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Review article

HPA axis, respiration and the airways in stress—A review in search of intersections

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ABSTRACT

Given clear connections between respiratory distress and subjective anxiety, it is not surprising that respiratory psychophysiologists have been interested in the psychobiology of anxiety. Given parallel links between anxiety and stress, it is not surprising that the hypothalamic-pituitary adrenal (HPA) stress system has also been a focus in anxiety research. However, despite extensive work in respiratory psychophysiology and stress neuroendocrinology – and evidence that these systems are jointly dysregulated in anxiety disorders – direct studies of their interactions are rare. This paper reviews evidence for scientific intersections, providing an overview of the HPA axis, its psychobiology, and shared neural substrates for HPA and respiratory control. We examine HPA hormone effects on respiration, immune/inflammatory mediators, and lung maturation. We also examine respiratory/dyspnea effects on HPA axis. There are clear points of intersection in the neuroscience of respiration and stress. Given the importance of both systems to an organism's ability to survive and adapt in challenging and changing environments, further study of their interactions is needed.

Contents

1. Introduction

Suffocation is among the most frightening experiences to which a human being can be exposed—witness the use of water boarding as torture and the outcry it has created. Being cut off from oxygen is an immediate and direct threat to life, but usually leaves the organism time to be aware of the threat and make efforts to escape, which is likely to generate intense emotional responses is humans. Given the intuitive connection between respiratory distress and fear, anxiety or the flight response, and the critical need for oxygen in stress adaptation, it is not surprising that the respiratory–anxiety link is of scientific interest (Wilhelm et al., 2006). Indeed, key theories of anxious psychopathology (e.g. panic disorder) have focused on respiratory control or monitoring systems (Klein, 1993); and the neurobiological relationships between critical emotion processes and respiratory control are now being characterized (Evans, 2009; Evans et al., 2009). If we all know

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what the acute distress of breath holding feels like, most of us also are familiar with the different set of feelings associated with prolonged stress—which is often subjectively characterized by anticipation of future calamity in the absence of an ability to control, shape or cope with the anticipated negative outcome. This is the quintessential type of situation that activates our central, neuroendocrine stress response system, the hypothalamic-pituitary adrenal (HPA) axis (Dickerson and Kemeny, 2004), leading to release of cortisol from the adrenal cortex. This stress system has been of central importance in the development of modern, biological psychiatry (Carroll et al., 1981). It is clearly critical for survival (McEwen, 1998), appears to suffer some degree of dysregulation across a wide range of psychiatric disorders (Khan et al., 2009) and plays a central role in the linkage between psychosocial stress and a wide range of general health problems (McEwen, 1998).

Though the psychophysiology of respiration and the neuroendocrinology of stress are both vibrant areas of research, there is little work done examining their intersections. This neglect may be partly due to lack of dialogue between the respective disciplines and a need to adequately develop each area separately before intelligently exploring intersections. However, given growing evidence linking neurobiological regions regulating emotional control with both respiratory phenomena and stress hormones (Jankord and Herman, 2008; Kristensen et al., 1997), and growing evidence that both systems are dysregulated in anxiety-related psychiatric disorders (Abelson et al., 2007; Wilhelm et al., 2001b; Young et al., 1994), further study of intersections may now be worthwhile.

To provide additional foundation for future attention to the intersections between respiratory psychophysiology and stress neuroendocrinology, we will provide an overview of the HPA axis and preliminary research from our group examining respiratory and neuroendocrine responses in panic disorder patients. We will then examine neuroanatomical intersections between HPA and respiratory control systems, physiological effects of HPA hormones on respiratory systems and development, and the impact of respiration on the HPA axis. Emerging themes suggest that the HPA axis and its end product cortisol play a major role in shaping biobehavioral capacities to adapt to changing and challenging environments, both through early programming of developing organ systems and through ongoing influences on acute and chronic responses to threats to survival; that a healthy and appropriately responsive respiratory system is equally critical to survival; and that these two systems have many points of intersection that warrant ongoing scientific attention.

2. Structure and function of the HPA axis

Stimulation of the hypothalamic-pituitary-adrenal (HPA) axis is precipitated by release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary. In response to stress, this results from synergistic stimulation of the pituitary by corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) from neurons originating from parvo- and magnocellular neurons in the peraventricular nucleus of the hypothalamus (PVN). CRH and AVP reach the pituitary through a circumscribed portal circulation where they trigger the release of adrenocorticotropin (ACTH) into general circulation. CRH provides the primary pathway for central control of ACTH release, but AVP plays an important role and can take over and help sustain acute reactivity under conditions of chronic stress, when CRH receptors may become desensitized (Herman et al., 2003). There is also neural input to the pituitary (Herman et al., 2003); and catecholamines, angiotensin II, serotonin and vasoactive intestinal peptide can also stimulate ACTH release, as can several pro-inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF-α) (Anisman and Merali, 1999; Besedovsky et al., 1991; Dantzer et al., 2008; Sapolsky et al., 1987; Venihaki et al., 2001).

ACTH has a relatively short half-life, acting quickly and briefly to stimulate the adrenal cortex (zona fasciculate) to release the glucocorticoid cortisol. It acutely stimulates cortisol production and secretion. With repeated bursts of ACTH release, it also stimulates the synthesis of cortisol producing enzymes and co-factors. Only 5–10% of circulating cortisol is free and active; the rest is bound to binding proteins (cortisol-binding globulin (CBG) and albumin). CBG levels vary across individuals and are affected by sex and gonadal hormones, possibly playing a regulatory role in glucocorticoid action (Kumsta et al., 2007). There are two types of cortisol receptors: Type I, mineralocorticoid (MR) and Type II, glucocorticoid (GR). Both are located in cell cytoplasm, where cortisol enters passively. After binding, the cortisol-receptor complex moves into the cell nucleus and binds to glucocorticoid receptor elements (GRE) on DNA sites, thereby inhibiting or promoting transcription of regulatory proteins. The density, binding affinity and regional distribution of GR and MR differ and play a role in cortisol effects, particularly at higher concentrations, when MR becomes saturated and occupancy and activation of GR rises. In addition to cytoplasmic, genomic effects, glucocorticoids also exert quick, non-genomic effects on cell signaling processes that shape homeostatic regulation more rapidly (Herman et al., 2003). This system is highly regulated in a very complex way, attesting to the considerable importance of its impact on effective adaptation and survival.

Primary physiological effects of glucocorticoids include energy mobilization (increasing glucose levels), suppression of immune responses, anti-inflammatory effects, growth inhibition, and inhibition of reproductive function. It directly stimulates glucose synthesis, stimulates other gluconeogenesis-mediating hormones (e.g. glucagon), and inhibits glucose uptake into cells by promoting insulin resistance. The organizing principle behind its widespread effects across physiological systems may be restoration of homeostasis following disruption (Herman et al., 2003), acutely allocating resources to address immediate challenges and shaping longer term adaptation to reduce the impact of future, similar challenges. These restorative processes are catabolic in nature and biologically expensive. If overused, they have secondary, deleterious consequences, contributing to the aging process, and producing organismic "wear and tear" (McEwen, 2002). Thus the system needs an efficient negative feedback mechanism, which is primarily provided by cortisol stimulation of GR and/or MR receptors in the pituitary, hypothalamus, hippocampus and frontal cortex, which leads to inhibition of ongoing activation.

3. Psychobiology of the HPA axis and intersections with respiratory control

Understanding of central control of the HPA axis has now expanded beyond the hypothalamus to include complex limbic and cortical inputs. Key additional brain regions of interest include those that subject sensory inputs to higher order processing involving memory, learning, emotion, cognition and their interactions (Herman et al., 2003). Given the fundamental importance of respiration to survival, and the critical need to efficiently match respiratory activity to immediate and anticipated physical need, one would expect that the same circuits would also be involved in the psychobiological control of breathing. Available data do suggest that neural circuits that allow higher order processing of incoming perceptual information to influence HPA axis activity may simultaneously shape respiratory patterns, with particular attention given to respiratory rhythms, inspiratory drive, and sighs—and to hypothalamic and hippocampal influences on them

(Evans et al., 2009). Studies directly examining a common neurocircuitry are quite limited. We recently re-analyzed a series of studies in our lab examining the effects of pharmacological and respiratory panicogens on endocrine measures. Though preliminary, the data indicate that common processes may regulate both endocrine and respiratory responses to novelty or anticipation in the context of a panic attack, providing empirical foundation for further studies into shared, modulatory neural circuits.

3.1. Panic disorder: links between endocrine and respiratory processes

Panic disorder (PD) is one psychiatric disorder with documented abnormalities in both respiratory control systems and the HPA axis. PD is characterized by acute and unexpected anxiety attacks and substantial anxiety over the possibility of experiencing another one. Symptoms include palpitations, shortness of breath, sweating and hyperventilation. Both neuroendocrine and respiratory systems have received extensive study in panic disorder but linkages between systems have rarely been examined. We have studied both respiration and stress neuroendocrinology in panic but until recently had not directly examined inter-relationships between them within our own data sets. Using a respiratory stimulant (doxapram) to trigger laboratory panic, we demonstrated persistent tidal volume irregularity in panic patients due to frequent sighs (Abelson et al., 2001). We also demonstrated elevated ACTH levels, strikingly present at baseline in a challenge study (Abelson et al., 2007) but absent after extended accommodation (Abelson and Curtis, 1996; Abelson et al., 2007). This suggests that pre-challenge levels are not a resting baseline for panic patients but instead reflect stressful anticipation of the pharmacological challenge to come. HPA axis hyperactivity in panic disorder could therefore represent an excessive reactivity to novelty or anticipation of future challenge (Abelson et al., 2007).

Might respiratory irregulatory also reflect reactivity to novelty/challenge? Could both respiratory and HPA axis dysregulation in panic be secondary to novelty sensitivity or anticipatory reactivity rooted in other emotion processing brain regions that influence both respiratory and neuroendocrine control centers? If so, then elevations in ACTH seen in panic patients in the doxapram study should be strongly correlated with their respiratory irregularity. Regression analyses confirmed that pre-challenge ACTH levels strongly predicted tidal volume irregularity ($r = .67$, $p < .0001$) and sigh frequency ($r = .53$, $p = .006$), but subjective distress or panic symptoms had no impact on respiration. These data suggest that elevated ACTH at the nominal baseline in a provocation study reflects increased anticipatory stress in the context of a novel challenge and that respiratory irregularity in that context may be another physiological manifestation of the same sensitivity (Abelson et al., 2008b). It further suggests that critical pathophysiological factors in panic may be found in brain circuits that modulate respiratory and HPA axis control rather than within respiratory and HPA control centers themselves.

3.2. An expanded view of the psychology of the HPA axis

These data and the hypothesis generated suggest potential value in further exploring linkages between respiratory and neuroendocrine phenomena. However, a better understanding of interactions between these systems requires a more sophisticated appreciation of the psychology of the neuroendocrine stress response and how hypothalamic, hippocampal and other limbic or cortical regions may modulate sensory/perceptual information to influence it.

Efforts to study the specific psychology of the human HPA axis have produced inconsistent results (Biondi and Picardi, 1999). The simplistic notion that what "feels" stressful subjectively should trigger cortisol release continues to influence thinking and experimentation. It is an appealing idea that has poor empirical support. There is some evidence that negative emotional states, which are often generated by stressful psychosocial challenges, can activate the HPA axis (Lovallo and Thomas, 2000); but there is also evidence that intense emotional distress (e.g., that generated by confrontation with a strongly feared object) does not always activate this system (Curtis et al., 1978, 1976). A recent meta-analysis documents that subjective distress is not a reliable predictor of HPA axis activation, whereas other, contextual aspects of task design are more relevant (Dickerson and Kemeny, 2004).

Animal work has identified specific factors that seem psychologically salient to the HPA axis. The system is highly sensitive to novelty (Armario et al., 1986; Hennessy and Levine, 1978; Hennessy et al., 1995); even small and benign increments in environmental novelty can evoke sustained release of cortisol (Hennessy et al., 1995). Social buffering, and access to control over a stressor or to coping responses to it can also modulate HPA reactivity to a stressor (Levine, 1992; Davis et al., 1977; Dess et al., 1983; Hanson et al., 1976; Peters et al., 1998; Weiss, 1968; Overmier and Murison, 2005).

Human work consistent with this animal literature is emerging. Meta-analysis of 208 laboratory studies supported the hypothesis that threat to achievement of meaningful goals, particularly involving social evaluation threat, when combined with a lack of access to behavioral responses that could control outcomes, provides the most potent trigger to ACTH and cortisol release in humans. Stressor duration or type and subjectively experienced distress showed little influence (Dickerson and Kemeny, 2004). A more recent meta-analysis of field studies of chronic stress (Miller et al., 2007) similarly suggests that the nature and physiological impact of a threat or stressor, and its controllability, shape the nature of the HPA response elicited. In a series of laboratory studies we have shown that familiarity, control and coping can significantly modulate HPA axis reactivity in humans, even when the system is directly activated pharmacologically (Abelson et al., 2005, 2008a, 2010).

3.3. Common neural processes in endocrine and respiratory response to stress

In order for psychologically complex phenomena like control, coping, familiarity and social support to modulate HPA axis activity, processing through limbic and cortical circuits is necessary. Animal work has shown that stressors of immediate physiological relevance to survival are processed through single synaptic neural circuits connecting sensory inputs through thalamus to hypothalamus (Herman and Cullinan, 1997). Complex stimuli with less immediate survival relevance are processed through cortical and limbic pathways that allow interpretation of meaning and salience, influenced by past experience (Herman et al., 2003). Critical nodes in this circuit likely include prefrontal cortex, hippocampus, and amygdala (Jankord and Herman, 2008), with final integration of incoming signals occurring in the "hypothalamic continuum" (preoptic area/hypothalamus/BNST (bed nucleus of the stria terminalis)) (Herman et al., 1996). Recent human neuroimaging work supports the emerging hypothesis that amygdala, hippocampus, temporal pole, and insula may provide activating inputs to the HPA axis, while medial prefrontal cortical regions may participate in inhibitory control (King et al., 2009).

The influence of limbic and higher inputs on respiratory control in humans has attracted less mainstream attention in biological psychiatry, despite evidence from the psychophysiological literature that respiration (and respiratory irregularity in particular) may provide a better marker of emotional states than other physiological channels (Wilhelm et al., 2006). Animal data has

implicated hippocampal and hypothalamic influences on breathing patterns, particularly sighs (Harper et al., 1998; Kristensen et al., 1997), though limbic and paralimbic influences on resting breathing in humans have not been extensively studied (Evans et al., 2009).

The use of neuroimaging to characterize neuroanatomical mediators of human respiration is in its infancy, but early evidence does suggest that activity in limbic and paralimbic networks is linked to spontaneous breathing. In addition, activity in insula, hippocampus, and hypothalamus, as well as brainstem, appear to be involved in a sighing pattern of breathing (Evans et al., 2009) which has been linked to anxiety (Abelson et al., 2001; Wilhelm et al., 2006). Thus, while a number of areas could be involved in mediating the co-regulation of endocrine and respiratory responses to stress, evidence is accumulating for a role for limbic–hypothalamic interactions.

3.4. Hypothalamus and limbic systems

The hypothalamus integrates information flowing from many brain regions and plays a major role in controlling effector systems required for adaptive behavior. This includes vegetative functions such as eating and sleeping, as well as active response channels required for instrumental behavior in the face of challenge, including cardiovascular function and autonomic activity more generally. It is not surprising that it has been implicated in respiratory control. CRH itself is a respiratory stimulant in humans (Krause et al., 1991; Nink et al., 1994). The periventricular region of the hypothalamus (PVH), which includes CRH neurons of the PVN, appears to have a particular role in phasic respiratory events, with activity changes that are temporally linked to sigh/apnea events (Kristensen et al., 1997).

Amygdala and hippocampus have also been linked to sighs, with hippocampal activity changes occurring just before sigh events (Harper et al., 1998; Poe et al., 1996). Connections from both amygdala and hippocampus to the hypothalamus, through the BNST (Herman et al., 2003) provide pathways through which experience and emotion can influence hypothalamic outputs, including perhaps some that control breathing rhythms, possibly through projections to the midbrain parabrachial region, which plays a role in respiratory phase switching (Kristensen et al., 1997). The PVH can also secondarily influence respiration through cardiovascular effects mediated by connections to the nucleus of the solitary tract (NTS) (Kristensen et al., 1997). Interestingly, CRH-related peptides (e.g. urocortin I and III), produce potent cardiovascular effects following direct infusion into the NTS (Nakamura et al., 2009; Yamazaki et al., 2008). The emerging picture supports the hypothesis that cognitive–emotional/cortical–limbic control regions that are critical modulators of HPA axis activity also have critical points of intersection and influence on respiratory control centers. Intriguingly, the converging circuits may have particular influence on phasic respiratory events, perhaps creating a particular link between emotion, breathing rhythms and sighs. This is an exciting possibility as it coincides with growing evidence that sighs may somehow be fundamental to the respiratory abnormalities documented in patients with panic disorder (Wilhelm et al., 2001a,b). It may explain the strong link described earlier between ACTH levels and sigh-based respiratory irregularity in a laboratory challenge study of panic (Abelson et al., 2008b). Shared cortical–limbic inputs to HPA axis and respiratory control systems – with a particular influence on phasic components of respiratory control – are consistent with the hypothesis that HPA axis abnormalities and respiratory irregularity seen in panic patients in laboratory studies could both reflect physiological consequences of a cortical or limbic-based hypersensitivity to particular psychological stimuli such as novelty.

Beyond effects in stimulating anterior pituitary and as a direct respiratory stimulant, CRH acts as a neurotransmitter in diverse areas, both centrally and peripherally. It is localized in amygdala and brain stem regions such as the locus coeruleus (LC), where it mediates arousal and behavioral activation. Effects in these regions could also link stress and respiration. Chronic and acute stress both reduce the threshold of LC activation by CRH (Curtis et al., 1999; Melia and Duman, 1991), and LC activation can be stimulated via glucocorticoid receptors on CRH neurons projecting from the amygdala (Lechner and Valentino, 1999). Recently, it was demonstrated that yawning induced by stimulation of the PVN was accompanied by increased LC CRH c-fos expression (Kita et al., 2006). The yawning induced arousal was reversed by central injections of a CRH antagonist (Kita et al., 2008). These findings support the presence of a CRH pathway from the PVN-LC that is involved in a respiratory-related process. Whether CRH as a neurotransmitter affects other respiratory processes and whether these might be linked to limbic-HPA pathways remains unclear and requires further investigation.

3.5. Olfactory system

Another intriguing hypothesis about the origins of the biological link between emotion and respiratory rhythms involves the shared influence of olfaction on both (Homma and Masaoka, 2008). Olfactory information is known to have direct access to limbic brain, likely due to its importance in detecting threat, finding food, and identifying sexual signals. A functional, bidirectional link between emotional arousal and respiratory rhythm may be rooted in the fact that odor detection/identification requires deep or prolonged inspiration. Neural circuitry linking orbital frontal cortex, amygdala, piriform and entorhinal cortex, and hippocampus to respiratory control centers may provide the substrate for these functional connections (Homma and Masaoka, 2008). The inspiration–olfaction–emotion link may explain the importance of respiration on brain rhythms more generally, including the impact of meditation on cognitive and emotional processes (Fontanini and Bower, 2006).

4. Cortisol and respiratory systems

4.1. Inflammatory and immune effects

In addition to points of intersection between HPA axis and respiratory control systems within the brain (described above), there are also potential interactions in the periphery involving glucocorticoid effects on inflammatory and immune function. Cortisol produces specific anti-inflammatory effects and, through these mechanisms, could potentially mediate a relationship between stress and airway inflammation. This complex relationship is discussed in greater detail elsewhere in this issue, but a brief description of one potential point of intersection is provided here.

Inflammatory and immune responses are activated during stress or threat as a defense against injury and foreign agents, and are critical for survival. Collectively, cytokines such as IL-1, IL-6, and TNF-alpha, through direct and indirect effects, serve to enhance the immune response and deal with particular inflammatory challenges such as allergens. When cytokine levels reach a certain level they elicit feedback inhibition to prevent them from overshooting or overcompensating to the detriment of the organism. Acute HPA axis activation reduces local inflammatory reactions and short term immunity and thus may play a critical role in constraining this system to prevent damage from excessive activation. Thus, IL-1, IL-6 and TNF-alpha also stimulate the HPA axis (Anisman and Merali, 1999; Besedovsky et al., 1991; Dantzer et al., 2008; Sapolsky et al., 1987; Venihaki et al., 2001), and the

resulting increase in plasma cortisol leads to suppression of immune and inflammatory responses.

Cortisol's anti-inflammatory effects include mobilizing circulating lymphocytes and granulocytes and inhibiting macrophages, as well as immunosuppressive effects, inhibiting proliferation of T-cells and suppressing Th1 cellular immunity. Cortisol also inhibits several pro-inflammatory cytokines and mediators, such as IL-1, IL-2, IL-3, IL-6, interferon-gamma, TNF-alpha (Beishuizen and Thijs, 2003; Beishuizen et al., 2001; Soni et al., 1995) and phospholipase A2 (Briegel et al., 1994), while stimulating anti-inflammatory factors such as IL-10 (Franchimont et al., 1999). The cortisol response to an acute stressor may thus protect against airway inflammation, through immunosuppressive and anti-inflammatory effects. Corticosteroid-based therapies take advantage of this physiological effect and have powerful therapeutic value. However, if the HPA axis was unable to respond normally to stress, then in the presence of airway inflammation, loss of its restraining influence could contribute to the further development and maintenance of respiratory diseases.

Whether reduced cortisol reactivity contributes to excessive airway inflammatory responses, particularly in response to stress, is not certain. However, several studies suggest it is a possibility. In ovalbumin-sensitized mice, stress induced airway inflammation was exacerbated in CRH knockout mice (Silverman et al., 2004). As well, early psychological stress in mice attenuated HPA responsiveness during ovalbumin challenge, eventually leading to exacerbated adult asthma (Chida et al., 2007). Numerous studies have also demonstrated that HPA axis reactivity is reduced – reflected in blunted HPA responses to ACTH stimulation and the Trier Social Stress test – in children, adolescents, and some adults with allergies, asthma or atopic dermatitis (reviewed by Priftis et al., 2008). Interestingly, the therapeutic effect of inhaled corticosteroid therapy in asthmatic patients is two-fold–it reduces asthma symptoms and it also restores a more normal cortisol response to stress (Priftis et al., 2006).

At this point, direct evidence for immune/inflammatory mediation of HPA effects on respiratory phenomena is limited. However intriguing hints of potentially important linkages suggest that further work in this area is warranted. A potential implication is that repeated activations of the HPA axis, through chronic stress or allergies, may produce blunted cortisol responses over time to a variety of stimulators including stress itself (Miller et al., 2007). This may protect the organism from excessive and expensive repeated activation of stress response systems, but may also have the consequence of reducing feedback inhibition of acute reactants, and exacerbating the reactivity of already sensitized airways. Work directly examining these relationships may be useful.

4.2. Lung development

In addition to affecting breathing, glucocorticoids also shape pre-natal and early life lung development. Glucocorticoid receptor gene expression is necessary for normal lung maturation (Cole et al., 1995). Stimulatory effects led to the common use of neonatal corticosteroid therapy to prevent or treat lung diseases of premature birth, though the risks of this practice are now clear (see below). Developmental effects of GCs are mediated by intracellular glucocorticoid receptors, which are highly expressed in the placenta (Sun et al., 1997) and found in most fetal tissue at an early embryonic stage (Cole, 1995; Speirs et al., 2004). In humans, fetal cortisol levels rise steadily in late gestation (Lye and Olson, 1996) when organ maturation accelerates. Glucocorticoids stimulate lung maturation via three processes, promoting synthesis of surfactant proteins that line the bronchioles and maintain alveolar integrity, directly stimulating adrenergic receptors in the alveoli, and stimulating synthesis of collagen and other connective tissue in the lungs (Liggins, 1994; Van Golde et al., 1988; Barnes et al., 1984; Schellenberg et al., 1987).

The HPA axis thus plays a critical role in stimulating pre-natal pulmonary development necessary to insure sufficient lung maturity at birth to support life. As a result, pre-natal administration of synthetic glucocorticoids to accelerate lung maturation in the context of risk for preterm birth has been accepted clinical practice (Roberts and Dalziel, 2006). However, growing evidence suggests that this has long term, detrimental effects on other physiological systems including the brain. Pre-natal overexposure to GCs leads to low birth weight and adult hypertension, metabolic syndrome, and cardiovascular vulnerability, as well as to impairments in social, motivational, motor and cognitive development (Hauser et al., 2008). There is growing evidence that pre- and perinatal stress, and associated excess GC exposure, can play a major role in programming the developing organism in ways that might be adaptive for surviving in similarly stressful environments in adulthood, but which have substantial potential for detrimental effects in average future environments (Seckl and Holmes, 2007). As with acute HPA reactivity in adulthood, this system appears critical for successful development but can be damaging when excessively activated. The risk of excessive GC exposure to the developing fetus is highlighted by the existence of a placental system (involving 11β-hydroxysteroid dehydrogenase type 2) designed to protect the fetus from maternal glucocorticoids (Seckl and Holmes, 2007). Detrimental effects on fetal development can result from excess GC exposure via maternal stress and/or a deficient or inhibited placental protective system, as well as by synthetic GCs that bypass this protective system (O'Regan et al., 2008). Detrimental effects are a consequence of altered gene programming, and more specifically altered expression of GR transcription factors (Seckl and Holmes, 2007). These findings are part of a growing body of evidence demonstrating the profound impact of early exposures in shaping life-long biological and behavioral functions of critical importance to health, and the central role of the HPA axis in this long-term programming (Meaney et al., 2007).

The impact of perinatal stress and early life programming on lung structure and function is addressed in more detail elsewhere in this issue. Careful attention and further study is needed, given the clinical value of GCs in enhancing lung maturation and the risks they create for brain and perhaps other organ system development. The possibility that early life programming of both respiratory and neuroendocrine control systems by early stress exposure might create some of the adult linkages we see between stress, neuroendocrine and respiratory systems also warrants further study. It is quite clear that intersections between the HPA axis and respiratory phenomena begin very early in life, even before birth, and play important roles in health and disease vulnerability throughout the life course.

5. The influence of respiration on the HPA axis

In addition to the impact of HPA-mediated stress and immune processes on pulmonary function and health, there is also evidence that respiratory function per se can impact health and that HPA axis function may be an important mediator of these effects. The primary role of the respiratory system is the vital function of gas exchange with the external environment in order to supply oxygen to the body and remove carbon dioxide (Hlastala and Berger, 2001). Respiratory system dysfunction perturbs homeostasis of carbon dioxide, oxygen and pH levels, with widespread effects on other physiological processes. The respiratory system is also directly coupled to cardiovascular systems via mechanical and neural pathways (Eckberg, 2003; Hirsch and Bishop, 1981), and may play

a role in moderating the impact of HPA axis on the cardiovascular function.

Hypercapnia (elevated partial pressure of carbon dioxide, pCO_2), is a common consequence of lung diseases that impair air exchange, but it also occurs with conditions that affect neural, muscular and circulatory components of the respiratory system. Hypercapnia generates mild anxiety in most people, but in those with anxiety disorders, especially panic disorder, it can produce intense anxiety and panic attacks (Papp et al., 1997; Woods et al., 1988). Prolonged exposure to low-dose CO_2 and single breath exposure to 35% CO_2 stimulate the HPA axis, anxiety symptoms, and cardiovascular reactions including systolic hypertension, increased pulse pressure, tachycardia and reduced total peripheral resistance (Argyropoulos et al., 2002; Kaye et al., 2004, 2006; Tenney, 1956, 1960). Neuroendocrine responses to 35% CO_2 include increases in ACTH, cortisol, and noradrenaline (Argyropoulos et al., 2002; Haxhiu et al., 2001; Sechzer et al., 1960; Woods et al., 1988; van Duinen et al., 2007). HPA axis activation in response to hypercapnia may be mediated by activation of the hypothalamic PVN via projections from CO_2 sensitive brainstem nuclei such as the ventrolateral medulla and locus coeruleus, which are important mediators of HPA stress activation, but higher cortical processing of CO_2 challenge also moderates HPA and anxiety reactions.

Hypocapnia (reduced levels of pCO_2) is a consequence of excessive ventilation, and also has non-pulmonary as well as pulmonary causes. It occurs during volitional or involuntary hyperventilation (e.g., preparation for exercise, labor and delivery, emotional stress). Acute hypocapnia increases levels of cortisol, insulin, free fatty acids and catecholamines, and is accompanied by psychological symptoms including anxiety, nervousness, tension, apprehension, derealization, and depersonalization (Laderach and Straub, 2001; Struder et al., 1996). Anticipatory anxiety is accompanied by both hyperventilation and HPA activation (Abelson et al., 2008b; Coplan et al., 1998; Ley, 1991), suggesting common neural pathways, perhaps involving the central nucleus of the amygdala and caudal efferent pathways that project both to PVN and pontine nucleus parabrachialis (Afifi and Bergman, 2005).

It thus appears that both excessive and inadequate ventilation can stimulate HPA axis activation, that there are both afferent and efferent pathways connecting the hypothalamus to respiratory control and monitoring centers in the brain, and that both HPA and respiratory systems are connected to emotion processing networks. The top-down connections through which cognitive–emotional processors in the brain (e.g., prefrontal cortex, ACC, insula, amygdala) can influence both HPA activity and respiration were discussed earlier. These connections also appear to be bidirectional, allowing respiratory phenomena to evoke emotional responses. Dyspnea, and in particular "air hunger" (an uncomfortable urge to breathe), is the most subjectively distressing respiratory symptom (Banzett et al., 2008). Neuroimaging studies of air hunger provocation in healthy subjects have implicated limbic and paralimbic regions, including anterior insula, anterior cingulate, operculum, cerebellum, amygdala, thalamus, and basal ganglia (Banzett et al., 2000; Evans et al., 2002). The finding of air hunger-related activity in anterior cingulate, anterior insula, and amygdala has recently been replicated (Evans, 2009). Exaggerated right anterior insula and right amygdala activity are associated with greater unpleasantness ratings of dyspnea during negative (vs. positive) affective visual stimuli under similar inspiratory resistive loads (von Leupoldt et al., 2008). There are suggestions that right insular cortex plays a similar role in both dyspnea and pain (Schon et al., 2008). Recent work confirms that with dyspnea, as with pain, the affective dimension is processed separately from the sensory intensity dimension (Banzett et al., 2008). These studies support dual processing models of homeostatic visceral sensations (Craig, 2002; Davenport and Vovk, 2009), with lateral thalamic-cortical pathways processing stimulus sensory qualities, and limbic pathways (involving insular cortex, amygdala, cingulate cortex and medial thalamus) processing their affective evaluation. Amygdala is critical in fear and salience processing, and probably mediates the pre-potent ability of breathing difficulty to stimulate fear and anxiety. Insular cortex is strongly and bi-directionally connected to other limbic and paralimbic structures, and is afferently linked to respiratory motor centers, chemoreceptors and stretch receptors, playing a role in integrating visceral sensory information with emotional processing and shaping autonomic and respiratory responses (Craig, 2009; Critchley, 2005).

Given the bidirectional flow of information in these circuits, it will likely take considerable effort to distinguish causes from consequences as the linkages between respiration and stress hormones are identified. We suggested earlier that respiratory irregularity and HPA axis activation may be linked due to common inputs to their respective control centers from cognitive–emotional processors in cortex and limbic brain, such that novelty sensitivity, for example, could simultaneously elicit HPA activation and respiratory changes. However, data reviewed in this section suggests that linkage could also be created due to the intense salience of respiratory distress to organismic survival, leading to rapid processing of dyspnea signals through an emotionally driven, rapid response system that then activates stress response systems and triggers potentially compensatory phasic respiratory responses such as sighs. Careful science will be needed to determine causal sequences, but such cross-system work may be critical in efforts to determine whether there are circumscribed, primary dysregulations in particular nodes within these complex circuits that can create complex disorders like panic, with manifestations seen in respiratory, neuroendocrine, and subjective response channels. Alternatively, circumscribed dysregulation in numerous places may be able to create similar phenomenological outcomes; or complex disorders like panic may require simultaneous, interacting disruption in multiple nodes. The strong connections and functional integration of breathing regulation and the HPA axis are likely critical in facilitating a coordinated homeostatic defensive response, and understanding their interactions may help us unravel the neurobiology of anxiety disorders.

6. Conclusions

Much remains to be learned about the complex interactions between stress response systems of the body involving hormonal, immunological, and physiological response channels. We have learned much from independent study of each of these systems, but the narrow focus required for deepened understanding of specific systems leaves us fairly ignorant of the interactions between systems. General systems theorists called on us decades ago to recognize the hierarchical organization of living systems, the artificial boundaries created by the initial need to study each level in the system separately, and the critical need to understand cross level interaction in order to truly understand a living system (Miller, 1978). A pioneering neuroanatomist translated this hierarchical thinking into brain structure terms (MacLean, 1985) and modern functional neuroimaging and neural connectivity tools are now allowing us to actually "see" the critical importance of "cross-talk" between levels in this highly complex command and control center (Bullmore and Sporns, 2009). Understanding linkages across brain areas, interactions across biological systems, and integrating language and techniques across disciplines and across the basic-clinical science interface are all critical in efforts to understand the neural bases of behavior and psychopathology.

One area of considerable interest and potential importance is the intersection between respiratory control systems and the HPA

axis. Both are critical systems in an organism's struggle to survive and thrive in challenging and changing environments. We now know that the neural systems that allow the HPA axis to utilize complex cognitive and emotional processors to shape acute and longer term adaptive behaviors to environmental threats and challenges (involving amygdala, insula, hippocampus and frontal cortex) may also play critical roles in shaping respiratory responses to perceived challenge. Intriguingly, the amygdala, hippocampus and hypothalamus may be particularly involved in phasic respiratory events, such as sighs, which may have particular relevance to anxiety. We also know that in the periphery, HPA axis end products modulate immune and inflammatory systems that are critical to healthy respiratory function. We also know that these same substances are critical for the healthy development of the lungs, and are also critical for developmental programming that shapes the brain and other physiological systems in ways that influence behavior and health over the entire lifespan. We also know that respiratory phenomena can influence HPA axis activity and that respiratory distress is processed through the same networks that process other distressing experiences, such as pain, and that provide cognitive/emotional inputs to effector systems that integrate our biobehavioral response to challenge. We have made huge strides in dissecting out and understanding a great deal about critical sub-systems within the complex structural–functional networks within the brain that control our biological and behavioral functions. The challenge for the future is to reassemble the dissected brain and understand how it all fits together. Clearly, how we breathe is of fundamental importance to the whole system, but studied in isolation tells us little about successful or unsuccessful adaptation.

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