A pharmacologically active monoclonal antibody against the human melanocortin-4 receptor : effectiveness after peripheral and central administration

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The hypothalamic melanocortin-4 receptor (MC4R) is a constituent of an important pathway regulating food intake and energy expenditure. We produced a monoclonal antibody (mAb) directed against the N-terminal domain of the MC4R and evaluated its potential as a possible therapeutic agent. This mAb (1E8a) showed specific binding to the MC4R in human embryonic kidney 293 cells expressing the human MC4R and blocked the activity of the MC4R under basal conditions and after stimulation with alpha-melanocyte-stimulating hormone (alpha-MSH). The inverse agonist action of Agouti-related protein was significantly enhanced in the presence of mAb 1E8a. After a single intracerebroventricular injection into the third ventricle, mAb 1E8a (1 microg) increased 24-h food intake in rats. After 7 days of continuous intracerebroventricular administration, mAb 1E8a increased food intake, body weight, and fat pad weight and induced hyperglycemia. Because the complete mAb was ineffective after intravenous injection, we produced single-chain variable fragments (scFvs) derived from mAb 1E8a. In pharmacokinetic studies it was demonstrated that these scFvs crossed the blood-brain barrier and reached the hypothalamus. Consequently, the scFv 1E8a increased significantly food intake and body weight in rats after intravenous administration (300 mug/kg). The pharmacological profile of mAb 1E8a and the fact that its scFv was active after peripheral administration suggest that derivatives of anti-MC4R mAbs may be useful in the treatment of patients with anorexia or cachexia.
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