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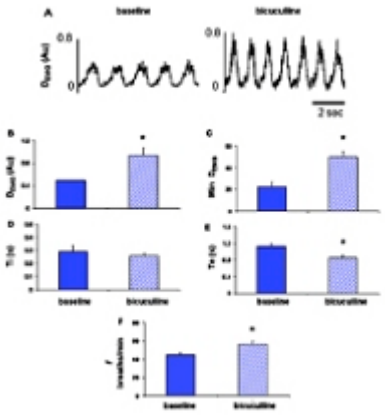
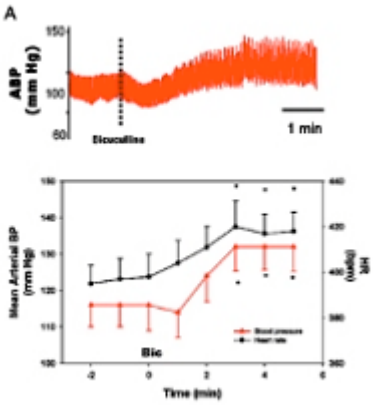
We are continuing studies that we began in my laboratory for a SNRP project (Type 1) on neuronal and chemical control of breathing. Our major interest is investigating central neuronal mechanisms that are involved in obesity-related respiratory disorders. It is well established that obesity results from an imbalance between energy intake and energy expenditure and that obese subjects commonly develop hypoventilation and sleep apnea syndromes with attenuated hypoxic and hypercapnic ventilatory responsiveness. We propose that these disorders may result, in part, from changes in neural input to regions of the brain that ultimately control the activity of respiratory muscles in the upper airways and chest wall. Our studies target specific hypothalamic nuclei because of their role as integrators of many peripheral signals and neural pathways that control energy homeostasis and body weight.

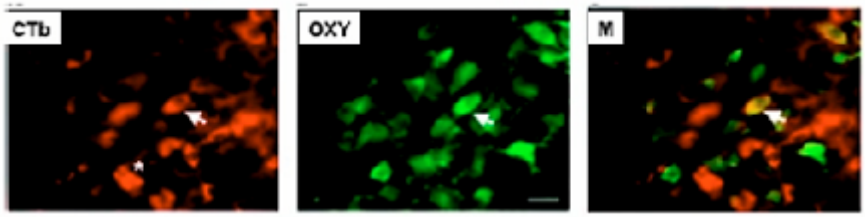
Recently, using integrative electrophysiology, we demonstrated that activation of the hypothalamic paraventricular nucleus (PVN) with GABAA receptor antagonist stimulates cardiorespiratory activity.





Admittedly, the critical neuronal circuitry required for generation and maintenance of respiration is located in the brain stem. Ultimately, changes in respiratory pattern or rhythm are derived through changes in the activity of brainstem neurons including a large population of cells known as the ventral respiratory group. This group of medullary neurons extends through the full rostrocaudal length of the ventrolateral medulla and contains the preBötzinger complex, the major proposed site for respiratory rhythm generation.

Our data show that oxytocin, a classic neurohormone with anorexigenic actions, is involved in modulating respiratory drive. First, using monosynaptic neuroanatomical tracers including cholera toxin B subunit (CTb) we showed that a subpopulation of PVN cells containing oxytocin project to neurons in the preBötzinger complex region.



Next, we demonstrated that microinjection of oxytocin into the the preBötzinger complex region dramatically stimulated respiratory frequency, while blockade of oxytocin receptors at the same site abolished this stimulatory effect. These studies suggest that loss of PVN neurons producing oxytocin or functional abnormalities in oxytocin or oxytocin receptor signaling may cause a decrease in respiratory drive, increased susceptibility to hypoventilation, and obstructive sleep apnea. Therefore, potentiation of central oxytocin dependent mechanisms, via activation of oxytocin receptors expressed by respiratory-related neurons in the rostral ventrolateral medulla, may represent targets for the development of new treatments for respiratory disorders associated with obesity and respiratory depression.