Flexible Double-Sided Neural Probe for Real-Time Dopamine Detection in Parkinson's Disease

Han Hee Jung*

*Hannam Univ.

*hanheejung18@hnu.kr

파킨슨병의 실시간 도파민 검출을 위한 유연한 양면형 뉴럴 프로브

정한희*
*한남대학교

Abstract

Accurate monitoring of neurotransmitters like dopamine (DA) is crucial for understanding brain activity and managing neurological disorders, as DA imbalance is associated with diseases such as Parkinson's, schizophrenia, and addiction. This research presents a highly adaptable multi-deformable double-sided (MDD) probe for detecting DA in real time. The probe integrates a three-electrode system-working, reference, and counter electrodes-into a single platform. Enhanced DA sensitivity and selectivity are achieved by immobilizing enzymes on 3D nanostructures fabricated on the working electrode. To improve flexibility and durability, a serpentine pattern is used for the electrodes, effectively reducing stress during deformation. Both experimental results and simulations verify this stress reduction. The probe has been successfully implanted in rodent brains, enabling in vivo DA detection, including dynamic changes observed before and after LDOPA administration in a hemi-PD mouse model. This innovative, stretchable probe minimizes brain tissue damage, making it a promising tool for studying and treating neurodegenerative conditions.

Ⅰ. Introduction

Accurately monitoring dopamine (DA) levels is critical for understanding Parkinson's disease (PD), as DA dysregulation is central to its pathology. Traditional techniques like micro-dialysis and FSCV enable real-time monitoring but often cause tissue damage due to rigid neural probes. [1] Flexible probes made from polymers like polyimide or PDMS reduce tissue damage but struggle to incorporate a minimally invasive three-electrode system. [2] To overcome these challenges, a novel double-sided, stretchable neural probe was developed, integrating all three electrodes into a compact structure. The serpentine electrode design ensures mechanical stability under deformation, while in vivo tests in rats and hemi-PD mice confirmed its high sensitivity, stability, and reliability. This probe offers a minimally invasive solution for real-time DA monitoring in neurodegenerative disease research.

Ⅱ. Method

The MDD dopamine-sensing probe integrates a working electrode (WE), reference electrode (RE), and counter electrode (CE) into a compact, flexible platform using a PDMS substrate with distinct top and bottom layers. The top side features serpentine-patterned Cr/Au electrodes, with the WE enhanced by ZnO nanorods (NRs) to increase surface area and improve dopamine detection. The RE is coated with Ag/AgCl paste, while the bottom layer houses a Ti/Pt bi-layer CE in a similar serpentine layout, ensuring stable electrochemical performance. This dual-sided architecture enhances mechanical durability and

signal quality, while minimizing tissue damage upon implantation. Tyrosinase (TYR) is immobilized on the ZnO NRs through a multi-step process involving silica coating, amine-functionalization via APTES, and cross-linking with glutaraldehyde. Structural and compositional confirmation of the immobilization is achieved through SEM and EDX analysis, while FTIR spectroscopy verifies TYR presence. The combination of 3D ZnO NR structures and successful TYR immobilization significantly improves DA detection sensitivity and accuracy, underscoring the probe's potential for real-time electrochemical sensing.

The electrochemical properties of the surface modification process were analyzed using cyclic voltammetry (CV). The bare Au electrode exhibited the highest current response due to its superior electrical conductivity compared to modified electrodes such as Au/ZnO seed layer, Au/ZnO NRs, and Au/ZnO—NH2 NRs/TYR. As modifications progressed, the current response decreased due to reduced conductivity, but the ZnO NRs enhanced the WE surface area. The enzyme-immobilized electrode showed further reduction in redox current, confirming successful TYR immobilization and the effectiveness of the modification process for the MDD DA-sensing probe.

The MDD DA-sensing probe demonstrated rapid DA detection (≈ 1 second response time) across concentrations from 1 to 9 μM, with TYR-immobilized probes exhibiting much higher sensitivity (4.299 nA μM^{-1}) and a lower limit of detection (150 nM) compared to enzyme-absent probes. The probe's anti-interference properties were confirmed, showing strong selectivity for DA while minimizing responses to ascorbic acid (AA) and norepinephrine (NE). Long-term stability tests indicated the probe retained ~90% of its initial sensitivity over four weeks. These findings demonstrate the MDD DA-sensing probe's excellent stability, sensitivity and selectivity, making it well-suited for long-term in vivo DA monitoring.

For in vivo, we applied this hemi-PD mice model to further validate the functionality of the MDD DA-sensing probe during the pharmacological synthesis of DA from its precursor L-DOPA. The MDD DA-sensing probe was implanted into the lesioned Str in the hemi-PD mice model under anesthesia status. Interestingly, the DA signal in the MDD DA-sensing probe was gradually increased after L-DOPA injection, as compared to no injection control. About 10 min post-injection, the DA level was saturated to the highest level and sustained for as long as about an hour. Collectively, these data demonstrated that the MDD DA-sensing probe is compatible with real-time measurement of pharmacological DA dynamics in the Parkinson's disease (PD) mice model.

Ⅲ. Conclusion

Recent advancements in neural probe technology have enabled real-time neurotransmitter monitoring, but challenges like brain tissue damage and the need for multiple electrodes remain. To address this, a highly stretchable, double-sided MDD DA-sensing probe with a three-electrode system was developed. The probe uses 3D nano-forest-like structures for enzyme immobilization, achieving high dopamine (DA) sensitivity (− 4.299 nA μM^{-1}) and a low detection limit (150 nM). Serpentine-patterned electrodes enhance mechanical stability, reducing stress during deformation. Validated in wild-type rats and hemi-parkinsonian (hemi-PD) mice, the probe reliably monitored DA dynamics, including changes after L-DOPA treatment. Its minimally invasive design ensures low tissue damage, offering a robust platform for studying neurological disorders like Parkinson's disease (PD) and advancing treatments through real-time monitoring.

ACKNOWLEDGMENT

This work was supported by 2024 Hannam University Research Fund.

REFERENCES

[1] Parasad, A., Xue, Q. -S., Sankar, V., Nishida, T., Shaw, G., Streit, W. J., Sanchez, J. C., " Comprehensive characterization and failure modes of tungsten microwire arrays in chronic neural implants," J. Neural Eng., 9, 056015, 2012.

[2] Roberts, J. G., Lugo-Morales, L. Z., Loziuk, P. L., Sombers, L. A.,"Real-time chemical measurements of dopamine release in the brain," MithodsMol. Biol., 964, 275, 2013.