ESSAYS ON APS CLASSIC PAPERS

Comroe’s study of aortic chemoreceptors: a path well chosen

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This essay looks at the historical significance of an APS classic paper that is freely available online:


I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.

From “The Road Not Taken” by Robert Frost

AS EARLY AS 1868, Pflüger (8) recognized that hypoxia stimulated ventilation, which spurred a search for the location of oxygen-sensitive receptors both within the brain and at various sites in the peripheral circulation. When Corneille Heymans and his colleagues (4) observed that ventilation increased when the oxygen content of the blood flowing through the bifurcation of the common carotid artery was reduced (winning him the Nobel Prize in 1938), the search for the oxygen chemosensor responsible for the ventilatory response to hypoxia was largely considered accomplished. The focus of research then shifted toward a search for the exact nature of the stimulus and the transduction process. However, the persistence of stimulatory effects of hypoxia in the absence of the carotid chemoreceptors led other investigators, among them Julius Comroe, to ascribe hypoxic chemosensitivity to other sites, including both peripheral sites (e.g., aortic bodies) and central sites (e.g., hypothalamus, pons and rostral ventrolateral medulla; see Ref. 7).

At the time this classic paper (1) was published in 1939, Comroe was a junior faculty member at the University of Pennsylvania, having recently been appointed in 1936 as an Instructor in the Department of Pharmacology (6). Working with Carl Schmidt, Comroe was interested in hypoxic chemosensors both in terms of their transduction mechanisms and the location of the extracarotid chemoreceptors. One of the first of his many major contributions was to show that the carotid body responded to reductions in PO2 and increases in PCO2 and did not respond to changes in oxygen concentration (3). However, he was struck by the fact that hypoxia, in the absence of intact carotid bodies, still produced an increase in ventilation, suggesting to him (and others) that an alternative receptor with hypoxic chemosensitivity must exist. Comroe was intrigued by the fact that, before their identification of the carotid site, Heymans and Heymans (5) had also reported that the aortic arch was chemosensitive, although this work was subsequently challenged. However, the observation that within the aortic arch there existed cells that greatly resembled carotid body cells supported the hypothesis and led many to propose that their structure was consistent with a chemosensitive function. The challenge, then, was to prove that these structures functioned physiologically as oxygen chemosensors and to characterize their specific responses.

The problem consisted of designing an experiment to first show that hypoxia excited respiratory and cardiovascular parameters in a “physiological” preparation without any influence from the carotid chemoreceptors and then to show that these responses could be induced by discretely stimulating cell bodies along the aortic arch. Important to the experimental design was an intimate understanding of the local anatomy with regard to both the location of the afferent nerves and the blood supply to the cell bodies. Comroe, a surgeon by training, undertook the daunting task of defining both the physiological responses to hypoxia and the neural and circulatory anatomy of aortic bodies in both dogs and cats. The “sophisticated tech-
nology” that he employed was to advance a small catheter along the aorta, creating local hypoxia at the tip of the catheter, noting the strength of the ventilatory and blood pressure responses, and documenting the catheter tip location. The outcome of these experiments was a definitive work localizing an important chemosensitive function in the aortic arch for the control of both respiratory and cardiovascular activity in dogs and cats. In general, he found that stimulation of the aortic chemoreceptors in the dog causes a greater effect on cardiovascular activity than ventilation (an observation that would later be made in humans as well), while in the cat stimulation produces relative increases in both ventilation and blood pressure.

There are several noteworthy points to make when comparing this 1939 work with current studies. First is the quality of the results despite the lack of “modern” technology. There was no confocal microscopy or high-powered imaging techniques to discern the microanatomy of the aortic bodies, no fluorescent dyes or isotopes to monitor blood flow or physiological activity, and no small interference RNA (siRNA) or antibodies to inhibit their responses. Certainly, in today’s world, such an experiment would likely employ state-of-the-art techniques, but I daresay they would not have been any more definitive in their findings than the original work. The innovation of the time was in the creativity involved in carefully thinking through an experimental plan that could yield interpretable results even in the context of physiological variability. Clearly, creative strategies were and still are the ingredient that marks breakthrough studies.

The ability to interpret results with significant physiological variability is another important quality of this paper. Comroe summarizes the “typical” results overall but repeatedly points out that the results were quite variable from animal to animal. He explicitly justifies this approach, sharing with the readers his philosophy on this issue. He writes, “Because of these natural variations individual investigators in this field, having different purposes in view, may arrive at conclusions which seem to be widely divergent but which actually are not at all at variance” (1). There is much scientific wisdom that underlies how Comroe chose to present the results of these experiments and makes this paper a valuable teaching tool for trainees today. In the long term, the presentation of the data and conclusions was important since it was the subtlety of the responses that provided the foundation for future studies that determined a mechanistic source for the variability.

Finally, it is the fundamental significance of this work, both in terms of basic physiology as well as clinical relevance, that makes this a classic paper. Interestingly, given the state of the field at the time, one might ask why Comroe chose to pursue the question of a chemosensitive receptor in the aortic bodies at all, given the rather definitive work by Heymans localizing hypoxic chemosensitivity to the carotids. Many would have thought the question resolved and considered investigation into the chemosensitivity of the aorta unworthy of further effort. In retrospect, aortic chemoreceptors have proven to be an important chemosensor in humans with significant influence on vascular tone and cardiac function. Clinically, there is no doubt that they are potential sites for therapeutic intervention in hypertension and heart failure. Yet nowhere in the paper does Comroe discuss the potential clinical relevance to his work.

Today, the clinical relevance is an important review criterion for grants and manuscripts. It is difficult to know whether this was an oversight on Comroe’s part or was the beginning of his adamantine belief that basic research, without any obvious clinical benefit, was worthy of pursuit and support. His thesis that the most significant clinical advances were the direct result of such basic research became a political cause later in his life. In the 1970s, Comroe was greatly disturbed by the influence of Congress and industry on directing the activities of the research supported by the National Institutes of Health. This growing concern led him to publish a “scientific” study with Dripps (2) in 1976 that found that a significant number of the major clinical breakthroughs in lung and heart diseases could trace their roots back to basic scientific research. As we prepare the next generation of scientists to tackle important biological problems, this is a lesson that seems well worth repeating.

In summary, Comroe’s paper of 1939 (1) stands as an enduring testament to thoughtful experimental design, intellectual honesty, and the value of basic research. He chose a path many would not have taken...and that has made all the difference.

REFERENCES