



Ag-Deposited Porous Silicon as a SERS-Active Substrate for the Sensitive Detection of Catecholamine Neurotransmitters

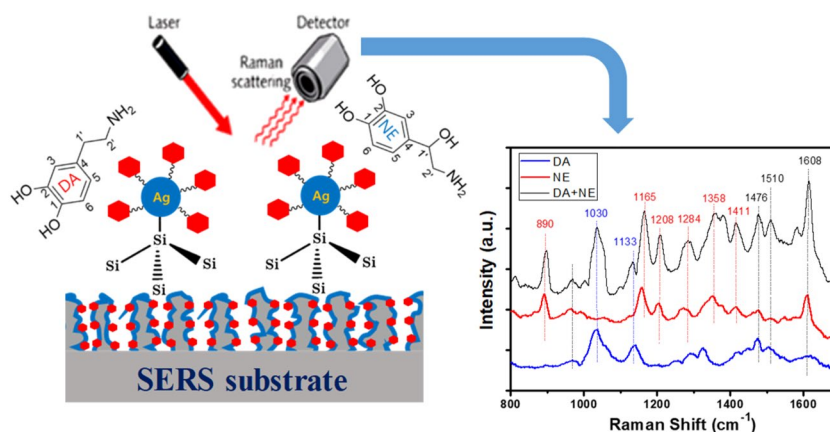
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Received: 27 December 2020 / Accepted: 28 February 2021 / Published online: 18 March 2021
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Abstract

The sensitive detection of various neurotransmitters is very useful in diagnosing diseases related to the dysfunction of the neurotransmitter system. Surface-enhanced Raman scattering (SERS) is one of the best methods for bio-analyte detection as it provides a molecular fingerprint at a trace concentration level. In this study, Ag-deposited porous silicon (Ag@pSi) was fabricated as a SERS-active substrate via metal-assisted chemical etching and electroless plating methods. Dopamine (DA) and norepinephrine (NE) neurotransmitters were tested as probing analytes. The Ag@pSi substrate demonstrated the sensitive detection of the neurotransmitters (DA and NE) over the wide concentration range (from 10^{-6} to 10^{-10} M), with a good linearity between the intensity of specific Raman peak and the log-scale concentration. The Ag@pSi substrate also distinguished the individual analytes in a mixture of DA and NE at 10^{-8} M, confirming the efficacy of the developed SERS substrate for the selective detection of neurotransmitters.

Graphic Abstract



Keywords Porous silicon · Ag-deposited · Dopamine · Norepinephrine · Surface-enhanced Raman scattering

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1 Introduction

Catecholamine neurotransmitters such as dopamine (DA), norepinephrine (NE), and epinephrine are crucial molecules in the central and peripheral nervous systems because they play key roles as neurochemical messengers to transmit signals from the nervous systems to targeted cells. These neurotransmitters are present in biological fluids at very low concentrations. Abnormal catecholamine levels are associated with various neuropsychiatric diseases such as Parkinson's disease, Huntington's disease, schizophrenia, and depression [1–3]. These compounds are active in the central nervous, cardiovascular, renal, and hormonal systems [4, 5]. DA is responsible for motor control, reward-based learning, motivation, and higher cognitive functions. Alterations in DA levels are involved in Parkinson's, Huntington's, and Alzheimer's diseases [6–10]. Epinephrine is synthesized in the medulla of the adrenal gland and is responsible for increases in blood pressure, heart rate, and respiration, which are also associated with emotional states [11, 12]. Norepinephrine (NE) is a precursor of epinephrine, which mobilizes the brain and body into action. The functions of NE include attention, learning, memory, and the sleep–wake cycle [13, 14]. Hence, fast and sensitive methods of detecting catecholamine neurotransmitters are very useful in the diagnosis and monitoring diseases related to the dysfunction of these neurotransmitters.

Many methods for detecting neurotransmitters have been reported, including high-performance liquid chromatography (HPLC) [15–17], enzyme-linked immunosorbent assay (ELISA) [18, 19], electrochemical detection [20–22], colorimetric/column-based methods [23–25] and surface-enhanced Raman scattering (SERS) methods [26–28]. Among them, HPLC is an effective method for quantitative detection of trace neurotransmitters, but is only suitable for laboratory studies because of its high cost and time-consuming process of sample preparation [29, 30]. ELISA technique has some limitation in providing information on chemical structures when the concentration of the analyte is very low [31]. As an inconvenience of the electrochemical detection method, ascorbic acid (AA) and DA are oxidized at the same potential, leading to the overlapped voltammetric responses [32]. In contrast, SERS bestows highly sensitive detection of analytes by providing a spectral fingerprint, even at the very low concentration, through the amplification of electromagnetic fields that are localized at nanoscale noble metals [33, 34].

It is well-known that noble metals (Au, Ag) can achieve enhanced Raman scattering signals [35]. Recently, Moody et al. fabricated Ag nanoparticles (NPs) by reducing silver nitrate with sodium borohydride, which was employed as SERS-active substrates for detecting melatonin, serotonin,

glutamate, dopamine, gamma aminobutyric acid (GABA), norepinephrine, and epinephrine. The limit of detection (LOD) was reported as ~ 1.0 nM [34]. Zhang et al. synthesized the thin gold film conjugated with 3,3'-dithiodipropionic acid di(*n*-hydroxysuccinimide ester) (DSP) and detected DA using a dual-recognition-directed hotspot strategy, i.e., DA was trapped by Ag NPs functionalized with 3-MPBA. Even though the LOD reached the pico-level concentration, the synthetic procedures were overly sophisticated [36]. Cao et al. synthesized Au-Fe(NTA) on a Si wafer for detecting catecholamines in serum, but the detection limit was restricted to $\sim 10^{-6}$ M [37]. Hence, it is necessary to develop a facile fabrication of SERS-active substrate that can detect trace neurotransmitters.

To quantify neurotransmitters using the SERS technique, a porous silicon (pSi) template was prepared by metal-assisted chemical etching of a Si wafer, followed by the electroless deposition of nanosized Ag inside the pSi template. The Ag-deposited pSi (Ag@pSi) was employed to detect DA and NE at nanomolar concentration with a good linearity over four orders of magnitude (from 10^{-6} to 10^{-10} M) between the intensity of typical Raman peak and the corresponding log-scale concentration. Notably, the Ag@pSi substrate distinguished the individual analyte in a mixture of DA and NE at 10^{-8} M, and the peak at 890 cm^{-1} served as a marker of the hydroxyl group in the NE structure. These results corroborated the efficacy of the developed SERS substrate on the sensitive and selective detection of trace neurotransmitters.

2 Experimental Details

All reagents were used as received without further purification. The following chemicals were purchased from Sigma-Aldrich: dopamine hydrochloride (98%), norepinephrine (97%), silver nitrate (99%, AgNO_3), hydrofluoric acid (48%, HF), nitric acid (70%, HNO_3), ethanol (99.5%, $\text{C}_2\text{H}_5\text{OH}$), acetone (99.5%), and ascorbic acid (99%). Boron-doped (p-type, resistance $< 0.005\ \Omega\text{ cm}^{-2}$) silicon wafers (polished on the (100) face) were purchased from Virginia Semiconductor.

The Si wafer was first cleaned with HPLC water in a sonication bath and subsequently immersed in a mixture of 0.2 M AgNO_3 and 5 M HF (1:1 volume ratio) for 2 h in a homemade Teflon cell (inside dia. = 3.1 cm). The freshly-etched pSi (so-called pristine pSi) was rinsed with 1.0 mM HNO_3 several times for 30 min to remove Ag aggregates deposited on the outer surface. After then, the pristine pSi was immersed in 5 mL of 0.01 M AgNO_3 solution in the Teflon cell for 30 min. After rinsing with ethanol, the sample was dried under a stream of nitrogen and then taken out from the etching cell. The dried sample was rinsed with 1.0 mM

HNO₃ solution for 3 min, followed by cleaning with ethanol and keeping in a desiccator. The final product was designated as Ag-deposited pSi (Ag@pSi). For SERS measurements, the circular Ag@pSi substrate was cut into four parts ($4 \times 1.94 \text{ cm}^2$) and each part was incubated in a solution containing analytes (DA and NE) with different concentrations (from 10^{-6} to 10^{-10} M), prior to a further characterization by Raman spectrometer.

The morphology of the samples was characterized by scanning electron microscopy (SEM, S-4700, Hitachi, 20 kV) to analyze the plain-view and cross-sectional morphologies of the samples. Energy-dispersive X-ray spectroscopy (EDX) was used to analyze the chemical components of the samples. The Raman spectra of the analytes adsorbed on the substrate were analyzed by micro-Raman spectroscopy (ANDOR Monora 500i, 632.8 nm) at the Smart Materials Research Center for IoT at Gachon University. The instrument was calibrated in reference to the Raman band of crystalline silicon at 520 cm^{-1} and the accumulation time of the Raman spectra was 5 s.

3 Results and Discussion

Metal-assisted chemical etching was initiated by depositing Ag nuclei on the Si wafer. The Si directly beneath the deposited Ag was dissolved by HF etchant solution [38]. In this process, Ag particles move vertically to generate a chip-based Si nanowire array. The most important parameters in this etching process are the etchant (AgNO₃/HF) concentration and etching time. As described in the experimental section, the pristine pSi was fabricated by the etchant solution of 0.2 M AgNO₃ and 5.0 HF (1:1 volume ratio) for 2 h. After removing Ag dendrites from the outer surface by rinsing with 1.0 mM HNO₃, Ag-deposited pSi was employed as a SERS-active substrate for the sensitive detection of trace analytes (Fig. 1).

Figure 2a, b shows SEM images of the pristine pSi and Ag-deposited pSi samples after rinsing with 1.0 mM HNO₃ solution. Interconnected pores propagated anisotropically perpendicular to the surface, which was similar to the pore morphology of electrochemically etched Si wafer. This observation indicates a strong dependence of the etching anisotropy on the geometry of the metal pattern. The most noticeable aspect is that generation of small isolated metal islands during etching was generally unpredictable, whilst larger islands and interconnected web-like patterns were etched nearly perpendicular to the surface. In the cross-sectional SEM images, Ag deposition and a columnar structure were clearly observed in the Ag@pSi substrate, displaying more heterogeneous morphology and larger pore variations in comparison to those of the pristine pSi. Figure 2c, d shows the EDX data, confirming the presence of Ag NPs in the Ag@pSi. The EDX mapping showed the presence of Ag component throughout the pSi template and the Ag content of the pSi was quantified as 5.21 wt.%.

Figure 2e shows the Raman spectra of Si wafer and pSi samples after removing the surface-deposited Ag aggregates. The standard Si is a flat and nonporous silicon wafer, and the pSi samples with and without Ag deposition are referred to as pristine pSi and Ag@pSi, respectively. The peak position and line-width in the Raman spectra of the pSi samples were compared with those of the standard Si that shows the Raman peak at 520 cm^{-1} and full-width-at-half-maximum (FWHM) of 2.3 cm^{-1} . The peak of the pristine pSi sample was located at the almost same position of 520 cm^{-1} with the FWHM of $\sim 13.5 \text{ cm}^{-1}$, whereas the peak of the Ag@pSi was slightly shifted to $\sim 525 \text{ cm}^{-1}$ with the FWHM of 15.5 cm^{-1} . Even though line-shape of the “pSi samples was broader than that of the standard Si, the presence of crystalline Si in the porous Si skeleton was confirmed by the appearance of Si–Si lattice mode at 520 cm^{-1} .

In the SERS measurement, the Ag@pSi substrate exhibited the characteristic Raman spectra of the

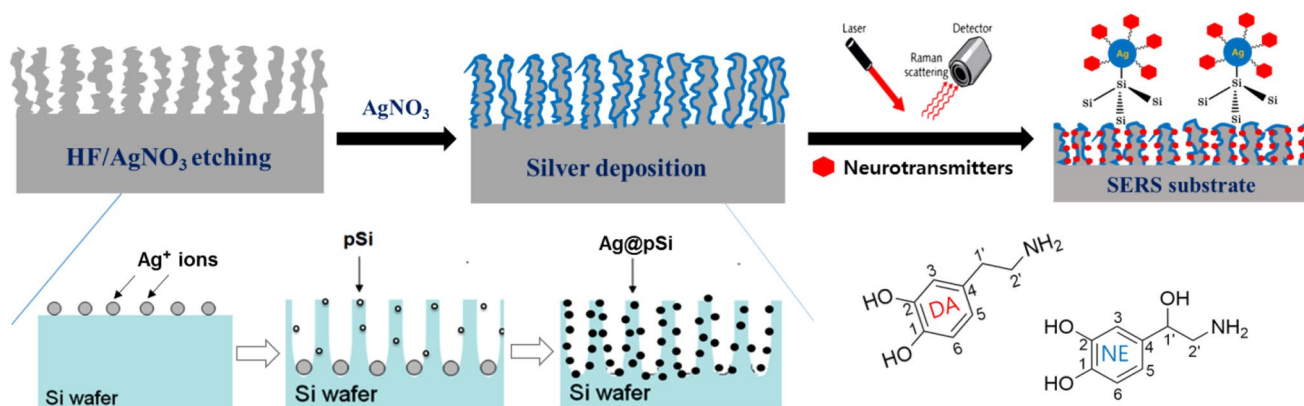


Fig. 1 Synthetic schemes for preparing the Ag@pSi substrate as a SERS-active substrate for detecting neurotransmitters

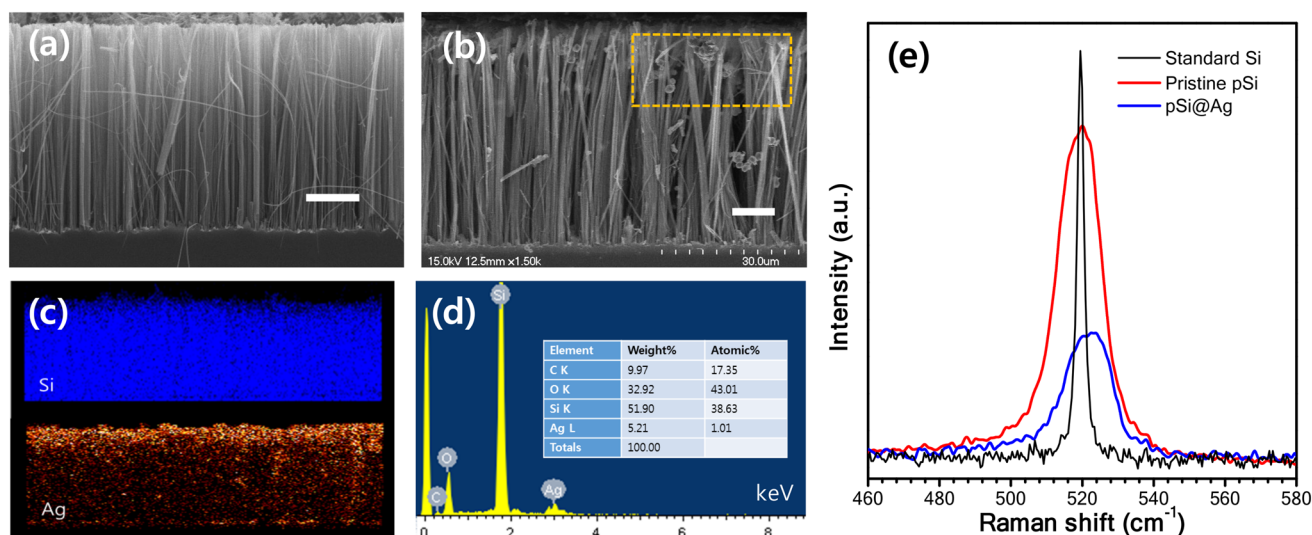
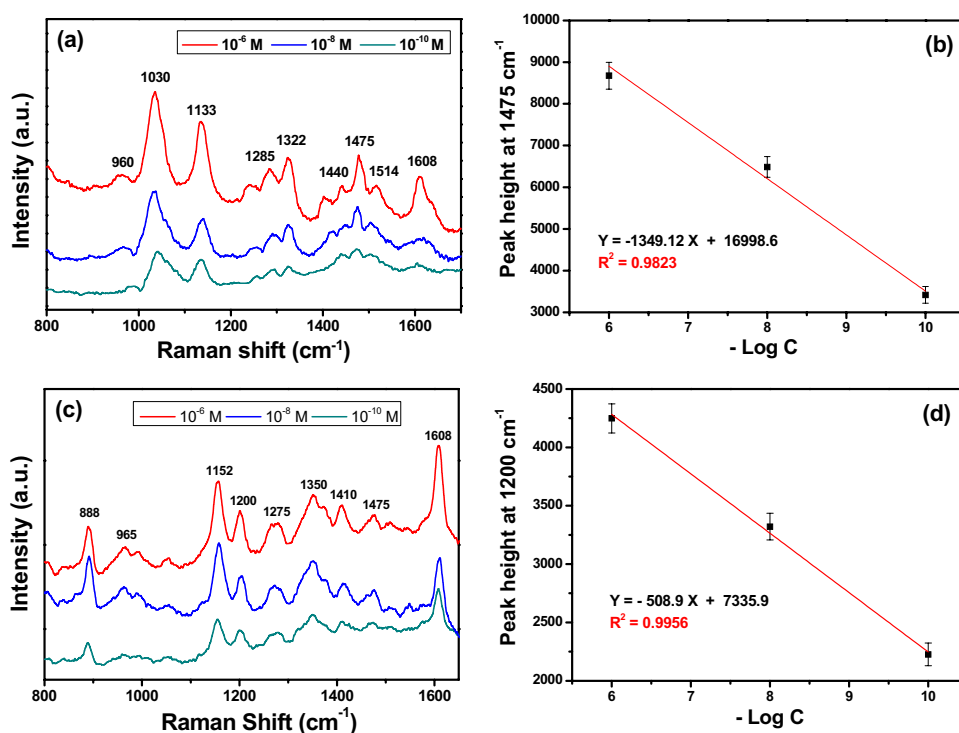


Fig. 2 SEM images of as-prepared samples: **a** freshly-etched porous Si (pSi) using AgNO_3/HF solution, **b** Ag-deposited pSi (Ag@pSi) after HNO_3 treatment, **c**, **d** EDX mapping and elemental composition

of the Ag@pSi, **e** Raman spectra of as-prepared Si samples without analytes. The scale bar is 10 μm

Fig. 3 **a** Raman spectra of DA adsorbed on the Ag@pSi substrate over the concentration range from 10^{-6} to 10^{-10} M, **b** standard curve between peak height at 1475 cm^{-1} versus log-scale concentration of DA, **c** Raman spectra of NE adsorbed on the Ag@pSi substrate over the concentration range from 10^{-6} to 10^{-10} M, **d** standard curve between the peak height at 1200 cm^{-1} versus log-scale concentration of NE



neurotransmitters (DA and NE) over the concentration range from 10^{-6} to 10^{-10} M. Figure 3a shows the Raman spectra of DA adsorbed on the Ag@pSi substrates, demonstrating the characteristics peaks of DA at 1030, 1133, 1285, 1322, 1475, and 1608 cm^{-1} , which were assigned to the C–O–H bending, C–N stretching vibration, ν_{15} , ν_3 , ν_{19b} , and ν_{8b} , respectively [3]. The peak at 1475 cm^{-1}

represents the typical ring stretching vibration of the C–C bond to which the oxygen is attached. Figure 3b shows the standard curve between the height of Raman peak at 1475 cm^{-1} versus log-scale concentration of DA, which was linearly regressed with a high reliability ($R^2=0.9823$): $y = -1349.12x + 16,998.6$ (y = peak height at 1475 cm^{-1} , x = logarithm of DA concentration).

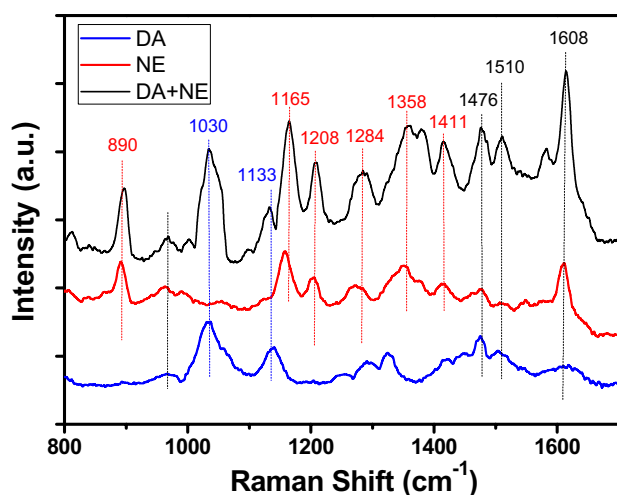


Fig. 4 Raman spectra of dopamine (DA), norepinephrine (NE), and the mixture of DA and NE. The concentration of each analyte was 10^{-8} M in the presence of ascorbic acid (10^{-5} M)

Figure 3c shows the Raman spectra of NE adsorbed on the Ag@pSi substrate at different concentrations. The Raman spectra showed peaks of NE at 1152, 1275, 1350, 1475, and 1608 cm^{-1} , which were assigned to CO stretching, CO asymmetric stretching, CH bending, CH_2 scissoring, and aromatic CC stretching, respectively [39, 40]. These results confirm the efficacy of the developed substrate for enhancing the Raman signals of the analytes for the sensitive detection of trace neurotransmitters. Figure 3d also shows the linear relationship between the peak height at 1200 cm^{-1} versus log scale concentration of NE. The standard curve was linearly regressed with a high reliability ($R^2 = 0.9956$): $y = -508.9x + 7335.9$ (y = peak height at 1200 cm^{-1} , x = logarithm of the NE concentration). The standard curves demonstrated the linear dynamic range over four orders of magnitude for the standard solution, suggesting a possible quantification of trace neurotransmitters (NRTs) in a bio-fluid.

To further extend the utility of the SERS technique, two neurotransmitters were simultaneously detected using the Ag@pSi substrate. The concentration of each neurotransmitter was set as 10^{-8} M in the presence of AA (10^{-5} M). Figure 4 shows all the Raman spectra of DA, NE, and the mixture. The characteristic peaks of DA and NE were observed in the Raman spectra of the mixture, in which the NE peaks at 890, 1165, 1208, 1284, 1358, and 1411 cm^{-1} appeared more distinctly in the mixed Raman spectra. On the other hand, some DA peaks at 1030 and 1133 cm^{-1} were apparent in the mixed Raman spectra, but some DA peaks disappeared due to overlapping with the strong NE bands. The peaks at 1476, 1510, and 1608 cm^{-1} for both DA and NE neurotransmitters were enhanced probably due to the existence of both neurotransmitters. The

distinct difference in the Raman spectra between DA and NE was due to the presence of characteristic peak of NE at 890 cm^{-1} , originating from the high polarizability of the $\text{C}_1'(\text{OH})\text{--}\text{C}_2'(\text{NH}_2)$ bond in the chemical structure of NE (see Fig. 1) [41]. The peaks of AA at 845, 1190, 1444, and 1656 cm^{-1} were not clearly observed, confirming the efficacy of the developed substrate on the sensitive detection of catecholamine neurotransmitters (DA and NE) [42]. Thus, it is highly anticipated that the optimally designed nanosilvers on the various substrates can enhance surface plasmon resonance and optical sensing capability [43–46].

4 Conclusion

Ag-deposited pSi (Ag@pSi) as a SERS-active substrate was fabricated using the combination of metal-assisted chemical etching and electroless plating methods. The Ag@pSi was employed to detect DA and NE neurotransmitters at nanomolar concentration. The standard curves demonstrated the linear dynamic range over four orders of magnitude (from 10^{-6} to 10^{-10} M) between the intensity of specific Raman peak and the log-scale concentration of the analyte. The developed Ag@pSi substrate demonstrated a promising capability for distinguishing the individual analytes in the mixed neurotransmitters (DA and NE at 10^{-8} M) in the presence of AA (10^{-5} M), corroborating the effectiveness of the developed SERS substrate for the reliable detection of trace neurotransmitters. Notably, the peak at 890 cm^{-1} served as a distinct marker for the hydroxyl group in the NE structure, which is quite different from non-polarized C–C bond of the DA structure.

Acknowledgements This research was supported by the Gachon University research fund of 2020 (GCU-202002730001), and also supported by the Korea Institute of Energy Technology Evaluation and Planning (KETEP) and the Ministry of Trade, Industry, and Energy (MOTIE) of the Republic of Korea [Grant No. 20194030202440].

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