An electronic proton-trapping ion pump for selective drug delivery

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The organic electronic ion pump (OEIP) delivers ions and charged drugs from a source electrolyte, through a charge-selective membrane, to a target electrolyte upon an electric bias. OEIPs have successfully delivered γ-aminobutyric acid (GABA), a neurotransmitter that reduces neuronal excitations, in vitro, and in brain tissue to terminate induced epileptic seizures. However, during pumping, protons (H+), which exhibit higher ionic mobility than GABA, are also delivered and may potentially cause side effects due to large local changes in pH. To reduce the proton transfer, we introduced proton traps along the selective channel membrane. The traps are based on palladium (Pd) electrodes, which selectively absorb protons into their structure. The proton-trapping Pd-OEIP improves the overall performance of the current state-of-the-art OEIP, namely, its temporal resolution, efficiency, selectivity, and dosage precision.

INTRODUCTION

The organic electronic ion pump (OEIP) (1–4) is an electrophoretic delivery device based on transporting charged species either at neutral or shifted pH through a cation or anion exchange membrane (CEM or AEM). The OEIP provides high spatiotemporal resolution and, potentially, also a high dosage precision (in principle, one electron corresponds to one delivered ion) and unlike analogous microfluidics-based techniques, no liquid flow (5). For these reasons, the OEIP has been proven as a promising technology for a variety of therapeutic challenges. The technology has been shown to trigger cell signaling in vitro (1, 6), terminate epileptiform activity in brain slice models (7–9), affect sensory function in vivo (10), work as a therapy for pain in awake animals (11), and even modulate plant growth via phytohormone delivery (12).

The basic cation-transporting OEIP contains two electrodes in two different electrolytes that are separated by a CEM (an AEM would be used for an anion-transporting OEIP). CEMs contain a high concentration of fixed negative charges, and their permeselectivity stands if the ion concentrations in the adjacent electrolytes are sufficiently lower (~10x lower) than the fixed charge concentration of the CEM (Donnan exclusion) (13). The ionic current through the membrane is represented by the combination of migration controlled by the electric field and diffusion along concentration gradients, with diffusion being most noticeable when no voltage is applied across the membrane.

CEM permeselectivity does not distinguish exclusive cationic species but is rather specific to charge. In addition, the relative contribution to the overall ion flux through the CEM will be dependent on the mobility of the various species through the membrane (or equivalently, their diffusion coefficients). H+ that are present in the source electrolyte are relatively more mobile and thus have a higher diffusion coefficient (due to transport based on the Grothuss mechanism) than other positively charged biomolecules like neurotransmitters (14). There is then a risk that cation transport through the CEM is dominated by H+. OEIP efficiency has been defined as the ratio of intended drugs transported (as opposed to, e.g., H+) compared to the electronic charge recorded in the driving circuit and taking the drug/ion’s charge number into account (5). In this way, 100% efficiency corresponds to only the intended drug being transported into the target system without cotransport of, e.g., H+. Many drugs and neurotransmitters present higher transport efficiency at low source pH (8, 10, 11). At pH 3, the structure of the neurotransmitter γ-aminobutyric acid (GABA) leads to a more globular conformation and thus higher mobility of the cationic GABA through the channel (15). This phenomenon results in the problem stated above since substantial shifts in pH lead to an abundance of H+. The excess H+ are delivered along with the neurotransmitter affecting channel selectivity and potentially leading to side effects of the treatment and/or negative effects on the device itself.

In this work, we develop a hybrid OEIP that specifically delivers a drug through the CEM to the target by selectively blocking the H+ along the CEM channel. The hybrid device uses palladium (Pd) contacts, patterned between source and target and located along the base of the CEM channel (Fig. 1). Pd has the ability to specifically extract H+ from a solution into its structure during electrochemical conversion to palladium hydride (PdH). Pd-based bioelectronic devices have been successfully used to study the transport of H+ in biomaterials (16–21), monitor and control biological reactions (22–24), and control and modulate pH in physiological relevant solutions (25). In this study, Pd contacts are used as H+ scavengers during delivery, thus enhancing the efficiency of the delivered drug.

We use the neurotransmitter GABA as the model delivery substance (as the cationic molecule that is transported through a CEM). GABA is one of the primary inhibitory neurotransmitters in the central nervous system and has been used in a variety of previous OEIP demonstrations (7, 8, 10, 11). The polyanion poly(4-styrenesulfonic acid-co-maleic acid) (PSS-co-MA or PSSA) cross-linked with the polyalcohol polyethylene glycol (PEG) was chosen as the model CEM material, where PSS is the primary ion exchange material. The hybrid “Pd-OEIP” delivers higher GABA concentration in the same amount of time as compared to a “normal” OEIP with the same geometry. Furthermore, its efficiency reaches 93 to 99%, nearing the ideal case of one electron for one GABA ion.
to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the ion channel and encapsulation layer (Fig. 1A).

RESULTS

Device fabrication was primarily achieved using photolithographic patterning and electrodeposition (see Materials and Methods). Following the Au electrode patterning, Pd was electrodeposited selectively on top of Au electrodes. Seven Pd electrodes of 100-μm length, 3-mm width (transverse to ion flow), and 50-μm spacing were patterned along the length of the PSS-co-MA channel (3 mm width, length of 1.12 mm, and thickness of 500 nm) (Fig. 2, A and B), through electrodeposition from palladium nitrate solution. The Pd electrodes were patterned along the channel at different positions with respect to the source electrolyte to investigate the Pd position dependence on the effective H\(^+\) absorption and thereby optimize the delivery efficiency (fig. S1). The change in color from gold to dark was observed during the Pd deposition. The dark color is a result of the rough structure of Pd on top of the gold electrodes. Following the Pd deposition, a layer of SU-8 of 10-μm thickness was used to define the areas of source, target, and to separate the Pd electrodes. Last, the PSS-co-MA CEM and a second SU-8 layer were patterned, defining the ion channel and encapsulation layer (Fig. 1A). Pd has the ability to absorb H\(^+\) into its bulk when it is at a negative potential versus the potential of the electrolyte, becoming PdH (Fig. 1B). In common electrolytes, H\(^+\) exist as hydronium ions (H\(_3\)O\(^+\)). Upon adsorption on the Pd surface, an H\(^+\) (in the form of H\(_2\)O\(^+\)) is reduced to H\(^+\) with an electron from the Pd. The H\(^+\) diffuses into the Pd contact and forms hydride PdH\(_x\) (Eq. 1 and Fig. 1B), with \(x\) being the atomic ratio of H to Pd with a maximum value of \(x\) ~ 0.6 to 0.7 in acidic electrolytes (26).

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Pd + H_3O^+ + e^- \rightarrow PdH_x + H_2O
\]  

This process is reversible, namely, PdH releases H\(^+\) back into the electrolyte, freeing its Pd sites when the voltage is 0 (fig. S1, B and C). The Pd → PdH and PdH → Pd reactions are stable processes, resulting in a reproducible transfer of H\(^+\) into and out of Pd over many cycles (16, 25).

The Pd → PdH onset potential is pH dependent; the lower the pH, the lower the potential difference between Pd and source electrolyte. In acidic solutions, H\(^+\) transfers into Pd when the Pd is no lower than ~0.4 V versus the source electrode in pH 1 as shown in cyclic voltammetry (fig. S1B) (23). In this scenario, H\(^+\) traversing the CEM from source to target are trapped in the Pd (at a local voltage minimum or ground) without accumulating in the CEM. However, since GABA does not transfer into Pd, it accumulates in the CEM near the active Pd electrode and is subsequently delivered to the target electrolyte (Fig. 1C).

Initially, we characterized the ability of the Pd to block H\(^+\) from delivery to the target electrolyte using an optical recording of pH changes. Acidic HCl solutions of different pH were placed in the source electrolyte, and KCl (aqueous) loaded with a methyl red pH indicator (pK\(_a\) of 5.1: the color becomes red for pH < 5.1, yellow for pH > 5.1) was placed in the target. When the device was operated as a normal OEIP, i.e., a voltage applied only between source and target electrolyte (Pd → PdH, PdH → Pd reactions are stable processes, resulting in a reproducible transfer of H\(^+\) into and out of Pd over many cycles (16, 25)).
indicating no substantial delivery of $\text{H}^+$ into the target after 300 s (Fig. 2B).

The difference between OEIP and Pd-OEIP can also be shown through their electrical characteristics. When the device is operated as a normal OEIP, a voltage $V = 1$ V is used as an input, and a current is measured as an output. When the voltage is on, the current has a value of several microamperes, and when the voltage is removed, the current drops rapidly to 0 µA (Fig. 2C). When a Pd electrode is used (Pd-OEIP), two positive voltages are applied as input: one voltage ($V_S = 0.7$ to 1 V) between source and Pd electrode and one smaller voltage ($V_T = 0.1$ to 0.5 V) between target and Pd. Pd is used as a common reference (ground; Figs. 1A and 2B). The corresponding currents $I_S$ and $I_T$ are recorded.

When both voltages are simultaneously applied (Fig. 2D), $I_S$, the current between source and Pd has a positive current value of several µA. Because of its noncapacitive character, $I_S$ indicates the transfer of $\text{H}^+$ into the Pd bulk, creating PdH. When $V_S = 0$ V, $I_S$ does not drop back to zero but rather has a characteristic behavior of Pd depletion with a negative nonzero value, indicating that $\text{H}^+$ transfer from Pd back to the source electrolyte and its magnitude is proportional to the $\text{H}^+$ concentration (Fig. S2A), which confirms $\text{H}^+$ transfer into the Pd bulk. When $V_S$ is positive ($V_S = 0.7$ to 1 V), $I_T$, which is defined as the current between target and Pd, is negative ranging from $-0.1$ to $-1$ µA, smaller than $I_S$ even when $V_T$ is positive (Figs. S2B and S8B). Note that $I_T < 0$ indicates that ions flow toward the target, i.e., intended drug delivery to the target. In an OEIP device, the PdH are transferred to the target electrolyte, while in a Pd-OEIP, PdH formation occurs in the channel blocking $\text{H}^+$ transfer to the target. As mentioned above, the maximum amount of PdH that can be transferred into the Pd is given by the ratio $x = 0.6$, namely, for three Pd atoms in a lattice, roughly two PdH can fit in between them (26).

So, the capacity of PdH depends on the amount of electrodeposited Pd, which can be controlled during deposition. In our devices, we attempted to reach the maximum capacity of Pd individual electrodes in the presence of 0.5 M HCl in the source electrolyte. However, even when $V_S$ was applied for 15,000 s, we only reached a ratio $x = Q_{PdH}/Q_{Pd} \sim 0.1$ (Fig. S3), indicating an excess of remaining sites for $\text{H}^+$ inclusion in the Pd electrode. To show that the Pd $\rightarrow$ PdH reaction causes the selectivity in trapping $\text{H}^+$ rather than a simple capacitive electrode, we used Au as a trapping electrode instead of Pd. Unlike Pd, Au is not selective to $\text{H}^+$. As in Fig. 2 (A and B), KCl with methyl red was used to visualize the pH changes in the target electrolyte, while HCl (pH 3) was placed in the source electrolyte (Fig. S4, A and B). We compared Pd and Au devices by applying the same voltage inputs ($V_S = 1$ V and $V_T = 0.5$ V). For the Au trapping electrode-based devices, the color change in the target electrolyte indicated a pH change, while no color change was observed for Pd-based devices. In addition, for Au trapping electrode-based devices, the output currents $I_S$ and $I_T$ (Fig. S4, C and D) showed an almost symmetrical behaviour, indicating that most of the $\text{H}^+$ were delivered to the target, while for Pd, the output currents $I_S$ and $I_T$ were not symmetrical, with $I_S$ having a larger magnitude than $I_T$.

The operating principle of the Pd-OEIP can be explained with a circuit model (Fig. S5). In the circuit, we assume that the channel comprises two resistances, one resistance from source to Pd ($R_{ch1}$) and one from Pd to target ($R_{ch2}$). The interface between the Pd electrode and the channel can be simplified by a reaction resistance ($R_R$) and a double-layer capacitance ($C_{DL}$) in parallel. The relative channel resistances can be modulated by the positioning of the Pd electrodes, while the reaction resistance and double-layer capacitance depend on the size and nature of the Pd electrode. Once the capacitor is charged up, a finite voltage is needed between the Pd electrode (~0.3 to 0.5 V) and the CEM channel to drive the reaction current (Fig. S1, B and C). This creates a potential difference between the Pd electrode (ground) and the CEM channel. When the potential in the channel is higher than $V_T$, cations will flow into the target and $I_T$ is negative.

The voltage threshold for PdH formation depends on multiple parameters such as the position of the Pd, as well as $V_S$ and $V_T$. By selecting only one Pd electrode at a time, we observed that the further the electrode is from the source electrolyte, the lower the $I_S$ becomes. PdH formation ($\text{Pd} \rightarrow \text{PdH}$) and Pd depletion current ($\text{PdH} \rightarrow \text{Pd}$) is observed. The opposite trend occurs with $I_T$. $I_T$ increases for Pd electrodes further away from the source electrolyte, indicating that more $\text{H}^+$ are transferred into the target electrolyte (Fig. S6). Last, there is a window of operation for $V_T$. If a high $V_T$ is applied, then $I_T$ is positive, indicating the transport of cations (Na+, K+, and H+ from target “backward” into the ion channel membrane (Fig. S7, A and B). If $V_T$ is lower than the voltage at the Pd electrode, then $I_S$ and $I_T$ are symmetrical, indicating $\text{H}^+$ delivery to the target and not trapping by the Pd electrodes. This is validated when $V_S$ returns to 0 V, and no Pd depletion is observed (Fig. S7C). Thus, by optimizing the values of $V_S$ and $V_T$, according to the specific geometry of the CEM and position and amount of Pd, one can control the amount of charge that will be delivered to the target electrolyte.

To test the drug delivery capabilities of the Pd-OEIP, we loaded the source reservoir with 100 mM GABA (aq) at pH 3.5, as this formulation has been reported to exhibit the highest mobilities (15). Devices were operated in a similar manner as in Fig. 2. Before device operation, the CEM channel was loaded with GABA by applying a constant voltage between the source and drain for 1 hour. Solutions were then replaced, with the target reservoir being washed multiple times to ensure complete removal of GABA from the target electrolyte and the source reservoir being replenished with a new GABA solution before every measurement. When the device was operated as a normal OEIP (no Pd), a pH-induced color change was observed in the target electrolyte after 300 s of delivery (Fig. 3A). This shows that protons were delivered in the target, indicating lower efficiency of the normal OEIP. However, when the Pd electrodes were used (all Pd electrodes shorted), no color change was observed (Fig. 3B).

The $I_S$ and $I_T$ profiles were similar to those in Fig. 2 (C and D) (Fig. S8); however, we applied $V_T = 0.2$ V to have a negative $I_T$ (Fig. S8B). The solutions from the target reservoir were collected, and the amount of delivered GABA was quantified by a commercially available enzyme-linked immunosorbent assay (ELISA) kit. Calibration curves show inverse proportionality of the absorption with the delivered GABA (fig. S9).

We delivered GABA for different operation times ranging from 5 to 300 s. Figure 3C shows the concentration of collected GABA versus time of device operation. Both curves show a linear delivery over time. By using Pd, we observe higher delivery of GABA, ranging from ~2 to ~8×, depending on device and operation time. The increased delivery rates can be used to reduce the delivery time for a desired amount of GABA. We repeated the experiments by using individual Pd electrodes and measured the GABA concentration. The highest GABA delivery was observed when all seven Pd electrodes were used as one electrode. Last, devices with Au, which were used as capacitively $\text{H}^+$ trapping electrodes, showed a poor GABA delivery (fig. S4E).
was not possible with traditional OEIPs. The amount of drug, without prior calibration curves, something that ter control and reproducibility toward delivering on-demand exact drug molecule. This is of high importance because it allows for bet-
ciency is between 93 and 99% over a wide range of S pulses.

Moreover, the ratio between the experimental concentration, based on the ELISA assay, and the expected concentration of delivered GABA, based on time-integrated \( I_T \), was defined as the delivery efficiency of the devices. When no Pd is used in the system, the efficiency starts from 20% and maxes out at 50% for long \( V_S \) pulses. Au \( H^+ \) trapping electrodes showed similar behavior with maximum efficiency of 55% (fig. S4F). In contrast, when Pd is used, the efficiency is between 93 and 99% over a wide range of \( V_S \) pulses (Fig. 3D). This shows a nearly 1:1 correlation between electron to a drug molecule. This is of high importance because it allows for better control and reproducibility toward delivering on-demand exact amount of drug, without prior calibration curves, something that was not possible with traditional OEIPs.

**DISCUSSION**

In this work, we have developed an OEIP that improves the delivery rate, specificity, and delivery efficiency of substances codelivered with \( H^+ \) such as neurotransmitters commonly used to treat epilepsy. This was achieved by the addition of \( H^+ \) traps, defined by Pd contacts patterned along the ion-selective channel/membrane of the OEIP. During delivery, the Pd absorbs the \( H^+ \) in its structure (Pd → PdH) and prevents them from being delivered all the way into the target electrolyte. This allows for selective delivery of the drug of interest while preventing undesired pH changes originating from delivered \( H^+ \) into a target such as biological tissue. The Pd-OEIP concept was used to deliver the neurotransmitter GABA and was shown to deliver more GABA compared to a control device (no Pd active) in less time. The ratio of transported GABA to transported charge in the electrical circuit (integrated \( I_T \) current) is nearly 1:1 when using the Pd-based \( H^+ \) traps, resulting in near-perfect control of the amount of delivered drug. As a result, the Pd-OEIP improves the current state of the art in terms of selectivity, efficiency, and reproducibility toward drug delivery to improve the treatment of conditions such as epilepsy and chronic pain.

**MATERIALS AND METHODS**

**OEIP fabrication**

Glass substrates were cleaned and rinsed in acetone and deionized water and then treated with \( O_2 \) plasma for 30 s [Advanced Vacuum Reactive Ion Etch; \( O_2 \) 400 standard cubic centimeters per minute (sccm), 250 W]. A 5-nm layer of Cr was deposited followed by the deposition of a 50-nm-thick Au layer using a thermal evaporator and a liftoff process [sonication in 80% (v/v) acetone and 20% (v/v) isopropanol for 5 min], defining the metal contacts and interconnects. An additional S1813 G2 photolithographic patterning process defined the area of the Pd contacts for Pd deposition, while the metal interconnects were insulated. After Pd deposition, the photoresist was stripped with acetone and the samples were activated with \( O_2 \) plasma for 2 min. The adhesion promoter 3-glycidoxypropyltrimethoxysilane (GOPS; Sigma-Aldrich, 1 ml) was added to ethanol (47.5 ml), water (2.5 ml), and acetic acid (50 μl) and mixed for 15 min. Immediately after \( O_2 \) plasma treatment, the substrates were soaked in the GOPS solution for 7 min. A quick rinse in ethanol and a baking step at 110°C for 15 min followed. SU-8 was spin-coated at 3000 rpm for 30 s, soft-baked for 10 min, including a ramping from 65°C to 95°C, exposed, postexposure baked for 2 min at 95°C, and developed in mr-Dev 600, resulting in approximately 10-μm-thick films.

The polyanion PSS-co-MA [Sigma-Aldrich; molecular weight (MW) of ∼20,000, transformed from Na+ form to H+ form by dialysis, 4 wt % (weight %)] was mixed with PEG (MW of ∼400, 1.5 wt %). A 0.5% (v/v) (3-mercaptopropyl) trimethoxysilane in water:1-propanol (1:1) was added to the solution to improve the adhesion of the CEM to Au or Pd electrodes. The CEM blend was then deposited by spin-coating at 1500 rpm ×2 to obtain a thickness of approximately 500 nm. The substrates were then baked at 110°C for 1 hour. A thin layer of poly(methyl methacrylate) (PMMA; Sigma-Aldrich; MW ∼12,000, 4 mg/ml in diethyl carbonate) was deposited on top of the PSS-co-MA/PEG film for improved adhesion of the photoresist followed by a layer of S1813 G2 photoresist (4000 rpm for 30 s, 5 min at 110°C bake). The photoresist was exposed using a Karl Suss MA6- BA6 Stuss mask aligner and developed in Microposit MF-319 developer to pattern the selective channel. Reactive ion etching (O2 100 sccm, CF4 200 sccm, 150 W, 95 s) was used to obtain the patterned PSS-co-MA/PEG CEM channels (1 mm long, 3 mm wide). The remaining photoresist and PMMA were removed using acetone. Substrates were then soaked in 0.1 M NaCl (aq) for 5 min to ensure that Na+ remained the dominant counterion before encapsulation with SU-8 3010 (MicroChem). A final encapsulation layer of 10-μm SU-8 (SU-8-3010, MicroChem) was spin-coated at 3000 rpm for 30 s, soft-baked for 10 min, ramping 65°C to 95°C, exposed for 20 s, post-exposure baked for 1 min at 95°C, developed in mr-Dev 600, and finalized by a 4-min hard bake at 150°C. The SU-8 pattern defined hydrophobic confinements for the two electrolytes and covered the channel region. Ag/AgCl (GWENT, Dupont) contacts were painted on the electrodes to ensure an electrochemically stable electrode (followed by 10-min bake at 100°C).

**Pd deposition**

Pd(NO3)2 (Sigma-Aldrich) was dissolved in 50 mM nitric acid to give a final concentration of 5 mM Pd. Pd was electrochemically deposited...
onto the Au contacts using a DC voltage of $V = -0.3$ V with a varied deposition time between 0.1 and 10 s (25). This resulted in a darkening of the contacts where the Pd clusters were successfully deposited.

**Electrical characterization**

Electrical characterization was performed using a Keithley 2602 SourceMeter (Keithley Instruments) with a custom-designed LabVIEW (National Instruments) software. A source voltage $V_S$ and a target voltage $V_T$ were applied, and, simultaneously, the current between source to palladium ($I_S$) and palladium to target ($I_T$) was recorded. A Gamry potentiostat was used to record electrochemical impedance spectroscopy. The H$^+$ entrapment was studied and evaluated for HCl (aq) at different pH (4, 3, 2, and 1) as well as 100 mM GABA (aq) at pH 3.5 with and without the Pd operation. Immediately before the main experiments, the ion-selective channels were loaded with the desired ions. The target solution of 10 mM KCl (aq) included the pH indicator methyl red. The methyl red indicator exhibits a gradual transition from yellow to red when the pH decreases. The color change has onset from pH 6.2 and becomes orange. Below pH 5, methyl red turns red.

**Quantification of GABA in the target electrolyte**

The source reservoir was filled with a 100 mM GABA in deionized water with adjusted pH 3.5 (adding HCl), and the target comprised 100 mM KCl (aq). A Keithley 2602 SourceMeter unit with customized LabVIEW software was used to drive the devices. Immediately before the main experiment, the channel was loaded with GABA (i.e., GABA actively transported). After the operation, the target solution was collected, and the target reservoir was thoroughly rinsed with deionized water, which was added to the collected target solution to ensure that most of the GABA was collected. The concentration of GABA was measured via ELISA kit (LDN/BA-E-2500) on a BioTek Synergy H1m plate reader according to the manufacturer’s instructions. The efficiency of the device was estimated by calculating the amount of delivered GABA divided by the number of electrons passed through the circuit and averaging the values obtained from the various experiments.

**SUPPLEMENTARY MATERIALS**

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/7/eabd8738/DC1

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