The Role of Hypothalamic Modulation in Obesity Hypoventilation Syndrome

Dylan Kupiec, Dr. Deanna Arble
Department of Biology, Marquette University, Milwaukee, WI 53201

Summary

Obesity hyperventilation syndrome (OHS) is a condition that afflicts 1 in every 220 US Americans, yet current treatments fail to cure the disease and have low compliance and effectiveness. The traditional hypothesis for OHS is that the physical effects of obesity is what causes respiratory issues, but recent evidence has shown that rather, a neuronal mechanism is more to blame for the symptoms of OHS. This neuronal connection has yet to be discovered, and the Arble lab's central goal is learning where this neuronal misfiring is and how to treat it.

Experimental Methods and Approach

1. The tissues must be "fixed" using formaldehyde, preventing the cells from changing during the procedure
2. Cells must be permeated, allowing the antibody to enter the cells and bind to the proteins
3. Primary antibodies are added to the cell
4. Secondary antibodies are then added, which target the primary antibodies, which creates a colorful compound that will be used as a marker for the protein

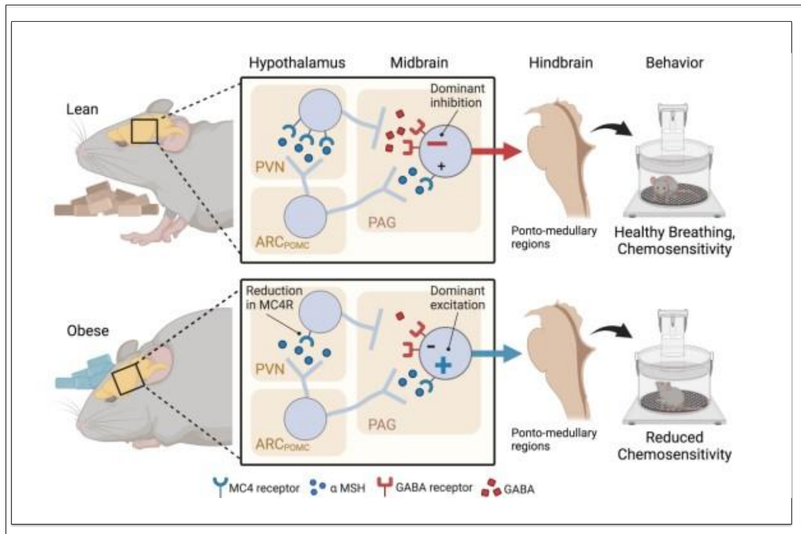
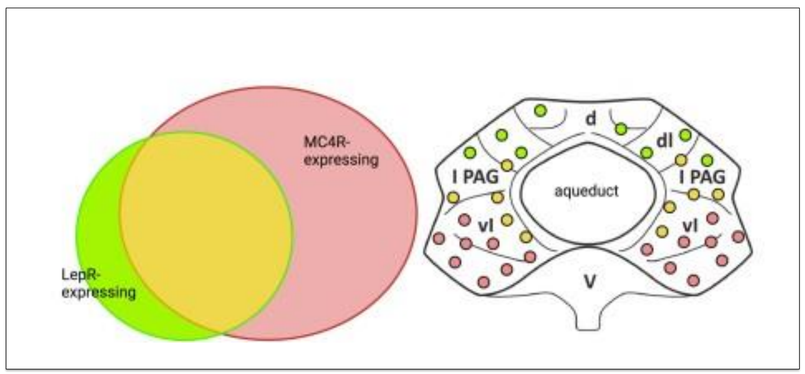


Figure 1. Hypothalamic modulation of chemosensitivity. ARCpomc neurons excite PVN and PAG neurons. PVN neurons then inhibit PAG neurons via GABA. In the lean state, the inhibited state of the PAG result in normal chemosensitivity. However, in the obese state, the downregulation of MC4 receptors prevents the PVN from sending inhibitory signals to the PAG, reducing chemosensitivity.

Background/Introduction

The hypothalamus is a small portion of the brain that sits right above the pituitary gland and is mainly involved in maintaining homeostatic regulation for the body, which includes the regulation of feeding. As such, it is hypothesized that obesity causes a dysregulation of feeding, which may affect the ponto-medullary region of the hindbrain, consequently impacting breathing. Our lab hypothesizes that this modulation is occurring in the midbrain periaqueductal gray (PAG), and a subpopulation of PAG neurons have been identified to play a critical role in chemosensitivity, impacting periodic breathing. In order to test these theories, the practice of immunohistochemistry (IHC) needs to be used to determine where in the PAG leptin-receptors and MC4R-receptors are being expressed. IHC is a technique that uses foreign antibodies binded to a protein or gene of interest, which in this case is MC4R, a part of the melanocortin system that has been correlated to regulation of chemosensitivity, to form a detectable compound in order to identify specific antigens in a sample.



Expectations of Experimental Methods. Co-expression of leptin and MC4 receptors are expected from a moderate number of cells in the lPAG. A smaller subset of cells are expected to only express leptin, and a large subset is expected to express only MC4, primarily in the vlPAG

Conclusion & Next Steps

Genome mice needed for IHC testing
Use IHC skills to identify the hypothalamic populations that are modulating the PAG