PERSPECTIVE

SENSITIVITY TO CARBON DIOXIDE AND TRANSLATIONAL STUDIES OF ANXIETY DISORDERS

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Abstract—Heightened concentrations of CO₂ in inhaled air provoke temporary acidification of the brain, followed by compensatory hyperventilation and increased arousal/anxiety. These responses are likely to map a basic, latent general alarm/avoidance system that is largely shared across mammals, and are sources of individual differences. By showing paroxysmal respiratory and emotional responses to CO₂ challenges, humans with panic and separation anxiety disorders lie at one extreme of the distribution for CO₂ sensitivity. This is also a developmental trait, sensitive to interference with parental cares. By sharing CO₂ sensitivity with humans, rodents constitute a valuable resource to model panic and separation anxiety in the laboratory. Advantages of modeling CO₂ sensitivity in rodents include non-inferential measurements (e.g. respiratory readouts) as proxies for human conditions, unbiased investigation of gene–environment interplays, and flexible availability of tissues for mechanistic studies. Data in humans and animals such as those reported in this issue of Neuroscience begin to reveal that CO₂-driven behavioral responses stem from anatomo-physiological systems that are relatively separated from those subserving general dispositions to anxiety. This supports the notion that sensitivity to suffocative stimuli and ensuing human panic are significantly independent from trait/cognitive anxiety, and corroborates newer conceptualizations that distinguish between fear and anxiety circuitries. © 2017 IBRO. Published by Elsevier Ltd. All rights reserved.

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Few, if any, fundamental biological traits are more universal across species than the behavioral and respiratory responses to heightened CO₂ concentrations in the environment. Except for blood-feeding insects that actively pursue CO₂ gradients in order to localize their host and tellingly carry the main CO₂-detecting sensors on the mandibulae (McMeniman et al., 2014) – for virtually all species, heightened [CO₂] is adversative and is adaptively shunned. As such, the study of CO₂ sensitivity is an investigational journey into one of the most basic and general alarm/avoidance systems within the realm of biology.

Once it permeates the blood–brain barrier, CO₂ is hydrolyzed and dissociated into HCO₃⁻ and H⁺: mammals’ responses to the ensuing temporary acidification of extracellular brain fluids (Guyenet, 2014) include: increased ventilation to restore PaO₂ and pH, enhanced arousal, and subsequent anxiety. These responses are not ‘all-or-none’ phenomena and are a source of individual differences. Genetic and gene-by-environment mechanisms explain variance for respiratory and emotional responses to CO₂ in animal and man, and people with panic and separation anxiety disorder lie at one extreme of the sensitivity distribution, showing paroxysmal hyperventilation and panic when they undergo CO₂ challenges (Battaglia et al., 2008).

On this basis, Sah and co-workers (Winter et al., 2017) assessed the CO₂-evoked behavioral responses of outbred vs. inbred rat strains. Since outbred strains approximate natural random mating conditions, they are more informative on continuously distributed traits such as the physiological responses to CO₂, while by virtue of their genetic homogeneity and reduced individual variability, inbred animals constitute a better tool to investigate mechanistic questions. They also assessed tryptophan hydroxylase-2 (TPH-2)-positive serotonergic neurons in anxiety/panic regulatory subdivisions of the dorsal raphe, and dopamine β hydroxylase (DβH)-positive noradrenergic neurons in the locus coeruleus. Serotonin is implicated in both fear and chemoreception, and noradrenaline has been classically implicated in anxiety.

There are several merits to this study. First, they addressed between strains’ variability. Inasmuch as the distribution of liability to CO₂ sensitivity is continuous and normally distributed in both animals and man, common genetic polymorphisms and environmental elements are expected to act additively to explain this variation. Studying the nature and the dynamics of this variance by comparing different strains is then central to address fundamental questions such the adaptive role, the pathology, and the evolutionary relevance of CO₂ sensitivity (Battaglia et al., 2014). Second, they tested animals in both unconditioned- and conditioned contexts.
This is important because behavioral reactivity to CO₂ in both animal and man can be thought of as a set of largely unconditioned responses that map one or more inner alarm systems (Klein, 1993). Third, they used immunohistochemistry to tie the behavioral data to the neurochemical analyses.

Multivariate analyses showed between-strains variability for freezing responses to breathing 10%-CO₂, matching previous findings of strain-dependent variation in CO₂-evoked ventilation in rodents. There was a large variation among outbred strains, and the highest sensitivity (as indexed by immobility) was seen in the inbred WK strain. These data simultaneously support the nature of CO₂ sensitivity as a quantitative trait and indicate the WK strain as a candidate for in-depth study of CO₂ hypersensitivity in rats. Quite interestingly, rearing behavior (an index of trait anxiety) was not enhanced in CO₂ hypersensitive rats, which parallels the finding of little correlation between human trait-anxiety and CO₂ hypersensitivity (Klein, 1993).

There was also a clear, unconditioned response to CO₂ in all strains, but no evidence of conditioned responses 24 h post inhalation. While this confirms CO₂ as a potent unconditioned adversative stimulus, it also indicates that multiple exposures are necessary to prime conditioned fear responses within this specific susceptibility. This may also resemble human trajectories, whereby several unexpected panic attacks at the onset of illness appear necessary before anticipatory anxiety and cue-contextual avoidance become visible. In a parallel fashion, experiments that showed conditioned/cued responses to CO₂ typically employed repeated exposures (D’Amato et al., 2011).

Turning to neurochemical analyses, altered TPH-2-positive cell counts (indicating reduced 5-HT immunoreactivity) were limited to the strains that had also shown enhanced CO₂ reactivity. Moreover, this was circumscribed to the chemoreceptive ventrolateral-and ventro-lateral periaqueductal gray regions of the dorsal raphe, but did not extend to other subdivisions (such as the dorsal raphe) subserving general trait-anxiety behavior, such as avoidance on the elevated T-maze. Coherently, CO₂-sensitive strains showed significantly enhanced D₁[H]-positive cell counts within the locus coeruleus.

Thus, neurochemical and behavioral data converge in showing CO₂-driven responses as stemming from a physiological system that is relatively separated and independent from those subserving general disposition toward anxiety. This supports the basic notion that sensitivity to suffocative stimuli and ensuing human panic cannot be equated to generalized anxiety (Klein, 1993), and current conceptualizations that distinguish between fear and anxiety circuitries (Ledoux and Pine, 2016).

Research on CO₂ sensitivity dovetails with both basic and clinical investigations (Wemnie et al., 2013; Lebold et al., 2016). The connections between chemoreception and essential survival-alarm systems, and the interspecific nature of the trait are solid assets for translational approaches. The manifest relationship with respiration physiology allows for measuring ventilatory parameters over and above behavioral responses to CO₂ challenges. Based on the knowledge that the phenotypes of CO₂ hypersensitivity and panic anxiety share a large proportion of causal agents (Battaglia et al., 2008), research questions and the associated procedures can be fruitfully converted from inferential (’is this animal anxious?’) into non-inferential (’how is this animal breathing?’).

Inasmuch as CO₂ hypersensitivity is affected by early-life adversities including parental separation and interference with maternal cares (Genest et al., 2007; Battaglia et al., 2014), this is a developmental trait. The gene-by-environment interplays common to animal and human CO₂ hypersensitivity may point toward conserved between-species’ phylogenetic bridges (Battaglia et al., 2014) and evoke further quests. These include the comprehension of the trade-offs between CO₂ hypersensitivity and better adaptation to hostile environments, and the possible epigenetic mediated. Without addressing these questions, the significance of this fundamental alarm system and its relevance to human panic disorder including its development, transmission, and age at onset (Battaglia et al., 1998) will hardly be understood.

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