

Targeted destruction of NPY receptor-expressing neurons in the arcuate nucleus of the hypothalamus increases food intake and body adiposity

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ABSTRACT

The arcuate nucleus of the hypothalamus (Arc) plays an important role in the regulation of appetite and metabolism. The orexigenic peptide, neuropeptide Y (NPY), is an integral part of the neural circuitry in the Arc. Previous work in our laboratory has shown that Arc microinjections of NPY-saporin (NPY-sap), a targeted neurotoxin that selectively destroys NPY receptor-expressing neurons, significantly increased food intake and led to rapid-onset obesity. The goal of the present experiment was to further understand the underlying mechanisms associated with this phenomenon. We microinjected NPY-sap into the Arc of male Sprague-Dawley rats and monitored them over the next 3-5 week period. We found that food intake, body weight and body adiposity were significantly increased, as were circulating leptin and insulin levels. In addition, the diurnal pattern of feeding was disrupted. Unlike the controls that ate mainly at night, lesioned rats ate nearly as much during the day as during the night. At the conclusion of the experiment, we analyzed the hypothalamus using immunohistochemistry to characterize the lesion produced by the NPY-sap microinjections. We found that the lesion caused a loss of NPY-Y1 and α -MSH immunoreactivity in the Arc, indicating that neurons known to express NPY receptors were destroyed at the injection site. Understanding the role of NPY and other neuropeptides associated with metabolism and feeding behavior in the rat can potentially open new doors for treatment and prevention of obesity, metabolic syndrome and type II diabetes in humans.