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Review

On the origins of sex-based differences in respiratory disorders: Lessons and hypotheses from stress neuroendocrinology in developing rats

Jean-Philippe Rousseau*,[1], Luana Tenorio-Lopes[1], Cécile Baldy, Tara Adele Janes, Stéphanie Fournier, Richard Kinkead

Department of Pediatrics, Université Laval, Institut Universitaire de Cardiologie et de Pneumologie de Québec, 2725 Chemin Ste-Foy, Québec, QC, G1V 4G5, Canada

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ABSTRACT

The environment plays a critical role in shaping development and function of the brain. Stress, especially when experienced early in life, can interfere with these processes. In the context of respiratory control, perinatal stress can therefore alter the ability to achieve the "fine-tuning" necessary for proper detection of chemosensory stimuli and production of an adequate motor (respiratory) command. Depending on the timing, intensity, and duration, the detrimental consequences of perinatal exposure to adverse conditions on the respiratory network become manifest at various life stages and can persist into adulthood.

During early life, respiratory diseases commonly associated with dysfunction of neural networks include apnea of prematurity (AOP) and cardio-respiratory failure leading to sudden infant death syndrome (SIDS). Sleep disordered breathing (SDB) can occur at various life stages, including adulthood. Regardless of age, a common element of these disorders is their greater prevalence in males. While this sexual dimorphism points to a potential role of sex hormones, our understanding of the neuroendocrine mechanisms remain poorly understood. In addition to their modulatory influence on breathing, gonadal hormones regulate sexual differentiation of the brain. Stress alters these effects, and over the years our laboratory has used various perinatal stress protocols to gain insight into the origins of sex-based differences in respiratory disorders. This review discusses our recent advances with a focus on the sex-specific impact of early life stress on O_2-chemoreflex function both in newborn and adult rats. We conclude by discussing the basic principles emerging from this work, potential mechanisms, and clinical relevance.

1. Introduction

The programming of the central nervous system (CNS) is a critical process occurring during development and lays the foundation for neural function and behaviour into adulthood. As the developmental encoding of the brain is extensive and in many cases persistent or permanent, disruption of this natural process has significant consequences for brain function and general health throughout life. Modern neuroscience has recognized the significant role of stress to direct aberrant neural programming and to interfere with the normal perception and responses to various inputs. The term "stress" describes a physiological event (e.g. blood loss, physical injury) or perceived threat (e.g. social aggression) to homeostasis which activates central neural circuits involved in cognitive processes as well as adaptive hormonal and autonomic responses (Joëls and Baram, 2009; Ulrich-Lai and Herman, 2009). However, the neural responses of different individuals to the same stressful stimulus may vary markedly, highlighting that the underlying signalling mechanisms are of key importance during stress-induced activation of neural circuits. Stress experienced early in development therefore has the capacity to persistently alter the function of many brain regions and is a key risk factor for the development of a variety of physical and psychological diseases (Rosmond and Björntorp, 2000; Tsigos and Chrousos, 2002; Jokinen and Nordström, 2009). Moreover, it is now accepted that developmental stress fundamentally alters homeostatic systems such as blood pressure regulation (hypertension) and glucose metabolism (metabolic syndrome), which have historically been considered as robust processes (Black, 2003; Rosmond, 2005; Nuyt and Alexander, 2009). However, there is a significant gap in knowledge at present regarding stress-mediated disruption of the developmental trajectory of respiratory behaviour; a process that is critical for health and homeostasis.

Respiratory diseases that involve neural network dysfunction affect

* Corresponding author.
E-mail address: jean-philippe.rousseau.3@ulaval.ca (J.-P. Rousseau).
[1] [1]These co-authors have contributed equally to the present manuscript.

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a significant percentage of the population worldwide at various life stages (Moon et al., 2007; Punjabi, 2008; Zhao et al., 2011). In newborns and infants, the most common (and studied) manifestations include apnea of prematurity (AOP) and cardio-respiratory failures leading to apparent life threatening events (ALTE) or sudden infant death syndrome (SIDS). Conversely, sleep disordered breathing (SDB) can be observed at various life stages whereas respiratory symptoms associated with panic attacks are commonly observed following puberty but are rare after menopause (Lovick, 2014). As a whole, respiratory disorders of neural origin impart considerable cost on health care systems and society as they result in hospitalization and premature death. Except for AOP, which mainly reflects interrupted development (Martin and Wilson, 2012), the etiology of these disorders is complex and involves numerous and inter-related risk factors and not surprisingly, comorbidities are common in each case. As a result, addressing the contribution of a specific neurobiological mechanism to the development of these respiratory diseases in isolation is very challenging in humans and to this day, animal models that offer a comprehensive view of the disease are limited. However, growing appreciation for sex-based differences in the manifestation of these respiratory disorders offers promising opportunities to address these challenges. For instance, we know that the prevalence of AOP, SIDS and SDB is significantly higher in males whereas respiratory manifestations of panic attacks are more prevalent in females (Mitchell and Stewart, 1997; Kapsimalis and Kryger, 2002; Paterson et al., 2006; Kinney and Thach, 2009; Lovick, 2014). Furthermore, this sexual dimorphism changes as endocrine function rises and then declines with ageing. The sum of these observations highlight an important role for sex hormones: estrogen, progesterone and testosterone in respiratory dysfunction.

The inference that aberrant sex hormone signalling contributes to the pathophysiology of respiratory diseases may seem novel, yet over a century of clinical and basic research support significant effects of sex hormones for the modulation of respiration (Behan and Wenninger, 2008; Behan and Kinkead, 2011). Several studies have reported that the functional outcomes of sex hormone-mediated neuromodulation are widespread within the CNS, including direct effects on ventilatory drive (Hasselbalch and Gammeltoft, 1915; da Silva et al., 2006), responses to hypoxia and hypercapnia (Jensen et al., 2005; Ahuja et al., 2007) and motoneuron plasticity (Zabka et al., 2006). Importantly, the differential effects of sex hormones on respiratory control are due to the high degree of sexual dimorphism in numerous brain regions and these patterns of dimorphism are set mainly during sexual differentiation of the brain. It is therefore plausible that disrupting the normal process of neuroendocrine programming of sexually dimorphic brain regions leads to persistent dysfunction of sex hormone signalling pathways, aberrant respiratory modulation, and ultimately sex-specific respiratory diseases. As research has shown, the most presumptive input capable of disrupting normal neuroendocrine programming is stress (Nelson and Lenz, 2017).

In this review, current evidence for a direct link between stress, sex-hormones and respiratory disorders is briefly introduced. We then discuss in depth recent advances from our lab confirming that stress results in sex-specific abnormalities in respiratory control which share key features in common with respiratory diseases encountered in the clinic. Using well-established mammalian models of non-systemic stress, our data show that in newborns and young pups, perinatal stress results in sex-specific increase in respiratory instability, apneas and abnormal maturation of the laryngeal chemoreflex. The observed respiratory dysregulations resulting from neonatal stress persist into adulthood leading to abnormal, sex-specific peripheral and central responses to hypoxia and other co-morbidities associated with SDB in adults. Our discussion will focus on outcomes for ventilatory reflexes at rest and under conditions of hypoxia; the effects of stress on hypercapnic ventilatory responses have been reviewed elsewhere (Battaglia et al., 2014; Kinkead et al., 2014).

2. Stress, sex hormones, and respiratory regulation

At the neural level, the stress response is coordinated by the hypothalamic-pituitary-adrenal (HPA) axis; activation of this axis by stressful stimuli initiates a cascade of signalling molecules ultimately leading to significantly augmented release of glucocorticoids from the zona fasciculata of the adrenal cortices (Smith and Vale, 2006). The glucocorticoids: cortisol (humans) and corticosterone (rats) are normally adaptive, playing important roles in fundamental processes such as glucose metabolism and immunity (Vegiopoulos and Herzig, 2007; Zen et al., 2011), but also readily cross the blood brain barrier (Behan and Wenninger, 2008). Within the brain, glucocorticoids exert a profound influence on neural function *via* mineralocorticoid receptors (MR's), which are highly expressed in brain structures involved in stress programming, and glucocorticoid receptors (GR's) which show ubiquitous expression. MR's and GR's, when activated, translocate to the nucleus to regulate gene expression and thus function at time scales from hours to days. However, rapid effects of these receptors through non-genomic process have been documented including changes in neuronal excitability, modulation of ion channel conductance's and glutamate receptor trafficking (Joëls and Baram, 2009; Oitzl et al., 2010; Oakley and Cidlowski, 2013). The functional consequences of glucocorticoids are clearly far reaching; but while basal levels of glucocorticoids are needed for cellular processes, the chronic elevation of glucocorticoids in the brain resulting from HPA axis hyper-activity is deleterious for neural function as it promotes oxidative stress and the release of pro-inflammatory cytokines (Spiers et al., 2015; Deak et al., 2015). Exposure to stress during development disrupts programming of the HPA axis, resulting in persistent sensitization of the axis and enhanced responsiveness to future stressors (Von Werne Baes et al., 2012; Maniam et al., 2014; Buschdorf and Meaney, 2015). In basic research, well established paradigms have been used to demonstrate the impact of developmental stress on short- and long-term neural function including gestational stress (stressing of a pregnant dam resulting in prenatal stress of the offspring) and neonatal maternal separation (NMS, acute separation of pups from the mother). An intriguing yet important observation to come out of these studies is that the functional and behavioural outcomes resulting from developmental stress are highly sex-specific (Lehmann and Feldon, 2000; Baker et al., 2009).

The hypothalamic-pituitary-gonadal (HPG) axis establishes neural control over circulating sex hormone levels produced and released from peripheral organs (gonads, adrenal gland, and placenta). Data from animal models have confirmed that sex hormones produced peripherally are readily transported across the blood-brain barrier (Pardridge and Mietus, 1979; Banks, 2012). In addition, many brain regions differentially express enzymes necessary for endogenous synthesis of neurosteroid equivalents of sex hormones (Lephart et al., 2001; Stoffel-Wagner, 2001). To the best of our knowledge, however, expression of these enzymes near key brainstem regions involved in respiratory control has yet to be investigated. Nevertheless, the presence of sex hormones in the CNS is significant and specific receptors for androgens, progesterone and estradiol, as well as receptors for neurosteroids, have been described in many structures, including those responsible for respiratory modulation (Simerly et al., 1990; Shughrue et al., 1997; Behan and Thomas, 2005) and rhythm generation (Ren and Greer, 2006). Importantly, the expression profiles of sex hormone receptors creating sexually dimorphic brain structures are dictated by the process of developmental programming, and are thus hypothesized to be altered by gestational stress and NMS. There is a growing body of research indicating that sex hormones significantly modulate HPA axis activity, with female and male hormones having divergent effects on HPA activation and glucocorticoid secretion (Goel et al., 2014). Similarly, chronic HPA axis activation depresses sex hormone release in both males and females (Norman and Smith, 1992; Chrousos et al., 1998). Significant functional connections thus exist between the HPA and HPG axes, however, the consequences of disrupting their coordi-