INSULIN RESISTANCE OF THE CENTRAL NERVOUS SYSTEM: RECORDING OF SPONTANEOUS ACTIVITY AND EVOKED MAGNETIC FIELDS WITH MAGNETOENCEPHALOGRAPHY (MEG)

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Obesity is associated with peripheral insulin resistance in muscle, liver, and adipose tissue. Animal studies suggest that the brain functions as an insulin-responsive organ and that central nervous insulin resistance induces hyperphagia and obesity. We hypothesize that the human brain is also insulin-responsive and that in obese subjects insulin effects are altered.

To investigate the role of central nervous effect of insulin we use whole-head magnetoencephalography (MEG) during a 2-step hyperinsulinaemic clamp (versus saline) to
1) assess cortical insulin effects in humans and to
2) compare these effects between lean (N=10) and obese subjects (N=15).
All subjects are investigated on two different days, receiving intravenous three levels of insulin under constant plasma glucose on one of the days, and placebo (saline) on the other day, in a simple-blind design. When a stable state after the insulin (or placebo) infusion is reached, the magnetoencephalographic recordings of cortical activity are performed. (fig.1)

In our first experimental design we recorded spontaneous cortical activity and evoked magnetic fields (auditory mismatch negativity paradigm). We found significant effects in the theta band for spontaneous activity and in the mismatch negativity (MMN) for the lean subjects. (fig. 2)
In lean subjects, the theta activity and MMN showed a significant enhancement during insulin administration compared to the placebo condition. During the placebo experiment theta activity decreased from 375 ± 37 to 326 ± 25 fT ($p = 0.03$) by the end of the second step. During the insulin experiment, in contrast, theta activity increased from 347 ± 44 to 401 ± 40 fT ($p < 0.001$, ANOVA).
MMN remained unchanged during the placebo experiment. During the insulin experiment, MMN increased from 7.31 ± 0.08 to 7.37 ± 0.07 fT ($p = 0.04$, ANOVA) during the second step.
In overweight subjects the insulin effect on theta activity and MMN was absent.

In our second experimental design we record visual evoked magnetic fields. For the visual stimuli we chose a set of pictures containing 64 food-relevant and 64 food-neutral photographs, which are visually presented to the subjects in a randomized order. These two categories of visual stimuli do not differ in the ratings of arousal and valence, but have significant different rating of potential to induce the feeling of hunger. Because obesity and insulin resistance are associated with certain types of eating behavior, we aim to analyse whether the resulting evoked magnetic fields differ between the two categories of stimuli (food-relevant vs. food-neutral), between the groups of subjects (lean vs. overweight) and in the hyperinsulinaemic condition compared with placebo.

Our results from the first experimental design confirm the hypothesis that insulin modulates cerebrocortical activity in healthy humans, which is absent in obese individuals. This suggests that cerebrocortical insulin resistance is involved in human obesity and possibly in the pathogenesis of type 2 diabetes.

Fig. 1

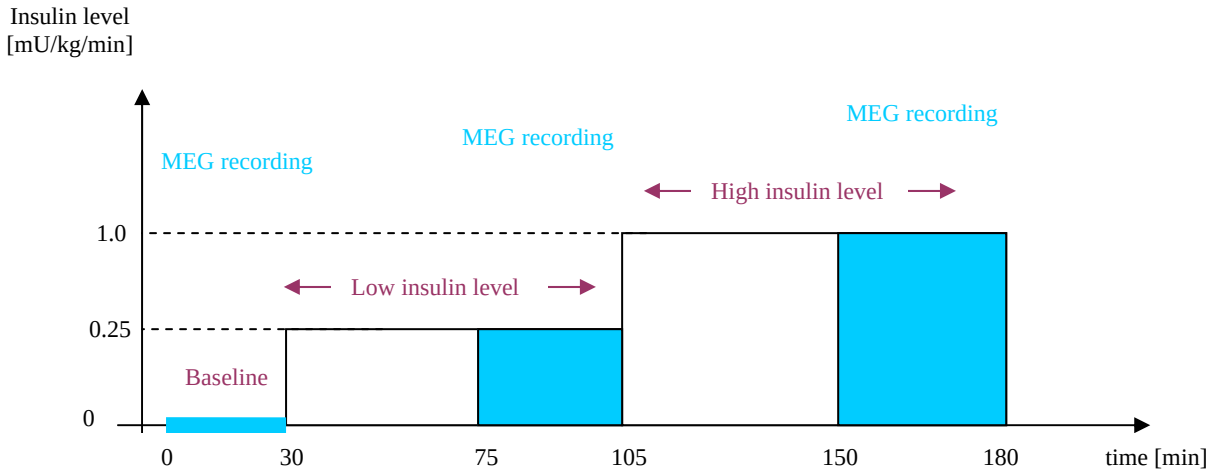
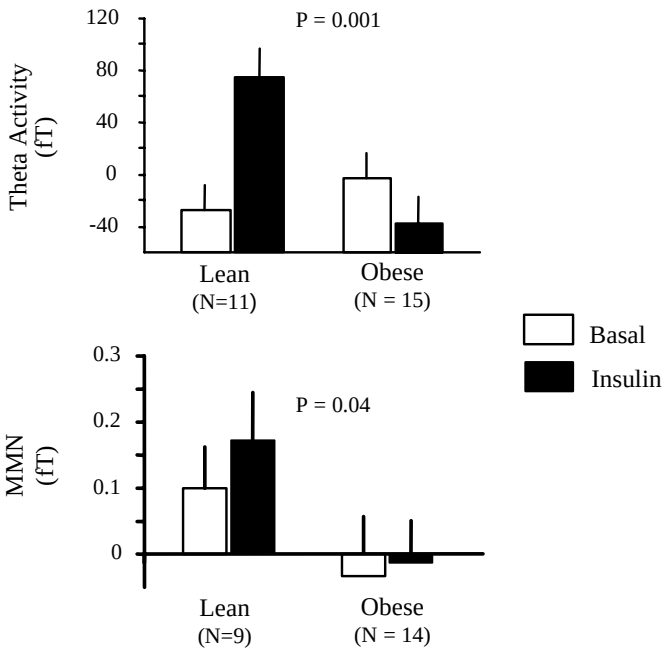

Insulin level
[mU/kg/min]
MEG recording
MEG recording
MEG recording
High insulin level
Low insulin level
Baseline
1.0
0.25
0
0
30
75
105
150
180
time [min]

Fig. 2


Theta Activity
(fT)
120
80
40
0
-40
P = 0.001
Lean
(N=11)
Obese
(N = 15)
Basal
Insulin
MMN
(fT)
0.3
0.2
0.1
0
P = 0.04
Lean
(N=9)
Obese
(N = 14)