Centrally administered MTII in mice ameliorates peripheral insulin sensitivity independent of food intake and body weight

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Melanocortin (MC) and neuropeptide Y (NPY) neurons in the arcuate nucleus are involved in the control of energy homeostasis. Genetic defects of the MC system have been linked to obesity and diabetes in rodents and humans.
Aim of the study: to evaluate the effects of central administration of MTII, a nonspecific agonist of the MC receptor, on insulin sensitivity, *independent* of food intake and body weight.
Experimental animals and methods: 75 ng of MTII (in 1.5 µl demi-water) was injected into the third cerebral ventricle 3 times (at 9 am, 5 pm and 9 am) in 24 hour fasted male wildtype mice. The control group received 3 demi-water injections. Whole body- and hepatic insulin sensitivity were measured using a ^{3}H labeled hyperinsulinemic euglycemic clamp.
Results: Plasma glucose and insulin concentrations were not significantly different between MTII treated (n=8) and control mice (n=10) before (5.8±1.0 vs 6.7±1.2 mmol/l; 0.31±0.11 vs 0.31±0.07 ng/ml, resp) and during the clamp (8.4±1.0 vs 8.3±2.1 mmol/l; 3.8±2.9 vs 3.7±2.7 ng/ml, resp). Basal endogenous glucose production was significantly higher in MTII treated mice compared to the control group (84±16 vs 43±12 µmol/min/kg respectively, $p<0.01$). During hyperinsulinemia, whole body glucose uptake was significantly higher in MTII treated mice compared to control mice (167±49 vs 110±11 µmol/min.kg respectively, $p<0.01$). The inhibition of endogenous glucose production by insulin was not different between groups (50± 20 vs 50±30%, $p=0.87$).
Conclusion: subacute activation of the MC pathway increases basal endogenous glucose production. In addition, MTII ameliorates peripheral insulin sensitivity without affecting hepatic insulin sensitivity. Therefore, MTII has tissue specific effects on insulin sensitivity, independent of food intake and body weight.

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