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Electrochemical Detection of Dopamine via Assisted Ion Transfer at Nanopipet Electrode Using Cyclic Voltammetry

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Abstract

We present here the detection of dopamine (DA) at nanopipet electrodes with radii of hundreds of nanometers ranging from 160 nm to 480 nm. Dibenzo-18-crown-6 (DB18C6) was employed as an ionophore to facilitate DA transfer, resulting in a half-wave transfer potential, $E_{1/2, DA}$, of $-0.322 (\pm 0.020)$ V vs. $E_{1/2, TBA}$. Well-defined steady-state sigmoidal cyclic voltammograms were observed for the transfer of DA. High resolution scanning electron microscopy was used to measure the size and taper angle of the nanopipet electrodes. The detection is linear with concentration of DA ranging from 0.25 mM to 2 mM; calculated diffusion coefficient at nanopipet electrodes with above mentioned sizes is $4.87 (\pm 0.28) \times 10^{-10} \text{ m}^2/\text{s}$. The effect of the common interferent ascorbic acid on DA detection with nanopipet electrodes was evaluated, where DA detection still shows linear behavior with well-defined sigmoidal CVs with $E_{1/2, DA}$ being $-0.328 (\pm 0.029)$ V vs. $E_{1/2, TBA}$. The diffusion coefficient for DA transfer in MgCl_2 with the presence of 2 mM AA was measured to be $1.93 (\pm 0.59) \times 10^{-10} \text{ m}^2/\text{s}$ on nanoelectrodes with radii from 161 nm to 263 nm, but the physiological concentration of 0.1 mM AA had no effect on DA's diffusion coefficient.

Dopamine (DA) is a small molecule that has many functions throughout the body. More specifically, DA functions as a neurotransmitter in the brain, and acts as a chemical messenger between neurons. DA has been attributed to playing a role in such processes as memory,¹ motor control,^{2,3} and reward.^{4,5} When the dopaminergic system is altered, certain disease states may occur, such as Parkinson's disease⁶ or Schizophrenia.^{7,8}

Electrochemical measurements, mainly on a carbon microelectrode, have proven to be a very useful technique for studying DA release during neurotransmission.^{9–22} There are however, several issues with the traditional electrochemical detection via the oxidation of DA, which primarily involve the presence of ascorbic acid (AA). Ascorbic acid is present in the brain at

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much higher concentrations compared to DA, and the two compounds are oxidized at similar potentials, thus ascorbic acid is a major interferent for the electrochemical detection of DA.²³ Furthermore, ascorbic acid can reduce dopamine's oxidation product back into DA, causing a signal larger than that is representative of the actual amount of DA in solution.¹⁸ Electrode modifications are needed to circumvent this issue, including the use of charge-selective polymer films, which can provide improved selectivity.^{18,24–27}

Pipet supported Interface between Two Immiscible Electrolyte Solutions (ITIES) provides a unique platform for detecting ionic species, such as DA, which has a pKa of 8.8–8.9 and 10.4–10.6 and is protonated under biological pH.^{28–30} The detection is based on ion transfer across a liquid-liquid interface rather than a redox process. Because of this, side reactions involving dopamine's oxidation product are not an issue. Furthermore, ion transfer at the ITIES offers the selectivity against AA that is necessary in DA detection without the use of modified electrode surfaces.^{31–34} We present here the detection of DA with nanometer sized ITIES pipet electrodes.

Ion transfer of several neurotransmitters has been previously reported at ITIES of various sizes, including macro- and micro-interfaces.^{31,35–39} Additionally, we have recently reported the detection of acetylcholine, tryptamine, and serotonin at nanopipet electrode with ITIES of only tens of nanometers via unassisted ion transfer.⁴⁰ The transfer of DA across the macroITIES (e.g. area $\approx 1 \text{ cm}^2$) has been demonstrated by Arrigan et al.,^{31–34} as well as by Samec and colleagues;^{41,42} and across the microITIES by Shao's group,³⁷ using ionophores such as dibenzo-18-crown-6 ether (DB18C6) to facilitate dopamine's transfer. DB18C6 complexes with dopamine via hydrogen bonds between the hydrogen atoms in DA's amino group and the oxygen atoms from the crown ether. This can lower the Gibbs energy of DA transfer,³⁵ allowing dopamine transfer to occur within the potential window of the background solution.^{34,43}

To the best of our knowledge, facilitated transfer of neurotransmitters at the nanometer scale ITIES has not yet been reported. Though DA transfer have been reported at macro and micro interfaces, the kinetic scaling of all processes involved in the facilitated transfer needs to be demonstrated in the challenging mass transfer conditions imposed by a nanoelectrode. Study at nano-ITIES provides insight regarding how the ion complexation reaction at the interface aligns with ion transfer and ion diffusion to the ITIES surface. This is critical at nanoelectrodes because when we decrease the size of the interface, the diffusion time decreases as well, (proportional to square of electrode radius divided by diffusion coefficient, a^2/D), thus challenging the kinetics of many processes involved, but importantly that of the interfacial formation of a complex. Besides, smaller electrochemical probes including those based on ion transfer at the ITIES have a few distinct advantages over their larger counterparts. First, micro- and nano-scale probes show better performance over macroelectrodes due to enhanced mass transport from spherical diffusion.^{44,45} Furthermore, small scale probes, particularly those that are on the nanoscale, are able to obtain high spatial resolution images using scanning probe techniques such as scanning electrochemical microscopy (SECM).^{46–48} For example, Sun et al. used disk-shaped Pt nanoelectrodes for the SECM imaging of a single Au nanoparticle's catalytic activity,⁴⁶ and Chen et al. reported the use of Pt nanodisk electrodes for the study of H_2 nanobubble nucleation.⁴⁸

Furthermore, nano-capillary supported ITIES have previously been used in imaging of ion transport across single nanopores within a nanoporous membrane by Shen et al.⁴⁷ Here we report the detection of DA via assisted ion transfer by DB18C6 at nanopipet electrode with sizes on the hundreds of nanometer scale. We also investigated selective detection of DA with the presence of ascorbic acid, a major interferent that co-exists with dopamine in the brain at high concentrations.

Experimental

Reagents

Potassium tetrakis(pentafluorophenyl)borate (TFAB) was obtained from Boulder Scientific Company (Mead, CO). Dopamine hydrochloride, dibenzo-18-crown-6 (DB18C6), tetradodecylammonium (TDDA) chloride, tetrabutylammonium chloride (TBACl), 1,2-dichloroethane (DCE), chlorotrimethylsilane were purchased from Sigma-Aldrich (St. Louis, MO). The TFAB salt of TDDA (TDDATFAB) was prepared by metathesis, as described elsewhere⁽⁴⁹⁾. Magnesium chloride (MgCl_2) was from Amresco (Solon, OH). Ascorbic acid was from Fisher Scientific (Pittsburgh, PA). All reagents were used as received, and solutions were prepared using 18.3 M Ω cm deionized water (ELGA, Woodridge, IL). The prepared solutions were passed through a 0.2 μm filter (Thermo Scientific, Waltham, MA) before use.

Nanopipet electrode preparation and characterization

Nanometer-scale pipet electrodes were fabricated by laser pulling of quartz capillaries (Sutter Instrument Co., Novato CA; O.D. = 1.0 mm, I.D. = 0.7 mm, length = 10 cm) using a P-2000 capillary puller (Sutter Instrument Co., Novato, CA). The pulled pipets were then silanized via vapor deposition as described elsewhere.^{40,45} Pipets were characterized using Scanning Electron Microscopy (SEM) and ion-transfer voltammetry. For SEM imaging, the nanopipets were coated with a thin Au/Pd film by a high-resolution sputter coater (Quorum Technologies LTD, Kent, UK), and the orifices were observed by high resolution field emission SEM (FEI dual-beam 235, FEI Co., Hillsboro OR, USA) under a 20 kV electron beam.

Electrochemical experiments

The transfer of protonated DA across the 1,2-DCE/water interface was studied by cyclic voltammetry. All electrochemical measurements were recorded using a CHI1205B Electrochemical Analyzer (CH Instruments, Austin, TX). The prepared nanopipets were backfilled with a solution of 5 mM TDDATFAB + 25 mM DB18C6 in 1,2-DCE using a 10 μL Hamilton syringe, and the organic solution was pushed to the tip of the pipet by creating a gentle vibration. When immersed in an aqueous solution, a liquid-liquid interface is formed at the tip of the pipet. Voltage was applied between two reference electrodes: one inside the pipet and one outside, which is immersed in the aqueous solution. A Pt wire (50 μm diameter) was used as the inner reference, and the external reference was a AgCl coated Ag wire (250 μm diameter). Cell diagrams representing each experimental setup used are the following:

Cell 1:

Pt | 5 mM TDDATFAB + DCE + 25 mM DB18C6 || 10 mM MgCl₂ + x mM DA | AgCl | Ag

Cell 2:

Pt | 5 mM TDDATFAB + DCE + 25 mM DB18C6 || 10 mM MgCl₂ + x mM DA + x mM ascorbic acid | AgCl | Ag

Characterization of steady-state limiting current

Nanopipet electrodes with radii of hundreds of nanometers were used to measure the steady-state current response for a range of dopamine concentrations, represented by⁵⁰

$$i = 4\pi n F D c a \quad [1]$$

where i is the steady-state limiting current, x is a function of the quantity $RG = r_g/a$ (r_g and a are outer and inner tip radii, respectively),⁵¹ here approximately $RG = 1.4$ and $x = 1.23$, n is the number of transferred charges in the tip reaction, F is Faraday's constant, a is the inner radius of the pipet, D is the diffusion coefficient of the neurotransmitter measured, and c is the concentration of neurotransmitter in solution. A proposed disk geometry for the nanopipet tip was used for the calculation. The slope, $m = i/c$ of calibration curves can be used in combination with Eq. 1 to determine the diffusion coefficient of dopamine.

Other calculations

To determine the half-wave transfer potential ($E_{1/2}$) of dopamine, TBACl was added at the end of experiments as an internal standard. This was calculated by subtracting the highest point of the first derivative of the DA CVs from the highest point of the first derivative of the TBA CV.

pH experiment

The pH of the bulk solution was monitored after subsequent additions of DA and AA. pH measurements were performed using a pH meter (Model # AB15, Fischer Scientific, Pittsburg, PA).

Results and Discussion

Overall matrix considerations

Here we report the detection of dopamine in a background solution of 10 mM MgCl₂, which provides a large potential window because divalent matrix cations (such as Mg²⁺) typically transfer at more negative potentials than monovalent matrix cations (such as Li⁺).³³ A background solution with a large potential window such as MgCl₂ was used in our study to provide the best condition in terms of background potential window to allow DA transfer at nanoITIES to be studied in a controlled manner. The study of this process facilitated by DB18C6 is possible in principle in other matrices, however it may prove more challenging given a larger overlap with the potential window.

Maintaining an appropriate pH environment for dopamine detection is a critical aspect of experimentation.⁴³ The electrochemical detection of DA at the ITIES is dependent on that dopamine, when protonated at its amine group, is cationic.⁴³ This allows dopamine to be detected by ion transfer at the ITIES.⁴³ Furthermore, it is necessary for dopamine to be positively charged in order to form a complex with DB18C6, the ionophore used in our study for the facilitated ion transfer of DA.⁴¹ In aqueous solution at physiological pH or lower, dopamine is protonated,³¹ since the pH of the environment is lower than the pK_a of DA's amino group, which is reported to be 8.8 to 8.9 and 10.4 to 10.6 in the literature.^{28–30} In order to ensure that DA will be in its cationic state for relevant ITIES experiments, the pH of the solution was monitored during various additions of DA and AA (Table S1, Supporting Information). These results indicate that DA exists in its cationic form in all of the experiments discussed below.

Dopamine detection using probes with radii of hundreds of nanometers

We present here dopamine detection with nanopipet electrodes with radii of hundreds of nanometers, ranging from 160 to 480 nm, using DB18C6 as an ionophore present in the organic phase. In the absence of DB18C6, DA does not transfer across the interface, and therefore is not detected (data not shown). Figure 1 shows the cyclic voltammograms for the facilitated DA detection with concentrations ranging from 0.25 mM to 2 mM in a background solution of 10 mM MgCl₂ at nanopipet electrodes with radii of 210 nm, 225 nm, and 480 nm for Figures 1a, 1b, and 1c, respectively. It can be seen that sigmoidal voltammograms with steady-state limiting currents were achieved for 0.25 – 2 mM DA at all of these nanoITIES pipets. The results shown in Figure 1 are representative of typical results that we observed in the lab for similar size ITIES, and it is important to note that all values reported in this paper were calculated from the results of pipets that were characterized via the electrochemistry of TBA as well as SEM imaging, to ensure that the pipets were working properly. The measured half-wave transfer potential for DA at these nanopipet electrodes is -0.322 ± 0.020 V vs. $E_{1/2, \text{TBA}}$ ($n = 5$). The insets of Figure 1 show the SEM micrographs of the nano-orifice at the end of nanopipet electrode (cross section) as well as the side view of the nanopipet positioned at 45 degrees with respect to the detector. These images allow for the pipet radius, r , and taper angle, θ , to be determined.

The current response corresponding to DA detection increases linearly with increasing concentration of DA for all of the nanopipet electrodes with various sizes studied, up to 2 mM. Past 2 mM, the current response still increases, but the response starts to slow down (data not shown). Calibration curves of the limiting current with respect to DA concentration shows an R^2 value of 0.99 for Figure 1a, of 0.98 for Figure 1b, and of 0.99 for Figure 1c, indicating linear response from the nanopipet electrodes for the detection of DA (Figure S1–3, Supporting Information). Using calibration curves for these pipets and others ($n = 6$), in combination with Eq. 1, the calculated diffusion coefficient for DA transfer is $4.87 (\pm 0.28) \times 10^{-10}$ m²/s for pipets with radii ranging from 175 to 480 nm. This value is very close to the value determined by flow injection analysis, $6 (\pm 0.25) \times 10^{-10}$ m²/s.⁵²

The taper angle, θ , is reported to influence the attainment of steady-state at the nanopipet-based ITIES; as θ increased from 0° to 90°, there is a gradual transition from linear to

hemispherical ion diffusion in the internal solution.⁵³ Using SEM images in the Figure 1 insets, θ was calculated to be 16.2° , 17.5° , and 17.5° for the nanopipets used in Figures 1a, 1b, 1c, respectively. These θ values observed in our quartz nanopipets are within the range of that reported typically for quartz nanopipets, i.e. 9° to 22° .⁵⁴ These values of θ could allow for the ingress and egress of DA transfer to reach steady-state, resulting in well-defined sigmoidal behavior in the voltammogram as observed with Figure 1. The taper angles of all pipets tested in this study ranged from 16° to 21° , with no effect in transfer behavior observed within this range of angles.

Dopamine detection with the presence of ascorbic acid using nanopipet electrodes with radii of hundreds of nanometers

As ascorbic acid is a substance present in the brain at high concentrations and is a known interferent for DA detection; we present here the detection of DA with AA present in the aqueous solution (Figure 2) at nanopipet electrodes with radii of 223 nm and 258 nm. As shown in Figure 2, there is no change on the potential window at the positive potential side after adding AA to background solution of MgCl_2 , indicating that ascorbate ion was not detected at our nanopipet electrode, thus not interfering with DA detection. However, the potential window on the negative side is slightly narrowed upon addition of AA, similar to previous reports at larger interfaces,³² which is likely due to the transfer of protons evidenced as decrease in pH with addition of AA (Table S1, Supporting Information). After the addition of 2 mM AA, DA with concentrations varying from 0.25 mM to 2 mM was added to the cell, where transfer behavior is similar to that shown in Figure 1 when no AA was present during DA detection. Cyclic voltammograms corresponding to transfer of DA with presence of AA show sigmoidal shape and steady-state limiting current increases linearly with increasing concentration of DA in multiple independent measurements ($n = 5$) on nanopipet electrodes with various radii ranging from 161 to 263 nm with R^2 values 0.98, e. g. R^2 for Figures 3a and 3b are 0.99 and 0.98, respectively (Figure S4–5, Supporting Information).

The measured half wave transfer potential for DA detection with presence of 2 mM AA was calculated to be -0.328 ± 0.029 V vs. $E_{1/2, \text{TBA}}$ ($n = 6$), showing no significant change in the presence of ascorbic acid. Based on calibration curves and Eq. 1, the diffusion coefficient for DA transfer with the presence of 2 mM AA was measured to be $1.93 (\pm 0.59) \times 10^{-10} \text{ m}^2/\text{s}$ from multiple independent measurements on nanopipet electrodes with various radii ranging from 161 nm to 263 nm ($n = 5$). We found few papers studying DA transfer at macro-ITIES^{31–33,41,42} and micro-ITIES,³⁷ with no diffusion coefficient reported based on calibration curves with the presence of AA. In the previously reported transient detection of DA at large pipet electrodes with radii on the scale of mm, the diffusion coefficient of DA with presence of 10 mM ascorbate was calculated from plots of peak current versus the square root of sweep rate.³² The results from Ref 32 indicated no significant change in D whether ascorbate is present in solution or not. The observed decrease in D of DA in our study with the presence of high concentration of AA, 2 mM, could be related to pH change in background solution after adding 2 mM AA (Table S1); in Ref 37, when the authors added $\text{Mg}(\text{OH})_2$ to a solution of DA in MgCl_2 after adding AA, not much change in dopamine current was observed with the addition of 20 mM AA. Although we observe a

decrease in the diffusion coefficient of DA when 2 mM AA is present, it is important to note that detection of DA is still linear with respect to its concentration, so determining an unknown concentration of dopamine in a solution with the presence of AA simply requires the use of this modified D in Eq. 1. Most importantly, steady state current of dopamine remains the same with presence of physiological concentration of 0.1 mM AA, as discussed in next paragraph.

While the concentration of AA present in biological environment is typically in the range of 0.1 mM,⁵⁵ we also investigated the electrode's response when AA was in even larger excess to DA, at 20 mM (Figure 3). As shown in Figure 3, there is no change on the potential window at the positive potential side after adding AA to background solution of MgCl_2 , indicating that even at 20 mM, ascorbate ion was not detected at our nanopipet electrode, thus not interfering with DA detection. Although the DA steady-state limiting current wave is cut off a little sooner than when compared to the presence of 2 mM AA, detection was still linear from 0.25 – 2 mM DA ($R^2 = 0.97$; Figure S6, Supporting Information). Interestingly, we measured D of DA in the presence of 20 mM AA to be $1.93 \pm 0.33 \text{ m}^2/\text{s}$ ($n = 5$), a value not statistically different from D when only 2 mM AA is present. In order to further explore the effect of AA, we performed experiments in which the current for 2 mM DA was monitored with respect to the addition of various concentrations of AA, ranging from 0.1 – 20 mM AA. The results are shown in Figure S7 of the Supporting Information, which show no significant change in DA current when 0.1 mM AA was added. This is important to note, because as mentioned previously, 0.1 mM is the typical AA concentration reported in biological environments. A steep drop in current is seen between 0.1 and 0.5 mM AA, but the decrease slows down with additions of higher concentrations.

Conclusions

We have shown the DB18C6 facilitated detection of dopamine at a nanopipet-supported ITIES interface consisting of water and 1,2-DCE using cyclic voltammetry. The steady-state limiting current corresponding to dopamine (DA) detection increases linearly with respect to concentration of DA. The diffusion coefficient of DA at interfaces of hundreds of nanometers was found to be $4.87 (\pm 0.28) \times 10^{-10} \text{ m}^2/\text{s}$ calculated based on independent measurements with nanopipets with radii ranging from 175 nm to 480 nm ($n = 6$), with a half-wave transfer potential of $-0.322 \pm 0.020 \text{ V}$ vs. $E_{1/2, \text{TBA}}$ ($n = 5$). We also show that with the presence of ascorbic acid (2 mM), DA detection at nanopipet electrodes still shows well-defined steady-state cyclic voltammograms, with current increasing linearly with respect to concentration of DA as well; no ascorbate was detected at nanopipet electrode. The half-wave transfer potential of DA was measured to be $-0.328 \pm 0.029 \text{ V}$ vs. $E_{1/2, \text{TBA}}$ ($n = 6$) with the presence of ascorbic acid. The presence of ascorbic acid doesn't affect the detection potential of DA at the nanopipet electrodes reported. These nano-ITIES electrodes provide an alternative to traditional DA detection at carbon electrodes, minimizing effects of ascorbic acid interference that traditionally results in a variety of problems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Cyclic voltammograms showing transfer of 0.25–2 mM dopamine (DA) across an ITIES with a radius of (a) 210 nm, (b) 225 nm, and (c) 480 nm using Cell 1. Insets: SEM micrographs of the pipet used for these experiments, showing tip geometry (radius, r , and taper angle, θ) with both cross-section view and side view at 45 degrees.

Figure 2.

Cyclic voltammograms showing transfer of 2 mM ascorbic acid (AA) followed by 0.25–2 mM dopamine (DA) across ITIES with radii of (a) 223 nm and (b) 258 nm, using 25 mM DB18C6; cell 2. Inset: SEM micrographs of the pipet used for these experiments, showing tip geometry (radius, r , and taper angle, θ) with both cross-section view and side view at 45 degrees.

Figure 3.

Cyclic voltammograms showing transfer of 20 mM ascorbic acid (AA) followed by 0.25–2 mM dopamine (DA) across an ITIES with radius = 350 nm using 25 mM DB18C6; cell 2. Inset: SEM micrograph showing cross section view of pipet used for this experiment.