HIGHLIGHTED TOPIC | Neural Control of Perinatal Respiration

Development of respiratory rhythm generation

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There have been very significant advances in our understanding of how respiratory rhythm is generated in mammals [see Feldman and Del Negro (2) for review]. This has provided the fundamental background on which to pursue investigations into how the system develops during the perinatal period. Respiratory rhythmogenesis is not only essential for postnatal survival but it is required in utero. Failure to generate adequate fetal breathing movements retards stretch-induced signaling within the developing lungs, resulting in lung hypoplasia and pulmonary hypertension at birth. Postnatally, neonatal intensive care units regularly deal with infants with inadequate maturation of the respiratory apparatus, resulting in obstructive, central, and mixed apneas. Indeed, as outlined in the following reviews, developmental abnormalities of respiratory control are a central component of an array of pathological conditions. Our understanding of the basic embryology, genetic control, neuropharmacology, physiology, and plasticity of respiratory neurons and muscles is providing a basis for an understanding of the pathogenesis and etiology of these disorders and the potential for therapeutic interventions.

Thoby-Brisson and Greer (7) focus on the anatomical and functional development of the pre-Bötzinger Complex (pre-BötC) in prenatal rodents. Independent studies examining rat and mouse pre-BötC development generated very consistent data between species. The time at which pre-BötC neurons begin to differentiate and migrate to their location in the ventrolateral medulla has been determined. Furthermore, a combination of electrophysiological recording and imaging techniques has characterized the inception of inspiratory rhythmogenesis and subsequent increases in respiratory frequency and stability during late gestation. The major factor leading to the age-dependent changes in inspiratory rhythmogenesis is the maturation of modulatory drive from regions that synapse onto and regulate pre-BötC function. It is noteworthy that there are marked similarities between prenatal in vitro respiratory developmental characteristics and those observed for fetal breathing movements measured in the rat via ultrasound recordings.

The genetic determination of pre-BötC and other respiratory neuronal population fate and phenotype is an emerging area in respiratory control. Paul Gray (4) provides an overview of how he and others are determining the combinatorial code of transcription factor regulation that defines respiratory neuronal subtypes. This includes examining genes that affect the anterior-posterior and dorsal-ventral patterning within the developing pons and medulla. This is a demanding task given that there are well over 100 different transcription factor genes expressed in subsets of brain stem neurons. Insights are arising from mouse models with specific deletions in transcription factors. A lack of defect on deletion of a neuronal population can itself be informative. An interesting case in point is mice deficient in a transcription factor necessary for the production of most serotonergic neurons. These mice have no significant alterations in breathing pattern in normoxia. This is surprising given the hypothesized critical role of serotonin for respiratory control and proposed link to Sudden Infant Death Syndrome (SIDS). In other cases, loss of a specific transcription factor results in mice with severe respiratory phenotypes. Those mouse models are the focus of the next paper in this series.

Gaultier and Gallego (3) provide an overview of the experimental strategies employed to examine mutant mouse models with breathing abnormalities. These include plethysmography to compare wild-type and mutant mouse breathing patterns in control conditions and after altering inspired oxygen and carbon dioxide levels. A defect in vivo could reflect abnormalities at many points in the respiratory system (e.g., chemoreception,afferent signaling, motoneurons, muscle, central neural networks). To determine if there is a defect in respiratory rhythmogenesis per se, brain stem-spinal cord and medullary slice in vitro preparations are employed where one can measure the basic respiratory drive within the pre-BötC and to motoneuron pools. In addition, one can determine if a defective rhythm can be normalized by the addition of appropriate neurochemical drive. Parallel anatomical studies reveal any structural defects. These strategies have been successfully employed to examine models with defects in transcription factors hypothesized to be important for brain stem development as well as genetic mouse models of Rett, Prader-Willi, and Congenital Central Hypoventilation Syndromes. It is noteworthy that many of the mutant mouse models have multiple abnormalities in structures that modulate pre-BötC function. Thus it is likely a combination of defects in the conditioning drive that causes the respiratory phenotype in many of these models rather than a specific defect within the pre-BötC or one single respiratory nuclei.

The genetic control of respiratory neural and muscular development does not work in isolation. Bavis and Mitchell (1) discuss how experiences during critical developmental periods (e.g., hypoxia, hyperoxia, exposure to chemicals associated with maternal habits, stress) lead to alterations in respiratory control. They describe a broad range of studies across several species to demonstrate that the perinatal environment can have a profound, long-lasting effect on respiratory control. However, the variable(s) of respiratory control modified (e.g., breathing frequency, tidal volume, chemoreception) in response to developmental exposure to the stressors is often inconsistent across vertebrate classes and within the sexes. This field of research is now advancing beyond cataloging examples of developmental plasticity. The emerging focus is now on identifying the underlying mechanisms of plasticity...
including changes in peripheral, central, and neuromuscular structure/function. Furthermore, consideration is being given to how environmental factors interact with transcription factor products and the epigenetic regulation of gene function.

The control of respiratory motoneuron and muscle is the final common path in the system. The primary muscle controlling rib cage expansion is the diaphragm. Drs. Mantilla and Sieck (5) provide a comprehensive overview of phrenic motoneuron-diaphragm development. There is a coordinated outgrowth of phrenic axons and the migration and fusion of diaphragm myoblasts during embryogenesis. Once formed, there is then a marked change in phrenic motoneuron morphology, electrophysiological properties, and firing patterns that is matched by concomitant changes in diaphragm muscle fiber biochemical and contractile properties. Thus by birth, motor units have developed sufficiently to regulate movement of a very compliant rib cage without running into difficulties of fatigue. Subsequent developmental changes increase the ability of phrenic motoneuron-diaphragm muscle units to generate higher levels and ranges of force. Mechanistically, this maturation process depends on innervation, activity, and regulatory actions of trophic and growth factors to stimulate postnatal differentiation of neuromuscular junctions and muscle hypertrophy.

Dr. Thach (6) concludes the series by relating the development of basic neural respiratory control mechanisms to the clinical realm. He focuses on two reflex mechanisms that are critical for surviving a host of insults, including transient hypoxemia, cerebral ischemia, and upper airway viral infection in newborns and indeed throughout life. The first involves cardiorespiratory brain stem-mediated interactions critical for autoresuscitation (AR). The power of AR and subsequent resiliency of the newborn is vividly demonstrated (e.g., Fig. 7 in Thach review). The second mechanism highlighted is a combination of swallowing, apnea, obstructed respiratory efforts, cough, hypertension, and arousal from sleep that are all components of the laryngeal chemoreflex (CR). This reflex protects the infant’s lungs from aspiration. The maturation of AR and CR and their potential importance in relation to apnea and SIDS is demonstrated by a range of data from animal studies and human case reports.

In the context of understanding the organization and function of mammalian motor systems, the respiratory field is at a relatively advanced stage. I believe this also applies to the developmental aspects. This series provides an overview of many of the key aspects of research in the development of respiratory neural control. Importantly, questions are being addressed at multiple levels from the genome to functional development and the key role of perinatal environment to clinically related problems. The novelty and emergent nature of this field is demonstrated by the fact that very little of the content in this series was available a decade ago. The fundamental foundation is now in place to allow for rapid growth, increased mechanistic understanding, and provisions of insights relevant to clinical respiratory problems during the newborn period and beyond.

REFERENCES