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Abstract

Serotonergic dysfunction is thought to enhance vulnerability to Sudden Infant Death Syndrome (SIDS) by compromising critical homeostatic reflexes. Rat dams fed a tryptophan deficient diet produce pups with low tissue serotonin (5HT) and a reduced ventilatory sensitivity to inspired CO2 *in vivo*. We use a perfused *in situ* brainstem model derived from pups of dams fed either a control or tryptophan deficient diet, to test the hypothesis that developmental tryptophan deficiency alters central CO2/pH chemosensitivity. Pups (P21-P83) developmentally exposed and maintained on the experimental diet had decreased ventilatory responses to arterial hypercapnia. Results indicate that central chemosensitive mechanisms are influenced by this treatment. We have proposed that raphé 5HT and GABA mediated mechanisms contribute to central CO2/pH chemosensitivity. Current experiments indicate that these mechanisms continue to contribute to the residual chemosensitivity remaining after tryptophan deficiency. These data further illustrate the contributions of 5HT dysfunction to SIDS vulnerability and enhance our understanding of the impacts of pre and postnatal nutrition.

Post Natal Impact of Maternal Tryptophan Deficiency on Central CO2/PH Chemosensitivity

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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/CO_2. 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 CO_2 (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.

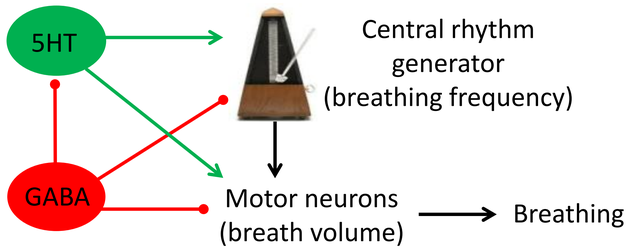
Methods

Rat dams are fed either a control diet or a diet ≈45% deficient in tryptophan beginning two weeks before mating through weaning of pups. Pups are, thus, maternally exposed to control or tryptophan restriction throughout pre and postnatal development . Subsequent experiments are conducted using male and female pups beginning on P21, using an *in situ* unanesthetized perfused decerebrate brainstem preparation (Paton 1996).

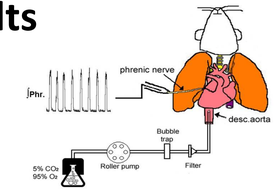
- Preparations are maintained with perfusate equilibrated with 5% CO_2 in 95% O_2 , and exposed to a 5 minute hypercapnic challenge (9% CO_2 balance O_2).
- Phrenic neurograms are recorded and analyzed for burst frequency and amplitude to illustrate neural equivalents of breathing frequency and amplitude, and sensitivity to the hypercapnic challenge.
- Hypercapnic sensitivities are compared between control and tryptophan restricted preparations.
- Hypercapnic sensitivities are also compared in control and restricted preparations pretreated with the 5-HT 2A receptor antagonist ketanserin (5 uM in perfusate).

"Push-Pull" model

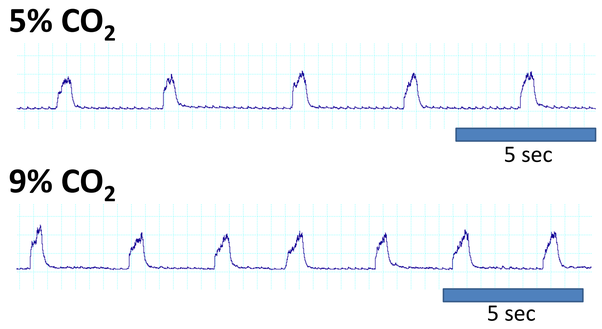
Both 5-HT and GABAergic mechanisms contribute to central chemosensitivity (Richerson 2004). We have proposed a model, illustrating raphé neuron contributions to central ventilatory chemosensitivity mediated by both 5-HT and GABA neurons.

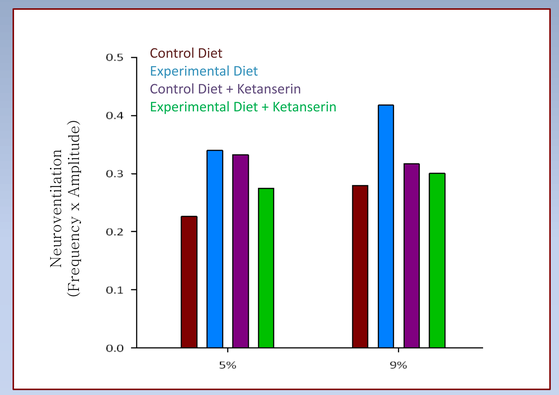


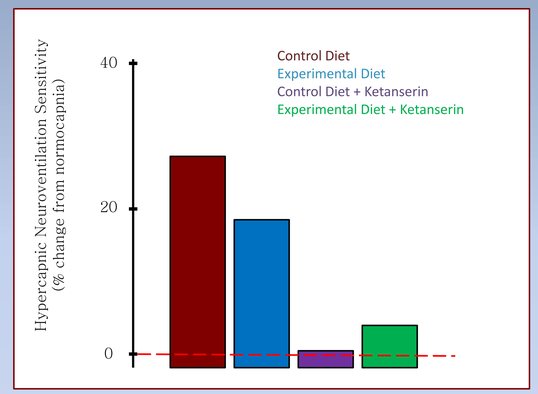
Results



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







Ventilatory 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 of 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 stregthening of the GABA-mediated processes.

References:

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