting. Neurons in which bursting depends on I_{CAN} stop bursting when exposed to flufenamic acid (FFA), lanthanum (105, 404) or cadmium, a blocker of calcium currents (554). Because of this pharmacological approach, these neurons are referred to as “cadmium-sensitive” (CS) pacemaker neurons (554). Neurons that rely on I_{NaP} to generate bursts continue to do so even in the presence of cadmium and are, therefore, called “cadmium-insensitive” (CI) pacemaker neurons (554).

It is important, however, to emphasize that this pharmacological approach identifies only the inward current that is critical to promote bursting in a given neuron. This does not imply that this inward current is the only inward current that is important in a particular neuron. In fact, the majority of respiratory neurons most likely possess both conductances (103, 105). Thus, CS pacemakers cease to burst following the blockade of I_{CAN} because the unblocked inward currents are not sufficient to promote intrinsic bursting, not because these neurons possess no other inward currents. Figure 4 proposes a cascade of different ionic currents contributing to the generation of bursting in these neurons. Indeed, following the blockade of I_{CAN} 22% of CS pacemakers continue to autonomously generate action potentials (404), most likely because of the presence of I_{NaP}. Moreover, both inward currents very likely interact closely with each other: within the same neuron, as well as within the population of neurons that are involved in the generation of the respiratory rhythm as proposed by modeling studies (558). Mounting evidence from *in vitro* and *in vivo* preparations indicates that respiratory activity persists following the blockade of I_{NaP} and I_{CAN} alone, and ceases only when both mechanisms are blocked (401, 404). Yet, the concept that both inward currents interact and together are critical for respiratory rhythm generation, is not shared by all laboratories in the field. Some laboratories emphasize I_{NaP}-dependent mechanisms (265), while others emphasize I_{CAN}-dependent mechanisms as the driving principle of rhythm generation within the preBötC (105, 392). Based primarily on computational modeling, some believe that I_{NaP} is essential only in the *in vitro*, but not in the *in vivo* network and they dismiss the I_{CAN} altogether (464), while others question the necessity of the I_{NaP} in the *in vitro* network, attributing rhythm generation primarily to I_{CAN}-dependent mechanisms (105, 392). Early characterizations of inward currents in the functional *in vivo* respiratory network provided convincing evidence that I_{NaP} plays a role in amplifying synaptic drive potentials in

medullary respiratory neurons of the intact network (341). Moreover, chelating intracellular calcium as well as elegant voltage- and current-clamp studies showed that calcium-dependent mechanisms that include low- and high-voltage-activated calcium currents and calcium-dependent potassium currents contribute significantly to the shape of ongoing drive potentials and are, therefore, likely to be critical for rhythm and pattern generation (419, 455). Thus, there are many different inward conductances that serve as building blocks of the respiratory network (Fig. 3).

Concluding remarks

The intrinsic firing properties of respiratory neurons are determined by a combination of various distinct inward and outward currents, leading to the phenotypes of silent, autonomous spiking, or autonomous bursting neurons. However, these firing properties are not fixed, but rather are constantly modulated by multiple mechanisms. In the functional network synaptic, intrinsic, and neuromodulatory mechanisms act in concert to promote the generation of respiratory activity. Understanding these intricate interactions requires a thorough understanding of the underlying cellular and molecular properties, as will be discussed in the following sections.

The Inward Conductances Within the Respiratory Network

This section will describe in more detail the physiology, pharmacology, and molecular biology of the inward currents that have been extensively studied within the respiratory network: the voltage-dependent sodium currents, nonselective cation “leak” currents, calcium currents, and calcium-dependent cation currents. Although these currents are described separately, we would like to reemphasize that this should not imply that they also function in separation. There is ample evidence indicating that all three types of inward currents are important building blocks in the generation of the respiratory rhythm.

The persistent sodium current (I_{NaP}) and its role in regulating neuronal excitability

Overview—Voltage-dependent sodium currents (Na_v) play critical roles in the generation of intrinsic excitability and information processing in general. These currents are important contributors to the autonomous generation of action potentials and bursts of activity. Thus, not surprisingly, these currents have received considerable attention, not only in the field of respiratory control, but also in most areas that deal with intrinsically active neuronal networks.

Molecular biology—Na_v channels are composed of a pore-forming α-subunit and one or two associated β-subunits (63, 64). Although nine functional types of α-subunit mRNAs have been identified, only five are expressed within the central nervous system ($Na_V1.1$, $Na_V1.2$, $Na_V1.3$, $Na_V1.5$, and $Na_V1.6$) (113, 175, 176). Single cell RT-PCR reveals the expression of multiple Na_V transcripts in acutely dissociated preBötC neurons from P0-P15 neonatal rats ($Na_V1.1$, $Na_V1.2$, and $Na_V1.6$) (424). Because I_{NaP} likely results from modal gating produced by conventional Na_v channels, any of these transcripts may potentially underlie I_{NaP} in the preBötC. Four different types of β-subunits are expressed in various combinations in different neurons (611, 613). They modify the biophysical and pharmacological properties of the α-subunit and thus seem to play important functional roles (38, 232). Yet, little is known about the role of β-subunits within the respiratory network. In the neocortex, mutations in the β1-gene (SCNA1B) have been associated with epilepsy (580) and the β-subunits seem to confer insensitivity to antiepilepsy drug therapy (567). The cytoplasmic tail of $Na_V\beta4$ acts as an endogenous blocking protein that delays Na_v channels from entering persistent fast-inactivated states by rapid, unstable binding upon activation and unbinding at negative voltages, resulting in a “resurgent” sodium current

upon repolarizations. This resurgent sodium current may mediate rapid repetitive firing in some neurons (8, 16).

Physiology—Na_v currents exhibit two distinct inactivation properties. The fast transiently activated Na_v current provides the initial depolarization of action potentials, while the noninactivating low-voltage-activated persistent Na_v current (I_{NaP}) gives rise to autonomous spiking and bursting. The I_{NaP} contributes to the generation of intrinsic activity in neurons distributed through-out the nervous system (44, 109, 542), and is typically activated at around −60 mV, reaching its peak current amplitude at −40 to −20 mV (7, 60, 103, 250, 321, 328, 424, 574). However, the voltage-operating range within which I_{NaP} is active may be extended to even more negative membrane potentials (opening at −80 mV) in some preparations, such as the presynaptic terminals at the Calyx of Held (221), offering the possibility of a larger influence of I_{NaP} at subthreshold potentials in more situations than were previously appreciated.

Due to its role in generating autonomous bursting, I_{NaP} has been extensively studied in the respiratory network (51, 103, 265, 465). Ptak and colleagues (424) found that the peak persistent sodium conductance, current density, and input resistance of preBötC neurons were greater than in neurons isolated from the neighboring region of the rostral VRG. The properties of I_{NaP} can explain many of the discharge characteristics of autonomously active respiratory neurons. The voltage dependency of the I_{NaP} can, for example, explain why the same neuron can assume different autonomous activity states. As demonstrated experimentally and computationally, increasing I_{NaP} density transitions a neuron from a silent to a bursting state and from a bursting into an autonomously active spiking state (51, 103, 554). Moreover, I_{NaP} density is greater in autonomously bursting neurons when compared to non-bursting neurons (103). However, it must be emphasized that the activity state does not necessarily depend on the absolute persistent sodium current density, but rather on the balance between I_{NaP} and outward leak currents (103, 265, 425).

Pharmacology—I_{NaP} can be blocked with riluzole (568) and low concentrations of TTX (160), which abolishes bursting in the majority of CI bursting pacemaker neurons. However, even with a bath concentration of 20 to 50 μmol/L riluzole plus 200 μmol/L cadmium, 29% of CI pacemaker neurons continue to burst (404). This means that there is currently no pharmacological tool available that blocks all autonomously bursting pacemaker neurons in slice preparations. This has the important, yet often overlooked, implication that no pharmacological approach in slices can prove that pacemaker neurons are not essential. Moreover, even though riluzole blocks 71% of CI pacemakers more than half of them (59%) continue to spike autonomously in the presence of riluzole. Thus, while riluzole reduces the number of bursting pacemakers, this substance can neither block bursting altogether, nor can it eliminate the impact of autonomously generated activity on driving network activity (404). Thus, it is not surprising that focal bilateral microinjection of riluzole into the preBötC fails to block respiratory rhythmic activity (390).

Another reason why it is difficult to test whether I_{NaP} is obligatory for respiratory rhythm generation is the challenge to experimentally separate the transient and persistent sodium currents. Riluzole modulates both of these components to approximately the same degree (424), but preferably binds to and stabilizes Na_V channels in late closed-state conformations, and thus can be used as a pharmacological tool to only preferentially block I_{NaP}, while minimizing the block of transient sodium currents. Yet, while riluzole leads to a relatively greater reduction of the persistent (I_{NaP}) versus transient sodium current component, there cannot be a selective blockade of I_{NaP} alone. The ratio between the blocked persistent versus blocked transient sodium current will be concentration dependent. This is particularly complicated in a slice preparation in which riluzole needs to reach its neuronal target via

diffusion. Thus, pharmacologically applied riluzole (as well as TTX) results in a spatially and temporally nonuniform pharmacological attenuation of I_{NaP} (265). This could explain why in slices respiratory rhythmic activity persists when riluzole is applied alone. Interestingly, one advantage of the respiratory network isolated in the *in situ* preparation is that substances can reach their neuronal targets not just by diffusion, but also via the artificial cerebrospinal fluid (CSF) that is infused into the nervous tissue through the still working heart and blood supply. Thus, limited diffusion is not an issue in this preparation. Importantly, this *in situ* preparation is exquisitely and consistently sensitive to riluzole applications (578). However, this finding seems to not be consistent with a study by St-John et al. (532). These authors found that riluzole does not block eupneic activity.

NALCN may be a significant component of the leak inward current within the preBötC

Another likely source of persistent inward cation current in the preBötC was recently revealed through a series of elegant studies, primarily from the laboratory of Dejian Ren at the University of Pennsylvania, combining molecular cloning and mouse molecular genetics. Lu and colleagues (315) reported the cloning and functional expression of a sodium-leak-channel (NALCN) channel, an unconventional member of the extended 4-domain Na_V/Ca_V gene family, which encodes a TTX-insensitive, nonvoltage-activated, nonselective cation channel. NALCN is evolutionarily conserved, with clear orthologs in *Drosophila (α-1U)* (302) and *Caenorhabditis elegans (nca-1, nca-2)* (518). Mutations of these orthologs in *Drosophila* and *C. elegans* result in behavioral phenotypes consistent with altered neuronal excitability and susceptibility to volatile anesthetics (367, 609). Following heterologous expression in HEK293 cells under bi-ionic recording conditions, NALCN produced constitutive currents with unusual ionic selectivity, conducting Na^+, K^+, and Cs^+ relatively indiscriminately, and to a lesser extent Ca^{2+} [$P_{Na}(1.3) > P_K(1.2) > P_{Cs}(1.0) > P_{Ca}(0.5)$] (315). This current exhibited unusual pharmacological properties, atypical of voltage-dependent Na_V or Ca_V channels. TTX (10 μmol/L) and several conventional organic Ca_V blockers (Nifedipine 100 μmol/L; dialtizem 1 mmol/L) failed to block NALCN currents. In addition, neither Ni^{2+} (1 mmol/L) nor La^{3+} (100 μmol/L) blocked NALCN. However, significant block (80%) was observed with Gd^{3+} (10 μmol/L), verapamil (1 mmol/L), Cd^{2+} (1 mmol/L), and Co^{2+} (1 mmol/L) (315). The sensitivity of NALCN to riluzole has not been reported. Significantly, targeted null mutations of NALCN in mice resulted in animals that died within 24 h after birth, due to an elevated rate of prolonged apneas (> 5–10 s), and, ultimately, respiratory failure (315). En bloc recordings from C4 phrenic nerves of isolated brainstem-spinal cord preparations revealed a 6-fold reduction of expiratory burst frequency in homozygous NALCN KO pups compared to wild type (WT), consistent with a central component to this respiratory defect. A central neuronal defect was further supported by recordings from WT and NALCN KO hippocampal neurons, which showed that NALCN underlies a native persistent inward current, which contributes a approximately 10 to 20 mV depolarization to WT resting membrane potentials (315).

As will be discussed in more detail below, neuromodulation is critical for sustaining respiratory rhythms in the preBötC (186) and regulating the state dependence of the respiratory neural network. Interestingly, NALCN activity is profoundly regulated by several G-protein coupled receptors (GPCRs), including the Neurokinin-1 receptor (NK1) that binds Substance P, the M3 muscarinic receptor, and the CaSR receptor that senses extracellular Ca^{2+} (315, 316) (267, 540). Activation of NK1 or M3 receptor greatly augments NALCN currents through an unconventional signaling pathway that utilizes a Src family kinase (SFK), instead of heterotrimeric G-proteins. This signaling pathway is absolutely dependent upon the assembly of the NALCN channel protein with UNC-80, a conserved intracellular scaffolding protein first discovered in *C. elegans* (491), into a functional signaling complex (316, 540) (Fig. 15). By contrast, activation of CaSR by

normal levels of extracellular Ca^{2+} (2.0 mmol/L), signals to inhibit NALCN through a conventional G-protein pathway, but again requires the assembly of NALCN with UNC-80 and a second related scaffolding protein, UNC-79 (317) (Fig. 15). Significantly, UNC-79 KO mouse lines also die perinatally, within 48 h of birth, and exhibit the same symptoms of respiratory failure as NALCN KO mice, although less severe. Independently, a forward genetic screen in mice also identified a dominant mutant allele of *unc-79 (Lightweight)* that dies perinatally as homozygous mutants. When assayed as heterozygous adults, these mutants exhibit altered sensitivity to acute isoflurane anesthesia and ethanol intoxication (525).

Taken together, these studies suggest that NALCN may contribute to a critical persistent inward cation current in respiratory neurons in the preBötC that is highly susceptible to regulation by neuromodulators are essential for sustaining respiratory rhythms. This channel may have gone unrecognized by earlier studies, due to the limitations of existing pharmacological tools. Further electrophysiological studies with preBötC slice preparations from NALCN and UNC-79 mutant mouse lines may prove highly revealing.

Voltage-dependent calcium currents and their roles in regulating respiratory network activities

Overview—Until early 2000 most studies using respiratory rhythmic brainstem slice preparations assumed that the persistent sodium current (I_{NaP}) was the major inward current responsible for generating autonomous pacemaker activity in respiratory neurons (103,331). Moreover, modeling studies provided convincing arguments that a rhythm could emerge through the activation and inactivation properties of I_{NaP} in these neurons (51, 102). The focus on I_{NaP} in *in vitro* studies created the impression that a *"simple"* respiratory rhythm is generated under *in vitro* conditions which emerges entirely through the persistent sodium current, a conclusion that is still implied by some studies (464). Yet, also for the *in vitro* network, it should be obvious that calcium currents play critical and heterogeneous roles. Calcium-sensitive dyes reveal that during periods of spontaneous bursting, Ca^{2+} concentrations within pacemaker neurons rise as Ca^{2+} ions enter through voltage-sensitive ion channels (265), and intrinsic calcium oscillations have been found in respiratory neurons (347). Not only *in vitro*, but also many *in vivo* studies indicate that voltage-dependent calcium currents and calcium-dependent mechanisms regulate various important aspects of respiratory rhythm generation (419, 450, 451). Some of the roles for calcium currents will be reviewed in this section. Molecularly, all voltage-dependent Ca^{2+} channels (Ca_v) contain a pore-forming α1-subunit that determines their main biophysical and pharmacologic properties. There are three major families of α1-subunits that contribute to the L, P/Q, N, R, and T-type calcium currents (22, 121, 156, 445). The R-type channels are known to contribute to exocytosis at many synapses (6, 246), including the mossy fiber-CA3 synapse in the hippocampus (169). But, to the best of our knowledge, the role of the R-type calcium current in the neuronal control of breathing remains unknown. Because it is very likely that this current also plays an important role in regulating respiratory activity, this issue clearly-deserves more in-depth studies.

The L-type channels—The L-type channels belong to the Ca_v1 subfamily. These channels have slow activation and inactivation kinetics (156, 301). For $Ca_v1.3$, it has been shown that it is involved in generating pacemaker activity in the substantia nigra (427), but it is unlikely that this subunit plays a critical role in generating autonomous pacemaker activity in the respiratory network. However, L-type calcium currents may still contribute to the generation of autonomous pacemaker activity. In the functional respiratory network, L-type calcium channels amplify drive potentials and increase spike frequency in some but not all respiratory neurons (297, 384). Calcium influx though L-type calcium channels is known

to increase during hypoxia in respiratory neurons (349, 351). This effect could potentially contribute to the augmentation seen during the initial phase of hypoxia (407).

Three respective members from the Ca_V2 subfamily contribute to the P/Q-, N-, and R-type calcium currents. Although the activation and inactivation kinetics of these channels are very similar, these channels are characterized by their differential sensitivity to blockade by a variety of biological toxins (307, 376, 383, 505). All of these antagonists act on the channels from the outside of the cell membrane.

The α1A (Cav2.1)-containing (P/Q-type) calcium channels—P/Q-type channels are sensitive to specific spider toxins (ω-Agatoxin IVA or TK) (346). These channels were first identified in Purkinje cells (307). They are expressed in the dendrites (215) and soma (346), where they play an important role in controlling the action potential firing rate (275, 570). As shown, for example, in other systems, P/Q-type channels can contribute to bursting in Purkinje cells (155) and other neurons. Within the respiratory network, P/Q-type calcium channels trigger neurotransmitter release at central excitatory synapses (297). Interestingly, the effect of P/Q-type calcium channel blockade was variable, as excitatory post-synaptic potential (EPSP) amplitudes were reduced in some respiratory neurons by only 8% and in others by more than 90%, suggesting that only a subset of excitatory synaptic connections within the respiratory network depends primarily upon P/Q-type channels (Fig. 6C). This finding may have important systems-level implications, because the P/Q-type channel blocker ω-agatoxin TK completely abolishes sigh generation at concentrations that do not eliminate normal respiratory activity in the preBötC (297). This raises the possibility that within the respiratory network, a subnetwork consisting of P/Q-type calcium-channel-dependent excitatory synapses may be critical for the generation of sighs (296, 297). Moreover, this subnetwork possesses metabotropic glutamate (mGluR8) receptors coupled to these P/Q-type Ca^{2+} channels (Fig. 6D,E). But, P/Q-type channels are not only involved in the generation of sighs. These α_{1A} ($Ca_V2.1$)-containing channels also augment the amplitude and duration of drive potentials of preinspiratory and inspiratory neurons, which in turn increases spike frequency during the respiratory burst (297, 384). P/Q-type calcium channels also contribute to an increased regularity of normal respiratory activity. Thus, P/Q-type channels serve a modulatory role for normal respiratory activity, and apparently are essential for the generation of sighs (297).

The α1B (N-type) calcium channels—N-type channels are not just modulatory, but essential for generating normal respiration (eupnea) *in vivo*. Acute blockade of the N-type calcium channel within the preBötC abolishes eupneic activity *in vivo* (440). By contrast, in *in vitro* systems, rhythmic respiratory activity persists following the blockade of N-type calcium currents with bath-applied ω–conotoxin GVIA (297). In the *in vitro* network, N-type calcium currents contribute to only 40% of the amplitude of glutamatergic EP-SCs generated between respiratory preBötC neurons (297). It is possible that the *in vivo* network depends more on N-type calcium-dependent synaptic mechanisms than the *in vitro* respiratory network. Although unproven, this hypothesis would be consistent with the idea that synaptic mechanisms are more important in the *in vivo* network, as proposed in the computational study by Rubin et al. (463). But many other possible reasons could explain the differences. These experiments were performed at significantly different ages (neonatal *in vitro* vs. adult *in vivo*) and species (mouse *in vitro* vs. cat *in vivo*).

N-type calcium currents activated during each action potential significantly influences their width and shape. The shape of action potentials in turn directly correlates to the amount of neurotransmitter release in presynaptic terminals. Calcium influx through N-type calcium currents also activates large (BK) and small (SK) conductance calcium-dependent K^+ channels (K_{Ca}) (26, 27, 326) or CAN cation channels. The coupling between N-type calcium

current and K_{Ca} currents could explain why respiratory frequency increases *in vitro* upon blockade of N-type calcium currents (297, 384). Block-ade of N-type calcium channels also increases the frequency of sigh activity, an effect associated with the elimination of the post-sigh apnea (297). Blockade of N-type calcium channels also augments respiratory drive potentials, which suggests that K_{Ca} currents play critical roles in shaping drive potentials *in vitro* (297, 384, 616). This conclusion is consistent with insights gained from the *in vivo* respiratory network. Under *in vivo* conditions, buffering intracellular calcium with 1, 2-bis(o-aminophenoxy)ethane-N,N,N′,N′- tetraacetic acid (BAPTA) resulted in blocking potassium currents. This revealed that intracellular calcium is important for activating calcium-dependent potassium currents that play critical roles in shaping the drive potentials of expiratory neurons (66, 451). These calcium-dependent mechanisms also seem to constitute an important off-switch mechanism involved in phase termination (416, 439, 451), but the molecular or pharmacological identity of these calcium channels remains unknown under *in vivo* conditions.

The Ca_V3 family encodes T-type channels—The T-type channels (Ca_V3) are located both on and near the soma and at more distal dendritic sites and can be detected in all brain regions including the neocortex, hippocampus, thalamus, cerebellum, and inferior olivary nucleus (244, 333, 485, 579). T-type channels have several unique properties that allow them to mediate pacemaker activity and rhythmic burst firing, as has been demonstrated in thalamic relay neurons (86, 226, 329, 536). However, so far no one has demonstrated this type of autonomous bursting activity within the respiratory network. But this does not mean that T-type calcium currents play no role in respiratory rhythm generation. Respiratory neurons within the preBötC possess T-type calcium currents (127, 385). Indeed, within the same anatomical location, the preBötC, rhythmic respiratory neurons express a larger T-type conductance compared to neurons not rhythmically active with respiration (126). When the resting membrane potential is below −70 mV, neurons expressing T-type currents can generate a high-frequency burst of action potentials (86, 234, 305). For medullary respiratory neurons, it was demonstrated that synaptic mechanisms are critical for removing inactivation from low-threshold calcium currents, which enables rebound excitation in inspiratory, as well as expiratory, neurons *in vivo* (419, 439, 451). This rebound depolarization persists after intracellular blockade of sodium currents, which demonstrates that they are mediated by calcium currents (451).

A new and exciting twist with regard to T-type calcium channels is their functionally significant window current. Although not shown for respiratory neurons, the window component of the T-type current can significantly contribute to the resting membrane potential of thalamic neurons, as well as to the up state of intrinsically generated slow oscillations (114). Moreover, in this study it was possible to evoke bursts of action potentials at depolarized potentials, where the majority of T-type calcium channels are known to be inactivated (114). This may also have important functional implications for the respiratory network, as rhythmically active preBötC neurons are characterized by a large T-type conductance with a large window current (126).

Calcium-activated nonselective cationic currents (I_{CAN}) and their roles in rhythm generation and neuromodulation

Overview—Until a decade ago, no model of respiratory rhythm generation considered I_{CAN} as a major cellular mechanism, and it was assumed that bursting in autonomous pacemaker neurons is primarily driven by the voltage-dependent characteristics of the persistent sodium current (I_{NaP}) (51, 102). While voltage-dependent calcium currents (Ca_V)were known to play critical roles in synaptic transmission and amplifying synaptic inputs, calcium-dependent mechanisms were thought to be modulatory in nature in

pacemaker neurons. The first indication that calcium-dependent mechanisms could also be critical for autonomous bursting came with the discovery that pacemaker neurons cease to burst in the presence of cadmium, a blocker of Ca_v (554). However, it was not possible to unambiguously link this bursting property to a specific voltage-dependent calcium channel, as this autonomous bursting was not reliably blocked by specific blockers of the L-, N-, P-, or Q-type calcium currents. It was subsequently demonstrated that bursting ceases in most (82%) CS pace-maker neurons in the presence of FFA and lanthanum (404). Because these substances block I_{CAN}, it was concluded that I_{CAN} gives rise to bursting in this type of pacemaker neuron (404). But it must be emphasized that FFA does not abolish bursting in 100%ofCS pacemakers, an important caveatwhen assessing the obligatory role of I_{CAN} (105, 554). Subsequent studies confirmed that I_{CAN} is critical for bursting in CS pace-maker neurons (105, 404), and attributed I_{CAN} as a major burst mechanism involved in amplifying synaptic drive potentials (392, 462).

I_{CAN}-type currents have been described in a variety of nonneuronal cells (81, 327) as well as neurons (82, 108, 397). Because I_{CAN} does not inactivate, it is ideal for promoting bursts and long-lasting plateau potentials (107, 359). I_{CAN} is calcium dependent, and may not be directly depended on membrane voltage to be activated. However, I_{CAN} is indirectly affected by voltage, because various Ca_v currents contribute to intracellular calcium currents and thus to the activation of I_{CAN} (282, 397). In addition, I_{CAN} can be activated by calcium released from internal stores (347). A recently published computational model by Toporikova and Butera (558) suggests that intracellular calcium oscillations may give rise to the autonomous bursting of CS pacemaker neurons, an interesting hypothesis that will need to be tested experimentally. Experimental evidence for intracellular dendritic calcium waves was demonstrated in isolated neurons from the preBötC. These calcium waves activated TRPM4/5 channels within the somatic compartment (347). These intracellularly generated calcium waves were facilitated by depolarization and activation of mGluR1/5 (347).

Molecular biology—I_{CAN} was identified pharmacologically in respiratory neurons and its molecular identity is still somewhat uncertain. But it is very likely this channel belongs molecularly to the *transient receptor potential* (TRP) family (21, 89). TRP channels consist of six transmembrane spanning segments (S1-S6) and a cation permeable pore (S5-S6) (345). The family of TRP channels is diverse, with seven subfamilies, six of which are functional in various mammalian tissues including nervous tissue (372). Within the brain, various forms of TRP channels are involved in temperature sensing (62), taste (622), hearing, and mechanosensation (88). They have also been implicated in neuronal outgrowth (TRPM7) (1) and cell survival (TRPC5) (189). In addition, a number of studies show that postsynaptic currents evoked by metabotropic glutamate receptors (mGluR1) are carried by TRPC1 channels, suggesting a role in synaptic plasticity and neuromodulation (23, 256, 560). The role of TRP and metabotropic receptors in neuromodulation will be discussed in a later section that describes in more detail interactions associated with G-protein coupled receptors.

It is possible that different isoforms of the TRP family contribute to different aspects of I_{CAN} within the respiratory network. It has been demonstrated that TRPM4 is regulated by phosphatidylinositol 4,5 (PIP_2), and that intracellularly applied PIP_2-analogues augment the inspiratory drive potential in respiratory neurons. Together with the observation that drive potentials are sensitive to FFA, this set of studies suggested that I_{CAN}, in the form of TRPM4, plays a critical role in boosting excitatory drive in respiratory neurons (89, 248, 371). Consistent with this hypothesis, some studies indicate that TRPM4 as well as TRPM5 is expressed in the preBötC. How-ever, Ben-Mabrouk and Tryba (21) were unable to reproduce expression of TRPM4 in Western Blots taken from the area that generates respiratory rhythmic activity. This negative result could have various methodological

reasons, as discussed by Ben-Mabrouk and Tryba (21), thus, single-cell RT-PCR approaches taken specifically from respiratory neurons may shed more light on this unresolved issue. In a characterization that focused on the modulation of respiratory activity by substance P, Ben-Mabrouk and Tryba (21) proposed that I_{CAN} depends on TRPC3 or TRPC7 channels. According to this study, the antagonist (SKF-96365) blocks NK-1 receptor activation by substance P, presumably via a blockade of TRPC channels. SKF-96365 specifically blocked the effects of substance P on CS pacemakers, further supporting the notion that TRPC channels may play a critical role in the NK1-mediated modulation of I_{CAN}-dependent bursting in pacemaker neurons.

Contribution of different inward currents to the onset of a respiratory cycle

While in the previous sections the different inward currents were separately discussed, they will likely all contribute to the onset of a respiratory cycle. This section will consider these currents in a more functional context.

Contribution of I_{NaP}-dependent bursting mechanisms to the onset of a respiratory cycle—I_{NaP}-dependent bursting neurons (CI pacemakers) were extensively studied in transverse slice preparations and their bursting characteristics simulated in computational models (51, 103–105, 268). According to these combined studies, I_{NaP} inactivation contributes to the termination of the burst. The slow kinetics of the recovery from this inactivation seem to determine the timing of burst onset. In the functional network, excitatory and inhibitory synaptic inputs and other inward and outward currents will influence this voltage-dependent recovery process. Synaptically evoked inputs will be able to slow or protract the recovery from inactivation, and an I_{NaP}-dependent intrinsic burst will be triggered either earlier or later in the respiratory cycle or not at all. Thus, the amount of synaptic excitation needed to trigger a protracted burst will depend on the inactivation state of the I_{NaP} current, but also on the presence and strength of other inward and outward currents that also will be described in this review. It will also depend on the amount of concurrent inhibition that these neurons receive. Immediately following a network burst, the threshold for activating the intrinsic burst will be highest and thus the probability for intrinsic bursting to contribute to the initiation of an inspiratory burst will be very small. But as time following the network burst increases, the likelihood that an I_{NaP}-dependent burst will be activated will also increase. This may explain why in autonomously bursting neurons ectopic bursts are often generated prior to the subsequent population burst (143, 404, 563). Assuming that bursting neurons are embedded in the respiratory network, these ectopic bursts may contribute to the initiation of the network burst (442). But to tease apart to what extent an ectopic burst is generated intrinsically or synaptically is difficult and it is most likely that the threshold for synaptic or intrinsic activation of a burst will vary among individual neurons and even individual respiratory cycles. The amount of available I_{NaP}, the inactivation status, the amount of synaptic inputs, and the location of ion channels and synaptic receptors on the dendrite and soma of the respiratory neurons will not be the same for any given neuron at any given time. This also explains why ectopic bursts are generated in some but not all neurons during some but not all respiratory cycles. This leads to another important conclusion. Bursting could potentially act as a nonlinear amplifier in some cycles and an initiating mechanism in other cycles, and the onset of each population burst will depend on the overall integration of all these intrinsic and synaptic factors at the cellular and network level. Thus, it will be impossible to know which neuron and what mechanism will contribute to what degree to the onset of the inspiratory activity at any given respiratory cycle. We conclude that there will unlikely be a situation in which a cycle onset will be purely determined synaptically or intrinsically, or only by one particular mechanism.

Contribution of I_{CAN}-dependent bursting to the onset of a respiratory cycle— While voltage-dependent properties are largely responsible for determining I_{NaP}-dependent bursting as described earlier, there are different parameters that determine the activation of I_{CAN}-dependent bursting. Indeed, much is already known about the various synaptic and metabotropic determinants (89, 100, 347, 392, 442). In principle, the onset of an I_{CAN} burst will be determined by an increase in intracellular calcium that will lead to the opening of TRP channels, which then results in the depolarizing influx of Na^+ (101). In addition to the spontaneous activation of intracellular dendritic calcium waves, as demonstrated in the dendrites of respiratory neurons (347), many processes are known to raise intracellular calcium and will, therefore, contribute to the opening of TRP channels. mGluR 1/5 receptors seem to be important for the activation of these calcium waves that in turn activate I_{CAN} (347). In one of the later sections, we will discuss in more detail various neuromodulators that have been implicated in the activation of channels in the TRP superfamily. Moreover, every action potential will open voltage-gated calcium currents. It follows that CS pacemaker neurons and I_{CAN} activation in general will have some voltage-dependent properties even though the TRP channels. However, the voltage dependency of the CS bursting may be different from that of CI bursting or the functionally activated I_{NaP} inward current (434). Action potentials generated during the population burst will create sufficient calcium influx to contribute to the activation of I_{CAN} current. Indeed, calcium-imaging studies have demonstrated that substantial and widespread somatic Ca^{2+} influx is generated by TTX-sensitive action potentials (358), which seem to complement the intrinsically generated dendritic calcium waves (347). Thus, the excitatory synaptic input contributes to the triggering of the I_{CAN} burst, in part through voltage-gated calcium currents that are activated by action potentials.

Contribution of a background current to the onset of a respiratory cycle— Bursting pacemaker neurons are continuously depolarized by a sodium-dependent background current that renders them spontaneously active (77, 566). This background current will contribute to the generation of action potentials that will intrinsically ramp up prior to the I_{CAN}-dependent burst. Assuming that approximately 50% of bursting neurons are excitatory (357), this intrinsic background current will contribute to an intrinsically generated ramp-up of EPSPs preceding the population burst (101). This ramp occurs not only from bursting pacemakers, but also from the numerous autonomously spiking neurons within the respiratory network. Clearly, in the functional network, spike generation will never be purely intrinsic, as autonomous spiking will evoke synaptic events in postsynaptic neurons. Thus, the onset of the respiratory cycle constitutes a synergy between intrinsic voltage- and calcium-dependent and synaptic mechanisms.

Contribution of calcium and other inward currents to the onset of respiratory cycle—Once initiated, the respiratory burst will bring the membrane potential to the voltage range that will also activate other voltage-dependent ionic conductances and channels, including the transient I_{Na} currents and the various voltage-gated calcium currents (P/Q-, L-, and N-type calcium channels) that were discussed in prior sections. The depolarization by these voltage-gated channels may suffice to remove Mg^{2+} block leading to the voltage-dependent opening of the NMDA receptor (NMDA-R), thus further contributing to the amplitude of the burst (439). The generation of the burst will become regenerative, as any of these currents will elevate the membrane potential to a level that will open more voltage-gated ion channels, which in turn will raise the calcium levels, which then will increase the activation of I_{CAN}. The earlier detailed cellular considerations focus on the generation of the inspiratory burst within the preBötC. But the reader should be reminded that this will be only one aspect in the generation of the respiratory rhythm. A very elegant study by Paarmann described in detail how different types of NMDA-R splice variants have

different deactivation kinetics in different regions of the medulla, which may have interesting functional implications (388, 389). Moreover, the exact type of NMDA-R subunit activated within the preBötC may change during development, which could also have functional consequences (303). In addition, it is known that NMDA-R play widespread differential roles in the generation of the respiratory rhythm (61, 84, 146, 154, 356, 417, 418) and the hypoxic response (382). Although, the ongoing quest for the obligatory mechanisms has demonstrated that NMDA-R are not essential for functional respiratory rhythm generation (164), it should be clear that these receptors are important building blocks in the generation of the respiratory rhythm, chemosensation, and motor patterning.

Concluding remarks—Several inward currents are important for the function of respiratory activity. These include not only voltage gated sodium and calcium currents (i.e., I_{NaP}), but also voltage-insensitive conductances (i.e., background currents, and leak channels). Inward currents have distinct activation and inactivation properties that have different functional consequences on the firing pattern of respiratory neurons. Although these properties shape the firing properties at the cellular level, they will ultimately affect the network output, which in turn will contribute to the generation of the different patterns of respiratory activity (i.e., eupnea, gasping, and sighs). Yet, our understanding of the functional integration of these cellular properties is still incomplete. While some currents, such as the I_{NaP} current, were extensively studied, we have much to learn about the integration of the different TRP channels and the NALCN current, and as yet nothing is known about the R-type calcium currents.

Potassium Currents and Their Contribution to Respiratory Rhythm Generation

The balance between inward currents as described in the Section “The Inward Conductance Within the Respiratory Network” and a large catalog of outward currents determines how a neuron drives synaptic and modulatory activity, and how it responds to its synaptic and modulatory inputs. As will be discussed in this section, potassium channels play critical roles in this complex and dynamic interplay. Potassium currents are known to determine key aspects of neuronal excitability, including basal subthreshold membrane potential, the shape of the repolarizing phase of action potentials, and the envelope of action potential bursts. Thus, potassium channels are expected to play equally important roles in respiratory rhythm generation. However, we are just beginning to appreciate the full extent of their numerous contributions. Initial studies of respiratory brainstem neurons relied nearly exclusively upon the application of various potassium channel blockers, many of which, however, offer relatively poor molecular specificity. More recently, molecular genetic approaches have been applied to identify and manipulate specific potassium channel genes, especially by employing genetically engineered mouse strains. Nonetheless, significant challenges remain in linking the role of individual potassium channels to the macroscopic electrical behavior of a circuit as complex as the respiratory network, even in its reduced form in the isolated brain slice. These challenges include the neuronal heterogeneity of circuit elements involved in rhythm generation, their potential redundancies, and the relative paucity of information about the detailed microcircuitry between these circuit elements. The development of further experimental tools, including additional molecular markers for specific key circuit elements, will undoubtedly help to overcome these challenges in the future.

Although, it is well established that the isolated preBötC can generate respiratory rhythmic activity at physiological potassium concentrations (165, 459, 460, 516, 564), isolated slices are usually investigated at elevated external $[K^+]o$, typically between 5 and 9 mmol/L. A number of studies have suggested that raising external $[K^+]o$ alters the balance between

potassium leak channels and sodium leak channels constitutively open at subthreshold membrane potentials (265, 390, 468). Elevated external $[K^+]o$ would be expected to depolarize the potassium reversal potential, thus reducing the normal driving force for a hyperpolarizing outward potassium conductance through an open potassium leak channel. In combination with a countervailing depolarizing drive from an inward sodium leak current, this reduction of potassium conductance may provide sufficient basal excitation to trigger additional cellular and/or circuit mechanisms to generate sustained patterned neuronal output. Support for this hypothesis is provided by computational and pharmacological studies of the preBötC circuit (468). A network model of 50 interconnected excitatory neurons (no contributions from inhibitory neurons was considered in this model) was simulated with varying ratios of potassium and sodium leak conductance, and subjected to a simulated step elevation in external $[K^+]o$. Computationally, synchronized network bursting was found to be triggered within a narrow window of elevated $[K^+]o$ (5–9 mmol/L), primarily determined by the ratio of potassium (g_K) to sodium leak (g_{Na}) conductance, and the size of excitatory synaptic conductance (g_{Edr}). This computational model was supported by experimental recordings from preBötC slices. Experimentally, rhythmic respiratory bursts were extracellularly recorded from slices in 7 mmol/L $[K^+]o$, then silenced in 3 mmol/L $[K^+]o$. Extracellular recorded rhythms could be subsequently reestablished by blocking potassium channels with [4-aminopyridine (4-AP), 100 μmol/L, or tetraethylammonium (TEA), 4 mmol/L]. Conversely, application of riluzole (25–50 μmol/L), a blocker of I_{NaP}, was sufficient to abolish rhythmicity. These experimental results were incorporated into a computational model that suggested that neuronal potassium and sodium leak conductances are critical determinants of preBötC rhythmicity. While this generalized conclusion is certainly correct, it must be emphasized that pharmacological blockade of all potassium channels can provide only a very coarse insight into the complex dynamics of potassium currents interacting with other membrane and network properties, in particular, because this study was based only on extracellular recordings. Unfortunately, this and many subsequent computational studies often overlooked important experimental evidence that could have provided a more refined view of network and pacemaker activity. As shown in Figure 7, pacemaker neurons possess a background Na^+ current which stabilizes their bursting activity against changes in extracellular K^+ currents. As shown in this figure, the pacemaker neuron can burst at 3 mmol/L extracellular K^+ (Fig. 7A,B) and its bursting does not change much when the extracellular K^+ concentration is raised to 8 mmol/L. This current can be revealed by long-lasting hyperpolarizing current injections (Fig. 7C). In response to this imposed hyperpolarization, the neuron ceases to burst, but as it depolarizes intrinsically bursting is resumed. Thus, unlike the neurons proposed in various computational models, biological pacemaker neurons do not require artificial elevation of extracellular potassium to autonomously burst (77, 564, 566). In the following section, we aim at providing a detailed overview of the role of potassium outward currents and their dynamic and complex interplay with inward currents.

Molecularly, potassium channels from the “two-pore” potassium channel gene family (177, 290) may encode, at least in part, the potassium leak conductance observed in neurons of the respiratory network. Voltage-clamp recordings from inspiratory preBötC neurons identify an outwardly rectifying, halothane-sensitive potassium leak current, and single cell RT-PCR reveal the presence of TASK1 and TASK3 potassium channel transcripts, consistent with this possibility (264). However, these results do not preclude the possibility that other “two-pore” subunits, or other classes of subthreshold potassium channels such as inward rectifiers (K_{IR}) may also contribute to the potassium leak current. Their potential roles in central chemosensitivity will be discussed later.

Voltage-dependent potassium currents can be broadly classified into noninactivating “delayed rectifier”-type (K_{DR}) and transient “A-type” (K_A) currents (192, 214, 612). 4-AP

preferentially blocks K_A currents, although a subset of noninactivating K^+ potassium channels encoded by *K_v3* genes are equally sensitive to blockade by 4-AP (447, 591). K_A currents were observed in inspiratory preBötC neurons, at a higher frequency than expiratory neurons (205). Space-clamp limitations precluded detailed biophysical analysis of this current in all whole-cell recordings, but steady-state activation and inactivation profiles of this current in well-clamped excised inside-out patches are consistent with potassium channels encoded by $K_v4.2$ or $K_v4.3$. In slice preparations, 4-AP reversibly broadens the width of individual action potentials and shortens the latency to first spike, in response to step injections of depolarizing current. Dramatically, in slices generating fictive eupneic rhythms, 4-AP disrupts the regularity of population bursts by inspiratory preBötC neurons (both amplitude and frequency are affected), as well as the efficacy of transmission of respiratory drive to downstream hypoglossal motor pools. The authors suggest that K_A currents in inspiratory neurons serve to buffer excitability against sporadic excitatory input. This allows neurons to respond only to highly synchronous and sustained excitatory synaptic input. Knock-out mouse strains for $K_v4.2$ and $K_v4.3$ are available (374, 375), but to our knowledge no obvious respiratory defects have yet been described.

DR-type K^+ channels

A large number of potassium channel species may underlie DR-type potassium currents (K_{DR}) in the preBötC, including members of the voltage-dependent *K_v1*, *K_v2*, and *K_v3* gene families among others (214, 470, 592), but few detailed molecular examinations specific for the preBötC exist yet in the literature. Among K_{DR} currents that may be found in preBötC, two non-K_v channels deserve particular notice. Because of the large and dynamic influxes of Na^+ and Ca^{2+} in respiratory neurons with underlying regular bursting potentials, repolarizing potassium channels sensitive to changes in the internal concentrations of these cations may play a particularly important role in shaping and terminating burst potentials. Two such potassium channels are large-conductance calcium-dependent potassium channels (BK-K_{Ca}) [composed of KCNMA1 (Slo1) α-subunits and KCNMB1-4 (BK-β) β- subunits], and sodium/chloride-dependent potassium channels (K_{Na}) [encoded by KCNT1 (Slo2.2 or SLACK) and KCNT2 (Slo2.1 or SLICK) α-subunits, in homo- or heteromeric combinations] (29, 52, 471, 615). Both BK-K_{Ca} and K_{Na} channels are widely distributed in the brain, and found in high abundance in the brainstem (29, 30, 116, 125, 260). The role for BK-K_{Ca} channels in preBötC activity was investigated with the highly selective BK-K_{Ca} blocker, paxiline (616, 619) and the less well-characterized BK-K_{Ca} activator NS-1619 (616). Blocking BK channels with paxiline significantly pro-longs the length and frequency of burst potentials in both autonomous pacemaker and nonbursting neurons recorded from the preBötC in synaptic isolation by a cocktail of postsynaptic blockers (blocking glutamatergic, GABAergic, and glycinergic receptors). Paradoxically, the BK-K_{Ca} activator, NS-1619, under similar conditions, also increases both duration and frequency of bursts in both neuronal types, for still unknown reasons. Interestingly, in preBötC slices neither pharmacological manipulation of BK-K_{Ca} channels dramatically altered measured parameters of fictive eupneic or hypoxic respiratory rhythms. This suggests that despite the ability of BK-K_{Ca} channels to shape the electrical properties of individual isolated neurons, in the context of intact preBötC circuits these perturbations are buffered by other compensatory cellular or circuit-wide mechanisms. More dramatic effects on fictive eupneic rhythms were reported with the application of quinidine (100 μmol/L), a nonselective blocker of K_{Na} channels (269, 606). Bath application of quinidine completely silenced eupneic bursts in a reversible fashion, concomitant with an approximately 14 mV depolarization of resting potentials in preBötC neurons. In synaptically isolated neurons, quinidine augments the size and slows the subsequent repolarization to a baseline potential of bursts, in response to step injections of depolarizing current. These results should be interpreted with caution because quinidine has been shown to be a broad spectrum K^+-

channel blocker (150, 209). In another study, voltage-clamp recordings, in combination with gene-specific siRNA knockdown transfections, from a variety of cultured neuronal cell types (olfactory mitral cells, striatal medium spiny neurons, and cortical pyramidal cells) indicate that a large component of noninactivating K_{Na} current is widely present in most neurons, spatially coupled to I_{NaP} provided by TTX-sensitive Na_V channels (47). Therefore, it would not be unreasonable to suspect that K_{Na} channels may play a major role in shaping respiratory rhythms. However, the findings of Krey et al. (269), as the authors note, need to be interpreted with caution because quinidine is a highly nonselective pharmacological agent, which can effectively block many species of potassium channels even at the relatively low concentrations used. Mouse knockout strains for Slo1 (339, 477) and Slo2.2 (Salkoff, unpublished) have been created that may be used to more directly address their roles in preBötC circuitry, but to the best of our knowledge, no specific respiratory defects have yet been described.

One other K_{DR} channel gene deserves note. This is the *KCNQ2* gene, which is a member of the five gene family in vertebrates (KCNQ1-5) (71, 271, 289, 487, 512, 581, 582, 607). This gene family encodes subunits that combine in homo- and heteromeric fashion to assemble "M-type" potassium channels (K_M) (42, 43). These potassium channels, by virtue of their unusually slow kinetics of activation and deactivation and relatively hyperpolarized conductance-voltage profiles, are thought to be major stabilizers of basal neuronal excitability. In addition, KCNQ potassium channels are exquisitely sensitive to modulation by various intracellular signaling pathways, including most prominently those coupled to muscarinic receptors. Consistent with their general importance, human mutations of four *KCNQ* genes (KCNQ1-4) are associated with a variety of hereditary diseases including epilepsy (Benign Familial Neonatal Convulsions or BFNC; KCNQ2, KCNQ3), long-QT syndrome (LQT1; KCNQ1), and congenital progressive deafness (nonsyndromic sensorineural deafness type 2 or DFNA2; KCNQ4) (238, 288, 534). Watanabe et al. (589) described a mouse knockout strain of KCNQ2 that exhibits hypersensitivity to epileptogenic drugs, when assayed as heterozygous individuals carrying only one functional copy of the gene. Interestingly, all homozygous KO neonates die within 24 h of birth due to pulmonary atelectasis and apparent respiratory failure. Whether respiratory failure can be attributed to a central defect in brainstem patterning mechanisms remains unexamined, to our knowledge. However, there is an increasing awareness that human epileptic patients suffer from a collateral risk of sudden unexpected death (SUDEP) at rates 24 to 40 times higher than the general healthy population (148). The underlying causes of SUDEP remain unknown. Conceivably, KCNQ2 may play a critical role in both cortical circuits controlling epilepsy and brain-stem respiratory neurons, and thus provide a mechanistic link between these two neural dysfunctions.

Small-conductance calcium-dependent K^+ Channels (SK-K_{Ca})

Respiratory phenotypes have been explicitly examined in several other mutant mouse strains engineered to delete or alter the expression of specific classes of potassium channels. These include apamin-sensitive SK3 potassium channels (34), neuronal ATP-sensitive potassium (K_{ATP}) channels formed by Kir6.2 (343, 353) and SUR1 subunits (4, 230), and pH-sensitive inward rectifier (Kir2.2; 387) and "two-pore" potassium channels [TASK1, TASK3; (363); TASK2, (172)]. In general, none of these genetic manipulations of single potassium channel genes yielded overtly catastrophic respiratory phenotypes, as all strains were viable, even if mutant phenotypes were observed in the context of isolated preBötC slices or single neuronal recordings. This may reflect the intrinsic subtlety or redundancy of control exerted by individual potassium channels within the intact preBötC respiratory circuit.

SK3 encodes one of four mammalian subunits that form nonvoltage-dependent, calcium-dependent SK potassium channels (SK1-4) (33, 263). Bond et al. (34) engineered a strain of

mice with a tetracycline-based genetic switch inserted into the 5' untranslated regulatory region of the *SK3* gene. This permitted conditional overexpression of SK3 under the control of its native promoter, triggered by the withdrawal of doxycycline (dox) chronically administered by feeding. Animals thus induced to overexpress SK3 were found to have a compromised response to moderate hypoxia (8% O_2), assessed by whole animal plethysmography. WT animals respond to this moderate hypoxic challenge with an elevated rate of breathing (~150 inspirations/min), but SK3 overexpression severely blunted this response (~55 inspirations/min) and produced prolonged periods of apnea. This effect was entirely reversible by reestablishing chronic dox treatment and shutting off SK3 overexpression. Although SK3 is abundantly expressed in brainstem structures including the preBötC, expression is also found in many non-neural tissues. Thus, these respiratory effects could result from either peripheral or central mechanisms mediated by SK3. Evidence supporting a central role for SK-type potassium channels in the generation of respiratory rhythms came from pharmacological studies with *in vitro* preBötC slices (616). Bath application of 1-ethyl-2-benzimidazolinone (1-EBIO), an SK-K_{Ca} channel activator, reduced the amplitude and frequency of inspiratory preBötC bursts in a dose-dependent manner, whereas apamin, an SK-K_{Ca} specific blocker, significantly increased burst rate and irregularity. Significantly, at low concentrations that did not decrease burst rate, augmenting SK-K_{Ca} channel activity with 1-EBIO selectively abolished fictive "sighs," one of several modes of bursting which can be observed from preBötC slices. Correspondingly, inhibiting SK-K_{Ca} activity with apamin increased the frequency of sighs, along with increasing the general excitability of the slice. Taken together, these studies suggest an important and perhaps uniquely selective role for SK-K_{Ca}-type channels in regulating the overall excitability of the preBötC respiratory network.

ATP-dependent K^+ channels

K_{ATP} potassium channels are regulated by intracellular concentrations of ATP and phosphoinositol signaling lipids (3, 4 phosphoinositol-*bis*-phosphate, PIP2), and thus they serve as sensitive effectors linking the metabolic status of cells with membrane potential. Decreases in cytosolic ATP activate K_{ATP} channels, and thus these channels may serve to produce a rapid protective hyperpolarization in response to acute hypoxia. In addition, these channels may also subserve continuous homeostatic regulation of excitability in cells designed to sense or experience high metabolic demand. Most notably, K_{ATP} channels have been studied in pancreatic β-islet cells in the context of compromised insulin release, but these channels are also widely distributed in the various brain regions, including glucose-responsive neurons of the ventromedial hypothalamus (342) and midbrain dopaminergic neurons (533). In preBötC slices, K_{ATP} channels were found in relatively high abundance, through a combination of patch-clamp recordings and single-cell RT-PCR, particularly in inspiratory respiratory neurons (200, 350). The high abundance of these channels allowed their activity to be simultaneously monitored in on-cell patches under voltage clamp, along with unclamped transients corresponding to action potentials generated by these neurons. Under normoxic conditions, the activity of K_{ATP} channels appeared to regularly fluctuate in phase with inspiratory bursts of action potentials. This discovery leads to the important concept that these channels dynamically modulate the firing patterns of these neurons in a cycle-by-cycle manner even under baseline conditions.

Concluding remarks—Like inward currents, K^+ currents act as diverse determinants of excitability. They provide stability to subthreshold V_m oscillations and these currents dynamically shape neuronal firing behavior. Both pharmacological and genetic manipulations of K^+ currents further demonstrate their roles in maintaining proper control over breathing and respiratory network activity. But our understanding of the differential physiological and pathophysiological roles of the highly diverse classes of potassium

channels is still very limited. Understanding, for example, how potassium currents contribute to the sudden unexplained death of epilepsy is one area of important clinical relevance.

The interactions between Intrinsic and Synaptic Properties

Overview

Synaptic mechanisms are cellular building blocks that are as important as the various inward and outward currents discussed in the previous sections. The search for the synaptic components that are critical for generating rhythmic activity patterns has been shaped by history. Following Graham Brown's (182) proposed concept of a CPG network came an equally influential publication in which he proposed a mechanism that could explain the emerging rhythmicity (182, 183). According to his proposal, two groups of functionally antagonistic groups of neurons are connected via reciprocal inhibition and Brown suggested that this so called "half-center" will give rise to the alternating rhythmic activity that characterizes many rhythmic activity patterns, including locomotion (182). This powerful hypothesis inspired many laboratories around the world to investigate the synaptic mechanisms in a variety of small and larger invertebrate and vertebrate neuronal networks. This quest led to the demonstration that indeed the majority of the networks reveal some degree of reciprocal organization involving synaptic inhibitory mechanisms (173, 203, 324, 400, 503). Moreover, early theoretical models confirmed the hypothesis that a network based purely on synaptic interactions could generate rhythmicity without the need to incorporate autonomously bursting neurons (411). However, as more experimental insights were gained, it became clear that certain intrinsic membrane properties were critical to control phase transitions in half center networks (588). Ionic mechanisms such as the hyperpolarization-activated cation current (I_h current) were discovered. This channel is activated during the inhibitory phase which is exerted by the functionally antagonist group of neurons (503, 514, 588). The depolarization caused by the I_h current could then activate low-voltage activated T-type calcium currents that would trigger the onset of the next rhythmic phase ["escape mechanism"; (503, 588)]. Alternatively, an active neuron could fall below the threshold to release the inhibitory transmitter that would release the silenced neurons from their inhibition ["release mechanism"; (514, 588)]. This half-center model also inspired many computational and experimental studies within the field of mammalian respiration (3, 14, 381, 466).

However, the idea that a reciprocally organized inhibitory network will generate "automatically" rhythmic activity alternating between two groups of neurons or between two or three phases of the rhythmical activity may be an oversimplification. Even if various intrinsic currents are incorporated in a network, it cannot be automatically assumed that a reciprocally organized inhibitory network will generate rhythmicity. Principle insights were gained into the constraints and requirements associated with the half-center network using the dynamic clamp or related approaches (503, 523). With these approaches, isolated neurons can be connected to a half-center network in which intrinsic and synaptic properties can be precisely regulated by a computer interface to explore the conditions that allow the generation of different activity patterns. This approach reveals that, depending on the time constants of the inhibitory potentials, the current density of the various inward and outward currents and various other parameters, the same half-center connectivity is capable of generating not only alternating stable rhythmic activity but also various other forms of activity patterns including synchrony, antiphase spiking, silence, or activity that was stuck in one particular phase [Figure 8B; (503, 523)]. Moreover, modeling studies suggest that reciprocal inhibition can play a critical role not only in generating antiphase activity, but also stable synchrony between bursting neurons (235). Thus, even if one were certain that the respiratory network is strictly organized in a reciprocal manner, it is impossible to

predict whether this network structure will promote the generation of alternating rhythmicity. However, irrespective of these uncertainties, it should be clear that massive synaptic inhibitory interactions are present within the respiratory network and it is very likely that they do play critical roles in various aspects of the respiratory rhythm. In this section, we want to highlight some of the hypothesized roles.

Inhibitory synaptic connections within the respiratory network

Synaptic inhibition in the in vivo network—There is much evidence for the role of synaptic inhibition within the respiratory network and many elegant *in vivo* studies have pioneered this research area. By employing different types of *in vivo* models, widespread inhibitory connections have been demonstrated between all types of respiratory neurons (484). Reciprocal inhibitory connections exist, for example, among expiratory neurons, as demonstrated by cross-correlation analyses (141, 504, 556). Inhibitory connectivity was also characterized by antidromic mapping, which showed that expiratory Bötzinger complex neurons with an augmenting firing pattern are extensively connected via inhibitory synapses to different classes of neurons (239). Elegant intracellular studies of respiratory rhythmic depolarization patterns revealed extensive inhibitory connections between all known types of respiratory neurons (14, 449, 484). By manipulating the drive potentials of intracellularly recorded neurons, it was demonstrated that synaptic inhibition plays a critical role in shaping expiratory activity *in vivo* (259). Moreover, glycinergic and GABAergic inhibition plays a critical role in generating the inspiratory ramp *in vivo* (199, 482, 483), and inhibition is critical for regulating the duration of inspiratory activity (146). Synaptic inhibition also has an important role in controlling the gain of respiratory drive potentials, as shown for various respiratory neurons (270, 624). Interestingly, there are various forms of inhibitory control mechanisms, which include phasic and tonic inhibition occurring during the silent and active respiratory phases that differentially regulate ongoing respiratory activity, and behaviorally associated changes in respiratory activity (110, 624). Over the past couple of years, there has been renewed interest in understanding how synaptic inhibition shapes respiratory activity and how different areas of the respiratory network communicate via synaptic inhibition. Most of these studies confirm the importance of synaptic inhibition in the generation of various characteristics of the respiratory rhythm (3, 12, 462, 515), and they also demonstrate that inhibition is an important determinant for the interaction between different areas of the respiratory network. One of these studies shows, for example, inhibitory interactions between the parafacial respiratory group (pFRG) and the preBötC (166). The pFRG seems to be critical for the generation of active expiration, as shown in a series of elegant studies using modern *in vivo* approaches (142, 144).

Inhibition in the in vitro network—While it is sometimes implied that synaptic inhibition is only important in the generation of the *in vivo* intact rhythm, it should be emphasized that the importance of synaptic inhibition has been extensively demonstrated within the isolated network. In the rhythmically active network, bursting neurons are bombarded by barrages of synaptic inhibition (441). Fifty percent of inspiratory neurons are thought to be glycinergic (600), and GABAergic inhibition by inspiratory neurons is also critical (278). When exposed to blockers of synaptic inhibition, the preBötC loses the ability to generate different phases of activity, and neurons that are active in phase with postinspiration begin to discharge in phase with inspiration (41, 299, 441, 496). The population activity generated by the isolated respiratory network changes from a bell-shaped, augmenting-like inspiratory activity to a decrementing short duration inspiratory activity upon blockade of synaptic inhibition (299). As also shown *in vivo*, synaptic inhibition occurs not only during the expiratory phase, but also concurrently during inspiration in the *in vitro* network (441). This inhibitory connectivity seems to contribute to the suppression of bursting in some but not all bursting neurons (564). Thus, inhibition

controls the degree of bursting within the respiratory network. In a modeling study, it has been demonstrated that weak inhibition concurrently arriving at bursting neurons cannot only suppress bursting, but also induce bursts and complete synchronization in networks that possess strong desynchronizing connections (20). This modeling study is an important reminder that synaptic interactions can result in network dynamics and activity patterns that are not necessarily expected by intuition. The role of concurrent inhibition and the regulation of pacemaker properties are presumably also important in the intact network. While it is known that concurrent inhibition does exist in the intact network (118), it remains difficult to unambiguously demonstrate pacemaker neurons in an intact animal.

Blockade of synaptic inhibition—Although reciprocally organized network structures were discovered in numerous neuronal networks and proposed to be the driving principle for many neuronal networks (11, 53, 161, 190, 330, 412, 413, 466, 493, 535, 546), it became increasingly clear that the majority of networks continue to generate rhythmicity even in the absence of synaptic inhibition (202, 252, 293). Thus, in retrospect it is not surprising that respiratory rhythmic activity persisted following the blockade of synaptic inhibition *in vitro* (441, 496) and *in situ* (443). Although these findings were confusing to many researchers who believed in the half-center organization as the only driving principle of rhythm generation, this discovery does not imply that all neuronal networks are pacemaker driven or that synaptic inhibition is not important in any neuronal network. The finding that respiratory rhythmic activity can be generated in the absence of synaptic inhibition should never be interpreted as proof that synaptic inhibition is not important. Instead, it is another example for the building block hypothesis, indicating that synaptic inhibition is one of several building blocks that establish rhythmicity in the respiratory network. Thus, it is important to emphasize that although the persistence of rhythmicity in the absence of synaptic inhibition was first discovered in the isolated respiratory network, it does not imply that the rhythm generated *in vitro* does not involve synaptic inhibition.

Consistent with the building block hypothesis, one can arrive at the following general statement: if the respiratory network or any network continues to generate rhythmicity in the absence of any given building block, it does not mean that this particular cellular property is unimportant for the generation of this particular rhythm. Nor does it imply that the rhythm functions in the network without this particular building block. This conclusion applies not only to the various glycinergic or GABAergic mechanisms but also to the I_{NaP} current, the I_{CAN} current, or any other current. This lesson has been learned not only from the respiratory network, but also from studies performed in neuronal networks across the animal kingdom over the past century. Therefore, it should be questioned whether the search for *the* obligatory rhythm generating mechanism or the building block on which the entire rhythm depends is really meaningful. Is this search merely a theoretical exercise that potentially causes more harm than benefit to the understanding of the mechanisms underlying rhythm generation? In analogy: will we better understand an airplane if we identify the part that is most critical? Can there be just one part that is critical? Is it not more important to understand how the different parts work together to make a functional airplane rather than trying to determine which part is the most critical one?

Synaptic inhibition and the control of the motor output—Synaptic inhibition plays not only a critical role in generating the respiratory rhythm, the respiratory patterns, and the different respiratory phases, but also in regulating the respiratory motor output. In fact, the search for the inhibitory mechanisms that shape motor output has an equally long history as the studies that characterized the inhibitory mechanisms of the respiratory network (e.g., reference 25). Although it is not within the scope of this review to cover this exciting research area in sufficient depth, it is important to emphasize that synaptic inhibition plays a critical role in actively shaping the respiratory motor output within the XII and phrenic

nucleus (35, 378, 395, 396, 511, 571, 572). One important source for the synaptic inhibition observed in the hypoglossal motoneurons arrives from GABAergic neurons located within the nucleus of roller (571, 572), which illustrates that the respiratory motor nuclei are not "follower nuclei" that are simple targets of the centrally generated respiratory rhythm and that relay this centrally generated activity simply to the muscles, but that instead these nuclei play a critical role in actively shaping the activity motor pattern, involving different sets of premotor nuclei.

Excitatory synaptic connections within the respiratory network

Excitatory synaptic transmission and the generation of normal respiratory activity (eupneic activity)—While the role of synaptic inhibition in respiratory rhythm generation has been a matter of ongoing debate, it was never questioned that synaptic excitation is critical for respiratory rhythm generation. AMPA receptors (AMPA-R) were identified early on as critical contributors to the generation of drive potentials in respiratory neurons (170, 501). Consistent with this conclusion, respiratory rhythmic activity at the level of the preBötC ceases upon the blockade of AMPA-R (165, 187, 296, 554). However, it is well established that multiple excitatory synaptic mechanisms are active within the respiratory rhythmic network. This multiplicity is critical for the generation of the large repertoire of behavioral functions that are served by this rhythm-generating network. A study by Ireland et al. (231) has elegantly demonstrated that the type of non-NMDA-R (probably AMPA) that mediate glutamatergic synaptic transmission within the preBötC are different from the non-NMDA-R mediating the drive to motoneurons (231).

For the generation of normal respiratory activity, there has been an increased understanding of how glutamatergic mechanisms and intrinsic membrane properties interact with each other to generate a burst of inspiratory activity. The activation of postsynaptic glutamatergic receptors leads to a transient Ca^{2+} influx that in turn activates a signaling cascade cumulating in the activation of I_{CAN} that then causes a dramatic amplification of the inspiratory drive potential (392). An elegant study by Mironov illustrates how metabotropic glutamate receptors (mGluR 1,5) interact with a dendritic, intracellularly generated calcium transient which propagates to the soma. There it causes the activation of I_{CAN} that then leads to a burst of activity, which is synchronized by non-NMDA-R, CNQX-sensitive synapses (347). The emerging calcium wave will lead to the activation of I_{CAN} that is synchronized by synaptic mechanisms.

Subsequent computational studies that were aimed at finding the obligatory mechanism suggested that respiratory rhythmicity emerges from an interconnected network of glutamatergic neurons without the ability for autonomous bursting (464). These theoretical considerations are consistent with the so-called group pacemaker hypothesis as first proposed by Rekling and others (143, 446). While there is no question that glutamatergic synapses play a critical role in triggering I_{CAN}, and thereby amplifying synaptic drive potentials, this hypothesis has been linked to a debate that questions the role of autonomous voltage-dependent bursting properties in respiratory rhythm generation. As discussed earlier, the usefulness of searching for the obligatory rhythm generation mechanism in a network that has a large catalogue of other synaptic, ionic, and modulatory mechanisms is questionable and potentially confusing to those outside the field. It is particularly confusing because nobody can deny the existence of bursting pacemaker neurons within the respiratory network. Moreover, there is currently no tool to unambiguously test the obligatory role of bursting pacemakers. Unfortunately, it is often overlooked that no pharmacological approach can specifically block all bursting neurons (404). As also discussed in this review, networks are highly dynamic and any manipulation of synaptic or intrinsic membrane properties will inevitably also alter the configuration of the network, making it impossible to

know to what extent a network follows the same rules as before the manipulation. Although the search for the obligatory mechanism may create the impression of wild disagreement between the different groups of researchers, there is really more agreement than disagreement. There is little disagreement that glutamatergic synaptic transmission is highly diverse and complex, that these mechanisms are essential for the formation of the eupneic network activity, and that the intrinsic membrane property reflected in the activation of the I_{CAN} is a critical mechanism in respiratory rhythm generation (143, 406). There is also general agreement that mGluR receptors are important contributors to respiratory rhythm generation (89, 296, 347, 392). Moreover, nobody disagrees that various forms of autonomous pacemaker activity do exist within the preBötC (243, 268, 404, 554, 563, 564, 566). Although there is little direct experimental evidence for direct recurrent excitation within the respiratory network, recent studies have demonstrated that isolated preBötC neurons can form small synaptically coupled micronetworks that can give rise to rhythmic bursts (347). Although the respiratory rhythm ceases in the presence of FFA and riluzole (404, 566), we do not know exactly why this is happening, in particular, since there is no drug available that specifically blocks all types of autonomously bursting neurons (as discussed earlier). Thus, any pharmacological manipulation will leave some bursting neurons functionally active. Aside from theoretical considerations of extreme conditions, there is not much evidence that the respiratory network will ever generate the rhythm based on only synaptic or only intrinsic membrane properties.

Differential synaptic and intrinsic mechanisms for the generation of normal and sigh respiratory activity—Within the preBötC, glutamatergic transmission differentially contributes to different forms of respiratory rhythms: in particular, in the simultaneous generation of eupneic and sigh activity (296, 297, 299). Both of these activities are generated in the isolated preBötC, and they are characterized by two distinct integrated waveform patterns and distinct population burst frequencies (299). Although distinctive at the activity level, there is not much evidence for two distinct populations of neurons, except for a small number of neurons that are active only during the sigh, but not eupneic activity (563). Indeed, as shown in Figure 1B, there is complete anatomical overlap between the areas involved in the generation of these activities. This poses the interesting issue of how the same population of preBötC neurons is capable of generating two distinct rhythms with very different timing and amplitude parameters: a fast, small amplitude eupneic and a slow, high-amplitude sigh activity (Fig. 2A,D). Lieske and Ramirez (296) proposed that the production of these two activities involves the differential activation of glutamatergic synapses with distinct properties. Fictive sigh burst generation seems to involve a glutamatergic synapse that is coupled to the P/Q-type Ca^{2+} channel and that is modulated by the activation of the group III metabotropic glutamate receptor (mGluR), mGluR8 (Fig. 6E). Moreover, sighs are more sensitive to the blockade of AMPA receptors (296). Thus, incomplete blockade of AMPA-R abolishes only fictive sighs. Based on these findings, it was suggested that sighs are emerging through excitatory connections with these specific properties that are different from those responsible for the generation of eupneic activity. The excitatory synaptic mechanisms contributing to the generation of fictive eupneic activity and, in particular, inspiratory drive potentials, are more dependent on the NMDA-R and also involve mGluR1 and mGluR5 (296, 297, 392), that is, metabotropic glutamate receptors that are distinct from those responsible for the generation of the sighs.

But, the differential generation of sigh and normal respiratory activities will not only depend on synaptic mechanisms. Blockade of the I_{NaP} current seems to abolish sighs (404), and Tryba et al. (563) identified a type of CI pacemaker neuron that depends on I_{NaP} and that concurrently exhibits two types of autonomous bursting with distinct characteristics (Fig. 9B): large amplitude bursts that are autonomously generated at a slow frequency, and small amplitude bursts that are generated at a faster frequency. As will be discussed in more detail

in the section on neuromodulation, oxotremorine selectively inhibits the faster, small amplitude bursts, while it selectively activates the generation of the large amplitude bursts (Fig. 9B). As shown in the slower time scale, the two types of bursts are concurrently generated as oxotremorine is being washed out (Fig. 9B, lower trace). This finding is very intriguing because at the network level oxotremorine inhibits the fast and small amplitude eupneic activity and dramatically increases the frequency of the large-amplitude sigh activity (Fig. 9A). This raises the question of whether these two burst types are transmitted via different types of glutamatergic synapses that differentially amplify these signals to generate two rhythmic activities. Although many questions remain unresolved, the differential generation of sighs and normal respiratory activity is clearly another example indicating that rhythm generation emerges through the differential integration of synaptic, intrinsic, and modulatory properties.

Concluding remarks—While synaptic inhibition, synaptic excitation, and intrinsic neuronal properties are known contributors to the functional output from respiratory networks, it must be recognized that these circuit and intrinsic properties do not function in isolation from one another. They are integrated to generate stability while at the same time retain the dynamic responsiveness of the network to changing intrinsic and external environments. Understanding the details of synaptic integration in the larger respiratory network that includes the various distributed brainstem components will be one of the important challenges for the future.

Cellular Properties and the Integration of Central Chemosensation to O_2 and CO_2

Overview

To guarantee adequate ventilation at any given time, the respiratory network needs to quickly respond to changes in O_2, CO_2, and pH. The discovery of peripheral chemoreceptors that are exquisitely sensitive to O_2, together with lesion experiments, led to the concept that peripheral chemosensors sense O_2, while the central nervous system (CNS), in particular, the ventral surface of the medulla, senses CO_2 (210, 212, 309, 310, 380, 478, 479, 480, 481). Although it has always been acknowledged that these different sites interact to form the respiratory responses (76, 171, 211, 285, 310, 325, 380), an anatomical separation between CO_2 sensitivity originating within the CNS and O_2 sensitivity originating in peripheral sensory organs dominated the field of respiration for many decades. Peripheral sensory neurons in the carotid body are thought to provide the primary neuronal input mediating acute respiratory responses, with central chemosensitive neurons contributing a secondary component and underlying more long-term adaptive responses. However, while it is widely considered as only a “secondary component,” there is an increased appreciation of the importance of the CNS in sensing both O_2 and CO_2.

Lessons learned from the central respiratory network can provide important insights that go beyond the immediate relevance for the neuronal control of breathing. As will be discussed in this section, the nervous system needs to maintain a very fine balance between hypoxia and hyperoxia to avoid the detrimental effects associated with any deviation from this balance. Any change in a network’s activity state will alter this balance if not concurrently coupled with an adequate network response. Depending on the particular behavioral, environmental, or intrinsic metabolic conditions, different neurons and different networks across the brain will be affected in a very differential manner. A “master peripheral or central sensor” for O_2 and CO_2 unlikely provides the adequate local sensitivity required for maintaining this fine homeostasis at the level of different neuronal networks distributed throughout the nervous system. Neuronal networks across the brain need to be capable of

adjusting and maintaining this balance locally and must, therefore, also be able to sense O_2 and CO_2 locally. This is particularly important because the majority of neuronal networks across the nervous system are continuously active (206, 279). These networks are, therefore, in continuous demand of an adequate supply of O_2 and CO_2. Slight shifts in this ongoing intrinsic activity will be associated with changes in oxygen consumption that varies from network to network and from moment to moment. Each network needs to adequately respond to slight changes in oxygen consumption andCO_2 production. Because 95% of the brain's metabolic energy is devoted to maintaining ongoing intrinsic activity that characterizes our resting state (429), the process of chemosensation cannot be turned on or off by a master regulator. More likely, chemosensation must be considered as a continuous process that forms an integral part of a network's ability to intrinsically generate activity.

Oxygen sensing and the integration within the preBötC network

Overview—The concept that chemosensation is an integral part of a network's ability to intrinsically generate activity is best exemplified by the preBötC. Known for its role in respiratory rhythm generation, the preBötC also integrates incoming sensory information and has an exquisite intrinsic sensitivity to changes in its biochemical environment. Moreover, neurons in the preBötC and ventral respiratory group are located in proximity to arterioles in newborn mice (139). The responsiveness and reconfiguration of the preBötC has been extensively studied in reduced slice preparations, which is perhaps the most direct demonstration that this rhythm generating network is capable of intrinsically sensing oxygen, as other peripheral mechanisms can be excluded (213, 437, 548). But, the conclusions gained from this *in vitro* network are also supported by *in vivo* studies in which experimentally induced central hypoxia mediates biphasic changes in ventilation and motor output (90, 521). Solomon et al. (521), in particular, demonstrated that focal hypoxia in preBötC leads to an initial excitation of respiratory motor output, further supporting the notion that this important rhythm-generating network is also involved in the chemosensory response.

What makes oxygen sensitivity a truly integral part of this network is that different aspects of the underlying rhythm generating mechanisms express different sensitivities to changes in the oxygen environment. Thus, we propose that the rhythm generating mechanisms themselves constitute important sensors of O_2. These sensitive mechanisms are the same cellular properties that are also discussed in this review in context of respiratory rhythm generation. Important for these considerations is the discovery that the isolated preBötC is capable of generating multiple patterns of rhythmic activity during changes in its experimental oxygen environment: eupneic activity, sigh activity, and gasping activity (299). Alterations in O_2 evoke a sequence of changes in various synaptic (Fig. 10B) and cellular mechanisms (Fig. 10C). These alterations result in a dramatic change in the firing patterns of the neurons that are embedded within the functional network (Fig. 11A) and the firing patterns of the autonomously active neurons as characterized independently from the network (Fig. 11B). These changes transform the network from a fully integrated, very complex network that depends on multiple network and autonomous mechanisms to one that is dominated by pacemaker neurons that are dependent on the persistent sodium current as first postulated by Pena et al. (404) (Figure 12).

The time courses of the hypoxic response—The hypoxic response begins with a biphasic response (48, 130, 198, 369). An initial frequency and amplitude augmentation and increased number of sighs is followed by a frequency depression (Fig. 10A). In severe hypoxia, this marks the beginning of a process that leads to a gasping state (548). The transition from eupnea into gasping can be gradual, both *in vitro* (213, 299) and *in vivo* (587). During the transition into gasping, respiratory bursts can vary in rise time and burst

duration. This transitory phase has been referred to as “pregasping” *in vivo* (587). Thus, one cannot assume that the respiratory network is fully reconfigured and in a gasping state when exposing the network to only very brief hypoxic or ischemic conditions or when exposing the network to mild hypoxia. In this pregasping state, some of characteristics of the network and modulatory response may still resemble that of the eupneic state, such as the duration of the inspiratory burst, while others like the rise time of the inspiratory burst may already look like gasping (530, 559). Figure 10 illustrates the matched time courses of the response of the network (Fig. 10A), of the synaptic excitatory (Fig. 10B1, excitatory post-synaptic currents (EPSCs)) and inhibitory activity (Fig. 10B1, inhibitory post-synaptic currents (IPSCs)), as well as the neurons that are autonomously active (Fig. 10C): the autonomously spiking neurons, CS pacemakers, and CI pacemakers (404, 554). The average responses reveal that autonomously spiking neurons cease to discharge first, followed by the cessation of CS pacemaker neurons, while CI pacemakers continue to be active throughout hypoxia. Thus, the pregasping state is characterized in part by the cessation of the autonomously active neurons and the continuously decreasing contribution from CS pacemaker neurons. But the gasping state is only reached when CI pacemaker neurons become the sole drivers (“State III”, Fig. 10B, blue). This network configuration becomes sensitive to riluzole, which blocks CI pacemaker neurons as well as the respiratory network during the gasping state [Figure 12; (401, 404)].

The hypoxic response and postnatal development—The time course of the hypoxic response changes during postnatal development. The augmentation phase of neonatal mammals, also including pre- and full-term human infants, is typically relatively brief, and it is followed by a sustained depression that can be maintained for a relatively long time (48, 191, 198, 283, 433, 473). In neonatal mammals, there is also an increased time to the first gasp, and autorescucitations are successful even after prolonged exposure to severe hypoxia (402). A sustained frequency depression with the generation of fictive gasps can also be seen in the neonatal *in vitro* preparations, suggesting that these effects are centrally generated and may originate within the medullary network. By contrast, adult mammals typically generate a sustained frequency augmentation followed by a depression that quickly leads to apnea (167, 227, 433, 452, 562). The time to the first gasp is shorter in mature compared to neonatal animals and the ability to resuscitate decreases with maturation (402). The shorter respiratory response leading to apnea, coupled with an enhanced augmentation in severe hypoxia is also similar to the response seen *in vitro* (437). As the mice mature, there seems to also be a decreased coupling between the rhythm that is generated within the preBötC and the XII motor output as demonstrated *in vitro* (402, 438).

The response to graded hypoxia—The respiratory network also shows a differential response when exposed to graded levels of sustained hypoxia. A dependency on the persistent sodium current (Fig. 12) is found only in severe hypoxia, and sustained severe hypoxia is also required to significantly alter the rise time of the inspiratory burst from an augmenting or bell-shaped bursting to a decrementing bursting (213). Both of these characteristics are the hallmarks of gasping. By contrast, the frequency of respiratory activity is altered even in moderate hypoxic conditions and is gradually affected as the hypoxic conditions become more severe. Thus, it is conceivable that the mechanisms governing the respiratory frequency have different oxygen sensitivity than those determining the rise time and riluzole dependency. The respiratory network begins to show a dramatic frequency increase as synaptic inhibition gets depressed and autonomously active neurons are beginning to shut down (Fig. 10A-C), but at a time when CS pacemakers are still active (Fig. 10C). This leads to the conclusion that the hypoxic response of the respiratory network is the consequence of multiple oxygen sensitivities inherent in the multiple synaptic,

cellular, and network mechanisms that govern the different aspects of neuronal network activity (213).

Differential network sensitivities to pharmacological blockade—It is hypothesized that under well oxygenated and moderately hypoxic conditions, the respiratory network is not dependent on riluzole-sensitive mechanisms (213, 404) because additional mechanisms exist, such as FFA-sensitive bursting mechanisms (including CS pacemakers), calcium-dependent mechanisms, GABAergic, glycinergic, and glutamatergic synaptic mechanisms, plus a host of metabotropic mechanisms that also contribute to respiratory rhythm generation (Fig. 12, integrated respiration). This network state is already complex under *in vitro* conditions, and it is even more complex in the *in vivo* state (112, 464, 515). As the network transitions into the gasping mode, it becomes sensitive to riluzole [(401, 404), Figure 12"I_{NaP}-driven gasping"]. Despite the caveats associated with the use of riluzole as discussed in this review, it is striking that experiments performed in all the available preparations ranging from slices to whole animals arrive at similar conclusions, that is, the respiratory network under well- to moderately oxygenated conditions is not sensitive to the blockade of riluzole either *in vitro* (390, 404), *in situ* (532), or *in vivo* (401). In all these studies, the authors conclude that in this oxygenated state the respiratory network depends on multiple network mechanisms (404). In this state, the respiratory network is able to generate frequency and amplitude changes that may involve partial changes in network configuration.

Role of ATP and KATP channels in the hypoxic response—The K_{ATP} channels seem to play a critical role in the biphasic response to hypoxia (200, 348). As ATP levels drop in moderate and severe hypoxia, the activation of K_{ATP} channels could protect the respiratory network against unmitigated Ca^{2+} influx that can lead to Ca^{2+} overload and neurotoxicity. This protective response has been studied not only within the respiratory network, but also in networks throughout the nervous system (15). Demonstrated by Mironov et al. (350), the opening of a K^+ conductance facilitates the closing of L-type Ca^{2+} channels during the frequency depression. The identity of this K^+ conductance was proposed to be K_{ATP}, as it was inhibited by tolbutamide and glibanclamide, and opened with diazoxide. Hypoxic activation of K_{ATP} will concurrently occur with the phasic activation of the K_{ATP} that was already present in well oxygenation conditions. This phasic activation is thought to be linked to the mitochondrial membrane potential ($\Delta\Psi$) that oscillates in phase with the population rhythm as a potential mechanism to prevent Ca^{2+} overload, via mitochondrial uptake of intracellular Ca^{2+} (352). Hence, the hypoxia-mediated increased Ca^{2+} influx is mitigated by the activation of K_{ATP} that is accompanied with mitochondrial Ca^{2+} uptake. This process will preserve and contribute to rhythmogenesis during the initial phase of hypoxia. The rundown of the I_{Ca} in inspiratory neurons of the preBötC was delayed with hypoxia. Moreover, pharmacological blockade of L-type Ca^{2+} channels eliminates the initial frequency augmentation, while accelerating the occurrence of frequency depression (351).

While a drop in intracellular ATP may activate K_{ATP} channels, it is also known that during hypoxia extracellular ATP is actually released throughout the ventrolateral medulla from glia sources, which may contribute to the hypoxic ventilatory response via purinergic receptors (178, 179). Putative inspiratory neurons of the preBötC express the metabotropic purinergic receptor ($P2Y_1R$) which when activated by ATP, opens an inward current that increases excitability, similar to that observed during the hypoxic frequency augmentation of the preBötC (312).

The role for K_{ATP} channels was also examined at the behavioral level using a mouse strain in which Kir6.2 was genetically deleted (353, 386). Deletion of Kir6.2 was found to clearly

abolish the gasping response induced by decapitation. In response to moderate hypoxia (5.5% O_2), Kir6.2 KO mice exhibited a significant intensification of the initial "augmentation" phase, manifested as an increase in both inspiratory frequency and length of the augmentation phase. In addition, the strength of "sighs" was diminished, although "sigh" frequency appeared unaffected in the Kir6.2 KO line. Oyamada et al. (386) suggested that the role for Kir6.2 in these hypoxic responses may be age dependent, as the respiratory effects of Kir6.2 deletion appear to be more prominent in older animals (4 weeks compared to 2 weeks postnatal). Future studies utilizing *in vitro* preBötC slices from Kir6.2 KO mice under controlled normoxic and hypoxic conditions may help unravel central versus peripheral contributions of K_{ATP} to respiratory control. It may also help to better integrate the findings at the behavioral level with those obtained at the cellular level.

The cessation of I_{CAN}-dependent burst mechanisms—It is conceivable that the transition into gasping involves a severe drop in ATP levels that may result in K_{ATP} channels potentially inhibiting I_{CAN}-dependent bursting mechanisms. The suppression of I_{CAN} dependent mechanisms during hypoxia is a hallmark of the network reconfiguration (404). Given the importance of I_{CAN}-dependent mechanisms in regulating the amplitude and shape of inspiratory activity (122, 392, 578), the loss of these mechanisms may contribute to the characteristic change in the shape of inspiratory activity from an augmenting, eupneic burst (Fig. 11, upper left panel) to a rapidly rising and decrementing gasping shape in severe hypoxia (Fig. 11, upper right panel).

The depression of synaptic inhibition—K_{ATP} may also mediate the inhibition of inhibitory neurons within the preBötC respiratory network. There is much evidence for the role of inhibitory neurons in the preBötC (69, 357), and it is known that many autonomously active respiratory neurons shut down at the onset of the hypoxic response (404). As shown in Figure 10C, the cessation of autonomously active neurons coincides with the dramatic decrease in the number of inhibitory postsynaptic potentials with hypoxia (299). As shown in the *in vivo* network, endogenously generated adenosine will accumulate and could also play a critical role in the generation of the depression of synaptic transmission (486). The decrease in synaptic inhibition and the cessation of autonomously active neurons also overlaps in part with the beginning of the frequency augmentation at the network level (Fig. 10A). However, based on *in vitro* experiments, the depression of synaptic inhibition seems not to be responsible for the frequency change, because pharmacological blockade of synaptic inhibition does not mimic the biphasic frequency changes (Lieske et al., 2000). By contrast, the hypoxia-induced synaptic depression seems to contribute to the alteration of the shape of the inspiratory burst from augmenting into decrementing (Fig. 11A, upper panel). This shape change can also be mimicked pharmacologically by blocking glycinergic mechanisms (299). Moreover, this decrease in synaptic inhibition will also contribute to the loss of expiratory activity and the phase switch of postinspiratory/ expiratory activity into inspiration, as can be seen in the isolated preBötC during exposure to severe hypoxia (438). Figure 11A exemplifies an expiratory neuron (11A, third panel on the left) as it loses the phasic inhibition and becomes rhythmically active in phase with inspiration [Figure 11A, third panel on the right (298, 299)]. This figure also illustrates the loss of IPSCs as the respiratory neurons are transiting into severe hypoxia (Fig. 11A, voltage clamp recording). Many of the in vitro findings resemble those obtained under *in vivo* conditions. A detailed characterization of changes as they occur within the *in vivo* respiratory network has been described by Richter et al. (452). At the behavioral level, the transition into severe hypoxia is also accompanied by a reconfiguration at the level of motoneurons. For example, the activity of the thyro-arythenoid muscle changes from expiratory to inspiratory, and a cessation of expiratory activity occurs at the level of the intercostal muscles (529).

For the preBötC, it was first proposed that in this reduced network state when I_{CAN}-dependent mechanisms and synaptic inhibition are significantly reduced, CI pacemaker mechanisms become the main driver of rhythmic activity and exposure to riluzole causes the cessation of respiratory activity (404). This network state characterizes gasping with all its properties including a shortened inspiratory rise time and duration, a reduction in inhibitory synaptic mechanisms, and a silencing of I_{CAN}-dependent bursting mechanisms. The aforementioned discussion also illustrates that the fact that this network state becomes riluzole sensitive is just one of many consequences associated with this network reconfiguration. In addition, I_{NaP} could become critical because hypoxia directly activates I_{NaP} as shown in other systems (245, 407). Clearly, the aforementioned changes in cellular properties are only some of the many changes that will contribute to the hypoxic response and network reconfiguration. There are many additional alterations that likely contribute but are not yet fully understood. Hypoxia is also associated with an increase in extracellular glutamate which will affect both ionotropic and metabotropic glutamate receptors. Moreover, hypoxia also activates Ca^{2+} channels (538) and as will be discussed in the Section "Cellular basis for chemosensing in preBotC neurons with a particular emphasis on the role of potassium currents" various K^+ currents also play critical roles in chemosensation (240, 291). These currents will likely contribute equally not only to respiratory rhythm generation, but also to the hypoxic response of this rhythm-generating network.

Conclusion: Hypoxia and the generation of three distinct network states—In this section, we describe how the cellular building blocks involved in respiratory rhythm generation are also involved in governing the hypoxic response of the respiratory network level, not only *in vitro*, but also *in vivo*. Many concurrent processes contribute to the orchestrated response seen at the network and behavioral level. Many of these changes are interactive and occur gradually, as the network is increasingly exposed to hypoxia. Yet, there are clearly marked changes that characterize distinct network states (Fig. 10D): the first distinct state is the control state, in which the network operates on multiple cellular and network mechanisms (Fig. 10D, State I). This state is not sensitive to the blockade of riluzole or FFA when applied alone (401, 404). State II is characterized by the cessation of the autonomously active spiking neurons and the cessation of synaptic inhibition (Fig. 10D, State II). During this distinct state, the network configuration is characterized by the loss of expiratory activity and the transition from a frequency augmentation to a frequency depression. State III occurs as the CS pacemakers cease to discharge, which renders the network dependent on the activity of the CI pacemaker neurons, making it sensitive to the blockade of riluzole (Fig. 10D, State III). During this third distinct state, the network is generating gasping in severe hypoxia that is an activity that is in many aspects significantly different from the activity of the well-oxygenated state I.

Cellular basis for chemosensing in preBötC neurons with a particular emphasis on the role of potassium currents

At the cellular level, changes in pH and O_2 are likely mediated by molecular mechanisms sensitive to protons (for hypercapnia), and immediate metabolic correlates of mitochondrial function, such as ATP, NAD^+/NADH redox potential, or reactive oxygen species (ROS) (for hypoxia and hyperoxia associated with reperfusion). Within the brainstem, several structures and cell types have been studied for intrinsic chemosensitivity, including the serotonergic neurons of the raphe (133, 494), noradrenergic neurons of the LC (133, 149, 456) and neurons (362, 363), and glia (135, 136, 178, 593) in the retrotrapeziod nucleus (RTN). Although chemosensitivity can clearly be demonstrated in many cases for cells in these individual brainstem nuclei, a unique role of any particular structure for *in vivo* respiratory regulation remains uncertain. It also remains unclear whether one particular region plays a dominant role, or whether chemosensitivity emerges through a distributed network response

involving all these and other nuclei (97, 197, 426, 448). In this context, several potassium channels have been examined as candidate chemosensors, particularly for acidosis within the normal physiological range produced under nonpathological hypercapnic conditions (pH 7.0–7.4). TASK1 (KCNK3), and TASK3 (KCNK9) are acidsensitive, outwardly rectifying "two-pore" potassium channels which contribute to constitutive K^+ leak (24). Potassium conduction through these channels is blocked by external protons (IC_{50} of pH 7.3 for TASK1 and pH 6.5 for TASK3), by protonation of a titratable histidine residue conserved in both channels near the outer mouth of the channel pore (361). Mulkey et al. (363) examined the role for TASK1 and TASK3 as central respiratory sensors for hypercapnia by generating mouse strains deleted for TASK1 and TASK3, as single and double homozygous KO strains. Despite the widespread expression of both channel transcripts in brainstem, homozygous TASK1/TASK3 KO mice were viable and displayed no gross behavioral phenotypes. Recordings from chemosensitive neurons from the raphe revealed a blunted pH response (between pH 6.9–7.5) in mutant neurons deleted for TASK1 and TASK3 (24). However, similar recordings in chemosensitive RTN neurons revealed no difference in the same mutant background. In addition, whole animal plethysmography failed to demonstrate respiratory differences between WT and mutant animals in response to progressive hypercapnic challenges (3%, 5%, and 10% CO_2). Thus, neither of these potassium channels appears to play an obligatory role for regulating normal respiratory responses to hypercapnia. More recently, a mouse KO strain was reported for TASK2 (KCNK5),which is actually a more structurally distant member of the two-pore gene family, despite its name (172). Although TASK2 is primarily expressed in non-neuronal tissue, lower expression was observed in restricted brain regions by driving the expression of lacZ (β-galactosidase) under the control of the native TASK2 promoter. A small bilateral cluster of neurons in the RTN were found to express TASK2, and these neurons were missing in the $Phox2b^{27Ala/+}$ mutant background which mimics human congenital central hypoventilation syndrome (CCHS). In the Phox2b mouse model of CCHS there is a developmental lost of pH-sensitive glutamergic neurons in the RTN. Several studies suggest that these neurons likely mediate, at least in part, reflexive increases in respiration in response to hypercapnia (2, 117). Functionally, the loss of TASK2 was found to both augment acute respiratory response to hypercapnia (< 15 min) and abolish long-term "acclimated" suppression of respiratory frequency (> 30 min). Recordings of phrenic motoneuron bursts from isolated "*en bloc*" preparations provided support for the hypothesis that these effects could be attributed, at least in part, to central mechanisms. TASK2 KO preparations failed to exhibit a normal 50% decrease in expiratory burst frequency with anoxia, although responses to hypercapnia, normocapnic acidosis, or normocapnic alkalinization were not significantly different from WT. The mechanism for how TASK2 channels may sense O_2, as suggested by these studies, as well as the details of how central mechanisms may integrate with peripheral mechanisms, remain to be explored more fully. Taken together, these studies suggest that the functional contributions of individual two-pore potassium channels to central respiratory circuits are probably redundant.

Although TASK channels are sensitive to external pH, chemosensitive raphe neurons, and perhaps other neurons, sense hypercapnia by changes in internal pH. Therefore, potassium channels that display demonstrated modulation by internal pH within the normal physiological range are attractive candidates for pH sensors in chemosensitive neurons. Among the class of inward rectifier potassium channels encoded by the large *Kir* gene family, heteromeric channels formed by Kir4.1 and Kir5.1 have emerged as a potential candidate for a pH-sensor active in respiratory neurons (240, 604). Heteromeric Kir4.1/Kir5.1 potassium channels are specifically inhibited by internal protons, with an IC50 of approximately 7.4 and an IC80 of approximately 7.1. This mirrors the normal nonpathological working range of internal pH experienced by neurons subjected to hypercapnia. Both Kir4.1 and Kir5.1 transcripts are found abundantly in brainstem, although

expression is widespread and does not appear restricted to respiratory-related regions (602). Specific blockers for Kir4.1/Kir5.1 are not available, so pharmacological manipulation to study the role for this channel in preBötC rhythmogenesis cannot be performed. In addition to its role as a neuronal pH sensor, this channel has also been proposed to serve as the pH sensor in astrocytes in the RTN, where it may contribute to chemosensitivity by modulating pH-dependent purinergic transmission between glia and respiratory neurons (178, 179, 593). Mouse lines null for either Kir4.1 or Kir5.1 have not been described, but respiration has been examined in a mouse KO line for Kir2.2 (387). Respiratory responses to hypercapnia were examined by whole animal plethysmography, but only modest differences were observed between WT and Kir2.2 mutants, and only transitory between postnatal days 14 and 15. This result is perhaps not unexpected since Kir2.2 does not exhibit overt pH sensitivity, although it likely can form heteromeric channels with Kir2.3 that does exhibit inhibition by external pH (569). Clearly, future experimentation with Kir4.1 or Kir5.1 mouse KO lines could be very revealing.

Concluding remarks—Central chemosensation emerges through the integration of the same cellular processes that are also involved in the generation of respiratory activity patterns. Ionic conductances such as K^+-channels possess properties sensitive to molecular cues for changes in local oxygen and carbon dioxide microenvironments. The different synaptic and intrinsic membrane properties have different sensitivities to changes in their metabolic environment. In the case of hypoxia, these differential sensitivities give rise to a complex reconfiguration of the respiratory network, resulting in the transition from eupneic into gasping activity. The integration of chemosensitive properties within the very mechanisms that are also responsible for the generation of respiratory activity preserves respiratory functionality during changes in the metabolic environment that ultimately promotes survival during common yet sometimes unexpected environmental challenges.

G-protein Coupled Receptors and the Modulation of Cellular Properties

Overview

The cellular properties that govern excitability, connectivity, and chemosensitivity within the respiratory network are under continuous influence from numerous endogenously released neuromodulators. The neuromodulators best studied within the respiratory network include NE, serotonin (5-HT), acetylcholine (ACh), substance P (SP), ATP, TRH, somatostatin (SST), dopamine (DA), endorphins, and adenosine. Yet, there are many potential modulators that have not been examined so far. The intracellular mechanisms that underlie a neuromodulator's action are diverse and interactive, and we are just beginning to appreciate this complexity. Indeed, for most neuromodulators very little is known about their specific actions within the respiratory network; thus, we can only infer from studies conducted in other systems. Almost all known neuromodulators act on G-protein coupled metabotropic receptors (Fig. 13, GPCRs). These metabotropic receptors are activated not only by neuromodulators, but also by the classical neurotransmitters glutamate and GABA, which creates a fascinating, highly complex interaction between metabotropic and ionotropic receptors (Fig. 3). Moreover, release of modulators and transmitters can be tonic and/or phasic, which adds a dynamic component to neuromodulation that is little understood. Neuromodulation targets tonically active and rhythmically bursting neurons and their synaptic interactions within the respiratory network, which results in a complex web of modulatory interactions inseparable from the rhythm generating and chemosensory functions of the rhythmically active respiratory network.

The isolated respiratory network containing the preBötC has contributed significantly to our current understanding of this dynamic interplay. Although portrayed by some as a "simple network," the preBötC when isolated in a slice preparation is continuously and

endogenously modulated by numerous neuromodulators, which include NE, 5-HT, Ach, and SP (405, 406, 497, 498, 499, 500, 563, 565, 578). These neuromodulators regulate different cellular mechanisms that are critical for rhythm and pattern generation, as well as chemoreception. As similarly discussed for chemosensation, neuromodulation is also an integral part of the respiratory rhythm generating process. Neuromodulators exert their dynamic influence via a multitude of receptors, second messenger systems, and regulatory processes that also alter intracellular calcium. The diversity of surface receptors coupled to a large number of diverse intracellular mechanisms allows neuromodulators to tightly regulate neuronal discharge patterns and to control many different aspects of network activity. Our understanding of these interactions within the respiratory network has benefited from lessons learned from the multineuromodulatory network located within the crustacean stomatogastric (STG) ganglion. Although composed of only 25 to 30 cells, more than 25 neuromodulators and neuropeptides were identified within this network (323, 492, 513). Many neuropeptides in the STG bind to GPCRs (CCAP, CabTrp, mACh, Proc, FLRF, and PRCH) and partly converge to the same cation channels (541). It is very likely that many of the rules identified in this small but not simple invertebrate network, also apply to the relatively small but not simple mammalian respiratory network.

To achieve a better appreciation of the complexity and diversity of neuromodulation, we will begin with a brief general overview of the molecular biology that underlies neuromodulation. Neuromodulators that bind to GPCRs are generally classified into Gq/11-protein coupling GPCRs (GqPCRs), Gs-protein coupling GPCRs (GsPCRs), and Gi/o-protein coupling GPCRs (GiPCRs) (Fig. 13). The so-called GqPCRs activate phospholipase C (PLC) that induces the hydrolysis of phosphatidylinositol 4, 5-biphosphate (PIP2). The product of PIP2 hydrolysis is diacylglycerol (DAG) and inositol- 1,4,5-trisphosphate (IP3), which is important for the activation of the IP3 receptor on intracellular Ca^{2+} stores. Production of DAG and elevated intracellular Ca^{2+} may typically lead to the activation of protein kinase C (PKC) (Fig. 13). As demonstrated in a variety of systems, Ca^{2+} store depletion activates several ion channels (403). By contrast, the GsPCRs and GiPCRs are coupled to adenylyl cyclase (AC), cAMP, and protein kinase A (PKA) activity, which can then directly regulate ion channels (373), among other effectors (Fig. 13).

All three GPCRs and their downstream pathways engage in extensive cross-talk (Fig. 14). This cross-talk significantly affects physiological functions, and must, therefore, be considered when trying to understand how neuromodulation and plasticity affect respiratory functions. Initial computational approaches described the existence of cross-talk between PKA and PKC and different GPCRs in the invertebrate Aplysia (17). Subsequent computational models also incorporated cross-talk between GqPCRs and GiPCRs (151). In addition, there is prominent experimental evidence for cross-talk between separate GPCR signaling pathways. For example, PKA-PKC cross-talk exists in the presynaptic terminals attached to the nucleus basalis of Maynert (272) and in heart cells (608). cAMP leads not only to the activation of PKA, but also to the elevation of intracellular Ca^{2+}, suggesting that this interaction results from cross-talk between PKA and PKC (457). These findings are very relevant for the respiratory system. Activation of both 5-HT1A (GiPCRs) and group mGluR (GqPCRs) results not only in PKA, but also PKC activation (157, 454). Cross-talk involving downstream cAMP has been reported for 5-HT1A and β-NE (GsPCRs) receptors (584). The cross-talk between these two receptors may also affect the level of voltage-gated Ca^{2+} influx (585). Additional examples of cross-talk exist between M3 ACh (GqPCRs) and β-NE, M3 ACh and M2 ACh (GsPCRs), kappa-opioid (GiPCRs), and β-NE receptors (220, 274, 408, 495). Within the respiratory network, cross-talk has also been identified in the neuronal control of long-term facilitation (218). Although cross-talk is highly relevant for understanding all aspects of neuromodulation, for simplicity, the next sections discuss these pathways separately.

The role of neuromodulators and G-protein coupled metabotropic receptors in regulating cation channels within the respiratory network

The activation of GPCRs modulates the gating properties of numerous ion channels (Fig. 3, Fig. 13). Several of these channels were discussed in previous sections, in the context of respiratory rhythm generation, chemoreception, and synaptic integration. Here, we will revisit some of these channels in the context of neuromodulation.

TRP channels and their modulation by GPCRs—TRP channels play critical roles in integrating not only intrinsic and synaptic properties, but also the modulatory inputs mediated by GPCRs. Our understanding of the diverse roles of TRP channels is still very limited for the respiratory system, However based on studies in a variety of other systems it can be expected that TRP channels will play equally important and diverse roles within the respiratory network. Activation of GqPCR can induce Ca^{2+} store depletion, which in turn facilitates the opening of store-operated nonselective cation currents (NSCCs) encoded by members of the TRP channel superfamily (152, 258, 469, 519, 601, 614), including TRPV6, and some TRPM and TRPC genes. The activation of TRPC channels by substance P could be mediated in part by this calcium-dependent mechanism (Fig. 15). Ben-Mabrouk and Tryba reported that the effect of NK1 receptor activation is inhibited by TRP channel blockers, and because the preBötC region contains TRPC3/7 immunostaining, it was suggested that TRPC3/7 receptors are a target NK1 receptor of modulation (21). Besides activating TRPC channels, GqPCRs also activate TRPV6 channels via their coupling to other second messenger cascades such as PIP2, DAG, and PKC (5, 561, 618). GqPCRs also activate TRPM4/5 through their coupling to DAG or IP3 induced Ca^{2+} release from internal stores (300, 576). This may be relevant for the neuronal control of breathing, since TRPM4/5 may be the I_{CAN}, as postulated by Crowder et al. (89) and Mironov (347). I_{CAN} was first described as a critical determinant of the respiratory network (404) at a time when the field was entirely focused on the role of I_{NaP} (51, 103, 104, 332, 446). Even though the exact molecular identity of I_{CAN} remains controversial, it seems to be modulated by mGluRs 1/5 (89, 347, 392). In the functional network, I_{CAN} is modulated by various modulators acting through GqPCRs. GqPCR receptors are known to activate TRPC (1, 2, 3, 5 and 6), TRPV6, and TRPM (3, 4, 5, 7, and 8) via a variety of second messenger systems (Fig. 15). It seems very likely that the effect of norepinephrine acting on the α-1 receptor is mediated through these GqPCR-activated pathways (Fig. 15). Norepinephrine specifically induces I_{CAN}-dependent bursting via α-1 adrenergic receptors in autonomously spiking neurons, which facilitates and amplifies inspiratory activity (578). Following the blockade of I_{CAN} with FFA, α-1-mediated amplification of inspiratory drive potentials was abolished (578). Interestingly, TRPM4/5 is activated by elevated internal Ca^{2+} that may result from receptor-mediated release of Ca^{2+} from internal stores (Liman, 2007; Vennekens and Nilius, 2007). This would be consistent with the hypothesized role of TRPM4 being activated in the soma of respiratory neurons following the activation of dendritic calcium waves (347). Because of their effects on cytosolic calcium, GqPCRs can activate TRPM4/5 in various ways, for example, by coupling to PIP2 or by IP3-induced Ca^{2+} release from intracellular stores (300, 576). Thus, in addition to phasic mGluR receptor-mediated activation of I_{CAN} (89, 347, 392), it seems likely that many of the known endogenously active neuromodulators will contribute to “tonic” activation of I_{CAN} within the respiratory network (578).

Modulation of channels of the K2P superfamily—GqPCRs are not only coupled to TRP channels, but they also modulate channels of the K2P superfamily which includes TREK, TASK, and TRESK (Fig. 15). Various forms of modulation have been described for these channels in a variety of systems. For example, both TREKs (1 and 2) are reported to be inhibited by the activation of PKC (131, 247, 364). But full suppression of TREK channels may also depend upon direct phosphorylation by PKA, acting through a reduction

in PIP2 sensitivity (311). A channel that has been implicated in the neuronal control of breathing is the TASK channel (18, 19, 264, 363). TASK channels are targeted by substance P and other neuromodulators, and they are directly inhibited by the activated Gq α-subunit itself, or via the Gq-induced PLC-PIP2 pathway which may directly suppress this channel without phosphorylation by PKC (72, 92). The GqPCR-dependent regulation of the TRESK channels seems to differ from the modulatory regulation of TREK and TASK (131) in that Ca^{2+}/calmodulin-dependent calcineurin directly affects TRESK, while TREK and TASK channels are unaffected by Ca^{2+} signaling (93). Although we are still at the beginning of our understanding of how respiratory neurons are modulated by different modulators, these examples illustrate that GqPCRs activation can potentially target many types of TRP and K2P channels which may be either activated or inhibited via various different intracellular mechanisms. These neurmodulators likely act by binding to GPCRs which then modulate TRP and/or K2P channels. Neutomodulators known to be critical for respiratory control include NE, 5-HT, ACh, SP, ATP, adenosine, TRH, dopamine, SST, GABA, and glutamate (112).

Norepinephrine and the modulation of GPCRs—Moreover, most of these modulators bind not only to GqPCRs, but also, to a variety of other GsPCRs or GiPCRs (Fig. 2; Fig. 14). NE receptors, for example, can be divided into three types of GPCRs, α-1, α-2, and β-NE receptors, which couple to Gq/11, Gi/o, and Gs-protein, respectively. From studies in a variety of systems we know that each of GPCRs affects a different complement of target ion channels. For example, NE binding to α-1 NE receptors (GqPCRs) suppress Cs^{+}- sensitive K^{+} channels in human osteoblast, Ba^{2+}- and TEA-sensitive heat-activated K^{+} channels in rat DRG neuron, and cardiac delayed rectifier K^{+} currents (262, 583, 605). α-2 NE receptors (GiPCRs) modulate, for example, N-type voltage-gated Ca^{2+} channels in cultured cerebellar neurons, delayed-rectifier K^{+} current, and Na^{+} current in rat sympathetic neurons (73, 292). β-NE receptors (GsPCRs) inhibit Ba^{2+}- and TEA-sensitive heat-activated K^{+} channels in rat DRG neurons (605). Within the respiratory network, we know that NE produces differential modulation on the two main types of respiratory pacemakers, resulting in an amplitude modulation of CS bursting pacemakers and frequency modulation for CI bursting pacemakers (578), but how exactly modulation of these bursting mechanisms is achieved remains unknown.

Serotonin, GPCRs, and implications for SIDS—A similar complexity of modulatory effects underlies modulation by serotonin. With the exception of the ionotropic 5-HT3 receptor, the various subgroups of 5-HT receptors can be classified according to their pharmacological profiles of binding to various synthetic agonists and antagonists (Fig. 3). Serotonin binding to 5-HT1A receptors regulates hyperpolarization activated non-selective cation channels (Ih) in rat DRG and N- and L-type Ca^{2+} channels in NTS (55, 233). Activation of 5-HT2 receptors decreases K^{+} conductance and Ca^{2+}- dependent K^{+} currents in subthalamic neurons (603). 5-HT4 receptors facilitate L-type Ca^{2+} channels in rat ventricular cardiomyocytes and I_h channels in CA1 pyramidal cells (32, 70). 5-HT7 receptors modulate I_h in rat DRG neurons (56). Within the respiratory network, 5-HT2, 5-HT4, and 5-HT7 receptors have been recognized as important modulators (201). In the preBötC, activation of 5-HT2 alters the bursting properties in CI and CS pacemaker neurons, effects that seem to be regulated through PKC (405). Bursting in CI pacemaker neurons seems to depend on activation by basally released serotonin, as blockade of 5-HT receptors abolishes bursting and reduces the persistent sodium current in CI bursting pacemaker neurons (405). As shown *in vivo*, *in vitro*, and *in situ*, the respiratory network becomes dependent on the persistent sodium current during hypoxia-induced gasping (399, 401, 404) and blockade of continuously activated 5-HT2 receptors abolishes gasping and abnormal respiratory activity (565). This is an interesting finding in the context of sudden infant death

syndrome (SIDS), as there is corroborative evidence that gasping is an important arousal and autoresuscitation mechanism, and that serotonergic mechanisms are significantly disturbed in SIDS patients (40, 46, 119, 120, 398, 444, 565, 590). Thus, a disturbance in serotonergic mechanisms could lead to a failure to autoresuscitate via a diminished drive for gasping (404, 565). Disturbances in serotonergic mechanisms could become particularly significant during hypoxic conditions when 5-HT levels are normally elevated. 5-HT levels rise coincident with the onset of respiratory depression (455), an observation that is consistent with c-FOS staining which indicates that raphe neurons are activated during hypoxia (132). However, it would be wrong to suggest that 5-HT2 activation is the only mechanism that determines respiratory activity during hypoxia. Activation of 5-HT1A receptors in the preBötC abolishes respiratory activity, which is consistent with *in vivo* data that suggest that 5-HT1A receptors are expressed on respiratory neurons and that receptor's activation suppresses excitability by activating on potassium currents (281, 453). Indeed, the existing data suggest a push-pull mechanism that relies on the differential activation of different serotonin receptors to determine the transitions from hypoxic augmentation to depression and, ultimately, to gasping. One possible scenario is that 5-HT1A receptor activation leads to the shutdown of the majority of respiratory neurons resulting in respiratory depression, thus protecting these neurons from excitotoxicity, as postulated by Richter et al. (455). By contrast, subsequent 5-HT2A activation may mediate the activation of bursting in persistent sodium-dependent pacemaker neurons which continue to be active to generate gasping, thus contributing to a critical role in autorescucitation, as postulated by Tryba et al. (565) and Pena et al. (404). But serotonin may not only play a critical role in hypoxic depression and autoresuscitation. A role of serotonin has also been implicated in recovery from opioid-mediated respiratory depression, since activation of 5- HT4 and 5-HT7 receptors can restore the respiratory rhythm and inhibition by opioids (322, 454).

Substance P and integration with other neuromodulators—Serotonin is coreleased with substance P (SP), and like 5-HT, SP also plays a critical role in generating hypoxic response (28, 273, 502, 547, 577, 597). SP activates the respiratory frequency at the network and behavioral level (105, 112, 185, 186, 405, 510, 555). In the *in vitro* and *in vivo* respiratory network SP stabilizes the respiratory rhythm. Like serotonin, SP slowly depolarizes spiking neurons and activates bursting in CS pacemakers. In CI pacemakers, it causes an increase in burst amplitude, frequency, and duration (406). SP activates neurokinin-1 (NK1) receptors (186) coupled to Gq/11-proteins that in turn activate phospholipase C (PLC). This intracellular cascade induces I_{CAN} which contributes to the SP effects on burst amplitude. As described above, these modulatory effects involve the activation of TRP channels. How serotonin, substance P, as well as norepinephrine interact in a state-dependent manner has recently been studied in both intact and *in vitro* preparations (112). Based on these studies, it was concluded that the activation of NK1 receptors may work only within a narrow range of the awake-sleep state, as the activity of NK1 receptors is completely masked by the concurrent activation of α-1 NE or 5-HT2 receptors (112). This study focused on the interaction and convergence of these neuromodulators at the level of the GqPCRs. More detailed information will be needed as it relates to the potential cross-talk and intracellular interactions that govern this convergence (111).

Acetylcholine and the modulatory control of breathing—Cholinergic inputs provide equally important modulatory drive to the respiratory system, where they modulate nicotinic and muscarinic receptors (50, 80, 174, 204, 368, 497, 498, 500). Muscarinic ACh (mACh) receptors can be classified into two types: (1) M2 and M4 ACh receptors acting as GiPCRs, while (2) M1, M3, and M5 Ach receptors act as GqPCRs. All of these ACh receptor subtypes are localized within the CNS. As shown in a variety of different systems, M2 AChRs generally increase K^+ and decrease Ca^{2+} conductances, while M3 AChR inhibit

TREK-2 channels (247), activate the NALCN channel (540), and inhibit the TASK-1 channel (37). Within the preBötC, M3 ACh receptor antagonists increase the input resistance of preBötC inspiratory neurons, suggesting that cation channels (K^+ channels) are closing under this condition (500). Muscarinic modulation has also been linked to SIDS, as prenatal nicotinic exposure seems to significantly suppress muscarinic receptor signaling and activates nicotinic modulation (80). This is interesting, as muscarinic receptor activation seems to be involved in the generation of sighs and concurrent depression of eupneic respiratory activity, thus representing another form of a push-pull mechanism for respiratory control (563). At the cellular level, cholinergic modulation differentially altered two types of bursting in a subset of CI pacemakers (563). As observed by recordings from a single neuron, cholinergic activation concurrently enhanced the frequency of large-amplitude bursting, while inhibiting the frequency of the relatively small-amplitude bursts. As demonstrated in a study by Tryba et al. (563), muscarinic activation altered not only the ratio of autonomously generated low and large amplitude bursts at the cellular level, but it also altered the ratio between small and large amplitude population bursts at the network level. The frequency of low-amplitude bursts representing fictive eupneic activity was inhibited, while the frequency of large amplitude bursts representing fictive sigh activity was increased. Thus, the shift in the autonomous activity generated within single neurons mirrored the activity of the network. The frequency of large amplitude sighs was significantly increased and small amplitude eupneic bursts were significantly decreased both in slices and the working heart brainstem preparation, which suggests that this is not just an "*in vitro* artifact" (563). This opens the intriguing hypothetical possibility that this modulatory push-pull mechanism may originate at the level of single neurons. These effects are likely mediated by M3 muscarinic receptors. But again, it must be emphasized that this most certainly is not the complete pictire, as ACh modulates respiratory activity not only via muscarinic, but also nicotinic receptors (497, 498, 499, 500, 563).

The generation of sighs has also been implicated in the arousal and autoresuscitation response, a failure of which may lead to SIDS (158, 404, 550, 551). Relevant for SIDS is also the fact that cholinergic mechanisms play a critical role at the interface between breathing and sleep (287). Intrinsic cholinergic drive is in part mediated by the pedunculo-pontine tegmental area, an area which is known to cause breathing instabilities and an increased generation of postsigh apneas (476). Thus, cholinergic modulation is not only relevant in the context of SIDS, but also sleep apnea (59, 253, 557). Carbachol injections into the peduncolo-pontine tegmental area significantly increase the apnea index in intact rats (59). Moreover, glutamate injection into this region causes erratic breathing and apneas (474, 475). These respiratory effects are possibly mediated by cholinergic action on the respiratory neurons within the preBötC, involving mechanisms studied by Tryba et al. (563), especially since the respiratory effects seem to be closely related to cholinergic neurons (557). Much like the situation already discussed for the preBötC, a complex integration with serotonergic modulation also plays a critical role in these pontine modulatory effects (476). Although it goes beyond the scope of this review, to fully understand the neuronal control of breathing and its state-dependent relationship to sleep and wakefulness, it will be important to integrate all modulatory processes not only within the medulla as emphasized in this review, but also within the pons, hypothalamus, and many other supraspinal regions (65). These modulatory processes potentially include cholinergic (94), serotonergic (575), cannabinoids (58), orexinergic (124, 228, 254, 276, 377, 549, 552, 598, 610), adenosine (573), and histaminergic mechanisms (123, 354).

Prenatal nicotine exposure and long-term plasticity—Given that sleep and breathing are closely linked by their common cholinergic mechanisms, and that nicotine is a major risk factor in SIDS, there is increased interest in understanding the consequences of prenatal nicotine exposure on the developing respiratory network (54, 80, 159, 223, 225,

420, 421). Indeed, it has been elegantly demonstrated that prenatal nicotine exposure decreases excitatory synaptic transmission within the XII nucleus and increases intrinsic excitability of XII motoneurons (421). Moreover, prenatal nicotine exposure increases the frequency of spontaneous apneas and, most dramatically it blunts the hypercapnic response and reduces the hypoxic response (137, 224). Prenatal nicotine exposure also alters long-term plasticity, an effect that becomes particularly relevant in the context of repeated hypoxic exposures (163). Direct effects on the respiratory network alter the respiratory frequency due to an effect on the α4/β2 nicotinic ACh receptors located presynaptically on glutamatergic neurons (319, 420). However, at the same time, prenatal nicotine exposure strengthens GABAergic synaptic transmission (318). An interesting opportunity to study the developmental impact of prenatal nicotine exposure is offered by the amphibian model system which exhibits different distinct developmental stages (45).

ATP and purinergic modulation—Neuromodulatory processes associated with ATP have also received considerable attention. In particular, this is the case, since ATP is the major energy source for the maintenance of cells, and also serves as an important extracellular agonist for ATP-specific receptors referred to as purinergic P2 receptors (P2Rs) (49). P2Rs can be divided into P2X and P2Y receptors. The former receptor type form non-GPCR ionotropic receptors, while the latter are metabotropic GPCRs. As discussed earlier for the other modulators, many different ionic mechanisms are associated with purinergic modulation. ATP binding to P2Y1 receptors (GqPCRs) affects I_h channels in trigeminal neurons (222), Ca^{2+} signaling in cultured rat hippocampal astrocytes (266), and inwardly rectifying cation permeability in Xenopus oocytes (379). The respiratory rhythm generated within the preBötC is sensitive to the activation of both P2X2 and P2Y1 receptors, which excite the respiratory rhythm during hypoxia conditions (179, 313). The P2Y1R-mediated increase in respiratory frequency appears to involve the activation of a mixed cationic conductance within the preBötC (312). The role of adenosine in mediating the hypoxic response has also been studied *in vivo* (453, 455, 486).

ATP is cleared from the extracellular space by being sequentially metabolized to ADP, AMP (595), and adenosine (257). Adenosine has long been known to reduce neurotransmitter release (207). Thus, metabolized adenosine that derives from ATP performs a negative feedback on both pre- and postsynaptic sites. Adenosine binds to adenosine (A) receptors classified as A1 (GiPCRs), A2A (GsPCRs), A2B (GsPCRs and GqPCRs), and A3 receptors (GiPCRs). Activation of A1 receptors inhibits neuronal excitability mediated by the modulation of N-type Ca^{2+} channels, both within the peripheral nerve system (PNS) and the CNS (365, 623), and facilitates G-protein-coupled inwardly rectifying K^+ (GIRK) channels and small conductance Ca^{2+}-dependent K^+ (SK-K_{Ca}) channels (79). A3 adenosine receptors attenuate the Ca^{2+} rise accompanying NMDA-R activation in retinal ganglion cells (619), and activate a PKC-sensitive Cl^- current in ciliary epithelial cells (508). Within the respiratory network, adenosine acting on A1 receptors hyperpolarizes respiratory neurons, whereas blockade of A1 receptors increases respiratory activity, suggesting that A1 receptors are tonically activated in preBötC respiratory neurons (486).

TRH, dopamine, and somatostatin—Early on, thyrotropin-releasing hormone (TRH) receptors have been implicated in respiratory control (99). Two types of TRH receptors (TRH1 and TRH2) have recently been recognized as GqPCRs (129). Within the respiratory network, TRH receptors are localized in NTS and the hypoglossal nucleus (XII nucleus). Further, it was recently published that TRH is coreleased with serotonin within the preBötC from the raphe obscurus (423). TRH induces rhythmic bursting in neurons within respiratory-related regions of the guinea pig NTS (99) and it stimulates central respiratory

rhythmic activity (219). However, it is still unknown what molecular type(s) of TRH receptors (TRH1 or TRH2) mediate(s) the effects on respiratory rhythms (111, 216).

Dopamine has also been implicated in respiratory control (280). The dopamine receptors are divided into two types: (1) D1-like (D1 and D5) (GsPCRs) and (2) D2-like (D2, 3 and 4) (GiPCRs). Much is known about the role of D1- like receptors in a variety of systems. These receptors modulate voltage-dependent Ca^{2+} channels in rat striatal aspiny neurons, I_h conductance in rat retinal ganglion cells, resting K^+ conductance in mouse subthalamic nucleus, and nonselective cation channel in primary cultured striatal neurons (10, 74, 314, 320). Within the respiratory network, D1-like receptor agonists prevent opioid receptor induced tonic discharges in expiratory neurons (280). D2-like (including D4) receptors activate nonselective cationic conductances in dorsal raphe serotonin neurons (9), and it has been demonstrated that D4 receptors disperse synchronization of respiratory neurons within the pFRG (162).

Somatostatin (SST) receptors have been used to define the anatomical limits of the preBötC (488). All SST receptor subtypes belong to GiPCRs. SST1 receptors activate inwardly rectifying K^+ conductance (75, 241, 255). In insulin-producing INS-1 cells SST2 and SST3 receptors suppress R-type voltage-gated Ca^{2+} channels (340). SST4 receptors inhibit spiking and L-type voltage-gated Ca^{2+} channels in rat retinal ganglion cells (140), and they couple to Kv7 (KCNQ) channels (M-currents) in hippocampal CA1 pyramidal neurons (428). SST5 receptors activate both K_{ATP} channels and GIRK channels in MIN-6 cells (517). Thus, in most systems Gi/o protein coupling of SST receptors has an inhibitory action. Not surprisingly, within the respiratory network SST receptors suppress the respiratory rhythm (308). But the specific subtypes of SST receptors are still not identified in the preBötC (308, 544).

Metabotropic GABA and glutamate receptors—GABA and glutamate receptors should also be considered in the context of neuromodulation. $GABA_B$ receptors are metabotropic receptors (GiPCRs), and within the respiratory network $GABA_B$ receptors modulate GIRK channels (415), Ba^{2+}-sensitive K^+ conductances (242), and voltage-dependent calcium currents (393). The mGluRs are generally divided into group I, II, and III receptors (296). Group I mGluRs are predominantly localized postsynaptically, while group II and III mGluRs are expressed at both pre- and postsynaptic sites (373). In a variety of systems it has been demonstrated that group I mGluRs modulate I_{CAN} currents, I_h currents, TRP-like channels, and K2P channels (39, 72, 82, 128, 138, 256, 391, 392). For inspiratory neurons, it has been demonstrated that glutamate binds to group I mGluRs, which supports I_{CAN}-dependent mechanisms (347, 392). Moreover, glutamate seems to bind also to group III mGluRs to modulate the generation of sighs [Figure 6 (296)]. Interestingly, group III mGluRs are known to exert their effects via the cAMP second messenger pathway involving the activation of Gi-proteins [Figure 13 (83, 366)]. However, pharmacological manipulations suggest that the effects on the sighs involve a direct inhibition of P/Q type calcium channels via the G-protein βγ-subunits because manipulating the downstream second messenger pathways had no effects on the sigh (208, 229, 296, 344).

The endogenous release of neuromodulators within the respiratory network—There is a large body of literature on the endogenous release of neuromodulators within the respiratory network. Nore-pinephrine is, for example, released from A5 and A6 nuclei, which provides the preBötC with local medullary input from noradrenergic neurons (112). Endogenous NE release continuously facilitates the respiratory rhythm through an integrated activation of α-1, α-2, and β-noradrenergic receptors (112). Under synaptically isolated conditions, NE differently affects different types of inspiratory neurons within the preBötC *in vitro* (578). NE induces I_{CAN}-dependent bursting properties in spiking neurons (Fig. 4),

and depolarizes CI bursting pacemakers and increases their burst frequency. In CS pacemakers, NE increases the burst amplitude of the depolarizing drive potential, as well as the number of action potentials during the burst. But NE does not affect the burst frequency of CS pacemakers (578). This differential effect is preserved at the network level, since only the modulation of population burst amplitude, but not frequency, depends on the activation of I_{CAN} (578). Therefore, by inducing bursting in pacemaker neurons, NE cannot only change the balance between bursting and spiking pacemakers, but also the differential modulation of frequency, amplitude, and burst shape among CI and CS pacemakers, which may have very specific consequences at the network level.

The preBötC receives, in addition, innervation from 5-HT and SP containing terminals derived from raphe nuclei, and it has been demonstrated that 5-HT and SP are indeed functionally co-released within the preBötC (423). Ruangkittisakul et al. reported that the preBötC generates eupneic rhythmic activity under the influence of caudal structures and tonically released TRH-like transmitters, while eupnea-sigh activity is predominantly controlled by the influence of rostral structures and SP-like transmitters (461). This raises the interesting concept that different rostro-caudal structures of the respiratory network may be associated with distinct modulatory influences that differentially regulate different modes of respiratory activities. Electrostimulation of the raphe magnus facilitates 5-HT release and leads to the activation of 5-HT2 receptors within the preBötC, which resulted in an increase in respiratory frequency (112). The respiratory rhythm within the preBötC is also continuously modulated by direct cholinergic projections. Physostigmine, an acetylcholinesterase inhibitor, microinjected into the preBötC, increases the respiratory rhythm, which suggests that the respiratory rhythm is continuously activated by basal endogenous ACh release (500). Although it is sometimes automatically assumed that modulatory effects within the preBötC are neuronal in nature, it must be emphasized that glia cells likely play an equally critical role in neuromodulation. ATP, for example, is stored and released from glia cells located at the ventral surface of medulla. These glia cells likely play an important role in respiratory rhythm generation, in response to changes in pH and hypoxic conditions (178, 528).

Concluding remarks—Complex modulation of cellular activity in respiratory neurons is achieved through a variety of neuromodulators. Various intracellular second messenger pathways are activated by G-protein coupled receptors, with the potential for interplay and cross-talk between these pathways. An understanding of these complex interactions will provide important insights into the modulation of respiratory activity and its ability to adapt to environmental and behavioral cues. Pathophysiological consequences may arise from disorders of these neuromodulatory mechanisms. While most existing studies focus on neuronal modulation, much needs to be learned about the modulatory role of glia cells.

Conclusion

This review provided a broad overview of the various cellular properties of brainstem respiratory neurons. We described the various inward and outward currents, G-protein coupled receptors, and intracellular mechanisms that modulate these ionic currents and the functional context in which these currents operate. The emerging picture is exceedingly complex and dynamic. This dynamic property applies not only for the processes that govern the generation of the respiratory rhythm, but also for the processes that adapt the respiratory network to changes in the behavioral and metabolic states of the organism. Indeed, all cellular properties are integrated to varying degrees into every aspect of respiratory function, and it is impossible to functionally separate roles such as rhythm and pattern formation, chemosensation, and neuromodulation. The various cellular properties described in this review function as building blocks of the respiratory network and it is safe to conclude that

there is no function that depends on just a single cellular property or principle. These building blocks are dynamically activated and deactivated, and they converge and diverge in the behaving animal. Even an apparently similar type of breathing behavior, such as eupnea, may involve different configurations of the respiratory network. The artificial removal of any of these building blocks will evoke transitions into different network states that may or may not replicate certain aspects of a given behavior. Although much has been learned about cellular integration within the preBötC, it is clear this network is integrated in a wider network that extends throughout the neuronal axis. Together, all these interactions are responsible for the generation of breathing, which is clearly one of the most integrated and important behaviors of any organism.

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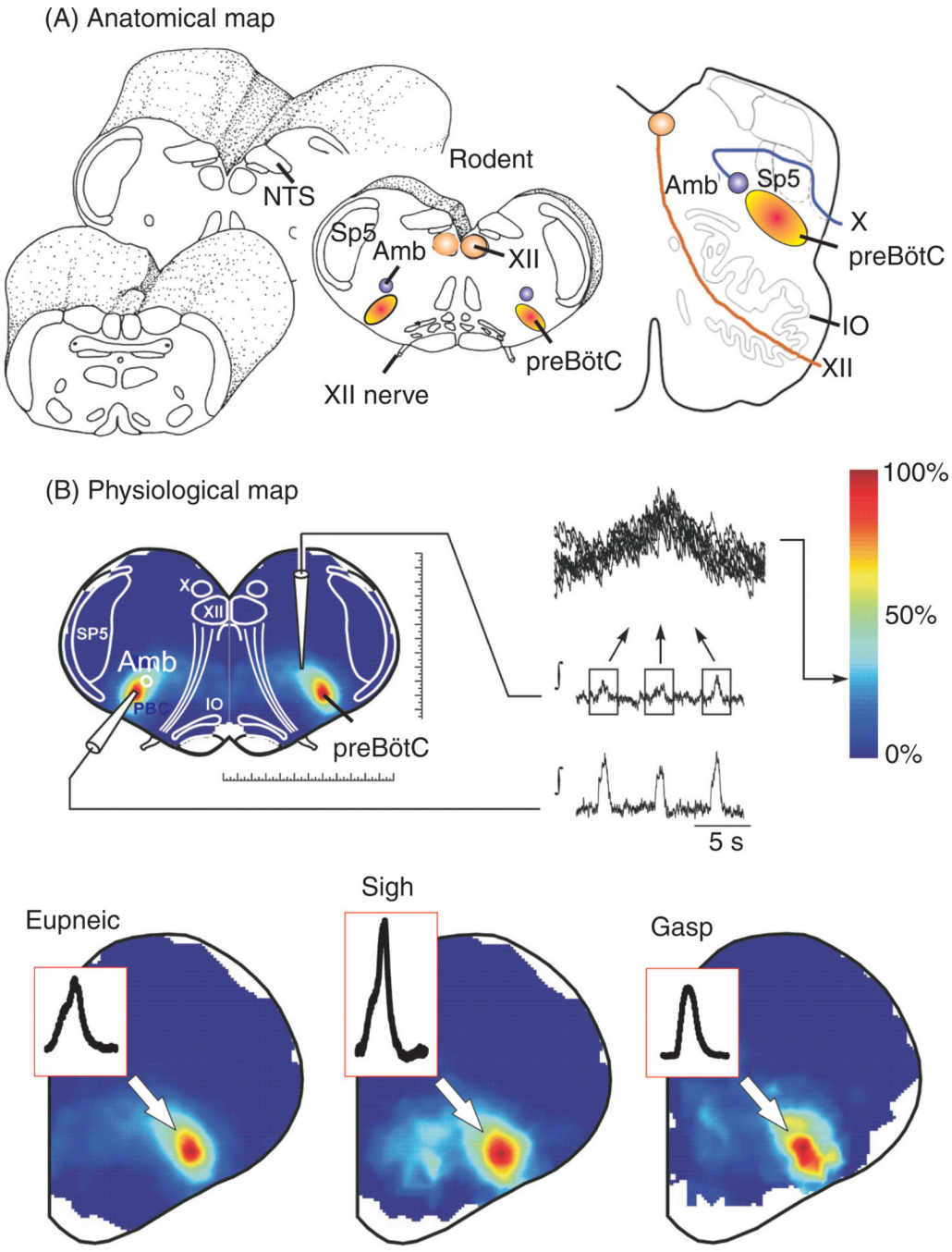

Figure 1.

Anatomical and physiological characterization of the pre-Bötzinger complex (preBötC) in the ventrolateral medulla. (A) Anatomical maps of brainstem regions from rodent [*left* (436)] and human (*right*, modified, with permission, from reference (489) containing the preBötC. The location of the preBötC is anatomically characterized by the same transverse section as the nucleus ambiguus (Amb), inferior olive (IO), nucleus tractus solitarius (NTS), and hypoglossal nucleus (XII). (B) Isolating the preBötC in a single medullary brainstem slice from rodents preserves rhythmic neuronal activity implicated in the generation of inspiratory activity. Heat maps of activity show both an anatomical and physiological

overlap of neuronal activities representing fictive eupnea (*left*), sighs (*center*), and gasps (*right*). Modified, with permission, from reference 299.

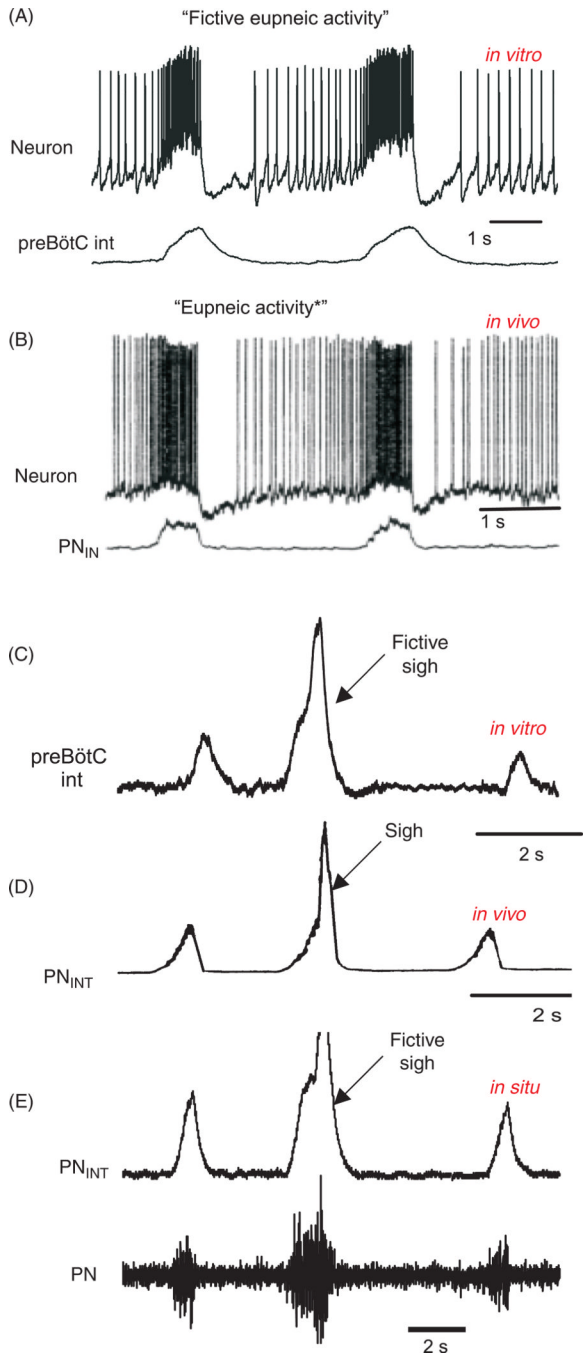

Figure 2.

Simultaneous intracellular whole cell recordings and integrated extracellular population recordings from pre-Bötzinger (preBötC) respiratory neurons (A) *in vitro* from a mouse brain slice exhibiting "fictive" eupneic activity and (B) *in vivo* from an anesthetized rat, during "eupneic activity" (modified, wih permission, from reference 490). (C) Integrated population recordings *in vitro* of a fictive sigh recorded with a surface electrode from the preBötC in a mouse brain slice and (E) from a working heart-brainstem preparation (WHBP). (D) A sigh recorded *in vivo* from the phrenic nerve (PN) from an anesthetized cat (modified, with permission, from reference 76).

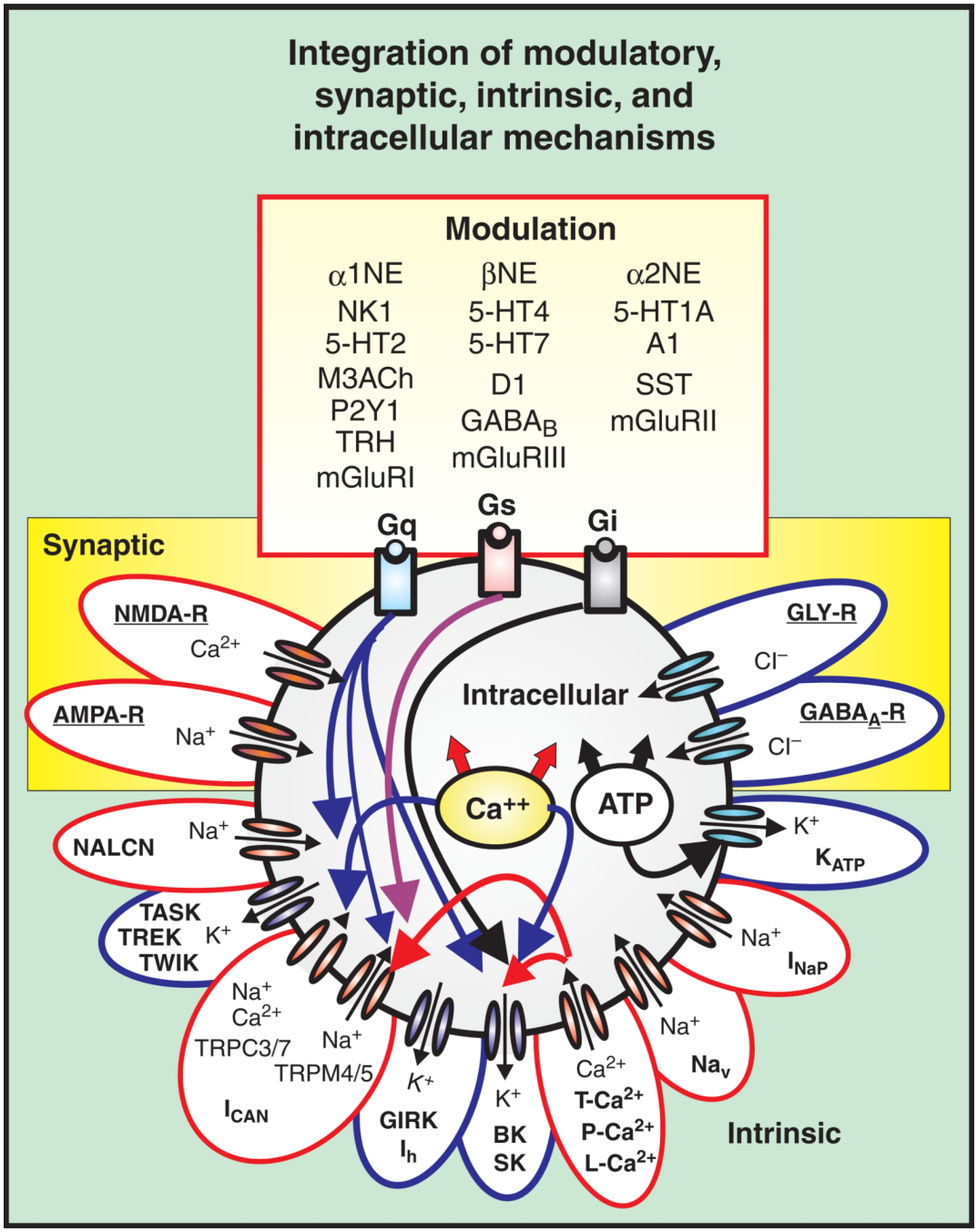

Figure 3.

Putative inspiratory neurons of the preBötC integrate modulatory, synaptic, intrinsic, and intracellular mechanisms that give rise to bursting. Modulation commonly involves a cascade of mechanisms mediated through metabotropic glutamate receptors (mGLUR-I, II, III), noradrenergic receptors (α1, α2, and β-NE), serotonergic receptors (5HT-1A, 2, 4, and 7), peptidergic (NK1-R), and purinergic receptors (P2Y1) that represent G-protein-coupled protein receptors (G_s, G_i, and G_q) and act on various intracellular signal transductions. Synaptic mechanisms involve ionotropic glutamatergic (AMPA-R, NMDA-R), GABAergic ($GABA_A$-R), and glycinergic receptors (GLY-R) that rapidly change membrane potential and hence, neuronal excitability when activated. Intrinsic mechanisms refer to other

membrane conductances that are not strictly synaptic, but also regulate neuronal excitability. These include, but are not limited to: (1) leak conductances, (TREK, TWIK, TASK, and NALCN); (2) calcium conductances (T, P, and L-Ca^{2+}); (3) K^+ conductances (K_{ATP}, BK, SK); (4) sodium conductances (Na_v, I_{NaP}); and nonspecific cation conductances, I_{CAN} (TRPC-3, 7, and TRPM-4,5). Intracellular mechanisms refer to the molecules and ions regulating intracellular signaling cascades and ultimately lead to changes in excitability. For example, Ca^{2+} and ATP influence neuronal excitability through indirect mechanisms affecting the conductances generated through various channels such as the K_{ATP}, and I_{CAN}. Blue outlines represent hyperpolarizing conductances, while red outlines represent depolarizing conductances.

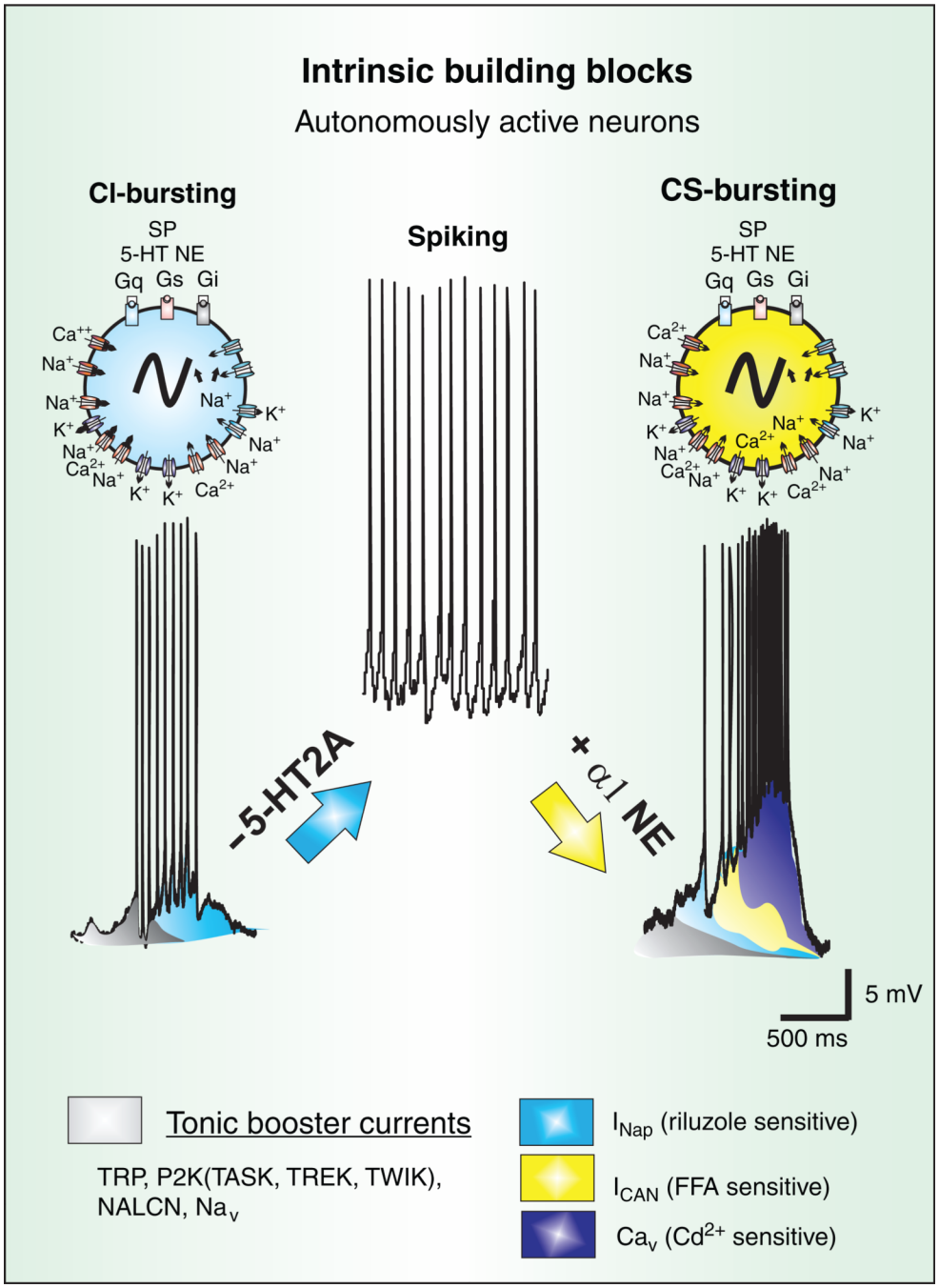

Figure 4.

Autonomously active neurons are part of the spectrum of intrinsic building blocks responsible for rhythmic population bursts in the preBötC. At the cellular level, a diversity of mechanisms exist to produce several forms of bursting that have different pharmacological properties. Some neurons express cadmium-insensitive bursting (CI) that is riluzole sensitive, and therefore, appears to be mediated by I_{NaP} (blue). Other neurons express cadmium-sensitive bursting (CS), predominantly mediated by both voltage-dependent Ca^{2+} currents (Ca_v) and a FFA-sensitive I_{CAN}. Moreover, pharmacological blockade of 5HT2A receptors can turn CI-bursting into tonic spiking while activation of a1-noradrenergic receptors in tonic spiking neurons into CS-bursting. This type of conditional

bursting demonstrates that the role of autonomously active neurons in the preBötC may not be fixed. Hence, while both forms of bursting, CI and CS, depend on dominant current(s) to drive spontaneous bursting, all putative inspiratory neurons of the preBötC appear to possess tonic boosting currents (grey), the I_{NaP} (blue), I_{CAN} (yellow), and Ca_v (purple).

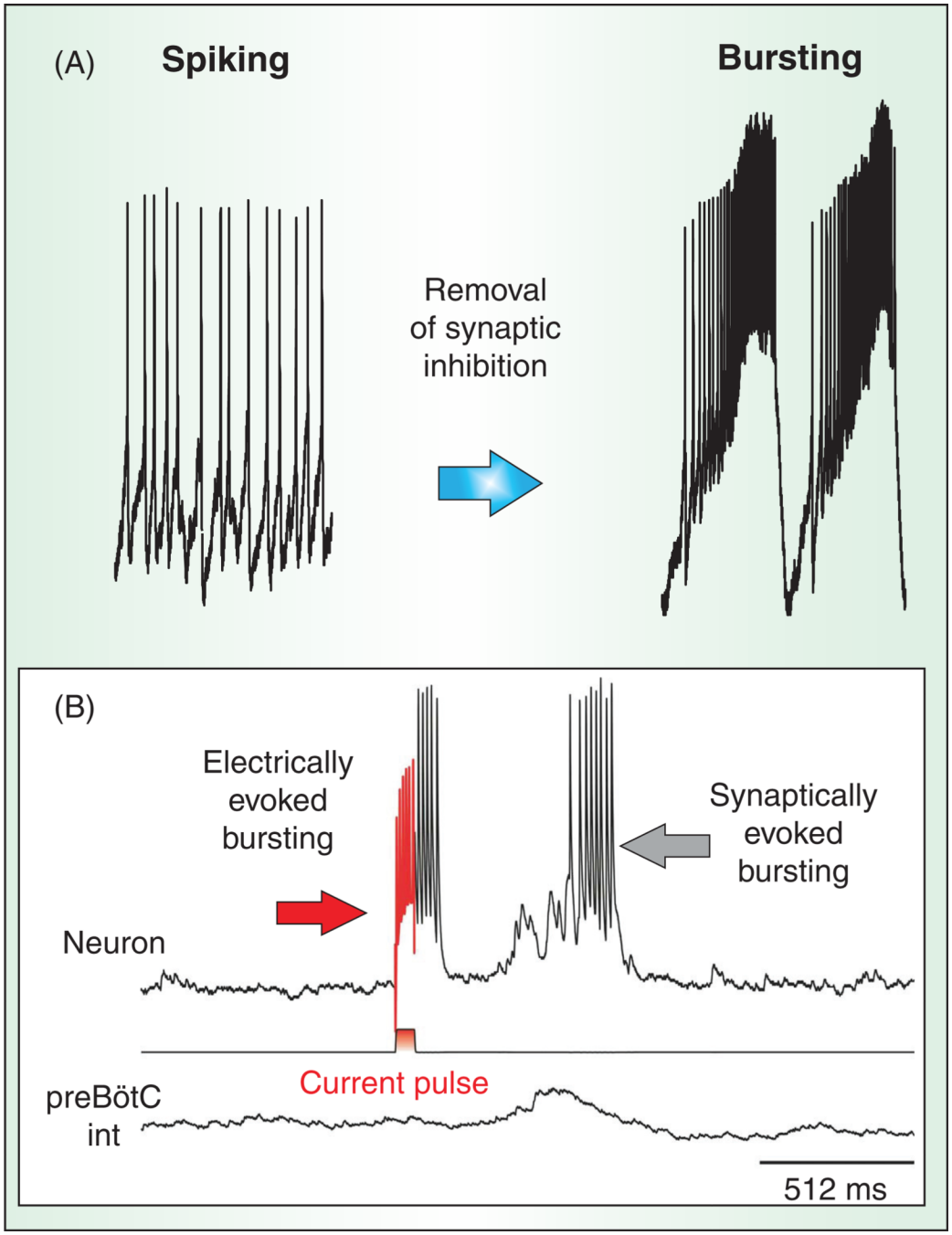

Figure 5.
Synaptic modulation of bursting properties. (A) Pharmacological removal of synaptic inhibition can alter the propensity of a respiratory neuron to switch from a tonic spiking into a bursting mode. (B) In a simultaneous intracellular and population recording, a burst of action potentials can be triggered in the cell by a brief positive current injection (rd) or by synaptic input occurring during the population burst.

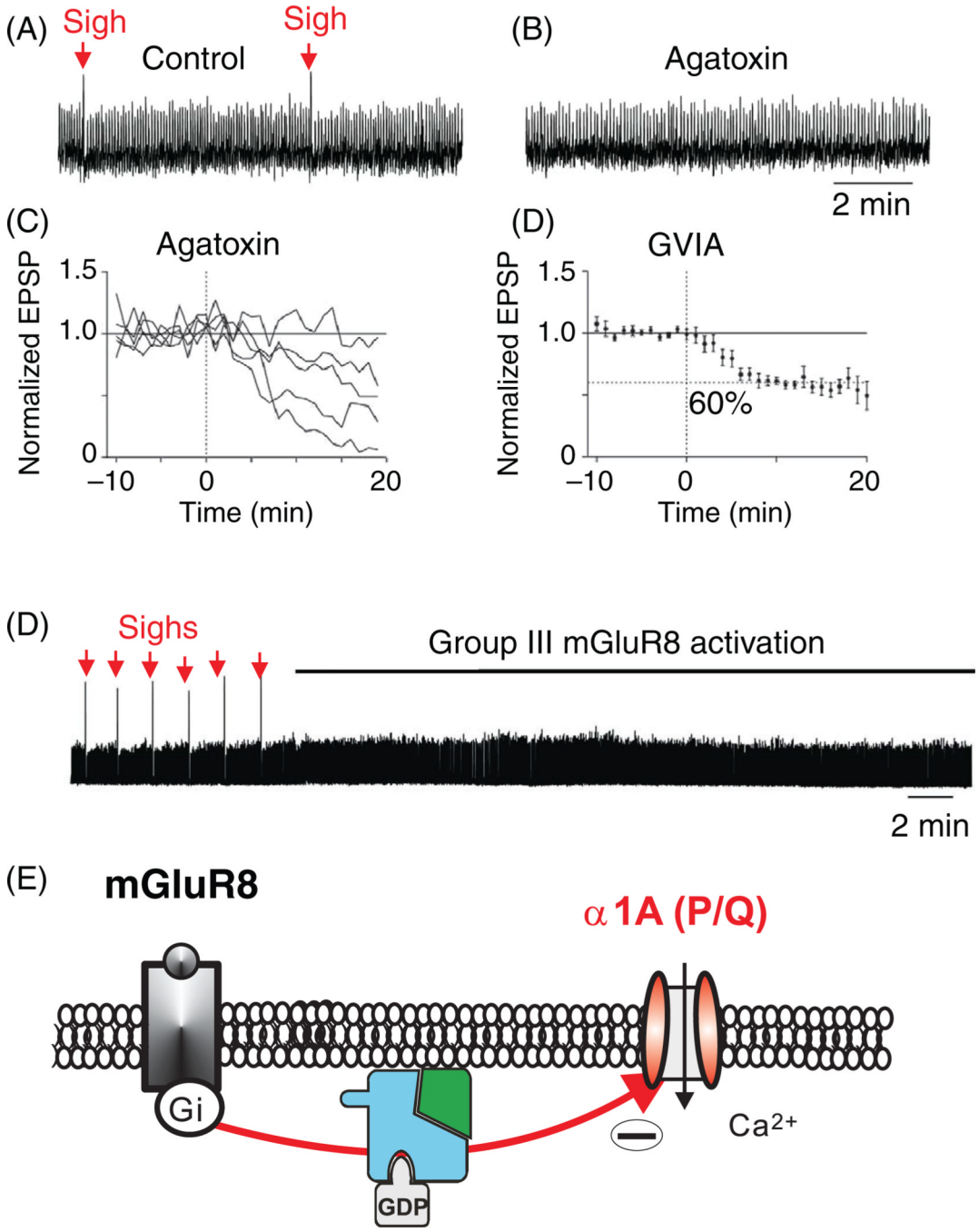

Figure 6.

Generation of fictive sighs depends on the activation of P/Q-type calcium channels. Pharmacological blockade of the P/Q type channels with ω-agatoxin TK specifically abolishes sighs. (A) Sighs recorded under control conditions in population recordings from the preBötC (sighs indicated by red arrows) and (B) after bath application of ω-agatoxin TK, at low concentrations (modified, with permission, from reference 297). (C) Reduction of the amplitude of intracellularly recorded evoked EPSPs (by electrical stimulation of the contralateral preBötC) in respiratory neurons by pharmacological blockade of P/Q-type calcium channels. Individual responses of five neurons to ω-agatoxin TK [120 nmol/L] show a variable response, with a minimum of 8% reduction and a maximum of 90%

reduction. (D) Individual responses to the N-type specific calcium channel blocker GVIA [0.5 μmol/L], showing a homogeneous 40% reduction of evoked EPSPs (modified, with permission, from reference 297). (E) Activation of the metabotropic glutamate receptors (mGluR8) leads to specific inhibition of "fictive sighs" recorded from the preBötC (modified, with permission, from reference 296). (F) Hypothesized mechanism of action for the inhibition of P/Q-type calcium channels by activated mGluR8 receptors, through a direct inhibitory interaction with the β-subunit of the heterotrimeric G-protein.

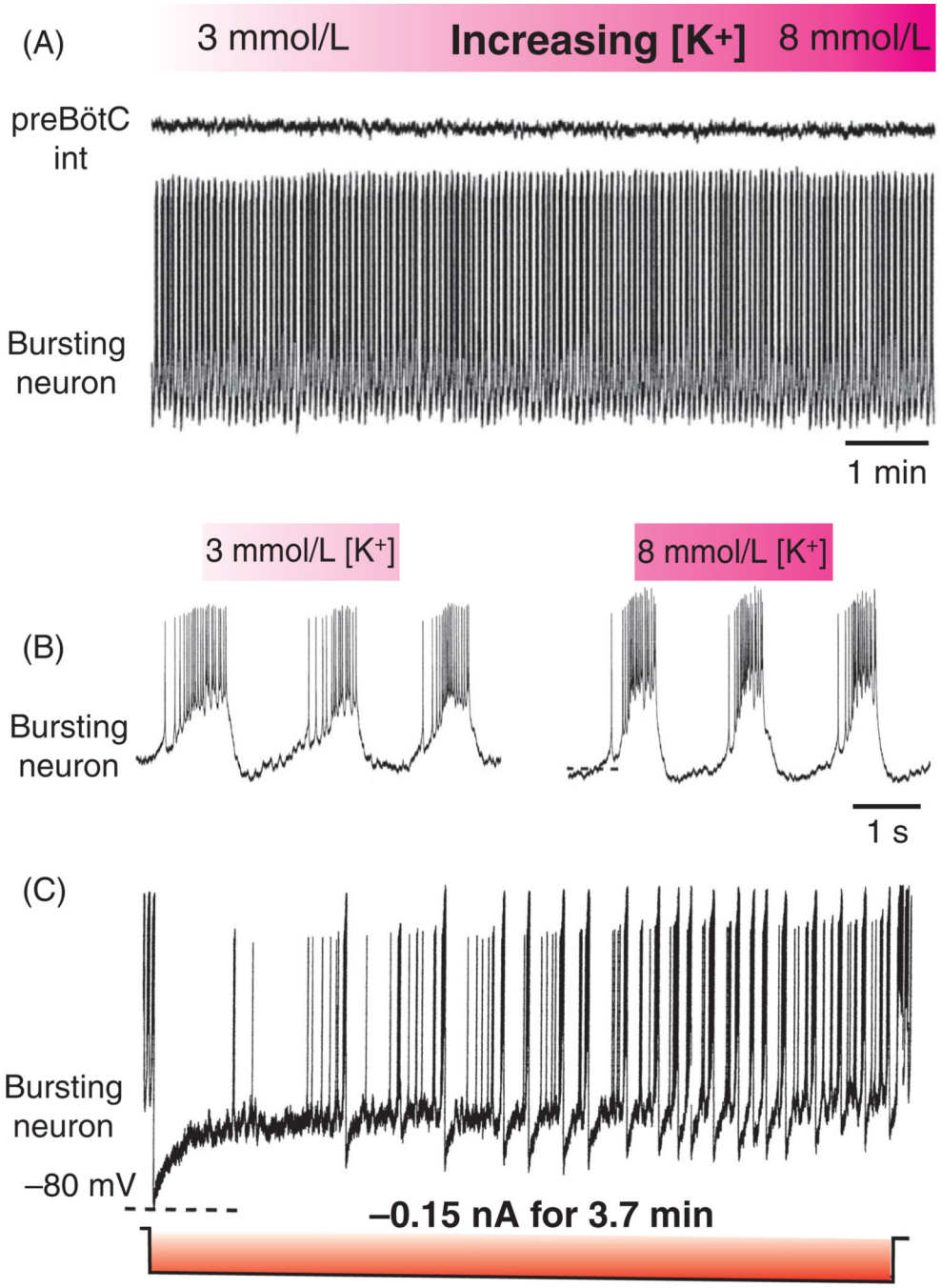

Figure 7.

Pacemaker neurons are able to burst throughout a range of extracellular potassium concentrations with the contribution of the persistent sodium current. (A) An intracellular recording from an individual pacemaker neuron illustrating autonomous bursting throughout a range of extracellular potassium concentrations (3–8 mmol/L) without significant changes to membrane potential. (B) Traces expanded from A of the autonomously bursting pacemaker at 3 mmol/L (*left*) and 8 mmol/L (*right*) extracellular K^+. (C) Autonomous bursting involves I_{NaP} as revealed by long-lasting hyperpolarizing current injections that cause the neuron to cease bursting, but as it intrinsically depolarizes bursting is resumed.

Hence, pacemaker neurons do not require artificial elevation of extracellular potassium to autonomously burst (77, 564, 566).

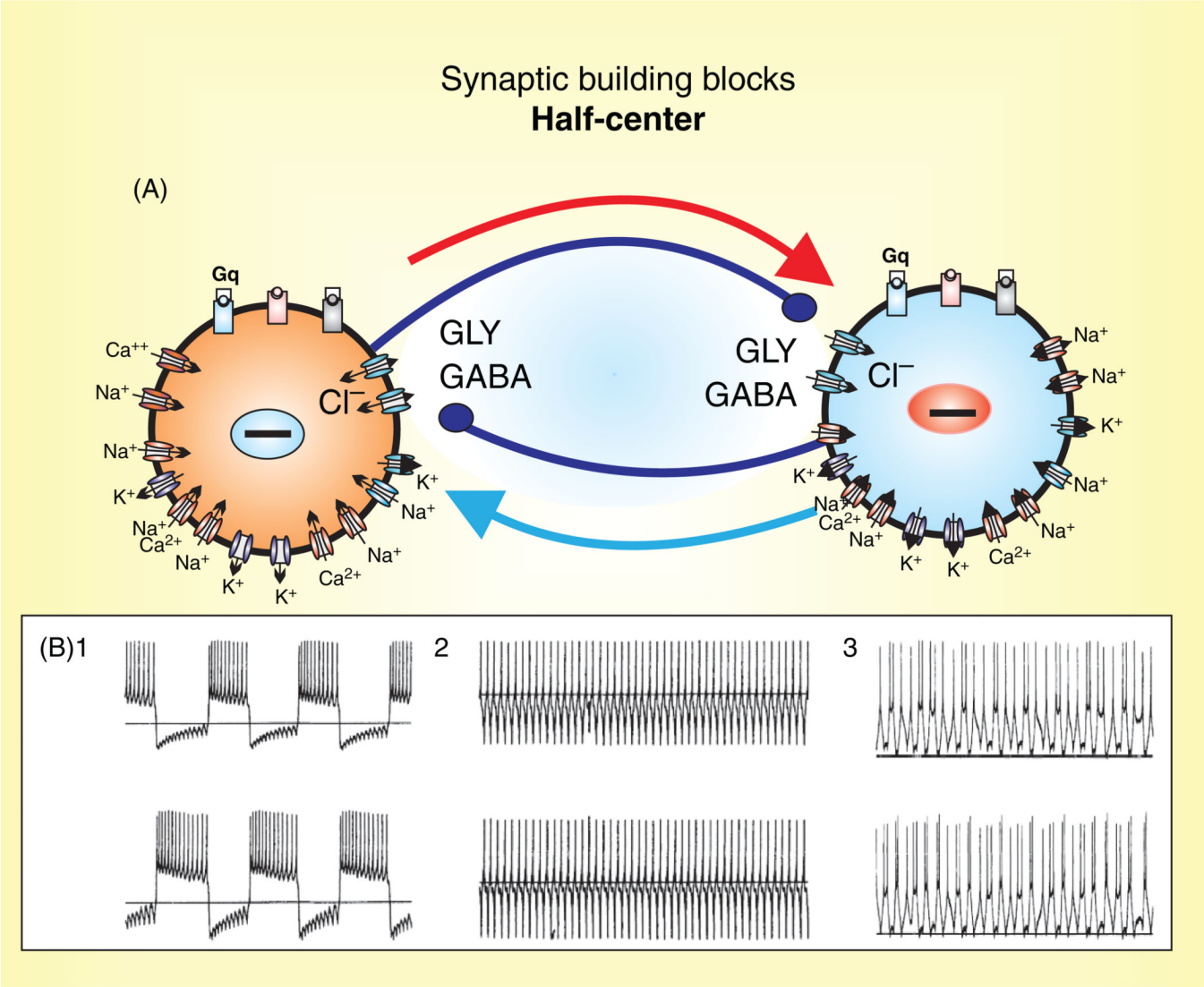

Figure 8.

Synaptic inhibition and its potential role in the generation of rhythmic network activity. (A) Schematic cartoon of a half center model with neurons connected by reciprocal inhibition. (B) Neurons connected to a dynamic clamp establish an artificial half center and can produce a variety of patterned outputs, as shown. Examples of a half-center model exhibiting (B1) alternating slow oscillations, (B2) antiphasic spiking, or (B3) high-frequency half-center oscillation. Output of the half-center model is highly dependent upon the synaptic and ionic conductance parameters defined by the dynamic clamp (modified, with permission, from reference 503).

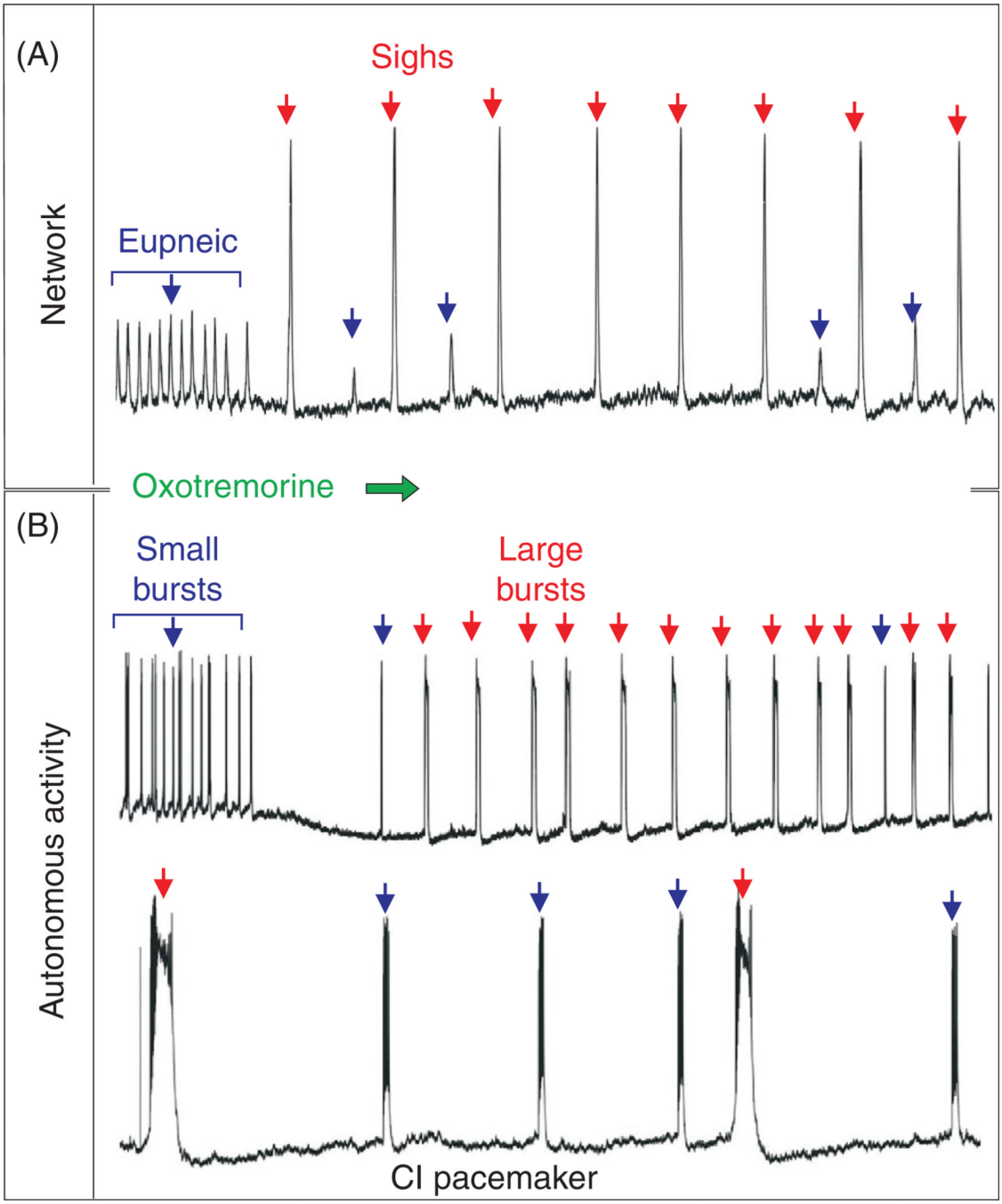

Figure 9.
Network and cellular responses of respiratory neurons to muscarinic receptor activation. (A) Bath application of the muscarinic agonist oxotremorine stimulates fictive sigh activity (*red arrows*), while inhibiting eupneic activity (*blue arrows*). (B) Bath application of oxotremorine induces the generation of two distinct burst patterns recorded from a CI pacemaker neuron, isolated from fast synaptic transmission (modified, with permission, from reference 563).

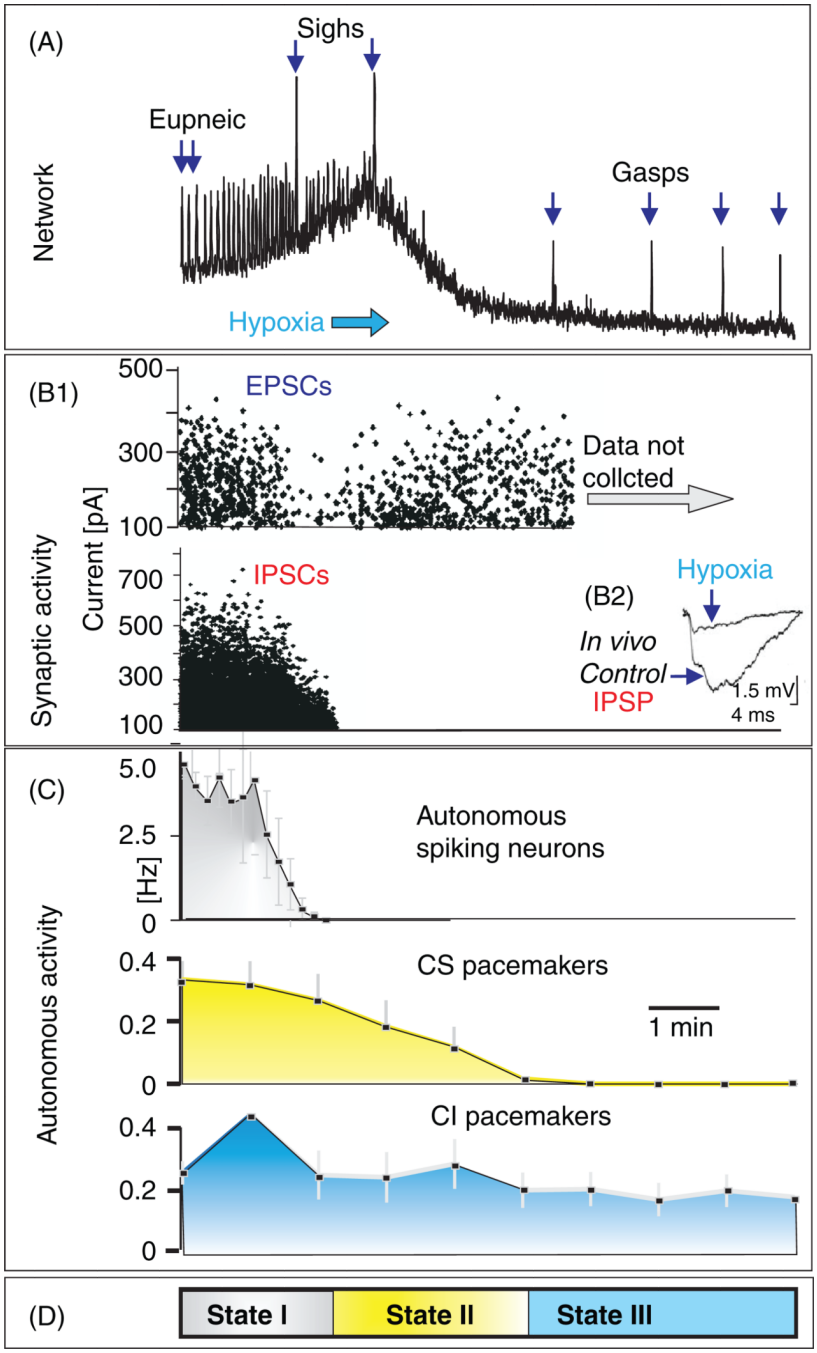

Figure 10.

Network reconfiguration of the preBötC during hypoxia, at the cellular and network level. (A) Typical biphasic network activity response of the preBötC during hypoxia, assessed by integrated population recording from the preBötC. After an early augmentation phase, activity enters a late depression phase. During this response, activity changes from a “fictive eupneic” to a “fictive gasping” mode of activity. Note the generation of multiple “fictive sighs” during the augmentation phase. (B1) Plot of spontaneous excitatory and inhibitory postsynaptic currents (ESPCs and IPSCs) recorded from a preBötC respiratory neuron in response to hypoxia. Note the dramatic reduction of IPSCs during hypoxia. (B2) IPSCs recorded *in vivo* from a respiratory neuron of an anesthetized cat, before and during hypoxia

(modified, with permission, from reference 486). (C) Average activity of three subsets of autonomous active neurons, in response to hypoxia. Tonically firing autonomous spiking and cadmium-sensitive (CS) pacemaker neurons hyperpolarize and cease firing during hypoxia (State I and State II). (D) By contrast, cadmium-insensitive (CI) pacemaker neurons continue to fire under hypoxia, even with persistent exposure to hypoxic conditions (State III) (modified, with permission, from references 404 and 553).

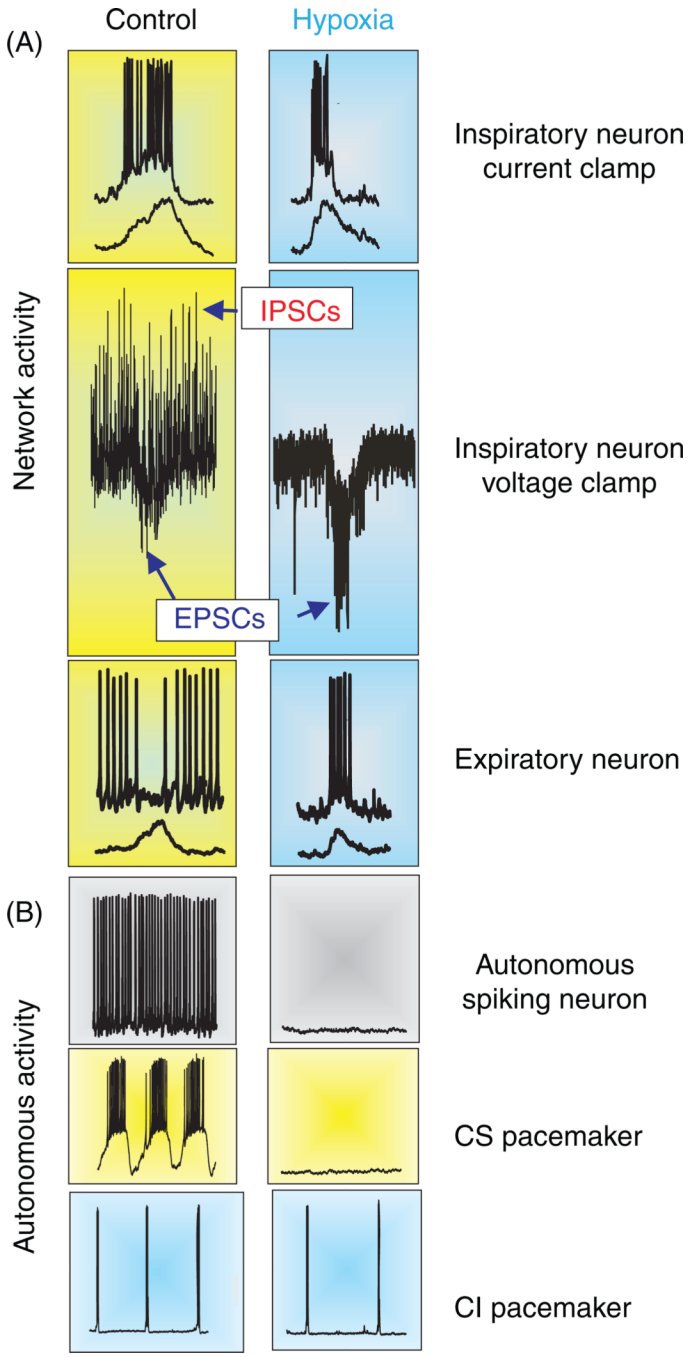

Figure 11.

Examples of activity pattern changes in respiratory neurons during hypoxia. (A1) Current-clamp recording from an inspiratory neuron showing an augmenting burst pattern under control normoxic conditions, switching to a sharply rising and decrementing burst under hypoxia. (A2) This change in network-initiated burst patterns coincides with a decrease in spontaneous inhibitory postsynaptic currents (IPSCs), measured in voltage clamp. (A3) Example of an expiratory neuron that receives inhibitory synaptic input under normoxic conditions, switching to excitatory synaptic input under hypoxia. (B) Examples of autonomous activity in three subsets of respiratory neurons isolated from fast synaptic transmission, before and during hypoxia. Tonic firing neurons and CS-pacemaker neurons

become silent, while CI-pacemaker neurons continue to generate bursting activity under hypoxia.

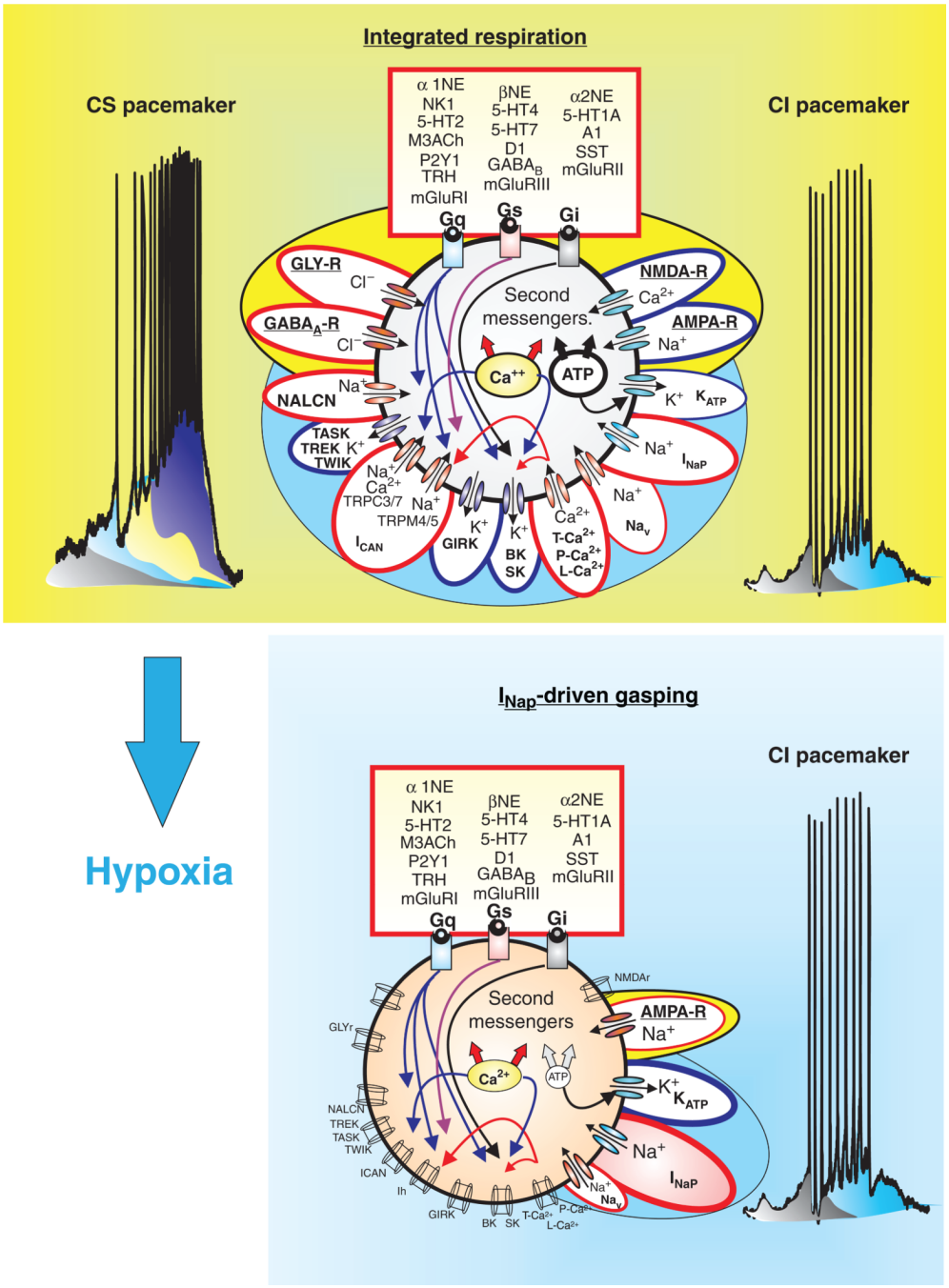

Figure 12.

The diverse interaction and relative contribution of multiple mechanisms (see Figure 3) in a single neuron gives rise to a neuronal population that possesses heterogeneous properties used to generate bursting and ultimately contribute to the eupneic rhythm. This integrated respiration during eupnea provides both stability and dynamic responsiveness. Hypoxia reconfigures the network to a state dominated by the I_{NaP}, K_{ATP}, and the AMPA receptor (AMPA-R) and various forms of neuromodulation. At the cellular level, I_{NaP} appears to be the basis for bursting involved with the gasping rhythm (i.e., I_{NaP}-driven gasping).

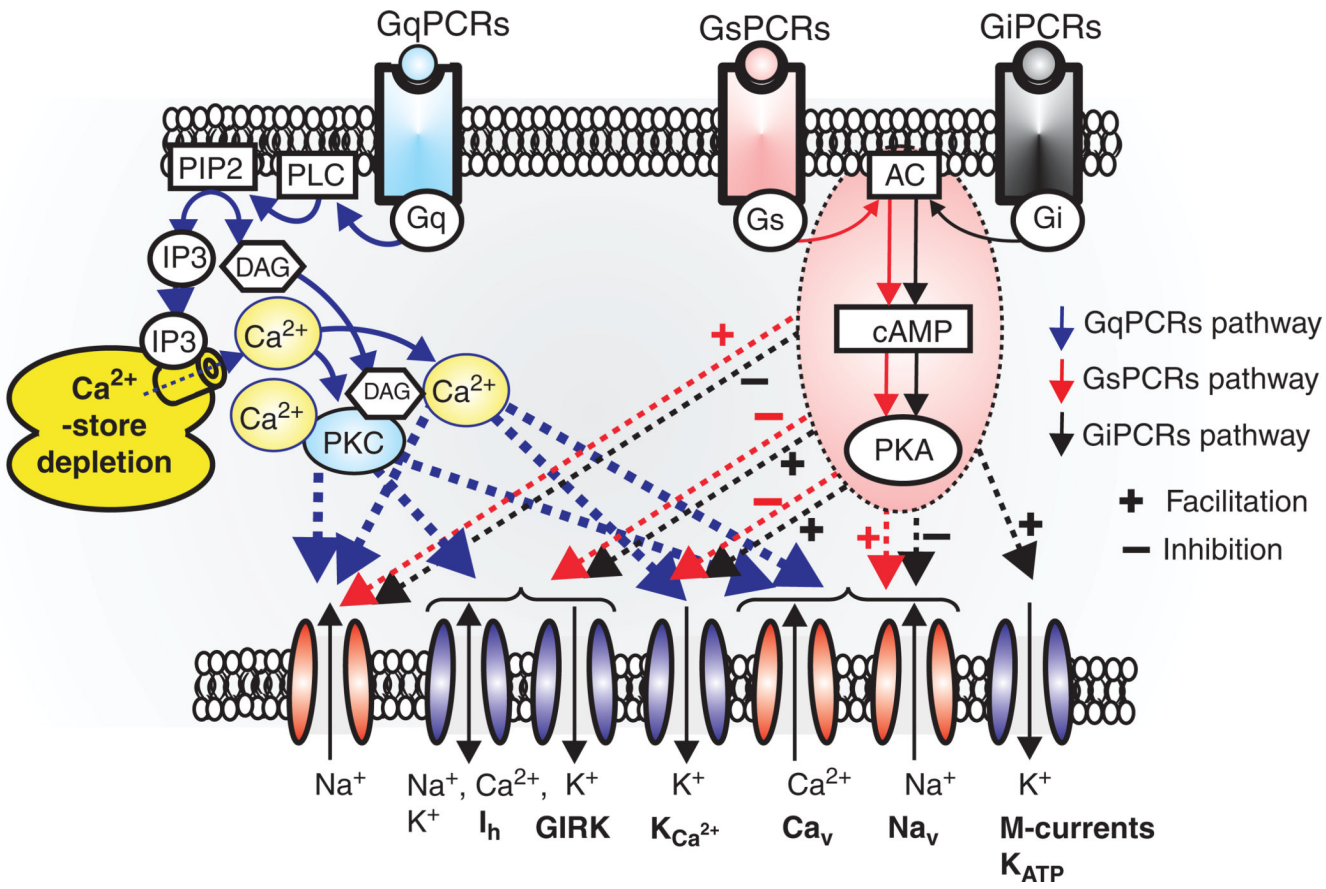

Figure 13.

Downstream pathways and effector channels for Gq/11, Gs, and Gi protein coupled receptors. Gs protein coupled receptors (GsPCRs) and Gq/11 protein coupled receptors (GqPCRs) are in general excitatory systems, and Gi protein coupled receptors (GiPCRs) are inhibitory systems. Both GsPCRs and GiPCRs regulate AC, cAMP, and PKA, and GqPCRs facilitate Ca^{2+} release from Ca^{2+} store and protein kinase C (PKC). These second messenger proteins up- and downregulate open probability of several voltage-dependent cation channels. PIP2 (phosphatidylinositol 4,5-biphosphate), PLC (phospholipase C), IP3 (inositol-1,4,5-trisphosphate), DAG (diacylglycerol), PKC, AC (adenylyl cyclase), cAMP (cyclic AMP), PKA (protein kinase A), I_{CAN} (calcium-activated nonspecific cation current), I_h (hyperpolarization activated non-selective cation channels), GIRK (G protein coupled inward rectifier K^+ channels), KCa^{2+} (Ca^{2+}-activated K^+ channels), Cav (voltage-dependent Ca^{2+} channels), Nav (voltage-dependent Na^+ channels), M-current (muscarinic receptor activated K^+ channels), and K_{ATP} (ATP-sensitive K^+ channels).

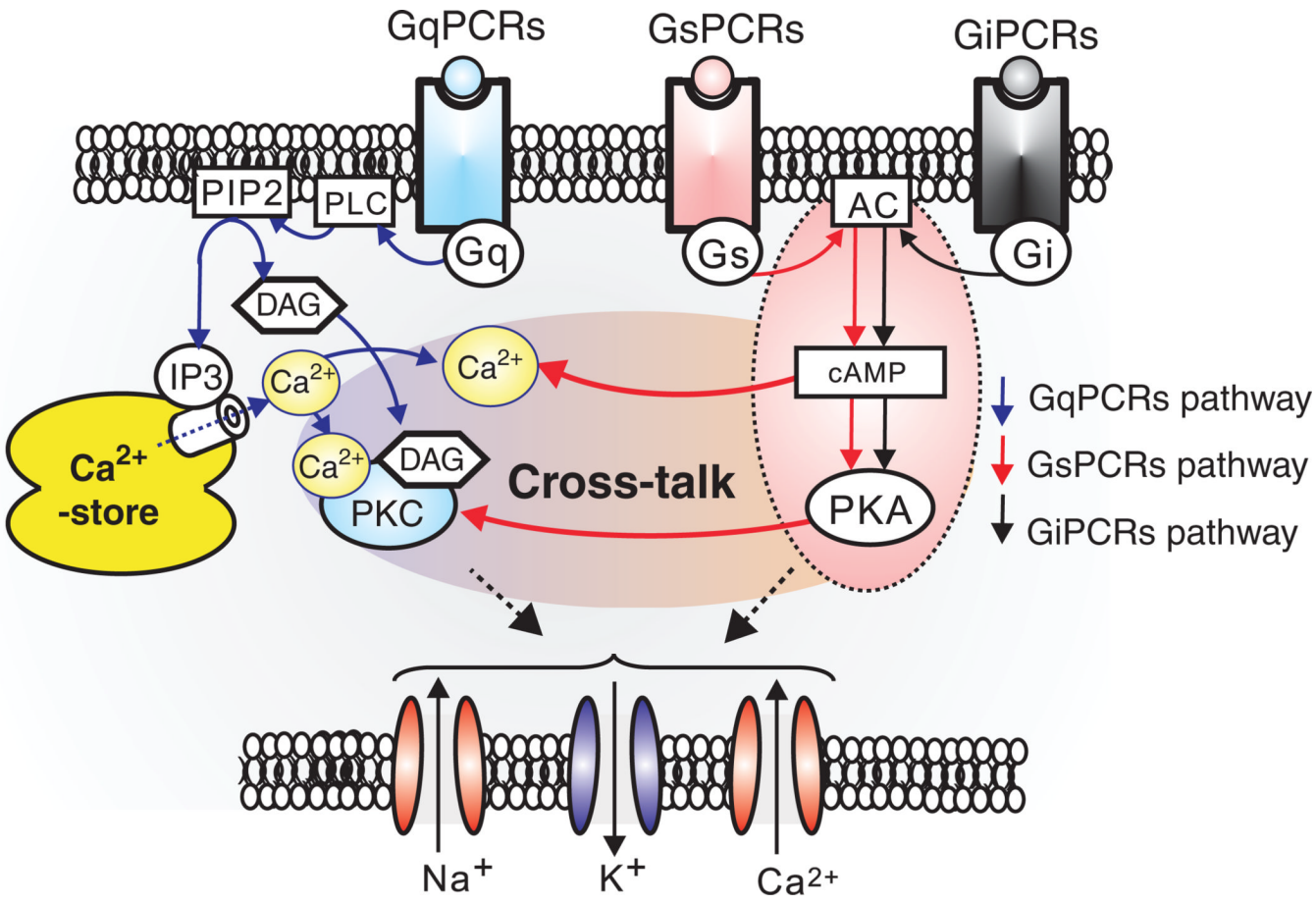

Figure 14.

Cross-talk between Gq/11 and Gs system. It has been thought that each of the GqPCRs and Gs(i)PCRs systems are separated. However, recent studies suggest GsPCRs-related cAMP production or activation of PKA stimulates elevation of intracellular Ca^{2+} and activation of PKC (17, 151, 272, 457, 608).

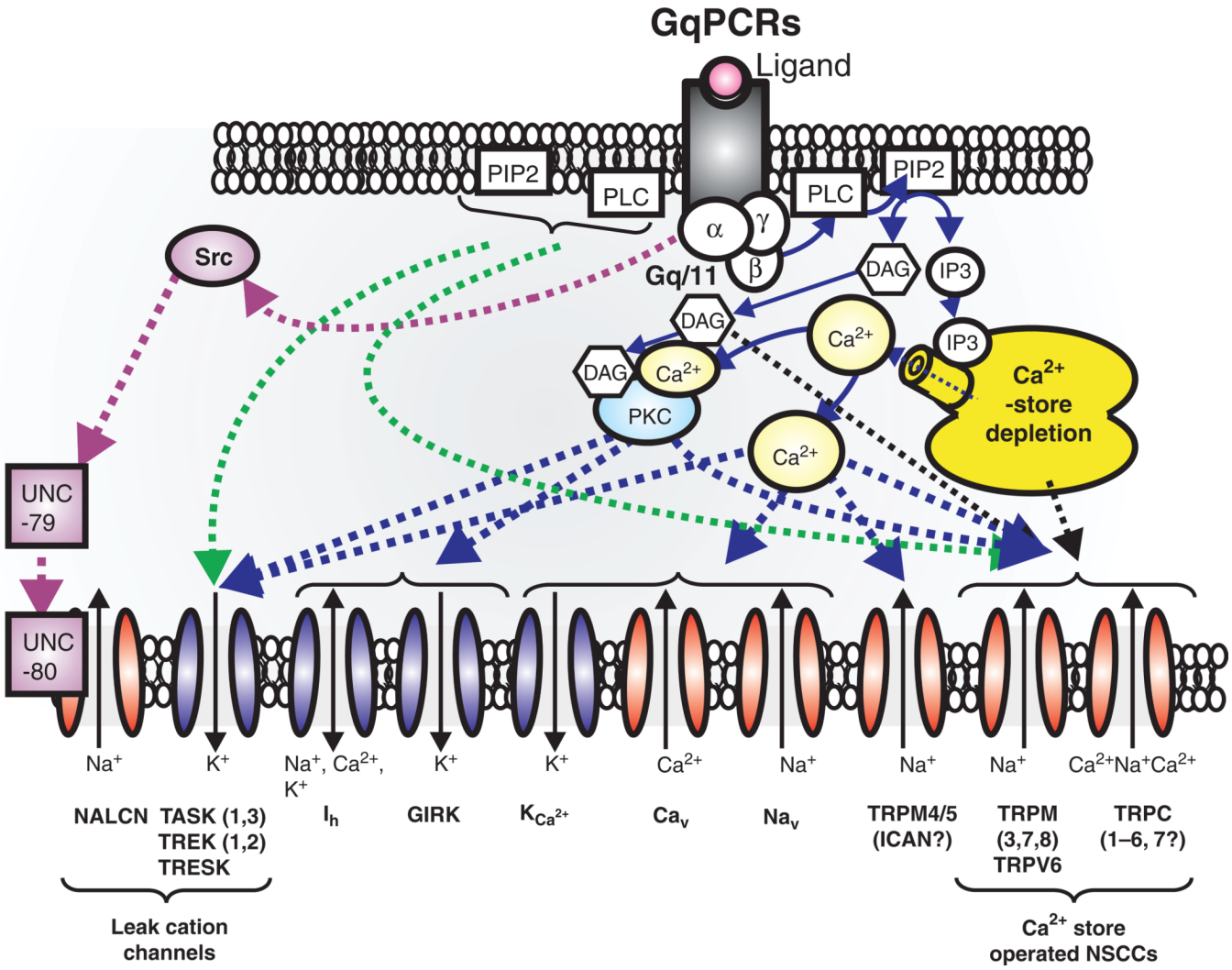

Figure 15.

GqPCRs regulates not only voltage-dependent cation channels, but also transient receptor potential (TRP) and leak cation channels. GqPCRs-induced depletion of Ca^{2+}-store facilitates activation of Ca^{2+}-store operated NSCCs, such as TRPC (1–6, 7), TRPM (3, 7, 8) and TRPV6. On the other hand, TRPM4/5 may be directly activated by elevation of internal Ca^{2+} concentration (300, 576). GqPCRs seem to modulate activity of K2P (TASK, TREK, and TRESK) and sodium-leak-channel-nonspecific (NALCN) channels. In particular, GqPCRs act through Src protein controls NALCN channels through both UNC-79 and UNC-80 (316, 317, 491, 540). Abbreviations; P2K (“two-pore” potassium channels, TASK, TREK, and TRESK channels), TRPM (transient receptor potential melastatin), TRPV(transient receptor potential vanilloid), TRPC (transient receptor potential canonical), Ca^{2+} store operated NSCCs (nonselective cation currents), and Src (sarcoma) is a proto-oncogenic and nonreceptor tyrosine kinase.