Glucose transporter 1 suppresses melanocortin 4 receptor activity

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Introduction and Aim of study

Overweight, obesity and associated diseases are global issues expanding in an epidemic way. Body weight is controlled by hypothalamic G protein coupled receptors (GPCRs). Especially the melanocortin 4 receptor (MC4R), expressed in the paraventricular nucleus (PVN) plays a crucial role in feeding behavior. MC4R knockout or loss-of-function variants result in hyperphagia and early-onset obesity [1]. One characteristic of GPCRs is the capability to form dimeric or oligomeric structures. It was demonstrated that MC4R interactions can have high impact on its signaling [2]. However, so far just a few interaction partners are known. Therefore we applied a screening based on protein complementation to detect further MCR interactions. The glucose transporter 1 was one potential MCR interactor. GLUT1 could represent a high sensitive glucose sensor at neurons that mediates the nutrition state between neurons, operating after the first important glucose maintenance by the GLUT3. A GLUT1 interaction with the most powerful food intake controlling MC4R and moreover an influence of blood glucose level on MC4R signaling (feeding behavior) would present a new neuronal circuitry. Aim of the study was to confirm and to characterize in a first step a hypothalamic MC4R/GLUT1 interplay.

Result I: GLUT1 expression on PVN neurons

Result II: GLUT1/MC4R co-expression on neuronal cell lines

Result III: GLUT1 interacts with the MC4R

Result IV: GLUT1 inhibits MC4R signaling and expression

Discussion

In the present study we could show GLUT1 expression on oxytocin expressing and non-oxytocin (supposed to be the MC4R expressing ones) [5]) PVN neurons. In addition we demonstrated GLUT1/MC4R co-expression in three neuronal cell lines (Fig 2B) facilitating a possible physiological MC4R/GLUT1 correlation. Further experiments confirmed a direct MC4R/GLUT1 interaction (Fig 3A) and a GLUT1 mediated inhibition of MC4R signaling by reduction of MC4R cell surface expression (Fig 4). Analyzing this receptor/transporter relationship in the background of high-fat diet we found strong down-regulation of GLUT1 expression after three days of HFD (Fig 5) representing a very physiological reaction at this point of research. HFD should mediate satiation. By decreasing GLUT1 expression in response to HFD the MC4R obtains higher cell surface expression and activity reducing food intake. By these data a new level of MC4R function was determined. Further studies could reveal if the GLUT1 expression is increasing after a longer period of HFD contributing to the development of overweight and obesity.