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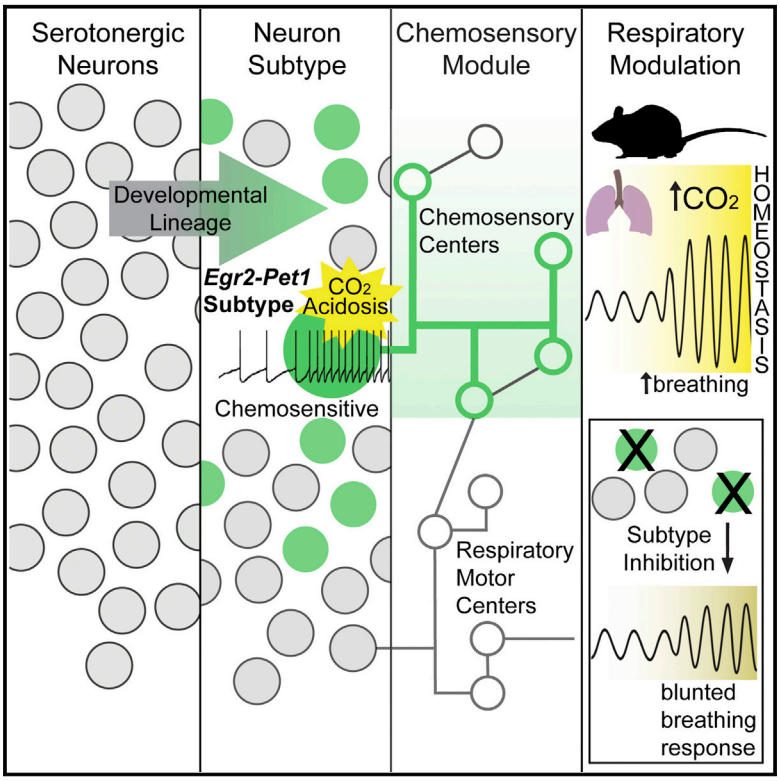
Functional and Developmental Identification of a Molecular Subtype of Brain Serotonergic Neuron Specialized to Regulate Breathing Dynamics

Graphical Abstract



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In Brief

Brust et al. show that the life-sustaining respiratory CO_2 chemoreflex is regulated by a specialized subtype of serotonergic neuron—the *Egr2-Pet1* subtype—and reveal its unique physiological, biophysical, and hogological properties centered around chemosensory processing and likely specified by genetic lineage developmentally. Thus, specialized modules contribute to serotonergic functional breadth.

Highlights

- Functional specializations map to distinct 5HT neuron developmental lineages
- Life-sustaining breathing reflex is specifically driven by *Egr2-Pet1* 5HT neurons
- *Egr2-Pet1* 5HT neurons function as frontline PCO_2/pH chemoreceptor
- 5HT neuronal system is found to have sensory and motor subdivisions

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Functional and Developmental Identification of a Molecular Subtype of Brain Serotonergic Neuron Specialized to Regulate Breathing Dynamics

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SUMMARY

Serotonergic neurons modulate behavioral and physiological responses from aggression and anxiety to breathing and thermoregulation. Disorders involving serotonin (5HT) dysregulation are commensurately heterogeneous and numerous. We hypothesized that this breadth in functionality derives in part from a developmentally determined substructure of distinct subtypes of 5HT neurons each specialized to modulate specific behaviors. By manipulating developmentally defined subgroups one by one chemogenetically, we find that the *Egr2-Pet1* subgroup is specialized to drive increased ventilation in response to carbon dioxide elevation and acidosis. Furthermore, this subtype exhibits intrinsic chemosensitivity and modality-specific projections—increasing firing during hypercapnic acidosis and selectively projecting to respiratory chemosensory but not motor centers, respectively. These findings show that serotonergic regulation of the respiratory chemoreflex is mediated by a specialized molecular subtype of 5HT neuron harboring unique physiological, biophysical, and hodological properties specified developmentally and demonstrate that the serotonergic system contains specialized modules contributing to its collective functional breadth.

INTRODUCTION

Serotonin (5HT), a monoamine neurotransmitter synthesized in the brain and gut, is involved in many neurological and psychiatric disorders and plays central, even life-sustaining, roles in controlling respiration, heart rate, and body temperature (Gingrich and Hen, 2001; Hilaire et al., 2010; Hodges and Richerson, 2010; Jacobs and Azmitia, 1992; Ray et al., 2011). Such a multiplicity of jobs underlies the unwanted effects often elicited upon deliberate therapeutic alteration of 5HT levels pharmacologically. Life-threatening cardiorespiratory dysfunction and hyperthermia can ensue, as can debilitative conditions involving depression, anxiety, anhedonia, bowel dysfunction, and diminished libido (Boyer and Shannon, 2005; Ferguson, 2001). Therapeutic strategies better tailored to specific aspects of 5HT-regulated physiology and behavior are needed. Advances would come through knowledge of serotonergic neuronal organization, including identification of specialized subtypes of 5HT neurons, the behaviors they regulate, and potential differentially expressed druggable substrates.

Molecular differences across brain serotonergic neurons and across serotonergic progenitor cells are indeed being uncovered (Gaspar and Lillesaar, 2012; Jensen et al., 2008; Wylie et al., 2010), and at least some of these gene expression differences may point to intrinsic functional differences and thus the possibility of identifiable, highly specialized subtypes of 5HT neurons. We recently developed genetic tools to test this prediction, now permitting linkage between a specific molecular subtype of 5HT neuron and function at the cellular, circuit, and organismal level. Applying these tools here, we sought to identify whether such functional modularity exists within and can be deconstructed from the 5HT neuronal system in mice.

We applied the intersectional feature of our recently engineered chemogenetic silencing allele, *RC::FPDi* (Ray et al., 2011), to target inhibitory DREADD receptor (hM_4Di; Armbruster et al., 2007) expression to the major molecularly and developmentally defined subtypes of 5HT neurons (Jensen et al., 2008), one subtype at a time, for in vivo activity modulation and subtype-specific functional probing in the awake mouse. Specifically, we queried each subtype for a role in regulating the respiratory chemoreflex. This reflex is responsible for increasing breathing in response to tissue CO_2 elevation (hypercapnia) and acidosis to restore these vital chemistries back within a normal range (Dean and Nattie, 2010; Guyenet et al., 2010; Nattie and Li, 2012), and it is dependent in part on serotonergic activity, as we revealed upon acute suppression of the 5HT neuronal system en masse (Ray et al., 2011) and as suggested in rodent