Continuous Glucose Monitoring in Interstitial Subcutaneous Adipose Tissue and Skeletal Muscle Reflects Excursions in Cerebral Cortex

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Continuous glucose monitoring (CGM) is being explored using several types of glucose sensors. Some are designed for subcutaneous adipose tissue. It is important to determine to which extent these glucose fluctuations in different tissues reflect changes taking place in the central nervous system, where glucose sensing is thought to occur. We studied the ability of subcutaneous adipose interstitial fluid measurements to parallel glucose propagations in blood, muscle, and central nervous system (CNS) during hyper- and hypoglycemia. A subcutaneous CGM system was applied in the CNS, subcutaneous adipose tissue, and skeletal muscle of nine Vietnamese potbellied pigs, and data were compared with frequent sampling in blood. Alterations in glucose levels were induced with intravenous glucose and insulin. During hyperglycemia, no difference was detected in delay between blood and interstitial glucose levels in subcutaneous adipose tissue (18.0 ± 0.8 min), muscle (18.0 ± 0.9 min), and CNS (20.3 ± 1.2 min), respectively. During hypoglycemia, we found no time difference between interstitial parameters in the three tissues. However, the amplitude of glucose changes varied considerably, with a smaller magnitude of glucose change taking place in the brain. The timing of glucose excursions in subcutaneous adipose tissue and muscle reflect excursions in CNS. The reduced magnitude of glucose excursions in the brain suggests that different mechanisms of glucose transport are operative in CNS compared with subcutaneous adipose tissue and muscle. *Diabetes* 54:1635–1639, 2005

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CGM, continuous glucose monitoring; CGMS, continuous glucose monitoring system; CNS, central nervous system.

During the last decade, technologies have emerged that enable continuous measurements of glucose. Many of these devices take measurements from a compartment different from blood, usually in the subcutaneous adipose tissue. However, physiological glucose sensing is known to occur at the level of the β-cell, in the hepatoportal vein (1) and in the brain, perhaps particularly in the hypothalamus (2). The question of comparability between blood, central nervous system (CNS), and subcutaneous adipose tissue is particularly important during dynamic glucose fluctuations.

Knowledge concerning glucose measurements in subcutaneous adipose tissue has hitherto concentrated on physiological delays in glucose propagations between this tissue and the blood compartment. An induced glucose variation, e.g., an intravenous glucose bolus, occurs at a later point in the interstitial fluid (delay), and furthermore the shape of the fluctuation changes in the tissue because of compartmental dilution, tissue vascularization, and local glucose consumption. Various groups have assessed this delay and expressed it by measuring the time until a detectable change in glucose occurred (detection limit) or the point at which 90, 95, or 100% of the amplitude change had occurred (referred to as T90, T95, or T100).

Rebrin et al. (3) addressed this issue in dogs and found a delay to detection limit to be ~5 min. The study used a continuous glucose monitoring (CGM) system (CGMS) prototype (Medtronic/Minimed), with minute-to-minute sampling during a hyperglycemic clamp. Moberg et al. (4) investigated the T100 in a human microdialysis study. The study focused on the time from an insulin infusion to glucose nadir. The glucose changes in adipose tissue were found to be delayed by 18 min compared with venous plasma, and in skeletal muscle, the delay was 30 min.

Regittnig et al. (5) performed a glucose infusion study in humans, using open-flow microperfusion, with the aim of investigating T95, and found a delay of ~28 min for both adipose tissue and skeletal muscle.

It could be hypothesized that tissues other than blood are better suited for glucose monitoring. The aim of the present study was to investigate the glucose excursions in interstitial fluid in subcutaneous adipose tissue, muscle, and brain during alternating conditions of hyper- and hypoglycemia.

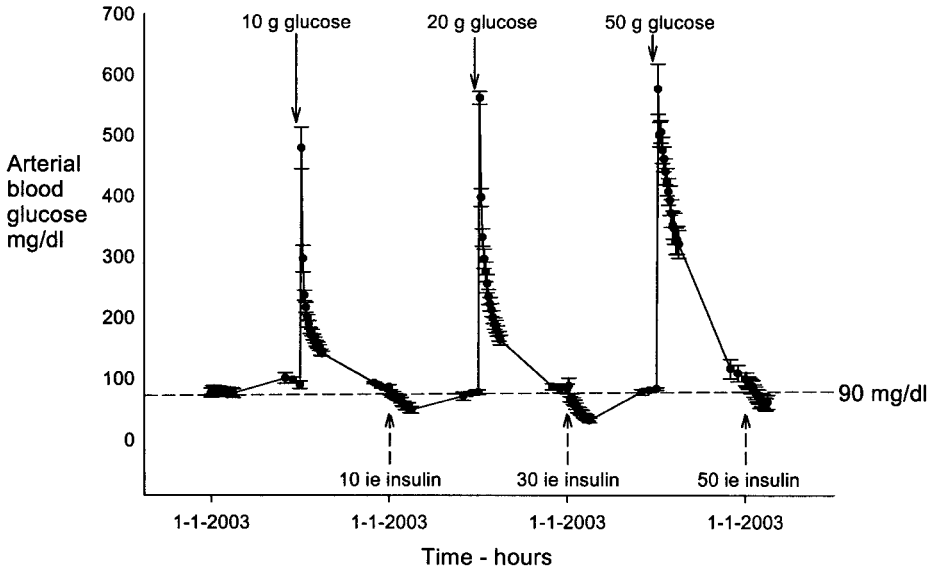

FIG. 1. Arterial blood glucose throughout the in vivo setup. Euglycemia is reached before each challenge. The error bars show standard error of the mean. The dotted line indicates glucose at 90 mg/dl (5 mmol/l). Arrows indicate timing and dose of either glucose (solid lines) or insulin (dashed line).

RESEARCH DESIGN AND METHODS

To investigate brief differences in time, we needed to apply a glucose sensor with a high sample frequency. The subcutaneous CGM (SCGM1; Roche Diagnostics, Mannheim, Germany) is based on a CMA-60 microdialysis catheter (CMA Microdialysis, Solna, Sweden) connected via short tubing directly to an extracorporeal glucose measuring device using mobilized glucose oxidase added to the dialysate, as described in detail previously (6). The device is strapped to the body and can easily be carried around. Because data are time averaged over 1 min, the device enables very high temporal resolution recordings of the interstitial glucose. The SCGM1 monitors glucose continuously for up to 5 days.

The perfusion of the microdialysis catheters is performed using Ringer's solution at a flow rate of 0.28 μl/min. With the given length of tubing, this corresponds to an inherent lag time of the system of ~30 min from membrane to analysis. A full equilibrium is believed to occur across the membrane because of the slow flow rate (4). To correct for the physical lag time, we performed a "lag time" experiment in vitro, before and after in vivo experimentation. The catheter was placed in Ringer solution and subsequently in a Ringer solution with glucose added to a concentration of 90 mg/dl. It was shifted between these solutions multiple times. The physical lag time of the sensors was found to be 29 ± 3 min (mean ± SD) before and 27 ± 3 min after the in vivo period (two-way ANOVA, $P = 0.4$). All presented data are corrected for the measured lag time, and physical lag time, therefore, does not constitute a confounding variable. Apart from enabling us to perform the lag time measurements, an in vitro calibration was also performed to allow comparison of relative concentrations between compartments. This was required because steady state between challenges was not obtained within all compartments (blood, subcutaneous adipose tissue, muscle, and CNS).

In vivo setup. Nine pigs of the race Wanton with an average weight of 65 ± 8 kg were used.

The study was approved by the authorities of animal welfare, Ministry of Justice. The pigs were sedated with 0.5 mg/kg midazolam and transported to the surgical research center. After arrival at the experimental research unit, anesthesia was commenced (midazolam, 5 μg/kg/min; fentanyl, 0.2 μg/kg/min; and ketamine, 0.25 mg/kg/min) and maintained throughout the experimentation period. Ventilation was maintained by a Servo 900 respirator (Siemens-Elema, Solna, Sweden). Arterial blood gas analyses were performed regularly throughout the study to ensure proper oxygenation (ABL 615; Radiometer, Copenhagen, Denmark).

Hereafter, intravascular sheaths were placed in the femoral artery and vein bilaterally for blood samples and infusions. Blood glucose was measured by a capillary blood glucose monitor that is a part of the SCGM1 system. To achieve a faster change in the level of glucose after insulin injection, a constant insulin infusion of 0.8 $mU \cdot kg^{-1} \cdot min^{-1}$ was initiated, and basal euglycemia was achieved by variable infusion of 200 g/l glucose.

An incision was made to the skin overlaying the skull of the animal at the frown just above and between the eyes. A hole was drilled through the osseous layer while care was taken not to penetrate the dura. A circular plate of ~5 cm in diameter was removed, thus providing a clear view of the dura mater with underlying vasculature. Hereafter, the microdialysis catheter was inserted in the cortex.

The intramuscular catheter was inserted into the gluteal muscle after prepuncture with a 16-gauge needle; muscle twitches ensured that correct placement was performed. The subcutaneous catheter was placed in the abdominal subcutaneous adipose tissue after prepuncture of the skin with a 16-gauge needle. After insertion, all three devices were allowed to settle for 60 min to ensure equilibration. No bleeding was observed with any of the catheters upon insertion.

After this, the in vivo protocol was commenced at $t = 0$ min. Euglycemia was maintained for 60 min at 90 mg/dl in arterial blood (Fig. 1). Thereafter, a 10-g glucose bolus at $t = 60$ min was given intravenously. After interventions, arterial and venous blood samples were drawn each minute for 15 min. An insulin bolus (10 IU Actrapid; Novo Nordisk, Bagsvaerd, Denmark) was given at $t = 120$ min, a time at which we estimated euglycemia had been reestablished, and at $t = 160$ min, a variable glucose infusion was started to reach euglycemia within 20 min. Hereafter, at each hour, alternating infusions with 20 g glucose, 30 units insulin, 50 g glucose, and 50 units insulin were given. Blood samples were drawn before and minute by minute for 15 min after each challenge and then every 10 min. At the end of the experiment the pigs were killed by KCl injection into the heart.

Analysis of glucose excursions from CGM. It is possible to measure different characteristics of a given increase in glucose, e.g., the detection limit, which is when the first changes becomes detectable. The peak time or T100 is the time when the glucose profile has reached its maximum/nadir, or the T90 or T95, reflecting the point when 90 or 95% of the change have occurred. We present only the T90 data but not the T95 and T100 data, because they were not sufficiently precise.

Statistical analysis. The Kolmogorov-Smirnov test of normal distribution of the data was performed. All data series were found to be normally distributed. Subcutaneous adipose tissue and muscle were compared with CNS by an independent samples t test. Differences in glucose delay between tissues and the physical lag time (in vitro) before and after in vivo testing were tested by a two-way general linear ANOVA model, including interactions between the individual animal, place of sampling, and dose of glucose/insulin (hyperglycemia or hypoglycemia) in the first model, and including interactions between the individual animal, place of sampling, and number of tests performed in the second model. We tested whether the different places of sampling or whether the different doses of glucose/insulin lead to differences in delay in T90 for glucose. P values <0.05 were considered significant. In vitro calibration computations were made with linear regression analyses between pre– and post–in vivo implantation of catheters.

RESULTS

The time from induced hyperglycemia to increased glucose concentrations in the tissues in comparison with blood glucose can be seen with minute-to-minute measurements (Fig. 2). From these data, we have established the time from glucose peak in arterial blood to T90 in the tissues. We found no significant differences between the delays in the various tissues in comparison with glucose

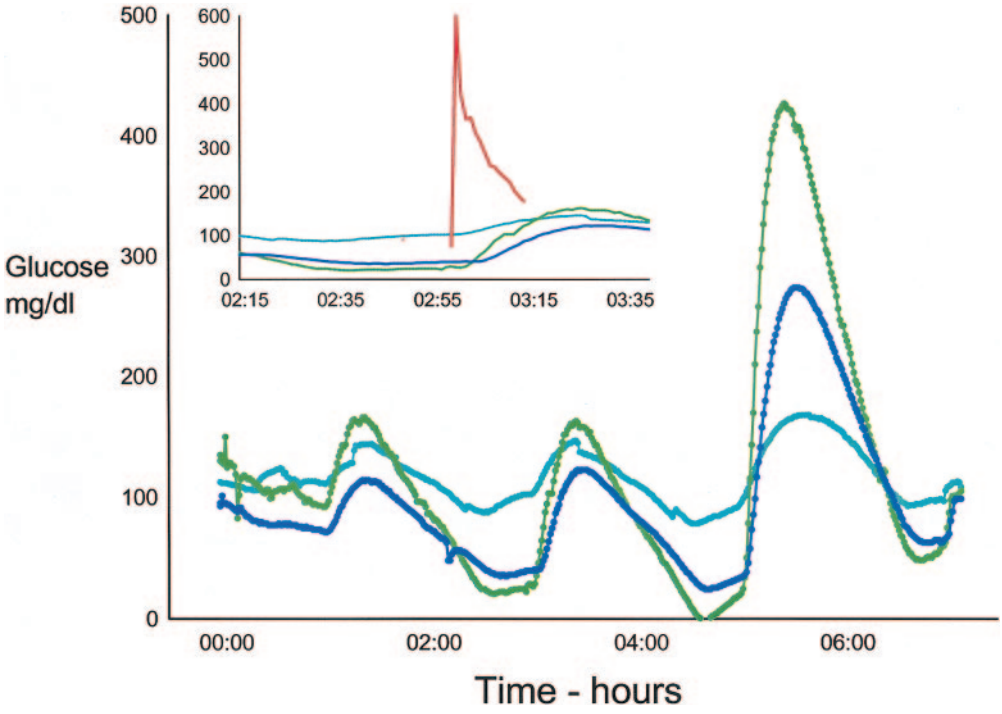

FIG. 2. Example of glucose excursion in one representative pig in different tissues during the study period. Data from muscle (blue line), subcutaneous adipose tissue (green line), and CNS (cyan line) are presented. Insert: Example of glucose excursion in the same pig in different tissues during a shorter span of time. At time 0300, an intravenous bolus of 20 g glucose was injected. An immediate response is seen in arterial blood (red line), and a response is seen after a few minutes in all tissues (muscle [blue line], subcutaneous adipose tissue [green line], and CNS [cyan line]).

appearance in blood (two-way ANOVA, $P = 0.1$). The delay was consistent during the different glucose challenges (average in all tissues): 19.1 ± 3.7 min (mean ± SD) for a 10-g bolus, 19.8 ± 4.1 min for a 20-g bolus, and 21.2 ± 5.3 min for a 50-g bolus. By two-way general linear ANOVA, the P value is 0.2, indicating that there was no difference in the delay between the three tissues due to different glucose boluses (Table 1).

During hypoglycemia, we sampled blood before the insulin challenge and minute by minute for the first 15 min and thereafter every 10 min. A nadir was not reached within the first 15 min after insulin injection; hence, we do not have exact data on blood glucose at nadir. However, the time from intervention to T90 nadir in the other tissues did not differ statistically (results not shown).

There was no significant difference in the actual concentrations of glucose between subcutaneous adipose tissue and muscle during either of the glucose challenges, but the amplitude of the glucose excursion in CNS clearly exhibited a dampened response during the 50-g bolus ($P < 0.01$) (Tables 2 and 3; Figs. 2 and 3). In other words, the amplitude of glucose changes was larger in fat and muscle in comparison with CNS, as seen in Tables 2 and 3. Furthermore, the lowest concentrations recorded in CNS during hypoglycemia tended to be higher than in subcutaneous adipose tissue and muscle.

TABLE 1
Glucose arterial peak to tissue T90

	CNS (min)	Muscle (min)	Adipose (min)
Hyperglycemia			
10 g glucose	19.5 ± 5.0	19.7 ± 3.6	17.2 ± 3.0
20 g glucose	20.1 ± 4.7	19.1 ± 4.0	19.4 ± 3.4
50 g glucose	23.9 ± 7.3	18.0 ± 4.4	19.7 ± 4.4
Hypoglycemia			
10 IU insulin	36.4 ± 8.3	38.3 ± 11.9	37.0 ± 11.0
30 IU insulin	30.0 ± 7.0	30.5 ± 8.3	29.9 ± 4.5
50 IU insulin	32.5 ± 2.5	34.0 ± 2.8	33.3 ± 4.6

Data are means ± SE for each challenge in each tissue.

DISCUSSION

The present study shows that changes in glucose concentrations in subcutaneous adipose tissue, muscle, and brain occur with the same delay in comparison with rapid induced excursions in blood during hyperglycemia. By using the T90 value, we found the delays to be ~20 min. Furthermore, we show that a change in amplitude of glucose in the CNS is different from that of subcutaneous adipose tissue and muscle, perhaps pointing toward a different handling of glucose in the brain in comparison with the periphery.

In a study by Rebrin et al. (3), evaluating data by the "edge detection" method (equivalent to T1 or 1% change in the level of glucose) in blood against the changes observed in subcutaneous adipose tissue, they found a delay of 4–12 min, corresponding to a delay similar to the values presented here determined by the T90 method. This corre-

TABLE 2
Absolute peak values of glucose during the hyperglycemic challenges in the interstitial tissues based on in vitro calibration data

	CNS (mg/dl)	Subcutaneous adipose tissue (mg/dl)	Muscle (mg/dl)
Baseline	46.9 ± 9.8	56.2 ± 10.0	56.6 ± 16.9
10 g glucose	85.0 ± 12.8*	84.0 ± 14.42*	97.8 ± 25.2*
20 g glucose	88.6 ± 9.3*	115.1 ± 15.2*	100.7 ± 20.1*
50 g glucose	123.0 ± 11.3*†	238.0 ± 20.2*	206.0 ± 54.0*

Glucose values are means ± SE. *$P < 0.05$ vs. baseline level of glucose in the same tissue. †$P < 0.01$, CNS vs. subcutaneous adipose tissue after a bolus 50-g glucose injection. There were no significant differences between the level of glucose in any of the remote tissues after the 10- and 20-g glucose challenges.

TABLE 3
Absolute values of glucose during hypoglycemic challenges (30 min after insulin challenge) in the interstitial tissues based on in vitro calibration data

	CNS (mg/dl)	Subcutaneous adipose tissue (mg/dl)	Muscle (mg/dl)
Baseline	46.9 ± 9.8	56.2 ± 10.0	56.6 ± 16.9
10 units insulin	43.0 ± 7.4	36.7 ± 7.4	35.9 ± 7.2*
30 units insulin	40.7 ± 7.8	32.4 ± 5.4	32.9 ± 7.2*
50 units insulin	53.0 ± 11.0	65.7 ± 15.6	42.8 ± 13.0

Glucose values are means ± SE. *$P < 0.05$ vs. baseline.

sponds very well with our data, considering the differences in assessment of changes in glucose. The same order of delay was found in the study by Regittnig et al. (5), albeit the T95 method was applied here, and, hence, an ~27-min delay was found. In contrast, recent findings of Boyne et al. (7) show delays of ~4–10 min using the Medtronic/Minimed CGMS, and analyzing the first derivative of the glucose concentration, their data would correspond to considerably shorter T90/T95 values. By definition, the point at which the first derivative equals zero corresponds to T100, and hence their data stand out compared with other data. However, as the authors state, considerable variation was observed intrinsically in the Medtronic/Minimed CGMS device, perhaps making in-depth analysis difficult (7). The results from that study are also in contrast with the data from the study by Rebrin et al. (3), applying a similar CGMS prototype.

Our analysis of time delays can only be influenced by changes in perfusion rate. We tested for the intrinsic lag time both before and after in vivo experimentation and found no difference between the two. We then calibrated the glucose monitor in vitro based on the data obtained during the physical lag time experiments. This approach could possibly lead to minor deviations from the "true" concentration in any given compartment, due to changes in sensitivity of the sensor after implantation and due to differences in environment between in vitro and in vivo settings. The latter has been found to be the case for a number of analytes when using microdialysis. Which direction this possible error might have remains speculative, and whether there might be differences among the three studied tissues is likewise not known. Nevertheless, the achieved concentrations are in accordance with other studies attempting to measure absolute concentrations. Regittnig et al. (5) found muscle and fat interstitial glucose values of 60 and 65% of blood glucose values during fasting conditions using the open-flow microperfusion technique. Interstitial values have been found to be identical to plasma values by some (8) and lower by 10–55% by others (9,10), and microdialysis studies have shown glucose values that were lower by 15–30% (11–13). This is the first study with simultaneous continuous measurement of glucose in the interstitial fluid of adipose tissue, muscle tissue, and brain. Because we have used the same technology in all three tissues, the reduced glucose excursions during hyper- and hypoglycemia in the brain and the apparent (but not statistically different) higher basal level of glucose in comparison with blood, fat, and muscle seem real, perhaps pointing toward some protective mechanisms coming into action during hypoglycemia in CNS, not allowing glucose levels to drop below a certain threshold. The fact that glycogen has been found in glia cells (14) could lead to the speculation that protective glycogenolytic processes are activated during cerebral hypoglycemia.

During experimental conditions, a wide range of glucose values in different areas of the brain have been found. With the microdialysis technique, the following glucose values have been found in rats: 0.3–0.5 mmol/l in the striatum (15,16), 1 mmol/l in the hippocampus (17), and 3.3 mmol/l in the neocortex (18). In pigs, the level of glucose has been found to be higher and in accordance with the present data. Using microdialysis in the cortex of pigs under different experimental conditions, values of 0.2–2.5 mmol/l have been found with simultaneous blood glucose values of 5–6 mmol/l (19–21). Here, we found basal cortical glucose levels of 3 mmol/l, which is somewhat higher than previously reported. This could be due to the placement of

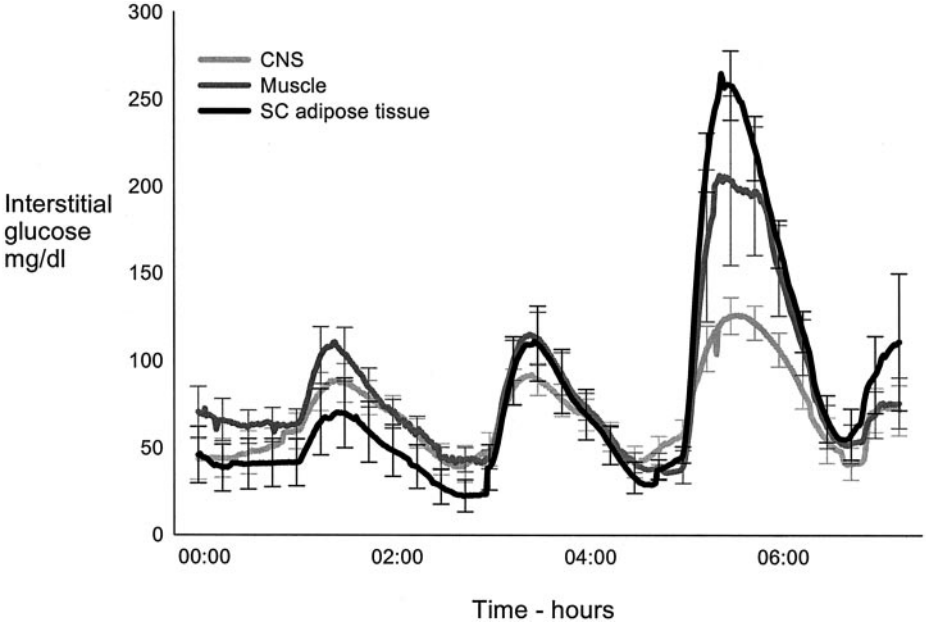

FIG. 3. The average glucose values of all experiments (n = 9) during the entire study period in subcutaneous adipose tissue, muscle, and the brain. The glucose values are calculated after in vitro calibration. Error bars show SE.

the microdialysis fiber, i.e., in the cortex, the methodology used, or the species of pigs used. CNS microdialysis is usually performed with membranes 2–10 mm in length. The size of the CMA-60 catheter is 30 mm, and thus an exact CNS area cannot be investigated. With the applied microdialysis technique, we were not able to place the sensor in the ventromedial hypothalamic nuclei, which is believed to have a central role in glucose sensing (2). However, cortical glucose sensing might be equally relevant, because cognitive dysfunction is a hallmark of neuroglycopenia. Transport from blood to interstitial tissue is thought to be by passive or facilitated diffusion. The brain may have a different transport system than adipose tissue and muscle. The presence of GLUT1 in the blood-brain barrier (22) and GLUT2 in the brain may point in that direction (2), but insulin-sensitive GLUT4, which is the most abundant glucose transporter in adipose tissue and muscle, has also been found in the brain.

Accurate measuring devices in the CGMS may allow a closed-loop insulin delivery system to be developed. This requires a real-time system or at least one with a short delay. In a closed-loop insulin delivery system, it is imperative to know what the relations are between the monitored tissue and the brain as the most critical tissue. The present study was designed to get exact results on the time delay from blood to tissue. Obviously, the intravenous bolus of glucose or insulin does not mimic daily life in the normal human being, and the physiological glucose release after a meal and the subsequent absorption in the tissues would be very interesting to look into in a later study. A number of issues must be taken into consideration when attempting to find the most ideal site for glucose monitoring. For instance, the permeability surface for glucose in muscle is low during postabsorptive conditions and rises at high physiological levels of insulin (23), compatible with local recruitment of capillaries.

In conclusion, we present simultaneous continuously sampled glucose data from pigs showing glucose dynamics under both hyper- and hypoglycemia. We show time-wise similar changes, thus making subcutaneous adipose tissue a sensible tissue to monitor glucose changes in patients with diabetes. Although this study was performed in pigs under experimental conditions, we have no reason to doubt that similar results would have been found in humans. Furthermore, the tendency of cortical glucose to be less oscillating than subcutaneous adipose tissue or muscle warrants further study.

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