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Facts and challenges in respiratory neurobiology☆

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Abstract

Respiratory neurobiology has been a lead discipline in the field of neuroscience for almost a century. Despite this, research studies on the fundamental synaptic and cellular processes underlying the generation and modulation of breathing movements suffered a significant decline during the last decade.

We still believe that respiratory neurobiology is one of the most exciting and imperative fields of neuroscience. With the first *white paper* concerned with the central control of breathing, we want to celebrate the global importance of breathing research.

☆The white paper 'Facts and challenges in Respiratory Neurobiology' was created during a discussion meeting at Melbourne in November 2014. However, this is a live manuscript and the final version of this first white paper for respiratory neurobiology will be published in fall 2015. Everyone is welcome to sign and support the paper. Please mail comments and additions to mathias.dutschmann@florey.edu.au.

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Keywords

Respiratory rhythm generation; Breathing pattern formation

1. Brain facts about breathing

- Breathing has well-defined input and output neuronal pathways.
- Breathing is 'learned' and requires circuit memory and plasticity.
- Breathing is the basis for multiple critical behavior.
- Breathing can be also entrained (modulated) by other rhythmic non-respiratory motor behaviors.
- The basic breathing circuitry is well-defined anatomically and functionally.
- Breathing provides the basis for communication of emotion.
- Breathing is a tool to modulate emotions and state.
- Breathing is strongly influenced by cognition.
- Breathing disturbance is linked to neurogenic diseases.

1.1. Breathing has well-defined input and output neuronal pathways

The motor pattern of breathing can be recorded from a variety of cranial (e.g. VII, X, XII nerves) and spinal motor outputs (phrenic nerve, intercostal nerves, abdominal nerves). The basic breathing activity is modulated by well-defined inputs from oxygen sensors (e.g. carotid body), carbon dioxide and pH sensors as well as a variety of lung receptors. Respiratory activity is rhythmic and therefore easy to measure via motor nerve recordings, EMGs, spirometry and plethysmography.

1.2. Breathing is 'learned' and requires circuit memory and plasticity

Breathing is continuous but adapts to changing needs across different time-scales. Short or long-term plasticity of breathing is associated with:

- Environmental challenges (e.g. hypoxia).
- Disease (lung and/or central).
- Short-term reflex habituation.
- Singing and speech.
- Playing wind and brass instruments.
- Breath-hold diving, snorkeling and swimming.
- Endurance exercise.

1.3. Breathing is the basis for multiple critical behaviors

Changes in respiratory airflow is the basis of, and/or adapted during:

- Phonation and vocalization.
- Olfaction and taste.
- Airway defensive maneuvers, such as expulsive sneezing, retching, cough, or protective breath-holding.
- Emesis.
- Parturition.
- Expectoration (spitting).

In addition, respiration is tightly linked to other homeostatic functions, such as blood pressure and heart rate regulation, and temperature control.

1.4. Breathing can be also entrained (modulated) by other rhythmic non-respiratory motor behaviors

The motor behaviors are as follows:

- Oropharyngeal behaviors e.g. swallowing and chewing.
- Respiratory-locomotor entrainment.
- Respiratory adaptation to posture.
- Endurance exercise and other athletic performance.

1.5. The basic breathing circuitry is well-defined anatomically and functionally

The neuronal network necessary and sufficient for generating automatic breathing is anatomically confined to the brainstem. Therefore, basic respiratory functions such as rhythm generation and pattern formation can be studied using reduced preparations (e.g. in vitro slice, brainstem-spinal cord (en bloc), in situ perfused brainstem preparations), as well as anesthetized and conscious animals.

The respiratory network is functionally well-organized into anatomical compartments. These compartments can be characterized by the co-expression of neuropeptides or their receptors (e.g. somatostatin, neurokinin-1 receptor, etc). Respiratory neurons can be further identified by developmental transcription factors. This makes the respiratory network amenable to genetic manipulation of the respiratory microcircuits using mouse models, optogenetics, pharmacogenetics, etc. These transcription factors include:

- dbx1 (dependent on the progenitor domain: glutamatergic, cholinergic and GABAergic).
- Lbx1 (dependent on the progenitor domain: glutamatergic, glycinergic or GABAergic).
- Pax2 (dependent on the progenitor domain: glutamatergic, glycinergic or GABAergic).
- Phox2b (dependent on the progenitor domain: glutamatergic or catecholaminergic neurons).

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- Lmx1b (dependent on the progenitor domain: serotonergic neurons, catecholamergic or glutamatergic).
- Pet1 (serotonergic neurons).
- FoxP2 (glutamatergic neurons).
- Atoh1 (glutamatergic neurons).

Given the well-defined anatomical and functional circuitry, the basic breathing network has greater tractability than the majority of other non-trivial motor behaviors. Moreover, the respiratory network is sufficiently complex to be a representative model for studies of neural signal generation and information processing. Therefore, it is highly probable that the respiratory network could be the first mammalian network to be understood in its entire anatomical and physiological entity.

1.6. Breathing provides the basis for communication of emotion

The basic breathing output is altered by higher brain centers for a range of higher functions. Modulation of breathing is required for the expression of emotions beyond speech. Respiratory acts can be related to a variety of different emotions, such as:

- Laughing, purring (indication of happiness or joy).
- Crying (indication of sadness).
- Gasping, or breath-holding (indication of surprise or shock).
- Sighing (indication of sorrow or weariness).
- Yawning (indication of boredom).
- Huffing, hissing, snorting (aggression).
- Hyperventilation/breath-holding (indication of fear or anxiety).
- Singing (can carry any form of emotion).

1.7. Breathing is a tool to modulate emotions and state

It is well accepted that certain breathing exercises, such as yoga (prayanama), slow deep breathing, or Lamaze (parturition), can help to overcome stress or pain.

1.8. Breathing is strongly influenced by cognition

- In human speech, the size of the breath taken anticipates the length of the subsequent sentence.
- All fine motor tasks are performed during breath-hold, e.g. threading a needle.
- Concentration is often associated with breath-holding.
- Other motor tasks can be synchronized with breathing to improve performance, e.g. in archery the arrow is released during exhalation.

1.9. Breathing disturbance is linked to neurogenic diseases

Impaired breathing function and, voice and speech disorders commonly occur in neurogenic diseases, such as:

- Alzheimer's disease.
- Parkinsonism.
- Frontotemporal dementia.
- Multiple sclerosis.
- Multiple systems atrophy.
- Amyotrophic lateral sclerosis (ALS).

Breathing disturbances in neurodevelopmental disorders can be associated with single gene mutations. These include:

- Congenital central hypoventilation syndrome (CCHS, Ondine's curse).
- Rett syndrome.
- Prader-Willi syndrome.
- Obesity hypoventilation syndrome.

Other neurodevelopmental disorders without identified genetic determinants include apnea of prematurity, and centrally-mediated upper airways obstruction in early childhood. In the extreme, respiratory failure is linked to sudden infant death syndrome.

Endemic breathing disorders can also be associated with emotional and mental instabilities, e.g. panic and anxiety disorders. Life-style dependent factors, such as obesity can trigger obstructive sleep apnea syndrome, and obesity hypoventilation. Finally, breathing disturbances are commonly seen in stroke and spinal cord injury.

2. Grand challenges

Although the field of respiratory neurobiology has made major progress, the neurophysiological principles are still not completely understood. We briefly reflect on the pertinent questions facing our field.

> I think there are two possibilities. Either we are both right, or one of us is wrong (but it is not me). I will consider a third very unlikely possibility that God has made a mistake—Wilhelm Feldberg.

2.1. The fundamental basis of breathing

2.1.1. Understanding inspiratory rhythm generation—Although major progress was made to establish the pre-Bötzinger Complex in the brainstem as a kernel for respiratory rhythm generation, more studies are required to fully understand its role, including:

- Further verification of identified cellular and circuit properties in the pre-Bötzinger Complex that focus on the multi-scale integration of intrinsic neuronal, synaptic, and glial mechanisms.
- Anatomical and physiological identification of the rhythmogenic sub-circuit within the pre-Bötzinger Complex.
- Validation of a definitive mechanism of in vitro respiratory rhythm generation in more intact systems (in situ brainstem preparations) and, in particular in vivo preparations.
- Confirmation of the pre-Bötzinger Complex as a kernel of respiratory rhythm generation, which requires exploration of the rhythmogenic capacity of other respiratory nuclei.
- Testing of existing and future data using computer simulations of different degrees of complexity.

2.1.2. Understanding the role of synaptic excitation and inhibition in respiratory rhythm generation and pattern formation—A controversial issue in respiratory neurobiology is the lack of consensus regarding a synaptic mechanism of inspiratory burst termination. Limited data suggest a biophysical mechanism for inspiratory burst termination in the pre-Bötzinger complex, while a much larger body of literature indicates that the inspiratory burst is terminated by synaptic inhibition (via sensory input or central mechanisms).

- A grand challenge is to find a definitive mechanism for inspiratory off-switching, that integrates cell intrinsic and network driven synaptic mechanisms. This mechanism also needs to be verified across states.

2.1.3. Understanding the formation of the respiratory motor pattern—The respiratory motor pattern is expressed by a large variety of motor outputs, and can be separated into several phases beyond inspiration and expiration. Important open questions that need to be addressed are:

- Verification of the existence of anatomically and functionally separate oscillators for distinct phases of breathing.
- Finding a role for such ‘single phase oscillators’ (rhythm generators) in the formation of the final respiratory motor pattern.

2.1.4. Identifying genetic and developmental determinants of respiratory neurons for use as tools to investigate the larger respiratory network and microcircuits—Technological breakthroughs allow for a sophisticated network analysis and can include:

Manipulation of respiratory circuits using optogenetics and/or DREADDs (Designer Receptors Exclusively Activated by Designer Drugs).

- By targeting identified developmental transcription factors (see brain facts) that are expressed in compartments of the respiratory network.
- Advanced viral tracing studies to understand the anatomical connectivity of respiratory microcircuits.
- Gene knock-out models lacking certain developmental transcription factors to investigate circuit assembly during gestation.
- Physiological investigations of non-lethal knock-out models to understand network plasticity and function during periods of postnatal development.

2.1.5. The neuronal basis of behavioral and emotional control of breathing—
The neural basis of the emotional control of breathing is an emerging field and requires studies of:

- The impact of the state of consciousness during sleep-wake cycles on the fundamental mechanisms of respiratory rhythm generation and pattern formation.
- Volitional control of breathing in animal models.
- A putative conscious respiratory pattern generator(s) located in the forebrain.

2.1.6. The homeostatic modulation of breathing—Great advances have been made in understanding the interaction between breathing and classic homeostasis. However, a full mechanistic understanding of classical cardio-respiratory reflexes is still pending. Future investigations should include:

- Determination of the optimal energy requirement for breathing.
- The molecular mechanisms of oxygen sensing (peripheral and central).
- The molecular mechanisms of carbon dioxide sensing (peripheral and central).
- The molecular mechanisms of temperature and lung mechanoreceptors.

2.2. Breathing and translational medicine

The respiratory motor pattern has to match neuro-mechanical constraints. As the latter change during development and aging, the underlying respiratory circuit must adapt. Such challenges make the system prone to maladaption. Understanding the origins of respiratory malfunction in neurogenic diseases, as well as disorders of non-neural origin, such as diabetes, obesity, chronic obstructive pulmonary disease (COPD), and chronic heart failure (CHF) are current major topics. However,

- The great challenge is to understand how changes in body function affect the central nervous system and vice versa. The brainstem circuits, particularly the primary respiratory network, play a key role in interfacing sensory feedback from the organs, and thus are a major hub for the *body and mind interface*. Deciphering how this hub functions will provide the basis for the development of new frontiers in medicine.

To facilitate endeavors in translational medicine, fundamental respiratory neurobiology must remain a lead discipline.

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