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Monitoring of histamine-induced calcium channel activity of a single cell using semiconducting carbon nanotube transistors

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Abstract. A method using transistors based on semiconducting carbon nanotubes were developed for the real-time monitoring of the electrophysiological responses of individual cells to histamine stimulation. Transistors with one or three floating electrodes were utilized to evaluate histamine-induced Ca^{2+} influx into Hela cells via recording the conductance changes of the transistors. The Hela cells were directly cultured on the semiconducting carbon nanotube junction area of the transistors. The Ca^{2+} influx resulted from the activation of histamine H1 receptors embedded on the cell membranes by histamine, which generated a temporary negative potential at the gap between the cell and the transistor. The addition of histamine therefore increased the conductance of the *p*-type transistors. Moreover, the antihistamine effects of chlorpheniramine on histamine-induced Ca^{2+} influx were also investigated using a transistor including three floating electrodes. The data showed that chlorpheniramine partial reduced the increase in the conductance of the transistor during the addition of histamine, indicating the antihistamine activity of chlorpheniramine. Especially, only a single transistor was applied to repeat the measurements of the responses of multiple Hela cells pretreated with chlorpheniramine to histamine stimulation. This allows us to acquire data without being suffered from device-to-device variations, implying that our method would be a simple yet powerful one for applications of nanoscale biosensors for electrophysiological studies.

Keywords: histamine, Ca^{2+} channel, single cell, semiconducting carbon nanotube.

Classification numbers: 2.2.2, 4.1.3.

1. INTRODUCTION

Calcium channels play vital electrophysiological roles in both excited and non-excited cell lines, which allows calcium ions (Ca^{2+}) to pass through plasma membranes. The electrophysiological activities of calcium channels are involved in various cellular functions as

well as cell growth [1 - 3]. Previous works reported that Ca^{2+} influx through membrane calcium channels could be caused by the stimulation of histamine H1 receptors on cell membranes using agonists [4, 5]. For example, when Hela cells are exposed to histamine, the cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) of the Hela cells increases rapidly. Since the histamine H1 receptors embedded within the plasma membranes of the Hela cells bind to histamine, some second messengers are produced to trigger Ca^{2+} influx through Ca^{2+} channels on the cell membranes [5, 6].

Ca^{2+} influx can be monitored by various methods such as dye labelling techniques, isotope tracer studies, and Patch-Clamp techniques. These methods have high sensitivity, high signal-to-noise ratio and quick response time. However, there are still some drawbacks such as time-consuming preparation, the nonlinearity relation between Ca^{2+} concentrations and light signals, complicated and invasive operation [7, 8]. Recently, the development of semiconducting material science has facilitated the application of semiconducting sensors to electrophysiological studies including Ca^{2+} flux measurement [9-11]. Among them, sensors based on carbon nanotubes (CNTs) have been reported to exhibit a distinct potential for monitoring the activity of ion channels [12, 13]. Unlike other semiconductor materials, the atomic layer structures of CNTs generate the unique electrical characteristics of CNTs, which brings many outstanding advantages of CNT sensors. For example, CNT sensors possess high sensitivity, quick response, free labeling, simple operation, and biocompatibility, which are necessary for biosensors [14]. In our previous work, we succeeded in using a CNT field-effect transistor to evaluate the effects of an antihistamine on the Ca^{2+} release from intracellular stores of floating Hela cells, which did not grow directly on a surface [11]. Since the cells did not spread on the surface, it resulted in the unnatural morphology of the cells. The modification in the cell morphology as well as plasma membrane structures may affect the activities of membrane proteins including ion channels [15]. Therefore, adherent cells should be naturally spread on a surface in order to properly estimate the activities of ion channels embedded on the cell plasma membrane.

Herein, a versatile method using semiconducting carbon nanotube (SCN) transistors is reported to monitor the activity of Ca^{2+} channels under the stimulation of histamine. In this work, Hela cells were first cultured on the floating electrode areas of SCN transistors for the monitoring of its electrophysiological responses to histamine. Since the Hela cells were naturally spread across the transistor surface, the morphology of the cells and the properties of membrane proteins were conserved. Therefore, the data obtained from this work could be used to compare with those from other works using conventional methods. These responses were evaluated by the conductance changes of SCN transistors including one and three floating electrodes, which were attributed to histamine-induced Ca^{2+} influx through ion channels embedded on a Hela cell membrane. The method was also utilized to monitor the electrophysiological responses of Hela cells pretreated with chlorpheniramine, an antihistamine, to histamine stimulation. The obtained results showed the reduction of Ca^{2+} influx into the cells, which was caused by the partial blocking of histamine H1 receptors by chlorpheniramine. Significantly, measured cells could be replaced with new cells for other measurements while using the same SCN transistor, enabling evaluation without errors from device-to-device variations. Moreover, these results indicated that the growth of cells on the sensor surface did not greatly affect the electrical characteristics of the SCN sensors, implying the high stability of CNT sensors. Importantly, this work should open up a promising approach to various biophysical studies at the single cell level.

2. MATERIALS AND METHODS

2.1. Materials

Semiconducting single-walled carbon nanotubes (ssCNTs), histamine, chlorphenamine, and other chemical reagents were purchased from Sigma-Aldrich and used as received. The ssCNTs had a diameter of 0.7 – 1.1 nm and a length of 300 – 2300 nm.

Hela cells were provided by the University of Science and Technology of Hanoi – USTH (Viet Nam). The Hela cells were grown in Dulbecco's Modified Eagle Medium (DMEM) media supplemented with 10 % v/v fetal bovine serum, 2 mM L-glutamine, 100 U/mL penicillin, and 100 µg/mL streptomycin at 37 ℃ in the atmosphere of 5 % CO_2.

2.2. Fabrication of SCN sensors

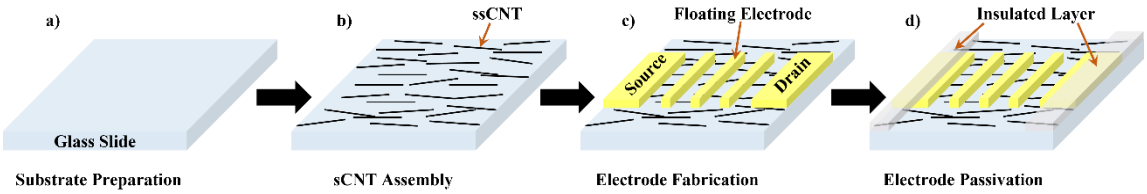

Figure 1. Schematic diagram depicting the experimental procedures of an SCN transistor fabrication. (a) Preparation of a clean glass substrate; (b) Absorption of ssCNTs on the glass surface; (c) Fabrication of metal electrodes including source, drain and floating electrodes; (d) Aluminum oxide isolation of the source and drain electrodes. The drawings are not for scaling.

In this work, SCN transistors were fabricated via conventional photolithography processes as reported in previous works (Figure 1) [11, 13]. Firstly, a substrate surface was prepared by soaking glass slides into a piranha solution and then cleaning with acetone and ethanol (Figure 1a). Subsequently, the ssCNT suspension in 1,2−dichlorobenzene was dropped onto the substrate while the glass slide was being spun to make a matrix of aligned ssCNTs (Figure 1b). After that, a palladium (Pd) layer (10 nm in thickness) and a gold (Au) layer (30 nm in thickness) were deposited on the CNT matrix to fabricate source, drain, and floating electrodes (Figure 1c). The electrode formation was performed using a thermal evaporator and liftoff processes. Finally, the SCN transistor surface was passivated by an aluminum oxide layer with a thickness of 100 nm except a floating electrode area (Figure 1d). The passivation was carried out using an atomic layer deposition system and an etching technique.

2.3. Measurements of the electrophysiological activity of a single cell

Figure 2 illustrates an experimental procedure for the monitoring of histamine-induced Ca^{2+} influx into a live cell using an SCN transistor. For the response monitoring of Hela cells to histamine stimulation, an SCN transistor was assembled in a framework, then Hela cells were transferred from a culture dish to the SCN transistor surface (Figure 2a). The Hela cells were cultured on the transistor surface at 37 ℃ in an atmosphere of 5 % CO_2 for 4 days. Randomly, there was a Hela cell growing on the floating electrode area, which was a target for the monitoring of electrophysiological responses to histamine stimulation using the SCN transistor (Figure 2b). Before electrophysiological measurements, the Hela cells were incubated in a Ca^{2+} free physiological buffer for 60 minutes and washed three times with the buffer. The electrophysiological responses of the target cell to histamine were evaluated via the conductance changes of the SCN transistor during the addition of a 100 μM histamine solution containing Ca^{2+} (Figure 2c). The electrical conductance (G) of the SCN transistor was recorded by a data acquisition system (National Instruments, NI−9215(A)) while the voltage bias of the source and

drain of the SCN transistor was set to 0.1 V. To estimate the antihistamine effects of chlorpheniramine on histamine-induced Ca^{2+} influx, Hela cells were incubated in a Ca^{2+} free buffer containing 10 μM chlorpheniramine for further 15 minutes before the addition of a 100 µM histamine solution containing Ca^{2+}. Measured Hela cells could be detached from the transistor surface using a 0.25 % trypsin-EDTA solution (Thermo Fisher Scientific) to reuse the transistor for other measurements.

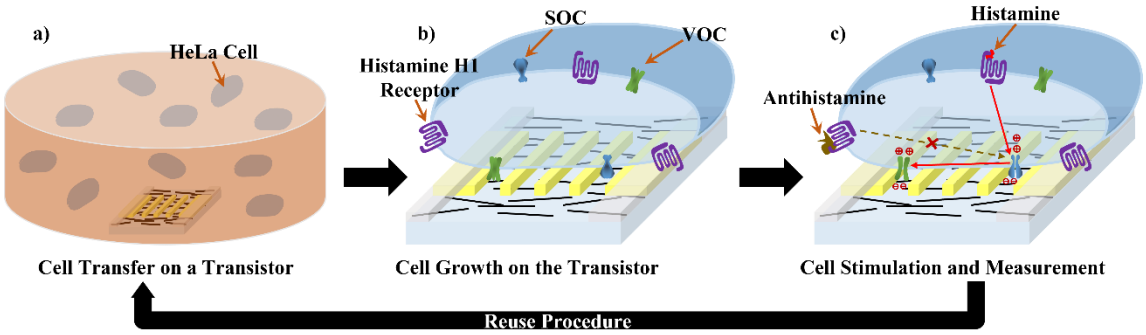

Figure 2. Schematic diagram depicting the monitoring procedures of histamine-induced Ca^{2+} influx. (a) Transfer of Hela cells on the SCN transistor surface; (b) Culture of the Hela cell on the CNT junction of the SCN transistor; (c) Simulation and monitoring of Ca^{2+} flow into the Hela cell by using the SCN transistor. The experimental procedures can be repeated using the same SCN transistor for different Hela cells. SOC and VOC stand for store-operated channel and voltage-operated channel, respectively. The drawings are not for scaling.

Since the electrical conductance (G) of CNT field-effect transistors depends on the density and width of CNT matrix between source and drain electrodes, the relative conductance changes ($\Delta G/G_0$) are used to assess the data obtained from different SCN transistors. The value of $\Delta G/G_0$ can be determined as follows,

$$\Delta G/G_0\,(\%) = \frac{G - G_0}{G_0} \times 100\% \qquad (1)$$

where, G_0 is the conductance value of the transistor at the time of adding histamine solution.

3. RESULTS AND DISCUSSION

3.1. Basic characteristics of SCN transistors

The quality of an SCN transistor was checked by imaging the surface structure of the transistor. Figure 3a shows the optical image of an SCN transistor without (i) and with (ii) Hela cells grown on the transistor surface. The images show that the width of the floating electrode area is around 15 µm, which is equivalent to the diameter of a single Hela cell. Therefore, our method could approach the monitoring of electrophysiological signals at the single cell level, which would be a significant advantage for biomedical researches and applications. Note that, unlike a patch clamp method, we do not need to form a hole or a high resistance seal on a cell membrane using a micropipette, and, thus, our method could be a convenient and non–invasive method.

Figure 3b shows the atomic force microscopy (AFM) image of a CNT junction area between floating electrodes. The topography image shows the high density and high alignment of a CNT matrix, which improves the conductance and sensitivity of semiconducting CNT transistors [16, 17]. This may be explained by the fact that the aligned CNT matrix reduces the lateral connection of CNTs. Furthermore, the presence of floating electrodes increases the number of Schottky barriers, enhances the transconductance capability between CNTs and metal electrodes as well as the sensitivity of our SCN transistors [18].

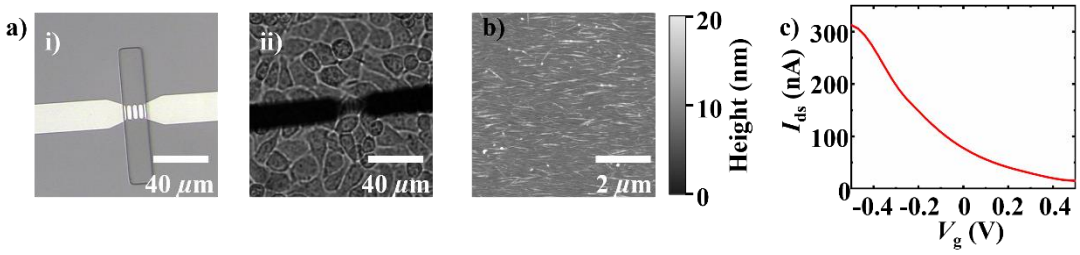

Figure 3. Basic characteristics of SCN transistors. (a) Optical image of a SCN transistor including three floating electrodes *without* (i) and *with* (ii) cultured Hela cells. (b) AFM image of the CNT junction of a SCN transistor. (c) I-V curve of a SCN transistor obtained by using as a liquid gate.

The electrical characteristics of an SCN transistor were investigated by applying a liquid gate bias (V_g) to the transistor through a physiological buffer containing Ca^{2+}. Here, the electrical current (I_{ds}) through the transistor was monitored while sweeping the liquid gate bias (V_g) from -0.5 V to 0.5 V using a Pt liquid gate electrode and maintaining the source-drain bias (V_{ds}) at 0.1 V. The SCN transistor responded to the changes of gate bias voltages with *p*-type transistor characteristics as shown in Figure 3c [19]. Significantly, when the gate bias was varied within a small range, the electrical current changed intensely, revealing the high sensitivity of SCN transistors.

3.2. Monitoring histamine-induced Ca^{2+} influx using SCN transistors

Previous works have demonstrated that Ca^{2+}influx into cells can be evoked by the activation of histamine H1 receptors [5, 20 - 22]. Figure 4a illustrates the mechanism of a histamine-induced Ca^{2+} influx via Ca^{2+} channels embedded on a cell membrane such as store-operated channels (SOCs) and voltage-operated channels (VOCs), which were regulated by the activation of histamine H1 receptors [23, 24]. Once histamine binds to its receptors, an intracellular signal transduction pathway is triggered to form inositol 1,4,5-trisphosphate ($InsP_3$). $InsP_3$ causes the emptying of intracellular Ca^{2+} stores, which induces the Ca^{2+} influx from an extracellular environment through the SOCs. In turn, it depolarizes the cells leading to Ca^{2+} influx through VOCs. The Ca^{2+} influx into the cell raises negative potential on the exterior side of a plasma membrane. Since the applying of a negative gate bias can increase the conductance of our SCN transistors (Figure 2b), the histamine stimulation of Hela cells can increase the conductance of the SCN transistors.

Figure 4b shows the relative conductance changes ($\Delta G/G_0$) of a bare SCN transistor without any grown Hela cell during the addition of a 100 μM histamine solution. The conductance of the bare SCN transistor in the measurement did not change significantly, implying that there is no effect of histamine addition on the transconductance of the SCN transistor. In contrast, Figure 4c and 4d show the conductance of SCN transistors with Hela cells

grown on surfaces immediately changed after histamine addition. For these measurements, SCN transistors with three and one floating electrodes were utilized to monitor the electrophysiological responses of individual cells to histamine as presented in Figure 4c and 4d, respectively. Although these two cases were performed under similar experimental conditions, the increase in the relative conductance of the three-floating electrode-based transistor of ~5.06 % was greater than that of the one-floating electrode-based transistor (~3.33 %). The changes of the transistors' conductance could be assigned to the histamine stimulation of histamine H1 receptors in cell membranes. The binding of histamine to the receptors triggered Ca^{2+} influx into cells via the above-described mechanism (Figure 4a), which made the exterior side of a cell membrane to become more negative. The negative exterior side acted as a gate bias to the SCN transistors, causing an increase in the conductance of the transistors due to the *p*-type characteristics of the SCN transistors (Figure 3c).

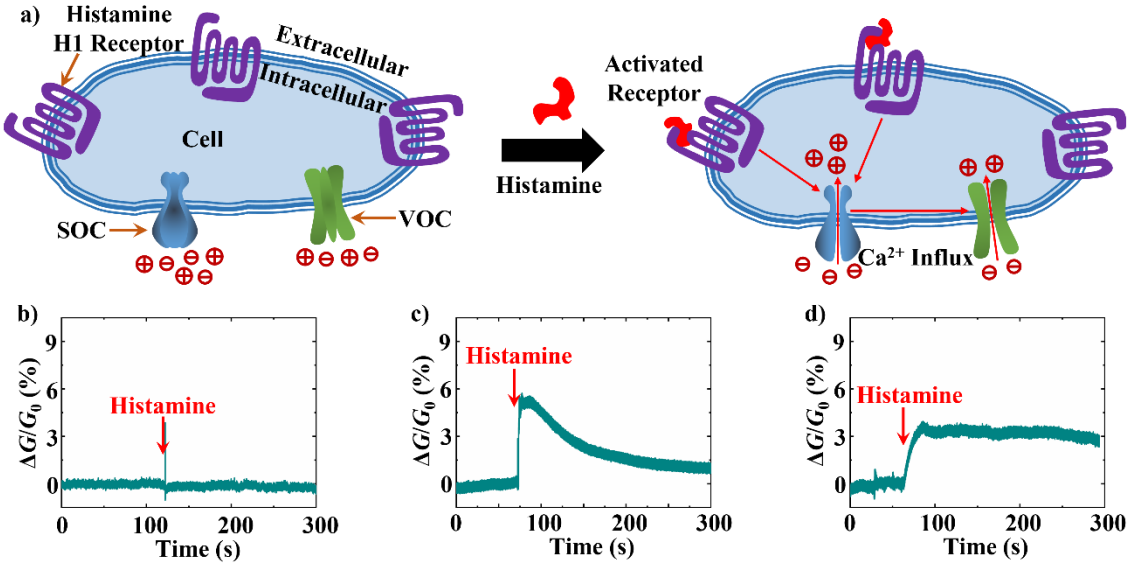

Figure 4. Monitoring of Ca^{2+} flow into a single Hela cell under the stimulation of histamine. (a) Schematic diagram depicting the influence mechanism of histamine on the activity of Ca^{2+} channels on a cell membrane. The drawings are not for scaling. (b) Real-time conductance measurement of a *bare* SCN transistor during the addition of a 100 μM histamine solution. (c) and (d) Real-time conductance measurement of SCN transistors including *three floating electrodes* and *one floating electrode*, respectively, with Hela cells cultured on the CNT junctions of the transistors during the addition of a 100 μM histamine solution.

Sometimes, the conductance increase was followed by a recovery to the initial conductance level, which probably resulted from the charge neutralization at the contact area between cells and CNTs. The neutralization could be attributed to the diffusion of ions in a bath solution and the repolarization of cell membrane. Significantly, these results indicate that the increase of floating electrodes could improve the sensitivity of the CNT field-effect transistors, which results from the increase in the numbers of Schottky barriers [25, 26]. The formation of floating electrodes creates Schottky barriers at the interfaces between the semiconducting CNTs and the metal electrodes. Previous works demonstrated that sensor sensitivity is mainly enhanced due to the increase in Schottky barrier numbers but not the shape or area of floating electrodes [18, 27]. This data clearly reveals that our SCN transistors can be used to monitor the electrophysiological

responses of Hela cells to histamine stimulation. Moreover, the measurement of changes in the membrane potential without cellular structure damage allows us to perform non-invasive electrophysiological studies on different cell types.

3.3. Monitoring the effects of chlorpheniramine on histamine-induced Ca^{2+} influx using a SCN transistor

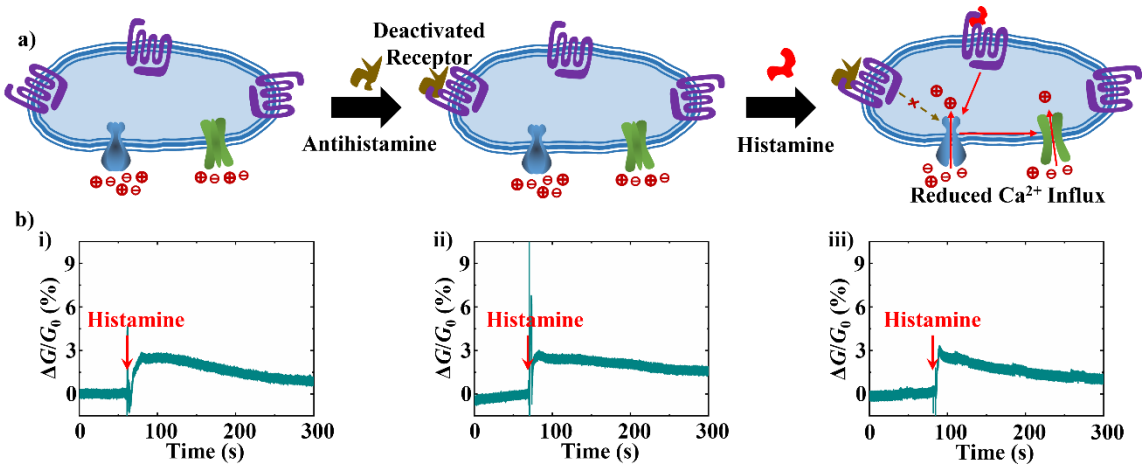

Figure 5. Evaluation of the effects of chlorpheniramine on histamine-induced Ca^{2+} influx through Hela cell membranes using a SCN transistor. (a) Schematic diagram depicting the inhibited mechanism of antihistamines on histamine-induced Ca^{2+} influx through membrane Ca^{2+} channels. The drawings are not for scaling. (b) Real-time response measurements of various Hela cells pretreated with a 10 μM chlorpheniramine solution to the addition of a 100 μM histamine solution using the same SCN transistor.

Figure 5a describes the effect mechanism of antihistamine on histamine-induced Ca^{2+} influx into a Hela cell. For example, histamine H1 receptors binding to chlorpheniramine, an antihistamine that acted as an inverse agonist, are transformed to deactivated states [28]. These receptors cannot be activated by histamine, resulting in the reduction of histamine-induced Ca^{2+} influx, probably due to the degradation of SOCs and VOCs [21]. Therefore, the antihistamine effects of chlorpheniramine on Hela cells can be estimated via the monitoring of membrane potential changes of the cells by using SCN transistors.

Figure 5b shows the real-time responses of a SCN transistor to Hela cells pretreated with chlorpheniramine under histamine stimulation. In these measurements, Hela cells grown on the SCN transistor surface were incubated with a 10 μM chlorpheniramine solution without Ca^{2+} for 15 minutes, followed by the stimulation of a 100 μM histamine solution containing Ca^{2+}. Three measurements were performed with different Hela cells using the same transistor to evaluate the reusability of our SCN transistor. The results showed the relative conductance change ($\Delta G/G_0$) of the SCN transistors of ~2.41 %, which was smaller than the response of the transistor to a non-pretreated cell (5.06 %) as shown in Figure 4c. This also indicated that chlorpheniramine had antihistamine effects on Hela cells [21, 28]. Significantly, the SCN transistor could be reused after every measurement by the detaching process of measured Hela cells. The obtained data show a similarity in the conductance changes of the SCN transistor in repeated measurements, implying that our transistor still maintained typical electrical characteristics despite undergoing various measurements. Moreover, the relative standard deviation of the relative conductance change values in Figure 5b was determined to be 1.90 %, indicating the

high sensitivity and repeatability of the SCN transistors. This allowed us to perform the real-time evaluation of antihistamine effects on the electrophysiological responses of a single cell without errors from device variations.

4. CONCLUSIONS

We report a strategy to monitor the real-time electrophysiological response of individual Hela cells under histamine stimulation using floating electrode-based semiconducting carbon nanotube transistors. SCN transistors were utilized to evaluate Ca^{2+} influx into Hela cells through membrane Ca^{2+} channels triggered by the activation of histamine H1 receptors. The results indicated that Hela cells grown on the surface of the SCN transistor caused changes in the conductance of the transistors during the addition of histamine. Moreover, the conductance changes of a SCN transistor with three floating electrodes were greater than that with one floating electrode, implying that the increase in the number of floating electrodes enhanced the sensitivity of SCN transistors. The effects of chlorpheniramine on histamine-induced Ca^{2+} influx were also detected using a SCN transistor. The increase in the conductance changes of the transistor with chlorpheniramine-pretreated cells was smaller than that with non-pretreated cells, confirming that Ca^{2+} influx could be inhibited by chlorpheniramine. Significantly, after a measurement, Hela cells cultured on the transistor could be easily removed, which allowed us to reuse the transistor for other measurements. It enables statistically meaningful evaluations without being suffered from the device characteristics of device-to-device variation. The obtained results demonstrated that SCN transistors could be used to monitor the activities of ion channels embedded on a cell membrane even in the presence of the interaction between cells and CNTs. Our work should suggest powerful applications of CNTs in biomedical studies and nanoscale semiconductor development.

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CRediT authorship contribution statement. Viet Anh Pham Ba: Methodology, Investigation, Funding acquisition. Ngoc Pham Van Bach: Methodology. Khoa Viet Nguyen: Methodology, Supervision.

Declaration of competing interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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