Experimental Neurology 287 (2017) 176–191

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Review Article

Developmental plasticity in the neural control of breathing

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ARTICLE INFO

Article history:
Received 22 February 2016
Received in revised form 13 May 2016
Accepted 26 May 2016
Available online 28 May 2016

Keywords:
Phenotypic plasticity
Neuroplasticity
Developmental plasticity
Critical window
Critical period
Control of breathing
Ventilatory response
Hypoxia
Hyperoxia
Hypercapnia

ABSTRACT

The respiratory control system undergoes a diversity of morphological and physiological transformational stages during intrauterine development as it prepares to transition into an air-breathing lifestyle. Following birth, the respiratory system continues to develop and may pass through critical periods of heightened vulnerability to acute environmental stressors. Over a similar time course, however, the developing respiratory control system exhibits substantial capacity to undergo plasticity in response to chronic or repeated environmental stimuli. A hallmark of developmental plasticity is that it requires an interaction between a stimulus (*e.g.*, hypoxia, hyperoxia, or psychosocial stress) and a unique window of development; the same stimulus experienced beyond the boundaries of this critical window of plasticity (*e.g.*, at maturity), therefore, will have little if any appreciable effect on the phenotype. However, there are major gaps in our understanding of the mechanistic basis of developmental plasticity. Filling these gaps in our knowledge may be crucial to advancing our understanding of the developmental origin of adult health and disease. In this review, we: i) begin by clarifying some ambiguities in the definitions of plasticity and related terms that have arisen in recent years; ii) describe various levels of the respiratory control system where plasticity can (or has been identified to) occur; iii) emphasize the importance of understanding the mechanistic basis of developmental plasticity; iv) consider factors that influence whether developmental plasticity is permanent or whether function can be restored; v) discuss genetic and sex-based variation in the expression of developmental plasticity; and vi) provide a translational perspective to developmental plasticity.

Contents

1. Introduction

An individual's phenotype is the product of both its genotype and its environment or, in other words, the product of both its nature and its nurture. This is well illustrated by striking examples of morphological plasticity in invertebrates and other taxonomic groups (*e.g.*, Greene, 1999; Nijhout, 2003), but this concept is equally relevant to homeostatic control systems in humans and other mammals. Thus, while the respiratory control system develops under strong genetic regulation and respiratory phenotypes exhibit significant heritability (*e.g.*, Han and Strohl, 2000; Strohl, 2003; Tankersley, 2003; Borday et al., 2004, 2005; Carmelli et al., 2004; Bloch-Salisbury et al., 2010), the neural pathways

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http://dx.doi.org/10.1016/j.expneurol.2016.05.032
0014-4886/

Table 1
Examples of developmental plasticity of respiratory control in rats.

Environmental stimulus[a]	Developmental stage	Respiratory phenotype[b]	Potential mechanisms for observed respiratory phenotypes[c]	Selected references
Sustained hypoxia	Prenatal	NX: hyperpnea, persists several weeks but not into adulthood HVR: increased initially, blunted by 9 weeks of age HCVR: not studied	Age- and region-specific changes in neurochemistry, *e.g.*: carotid body dopamine content reduced; brainstem (A1) noradrenaline reduced (at 3 weeks) then enhanced (at 9 weeks); CB and PG TH activity reduced (≤1 week) then enhanced (≥3 weeks), but opposite pattern in brainstem catecholaminergic regions.	Peyronnet et al. (2000, 2007)
Sustained hypoxia	Postnatal	NX: hyperpnea, persists several weeks but not into adulthood HVR: decreased, persists into adulthood in males only HCVR: no change or increased	Reduced glomus cell O_2 sensitivity correlated with decreased K^+ channel expression and increased dopamine turnover; glomus cell O_2 sensitivity recovers after re-exposure to normoxia; TH activity increased in CB and decreased in brainstem (high altitude)	Okubo and Mortola (1990); Hertzberg et al. (1992), Wyatt et al. (19950, Sterni et al. (1999), Joseph et al. (2000), Bavis et al. (2004), Mayer et al. (2014)
Intermittent hypoxia	Postnatal	NX: no change or hyperpnea depending on model; hyperpnea may persist several weeks after re-exposure to normoxia HVR: generally increased, but decreased or no change in some models HCVR: no change	Enhanced CB response to hypoxia.	Peng et al. (2004), Reeves and Gozal (2006a), (2006b), Reeves et al. (2006), Julien et al. (2008), (2011), Pawar et al. (2008), Nanduri et al. (2012)
Sustained hypoxia + intermittent hypoxia	Postnatal	NX: hyperpnea secondary to increased metabolic rate HVR: decreased HCVR: no change	Reduced CB O_2 sensitivity; increased nTS neuron excitability.	Mayer et al. (2013), (2015)
Sustained hyperoxia	Postnatal	NX: hypopnea/hypoventilation, generally does not persist into adulthood HVR: initially increased (≤P7), then decreased through adulthood HCVR: no change	Decreased CB size (persists into adulthood); decreased glomus cell O_2 sensitivity (recovers after re-exposure to normoxia), correlated with changes in K^+ channel mRNA expression; decreased whole-nerve CSN responses to hypoxia, likely due to CSN neuron degeneration; decreased neurotrophin expression in CB, PG, and nTS; neonatal brainstem exhibits slowed respiratory rhythm *in vitro*.	Ling et al. (1996), Erickson et al. (1998), Bisgard et al. (2003), Bavis et al. (2010), (2011b), (2014b), Dmitrieff et al. (2011), 2012, Chavez-Valdez et al. (2012), Bierman et al. (2014a), (2014b)
Intermittent hyperoxia	Postnatal	NX: no change or hyperpnea depending on age, does not persist into adulthood HVR: initially increased (P4), then decreased (P14–P15); blunting may persist into adulthood depending on model HCVR: not studied	Decreased CB size (persists into adulthood); single-unit carotid chemoafferent nerve activity reduced under baseline conditions, but hypoxic response only reduced in the youngest age groups tested (*i.e.*, P4, not P13–P14).	Bavis et al. (2007), Logan et al. (2016)
Maternal separation stress	Postnatal	NX: increased in females only; increased apnea frequency and breath-to-breath variability in males HVR: decreased in females, increased in males; effects are not apparent in neonates (*i.e.*, emerge in adults) HCVR: increased in females, decreased in males	Females: no change in basal stress hormone levels; increased CB dopamine D_2 receptor mRNA expression; increased estradiol during acute hypoxia, but no effect on progesterone Males: increased basal stress hormone levels; enhanced gain for central integration of CSN activity; altered balance between glutamatergic and GABAergic modulation in the nTS and/or PVN; increased BDNF expression in PVN; increased CB TH and dopamine D_2 receptor mRNA expression; reduced Hering-Breuer reflex; increased testosterone during acute hypoxia, but no effect on estradiol or progesterone; greater expression of androgen receptors in the caudal nTS.	Genest et al. (2004), 2007, Dumont and Kinkead (2011), Gulemetova and Kinkead (2011), Gulemetova et al. (2013), Fournier et al. (2014), (2015), see also Behan and Kinkead (2011) and references therein.
Predator-induced stress	Prenatal	NX: increased frequency and severity of apneas, increased respiratory instability HVR: decreased HCVR: increased in females only	Decreased medullary 5-HT and NA concentrations at birth; neonatal brainstem exhibits slowed (males only) and more variable respiratory rhythm *in vitro*; more sensitive to serotonergic modulation of respiratory stability *in vitro* and *in vivo*; delayed maturation of GABAergic neuromodulation, potentially within peripheral nervous system or pons.	Fournier et al. (2013) Delhaes et al. (2014)
Caffeine	Postnatal	NX: no change (males and females) or hyperpnea (males), persists into adulthood HVR: altered pattern (increased frequency response) in adult males only HCVR: increased in young rats; as adults, change in pattern only (only in males) or decreased (males)	Females: increased CB adenosine A_{2A} receptor mRNA expression. Males: increased CB adenosine A_{2A} receptor, dopamine D_2 receptor, and TH mRNA expression; increased hypoxic frequency response blocked by A_{2A} receptor antagonist; HCVR less sensitive to adenosine A_1 receptor antagonist	Montandon et al. (2006), (2007), (2008), (2009)

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