

Network: Obesity and Related Disorders**Project: Neuroimaging of Hunger and Satiety and Assessment of Sympathetic Nerve Activity in Carriers of a MC4-R Gene Mutation**

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Introduction

The central melanocortin system is critically involved in the control of food intake and body weight. Recently the importance of melanocortins in complex pathways such as memory, sexual behaviour, and inflammatory response has also been demonstrated. Investigations in this subproject will be done to assess the functional importance of mutations in identified candidate genes of obesity on sympathetic nervous system and functional neuroimaging by MRI techniques. Our focus is set on central melanocortinergic system because mutations in the MC4-R until now represent the most important monogenetic cause of obesity. Beside subjects with MC4R mutations leading to a diminished receptor signalling carriers of the Polymorphism V103I were recently recognized rather to exhibit a decreased body weight.

Sympathetic nervous activity

The sympathetic nervous activity plays a critical role in the etiology of obesity through its impact on energy expenditure and food intake. Individuals with low resting muscular sympathetic nervous activity (MSNA) may be at risk for body weight gain resulting from a lower metabolic rate. In the animal models (heterozygous and homozygous MC-4R knock-out mice) the the sympathetic nervous activity is attenuated in response to intracerebroventricular application of leptin and insulin respectively.

We employ microneurography to directly record sympathetic nerve activity to muscle. The efferent sympathetic nerve activity is recorded with insulated tungsten microelectrodes with a shaft diameter of 0.2 mm and an uninsulated tip of a few micrometers. The recording electrode is inserted into a muscle nerve fascicle of the peroneal nerve below knee. A reference electrode is inserted subcutaneously a few centimeters away. The signals are amplified (gain 50 000), filtered, and passed through an amplitude discriminator to obtain a mean voltage display of the multiunit nerve activity.

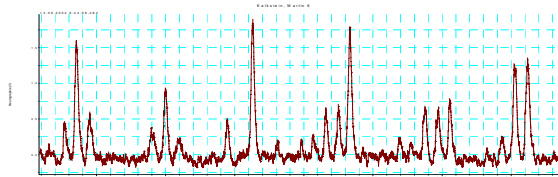


Fig 1: Visualization of muscular sympathetic nervous activity bursts (MSNA) by microneurography.

Relative blood pressure changes are monitored with blood pressure measurements from a finger with the hand resting at the level of the heart, with the volume-clamp technique (Finapres). Respiratory movements are monitored with a strain gauge strapped around the chest with a rubber band to control for inadvertent apneas and irregular breathing, which are known to affect MSA. Nerve activity is expressed as the number of bursts per minute and bursts per 100 heartbeats.

Functional magnetic resonance imaging using (fMRI)

Advances in neuroimaging technology by functional magnetic resonance imaging (fMRI) have increased the possibility to study brain function in vivo. Differences of regional cerebral blood flow and regional cerebral blood oxygenation in response to various stimuli can be demonstrated with high resolution. In obesity research fMRI has been used to study human brain response in relation to food intake. Neuroimaging studies done over the past years have shown that different brain activity occurs in response to food intake between obese and lean individuals. These differences include brain activity locations as well as timing and strength of the brain response. The importance of hypothalamic areas and parts of the limbic system is well known. Especially the network of several neuropeptides like Neuropeptide Y and Melanocortin modified by signalling of insulin and leptin in the Nucleus arcuatus and Nucleus paraventricularis plays a critical role in appetite regulation. It has been demonstrated that circulating insulin levels modulate the brain activity that controls food intake. Probably this regulatory mechanism is impaired in obese subjects. One important finding in previous studies is a delay and diminishing of the hypothalamic response after glucose. This has been demonstrated in rodents and also in men. Because the secretion of insulin increases immediately after a meal, this suggest that meal dependent insulin release may modulate the later brain response.

Neuroimaging studies done over the past years have shown that different brain activity occurs in response to food intake between obese and lean individuals. Furthermore with availability of a high resolution MRI scan (7 Tesla) we will try to demonstrate differences in central regions correlated with sympathetic activity such as the the nucleus of the solitary tract.

In summary our goal is to describe phenotypic characteristics of subjects with certain MC4R-mutations. Beside phenotypic description of obese individuals in regard to sympathetic nervous activity functional neuroimaging is planned to reveal differences in brain activity.

The technique of microneurography is well established in Lübeck (cooperation with Prof. Dodt) and functional MRI is practiced in Magdeburg at a very high standard.

Results/Project Status

In a group of subjects harbouring MC4R-mutations sympathetic nervous activity has been assessed by microneurography. Microneurography has been performed after an overnight fast. Blood pressure, heart rate and muscle sympathetic nerve activity (MSNA) from the peroneal nerve were recorded. Subjects were asked to perform an inspiratory apnea of maximal length, a procedure to search for a suitable intraneural recording site. Subjects were investigated in the supine position with 1 leg slightly elevated. The ECG was recorded with standard chest leads. Blood pressure was measured oscillometrically.

During resting conditions burst frequency was similar in obese subjects with and without MC4R mutations. When normalized for the different baseline values, baroreflex-mediated changes in MSNA were similar in both groups. Maximal MSNA levels in response to inspiratory apnoea and the cold pressor test did not differ between the groups. This data have surprisingly demonstrated that a lower sympathetic nervous activity under resting conditions is probably not responsible for weight gain in subjects harbouring MC4-R mutations. Nevertheless a lower MSNA in children of all obese families was remarkable.

In one of our neuroimaging studies the impact of insulin on neuronal activity using a picture encoding task in a functional magnetic resonance imaging approach has been investigated. Ten subjects performed two independent scanning sessions, each session divided into one part of four baseline runs and a second part of four runs during either insulin or saline was infused. A hyperinsulinemic-euglycemic clamp technique was applied to keep the blood glucose concentrations normal during insulin infusion. Contrast images between the two parts revealed identical activation patterns during baseline and saline conditions while during the insulin condition a higher level of activation was detected within the fusiform gyrus in both hemispheres. Shorter reaction times during the insulin condition underlined the cognitive benefit. It has been shown that insulin enhances neuronal activity within the medio-temporal lobe and increased performance in humans under in-vivo conditions.

We have established different procedures to investigate differences in MRI neuroimaging in relation to meal ingestion. Utilising this approach influences of different pharmaceutical agents on in vivo brain function can be studied. Subjects will be characterized in regard to metabolic parameters of insulin sensitivity. Psychological tests were performed to assess the eating behaviour of the probands and to correlate with the results of neuroimaging.

In one of these investigations scans were performed after a 15 h fasting period in obese and lean individuals. In obese individuals a stronger activation of different limbic and paralimbic areas perception of palatable meals has been demonstrated (fig. 2).

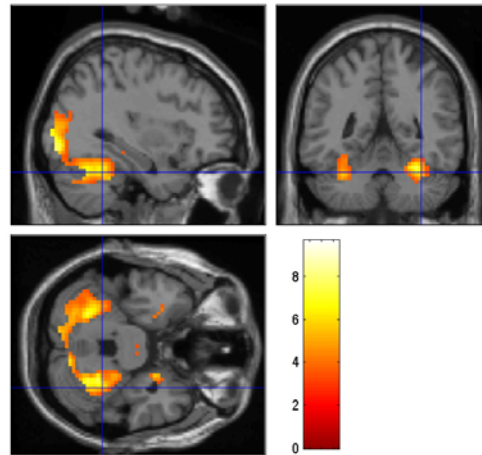


Fig 2: Increased activation of limbic/paralimbic areas in obese individuals during apperception of palatable food.

Outlook

Besides controlling metabolic processes such as energy homeostasis by the regulation of food intake through hypothalamic receptors, melanocortin also appears to be capable of modulating cognitive functions. Experimental and clinical evidence for melanocortin supports effects on learning and memory.

Recently the melanocortins and their receptors have been recognized as a target for drug-based treatment of human obesity.

Intranasal delivery provides a noninvasive method to deliver therapeutic agents not crossing the blood-brain barrier in to the brain. Applying this method we will studying effects of melanocortin on in vivo brain function by fMRI.

Lit.: 1. Rotte M, Baerecke C, Pottag G, Klose S, Kanneberg E, Heinze HJ, Lehnert H. Insulin affects the neuronal response in the medial temporal lobe in humans. Neuroendocrinology 2005;81(1):49-55 2. Paulus K, Schulz C, Lehnert H. Central nervous effects of leptin and insulin on hippocampal leptin and insulin receptor expression following a learning task in wistar rats. Neuropsychobiology. 2005;51(2):100-6.