Diamond Electrodes for Neurochemical Sensing

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Carbon-based electrodes combined with fast-scan cyclic voltammetry (FSCV) enable neurochemical sensing with high spatiotemporal resolution and sensitivity. While their attractive electrochemical and conductive properties have established a long history of use in the detection of neurotransmitters both in vitro and in vivo, carbon fiber microelectrodes (CFMEs) also have limitations in their fabrication, flexibility, and chronic stability. Diamond is a form of carbon with a more rigid bonding structure (sp3-hybridized) which can become conductive when boron-doped. Boron-doped diamond (BDD) is characterized by an extremely wide potential window, low background current, and good biocompatibility. Additionally, methods for processing and patterning diamond allow for high-throughput batch fabrication and customization of electrode arrays with unique architectures.

Keywords: diamond ; neurotransmitter ; FSCV ; electrode ; sensing

1. Introduction to Carbon-Based Sensors for Neurochemical Sensing

Disruption of chemical or electrical signaling in the brain underlies neurological disorders such as addiction [1][2][3], Alzheimer's disease [4][5][6], amyotrophic lateral sclerosis [7][8][9][10][11], chronic pain [12][13][14][15], depression [16][17][18], Huntington's disease [19][20][21], Parkinson's disease [22][23][24], and schizophrenia [25][26][27]. Detection methods for sensing neurochemicals in vivo for the study of neurological disorders would ideally be simultaneously sensitive, minimally-invasive, chronically stable, and relatively inexpensive. In a recent review by S. Niyonambaza et al., techniques for neurotransmitter (NT) identification and quantification were discussed in depth [28], including positron emission tomography and single photon NT identification and measurement [29][30][31], single-photon emission computed tomography [32][33], surface-enhanced Raman spectroscopy [34][35], fast-scan cyclic voltammetry (FSCV) [36][37][38], amperometry [39][40], high performance liquid column chromatography (HPLC) [41][42][43], fluorescence [44][45], optical fiber sensing [46][47], and colorimetric measurements [48][49][50], as seen in Table 1. Longitudinal positron emission tomography (PET), while non-invasive, is not adequately sensitive to detect subtle changes in dopamine (DA) levels. While each available technique yields useful information, it is fast-scan cyclic voltammetry (FSCV) and HPLC coupled with microdialysis that allow for high temporal and spatial resolution for the detection of neurotransmitters (NTs) [51][52][53][54]. Of these two techniques, HPLC-coupled microdialysis can have a temporal resolution of up to 1 min by combining injection and analysis, separating and quantifying various NTs. Microdialysis is a powerful technique due to its sensitivity, selectivity, and number of simultaneous metabolites that can be separated and quantified [55]. Classically, however, microdialysis lacks spatiotemporal resolution because it has a relatively large probe diameter (~200 µm) and a typical sample collection time of every ~5–20 min [55][56]. Likewise, microdialysis probes are associated with pronounced glial encapsulation and disruption of blood vessels in comparison to small-diameter carbon fiber microelectrodes (CFMEs) traditionally used for FSCV [57]. CFMEs detected a ~90% decrease in DA concentration within the immediate vicinity of a microdialysis probe (~200 microns) in comparison to levels measured ~1 mm away following probe insertion [58]. The relatively large scale of the microdialysis probe may disrupt release and reuptake of the neurochemicals of interest. These results imply that the accuracy of NT detection may be influenced by the tissue damage caused by microdialysis probes, motivating the development of improved technology.

As an alternative, FSCV has been used to measure sub-second neurochemical signaling through electrochemical detection in situ [59]. FSCV has been widely used for real-time detection of NTs and other important bioanalytes, including oxygen (O_2) and pH change. It provides improved spatiotemporal resolution compared to other short-time scale electroanalytical techniques such as chronoamperometry (CA). The technique uses an ultramicroelectrode with a small biological footprint (~7 µm in diameter) to produce a background-subtracted signal with high temporal resolution and nanomolar sensitivity [60][61][62][63][64][65][66]. FSCV involves two central steps: (1) adsorption of electroactive species of interest (e.g., neurochemicals) to the electrode surface is favored by the application of a small DC holding potential, and (2) a triangular voltage pulse is repeatedly swept across the interface to produce signature peaks in Faradaic current which result from oxidation/reduction of adsorbed neurochemicals. These peaks can be used to identify the specific

neurochemical (based on the corresponding potentials) as well as its concentration (based on current amplitude). The typical voltage waveform that has been optimized to achieve selectivity, sensitivity, and stability for measuring DA with CFMEs is an applied potential swept from −0.4 to 1.3 to −0.4 V at 400 V/s, and reapplied at a frequency of 10 Hz [67][68]. Using this waveform and other developed waveforms, FSCV has been used to probe not only DA and serotonin (5-HT), but also other oxidizable neurochemicals, such as 3,4-dihydroxyphenylacetic acid (DOPAC), purines, ascorbic acid (AA), adenosine, norepinephrine (NEP), oxygen, pH changes, and hydrogen peroxide in vivo . Improvements in selectivity and sensitivity have been achieved through further development of FSCV waveforms and application rate optimization. Development has also expanded NT measurement from phasic to tonic quantification and worked to increase technique safety and address biofouling effects on the chemical measurement [69][70][71][72][73][74].

2. CFME

The most commonly used materials for NT measurement with FSCV are carbon fibers due to their biocompatibility, electrochemical, and conductive properties [75][76][77][78]. CFMEs have been the cornerstone of in vivo FSCV and a bevy of data exist for the detection of electroactive NTs like DA, serotonin (5-HT), DOPAC, and others. Ralph Adam's lab was the first to electrochemically measure DA in vivo using a carbon electrode consisting of graphite mixed with mineral oil [79]. Later, CFMEs were developed and used for dopaminergic and electrophysiological measurements in vivo, first published by Gonon [80], and then by Armstrong-James and Millar in 1979 [81]. Using the CFME, in 1981, Millar developed the technique of FSCV that was later popularized by Wightman [81][82][83]. A typical CFME consists of a carbon fiber that is aspirated into either a glass or silica capillary, or encased in some other insulating medium, such as parylene-C [84][85][86]. Electrodes also can be coated with polymers and other carbon-based materials to enhance the sensitivity and selectivity for various NTs [87][88][89]. Additionally, CFME surfaces can be functionalized with ease to tune the electrode to increase selectivity and decrease biofouling. Such coatings include: Poly(3,4-ethylenedioxythiophene) (PEDOT):Nafion, PEDOT:phosphorylcholrine [90], PEDOT: poly(ethyleneimine) (PEI) [88], CFME:gold nanoparticle [91], carbon nanospikes [92], Nafion carbon nanotubes [93][94], polycrystalline boron doped diamond [95][96], and carbon nanotube yarn [97][98]. Each coating has been tailored to not only increase sensitivity to NTs such as DA, but also to decrease the effects of biofouling and increase in vivo sensor lifetime.

Table 1. Summary of neurotransmitter detection techniques.

Techniques	Advantages	Shortcomings	Reported LOD
PET	High spatial resolution	Complex manipulation Very high cost	Dopamine: 200 nM [99]
SPECT	High spatial resolution	Complex manipulation Very high cost	
SERS	Very high sensitivity and selectivity	Can be inapplicable in vivo depending on used material	Choline: 2 µM Acetylcholine: 4 µM Dopamine: 100 Nm Epinephrine: 100 µM
FSCV	High sensitivity	Low selectivity Electrode short lifetime	Dopamine: 50 nM
Amperometry	Low implementation cost	Low sensitivity and selectivity	Dopamine: 10 nM [100]
HPLC	High sensitivity and selectivity	High cost and complex manipulation	
Fluorescence	High sensitivity and selectivity	May not be usable in vivo	Dopamine: 10 pM

Techniques	Advantages	Shortcomings	Reported LOD
Chemilumin-escence	High sensitivity, and ease to couple with other methods	Indirect measurement through the loss of a signal due to a binding event	6 nM
Optical Fiber Sensing	High selectivity	Low sensitivity	Glutamate: 0.22 µM
Colorimetric	High sensitivity and selectivity, low cost	Not usable in vivo	Dopamine: 1.8 nM Noradrenaline: 20 µM Adrenaline: 2.5 µM

Table based on S. Niyonambaza et al. (reproduced from [28] under a Creative Commons Attribution 4.0 International License).

Despite their advantages, CFMEs have drawbacks which have motivated the search for alternative materials for in vivo FSCV. CFMEs are brittle and easily broken during insertion into the brain. Likewise, their long-term stability is compromised by dissolution of the carbon fiber electrode material that can result in significant degradation and loss of sensitivity over time. CFMEs are often fabricated through proprietary mechanisms, using low-throughput assembly methods, and are designed for industrial processes rather than electrochemical purposes[101]. Recently, boron doped diamond (BDD) deposition and growth processes were developed that enable the wafer patterning and growth of custom-deposited carbon electrodes [102][103][104][105]. Through these growth processes, BDD was grown on tungsten wires and carbon fiber surfaces. More recently, custom BDD microelectrodes (BDDMEs) encapsulated with polycrystalline diamond were developed [106][107]. BDD is an attractive material because it has a low background current, a wide potential window, and good biocompatibility [108][109][110]. Using BDD, Rusinek et al. showed that BDDMEs were suitable for neurochemical measurement using an all-diamond-electrode rather than the deposition of BDD onto another medium [103]. As carbon fibers are proprietarily fabricated, limiting the modification of the material for an optimized structure–function relationship, BDD electrodes are attractive due to the tunability of the carbon sp^2 to sp^3 ratio [111][112][113][114]. Increasing the sp^2 character of the BDD increases the density of electronic states, and provides catalytic sites for redox reactions through adsorption sites. By using the BDD growth process, electrodes can be further tailored to enhance specific electrochemical properties. Such modifications include adjusting the structure–function relationship of the material to enhance conductivity, decrease capacitance, and increase chemical functionalization for selectivity and sensitivity. Additionally, recent advances in electrode array technologies for voltammetric measurements include multi-barrel glass capillary arrays [115][116], patterned arrays on silicon wafers [117][118], or parylene-C insulated multichannel carbon fiber electrode arrays [119]. While these arrays are powerful, most rely on hand fabrication processes under a microscope and are cumbersome, and slow. Open opportunities remain to improve the design and performance of carbon-based neurochemical sensors, including the development and optimization of diamond-based electrodes.

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