Extended Abstracts of the 2015 International Conference on Solid State Devices and Materials, Sapporo, 2015, pp382-383

Development of a Novel Device for Allergy Test Based on Semiconductor Principle

Haoyue Yang[1], Akiko Saito[1], Taira Kajisa[2], Yuki Yanase[3] and Toshiya Sakata[1]

[1] School of Engineering, Univ. of Tokyo
7-3-1Hongo, Bunkyo-ku, Tokyo 113-8656, Japan
[2] PROVIGATE Inc.
Entrepreneur Plaza, Univ. of Tokyo 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
[3] Hiroshima Univ., Department of Dermatology, Integrated Health Sciences, Institute of Biomedical and Health Sciences, 1-2-3, Kasumi, Minami-ku, Hiroshima 734-8551, Japan
Phone: +81-3-5841-1842, E-mail: sakata@biofet.t.u-tokyo.ac.jp

Abstract

Allergy is a widely infected disease which is induced by various allergen sources. At present, the methods of allergy detection are still less of accuracy. To find a quicker and more accurate way to detect allergy, this research aims on making a new device based on semiconductor principle. In this research, we consider histamine as the mainly signal source secreted when allergy reaction happens. The histamine can be detected as the charge change based on dissociation using a field effect transistor (FET), and moreover modifying molecular imprinted polymer (MIP) film on the gate surface of the FET. Thus, the MIP film would help distinguish histamine from other chemicals caused by allergy reaction. In this study, we would get a new concept for practical use by use of the FET, which could detect histamine from allergy reaction precisely.

1. Introduction

Allergy is one of the closest diseases at the present day. Almost half of the population are affected with some types of allergy in Japan, and the number of patients are increasing throughout the world. There are still a lot of problems, which remain unexplained on its mechanism and strong demands for approach to treatment. That is, the present diagnosis for allergy still requires not only a lot of time but also collection of large amounts of blood from patients. Diagnostic test kit lacks precision because it assesses only the presence of antibody using enzyme. Therefore, easy-to-use and precise evaluation approaches are expected in clinical test and drug discovery. In this study, we focused on type I reaction, the immediate allergic reaction such as food allergy and pollen allergy. We investigated the cellular activities based on allergic antigen-antibody reaction at mast cells in an easy, quantitative, and label-free way by use of semiconductor-based biosensor.

2. Methods

2.1. Materials

In the electrical measurement, we used N channel depression type ion sensitive filed effect transistor (ISFET) with $Ta_2O_5/Si_3N_4/SiO_2$ as the gate insulator.

2.2. MIP film on FET

To make MIP film on the gate of FET sensor, monomers containing histamine were copolymerized by radical polymerization. The composition of MIP film was shown as the Table.1.The monomer solution was degassed with N_2 bubbling for 10 minutes, and then the 10 μL of gel was spread on the FET surface by covering with PET film. After it was polymerized under UV light (365 nm) for 10 minutes, we put the MIP film on the gate electrode into methanol for 24 hours, a mixture of acetic acid/acetonitrile (1:1) for 24 hours, and methanol again for 12 hours to remove histamine in the polymerized MIP film.

Table 1 The composition of monomer solution for polymerization of MIP film.

Monomer	Volume
Acrylic acid	0.05 g
Ethylene Glycol dimethacrylate	0.40 g
Histamine	0.01 g
Dimethyl Sulfoxide	Add up to 1.00 g
2,2'-Azobis(isobutyronitrile)	0.01g

2.3. Cell experiments

In this study, we used mast cells, Rat basophilic leukemia (RBL), which both have been commonly used in allergy studies. Firstly, RBL cells of 1×10^5/mL were incubated on the gate insulator of FET in the culture medium (RPMI+10%FBS+1%PS/SM) including IgE (40ng) overnight. Then, IgE is adhered at RBL cell membrane. On the next day, the cell culture medium was exchanged before measurement. After keeping the device in the CO_2 incubator for the electrical stability, we added antigen, Ag (DNP-HAS) of different concentrations (100ng, 50ng, 10ng, 1ng) included in the culture medium on the IgE-RBL-based FET. Moreover, β-hexosaminidase, which is widely used for evaluating histamine, was fluorescently labeled in the medium to investigate quantitatively histamine secretion from RBL following the antigen-antibody reaction at the cell membrane.

3. Results

3.1. Electrical characteristics of FET for histamine detection

As the measurement depending on the positive charge of histamine, we first measured to check how the concentration of histamine works on ISFET device. The concentration of histamine was varied in the range of 1×10^{-4} to 1 mM to check the properties on the ISFET device by the semiconductor parameter analyzer. (Agilent) (Fig. 1). Actually, the histamine could be detected as the change of pH by use of FET device because of its basic property.

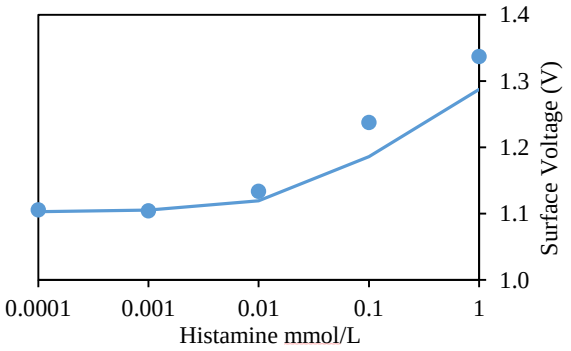

Fig. 1 The effect on pH of the solution depending on histamine concentration using ion-sensitive FET (ISFET).

Regarding the electrical characteristics of the FET with MIP film, we used real-time monitoring system to detect the signal when adding histamine solution with different concentrations (Fig. 2). In this case, histamine could be selectively detected at 1 mmol/L, but the detection sensitivity should be improved in the future.

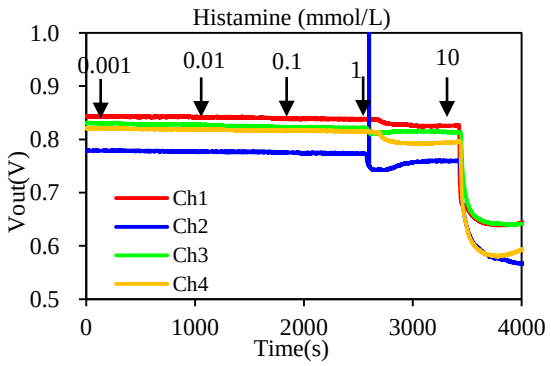

Fig. 2 The time course for gate surface potential changes of MIP film gated FET in time of histamine addition.

3.2. Monitoring of allergy reaction using IgE-RBL-based FET

Moreover, we added the allergen solution on the IgE-RBL-based FET. As a result of that, the gate surface potential of IgE-RBL-based FET decreased continuously and specifically after introduction of antigen, as shown in Fig. 3. This result indicates that the electrical activity of RBL was monitored on the basis of pH changes at the cell/gate interface using the IgE-RBL-based FET, because histamine is basic compound. From this research, it became clear that the allergy reaction could be evaluated by principle of semiconductor. Moreover, we are investigating the possibility of allergy detection using the FET with MIP film now.

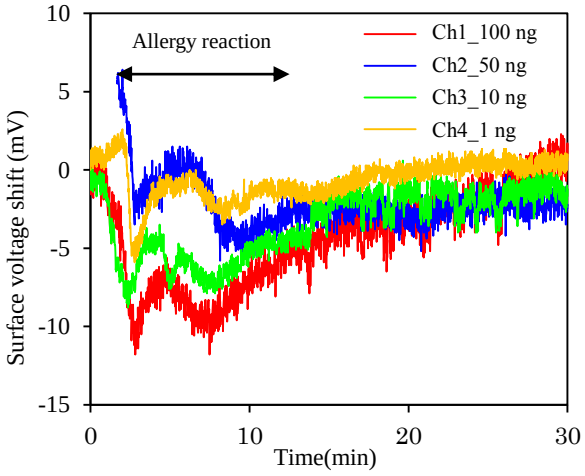

Fig. 3 Change of respiration activity of RBL cell by ISFET when the each amount of allergen was added.

4. Conclusion

In this study, we have clarified the detection of histamine using the FET biosensor. In particular, the allergy response for addition of antigen was monitored using the IgE-RBL-based FET. This method is available for the label-free detection of allergy response, particularly the low molecular weight antigen such as histamine.

Additionally, the FET with MIP film may enhance the selectivity of histamine detection, but this result is now under consideration and we need to discuss in the conference.

References

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[2] M. Peeters *et al. Anal. Chem.* 2013, **85** (2013) 1475.