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ARTICLE

Maternal insulin sensitivity is associated with oral glucose-induced changes in fetal brain activity

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Abstract
Aims/hypothesis Fetal programming plays an important role in the pathogenesis of type 2 diabetes. The aim of the present study was to investigate whether maternal metabolic changes during OGTT influence fetal brain activity.
Methods Thirteen healthy pregnant women underwent an OGTT (75 g). Insulin sensitivity was determined by glucose and insulin measurements at 0, 60 and 120 min. At each time point, fetal auditory evoked fields were recorded with a fetal magnetoencephalographic device and response latencies were determined.
Results Maternal insulin increased from a fasting level of 67±25 pmol/l (mean ± SD) to 918±492 pmol/l 60 min after glucose ingestion and glucose levels increased from 4.4±0.3 to 7.4±1.1 mmol/l. Over the same time period, fetal response latencies decreased from 297±99 to 235±84 ms (p=0.01) and then remained stable until 120 min (235±84 vs 251±91 ms, p=0.39). There was a negative correlation between maternal insulin sensitivity and fetal response latencies 60 min after glucose ingestion (r=0.68, p=0.02). After a median split of the group based on maternal insulin sensitivity, fetuses of insulin-resistant mothers showed a slower response to auditory stimuli (283±79 ms) than those of insulin-sensitive mothers (178±46 ms, p=0.03).
Conclusions/interpretation Lower maternal insulin sensitivity is associated with slower fetal brain responses. These findings provide the first evidence of a direct effect of maternal metabolism on fetal brain activity and suggest that central insulin resistance may be programmed during fetal development.

Keywords Brain insulin resistance · Fetal programming · Gestational diabetes

Abbreviations

AER	Auditory evoked response
CTG	Cardiotocography
ER	Evoked response
fMEG	Fetal magnetoencephalography

Introduction

The effects of insulin on the central nervous system play an important role in the pathogenesis of obesity and diabetes mellitus. Recently it has been suggested that changes in insulin action in the brain not only affect the regulation of appetite and body weight but are also crucial in controlling glucose metabolism [1–3]. There is evidence in humans that brain insulin resistance is not the consequence of peripheral metabolic changes but may itself contribute to the development of

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diabetes and obesity [4–6]. By recording brain activity with magnetoencephalography during a euglycaemic–hyperinsulinaemic stepwise clamp, we showed in adult humans that obesity, peripheral insulin resistance, age and genetic background are all associated with impaired central insulin sensitivity [7, 8].

The prevalence of obesity and type 2 diabetes mellitus is rising worldwide and the percentage of young people affected is increasing. The reasons for these changes are unclear, although environmental and epigenetic mechanisms are likely to be involved. A major epigenetic mechanism is the so-called fetal programming [9, 10]. Maternal environment and metabolism are of particular importance for the development of obesity and type 2 diabetes in offspring [11, 12]. Nutritional factors can alter fetal growth and glucose metabolism [13]. Furthermore, maternal metabolic changes related to type 2 diabetes or obesity influence the fetal phenotype [14]. Children of obese or diabetic mothers have an increased risk for type 2 diabetes and obesity in adulthood, independent of their genetic background [15, 16]. Also, in fetuses of obese mothers peripheral insulin resistance is already developing in utero [17]. At present, it is unclear whether changes in maternal glucose metabolic status also have an influence on fetal brain activity.

Our aim was to study fetal brain activity during an OGTT in pregnant women. We hypothesised that the postprandial metabolism of the mother influences, or is associated with, fetal brain activity. Fetal magnetoencephalography (fMEG) enables us to non-invasively record brain activity in utero [18]. Fetal brain activity has mainly been studied as evoked activity to visual [19] and auditory stimulation [20, 21]. Response latencies to auditory stimuli decrease with fetal age and provide quantitative information on fetal functional brain maturation [22, 23]. Therefore, in the present study we evaluated changes in fetal response latencies to auditory stimulation during the course of a routine OGTT in healthy, normal pregnancies. In addition, we determined correlations between fetal response latencies and maternal blood glucose and plasma insulin levels as indicators for the influence of maternal metabolic changes on fetal brain activity.

Methods

Participants Twenty-two healthy pregnant women participated in this study. Gestational age ranged from 27 to 36 weeks (mean 30.9 weeks). Informed consent was received from the participants before any measurements were made. The Ethical Committee of the Medical Faculty of the University of Tübingen approved the study plan.

Of the 22 participants, four had to discontinue the study due to fatigue and data analysis was not possible for a further five due to weak fetal signals, maternal muscle activity or movement artefacts. Therefore, data from 13 women was analysed. All pregnancies were uncomplicated singleton pregnancies according to maternal pregnancy record books. None of the fetuses were macrosomic at birth. Two out of 13 women declared smoking up to five cigarettes a day.

Paradigm All measurements were started at 08:00 hours at the fMEG Center at the University of Tübingen. After an overnight fast of at least 5 h, each participant ingested a solution containing 75 g glucose (Accu-Chek Dextrose O.G-T.; Roche Diagnostics, Germany). Venous blood samples were obtained before ingestion of the glucose solution (0 min) and after 60 and 120 min. In one participant, a venous blood sample could not be obtained at 60 min. Blood glucose and plasma insulin concentrations were determined in the laboratory.

Each blood extraction was preceded by an fMEG measurement. The baseline fMEG measurement was performed before the baseline blood extraction. The second and third fMEG measurement was started after 50 and 110 min, respectively.

Before the first and after the last fMEG measurement an ultrasound scan was performed to determine the fetal head position. Between measurements, the medical history of the participants was recorded and cardiotocography (CTG) was performed. The relevant steps of the paradigm are shown in Table 1.

Laboratory measurements and calculations Blood glucose concentrations were determined using a glucose analyser (glucose oxidase method; Yellow Springs Instruments, Yellow Springs, OH, USA). Plasma insulin was analysed using the ADVIA Centaur XP immunoassay system (Siemens AG, Erlangen, Germany). Insulin resistance was calculated by means of the HOMA-IR [24]. For better characterisation of the postprandial insulin sensitivity, the following index was

Table 1 Paradigm

Measurement time point	Timing (min)	Procedure
		Ultrasound scan
1		First auditory fMEG measurement (baseline)
		Laying of venous access First blood extraction (baseline)
2	0	Drinking OGTT solution
	50+	Second auditory fMEG measurement
	60	Second blood extraction
3	110+	Third auditory fMEG measurement
	120	Third blood extraction
		Ultrasound scan
		Breakfast

calculated (as recommended by Stumvoll et al [25]) for a three-point OGTT in units of μmol kg^{-1} min^{-1} pmol/l:

$$0.156 - 0.0000459 \times Ins_{120\ min} - 0.000321 \times Ins_{0\ min} - 0.00541 \times Gluc_{120\ min}$$

fMEG measurement fMEG data were recorded with the SARA system (SQUID Array for Reproductive Assessment, VSM MedTech, Port Coquitlam, BC, Canada) installed at the fMEG Center at the University Tübingen. In this system biomagnetic signals generated by electrical currents in the body are recorded with 156 primary magnetic sensors, which are distributed over a concave array, shaped to match the form of the gravid abdomen.

Based on the first ultrasound measurement (Ultrasound Logiq 500MD; GE Healthcare, Pollards Wood, UK), the position of fetal head was marked by a localisation coil placed directly on the abdomen. This location was reconfirmed via ultrasound after the last measurement. Three additional localisation coils were placed on the mother's spine and on her left and right side. At the beginning and end of each recording, localisation coils were activated at a certain frequency to determine their coordinates in relation to the sensors. Data were recorded with a sampling rate of 610.352 Hz.

During each fMEG measurement, an auditory sequence was presented for 6 min and the evoked fetal brain activity was recorded.

Auditory stimulation procedure Two tones were presented in an auditory oddball paradigm. A frequent 'standard' tone with a frequency of 500 Hz was presented 75% of the time. This was randomly interspersed with an infrequent 'deviant' tone (frequency of 750 Hz, presented 25% of the time) to prevent habituation to the standard tone. Tone duration was 500 ms, tone intensity was 95 dB (3.2×10^{-3} W/m^2). Attenuation of the sound intensity by maternal tissue implies that tones with an intensity of about 65 dB (3.2×10^{-6} W/m^2) reach the fetus [26]. Stimuli were generated as tone bursts with 10 ms rise and fall times. The inter-stimulus interval was set to 1,500 ms. Stimulus delivery was controlled using the Presentation program (version 12.2, www.neurobs.com). The sound was generated by a speaker and transmitted by means of plastic tubing to an inflated plastic bag (height approximately 3 cm) placed between the sensor array and maternal abdomen. Reported results refer to the standard tone.

Fetal data analysis Data were collected in continuous mode. Maternal and fetal heart signals were attenuated with standard algorithms [27, 28]. A bandpass filter between 0.5 and 10 Hz was applied to the data. Data were split into trials based on stimulus type (200 ms before, 1,000 ms after stimulus onset). Trials containing amplitudes above 2 pT were rejected. Trials were then averaged according to stimulus type.

Evoked responses (ERs) to the standard tone were identified by visual inspection. The evoked activity had to be located in the area near the position of the head coil [29]. The five channels with the highest amplitude of the ER were selected and latencies were determined by the peak root mean square amplitude of those channels.

Statistical analysis Statistical tests were performed with SPSS (version 20.0; IBM SPSS Statistics for Windows, Armonk, NY, USA) and results with $p<0.05$ were regarded as statistically significant. Missing values were excluded pairwise.

A repeated measures ANOVA of measurement time point (oral glucose) on ER latency was performed. Additionally, paired *t* tests were used to compare variables between time points. Since a possible effect on ER latencies could be caused by a change in either maternal blood glucose or plasma insulin level, linear regressions analyses were performed to examine the influence of glucose and insulin levels on response latencies of the fetus for the different time points.

For the second measurement time point, Pearson correlations were used to explore the connection between maternal insulin sensitivity and fetal auditory response latency. Response latencies between two insulin sensitivity subgroups were compared with two-sample *t* tests.

Results

Participants Data from 13 pregnant healthy women were included in this study. The metabolic and clinical characteristics of the participants are shown in Table 2.

Table 2 Characteristics of the study participants

Characteristic	Value
n	13
Age (years)	32±3
Duration of pregnancy (weeks)	31±3
BMI before pregnancy (kg/m^2)	23.6±3.3
Absolute weight gain during pregnancy (kg)	10.0±2.2
Relative weight gain during pregnancy (kg/week)	0.32±0.07
Fasting glucose (mmol/l)	4.4±0.3
2 h glucose (mmol/l)	6.4±1.1
Fasting insulin (pmol/l)	67±25
2 h insulin (pmol/l)	792±368
HOMA-IR	1.9±0.7
Insulin sensitivity index (μmol kg^{-1} min^{-1} pmol/l)	0.063±0.026

Data are presented as means ± SD

Auditory measurements Fetal auditory evoked responses (AERs) could be analysed for 13 participants. For two participants, no AER was detectable at time point 1, for a further two participants, no AER was detectable at time point 2.

Table 3 shows mean AER latencies to standard tones, as well as maternal blood glucose and plasma insulin levels for all three measurement time points, including values from all participants.

As expected during an oral glucose challenge, maternal blood glucose and plasma insulin levels increased from baseline to 60 min and decreased again at 120 min. There was also a change in fetal ER latency during the course of the oral glucose challenge. A repeated measures ANOVA revealed a significant main effect of the oral glucose challenge on AER latency (F[2]=4.8, p=0.024). Response latency was shortened during the OGTT from a fasting level at 0 to 60 min after glucose administration (297±99 vs 235±84 ms, t[8]=3.3, p=0.01). There was no significant change in response latency between 60 and 120 min (235±84 vs 251±91 ms, t[10]=0.9, p=0.39). Linear regression analysis revealed an association between maternal insulin level and the ER of the fetus at 60 min after glucose ingestion (F[1]=5.45, p=0.05). There was no significant effect of maternal insulin level at 0 and 120 min and maternal glucose level at 0, 60 and 120 min on corresponding ERs.

There was a significant correlation between maternal insulin sensitivity and response latency of the fetus (r=0.68, p=0.02) 60 min after ingestion of glucose: the higher the insulin sensitivity of the mother, the shorter was the response latency of the fetus (Fig. 1). The correlation remained significant after controlling for relative weight gain of the mother, gestational age or weight of the child at birth.

There was no significant correlation between maternal insulin sensitivity index and response latency of the fetus at baseline or after 120 min (r=0.03, p=0.93 and r=0.21, p=0.48, respectively).

The women were split into two groups based on the median of the insulin sensitivity index—insulin resistant (0.081±0.023 μmol kg^{-1} min^{-1} pmol/l) and insulin sensitive (0.043±0.008 μmol kg^{-1} min^{-1} pmol/l). The insulin sensitivity index differed significantly between groups (t[8]=4.1, p=0.004). The response latency of fetuses 60 min after glucose ingestion by insulin-resistant mothers was delayed in comparison with the response latency of fetuses of insulin-sensitive mothers (283±79 vs 178±46 ms, t[9]=2.6, p=0.03). Figure 2 shows mean maternal glucose and insulin levels and mean fetal response latencies during the OGTT in both insulin-resistant and insulin-sensitive groups. There was

Table 3 Maternal blood glucose and plasma insulin levels and corresponding ER latencies to standard tones for all three measurements

Variable	Measurement time point		
	1 (0 min)	2 (60 min)	3 (120 min)
ER latency to standard tone (ms)	297±99	235±84	251±91
Insulin (pmol/l)	67±25	918±492	792±368
Glucose (mmol/l)	4.4±0.3	7.4±1.1	6.4±1.1

Data are presented as means ± SD, n=13

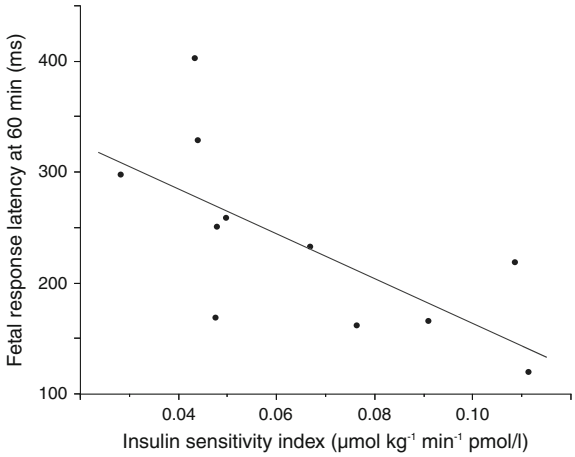

Fig. 1 Maternal insulin sensitivity index and fetal response latency 60 min after glucose ingestion

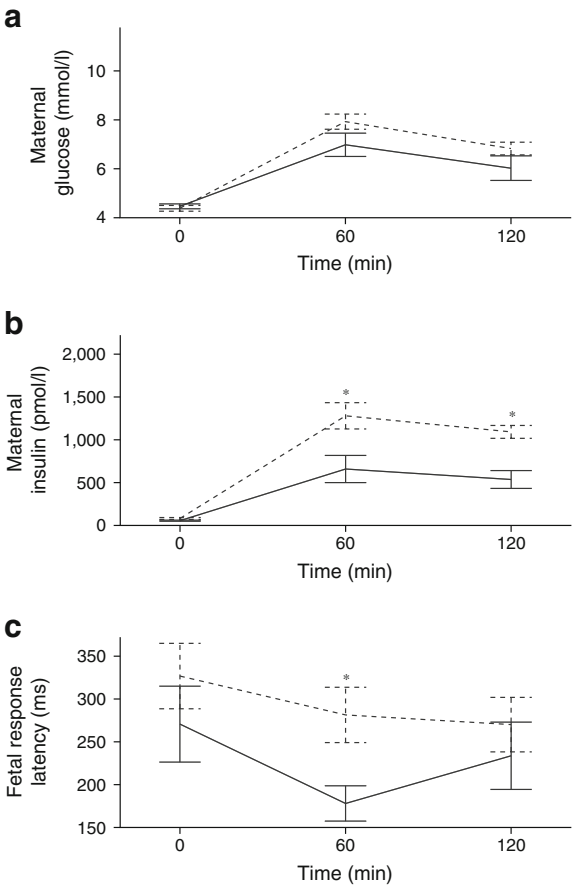

Fig. 2 Maternal glucose levels (**a**), maternal insulin levels (**b**) and fetal response latencies (**c**) during OGTT in insulin-resistant (n=6, dashed line) and insulin-sensitive women (n=7, solid line). Data are shown as mean ± SEM; *p<0.05 between groups

a significant difference in insulin level between groups after 60 min (t[10]=2.71, p=0.02) and after 120 min (t[11]=4.19, p=0.002).

A similar association was observed when maternal insulin sensitivity was calculated from fasting glucose and insulin levels using HOMA-IR. Insulin-sensitive and -resistant women differed significantly in HOMA-IR (1.29±0.34 vs 2.44±0.51, t[11]=−4.69, p=0.001). The HOMA-IR of mothers and response latency of fetuses 60 min after ingestion of glucose by the mother correlated significantly (r=0.71, p=0.01); the response latency was delayed in fetuses of insulin-resistant mothers when compared with fetuses of insulin-sensitive mothers (281±81 vs 179±45 ms, t[9]=2.5, p=0.03).

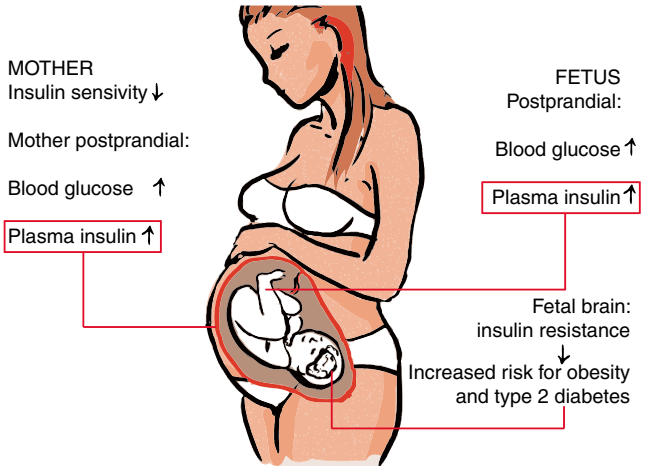

Fig. 3 Possible pathogenesis of fetal brain insulin resistance

Discussion

In the present study, we showed for the first time that fetal brain activity is altered in the postprandial state during an oral glucose challenge and also that maternal insulin sensitivity is associated with fetal brain activity. In particular, we showed that 60 min after glucose ingestion, fetuses of pregnant woman with lower insulin sensitivity (insulin-resistant group) have longer response latencies than fetuses of pregnant woman with higher insulin sensitivity (insulin-sensitive group).

AERs in fetuses, recorded using fMEG, have previously been demonstrated [18, 22] and the latencies of AERs decreasing with gestational age have been interpreted as an indicator of brain maturation. A recent study showed that intrauterine growth restriction caused by placental insufficiency leads to an increase in the latency of fetal AERs with a similar paradigm [23]. Both of these findings clearly show that the nutrient supply to the fetus has an effect on fetal brain activity. Interestingly the current study showed a differential effect of the OGTT for insulin-sensitive and -resistant pregnant women on fetal functional brain activation in the postprandial maternal state.

Speculation concerning the mechanisms for this differential effect can be based on the findings shown in Fig. 2 (visualised in Fig. 3), demonstrating that insulin-resistant mothers have higher glucose levels accompanied by increased insulin levels in the postprandial state. As glucose passes the placenta, these postprandially increased glucose levels induce hyperinsulinaemia in the fetus (Pedersen hypothesis [30]). Therefore, high insulin levels in the mother may correspond to high insulin levels in the fetus. It is possible that high insulin levels are a prerequisite for appropriate brain maturation. However, chronic hyperinsulinaemia, which is present in insulin-resistant mothers and corresponds to high insulin levels in the fetus, might induce insulin resistance in the fetal brain. Of course, there are several other possible mechanisms explaining the association between the change in response latency in the fetal brain and the insulin sensitivity of the mother: the insulin resistance of the mother may be associated with a limited insulin transport into the fetal brain; alternatively, the insulin resistance of the mother may be associated with a variety of other hormonal and metabolic fuel effects, which actually mediate the change in response latency [31]. Therefore, at present we can only speculate that the high insulin levels in the fetus associated with maternal insulin resistance induce primary insulin resistance of the fetal brain.

The insulin resistance of the fetal brain may be interpreted as metabolic imprinting of insulin resistance with important consequences for later life. The consequent effect of hyperinsulinaemia on fetal development has already been shown. Compared with newborns of non-diabetic women, children of diabetic mothers with poorly controlled glycaemia show neurophysiological impairment and have a higher risk for metabolic syndrome, obesity and type 2 diabetes mellitus in later life [15, 16, 32].

The assumption that an insulin-resistant fetal brain may have an impact on the development of metabolic syndrome, obesity and type 2 diabetes mellitus in later life is supported by recent studies investigating the effect of impaired insulin action on the central nervous system in adults. The action of insulin in the brain is thought to control metabolism and behaviour, and insulin resistance of the brain may be associated with obesity, diabetes and cognitive impairment [1]. For example, we recently demonstrated cross-sectionally that a reduced cerebrocortical response to insulin during a hyperinsulinaemic clamp, in overweight compared with lean humans, is associated with obesity and increased NEFA [7, 8]. Furthermore, insulin resistance of the brain prospectively predicts less weight reduction in individuals taking part in lifestyle intervention programmes [6].

A limitation of the present study is the small number of participants. Additionally, direct measurement of insulin levels in the amniotic fluid would have been desirable, although this was not possible for ethical reasons. The

gestational age in the present study varied between 28 and 36 weeks. According to previous fMEG studies, ER latencies seem to decrease with fetal age, and are interpreted as an indicator of brain maturity. Since our results remained significant after adjustment for gestational age, it is unlikely that the increased response latency is caused by differing gestational age.

In summary, our study showed that fetal brain activity increases postprandially, as indicated by shorter fetal response latencies to auditory stimuli. Furthermore, the level of maternal insulin resistance affects the fetal brain activity in postprandial conditions. This finding constitutes important evidence supporting the fetal programming theory. Central insulin resistance could already be developed in utero. Future investigations will further examine the effects that pathological insulin resistance and chronic exposure to higher insulin levels in diabetic mothers have on fetuses and children.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement KL and FS contributed equally to this work, were involved in the design of the study, data acquisition and analysis and interpretation of data and drafted and revised the article. CK contributed to the study design and revised the article. LF and IKS were involved in data acquisition and revised the article. AH contributed to the conception and design of the study and revised the article. HUH contributed to interpretation of the data and revised the article. HP and AF contributed to the conception and design of the study and to the analysis and interpretation of data and drafted and revised the article. All authors approved the current version of the article. HP and AH are the guarantors of this article.

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