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Development of intraoperative electrochemical detection: wireless instantaneous neurochemical concentration sensor for deep brain stimulation feedback

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Abstract

Deep brain stimulation (DBS) is effective when there appears to be a distortion in the complex neurochemical circuitry of the brain. Currently, the mechanism of DBS is incompletely understood; however, it has been hypothesized that DBS evokes release of neurochemicals. Well-established chemical detection systems such as microdialysis and mass spectrometry are impractical if one is assessing changes that are happening on a second-to-second time scale or for chronically used implanted recordings, as would be required for DBS feedback. Electrochemical detection techniques such as fast-scan cyclic voltammetry (FSCV) and amperometry have until recently remained in the realm of basic science; however, it is enticing to apply these powerful recording technologies to clinical and translational applications. The Wireless Instantaneous Neurochemical Concentration Sensor (WINCS) currently is a research device designed for human use capable of in vivo FSCV and amperometry, sampling at subsecond time resolution. In this paper, the authors review recent advances in this electrochemical application to DBS technologies. The WINCS can detect dopamine, adenosine, and serotonin by FSCV. For example, FSCV is capable of detecting dopamine in the caudate evoked by stimulation of the subthalamic nucleus/substantia nigra in pig and rat models of DBS. It is further capable of detecting dopamine by amperometry and, when used with enzyme linked sensors, both glutamate and adenosine. In conclusion, WINCS is a highly versatile instrument that allows near real-time (millisecond) detection of neurochemicals important to DBS research. In the future, the neurochemical changes detected using WINCS may be important as surrogate markers for proper DBS placement as well as the sensor component for a “smart” DBS system with electrochemical feedback that allows automatic modulation of stimulation parameters. Current work is under way to establish WINCS use in humans.

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Disclosure

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Keywords

deep brain stimulation; dopamine; adenosine; serotonin; fast-scan cyclic voltammetry; amperometry; electrochemistry

Although DBS use has increased dramatically, with clinical indications expanding to neurological and psychiatric diseases, there is a great need to improve this functional neurosurgical technique. A major challenge is incomplete understanding of the DBS mechanism, especially why stimulation of specific targets is effective. Furthermore, DBS technology and procedures have remained largely unchanged for the past 20 years.³⁰ Subsecond monitoring of the neurochemical efflux secondary to DBS-targeted regions has the potential to advance functional neurosurgical procedures. Surrogate neurotransmitters involved in the clinical effectiveness of DBS may directly correlate with treatment outcomes.³⁰ In turn, one could conceive of chemically guided placement of DBS electrodes in vivo to assist our current practice of electrophysiologically guided placement.³⁰ This review addresses one such step toward neurochemically guided or modulated functional neurosurgery.

Neurochemical Monitoring

Microdialysis and voltammetry are the 2 most widely used techniques for neurochemical monitoring.⁷ Microdialysis has excellent selectivity and sensitivity but is limited in temporal resolution and has been the workhorse technique for sampling brain neurotransmitters over the last 3 decades.⁴⁷ Unfortunately, there are limitations to microdialysis; for instance, microdialysis requires multiminute collection times and may monitor trends in neurochemicals but not second-to-second changes necessary to investigate the subsecond changes in neuronal transmission evoked by electrical stimulation.^{17–20,28,43,44} Therefore, in relation to DBS, in which stimulation is applied 5 to 100s of times per second, microdialysis may not have the temporal resolution to determine neurochemical changes that are important for DBS feedback. Although predating microdialysis and offering the enticing potential of faster measurements with smaller probes and improving spatial resolution, voltammetry had initially struggled to compete with microdialysis due to poor selectivity.⁵ However, the modern era of electrochemistry has seen the rise of rapid sampling voltammetry, such as amperometry and FSCV. While microdialysis has been used in humans, electrochemical techniques have not. The same analytical attributes that have made this neurochemical monitoring technique attractive for brain behavior studies in awake laboratory animals may be valuable for human research.^{1,14,15,21–23,37–40}

Electrochemical Detection

In vivo electrochemistry most often uses microelectrodes of various fabrications that can be implanted into the brain and record relative changes in neurochemicals of interest. These electrodes are similar to contemporary extracellular electrodes used for electrophysiology with slight modification. The microelectrode can oxidize or reduce compounds of interest. Currents generated from these oxidation and reduction reactions may linearly be correlated to concentration of the electroactive molecule(s) in the extracellular environment. It is important to note that, while microdialysis allows for absolute determination of the concentration of a specific neurotransmitter, FSCV and amperometric techniques are limited to detect relative changes in neurotransmitters concentrations.

Amperometry

Fixed-potential amperometry, one of the simpler types of in vivo electrochemistry, involves the measurement of current at a fixed constant potential. The current is monitored continuously;

therefore, measurements can occur as frequently as ≤ 1 msec. Furthermore, amperometry has superb specificity when enzymes are applied to the recording surface to produce an electrochemically active reporter molecule, such as H_2O_2 , to allow measurements of molecules that are not naturally electrochemically active, such as glutamate. Currently, commercially available biosensors, not for use in humans, are sensitive to adenosine and glutamate (from both Sarissa Biomedical Ltd. and Pinnacle Technology, Inc.).³ As seen in Fig. 1, platinum recording electrodes that are coated with glutamate oxidase, an enzyme that reacts with glutamate to ultimately produce H_2O_2 , are capable of amperometrically measuring glutamate concentration changes. In addition, for oxidizable neurotransmitters such as dopamine, these amperometric techniques when coupled to carbon fiber microelectrodes can measure analytes of interest on rapid time scales (1–1000 msec), allowing for uptake and release kinetics of neurotransmitters to be easily studied. Thus, amperometry may be superior to microdialysis as a technique for monitoring neurochemicals in DBS.

Fast-Scan Cyclic Voltammetry

Like all voltammetry, a potential is applied to the electrode, and the current is measured. However, in contrast to amperometry where the potential is fixed, the potential is linearly changed with respect to time in FSCV. This novel detection scheme generates a voltammogram (that is, a plot of measured current versus applied potential) that serves as a chemical signature to identify an analyte. For example, dopamine oxidation occurs during a positive scan at approximately +0.6 V, and reduction of the electro-formed DOQ back to dopamine occurs during the negative scan at –0.2 V (Fig. 1). These electrically induced changes create 2 distinct peaks of current out of proportion to the background scan. The FSCV can detect other neurotransmitters such as serotonin, adenosine, norepinephrine, epinephrine, histamine, and nitric oxide.^{8,31,45} Furthermore, nonneurotransmitter phenomena such as pH shift or oxygen concentration can be measured.^{5,6,8}

Wireless Electrochemistry

Based on previous instrumentation by Garriss et al., our laboratory has developed WINCS (patent pending by Mayo Clinic) designed to perform human FSCV and amperometry.^{3,8,24,29} The device in its current form is pictured in Fig. 2. The WINCS is composed of front-end analog circuitry for FSCV/amperometry, a microprocessor, and a Bluetooth transmitter that is battery powered.^{3,8,29} The device works either with amperometric biosensors, or may be used with a carbon fiber microelectrode to perform FSCV as detailed above. These sensors require a reference electrode, consisting of silver/silver chloride in animal experiments (in humans, the reference electrode is made of stainless steel or carbon rather than silver/silver chloride). This device is controlled by a base station computer in a Windows-XP environment and custom software controlling the operational parameters of WINCS. Wireless data acquisition may occur at a rate up to 100 kilosamples per second. This system is described in detail in previous publications and has been shown to be equivalent to wired devices that would be incapable of human use.^{3,8,29} The WINCS-driven electrochemistry is summarized in Table 1.

Adenosine

Adenosine has been shown to be an important neurotransmitter in tremor, as well as epilepsy.^{4,9,10} Indeed, Bekar et al.,⁴ using adenosine amperometric electrodes, demonstrated that adenosine may be crucial for DBS effects for abolishing tremor in rat models. Amperometric detection of adenosine utilizes a multiple enzyme–linked biosensor consisting of adenosine deaminase, nucleoside phosphorylase, and xanthine oxidase to confer specificity to adenosine. This multienzymatic reaction results in a 2-second delay of adenosine detection.³³ On this biosensor, adenosine deaminase converts adenosine to inosine, which is subsequently converted to hypoxanthine by nucleoside phosphorylase, and ultimately, xanthine oxidase

oxidizes hypoxanthine to xanthine then uric acid which results in the production of H_2O_2 .³³ Again, H_2O_2 generates a signal by oxidation and release of 2 electrons detected at the platinum wire.³³ The WINCS has shown the ability to detect adenosine in in vitro experiments as well as in vivo rat experiments where adenosine is evoked by stimulation of the ventrolateral thalamus by amperometry.^{2,3} Recently, Swamy and Venton⁴⁵ described FSCV as a viable technique to measure adenosine, establishing it as the fastest technique to monitor adenosine. The subtracted voltammogram and pseudocolor plot are distinguished from dopamine in Fig. 3. Our laboratory has used this technique to demonstrate the ability to detect, within the physiological range, in vitro adenosine alone, as well as in the presence of supraphysiological dopamine.⁴¹ Moreover, it has been demonstrated that rat ventral tegmental/substantia nigra stimulation evoked release of adenosine in a time-locked manner in the caudate.⁴¹ Finally, FSCV has been proven as an effective method of detecting adenosine release during microthalamotomy in rats.¹⁶

Dopamine

Dopamine is essential in the pathophysiology of Parkinson disease. Clinically, STN DBS may reduce or perhaps eliminate the need for oral dopamine and is most effective in patients with Parkinson disease who respond well to levodopa, suggesting that effective DBS requires endogenous dopamine production.^{11,35} Moreover, DBS may induce dyskinesias, suggesting that there is excess dopamine present.³² Clinical observations such as these imply that an increase in dopamine may account for the therapeutic efficacy of STN DBS in patients with Parkinson disease. Indeed, amperometric recordings in the caudate nucleus during STN stimulation has been demonstrated to release dopamine in the rat.³¹ However, to date, human recordings of dopamine have not been obtained.

Due to the relative ease at which dopamine is oxidized to DOQ, dopamine is the ideal neurotransmitter to study with FSCV.⁵ The typical appearance of dopamine in FSCV is seen in Fig. 3. A triangular waveform is typically applied from -0.4 V to at least $+1.0$ but up to $+1.5$ V and then back to -0.4 V (Fig. 4).^{8,29,41,42} The WINCS has been shown to reliably detect dopamine in both in vitro and in vivo (rat) models in the context of interferents such as norepinephrine and serotonin.⁸ Moreover, dopamine is detected in the caudate of laboratory animals such as the rat, mouse, and pig in response to stimulation of the medial forebrain bundle, ventral tegmental area, and substantia nigra.^{3,8,41} Furthermore, WINCS is capable of measuring dopamine with a carbon fiber electrode by using fixed potential amperometry.³ Although this technique is not specific, drug manipulations may be used to verify dopamine as the source of the amperometric signal.³ Therefore, the use of WINCS to measure dopamine in humans undergoing STN DBS may prove to be valuable in proving or disproving the dopamine release hypothesis for therapeutic efficacy in patients with Parkinson disease.

Serotonin

Serotonin is thought to be an important neurotransmitter in depression due to the effectiveness of serotonin reuptake inhibitor therapy for depression.³⁶ Recently, DBS therapies have been approved for treatment-resistant depression.³⁴ Although it is uncertain if DBS contributes to local or remote serotonin release, we have demonstrated WINCS FSCV parameters that allow detection of a physiological level of serotonin in real time. Initially, FSCV parameters for serotonin were described using a V-shaped scanning protocol as is done with dopamine and adenosine; however, it was quickly realized that detection in this manner was inaccurate due to rapid and irreversible accumulation of oxidation byproducts at the carbon fiber electrode.^{25–27} To counteract this, an N-shaped wave-form, having a resting potential of $+0.2$ V, scanning to $+1.0$ V, then to -0.1 V and finishing at $+0.2$ V at a rate of 1000 V/second, was developed to measure serotonin.^{12,13} We have shown, using WINCS, that bipolar electrical stimulation

of the dorsal raphe nucleus in rats results in local efflux of serotonin detectable with this technique.²⁵ Future applications of WINCS to measure serotonin in humans undergoing neurosurgery for depression may prove to be valuable in assessing serotonin neuromodulation with DBS.

Glutamate

Glutamate is an excitatory neurotransmitter most commonly associated with epilepsy; however, its release may be important to essential tremor and other movement disorders.^{2,31} Fast-scan cyclic voltammetry is not capable of detecting glutamate because glutamate is not electrochemically active; however, fixed potential amperometry is relatively straightforward for this neurochemical as it requires only 1 enzyme to couple this for bioelectric detection. Our laboratory has shown that local thalamic stimulation results in glutamate release in rats.² This stimulated release is dependent on intensity, time, and frequency.² Furthermore, implantation of electrodes into the thalamus of the rat resulted in transient rise in adenosine and glutamate level by mechanical stimulation; this again may be involved in the microthalamotomy effect experienced by some patients after DBS surgery.¹⁷

Large Animal Model of DBS Surgery in Pigs

Deep brain stimulation has been demonstrated to be an effective therapy for medically intractable Parkinson disease, dystonia, and essential tremor.⁴⁶ Furthermore, there is accumulating evidence that DBS is effective for a plethora of conditions including cluster headache, epilepsy, depression, and Tourette syndrome. Using a large animal model (swine) of human DBS surgery, our laboratory is currently studying the mechanism of DBS. In this model, swine were placed in a custom-made stereotactic frame, and MR imaging was performed for targeting.⁴² After imaging, STN targets were confirmed using electrophysiological mapping of the STN followed by placement of a Medtronic 3389 DBS electrode.⁴² Subsequently, a carbon fiber microelectrode was placed into the caudate that was capable of detecting—by FSCV driven by WINCS—evoked dopamine in response to varying stimulation parameters.⁴² In response to stimulation, there was a consistently delayed increase in dopamine relative concentration in the caudate which was dependent on stimulus intensity, duration, and frequency (see Fig. 5).⁴² Interestingly, compared with similar work in rat studies, stimulation parameters were more consistent with human parameters, demonstrating the value of having a large animal model for DBS research.⁴² This experimental system suggests that we may be capable of detecting dopamine changes elicited remotely by DBS and use this information for modulation and stimulation feedback. Currently, this experimental setup is being evaluated in humans by our group with the approval of the institutional review board.

Future Directions

Deep brain stimulation likely evokes changes in neural activity and neurochemical transmission in interconnected structures within the neural network, which ultimately underlie clinical benefit. Nevertheless, our understanding of these electrochemical effects remains far from complete, in large part because of the technical difficulties in measurement modalities for global assessment of neural activity and chemical-specific sensing. There is a critical need to develop and integrate novel investigative approaches with animal models and in humans to bring new insights on the mechanisms of this powerful neurosurgical treatment. The WINCS has shown promise and versatility. Furthermore, WINCS has proven to be a highly versatile instrument that allows near real-time (subsecond) detection of neurochemicals important to DBS research. In the future, the neurochemical changes detected using WINCS may be important as surrogate markers for proper DBS placement as well as the sensor component for a “smart” DBS system with electrochemical feedback that allows automatic modulation of stimulation parameters. Current work is underway to establish WINCS use in humans.

Abbreviations used in this paper

DBS	deep brain stimulation
DOQ	dopamine ortho-quinone
FSCV	fast-scan cyclic voltammetry
STN	subthalamic nucleus
WINCS	Wireless Instantaneous Neurotransmitter Concentration Sensor

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FIG. 1.

Examples of electrochemical techniques. **Left:** Amperometry is performed by applying a constant potential to the biosensor, which, in this setup, is a platinum wire (PT). When used to measure glutamate as in the example, an enzymatic layer is applied to confer specificity. Here, local glutamate comes in contact with an immobilized glutamate oxidase (Glu-Ox) layer (fixed to surface with bovine serum albumin [BSA] and glutaraldehyde [glut]). Interfering molecules are blocked from the platinum wire by Nafion. Glutamate is enzymatically converted to H_2O_2 , which breaks down to 2 hydrogen molecules and oxygen releasing 2 electrons (e^-) that increase the current recorded in the platinum wire. **Right:** Fast-scan cyclic voltammetry is performed by applying a changing potential over a short period of time. For dopamine (DA) in this example, 10 times a second a potential is applied to a carbon fiber from -0.4 to $+1.3$ V and back to -0.4 V. During this cycle, dopamine is converted to DOQ releasing 2 electrons. The 2 electrons are returned (reduced) on the return to baseline potential. These electron transfers cause perturbations in the raw voltammogram. Where these perturbations occur is unique to the analyte and allows us to target specific neurotransmitters of interest. a-KG = α -ketoglutarate; $E(\text{V})$ = the voltage applied is varied.

FIG. 2.

Photograph of the intraoperative human use WINCS transmitter and device housing (A), hermetically sealed and capable of ethylene oxide sterilization. Note that each device after rigorous internal engineer testing is approved for human use only as noted on the main housing. The cable connection to the device is a single-orientation connection (B), as are the pin connections to the implantable biosensor (C). This ensures that connection setup can only be done in one manner for correct use.

FIG. 3. Typical subtracted voltammograms (**A1**, **B1**, and **C1**) and pseudocolor plots (**A2**, **B2**, and **C2**). Each neurotransmitter has a distinct voltammogram when the FSCV parameters are set to detect the respective analyte.

FIG. 4.

Applied FSCV waveforms for adenosine (400 V/second) (**A**), dopamine (400 V/second) (**B**), and serotonin (1000 V/second) (**C**). Each waveform is applied 10 times a second, which is represented in the main graphic depiction (100 msec). **Insets** are the waveform seen relative to 20 msec.

FIG. 5.

A: Fast-scan cyclic voltammetry dopamine measurements obtained in an anesthetized pig. The dopamine signal is shown on a pseudocolor plot, recorded at a carbon fiber microelectrode implanted in the caudate. This dopamine release was seen in response to electrical stimulation of the subthalamic nucleus (at various voltage strengths (1, 3, and 5 V) from a hand-held Medtronic stimulator (held constant 120 Hz, 2-second stimulation, 0.5-msec pulse width). The varying color intensities represent the voltage. Immediately after stimulation (artifact is the *rectangular signal* at 3–5 seconds), increasing levels of evoked dopamine (*green oval* seen from 5 to 10 seconds) are seen with increasing strengths of stimulation at 1, 3, and then 5 V. There is no visible release with 1 V. **B:** This signal is identified as dopamine by the characteristic shape in the cyclic voltammogram (increasing voltage stimulations increase the relative amount of dopamine released in response to stimulation). **C:** Current versus time plot showing the increasing release of relative dopamine with increasing stimulation voltages.

TABLE 1

Summary of WINCS FSCV and amperometry detection parameters*

Neurochemical	Mode	Wave	Parameters (V)	Scan Rate (V/sec)	Oxidation Peaks (V)	Reduction Peaks (V)
dopamine	FSCV	V shape	-0.4→+1.3→-0.4	400	+0.6	-0.2
dopamine	AMP		+0.8			
adenosine	FSCV	V shape	-0.4→+1.5→-0.4	400	+1.4, +1.0, +0.5	
adenosine	AMP		+0.5→0.6			
serotonin	FSCV	N shape	+0.2→+1.0→-0.1→+0.2	1000	+0.8	0
glutamate	AMP		+0.5→0.6			

* AMP = amperometry; sec = second.