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Detection of Transmitter Release from Single Living Cells Using Conducting Polymer Microelectrodes

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The advent of organic electronics has made available a host of materials and devices with unique properties for interfacing with biology.^{1–2} One example is the use of conducting polymer coatings on metal electrodes that are implanted in the central nervous system and interface electrically with neurons, providing stimulation and recording the neuron's electrical activity.^{3–5} Coating a metal electrode with a conducting polymer has been shown to lower the electrical impedance and decrease the mechanical properties mismatch at the interface with tissue, with beneficial effects on the lifetime of the implant.^{3, 6} Conducting polymers can also be functionalized with biomolecules that stimulate neural growth and minimize the immune response to the implant.^{3–5, 7} Other examples are organic electronic ion pumps,⁸ and ion transistors,⁹ which are recently invented devices capable of precise delivery of neurotransmitters to neurons. These devices were recently implanted in the ear of a guinea pig and were shown to control its hearing.¹⁰ Conducting polymers such as poly(3,4-ethylenedioxythiophene) doped with poly(styrene sulfonate) (PEDOT:PSS), a material that has been shown to be biocompatible with a variety of different cells,¹ have

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been used for these applications. These examples highlight the main advantages that organic electronic materials bring to the interface with biology, including their “soft” nature, which offers better mechanical compatibility with tissue than traditional electronic materials, and natural compatibility with mechanically flexible substrates, which paves the way for the development of implants that better conform to the non-planar shape of organs. Finally, the ability of organics to transport ionic in addition to electronic charge creates the opportunity to interface with electrically active cells in novel ways, as the work on ion pumps indicates.

Many cell types in the human body release specific transmitter molecules that are recognized by specific receptors in the target cell membrane. In a variety of excitable cells, such as neurons and neuroendocrine cells, the transmitter molecules are stored in membrane-bound vesicles. In response to stimulation, these vesicles fuse with the cell's plasma membrane, thereby releasing their contents in the form of quantal events.¹¹ This mechanism of vesicle fusion with the plasma membrane has been termed exocytosis. Exocytosis plays a central role in communication of neurons: Electrical excitations, which propagate in the axon of a neuron in the form of action potentials, induce the release of transmitters in the synapse formed between the axon terminal of the pre-synaptic neuron and a dendritic spine of the post-synaptic neuron (Fig. 1(a)). The receptors in the post-synaptic membrane, subsequently, transduce the biochemical signal into an electrical excitation. Our aim here is to develop an organic device that performs this transduction, on the level of a single cell and with adequate temporal resolution to detect individual exocytosis events. The idea is to create a semi-artificial synaptic cleft, in which the secreted transmitter molecules released by a cell diffuse to a PEDOT:PSS microelectrode surface where they are detected electrochemically (Fig. 1(b)). Such a transducer will enable a chemo-electrical way to interface with excitable cells. Combined with conducting polymer electrodes, which record and stimulate electrically, and with organic electronic ion pumps, which stimulate biochemically, it will expand the repertoire of possibilities for interfacing organics with biology. It will also pave the road for new concepts, such as the design of all-organic artificial synapses, in which the capability of conducting polymers to deliver neurotransmitters for cell stimulation or inhibition is combined with their ability to detect the release of neurotransmitters.

It is not, however, *a priori* clear that such devices can be developed using conducting polymers, as the electrodes need to be patterned to single cell dimensions and meticulously insulated to reduce background noise. Nor is it clear whether conducting polymer electrodes can accurately capture the kinetics of transmitter release and resolve the small currents associated with amperometric detection of individual release events. Exocytosis is usually monitored with carbon fiber microelectrodes (CFEs),¹² or with microfabricated electrodes made of platinum (Pt)^{13–14} or indium tin oxide (ITO)^{15–16}. Both approaches rely on electrode materials that are highly conducting, and on well-developed processes for their miniaturization and insulation. Implementing the semi-artificial synapse concept of Fig. 1(b) involves subsequent patterning of conducting polymer electrodes and insulator films with feature sizes of the order of 10 μm . Although this length scale is easily addressed with photolithography, the choices of materials and processes are not trivial.

In this Communication we show that PEDOT:PSS microelectrodes can be used as sensitive sensors for the detection of individual transmitter release events from single cells. Our approach is shown in Fig. 1(c). The device consists of a photolithographically patterned PEDOT:PSS thin film which is connected to a platinum (Pt) pad that provides contact with external electronics, and is covered with an insulator, except from a small window (not visible here, see next paragraph) on top of which a single chromaffin cell was placed. Chromaffin cells were chosen as they are a widely-used model system to study neuronal exocytosis.¹⁷ These cells release transmitters which are redox active and can be detected by

amperometric measurements, which involve oxidation of the released molecules at the electrode surface. For norepinephrine, a catecholamine released by chromaffin cells, the oxidation involves transfer of two electrons and generates its o-quinone. The oxidized compounds may again diffuse away or adsorb to the electrode surface. As reported for Pt microelectrodes, such adsorption interferes with dynamic detection by fast scan cyclic voltammetry but does not impair the ability to perform continued recordings of amperometric spikes at constant voltage.¹⁸ A micropipette was used to gently press on the cells and stimulate the exocytosis process.¹⁹

In an effort to achieve high quality signal detection, we progressed through three different device architectures, shown in Figs. 2(a), (b) and (c). The fabrication details are described in *experimental*. Each device consists of the patterned PEDOT:PSS thin film, which is covered with an insulator, except for a small window that allows the PEDOT:PSS film to contact the electrolyte. The difference between the three devices lies in the area of the PEDOT:PSS film and in the type of insulator used: Devices of type **1** and **2** had the same insulator (a commercially available photoresist), but differed in the architecture of the PEDOT:PSS film, which had a smaller area in the device of type **2**. As a result, the microelectrode area was $100\ \mu\text{m}^2$ in the device of type **1**, and $40\ \mu\text{m}^2$ in the device of type **2**. The device of type **3** utilized a geometry similar to device type **2** but had a slightly smaller PEDOT:PSS film area (the microelectrode area was $30\ \mu\text{m}^2$), as well as a bilayer insulator that included a fluoropolymer (insert of Fig. 2(d) shows its chemical structure) between PEDOT:PSS and the photoresist. By gently pressing on the cell with a micropipette for stimulation,¹⁹ amperometric spikes representing the oxidation of catecholamines released from individual vesicles were recorded with the PEDOT:PSS microelectrodes: The spikes in the traces of Figs. 2(a)–(c) correspond to individual exocytosis events. These results indicate that PEDOT:PSS microelectrodes have the ability to detect the release of transmitter molecules such as catecholamines. They also show that the device architecture has a significant influence on the background electrode current noise during the measurement. Fig. 2(d) shows the averaged current noise from seven microelectrodes for devices of type **1** and **3**, and from six microelectrodes for devices of type **2**. The mean electrode current noise of type **1**, **2** and **3**, measured before placing the cells on the electrodes, were 14.34 ± 4.37 (N=7), 8.37 ± 1.84 (N=6) and 3.29 ± 0.24 pA (N=7), respectively. The background noise (between current spikes from transmitter release events) was practically unchanged when a cell was placed on the electrode.

Electrode current noise increases with electrode area. Therefore, devices of type **3** which have the smallest PEDOT:PSS films are expected to show the lowest noise. Fabrication issues also play a role in determining electrode current noise: Patterning of the insulator layer of devices of type **1** and **2** (a positive-tone photoresist) to expose the PEDOT:PSS microelectrode surface necessitates a basic developer solution with a high pH (~14). It is known that the surface of PEDOT:PSS thin films consists of an excess PSS layer with acidic properties.²⁰ We found that the ensuing acid-base reaction that takes place at the surface of the PEDOT:PSS film causes a poor quality interface with the overlying photoresist layer. This effect can deteriorate the final pattern and lead to defects in the insulation of the PEDOT:PSS film, as indicated by white arrows in the micrograph of a device of type **1** in Fig. 2(a). As a result, the r.m.s. electrode current noise was on average ~15 pA and showed considerable variability as indicated by the high standard deviation in Fig. 2(d). Decreasing the size of the PEDOT:PSS film in devices of type **2** helped reduce the noise level. A further substantial reduction was achieved when a fluoropolymer interlayer was introduced between it and the photoresist layer in devices of type **3**, as seen in Figs. 2(b) and (c). The reduction by 60% in electrode current noise is much larger than that expected from the 25% decrease in electrode area. The success of the fluoropolymer lies in the fact that it can be processed from fluoroethers – solvents that are orthogonal to, hence do not affect the properties of

most organic electronic materials.²¹ Therefore, the use of a fluoropolymer interlayer avoids the direct exposure of the PEDOT:PSS surface to the basic developer and prevents any damage at the PEDOT:PSS/insulator interface. Fig 2(d) shows that the electrode current noise in devices of type **3** was dramatically reduced down to 3.27 pA, a factor of 4 smaller compared with that in devices of type **1**. In addition, there was a concomitant improvement in device-to-device reproducibility, as indicated by the small standard deviation. The reduced noise level in devices of type **3** improved drastically the signal-to-noise ratio during measurement of exocytotic events from a single chromaffin cell as shown in Figs. 2(a)–(c).

Fig. 3(a) shows an amperometric recording of transmitter release events from a single chromaffin cell placed on a PEDOT:PSS microelectrode of device type **3** in more detail. These amperometric spikes show a half width of a few milliseconds, as previously reported for CFE recordings from bovine chromaffin cells^{24–27}. It also shows two amperometric spikes on expanded time scale. One of these shows a foot signal, similar to those previously reported for recordings with conventional CFEs²². It has been shown that these amperometric foot signals reflect the slow flux of transmitter through the early narrow fusion pore.²³ We quantified the temporal response of the PEDOT:PSS microelectrodes by analyzing the spike width at half maximum ($t_{1/2}$), which is related to the kinetics catecholamine release from the vesicle. The histogram in Fig. 3(b) shows the distribution of $t_{1/2}$ measured with PEDOT:PSS microelectrodes of type **3**. Nine cells each (N=9) were tested, and a total of 1486 events were analyzed individually to determine amperometric spike parameters for the PEDOT:PSS microelectrodes. It is worth noting that the mean of each parameter was determined for each cell and then, the parameters determined for each cell in a group were averaged to calculate the mean and the standard error of the mean (SEM) of a parameter.²⁴ The mean value of $t_{1/2}$ for PEDOT:PSS (8.39 ± 1.05 ms; mean $\pm$ SEM) was not significantly different from that for Pt microelectrodes (10.97 ± 0.96 ms), as well as the reported mean values of $t_{1/2}$ for conventional CFEs,^{25–28} indicating that PEDOT:PSS microelectrodes correctly report the kinetics of quantal release events.

In addition to demonstrating the capability of PEDOT:PSS microelectrodes to accurately monitor the time course of release of catecholamines from single vesicles, we quantified the amperometric spikes by determining the amperometric charge (Q_{amp}), which corresponds to the number of catecholamine molecules collected by the PEDOT:PSS microelectrode during an individual event. The mean Q_{amp} obtained with PEDOT:PSS microelectrodes (1.43 ± 0.18 pC; mean $\pm$ SEM) is within the range of values previously reported for conventional CFE recordings.^{29–31} The frequency distribution of events showed a Gaussian distribution when plotted as a function of $Q^{1/3}$, as seen in Fig. 3(c). This is expected, as the distribution of vesicular radii in a chromaffin cell is approximately Gaussian, and $Q^{1/3}$ is proportional to vesicular radius.^{23, 32} Analysis of the foot signals measured with PEDOT:PSS microelectrodes provided a mean foot duration and foot charge (integral of foot current) of 17.04 ± 5.31 ms and 0.25 ± 0.08 pC (mean $\pm$ SEM, 28 of total 1486 events), respectively, consistent with data from CFE recordings from bovine chromaffin cells.^{22, 30} These results indicate that our analysis was based on sufficient data collection, and that the PEDOT:PSS microelectrode provides a good means for monitoring secretion phenomena from chromaffin cells without distorting their properties.

In conclusion, we demonstrated that PEDOT:PSS microelectrodes have the ability to detect transmitter release from single chromaffin cells during exocytosis. The microelectrodes were fabricated using photolithography, and it was found that the addition of a fluoropolymer between the conducting polymer and the photoresist insulator was crucial for being able to record the oxidation of released catecholamines with a high signal-to-noise ratio. These microelectrodes accurately reported the kinetics of release and were shown to be a good means for monitoring secretion phenomena from chromaffin cells without distorting their

nature. The detection of transmitter release from living cells represents a new capability for interfacing with the nervous system using organic electronics, and one that allows new bioelectronic devices to be envisioned. One example is the combination with organic electronic ion pumps, devices that control the release of neurotransmitters, to yield an all-organic artificial synapse.

Experimental

Fabrication of the microelectrodes

For the fabrication of the PEDOT:PSS microelectrodes, 15 nm thick Pt pads were defined on a glass substrate by conventional photolithography and electron-beam evaporation. A 5 nm thick titanium film was used as the adhesion layer. The PEDOT:PSS microelectrodes were subsequently fabricated by means of subtractive patterning: First, a PEDOT:PSS (Clevios PH500, HC Starck) solution which was formulated with ethylene glycol (EG, PEDOT:PSS/EG = 80/20 by volume percent) was spin-coated on the glass substrate with the Pt pads, and then dried at 140 °C for 60 min. A protective layer that consisted of a fluorinated polymer (see inset of Fig. 2(d)²¹) was then spin-coated on the PEDOT:PSS film from a ~ 9.1 wt% solution in 3M Novec Engineered Fluid HFE-7600, and baked at 110 °C for 10 min. On top of this fluorinated polymer film, photolithography was carried out using a AZ nLOF 2020 photoresist. PEDOT:PSS was patterned by etching the region where PEDOT:PSS was not covered by resist with oxygen plasma. The fluorinated polymer/photoresist layers were then removed by lift-off in 3M Novec Engineered Fluid HFE-7200. The substrates were subsequently insulated, leaving only a small window open that defined the area of the microelectrode. For devices of type **3**, a fluorinated polymer film (same as used above) was deposited on the substrates and was subsequently coated with Shipley 1805 (S1805) photoresist. The latter was exposed to UV in a contact aligner (ABM) to define a window over which the photoresist was removed to expose the PEDOT:PSS microelectrode. Development with aqueous alkaline developer (Shipley 300MIF) did not dissolve the underlying fluorinated polymer film, but did only the UV exposed areas of S1805 resist. The pattern in the S1805 resist was then transferred to the underlying fluorinated polymer layer by spin-coating HFE-7200 solvent for 10 seconds. Therefore, the final structure of the insulator consisted of a bilayer of the fluorinated polymer (~ 460 nm thick) and the S1805 layer (500 nm thick). The fabrication of devices of type **1** and **2** followed the same steps, but without the fluorinated polymer interlayer. For details on the patterning of PEDOT:PSS-based devices, including the influence of patterning on morphology and properties, the reader is also referred to our previous work.²⁰

Cell preparation, electrochemical recording and analysis

Bovine adrenal glands were obtained from a local slaughter house and chromaffin cells were cultured on 8 mm cover slips as described in literature.³³ A cover slip with cultured cells was placed near the PEDOT:PSS microelectrodes, and a drop of buffer solution (~200 µl) was applied to cover the area including the microelectrodes and the cover slip with the cells. The buffer solution was composed of 140 mM NaCl, 5 mM KCl, 5 mM CaCl₂, 2 mM MgCl₂, 10 mM HEPES-NaOH and 10 mM D-glucose (pH 7.4). A healthy cell (shiny and roundish) was picked up from cover slip by applying gentle suction (~50 mBar) with a glass micropipette and was carefully moved and placed on a PEDOT:PSS microelectrode. The glass micropipette was also used to mechanically stimulate the exocytotic process by gently pressing on the cell. The amperometric current was measured by single channel current amplifier (HEKA EPC-8, HEKA Instruments Inc.). The microelectrode was held at 700 mV relative to a Ag|AgCl reference electrode (a value comparable to the ones used with CFEs^{25–28} and Pt microelectrodes.^{13, 19, 34}) immersed in the buffer solution. The sampling rate for data acquisition was 2 kHz under the application of 500 Hz low-pass filter.

Amperometric signals were further digitally filtered with a 500 Hz low pass Gaussian filter to reduce the background noise. Parameters obtained from amperometric spikes such as spike width at half maximum and amperometric charge were analyzed using Mosharov's Quanta Analysis software (open source program available online, version 8.0).³⁵ For a consistent comparison of analyzed parameter among different microelectrodes, standard deviations of noise (SD_I) for PEDOT:PSS microelectrodes were averaged and the cutoff peak height during analysis was set as four times of averaged SD_I (~12.84 pA).

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Figure 1.

Analogy between a synapse in neurons (a) and a semi-artificial synapse at a cell/PEDOT:PSS interface, in which transmitter release from the cell results in the flow of a hole (h^+) current in the PEDOT:PSS film (b). Optical micrograph of the test configuration with a single chromaffin cell placed on a PEDOT:PSS microelectrode. The micropipette was used to mechanically stimulate the exocytotic process by gently pressing on the cell.

Figure 2.

Optical micrograph (top left panel), schematic side-view (lower left panel) of different architectures of PEDOT:PSS microelectrodes and the corresponding current recording traces (right panel) (a–c). The arrows in the electrode image of panel (a) show the damaged part of the insulator. Quantification of electrode current noise for the three PEDOT:PSS microelectrode architectures (d). The error bars indicate the standard deviation. The inset in (d) displays the chemical structure of the fluoropolymer.

Figure 3.

An amperometric trace recorded during the release of catecholamines from a single chromaffin cell with a PEDOT:PSS microelectrode of type **3** (a). Two individual amperometric spikes with (left) and without (right) a foot signal are shown on expanded time scale. Histogram representing the distribution of spike width at half maximum (b). Histogram of the cube root of amperometric charge (c), in which the solid line is a Gaussian fit.