The following letters are in response to the Point:Counterpoint “Medullary pacemaker neurons are essential for both eupnea and gasping in mammals vs. medullary pacemaker neurons are essential for gasping, but not eupnea, in mammals” that appears in this issue.

To the Editor: Eupnea is characterized by several systems criteria important for breathing, including specific shapes of discharge patterns in phrenic and other nerves and temporal relationships between them (1, 3, 5, 6). Identification of eupnea in slice based on firing patterns of single neurons or mass activity in the pre-Bötzinger complex (2, 4) does not meet these criteria and makes no sense. The statement that “the pre-Bötzinger complex is critical for generating eupnea” (4) is not debated. The pre-Bötzinger complex is indeed a necessary but not sufficient part of the brain stem involved in generating eupnea. Other necessary regions, including the pons, are involved (1, 3, 5, 6). Moreover, the state and performance of the pre-Bötzinger complex depend on interactions with other necessary brain stem regions, such as the Bötzinger complex, RTN, pontine structures. The assumption that the pre-Bötzinger complex operates within reduced preparations in the same way (i.e., engages the same cellular/pacemaker/network mechanisms) as within the intact brain stem has no evidence. Specific pacemaker activities may be evoked under certain conditions [e.g., in reduced preparations (2, 4) or during gasping (3, 5, 6)], but suppressed by network mechanisms or not expressed during eupnea (3, 5, 6). It is also not obvious why any rhythmic activity should be necessarily generated by pacemakers (2, 4). Network rhythmic mechanisms may operate instead (1, 5). All the above does not allow “in-depth comparison of pacemaker activity during different states of the network” (eupnea vs. gasping) in vitro (4), but supports the statement that an isolated medulla can generate various rhythms (with or without pacemakers) under different conditions but cannot generate eupnea (6).

REFERENCES

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To the Editor: With the knowledge available today there is no final answer whether under eupnic conditions pacemaker neurons are essential for the generation of the respiratory rhythm. Nevertheless, the authors of the Point:Counterpoint articles (4, 5) should take additional points into consideration that are essential for a final conclusion.

Due to the immense relevance of glycinergic and GABAergic inhibition in the adult network (6), respiratory neurons are slightly hyperpolarized and, under this condition, the threshold potential of the pacemaker will not be reached. But, whenever the synaptic inhibition is weakened by specific experimental conditions like (1) neonatal age, where the synaptic inhibition is not fully developed; (2) the use of brain slices, where some inhibitory synaptic connections are literally cut off; (3) under pharmacologic manipulations; or by physiological reactions to overcome a weaker drive within the network, e.g., initiated by an acidification when Pco2 increases; potential pacemaker properties of the neurons will be uncovered and therefore bring an additional “drive” to the network. To guarantee survival in a more crucial situation (e.g., loss of glycinergic inhibition) the activation of pacemakers reorganizes the network (1-3) to a simpler—but functional—rhythm generation.

Therefore, I consider the potential pacemaker properties of respiratory neurons as an older phylogenetic “backup-program,” which will be activated whenever the membrane potential is depolarized. Having this concept in mind, a counterpoint debate whether pacemaker neurons are essential for eupnea is not fruitful, since they also guarantee breathing, while they are suppressed whenever the membrane potential is sufficiently hyperpolarized.

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therefore may have arrived at partial conclusions (5). In vitro experiments have shown that blocking the two groups of pacemakers abolishes fictive eupnea, and blocking the riluzole-sensitive group abolishes gasping (3). Without sharing all the critiques expressed to the in vitro approach (5), which, by the way, allowed the identification and characterization of respiratory pacemaker neurons, we decided to test if the heterogeneous pacemaker population is necessary for rhythm generation in vivo. We recently showed that coapplication of riluzole plus flufenamic acid abolishes eupnea in vivo and that riluzole blocks gasping generation and autoresuscitation as well (2). The similarities between the findings in vitro and in vivo are appealing and suggest that eupnea generation requires a heterogeneous set of pacemaker neurons and that gasping relies on a more restricted set of pacemaker neurons (2–4, 6).

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To the Editor: The main assertions of the Point:Counterpoint articles (4, 5) emphasize the essential role of pacemaker neurons in the generation of either eupnea or gasping. Since the neural networks generating both rhythms are comprised of pacemaker and nonpacemaker neurons, an irrefutable demonstration of the articles’ assertions can best be derived from experiments using a “magic bullet” specifically to turn off the pacemaker neuron population. Although riluzole and flufenamic acid have revealed important properties of the pacemaker population (2, 3), their effects on the remainder of the network comprised of nonpacemaker neurons should be considered (1, 2). It may be that subtle changes in the properties of each element of the remaining network could generate a rhythm with altered patterns or abolish the existing rhythm.

REFERENCES


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To the Editor: Ramirez and Garcia (4) argue that pacemakers in the pre-Bötzinger Complex are critical for eupnea and gasping. In switching from eupnea to gasping during hypoxia, an I-Can pacemaker is suppressed, while an I-NaP pacemaker persists. Within the confines of their experimental conditions, this pacemaker mechanism seems reasonable and is not without precedent. Multiple pacemakers are present in cardiac tissue and in the gut. One or the other type of pacemaker plays the dominant role over other pacemakers in controlling rhythmic contractions (1, 2). The essential participation of I-NaP during “fictive gasping” under hypoxic conditions is well supported by their data. I have trouble, however, with the insinuation that if eupnea characterizes plastic-ity and adaptation to environmental change, pacemakers are essential for generating eupnea and gasping. St-John and Paton (5) argue that there are multiple bulbarrhythm generators, there are problems in determining what the rhythms of in vitro preparations are, and others argue against the existence of respiratory pacemakers. Nonetheless, they indicate that med-ullary pre-inspiratory neurons are “rhythmic bursters” that are active in gasping during hypoxia. They argue that “pre-inspira-tory neuronal activities” have the capacity for intrinsic rhythmic bursting and that the rhythmic bursting and gasping are eliminated by blockers of persistent sodium channels. They present in situ evidence (3) to support intrinsic bursting of Pre-I neurons and suppression with I-NaP blockers. In the end, however, I am left without a good definition of what a med-ullary pacemaker is: autorhythmic cell? A group of neurons? Is a burster a pacemaker?

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To the Editor: The focus of this debate is grounded in the notion that a single population of respiratory neurons located in the pre-Botzinger Complex (Pre-BöC) is essential for both eupnea and gasping. Both sides of this Point:Counterpoint debate raised a number of important issues. However, one aspect that did not receive much attention was the spatial pattern of respiratory activity when breathing is shifted from eupnea to gasping. If a shift in spatial activity occurs, this may indicate that a second “population” of respiratory neurons is needed to drive inspiration during gasping. Using optical imaging techniques, we recently reported that there was a marked shift in the spatial pattern of optical activity when gasping was produced by hypoxia in the in situ perfused rat (3). In association with a dramatic increase in optically related respiratory activity, we found that the core of peak optical activity shifted dorsomedially during gasping. This gasping-related region was similar to the region described in an earlier study that, when lesioned, eliminated gasping but not eupnea (1). Interestingly, this lesioned region was located dorsomedial of the pre-BöC. Since the region imaged during eupnea in our study also corresponded with the pre-BöC, the spatial shift in optical activity away from this region suggests that respiratory neurons in the pre-BöC (whether pacemakers or not) were not involved in hypoxic-induced gasping. Furthermore, since the magnitude of the spatial shift in optical activity (168 um dorsal and 63 um caudal of Pre-BöC) was significant, it seems likely that separate respiratory populations provide inspiratory drive during eupnea and gasping.

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