Influence of Paracetamol, Sulfanilamide and Ascorbic Acid on the Electrocatalytic Glucose Sensor

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Summary

An electrocatalytic glucose sensor for in vivo application has been developed. The principle of measurement is based on the direct electrochemical oxidation of glucose at a platinum electrode without an enzymatic reaction.

In an in vivo experiment with sheep the glucose sensor was tested with respect to its cross-sensitivity towards ascorbic acid, paracetamol and sulfanilamide. The influence of these substances could be reduced by an adapted calibration to such an extent, that the sensor performance could be ensured.

Key words

Electrocatalytic Glucose Sensor – In-Vivo-Measurement – Cross-Sensitivity – Drugs – Sensor Performance

Introduction

A critical part of an artificial endocrine pancreas is a glucose sensor intended for the continuous measurement of the blood glucose concentration. It is envisaged that the measurements from the sensor should control the amount of insulin units to be delivered by an insulin pump. To achieve best possible coordination of the insulin supply to the physiological condition of the patient, it is necessary to know the effect of other substances on the sensor response.

The influence of different blood ingredients, such as amino acids and urea, on the glucose oxidation at a noble metal electrode has been investigated by several groups: *Giner, Marincic* and *Soeldner* (1981); *Guyton, Chang, Aisenberg* and *Soeldner* (1975); *Rao, Richter, Luft* and *von Sturm* (1978). Good results in eliminating the interfering influences have been achieved by the use of selectively permeable membranes and by separation of the different potential dependent reactivity of these substances, as published by *Gebhardt, Luft, Mund* and *Richter* (1983) and by *Richter, Luft* and *Gebhardt* (1982).

In order to study the cross-sensitivity of the electrocatalytic glucose sensor towards pharmacological agents, we have focused on three substances which are small enough to penetrate the membrane in front of the sensor electrode and are administered in higher doses. These three substances are ascorbate, paracetamol and sulfanilamide; the first two of them being known to have considerable influence on the enzymatic glucose determination as reported by *Kruse-Jarres* (1979) and *Velho, Moatti* and *Reach* (1990).

The tests were conducted during an in vivo implantation of the sensor in a sheep (*Preidel, Saeger, Ruprecht, von Lucadou* and *Lager* 1991). This provided the possibility to compare the dependency of the electrocatalytic and the enzymatic measuring methods on other blood substances which interfere with the glucose oxidation.

Material and Methods

The electrocatalytic glucose sensor is constructed as a flow-through-cell (cylindrical, diameter 2.5 cm, size 1.8 cm). It was implanted via a vessel prothesis (FEP ring removable Gore-Tex graft, Gore-Tex, Munich, Germany) into the carotid artery of a sheep. The principle of measurement is based on the direct electrochemical oxidation of glucose at a platinum electrode which is covered by a membrane (*Gebhardt, Luft, Mund, Preidel* and *Richter* 1983). The glucose concentration is determined by measuring the impedance of the electrode/membrane system. The impedance at certain potentials is directly proportional to the glucose concentration in the solution. Selectivity of the sensor is achieved by adequate choice of the membrane properties (i.e. cut-off, hydrophilicity and covalently linked chemical groups) and by selection of special impedance parameters in calculating the glucose concentration. These parameters are the double layer capacity and the charge transfer resistance at certain potentials. The detailed principle of sensor design and method of measurement are described elsewhere (*von Lucadou, Luft, Preidel* and *Richter* 1988; *Preidel* and *Saeger* 1989; *Preidel* and *Saeger* 1990).

The sensor was implanted over a period of 90 days to observe the blood sugar level. During this long-term experiment we examined the cross-sensitivity of the sensor towards paracetamol, sulfanilamide and ascorbic acid (all from Sigma Chemicals, Munich, Germany) by infusing the respective agent in pharmacological amounts. The influence of the three substances was tested at different times of the implantation period. Prior to each experiment, the sensor was recalibrated using an intravenous glucose tolerance test (IVGTT). A similar IVGTT was conducted after the intravenous administration of the test substances via a jugular vein catheter to verify the sensor function. The infused substances were 5 g ascorbic acid dissolved in 100 ml, 3.1 g paracetamol in 31 ml and 1.5 g sulfanilamide in 120 ml of buffered

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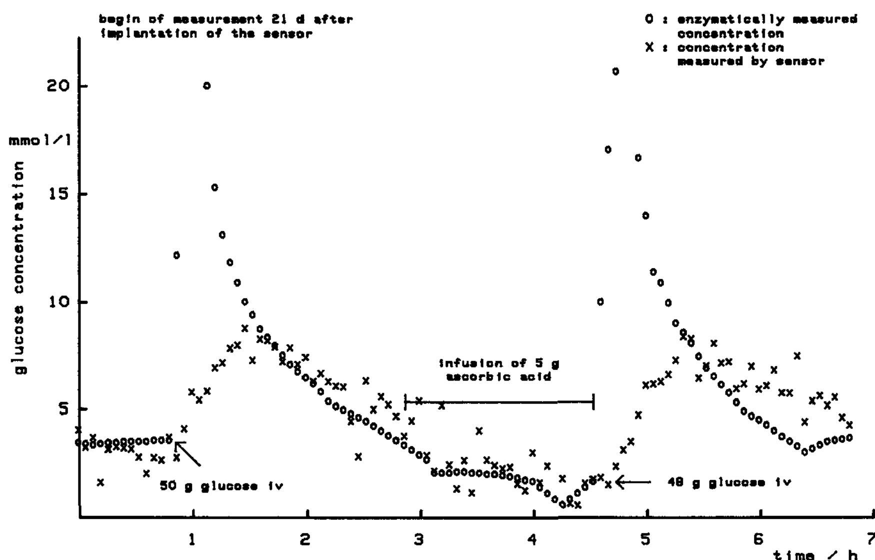

Fig. 1 Influence of ascorbic acid on glucose sensing by the electrocatalytic sensor in a sheep. Infusion of 5 g ascorbic acid dissolved in 100 ml saline solution. Calibration over 4 days of measurement.

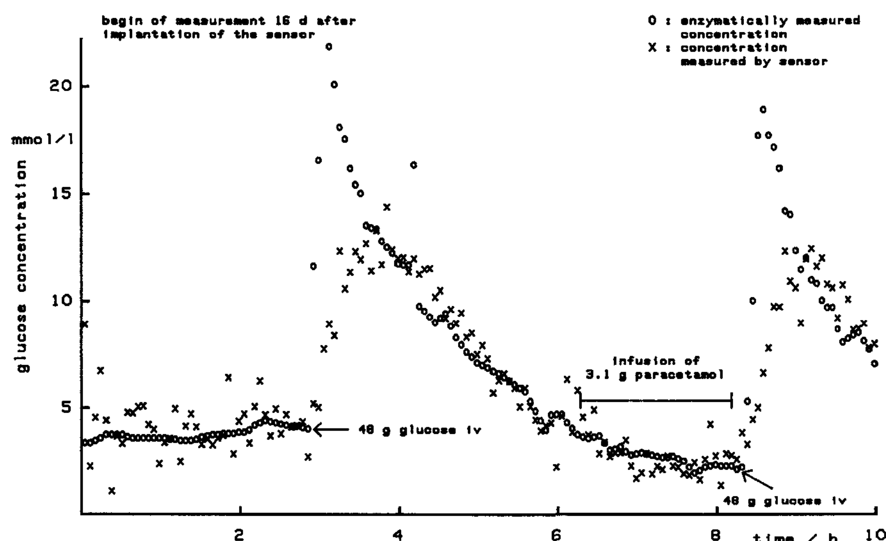

Fig. 2 Influence of paracetamol on glucose sensing by the electrocatalytic sensor in a sheep. Infusion of 3.1 g dissolved in 31 ml saline solution. Calibration over 1 day of measurement.

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saline solution. Blood samples for the glucose analysis were also taken from the jugular vein catheter. Glucose concentration was measured by a standard enzymatic method (GOD-POP method, Merck, Darmstadt, Germany).

Results

The recorded glucose measurements and the influence of ascorbic acid, paracetamol and sulfanilamide are shown in Figs. **1**–**3**. The glucose concentrations calculated by the sensor by impedance measurement are represented as crosses, the enzymatically determined concentrations correspond to the circles. The enzymatic glucose measurement was used as a reference to check the sensor performance, though this method is not unaffected by the test substances as will be demonstrated later.

The test with ascorbic acid was conducted after 21 days of implantation (Fig. **1**). The sensor response rapidly levelled out and the measured values were in accordance with the enzymatically determined glucose concentration. After an IVGTT, 5 g ascorbic acid were infused into the jugular vein over a period of nearly 2 hours. As illustrated in Fig. **1**, the sensor performance was not affected by ascorbic acid. The error in measurement of the sensor, which was on average 1.5–2 mmol/l glucose, was not increased. Also the subsequent IVGTT was recorded by the sensor. In the range of high glucose concentrations (above 15 mmol/l) there is a significant difference between both values and hence a deviation; it is due to different sites of sensor implantation (carotid artery) and glucose infusion (jugular vein), where the blood samples for the analysis were also taken (*Kruse-Jarres* 1979).

At the end of the ascorbate infusion, a slight decline of the enzymatically determined values can be observed. This effect cannot be ascribed to the metabolic resorption of glucose, but to an interference of increased ascorbate

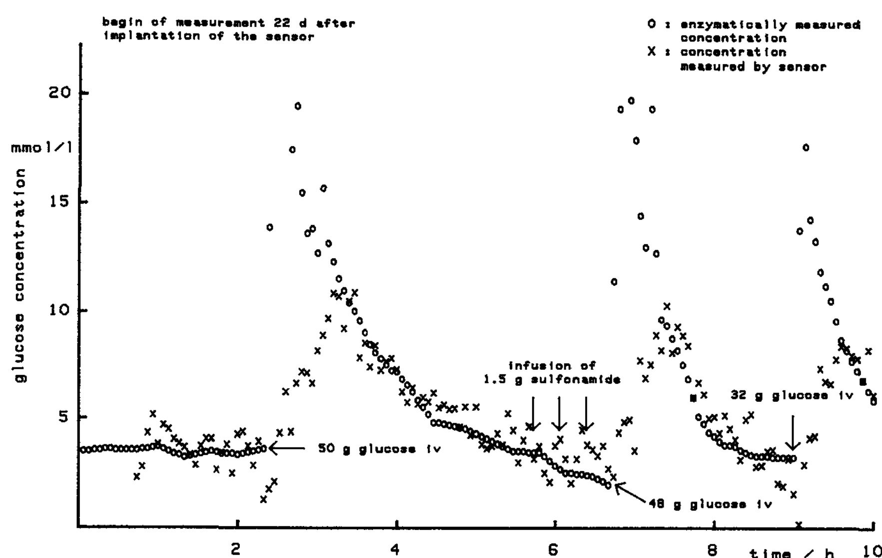

Fig. 3 Influence of sulfonamide on glucose sensing by the electrocatalytic sensor in a sheep. Infusion of 1.5 g dissolved in 120 ml saline solution. Calibration over 1 day of measurement.

concentrations with the oxidation of the chromogene used in the photometric analysis (*Kutter* 1961).

The influence of paracetamol and sulfonamide was examined 16 and 22 days after the implantation. These tests followed the same experimental procedure as described for ascorbic acid. There is no detrimental effect of paracetamol on sensor performance, as shown by Figure **2**. 1.5 g sulfanilamide, administered as three boli of 500 mg each, showed a slight influence on the sensor response, though it can hardly be distinguished from the average error in measurement (Fig. **3**). As the figures show, there is in general a good correlation between the enzymatically measured glucose concentration and the values calculated from the sensor. Deviations of the sensor response can be explained by variations in the sheep's body temperature, which were in the range of 1–3 °C. These fluctuations were not taken into consideration in calculating the glucose concentration and may lead to variations in the sensor's accuracy.

Discussion

This investigation not only revealed the potential long-term stability of an electrocatalytic glucose sensor but also its negligible cross-sensitivity towards ascorbic acid, paracetamol and sulfanilamide despite their unusually high concentrations. Though these substances are able to penetrate the membrane which covers the electrode, their effect can be suppressed. This can be achieved by selection of certain impedance parameters at particular potentials, which show a weak interference with the test substances. It may sometimes lead to a slight increase of the average error in measurement. Difficulties in calibrating the sensor may occur during simultaneous fluctuations of the concentration of several blood substances effecting the sensor performance. However, such drastic physiological changes can hardly occur to be critical for the development of an implantable electrocatalytic sensor. Such effects are also being investigated.

The intrinsic selectivity of an enzymatic glucose sensor is a generally accepted argument for the preference of this principle of measurement. However, recent experiments conducted by *Velho, Moatti* and *Reach* (1990) demonstrated a major influence of ascorbate and paracetamol on the glucose sensing by an enzymatic sensor. The use of selectively permeable membranes for an enzymatic sensor can diminish the interference, but increases the sensor complexity. Taking these factors into consideration the long-term stable electrocatalytic glucose sensor which has a simple construction becomes more attractive.

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