Extended-gate-type Organic Field-effect Transistors for the Detection of Potential Psychological Stress Markers

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Organic field-effect transistors (OFETs) are promising electronic devices owing to their attractive features such as a low cost, solution processability, and ease of use. In this regard, we have fabricated extended-gate-type OFETs functionalized with natural molecular recognition materials as biosensors for the detection of biomarkers. Toward the development of a potential psychological stress monitoring method based on OFETs, we have successfully detected three types of psychological stress biomarkers: chromogranin A (CgA), immunoglobulin A (IgA), and nitrate (NO_3^-). The OFETs reproducibly respond to the biomarkers, demonstrating their ability to detect potential psychological stress in individuals. Notably, the detectability of the OFETs makes them suitable for the analyses of real samples. Thus, we strongly believe that the developed system based on extended-gate-type OFETs could be employed as a sensor platform for biosensor applications in the field of healthcare.

1. Introduction

Psychological stress is caused by various stressors that disturb internal processes for the functioning of living organisms. The peripheral and central nervous systems react to this psychological stress through complex mechanisms such as physiological or behavioral adaptation to restore homeostasis and to prevent excessive responses.[1] Short-term psychological stress boosts the immune system, while chronic psychological stress causes the overdrive of multiple systems.[2] The latter stress can lead to suppression of the immune system,[3] atherosclerosis (plaque buildup in arteries), increased risk of diabetes mellitus,[3] or abnormal secretion of gastric acid, which can cause peptic ulcers.[3,4] Psychological stress can also lead to epigenetic changes such as methylation of cytosine nucleobases[5] or amino acid residues of histones (i.e., lysine and arginine).[6] Although the DNA sequence remains unchanged, the methylated nucleobases and histones lead to gene silencing. As a consequence, abnormal protein production can affect

behavioral and physiological traits. Another serious problem of psychological stress is that it affects the economy. In the U.K., 13.4 million working days were lost by 1.3% of the workforce who were negatively influenced as a consequence of psychological stress such as depression and anxiety.[7]

Saliva, which is also called "the mirror of the body",[8,9] is already used in many studies for measuring psychological stress biomarkers because it can be collected easily and noninvasively.[10,11] In comparison with blood and urine, saliva has many advantages as a real sample,[12] because it can be used as responses to acute[13] and long-term mental stresses.[14] This body fluid is derived from the ultrafiltration of blood[15] and is secreted by the glandula sublinguallis, the glandula submandibularis, and the parotid gland. Even though many markers are also present in blood, saliva is preferred for noninvasive diagnoses because it shows the highest variability in concentration due to acute psychological stress. Many different biomarkers related to psychological stress such as α-amylase,[16] cortisol,[10] and cortisone hormones[17] can be investigated using saliva. In addition, saliva has the advantage for laboratory technicians and clinical staff because they are not exposed to pathogens.

To realize simple methods for psychological stress detection, we believe that organic field-effect transistors (OFETs) are among the most promising electronic devices. OFETs have several attractive features including light weight, flexibility, durability, solution processability, and compact integration.[18–23] Furthermore, OFET-based devices can directly read out molecular recognition phenomena of receptors as electrical signals, suggesting that the devices can be employed for psychological stress detection. To date, several psychological stress biomarkers have been successfully detected using OFET-based sensors.[24–27] In this Perspective, we summarize our recent progress in detecting psychological stress biomarkers based on extended-gate-type OFETs. The detectability of three types of psychological stress biomarkers [i.e., chromogranin A (CgA),[28] immunoglobulin A (IgA),[29] and nitrate (NO_3^-)[30]] using OFETs is reported.

2. Extended-gate-type OFETs as Sensing Platform for Biomarkers

An OFET consists of two distinct parts, the drive part (i.e., the OFET device) and the detection part (i.e., the functionalized extended gate) as shown in Fig. 1.[31,32] The extended gate can be functionalized by immunoproteins or enzymes for the corresponding analytes. By employing a floating-gate electrode structure, the electrical properties of the OFET vary upon the addition of an analyte on the extended gate.[26,27] The changes in the electrical characteristics of the OFET stemming from the molecular recognition phenomena can be quantified using Eq. (1):[33]

$$I_{DS} = \left(\frac{W}{2L}\right)\mu C(V_{GS} - V_{TH})^2 , \tag{1}$$

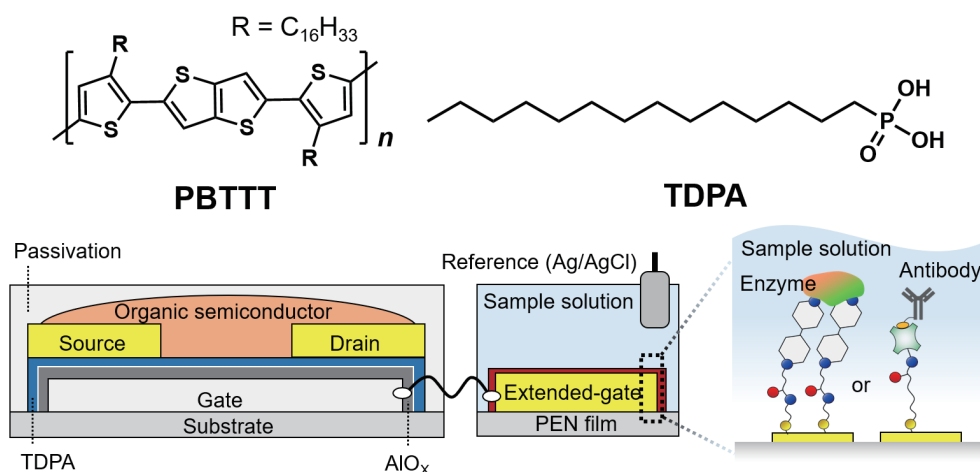where I_{DS} is the measured drain current, W and L are respectively the width and length of the

Fig. 1.   (Color online) Schematic illustration of the extended-gate-type OFET.

channel, μ is the field-effect mobility, C is the capacitance of the dielectric layer, V_{GS} is the voltage applied through the gate electrode, and V_{TH} is the threshold voltage.

With the accumulation of positively or negatively charged analytes on the electrode, electrical charge (Q) and V_{TH} correlate according to the following equation:

$$\Delta V_{TH} = \frac{\Delta Q}{C}. \tag{2}$$

Using this principle, we have successfully detected small ionic species and biomacromolecules. More information on OFET-based chemical sensor devices has been given in recent review articles.[24–27]

To operate at low voltages (<|3 V|) and prevent the electrical degradation of the developed OFET, the design and optimization of the drive part are necessary. One way to achieve this is to improve the capacitance of the dielectric layer.[34] To enhance the capacitance, we first deposited an aluminum gate electrode, which was oxidized by an oxygen plasma treatment involving reactive ion etching (RIE). Then, we employed a self-assembled monolayer (SAM) composed of tetradecylphosphonic acid (TDPA)[35] as a dielectric bilayer for the gate electrode to increase the carrier concentration in the channel. Source and drain electrodes were then deposited by thermal vacuum deposition on the dielectric layer. One of the critical factors determining the properties of OFETs is the selection of the material for the organic semiconductor layer. Poly{2,5-bis(3-hexadecylthiophene-2-yl)thieno[3,2-*b*]}thiophene (PBTTT) is frequently used as the semiconductor material owing to its atmospheric stability and uniform electrical properties.[36] PBTTT was drop-casted and baked, followed by the passivation of the semiconductor layer using Cytop^TM (CTL-809M in CT-Solv 180). The extended gate, which is the detection part of the developed device, was obtained after Au deposition by thermal vacuum deposition on a polyethylene naphthalate (PEN) film. The extended gate can be subsequently functionalized by recognition materials to detect analytes.

To evaluate the properties of the OFET, we obtained the initial transfer and output curves by measurement. The source electrode was connected to the ground, and then a sweep voltage was applied to the drain electrode. The gate voltage was applied through an Ag/AgCl reference electrode.[37] The OFET presented reproducible properties without any hysteresis after repeated measurements, demonstrating that it can be used as a biosensor.

3. Low-voltage-operable Extended-gate-type OFET Used as a Psychological Stress Marker Sensor

3.1 Detection of CgA

Chromogranin A (CgA; molecular weight = 48 kDa; made of 439 amino acid residues)[38,39] is an important soluble[38,40] acidic glycoprotein,[41] existing in the secretory granules of many endocrine and neuroendocrine cells. When an individual is exposed to a stressor, psychological stress can be observed by an increase in the CgA level. The benefits of CgA are its independence of the salivary flow rate and temperature, the short time lag between the stimulation and the maximum CgA level,[10] and its durability.[42] Importantly, salivary CgA is not bound to other proteins, in contrast to blood samples,[38] and remains for a long time (up to 60 min) in saliva after stimulation.[43] Thus, CgA is a sensitive biomarker for psychophysical stress,[44] such as exposure to situations inducing anxiety and depressive moods.[45] In addition, serum CgA is an early biomarker for the monitoring of endocrine tumors,[46] hypertensive heart failure,[38] and neurodegenerative/neuropsychiatric diseases (e.g., amyotrophic lateral sclerosis (ALS),[10] Alzheimer's disease,[38] and Parkinson's disease.[47] In other words, CgA is important for diagnosing chronic psychological stress and malfunction of the sympathetic nervous system. Although CgA can be detected by conventional biochemical methods such as immunoassay,[48] they require relatively complicated treatments of samples (i.e., labeling prior to detection) and large equipment. Therefore, we developed an OFET-based biosensor, the extended gate of which was functionalized by an anti-CgA antibody [Fig. 2(a)].[28] The anti-CgA antibody was immobilized on the surface of the extended gate by avidin–biotin binding. The OFET exhibited changes in the transfer characteristics depending on the concentration of CgA in phosphate-buffered saline (PBS) containing 0.1 wt% human serum albumin (HSA). The observed changes stemmed from the changes in the nature of the charged surface of the extended gate, which leads to a positive shift of the transfer characteristics when the analyte is bound to the antibody on the extended-gate-type electrode. The limit of detection (LoD) and the limit of quantification (LoQ) are 0.31 $\mu g \cdot mL^{-1}$ (~6 nM) and 1.0 $\mu g \cdot mL^{-1}$ (~19 nM), respectively. These tests were also performed in artificial saliva (Saliveht®, Teijin Pharma), in which the OFET device showed LoD and LoQ values of 0.11 $\mu g \cdot mL^{-1}$ (~2 mM) and 0.38 $\mu g \cdot mL^{-1}$ (~7 nM), respectively. Note that the developed OFET device needs an assay time of ca. 0.5 h, which is approximately one-fifth of that of the conventional ELISA method (ca. 2.5 h). Furthermore, the sensor showed only small cross-reactive responses, as evident from a selectivity study with α-amylase, IgA, and myeroperoxidase, implying the potential applicability of the OFET device for rapid CgA detection in a mixture [Fig. 2(c)].
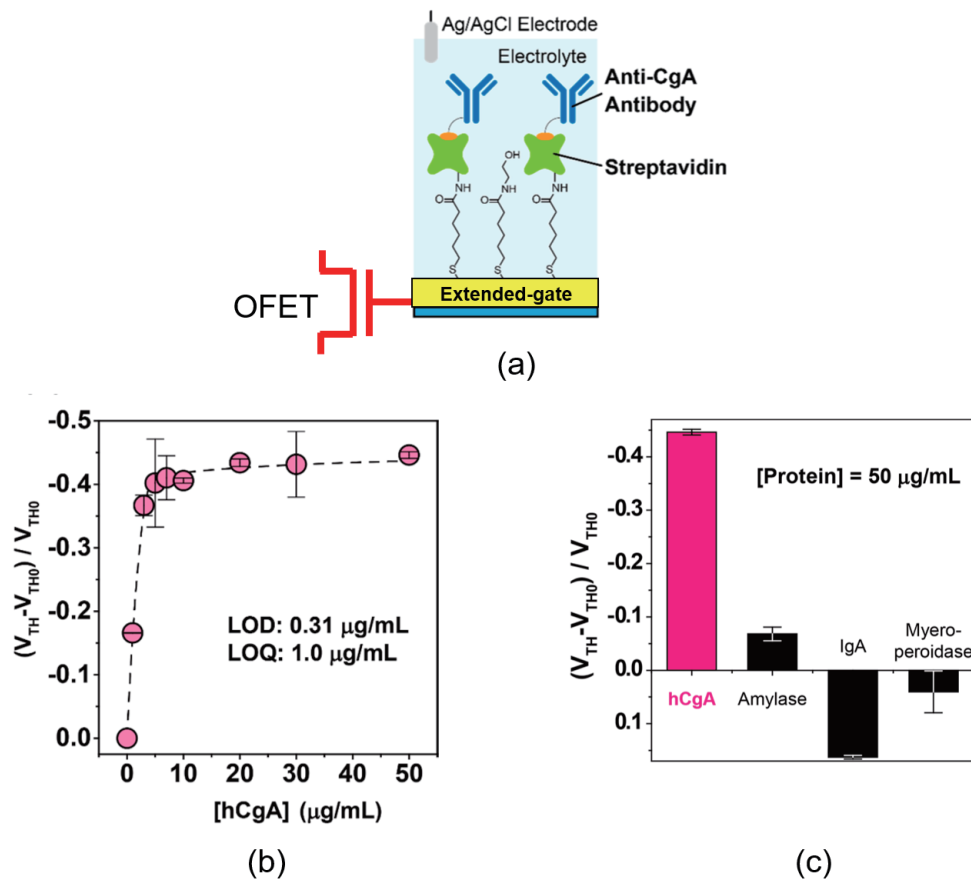
Fig. 2. (Color online) (a) Schematic illustration of the OFET functionalized by anti-CgA antibody. (b) Transfer characteristics (I_{DS}–V_{GS}) of the OFET upon the addition of label-free human CgA in a PBS solution with 0.1 wt% HSA. [CgA] = 0–50 µg·mL^{-1}. (c) Selectivity study for human CgA (hCgA) Reprinted with permission from Ref. 28. Licensed by Creative Commons Attribution 4.0 International (CC BY 4.0).

3.2 Detection of salivary IgA

IgA can be found in blood serum and in mucous secretion (i.e., saliva and tears). Several IgA can be found in blood serum and in mucous secretions (i.e., saliva and tears). Several studies have shown that the concentration of secretory IgA in saliva is altered in the case of infection and psychological stress,[10,49–51] suggesting that the determination of the IgA level is crucial to manage such risks. To this end, we demonstrated the ability of an OFET-based sensor to detect IgA.[29] We prepared a simulated saliva solution containing several interfering proteins (α-amylase, lysozyme, lactoferrin, and myeloperoxidase). To comply with real biological conditions, the interferants were present at practical concentrations ([α-amylase] = 0.4 µg·mL^{-1}, [lysozyme] = 0.4 µg·mL^{-1}, [lactoferrin] = 1.0 µg·mL^{-1}, and [myeloperoxidase] = 3.6 µg·mL^{-1}). To detect IgA with an OFET-based device in saliva, a biotin-conjugated IgA antibody was immobilized on the extended-gate-type electrode as shown in Fig. 3(a). Because IgA is a dimeric biomolecule (molecular weight = 162 kDa),[52] the distance between the Au electrode and the anti-IgA
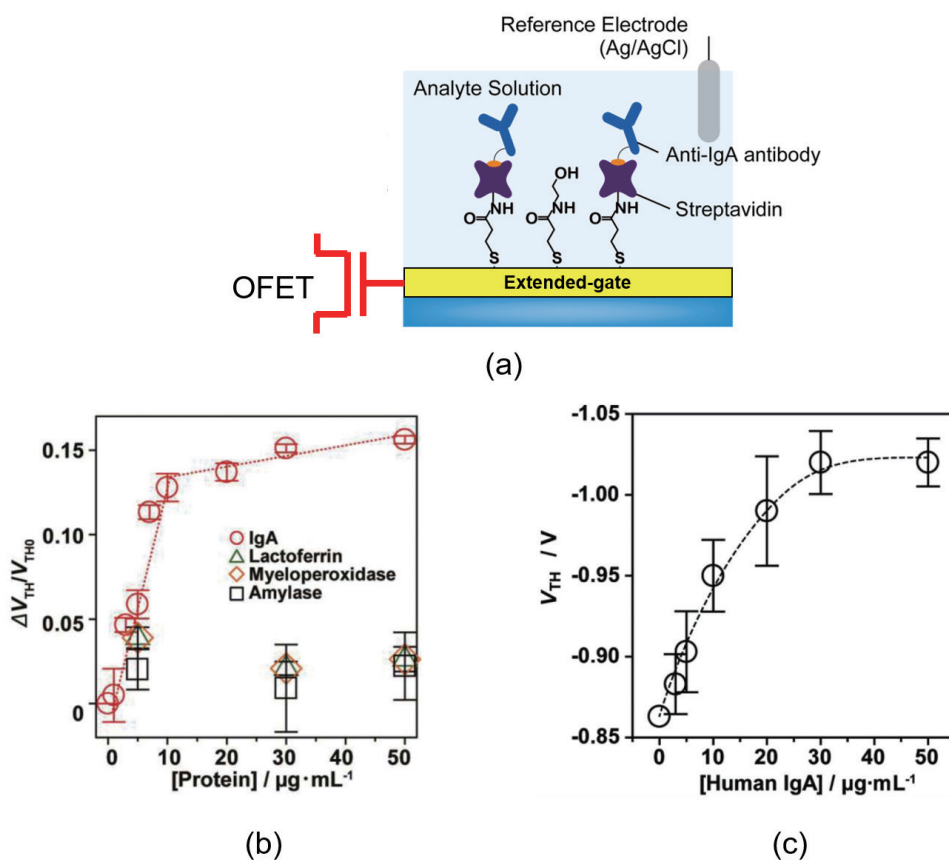
Fig. 3.　(Color online) (a) Schematic illustration of the extended-gate-type OFET functionalized with anti-IgA antibody. (b) Changes in the V_{TH} value of the OFET device upon the addition of IgA (circles), lactoferrin (triangles), myeloperoxidase (diamonds), or α-amylase (squares) in a PBS solution with 0.1 %wt HSA. [Proteins] = 0–50 µg·mL^{-1}. (c) Changes in the V_{TH} value of the OFET in the presence of various concentrations of IgA in a PBS solution containing α-amylase (0.4 µg·mL^{-1}), lactoferrin (1.0 µg·mL^{-1}), lysozyme (0.4 µg·mL^{-1}), and myeloperoxidase (3.6 µg·mL^{-1}). [IgA] = 0–50 µg·mL^{-1}. Reprinted with permission from Ref. 29. Copyright 2015 Japan Society for Analytical Chemistry.

antibody was shortened to similar to that for CgA to avoid adverse effects arising from Debye shielding [Figs. 2(a) and 3(a)].[53] Figure 3(b) shows the relationship between the concentration of the analytes and the V_{TH} value. The titration was performed in a PBS solution containing 0.1 wt% HSA, where the analyte concentration ranged between 0 and 50 µg·mL^{-1}. The OFET device provided a higher response to IgA than to the interfering species [Fig. 3(b)]. The LoD value was calculated as 2.1 µg·mL^{-1}, while saturation of the response was observed above a concentration of 10 µg·mL^{-1}. Furthermore, we realized the detection of human IgA in simulated saliva containing the above-mentioned interferants [Fig. 3(c)]. We also observed the change in V_{TH} with increasing IgA concentration. The titration isotherm showed a linear response of the OFET to IgA in the concentration range from 0 to 20 µg·mL^{-1}. Because the concentration of salivary IgA is higher than 40 µg·mL^{-1} under healthy conditions, the developed OFET could be employed for monitoring the decrease in the IgA concentration under psychological stress.[54]

3.3   OFET-based sensor for the detection of NO_3^- in human saliva

Despite being used as a food additive and found in drinking water, NO_3^- can cause several diseases such as bladder cancer,[55] stomach cancer,[56] and infant methemoglobinemia[57] in the case of overingestion. Moreover, numerous studies have shown that the NO_3^- concentration is closely related to the physical and psychological stresses of humans.[58,59] NO_3^- detection techniques based on colorimetric[60] and fluorometric spectroscopy[61] and inorganic field-effect transistors[62,63] have been widely studied. On the other hand, NO_3^- detection by OFETs would enable the realization of low-cost and flexible organic sensor devices for daily monitoring of psychological stress. The mechanism of NO_3^- detection of the proposed OFET device is based on the reduction of NO_3^- by a nitrate reductase with a bipyridinium derivative (BP^{2+}) as an electron mediator [Fig. 4(a)]. The BP is converted to BP cation radicals through one-electron reduction by $Na_2S_2O_4$. The reduced form of BP is a source of electrons for the enzymatic
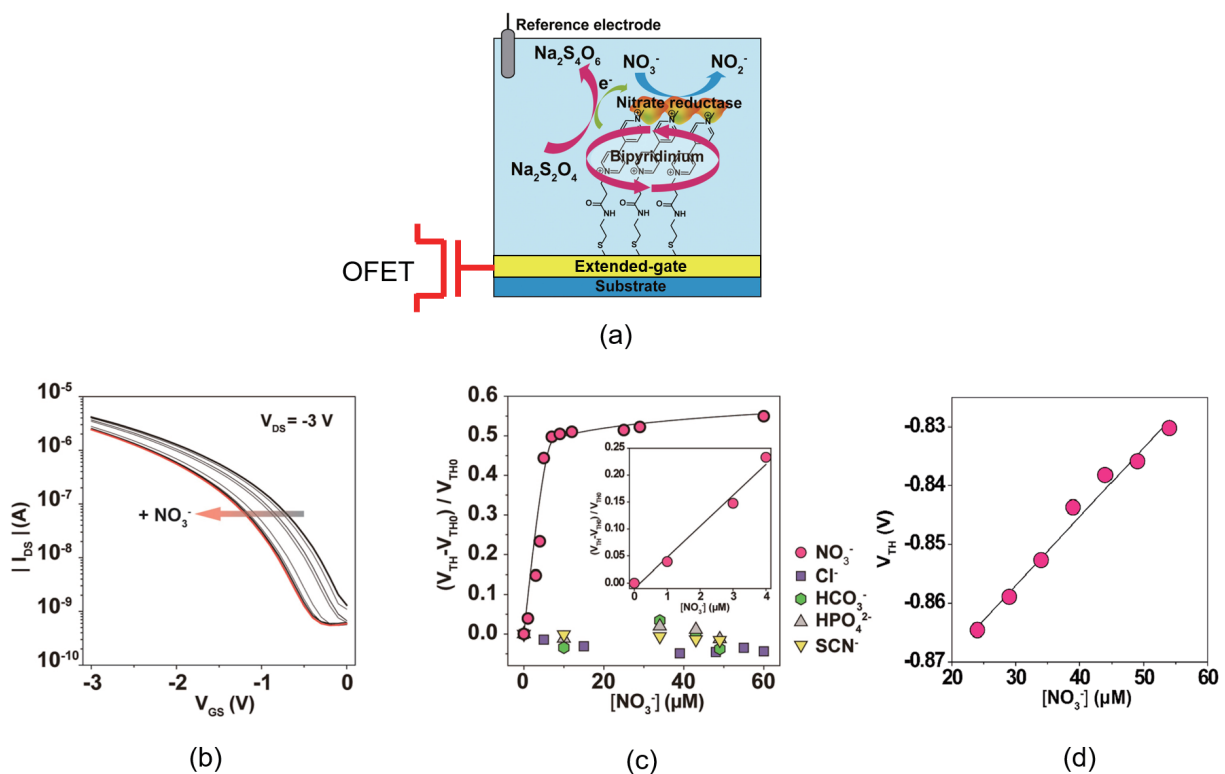

Fig. 4.   (Color online) (a) Schematic illustration of the extended-gate-type OFET functionalized by nitrate reductase and a bipyridinium derivative for NO_3^- detection. (b) Transfer characteristics of the OFET upon titration with NO_3^- in a HEPES buffer solution (10 mM) at pH 7.4 at room temperature. $[NO_3^-]$ = 0–60 μM. (c) Changes in the V_{TH} value of the OFET upon the addition of NO_3^- (circles), Cl^- (squares), HCO_3^- (hexagons), HPO_4^{2-} (triangles), and SCN^- (down-pointing triangles) at various concentrations in a HEPES buffer solution (10 mM) at pH 7.4 at room temperature. [anions] = 0–60 μM. (d) Changes in the V_{TH} value of the OFET in the presence of different concentrations of NO_3^- in diluted human saliva. $[NO_3^-]$ = 24–54 μM. $R^2 > 0.98$. Reprinted with permission from Ref. 30. Copyright 2016 Elsevier Inc.

reduction of NO_3^- [Fig. 4(a)]. After obtaining evidence that the extended-gate-type electrode was functionalized by the enzyme, we first performed NO_3^- titration in a HEPES buffer solution in a concentration range of 0 to 60 μM. Consequently, the transfer characteristics of the OFET showed a negative shift with increasing NO_3^- concentration [Fig. 4(b)]. The 90% response time of the OFET to NO_3^- was within 20 s, which is comparable to that of an inorganic FET-based NO_3^- sensor.[62] The absence of $Na_2S_2O_4$ did not cause changes in the OFET characteristics, demonstrating the proof of concept. Subsequently, we investigated the selectivity of the device for NO_3^- using four other types of anionic species (i.e., Cl^-, HCO_3^-, HPO_4^{2-}, and SCN^-). Figure 4(b) shows the change in V_{TH} as a function of the anion concentrations in the HEPES buffer solution. No responses were observed with the four other types of anionic species. From the titration isotherm in the linear range (~4 μM), the LoD value for NO_3^- was estimated as 45 ppb. Finally, we detected NO_3^- in diluted human saliva [Fig. 4(c)]. Although human saliva contains a variety of organic and inorganic ions and biomacromolecules,[64] the V_{TH} value of the OFET device changed with the NO_3^- concentration. The recovery for the standard NO_3^- solution added to the saliva samples was estimated to be 97.4 ± 1.8%, confirming that the developed OFET-based sensor could be employed to detect NO_3^- in a real sample.

4.   Conclusions

In this Perspective, we summarized the development of extended-gate-type OFETs functionalized by antibodies or enzymes as biosensors for the detection of potential psychological stress biomarkers (IgA, CgA, and NO_3^-). The electrical properties of the OFET changed with the recognition of the analytes by the immune interaction or the enzymatic reaction for the analyte. Notably, the proposed biosensor allowed the detection of an analyte in mixtures, and may offer rapid analyses compared with the conventional immunoassays (i.e., ELISA). To accelerate the practical application of OFET-based sensor devices for psychological stress monitoring, we need to address the following points. (1) The chemical and thermal stabilities of the molecular recognition materials on the OFET need to be improved. In this regard, we have recently developed artificial molecular recognition materials for the detection of phosphoprotein,[27,65] serum albumin,[27,66] and lactate.[67] Because these artificial materials have greater stability than natural materials, artificial materials for psychological stress markers also need to be developed toward future applications. (2) Detection accuracy should be considered from the viewpoint of stress diagnosis. Although OFET-based sensors show selectivity for target analytes due to the molecular recognition materials on the extended gate, pattern recognition[68] combined with multiple measurements with the OFET sensor array would be effective to enhance the detection accuracy.

In our daily lives, simple, low-cost, and easy-to-use sensor devices to help manage daily stress are desirable. To this end, the proposed OFET devices functionalized by biomaterials are expected to pave the way for such sensor devices. Hence, we believe that our results will be useful for the future realization of OFET-based biosensors for healthcare applications.

Acknowledgments

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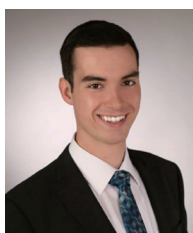
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