Advances in Parasympathetic Control of Heart Rate and Cardiac Function

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It is well known that the neuronal projections from the brain to the heart strongly influence cardiac function, and an abnormal activity has been implicated in diseases such as cardiac arrhythmia and sudden infant death syndrome. This short review describes recent advances focused on the neurobiology of cardiac vagal neurons, utilizing cellular techniques.

Heart rate is dominated by the activity of the cardioinhibitory parasympathetic nervous system (4). In conscious and anesthetized animals, including humans, dogs, cats, rats, and mice, there is a tonic level of parasympathetic cardiac nerve firing and little, if any, sympathetic activity to the heart at rest. During increases in arterial pressure, the initial reflex-induced slowing of the heart is caused primarily, if not exclusively, by increases in cardiac vagal nerve activity. During decreases in arterial pressure, the baroreflex-induced tachycardia is caused by decreases in parasympathetic nerve activity in addition to increases in sympathetic nerve activity (4).

When both parasympathetic and sympathetic activity are present, parasympathetic activity generally dominates. Increases in parasympathetic activity to the heart evoke a bradycardia that is more pronounced when there is a high level of

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References


sympathetic firing. When there is a moderate or high level of parasympathetic activity, changes in sympathetic firing elicit negligible changes in heart rate. There are a number of hypotheses concerning the mechanisms responsible for this interaction. The release of acetylcholine from parasympathetic neurons might act presynaptically to inhibit the release of norepinephrine from sympathetic nerve terminals. The parasympathetic-sympathetic interaction might also be the result of competition postsynaptically between different guanine nucleotide-binding (G) proteins within the membranes of sinoatrial pacemaker cells.

In many diseases, including hypertension and heart failure, cardiac vagal activity is diminished and unresponsive (14). The relative absence of cardiac vagal activity, or a diminished respiratory modulation of cardiac vagal activity, is often used clinically as an index of pathophysiology and the likelihood of sudden cardiac death. Restoration of cardiac vagal activity lessens ischemia and reperfusion-induced arrhythmias and decreases risk of sudden death after myocardial infarction, suggesting that increases in cardiac vagal activity could be an effective clinical target in heart diseases (13).

Neurophysiology of cardiac vagal neurons

It is widely accepted that parasympathetic activity originates from the central nervous system rather than from peripheral ganglia (5). Pre-ganglionic cardiac vagal fibers are tonically active, with a firing pattern that is pulse synchronous and most active during postinspiration and reduced during inspiration. Section of the pre-ganglionic fibers, leaving only postganglionic innervation intact, releases the heart from parasympathetic inhibition.

The study of cardiac vagal activity in the central nervous system has been exceptionally difficult in vivo. This is caused by many factors, including the relatively small population of cardiac vagal neurons, experimental difficulties antidromically activating these neurons from their cardiac fibers projecting to the heart, and the location of their soma deep within the brain stem in a poorly defined and heterogeneous nucleus ambiguus. Furthermore, these studies have been hampered by the deleterious effects of the required surgical procedures, which include opening the chest, exposing the brain stem, anesthesia, and the difficulty of controlling the experimental conditions in these in vivo preparations.

More recent attempts at examination of cardiac vagal neurons, especially at the cellular level, have been greatly advanced with new methodological strategies including infrared visualization of neurons in in vitro brain stem slices coupled with the retention of physiological identity using retrograde fluorescent tracers. Using these techniques in this laboratory, we can visually identify and electrophysiologically manipulate cardiac vagal neurons with patch-clamp methodologies (6, 9–11).

Among the first hypotheses tested in this laboratory was whether cardiac vagal neurons in the rat possess pacemaker-like activity (6). The results, as illustrated in Fig. 1, demonstrate that in the absence of synaptic activity, cardiac vagal neurons in the nucleus ambiguus are normally silent. Cardiac vagal neurons do not display any pacemaker-like activity such as repetitive or phasic depolarizations or action potentials. However, depolarizing currents (as little as 100 pA) are sufficient to evoke repetitive firing in cardiac vagal neurons. This activity occurs with little delay and minimal spike frequency adaptation during maintained depolarizing currents.

The voltage-gated currents that have been characterized in these neurons and are responsible for these firing properties include a rapidly activating and inactivating Na current (9). Surprisingly, this Na current is relatively resistant to tetrodotoxin (TTX), requiring 10 mM TTX for complete blockage. Voltage-gated K currents include a transient K current.
that can be blocked by 4-aminopyridine (4-AP) and a tetraethylammonium (TEA)-sensitive delayed rectified K channel. Also present, and responsible for the afterhyperpolarization that occurs after firing, is a Ca-activated K channel that is blocked by apamin (6). These currents, among others, are responsible for the firing characteristics of cardiac vagal neurons and enable them to follow fast synaptic drive closely, without adaptation, as well as integrate long lasting modulatory influences.

The absence of pacemaker activity in cardiac vagal neurons in vitro is consistent with the results from the rare successful in vivo studies. In such studies that have successfully identified and examined cardiac vagal neurons with extracellular electrodes, the great majority (identified by antidromic stimulation) were silent (5, 6). Only two cardiac vagal neurons have been recorded intracellularly in vivo, and these neurons were silent (6). The lack of ongoing cardiac vagal activity in these anesthetized in vivo animals is, at first, somewhat unexpected, because in conscious animals there is a high level of tonic cardiac vagal activity. However, in the in vivo experiments excitatory pathways to cardiac vagal neurons were likely inhibited because of the trauma of the acute open-chest surgery or anesthesia, which, in general, inhibits excitatory and augments inhibitory pathways. The tonic ongoing parasympathetic activity that is present in unanesthetized animals is therefore likely initiated, to a large extent, by an excitatory synaptic input that also appears susceptible to trauma and/or anesthesia.

One interpretation of the findings discussed above is that cardiac vagal neurons possess follower cell-like properties. Unlike other brain stem neurons, which may be involved in maintaining blood pressure or respiration in the absence of sensory information, such as those neurons in the nucleus tractus solitarii (NTS) that fire spontaneously even when impinging sensory synapses are silenced, or neurons in the pre-Botzinger complex that may have intrinsic respiratory rhythmogenic activity, the firing of cardiac vagal neurons is totally dependent on critical synaptic input to these neurons. The synaptic inputs to cardiac vagal neurons are therefore important in maintaining normal heart rates and cardiac function but seem to be easily silenced with stressful conditions, such as anesthesia or pain, consistent with the high heart rates and lack of respiratory sinus arrhythmia under these conditions.

**Mechanisms responsible for generating cardiorespiratory interactions**

In each respiratory cycle the heart beats more rapidly in inspiration and slows during postinspiration and expiration, often referred to as respiratory sinus arrhythmia. Respiratory sinus arrhythmia is present in healthy fetuses, newborns, and mature animals and humans. However, respiratory sinus arrhythmia is diminished in many disease states. In distressed fetuses, as well as partially asphyxiated newborns, respiratory sinus arrhythmia is diminished and is strongly correlated (independent from absolute heart or respiratory rate) with low Apgar scores and subsequent neonatal mortality. It has been speculated that an exaggeration of cardiorespiratory interac-

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“**These prevagal neurons . . . are mostly located in the ventral region of the NTS.”**
 FIGURE 2. Stimulation of the nucleus tractus solitarii (NTS) evoked excitatory postsynaptic currents (EPSCs) in identified cardiac vagal neurons. These EPSCs were comprised of a rapidly activating (spikelike) component and a long lasting current that lasted >100 ms as shown in top left trace (traces illustrate average response from 3 consecutive stimulations). To examine the postsynaptic receptors responsible for these EPSCs, d-2-amino-5-phosphonovalerate (AP5) and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) were used to block N-methyl-D-aspartate (NMDA) and non-NMDA receptors, respectively. Addition of 50 mM AP5 decreased the EPSC amplitude by approximately one-half (top and middle graphs), and the synaptic decay time (defined as duration from 90% of peak amplitude to 10% of peak amplitude) was nearly completely inhibited (bottom graph). The spikelike rapidly activating and inactivating component was unchanged by the presence of AP5. Subsequent addition of 50 mM CNQX (or in 1 experiment, tetrahydro-6-nitro-2,3-dioxo-benzo[f]quinoxaline-7-sulfonamide [NBQX]), in the continued presence of AP5, blocked the spikelike EPSC completely. Similar results were obtained in 15 cardiac vagal neurons. Reprinted from Ref. 11.

...the dominant source of respiratory sinus arrhythmia originates from the brain stem....
arrhythmia persists in experimental animals upon section of sympathetic pathways and in quadriplegic patients with spinal cord injury and sympathetic dysfunction. The respiratory system also influences heart rate by modulating the baroreceptor and chemoreceptor input to cardiac vagal neurons. In animals, including humans, the baroreceptor and chemoreceptor reflexes are inhibited during inspiration and are facilitated during postinspiration and expiration or during a maintained phase of postinspiration and apnea (5). This respiratory modulation of both reflexes persists after pulmonary denervation, as well as ventilatory paralysis, suggesting that this “gating” of the baroreceptor and chemoreceptor reflexes also occurs within the brain stem.

Cardiac vagal neurons (recorded either at their soma in the nucleus ambiguus or from their axons in the vagus nerve) have pronounced respiratory modulation. Cardiac vagal neurons fire most rapidly in postinspiration and are often silent in inspiration and stage 2 expiration (5). However, the neurons and mechanisms within the central nervous system responsible for any type of cardiorespiratory interaction are largely unknown. Respiratory inputs do not alter baroreceptor neurons at either their soma or their presynaptic terminals. The presynaptic excitability of baroreceptor terminals in the NTS is not modified by the respiratory cycle, because baroreceptor-evoked post-synaptic responses in NTS neurons are unaltered by lung inflation or by stimulation of chemoreceptor fibers (8). The NTS neurons that receive synapses from baroreceptors also do not seem to be significantly modified by the respiratory cycle, because few, if any, NTS neurons receive converging input from baroreceptors and chemoreceptors. These observations indicate that respiratory modifications of the baroreceptor reflex do not occur early in the reflex pathway. Rather, the few data that exist suggest that cardiorespiratory interactions occur within the nucleus ambiguus.

Central nervous system acetylcholine is likely involved in respiratory sinus arrhythmia

Cardiac vagal neurons recorded in vivo receive inhibitory synaptic input during inspiration, which is then followed by a rapid depolarization caused by excitatory synaptic input during postinspiration (3). Acetylcholine receptors within the central nervous system are likely involved, because centrally acting, but not peripherally acting, cholinergic antagonists reduce respiratory sinus arrhythmia in humans. However, the respiratory phase in which acetylcholine is presumably involved and the neurons responsible for this modulation are unknown (see Fig. 3). Acetylcholine microinjected into the nucleus ambiguus in vivo inhibited cardiac vagal activity in one study but increased cardiac vagal activity in other work. Consistent with the excitatory action of acetylcholine, cholinesterase inhibitors administered centrally decrease heart rate and increase the baroreflex control of heart rate. This augmentation is prevented by nicotinic antagonists.

Recent work from this laboratory (10) has shown that activation of cholinergic receptors on cardiac vagal neurons is excitatory, and this occurs by activation of both presynaptic and postsynaptic mechanisms (see Fig. 4). Nicotine, but not muscarinic agonists, activates postsynaptic receptors and a depolarizing inward current in vagal cardiac neurons. In addition, nicotine acts at different presynaptic and postsynaptic sites to facilitate glutamatergic neurotransmission. Presynaptic nicotinic receptors increase the frequency of transmitter release, and are sensitive to block by α-bungarotoxin (αBgtx), indicating that these presynaptic receptors likely contain the α7 subunit of the nicotinic receptor (10). Nicotine also augments postsynaptic non-NMDA currents via a αBgtx-insensitive receptor.

One possibility is that there are cholinergic neurons active in postinspiration that project to cardiac vagal neurons. These neurons could influence cardiac vagal neurons via three independent mechanisms. One site of action would...
be via a direct activation of postsynaptic ligand-gated nicotinic channels in cardiac vagal neurons, which would act to depolarize and excite cardiac vagal neurons during postinspiration. An additional site of action would be presynaptic and would evoke a nicotinic facilitation of presynaptic release of glutamate. A third action of the postinspiratory neurons would be to augment glutamatergic neurotransmission by activating nicotinic receptors that facilitate postsynaptic non-NMDA receptors in cardiac vagal neurons. These latter two effects could constitute mechanisms by which respiratory inputs gate, or facilitate, the baroreflex during postinspiration.

In summary, during the last 5 years there has been considerable progress in our understanding of the voltage-, Ca-, and ligand-gated channels, synaptic pathways, transmitters, and receptors involved in the central control of cardiac vagal activity. It is apparent that cardiac vagal neurons are inherently silent and depend on excitatory synaptic input for their activity. Synaptic inputs to cardiac vagal neurons include NTS neurons, which activate both NMDA and non-NMDA receptors in cardiac vagal neurons. It is also likely that postinspiratory cholinergic neurons activate postsynaptic nicotinic receptors and directly excite these neurons, which may be a mechanism responsible for respiratory sinus arrhythmia. Postinspiratory cholinergic neurons also likely activate presynaptic nicotinic receptors on glutamatergic terminals, which could facilitate, or gate, the baroreflex during postinspiration. However, much work is still needed, especially investigations concerning the presynaptic and postsynaptic receptors activated upon stimulation of identified synaptic pathways to cardiac vagal neurons and alterations in these receptors and channels during pathological disease states. It is hoped that a further understanding of the functional importance and pharmacological properties of presynaptic and postsynaptic receptors that determine cardiac vagal activity in the brain stem may allow us to identify agents that can reduce cardiac vagal activity in pathological conditions with abnormally low heart rates and cardiac function, such as SIDS, as well as increase vagal cardiac activity and reduce the fatality associated with cardiac hyperexcitability.

References


