ABSTRACT

MELANOCORTIN-4 RECEPTOR SIGNALING IN THE PARAVENTRICULAR NUCLEUS: LINKING OBESITY AND RESPIRATORY HYPERCAPNIC CHEMOSENSITIVITY

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Responding to metabolic demands such as increased breathing in response to hypercapnia is essential for sustaining life. An obese, high-fat diet-fed state induces central changes in the brain that increases the risk of diseases, including those associated with a reduced hypercapnic respiratory chemosensitivity. While this is a prevalent problem, a mechanism outlining obesity-induced reduction in hypercapnic chemosensitivity remains to be discovered. To begin understanding the extent of central changes involved in respiratory hypercapnic chemosensitivity, we present data illustrating that diet-induced central changes at the level of the paraventricular nucleus of the hypothalamus are involved in chemosensitivity. We first illustrate that a high-fat diet causes significant neural changes in the arcuate nucleus, paraventricular nucleus and periaqueductal grey that are key contributors to bodyweight and energy regulation. Then using DREADD technology to target melanocortin-4 receptor-expressing neurons in the paraventricular nucleus of high-fat diet-fed (obese) and chow-fed (lean) animals, we found that inhibiting melanocortin-4 receptor-expressing neurons in the paraventricular nucleus in lean animals is sufficient to blunt chemosensitivity to the same degree as an obese phenotype. Similarly, we found that exciting melanocortin-4 receptor-expressing neurons in the paraventricular nucleus in obese animals partially improves chemosensitivity, such that a lean phenotype is nearly recapitulated. Collectively these findings elucidate that melanotcortin-4 receptors-expressing neurons in the paraventricular nucleus are sufficient to influence hypercapnic chemosensitivity, indicating that high-fat diet-induced central changes at this node can affect chemosensitivity. Then we illustrate how system stimulation of melanocortin-4 receptors via setmelanotide improves hypercapnic chemosensitivity to the same extent as prolonged weight loss. These experiments outline for the first time that central changes in the hypothalamus involved in bodyweight and energy regulation are also key contributors to blunted hypercapnic chemosensitivity under a high-fat diet, obese model. Overall, this work presents novel findings that expands the current field by demonstrating for the first time the role of melanocortin-4 receptor-expressing neurons in the paraventricular nucleus as a significant contributing factor of chemosensitivity that are disrupted in an obese, high-fat diet-fed state.