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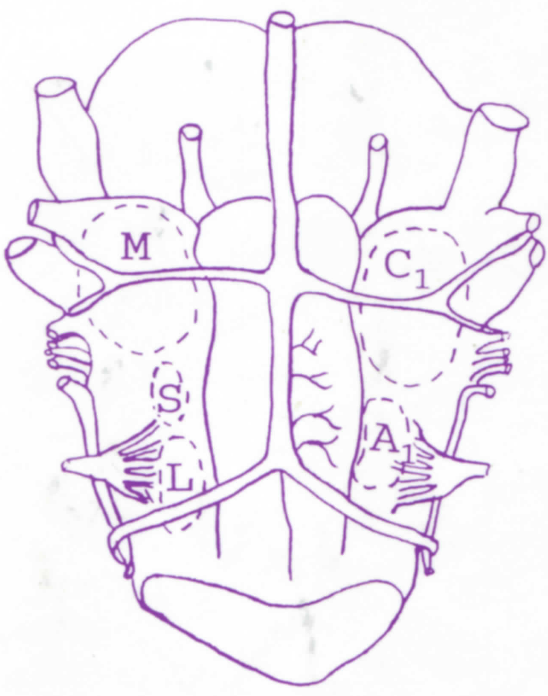
Executive Editor: Claude Lenfant

Ventral Brainstem Mechanisms and Control of Respiration and Blood Pressure



edited by

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about the book . . .

This **outstanding** reference—based on a symposium held at Howard University in Washington, D.C.—presents **in-depth** information on ventral brainstem involvement in the neural and chemical regulation of respiration, blood pressure, and numerous other bodily functions—investigating the **unique** effects of neurotransmitters and neuromodulators as well as the complexity of their interaction.

about the editors . . .

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VENTRAL BRAINSTEM MECHANISMS AND CONTROL OF RESPIRATION AND BLOOD PRESSURE

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INTRODUCTION

Few topics in physiology have attracted as many great scientists over the centuries as the neural control of respiration. As one ponders why this is so, the views of one contemporary researcher and clinician, Dr. Fred Plum, come to mind: "Breathing, the only autonomic function regulated entirely by skeletal muscle, serves two great homeostatic systems, metabolism and behavior." Dr. Plum further noted that there are "separate neurological structures mediating behavioral and metabolic influences on the respiratory act at almost every level of the brain, from the cerebral hemispheres to the medulla and even the upper cervical spinal cord" (1).

Galen (ca. 129–200), through his pioneering studies of the human body, was the first to elucidate the effect of transection of the spinal cord: all respiration ceases, but the heart continues to beat! It is of further interest that his studies led him to characterize a particular personality type as "sanguine" or "melancholic," expressions that today portray quite different temperaments!

Most likely, the first precise location of the respiratory center may be attributed to Julien Jean Cesar LeGallois, who reported in *Experiences sur le principe de la vie* (1912): "If we open the cranium of a young rabbit, and extract the brain in successive portions, beginning by the anterior part, cutting it into slices, we may then take away the whole cerebrum, then all the cerebellum, and part of the medulla oblongata, without stopping respiration. But, it instantly ceases when we cut the origin of the nerves of the eighth pair." And so, over the centuries, a wealth of discoveries has been made. Sometimes controversies developed, but, undoubtedly, they too contributed to our understanding of the brainstem mechanisms controlling respiratory and circulatory processes.

This volume brings together the experience and the vast knowledge of a great number of experts from the United States and Europe. It is the end product of a symposium held at Howard University in Washington, D.C., and organized by Drs. Trouth, Millis, Kiwull-Schöne, and Schläfke, who are also editors of this monograph. There is no question that this volume constitutes a landmark in the complicated field it addresses. For this reason, it occupies a unique place in the Lung Biology in Health and Disease series. As executive editor of this series, I am grateful to the editors and the authors for the opportunity to include this very important contribution.

Claude Lenfant, M.D.
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Reference

Plum, F. Neurological integration of behavioral and metabolic control of breathing. In: Breathing. Porter, R., ed. Hering Breuer Century Symposium. London: J & A Churchill, 1970.

FOREWORD

Much has been learned over the past century about how the body operates and how different organ systems are integrated. Although there is more to be learned, certain principles, such as homeostatic control, are well accepted. We have a good appreciation of adaptive processes and how the same functions, such as the body's CO_2 intake, can be subserved by different structures in various species.

Also, over a much shorter time span, we have become quite knowledgeable about cellular mechanisms—about the basic principles of the genetic code and the complexity of intracellular processes—which at this time seem to require amazingly intricate interlocking processes for cells to grow and develop in an active individual. Although, again, there is much that remains unknown.

The relative wealth of information that exists at the cellular level and at the level of the body's behavior contrasts with the scarcity of data concerning the translation of cellular mechanisms to the responses of intact humans or to even less sophisticated multicellular species.

We know very little of the connection between complex cellular mechanisms and the amazing variety of whole-body responses that allow the organism to adapt to equally complex environmental changes. We do not know very much about the relationship of cellular processes to the development of the hormonal and neural connections that play such an important role in the integration of responses of different organ systems.

This volume deals with one small area of the brain, the ventral medulla, which seems to be involved in a multiplicity of physiological responses, including airway responses, secretory behavior, the defense reaction, and especially respiratory and circulatory behavior. This area may prove to be a region that can provide the clues leading to an understanding of the linkages between cellular and whole-body responses.

As a result of the pioneering efforts of Loeschcke and Feldberg and their coworkers (many of whom have made contributions to this volume), it has been established that the ventral medulla plays a significant role in both vasomotor and circulatory responses and possibly in the integrated behavior of these two systems. That this integration takes place commonly is evident. The integrated responses of the whole body to stresses, such as exercise and hypoxia, demonstrate that there is important coordination of the two systems and that to a degree one system can compensate for deficiencies in the other caused by disease affecting the main cellular metabolism. Study of the ventral medulla may provide an opportunity to understand the signals at the cellular level that evoke these responses. Tissue P_{O_2}, or pH, or some complex weighting of the two, in addition to other factors, may be important.

The presentations in this volume record the progress that has been made and indicate the enormous gaps of information that remain. Fortunately, tools necessary to obtain fundamental information are now available. These tools include the reduced preparations that can now be used to study respiratory behavior. Novel genetic techniques now exist that allow the removal or insertion of specific genetic information, leaving the rest of the animal intact so that whole-body responses can be examined. With new imaging techniques, such as magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and optical imaging, cellular behavior, or at least the behavior of small groups of cells, can be examined in the intact animal.

Ultimately, we would like to describe the transformation of information from cell to system quantitatively. The advances in computer technology as well as those that have been made in the mathematical analysis of alinear and fuzzy systems make this quantitative description a foreseeable possibility.

The chapters in this book should provide us a better understanding of the possibilities and know-how to frame our questions more sharply so that we can develop further testable hypotheses.

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PREFACE

The idea of an arrangement of brainstem neurons in chemosensitive regions exquisitely sensitive to pH and P_{CO_2} changes in their microenvironment was not new to biomedical researchers and clinicians working in the 1990s. But in the 1960s little was known about the role of the ventral brainstem in regulating ventilatory and vasomotor reflexes. This volume is dedicated to all the biomedical researchers of the past 30 years who have advanced our understanding of the brainstem mechanisms underlying ventilatory and vasomotor control. We have singled out Professors Koepchen and Loeschcke for their outstanding contributions, both being originally influenced by Hans Winterstein's fundamental "reaction theory" to explain the chemical control of breathing by the unique principle of H^+ homeostasis. Their leadership and foresight brought about pioneering experiments in both Germany and the United States that led directly to the first localization of what might be called the chemosensitive components of brainstem cardiorespiratory control mechanisms. Their original hypotheses have provided a structural framework for experiments addressing the significance and diversity of ventral brainstem control phenomena.

The location of vital centers controlling respiration and blood pressure have long been recognized within the reticular formation of the brainstem.

The control functions of these centers have been modeled as pattern generators, and they may have rhythmic characteristics common to those described for locomotor regulation in other parts of the central nervous system. In addition, the reflex activities of these ventilatory and vasomotor control centers are dependent upon numerous peripheral inputs from cranial nerve afferents and higher centers. Significant inputs to these cardiorespiratory control centers have also been traced to discrete regions of the ventral medullary surface, where the central respiratory chemoreceptors are presumed to reside. This anatomical arrangement presents several significant research problems. There appear to be interspecies differences with respect to the localization of the reticular centers and their connections to the ventral medullary surface. It also appears that the control functions of these centers might be observable at several different sites. This could represent redundancy in control of vital functions. However, it also suggests that the observed activity might not be that of the control center per se. In analogy to an electric circuit arrangement, a control switch might lie some distance from either a single electrical appliance or a group of appliances. Although electrical activity might be controlled individually at the appliances, another switch might, at some significant distance, be the critical control trigger for all of the appliances. At the ventral brainstem, the reticular rhythm generators and control centers that have been described all seem to have significant connectivity to the chemosensitive zones of the ventral medullary surface. Studies in the laboratories of Koepchen and Loeschcke were among the earliest to localize what might be found to represent the cardiorespiratory control trigger of the ventral brainstem.

The advances documented in this volume have brought to mind the enormous technical difficulties overcome during the 1960s by Professors Koepchen and Loeschcke in attempting to identify the signposts for chemosensitive control activity at the brainstem level. Their initial hypotheses concerning central respiratory chemosensitivity were insightful and greatly advanced our ability to explain the participation of the brainstem in cardiorespiratory reflex control mechanisms. Techniques had to be developed for maintaining physiological conditions suitable to these studies. This was accomplished by developing electrodes for monitoring the acid–base balance of body fluids and artificial cerebrospinal fluid solutions at and beneath the ventral brainstem surface. The chemosensitive regions had to be demarcated and the morphology of the chemosensitive substrates determined. Recordings of neuronal activity were made from regions where the neuronal density was sparse, requiring tedious experiments to search for a few chemosensitive units. Peripheral inputs from redundant systems, such as carotid and aortic chemoreceptors, had to be separated from their central brainstem components.

This book is based on a symposium held at Howard University to summarize the current knowledge base on ventral brainstem mechanisms. The symposium comprised an international group of researchers whose experience in

studying ventral brainstem control mechanisms spanned the past 30 years. Advances in the understanding of neuroregulatory chemicals, cellular transductive, and rhythm generator mechanisms provided a strong infrastructure for workshop discussions on the significance of various research and clinical models for ventral brainstem participation in ventilatory and vasomotor control processes. Each workshop offered an opportunity for scientific enrichment and debate, thereby focusing the writing of the summary chapters.

We are hopeful that this volume will provide an insightful overview for a state-of-the-art scientific summary of our current knowledge of ventral brainstem mechanisms and control of breathing and blood pressure.

The tasks of producing this work have been facilitated by contributions from our colleagues. We wish to give special acknowledgment to the supportive efforts of Dr. Charles H. Epps, Jr., Dean of the Howard University College of Medicine, Dr. LaVal N. Cothran, Chairman of Howard's Department of Physiology and Biophysics, and Pfizer, Inc. This book could not have been produced without the devoted editorial assistance of Drs. Leroy Penix, Nanduri Prabhakar, and David Bernard and of Ms. Deepa Soni, Mr. C.S. Vasudevan, and Ms. Rosalyn Larkin. We have been encouraged in this endeavor by the superb performance of Mr. Paul Dolgert and Ms. Connie Casella and the expert production staff at Marcel Dekker, Inc. We are most grateful for the scientific foresight of Dr. Claude Lenfant, Executive Editor of this Lung Biology in Health and Disease series, and the clarity of each scientist-author's contribution.

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