

Continuous glucose monitoring in subcutaneous tissue of rats using glucose oxidase based sensors

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INTRODUCTION: Glucose monitoring is of great importance for the success of complex therapeutic interventions to achieve near normoglycemia in diabetic patients. The substitution of the numerous daily blood glucose measurements by a continuous monitoring system would lead to a considerable progress in the control of the patients' disturbed metabolism.

Aim of our study was to establish an animal model for testing of continuous glucose monitoring systems in normo- as well as hypo- and hyperglycemia. Rats, easy in handling and fast reacting to metabolic changes, were used for verifying the glucose sensor's function.

METHODS: The needle type sensor was composed of a base foil, conduction path, a cover layer for electronic insulation, carbon paste with glucose-oxidase for working electrode and silver/silver chloride for the reference electrode. For improving biocompatibility the sensor was covered with MPC (2-methacryloyloxyethyl phosphorylcholine, for details see Woderer et al. 2007). Male SPF Sprague-Dawley rats with a body weight of about 500 g were used for the study. For substance application and blood sampling catheters were inserted into the femoral vein and artery, tunnelled subcutaneously and exteriorized at the back of the neck. The sensors were implanted into the subcutaneous tissue between the scapulae and sutured to the skin. Animals were kept in a rodent work station during the experiment. To achieve hyperglycemia two different kinds of glucose profiles were run: single intravenous injection of glucose (400mg/kg) and repeated injections (100mg/kg) every 2min for a time period of 30min. After decline to normoglycemia, hypoglycemia was induced by intravenous application of insulin (2U/kg). For reference measurements with an Accu-Check® sensor instrument arterial blood was used.

RESULTS: A close correlation is given between the glucose levels in interstitial fluid (ISF) and the conventional blood glucose readings in hypo- as well as normoglycemia and concentrations up to 300mg/dL (Fig. 1). Error grid analysis (Table 1) showed the vast majority of data in zone A and B,

demonstrating a good comparability of both methods even over a period of 5 days.

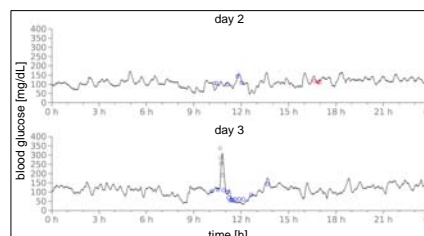


Fig. 1: Continuous glucose monitoring in rat's subcutaneous interstitial fluid (ISF) over a time period of 5 days. Given are the courses of day 2 and 3. Circles indicate spot measurements.

Table 1: Error grid analysis of continuous glucose monitoring in ISF vs. blood glucose (n=3; 5 days)

zone	error grid zones					
	total	A	B	C	D	E
absolute	110	71	30	3	6	0
relative [%]	100	64.5	27.3	2.7	5.5	0

DISCUSSION & CONCLUSIONS: Good comparability of the sensor readings with the conventional blood glucose measurements in normo- and hypoglycaemic status demonstrates the usefulness of the sensor for in vivo glucose monitoring over at least 5 days. The discrepancy of glucose values above 300mg/dL may be rather the consequence of fast glucose flux from ISF into cells in metabolically healthy rats than insufficiency of the sensor. Appropriate test systems are essential prerequisites for development and improvement of glucose monitoring systems. Our results demonstrate the rat as a suitable test model for continuous glucose monitoring even over a long time period.

REFERENCES: S. Woderer et al. (2007) *Continuous glucose monitoring in interstitial fluid using glucose oxidase-based sensor compared to established blood glucose measurement in rats* Analytica Chimica Acta, 581 (1), pp 7-12

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