Wireless Neurochemical Monitoring in Humans

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Key Words

WINCS • Electrochemistry • Humans

Abstract

Electrochemical techniques have long been utilized to investigate chemical changes in the neuronal microenvironment. Preclinical models have demonstrated the successful monitoring of changes in various neurotransmitter systems in vivo with high temporal and spatial resolution. The expansion of electrochemical recording to humans is a critical yet challenging goal to elucidate various aspects of human neurophysiology and to create future therapies. We have designed a novel device named the WINCS (Wireless Instantaneous Neurotransmitter Concentration Sensing) system that combines rapid scan voltammetry with wireless telemetry for highly resolved electrochemical recording and analysis. WINCS utilizes fast-scan cyclic voltammetry and fixed potential amperometry for in vivo recording and has demonstrated high temporal and spatial resolution in detecting changes in extracellular levels of a wide range of analytes including dopamine, adenosine, glutamate, serotonin, and histamine. Neurochemical monitoring in humans represents a new approach to understanding the neurophysiology of the central nervous system, the neurobiology of numerous diseases, and the underlying mechanism of various neurosurgical therapies. This article addresses the current understanding of electrochemistry, its application in humans, and future directions.

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Introduction

Current methods of functional brain monitoring rely heavily on electrophysiological measurements. Similar to electrophysiological recording, electrochemical recording has demonstrated versatility in evaluating the neuronal microenvironment with high temporal and spatial resolution. Functional brain surgery aimed at modulation of subcortical brain structures, named deep brain stimulation (DBS), has provided a unique window of opportunity to apply electrochemical methods for monitoring changes in the neuronal milieu. DBS has demonstrated clinical efficacy in a multitude of neurological and psychiatric conditions including Parkinson's disease [1–3], dystonia [4–6], essential tremor [7–9], chorea [10, 11], epilepsy [12–14], chronic pain [15, 16], depression [17, 18], obsessive compulsive disorder [19–21], and Tourette's syndrome [22–25]. Although previously confined to animal research models, electrochemical methods have recently been successfully applied in humans to monitor real-time neurochemical changes during functional neurosurgery [26].

The application of electrochemical methods in humans is of considerable importance. The clinical efficacy of DBS in relieving symptoms of various neurological disorders is well established. This fact notwithstanding, the mechanism of action of DBS in such disorders is incompletely understood. Numerous studies have demon-

strated the robustness of electrochemical methods in assessing the modulatory mechanisms of DBS through analysis of changes in various neurotransmitter systems, including dopaminergic [27, 28], glutamatergic [29–31], adenosinergic [30, 32, 33], and serotonergic [34] systems. In contrast, other techniques, such as PET, have been unable to demonstrate changes in extracellular dopamine levels following DBS in humans [35–37]. Integrating electrochemical methods in human neurosurgery will help further elucidate the specific impairment of neurotransmitter systems in various neurological disorders. Furthermore, sustainable chronic neurochemical recording may serve as a novel technique allowing long-term monitoring of neurochemical imbalances underlying various disease states. Moreover, electrochemical methods applied in human neurosurgery will facilitate the development of next-generation, closed-loop neural interface devices based on neurochemically guided placement and control [38].

Electrochemical Recording

Electrochemistry has been shown to overcome the limitations of microdialysis, a nonelectrochemical method of recording analytes and the pillar of neurochemical recording for the past several decades. Indeed, electrochemistry has been shown to detect analytes in tissue with sensitivity, selectivity, subsecond temporal resolution, and minimal tissue damage [39–43]. These qualities of electrochemistry are vital for such studies as investigating the effects of high-frequency stimulation on neurotransmitter systems and correlating behavioral phenomena with neurochemical changes, where utilizing microdialysis would be problematic. In voltammetry, oxidation and reduction of analytes occur at an electrode surface when an electrical potential is applied. The transfer of electrons in these reactions results in currents with magnitude proportional to the concentration of the electroactive analyte [40], allowing for calculation of changes in the level of the analyte.

Of the various electrochemical approaches, fast-scan cyclic voltammetry (FSCV) has emerged as a robust technique for *in vivo* electrochemistry. In FSCV, linear changes in electrical potential are applied to the recording electrode at rates of hundreds of times per second, and the resultant oxidative and reductive currents of the analytes of interest are recorded. FSCV is applied through carbon-fiber electrodes with small diameters ($\approx 5 \mu\text{m}$), allowing for rapid diffusion of analytes around the electrode and

very high scan rates. The bidirectional nature of the applied potentials confers exquisite analyte specificity to FSCV. Indeed, numerous electroactive analytes are detected with FSCV such as dopamine, serotonin, adenosine, epinephrine, norepinephrine, and histamine. Together, these characteristics render FSCV an exceptional electrochemical technique for *in vivo* electrochemistry in humans preferable over other techniques such as fixed potential amperometry or differential pulse voltammetry [28, 34, 41, 44–46].

WINCS: Wireless, Real-Time FSCV

Transferring FSCV technology to the human brain in the operating room has been challenging. The intricacies and safety requirements of the neurosurgical operating room make integration of novel devices problematic, and no telemetry device was previously available. To meet these challenges, we developed the WINCS (Wireless Instantaneous Neurotransmitter Concentration Sensing) system, a device that combines rapid scan voltammetry with wireless telemetry. WINCS utilizes FSCV coupled with carbon-fiber microelectrodes, and has demonstrated high temporal and spatial resolution in detecting numerous neurotransmitters. Indeed, preclinical studies using this novel device have revealed considerable versatility, demonstrating the ability to detect changes in extracellular levels of a wide range of analytes including dopamine, adenosine, glutamate, serotonin, and histamine in addition to pH change [30, 28, 33, 34, 44, 47–49].

The WINCS apparatus is composed of four units, a microprocessor, a battery, a front-end analog circuit, and a Bluetooth transceiver, and is controlled using custom-designed software (WINCSware) [47, 48]. Specialized sensors have been fabricated for various applications, with one sensor, the WincsTrobe, specifically designed for human use. When compared with a conventional hardwired electrochemical recording system, WINCS demonstrated comparable sensitivity and release and uptake kinetics [44, 47]. Moreover, WINCS maintains high signal fidelity in the operating room environment, a finding attributed to signal digitization near the point of acquisition and utilization of digital telemetry for data transfer. Analysis of electromagnetic interference of the operating room setting on electrochemical recording revealed lower levels of interference with WINCS compared with conventional electrochemical monitoring systems [44]. Designed as a wireless device, WINCS does not

Fig. 1. WINCS attached to the neurosurgical stereotactic frame where it is coupled with the WincsTrobe implanted in the brain. WINCS is operated at a remote support station laptop computer with custom software.

contribute to crowding in the operating room, and is of a small size that allows attachment to the stereotactic head frame (fig. 1). The high signal fidelity precludes the need to use the Faraday cage routinely used with hardwired devices to reduce interfering electrical noise. Additionally, WINCS enjoys other critical advantages over commercially available wireless recording systems. These include a more advanced microprocessor with faster clock speed, greater internal memory, and superior analog-to-digital conversion. Furthermore, WINCS allows wireless programming of waveform parameters via an advanced Bluetooth module. WINCS also possesses superior battery life and higher precision voltage reference for the microprocessor [47, 50]. A critical feature of WINCS is the demonstrated functionality in the bore of a 3-Tesla MRI unit [48]. Collectively, these features render WINCS suitable for integration into functional neurosurgical procedures for intraoperative real-time neurochemical monitoring in humans.

FSCV in Humans

Recently, Kishida et al. [26] developed an electrochemical sensing electrode for use in humans. Their developed electrode was biocompatible, comparable in electrochemical performance to conventional carbon-fiber recording electrodes, and sterilizable with no effect on performance. The designed electrode incorporated a reference electrode, precluding the need for a further surgical implant. The electrode was comparable in dimensions to

electrophysiological electrodes used in DBS surgery, making it compatible with currently-used neurosurgical equipment. In order to examine the use of such an electrode assembly in humans, a proof-of-principle study with a single human subject was performed. The patient suffered from late-stage Parkinson's disease and was planned to undergo STN nucleus DBS surgery. The electrode assembly was inserted in the patient's right caudate nucleus, and a behavioral investment task was performed by the patient to stimulate reward systems. Concurrent measurement using FSCV at the electrode successfully demonstrated voltammetric traces consistent with dopamine release. Noteworthy, no side effects were described as the patient followed the projected clinical course. In this study, sustained electrochemical recordings suggest the feasibility of the use of this electrode for the duration of the surgical procedure.

WINCS for Wireless FSCV in Humans

Utilizing the WINCS system, we recently reported on the first use of electrochemistry in humans for measurement of adenosine in the thalamus [51]. In 8 patients diagnosed with essential tremor, WINCS was used during DBS of the ventral intermediate nucleus (VIM) of the thalamus for tremor control. Following MRI and electrophysiologic identification of VIM of the thalamus, the WincsTrobe (a column-type carbon-fiber microelectrodes coated with polyamide with an exposed length of less than 50 μm) was implanted in the VIM via a micro-

Fig. 2. **a** Representative pseudocolor plot demonstrating in vivo adenosine. The x-, y-, and color gradient axes represent time, applied voltage, and resulting current changes, respectively. Oxidation currents are detected at +1.4 V and +1.2 V, with a smaller current detected at +0.5 V, characteristic of adenosine FSCV.

b Current vs. time plot of first (black curve, corresponding to horizontal black line in **a**) and second (red curve, corresponding to horizontal red line in **a**) adenosine oxidation currents. **c** Background-subtracted cyclic voltammogram characteristic of adenosine.

drive through the same surgical trajectory as the electrophysiology electrode, averting the need for multiple surgical pathways. Following insertion of the WincsTrobe, FSCV was performed beginning with a resting potential of -0.4 V, increased to $+1.5$ V, and returned to the resting potential at a rate of 400 V/s and scanned at 10 Hz. Such a triangular waveform has been shown to detect adenosine in preclinical models [30, 33]. Application of this triangular current demonstrated a significant increase in adenosine oxidation current in addition to the signature cyclic voltammogram of adenosine with the characteristic twin current peaks at $+1.4$ V and $+1.2$ V (fig. 2). Importantly, in 7 of 8 patients undergoing awake DBS, a reduction of contralateral arm and hand tremor amplitude, as measured by a custom-built wireless three-axis accelerometer, was measured upon electrode insertion into the VIM, consistent with the microthalamotomy effect [30, 52]. In parallel with this reduction in tremor amplitude was a noticeable increase in recorded FSCV oxidation current peaks corresponding to adenosine and its oxidation catabolic product. In all patients in this series, no intraoperative or postoperative complications were noted related to the use of WINCS. These findings support the potential safety and feasibility of WINCS for acutely evaluating the neurochemical changes underlying improvement of motor symptoms following DBS surgery in humans.

Future Directions

The use of in vivo voltammetry continues to evolve. In spite of the established clinical efficacy of DBS in various neuropathologies, our understanding of the mechanisms underlying the clinical benefit of DBS is incomplete. Pre-clinical studies have demonstrated the value of applying neurochemical analysis during HFS. In humans, neurochemical monitoring will offer a novel avenue that will contribute to elucidating the neurochemical changes underlying the therapeutic effects of DBS. Therefore, one immediate objective is to utilize WINCS to investigate the mechanisms underlying the efficacy of DBS in the multitude of neurologic and psychiatric conditions treated by DBS. Expanding the functionality of WINCS to include detection of other important analytes, such as molecular oxygen and nitric oxide, is also a key objective. Furthermore, a deeper understanding of the chemical dynamics in various neuropathologies will allow for optimizing targeting of electrodes in functional neurosurgical procedures through chemically guided electrode placement.

Several lines of evidence converge on the axonal activation hypothesis as the mechanism of DBS [27, 53–56], where soma inhibition and axonal stimulation occur at the DBS electrode site with resultant modulation of neural network activity and neurotransmitter signaling in the brain. However, a better understanding of the mech-

anism of DBS is limited in part by the challenge of combining the evaluation of widespread neural network changes and specific neurochemical changes. Toward this end, ongoing studies by our group aim at combining functional MRI (fMRI) and electrochemical recording with WINCS. Such an approach is primed to uncover the region-specific effects of DBS on neurotransmitter systems. Preliminary studies have demonstrated that striatal dopamine release following STN DBS in a large animal model coincides with fMRI-identified increased striatal activation [57]. Studies combining fMRI and electrochemical analysis will allow the identification of specific neuroanatomical and neurochemical substrates of DBS, thereby allowing the refinement of surgical targeting to achieve optimal clinical benefit.

One crucial objective is the realization of long-term neurochemical monitoring in humans. Achievement of such a milestone would allow for a more comprehensive understanding of the correlation between alterations in neurotransmitter systems and clinical outcomes following DBS. WINCS is posed to serve as a neurochemical interface device that would allow for such long-term neurochemical monitoring. Furthermore, such a setup would pave the way for the development of next generation, in-

telligent DBS devices. Current DBS systems use open-loop stimulation, where stimulation is constantly running independent of any neurophysiological control. We envision closed-loop neuromodulation devices where neurochemical input would serve as feedback to regulate stimulation parameters for maintaining optimal neurotransmitter levels and behavioral control. Such a closed-loop device has been developed for the electrophysiologic control of medically refractory epilepsy (NeuroPace, Mountain View, Calif., USA). Here, subdural or depth electrodes recording cortical electrical activity serve as the afferent limb of the closed-loop device, providing input to the release of normalizing bursts of stimulation to abort the seizure [58]. A similar platform, with WINCS as the neural output device, may be key in realizing long-term neurochemical monitoring and control. These endeavors remain stimulating frontiers in neuroscience.

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