Respiratory Physiology & Neurobiology 185 (2013) 75–86

Contents lists available at SciVerse ScienceDirect

Respiratory Physiology & Neurobiology

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

Review

Sex, hormones, and stress: How they impact development and function of the carotid bodies and related reflexes☆

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ARTICLE INFO

Article history:
Accepted 3 July 2012

Keywords:
Sex
Hormones
Stress
Progesterone
Corticosterone

ABSTRACT

Progesterone and corticosterone are key modulators of the respiratory control system. While progesterone is widely recognized as an important respiratory stimulant in adult and newborn animals, much remains to be described regarding the underlying mechanisms. We review the potential implication of nuclear and membrane progesterone receptors in adults and in newborns. This raises intriguing questions regarding the contribution of progesterone as a protective factor against some respiratory control disorders during early life. We then discuss our current understanding of the central integration of stressful stimuli and the responses they elicit. The fact that this system interacts with the respiratory control system, either because both share some common neural pathways in the brainstem and hypothalamus, or because corticosterone directly modulates the function of the respiratory control network, is a fascinating field of research that has emerged over the past few years. Finally, we review the short- and long-term consequences of disruption of stress circuitry during postnatal development on these systems.

1. Introduction

Regulation of sexual function and behavior, as well as physiological stress responses mainly rely on integrated neuroendocrine systems that share some basic properties. Amongst these systems there is a key implication that steroid hormones are the chemical messengers carried by the blood from a site of synthesis, and released to the target tissues which are either peripheral organs or elements of the central and peripheral nervous system. A variety of effectors are necessary for the expression of the related processes allowing an efficient response. For example, corticosteroid release from the adrenal cortex following exposure to stress activates glycolysis from the liver and glucose uptake by muscles to sustain the high energy demand associated with the "fight or flight" response. At the same time, these hormones act on hippocampal neurons contributing to the cognitive processes that create and strengthen memory information related to the stressful events and the appropriate behavioral responses (Gore and Roberts, 2003; McEwen, 2008; Joels and Baram, 2009). Similarly, ovarian and placental steroid hormones promote growth of uterine tissue throughout gestation, suppress uterine contractions, and modulate catecholamine synthesis in uterine arteries to maintain a high blood flow. These hormones also act on the central nervous system to ensure timely expression of maternal behavior related to care and feeding of the offspring. The objective of this review is to discuss how these neuroendocrine systems act to modulate the peripheral and central structures that regulate breathing.

1.1. Historical perspective of the impact of hormones on breathing

In the early 20th century it was reported that adult women had lower alveolar PCO_2 than men (Fitzgerald and Haldane, 1905). Interestingly, this difference was also apparent in young girls *vs.* boys (8–15 years). To visualize the full extent of this difference we took the raw data and group categories published by Fitzgerald and Haldane (1905) to construct a graph (Fig. 1) and run a statistical analysis (ANOVA). Corresponding to Tables I–IV in the original paper, adults are subjects above 17 years, whereas boys and girls are those ranging from 7.5 to 15.5 years. Using these criteria, we found that there are sex ($p = 0.0003$) and age ($p = 0.015$) effects on PA_{CO_2}, but no sex × age interaction ($p = 0.4$).

Following a study published a few years later by Hasselbach showing the hyperventilation associated with pregnancy in women (Hasselbalch and Gammeltoft, 1915), many subsequent studies focused on the function of ovarian hormones on respiratory control in adult subjects, providing remarkable advances in our understanding of the contribution of these hormones to the respiratory

☆ This paper is part of a special issue entitled "Development of the Carotid Body", guest-edited by John L. Carroll, David F. Donnelly and Aida Bairam.

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http://dx.doi.org/10.1016/j.resp.2012.07.001

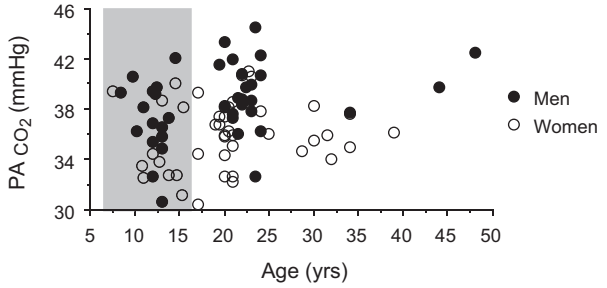

Fig. 1. Illustration of sex-specific effect of ventilatory control in adult (white area) and pre-pubertal boys and girls (grey area). Alveolar PCO_2 plotted as a function of age.

Data taken from Fitzgerald and Haldane (1905).

control system. In 1935, the factor necessary for the morphological transformation of the uterus to prepare for, and maintain gestation was isolated, crystallized, and named "progesterone" (Allen, 1935). It was later confirmed that fluctuating levels of plasma progesterone correlated with cyclical ventilatory stimulation (see Dempsey et al., 1986 for review). The respiratory stimulant effect of progesterone during gestation likely ensures adequate outflow of CO_2 from the fetus to the maternal circulation, avoiding a potentially harmful fetal acidosis. Several reviews of the respiratory effects of progesterone have been published (Dempsey et al., 1986; Saaresranta and Polo, 2002; Soliz and Joseph, 2005; Behan and Wenninger, 2008) giving a substantial overview of the implication of progesterone on respiratory control and some underlying mechanisms. This part of the current review will mainly discuss the receptor subtypes that are involved in these effects and the relevance of progesterone in the newborn. While most of this section relates to progesterone, the reader should keep in mind that other sex hormones (estradiol and testosterone) are also involved in respiratory control (White et al., 1985; Lefter et al., 2008), and where relevant, some of their effects will be mentioned.

2. Impact of progesterone on respiratory regulation

2.1. In adults

In adults, exogenous administration of progesterone reduces CO_2 retention in patients suffering from chronic obstructive pulmonary disease (COPD), decreases the occurrence of periodic breathing and episodic apneas in subjects sleeping at high altitude, and, in patients with chronic mountain sickness, improves arterial oxygen saturation and decreases the frequency of episodes of severe desaturation during sleep (see Dempsey et al., 1986 for review). The prevalence of sleep apnea is higher in adult men compared to women (Block et al., 1979), and because the risk factor for sleep apnea increases after menopause (Young et al., 2003), it was proposed that hormone replacement therapy in women could reduce apnea frequency. This hypothesis was firmly supported in a study that analyzed the frequency and severity of apneic events during sleep in a total of 2854 women aged 50 years and older, of whom 525 were taking estrogen alone and 382 were taking estrogen and progesterone. Overall, the odds ratio for an apnea index > 15 episodes/h was 0.55, and the odds ratio of arterial oxygen saturation < 90% for 10% or more of the recording time was 0.75 in women taking estradiol and 0.41 in women taking estradiol + progesterone as compared with women not taking any hormones (Shahar et al., 2003). The authors concluded that these data indicate that hormone replacement therapy could have a significant role in the prevention or treatment of sleep-disordered breathing in postmenopausal women. Despite this clear demonstration, the underlying mechanisms remain poorly understood.

2.2. In newborn

High levels of progesterone during pregnancy are also encountered in the fetal circulation. This is an important concern in preterm neonates because the circulating levels of progesterone and other placental hormones are much lower than in *in utero* fetuses (Trotter and Pohlandt, 2000). In parallel, preterm neonates have an extremely elevated frequency of apnea and unstable breathing patterns (Finer et al., 2006) due to the immaturity of the respiratory control system. In this population, tactile and mechanical respiratory support can be used to reduce apnea frequency, and when these approaches fail, the most common practice is to use methylxanthines (caffeine or theophylline) as respiratory stimulant drugs. While methylxanthines are thus far considered safe drugs, they are not always effective to relieve apneas, and it has been suggested that progesterone (or progestins in general) might be used as alternative or supplemental drugs (Finer et al., 2006). While this suggestion is based on a wealth of relevant data in adults, much less is known about the effects of progesterone as a respiratory stimulant in the newborn. By using 10 day old rats, fed by mothers implanted 1 day after delivery with osmotic mini-pumps delivering progesterone, estradiol, or estradiol + progesterone, we reported that progesterone increases the hypoxic ventilatory response and reduces apnea frequency in newborn rats (Lefter et al., 2007). Surprisingly, the frequency of sighs, a specific breathing pattern characterized by high inspiratory volume and a very rapid expiration, was increased by estradiol (by about 75%), while estradiol + progesterone increased sigh-frequency three-fold (Lefter et al., 2008). In control animals about 30% of these sighs were followed by an apnea, but remarkably, this effect was balanced by the progesterone treatment such that apnea frequency did not increase in proportion to sigh frequency (Lefter et al., 2008).

One particularly intriguing question in newborns is whether, without pharmacological intervention, progesterone that is present in breast milk at concentration equal to or lower than in maternal plasma (Grosvenor et al., 1993), or progesterone that is directly synthesized by neurons and glial cells (Zwain and Yen, 1999), could have a role in respiratory control during development. From a clinical perspective, it is striking to observe that preterm birth – which deprives the newborn of maternal progesterone secretion – is an important risk factor for Sudden Infant Death Syndrome (SIDS), while breastfeeding notably reduces the risk of SIDS (Vennemann et al., 2009). Along the same line of evidence, whereas preterm birth is a risk factor for development of sleep apnea during infancy (Hibbs et al., 2008), breastfeeding also decreases sleep-disordered breathing in 4–10-year-old infants (Montgomery-Downs et al., 2007). Hence, it is tempting to postulate that one of the potential links between these outcomes might be perinatal exposure to progesterone contributing to an enhanced respiratory chemoreflex, protective responses to hypoxia, and long-term modulation of the respiratory control system.

To address this hypothesis of an endogenous stimulatory effect of progesterone on the hypoxic chemoreflex in newborn rats, we recently performed a study with mifepristone, a progesterone receptor antagonist (Joseph et al., 2012). Unfortunately mifepristone is not specific, being a progesterone and a glucocorticoid receptor antagonist with weak anti-androgenic activity. With these limitations in mind, we used mifepristone to ask whether it would affect the function of peripheral chemoreceptors in newborn rats. After daily gavage between postnatal days 3–15, we used the *ex vivo* carotid body/carotid sinus nerve preparation and whole body plethysmography to determine whether this treatment would alter hypoxic sensitivity. Carotid body responses to both hypoxia and a cholinergic nicotinic agonist as measured in the *ex vivo* carotid