Antibodies against the melanocortin-4 receptor act as inverse agonists in vitro and in vivo

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Functionally active antibodies (Abs) against central G-protein-coupled receptors have not yet been reported. We selected the hypothalamic melanocortin-4 receptor (MC4-R) as a target because of its crucial role in the regulation of energy homeostasis. A 15 amino acid sequence of the N-terminal (NT) domain was used as an antigen. This peptide showed functional activity in surface plasmon resonance experiments and in studies on HEK-293 cells overexpressing the human MC4-R (hMC4-R). Rats immunized against the NT peptide produced specific antibodies, which were purified and characterized in vitro. In HEK-293 cells, rat anti-NT Abs showed specific immunofluorescence labeling of hMC4-R. They reduced the production of cAMP under basal conditions and after stimulation with a synthetic MC4-R agonist. Rats immunized against the NT peptide developed a phenotype consistent with MC4-R blockade, that is, increased food intake and body weight, increased liver and fat pad weight, and elevated plasma triglycerides. In a separate experiment in rats, an increase in food intake could be produced after injection of purified Abs into the third ventricle. Similar results were obtained in rats injected with anti-NT Abs raised in rabbits. Our data show for the first time that active immunization of rats against the NT sequence of the MC4-R results in specific Abs, which appear to stimulate food intake by acting as inverse agonists in the hypothalamus.
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