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## Enhanced dopamine detection sensitivity by PEDOT/graphene oxide coating on in vivo carbon fiber electrodes

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## ABSTRACT

Dopamine (DA) is a monoamine neurotransmitter responsible for regulating a variety of vital life functions. In vivo detection of DA poses a challenge due to the low concentration and high speed of physiological signaling. Fast scan cyclic voltammetry at carbon fiber microelectrodes (CFEs) is an effective method to monitor real-time in vivo DA signaling, however the sensitivity is somewhat limited. Electrodeposition of poly(3,4-ethylene dioxythiophene) (PEDOT)/graphene oxide (GO) onto the CFE surface is shown to increase the sensitivity and lower the limit of detection for DA compared to bare CFEs. Thicker PEDOT/GO coatings demonstrate higher sensitivities for DA, but display the negative drawback of slow adsorption and electron transfer kinetics. The moderate thickness resulting from 25 s electrodeposition of PEDOT/GO produces the optimal electrode, exhibiting an 880% increase in sensitivity, a 50% decrease in limit of detection and minimally altered electrode kinetics. PEDOT/GO coated electrodes rapidly and robustly detect DA, both in solution and in the rat dorsal striatum. This increase in DA sensitivity is likely due to increasing the electrode surface area with a PEDOT/GO coating and improved adsorption of DA's oxidation product (DA-o-quinone). Increasing DA sensitivity without compromising electrode kinetics is expected to significantly improve our understanding of the DA function in vivo.

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### 1. Introduction

Neurochemicals, such as dopamine (DA), are responsible for the regulation of a myriad of physical and cognitive functionality (Brooks, 2001; Hull et al., 1999; Urban et al., 2012). Observing the real-time kinetics of in vivo neurochemical signaling is paramount to uncovering these functionalities and furthering our understanding of brain function and dysfunction. Electrochemical methods, such as fast scan cyclic voltammetry (FSCV) and chronoamperometry, have been widely employed for the sub-second detection of electroactive neurochemicals such as dopamine (Jones et al., 1995; Kawagoe et al., 1992; Larsen et al., 2011; Taylor et al., 2013, 2015; Wightman et al., 1988), ascorbic acid (Cofan and Radovan, 2008; Yoshimi and Weitemier, 2014), norepinephrine (Park et al., 2011), adenosine (Nguyen et al., 2014; Ross et al., 2014) and serotonin (Hashemi et al., 2012, 2009, 2011). The high temporal resolution afforded by these electrochemical detection techniques allows for in vivo concentration monitoring of neurochemicals on

a physiologically relevant timescale (Robinson et al., 2011). Chronoamperometry provides superior temporal resolution but lacks analyte selectivity, while FSCV forfeits temporal resolution for the ability to discern specific analytes via a diagnostic cyclic voltammogram fingerprint. Due to the importance of selectivity, FSCV is often considered a more favorable detection method.

Carbon fiber microelectrodes (CFE) have been used as an electrochemical detector for in vivo neurochemical monitoring for decades (Gonon et al., 1978) due to its efficient electrical conductivity, adsorptive capabilities, and small size (McCreery, 2008). In fact, in vivo monitoring of cerebral systems using CFEs has significantly enhanced our understanding of a wide range of cognitive functionalities such as reward (Ambrosi and Pumera, 2013), addiction (Phillips et al., 2003a) and motor control (Giros et al., 1996). The use of a small electrode imparts many advantages for in vivo electrochemical detection. First, the small size of the electrode allows for rapid alteration of applied potential. Rapid potential sweeping is necessary for the use of FSCV. Second, the small dimensions of the CFE mitigates damage caused by electrode insertion. The insertion of a 7 μm diameter CFE has been shown to elicit significantly less immune response than a 200 μm diameter microdialysis probe in the rat dorsal striatum (Jaquins-Gerstl and

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Michael, 2009; Peters et al., 2004). It is well documented that the introduction of large foreign bodies into healthy neural tissue elicits a substantial immune response localized to the damage site immediately upon penetration (Borland et al., 2005; Jaquins-Gerstl and Michael, 2009; Jaquins-Gerstl et al., 2011; Kozai et al., 2015). This host tissue response disturbs the “healthy” neuronal tissue, subsequently altering the kinetics of neurotransmitter release, uptake, and diffusion (Borland et al., 2005; Mitala et al., 2008; Nesbitt et al., 2013, 2015; Wang and Michael, 2012). Third, the small size of the CFE allows for the detection of individual groupings of neurons. This provides the high spatial resolution necessary to map regions of discrete neurotransmitter kinetics throughout the brain (Moquin and Michael, 2009; Shu et al., 2013; Taylor et al., 2015). While these features make the CFE an attractive *in vivo* detector, there is still room for improvement. CFEs exhibit a 200 nM limit of detection and a moderate sensitivity for DA (sensitivity dependent on the length of the exposed carbon fiber). Recent efforts have been made to improve the performance of carbon based electrodes, such as incorporation of single wall carbon nanotubes onto the CFE surface (Ross and Venton, 2012; Swamy and Venton, 2007; Xiao and Venton, 2012), the development of carbon nanotube fibers and yarns (Jacobs et al., 2014; Schmidt et al., 2013; Zestos et al., 2014, 2013), the advancement of carbon nanopipettes (Phillips et al., 2003b) and the deposition of conductive polymers and coatings (Gerhardt et al., 1984; Vreeland et al., 2015).

Conductive polymers can be controllably deposited on a substrate surface via the application of a potential sufficient to oxidize and polymerize the specific monomer. The introduction of a thin conductive polymer film increases the effective surface area in addition to incorporating a specific reactive surface on the electrode substrate without sacrificing the conductive property of the electrode. Poly(3,4-ethylene dithiophene) (PEDOT) is electropolymerized from 3,4-ethylene dithiophene (EDOT) monomers. The oxidative polymerization of PEDOT results in positive charges on the polymer backbone, this allows for the incorporation of negatively charged doping agents, such as graphene oxide (GO) (Luo et al., 2013a; Wang et al., 2015, 2014; Weaver et al., 2014a, 2014b), polystyrene sulfonate (PSS) (Alemu et al., 2012; Tait et al., 2013), carbon nanotubes (CNT) (Gerwig et al., 2012; Luo et al., 2011; Xu et al., 2013), Nafion (Vreeland et al., 2015; Wang and Olbricht, 2010) and tosylate (Larsen et al., 2012; Vreeland et al., 2014), for the purpose of charge balancing. The introduction of a doping agent also has the added benefit of incorporating additional reactive functional groups. GO, a negatively charged molecule, has great potential in the fields of biosensing, tissue engineering, and drug delivery. The extensive oxidative functionalization of the GO surface inhibits electrical conductivity due to the interruption of conjugated pi bonding (Dreyer et al., 2010). Incorporating GO into the PEDOT conductive polymer coating as a dopant allows for it to be used in an electrode material without the associated drawbacks of an electrical insulator.

PEDOT functionalized materials are widely used as electrochemical sensors (Nie et al., 2013; Zhang et al., 2014, 2015). In particular, PEDOT/GO and its PEDOT/reduced GO counterpart have been shown to be effective for the selective chemical sensing of DA on 3 mm diameter glassy carbon macroelectrodes using conventional cyclic voltammetry (100 mV/s sweep rate) (Wang et al., 2014; Weaver et al., 2014b). In addition, PEDOT/GO coatings can undergo controlled drug delivery upon the application of a trigger potential (Weaver et al., 2014a) or be functionalized to promote cellular interactions for tissue engineering applications (Luo et al., 2013b). These factors make PEDOT/GO a desired coating for CFE modification.

## 2. Materials and methods

### 2.1. Carbon fiber electrodes

Single carbon fibers (7  $\mu\text{m}$  diameter, T650; Cytec Carbon Fibers LLC, Piedmont, SC, USA) were threaded into borosilicate glass capillaries (0.4 mm ID, 0.6 mm OD; A-M systems Inc., Sequim, WA, USA) and pulled to a fine tip (8  $\mu\text{m}$  OD) using a vertical electrode puller (Narishige puller, Los Angeles, CA, USA). Electrode tips were sealed using low viscosity epoxy (Spurr Epoxy; Polysciences Inc., Warrington, PA, USA). The exposed carbon fibers were trimmed to 400  $\mu\text{m}$  length and electrical connection was established via a drop of mercury and a single nichrome wire (annealed nichrome; Goodfellow, Oakdale, PA, USA). Fully assembled electrodes were soaked in isopropanol (Bath et al., 2000) for 15 min prior to bare electrode calibration, prior to PEDOT/GO coating and prior to calibration post PEDOT/GO coating.

### 2.2. GO synthesis and PEDOT/GO electropolymerization

GO was synthesized via the modified Hummer's method used in previous work (Hummers and Offeman, 1958; Luo et al., 2013a; Weaver et al., 2014a, 2014b) and stored as a concentrated stock in water until use. Prior to use, GO was diluted to 5 mg/mL with water and spiked with 1  $\mu\text{L}/\text{mL}$  EDOT monomer. The EDOT/GO solution was stirred vigorously overnight at 4  $^{\circ}\text{C}$  prior to 60 min (Weaver et al., 2014b) of continuous probe sonication. Probe sonication serves to mechanically exfoliate the GO nanosheets, altering the size and thickness of the GO nanoparticles (Weaver et al., 2014a, 2014b), in addition to aiding the dissolution of the EDOT monomer. The EDOT/GO solution was prepared in an aqueous solution in the absence of salt to ensure that GO was the sole dopant (Luo et al., 2013a). Conductivity within the EDOT/GO solution was maintained by the presence of negatively charged GO molecules. PEDOT/GO films were electrochemically deposited onto CFE surfaces via chronopotentiometry using a three electrode setup (isopropanol soaked CFE: working, Pt sheet: counter, Ag/AgCl wire: reference) at a Gamry potentiostat, FAS2 femtostat (Gamry Instruments, Warminster, PA, USA). Chronopotentiometry consisted of a single current step from 0 to 12.55 nA for a period of 5, 10, 25, 50, or 100 s. Coated electrodes were rinsed in water and soaked in isopropanol for 15 min prior to calibration. The reference electrode was stable upon repeated polymerizations, both within and between days, when stored in 1 M KCl between uses. Electrochemical impedance measurements were collected from  $n=3$  individual electrodes from each PEDOT/GO deposition duration condition in PBS using a three electrode setup (PEDOT/GO coated CFEs: working, Pt sheet: counter, glass enclosed Ag/AgCl: reference) at an Autolab potentiostat/galvanostat PGSTAT128N (Metrohm, Herisau, Switzerland). Impedance values were in response to a series of 15 mV sinusoidal alternating currents applied in a frequency range between 1 Hz and 100,000 Hz.

### 2.3. Fast scan cyclic voltammetry

FSCV was performed using a two electrode system (CFE: working, glass enclosed Ag/AgCl: reference) at a locally built potential driver (University of Pittsburgh Electronics Shop, Pittsburgh, PA, USA) and a Keithley 428 current amplifier (Keithley Instruments, Cleveland, OH, USA) controlled by the CV Tar Heels LabVIEW program (CV Tar Heels v4.3, courtesy of Dr. Michael Heien, University of Arizona, Tucson, AZ, USA). The potential waveform consisted of a 400 V/s sweep from the 0 V resting potential up to +1.0 V, down to  $-0.5$  V, and back to the 0 V resting potential applied at 10 Hz. DA detection was confirmed via identification of the background subtracted cyclic voltammogram. The

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