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Estrogens, age, and, neonatal stress: panic disorders and novel views on the contribution of non-medullary structures to respiratory control and CO_2 responses

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CO_2 is a fundamental component of living matter. This chemical signal requires close monitoring to ensure proper match between metabolic production and elimination by lung ventilation. Besides ventilatory adjustments, CO_2 can also trigger innate behavioral and physiological responses associated with fear and escape but the changes in brain CO_2/pH required to induce ventilatory adjustments are generally lower than those evoking fear and escape. However, for patients suffering from panic disorder (PD), the thresholds for CO_2-evoked hyperventilation, fear and escape are reduced and the magnitude of those reactions are excessive. To explain these clinical observations, Klein proposed *the false suffocation alarm hypothesis* which states that *many spontaneous panics occur when the brain's suffocation monitor erroneously signals a lack of useful air, thereby maladaptively triggering an evolved suffocation alarm system*. After 30 years of basic and clinical research, it is now well established that anomalies in respiratory control (including the CO_2 sensing system) are key to PD. Here, we explore how a stress-related affective disorder such as PD can disrupt respiratory control. We discuss rodent models of PD as the concepts emerging from this research has influenced our comprehension of the CO_2 chemosensitivity network, especially structure that are not located in the medulla, and how factors such as stress and biological sex modulate its functionality. Thus, elucidating why hormonal fluctuations can lead to excessive responsiveness to CO_2 offers a unique opportunity to gain insights into the neuroendocrine mechanisms regulating this key aspect of respiratory control and the pathophysiology of respiratory manifestations of PD.

KEYWORDS

hyperventilation, sex-based differences, control of breathing, orexin, estradiol (17ß-estradiol), maternal separation anxiety

1 Introduction and overview

As a chemist, Antoine Lavoisier was the first to acknowledge CO_2 as a "fundamental component of living matter". While his significant contributions to modern physiology did not save him from the guillotine, CO_2 is now acknowledged as a chemical signal that requires close monitoring to ensure proper match between metabolic production and elimination by lung ventilation. Although accurate, this approach neglects the fact that CO_2 accumulation is a sign of an impoverished air quality such that in many species (including rodents and humans), CO_2 can trigger innate behavioral and physiological responses associated with fear and escape. These responses are highly adaptive because leaving the room (rather than hyperventilating) is perhaps the simplest (and most efficient) way to deal with a hypercarbic environment! Clearly, the changes in brain CO_2/pH required to induce ventilatory adjustments are far lower than those evoking fear and escape (Guyenet and Bayliss, 2022), but in a subpopulation of patients suffering from anxiety disorders, the thresholds for CO_2-evoked hyperventilation, fear and escape are reduced and the magnitude of those reactions are excessive. This trait can then initiate a vicious circle: if the increase in breathing is disproportionate, the perception of respiratory efforts along with the excessive CO_2 loss (hypocapnia) can trigger a variety of physical sensations ranging from headaches to chest pain/discomfort (Gardner, 1996). Panic disorder (PD) patients misinterpret these physiological signals as life-threatening and experience strong emotional reactions that can lead to full-blown panic attacks encompassing fear of dying, shortness of breath, and a choking sensation (Gardner, 1996; Gorman et al., 2000; Nardi et al., 2009). To explain these clinical observations, Donald Klein proposed "*the false suffocation alarm hypothesis*" which states that "*many spontaneous panics occur when the brain's suffocation monitor erroneously signals a lack of useful air, thereby maladaptively triggering an evolved suffocation alarm system*" (Klein, 1993). This model has been refined (Feinstein et al., 2022; Kinkead et al., 2022), but has generally stood the test of time. After 30 years of basic and clinical research, it is now well established that anomalies in respiratory control (including the CO_2 sensing system) are key to PD. Moreover, the intense fear and anxiety experienced by PD patients highlight the functional and anatomical overlaps that exists between the neural circuits that control breathing and those that regulate emotions, fear and escape responses (Schenberg, 2016; Venkatraman et al., 2017). Each of these systems has been studied extensively in isolation, but in recent years, the study of their functional intersection has offered a novel and broader view of respiratory neurobiology. Recent work from Feldman and collaborators has deciphered the pathways by which inspiratory rhythm originating from the pre-Bötzinger complex affects emotions (Ashhad et al., 2022). Here, we will look at this relationship from a different angle; namely, we will explore how a stress-related affective disorder such as PD can influence respiratory control. We focus on rodent models of PD as the concepts emerging from this research has influenced our comprehension of the CO_2 chemosensitivity network and how factors such as stress and biological sex modulate its functionality.

2 Panic disorder: Definitions and sex-based differences in respiratory manifestations of neural control dysfunction

Panic disorder is an anxiety disorder characterized by recurrent panic attacks that are acute, unexpected, and that occur without a clear trigger (World-Health-Organization, 1992; American-Psychiatric-Association, 1994). A panic attack is defined as an episode of overwhelming physical distress and cognitive anxiety during which the patient rapidly develops intense symptoms such as air hunger, sweating, heart palpitations, shortness of breath, hyperventilation, and fear of dying (Hoppe et al., 2012). As such, PD is perhaps one of the most overwhelming experiences that a person can endure (Moreira et al., 2013). While the DSM-V definition of PD spans across 13 different symptoms, the respiratory PD subtype has been identified as the most common, the most pervasive, and the most disabling form of PD (Roberson-Nay and Kendler, 2011). This demonstrates the prominence of the respiratory distress symptoms in PD (Wilhelm et al., 2001; Roberson-Nay et al., 2010; Hoppe et al., 2012; Rappaport et al., 2017) and, depending on theoretical standpoints, hyperventilation can thus be viewed as a cause, a correlate, or a consequence of panic attacks (Nardi et al., 2009).

During World War I, it was observed that CO_2 rebreathing while wearing a gas mask can bring some soldiers to remove the gas mask and/or induce a panic attack (Ritchie, 1992); it was proposed at the time that soldiers prone to the "irritable heart" are excessively sensitive to this stimulus (Drury, 1918). Today, CO_2 inhalation is commonly used as a diagnostic tool for PD (Battaglia and Perna, 1995; Gorman et al., 2001; Hoppe et al., 2012). An increased CO_2 response is acknowledged as a distinctive biomarker of this population and remains a central readout of PD that is easily and non-inferentially modeled in the laboratory. Furthermore, PD patients show an abnormally elevated respiratory variability owing to excessive sighing and an increased rate of apnea both during sleep and wakefulness (Stein et al., 1995; Bystritsky et al., 2000; Abelson et al., 2001; Nardi et al., 2009; Garbarino et al., 2020; Feinstein et al., 2022). The sum of these physiological symptoms indicate that both the regulation and perception of breathing are dysfunctional in PD patients (Gorman et al., 2000; Sinha et al., 2000; Katzman et al., 2002; van Duinen et al., 2007; Abelson et al., 2008; Nardi et al., 2009; Abelson et al., 2010; Grassi et al., 2013).

In North America and Europe, PD affects ~5% of the general population (Hoppe et al., 2012; Meng and D'Arcy, 2012; Bandelow and Michaelis, 2015) and its sexual dimorphism is striking: the prevalence rate of women who have PD or with excessive physiological and behavioral responses to CO_2 inhalation is 2–3 times that of men (Wilhelm and Roth, 2001; Pigott, 2003; Donner and Lowry, 2013). The incidence of PD rises at puberty (Reardon et al., 2009) and in young adolescent girls, pubertal stage predicts panic attack occurrence (Hayward et al., 1992). Furthermore, the panicogenic effects of CO_2 inhalation are highest during the pre-menstrual phase (Nillni et al., 2017), thus indicating that, by comparison with healthy subjects, women suffering from PD are more sensitive to the sudden drop in ovarian hormones taking place during the last days of the luteal phase (Reardon et al., 2009; Nillni et al., 2011; Nillni et al., 2017).

Cyclic fluctuation in ovarian hormones is a normal physiological process, but in a subpopulation of women, they contribute to the onset of PD and its recurrent exacerbations (Reed and Wittchen, 1998; Gorman et al., 2001; Lovick, 2014). Thus, elucidating why hormonal fluctuations can lead to excessive responsiveness to CO_2 offers a unique opportunity to gain insights into the neuroendocrine mechanisms regulating this key aspect of respiratory control and the pathophysiology of respiratory manifestations of PD.

3 Early life stress and PD-related respiratory disturbances in rodents and humans

In mammals (including humans), exposure to adversities during early life alters brain development and is a significant risk for disease (Graham et al., 1999; Buitelaar et al., 2003; Fumagalli et al., 2007; Shonkoff et al., 2009; Charil et al., 2010). Conditions such as maternal depression, unstable parental environment, and special medical care at birth that interfere with mother-infant interactions are stressful to the infant. The sum of current data from clinical and basic research indicates that these forms of early life stress predispose to behavioural and cognitive disorders as well as excessive CO_2 sensitivity and PD that emerge at adolescence, especially in females (Battaglia et al., 1995; Gunnar, 2003; Battaglia et al., 2009; Shonkoff et al., 2009; D'Amato et al., 2011). Thus, the deleterious impacts of early life stress remain latent and are revealed by the rise in ovarian function that takes place at puberty; subsequent fluctuations of ovarian hormones exacerbate PD-related respiratory symptoms in a cyclic fashion. To gain insight into the basic neuroendocrine mechanisms of PD, repeated cross fostering (RCF) and neonatal maternal separation (NMS) have been use in mice and rats (respectively) as clinically relevant models of early life stress and using the ventilatory response to CO_2 as a main physiological outcome (Battaglia et al., 2014).

The hypercapnic ventilatory response (HcVR) changes significantly during development (Putnam et al., 2005; Tenorio-Lopes et al., 2020) and progressive increase in the expression TASK 1 and TASK 2 channels in the hypothalamus likely contribute to this process (Wang et al., 2021); however, the molecular signal initiating their expression remains unknown. In sexually mature mammals (including humans), sex-based differences in the intensity of the CO_2 response are well documented but are highly heterogeneous (Gargaglioni et al., 2019). In mice, RCF augments the HcVR of pups (P16-20) and adults mainly by augmenting the tidal volume response; however, this effect is similar in both sexes (D'Amato et al., 2011; Luchetti et al., 2015; Cittaro et al., 2016; Battaglia et al., 2018). In adult C57BL6 mice, NMS elicits a modest increase of the HcVR only in females (Elliot-Portal et al., 2021). In rats, the ventilatory response to 5% CO_2 of pre-pubertal rat pups (P14 - P15) is very weak with no evidence of sex- or NMS-related effects (Tenorio-Lopes et al., 2020). At adulthood, the HcVR of control (non-stressed) male and female rats is similar, but the effects of NMS on the CO_2 response differ strikingly between sexes in ways that are very similar to clinical observations of PD. Specifically, the minute ventilation response to CO_2 inhalation (5% CO_2; 10 min) of NMS females is 60%–80% larger than controls and NMS-related increase of the CO_2 response is ***i***) sex-specific (limited to females), ***ii***) peaks during proestrus, and ***iii***) is not observed prior to puberty (Genest et al., 2007; Kinkead et al., 2009) (Figure 1). These differences in the developmental and sex-specific effects of early life stress on the HcVR of mice and rats likely reflect inter-species differences in stress responses of rodents (Beery and Kaufer, 2015). Regardless, both models have advanced our comprehension of the pathophysiology of PD. What follows is a summary of the main mechanisms that contribute to stress-related increase in CO_2 response.

4 Early life stress alters non-medullary structures with CO_2 sensing properties

4.1 The amygdala

Within the medial temporal lobes, the amygdalar complex is responsible for perception and processing of stimuli; it also initiates and terminates emotional reactions (Marek et al., 2013). Briefly, this complex is composed of three main structures: the medial amygdala (MeA), the central amygdala (CeA) and the basolateral amygdala (BLA) (Figure 2). The basolateral part of the amygdala (BLA) is of great interest to this mini-review because it has inherent CO_2 sensing properties; much like "classical" CO_2-sensing neurons of the medulla, BLA neurons can detect CO_2 (Ziemann et al., 2009). While direct comparisons are not possible, we can estimate that the CO_2/H^+ sensitivity of BLA neurons is ~ 10 times less than that of the retrotrapezoid nucleus (RTN), the main CO_2 sensing structure in respiratory control (Guyenet et al., 2019). Nonetheless, CO_2-induced stimulation of the BLA elicits emotional and physiological responses associated with fear and panic-related states (Ziemann et al., 2009). The BLA interacts with the medial amygdala (MeA) that regulates innate emotional behaviors; it relays olfactory information to hypothalamic nuclei involved in reproduction and defense behaviors. Interestingly, sex-based differences in anatomy, laterality, function, and sensitivity to steroid hormones of the MeA are well documented in humans and rodents (Rodrigues et al., 2009; Cahill, 2010; Goldstein et al., 2010; Edelmann and Auger, 2011; Buss et al., 2012). Both regions project to the central amygdala (CeA) (Keshavarzi et al., 2014), which is the amygdala's output pathway because it initiates autonomic and respiratory responses (Veening et al., 1984). The CeA projects directly onto rhythmogenic neurons of the pre-Bötzinger complex, the nucleus of the solitary tract (NTS), and the RTN (Petrov et al., 1995; Rosin et al., 2006; Ulrich-Lai and Herman, 2009; Yang et al., 2020). Furthermore, stimulation of the CeA excites the inspiratory cycle (Harper et al., 1984). In our studies using *c-fos* mRNA as a marker of neuronal activation, the CeA has emerged as an important candidate in the initiation of an excessive ventilatory response to CO_2 in NMS, especially in female rats (Kinkead et al., 2014).

Owing to its role in the regulation of emotional reactions, the amygdala contributes to the pathogenesis of anxiety (Feinstein et al., 2022); however, observations made on patients with Urbach–Wiethe disease, a rare genetic disorder leading to focal bilateral amygdala lesions, have raised questions concerning its contribution to PD. Briefly, Urbach–Wiethe patients show no fear and avoidance behavior to external threats such as snakes,

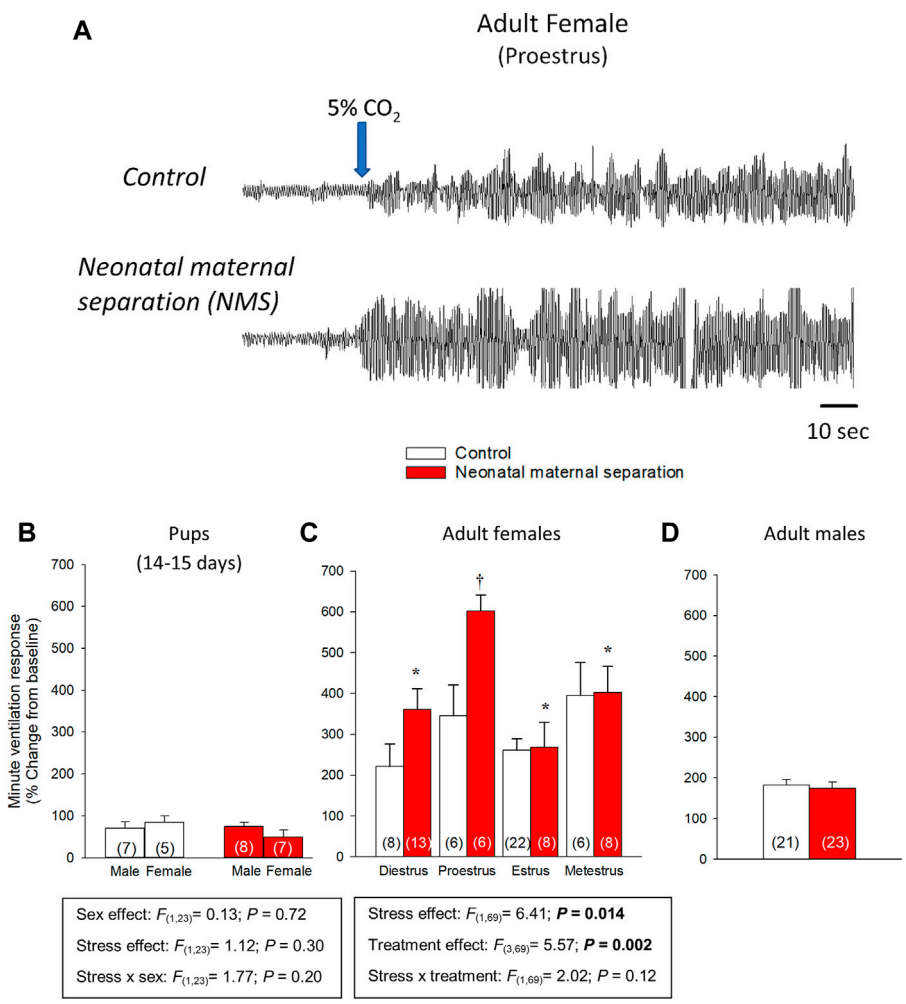

FIGURE 1
Influence of neonatal stress and reproductive status on the magnitude of ventilatory response to CO_2 in rats. **(A)** Original plethysmography recordings comparing ventilatory activity at rest and upon exposure to hypercapnia (5% CO_2 in air). Recordings were obtained from adult rats during the proestrus phase; females were either raised under standard conditions (top trace) or subjected to neonatal maternal separation (bottom trace; 3 h/day, postnatal days 3–12). Blue arrow indicates the onset of the exposition to 5% CO_2 for 10 min. Comparison of the minute ventilation responses to hypercapnia between control rats (white bars) and rats subjected to neonatal maternal separation (NMS; red bars). Data expressed as percent change from baseline (room air) in **(B)** pups, adult **(C)** females and **(D)** males. Data from males are from (Genest et al., 2007; Tenorio-Lopes et al., 2017); they are reported for comparison and were not included in the statistical analyses. Data are reported as means ± SEM * indicates a value significantly different from corresponding proestrus value at $p < 0.05$; † indicates a value significantly different from corresponding control value at $p < 0.05$. Adapted with permission from (Tenorio-Lopes et al., 2020).

tarantulas, and a range of traumatic life events, but exhibit a significantly higher rate of CO_2-evoked fear and panic than a sample of demographically-matched healthy participants (Feinstein et al., 2013; Feinstein et al., 2022). In mice, electrolytic lesions of the amygdala inhibited fear-like behavior (freezing); however, the ventilatory response was not tested (Taugher et al., 2020). In pediatric subjects, electrical stimulation of the medial subregion of the basal nuclei, cortical and medial nuclei induces apnea (Rhone et al., 2020); similar procedures in the lateral and basolateral amygdala of adults also results in respiratory inhibition (Dlouhy et al., 2015). The fact that these patients do not notice respiratory arrest or report dyspnea indicate that their ability to perceive the rise in CO_2 is blunted; the inverse relationship between CO_2 activation of the MeA and the HcVR of male rats is in line with this observation (Tenorio-Lopes et al., 2017). Although compelling, this interpretation requires caution because amygdalar lesions in humans and mice were heterogeneous and clinical studies generally involve a limited number of participants. Nonetheless, the sum of these observations ***i***) highlights an important neural distinction between "external" threats conveyed via visual and auditory pathways, *versus* threats conveyed through "internal" sensory channels (e.g., chemoreceptive); ***ii***) suggests that rather than inducing panic, the amygdala inhibits it, especially when it is evoked by an internal threat such as elevated levels of CO_2, and ***iii***) this inhibition likely originates from a subpopulation of CeA neurons considering that as discussed previously, the CeA is generally acknowledged for its stimulatory influence on breathing.

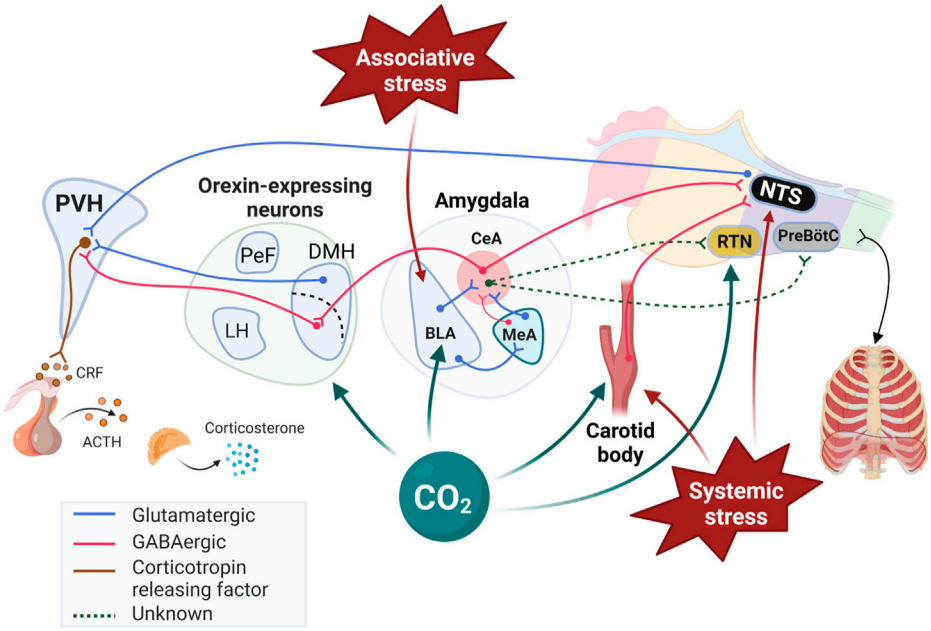

FIGURE 2
Schematic representation of stress-related neuronal inputs and CO_2 chemosenstivity in cardiorespiratory control. While retrotrapezoid nucleus (RTN) of the medulla is well established as a highly sensitive to CO_2/H^+ responsible for fine respiratory adjustments, the Figure 1) highlights other "non-medullary" sites that respond to CO_2/H^+, 2) identifies the pathways by which they initiate significant cardiorespiratory and behavioral responses, and 3) illustrates how these structures are part of the neural network initiating and regulating the response to stress. Note that the interactions between the PVH and medullary structures regulating breathing are not shown for simplicity. The review by (Zhang et al., 2021) provided valuable informations on network and the neurotransmitters contributing to those interactions. PVH: paraventricular nucleus of the hypothalamus; BLA: Basolateral amygdala; CeA: Central nucleus of the amygdala; MeA: Medial nucleus of the amygdala; ORX; Orexin producing neurons; DMH: Dorsomedial hypothalamic nucleus; PeF: Perifornical area; LH: Lateral hypothalamus; NTS: Nucleus of the solitary tract; CRF: Corticotropin releasing factor; ACTH: Adrenocorticotropic hormone; PreBötC: Pre-Bötzinger complex. Created with BioRender.com.

4.2 Orexin neurons

Orexins A and B (ORX; also known as hypocretins) are regulatory peptides produced by neurons located in the dorso-medial, perifornical, and lateral hypothalamus (DMH, PeF, and LH, respectively). Orexin neurons have extensive projections throughout the central nervous system; however, the organisation of this system is dichotomous: LH neurons stimulate motivated behaviors such as appetite for food and other rewards such as abused drugs (Harris and Aston-Jones, 2006), whereas neurons of the PeF and DMH act in parallel to influence arousal, sleep/wake states, and cardiorespiratory function (Johnson et al., 2010; Nattie and Li, 2012; Ciriello et al., 2013; Barnett and Li, 2020). Interestingly, the DMH/PeF region was initially termed the "panic area" because its activation induced a "panic-like state" in experimental animals (DiMicco et al., 2002; Díaz-Casares et al., 2009). Today, a "hyperactive" ORX system is a leading hypothesis in the pathophysiology of PD (Johnson et al., 2010; Abreu et al., 2020). This is based on the fact that ORX levels in the cerebrospinal fluid of PD patients is elevated by comparison with healthy subjects (Johnson et al., 2010) (Figure 3) and in adult rats, previous exposure to early life stress (maternal deprivation/separation) augments ORX_A levels in hypothalamus extracts (Feng et al., 2007; Tenorio-Lopes et al., 2020). Furthermore, PD patients show abnormal levels of expression the HCRTR1 gene which encodes for ORX_1 receptors (Johnson et al., 2010; Gottschalk et al., 2019).

Orexin acts on two receptors (ORX_1 and ORX_2) and their expression in the pontomedullary areas of the autonomic and respiratory network overlap partially (Marcus et al., 2001). ORX_A can bind to both receptors whereas ORX_B binds primarily to ORX_2 (Carrive and Kuwaki, 2017). The fact that the basal respiratory activity of ORX-knock out mice is similar to that of wild-type indicates that ORX neurons have limited impacts on breathing at rest (Nakamura et al., 2007; Berteotti et al., 2020) and while there is evidence indicating that deletion of ORX neurons increases apneic events during sleep (Nakamura et al., 2007), this effect is not always observed (Berteotti et al., 2020). However, activation of ORX neurons potentiates chemoreflexes and there is growing evidence indicating that ORX neurons have CO_2-sensing properties (Gestreau et al., 2008; Li and Nattie, 2014; Carrive and Kuwaki, 2017). In mice, exposure to CO_2 (10% CO_2; 3 h) augments the number of *c-FOS* immunolabeling in ORX_A expressing neurons of the PeF and DMH (but not LH) (Sunanaga et al., 2009). Results from electrophysiological experiments provide more direct support as they show that acidification of the extracellular milieu increases intrinsic excitability and firing rate of ORX cells, whereas alkalinization depresses it. Furthermore, this effect involves acid-induced closure of K^+ channels in the orexin cell membrane (Williams et al., 2007). These responses resemble those of known chemosensory neurons; however, the authors did not specify the specific location of the populations of ORX neurons that were recorded. Regulation of ORX neurons is greatly influenced by

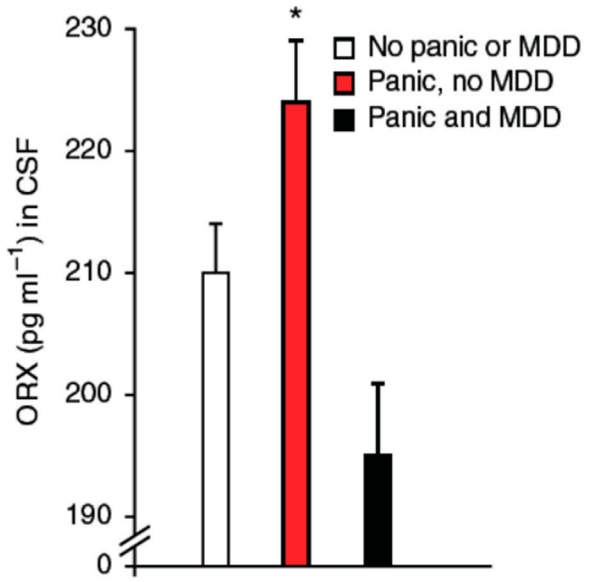

FIGURE 3
Orexin concentrations in cerebrospinal fluid (CSF) obtained by lumbar puncture in subjects with panic anxiety with or without major depressive disorder (MDD). Subjects who presented with acute suicidal behavior were systematically assessed for psychiatric symptoms utilizing the comprehensive psychopathological rating scale (CPRS), where item 3 (inner tension) assesses panic anxiety. A threshold cut off at 1.5 on this item was used to define a subject as having significant panic symptoms. All subjects with substance abuse and traces of anti-depressive, neuroleptic or anxiolytic medication in the blood were excluded from the analysis. Subjects with panic anxiety without MDD (n = 12); subjects with both panic and co-morbid MDD (n = 13); and subjects without panic, without MDD (n = 28). Data are reported as means ± SD; * indicates significant differences from other groups, using Kruskall Wallis ANOVA (p = 0.004); and two-tailed Mann-Whitney U-test (subjects with panic and MDD, p = 0.002; subjects without panic, p = 0.01). Reproduce with permission from Johnson et al. (2010).

gonadal hormones and data show that the intensity of expression of ORX_1 receptors in the hypothalamus parallels ovarian hormone levels. In rats, their expression peaks during the proestrus phase (Silveyra et al., 2009). As a result, Grafe and Bhatnagar proposed that the ORX system is fundamental to sex-based differences in stress-related neurological disorders such as PD (Grafe and Bhatnagar, 2018). Estradiol (E_2) is of great interest in this context because E_2 levels rise during proestrus and its inhibitory actions on ORX neurons reduce their responsiveness to stress (Shors et al., 2001). To evaluate the role of E_2 in regulating ORX neurons we first used immunohistochemistry and data convincingly show that under resting conditions, OVX augments the ratio of *c-FOS*/ORX_A immunolabeled cells in control females, especially in the DMH. Conversely, OVX had no significant effect in NMS females because the number of labeled cells was already elevated in intact females (Tenorio-Lopes and Kinkead, 2021). We then used whole cell recording to evaluate how changes in E_2 across the estrus cycle affects synaptic inputs converging onto ORX neurons and our results showed that NMS reduces E_2-mediated inhibition of ORX neurons (Figure 4). During proestrus, the excitatory post-synaptic current (EPSC) frequency of control females was the lowest whereas in NMS females the frequencies were the highest observed in this group. These observations provide a plausible explanation for the higher *c-FOS*/ORX_A immunolabeling, greater ORX_A levels measured in hypothalamic extract, and the high efficacy of systemic administration of the selective ORX_1 receptor antagonist SB-334867 (15 mg/kg; IP) at reducing the HcVR of NMS female rats. Of note, this drug-induced attenuation of the HcVR was most important during the proestrus phase; in controls, this treatment had no significant effect on the HcVR, regardless of the estrus phase (Tenorio-Lopes and Kinkead, 2021). The sum of these data indicates that stress-induced disruption of E_2 signalling is an important mechanism in a rat model of PD and that ORX neurons is an important site of action (Figures 2, 5).

5 Early life stress and its impacts on other mechanisms contributing to CO_2 sensing

5.1 Acid-sensing ion channels (ASICs)

The ventilatory response to CO_2 is determined by multiple chemosensory structures with specialised capacity for detecting changes in CO_2/H^+ in their vicinity that project to respiratory neurons to initiate a robust increase in breathing. Acid-sensing ion channels (ASICs) are widely expressed in the brain, including the ventrolateral medulla, where they play a pivotal role in driving CO_2/H^+ chemosensing and triggering emotional and physiological responses (Song et al., 2016). Regardless of their biological sex, PD patients show variation of the ACCN2 gene, the human ortholog of the *Asic1a* (Smoller et al., 2014). Consistent with human data, mRNA transcript analysis of the brainstems of male and female mice show heightened ASIC expression in RCF exposed animals (Cittaro et al., 2016); although ASICs are comprised of multiple subunits the authors presumably refer to ASIC1A but this was not specified.

The fact that inactivation of ASIC channels with amiloride attenuates the HcVR of RCF animals but not controls strongly suggests that overexpression of these ion channels is an important mechanism in the abnormal respiratory phenotype associated with PD (Battaglia et al., 2018). However, the fact that amiloride has non-specific effects on a number of other receptors and transporters needs to be considered.

5.2 The carotid bodies

Strategically located at the bifurcation of the carotid arteries, the carotid bodies are main sensors of O_2 levels in the arterial blood; however, they also respond to changes in arterial CO_2/H^+ (Iturriaga et al., 2021). They project to the medulla where they provide powerful chemosensory signals to the respiratory network. Because carotid body stimulation by potassium cyanide injection stimulates fear and escape responses (Schimitel et al., 2012), we determined whether these chemosensors contribute to the excessive HcVR of NMS females. To do so, we compared the responsiveness of the carotid bodies to changes in O_2 and CO_2 using an *ex vivo* preparation and the results convincingly showed that NMS does not affect peripheral CO_2 sensing in either sex (Soliz et al., 2016). We

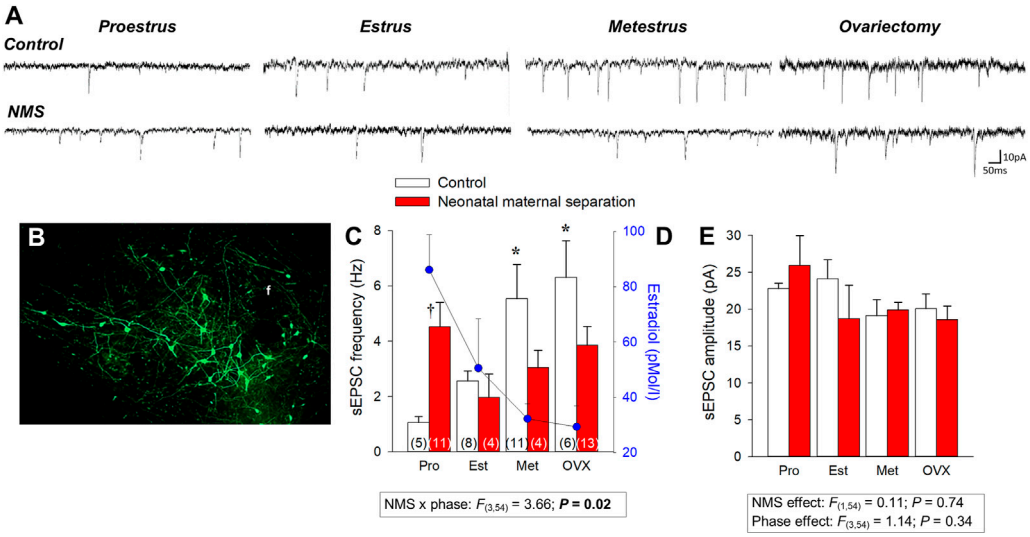

FIGURE 4
Neonatal maternal separation stress (NMS) reduces the spontaneous excitatory postsynaptic currents (sEPSC) recorded in GFP-labeled orexin neurons in response to changes in 17β-estradiol (E_2) level in intact and ovarectomized rats. **(A)** Comparison of sEPSC recordings from orexin neurons between cells during different phase of the estrus cycle and 2 weeks following ovariectomy (OVX); tissue slices originated from females raised under control conditions (top traces) or subjected to NMS (bottom traces; 3 h/day, postnatal days 3–12). **(B)** Photomicrograph illustrating GFP-labeled orexin neurons; the fornix (f) is shown as a landmark. **(C)** Population data of EPSC frequencies recorded during 3 distinct phases of the estrus cycle and following OVX. **(D)** Baseline E_2 values are reported for comparison; values from NMS and controls were pooled since they are not statistically different. **(E)** Reports sEPSC amplitudes. Data are reported as means ± SEM; *$p < 0.05$ compare to corresponding proestrus value; † $p < 0.05$ compare to corresponding control. *Adapted from* Tenorio-Lopes *et al* (2020).

therefore concluded that anomalies in the CO_2 chemoreflex takes place within the brain.

We first evaluated the contribution of the central nervous system (CNS) to this phenotype using anesthetised rats (Dumont and Kinkead, 2010; Dumont et al., 2011; Dumont and Kinkead, 2011), but this approach eliminated the NMS-induced increase of the ventilatory response to CO_2 reported in awake females (Dumont et al., 2011). This led us to propose that NMS disrupts anesthesia-sensitive structures responsible for the cognitive and/or emotional perception of the CO_2 stimulus (Dumont et al., 2011). This inference was first based on the notion that CO_2 is both a systemic and associative stressor. In other words, CO_2 is capable of stimulating both physiological (*i.e.,* respiratory) reflexes via conventional pathways and strong emotional and associative reactions, such as fear and escape responses that, in turn, further stimulate breathing (Schenberg, 2016). These observations and the current background knowledge brought our attention to the amygdala.

5.3 Microglia

Microglia are the immune cells of the brain that are mainly known for scavenging the CNS for infectious agents, damaged or unnecessary neurons and synapses. However, there is growing evidence indicating that uncoupling neuron–microglia interactions alters neuroplasticity and contributes to anxiety- or depressive-like behaviors (Koo and Wohleb, 2021). Microglia express cell death–associated gene-8 (TDAG8), an acid-sensing G-protein coupled receptor which is necessary for full expression of CO_2-evoked fear (Vollmer et al., 2016). Specifically, freezing and blood pressure responses to CO_2 inhalation (5% CO_2; 10 min) of TDAG8 deficient mice are lower than those reported in wildtype animals; however, the HcVR does not differ between genotypes (Vollmer et al., 2016). Subsequent experiments demonstrated that upon CO_2 exposure, microglia release the proinflammatory cytokine IL-1β which then activates neurons. Quantification of microglial activation and electrophysiological assessment of the CO_2 responses were performed in the subfornical organ, a circumventricular organ that lacks a blood brain barrier. Based on comparisons of the cell's firing rate response of subfornical neurons, the sensitivity to CO_2/H^+ is ~10 times less than that reported for the RTN (Guyenet et al., 2019). It was argued that blood-born compounds can have access to the CNS via this route such that this structure acts as an integrative site for the maintenance of homeostasis (Vollmer et al., 2016). This explanation raises the possibility that the area postrema plays a similar role in respiratory manifestations of PD. The area postrema is a medullary circumventricular organ with chemosensing properties located above the NTS; it expresses inward rectifier K^+ channels (Kir) associated with CO_2 chemosensitivity (Wu et al., 2004) and projects to the RTN, a key medullary structure in CO_2 chemodetection (Rosin et al., 2006). This idea is certainly worth exploring.

5.4 Estrogens

Gonadal hormones are "the usual suspects" in mechanistic studies aiming to explain sex-based differences in physiological function. The contribution of 17β-estradiol (E_2) is intriguing owing to its multiple and heterogeneous influences on the stress

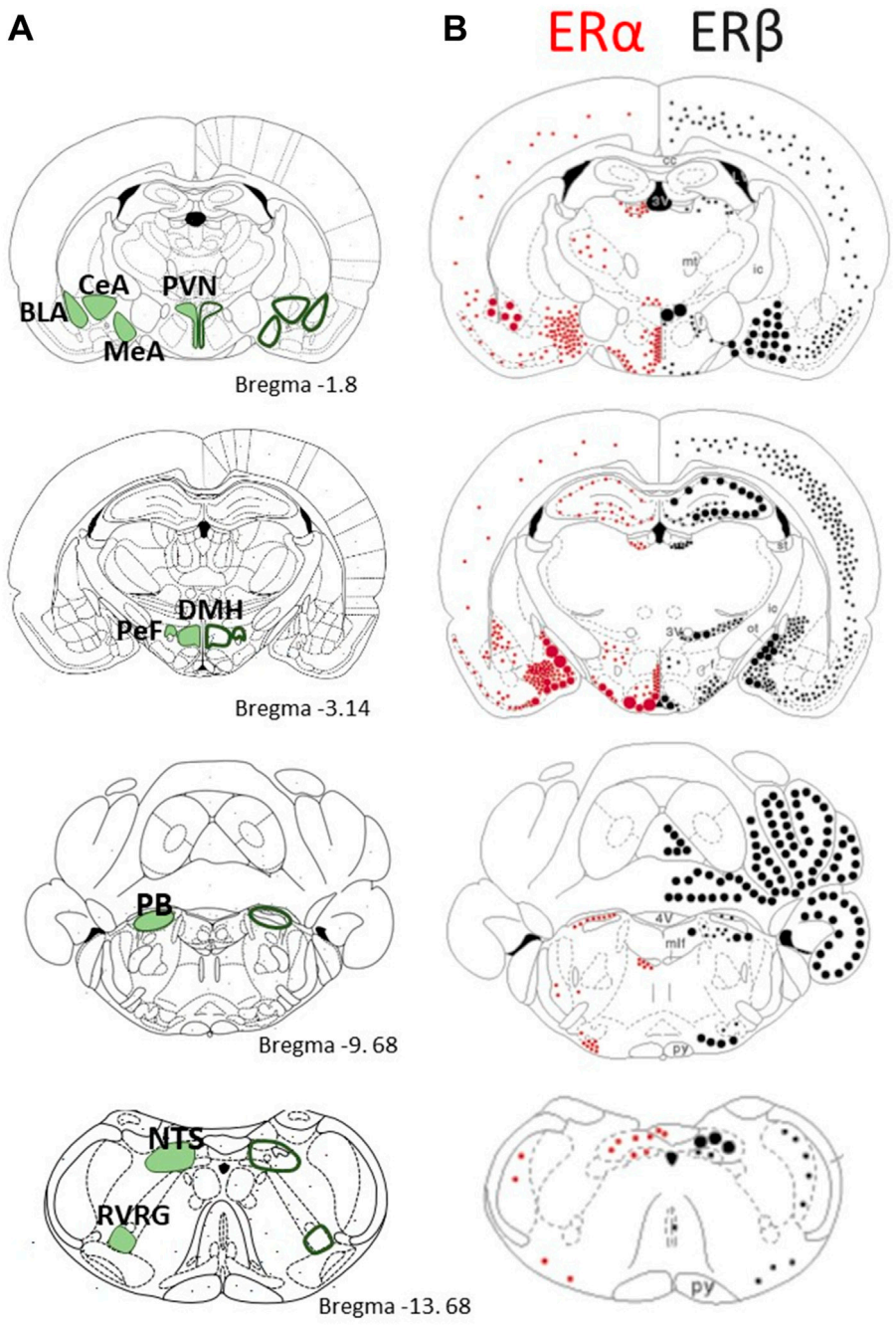

FIGURE 5
Comparison of the distribution of estrogen receptors α and β in brain regions that are responsive to CO_2/H^+ sensing and/or contribute to the stress response **(A)** Schmatics on the left present a series of coronal section modified from the rat brain atlas of Paxinos and Watson (1998) with emphasis on key structure with CO_2 sensing properties or with established roles in respiratory control; the stereotaxic reference (distance from bregma) is indicated. **(B)** Schematics on the right present the distribution of ERα (red dots) and ERβ (black dots) mRNA in the rat brain. Small dots represent 1–5 labeled cells; medium dots 6–10 labeled cells; large dots represent approximately 50 labeled cells. Adapted with permission from Shughrue et al., 1997. PVH: Paraventricular nucleus of the hypothalamus; BLA: Basolateral amygdala; CeA: Central nucleus of the amygdala; MeA: Medial nucleus of the amygdala; DMH: Dorsomedial hypothalamic nucleus; PeF: Perifornical area; PB: Parabrachial nucleus; NTS: Nucleus of the solitary tract; RVRG: Rostral ventral respiratory group.

response. On the one hand, the onset of PD-related respiratory disturbances coincides with the rise in circulating E_2 at puberty and reports of panic attacks in *some* women receiving E_2-replacement therapy (Price and Heil, 1988; Hayward et al., 1992). This is consistent with the view that E_2 is a potent stimulant of the hypothalamic pathways regulating the stress response; female rats in proestrus (high estradiol, high progesterone) and estrus (recent exposure to peak estradiol), have elevated basal and stress induced corticotropic hormone (ACTH) and corticosterone (Viau and Meaney, 1991; Heck and Handa, 2019). On the other hand, E_2-

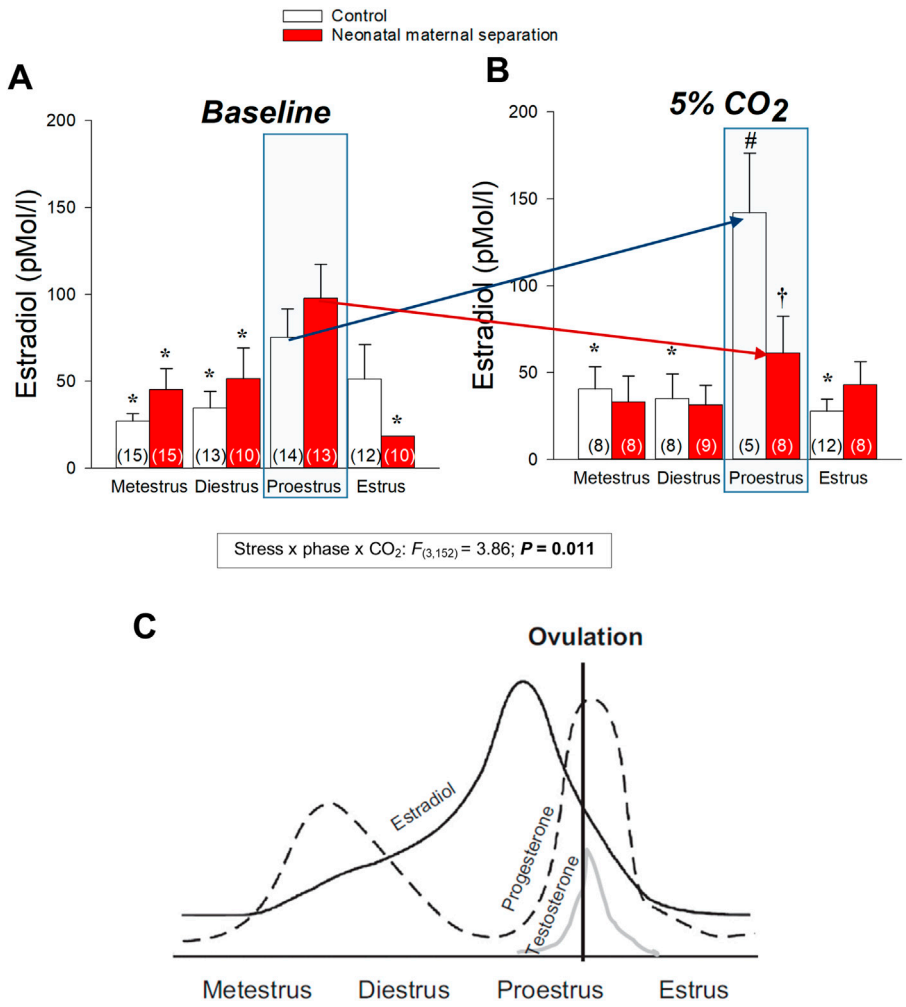

FIGURE 6
Neonatal stress disrupts the plasma 17β-estradiol (E_2) response to CO_2 inhalation of female rats. Plasma E_2 levels measured across the different phases of the estrus cycle **(A)** in room air and **(B)** 30 min following exposition to 5% CO_2 for 10 min. The numbers in brackets indicate the number of replicates in each group. **(C)** Schematic representation of the changes in estradiol, progesterone, and testosterone across the estrus cycle in rat. Repreoduc with persmission from (Pfaus et al., 2015). Data are reported as means ± SEM; * indicates a value different from corresponding proestrus value at $p < 0.05$; † indicates a value different from corresponsing control value at $p < 0.05$; # indicates a value signifincatly different from corresponsing baseline value at $p < 0.05$ compare to baseline value. Reproduced with permission from (Tenorio-Lopes et al., 2020).

replacement therapy may reduce panic symptoms in women and transdermal E_2 treatment in menopausal women has been reported to blunt the acute stress response (Lindheim et al., 1992; Chung et al., 1995). In rats, E_2-supplementation of ovariectomized females can reduce the response to chronic recurrent stress by attenuating the output of the paraventricular nucleus of the hypothalamus (PVN) (Gerrits et al., 2005). The sum of these observations underlies the view that E_2 has anxiolytic properties (Österlund, 2010; Borrow and Handa, 2017). Thus, there is no clear consensus and these apparent discrepancies reflect challenges commonly encountered in stress studies in which the responses vary depending of the intensity, nature, and duration of the challenge used. Furthermore, the sex, species, age/ovarian status of the female along with environmental factors such as nutrition contribute to the variability of estrogen's actions (Borrow and Handa, 2017; Heck and Handa, 2019). As we discuss below, the two main E_2 receptors (ERα and ERβ) have opposing actions on network function, such that slight changes in their relative expression can alter E_2's net effects and thus explain the heterogeneity in its effects (Kunte et al., 2014; Borrow and Handa, 2017).

E_2 was initially shown to act via "classical" ERα and ERβ that are ligand-activated transcription factors influencing gene expression; however, both receptors are also expressed outside the nucleus where they induce non-genomic actions. E_2 binds equally well to ERα and ERβ, but the two receptors are not functionally interchangeable; the differences in their localisation throughout the rodent brain support this functional divergence (Figure 5; adapted from (Shughrue et al., 1997). Interestingly, the distribution of ERα and ERβ is similar between sexes (Hara et al., 2015), but the levels of expression are generally greater in females (Garcia-Segura et al., 2001). E_2 also exerts rapid effects via membrane-bound G-protein estrogen receptors (GPERs); their discovery being more recent (1990s), the responses induced by GPERs are less documented (Hara et al., 2015; Barton et al.,

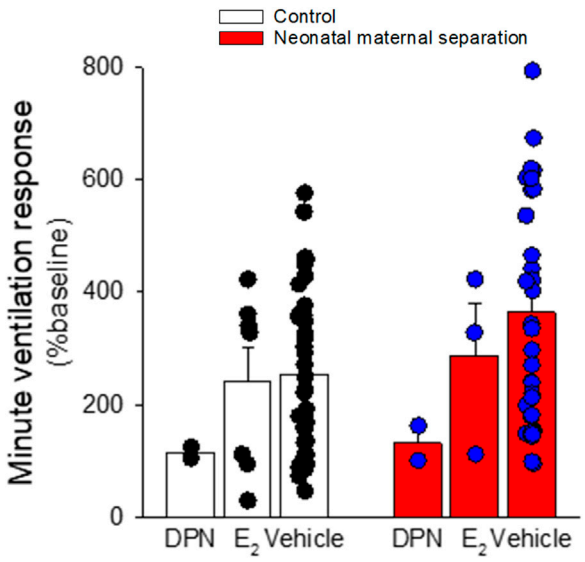

FIGURE 7
17-β estradiol supplementation attenuates the ventilatory response to the CO_2 inhalation (5% CO_2; 10 min) in female rats. Rats with intact ovaries either received vehicle, 17-β estradiol (40 μg/kg), or the ER-β agonist diarylpropionitrile (DPN; 0.1 mg/kg) 1 h before the onset of the experiment. Data are reported as means ± SEM; all phases of the cycle are combined. The low number of replicates in DPN treated rats did not allow proper statistical analysis.

2018). Together, these receptors allow E_2 to alter the structure and function of neuronal networks via multiple mechanisms with time courses ranging from seconds to days (Evrard and Balthazart, 2004). We know for instance that E_2 facilitates the transmission of electrical signals by promoting synaptic transmission via ERα. The concurrent actions of E_2 on ERβ promote the formation of dendritic spines such that in the hippocampus, the spine density fluctuates with the estrus cycle and peaks on the day of proestrus (Woolley and McEwen, 1992; Tan et al., 2012), which is the phase when the largest CO_2 response in NMS females were observed (Figure 1) (Tenorio-Lopes et al., 2020). E_2 is strongly linked with anxiety disorders and a common view is that activation of ERβ is responsible for its anxiolytic effects whereas ERα initiate fear and anxiety-like behaviors (Walf and Frye, 2006; Frye et al., 2008; Borrow and Handa, 2017). Such generalisation requires caution, however, because each receptor type has distinct effects on glutamatergic and GABAergic signalling. The relative expression of each receptor type thus determines the balance between excitation and inhibition and E_2's net effect on a system (Woolley, 2007; Liu et al., 2008; Tan et al., 2012; Tian et al., 2013). Still, this balance is plastic and factors such as E_2 levels and stress influence the relative expression of ERs. For instance, acute immobilization stress augments ERα immunolabeling in the PVN and medullary noradrenergic neurons (A2 area) of females (Estacio et al., 1996). Conversely, E_2 generally reduces ERs in the hypothalamus (Simerly and Young, 1991; Garcia-Segura et al., 2001). GPERs also contribute to anxious phenotypes but their role remains unclear because opposing behavioral responses have been reported (Tian et al., 2013; Borrow and Handa, 2017).

Disruption of E_2-signalling has therefore emerged as a key mechanism in anxiety disorders (Östlund et al., 2003; Albert et al., 2015) and although respiratory symptoms are an important feature of PD, our comprehension of the actions of E_2 on the respiratory control system (including CO_2 sensing) is still in its infancy, especially in females. Because female rats previously subjected to NMS closely replicate ontogenic and cyclic features of respiratory manifestations of PD, we took advantage of this model to further our understanding of the contribution of E_2 on the ventilatory response to CO_2.

Comparison of basal E_2 and progesterone levels between NMS and controls across the estrus cycle does not indicate that NMS affects the gonadotropic axis at rest (Figure 6) (Dumont et al., 2011; Tenorio-Lopes et al., 2020). However, analysis of samples harvested following CO_2 inhalation shows that this acute challenge stimulates E_2 release during proestrus in controls but not in NMS females (Tenorio-Lopes et al., 2020) (Figure 6). We then noted that during proestrus, the intensity of the hyperventilatory response observed in NMS females was inversely proportional to E_2 levels observed following CO_2 exposure (Tenorio-Lopes et al., 2020). These data indicate that high E_2 is a powerful inhibitor of the ventilatory response to CO_2 but the E_2 level achieved in NMS females is insufficient to prevent an excessive HcVR, especially during proestrus (Tenorio-Lopes et al., 2020). We then tested those conclusions by injecting E_2 (3, 10, or 25 μg) in ovariectomized (OVX) females once per day every 4 days to restore E_2 level within physiological range and mimic cyclic fluctuations. The last injection was performed ~2 h prior to ventilatory measurements. Consistent with previous observations in rats, OVX reduced the HcVR (Marques et al., 2015), but the drop was greater in NMS females such that their HcVR (post-OVX) was comparable to that of controls with intact gonads (Tenorio-Lopes et al., 2020). Results from supplementation experiments clearly show that in NMS females, E_2's actions are biphasic with an increasing stimulatory effect until plasma levels reached the range observed during proestrus (~150 pMol/l); higher doses no longer stimulated the HcVR. In contrast, E_2's influence on the HcVR of controls was limited. In a preliminary and unpublished experiment, we determined whether ERβ contributes to this process by testing the effect of acute IP injection of E_2 (40 μg/kg) and the selective ERβ agonist diarylpropionitrile (DPN, 0.1 mg/kg) 1 h prior to CO_2 inhalation test. Preliminary observations suggest that, at these doses, this treatment is more effective than E_2 at reducing the HcVR, especially in NMS females (Figure 7). These results require further validation and raise questions about the stimulatory actions of a selective ERα agonist on the HcVR. Notwithstanding, E_2 can be an important modulator of the neural pathways regulating the CO_2 response; it would be interesting to determine whether those actions take place within "classical" medullary circuits or involve more rostral structures. As we discuss below, recent data revealed orexin producing neurons of the hypothalamus as key players in the process.

6 Conclusion and future directions

CO_2 monitoring is essential to respiratory homeostasis and health; consequently, deciphering the cellular and molecular

underpinnings of CO_2 sensing and the neural networks driving reflexive responses has been a long-standing quest for physiologists. The presence of CO_2 sensing neurons on the ventral surface of the medulla has been suspected since the 1960s and today, the RTN is firmly established as a primary structure in feedback regulation of breathing (Guyenet and Bayliss, 2022). The use of modern, "state of the art" approaches has led to important discoveries regarding the role and function of the RTN and we now know that this structure responds to very small changes in CO_2/H^+ to induce precise respiratory adjustments without producing any conscious aversive sensation (dyspnea), stress, or arousal (Guyenet and Bayliss, 2022). This mini-review and other contributions to this special issue demonstrate that other (non-medullary) brain regions are important contributors to central CO_2 chemosenstivity (Nattie and Li, 2011). Figure 2 illustrates how these various structures interact to influence breathing and how E_2 related signalling influences network function. While the evidence indicating that these structures can reflexively induce arousal and behavioral responses is compelling, further experiments are necessary to determine their specific contribution to respiratory control since the threshold for their activation seems greater than the RTN. Moreover, it is imperative to determine whether their response to CO_2 is the result of a direct action of CO_2/H^+ or "network driven" changes. Although the contribution of these structures to homeostasis maybe limited under "standard" (healthy) conditions, their contribution to various respiratory disorders is convincing. For instance, CO_2-induced arousal contributes to sleep fragmentation during sleep apnea (Kaur et al., 2017; Kaur and Saper, 2019; Kaur et al., 2020) and impairment of this arousal response may be important in the pathophysiology of sudden unexpected death in epilepsy, sudden infant death syndrome, and sleep apnea (Buchanan and Richerson, 2010; Smith et al., 2018; Buchanan, 2019). Here, our discussion focused on PD and the mechanistic studies performed in this context brings further support to this notion as they show that the excessive HcVR observed in stressed female rats reflect abnormal CO_2 sensing taking place in structures near the hypothalamus.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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