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Biomedical soft contact-lens sensor for *in situ* ocular biomonitoring of tear contents

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Abstract A soft contact-lens biosensor (SCL-biosensor) for novel non-invasive biomonitoring of tear fluids was fabricated and tested. Wearing a biosensor on eye enabled the *in situ* monitoring of tear contents. The biosensor has an enzyme immobilized electrode on the surface of a polydimethyl siloxane (PDMS) contact lens. The SCL-biosensor was fabricated using microfabrication techniques for functional polymers (PDMS and 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer). In investigation of *in vitro* characterization, the SCL-biosensor showed excellent relationship between the output current and glucose concentration from 0.03 to 5.0 mmol·L^{-1}, with a correlation coefficient of 0.994. The calibration range covered the reported tear glucose concentrations (0.14 mmol·L^{-1}). Based on the result, ocular biomonitoring with the SCL-biosensor was carried out. The SCL-biosensor well worked both in the static state and the dynamic state. The tear glucose level of rabbit was estimated to 0.12 mmol·L^{-1} at first and then the tear turnover was successfully calculated to be 29.6±8.42% min^{-1}. The result indicated that SCL-biosensor is useful for advanced biomonitoring on eye.

Keywords Contact-lens · Biosensor · Non-invasive · Ocular biomonitoring · Glucose

1 Introduction

Recent advances in information, communication and device technologies have modernized logistics, emergency services and other essential utilities in developed countries. Particularly, rapid spread of portable network devices (e.g. mobile phones) and communication infrastructures drastically changed our daily lives since they allow individuals to be available for constant access to network systems. It enables us to carry our own personal data as relatively-secure

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electronic information, which is useful for administrative, medical or commercial network services. Utilization of physiological information with the information systems is expected to provide proactive management of health that can improve public health, and reduce medical expenditure. For this purpose, technical fusion and innovation in advanced non-invasive biomonitoring sensors and suitable communication technologies are requested. With the aim of health monitoring applications, several types of radio technologies for transmitting physiological information to create a wireless or body-wired personal/body area networks (PAN/BAN) in/on the body have been investigated (Javanov et al. 2003; Milenković et al. 2006). Those networking technologies assume to connect sensors and other devices each other and provide feedback to maintain optimal health status (*ubiquitous biomonitoring*). It is also expected to free certain patients from inconveniences due to frequent clinical tests or clinical treatments.

Some of modern portable devices (or computers) utilize biological information (e.g. vocal recognition, fingerprint, etc.) and are successful in the marketplace. However, it is still difficult to utilize biochemical information with those systems. Many kinds of miniaturized physical sensors were improved in reliability and sensitivity so that being suitable for *in vivo* purposes by recent advances in micro-fabrication techniques. In contrast, biochemical sensors are still difficult to use wearing purposes because many of them have wet components like Clark's oxygen electrodes, or biocatalysts like an enzyme. Considering health monitoring purposes, it is also requested to be non-invasive, highly-selective to chemicals existing together, comfortable in measurement, useful in a humid atmosphere and safe to be attached on the body surface. Particularly, flexible sensors that can follow to the transformation and expansion by the movement of human bodies are the most promising devices to measure biological information with minimum consciousness of sensor attachment to the subjects. For this reason, techniques to add flexibility to chemical sensors are also expected for ubiquitous biomonitoring. Recently, Gray et al. had developed a wavy gold wiring for flexible devices (Gray et al. 2004). A stretchable transistor formed on a polydimethylsiloxane (PDMS) panel was also developed for further flexible devices (Khang et al. 2006). Wearable applications in mind, flexible chemical sensors using polymer film such as conductimetric sensor (Mitsubayashi et al. 1993), oxygen sensor (Iguchi et al. 2005), moisture, hygrometric and biosensors (Mitsubayashi et al. 1995; Kudo et al. 2006; Iguchi et al. 2007) was reported.

On the other hand, body fluid for non-invasive biomonitoring is also important for biochemical sensors. For instance, continuous glucose monitoring does not measure blood sugar directly, but rely instead on other body fluids that reflect blood sugar levels (Wilson and Gifford 2005). Thus, we focused on tear fluids as a target of non-invasive biomonitoring. Tear is secreted from lacrimal grands (Tiffany 2003). It contains various chemicals such as glucose (Ridley 1930; Giardini and Roberts 1950; Daum and Hill 1982, 1984), ascorbic acid (Kuizenga et al. 1987; Paterson and O'Rourke 1987; Choy et al. 2000; Bilgihan et al. 2001) and various proteins (e.g. albumin (Sapse et al. 1969; Li et al. 2005), lysozyme (Mackie and Seal 1976; Aviser et al. 1979; Farris 1985), epidermal growth factor (Wilson 1991; Van setten et al. 1991; Pflugfelder et al. 1999; Ohashi et al. 2003)). Tear contents are known to reflect physiological conditions. For instance there appears to be a relationship between blood glucose levels and tear glucose levels (Daum and Hill 1982; Lewis and Stephens 1958; Sen and Sarin 1980). However, the reported tear glucose concentration differs between studies, which are thought to be due various collection methods (Daum and Hill 1982). Thus, *in situ* real-time biomonitoring would be advantageous.

In this study, we developed a soft contact-lens electrochemical biosensor (SCL-biosensor) for monitoring of glucose levels in tear fluids. The biosensor measures glucose as concentrations of hydrogen peroxide, which is the product of glucose oxidase (GOD) reaction. Microfabrication technique for fabrication of the SCL-biosensor was advanced from that of previously reported paper (Iguchi et al. 2007). An enzyme electrode was formed on the rounded surface of the flexible PDMS contact lens. Also, a new ocular biomonitoring that uses the advantage of the contact lens-shaped device was demonstrated. At first, the glucose level in tear fluids was monitored by wearing the SCL-biosensor. In order to assess the dynamic state of tear fluids, tear turnover was also investigated by dropping glucose solution into eye. Tear turnover rate is defined as a percentage value of tear volume which is replaced by tear flow per minute. The rate is used as an important factor to diagnose xerophthalmia. Previously, tear turnover was measured by a strip filter paper or fluorophotometric method (Schirmer 1903; Lamberts et al. 1979; Krupin et al. 1977; Farris et al. 1986; McGavin et al. 1976; Waltman and Kaufman 1970; Townsend and Brubaker 1980; Polse 1979). In this study, it was monitored in real-time using the SCL-biosensor. This paper reports design, fabrication, *in vitro* characteristics and the result of animal tests using the SCL-biosensor in detail.

2 Experimental

2.1 Chemicals

Hydrophobic PDMS (Silpot 184, Dow Corning Toray Co., Ltd., Japan) was used as the structural material of the

contact-lens sensor. In order to form the sensing region, 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer was prepared for immobilization of glucose oxidase (GOD: EC 1.1.3.4, 146000 units g^{-1}, Sigma-Aldrich Co. USA). The MPC polymer was polymerized by free-radical polymerization method as previously reported (Kudo et al. 2008). Monomer solution (MPC and 2-ethylhexyl methacrylate (EHMA)) was prepared with ethanol and tetrahydrofuran. The total concentrations of the monomers were adjusted to be 1 mol L^{-1} (MPC : EHMA=3 : 7). 1.5×10^{-4} mol of α, α'-azobisisobutyronitrile (AIBN) was added as a polymerization initiator to the monomer solution and free radical-polymerization was conducted at 60°C in a sealed polymerization tube. After that, dialysis treatment was performed using a dialysis membrane (MWCO: 15000) to remove unreacted monomer and PMEH was obtained. Phosphate buffer (PB, pH 7.4, 20 mmol L^{-1}) was used for characterization of the biosensors. HCl solution for forming Ag/AgCl was prepared by dilute hydrochloric acid solution (083-02715, Wako Pure Chemical Industries, Ltd., Japan). Standard glucose solution was prepared using D(+)-Glucose (Wako Pure Chemical Industries Ltd., Japan). Physiological sodium chloride solution (OTSUKA Pharmaceutical CO., Ltd., Japan) was used to clean the sensor before animal experiments.

2.2 Construction and characterization of the biosensor

Figure 1 shows the design and the method for application of the contact lens biosensor. The contact lens biosensor has a rounded surface as well as a conventional soft-contact lens (base curve radius: 8.6). PDMS was used as the body of the sensor while poly 2-hydroxyethyl methacrylate (HEMA) is commonly used as a contact lens material. The use of PDMS prevented electrodes from pealing-off or cracking due to large transformation of HEMA by containing water. Tentatively, metal wirings were formed on a flexible PDMS membrane (width: 3.0 mm, length: 45 mm, thickness: 70 μm) for the purpose of characterization and convenience of animal experiments. The contact lens sensor placed on the eye as shown in the figure.

In the experiment, a flexible biosensor was first constructed and tested. It was then integrated on a PDMS contact lens and applied to monitoring of real tear fluids.

2.2.1 Flexible biosensor using PDMS and PMEH

As shown in Fig. 1, the SCL-biosensor is a combination of the PDMS contact lens and the biosensor formed on a flexible membrane. The characteristics of the SCL-biosensor were assessed using a thin and flexible biosensor strip as a preliminary experiment. Figure 2 represents the fabrication processes of the flexible biosensor (I) and the SCL-biosensor (II).

The flexible biosensor was fabricated using micro-fabrication techniques. A 70 μm thick PDMS membrane was first formed on a dummy silicon wafer by spin-coating system (1H-DX II, Mikasa Co., Tokyo, Japan). The PDMS resin was degassed using a conditioning mixer (AR-100, THINKY Co., Japan) and cured at 80°C. Then a 200 nm thick Pt electrode was deposited on the PDMS surface through a 40 μm thick titanium stencil mask, which was prepared by direct patterning on a titanium substrate (Nilaco Co., Japan) with an YVO_4 laser marking system (MD-V 9610, Keyence, Co., Japan). An Ag electrode (thickness: 300 nm) was also formed as well. The electrodes were then covered with PDMS except the sensing region and the contacting region. Ag/AgCl electrode at the sensing region was electrochemically formed in an HCl solution (Suzuki et al. 1999). Finally, PMEH solvent (10 wt.%) containing GOD was spread on the sensing region. The concentration of GOD was optimized to 38.9 units/cm^2. The sensing region was overcoated with 1.0 μL of PMEH solvent (3 wt.%).

In vitro characterization of the flexible biosensor was carried out using a batch measurement system. The sensor strip was put into a measurement cell filled with PB (pH 7.4, 20 mmol L^{-1}), which was saturated with oxygen using an oxygen supply device (MS-X1, Panasonic, Co., Japan) for 2 h. Then, a potential of +400 mV was applied to the Pt electrode using a potentiostat (MODEL 1112, Fuso Inc., Japan). The standard glucose solution was dropped into the measuring cell, and the output current was recorded using computer via 16 bit A/D converter (ADC-16, pico Technology Ltd., UK).

2.2.2 SCL-biosensor

The SCL-biosensor was constructed by attaching the flexible biosensor to the surface of a PDMS contact lens. The PDMS lens was formed using a molding method. The casting mold was filled with PDMS resin and the resin was degassed in a vacuum chamber to remove gaseous substances in PDMS resin for 30 min. The soft PDMS contact lens was obtained by curing at room temperature for 24 h. The flexible biosensor was attached on the outer surface of the PDMS lens using a PDMS resin as a binder material, and cured for 24 h at the room temperature (Fig. 2). Prior to the animal tests, characteristics of the SCL-biosensor were also investigated at 35°C to assess the possibility for animal tests.

2.3 *In situ* tear monitoring with SCL-biosensor

Tear glucose monitoring was conducted on a Japan white rabbit (age: 55 month, weight: 3.7 kg) using the SCL-biosensor (approval number: 100010, Tokyo Medical and Dental University Ethics Committee). In the animal test, any anesthetic was not used to the rabbit. As the first stage

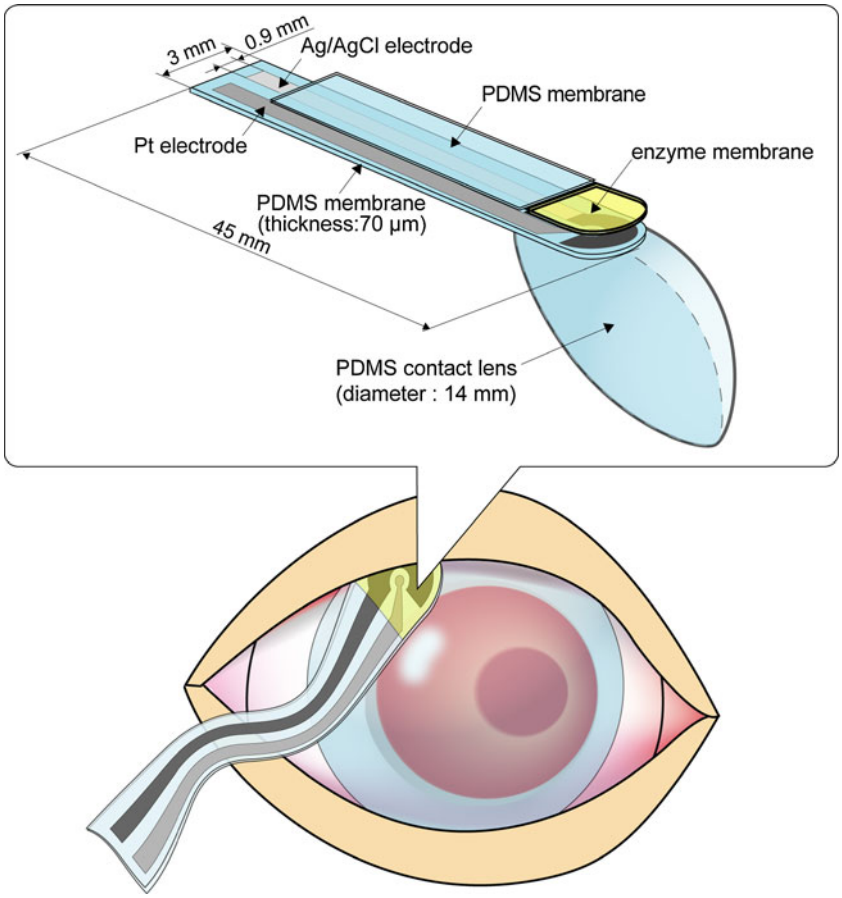

Fig. 1 Structure of the SCL-biosensor. The SCL-biosensor has an enzyme electrode on the surface of a PDMS contact lens

of animal testing, static glucose level in tear fluid was monitored directly. The SCL-biosensor was attached on the eyeball of the rabbit, which was fixed using a fixation device (Hara et al. 2002; Mitsubayashi et al. 1993). The SCL-biosensor was cleaned with physiological sodium chloride solution before ocular application. After confirming the rabbit to be settled, a constant potential of +400 mV was applied to the Pt working electrode via readout and the output current was monitored and recorded.

At the second stage, the tear dynamics were monitored using the SCL-biosensor. Various concentrations of standard glucose solutions (volume: 50 μl) were instilled into the eye of the rabbit (Fig. 3). In order to reduce stimulus-secretion, the temperature of the dropping solution was adjusted to 35° C. Tear turnover rate of the rabbit was assessed from the dilution curve due to steady secretion of tear fluids.

3 Results and discussion

3.1 Characteristics of the flexible biosensor

Due to flexibility of PDMS, the body of the flexible biosensor showed sufficient flexibility to be used as a wiring of the SCL-biosensor as shown in the photograph of Fig. 4. The electrodes were highly adhesive to the PDMS membrane and no significant damages were observed after bending. Figure 4 represents the relationship between glucose concentrations and output currents of the flexible biosensor. Despite thinner structure, the flexible biosensor showed rapid response to glucose solution. Due to production of hydrogen peroxide by enzyme reaction at the sensing region, the output current increased immediately as the glucose level increased. According to the regression analysis, the output current of the flexible biosensor was given by following equation with the correlation coefficient of 0.994:

$$\text{output current}(\mu\text{A}) = 0.133 \times \left[\text{glucose}\left(\text{mmol}\cdot\text{L}^{-1}\right)\right]^{0.913} \quad (1)$$

The calibration range was 0.03–5.0 mmol·L^{-1}, that included normal tear glucose level (0.14 mmol·L^{-1}). The mean value of standard deviations (S.D.) in the measured glucose concentrations (0.03–5.0 mmol·L^{-1}) was 0.03 μA. In case of patients with diabetes (tear glucose conc.: 0.3 mmol·L^{-1}) and normal subjects (tear glucose conc.: 0.14 mmol·L^{-1}), S.D. was ~0.0028 μA. It is enough for ocular glucose monitoring.

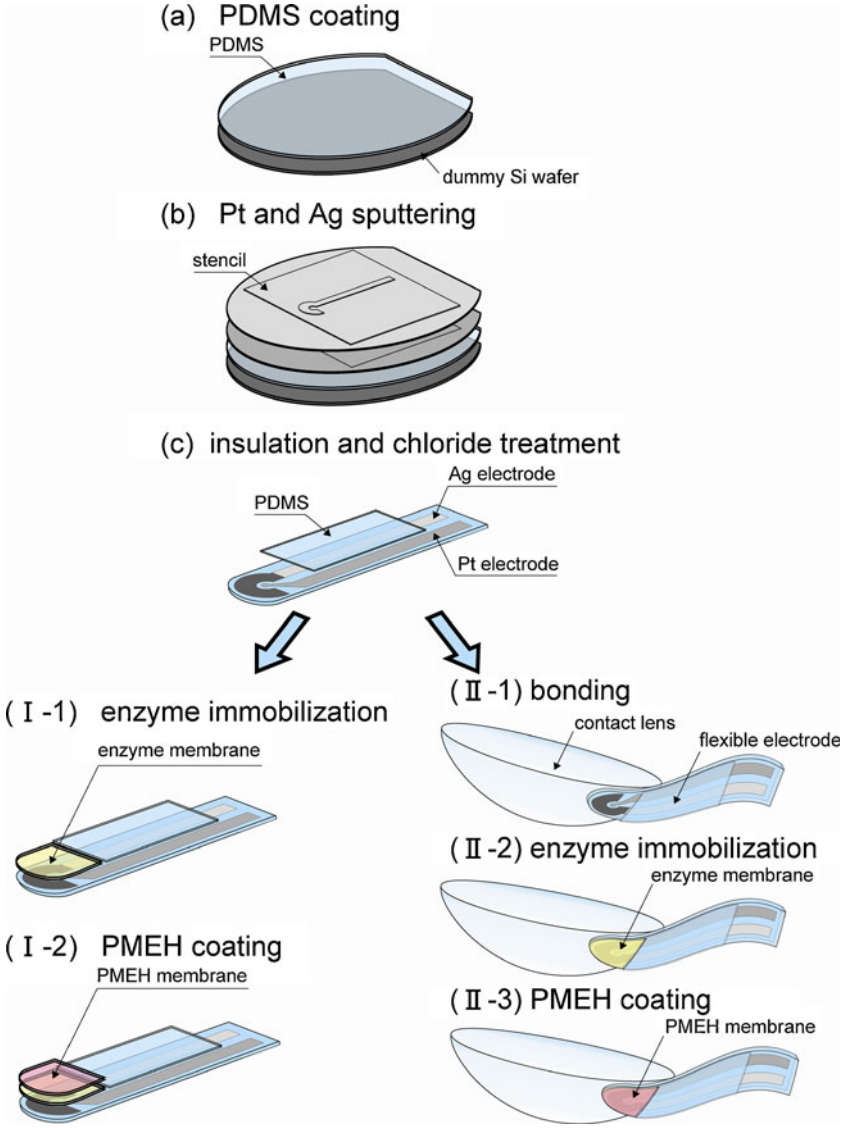

Fig. 2 Fabrication process of the SCL- biosensor. The flexible hydrogen peroxide electrode was formed onto a 70 μm thick PDMS membrane by ion beam sputtering. The left hand (I) indicates the fabrication process of the flexible electrodes. The right hand (II) represents the process to construct the SCL- biosensor

3.2 Characteristics of the SCL-biosensor

In vitro characterization of the SCL-biosensor was also carried out using the batch measurement system. Figure 5 shows the calibration curve of the SCL-biosensor. Typical responses to various concentration of glucose (0.03, 0.05, 0.1, 0.3, 0.5, 1.0, 3.0, 5.0, 10, 20 mmol·L^{-1}) are shown in the small box of Fig. 5. The SCL-biosensor showed rapid responses in each glucose concentration. The time to reach to 95% of the steady current (T_{95}) was approximately 21 s and the mean standard deviation (S.D.) was 5.1 s (variation range of T_{95} : 13–26 s). The response was sufficiently fast to monitor the change of blood glucose levels since blood glucose varies in 2.25 mg dL^{-1} min^{-1}or slower (Stefan et al. 2003). Similar to the testing of the flexible biosensor, the SCL-biosensor was useful for between 0.03 and 5.0 mmol·L^{-1}. In the higher concentrations (10.0 mmol·L^{-1} or higher), the output current was saturated and overshoots were observed at that concentration. Although the dynamic range was not sufficiently wide to be used for measurement of blood sugar, it was expected to be useful for monitoring of tear glucose because it included the reported tear glucose concen-

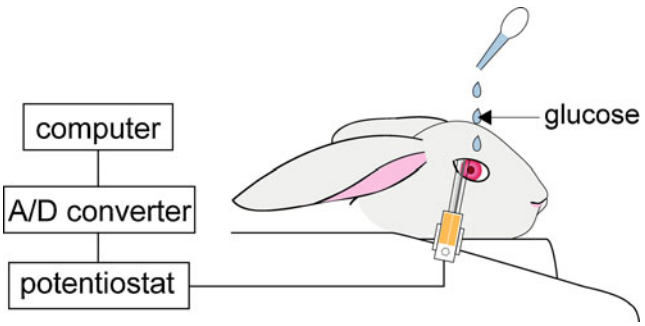

Fig. 3 Experimental setup for ocular biomonitoring with the SCL-biosensor

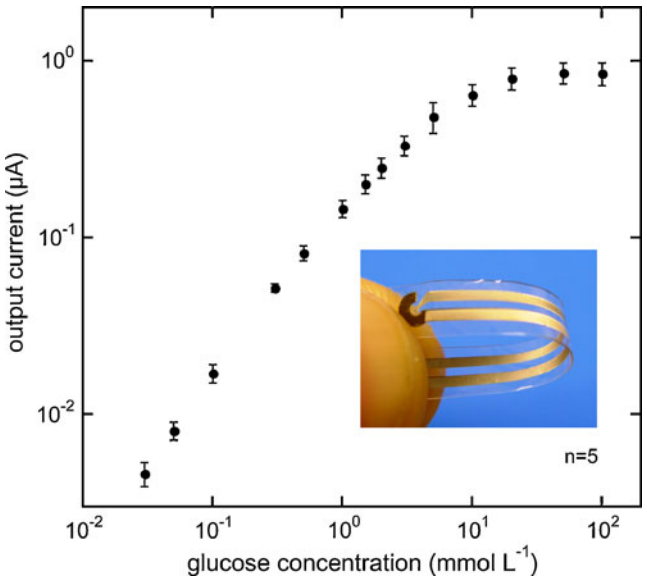

Fig. 4 Calibration curve of the flexible biosensor obtained by *in vitro* characterization (pH 7.4, 20 mmol·L^{-1} PB). The calibration range was 0.03–5.0 mmol·L^{-1}, with a correlation coefficient of 0.994. Inset photograph shows the flexible biosensor

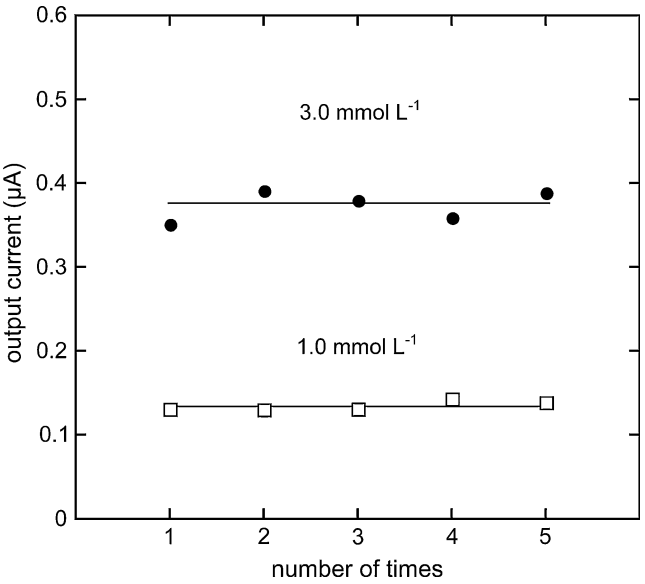

Fig. 6 Reproducibility of the biosensor for 3.0 mmol·L^{-1} (upper) and 1.0 mmol·L^{-1} (bottom) glucose

trations of normal and diabetic patients (Giardini and Roberts 1950; Alexeev et al. 2004; Daum and Hill 1982, 1984).

Reproducibility of SCL-biosensor was also investigated (Fig. 6). As the figure indicates, sufficient repeatability was obtained. The mean values of the current were 0.135 (1.0 mmol·L^{-1}) and 0.374 μA (3.0 mmol·L^{-1}) with coefficients variation of 3.7% and 4.5%, respectively.

3.3 Tear glucose monitoring with SCL-biosensor

After *in vitro* investigation, the SCL-biosensor was applied to monitoring of tear fluids. As already mentioned, the SCL-biosensor was just attached on the eyeball of the rabbit and the glucose level in steady tear fluids was monitored. Figure 7 shows the result of tear glucose monitoring by the SCL-biosensor. During this experiment, the rabbit was well settled. The output current of the SCL-biosensor was

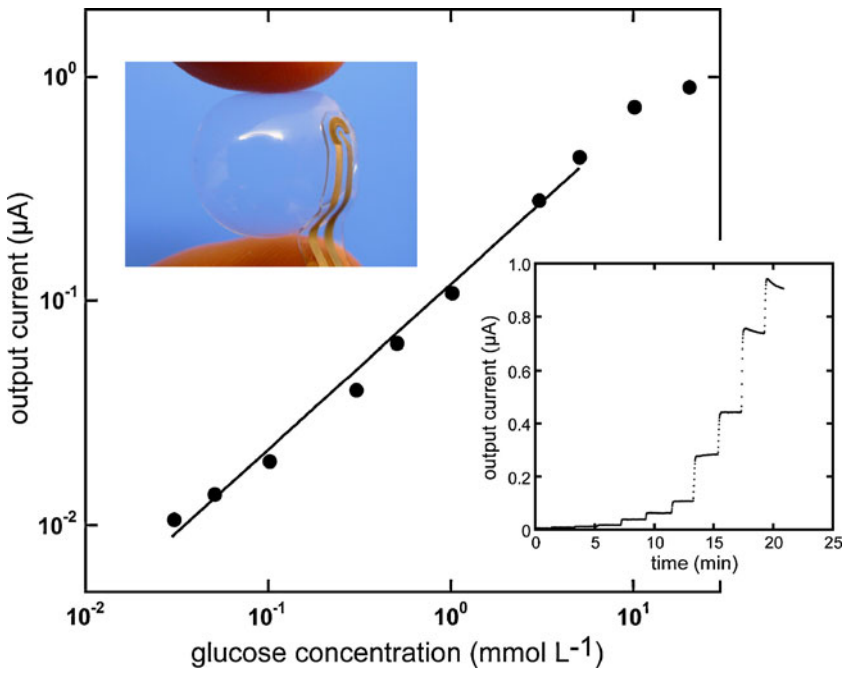

Fig. 5 Calibration curve of the SCL-biosenosr. The calibration range was 0.03–5.0 mmol·L^{-1} which included the normal tear glucose level of humans (0.14 mmol·L^{-1})

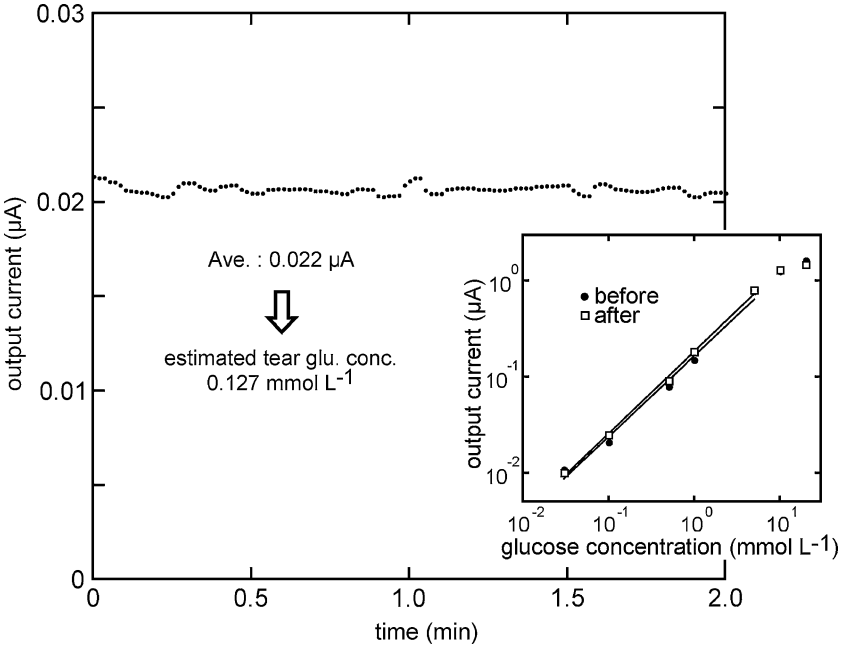

Fig. 7 Result of tear glucose monitoring with the SCL-biosensor. The small box shows the characteristics before- and after ocular biomonitoring. The output signal was successfully stable and the glucose level was estimated to 0.127 mmol·L^{-1}

approximately 0.022 μA and the value was almost stable as indicated. According to the current output, the tear glucose level of the rabbit was estimated to be 0.127 mmol·L^{-1}, which value was consistent with previous reports (Ridley 1930; Giardini and Roberts 1950; Daum and Hill 1982, 1984; Iguchi et al. 2007). The small box indicates the characteristics of the sensor before- and after- glucose monitoring at the rabbit's eye. There was no significant difference in both calibration ranges and sensitivities. This indicates that the SCL-biosensor was operational during the measurement on eye and was durable enough for the test. We also inspected the eye of the rabbit after experiment and no inflammation was observed around the eye. Thus, the biosensor was appropriate and stable for monitoring of steady tear fluids. In the present device, measurement results can be influenced by interferences such as ascorbic acid. This can be improved by applying a selective film at the sensing region in future work.

3.4 Assessment of tear turnover with SCL-biosensor

Based on the result of steady tear monitoring, the tear turnover that reflects tear secretion dynamics was assessed by ocular instillation of glucose solution. As shown in Fig. 8, the initial current was confirmed to be stable for 150 s, with the averaged value of 0.021 μA, which was almost same as above mentioned result. The basal concentration of tear glucose was calculated to be 0.121 mmol·L^{-1}. According to ocular instillation of standard glucose solution (0.5, 1.0, 1.5 mmol·L^{-1}, diluted with physiological saline), the signal rapidly increased and gradually decreased to initial value. At the fourth instillation, physiological sodium chloride solution was instilled. In this case, the output current first decreased to nearly zero and gradually increased up to initial value. As the glucose level increased, peak value of the output signal also increased.

Above results suggest that the output current reflects changes of glucose level on eye. The rapid change due to ocular instillation represents replacement of tear fluids by dropped solutions and the recovery curve to the initial current indicates dilution of the dropped solutions by tear secretion. The inset box of Fig. 8 shows a semi-log plot of the output signal (1.5 mmol·L^{-1}) and the regression curve derived from the following powerlaw equation:

$$\text{output current}(\mu\text{A}) = 0.247 \times 0.644^{t}(1.5\,\text{mmol}\cdot\text{L}^{-1})$$

where t is the time after instillation. The other curves (1.0, 0.5, 0 mmol·L^{-1}) can be also given as follows:

$$\text{output current}(\mu\text{A}) = 0.090 \times 0.729^{t}(0.5\,\text{mmol}\cdot\text{L}^{-1})$$
$$\text{output current}(\mu\text{A}) = 0.169 \times 0.631^{t}(1.0\,\text{mmol}\cdot\text{L}^{-1})$$
$$\text{output current}(\mu\text{A}) = 0.010 \times 1.187^{t}(\text{sodium chloride solution})$$

The correlation coefficients of above equations were 0.990, 0.953, 0.915, 0.900 for 1.5, 1.0, 0.5 mmol·L^{-1} and sodium chloride solution, respectively. Based on those equations, the tear turnover rates (% min^{-1}) were estimated (Table 1). As a result, the mean turnover rate was calculated to be 29.6%±8.42% min^{-1}. Previously, the tear turnover rate

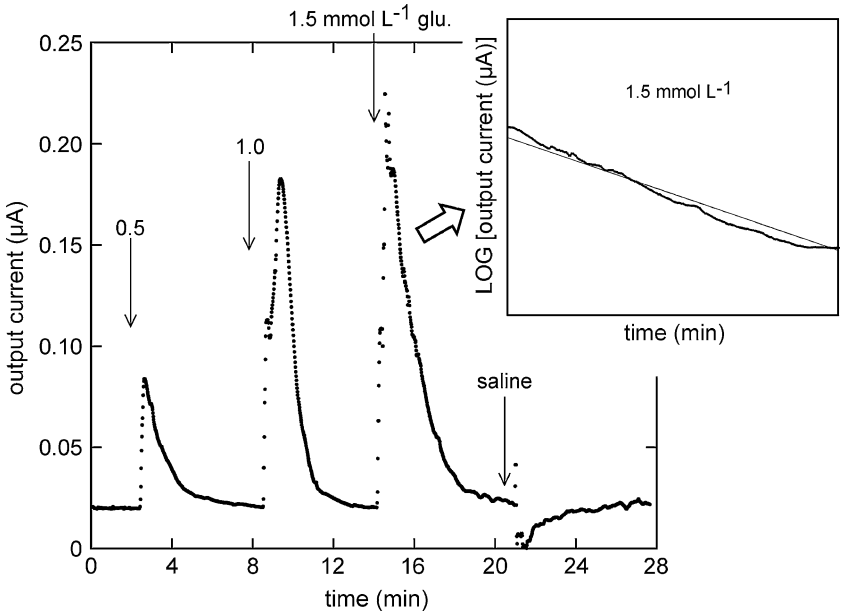

Fig. 8 Change of tear glucose level due to instillation of standard glucose. Three higher peaks indicates instillation of 0.5, 1.0 and 1.5 mmol·L^{-1} glucose, respectively. The inverse peak indicates dilution of tear glucose by instillation of physiological sodium chloride solution

of humans was reported to be approximately 40% min^{-1} (Mitsubayashi et al. 1993). There were difference between the result of animal test and the turnover rate of humans. The major reason is considered to be difference in the human turnover rates and the rabbit turnover rate. The turnover rate also varies by experimental conditions such as temperature, humidity, etc. Considering the estimated glucose levels calculated by above equations, the tear turnover was successfully assessed by the SCL-biosensor.

The SCL-biosensor was thus confirmed to be useful for monitoring of both static tear fluids and dynamics of tear components. This indicates that the SCL-biosensor is not only useful for tear glucose monitoring, but also useful for other tear contents by modifying the sensing region. Since PDMS is a flexible and workable polymer, the SCL-biosensor can be optimized to any surface of the human body. Although there are design challenges that need to be addressed such as power supply or communication techniques, the SCL-biosensor has demonstrated a possibility of 'ubiquitous biomonitoring'.

4 Conclusions

The novel SCL-biosensor for ocular biomonitoring was developed. Using microfabrication techniques for functional polymers, the flexible electrodes on which GOD was immobilized were successfully formed on the PDMS contact lens. The SCL-biosensor showed sufficient relationship for monitoring of tear glucose on eye. The calibration range was 0.03 to 5.0 mmol·L^{-1}, which included normal tear glucose level of humans (0.14 mmol·L^{-1}). Novel ocular biomonitoring with the SCL-biosensor was also carried out. The SCL-biosensor worn on the eye of the rabbit and the glucose levels in tear fluids were monitored *in situ*. The SCL-biosensor was confirmed to be useful both in the static state and the dynamic state. According to the result of animal test, the tear glucose level of rabbit was estimated to 0.12 mmol·L^{-1}. Also, the tear turnover rate was assessed using the SCL-biosensor. The rabbit's tear turnover rate due to secretion of fresh tears was 29.6±8.42% min^{-1}, which is slightly slower than the human quoted rate of 40% min^{-1}. The result indicated that SCL-biosensor is useful for

Table 1 Tear turnover rate estimated by the result of ocular biomonitoring with SCL-biosensor

dropped glu. (mmol·L^{-1})	turnover rate (% min^{-1})	estimated glu. (mmol·L^{-1})	accuracy (%)
0.5	27.1	0.494	98.8
1.0	36.9	0.992	99.2
1.5	35.5	1.490	99.3
0 (saline)	18.7	0.009	–
Ave.	29.6		99.1

advanced biomonitoring on eye. Since PDMS is a flexible and workable polymer, the SCL-biosensor can be optimized to any surface of the human body. It is expected to realize 'ubiquitous biomonitoring' by further studies such as communication techniques.

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