Background

Cells and mechanisms underlying central chemosensitivity, are poorly understood and can be controversial. Our overarching hypothesis is that brainstem 5-HT and/or GABA neurons contribute to detection and response to changes in pH/CO₂. Our experiments are designed to provide insight into respiratory physiology, and pathologies thought to result from chemosensory dysfunction such as the Sudden Infant Death Syndrome (SIDS). A deficiency of 5-HT resulting from maternal dietary restriction could enhance vulnerability to SIDS. It was recently shown that rat pups born to dams fed a tryptophan deficient diet have a reduced number of central 5-HT neurons and reduced ventilatory sensitivity to CO₂ (Nattie et al. 2011). Unknown are the relative contributions of central vs peripheral chemoreceptors to this observation, or the residual contributions of 5-HT in the face of this deficiency. In the present study we are extending this initial description using a perfused in situ brainstem model to determine the degree of central chemosensory deficit imparted by maternal tryptophan restriction. We also repeat these studies with pharmacological blockade of a population of 5-HT receptors to illustrate remaining 5-HT and non-5-HT contributions to chemosensitivity. This work reveals important interactions between nutrition and ventilatory control that may aid in the understanding of SIDS.

Methods

Rat dams are fed either a control diet or a control diet ≈45% deficient in tryptophan, to test the hypothesis that developmental tryptophan deficiency alters cardiorespiratory control or tryptophan deficient dams, to test the hypothesis that developmental tryptophan deficiencies alters CO₂/pH chemosensitivity. Pups, 30-40 days developmentally exposed and maintained on the experimental diet had decreased ventilatory responses to arterial hypercapnia. Results indicate that central chemosensory mechanisms are influenced by this independent variable. In the present study we are extending this initial description using a perfused central CO₂/pH chemosensitivity. Current experiments indicate that these mechanisms are influenced by this independent variable. In the present study we are extending this initial description using a perfused central CO₂/pH chemosensitivity. Current experiments indicate that these mechanisms are influenced by this independent variable. In the present study we are extending this initial description using a perfused central CO₂/pH chemosensitivity. Current experiments indicate that these mechanisms are influenced by this.

“Push-Pull” model

Both 5-HT and GABAergic mechanisms contribute to central chemosensitivity (Richardson 2004). We have proposed a model, illustrating raphe neuron contributions to central ventilatory chemosensitivity mediated by both 5-HT and GABA neurons.

Results

5% CO₂

Increases in phrenic discharge with hypercapnia in the in situ preparation illustrate the product of central chemosensitivity

9% CO₂

Ventriculosity Sensitivity to CO₂: Effect of tryptophan deficient diet and 5-HT²A antagonist ketanserin.

- In control animals, hypercapnia increases neuroventilation by 27%.
- Tryptophan deficiency reduces hypercapnic ventilatory response by 32.3% when compared to control.
- In control animals, ketanserin decreases hypercapnic ventilatory sensitivity by 98.8%.
- In tryptophan deficient animals, ketanserin decreases hypercapnic ventilatory sensitivity by 80.15%.

Preliminary Conclusions:

- Rats born to tryptophan deficient dams have attenuated central chemosensitivity
- Chemosensitivity of control rats is greatly attenuated/abolished by ketanserin, suggesting 5HT 2A receptor mediated mechanisms are critical for central chemosensitivity.
- Ketanserin insensitive mechanisms contribute to chemosensitivity in rats born to tryptophan deficient dams, suggesting non-5-HT mechanisms are up regulated to accommodate for the 5-HT deficiency. We speculate that this is achieved through a strengthening of the GABA-mediated processes.

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