Available online at www.sciencedirect.com
SCIENCE DIRECT®
Respiratory Physiology & Neurobiology 149 (2005) 99–109
RESPIRATORY PHYSIOLOGY & NEUROBIOLOGY
www.elsevier.com/locate/resphysiol

Regulation of respiratory neuron development by neurotrophic and transcriptional signaling mechanisms

David M. Katz *

Department of Neurosciences, School of Medicine, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106, USA

Received 15 December 2004; received in revised form 7 February 2005; accepted 8 February 2005

Abstract

Functionally diverse populations of respiratory neurons appear to be targets of common neurotrophic and transcriptional signaling pathways. For example, peripheral chemoafferent neurons and noradrenergic neurons in the pontine A5 cell group both require co-signaling by brain derived neurotrophic factor (BDNF) and glial cell line derived neurotrophic factor (GDNF) for survival, growth and/or phenotypic differentiation. Moreover, these same cell groups are dependent on the Phox2 family of transcription factors for early cell type specification. In addition, BDNF and its receptor, TrkB, are expressed in the preBotzinger complex (pBC), a critical site for respiratory rhythm generation, and exogenous BDNF can modulate the activity of pBC neurons. This convergence of BDNF, GDNF and Phox2 dependencies may help to explain how mutations in each of these pathways can result in human developmental disorders of breathing.

Keywords: Brain derived neurotrophic factor (BDNF); Glial cell line derived neurotrophic factor (GDNF); Phox2a; Phox2b; Chemoafferents; PreBotzinger complex; A5; Congenital hypoventilation syndrome; RETT syndrome

0. Introduction

The critical importance of neurotrophic factors in regulating neuronal development and plasticity is well established (Thoenen, 1995; Black, 1999; Lu et al., 1999; McAllister et al., 1999; Huang and Reichardt, 2001). A key principle that has emerged from these studies is that neuronal growth factors exhibit spatial and temporal specificity for different populations of neurons based on unique patterns of expression of ligands and receptors. Work in our laboratory has demonstrated that two factors in particular, brain derived neurotrophic factor (BDNF) and glial cell line derived neurotrophic factor (GDNF), are required for the development of specific subsets of primary sensory and brainstem neurons involved in respiratory control and for the expression of normal breathing after birth (Katz et al., 1997; Katz, 2003). More recent studies have identified other mechanisms, including activity dependent signaling and transcriptional cascades that work in concert with neurotrophic factors to orchestrate the survival, growth and phenotypic differentiation

* Tel.: +1 216 368 6116; fax: +1 216 368 4650.
E-mail addresses: dmk4@cwru.edu, dmk4@case.edu (D.M. Katz).

1569-9048/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.resp.2005.02.007

of respiratory neurons. In addition, linkage analyses have demonstrated that gene mutations affecting neurotrophic and transcriptional signaling molecules are associated with developmental disorders of breathing in humans. The goal of this review is to synthesize these findings and to identify key questions that remain to be addressed.

1. Neurotrophic mechanisms

1.1. Regulation of developmental cell death

Metabolic homeostasis is critically dependent on the ability of the cardiorespiratory system to adapt to acute and long-term changes in oxygen availability and systemic arterial pressure. Chemoafferent neurons in the petrosal ganglion (PG) provide the afferent link between the carotid body, the principle site for neural sensing of arterial p_{O_2}, and cardiorespiratory control systems in the brain. Baroreceptor afferents, arising primarily from sensory neurons in the nodose ganglion (NG), innervate specialized regions of the cardiac outflow tract and transmit information about arterial pressure. Thus, elucidating mechanisms that regulate chemoafferent and baroreceptor differentiation, growth and survival are critical for understanding functional maturation of homeostatic cardiorespiratory control.

1.1.1. Chemoafferent neurons

Studies in our laboratory demonstrated that, in addition to its role as a chemosensory organ, the carotid body also provides trophic support that is required for survival of chemoafferent neurons during perinatal development (see Katz, 2003 for review). Moreover, because of this trophic dependence, and because growth of the carotid body is oxygen sensitive, survival of chemoafferent neurons can be profoundly altered by changes in oxygen availability after birth (Erickson et al., 1998). For example, exposure to hyperoxia after birth results in marked hypoplasia of the carotid body which is associated with selective degeneration of chemoafferent neurons (Erickson et al., 1998).

Two growth factors, BDNF and GDNF, are synthesized in the developing carotid body and mediate trophic support of chemoafferent survival. Genetic deletion of BDNF or GDNF results in loss of 50–60% of dopaminergic chemoafferent neurons and severe disruptions of breathing in newborn mice (see Katz, 2003 for review). Thus far, BDNF and GDNF are the only growth factors known to be required for survival of chemoafferent neurons in vivo.

Mutant mice carrying targeted deletions of either BDNF or GDNF exhibit the same loss of chemoafferent neurons as BDNF/GDNF double null mutants (Erickson et al., 2001). In other words, both factors support survival of the same population of cells. Moreover, BDNF and GDNF act simultaneously, rather than sequentially, to promote chemoafferent survival during the third trimester of fetal development in the mouse. However, it is currently unknown whether BDNF and GDNF act through similar or distinct mechanisms. For example, both factors may promote chemoafferent survival by suppressing a common proapoptotic pathway. Alternatively, one factor may promote responsiveness to the other, e.g., by activating receptor expression or downstream signaling.

1.1.2. Baroreceptor neurons

BDNF is also required for survival of baroreceptor afferent neurons in the nodose ganglion, the vagal homologue of the PG (Brady et al., 1999). As in the carotid body, BDNF is expressed in baroreceptor target regions of the developing cardiac outflow tract, including the aortic arch, the origin of the right subclavian artery and carotid sinus, during late fetal development (peak expression occurs between embryonic days 14.5 and 16.5 in the rat) (Brady et al., 1999). Baroreceptor innervation is completely absent in BDNF null mutants (Brady et al., 1999) and unaffected in GDNF nulls (Katz, D.M., unpublished observations).

1.1.3. Regulation of target innervation and transmitter phenotype

Chemoafferent and baroreceptor innervation of peripheral target tissues is established during the third trimester of gestation in the rat, between E13.5 and E16.5 (Hertzberg et al., 1994). The onset of target innervation is coincident with the appearance of BDNF and GDNF in the carotid body (Brady et al., 1999; Erickson et al., 2001) and BDNF in the cardiac outflow tract (Brady et al., 1999). This period of peripheral target innervation marks the onset of other key events in the maturation of PG and NG neurons as well, including (1) dependence on trophic support (Hertzberg et al., 1994; Erickson et al., 2001), (2) increased axonal branching